ISTITUTO NAZIONALE TUMORI "REGINA ELENA" • Roma
"REGINA ELENA" NATIONAL CANCER INSTITUTE • Rome

SCIENTIFIC REPORT 2003

Codice Anagrafe Ricerca: L123003Z

IRE
ISTITUTO NAZIONALE TUMORI REGINA ELENA

ISTITUTO NAZIONALE
TUMORI "REGINA ELENA"

Via Elio Chianesi, 53
00144 Roma
Tel. +39 06 52662728-5330
Fax +39 06 52665523
e-mail: dirscire@ifo.it
www.ifo.it

Center for Experimental Research

Via delle Messi d'Oro, 156/158
00158 Roma
Tel. +39 06 52662538
Fax +39 06 52662502
email: dirsci@ifo.it
www.ifo.it

Intermedia editore
Healthcare Communication Network
via Malta 12B - 25124 Brescia
Tel. 030.226105 - Fax. 030.2420472
imediabs@tin.it
Via C. Morin, 44 - 00195 Roma
Tel. 06.3723187
intermedia@intermedianews.it
www.medinews.it

Index

Scientific Director's Reports

Francesco Cognetti

Scientific Director

Professor Francesco Cognetti is currently the Scientific Director of the Regina Elena Cancer Research Institute in Rome.
Professor Cognetti designed and conducted relevant clinical studies in 1980's and 90's in the field of the treatment of head and neck cancer leading to significant contribution in the development of combined treatments in localized disease and new drugs in the advanced or metastatic setting. He also conducted studies on supportive care in neoplastic patients mainly on control of emesis during chemotherapy.
He is presently conducting large scale controlled clinical trials on adjuvant chemotherapy in operable breast cancer as chairman of the GIM (Gruppo Italiano Mammella), which is the unique national cooperative group for clinical research on breast cancer.
He obtained a Master's degree in Medicine and Surgery in 1975, and went on to specialize in Internal Medicine in 1981. Then from 1984, he followed a career in Oncology, and gained European Certification in Medical Oncology in London in 1989.
Professor Cognetti is a member of several international organizations such as ESMO (the European Society for Medical Oncology) where he was Chairman of the Membership Committee. He was a member of the Executive Board and the Steering Committee and is the national representative for Italy, as well as being an active member of the Head and Neck Cooperative Group of EORTC (the European Organization for Research and Treatment of Cancer), where he was secretary.
He also represents Italy through his involvement in several prestigious organizations including AIOM (the Italian Association of Medical Oncology) where he was President until October 2003, as Secretary and Treasurer of the Italian Alliance against Cancer Association, as an elected member of the Italian Health Governing Council and as a member of the Italy-USA Executive Committee for Research in Oncology. He is also member of the National Committee for Oncology, appointed by the Minister of Health.
Professor Cognetti is the author and co-author of more than 200 publications. He is also a Peer Reviewer of the Annals of Oncology, the official journal of the European Society for Medical Oncology.

Staff:

Secretariat:
Federica Cervini
Sandro Genovesi
Carmela Matrascia
Giovanna Santuccio
Antonio De Paolis

Fund raising office:
Anne Sonia Convers

International Affairs Bureau:
Ilaria Vallati

Research Administration Office (Unità amministrativa per la ricerca - S.A.R.):
Tommaso Coppola - Director
Piera Brugnoli
Sabrina Del Pesco
Maria La Rosa
Doriana Salvati

Education (CME) and Training, Congress Center Management:
Eugenio Poggi
Carol Scioscia
Sabrina Soresi

Data Center for Clinical Trials:
Diana Giannarelli - Director
Federica Falcioni
Barbara Matrascia - Contracted staff
Mario Pellicciotta - Contracted staff
Isabella Sperduti - Contracted staff

Office for the Management of the Regional clinical and scientific activity:
Italo Lorenzon

Library, scientific information and documentation:
Gaetana Cognetti - Director
Emanuela Dimiziani - Director
Giovanni Cavallotti
Giuseppe Filardo
Antonio Verbicaro

Photographers - Tecnical Service:
Ivana Zardin
Mauro Di Giovanni

During 2003 a notable expansion has been realized in the scientific research and clinical activity, in the educational projects of the Regina Elena, as well as the structuring and organization of various sections in which the Scientific Directorship is organized.
Our intention in this volume is to present in detail the scientific activity of the various Divisions and Centers which comprise the Institute. As shown in the tables to be found herein, 179 scientific papers have been published in journals with - quoted impact factor - compared to 134 the preceding year, and includes a rise in impact factor (617 vs. 543). This increase pertains to all the Departments of the Institute. Instead, there has been a decrease in papers published in journals without a quoted impact factor compared to those with impact factor. Moreover, 19 books or chapters of books have been published. Compared to the preceding year, there has also been a significant increase in participation on behalf of the researchers of the Institute at national and international congresses, and 253 abstracts have been presented therein.
The high level of activity of the researchers of the Regina Elena Institute is testified by their ability to obtain resources as illustrated in the following tables and graphs. The Ministry of Health, AIRC, the Italian Tumor League, Lazio Region, CNR-MIUR, the Italian Institute of Health, CEE, and others were the most contributing Institutions.
The Research activity of the Experimental Oncology Department has mainly been focused on new molecular indicators useful in the diagnosis and prevention of tumors, on new approaches to preclinical drug, on the genetics of tumors, immunotherapy, vaccines and gene therapy. The use of animal models (transgenic mice and nude mice with human tu-

mor transplants) has permitted the production of specific antibodies for functional domains of oncoproteins.

During 2003, the Institute has proceeded with the projects of Alliance Against Cancer - and cooperation has been consolidated with the other six oncologic IRCCS divisions on these studies.

Furthermore the clinical activity has been significantly increased in 2003, as illustrated in the graphs with 13,119 normal and daily admissions and 738,937 outpatient services.

The establishment of a Data Center for Clinical Trials enabled remarkable development of clinical research in our Institute, which gained second place amongst all the Italian Institutes (IRCCS, Universities and General Hospitals) for the number of clinical trials in the oncological field according to the special classification recently published by the National Observation Center for clinical trials on drugs.

The Epidemiology Division in particular has intensified its research on risk factors and lifestyles related to primary prevention, has cooperated with the European investigation – Eurocare – on the incidence and survival of tumors and the genetic risk of some tumors.

One hundred and fifty three clinical studies have been initiated during 2003, and 1,387 new patients have been enrolled. The Regina Elena has sponsored 23.5% of these trials.

The Data Center for Clinical Trials has dedicated a great deal of its activity this year for the adaptation of new norms for Clinical Trials introduced in our country according to European Directives (instituted in January 2004). Furthermore, the Data Center for Clinical Trials has worked on establishing a clinical data base along with a tissue and biological data base within a sigle Date Bank system.

Moreover 111 educational and scientific events have been organized, 6 of which concerned mainly the training of non-graduate personal and 105 with clinical and experimental research personal, totaling 531 CME points.

I must thank all those in charge of Clinical and Experimental research, the Directors of Departments and all the personal for their active service carried out during the course of the year 2003.

My thanks also go to Ada Sacchi, Diana Giannarelli and Massimo Zeuli as well as all the staff of the Scientific Director for their invaluable contribution with the editing.

The research activity presented in this volume has been made possible also thanks to the contributions of the Ministry of Health, the Italian Association for Cancer Research (AIRC) and the Italian League for the Fight Against Tumors, as well as the other Authorities/Corporations and Private companies.

Francesco Cognetti
Scientific Director

Scientific Activity

Publications

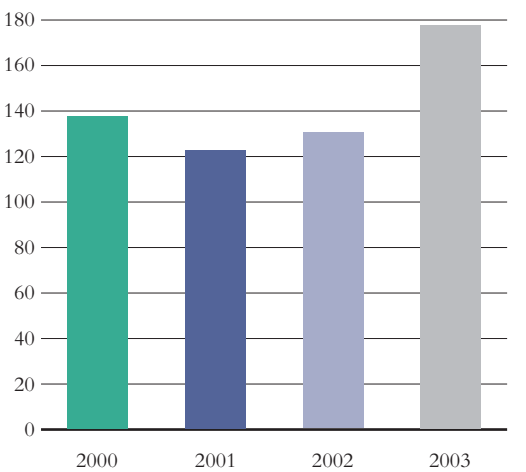
Departments	2000	2001	2002	2003
Central Facilities	17	25	21	41
Surgical Oncology	28	34	23	36
Medical Oncology	30	29	33	47
Prevention and Diagnosis	39	32	41	35
Neuroscience & Head - Neck Pathologies	8	4	5	9
Critical Area	7	15	2	13
Experimental Oncology	47	35	43	46
Therapeutic Programs Development	31	30	26	31
Total	**207**	**204**	**194**	**258**

Impact Factor *

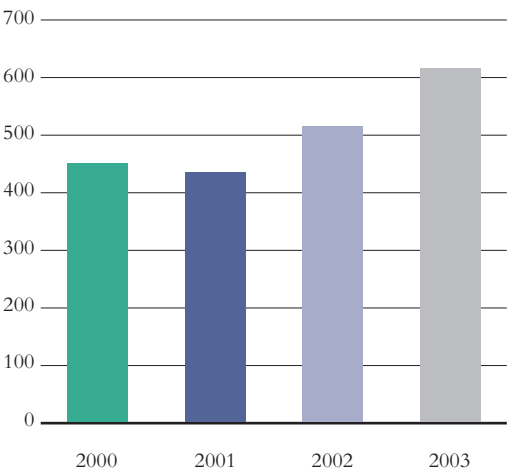
Departments	2000	2001	2002	2003
Central Facilities	36,14	62,62	49,30	60,12
Surgical Oncology	22,87	21,13	26,80	34,02
Medical Oncology	45,62	46,11	106,10	124,65
Prevention and Diagnosis	60,53	65,20	71,30	44,05
Neuroscience & Head - Neck Pathologies	9,49	2,83	13,00	15,08
Critical Area	6,95	0,00	2,50	25,37
Experimental Oncology	170,02	141,23	188,42	158,24
Therapeutic Programs Development	100,51	101,84	85,58	155,32
Total	**452,1**	**441,0**	**543,0**	**616,9**

*Normalized according to the Italian Ministry of Health's indications

Publications



Impact Factor*



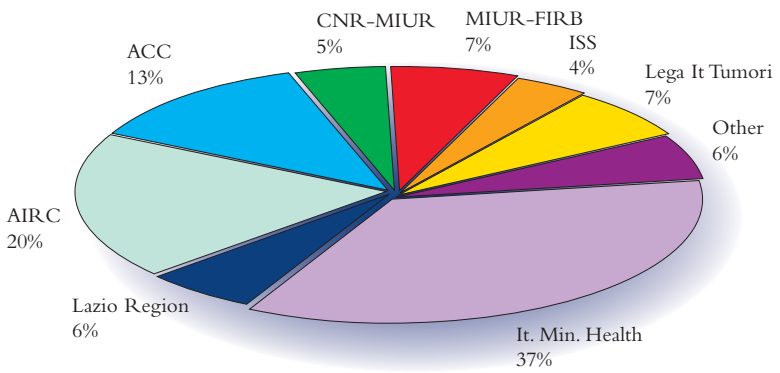
*Normalized according to the Italian Ministry of Health's indications

Educational activity (CME) 2002-2003

Intramural educational activity	2002		2003	
Events	n°	Total credits	n°	Total credits
Breakfast meetings	33		36	
Multidisciplinary panels	9		9	
Lectures	2		7	
Experimental research seminars	15		13	
Meetings, courses	43		46	
Total	**102**	**321**	**111**	**531**

Institutional Grants

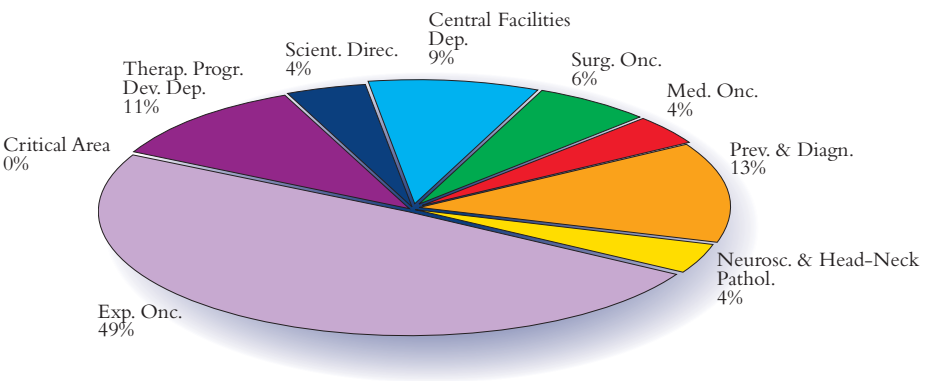
Institution	Project No.	Financial support
Italian Ministry of Health	15	€ 1.231.035,00
Lazio Region	2	€ 210.000,00
AIRC	16	€ 760.000,00
ACC	16	€ 497.000,00
CNR-MIUR	8	€ 183.342,00
MIUR-FIRB	2	€ 261.200,00
ISS	4	€ 119.651,00
Lega It Tumori	4	€ 282.962,00
Other	2	€ 242.200,00
Total year 2003	**69**	**€ 3.787.390,00**



Founded Projects

Departments	P.I.*	External Units P.I.*	Total
Central Facilities	4	4	8
Surgical Oncology	3	1	4
Medical Oncology	2	4	6
Prevention and Diagnosis	6	5	11
Neuroscience & Head - Neck Pathologies	2	0	2
Critical Area	0	0	0
Experimental Oncology	23	6	29
Therapeutic Programs Development	5	1	6
Scientific Direction	2	1	3
Total year 2003	**47**	**22**	**69**

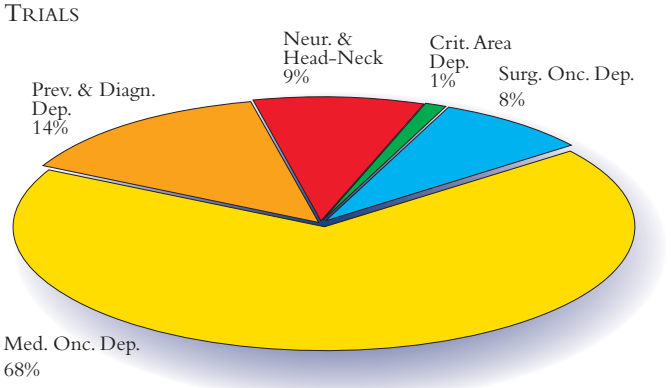
*Principal investigator



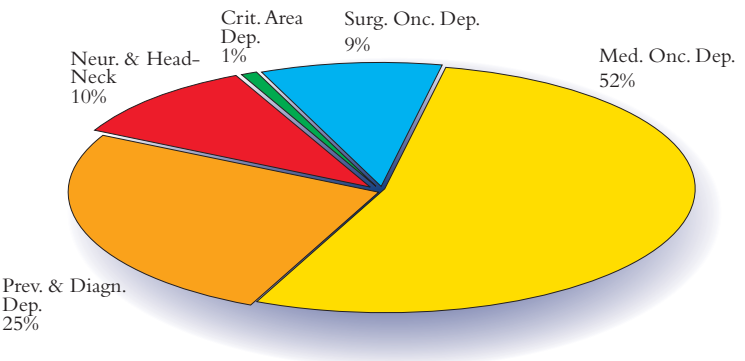
Active Clinical trials (2003)

Department	Trial No.	Patient No.
Surgical Oncology	13	141
Medical Oncology	103	727
Prevention and Diagnosis	21	349
Neuroscience & Head - Neck Pathologies	14	164
Critical Area	2	6
Total year 2003	**153**	**1387**

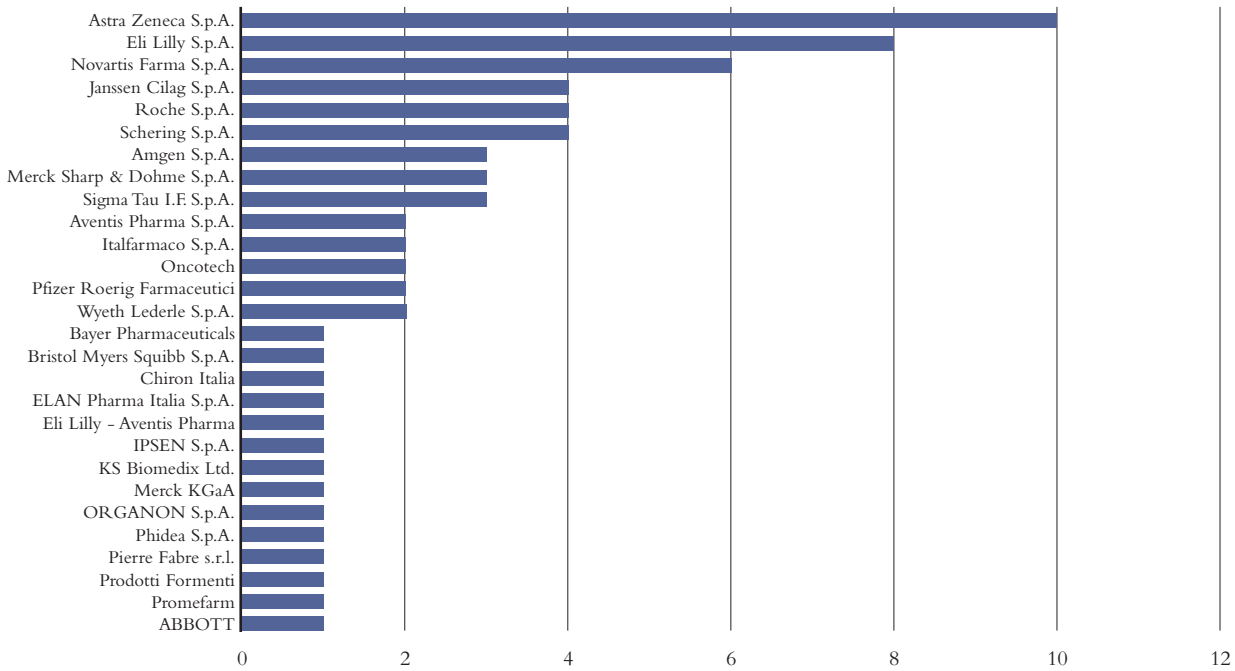
Trials



Patients



Number of supported clinical trials (2003)



Publications 2002-2003

	2002	2003
Full Papers		
Journals with Impact Factor	134	179
Total Impact Factor (*)	542,960	616,85
Full Papers		
Journals without Impact Factor	28	15
Total Full Papers	162	194
- Abstract: International Congresses	74	96
- Abstract: National Congresses	75	157
- Books, chapters	20	19
Total publications	**231**	**466**

* Normalized according to the Italian Ministry of Health's indications

Clinical Activity

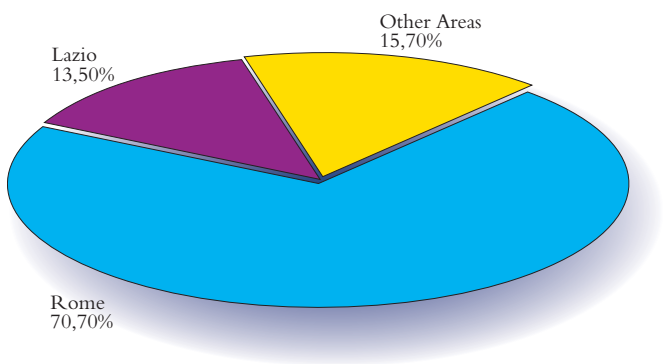
In patients

	1995	1996	1997	1998	1999	2000	2001	2002	2003
Inpatient admissions	7220	7755	8627	8374	8083	6673	6721	8080	9478
Inpatient Days	79022	75933	76092	73510	67728	55064	54832	65706	72314
Alos	11	10	8,82	8,78	8,38	8,25	8,16	8,13	7,63
Surgical index %	52	55	52	53	51	50	51	51	51
Day Surgery Admissions						752	828	1079	1305
Day Hospital Cycles						1674	2003	2084	2335
Day Hospital Treatments						16634	16626	17865	17059
Average n. of Treatments/Cycle						994	830	857	7,5
Total Admissions	**7220**	**7755**	**8627**	**8374**	**8083**	**9099**	**9552**	**11243**	**13119**

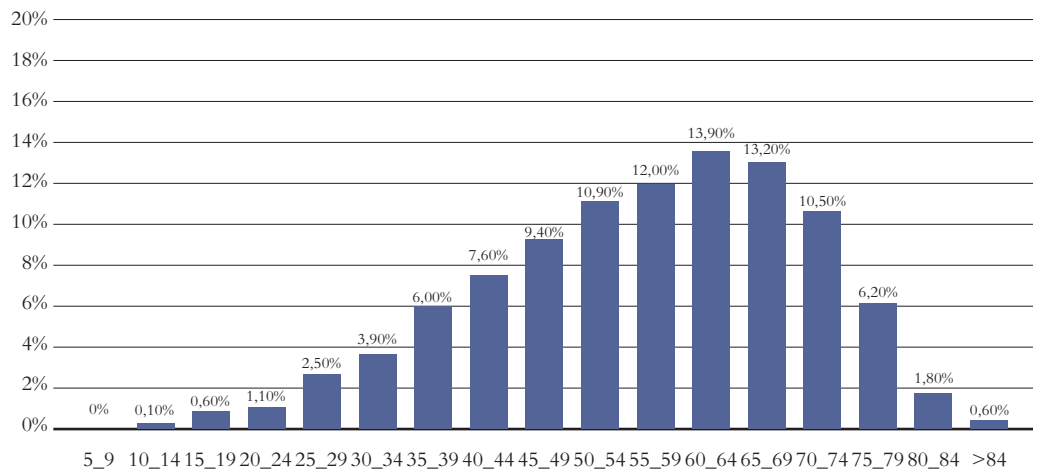
Case-mix by speciality (2003)

	Beds	Admissions	Days	ALOS	Surgical Index	Average Weight
General & Mammary Surgery	22	936	6237	6,66	92,7	1,303
Abdominal Surgery	37	858	12627	14,71	63,3	2,746
Chest Surgery	22	789	5636	7,14	65,7	2,207
Plastic Surgery	8	517	2463	4,76	92,8	1,049
Neurosurgery	16	424	447	10,6	68,9	2,2
Gynecology	22	807	6421	7,96	80,3	1,24
Otorhinolaryngology	18	519	5100	9,83	72,1	1,97
Urology	22	855	6708	7,85	87,8	1,77
Intensive Care	8	92	1688	18,35	47,8	5,24
Nuclear Medicine	8	486	1854	3,81	0	0,96
Medicine Oncology and Ematology	64	3195	19130	5,99	4,7	1,23
Day Hospital		2335	17059	7,3		0,78
Day Surgery		1305	5722	4,38		0,8

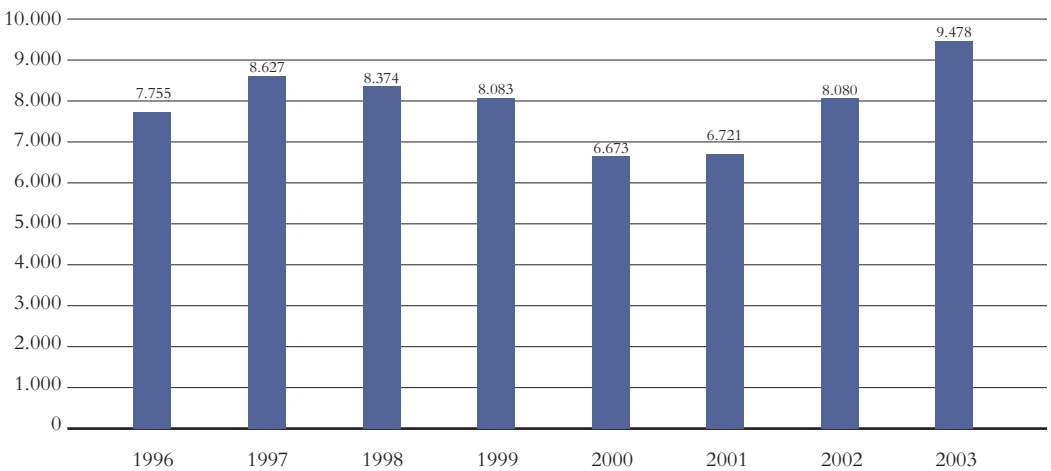
Inpatient Admissions by Geographical Area (2003)



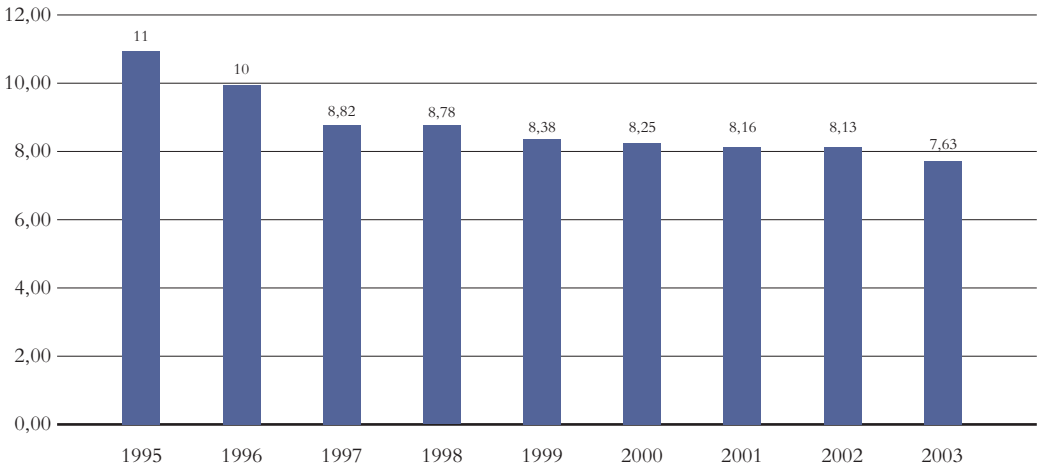
Inpatient Admissions by age (2003)



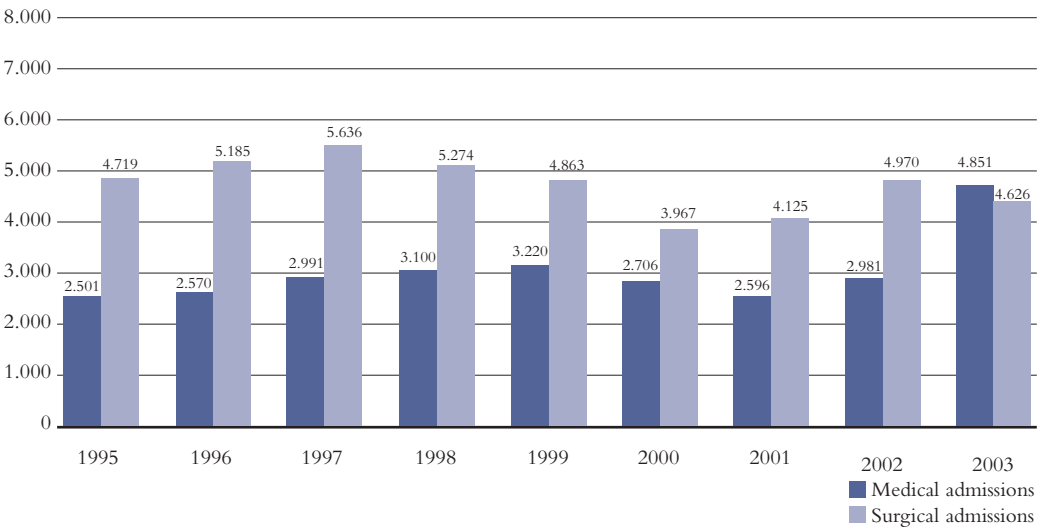
Inpatient Admissions



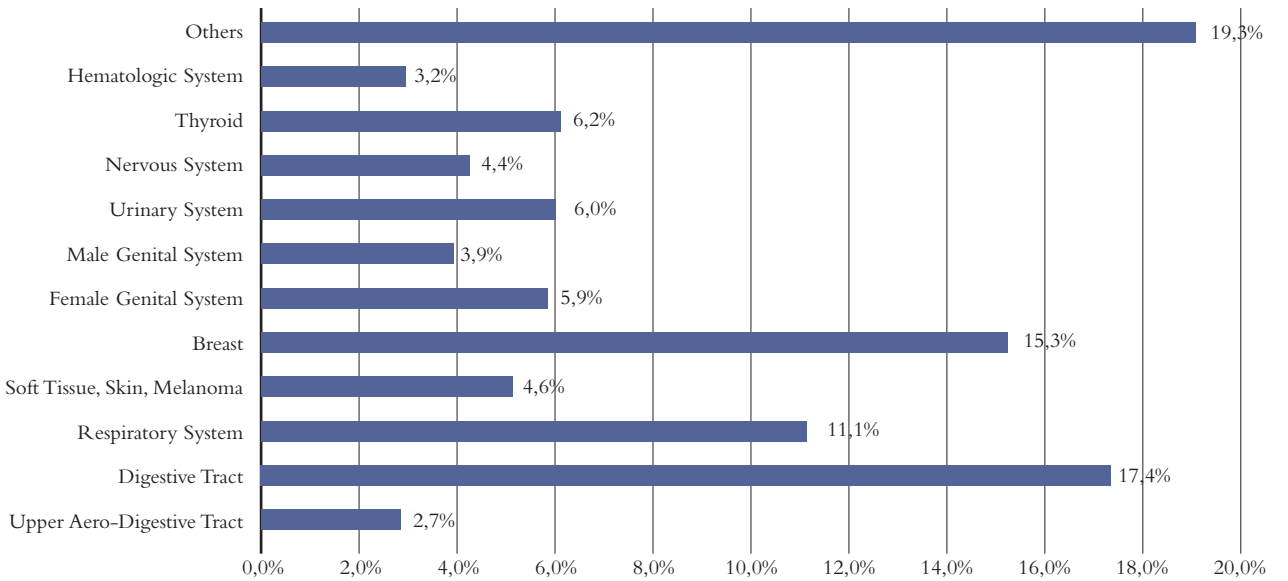
Average Length of Stay



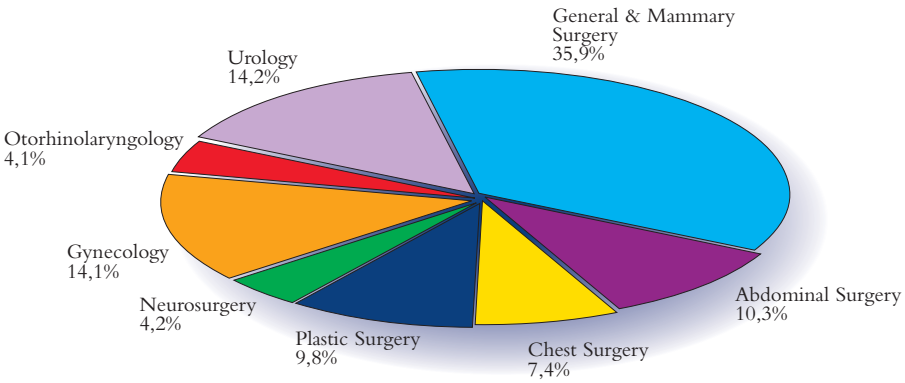
Hospital Admissions



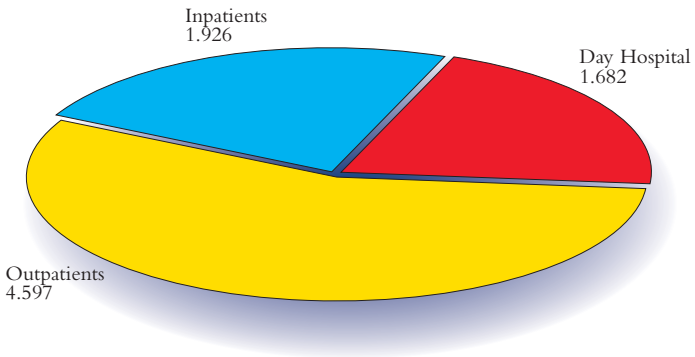
Neoplastic Pathology (140-208, ICD9CM) distribution by site of 8.515 (76% of the total No. of 2003 hospitalizations)



Surgical Interventions (2003)



Systemic Treatments (2003)



	Outpatients (visits and performances)
Breast surgery	12.622
Abdominal surgery	3.398
Thoracic surgery	1.356
Plastic and reconstructive surgery	3.316
Gynaecology	14.854
Urology	5.780
Medical Oncology	37.610
Hematology Oncology	3.155
Radiotherapy	143.946
Radiology and diagnostic imaging	26.283
Nuclear medicine	20.374
Clinical pathology	371.737
Histo and cytopathology	24.903
Digestive endoscopy	9.376
Endocrinology	5.100
Oncologic dermatology	8.917
Neurosurgery	852
Neurology	22.265
Head&Neck surgery	4.309
Intensive care, pain therapy and palliative care	1.300
Pulmonary physiopathology	6.803
Cardiology	8.756
Psychology	1.925
Total	**738.937**

Departments s.c. • s.s.d.

Clinical Research Area

Services
Ettore Maria Salvatore Conti

- Cancer Prevention Institutional and External Affairs and Educational Programs *(Silverio Tomao)*
- Integrated Service of Epidemiology and Information Systems *(Ettore Maria Salvatore Conti)*
- Pharmacy *(Felice Musicco)*
- Medical Physics and Expert Systems *(Marcello Benassi)*
- Psychology *(Patrizia Pugliese)*
- Laboratory Animal Center *(Gennaro Citro)*

Department of Oncological Surgery
Eugenio Santoro

- General Surgery A - Breast - Melanoma - Soft Tissue Sarcomas *(Franco Di Filippo)*
- General Surgery B - Digestive and Hepaticopancreatic Disease Disorders *(Eugenio Santoro)*
- Thoracic Surgery *(Francesco Facciolo)*
- Gynaecology *(Carlo Sbiroli)*
- Urology *(Michele Gallucci)*
- Plastic and Reconstructive Surgery *(Roy De Vita)*

Department of Medical Oncology
Edmondo Terzoli

- Medical Oncology A *(Francesco Cognetti)*
- Medical Oncology B *(Massimo Lopez)*
- Medical Oncology C *(Edmondo Terzoli)*
- Hematology Oncology *(Maria Concetta Petti)*
- Radiotherapy *(Giorgio Arcangeli)*

Department of Oncological Prevention and Diagnoses
Raffaele Perrone Donnorso

- Radiology and Diagnostic Imaging *(Marcello Crecco)*
- Nuclear Medicine *(Carlo Ludovico Maini)*
- Clinical Pathology *(Fiorella Guadagni)*
- Histo and Cytopathology *(Raffaele Perrone Donnorso)*
- Digestive Endoscopy *(Vincenzo Casale)*
- Endocrinology *(Maria Luisa Appetecchia)*
- Oncologic Dermatology *(Pasquale Frascione)*

Department of Neurosciences and Head & Neck
Bruno Jandolo

- Neurosurgery *(Emanuele Occhipinti)*
- Neurology *(Bruno Jandolo)*
- Head & Neck Surgery *(Giuseppe Spriano)*

Department of Critical Area
Luigi Aloe

- Intensive Care, Pain Therapy and Palliative Care *(Edoardo Arcuri)*
- Pulmonary Physiopathology *(Vincenzo Cilenti)*
- Anaesthesiology *(Luigi Aloe)*
- Cardiology *(Italo Sacchi)*

Experimental Research Area

Department of Experimental Oncology
Ada Sacchi

- Laboratory "A" of Experimental Chemiotherapy *(Gabriella Zupi)*
- Laboratory "B" of Immunology *(Pier Giorgio Natali)*
- Laboratory "C" of Molecular Oncogenesis *(Ada Sacchi)*
- Laboratory "D" of Virology *(Aldo Venuti)*

Department for the Development of Therapeutic Programs

- Laboratory "A" associated to Surgical Oncologic Department *(Pier Giorgio Natali)*
- Laboratory "B" associated to Medical Oncology Department *(Gabriella Zupi)*
- Laboratory "C" associated to Prevention and Diagnoses Department *(Marco Giorgio Paggi)*
- Laboratory "D" associated to Neurosciences, Head & Neck and Facial Pathologies Department *(Ada Sacchi)*

Administrative Chairman
Luigi Giusto Spagnoli

Deputy Administrative Chairmen
Francesco Vaia, Guido Rasi

General Medical Director
Patrizio Valeri

Medical Director
Costanza Cavuto

Scientific Director
Francesco Cognetti

- Secreteriat Office
- Cancer Research Projects
- International Affairs Bureau
- Administrative Service for Research (S.A.R.- Servizio Amministrativo per la Ricerca) (*Tommaso Coppola*)
- Unit for Lectures and CME Programs, Congress Center Management
- Clinical Trials Data Center/Biostatistics Office (*Diana Giannarelli*)
- Library, Scientific Documention and Information Service I.R.E. (*Gaetana Cognetti*)
  C.R.S. (*Emanuela Diniziani*)
- BioInformatics and Telemedicine Center
- Technical Photography Service
- Unity for the Management of Clinical and Scientific Activities (*Italo Lorenzon*)

Administrative Director
Elisabetta Paccapelo

Independent Ethical Committee

Chairman:	Gianfranco Turchetti
Members:	Raffaele Argentieri, Silvio Damiani, Silverio Tomao, Filippo De Marinis, Mario Roselli, Luca Marini, Lucia Negri, Marina Cicerone, Romana Gianvenuti
ex-Officio Members:	Francesco Cognetti, Mauro Picardo, Patrizio Valeri, Felice Musicco
Secretary:	Anna Maria D'Ambrosio

Cancer prevention institutional and external affairs and educational programs

Director:
Silverio Tomao, MD

Silverio Tomao graduated in Medicine and Surgery in 1978 and later obtained his specialization in Clinical Obstetrics and Gynecology (1982) and Oncology (1986). After having held the position of Public Health Physician from 1980 to 1986, he then went on to develop his own clinical and scientific activity at the National Institute for Cancer Research, Genoa, and at the Department of Experimental Medicine and Pathology at La Sapienza University, Rome, as assistant in Medical Oncology from 1986 to 1992 and Chief of Medical Oncology from 1993 to date. Since 2003, Dr. Tomao has been responsible for the promotion of preventative, institutional, teaching and training activities as well as the external relations of the Regina Elena Institute. As such, he coordinates and directs the primary and secondary prevention initiatives of the Institute as well as the teaching and training programs in cooperation with the Scientific Department. He is a member of numerous commissions and technical-scientific work groups and holds various teaching positions at the Universities of Rome, Genoa and Cassino. He is the author of nearly 200 scientific works published in national and international journals and has been the speaker and moderator in numerous scientific congresses, many of which he organized.

Staff:
Oreste Aronadio - M.D.
Maurizio De Santis - M.D.
Giuseppe La Ferla - M.D.
Giacomo Carlo Rispoli - M.D.

Aim and mission

The 2003 organizational, clinical and scientific activity of the Department for the Promotion of the Preventive, Institutional, Teaching and Training Activities as well as External Relations was carried out via the joint development of different institutional initiatives aimed at promoting and implementing events dedicated to oncologic prevention, the relationships with other countries in the promotion of institutional activities, the development of training and educational activities in the field of oncology.
The service stood out as a Provider of teaching and training activities in and out of the companies within the ECM Commission of the Ministry of Health, using the scientific and clinical knowledge of the IRCCS oncology as well as the availability of the Bastianelli Congress Center, a high level multipurpose teaching center, in cooperation with other institutes and scientific establishments. In line with these initiatives the Department has also organized and developed training events in cooperation with the Scientific Department of the IRCCS Regina Elena, Rome, dedicated to in-depth scientific research and the promotion of initiatives of internal and external cooperation for the creation of clinical and experimental research protocols in the field of neoplastic pathology.
Based on this program, other training initiatives have been organized, such as: courses, seminars, workshops, meetings, etc. for personnel and external nurses, including different professional categories (doctors, nurses, socio-health assistants, psychologists), all involved in the oncologic field.
During recent years the Center for Training of the IRCCS Regina Elena, has become the regional structure of reference in the organization of teaching/educational activities in the oncologic field, guaranteeing a varied and high level training program which is carried out by the organization of brief weekly encounters and monthly seminars, as well as other training events (courses, workshops, meetings) which take place throughout the year.

The activity of the Center for the Prevention of Tumors has always been considered a point of reference in the region for the prevention of neoplastic illnesses due to its complete and qualified services, and thanks to the availability of high-level human and structural resources at the IRCCS Regina Elena.
The Center's mission has always been, and still is, the possibility of offering a range of services for primary and secondary high-level prevention, as well as institutional and country wide initiatives aimed at health information and education for responsible prevention and improved health.

Activity

The Center is organized in two levels of intervention; a multidisciplinary strategy aimed at the early diagnosis of tumors and precancerous states and a strategy of training and educational intervention aimed at primary prevention and the maintenance of health.
Furthermore, the center is focused on initiatives which promote intervention in the country aimed at promoting prevention for corporations, institutes and businesses through the functional and operational partnership with other medical institutes thanks to common strategic objectives within the public health system.
From a clinical point of view, the Department for preventative activities is structured according to the following functional framework:

- Preventive visits for general oncology
- Control of oncologic patients apart from follow-ups
- Service for first stage breast prevention
- PSA dosage and urinary cytology
- Specialized gynecologic and oncologic dermatology visits
- Early diagnosis of pulmonary tumors
- Diagnosis and control of hereditary/familial tumors
- Clinic of oncologic drug prevention
- Service of psycho oncology

In 2003, almost 10,000 diagnosis were carried out through visits and general testing, breast controls, diagnostic testing and follow ups. Only 200 breast examinations were carried out due to the fact that the service only begun its full activity in October of 2003. It is important to state that in the first semester of 2004, with only two part-time specialists available 2,000 visits breast examinations were carried out.
Over 25% of the general preventive visits include first visits, so much so that, the limited staff (only one doctor now) has had to limit the age of entrance to the program to individuals 70 years of age and younger.
Thanks to its important instrumental clinical/diagnostic activity, the center has been able to identify numerous cases of neoplastic and preneoplastic pathology, both in first and second level screening.
As regards the scientific research activity, priority has been given to certain subjects, such as the early diagnosis of pulmonary tumors with spiral CT (ELCAP project), the prevalence and incidence of genital infection from HPV, the study of hereditary predisposition to breast and ovarian tumors, the familiarity for melanoma and colon rectal tumors.
The Medical Directors of the Center have taken part in research projects in cooperation with institutional corporations of national importance (Istituto Superiore di Sanitá) and have developed original guidelines for research on the relationship between lifestyle and tumor (eating habits, smoking, environmental pollution).
The center has also developed training and educational health initiatives on a country-wide basis, organizing events dedicated to this subject and setting up projects in cooperation with sectors of reference in the educational field, aimed at the health education of professors and students from middle and high schools. In this regard, Dr. Rispoli has concentrated on a training and educational health project in educational institutions and cultural associations, using his experience and the competence of the Regina Elena Institute. Dr. La Ferla has completed this educational project by applying his personal competence

to seminars dedicated to the subject of oncologic prevention and health education in scholastic structures and scientific associations. In order to improve the epidemiologic competence of the Service, Dr. Oreste Aronadio was introduced to the level 2 masters in epidemiology at the Sacro Cuore Catholic University. By the end of the project, Dr. Aronadio had completed an interesting case control study on 6,609 females, aimed at highlighting the familial role in breast cancer in a well-defined geographic area.
During training, the doctors of the Center have respected the internal and external training initiatives of the Institute. In 2003, Dr. Rispoli, managed to obtain 120 credits for further medical education from the commission.
Professor Tomao, director of the Center, has attended and finished the managerial training course for the directors of complex structures in the Liguria Region. He has taken part in many studies and research groups as well as the Executive Boards of Scientific societies (SIT, AIOM). He has organized training events and congresses, in which he was also a speaker and moderator. He is responsible for the operative unit for the 'Epidemiological, biological and clinical evaluation of the risks of occupational exposure to chemotherapeutics in a hospital context' in a project on the evaluation of the risks of manipulating antiblastic chemotherapeutics in the health system financed by the Ministry of Health.
He is an expert on the Ministry of Health's national commission for further training, he is vice president of the Committee of ethics of the Istituti Fisioterapici Ospedaleari, Rome, Oncologic Consultant at the Center for Tumor Prevention of the La Sapienza-Palazzo Baleani, University of Rome. He is responsible for the Research project financed by the Italian League in the fight against tumors, entitled 'Progetto pilota integrato di formazione, educazione sanitaria e formazione oncologica per il personale docente della scuola media superiore'. He is also in charge of the operative unit n.4 for the project on Tumor Biomarkers (BT), as well as doctor for General Medicine (MMG); 'Efficenza ed appropriatezza di utilizzo clinico', financed by the Ministry of Health.
Professor Tomao is a contract professor at the Universtitá degli Studi, Rome in the schools of medical and oncologic specialization, at the University of Genoa in the school of oncologic specialization and at the Facoltá di scienze motorie di Cassino in Farmacologia.

Publications 2003

A. Zullo, A. Romiti, S. Tomao, C. Hassan, V. Rinaldi, M. Giustini, S. Morini, F. Taggi.

Gastric cancer prevalence in patients with liver cirrhosis.

Eur J Cancer Prev 2003, June, 12(3):179-182

Frati L., Faggioni A., Gulino A., Nuti M., Ragona G., Saccani jotti G., Santoni A., Screpanti I. and Tomao S.

New trends in molecular oncology-"Tumor markers in the era of molecular medicine.

J Tumor marker oncol 2003, 18(3):124-131

Carlini P., Ferretti G., Di Cosimo S., m Colella E., Tonacella R., Romiti A., Tomao S. Frassoldati A., Papaldo P., Fabi A., Ruggeri E.M., Cognetti F.

Is there a benefit by the sequenze anastrazole-formestane for postmenopausal metastatic breast cancer women?

J Steroid Biochem Mol Biol, 2003 Jul; 86(1):107-109

Integrated service of epidemiology and information systems

DIRECTOR:
ETTORE MARIA SALVATORE CONTI, MD

Ettore Conti received his MD in 1978 and specialised in Diseases of the digestive tract in 1983 at La Sapienza. University, Rome. In 1987 he also specialised in Oncology.
From 1983 to 2003 he was Director of the Cancer Registry of Latina Province. From 1981 he worked at Regina Elena National Cancer Institute and since 1982 he has been at the Department of Environmental Carcinogenesis Epidemiology and Prevention (SOAEP). From 1995 he has worked at the Regina Elena National Cancer Institute as Responsible of the Department of Network on Clinical and Administrative Data (SIO, SIAS). From 2001 to 2003 he was Director of the Department of Epidemiology and Network on clinical and administrative data (S.Int.E.S.I.). From 2001 to 2002 he was also Corporate Health Director.
From 1999 to 2003 he taught Cancer Epidemiology and Prevention at Tor Vergata University, Rome.
Dr. Conti's research interests were focused on Cancer Epidemiology with a particular concern for Cancer Registration, with the issue of incidence, prevalence and survival data; other subjects of interest were analytical studies on diet and risk of cancer.
He was also a member of board of the Italian Association of Cancer Registries (AIRT); voting member of the International Association of Cancer Registries (IACR) of WHO; member of EUROCARE, EUROCIM and EUROPREVAL European Projects.
Unfortunately Dr. Ettore Conti passed away August 2, 2003. All his colleagues and assistants wish to remember his commitment, devotion and great professional competence.

Staff:

VALERIO RAMAZZOTTI - M.D. Epidemiologist
MARIA CECILIA CERCATO - M.D. Epidemiologist
MARCO CAPERLE - M.D. Epidemiologist

Epidemiology activities:
MINA LOMUSCIO - Administrative Assistant
FULVIA AZZOLINA - Administrative Assistant

Research Staff under contract:
ANNA SESSA - Graduate
CHIARA MANFREDINI - Graduate
ALESSANDRA D'IPPOLITO - Graduate
MARCO CANFORA
CECILIA FAGIOLI
FRANCESCA GABRIELLI
ANA ISABEL CALVO ABAD
SIMONA SBRAGA

Activities of S.I.O. and S.I.A.S.:
ELENA GATTEI - Administrative Assistant
FRANCESCA MORETTI - Administrative Assistant
SILVIA MALVEZZI - Administrative Assistant
DANIELA RENNA - Administrative Assistant
ADRIANA SANGUIGNO - Administrative Assistant
ANNA LISE DI BELLA - Administrative Assistant
SIMONETTA ROSCIONI - M.D. Post-graduate under Contract

Activities 2003

ACTIVITIES OF S.I.O. AND S.I.A.S.
During 2003 the database on inpatient hospital admissions, S.I.O, and the database on outpatient hospital procedures, S.I.A.S, have assured the institutional link with national and regional authorities and have given their support to internal decision-making process in medical as well as administrative management.

Epidemiology Activities

CANCER REGISTRY
The registration of oncological cases connected to IRE has been carried out in accordance

with the Sistema Informativo Ospedaliero database. This will allow us to update acquired data concerning the previous period.
The Cancer Registry of Latina Province afferent to S.Int.E.S.I. continued its routine activities of registration and coding of incident cases of malignant tumors in the Province of Latina. In 2003 the activities of the Cancer Registry and co-operation with other Italian and European Cancer Registries and Registries of Pathology enabled the publication of many studies.

EUROCARE AND ITACARE

S.Int.E.S.I., through the Cancer Registry of Latina, participated in the Eurocare study, a European Co-operative Project based on data collected from the cancer registries for the study of survival in oncological patients. This study involved the Istituto Superiore di Sanità of Italy and 67 European Cancer Registries. Latina Cancer Registry contributed with 14,597 validated cases from 1983 to 1994. In 2003 a study called EUROCARE 3, concerning incident cases from 1990 to 1994, has been published.
The study is based on the calculation of relative survival, that is the ratio between survival observed in registered cases and survival expected in the general population with the same characteristics of age, gender and residence. Relative survival can be meant as a method to estimate survival after correction for non-neoplastic causes of mortality.
The population-based survival derived from the Cancer Registries is a public health indicator, resulting from different factors; effectiveness of treatment, accessibility to health structures, the socio-cultural and economic level of the populations under study.
Some geographical differences in survival have been highlighted. They could depend on different factors such as stage of disease at diagnosis, accessibility to the best treatment, the macroeconomic determinants including health and public health investments.
In order to take these variables into account we joined the co-operative ITACARE study, which includes the Istituto Superiore di Sanità of Italy and other Italian Cancer Registries. The study involves high resolution analysis to evaluate the role of stage at diagnosis, treatment and the socio-economic variables related to census data.

SKIN CANCER PREVENTION PROGRAMME IN SCHOOL-AGE CHILDREN. THE AUTO-DIAGNOSIS OF CHILDREN.

A Skin Cancer Prevention Program for children of the nursery schools of the Lazio region has been carried out with the support of the Administrative Office of Lazio region. The choice of a population of pre-school children is aimed at earlier preventive action during the child's life. The program undertook to make personalized guidelines for sun exposure available to each child, based on a questionnaire to be completed on skin photosensitivity, which was handed out in the schools. One thousand and sixty nine schools took part in the initiative. Out of a population of 150,000 children 127,940 participated and 75,266 completed the questionnaire, corresponding to a compliance of about 60%. After recording the data obtained from the questionnaires, 74,908 letters of recommendations were sent to each school at the end of the school year. From the questionnaire children who showed problems of certain prominence, were invited to S. Maria and S. Gallicano Institute for a dermatology visit.
We also carried out the same program for foreign children in the following countries: Tunisia, Russia, Spain (Valencia) and Hungary. The analysis of data resulting from the questionnaires, allowed us to process and send personalized guidelines to all children involved in the project and send the results of the analysis of the sample to those responsible in the foreign countries involved.
We also signed an agreement with Instituto Valenciano de Oncologia (Spain), school year 2003-2004, and with the Hellenic Cancer Society of Athens (Greece) to introduce the project in their countries.
The Province of Rome allocated a budget for the development of the Project on the dermatologic evaluation and control of the extent that the message was received, to be carried out in the school year 2004-2005 on a sample of children from nursery schools.

Survey Of The Frequency Of Risk Habits In A Population Through Interviews On A Familial Sample Of School-Age Children

The database containing the data of a sample of families (approx. 3000 people) from the Lazio region, who gave their consent to participate in initiatives of prevention and health education during the program to prevent damage derived from sun exposure spreading in the schools. An evaluation of the interventions that could be carried out in prevention and health promotion it is also in progress.

Alliance Against Cancer

Project No. 15: The network on economic-health, etiopathogenetic and epidemiological analysis of the population with thyroid tumor and thyroid oncological pathology afferent to IRCCS.

For this project, S.Int.E.S.I. together with the National Cancer Institute of Milan were the coordination centers. The main purpose being to establish a network among the participating Institutions (national IRCCS), which will enable us to share a database of the cases concerning thyroid cancer afferent to each center.

As a consequence, we have pursued two lines of work:

a) setting up of an electronic medical record containing the patient's information (personal data, familial history, clinical tests, surgical procedures, histological data, therapies, follow-up data, etc.). In this database the National Cancer Institute of Milan collected data on case histories for 2003. A demo version is available on the website www.e-oncology.it.

b) at Regina Elena National Cancer Institute (S.Int.E.S.I.) a file based on a record-linkage among the different databases of the Institute has been set up. In particular. The records relevant to the pathology under discussion taken from the SIO database concerning inpatient admissions from 1995 to 2003 have been selected. To these records we linked the records provided by SIAS concerning the data on outpatients, available from 1998 and the records on about 600 patients obtained from an ad hoc database provided by the Nuclear Medicine Department.

This experimental phase has involved over 1,400 patients, the main diagnosis being thyroid cancer, which has generated over 2,400 hospital admissions and over 46,000 outpatient procedures.

As to records provided from Nuclear Medicine, the linkage allowed the optimal integration of available information on each patient, overcoming the lack of a single database, such as the lack of histological data in the SIO database obtained from the Nuclear Medicine files, and the lack of data concerning the economic data typical of clinical databases.

Moreover, the possibility of assigning to each inpatient the total number of procedures received as an outpatient, thanks to information technology was of particular relevance.

The results obtained during this experimental phase have been submitted to other centers involved with whom we defined the structure of a shared database for storage of data. This will enable the setting up of a common database for all the Institutes involved.

Alliance Against Cancer

Project No. 7: Epidemiology for health education and information. The project "Tumours in Italy" is a Epidemiology E-oncology site.

S.Int.E.S.I. participated as co-operative center in the project based on the E-Oncology, Alleanza contro il Cancro portal, set up with the aim to make oncological information for an acquainted and specific health education available on the web.

The project "Tumors in Italy" (www.tumori.net), supported by Alleanza contro il Cancro, aims to produce, in cooperation with E-Oncology, the Epidemiology portal of Italian Oncology. The portal can be reached on the web and already provides the initial results of the project.

The activities involve IRCCS, experts and oncological networks divided in Gruppi Obiettivo (GO).

The main aims are: the epidemiological description of cancer through a network of Cancer Registries to produce estimates both on national and regional bases, as well as the description

of the activities of early diagnosis and of risk factors related to specific neoplasms.
GO "Stime Epidemiologiche" resulted from the cooperation between the National Cancer Institute of Milan and Istituto Superiore di Sanità of Rome with the aim of producing estimates of epidemiological indicators at the regional and national level. It has benefited from the cooperation of the Cancer Registries, among them the Cancer Registry of Latina Province connected to S.Int.E.S.I. As a consequence, it has been possible to produce estimates on incidence and prevalence on a regional base for ten different tumors and for the total number of tumors. Data are already available on the web.
The Latina Cancer Registry, together with the Italian Association of Medical Oncology, IRCCS of Naples and Bari, and with Ragusa Cancer Registry participated in "GO SUD ITALIA". The main purpose of the project is to detect the principal faults of the cancer registration networks in the regions of Southern Italy.

Other Activities

Co-operative epidemiological studies were published in 2003. In particular analytical studies such as:

- the case-control study on "Dietary glycemic index, glycemic load and ovarian cancer risk: a case-control study in Italy", that supports the hypothesis of a direct association between glycemic index and glycemic load and ovarian cancer risk and of the possible role of hyperinsulinemia/insulin resistance in ovarian cancer development;
- the case-control study on "Familial history of cancer and risk of ovarian cancer" that confirms higher ovarian cancer risk in women with a familial history of ovarian and breast cancer;
- the case-control study on "Folate intake and risk of oral and pharyngeal cancer" that supports a protective role of folate against oral and pharyngeal carcinogenesis;
- the case control study "Does pizza protect against cancer" on protective role of pizza for digestive tract neoplasms;
- the case-control study on "Cigarette tar yield and risk of upper digestive tract cancers: case-control studies from Italy and Switzerland" that confirms the direct relationship between the tar yield of cigarettes and upper digestive tract neoplasms with clear indications for stopping smoking as a priority for prevention;
- the case-control study on "Delayed infection, late tonsillectomy or adenoidectomy and adult leukemia: a case-control study" that pointed out that a later age at adenoidectomy and tonsillectomy increased the risk considerably of lymphocytic (but not myeloid) leukemia;
- the case-control study on "Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study" that suggest an increased risk for NHL and leukemia for some chemical classes of pesticides;
- the study on "Prostate cancer in Italy before and during the 'PSA era': survival trend and prognostic determinants" that pointed out a striking prognostic improvement between the late 1980s and the early 1990s occurred in almost all Cancer Registries.

Further studies were carried out by record linkage between the National Registry of AIDS and 19 Cancer Registries focusing on the risk of cancer, and the incidence of AIDS-Defining Cancer in persons with AIDS in Italy.

European Competition "Quit & Win! 2003" Start Smoking And Win A Prize

S.Int.E.S.I. and the Pulmonary Physiopathology Service of Regina Elena National Cancer Institute carried out this European Project promoted by ENYPAT (European Network Young People Against Tobacco).
The aim of the project was to help young smokers (aged 14-21) to quit smoking through a competition held in the High Schools of Rome and the province.
Young people who quit smoking for a month receive a prize.
The project aimed at informing young people and making them aware of the damages provoked by smoking involving teachers, parents, schoolmates and friends. The project gave an insight into the characteristics of Italian young smokers and permitted the planning targeted interventions for the prevention of damage caused by tobacco.

As to the activities of Epidemiology S.Int.E.S.I. is also involved in other research projects with the Clinical and Scientific Departments of the Institute.

Publications 2003

Capocaccia R., Gatta G., Roazzi P., Carrani E., Santaquilani M., De Angelis R., Tavilla A. and the EUROCARE Working Group Conti E. (Latina Cancer Registry)

The EUROCARE-3 database: methodology of data collection, standardization, quality control and statistical analysis.

Annals of Oncology 14 (Supplement 5): v14-v27, 2003

Sant M., Aareleid T., Berrino F., Bielska Lasota M., Carli P.M., Faivre J., Grosclaude P., Hédelin G., Matsuda T., Møller H., Möller T., Verdecchia A., Capocaccia R., Gatta G., Micheli A., Santaquilani M., Roazzi P., Lisi D. and the EUROCARE Working Group. (Conti E. (Latina Cancer Registry)

EUROCARE-3: survival of cancer patients diagnosed 1990-94-results and commentary

Annals of Oncology 14 (Supplement 5): v61-v118, 2003

Gatta G., Corazziari I., Magnani C., Peris-Bonet R., Roazzi P., Stiller C. and the EUROCARE Working Group Conti E. (Latina Cancer Registry)

Childhood cancer survival in Europe.

Annals of Oncology 14 (Supplement 5): v119-v127, 2003

Coleman M.P., Gatta G., Verdecchia A., Estève J., Sant M., Storm H., Allemani C., Ciccolallo L., Santaquilani M., Berrino F. and the EUROCARE Working Group. Conti E. (Latina Cancer Registry)

EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century.

Annals of Oncology 14 (Supplement 5): v128-v149, 2003

Roazzi P., Capocaccia R., Santaquilani M., Carrani E. and the EUROCARE Working Group. (Conti E. (Latina Cancer Registry)

Electronic availability of EUROCARE-3 data: a tool for further analysis.

Annals of Oncology 14 (Supplement 5): v150-v155, 2003

Augustin L.S.A., Polesel J., Bosetti C., Kendall C.W.C., La Vechia C., Parpinel M., Conti E., Montella M., Franceschi S., Jenkins D.J.A. & Dal Maso L.

Dietary glycemic index, glycemic load and ovarian cancer risk: a case-control study in Italy.

Annals of Oncology 14: 78-84, 2003

Negri E., Pelucchi C., Franceschi S., Montella M., Conti E., Dal Maso L., Parazzini F, Tavani A., Carbone A., La Vecchia C.

Family history of cancer and risk of ovarian cancer.

European Journal of Cancer 39(4): 505-10, 2003

Pelucchi C., Talamini R., Negri E., Levi F., Conti E., Franceschi S., La Vecchia C.

Folate intake and risk of oral and pharyngeal cancer.

Annals of Oncology 14: 1677-1681, 2003

Gallus S., Bosetti C., Negri E., Talamini R., Montella M., Conti E., Franceschi S., La Vecchia C.

Does pizza protect against cancer?

Int J Cancer 107(2): 283-284, 2003

Gallus S., Altieri A., Bosetti C., Franceschi S., Levi F., Negri E., Dal Maso L., Conti E., Zambon P., La Vecchia C.

Cigarette tar yield and risk of upper digestive tract cancers: case-control studies from Italy and Switzerland.

Annals of Oncology 14: 209-213, 2003

Franceschi S., Dal Maso L., Pezzotti P., Polesel J., Braga C., Piselli P., Serraino D., Tagliabue G., Federico M., Ferretti S., De Lisi V., La Rosa F., Conti E., Budroni M., Vicario G., Piffer S., Pannelli F., Giacomin A., Bellù F., Tumino R., Fusco M., Rezza G. for the Cancer and AIDS Registry Linkage Study.

The members of the Cancer and AIDS Registry Linkage Study (Ramazzotti V. Registro Tumori di Popolazione della Provincia di Latina, Italy)

Incidence of AIDS-Defining Cancer After AIDS Diagnosis Among People with AIDS in Italy, 1986-1998.

J Acquir Immune Defic Syndr 34, (1) 84-90, 2003

Vineis P., Miligi L., Crosignani P., Davico L., Fontana A., Masala G., Nanni O., Ramazzotti V., Rodella S., Stagnaro E., Tumino R., Viganò C., Vindigni C., Costantini A.S.

Delayed infection, late tonsillectomy or adenoidectomy and adult leukemia: a case-control study.

British Journal of Cancer 88, 47-49, 2003

Quaglia A., Vercelli M., Puppo A., Casella C., Artioli E., Crocetti E., Falcini F., Ramazzotti V., Tagliabue G. and Prostate Working Group. (Conti E.M.S. Latina Cancer Registry, Regina Elena Institute, Rome).

Prostate cancer in Italy before and during the 'PSA era': survival trend and prognostic determinants.

European Journal of Cancer Prevention 12 (2), 145-152, 2003

Miligi L., Costantini A.S., Bolejack V., Veraldi A., Benvenuti A., Nanni O., Ramazzotti V., Tumino R., Stagnaro E., Rodella S., Fontana A., Vindigni C., Vineis P.

Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study.

American Journal of Industrial Medicine. 44(6):627-636, 2003

Dal Maso L., Franceschi S., Polesel J., Braga C., Piselli P., Crocetti E., Falcini F., Guzzinati S., Zanetti R., Vercelli M., Rezza G. for the Cancer and AIDS Registry Linkage Study.

Cancer and AIDS Registry Linkage Study: (Conti E., Ramazzotti V. Registro Tumori di Popolazione della Provincia di Latina)

Risk of cancer in persons with AIDS in Italy, 1985-1998. British Journal of Cancer 89, 94-100, 2003

Dal Maso L, Polesel J., Serraino D., Franceschi S. for the Cancer and AIDS Registry Linkage Study.

Cancer and AIDS Registry Linkage Study:(Conti E. Registro Tumori di Popolazione della Provincia di Latina, Italy)

Lung cancer in persons with AIDS in Italy, 1985-1998. AIDS 17, 2117-2119, 2003

Medical Physics and Expert Systems

DIRECTOR:
MARCELLO BENASSI, PHD

Study: Marcello Benassi received his Ph.D. at the La Sapienza University of Studies, Rome. He became a member of Qualified Experts in Radiation protection of the Italian Ministry of Labor (ex art.77 D.Lgs.230/95).
Curriculum: From 1969 to 1978 he worked in the Laboratory of Medical Physics and Expert Systems of the Regina Elena National Cancer Institute in Rome, Italy and since 1979 he has been Laboratory Director. He also served as Scientific Consultant on Radioprotection and Security for the Tor Vergata University in Rome and the Institute Superiore Sanità of Rome.
From 1985 he has also been Professor at the school of specialization of Medical Physics at the Tor Vergata University in Rome.
Scientific Society: Past President of AIFB, Associazione Italiana di Fisica Biomedica (1992-1996); member of ESTRO, European Society for Therapeutic Radiology and Oncology, ESHO, European Society for Hyperthermic Oncology, SIF**,** Società Italiana di Fisica, AIRP, Associazione Italiana di Radioprotezione, SIRR, Società Italiana Ricerca Radiazioni, SIRM, Società Italiana Radiologia Medica, AIFB, Associazione Italiana di Fisica Biomedica, ANPEQ, Associazione Nazionale Professionale Esperti Qualificati, AIFM**,** Associazione Italiana Fisica in Medicina.
Dr. Benassi's research interests are focused on basic and clinical dosimetry of ionizing radiation, radiobiology, hyperthermia, quality assurance and radioprotection, elaboration of biomedical imaging, the Monte Carlo simulation of physical and biological phenomena, expert systems and medical informatics. He has been in charge of many research projects related to physical and mathematical applications to radiotherapy and oncology.

Staff:
VICENTE BRUZZANITI - PH.D.
ANNA DI NALLO - PH.D.
GIUSEPPE IACCARINO - PH.D.
VALERIA LANDONI - PH.D.
SIMONA MARZI - PH.D.
LUIS PEDRO ORDONEZ - PH.D.
ANTONELLA SORIANI - PH.D.
LIDIA STRIGARI - PH.D.

Post graduate contract researcher:
MARCO D'ANDREA - PH.D.

On training:
FIORE BAZZARELLI - Engineering
DANIELA D'ALESSIO - Physicist
PATRIZIA FERRO - Engineering
ELISABETTA GENOVESE - Physicist
CARMELINA SALIERNO - Engineering

Activities 2003

INTRAOPERATIVE RADIOTHERAPY

Intraoperative radiotherapy (IORT) is becoming an increasingly common procedure for treating tumors or tumor beds after resection and areas of possible local regional spread. IORT is used in most modern protocol studies as a component of multidisciplinary treatment approaches. In the last years there has been an increasing interest on IORT technique, also because of the development of dedicated mobile accelerators.
A large single dose of irradiation is delivered to a surgically defined area, while uninvolved and dose-limiting tissues are displaced, with the ability to shield or physically move normal tissues and organs out of the treatment volume. The final goal of IORT is enhanced locoregional tumor control.
IORT is feasible for various intraabdominal, retroperitoneal, pelvic and other malignancies. More recently, clinical experience has shown that IORT may improve local control and

disease-free survival, especially when used in an adjuvant setting, combined with external beam irradiation in cancer of the stomach, pancreas, colorectal and soft tissue sarcoma.
Widespread applications for IORT at various disease sites are feasible due to improved technology. Increasing the maximum energy of the linear accelerators IORT and the total radiation dose it is possible to improve the therapeutic ratio and the local tumor control without increasing morbidity.
In the world IORT is generally used as an adjuvant therapy, i.e., it is given as a boost after conventional fractionated radiotherapy. A task group (No. 48) of the AAPM has developed guidelines for IORT. Also an International scientific Society has been founded (ISIORT) with the principal aim of gathering specific experiences and methods.
In the framework of a national project on quality assurance in Radiotherapy, the Italian National Institute of Health established a multidisciplinary working group, with experience in clinical practice, in order to develop guidelines on quality assurance for IORT technique. In this context, new requirements have come out, for both specific clinical application as well as an increased or decreased accelerator usability.

IORT STUDIES:
Prostate cancer: a dose-finding study in patients with intermediate risk prostate cancer, who have undergone radical prostatectomy, were treated with doses of 16Gy, 18Gy and 20Gy, following a dose-escalation program by Fibonacci.
Breast cancer: patients, who have undergone conservative surgery for small mammary carcinomas are randomized to receive IORT on the tumor bed or conventional EBRT. The main objectives of this study are to evaluate the local recurrence rate and second ipsilateral tumors, as well as the local recurrence free interval.
Head and neck: proposed protocols:
Feasibility Study on the use of Intra-Operative Radiation Therapy (IORT) as an early boost on locally advanced head and neck cancers. The goal of this study is to evaluate the feasibility and eventual side effects of this modality used as a booster dose on the tumor bed in patients with locally advanced tumors (>T3 or >N2) of the oral cavity, oropharynx, hypopharynx and larynx that undergo resection with curative intent. Standard post operative 3D wide field radiation therapy will follow for all the patients. The protocol was approved by the ethical committee and the patients accrual started in 2004.
A feasibility study on the integrated use of Salvage Surgery, Intra-Operative Radiation Therapy (IORT) and External Beam Radiation Therapy (EBRT) on head and neck cancers recurred after radiation therapy. IORT is used at the end of the resection with the intention of delivering a single tumoricidal dose and at the same time spare organs at risk. The goal of our study is to evaluate the feasibility and eventual side effects of this modality, used to improve local control in otherwise palliative patients. External beam radiation therapy will follow where possible. The protocol was approved by the ethical committee and the patients accrual started in 2004.

INTENSITY MODULATION RADIATION THERAPY
With the advent of advanced techniques to design and deliver 3D dose distributions, based on multi-modality imaging and on computer plan optimization, the use of biological criteria and the correlation between it and the clinical outcome becomes impellent. High conformity of IMRT plans, characterized by steep gradient dose regions, allows the sparing, total or partial, of normal tissues surrounding the tumor, especially at the highest doses. Consequently, the dose-volume histograms (DVHs) of the sensitive structures typically show a inhomogeneous dose distribution, which is difficult to interpret and requires a greater awareness of the radiobiologic properties of tissues. IMRT has also induced new dose escalation protocols, increasing the necessity to define more appropriate dose-volume constraints for critical structures. The dose-response index TCP (Tumor Control Probability) and NTCP (Normal Tissue Complication Probability) provide valid help in evaluating the treatment and comparing different treatment plans.

IMRT STUDIES:

Head and Neck cancer: Observational Study on Xerostomia evaluation on patients with oral cavity and oropharyngel cancer treated with Intensity modulated radiation therapy (IMRT). IMRT is a complex, relatively new technique that allows the delivery of a highly conformal dose to the target with a better sparing of organs at risk, such as the parotids. The goal of our study is to evaluate subjectively and objectively, through a patient filled questionnaire, the real efficacy of this technique to reduce xerostomia and improve the patient's comfort with the collection of saliva before and up to 12 months after the end of the treatment. The ethical committee has approved the protocol and patients accrual has already started.

Prostate: Multi-institutional Phase II trial of Hypofractionated Accelerated Radiotherapy in Prostate Cancer. The aims of the present study are to evaluate the effect of set-up errors and organ motion on DVHs and to introduce radiobiological considerations by evaluating Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) in a group of patients undergoing IMRT for prostate cancer.

BREAST CANCER

Observational study on correlation between the 2-D and 3-D measurement of the irradiated lung in the postoperative treatment of breast cancer. The objectives of the study are to find a correlation between 2-D and 3-D lung volumes and to evaluate the normal tissue complication probability for the organs at risk by means of mathematical models.

PROSTATE CANCER

An institutional, multidisciplinary project with the participation of radiation oncology, urology, radiology, pathology, physics, and gastroenterology division, has already been conducted with the aim of establishing standard evaluation methods and criteria for all the future planned studies on prostate cancer.

Phase II randomized study of hypofractionation versus standard fractionation radiotherapy in unfavorable risk prostate cancer: The main objectives of this study are the evaluation of the biochemical control, acute and late toxicity. One hundred and eighty patients are required for the specimen size.

Phase II randomized study on the use of antiCox 2 vs standard treatment to reduce the radiation therapy acute and late side effects in prostate cancer: The patients are randomized between the standard supportive treatment and the use of COX 2 inhibitors throughout the entire treatment and a week later. The aim of the study is to evaluate the eventual reduction of acute and late side effects on rectal and vesicle mucosa.

NUCLEAR MEDICINE

Patient specific Dosimetry must be referred to the estimation of dose to tissue of a specific patient based on individual body habitus and radiopharmaceutical kinetics. In fact MIRD formalism implicitly assumes that activity and cumulated activity are uniformly distributed within organ size source regions and that radiation energy is uniformly deposited within organ size target regions. Therefore this method is not able to calculate the dose released by low energy Auger electrons emitted by radiopeptide internalized within the tumor, which is the most important component of an accumulated dose in the intracellular level. To overcome this limitation of MIRD formalism, MIRD Pamphlet No.17 introduced the Voxel Dosimetry, which calculates the absorbed dose to tissue regions with dimensions ranging from a few centimeters to hundreds of micrometers. Voxel Dosimetry refers to radiation doses to specific points in a tumor or organ and thus reflects the spatial variation in dose within a target tissue. A more precise determination of temporal distribution of activity administered in tissues can be derived either from SPECT or planar sequential images. The dose point kernel is currently the most widely used method to calculate macroscopic not uniform dose distributions, primarily because of the demanding computational requirements of the Monte Carlo simulation. This calculation approach is mainly designed for internal dosime-

try in patients with solid tumors. The Biodistribution is given from measurements on the patient's biological samples and from planar images, acquired at prefixed times, applying an opportune calculation method to evaluate the residence times from compartmental models. We have developed a dosimetric tool, based on dose point kernel, derived from Monte Carlo simulations using the EGSnrc code, to calculate 3D dose distributions. Dose released by ?, ? radiation and low energy Auger electrons is provided by activity distribution obtained from SPECT and sequential planar images. Coregistered or matched CT/ SPECT images allow identification of tumor and organ at risk volumes, based on both morphologic and functional images. The Volumes of Interest Tumor and Organ at risk (liver, kidneys etc.) can be contoured by the physician, as in external beam radiotherapy, to obtain integral and differential dose-volume histograms (DVHs). DVHs show what percentage of any chosen volume is irradiated with a given dose and allow the application of predictive radiobiological models. The tumor control probability (TCP) for inhomogeneous dose distribution can derived from DVHs applying the linear quadratic model. We have also derived the TCP taking into account the dose rate variability between voxels.

Magnetic Resonance Physics

The activity is concerned essentially with:

Procedures and analysis tool for MRI quality assurance, quality control and protection. Guidelines and recommendations for MRI users, related to the acceptance test of systems utilized in the clinical practice, have been proposed to verify the performances;

Study of the functional imaging techniques and spectroscopic ones, both implemented in the high field MRI. The possibility to integrate morphologic patient data of the conventional Magnetic Resonance with metabolic-functional data and with spectroscopic analysis of the nucleotides present in the tissues, permit the diagnosis implementation;

Bayesian analysis of the dynamic Magnetic Resonance
images of the breast to extract useful information about
tumor morphology and pathophysiological features in the patients.

Ultrasound Physics

Protocols for B-mode ultrasound quality assurance have been produced by international associations, while Doppler ultrasonography uses a qualitative approach and suffers from lack of suitable guidelines. Therefore, specific quantitative quality assurance program have been proposed for optimizing diagnosis;

The applications of color and power Doppler ultrasound are in progress to visualize hypervascolarization areas for morphologic-functional diagnoses.

Radiation imaging

The medical physics laboratory co-operates with the radiology department in the maintenance and constant actualization and optimization of a quality assurance (QA) program concerning the technical and physical aspects of the medical imaging with ionizing and non-ionizing radiation.

This means that in order to reach and keep high standard levels of medical image quality and to minimize the risks for patients, the planning, execution and evaluation of many quality control measurements concerning image quality and the assessment of dose in diagnostic radiology are frequently performed in the analogical and digital domain of medical imaging.

The QA program includes some specialized branches concerning both: the screening programs (breast, lung) and observational studies.

The laboratory also co-operates in the evaluation and optimization of the radiology department computer network.

Publications 2003

Guidelines for quality assurance in intraoperative radiation therapy ISSN 1123-3117
07/1 Rapporti ISTISAN

Psychology

DIRECTOR:
PATRIZIA PUGLIESE, MD

Patrizia Pugliese graduated in 1984 at the University of Rome and specialized in psychodynamic psychotherapy in 1994. From 1989 to 2001 she worked in the Department of Oncology at the Regina Elena Cancer Institute. From 2002 she has been Director of the Service of Psychology at IFO. Dr. Pugliese's research focuses on an integrated approach regarding the Quality of Life for oncological patients. In 1995 Dr. Pugliese became a member of the Italian Society of Psycho-Oncology (SIPO) and in 1998 of the Italian Association of Medical Oncology (AIOM).

Staff:

Attending Ph.D:
DR. PAOLA TORTI

Post-Doctoral Ph. D (time-limited contract psychologist):
DR. MARIA PERRONE
DR. GABRIELLA MAGGI
DR. MARIA CONDOLEO

Time-limited contract:
DR. FEDERICO BUSSOLETTI

Fellow Ph. D in training:
DR. SANTINA TRAVO

Student:
DR. CHIARA FALCICCHIO

Activities 2003

Greater awareness of the complexities of oncological disease and treatment has led to a significant shift from an organ-centered objective to a person-centered medicine integrating bio-psycho-social factors into the diagnostic-therapeutic process. This new approach calls for the utilization of a multi-dimensional team both in the clinical and research process, with the following objectives in mind: prevention, cure and rehabilitation. This represents the new clinical and scientific guide-lines observed by both the international community and our Institute. The multidimensional aetiology (organic, psychological, disease and related treatments) of Quality of Life (QoL) necessitates a multidisciplinary approach. The QoL evaluation should utilize longitudinal studies which help to relieve the treatment related side-effects, their natural evolution and impact on QoL. Research activities in 2003 were based prevalently on QoL projects following these characteristics.

The assessment strategy is multidimesional and consists of structured and semi-structured interviews (to evaluate personality and social variables, sexuality, menopause, sterility/infertility, lymphedema, transplant meaning and integration with the new organ and quality of care) and psychometric instruments (to evaluate personality, QoL, anxiety and depression) All the instruments were administered before, during and after the treatment as well as in the follow-up.

During 2003, 908 new patients (592 in-patients and 316 out-patients) have been accepted and 3,345 activities (psychotherapy, clinical interview and tests) have been carried out. Emotional distress was focused on an important area of QoL, disease adaptation and treatment compliance. The aims of the study entitled "Emotional distress in advanced cancer patients treated with chronomodulated chemotherapy", were to describe the course of distress and QoL in 2 groups of patients with advanced cancer; to assess the distress as prognostic factor of QoL. Forty four advanced colorectal cancer patients were evaluated during chronomodulated therapy. Group 1 consisted of 22 patients with high levels of anxiety and depression symptoms (HADs ≥8; 10 male/ 12 female; median age: 61); Group 2 consisted of 22 patients with low levels of anxiety and depression symptoms (HADs ≤ 8; 10 male/12 female; median age: 62). The whole population were followed by an integrated team (psychologists and oncologists) with a supportive function during the therapy. The psychological intervention was a brief crisis intervention.

The results showed that a high level of anxiety and depression symptoms negatively impacted many QoL domains. At the end of treatment the improvement of emotional distress could be related to the supportive function of the integrated team or to the natural development of adaptation in a crisis situation.
The study gave rise to an abstract which was presented and accepted at the 7th World Congress of Psycho-Oncology.
A retrospective study "Lymphedema and QoL", concerning the lymphedema impact on QoL in collaboration with the Department of Neurology, is in agreement with the importance of prevention and management of treatment sequelae.
The research in literature showed that the interruption of the axillary lymphatic system by surgery or radiation therapy, may also cause severe morbidity such as edema, pain, numbness, loss of strength and impaired range of motion. Patients with lymphedema may experience a substantial degree of functional impairment and psychological morbidity. Early diagnosis, rehabilitative treatment and information for the patients are important to prevent worsening of the conditions and to increase their ability to adapt themselves to the changes of life. We enrolled 80 breast cancer patients during follow-up, comparing them with a group of patients without lymphedema. The results showed that mild or moderate lymphedema worsened all QoL areas, particularly distress and body image. This led to a longitudinal study on evaluation and improvement of lymphedema.
The study gave rise to an abstract which was presented and accepted at the 7th World Congress of Psycho-Oncology.
Treatment induced menopause represents a main area of long-term QoL. A retrospective study on "Evaluation and improvement of treatment related menopause" in breast and gynaecological women during follow-up was carried out with the Department of Gynaecology (Programma Prometeo). The aim of the study was to evaluate the impact of early menopause on QoL (sexual functioning, couple relationship, distress), the prevalence and the persistence for a prolonged period.
The results showed menopausal physical and psychological symptoms are related to high distress levels and sexual dysfunction after a long period of treatment.
The high percentage of patients who requested psychological therapy underlines the subjective significance of both QoL areas.
The study "QoL and liver transplant" is one of the few longitudinal studies which evaluated the psycho-social variables of transplant patients and the meaning that these patients attribute to the various phases of the therapeutic process. Each phase of the transplant (the candidature, the waiting, the day of transplant, the intensive unit care, the hospital stay, the discharge, and the following care) influences body image, daily activity, interpersonal relationships and life values and expectations.
The aim of the study was to evaluate the psychosocial variables and the psychological impact of the phases of the transplant. This evaluation represents the basis for the QoL improvement.
The results showed a worsening of QoL and distress during the first admission to hospital but an improvement during the following phases.
The project "Quality of life in early breast cancer patients receiving adjuvant chemotherapy" responds to the need for monitoring and dealing with the physical, psychological, social and sexual long term side-effects of disease and treatment. This results in the consideration of the QoL evaluation as an endpoint as important as survival and objective response.
The aim of the study was to evaluate QoL, anxiety, depression and patient perception of treatment sequelae during adjuvant chemotherapy. Patients were followed by a team including psychologists and oncologists.
The most affected QoL domains were anxiety, depression, sexuality. On the contrary, fatigue and QoL were stable during the course of treatment.
According to Kajat (2002), patients experienced the worst psychological symptoms.
The study gave rise to an abstract which was presented and accepted at the 7th World Congress of Psycho-Oncology.

The results of retrospective studies led to the "Global Project for QoL evaluation and improvement in oncological long-survivors". The aim of this project is to work out and circulate guide lines for multidisciplinary evaluation and treatment of some QoL domains such as sexual and reproductive functioning, distress and fatigue in long survivors.
The meetings of team members are the basis of QoL improvement. This ongoing formative training facilitates adequate communication skills and thus good quality of care.
The guide lines arise from previous experience at the Regina Elena Cancer Institute and from future collaboration with other oncological IRCCS and will be circulated through E-Oncology, the portal of Alleanza Contro il Cancro.
The circulation of guidelines will be utilized as a net to link Cancer Institutes with SSN, Universities, patients and their families.
The knowledge acquired during course of the project will be utilized for educational purposes with training courses and updating regarding the quality of life of the cancer patient defined on the basis of each single specialized competence and arranged within a program of ongoing training and credit for health workers established by the Ministry of Health.
Another specific field of our Service regards screening and life style improvement strategies.
Literature has shown that early diagnosis and smoking cessation are principal aims of lung cancer prevention and cure. The evaluation of lung cancer screening psychological issues is part of a program, which uses Low Dose Spiral Computerized Tomography (LDSCT) for early diagnosis. Our purpose was to evaluate the screening impact on QoL and anxiety of enrolled subjects and to evaluate the subjective perception of the quality of the screening program and the relationship between participation in the program and the motivation to quit smoking.
In this program the psychologist intervention is both educational, with the aim of preventing the crisis related to LDSCT response as well as supportive, aiming at containing the patient crisis with a positive diagnosis.
The results showed that in 296 individuals prevention above all motivated participation. Individuals referred, moreover, that participating in this program motivated the decision for quitting smoking in the following months. The annual repeat screening made on 102 individuals showed a positive perception of the quality of the program, particularly with the information provided by the health care staff. Finally, in most patient, participating in this program didn't cause anxiety symptoms and thus a worsening of QoL.
Literature on the smoking habit shows that the combined use of substitute nicotine therapy (NRT) with psychological support has a 16% increase in the probability of an effective attempt at cessation. Therefore this study used an integrated pharmacological and psychological approach with Service of Pneumology for the smoking cessation program.
The psychological intervention is based on a cognitive-behavioral approach, with the aim of increasing or maintaining the motivation to quit smoking.
Concerning the stage of change as described by Prochaska (1991) the results in 144 subjects showed:
44% of the sample were in the "contemplative" stage, 31% in the "precontemplative" and the remaining 35% in the "preparation" stage. Most of the individuals highlighted a psychological dependence to smoking: 41% considered cigarettes a pleasure, 28% as a way to control anxiety, 16% as a habit, and the remaining 15% as able to give self-confidence. After six months 35% of the sample still abstain from smoking.
These results focus on the necessity to create an integrated perspective among screening and smoking cessation programs.
The study gave rise to an abstract which was presented and accepted at the 7th World Congress of Psycho-Oncology.

Future perspectives:

Our interest in the multidisciplinary approach is based on the integration between clinical, research and formative areas. QoL research is derived from the direct impact of disease diagnosis and treatment and the importance of team communication.

The formative process of the team deals with bio-psycho-social side-effects as this facilitates a better doctor-patient communication and an earlier diagnosis as well as improvement of QoL problems. At our Institute the increase of longitudinal studies and their use in different neoplasms and disease phases could be linked with randomized studies on the clinical effectiveness of integrated intervention.

The clinical activity of our service provides for group psychotherapy in addition to individual therapy. Group psychotherapy can address the major issues facing persons with cancer in a way that members can garner the emotional support of persons with similar experiences and use the experiences of others to buffer the fear of future unknowns. Yet beyond it's effectiveness, group therapy, is also extremely time-and-cost efficient. This therapy facilitates treatment awareness and compliance (educational groups), specific symptom management and lifestyle and behavior change (cognitive-behavioral groups), the open expression of emotion and a new meaning for the disease (psychodynamic groups).

Laboratory animal center (S.AF.U.)

DIRECTOR:
GENNARO CITRO, PHD

Dr. Gennaro Citro is actually director of S.A.F.U. Stabling, raising, supplying and managing animal models for Regina Elena National Tumor Institute-Rome. July 1975 Graduated in Biological Science, 110/110 summa cum laude from the University of Studies Rome, gained considerable experience in research both in Italy and overseas. Since 1969 Visiting Investigator at Zoological Facility of Naples on behalf of the Swedish National Cancer Society. Then in 1975 Visiting Investigator at the Immunology Laboratory of Guy's Hospital Medical School in London, and in 1987 Senior Investigator at the Genetic Engineering Laboratory of the Max-Planck Institute in West Berlin.
In the 1990 Senior Investigator-Department of Chemical Cancerogenesis at the Dutch National Institute of Cancer
Amsterdam. During 1992 Senior investigator, Department of Microbiology and Immunology, Jefferson Cancer Institute, Philadelphia, USA (National Institute of Health, Bethesda grant).

Teaching Experience

Professor: Chemical Cancerogenesis, Faculty of Medicine and Surgery, Tor Vergata 2nd University of Rome.
1988-89 Professor: Applied Immunology, Faculty of Medicine, University of Camerino
1989-9 Professor: Immunochemical and biological marker detection Techniques, Faculty of Science, University of Aquila.
1990-93 Professor: Bio-organic Mechanisms of Reaction in Toxicology, Faculty of Medicine, La Sapienza University Rome.

Research Unit Management.

In charge of the research project for A) the Italian Association of Cancer Research; B) the CNR Bio-material Research Unit and of the CNR Project for Strategic oligonucleotide antisense research; C) the CNR Special Project - Vegetable Toxins; D) the Unit for the MURST Project 'National Biotechnological Project' law 46 D. Min. 995 31/1/96; E) the Operative Unit, Ministry of Health Project; F) Project Coordinator, Ministry of Health; G) the Operative Unit, Ministry of Health Project

Staff:
DR. GIANCARLO CORTESE
DR. ENRICO SPUGNINO (veterinary consultant)
MR. GIUSEPPE BERTINI
MR. PIERINO PICCOLI
MR. DEMETRIO SPOSATO

Activies 2003

The work carried out for S.A.F.U. has mainly been in support of the clinical as well as experimental departments of the facility, using animal models for the development of completed and current research projects.
The availability of animal breading models permits the study of drug kinetics and drug distribution, supplying important information such as:

- the activity and duration of the effect of a drug;
- metabolic end of a molecule in an individual;
- early signs of further intervention to be undertaken in a treatment protocol in the case of an unsatisfactory response of a patient;
- the eventual interference of drug effects, administered in combination/association with other drugs.

Furthermore, specific antiserum is produced in rabbits through the synthesis of peptides

that reproduce the protein antigenic activity sites of biological interest. These reagents aid in highlighting both the presence of natural antigens in the biological areas where they are expressed as well as determine the quantity. Moreover, the possibility to use the reagents as drugs in new therapeutic strategies from the peptides produced, are experimentally evaluated. In particular synthetic peptides, the amino-acid sequence of which is able to inhibit the links with oncogene products and other functional proteins, are produced.

Current Research Projects

- Transgenic Models (2000-2002 Coordinator in charge of End Project Ministry of Health)
- "Lead Molecules" inhibitors of some Signaling Proteins affected by excess/deregulation of function. (2002-2004 In charge of the End Project, Ministry of Health)

Cooperation/Conventions:

Department of Experimental Medicine, University Tor Vergata Rome
Biology Department Tor Vergata.
La Sapienza University, Department of Motor Science and traumatology
Department of Biochemical Science 2nd Faculty Sant'Andrea Hospital

Publications 2003

Expression of OP4 (ORLLLL1, NOP1) receptors in vascular endothelia.
Eur J Pharmacol. 2003 Dec 15;482 (1-3): 17-23.

Glucosyleceramide synthase and its functional interaction with lC regulate chemotherapeutic induced apoptosis in neuroepithelial cells.
Cancer res. 2003 15;63 (14): 3860-5

Division of general surgery A

Director:
Franco Di Filippo, MD

Franco Di Filippo received his MD in 1975 and specialized in General Surgery, in 1979 at the University of Trieste, in vascular Surgery in 1982 at the University of Rome and in Surgical Oncology in 1986 in the University of Naples.
From March to September 1983 he worked as follows at MD Anderson Hospital, Houston Texas and at MSKCC, New York. From April 1997 to June he worked at Washington Cancer Center, Chaired by Prof. Paul Sugarbaker in order to specialize in the combined treatment of peritoneal carcinomatosis.
From 1999 he has been teaching in the school of General Surgery at the University of Rome. Since March 1999 he has been director of the department of Surgical Oncology of the National Cancer Institute of Rome.
He is a member of the Italian Society of Surgery, Italian Society of Surgical Oncology and President of the Italian Society of Integrated Locoregional Therapies in Oncology.
Prof. Franco Di Filippo's interests are focused mainly on basic and clinical research of breast cancer, melanoma, soft tissue sarcoma and peritoneal carcinomatosis.

Medical Staff:
Michele Anzà - M.D.
Claudio Botti - M.D.
Pietro Bruno - M.D.
Alfredo Callopoli - M.D.
Francesco Cavaliere - M.D.
Fabrizio Frezza - M.D.
Rosa Garinei - M.D.
Roberto Maialetti - M.D.
Loredana Piarulli - M.D.
Angelo Psaila - M.D.
Pasquale Perri - M.D.
Fabio Massimo Sega - M.D.
Carlo Viticci - M.D.
Vanessa Patrizi - M.D. Student
Francesco Priore - M.D. Student
Giuseppe Curinga - M.D. Student
Tiziana Piccolo - Department secretary

Nurse:
Giovanna Grazioli - Chief of Nurses

Nurses:
Castaldo Agostino
Chiarabini Gianni
De Vecchis Romeo
Di Cecio Maria
Di Ceglie Antonietta
Di Paolo Daniela
Gemma Giuseppina
Melis Roberta
Panzieri Giulia
Tirimagni Aurelio

Activities 2003

The activities of our department will be focused on 4 topics: breast cancer, melanoma, soft tissue sarcoma and peritoneal carcinomatosis.

Breast cancers

Randomized multicenter giscris Study.
This is a phase III randomized protocol that compares axilliary nodes dissection vs.. sentinel node biopsy followed by node dissection only if SN is involved.

Eligible patients were those with T1 cancer with clinically negative axillary nodes. The main objective of the study was the loco-regional relapse rate and survival in the two arms. The accrual of the patients was ended in 2003.

Nipple skin sparing mastectomy.

Background

Breast cancer treatment is carried out with conservative surgery in the majority of the patients. There still are patients in which radical mastectomy is mandatory. In these cases breast reconstruction is always performed, but the cosmetic results are not always satisfactory, due to the removal of skin and NAC complex. Therefore, we have begun a new protocol that foresees the nipple-skin sparing mastectomy in selected patients.

Methods and Results

Eligible patients are those candidates to radical mastectomy without Paget diseases, NAC infiltration or tumor located immediately below NAC complex. During the operation frozen sections of tissue underlying the NAC are always carried out to exclude the infiltration of subareolar ducts. The results will be evaluated in terms of feasibility, rate of complication (skin or NAC necrosis) cosmetic and oncological results (recurrence).

At the present time 30 patients have been treated with this technique. Partial necrosis of NAC complex has been observed only in one patient, the cosmetic results have been excellent.

Multicentric randomized study: IORT vs. external radiotherapy

Background

Our department is participating in a prospective randomized trial that compares the effectiveness of IORT vs. external radiotherapy in breast cancer patients submitted to conservative surgery. It is a well known fact that radiotherapy is mandatory after breast conserving surgery. A randomized study carried out at the National Cancer Institute of Milan has compared conservative surgery and radiotherapy vs. surgery only. There was a greater recurrence rate in the surgery arm. Interestingly, a high frequency (80%) of recurrences occurred in the surgical field. On the basis of these observations a randomized multicenter study that compares IORT vs. external radiotherapy was undertaken.

Methods and Results

Patient affected with breast cancer $\leq$2.5 cm, age $\geq$48 and already in menopause are intraoperatively randomized (frozen section of margins are carried out during operation). After conservative surgery, breast parenchyma is reconstructed, a perspex disk is located between breast tissue and chest wall to protect the underlying structures.

IORT is carried out.

The aim of the study is to demonstrate an equivalence in the two techniques in terms of efficacy (locoregional relapse); side effects IORT-related and cosmetic results will also be evaluated.

Sentinel node biopsy: relevance of immunohistochemical examination for micrometastases detection.

Background

It is a well known fact that the reliability of sentinel node biopsy is also based on the histopathological examinations. Thus, immunohistochemistry is routinely employed. We have compared the rate of micrometastases identified by E.E. and IHC.

Methods and Results

From our database we have selected 178 patients, all submitted to sentinel node biopsy. The sentinel node was examined according to histopathological rule established by Foncam. All the sentinel nodes were also examined with IHC (antibodies anticytocheratin).

The percentage of sentinel node involvement was 26% (47 out of 178).

Forty-two sentinel nodes were positive both to E.E. and IHC, and positive to IHC only in just five cases. Therefore, the use of IHC allowed us to identify only 10% of patients negative to conventional E.E.
Taking into account that the real impact of micrometastases on patient outcome does not seem to be relevant, the routine use of IHC should probably be abandoned.

Melanoma

The clinical impact of sentinel node micrometastases on the outcome of melanoma patients: prospective multicenter study (IDI Institute – S. Gallicano Institute – University of Tor Vergata).

Background

The sentinel node (SN) biopsy technique has become a routine procedure in the treatment of melanoma patients. The pathological examination of SN has been carried out with the E.E. technique, but employing immunohistochemistry or the RT-PCR technique it is possible to increase the sensitivity and therefore to identify a higher number of positive SN. The aims of the study were:
to evaluate the rate of increased sensitivity of immunohistochemistry and RT-PCR technique as compared to E.E.
to evaluate the clinical impact of micrometastases on the outcome of patients.

Methods and Results

From March 2001 to June 2003, 395 patients were enrolled in the study. Eligible patients were those with tumor thickness ≥1mm, Clark level IV and/or ulcerated tumors. All the patients were submitted to SN biopsy, lynphadenectomy was carried out only if SN was involved. The SN was examined with E.E., immunoistochemistry (HMB45 and MART-1) and RT PCR technique (MART-1 and HTYR).
The Breslow thickness ranged between 1 and 10 mm, with an average of 1.9 mm.; most of the patients (93%) had a tumor thickness between 1 and 4 mm. In 97% of the patients Clark level ranged between III and IV, ulceration and regression were present in 28% and 24% of patients respectively. The rate of SN positivity is 16.7%.
There was a close correlation between SN positivity and tumor thickness: 7.5% in tumor thickness 1-2 mm; 12.6%, >2 mm; 32%, >3mm and 33%, >4 mm.
The examination of SN with IHC permitted to identify micrometastases in 20% of the patients negative to E.E.
In the SN examined with RT-PCR a positivity for MART-1 was found in 55% of SN; a positivity for both primers (HTYR-MART-1) was found in 45% of cases.
The RT-PCR was able to identify a positivity of 25% of SN negative to E.E. and IHC.
In a small subset of patients with a median follow-up of 22 months, we have compared the relapse rate in SN negative and SN positive with IHC, the rates were 14% and 33% respectively. These preliminary data seem to indicate that micrometastases may have an impact on the outcome of melanoma patients.
Hyperthermic Isolation Limb Perfusion (HILP) with TNFα (1 mg) and Melphalan in the treatment of locoregional spreading melanoma.
Background
HILP with TNFα and Melphalan has proven to be very effective in the treatment of advanced limb melanoma. Unfortunately, the TNFα dosage (3-4 mg) was established empirically. Moreover, it was extremely important to identify patients who really benefit from TNFα HILP.
Methods and Results
We have carried out a phase I-II study starting with a TNFα dose of 0.5 mg (the systemic MTD) up to 3.3 mg. No correlation with TNFα dose and tumor response was observed; evaluating all the patients treated with 1 mg of TNFα, the pathological tumor response was: CR 70%, PR 20%, SD 10%, with on OR of 90%. These results are almost identical to those obtained with 3-4 mg, demonstrating that high TNFα dosages are not necessary.

We have also carried out a retrospective study comparing patients with low tumor burden and high tumor burden treated with HILP and Melphalan or with Melphalan and TNFα. The retrospective comparison seem to show that only patients with high tumor burden (≥10 nodules or nodules with a diameter > 3cm) really benefit from HILP with TNFα. In fact, in those patients the CR rate was 67% with Melphalan and TNFα as opposed to 28% with Melphalan alone.
This is an important issue because we have established the eligibility criteria and TNFα dosage (1 mg) to be employed during HILP.
Hypoxic pelvic and limb perfusion with melphalan and mitomycin-C for recurrent limb melanoma: a pilot study.

Background
In-transit metastases from limb melanoma can occur in the proximal third of the thigh or arm; sometimes unresectable pelvic nodes can develop.
These patients are not eligible for hyperthermic isolated limb perfusion (HILP).
Recently, a new technique hypoxic limb perfusion has been performed, able to treat patients not eligible for HILP. We have participated to a pilot study conducted on the behalf of Italian Society of Integrated Locoregional Treatment in Oncology.

Methods and Results
Hypoxic pelvic and limb perfusion by means of a balloon occlusion technique was performed in 17 patients, melphalan (50 mg/m^2) or melphalan and mitomycin C (50 mg/m^2 and 25mg/m^2 respectively) were employed as antineoplastic drugs.
Each procedure was followed by hemofiltration. A leakage monitoring study was performed in 5 out of 17 patients. The response rate and time to disease progression were the primary end points, with overall survival as a secondary endpoint. No technique-related complications or deaths were observed in the postoperative period. Significant leakage (median 40%) was recorded in five patients. No severe systemic or regional toxicity was observed.
After one course of treatment, the OR rate was 47%, the median time to disease progression was 10 months (range 2-40 months), and the 3 year overall was 20%.
Hypoxic pelvic and limb perfusion seems to be a safe and effective treatment for patients with unresectable recurrent limb melanoma not eligible for HILP.

Soft tissue sarcoma

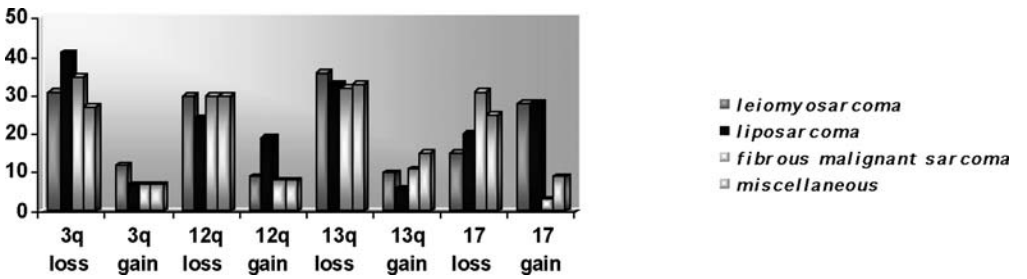
Liposomal doxorubicin in the perfusional treatment of advanced soft tissue limb sarcoma.

Background
We have previously carried out a phase I-II study in the perfusional treatment of advanced limb soft tissue sarcoma with adriamycin and TNFα. The results were: CR 25%, PR 75% with an OR of 80%. Moreover, limb sparing surgery was carried out in 77% of patients candidate to amputation. Unfortunately, in some patients a grade 3-4 limb reaction was observed due to hyperthermia-adriamycin synergism that also involves healthy tissues.
Recently, adriamycin encapsulated in liposomes has become commercially available. Liposomes have particular physical-chemical properties because they release the drug preferentially in hypoxic tissue (tumor) instead of euoxic tissue (healty tissue).

Methods and Results
We have carried out a phase I-II study with a starting dose of 10 mg/L of limb volume. The dosage was increased with 2 mg for each triplet of patients, whereas tumor and muscle temperature remained constant (41.5°C). The MTD was 16 mg/L because at 18 mg/L two grade IV limb reactions were observed. In all the patients treated with a dosage between 10 and 16 mg/L a grade I-II was observed.
A tumor necrosis >50% was recorded in 7/15 patients. All patients were submitted to conservative surgery, with the exception of a patient affected with a multifocal synovial sarco-

ma with a poor response to treatment.
At the present time 2 out of 15 patients developed lung metastases, no recurrences have been observed thus far. The next protocol foresees the association of liposomal doxorubicin with 1 mg of TNFα.

GENETIC EVALUATION OF SOFT TISSUE SARCOMA.
Background
Cytogenetical analysis of soft tissue sarcoma is of paramount relevance both in basic and clinical research.
Molecular cytogenetical techniques have identified many genotypic aberrations in benign and malignant soft tissue sarcomas.
Methods and Results
To improve prognostic data patterns, 30 soft tissue sarcomas biopsies were cytogenetically evaluated by Fluorescent in Situ Hybridization (FISH). Distribution of histological subtypes is as follows: 25% lyposarcomas, 39% Malignant fibrous lesions, 18% leiomyosarcomas and 18% miscellaneous sarcomas.
As negative prognostic factors, chromosome 3q, 12q, 13q losses and HER2/neu gene together with chromosome 17 status were genetically analyzed in each sample (Fig. 1).



Peritoneal carcinomatosis

Peritoneal Carcinomatosis from colorectal cancer: clinical prognostic factors.

Background
A high number of colorectal cancer patients often experience a peritoneal recurrence as the only site of relapse. Recent studies on the natural history of peritoneal carcinomatosis from colorectal adenocarcinoma show a median survival that does not exceed 7 months.
In recent years it has been realized that some peritoneal carcinomatosis have to be considered as a locoregional disease to be treated with locoregional instead of systemic therapy. A new therapeutic approach has been carried out that foresees the cytoreduction of all visible disease followed by intraoperative hyperthermic chemoperfusion (IHCP) or early postoperative intraperitoneal chemotherapy (EPIC).
Encouraging results were obtained in many phase II studies, the 3 year survival ranging from 22% up to 65%. Despite the increased survival, the wide range of results obtained still remain an open question regarding patient selection and prognostic factor identification.

Methods and Results
On behalf of the Italian Society of Integrated Locoregional Treatment in Oncology we have conducted a prospective study on the treatment of peritoneal carcinomatosis by peritonectomy and perioperative chemotherapy. Sixty-nine consecutive patients were enrolled in the study. The median age was 52 years (range 19-76), most of the patients (75%) had been previously treated with adjuvant or palliative systemic chemotherapy. The peritoneal cancer index (PCI) ranged between 11 and 20 in 47% and was more than 20 in 19% of the patients.
The cytoreductive surgery was synchronous with the resection of the primary tumor in 29 patients (42%); total peritonectomy was performed in 12 cases (18%). A complete cytoreduction ($CC\text{-}_0$) was achieved in 75% optimal ($CC\text{-}_1$) in 7%, while in 18% of the patient peri-

tonectomy resulted in macroscopic residual tumor with nodules larger then 0.5 cm ($CC-_2$).
The IHCP was routinely performed except in 4 cases because of the bulky residual disease. The technique was open (Coliseum) in 85% of the procedures and closed in 15%, lasting 90 minutes in 68% and 60 minutes in the remaining 32%.
Morbidity was 21.7% and was directly correlated with the extension of cytoreduction (Chi square for trend. 04). The most important events were represented by anastomotic leak (4.3%), perforation (2.9%) and sepsis (2.9%). Surgery was required in 40% of the complicated cases. Locoregional toxicity, evaluated according to modified Ozol's classification, was G1 in 21.7% of the patients, G2 in 1.4%, G3 in 1.4% and G4 in 2.8%; the observed systemic toxicity (WHO) was only hematologic G1 in 2.8% and G2 and G3 in 1.4%. No G4 toxicity was registered.
Perioperative mortality was 2.9%.
The 3-year overall survival for the entire series was 26.7% with a median survival of 19 months.
Evaluating only those patients who could be cytoreducted to $CC-_{0-1}$, the 3-year survival rose to 31.3%.
Synchronous resection of primary adenocarcinoma did not modify overall and disease-free survival (p=ns).
No differences either in survival or in recurrent rate have been registered performing IHCP with the 'open' vs. 'closed' technique (p=.08) or modifying the duration of chemoperfusion from 60 to 90 minutes (p=.07).
A PCI cut-off of 10 has a significant impact (p=.02) on survival which was 42% at three years (PCI≤10) vs. 23% (PCI>10).
Evaluating patients with a low PCI (≤!0) and complete or optimal cytoreduction ($CC-_{0-1}$) vs. patients with a PCI>10 and residual disease larger than 0.5 cm (CC-2) the 4-year survival was 44.7% and 0% respectively (p=.008). in the first group the median survival was 28 months.
Finally we analyzed the influence of the disease-free interval (DFI) between resection of primary tumor and the onset of peritoneal carcinomatosis: the DFI longer than 24 months showed a 5-year overall survival of 60% (p=.04) and a 5-year disease-free survival of 50% (p=.01).
The analysis of recurrence distribution pointed out that the incidence of relapses is still locoregional in 80% of the patients.

Publications 2003

Cavaliere F., Perri P., Rossi C.R., Pilati P.L., De Simone M., Vaira M., Deraco M., Di Filippo F.

Indications for integrated surgical treatment of peritoneal carcinomatosis of colorectal origin: experience of the Italian Society of Locoregional Integrated Therapy in Oncology.

Tumori. 2003 Jul-Aug;89(4 Suppl):21-3. *I.F. 0.267*

Cavaliere F., Perri P., Rossi C.R., Pilati P.L., De Simone M., Vaira M., Deraco M., Aloe S., Di Filippo S. and Di Filippo F.

Sitilo Experience on Peritoneal Carcinomatosis From Colorectal Cancer: Clinical Prognostic Features

J. Exp. Clin. Cancer Res., 22, 4, 2003-Supplement *I.F. 0.703*

Deraco M., De Simone M., Rossi C.R., Cavaliere F., Di Filippo F., Vaira M., Piatti P. and Kusamura S.

An Italian Multicentric Phase II Study on Peritonectomy and Intra Peritoneal Hyperthermic Perfusion (IPHP) to treat patients with Pseudomyxoma Peritonei

J. Exp. Clin. Cancer Res., 22, 4, 2003 - Supplement *I.F. 0.703*

Deraco M, De Simone M., Rossi C.R., Cavaliere F., Difilippo F., Scuderi S., Pilatti P. and Kusamura S.

An Italian Multicentric Phase II Study on Peritonectomy and Intra Peritoneal Hyperthermic Perfusion (IPHP) to Treat Patients with Peritoneal Mesothelioma

J. Exp. Clin. Cancer Res., 22, 4, 2003 - Supplement *I.F. 0.703*

Di Filippo F., Garinei R., Anzà M., Cavaliere F., Giannarelli D., Cagol P.P., Rossi C.R., Santinami M., Deraco M., Botti C., Perri P., Di Filippo S., Piarulli L., Bruno P.

Doxorubicin in Isolation Limb Perfusion in the Treatment of Advanced Limb Soft Tissue Sarcoma

J. Exp. Clin. Cancer Res., 22, 4, 2003 - Supplement *I.F. 0.703*

Di Filippo F., Garinei R., Giannarelli D., Anzà M., Cavaliere F., Botti C., Perri P., Di Filippo S., Psaila A., Callopoli A., Maialetti R., Sega F., Frezza F., Viticci C.

Hyperthermic Antiblastic Perfusion in the Treatment of Loco- Regional Spreading Limb Melanoma

J. Exp. Clin. Cancer Res., 22, 4, 2003 - Supplement *I.F. 0.703*

Di Filippo F., Garinei R., Anzà M., Cavaliere F., Botti C., Perri P., Di Filippo S.

Anti-blastic hyperthermic perfusion in the treatment of melanoma of the extremities in the loco-regional diffusion phase.

Tumori. 2003 Jul-Aug;89(4 Suppl):241-3. *I.F. 0.267*

Di Filippo F., Rossi C.R., Garinei R., Anzà M., Cavaliere F., Botti C., Perri P., Di Filippo S., Di Angelo P., Principi F., Laurenzi L.

Hyperthermic Antiblastic Perfusion with TNFα and Melphalan in Stage III Limb Melanoma Patients: A Phase I - II SITILO Study

J. Exp. Clin. Cancer Res., 22, 4, 2003 - Supplement *I.F. 0.703*

Guadagni S., Santinami M., Patuzzo R., Pilati P.L., Miotto D., Deraco M., Rossi C.R., Fiorentini G., Di Filippo F., Valenti M., Amicucci G.

Hypoxic pelvic and limb perfusion with melphalan and mitomycin C for recurrent limb melanoma: a pilot study.

Melanoma Res. 2003 Feb;13(1):51-8. *I.F. 1.773*

Papaldo P., Lopez M., Cortesi E., Cammilluzzi E., Antimi M., Terzoli E., Lepidini G., Vici P., Barone C., Ferretti G., Di Cosimo S., Nistico C., Carlini P., Conti F., Di Lauro L., Botti C., Vitucci C., Fabi A., Giannarelli D., Marolla P.

Addition of either lonidamine or granulocyte colony-stimulating factor does not improve survival in early breast cancer patients treated with high-dose epirubicin and cyclophosphamide.

J.Clin. Oncol. 2003 Sep 15;21(18):3462-8. *I.F. 9.868*

Visca P., Sebastiani V., Pizer E.S., Botti C., De Carli P., Filippi S., Monaco S., Alo P.L.

Immunohistochemical expression and prognostic significance of FAS and GLUT1 in bladder carcinoma.

Anticancer Res. 2003 Jan-Feb;23(1A):335-9. *I.F. 1.447*

Division of gastro-intestinal surgical oncology and liver transplantation

DIRECTOR:
EUGENIO SANTORO, MD

Eugenio Santoro graduated in medicine cum laude at the University of Rome in July 1962. He received his post-graduate specialization in General Surgery (1967), Thoracic Surgery (1969) and Pediatric Surgery (1973) from the University of Rome. He was a visiting surgeon in Stockholm (1964), Paris (1966-1968), Minneapolis (1976) and Houston (1984 and 1986). From 1976 to 1989 he was director of the division of general surgery at Cristo Re hospital in Rome and from 1990 till 2000 he was director of the Division of Surgical Oncology at Regina Elena Cancer Institute of Rome. From 2000 he has been the Director of the Division of Digestive Surgical Oncology and Liver Transplantation and from 2001 the Director of Surgical Oncology Department, always at Regina Elena Cancer Institute.

Prof. Santoro was president of the Italian Surgical Society (SIC) for a period of two years 1998-2000 and A.C.O.I (Associazione Chirurghi Ospedalieri Italiani) for the period 1993-1996.

He has been on the teaching staff of La Sapienza University, Rome since 1969 and the Catholic University since 1984.

He is the President of *Federchir* (Federazione Società Scientifiche Chirurgiche) and International Association for Gastric Cancer and Gastric Disease and Vice-president of the European Association for Videosurgery.

He is a member of the executive council of Lega Italiana Lotta Tumori, the commission for medical devices of Ministry of Health and the managing council of Tel.ma. University.

In 2004 Prof. Santoro was decorated with a gold medal by the Minister of Health. He was a member of the Consiglio Superiore di Sanità from 1997 to 2002, and he has been included in the National Commission of ECM (Educazione Continua in Medicina) since 2000.

He was an honorary member of the Medical Association of Argentina (1993), Surgical Society of Lebanon (1999), French Surgical Academy (1999), Surgical Society of Peru (2000) and Surgical Society Rumania (2000) and Fellow of American College of Surgeons (1998). He has been treasurer of International Surgical Club since 1991.

He is member of board of numerous Italian and foreign journals (Chirurgia Italiana, Hepato-gastroenterology, Journal of Experimental and Clinical Cancer Research, Laparoscopic Surgery, Hepatology, Gastric Cancer).

He has promoted numerous national and international meetings and courses in the field of general surgery and surgical oncology.

Prof Santoro's main area of interest is General Surgical Oncology, Liver Transplantation and Liver Surgery. In August 2002 he performed the first liver transplant in a HIV positive patient in Italy.

He is in charge of several research projects of CNR, Ministry of Health and Lega Italiana Lotta ai tumori. He is the Author of more than 200 full papers and eight books, including one on the history of Italian surgery (Cento anni di Chirurgia).

Staff:

FABIO CARBONI - M.D. PHD Assistant
MAURIZIO COSIMELLI - M.D. Assistant
MARCO D'ANNIBALE - M.D. Assistant
GIUSEPPE ETTORRE - M.D. Assistant
FRANCO GRAZIANO - M.D. Assistant
PASQUALE LEPIANE - M.D. Assistant
ROBERTO SANTORO - M.D. PHD Assistant
GIOVANNI VENNARECCI - M.D. Assistant
ARIANNA BOSCHETTO - M.D. Fellow
VALERIO CORAZZA - M.D. Fellow
ALESSANDRO ESPOSITO - M.D. Fellow
RICCARDO LORUSSO - M.D. Fellow
PIETRO MANCINI - M.D. Fellow
RAFFAELLO MANCINI - M.D. Fellow

Clinical 2003 Activity

The Division is dedicated to the cure of abdominal and gastrointestinal oncological disease, from the esophagus to the anus. The ward has 37 in-patient beds, three of which are totally dedicated to patients undergoing liver transplantation. During 2003, 858 patients were admitted and 560 underwent a surgery. We are very active in dealing with a multimodal and multidisciplinary approach to cancer of the stomach, colon-rectum and liver. The unit is also dedicated to the treatment of tumors of the biliary tract and pancreas. Patients with cancer of the lower rectum are candidate for pre-operative local radiotherapy and systemic chemotherapy with the aim of loco-regional reduction of tumor extension. In the year 2003 the division performed 55 gastrectomies, 130 colectomies, 24 pancreasectomies and 75 hepatectomies and 23 liver transplantations. The majority of gastrointestinal operations were performed laparoscopically.

The Division in the year 2000 started the liver transplant program for hepatocellular carcinoma grown on cirrhosis. Since then the Division, well know thorough out Italy and abroad, has increased its activities in the field of treating liver cancers and liver metastases. The Division has a extensive experience in major liver resection for hepatocellular carcinoma on cirrhosis and liver metastases, treating liver cancers by trans-arterial-chemo-embolization (TACE), radiofrequency ablation and alcolization.

The Division has a very active out-patient clinic (one clinic is dedicated to patients with gastrointestinal oncologycal disease, one to patients with liver cancer (primary and metastases) and four to follow-up of operated patients (stomach and pancreas, colon-rectum, liver and liver transplant respectively). The overall activity for 2003 accounts for over 3000 out-patient visits.

Research Activity

Research on liver cancer

In 2003, 58 patients with liver neoplasms have been submitted to surgery: 28 for HCC, 24 for metastases and 6 for cholangiocarcinoma, including gallbladder cancer. Furthermore, 23 liver transplantations have been performed in the Department for liver cirrhosis, 11 of them with associated HCC, and 14 other patients underwent surgery for benign disease.

During the year a larger number of liver patients have been observed but excluded for surgery because of the extension of neoplastic disease or very poor general conditions. Part of the un-resected HCC have been submitted to chemoembolization (TACE).

The clinical research has involved two main fields of interest:

HCC in patient with HBV or HCV hepatitis;

Liver metastasis from colorectal cancer previously submitted to chemotherapy with response.

The current studies are as follows: **Liver transplantations in HCC patients: evaluation of histologic vascular invasion as prognostic factor.** Eleven patients have been included in the study during the year. In 2002 another 9 patients have been included. The study will require at least 20 HCC with vascular invasion and 20 HCC without it, with a follow-up not shorter than three years for each case. A the moment only one HCC with vascular invasion submitted to liver transplantation in 2002 died from progression of neoplastic disease. No death or recurrent disease was observed in the other patients.

Chemotherapy and liver surgery in the treatment of colorectal metastasis. 24 pts with liver metastasis have been resected during the year in patients previously submitted to colorectal resection of primary and postoperative chemotherapy for synchronous liver metastasis. Chemotherapy protocols included FOLFIRI and FOLFOX according to response with continuous infusion. One arm of this study included patients in which a two-step surgery was performed: first, legation of the right portal vein and removal of one or two metastases in the left lobe; secondly, (2 months later), right hepatectomy and remnant hypertrophic left lobe remnant.

Multicenter Study on primary and secondary HCC (promoted by ESMO and

supported by LILT). This observational study has been approved by the Ethical Committee and should start in the near future.

New biomolecular markers of HCC associated with liver cirrhosis, in relation to different treatments. The aim of the study is to obtain a better knowledge of the biological behavior of HCC in order to select a tailored specific treatment, through: a) evaluation of new biomolecular markers such as DCP and VEGF, Ki-67 nuclear antigen, NGF, metalloproteinasis and specific inhibitors; b) detection of circulating neoplastic cells by RT-PCR; c) evaluation of HVPG by selective supra-hepatic catheterism. Patient accrual is currently ongoing.

Research on colo-rectal cancer

In 2003, 112 patients affected by primary, resectable colorectal cancer were admitted and underwent surgery at our department. Moreover, 743 follow-up clinical examinations in an outpatient setting were performed. The translational and clinical research activity on colorectal cancer was carried out for the Regina Elena Colorectal Cancer Project. The sections of activity were as follows: **Neoadjuvant pelvic chemoradiation in extraperitoneal, resectable T3 rectal cancer**: in April 2003, a multicenter, phase II randomized clinical trial was started to evaluate rates of pathologically complete response to two different regimens of neoadjuvant treatment (XRT, Tomudex and Oxaliplatin vs. XRT, Cisplatin and Fluorouracil). Secondary endpoints were the chances of sphincter-saving surgical procedures and overall, local-recurrence and disease-free survival rates. Up to December 2003, 14 pts. were enrolled and randomized (7 tomox, 7 plafur) at our institute. By June 2004 the overall patient accrual of the multicenter study was 130 and preliminary results will be soon available.

Ultraconservative sphincter-saving surgery in very low rectal cancer responding to neoadjuvant chemoradiation: to date, 12 patients have undergone a transanal, full-thickness rectal excision of the microscopic, residual rectal cancer or fibrotic scar tissue after neoadjuvant chemoradiation. Patients were selected on the basis of age (72 as a median), clinical negativity of mesorectal nodes evaluated by CT scan and endorectal sonogram. The median follow-up and size of this series are too small and do not allow a prognostic evaluation. Nevertheless, up to now 4 loco-regional (3 local, 1 mesorectal) relapses were observed after a median time of 7 months. No distant events were recorded.

Sentinel lymph node study in rectal cancer (AIRC project: Impact of biological profile, chemoradiation and surgery of rectal cancer on downstaging and quality of life): many attempts aimed to better define site, route of lymphatic drainage and clinical value of the sentinel lymph node in resectable rectal cancer were published in literature in the last 5 years. Unfortunately all failed to demonstrate the pathological and prognostic role in the clinical management of disease. Within the prospective study supported by AIRC, a very preliminary series of 10 pts. were submitted to lymphoscintigraphy at observation and after neoadjuvant chemoradiation, immediately before surgery, always performed by an endoscopic approach to four cardinal points around the tumor. Furthermore, a pathological study on fresh surgical specimens was also carried out using a Neoprobe device to detect the potential, mesorectal sentinel node and to correlate this finding with lymphoscintigraphy.

Project C.N.R.-MIUR Oncologia SP5: Adjuvant therapy based on biological profile in curable colorectal cancer: the aims of this study was a) to validate a model of prognostic risk based on a combined biological profile (multiploidy, ki67, p53, bcl-2) of colorectal cancer; b) to evaluate the predictive value of response of those biological variables to different treatments; c) to modulate adjuvant strategy by biological profile; d) to verify clinical impact of new strategies on tumor progression. Three Groups of patients (1, 2 and 3) with different biological profiles (with none or 1, 2 or 3, 4 unfavorable variables respectively) were identified within the same pathological TNM stage II. The overall survival of the three Groups was significantly different (96.1%, 88.8% and 78.8% respectively; p=.04) and it suggested to modulate adjuvant strategy on their different prognostic pro-

files. Therefore, the Group 3 patients were assigned to a chronomodulated regimen of systemic chemotherapy, potentially able to reduce the risk of relapse, as demonstrated in advanced colorectal cancer. On the contrary, preliminary results on the prognostic value of intraoperative, peritoneal washing in 114 patients with a minimum follow-up of 2 years after radical surgery did not show any difference between those with cytologically positive or negative washing.

Project Italian Minister of Health Global Project for evaluation and improvement of QoL in oncological patients with long-term life expectancy: the study started recently and no data are yet available.

Research on gastric cancer

In 2003, 64 patients affected by primary gastric cancer were admitted and underwent surgery at our department. Moreover, about 240 follow-up clinical examinations in an outpatient setting were performed. Sections of clinical activity were as follows:

Lymphatic Spread and Sentinel Node Study in Gastric Cancer Surgery: a clinical trial evaluating the lymphatic pathways and spreading, the existence of a SN node and its clinical value in tailoring a less aggressive lymphadenectomy in gastric cancer was carried out. Preliminary results on the feasibility, efficacy and reproducibility have been previously reported and patient accrual is ongoing. The secondary endpoint are the long-term oncologic results.

Laparoscopic versus Open Surgery in Early Gastric Cancer: a clinical trial evaluating feasibility, efficacy and reproducibility of laparoscopic surgery in EGC was started. In the first 2 patients operated, the number of harvested lymphnodes and operation time were comparable to those of traditional open surgery as early clinical results, but several advantages have been demonstrated in terms of the patient's postoperative outcome, hospital stay and quality of life. Patient accrual is ongoing and the secondary endpoint will be long-term oncologic results.

Laparoscopic Surgery in Palliative Treatment of Advanced Gastric Cancer: as for EGC, a clinical trial evaluating the feasibility, efficacy and reproducibility of laparoscopic surgery in advanced gastric cancer was started. Early clinical results in the first 2 patients were comparable to those of traditional open surgery, but several advantages have been demonstrated in terms of the patient's postoperative outcome, hospital stay and quality of life. Patient accrual is ongoing.

Neoadjuvant Treatment in Advanced Gastric Cancer: a clinical trial evaluating the value of neoadjuvant chemotherapy in advanced gastric cancer was started. In the first 4 operated patients, treatment did not negatively influenced the surgical outcome. Patient accrual is still ongoing and the secondary endpoint will be the long-term oncologic results.

Research on pancreatic cancer

In 2003, 45 patients affected with peri-ampullary and pancreatic neoplasms were admitted and studied in our Department. Of these, 15 were submitted to conservative treatment only, 8 underwent an exploratory laparotomy or palliative procedures and 22 surgical resection. Clinical trials were as follows:

Role of spiral CT with vascular reconstruction in diagnosis and staging of peri-ampullary neoplasms: a high incidence of peri-ampullary tumors were diagnosed in a locally advanced stage, with suspected spleno-portal confluence infiltration representing a relative contraindication to surgical resection. The aim of this clinical study was to evaluate the diagnostic accuracy of spiral CT with respect to traditionally invasive visceral angiography in operated patients. Patient accrual is ongoing and preliminary results seem to confirm the very good accuracy reported in literature.

Observational clinical study of non-adc pancreatic neoplasms: incidence of non-adc neoplasms is increasing worldwide and their treatment has not yet been standardized. From the start, we have observed 6 different cystic tumors and 1 non functioning en-

docrine tumor. All the patients were submitted to different kinds of operations, depending on tumor type and the patient's characteristics, but as conservative as possible, to preserve pancreatic function when indicated. Patient accrual is ongoing, and the preliminary results are promising.

Selected publications 2003

PAPERS

Ettorre G.M., Vennarecci G., Santoro R., Antonini M., Lonardo M.T., Carlini M., Santoro E.

Modified liver hanging maneuver during orthotopic liver transplantation with inferior vena cava preservation.

TRANSPLANTATION. 2003 Jan 27;75(2):247-9.

VENNARECCI G., ETTORRE G.M., ANTONINI M., MARITTI M., MORICCA P., D'OFFIZZI G., NARCISO P., LONARDO M.T., BOSCHETTO A., DEL NONNO F., PERRACCHIO L., PALMIERI G.P., VISCO G., SANTORO E.

Acute liver toxicity of antiretroviral therapy (HAART) after liver transplantation in a patient with HIV-HCV co-infection and associated hepatocarcinoma (HCC)

Tumori. 2003 Jul-Aug;89(4 Suppl):159-61.

ETTORRE G.M., VENNARECCI G., LONARDO M.T., BOSCHETTO A., ANTONINI M., CARBONI F., CARLINI M., SANTORO E.

The modified hanging maneuver during orthotopic liver transplantation using a technique for conserving the inferior vena cava.

Tumori. 2003 Jul-Aug;89(4 Suppl):63-5.

CATALDI C., VENNARECCI G., TUCCIMEI U., BALLATORE S., MAZZARELLA FARAO R.

Trauma of the liver and hepatic pedicle Minerva Chir.

2003 Aug; 58(4):615-20.

Ettorre GM, Vennarecci G, Boschetto A, Giovannelli L, Antonini M, Carboni F, Santoro R, et al. Resection and Transplantation: evaluation of Surgical prospectives in HIV positive patients affected by end-stage liver disease. J. Exp. Clin. Cancer Res.. 22, 4, 2003 - Suppl.

Santoro R., Carlini M., Carboni F., Nicolas C., Santoro E.

Delayed massive arterial hemorrhage after pancreaticoduodenectomy for cancer. Management of a life-threatening complications.

Hepato-Gastroenterology 2003; 50: 2199-2204.

VENNARECCI G., ETTORRE G.M/, BOSCHETTO A., CARBONI F. ET AL.

Liver transplantation for primari and secondary liver tumors. Review and perspectives.

Chir Ital 2003; 55: 797-810.

CARBONI F., CARLINI M., SCARDAMAGLIA F. ET AL.

Gastrointestinal Stromal Tumors of the stomach. A ten-year surgical experience.

J Exp Clin Can Res 2003; 22: 379-384.

Carlini M., Lonardo M.T., Boschetto A., Carboni F. et al.

Adrenal gland metastases from malignant melanoma. Laparoscopic bilateral adrenalectomy.

J Exp Clin Can Res 2003; 22: 141-145.

Mancini R., Tedesco M., Garufi C., Filippini A., Arcieri S., Caterino M., Pizzi G., Cortesi E., Spila A., Sperduti I. and Cosimelli M.

Hepatic arterial infusion (HAD) of Cisplatin and systemic Fluorouracil in the treatment of unresectable colorectal liver metastases.

ANTICANCER RESEARCH, 23: 1837-1842, 2003. *IF 1.4*

Aloe S., D'Alessandro R., Spila A., Ferroni P., Basili S., Palmirotta R., Carlini M., Graziano F., Mancini R., Mariotti S., Cosimelli M., Roselli M., Guadagni F.

Prognostic Value of serum and tumor tissue CA 72-4 content in gastric cancer.

INT. J BILO. MARKERS, 18(1): 21-27, 2003. *IF 1.5*

Roselli M., Guadagni F., Martini F., Spila A., Mariotti S., D'Alessandro R., Aloe S., Gazzaniga P.P., Basili S., Cosimelli M., Ferroni P.

Association between serum Carcinoembryonic antigen and endhotelial cell adhesion molecules in colorectal cancer.

ONCOLOGY, 65: 132-138, 2003. *IF 3.0*

Esposito A., Mancini R., Ettorre G., Garufi C., Saracca E., Arcieri S. and Cosimelli M.

A combined approach of Neoadjuvant chemotherapy and surgery for colorectal liver metastases.

J. EXP. CLIN. CANCER RES, 22, 4, 197-202, 2003. *IF 0.7*

Mancini R., Ettorre G., Vennarecci G., Sperduti I., Garufi C., Esposito A., Cosimelli M.

Treatment of colorectal liver metastases: a multidisciplinary approach.

J. exp. clin. cancer res, 22, 4, 213-217, 2003. *IF 0.7*

Cianciulli A.M., Marzano M.D., Merola R., Guadagni F., Piperno G., Sperduti I., De la Iglesia F., Mancini R., Cosimelli M.

Genetic and pathological significance of status of chromosomes 1p, 17p, 18q and HER-2 gene in colorectal cancer and related normal colonic mucosa.

CANCER GENETICS, 2003.

Greco C., Vona R., Cosimelli M., Matarrese P., Straface E., Scordati P., Giannarelli D., Casale V., Assisi D., Mottolese M., Moles A. and Malori Walter.

Cells surface expression of Galectin-3 differentiates adenmatous from carcinomatous lesions of colonic mucosa.

BRIT. J CANCER, 2003.

Santoro E., Carlini M., Lepiane P.

Tumours of the Stomach. Chapter in: Mazzeo F.

Trattato di Chirurgia, Piccin 2003, vol III

Gentileschi P., Di Paola M., Catarci M., Santoro E. et al.

Bile duct injuries during laparoscopic cholecystectomy: a 1994-2001 audit on 13,718 operations in the area of Rome.

Surg Endosc. 2003 Dec 29.

Division of thoracic surgery

DIRECTOR:
FRANCESCO FACCIOLO, MD

Francesco Facciolo, MD was born in 1953. He received his MD Degree in 1977 and specialized in Thoracic Surgery and General Surgery in 1981 and 1987 respectively. From 1977 to 1993 he attended the Chair of Thoracic Surgery at the University of Rome "La Sapienza" as Student first and than as Assistant. In 1993 he became First Assistant at Division of Thoracic Surgery of S. Camillo Forlanini Hospital were he has been working until 2001. In 2001 he became Chief of Thoracic Surgery at Department of Surgical Oncology of Regina Elena Cancer Institute of Rome. Professor at post Degree Specialization Schools of Thoracic Surgery, General Surgery, Thysiology and Respiratory disease at the University of Rome "La Sapienza. Actually member of European Association for Cardio-Thoracic Surgery, European Association for Endoscopic Surgery, Italian Society for Thoracic Surgery, Italian Society for Endcoscopic Surgery, Italian Association for Hospital Surgeons.

Staff:

SANDRO CARLINI - M.D.: Assistant
MASSIMO FILIPPETTI - M.D.: Assistant
FELICITA CORZANI - M.D.: Assistant
VIRNA CERASOLI - M.D.: Assistant
ENRICOMELIS - M.D.: Assistant
LUIGI IONI - M.D.: Fellow
GABRIELE ALESSANDRINI - M.D.: Fellow
MARIO MICELI - M.D.: Fellow

Scientific activity

THYMOMA AND AUTOIMMUNE SYNDROMES.

Mediastinal tumors especially Thymic Epithelial tumors, (TET) are very rare diseases but find a particular interest as they are often associated to autoimmune diseases. A good diagnostic approach to these lesions requires a multidisciplinary team and multistep decisions.
Thymoma classification has been over the years a controversial field in pathology, as these rare significantly heterogeneous tumors in their microscopical features; in 1999, the World Health Organization published a proposal for a Thymic Epithelial Tumor,s (TET) nomenclature not aimed to be a new classification, which proved to be reproducible and easily applicable by pathologists.
As thymoma are rare tumors, clinicopathological statistically significant data could be better acquired by multicenter studies; furthermore, a multidisciplinary approach could provide additional instruments to our understanding of biological / immunological thymoma features of relevant interest for therapeutical options.
A multicenter, multidisciplinary collaborative thymoma study has been recently undertaken by thoracic surgeons, pathologists, neurologists, oncologists and immunologists from three large Institutions (Regina Elena Cancer Institute of Rome, Catholic University of Rome and Federico II University of Naples) particular interested in mediastinal and thymic pathology in Italy. We are now evaluating in a preliminary phase of a retrospective study the clinicopathological, biological, immunological and oncological characteristics of thymoma patients over the last years. In the years 2001-2002, 53 cases of Thymic Epithelial Tumors were diagnosed in the three Institutions; paraneoplastic syndromes were observed very frequently, MG being present in 27/53 cases.

INTERNATIONAL EARLY LUNG CANCER ACTION PROGRAM (I-ELCAP).

This study was performed to study and develop low-dose CT screening for lung cancer. The institutions participating in this study have been using a common protocol for the screening itself, though different entry criteria, so that the resulting data can be pooled to provide up-to-date information for protocol updates, and on the resulting diagnostic distribution (primarily in terms of stage and size) of the diagnosed cases of lung cancer. After sufficiently long follow-up of the diagnosed cases it will be possible to assess the cur-

ability of the screen-diagnosed lung cancers. To date, about 27000 participants have been screened, including in over 16000 repeat screenings, and more than 400 cases of lung cancer have been diagnosed. Until now we enrolled 790 patients and 18 (2.27%) NSCLC, 15 (83%) of whom at stage I were diagnosed

CHEMOTHERAPY FOR EARLY STAGES (CH.E.S.T.).

The aim of this study is to assess whether preoperative CT improves progression-free survival compared to surgery alone in clinical stage IB, II and selected IIIA (cT3-N1) NSCLC. Inclusion criteria involve a pathologic documentation (either histologic or cytologic) of non small cell lung cancer, no prior chemotherapy or radiotherapy, bidimensionally measurable or evaluable disease; pancost tumors are not elegible. 700 patients in total will be randomized to arm A (chemotherapy plus surgery) and arm B (surgery).
Our institute is the first one for accrual.

SERUM-PROTEOMIC PROJECT (ITALY-USA PROJECT).

The behaviour and outcome of lung cancer is highly variable. The molecular basis of this variability is unknown; neither standard histopathology nor currently available molecular markers can predict these characteristics. The identification of novel biomarkers to differentiate tumors from normal cells and predictors of tumors' behaviour, such as pathological stage, response to chemotherapy and site of relapse, is very important in clinical practice. To date, none of the hundreds single markers evaluated have provided a significant clinical utility, but by surveying thousands of genes, at once with use of microarrays or proteomic technologies, now it is possible to read the molecular signature of an individual tumor.

Proteomics-based approaches allow examination of expressed proteins of a tissue or cell type, complement the genome initiatives, and are increasingly being used to address biomedical questions. The growing knowledge of the tight connection between apoptosis and cancer has lead to an explosion of researchs around apoptotic induction with chemotherapeutic agents and small molecule inhibitors; the chemotherapeutic agent paclitaxel (Taxol) activates mitogen-activated protein kinase (MEK), extracellular signal-regulated kinase, and combined with MEK inhibition, synergistically enhances apoptosis.

The most effective treatment for lung cancer remains surgical resection of early stage disease; however, sporadic lung cancer is rarely diagnosed in its earliest stages. The promise of screening techniques for increasing rates of early stage lung cancer detection, and thus the expectation of more treatable cases, has driven considerable research and ongoing development of screening technologies.

Randomized controlled trials (RCTs) of CXR and sputum cytology have failed to demonstrate a mortality benefit for either technique, and we do not recommended screening with serial CXR or sputum cytology for asymptomatic individuals or individuals without a history of cancer.

LDCT scanning is a promising technology due to its sensitivity and ability to assess growth of nodules, and ongoing studies may provide additional information about the costs and benefits of screening with this technology.
A proteomic approach, using two-dimensional gels coupled with mass spectrometry to identify altered proteins in primary lung tumors with matched adjacent normal tissue, could be the right way to identify the proteomic profile, allowing us to discover novel molecular targets and potential cancer cell-specific biomarkers.
Italy-USA serum-proteomic project for lung cancer enrols smokers and no smokers with NSCLC divided in four groups.
P1: smokers and nonsmokers with NSCLC histologically proved (100 patients);
P2: smokers and nonsmokers with negative spiral CT scan (300 patients);
P3: people with spiral CT scan suspicion for lung cancer followed by negative histologic findings (20 patients);
P4: people with spiral CT scan suspicion for lung cancer and positive histologic findings (100 patients);

NEW APPROACH TO MALIGNANT PLEURAL MESOTHELIOMA.
This study was designed with the aim to assess whether preoperative CT followed by surgery and postoperative radiotherapy improves survival for stage I-III (T1-3 N0-2) malignant pleural mesothelioma. This phase II study will include an induction chemotherapy with pemetrexed + cisplatin for 3 cycles (q 21 days) followed by extrapleural pneumonectomy and postoperative hemithoracic radiotherapy (54 Gy).
It will start next year.

Selected Publications 2003

ASCOLI V., BELLI S., CARNOVALE-SCALZO C., CORZANI F., FACCIOLO F., LOPERGOLO M., NARDI F., PASETTO R., COMBA P.

Malignant mesothelioma in Rome and Latium region, 1993-2001.

Tumori. 2003 Jul-Aug;89(4):377-81.

CARDILLO G., REGAL M., SERA F., DI MARTINO M., CARBONE L., FACCIOLO F., MARTELLI M.

Videothoracoscopic management of the solitary pulmonary nodule: a single-institution study on 429 cases.

Ann Thorac Surg. 2003 May;75(5):1607-11; discussion 1611-2.

Clinical Activity

Our activity enroles all the general thoracic surgery procedures with special interest in surgery for malignant pleural mesothelioma and extended chest wall resections for lung cancer. In 2003, we observed 984 patients in the outcome patients referring 785 of them. We performed 516 surgical interventions (D.M. 7.12) (O.M. 69.6%) (I.T.O. 3.1) (I.R. 35.7) (Median Weight D.R.G. 2.840). We also performed 357 diagnostic endoscopic procedures.

Division of gynecology

DIRECTOR:
CARLO SBIROLI, PHD

Carlo Sbiroli graduated in Medicine in 1964 and completed the Specialty School in Obstetrics and Gynecology in 1980. Since 1969 he has been a Lecturer on Obstetrics and Gynecology. Between 1970-72 he was an assistant professor in the Department of Obstetrics and Gynecology, La Sapienza University of Rome. From 1972 to1977 he has served as senior registrar in the Division of Obstetrics and Gynecology, S.Giovanni Calibita-Fatebenefratelli Hospital, Rome and from 1977 to 2001 director of the Division of Gynecology, S.Carlo di Nancy-IDI hospital, Rome. From June 2001 to date he has been the director of the division of Gynecologic Oncology at the Regina Elena National Cancer Institute. During 1968-70, Prof. Sbiroli was involved in the study of ovarian steroids at the Chelsea Hospital for Woman in London.. During 1974-78, he attended the Department of Urology, University of California, Los Angeles, doing research in the field of urogynecology. He completed his preparation on pelvic and oncologic surgery attending European as well as American institutions. He is professor of Gynecologic Oncology at the Specialty School on Oncology, La Sapienza University of Rome. He has published three books on gynecology and 186 papers. Between 1983-89 was Editor in Chief of the medical journal "Impegno Ospedaliero". From 1990 till 1998 he was a member of the editorial board of the *International Urogynecological Journal*. Since 2004 he has been president of the Italian Association of Obstetrics and Gynecology.

Staff:

ENRICO VIZZA - M.D. Assistant
MARIO ANTONIO CONGIU - M.D. Assistant
GIUSEPPE CUTILLO - M.D. Assistant
FABIO F. DIOTALLEVI - M.D. Assistant
LUCIANO MARIANI - M.D. Assistant
DOMENICA MAZZA - M.D. Assistant
ROBERTO SINDICO - M.D. Assistant
CRISTINA VINCENZONI - M.D. Assistant
GIUSEPPE VOCATURO - M.D. Assistant
GREGORIO MARCO GALATI - M.D. Fellow
MARCO ATLANTE - M.D. Fellow
GIACOMO CORRADO - M.D. Student

The division of Gynecologic Oncology is mainly dedicated to the screening, diagnosis, treatment and follow-up of gynecologic cancer. It has eleven permanent medical staff, two research fellows and a PhD. Student. The Division is organized in a second level outpatients clinic, a ward with 24 beds and includes a Minimally Invasive Surgery Unit mainly dedicated to the application of new minimally invasive technologies in the field of Gynecologic Oncology Surgery. During 2003, various clinical research protocols as well studies in the field of biology of tumors has been conducted.

Activities in progress

CLINICAL SIGNIFICANCE OF GENETIC ALTERATIONS OF CHROMOSOME 3,7,X E EGFR GENE IN UTERINE CERVICAL CANCER PROGRESSION

The primary objective of the study is to identify the genetic alterations of chromosome 3,7,X and EGFR genes expressed by squamous cells during transformation and progression from L-SIL and H-SIL to invasive cervical carcinoma. Aberrations of chromosomes 3,7,X and EGFR gene status is assessed by FISH in samples coming from patients affected by L-SIL, H-SIL and invasive squamous cell carcinoma. Data obtained from the first set of 60 patients has revealed a strong correlation between chromosomes 3,7 and X polysomy and development and progression of a H-SIL to invasive carcinoma. Therefore, the present observations seem to suggest an emerging role of chromosomes 3,7 and X status as a predictive marker of H-SIL progression to invasive cancer.

Metalloproteinase(MMP) and c-Kit protein expression in Mesenchymal tumors of the uterus and their evaluation as biological markers predictive of outcome

Recent studies demonstrated that Gastrointestinal Stromal Tumor (GISTs), a rare form of soft tissue tumor of the gut arise because of a mutation in a gene called ***c-kit*** that encodes a transmembrane receptor for a growth factor termed **scf** (stem cell factor). Mutations make c-kit function independent of activation by scf, leading to a high cell division rate and possibly genomic instability. The aim of the present study is: 1) to evaluate the expression of Metalloproteinase (MMP) and c-Kit protein in mesenchymal tumors of the uterus, 2) to correlate the expression of Metalloproteinase (MMP) and c-Kit protein with the DFS and OS 3) to correlate the expression of Metalloproteinase (MMP) and c-Kit protein with the stages of the new classification of soft tissue tumors proposed by the *French Federation of Anticancer Centers*. The immunohistochemical expression of Metalloproteinase (MMP) and c-Kit protein is assessed in 25 cases of mesenchymal tumor of the uterus subjected to hysterectomy in the last ten years with a minimum follow-up of 5 years. If the results confirm a role of c-Kit protein in the mesenchymal tumor of the uterus as demonstrated in GISTs, it will be possible to hypothesize a therapeutic role of STI 571 (inhibitor of c-Kit/117 receptor).

Randomized phase III study comparing standard combination chemotherapy versus Extreme Drug Resistance assay-sorted chemotherapy following upfront debulking surgery in advanced epithelial ovarian cancer

The division of Gynecologic Oncology participates together with the division of Oncology A in an prospective international multicenter phase III study. After surgical debulking, the results of an *in vitro* assay for drug resistance is used to individually select chemotherapy for the patient in order to avoid ineffective treatments, needless toxicity, and loss of quality of life. Patients are randomly assigned to receive the TP regimen (Paclitaxel at a dose of 175 mg/m^2 as a 3-hour infusion followed by Carboplatin AUC=6) or the EDRA-sorted regimen (Carboplatin, Cisplatin, Paclitaxel, Topotecan, Doxil, Etoposide, Gemcitabine, Cyclophosphamide: single-drug vs multidrug therapy à open to discussion). Stratification factors will include the treating institution, the FIGO stage (IIB–C, III, or IV). This study will try to demonstrate that it is feasible to use an *in vitro* assay in routine clinical practice to eliminate ineffective chemotherapeutic agents.

Italy-USA project on pharmaco-genomic

This study is structured in two parts: 1) determination of protein serous pattern alterations correlated with pathogenesis, prognosis using proteomic spectra generated by mass spectroscopy. 2) identification of specific clusters of proteins predictive of early diagnosis and on which to tailor the treatment using phosphoproteomics. In this prospective study, the protein serous pattern alteration of 200 patients collected at the time of first diagnosis of ovarian cancer is analyzed comparing the proteomic spectra with that obtained from the serous belonging to 200 cancer-free women used as control. The study is ongoing and at the moment 40 cases have been enrolled.

Prognostic value of FAS and FAS Ligand in ovarian carcinoma

Fas (CD95 / APO-1) and FAS Ligand are two transmembrane proteins belonging to the family of tumor necrosis factor and tumor necrosis factor receptor. When FAS is activated by its ligand FAS-L, it modulates apoptosis. Alteration of the FAS/FAS-Ligand system seems to be one of the possible mechanism by which tumoral cells escape immunosurveillance. The aim of the present study is: 1) to evaluate the phenotypic expression of Fas and Fas-L in ovarian carcinoma; 2) to determinate if there is any correlation between the expression of Fas and Fas-L and the other clinico-pathologic parameters (FIGO stage, histotype, grading, residual disease after surgery, DFS, OS). The preliminary results on a retrospective analysis of 95 ovarian carcinomas seems to suggest a prognostic value of FAS and FAS Ligand in ovarian carcinoma.

Immunogenicity and safety of prophylactic quadrivalent HPV (types 6,11,16,18) virus-like particles

Research shows that women who are infected with these strains of HPV, have a tendency to develop cervical dysphasia (L-SIL, H-SIL and ca. in situ) which, if left untreated, may develop further into invasive cervical cancer. The Division of Gynecologic Oncology is participating in a prospective randomized multicenter phase III study, the aim of which is to demonstrate the efficacy of immunization against HPV6, 11, 16, 18 to prevent the onset of cervical carcinoma. The study also evaluates the safety of the vaccine. Healthy, non-pregnant, females between the ages of 16-23 are enrolled in this study and immunized against HPV6, 11, 16, 18.

Laparoscopic Staging and Restaging of gynecologic tumors

Continuing worldwide interest clearly demonstrated that laparoscopic techniques are now part of the armamentarium of gynecological oncologists. Therefore, a great effort has been made to introduce laparoscopic and related mininvasive techniques in staging and surgery of gynecologic tumors. The main fields of exploration and application are: pelvic and lomboartic extraperitoneal and transperitoneal lymphadenectomy as a staging or a restaging procedure; differential diagnosis in carcinosis; selection of patients candidate to primary cytoreductive surgery in advance ovarian cancer; intensive surgical staging of cervical and endometrial cancer, totally laparoscopic; restaging of borderline ovarian tumors after primary incomplete surgery.

Menopause in oncologic patients and Quality of Life

In order to improve the Quality of Life (QoL) of oncologic patient in menopause or those who suffer from early menopause induced by medical/surgical treatments, the Division of Gynecologic Oncology has two experimental protocols on the non-hormonal therapy of menopausal symptoms on going.

1 Effectiveness of low-dosage Fluoxetine for hot-flashes in breast cancer survivors: a pilot study.

The aim of this study is to identify molecules of the serotonin-selective re-uptake inhibitors ssris family (such as Fluoxetina and Venlafaxina) that could have a role in the control of hot-flushes in breast cancer survivors.

2 A multicenter, randomized, parallel-group, double-blind, placebo-controlled trial to evaluate the efficacy and safety of four different doses of Org 50081 in the treatment of moderate to severe vasomotor symptoms associated with menopause.

The present study intends to investigate the efficacy and safety of a new molecule (mirtazapina), in the control of moderate to severe vasomotor symptoms associated with menopause in oncologic patients

Publications 2003

Sbiroli C., Corrado G., Merola R., Vizza E., Marzano R., Vincenzoni C., Galati M., Cianciulli A.M.

Genetic alterations accumulate during cervical tumorigenesis.

Ann Oncol;14(S4):73 2003

Corrado G., Mottolese M., Carosi M., Bavarese A., Giannarelli D., Vizza E., Zerbini V., Vincenzoni C., Natali P.G., Sbiroli C.

Altered expression of Fas system in ovarian carcinomas: correlation to conventional prognostic parameters.

Int J Gynecol Cancer:13(S1):19 2003

Savarese A, Corrado G, Felici A,Vizza E, Di Cocco B, Carosi MA, Sbiroli C, Cognetti F, Mottolese M.

Expression of FAS and FAS Ligand in patients with ovarian cancer.

Ann Oncol 2003;14(S4):73

De Capoa A., Muscolino A., Della Rosa S., Caiafa P., Mariani L., Del Nonno F.,Vocaturo A., Perrone Donnorso R., Niveleau A., Grappelli C.

DNA demethylation is directly related to tumor progression: evidence in normal, premalignant and malignant cells from uterine cervix samples.

Oncology Reports 10:545-549,2003

Branca M., Costa S., Mariani L., Sesti F., Agarossi A., di Carlo A., Galati M., Benedetto A., Ciotti M, Giorgi C., Criscuolo A.,Valieri M., Favalli C., Paba P., Santini D., Piccione E., Alderisio M., De Nuzzo M., di Bonito L., Syrjänen K.

Assessment of risk factors and human papillomavirus (hpv) related pathogenetic mechanisms of cin in hiv-positive and hiv-negative women. study design and Vaseline.

Data of the HPV-Pathogen ISS Study. Eur. J. Gynecol. Oncol.

Vizza E., Galati M., Corrado G., Sbiroli

Role of pelvic lymphadenectomy in the management of stage I endometrial cancer: our experience.

Eur J Gynaecol Oncol;vol24(2):126–128 2003

Division of urology

DIRECTOR:
MICHELE GALLUCCI, MD

Michele Gallucci received his MD in 1974 and specialized in Urology in 1977 and in General Surgery in 1984 at La Sapienza Medical School, Rome. From 1981 to 1994 he was Assistent Professor of the Dpt. of Urology U. Bracci, La Sapienza University, Rome. From 1990 to 1994 he was Associate Professor at the School of Specialization in Urology, La Sapienza University, Rome.
From 1994 to 1999 he was the Director of the Urology Division of Cristo Re Hospital, Rome. From 1994 to 2000 he was Associate Professor at the School of Specialization in Urology, Sacro Cuore University, Rome. From 1999 to 2001 he was Director of the Urology Division, the University Biomedical Campus, Rome. From 2001 he has been Director of the Urology Division, Regina Elena Cancer Institute Rome.

Staff:
RUGGERO CANTIANI - M.D.
GIUSEPPE CUSUMANO - M.D.
PIERO DE CARLI - M.D.
LUCIANO LA MANNA - M.D.
GIOVANNI MAINIERO - M.D.
VINCENZO POMPEO - M.D.

Activities 2003

We studied and proposed a new technique to prepare the upper cave for surgery in caval thrombosis.
Caval thrombosis is a relatively common event occurring in about 10% of patients affected by renal tumor. Extension does not take place by vascular invasion but via tumor progression inside the lumen of the renal vein and subsequently of the IVC. Caval thrombosis is not considered a contraindication to radical surgical treatment; on the contrary surgical removal of the tumor and the thrombus, improves the prognosis, even in the presence of distant metastases. Five-year survival rates of patients with renal tumor and caval thrombosis undergoing radical surgery range from 25% to 64%. The validity of this treatment in the presence of disease extension to perinephric tissues and regional nodes remains unclear. Despite the oncological effectiveness, surgical treatment of patients with a cephalic thrombus extension above of the suprahepatic tract of the IVC (level II and III lesions) is affected by significant rates of morbidity and morality. In the past, several different surgical approaches to Level II-III caval thrombosis have been proposed to improve perioperative results. Only surgical approaches including large cavotomy, usually with cardio circolatory arrest, significantly lowered mortality rates, reducing blood loss, thrombus fragmentation and pulmonary embolism. Retro-hepatic IVC is a complex anatomical region. As a consequence, the surgical removal of a thrombus extended to this tract is a high-risk procedure requiring an effective complete surgical control of the vessel. The shortness of the main suprahepatic veins, the presence of hyper-vascularized tissue and of a variable number of accessory suprahepatic veins are the cause of the strict anatomical connection between the IVC and the posterior margin of the liver. In addition, the caval wall in this portion is fragile; in spite of several attempts a systematic classification of accessory suprahepatic veins has never been achieved because of an extreme variability of number, diameter and site of confluence in the IVC. The removal of a thrombus extended to this portion of the IVC without adequate control can be the cause of two undesirable events; thrombus fragmentation with possible pulmonary embolism and uncontrollable hemorrhages due to lumbar, adrenal and suprahepatic vein bleeding. Tumor fragmentation is a well-described life-threatening event that can determine the detachment of the thrombus and massive pulmonary embolism. Blind removal of the thrombus can determine an intraluminal persistence of a thrombus fraction with possible postoperative embolism and early disease recurrence. According to previous papers, our experience confirmed that surgical strategy and perioperative results radically change according to the cephalic extension of the thrombus. An infrahepatic-thrombus (Level I) can be safely removed via a completely ab-

dominal isolation of the IVC, clamping and cavotomy. On the other hand, a thrombus extended to the right atrium requires a mandatory large thoracol-abdominal access with cardio-circulatory arrest. The surgical approach to Levell II caval thrombosis remains a debatable issue. Involvement of the retro-hepatic tract represents approximately 50% of all patients with caval thrombosis from renal tumors. In the past, surgical removal of these lesions was usually done through an infrahepatic-cavotomy and thrombus extraction with cephalic Foley's catheter passing up to the thoracic IVC. However, this technique leads to an increased risk of pulmonary embolism and early recurrence of disease because of frequent tumor fragmentation. More recently, IVC has also been approached through an infrahepatic cavotomy and thrombus extraction with or without use of cardio-circulatory arrest. An alternative approach has been described by Ohwada who completely isolated the retro-hepatic IVC via segmentectomy of the caudate lobe. Thoraco-frenolaparotomy is now widely accepted for the treatment of retro-hepatic thrombosis, but the use of double thoracic and abdominal access without complete liver isolation from the IVC does not seem to significantly decrease perioperative risks. In a series of 53 patients with caval thrombosis undergoing thoraco-abdominal approach in the presence of retro-hepatic lesions, Skinner reported an overall morality (including Level I cases) of 13.2% and an average blood loss of 5,466 ml. Langenburg described a similar approach in 1994 with an overall mortality of 8%. In a series of 26 patients affected by retro-hepatic caval thrombosis undergoing thoraco-abdominal access. Nesbitt reported a significantly lower rate of mortality (overall 2.7%) and the reduction of intraoperative blood loss. The surgical strategy reported by Nesbitt included a careful mobilization of the liver and a large cavotomy in all cases, as described in the present study. The combined use of thoraco-abdominal access and cardio-circulatory arrest for the treatment of retro-hepatic and thoracic lesions has also been recently suggested by other authors. This approach allows minimal intraoperative blood loss with reduced rates of major morbidity and mortality. However, an increase in invasivity and economical costs can be assumed. Chest opening can result more frequently in respiratory postoperative complications with a delay in the patient's recovery and discharge. The present study reports the results of a fully abdominal surgical technique used for the treatment of patients affected by Level II caval thrombosis. Our approach is directly imported from liver transplant surgery. It includes the complete over turning of the liver and the isolation of the entire tract of the infra-, retro- and suprahepatic IVC as commonly used for the removal of both donor and recipient liver. Recently Ciancio showed that this technique can also be used for the removal of caval thrombosis. For retro-hepatic caval thrombus, the isolation of the IVC from the liver offers the surgeon the possibility to entirely isolate the tract of IVC filled by the thrombus. After proximal and distal IVC and hepatic pedicle clamping, a large cavotomy including the entire thrombus is performed. At which time the surgeon can safely remove the entire thrombus through a small buttonhole of the caval wall close to the renal vein confluence and the kidney. Minimal blood loss and the complete opening of the IVC reduces the risk of thrombus fragmentation during the removal. In our experience no perioperative clinical, laboratoristic or instrumental signs of pulmonary embolisms were observed. Perioperative mortality was absent and macroscopic examination of all lesions extended to retro-hepatic IVC revealed no evidence of rupture or fracture. The vein wall can be accurately explored in a bloodless field. Moreover, blood loss can be avoided by the careful section of all accessory suprahepatic veins and the effective vascular control of renal, adrenal, lumbar and major suprahepatic veins. During removal of Level II lesions we experienced a mean blood loss of less than 500 ml, not significantly higher than observed for surgical treatment of Level I thrombosis. In 2 of 10 Level II patients, the thrombus extended to the confluence of the major suprahepatic veins and reached the intra-thoracic tract of the IVC. In this situation a thoraco-abdominal access with cardio-circulatory arrest has been proposed by several authors. In our experience, our surgical approach can be safely performed even in the case of thoracic extension of the thrombous. After detachment of the diaphragmatic peritoneum from the liver and complete isolation of the suprahepatic portion of the IVC, a

small incision of the pericaval diaphragmatic muscle is made and a thoracic window is created. In this way the level of caval clamping can be further extended. According to our results, the avoidance of chest opening reduces the length of postoperative stay and overall recovery time of patients. Finally, our results suggested that a complete thrombus removal in absence of fragmentation can also reduce tumoral cell spread and intracaval recurrence of the disease. This hypothesis seems to be confirmed by our follow-up results. After a mean follow-up of 53.9 months 14/15 patients (93.3%) are still alive; only 2 patients developed distant metastases and 12 patients are alive and disease free. Postoperative and long-term work-up never showed intra-caval tumor recurrence. In conclusion, our study confirms that careful detachment of the IVC from the liver as commonly performed in transplant liver surgery is a safe and effective surgical procedure for patients affected by Level II caval thrombosis.

Clinical Activity

For patients at risk a protocol for intraoperative adjuvant radiotherapy (IORT), agreed with Department of Radiotherapy was proposed.
Twenty five patients were treated with gradual doses to obtain the right dose. The activity of radiotherapy was carried out with relievetors in the rectum and bladder.
The results are very interesting:
With 2000 Gray (maximum dose) there were no side effects, in fact no activity in the relievetors of the rectal and bladder, was registered.
Therefore, a national clinical research project in cooperation with other centers using IORT equipment was started. The first research in this connection, was begun in May 2003, in collaboration with the Division of Radiotherapy.
A study of the effect of set up errors and organ motion on IMRT dose distributions for prostate cancer.

Valeria Landoni PhD
Bianca Saracino M.D.
Simona Marzi PhD
Michele Gallucci M.D.
Maria G. Petrongari M.D.
Enrico Chianese M.D.
Michela Benassi M.D.
Giuseppe Iaccarino PhD
Antonella Soriani PhD
Giorgio Arcangeli M.D.

Purpose
Assessment of the influence of set up errors and organ motion on the probability of tumor control and normal tissue complications by TCP (Tumor Control Probability) and NTCP (Normal Tissue Complication Probability).

Materials and Methods
12 patients were treated for prostate cancer with IMRT (Intensity Modulated Radiation Therapy). Two ortogonal portal images were taken daily. All patients underwent 3 CT scans at different times during the 8 week period of the treatment (i.e. baseline, intermediate and final). The original treatment plans were re-evaluated taking into account set-up errors and organ motion.

Results
The mean shift+ std deviation of the whole patient population in the lateral, anterior-posterior and cranio-caudal direction were 0.8+1.5 mm, 1.0+2.0 mm, 1.4+2.1 mm respectively. In most of the recalculated DVHs (Dose-Volume Histograms) the coverage of CTV

(Clinical Target Volume) was grated despite organ motion, While the rectal wall histograms were often very different from the planned ones.

Conclusion
Prostate and rectum motion seem to have a heavier impact on DVHs than set up errors. Tumor control probability is granted but only future follow-up will tell the real influence of these deviations on the probability of normal tissue complication.

Scientific activity

We evaluated a panel of well-known genetic alterations for frequency of changes in bladder cancer that could be considered as genomic instability determinant or **adjunctive prognostic predictors.**

Methods
FISH (fluorescent in situ hybridization) analysis for evaluation of 3,7,9,17 chromosomes and 9p21, 17p13.1, 13q14, 17q11.2 chromosomal loci in 48 muscle invasive bladder cancer specimens and adjacent normal mucosae was performed.

Results
A statistical difference was observed when chromosome 7 monosomy and polysomy and 17 monosomy frequencies in two groups (tumors and adjacent mucosae) were compared. No difference in the frequency of gene deletions between tumors and adjacent mucosae was found. The 17q11.2 amplification was found in 14.5% of examined tumors but in no evaluated nonmalignant epithelium. The 3,7,17 monosomy and RB1 heterozygous deletion were significantly associated with T3-4 stage.

Conclusions
Our results demonstrate the importance of chromosomes 3,7,17 and gene alterations in bladder cancer progression, highlighting their usefulness as significant prognostic markers. Only future larger studies, with long-term follow-up of these patients can determine the validity and clinical relevance of these genetic findings with resultant incorporation of molecular prognostic markers in phase II and III trials to define their role in clinical outcome.

Publications 2003

Cianciulli A.M., Leonardo C., Guadagni F., Marzano R., Iori F., De Nunzio C., Franco G., Merola R., Laurenti C.

Genetic instability in superficial bladder cancer and adjacent mucosa: an interphase cytogenetic study.

Hum. Pathol. 2003 Mar;34(3):214-21. *I.F. 3.049*

Sternberg C.N., Pansadoro V., Calabro F., Schnetzer S., Giannarelli D., Emiliozzi P., De Paula F., Scarpone P., De Carli P., Pizzo M., Platania A., Amini M.

Can patient selection for bladder preservation be based on response to chemotherapy?

Cancer. 2003 Apr 1;97(7):1644-52. *I.F. 3.941*

Visca P., Sebastiani V., Pizer E.S., Botti C., De Carli P., Filippi S., Monaco S., Alo P.L.

Immunohistochemical expression and prognostic significance of FAS and GLUT1 in bladder carcinoma.

Anticancer Res. 2003 Jan-Feb;23(1A):335-9. *I.F. 1.447*

Division of plastic and reconstructive surgery

DIRECTOR:
ROY DE VITA, MD

Roy de Vita received his Medical Degree in 1981 at the University of Naples Medical School and obtained a full specialization in Plastic and Reconstructive Surgery, in 1986 at the same University.
He worked from 1981 to 1987 as Assistant of the Clinical Plastic Surgery Department at the University of Naples.
During that time, from 1985 to 1986 he did his surgical training in Great Britain, at East Grinstead-Queen Victoria Hospital.
Then in 1987 he moved, as Senior Registrar to the Clinical Department of Plastic Surgery at La Sapienza University, Rome, where he worked until May 2002.
From the following June he has been the Director of Plastic Reconstructive Surgery Department at Regina Elena National Cancer Institute in Rome.
During his career Dr. De Vita has performed more than 6,000 operations as first surgeon.
His major interests are focused on breast, head, neck and limb surgery.

Medical Staff:
MAURIZIO COSTANTINI - Assistant
PIERPAOLO GULLO - Fellow
MASSIMO PANIMOLLE - Fellow
MARCELLO POZZI - Assistant
ANTONIO VARANESE - Assistant

Activities

BREAST RECONSTRUCTIVE SURGERY
Immediate and delayed breast reconstructive surgery is performed in the Department using high specialty techniques.
Microsurgery is a routine method in our Plastic Surgery Department, especially for delayed reconstruction such as post-QUART and radical mastectomy after radiotherapy.
In 2003 we performed almost 500 surgical treatments for breast reconstruction.
As first choice, both in immediate and delayed reconstruction, we prefer using tissue expanders. Even though it is a two stage procedure, there is very limited physical and psychological stress for the patient.
In the cases in which tissue expanders cannot be used, we are able to choose from a very large spectrum of surgical methods. From myocutaneous pedicle flaps such as the Latissimus dorsii flap or TRAM flap, to microsurgical free flaps such as TRAM, DIEP or SIEA.
As is well known, clinical research in breast cancer surgery points towards a more conservative operation versus an aggressive one.
Starting from this concept, in co-operation with the General Surgery Department and only in selected cases, we began to perform a very conservative surgery for breast cancer in which we preserve not only the skin, but also the nipple-areola complex.
This technique is called Nipple sparing mastectomy.
Objective - Nipple Sparing Mastectomy (NSM) was part of the evolution of breast conservative treatment, for cancers located outside of the central area and also to obtain the best psychological impact in breast surgery.
The surgical possibilities indicated for this treatment are also numerous.
Background data - From a review of the literature we know that this procedure has been studied for many years by different authors, and does not have an increase of local recurrence in NSM than traditional surgery treatment.
Methods - We divided our study in two parts. The first including 50 patients reconstructed with implants over 24 months. The second includes a group of patients with autologous reconstruction.
Our indication for NSM are: T0-T1, N0, M0 tumors; little breast where conservative treatment does not have good cosmetic results; T2, N0, M0 tumors, and recurrence after conservative surgery. All tumors must have a peripheral localization and multiple negative frozen sections of the sub-areolar tissue.

In order to carry out axillary node dissection and conservative treatment as well as for subcutaneous mastectomy and implant introduction, we use the skin access for the biopsy. Only for QII do we use a different scar for axillary dissection.
Results-The patient data is presently under review. The preliminary results, however have been excellent, both for cosmetic management and for recurrence rate as well as for the psychological impact.
In fact, in 48 patients we only observed one total and two partial necroses of the areola probably due to an over aggressive retroareolar dissection.
Considering the short term results (24 months) and comparing them with the literature, we did not register an increase of local recurrence nor any other complication.
Conclusions - Our preliminary results in patients candidate for mastectomy are very good. Compared to traditional surgery, we have noticed a lower number of recurrences, better cosmetic results and more satisfaction from our patients.

Head and Neck Reconstruction

Reconstruction of head and neck wounds due to surgical resection for cancer or head and neck trauma creates numerous challenges for the microsurgeon.
Defects are both functional and cosmetic, defying the reconstructive surgeon to minimize any loss in speech or motor capacity while maintaining a normal appearance.
Advances in microsurgical transplantation have improved reconstructive efforts considerably from a time when reconstruction meant only filling a defect.
The complex anatomy of the head and neck area creates numerous functional mechanisms involved in:

- Speech
- Swallowing
- Sensation
- Oral continence
- Airway protection
- Facial expression

The goal of reconstruction is to preserve and protect all these mechanisms as much as possible while obtaining reasonable restoration of function and morphological reconstruction. This must frequently be done in co-operation with other surgical departments who must attempt to achieve an ablative cure. Using microsurgical reconstruction, resection of tumor can often be even more aggressive since repair of even large defects is possible. Many patients with head and neck cancer require radiation treatment or chemotherapy, increasing the need for a well vascularized tissue reconstruction.
Although many factors are involved for choosing a reconstruction method. Micro-vascular transplantation often results as the most consistent and rewarding kind of reconstruction.
In our department, major surgical reconstruction are usually carried out with radial forearm flaps, being very thin and big enough to cover large areas, but Latissimus dorsii is also used as a free flap, more than the antero-lateral thigh flap (always as micro-surgery).

Mandible Reconstruction

Mandible reconstruction after tumor resection is performed to replace any excised section of the mandible with vascularized bone. Soft tissue defects can be filled with skin and subcutaneous tissue based on perforators from the vascular pedicle accompanying the bone graft. Vascularized bone reconstruction promotes primary healing and increased resistance to infection and resistance to adjuvant radiation therapy necrosis. It also lends itself to bone-integrated implant dental restoration. Often, patients can begin an early range of motion exercises and minimize stiffness in the temporal-mandibular joint.
Options for vascularized bone micro-vascular reconstruction most commonly include:

- Circumflex iliac artery osteocutaneous flap
- Radial forearm osteocutaneous flap

- Serratus with rib flap
- Scapular bone osteocutaneous flap
- Fibula osteocutaneous flap

Our first surgical choice is the fibula free flap transfer, and we have performed one every two weeks this year. The fibula is a wonderful bone to model and a large portion can be obtained to reconstruct the entire mandible.
Furthermore, little damage is caused to the donor site.
In cases where the fibula is not available or only a small piece of bone is required, other options are considered.

Skin cancer

Skin cancers are known to be the most frequent of human cancers and can sometimes be very aggressive.
BCC excisions are usually considered as minor surgery and performed in the out-patient department.
SCC on the contrary very often needs a quite and careful approach.
Notwithstanding the fact that we find ourselves in the third millennium, unfortunately large underestimated tumors that required major surgery can still be observed.
In such cases local flaps are usually employed and when they are not enough we use free micro-surgical flaps.
Malignant Melanoma is to be mentioned.
The lesion excision is made according to international protocols and when the Breslow classification of the lesion is equal or over 1 mm, a control is made of the sentry node closest to the skin excision.
An important co-operation is underway with the Departments of Dermatology, Epidemiology an Radiotherapy for the best treatment and follow-up of our patients.

Division of medical oncology A

DIRECTOR:
FRANCESCO COGNETTI, MD

Professor Francesco Cognetti is currently the Scientific Director of the Regina Elena Cancer Research Institute in Rome.
Professor Cognetti obtained a Master's degree in Medicine and Surgery in 1975, and went on to specialize in Internal Medicine in 1981. He then followed a career in Oncology from 1984, and gained European Certification in Medical Oncology in London in 1989.
Professor Cognetti is a member of several international organizations such as ESMO (the European Society for Medical Oncology) where he was Chairman of the Membership Committee. He is a member of the Executive Board and the Steering Committee as the national representative for Italy, as well as being an active member of the Head and Neck Cooperative Group of EORTC (the European Organization for Research and Treatment of Cancer).
He also represents Italy through his involvement in several prestigious organizations including AIOM (the Italian Association of Medical Oncology) where he was President until October 2003, as Secretary and Treasurer of the Italian Alliance against Cancer Association, as an elected member of the Italian Health Governing Council and as a member of the Italy-USA Effective Committee for Research in Oncology.
Professor Cognetti is the author and co-author of more than 200 publications. He is also a Peer Reviewer of the Annals of Oncology, the official journal of the European Society for Medical Oncology.

Staff:
PAOLO CARLINI - M.D. Assistant
ANNA CERIBELLI - M.D. Assistant
ALESSANDRA FABI - M.D. Assistant
VIRGINIA FERRARESI - M.D. Assistant
GIANLUIGI FERRETTI - M.D. Assistant
MICHELE MILELLA - M.D. Assistant
PAOLA PAPALDO - M.D. Assistant
ENZO MARIA RUGGERI - M.D. Assistant
ANTONELLA SAVARESE - M.D. Assistant
MASSIMO ZEULI - M.D. Assistant
ALESSANDRA FELICI - M.D. Senior Fellow
ALAIN GELIBTER - M.D. Senior Fellow
CHIARA NARDONI - M.D. Senior Fellow
MARIANGELA CICCARESE - M.D. Fellow
FABIANA CECERE - M.D. Fellow
BARBARA DI COCCO - M.D. Fellow
NELLO SALESI - M.D. Fellow
ANDREA ALIMONTI - M.D. Fellow
SERENA DI COSIMO - M.D. Fellow
SIMONA PINO - M.D. Fellow
SUSANNA DI SEGNI - Pharmacist Fellow
LUCA PAOLUZZI - M.D. Fellow

Activities 2003

The clinical activity performed by the Division of Medical Oncology A guarantees treatment and assistance to cancer patients requiring drug administration and clinical follow up. In particular, the Division develops clinical research and new treatment strategies on solid tumors, especially gastrointestinal, lung, breast, gynecologic tumors and melanomas, using either biology response modulators or drugs molecularly targeted to specific biologic targets for different tumors, in addition to the classic antineoplastic drugs. The Division preferentially adopts regimens with optimal efficacy and a low toxicity profile, such as continuous infusion regimens which produce a lower burden of individual toxicity and offer the patients an acceptable quality of life. Several study protocols, each devoted to a single tumor, have been designed with this aim. Other fields of interest include the treatment of cancers requiring a wide experience in med-

ical oncology (e.g. gonadal or extragonadal germinal cell tumors and soft tissue sarcomas). In 2003, 1,738 new patients have been accepted and 12,241 activities (visits and treatments) have been carried out. There have been 1,324 in-patient admissions and 5,009 out-patient admissions. The main research topic of the Division of Medical Oncology A has been the study of new drugs, their combinations and/or sequence and new strategies of integrated treatments. During the past year the Division of Medical Oncology A has produced 23 indexed publications (total impact factor: 76.41) and 15 communications at international congresses.

Non Small Cell Lung Cancer

A multicentric phase III study investigating the role of a novel antisense oligonucleotide (LY900003), with a kinase inhibitor mechanism interacting with the Vascular Epidermal Growth Factor, used with conventional first-line chemotherapy, is underway in the Division of Medical Oncology A.

Two phase II studies, with the combination of CDDP-Gemcitabine followed by weekly Docetaxel and with the combination of Gemcitabine and Paclitaxel in the elderly, are ongoing. Another study on the EGFR inhibitor ZD1839 (Gefitinib) in patients resistant to conventional treatment is still open.

A multicenter phase II study (GEMOXA trial) with Gemcitabine and Oxaliplatin as front-line therapy was activated in 2003.

A phase III trial comparing Docetaxel administered every three weeks versus weekly administration (DISTAL study) as second-line treatment is also ongoing.

Breast Cancer

Adjuvant

Regarding node-positive early breast cancer, a randomized multicenter study (TXT-01) on adjuvant chemotherapy containing Epirubicin followed by CMF compared with Epirubicin followed by Docetaxel followed by CMF has recently been closed and data analysis is in process.

Our Department leads an Italian breast cooperative group called GIM (Gruppo Italiano Mammella), that promotes large randomized studies, and Prof. Cognetti is one of the chairmen. Two randomized studies are actually open and are enrolling node-positive and node-negative women. The first, a study for patients with node positive breast cancer (GIM-2) concerns adjuvant chemotherapy with anthracyclines and taxanes given at different dose-density. This is an important randomized multicenter phase III study of EC followed by Paclitaxel versus FEC followed by Paclitaxel, all given either every 3 weeks or 2 weeks supported by Pegfilgrastim. The study will accrue 2,000 patients in two years, and is intended to determine whether the 5-Fluorouracil addition to EC combination followed by Taxol and a dose-dense schedule (every 2 weeks) will improve disease-free and overall survival.

The other important, international, randomized, multicenter study on women with HER2-overexpressing breast tumors, who have completed adjuvant chemotherapy, designed in 3 arms (Herceptin for 1 year vs Herceptin for 2 years vs follow up only) is ongoing, and will address important questions on the use of Herceptin in the adjuvant setting.

Screening and prevention

A screening and chemoprevention program for women at genetic risk of breast cancer has been activated. The Division of Medical Oncology A coordinates a genetic counseling unit at the Regina Elena Cancer Institute and data regarding this activity and its impact on the population studied is being analyzed. From April 2002 to November 2003,191 subjects (188 females, 3 males, median age 52 yrs) belonging to 140 families with a history of breast or ovarian cancer underwent genetic counseling, and agreed to intensive screening after being informed of the results of the mutation tests.

Advanced breast cancer

Hormonetherapy

A study on the combination of the aromatase inhibitor Anastrozole with the EGFR inhibitor ZD1839 (Gefitinib-Iressa®) is open. Furthermore, a study on the optimal sequence of aromatase inhibitors (AI) (non-steroidal/steroidal) and also a retrospective study on the efficacy of these inhibitors in receptor-negative breast cancer patients were performed. This analysis on new aromatase inhibitors as 2nd-line endocrine therapy (ET) in metastatic breast cancer (MBC) was presented at the ASCO 2004 meeting. When all the subgroups were analyzed for ORR and TTP, no significant differences were found. AIs in 2nd-line ET for MBC pts did not seem to add any significant benefit to the standard comparator arm in terms of ORR and TTP.

Chemotherapy

We are currently participating in an international multicenter randomized phase 2 trial with Trastuzumab (Herceptin) given with weekly Paclitaxel (Taxol) versus weekly Paclitaxel as single agent in first-line therapy metastatic breast cancer (MBC) patients with HER-2/neu overexpression. This protocol will determine the safety profile and the overall response rate in each treatment arm.

Furthermore a Phase II study with Pegylated Liposomal Doxorubicin (PLD) in combination with Gemcitabine (G) in metastatic breast cancer (MBC) patients is active in our Division. Pegylated Liposomal Doxorubicin and Gemcitabine have recently demonstrated a promising clinical efficacy in MBC when used as single agents. We conducted a phase II clinical trial to determine the activity and safety of the two drugs in combination either in untreated or previously treated metastatic breast cancer.

Advanced Colorectal Cancer

Two multicenter studies, both coordinated by the Division of Medical Oncology A, are ongoing. A phase II study on the combination of the EGFR inhibitor ZD1839 (Gefitinib - Iressa®) with Oxaliplatin and Capecitabine and a phase III study on the combination of Oxaliplatin, Fluorouracil by continuous infusion and a new inhibitor of cancer angiogenic activity PTK787/ ZK222584.

The combination Oxaliplatin and Capecitabine in advanced colorectal cancer was previously extensively studied in the Division of Medical Oncology A resulting in two indexed publications in recent years and the phase II study on the combination of Oxaliplatin and Capecitabine with the EGFR inhibitor ZD1839 (Gefitinib - Iressa®) is close to conclusion. The most common side-effect was diarrhea and the efficacy of treatment seems to be very interesting with an overall response rate of up to 50%

The multicenter phase III study with PTK787/ ZK222584 was activated in 2003 with the accrual of 8 patients by the Division of Medical Oncology A. A very tolerable safety profile with interesting clinical activity was noted.

Advanced Pancreatic (pdac) and Biliary Tree (btc) Carcinomas

A phase II study for advanced pancreatic and biliary tree carcinoma was concluded in 2003. Patients were treated with Gemcitabine 1,000 mg/m^2 at the fixed dose-rate of 10 mg/m2/min for 7 consecutive wks and weekly x 3 q4 wks.

The analysis of preliminary results showed a mild toxicity with clinical benefit in 44% of patients.

A multicenter phase III study investigating the role of the adjunct of Cisplatin to Gemcitabine (Gip-1 Study) as first-line chemotherapy in unresectable advanced pancreatic cancer is also active.

Urothelial Bladder Carcinoma

In urothelial bladder carcinoma the enrollment of patients in a phase III randomized study on adjuvant chemotherapy with CDDP plus Gemcitabine versus observation alone is in process. Our division, together with the Genova Cancer Institute, are coordinating the study, that is addressing important questions on the use of adjuvant chemotherapy in bladder cancer.

Melanoma

For malignant melanoma, two studies were finalized in 2003. An EORTC phase III study evaluating the role of Pegylated Interferon (PEG-Intron) in an adjuvant setting and a phase II study with Temozolamide after whole brain radiotherapy in patients with brain metastases. The analyses are in progress.
A phase III randomized study promoted by EORTC is evaluating the efficacy of vaccination with Ganglioside GM2-KLH/ QS-21 in patients with stage II disease.
A randomized phase II study in patients with metastatic melanoma is comparing DTIC plus IFN-alfa at low dose with DTIC plus Timosine alfa-1 or with DTIC plus IFN-alfa plus Timosine alfa-1. In addition, in advanced melanoma another study using chemoimmunotherapy including Fotemustine, CDDP, IL2 and IFN-alfa with a simultaneous biological study is ongoing.

Ovarian Carcinoma

Two phase III studies are active.
A multicenter phase III study comparing conventional first-line chemotherapy with Carboplatin and Paclitaxel versus the innovative combination Carboplatin and Liposomial Doxorubicin and a multicenter phase III study (Mito-2 Study) comparing Topotecan, Gemcitabine and Liposomial Doxorubicin in patients with refractory ovarian carcinoma are underway in our division.

Brain Tumors

Regarding cerebral tumors, a dose-finding study on the weekly administration of Gemcitabine as radiosensitizer is enrolling patients with glioblastoma multiforme.

Supportive Care

Concerning supportive care, two studies using Eritrhopoietin and Darbopoietin in different tumors and chemotherapeutic treatments, are in process with the aim of evaluating the quality of life of long-term cancer survivors.

Publications 2003

Alimonti A., Ferretti G., Di Cosimo S., Cognetti F., Vecchione A.

Can colorectal cancer patients with thymidylate synthase-overexpressing liver metastases have an overall survival advantage with hepatic arterial infusion alone?

J. Clin. Oncol. 2003 Sep 15;21(18):3543-4; author reply 3544-5. *I.F. 9.868*

Alimonti A., Di Cosimo S., Di Stani F., Vecchione A., Di Palma M., Ferretti G.

Subacute motor weakness and left renal mass.

Am. J. Med. 2003 Jun 1;114(8):706-8. *I.F. 4.904*

Boogaerts M., Coiffier B., Kainz C., and the Epoetin b QOL Working Group; (Cognetti F.)

Impact of epoetin b on quality of life in patients with malignant disease.

Br. J. Cancer 2003, 88, 988-995. *I.F. 3.639*

Carlini P., Ferretti G., Di Cosimo S., Colella E., Tonachella R., Romiti A., Tomao S., Frassoldati A., Papaldo P., Fabi A., Ruggeri E.M., Cognetti F.

Is there a benefit by the sequence anastrozole-formestane for postmenopausal metastatic breast cancer women?

J. Steroid Biochem. Mo.l Biol. 2003 Jul;86(1):107-9. *I.F. 2.637*

Carlini P., Di Cosimo S., Ferretti G., Papaldo P., Fabi A., Ruggeri E.M., Milella M., Cognetti F.

Alopecia in a premenopausal breast cancer woman treated with letrozole and triptorelin.

Ann. Oncol. 2003 Nov;14(11):1689-90 *I.F. 3.114*

Ceribelli A., Gridelli C., De Marinis F., Fabi A., Gamucci T., Cortesi E., Barduagni M., Antimi M., Maione P., Migliorino M.R., Giannarelli D., Cognetti F.

Prolonged Gemcitabine infusion in advanced non-small cell lung carcinoma: a randomized phase II study of two different schedules in combination with Cisplatin.

Cancer. 2003 Jul 15;98(2):337-43. *I.F. 3.941*

Cocconi G., Passalacqua R., Foladore S., Carlini P., Acito L., Maiello E., Marchi M., Gebbia V., Di Sarra S., Beretta M., Bacchi M.

Treatment of metastatic malignant melanoma with Dacarbazine plus Tamoxifen, or Vindesine plus Tamoxifen: a prospective randomized study.

Melanoma Res. 2003 Feb;13(1):73-9. *I.F. 1.773*

Cocconi G., Carlini P., Gamboni A., Gasperoni S., Rodino C., Zironi S., Bisagni G., Porrozzi S., Cognetti F., Di Costanzo F., Canaletti R., Ruggeri E.M., Camisa R., Pucci F.

Cisplatin, Epirubicin, Leucovorin and 5-fluorouracil (PELF) is more active than 5-fluorouracil, Doxorubicin and Methotrexate (FAMTX) in advanced gastric carcinoma.

Ann. Oncol. 2003 Aug;14(8):1258-63. *I.F. 3.114*

Di Cosimo S., Ferretti G., Fazio N., Silvestris N., Carlini P., Alimonti A., Gelibter A., Felici A., Papaldo P., Cognetti F.

Docetaxel in advanced gastric cancer-review of the main clinical trials.

Acta Oncol. 2003; 42(7): 693-700. Review. *I.F. 1.909*

Di Cosimo S., Ferretti G., Papaldo P., Carlini P., Fabi A., Cognetti F.

Lonidamine: Efficacy and safety in clinical trials for the treatment of solid tumors.

Drugs Today (Barc). 2003 Mar;39(3):157-74. *I.F. 0.258*

Fabi A., Barduagni M., Lauro S., Portalone L., Mauri M., Marinis F., Narduzzi C., Tonini G., Giampaolo M., Pacetti U., Paoloni F., Cognetti F.

Is delayed chemotherapy-induced emesis well managed in oncological clinical practice? An observational study.

Support Care Cancer. 2003 Mar;11(3):156-61. Epub 2003 Jan 25. *I.F. 1.299*

Gelibter A., Ceribelli A., Milella M., Mottolese M., Vocaturo A., and Cognetti F.

Clinically Meaningful Response to the EGFR Tyrosine Kinase Inhibitor Gefitinib (Iressa, ZD1839) in Non Small Cell Lung Cancer

J. Exp. Clin. Cancer Res., 22, 3, 2003 *I.F. 0.703*

Leonetti C., Biroccio A., Gabellini C., Scarsella M., Maresca V., Flori E., Bove L., Pace A., Stoppacciaro A., Zupi G., Cognetti F., Picardo M.

Alpha-tocopherol protects against Cisplatin-induced toxicity without interfering with antitumor efficacy.

Int. J. Cancer. 2003 Mar 20;104(2):243-50. *I.F. 4.056*

Mandala M., Ferretti G., Cremonesi M., Cazzaniga M., Curigliano G., Barni S.

Venous thromboembolism and cancer: new issues for an old topic.

Crit. Rev. Oncol. Hematol. 2003 Oct;48(1):65-80. *I.F. 2.758*

Milella M.

Relevance of cytoplasmic intermediates (MAPK-PI3K) in signal transduction.

Tumori, suppl. 2(2): S35-S36, 2003 *I.F. 0.267*

Mouridsen H., Gershanovich M., Sun Y., Perez-Carrion R., Boni C., Monnier A., Apffelstaedt J., Smith R., Sleeboom H.P., Jaenicke F., Pluzanska A., Dank M., Becquart D., Bapsy P.P., Salminen E., Snyder R., Chaudri-Ross H., Lang R., Wyld P., Bhatnagar A.

Phase III study of Letrozole versus Tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group (in addition to listed authors) were as follows: Italy: P. Carlini et al..

J. Clin. Oncol. 2003 Jun 1; 21(11): 2101-9. *I.F. 9.868*

Pace A., Savarese A., Picardo M., Maresca V., Pacetti U., Del Monte G., Biroccio A., Leonetti C., Jandolo B., Cognetti F., Bove L.

Neuroprotective effect of vitamin E supplementation in patients treated with Cisplatin chemotherapy.

J. Clin. Oncol. 2003 Mar 1;21(5):927-31. *I.F. 9.868*

Papaldo P., Ferretti G.L. Di Cosimo.

Indicazioni nella pratica clinica della chemioterapia nelle pazienti con tumore della mammella operato con linfonodi negativi. contro

Tumori, suppl. 2(4): S11-S12, 2003 *I.F. 0.267*

Papaldo P., Lopez M., Cortesi E., Cammilluzzi E., Antimi M., Terzoli E., Lepidini G., Vici P., Barone C., Ferretti G., Di Cosimo S., Nistico C., Carlini P., Conti F., Di Lauro L., Botti C., Vitucci C., Fabi A., Giannarelli D., Marolla P.

Addition of either Lonidamine or Granulocyte colony-stimulating factor does not improve survival in early breast cancer patients treated with high-dose Epirubicin and Cyclophosphamide.

J.Clin. Oncol. 2003 Sep 15;21(18):3462-8. *I.F. 9.868*

Quattrini M., Del Nonno F., Pacetti U., Visca P., Atlante M., Brenna A., Romagnoli F., Marandino F., Sbiroli C., Mariani L..

Rapid Modification of Aggressiveness of a Primary Non-Hodgkin Lymphoma of Uterine Cervix

J. Exp. Clin. Cancer Res., 22, 4, 2003 Case Report *I.F. 0.703*

Savarese A., Cognetti F.

New drugs in the treatment of recurrent or metastatic cervical cancer.

Crit. Rev. Oncol. Hematol. 2003 Dec; 48(3): 323-7. *I.F. 2.758*

Scagliotti G.V., Fossati R., Torri V., Crino L., Giaccone G., Silvano G., Martelli M., Clerici M., Cognetti F., Tonato M.

Adjuvant Lung Project Italy/European Organization for Research Treatment of Cancer-Lung Cancer Cooperative Group Investigators.
Randomized study of adjuvant chemotherapy for completely resected stage I, II, or III A non-small-cell Lung cancer.

J. Natl. Cancer Inst. 2003 Oct 1;95(19):1453-61. *I.F. 14.500*

Zeuli M., Nardoni C., Pino M.S., Gamucci T., Gabriele A., Ferraresi V., Giannarelli D., Cognetti F.

Phase II study of Capecitabine and Oxaliplatin as first-line treatment in advanced colorectal cancer.

Annals of Oncology 14: 1378-1382,2003. *I.F. 3.114*

Totale= 76.41

Division of medical oncology B

DIRECTOR:
MASSIMO LOPEZ, MD

Massimo Lopez graduated in Medicine on November 15, 1967 at the University of Rome Medical School, and specialised in medical oncology and internal medicine at the same University. From 1969 to 1986 he worked at Regina Elena Institute for Cancer Research in Rome. His main interest was in the field of medical treatment of solid tumors with special attention to clinical evaluation of new drugs. In 1982, he reported for the first time the clinical activity of cyproterone acetate in male breast cancer. In 1986, he moved to "G. Porfiri" Oncologic Center, Latina, as Director of Division of Medical Oncology. He left Latina and went to Regina Elena Institute for Cancer Research in 1990 to work as Director of Division of Medical Oncology B. During the last years, his research interests were focused on chemotherapy and targeted therapy of breast cancer, soft tissue sarcomas, and melanoma.
Dr. Lopez is a member of the Italian Association of Medical Oncology (AIOM), European Society for Medical Oncology (ESMO), and American Society for Clinical Oncology (ASCO). He is Scientific Director of the journal *La Clinica Terapeutica*, editor of the textbook *Oncologia Medica Pratica*, and co-editor of the books *TEODORI-Trattato italiano di Medicina Interna*, and *Prontuario Terapeutico Universo*.

Staff:

ANTONELLA AMODIO - M.D. Assistant
CAROLINA CAUCHI - M.D. Fellow
SILVIA CARPANO - M.D. Assistant
SONJA CONDORELLI - M.D. Fellow
FRANCESCA CONTI - M.D. Assistant
MARIA CLAUDIA MASI - M.D. Fellow
MARINA DELLA GIULIA - M.D. Assistant
DOMENICO SERGI - M.D. Fellow
LUIGI DI LAURO - M.D. Assistant
GIUDITTA VIOLA - M.D. Fellow
PAOLO FOGGI - M.D. Assistant
SERENA CORSETTI - M.D. Fellow
GIANCARLO PAOLETTI - M.D. Assistant
SIMONA APICELLA - Student
MASSIMO RINALDI - M.D. Assistant
LUIGI CARMINE ROMA - Student
IRENE VENTURO - M.D. Assistant
WALTER CHIERICHETTI - Student
PATRIZIA VICI - M.D. Assistant
SILVIA ILEANA SARA FATTORUSO - Student
ROSITA CAPONETTI - M.D. Senior Fellow

Activities 2003

Among the fields of interest of the Division of Medical Oncology B (MOB) is to maintain liasons with other oncological associations, universities, and to cooperate with the pharmaceutical industry in areas of mutual interest.
During 2003 several clinical trials concerning a lot of oncologic fields have been carried out. In particular, the Division of MOB served as coordinator center of various breast cancer clinical trials in adjuvant, neoadjuvant and advanced setting, in collaboration with other Italian oncologic centers.
In the adjuvant setting we are currently investigating in a phase III multicenter randomized trial, the efficacy of 4 cycles of epirubicin/cyclophosphamide regimen versus the same regimen preceded by 4 cycles of docetaxel in node positive breast cancer patients. In 2003 we continued the enrollment of the patients. The accrual will be completed in 2004 and final data will be analysed.
Another relevant field of interest was primary chemotherapy in locally advanced breast cancer. We designed a multicenter trial with a regimen of epirubicin 80mg/m^2 and doc-

etaxel 80 mg/m^2, every 3 weeks, with G-CSF support, followed whenever possible by surgery or, in case of no change or progression, by radiotherapy, and a subsequent adjuvant regimen with vinorelbine, 25 mg/m^2 d 1,8 and mitomycin C 10 mg/m^2 d 1, every 4 weeks. Estrogen receptor positive patients receive at the end of chemotherapy an hormonal treatment. The enrollment is ongoing; in the first 29 evaluable patients there was a response rate (RR) of 76%, and surgery was feasible in 93% of the patients.

In one of our most recent articles on treatment of advanced breast cancer (JCO 2002, Vici et al.), we reported a very active regimen consisting of epirubicin (100 mg/m^2 d 1) combined with vinorelbine (25 mg/m^2 d 1 and 5), with G-CSF support and cycles repeated every 3 weeks. The overall response rate was 71%, with median TTP and median OS of 16 and 21 months, respectively. Toxicity was manageable, consisting mostly in neutropenia and mucositis. On the basis of the above previous work, in 2003 we designed and activated a new clinical trial, a prospective multicenter phase II randomized study of the above combination, at a lower dose of epirubicin, versus the combination of pegylated liposomal doxorubicin and vinorelbine (L-DOX 40 mg/m^2 d 1, VNB 30 mg/m^2 d 1, 15, every 4 weeks), as first line chemotherapy in anthracycline naïve patients. The enrollement is ongoing, and many Italian oncologic centers are participating in the trial.

We are also interested in clinical evaluation of new drugs, and we designed and activated several clinical trials, most of which multicentric, with gemcitabine in advanced breast cancer patients. In 2003 we closed the enrollment and elaborated data of two clinical trials. The first one was a combination of docetaxel 80 mg/m^2 d 8 and gemcitabine, 1000 mg/m^2 d 1, 8, every 3 weeks in 53 anthracycline pretreated patients, with a RR of 53%, TTP of 7.5 months and OS of 16 months. This trial was published in Seminars in Oncology (April 2004). The second one is an interesting combination of paclitaxel 150 mg/m^2 and gemcitabine 1500 mg/m^2 d 1, 15, every 4 weeks, in heavily pretreated advanced breast cancer patients. We enrolled 39 patients, and we observed 45% of response, a TTP of 9 months, an OS of 21 months, with a very mild toxicity. These data are very encouraging and supported by a synergistic activity between the two drugs, as demonstrated by preliminary results of in vitro and in vivo studies which are ongoing in the Department of Preclinical Pharmacology of our Institute.

In 2003 we also continued the enrollment in another phase II multicenter clinical trial with the combination of docetaxel 80 mg/m^2 d 8 and gemcitabine 1000 mg/m^2 d 1, 8, as first-line chemotherapy in patients treated with adjuvant anthracyclines. Preliminary results showed objective responses in 52% of the patiens with negligeable toxicity. We are now evaluating final data.

On the basis of our previous experience, in 2003 we activated another phase II multicenter randomized trial of docetaxel 75 mg/m^2 d 8 and gemcitabine 1000 mg/m^2 d 1, 8 versus docetaxel 75 mg/m^2 d 1 and capecitabine 1,250 bid d 1à14, with cycles repeated every 3 weeks, as first-line treatment for advanced disease, in patients previously treated with adjuvant anthracyclines. The enrollment is ongoing.

Moreover, another clinical multicenter phase II trial is ongoing as 2nd line treatment in advanced breast cancer, consisting of the combination of docetaxel 75 mg/m^2 d 1 and vinorelbine 25 mg/m^2, every 3 weeks and with G-CSF support, in patients pretreated with anthracyclines. In 33 evaluable patients we observed a RR of 45%, with a median TTP of 8 months, and a manageable toxicity. Preliminary data have been accepted for ASCO meeting 2003 as an abstract pubblication.

Another field of interest of the 2nd Division of Medical Oncology is the treatment of **lung cancer**. A lot of multicenter international clinical trials have been carried out, and our Division is the coordinator center of some of these trials. The results of two trials have been published in international journals in 2003 (see selected publications).

We are also interested in several other oncologic fields, including soft tissue sarcomas, melanoma, gastric cancer, colorectal cancer, and molecular targeted therapy.

Selected publications 2003

Papaldo P, Lopez M, Cortesi E, Cammilluzzi E, Antimi M, Terzoli E, Lepidini G, Vici P, Barone C, Ferretti G, Di Cosimo S, Nistico C, Carlini P, Conti F, Di Lauro L, Botti C, Vitucci C, Fabi A, Giannarelli D, Marolla P.:

Addition of either lonidamine or granulocyte colony-stimulating factor does not improve survival in early breast cancer patients treated with high-dose epirubicin and cyclophosphamide.

J Clin Oncol 21: 3462-3468, 2003

Gebbia V, Galetta D, Caruso M, Verderame F, Pezzella G, Valdesi M, Borsellino N, Pandolfo G, Durini E, Rinaldi M, Loizzi M, Gebbia N, Valenza R, Tirrito ML, Varvara F, Colucci G, Gruppo Ocologico Italia Meridionale.

Gemcitabine and cisplatin versus vinorelbine and cisplatin versus ifosfamide+gemcitabine followed by vinorelbine and cisplatin versus vinorelbine and cisplatin followed by ifosfamide and gemcitabine in stage IIIB-IV non small cell lung carcinoma: a prospective randomized phase III trial of the Gruppo Oncologico Italia Meridionale.

Lung Cancer 39: 179-189, 2003

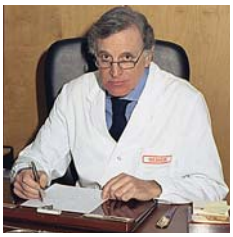
Rosell R, Scagliotti G, Danenberg KD, Lord RV, Bepler G, Novello S, Cooc J, Crino L, Sanchez JJ, Taron M, Boni C, De Marinis F, Tonato M, Marangolo M, Gozzelino F, Di Costanzo F, Rinaldi M, Salonga D, Stephens C.

Transcripts in pretreatment biopsies from a three-arm randomized trial in metastatic non-small-cell lung cancer.

Oncogene 22: 3548-3553, 2003

Division of medical oncology C

DIRECTOR:
EDMONDO TERZOLI, MD



Prof. Edmondo Terzoli, MD graduated in Medicine and Surgery in 1969 at La Sapienza University, Rome. He also received fellowships for Hematology, Medical Oncology and Pulmonary diseases, during 1972, 1974 and 1976, respectively at La Sapienza University, Rome. From 1970 to 1979 he worked at the Regina Elena National Cancer Institute, Rome as Attending MD, during 1979, he became the Head of Division, and in 1991 Head of the Complementary Medical Oncology Division. From 2000 he has been Director of the Medical Oncology C Division, and from 2003 has been Head Director of the Department of Medical Oncology of the Regina Elena National Cancer Institute of Rome. Over the years Prof. Terzoli has held several roles in the Italian Association of Medical Oncology (AIOM).

Staff:

Attending / Assistant M.D.:
DR. ANNA MARIA ASCHELTER - M.D.
DR. ALESSANDRO CASALI - M.D.
DR. CARLO GARUFI - M.D.
DR. FIORENTINO IZZO - M.D.
DR. CECILIA NISTICÒ - M.D.
DR. FRANCESCO TROPEA - M.D.

Post-Doctoral MD (Senior Fellow):
DR. EMILIO BRIA - M.D.
DR. ANGELA TORSELLO - M.D.
DR. BARBARA VANNI - M.D.

MD Fellows (in Training):
DR. FRANCESCA CALABRETTA - M.D.
DR. CARLA CAMPANELLA - M.D.
DR. FEDERICA CUPPONE - M.D.

Activities 2003

The division of Medical Oncology C has focused its major scientific activity during 2003 in breast and colorectal cancer.
In particular, the development of weekly chemotherapy and the chronomodulated infusion of chemotherapy in breast and colorectal cancer respectively, represent more than 12 years of experience of the Department directed by Prof. Terzoli, and a cultural and scientific treasure for the Regina Elena National Cancer Institute of Rome. As with old drugs, new chemotherapeutic and molecular targeted agents have been developed for weekly and chronomodulated application. These two research lines have been enriched by several international peer-reviewed publications and by meetings in which national and international authorities in the profession were present.
In order to follow the rapidly growing need to update knowledge and research required by medical oncology, our division has also distinguished itself by organizing courses on several skills, strictly focused on weekly schedules. Doctors throughout the country participated interactively in a discussion of issues which were raised during the courses, regarding the most recent clinical studies and their application to real clinical cases. With these criteria, ideal skilled training of research and clinical practice has been followed. The international consensus about weekly chemotherapy for breast cancer, has recently been reached at the last meeting of the American Society of Clinical Oncology (ASCO 2004), where a phase III trial showed the benefit in activity and efficacy of this approach, when compared to conventional 3-weekly chemotherapy. Thanks to these important results, the experience and the size, in terms of enrolled patients of our Division, regarding weekly chemotherapy of breast cancer, can be considered as one of the largest and most skilled worldwide, stressing again the relevance of the Regina Elena National Cancer Institute of Rome in clinical research.
As concerns chronomodulated infusion of chemotherapy in the treatment of colorectal

cancer, our Division can be considered a national and international reference center, and as a member of EORTC, our division coordinates an international trial.
Both research lines conducted in the Division directed by Prof. Terzoli, find continuous support in the Scientific Director of the Regina Elena National Cancer Institute.
During 2003, 950 new patients have been accepted and 14,400 activities (visits and treatments) have been carried out. 478 in-patient- and 2,689 out-patient-admissions were recorded, respectively.

Breast Cancer.
Until recently, weekly chemotherapy was considered to be a treatment restricted to particular sub-classes of patients, such as the elderly or unfit, or for those affected by concomitant life-threatening co-morbidities.
Conversely, today it is recognized as a new administration option for chemotherapeutics, built on theoretical roots based on a dose-dense theory developed in the Memorial Sloan Kettering Cancer Institute of New York (US).
Cancer cells follow a non-exponential Gompertzian curve model, with a doubling time which progressively grows in the most advanced periods. When increasing chemotherapy dosages with 3-weeks of rest, we theoretically obtain an increase in cell deaths for each cycle; however, the re-growth between 2 courses, as described by the Gompertzian model, should explain the failure of any strategy based exclusively on dose-augmentation. Furthermore, the endothelial cells of new born vessels can begin to proliferate again, favoring neoplastic cell growth through neoangiogenesis empowerment.
More recently, as hematopoietic growth factors became available, new dose-intensification strategies based on the time-reduction between two consecutive doses (dose-density) was born. This approach has the theoretical advantage of reducing the re-growth effect of cancer cells between cycles, thereby increasing the efficacy of such drugs. In fact, cytotoxicity does not follow a linear dose-response curve in these drugs. Besides, the prolonged exposure of cancer cells to agents which interfere with mechanisms of cellular proliferation could permanently damage the ability for regrowth, even in the absence of chemotherapy. This approach offers pharmacokynetic advantages too, as it permits the drug-concentration peak, which is often toxicity-related, to be reduced, while maintaining overall AUC.
In conclusion, the weekly administration of chemotherapeutics theoretically increases the frequency of cancer-cell exposure to drugs and reduces the non-exposure time-interval, in which neoangiogenesis and cancer cell re-growth are supposed to happen.
In the treatment of metastatic breast cancer, a weekly schedule has demonstrated to be active in both mono- and poly-chemotherapy. The toxicity of this approach seems to be lower than with 3-weekly chemotherapy. The constant and prophylactic administration of growth factors (G-CSF) allows to avoid hematologic toxicity through bone-marrow recovery and, above all, to maintain the frequency of a weekly administration, which is crucial for dose-intensity maintenance. Indeed, the delay of one administration per month implies a 25% reduction of dose-intensity, and it is well known that this decrease has a negative impact on adjuvant treatment and it is likely to happen in a metastatic setting. All these theories have recently been supported and finally assessed in an important clinical setting, the CALGB 9840 phase III trial, which clearly demonstrated the advantages of weekly over 3-weekly paclitaxel in terms of objective response rate, duration of response and time to progression.
From 1990, our Division has been working on the development of weekly schedules in metastatic breast cancer. During 2003, a phase II study was completed in which patients affected by previously untreated advanced or metastatic breast cancer underwent weekly combination chemotherapy with Epirubicin and Paclitaxel. Furthermore, two ancillary studies have also been conducted to evaluate cardio- and neuro-toxicity of this schedule from a clinical, serological and instrumental perspective.
Anthracycline-resistant or refractory patients, were enrolled onto a phase II study with weekly Gemcitabine and Paclitaxel; Gemcitabine was also administered as fixed dose rate (FDR) of 10 $mg/m^2/min$, owing to the extremely recent pharmacokynetic and clinical news about this drug.

As concerns the results achieved with monoclonal antibodies, patients expressing HER +++ or FISH positive, were treated with weekly Trastuzumab in combination with Epirubicin and Paclitaxel in 1st line or with Gemcitabine and Paclitaxel, if resistant or refractory to anthracyclines.
As concerns adjuvant treatment of breast cancer, our Division partook in 2 trials coordinated by the Gruppo Italiano Mammella (GIM); node-positive patients after surgery for early stage breast cancer have been randomized in the GIM 2 protocol, while the GIM 1 trial which refers to node-negative patients is scheduled to start in early 2004.

COLORECTAL CANCER.

Chrono-biology is the study of biologic rhythms that are spontaneously present in nature and how they interact with normal physiology and physiopathology. Chronotherapy aims at synchronizing medical therapies with endogenous physiologic rhythms to increase the therapeutic index of administered drugs. In oncology too, this discipline finds a very notable application. Many endogenous rhythms have a genetic origin: in mammalians many physiologic, biochemical and behavioral processes varying in a regular and predictable periodical way in function of time. Some of more common rhythms of the human species are ultradian (circadian rhythm that go on through 24 h, such as the sleep-awake rhythm or cortisole rhythm), infradian (> 24 h, such as the menstrual cycle in woman) and seasonal rhythms. The suprachiasmatic nucleus of anterior hypothalamus (SCN) coordinates circadian rhythms and, through connections with the retinal epithelium, is responsible of melatonin synthesis, a pineal hormone involved in the circadian sleep-awake rhythm. Organisms philogenetically distant, such as Synechoccus, Neurospora, Drosophila and mammalians, share a common mechanism and, in part, homologous genes for circadian rhythm control. In mammalians five 'clock genes' were cloned (clock, Per, Bmal 1, Tim and Cry) and their role in intracellular transcriptional/traductional regulations was demonstrated. These clock genes are expressed both in neuronal tissues and in oral mucosa and the skin, with a time lag of 4-6 hours compared to the SCN rhythm. Recent studies have demonstrated that expression of hundreds of genes is under clock-gene control. These data suggest that human clock-genes can be functionally important for molecular control of the human circadian pacemaker. Circadian organization modulates numerous cellular functions involved in metabolism and/or citotoxicity of antiblastic drugs, for example enzymatic activities responsible for catabolism and anabolism of 5-Fluorouracil (5-FU), cellular concentrations of GSH, expression of proteins involved in cell cycle regulation and apoptosis. As cancer can change circadian functions both in experimental models and in patients, so it seems that cortisole and melatonin and sleep-waking rhythms are implied in neoplastic progression. The more notable results of the application of chronotherapy concepts were documented in various studies carried out during 1990, and still in course, about metastatic colorectal cancer. Strategic lines developed in studies carried out in individual institutions and also in a cooperative way were the following: a) development of chronomodulated infusion of 5-Fluorouracile (5-FU), associated to Folinic Acid (FA) in FF schedule, and Oxaliplatin (l-OHP) as single agent and in combination in a FFL schedule, obtaining an intensification of treatment; b) introduction of neoadjuvant chemotherapy concept for patients with liver metastases unresectable at time of diagnosis; c) development of models of new psychological interventions for patients with metastasis; d) evaluation of the role of circadian rhythms as an independent prognostic factor in patients with advanced disease. Now the activity of the chronotherapy centers has been institutionalized by the EORTC Cronotherapy Group that include more of 40 centers in Europe, Canada and Israel. Treatment of colorectal cancer as first line came about from participation in the European multicenter study EORTC 05011 (of which our Division is the co-ordinating centre), that consists of chronomodulated infusion of 4 drugs, CPT-11, 5-FU, FA and L-OHP, in patients randomized to receive Irinotecan in 6 different peaks of infusion to evaluate the time of better tolerability of this drug. Thirty patients were recruited in this study, five of which were subjected to resection of hepatic metastasis. The development of this study arose from our previous experience, published on BJC 2003, where the synergism between CPT-11 and L-OHP was evaluated in animals with transplanted tumor in collaboration with Villejuif

(France). In these study pre-treated patients received L-OHP, 5-FU and FA in chronomodulated infusions and CPT-11 in i.v. 90 minute infusions. Moreover, in pre-treated patients a phase II study that compared CPT-11 standard infusion with chrono-infusion of 5-FU/FA plus CPT-11, according to our previous phase I study published on Cancer 2001. Highly treated patients made a therapy with Mytomicin C plus chronomodulated oral Fluoropirimydine (20% of total dose in the morning and 80% of dose in the evening) or oral Fluoropirimydine plus COX-2 inhibitors. Regarding adjuvant chemotherapy for colorectal cancer, the protocol of our Institute is ongoing for patients with Dukes B2/C stage of colorectal cancer. Patients with extraperitoneal rectal cancer are including in the protocol of neoadjuvant radio-chemotherapy (PLAFUR vs TOMOXRT) in collaboration with the Radiotherapeutic and Surgical Divisions. Moreover, we have participated in a phase II randomized, multicenter, explorative and double-blind study to evaluate the efficacy of Acetil-L-Carnitine (ALCAR) to significantly reduce neuropathy in patients with advanced colorectal cancer, treated with chemotherapic regimen with L-OHP for G3 neuropathy.

Other diseases.

During 2003, patients affected by advanced untreated pancreatic carcinoma were enrolled in an international randomized phase III trial in which standard Gemcitabine chemotherapy was compared to the experimental combination of Gemcitabine plus Pemetrexed. Our center enrolled the largest number of patients in Italy. Patients not-eligible for this trial, were enrolled in a study with Gemcitabine FDR (10 mg/m^2/min), designed and coordinated by the Medical Oncology "A" Division. Thanks to the recent news about the role of Cyclo-oxigenase-2 (COX-2) inhibitors in the treatment of pancreatic carcinoma, pretreated patients were enrolled in a pilot study with 5-fluoruracil in continuous infusion in combination with the selective COX-2 inhibitor Celecoxib.
Concerning non-small-cell lung cancer, a pilot study of sequential chemotherapy with non-cross resistant drugs has been completed.

Publications 2003

Nisticò C., Bria E., Vanni B., Terzoli E.

Le terapia settimanali - NPT

Dompè Biotec, 2003.

Garufi C., Bria E., Vanni B., Zappala A.M. Sperduti I., Terzoli E.

A phase II study of irinotecan plus chronomodulated oxaliplatin, 5-fluorouracil and folinic acid in advanced colorectal cancer patients.

Br J Cancer. 89(10): 1870-5 Nov 17; 2003.

Garufi C., Cristaudo A., Vanni B., Bria E., Aschelter A.M., Santucci B., Terzoli E.

Skin testing and Hypersensitivity reactions to oxaliplatin.

Ann Oncol. 14(3): 497-8, Mar 2003.

Mancini R., Tedesco M., Garufi C., Filippini A., Arcieri S., Caterino M., Pizzi G., Cortesi E., Spila A., Sperduti I., Cosimelli M.

Hepatic arterial infusion (HAI) of Cisplatin and systemic Fluorouracil in the treatment of unresectable colorectal liver metastases.

Anticancer Res.; 23(2C): 1837-4, Mar-Apr 2003.

Garufi C., Vanni B., Bria E., Zappalà A.R., Aschelter A.M., Terzoli E.

Terapia cronomodulata-Capitolo 26, pp. 413-420

Da: I tumori dell'apparato gastroenterico, A. Zaniboni, L. Gennai, P. Olmi, Ed. Masson 2003.

Division of haematology oncology

DIRECTOR:
MARIA CONCETTA PETTI, MD

Dr. Maria Concetta Petti graduated as MD from the Medical School of La Sapienza University Rome, Italy, in 1972. After training in Internal Medicine, she obtained the Specialty Board Certification in Clinical and Laboratory Hematology at La Sapienza University, Rome, where she was Assistant Professor in the Department of Cellular Biotechnology and Hematology until January 2001. Since 2001 she has been serving as Head of Hematology and the Stem Cell Transplant Division in the Regina Elena Cancer Institute of Rome. In 1979 she was Visiting physician in the Unitè de chemiotherapy, Hopital S. Louis, Paris, Dr Petti is Professor at La Sapienza University and the Campus Biomedico, Post graduate School of Haematology and Gastroentherology.
Dr Petti is a member of many prestigious societies including the Italian Society of Hematology, the Italian Society of Experimental Hematology, the European Society of Haematology, the Italian Society of Clinical Oncology.

Areas of Research Interest:

Biology of acute leukaemias, myeloproliferative disorders and myelodisplastic syndromes. Clinical trials on the role of chemotherapies, BRM's, differentiative agents and growth factors in leukaemias, lymphoproliferative and myeloproliferative disorders, myelodisplastic syndromes.

Staff:

ANDREA MENGARELLI - M.D.
FRANCESCO PISANI - M.D.
ATELDA ROMANO - M.D.
ANTONIO SPADEA - M.D.
PAOLA ANTICOLI BORGIA - M.D. Fellow

Activities 2003

The effort of the our Unit (S.C. Ematologia) was mainly aimed at designing and carrying out clinical trials of primary relevance in different hematological malignancies working in cooperation with other hematological institutions. In particular, our Unit is a member of the following cooperative groups:

- Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA)
- The European Organization for the Research and Treatment of Cancer (EORTC)
- The Italian Cooperative Study Group on Chronic Myeloid Leukemia (ICSG on CML)
- The Non-Hodgkin Lymphoma Cooperative Study Group (NHLCSG)

CHRONIC MYELOGENOUS LEUKEMIA

(CML) is a malignant clonal disorder of the hemopoietic stem cell due to reciprocal translocation of genetic material between chromosome 9 and 22 (t(9;22) (q 2.2;q 2.1). The translocation causes the formation of a new hybrid gene (bcr/abl) that codes for a 210 kb cytoplasmic protein (P210) that by autophosphorylation activates a number of signaling pathways involved in cell proliferation, maturation, apoptosis and adhesion, leading to the malignant cell transformation. The course of the disease goes on through a chronic phase (CP), usually lasting some years, that is characterized by a massive myeloid hyperplasia with hyperleukocytosis and splenomegaly. The CP is almost always followed by an accelerated or blastic phase (ABP) where the leukemic process acquires the characteristics of acute leukemia. The ABP usually lasts some months and terminates with the death of the patient. Imatinib mesylate (Glivec, Novartis) is a phenylaminopyrimidine derivative with specific property of binding to the ATP-docking site of the P210 oncoprotein, preventing autophosphorylation and all subsequent transforming effects. Imatinib has been investigated in phase II studies of CML in ABP and of CML in CP, resistant to or intolerant of alfaIFN, and in a phase III study (IRIS trial) where previously untreated patients are randomly assigned to imatinib or to a combination of alfaIFN and LDAC. The bulk of evidence of the efficacy of imatinib in CML comes from the results of clinical trials where imatinib was given alone in CML patients.

In 2003, the Italian Cooperative Study Group on Chronic Myeloid Leukemia (ICSG on CML) has launched two different protocols that are currently open to enrollment by 73 hematological institutions and our unit is among those participating centers.
Protocol ICSG/CML 021 is a phase II multicenter, open-label study designed to investigate the efficacy (hematological, cytogenetic and molecular responses) and feasibility of imatinib at high dose (800 mg/daily) in patients with Ph+ CML in CP previously untreated, at intermediate Sokal risk.
Protocol ICSG/CML 022 is a phase III multicenter, open-label study designed to investigate the efficacy and feasibility of imatinib at conventional dose (400 mg/daily) if compared with high dose (800 mg/daily) in patients with Ph+ CML in CP previously untreated, at high Sokal risk.
Both protocols are enrolling patients according to the investigation plan; however, clinical data on both protocols are not yet available.
Since the introduction of the vitamin A derivative all-trans retionoic acid (ATRA) in front line therapy, the outcome of **acute promyelocytic leukemia** (APL) has changed from the state of a most frequently fatal leukemia to the condition of a highly curable disease. The Italian cooperative group GIMEMA (comprising more than 50 hematologic institution, including our unit) designed in 1993 the AIDA (Atra + IDArubicin) protocol for newly diagnosed APL. Updated results on over 800 patients showed a CR rate >90% and an overall survival of 73%. These data show that the best results in terms of CR, EFS and DFS rates are obtained combining ATRA with chemotherapy during the induction treatment and that the concomitant administration of ATRA and chemotherapy is more effective than the sequential administration.
Following preliminary reports of the AIDA study, in 1996 the Spanish cooperative group PETHEMA designed a protocol for APL (LPA96) including ATRA and Idarubicin for induction as in the original AIDA protocol. However, differently from the Italian protocol, in the LPA96 study, the non-intercalating chemotherapy agents (cytarabine, VP-16 and 6-thioguanine) where excluded from the consolidation treatment, maintaining the same dose and sequence of IDA and mitoxantrone as in the AIDA. Moreover, all patients received maintenance treatment with methotrexate, 6-mercaptopurine and ATRA. A preliminary report of the PETHEMA showed that this modified regimen yielded similar results as compared to the original AIDA protocol and was associated with less toxicity. In order to identify the prognostic factors influencing the relapse-free survival (RFS), a joint study of the two groups was carried out which included all PETHEMA patients together with those patients in the GIMEMA AIDA series who had received the same maintenance (ATRA + MTX + 6-MP). This analysis indicated that initial leucocyte and platelet counts were the most relevant variables with independent prognostic factors for RFS in the multivariate analysis, allowing to stratify patients in different risk groups as follows:
Low risk (RFS ~ 100%): leukocytes <10.000/mmc and platelets > 40.000/mmc.
Intermediate risk (RFS ~90%): leukocytes < 10.000/mmc and platelets <40.000/mmc.
High risk (RFS ~ 70%): leukocytes> 10.000/mmc.
As a results of these findings, the GIMEMA cooperative group designed a new protocol named AIDA 2000 differentiating treatment intensity according to the relapse risk. With regard to the induction phase, the combination of ATRA and Idarubicin of the original protocol was not modified, in light of the excellent results previously obtained especially in terms of antileukemic efficacy (less than 1% of resistant cases). In the new protocol the most relevant modification from the original AIDA scheme is the new consolidation strategy. In the low and intermediate risk groups, the original PETHEMA schedule will be adopted, consisting of 3 sequential chemotherapy cycles as in the original AIDA protocol but omitting non-intercalating drugs (AraC and VP-16), with the aim of reducing toxicity. The classic consolidation schedule of the AIDA protocol will be utilized in the high risk group. All patients in the 3 risk categories will also receive ATRA during consolidation, on the basis of the suggested synergistic effect of this agent with chemotherapy.
As to the choice of maintenance there is no clear alternative to the AIDA protocol sched-

ule, consisting of daily mercaptopurine, weekly methotrexate and ATRA given for 15 days every 3 months, this type of maintenance being the best of the known regimens.
At present the study is open to the enrollment and clinical data are not yet available.
Despite advances in first-line treatment, relapsed and resistant APL is still a clinical reality. Various treatments have been explored, including ATRA, experimental chemotherapy, and antibody-targeted therapies, with varying success. Second CRs are seldom durable. However the outlook for patients with relapsed APL has been greatly enhanced by the recent introduction of arsenic trioxide (ATO) as a single agent for relapsed disease. Results from clinical trials using ATO in patients with relapsed APL are impressive: CR rates of 85% to 95% have been reported.
We published our experience on ATO treatment in eleven patients with advanced APL. Eight patients (73%) achieved hematologic complete remission (HCR) after induction treatment while three patients died of cerebral hemorrhage. All but one of the patients in HCR received one cycle of consolidation with ATO; among the 8 patients in HCR, 6 achieved molecular remission (MCR) after the first cycle of ATO and the remaining 2 after consolidation. As to follow-up, 1 patient was lost to follow-up after 2 months while in MCR, 1 patient did not receive any other treatment and relapsed after 3 months, 2 patients received further treatment with ATRA + Idarubicin and both relapsed after 3 and 4 months. The remaining 4 patients underwent transplant procedures: 2 received an autologous BMT and both relapsed, after 13 and 22 months, while 2 received an allogeneic BMT (1 died in MCR from second neoplasia after 20 months and 1 is still alive in MCR after 24 months). These data highlight the efficacy of ATO in advanced APL and the need to use allogeneic transplantation to consolidate the remission; results of ATO as front-line treatment of APL are awaited.
Modern combination chemotherapy in **acute myeloid leukemia** (AML) can induce a complete remission in 70-80% of adult patients (age less than 60 years), with 25 to 35% long-term leukemia-free survivors. Results in elderly patients are still consistently worse in terms of response rates, duration of response and survival time.
The improved results with alogeneic bone marrow transplantation using high-dose chemo-radiotherapy followed by stem cell infusion from an HLA identical sibling as well as recent results with some induction and consolidation schedules followed by autologous stem cell transplantation support a dose-response relationship in the treatment of AML. Nevertheless, depending on the type and stage of leukemia at the time of transplantation, 20% to 60% of patients will eventually suffer relapse, with the greatest risk in the first two years post grafting. Further intensification of the remission induction /consolidation program may help to decrease the relapse risk.
In the EORTC/GIMEMA trial AML-10, the value of intensification of the remission induction by one of the 3 intercalating agents (Idarucin vs Mitoxantrone vs Daunorubicine) in combination with standard dose AraC for 10 days and Etoposide for 5 days was tested. The final analysis of the study was presented at the 2003 ASH meeting in San Diego (December 2003). Complete response rate was 72% and no significant difference (in terms of CR) was detected between the three arms. Toxicity consisted of 3 weeks of pancytopenia, frequent severe oral and gastrointestinal mucositis, infections and skin abnormalities. Induction death rate was 14%. The consolidation regimen consisted of intermediate dose Ara-C (0.5 g/sqm every 12 hr for 12 doses) combined with an anthracycline (the same as was used in the induction course). This regimen was well tolerated with a mortality rate of less than 5%. Subsequently, harvest of autologous peripheral stem cells in patients without an HLA-identical donor was successful in 65% of cases. The daunorubicin arm showed the highest percentage of patients in which stem cells can be harvested (79%) and transplantation could be performed. Current relapse rate is 50% in patients for whom an autologous stem cell transplantation should be performed in first CR and 25% for those receiving an allogeneic stem cell transplantation.
An increase in the CR rate after the induction, improvement of the applicability of a stem cell transplantation, a reduction in the relapse rate, and monitoring of minimal residual disease are the main aims of the current phase III randomized trial of the EORTC/GIMEMA (AML 12).

A reduction of the relapse risk in comparison with the AML-10 trial may be achieved through further intensification (high dose Ara-C) of the induction phase and by immunological manipulation of the post-transplantation phase (Interleukin-2). Improvement of the stem cell harvest procedure and subsequent transplantation may be realized by decreasing the stem cell damage by choosing the least stem cell toxic intercalating agent for the consolidation course (according to AML 10) and allowing SCT with autologous peripheral blood stem cells. However, the intercalating agent may be changed if one of the future analyses of the AML-10 protocol detects a superior arm.
All patients with an HLA identical family donor will undergo an allo-SCT. In the small subgroup of patients with high-risk leukemia under the age of 40 even a SCT with stem cells of an unrelated donor will be allowed.
In recent years, Rituximab has been widely tested as single agent or in combination with the CHOP regimen for the treatment of patients with newly diagnosed aggressive **non-Hodgkin's lymphoma** such as diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma. Synergism may be demonstrated with other chemotherapy regimens. In our phase II study, presented at the XXXIX Congress of the Italian Society of Hematology on October 26-29,2003, eleven patients with previously untreated DLBCL received Rituximab from the 9th to 12th week of the MACOP-B regimen as intensification. The objectives of the trial were to evaluate the safety and efficacy of the addition of Rituximab to the conventional MACOP-B regimen for young adult patients with previously untreated DLBCL. Response was evaluated before the 1st administration of Rituximab and at the end of the combination regimen. Of the 11 patients, 8 were in partial remission at the beginning of Rituximab and 3 were in complete remission. Two patients died during treatment with Rituximab: 1 of acute liver failure following HCV-related hepatitis and 1 of acute heart failure 3 days after the end of the immuno-chemotherapy treatment. Of the 9 patients evaluable at the CT evaluation performed 1 month after the MACOP-B/Rituximab, 8 were in complete remission and 1 patient showed progressive disease. Although a significantly larger number of patients and longer follow-up are requested, the MACOP-B/Rituximab schedule seems to be an effective and feasible combination for the treatment of aggressive B lymphomas.

Publications 2003

Breccia M., Carmosino I., Diverio D., De Santis S., De Propris M.S., Romano A., Petti M.C., Mandelli F., Lo-Coco F

Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count.

Br. J. Haematol. 2003 Jan;120(2):266-70. *I.F. 3.052*

De Sanctis V, Mazzucconi MG, Spadea A, Alfo M, Mancini M, Bizzoni L, Peraino M, Mandelli F.

Long-term evaluation of 164 patients with essential thrombocythaemia treated with pipobroman: occurrence of leukaemic evolution.

Br J Haematol. 2003 Nov;123(3):517-21. *I.F. 3.052*

Girmenia C., Lo Coco F., Breccia M., Latagliata R., Spadea A., D'Andrea M., Gentile G., Micozzi A., Alimena G., Martino P., Mandelli F.

Infectious complications in patients with acute promyelocytic leukaemia treated with the AIDA regimen.

Leukemia. 2003 May;17(5):925-30. *I.F. 4.693*

Lo-Coco F, Romano A., Mengarelli A., Diverio D, Iori AP, Moleti ML, De Santis S, Cerretti R, Mandelli F, Arcese W.

Allogeneic stem cell transplantation for advanced acute promyelocytic leukemia: results in patients treated in second molecular remission or with molecularly persistent disease.

Leukemia. 2003 Oct;17(10):1930-3. *I.F. 4.693*

Mandelli F., Latagliata R., Avvisati G., Fazi P., Rodeghiero F., Leoni F., Gobbi M., Nobile F., Gallo E., Fanin R., Amadori S., Vignetti M., Fioritoni G., Ferrara F., Peta A., Giustolisi R., Broccia G., Petti M.C., Lo-Coco F.

Italian GIMEMA Cooperative Group. Treatment of elderly patients (> or =60 years) with newly diagnosed acute promyelocytic leukemia. Results of the Italian multicenter group GIMEMA with ATRA and idarubicin (AIDA) protocols.

Leukemia. 2003 Jun;17(6):1085-90. *I.F. 4.693*

Division of radiotherapy

DIRECTOR:
GIORGIO ARCANGELI, MD

Prof G. Arcangeli received his MD degree in 1965. He specialized in Gastroenterology in 1967, University of Rome and in Radiology in 1969 at the University of Cagliari.
From 1970 to 1974 he worked as Researcher; and from 1974 to 1976 as Assistant Professor in the Division of Radiotherapy IRE, Rome. From 1977 to 1985 he was Head of the Department of. Radiotherapy, Ist. Doctor of Scientific Research, Rome and from 1985 to 1996 of the Department of Radiotherapy S. Maria Goretti Hospital, Latina. Since 1996 he has been the head of the Department of Radiation Oncology IRE, Rome. From 2001 to 2003 he was the Head of the Department of Medical Oncology, IRE, Rome.
He is member of the following associations: American Society of Clinical Oncology (ASCO); American Society of Therapeutic Radiology and Oncology (ASTRO); American Radium Society (ARS); European Society for Hyperthermic Oncology (ESHO); European Society for Therapeutic Radiology and Oncology (ESTRO); Soc. Italian Society for Research into radiation (SIRR); EORTC Radiotherapy Group; New York Academy of Sciences; the Italian Ass. of Medical Oncology (AIOM); Medical Soc. for Lazio; Italian Ass. of Oncologic Radiotherapia.
In 2002-2003 he was President of the "Associazione Italiana di Radioterapia Oncologica Sezione Lazio/Abruzzo"; and 2003 Vice president of the "Società Italiana di Urologia Oncologica" (SIUrO).
Prof Arcangeli's main interests are: the treatment of Prostate and Head and Neck Cancer, and the use of Intensity Modulated Radiation Therapy.

Director:
GIORGIO ARCANGELI - M.D.

Time limited contract physician:
SARA GOMELLINI - M.D.

Staff:
FABRIZIO AMBESI IMPIOMBATO - M.D.
ROSARIA DEL VECCHIO - M.D.
PAOLA PINNARÒ - M.D.
GIUSEPPE GIOVINAZZO - M.D.
BIANCAMARIA SARACINO - M.D.
RITA RAMBONE - M.D.
MARIA ALESSANDRA MIRRI - M.D.
MARIA GRAZIA PETRONGARI - M.D.
ADRIANA MICHELI - M.D.
LAURA MARUCCI - M.D.

Physicians in training:
ANTONIO FARELLA
MAURO MESSINA
CATERINA VACCARO
MICHELA BENASSI
TERESA PARRETTA
CAROLINA GIORDANO

Activities 2003

The recent installation of high technology equipment in our division allowed us to start several clinical studies to implement and validate the latest radiation therapy techniques in the treatment of various cancer sites.
IORT STUDIES: this technique was implemented thanks to a movable, dedicated linear accelerator installed in the operating room.
Prostate cancer: Since February 2002 we have been conducting a dose-finding study in patients with intermediate risk prostate cancer, who underwent radical prostatectomy. Initially 3 groups of 6 patients were treated with doses of 16 Gy, 18 Gy and 20 Gy, following a dose-escalation program by Fibonacci. As no acute or subacute toxicity was observed, 10

more patients were treated with the highest tested dose of 20 Gy and, again no toxicity was observed. We decided to increase the dose to 22 Gy.
Breast cancer: in March 2003 a national multicenter trial on the use of IORT in breast cancer was started under the co-ordination of our division. Post menopausal patients who have undergone conservative surgery for small mammary carcinomas are randomized to receive IORT on the tumor bed or conventional EBRT. The main objective of this study is to evaluate the local recurrence *rate* and second ipsilateral tumors, as well as the local recurrence free interval. Seventy five patients were accrued in this study (23 from our institute).

HEAD AND NECK: PROPOSED PROTOCOLS:

Feasibility Study on the use of Intra-Operative Radiation Therapy (IORT) as an 'early boost' on locally advanced head and neck cancers.

IORT is a technique that permits the delivery of a single dose of radiation (electrons) on the tumor bed immediately after resection without any delay. This technique also consents to better spare the organ at risk thanks to the possibility of removing or shielding the same from the radiation field and the typical electron limited dose penetrance.
The goal of our study is to evaluate the feasibility and eventual side effects of this modality used as a dose boost on the tumor bed in patients with locally advanced tumors (>T3 or >N2) of the oral cavity, oropharynx, hypopharynx and larynx that undergo resection with curative intent. Standard post operative 3D wide field radiation therapy will follow for all the patients.
The protocol was approved by the ethical committee and the patients accrual started in 2004.

Feasibility study on the integrated use of Salvage Surgery, Intra-Operative radiation Therapy (IORT) and External Beam Radiation Therapy (EBRT) on head and neck cancers recurred after radiation therapy.

The prognosis of patients with head and neck cancer, relapsing after radiation therapy are dismal. Surgery alone can rarely achieve a complete resection and an external beam cannot be used with curative doses because of the limited tolerance of the organ at risk.
As with the previous protocol, IORT is used at the end of the resection with the intent of delivering a single tumoral dose and at the same time spare organs at risk. The goal of our study was to evaluate the feasibility and eventual side effects of this modality used to improve local control in otherwise palliative patients. External beam radiation therapy will follow where possible. Six patients have been enrolled in the study. No complications have been registered.
The protocol was approved by the ethical committee and the patients accrual started in 2004.

IMRT STUDIES:

Head and Neck cancer:

Observational Study on Xerostomia evaluation on patients with oral cavity and oropharyngel cancer treated with Intensity modulated radiation therapy (IMRT).

IMRT is a relatively new, complex technique that allows the delivery of a highly conformal dose to the target with a better sparing of organs at risk, such as the parotids. The goal of our study is to evaluate a patient filled questionnaire, both subjectively and objectively, through the collection of the saliva before and up to 12 months after the end of the treatment, which is the real efficacy of this technique in reducing xerostomia and improving the patient's comfort.
The ethical committee has approved the protocol and patients accrual has already started.

PROSTATE CANCER:

Observational study on the accuracy and reproducibility of the IMRT technique in patients treated for prostate cancer

The aims of the present study are to evaluate the effect of set-up errors and organ motion on DVHs and to introduce radiobiological considerations by evaluating Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) in a group of patients undergoing IMRT for prostate cancer.
12 patients have already been enrolled in the study

PROSTATE CANCER:
An institutional, multidisciplinary project with the participation of the radiation oncology, urology, radiology, pathology, physics, and gastroenterology division, has already been conducted in our institution with the aim of establishing standard evaluation methods and criteria for all future planned studies on prostate cancer.
Phase II randomized study of hypofractionation versus standard fractionation radiotherapy in unfavorable risk prostate cancer:
The study started in February 2003. All patients undergo Total Androgenic Suppression and are randomized to receive 62 Gy in 20 fractions in 5 weeks, or 80 Gy in 40 fractions in 8 weeks by 3-D conformal radiotherapy. The main objective of this study is the evaluation of the biochemical control, acute and late toxicity. One hundred and eighty patients are required for the specimen size. Fifty patients have been accrued in this study to date.
Phase II randomized study on the use of anti Cox 2 vs standard treatment to reduce the acute radiation therapy and late side effects in prostate cancer.
The patients are randomized between the standard supportive treatment and the use of COX 2 inhibitors throughout the entire treatment and then after a week. The aim of the study is to evaluate the eventual reduction of rectal and genito urinary acute and late side effects.
The ethical committee has approved the protocol and patients accrual was started in 2004.

BREAST CANCER:
Prospective phase III randomized study of immediate versus delayed radiotherapy in patients undergoing conservative surgery and CMF chemotherapy:
The objective of this study was the evaluation of the efficacy and tolerance of 2 different radiotherapy timings in patients receiving adjuvant CMF. The study started in January 1998 after the accrual of 207 patients and ended in December 2003 because of the very low accrual of CMF patients in the last year. The results are currently under analysis and will be published as soon as the evaluation is completed.
Observational study on correlation between the 2-D and 3-D measurement of the irradiated lung in the postoperative treatment of breast cancer
The objectives of the study are to look for a correlation between a 2-D and 3-D lung volume and to evaluate the normal tissue complication probability for the organs at risk using mathematical models. The study started in September 2003 and 143 patients have been accrued to date.

RECTAL CANCER:
For several years our division has been participating in a departmental and interdepartmental project on the use of chemo-radiotherapy to obtain sphincter preservation in locally advanced rectal cancer. Several studies have already been published by our institution.
Our institute is presently participating in a multicenter phase III trial of preoperative Raltitrexed + Oxaliplatin + RT (TOMOXRT) VS. CDDP + 5FU + RT (PLAFUR) in extra-peritoneal T3 rectal cancer. The purpose of this study is to comparatively evaluate the downstaging ability of the chemo-radiotherapy combinations. Eighteen patients were accrued for this study by our institute.

BONE METASTASIS:
Randomized study between two different fractionation schemes in patients with symptomatic bone metastasis.

The patients with symptomatic bone metastasis enrolled in the study are randomized to receive 1 single fraction of 800cGy or a single fraction of 800cGy plus another 4 fractions of 400cGy. The aim of the study is to evaluate which fraction is more effective in decreasing or eliminating the symptoms using the VAS score and the Barthel index.

BRAIN TUMORS:

Phase II trial of dose finding on the concomitant use of Radiotherapy and Gemcitabine in the treatment of malignant gliomas.

The aim of the study was to evaluate the limiting dose-toxicity and the maximum tolerated dose of Gemcitabine in association with radiotherapy in patients affected by glioblastoma multiforme with measurable residue after surgery or biopsy. The planned total dose of radiotherapy is 60 Gy delivered in 2 Gy per. Gemcitabine is administered weekly during the 6 weeks of treatment.

Since November 2003 nine patients have been enrolled in this study. In the first dose level (200 mg/mq/min) there were two possible treatment-related toxicities, therefore the doses for the next three patients were reduced to 175 mg/mq for 4 weeks instead of 6 weeks. As there were no major toxicities with that schedule of treatment, in the last three patients the 175 mg/mq dose was extended for 6 weeks. The study is ongoing.

Division of Radiology and Diagnostic Imaging

DIRECTOR:
MARCELLO CRECCO, MD

Marcello Crecco, 54, graduated in medicine in 1974 at La Sapienza University, Rome. From May 1975 to April 1976 he worked as a junior registrar in the intensive care unit at the Catholic University, Rome. From August 1976 to July 1977 he served as a second lieutenant medical officer and from July 1978 to July 1979 he worked as a radiologist at the Policlinico Umberto I University Hospital, Rome. From July 1979 to August 1989 he was a radiologist in the Department of Diagnostic Radiology at the Regina Elena Institute, Rome and from September 1989 to December 1999 he worked as Senior Radiologist at the Regina Elena Institute, Rome. From November 1999 he was given a five-year appointment as Consultant Radiologist at the Department of Diagnostic Radiology at the Regina Elena Institute, Rome. He specialized in Radiology (Diagnostic, Radiotherapy, Nuclear Medicine) in 1984 and in Oncology in 1988 at La Sapienza University, Rome. He lectured in Diagnostic Radiology at Tor Vergata University in 1990-91, 1991-92, 1993-94. He has participated in many professional refresher courses, congresses and seminars. He was responsible for the Research project CNR ACRO in Instrumental Diagnosis "Clinical applications of oncological research". He is the author of numerous publications.

Staff:

LAURA ANGELONE - M.D.
MAURO CATERINO - M.D.
LIVIO CARPANESE - M.D.
CARLO DE MUTIS - M.D.
FRANCESCA ROMANA FERRANTI - M.D.
SALVATORE GIUNTA - M.D.
MARCELLO GRECO - M.D.
RAMY KYAL - M.D.
ANTONIETTA MAZZONE - M.D.
GIUSEPPE PIZZI - M.D.
ELENA SARACCA - M.D.
MIRELLA TERAMO - M.D.
GIULIO VALLATI - M.D.
ANTONELLO VIDIRI - M.D.

Activities 2003

The activity of the Division of Radiology is organized according to interest areas regarding organ pathology as well as multidisciplinary areas such as pre-hospitalization or interventional radiology.
During 2003 approximately 50,000 radiological examination, 6,500 mammography and 460 CT of the Thorax for screening were performed.

ABDOMINAL IMAGING

A study about the use of superparamagnetic iron-oxide in the evaluation of liver colorectal metastases has been closed. The purpose of the study was to compare the results obtained with iron-oxide MR and plain-MR with that of spiral CT in order to select patients for liver resection; intraoperative-echothomography being the gold standard.
Another study on the evaluation of primitive and secondary liver lesions with Mn-DPDP contrast medium has been carried out. The purpose of this study was to recognize small dimension lesions (< 5 mm) and also a possible characterization.
Regarding liver metastases, a study comparing bidimensional versus 3D measurements with volumetric spiral-CT was performed. Our preliminary results show the superiority of 3D measurement (in particular in lesions with irregular edges).
From November 2003 our Radiology Service has taken part in an Italian multicenter study, based on 18 Groups, selected from 50 university and hospital centers, promoted by SIRM (the Italian Society of Medical Radiology) with the aim of identifying hepatic metastasis through echothomographic contrast medium.

Specific studies on hepatic metastases in colorectal disease are being carried out on patients treated with different chemiotherapics concerning the drug used and the administration method (bolus, chronomodulated. Director Lévi F. (Villejuif) EORTC
In collaboration with the Department of Abdominal Surgery, a study is underway regarding the evaluation of hepatic vascular anatomy with CT angiography in liver transplant patients to compare it with digital angiography.
The Radiology Service is taking part in the following plans:
1) "Impact of biological profile, chemoradiation and surgery of rectal cancer on downstaging and quality of life". AIRC Coordinator: Dr. Maurizio Cosimelli.
2)" Clinical impact of an innovative strategy of adjuvant therapy in high risk Aster Coller B2 colorectal cancer patients selected by biological profiles" AIRC Coordinator: Dr.Maurizio Cosimelli.
3) 'The role of new biomolecular markers of liver cancer on cirrhosis in relation to the efficiency of different therapies'. Coordinator: Prof E. Santoro.
4) Neuroendocrine tumors of the digestive system: clinical-pathological coordinator: Dr P. Perri
Recently a cooperation was initiated with La Sapienza University (Prof. R. Passariello) concerning virtual colonoscopy with spiral-CT.

Senologic imaging and breast mini invasive diagnostics

A research project: 'A screening program for the identification and prevention of breast tumors in subjects at high genetic risk has been carried out. The project was initiated by the Ministry for Health and will be concluded in 2004. The scientific director of the project is Prof Franceso Cognetti and the operative unit service is taking part with Dr Marcello Crecco in charge.
In the field of mini-invasive diagnostics, biopsy technologies with new needles with greater caliber, about 8 G. as opposed to the previous 11 G using the digital stereotactic breast biopsy systems with forced vacuum (Mammotome). A positive response was obtained in 50 cases following 155 procedures with stereotactic biopsies with Mammotome.

Neuroradiology - Head and Neck Imaging

In 2003 research data was published regarding the clinical benefit and radiological response of treatment with Temozolamide on low-grade neoplasias, both in the form of an abstract at international congresses such as A.S.C.O and the European Congress of Neurosurgery and as publications in the Annals of Oncology.
The study relating to the MR evaluation of high-grade early glial neoplasia is drawing to a close.
A study in collaboration with the Department of Radiotherapy is underway regarding the possibility of the fusion of MR and CT stereotactic in glial brain tumors and pharyngeal tumors with the aim of obtaining more precise and limited irradiation fields. Only a few patients have been enrolled in the study this year in order to evaluate its feasibility.
A study regarding the evaluation with MR of the response to treatment of combined radiotherapy and extended infusion of Gemcitabine in the treatment of multiform glioblastoma was initiated in collaboration with the Department of Radiotherapy, Clinical Oncology A, Neurosurgery and Neurology.
The Department of Radiology is taking part in the Interphone Study. This study has been commissioned by the WHO and coordinated by the International Cancer Research Agency in Lyon. It regards a case-controlled study of the eventual association of the use of mobile phones and the incidence of tumors in organs closest to the source of radio frequency (RF).
In collaboration with the Department of Maxillo-Facial surgery a study is underway regarding the comparative evaluation of MR, T clinical and T pathological reports in the study of patients with mouth and oropharynx tumors.

In addition, a study which includes the Departments of Diagnostic Radiology, Radiotherapy, Maxillo-Facial surgery, Clinical Oncology A and Histology has begun. This study concerns MR evaluation of the patients undergoing chemo-radiotherapy for oropharynx neoplasms.

Angiography Imaging and Interventional Radiology
Percutaneous tumor ablation with radio frequency.
In 2003, following current trends and technological and material developments, patients with inoperable lung and renal tumors were enrolled in the study. In accordance with emerging indications, the patients with secondary osteo structural lesions, painful and resistant to analgesic treatment, underwent treatment with RF with percutaneous ablation.
Percutaneous treatment of ureteral stenosis through self expandable metallic stents were routinely performed, such as treatment with self expandable metallic stents in malignant bilary obstruction in patients with controindications for surgery.
In collaboration with the Department of Urology, a study about pre-surgical embolization of renal tumors undergoing laparoscopic surgery is underway

Urologic and Gynecologic Imaging
In 2003 an interdisciplinary prostate work group was set up and coordinated by Prof. Arcangeli. The aim of the project was to optimize radiotherapy for prostate carcinoma with conformational techniques. In the project, diagnostic radiology utilized the multicore method with transrectal echothomography in collaboration with pathologists and urologists. This method allows a large number of bioptic samples from the prostate (up to 20) with a greater accuracy in the detection of nodules and grading.
A trial regarding the study of the T stage of bladder tumors with spiral CT with air insufflation was concluded.
Another study for the evaluation of cervical tumors before and after chemo-radiation therapy with MR is ongoing

Thoracic Imaging
The study "Low dose spiral CT in the early diagnosis of lung cancer in patients at risk" (sponsored by Enel-AdR-Telecom) has enrolled 725 patients. Of these more than 260 have undergone multiple examinations. The aims of the study are: a) to assess the incidence and the radiological characteristics of cancers revealed at an early stage b) to assess the disease free and global survival rate in subjects with stage I and II lung cancer d) to evaluate the impact of screening on the quality of life and smoking cessation The study is part of ELCAP (International Early Lung Cancer Action Program) which involves numerous international institutions and has its headquarters in New York at Cornell University (Director: Prof. C. Henscke).
In addition, a Siemens prototype CAD for the automatic observation of pulmonary nodules has been tested. Some previously screened cases were evaluated. The sensitivity of radiological reading alone was 35%, while radiological reading + CAD showed a sensitivity of 93%.
The Radiology Department, is participating in a project directed by the Ministry for Health, "Proposal for a lung cancer screening program for the Regione Lazio"

Publications 2003

E Galiè, A. Pietrangeli, M. Maschio, A. Pace, A. Vidiri, M. Carosi, B. Jandolo
Demyelinating disease in monoclonal gammopathy of undetermined significance.
J Exp. Clin. Cancer Res. 22, 2: 337-339, 2003.

A. Pace, A. Vidiri, E. Galiè, M. Carosi, S. Telera, A.M. Cianculli, P. Canalini, D. Giannarelli, B. Jandolo, C.M. Carapella.

Temozolamide chemoterapy for progressive low-grade glioma: clinical benefits and radiological response.

Annals of Oncology 14:1722-1726, 2003.

Mancini R, Tedesco M, Garufi C, Filippini A, Arcieri S, Caterino M, Pizzi G, Cortesi E, Spila A, Sperduti I, Cosimelli M.

Hepatic arterial infusion (HAI) of cisplatin and systemic fluorouracil in the treatment of unresectable colorectal liver metastases.

Anticancer Res. Mar-Apr;23(2C):1837-41, 2003.

Division of nuclear medicine

DIRECTOR:
CARLO LUDOVICO MAINI, PHD

Prof Maini received his MD from the University of Rome in 1975, and then specialized in Nuclear Medicine, Cardiology and Diagnostic Radiology. He worked as assistant Professor of Nuclear Medicine at the Catholic University of Rome till 1987 when, after receiving a PhD in Radiology and Nuclear Medicine, he moved as associate Professor of Nuclear Medicine to the University of Ancona.
His Research activity in Nuclear Medicine led to over 350 publications with over 95 published in international peer-reviewed journals.
From 1992 he developed and organized the Nuclear Medicine Division at Regina Elena National Cancer Institute in Rome. This Department, staffed by young and energetic physicians from different professional backgrounds, has achieved national and international standards in nuclear oncology including therapy with unsealed sources and a leading-edge thyroid clinic practice.

Staff:

ROSA SCIUTO - M.D. Deputy Director and Head of Radiometabolic Therapy Unit
ANNA FESTA - M.D. Assistant
ROSELLA PASQUALONI - M.D. Assistant
SANDRA REA - M.D. Assistant
ALESSANDRO SEMPREBENE - M.D. Assistant
ANNA TOFANI - M.D. Assistant
SERENELLA BERGOMI - M.D. Assistant
LUISA ROMANO - M.D. Assistant
GIANLUCA LOPES - Chief Technician

Activities 2003

The activities of the Nuclear Medicine Division are focused on clinical research oriented to therapy and diagnostics. Therapy includes radionuclide treatment of thyroid carcinoma, neuroblastoma, pain from bone metastases and lymphoma. Diagnostics includes, besides routine oncological studies, radioreptorial scintigraphy with ^{111}In-octreotide and ^{99m}Tc-depreotide, sentinel node mapping, cardiac gated-SPET and neurological DAT scanning. In 2003 a total of 13,800 therapeutic and diagnostic procedure were performed with more than 390 cancer radionuclide treatments.

1. ADJUVANT RADIOIODINE THERAPY SIGNIFICANTLY IMPROVES SURVIVAL AND DECREASES MORBIDITY OF BOTH HIGH AND LOW RISK DIFFERENTIATED THYROID CANCERS: A RETROSPECTIVE ANALYSIS ON A SERIES OF 1,350 PATIENTS

Our main clinical and research interest from 1992 until today has been focused on thyroid cancer management and the role of radioiodine therapy. Current studies on radioiodine efficacy, demonstrating decreased recurrence and disease-specific mortality are largely confined to higher risk populations and strongly biased by inhomogeneous criteria of treatment and evaluation. We investigated the role of adjuvant radioiodine therapy (ARIT) routinely performed after surgery on a large series of differentiated thyroid cancer (DTC) homogeneously managed and evaluated at a single institution. A cohort of 1,350 patients with DTC, directly managed by the IRE Nuclear Medicine Division from 1992 until today, was retrospectively analyzed. Complete data were available in over 1,300 patients and evidenced that ARIT routinely performed after surgery significantly impacts on DTC clinical management as:

- post-operative pTNM staging system understages DTC patients, particularly low-risk T1 patients so that diagnostic and post-therapeutic ^{131}I whole-body scan is mandatory to avoid possible undertreatment
- radioiodine therapy improves recurrence rate and specific cancer mortality both in low-risk and high risk patients.

These data are currently in press.

2. VALUATION OF THE COST-EFFECTIVENESS OF RECOMBINANT HUMAN TSH IN THYROID CANCER FOLLOW-UP

The large experience in the use of recombinant human TSH obtained in over 400 patients

followed at our Institution for differentiated thyroid cancer led to technical and health-economy optimization of the procedure, as formalized in the I.R.E Guidelines for differentiated thyroid cancer management.

3. Radionuclide therapy for bone pain palliation in skeletal metastases

Personal experience includes more than 450 treatments for bone metastases performed with all the three available bone seeking radioisotopes (^{89}Sr; ^{186}Re; ^{153}Sm) from late 1992 using the same clearly defined criteria for entry into the treatment and for response evaluation. This rigorous standardized and reproducible methodology has produced a great wealth of comparable data leading to impressive original contributions in this field. The results contribute both in clarifying clinical indications using standard procedures and exploring innovative strategies by a series of clinical trials. In addition, a focus on radiation protection issues has been summarized for national guideline purposes and is in press. In particular, published results in 2003 were a review of our experience with the three commercially available radionuclied and original data on ^{153}Sm-EDTMP obtained in over 80 treatments performed in 60 patients with painful bone metastases from different tumors.

4. Staging of neuro-endocrine tumors (NET) using somatostatin receptor scintigraphy.

Somatostatin receptor scintigraphy (SRS) is considered the gold standard imaging procedure in patients with NET. Our group is considered a referral center for radioreceptorial scintigraphy having the largest series of NET patients (> 400 pts.) in Italy.

In the first study we determined the diagnostic accuracy and the ability to modify the surgical management of CT, alone or combined with SRS and demonstrated that both techniques should be used in the pre-operative work-up of digestive endocrine tumors. Further results of our experience confirm the primary role of SRS also in the post-operative follow-up and specifically for the following indications:- identification of the site of unknown primitive tumor in patients with clinical evidence of NET or histological diagnosis of metastasis from NET; - early diagnosis of recurrence in patients with negative CT/RM; - monitoring of clinical response after somatostatin analogues and/or radioreceptorial therapy with ^{90}Y-DOTATOC; - re-staging of disease after recurrence; - selection of patients eligible for radioreceptorial therapy with ^{90}Y-DOTATOC.

Our Division in also involved in a Italian multicenter trial on NET diagnosis and therapy (CROMaNET) aimed at evaluating the validity of cromogranine A as marker for disease monitoring.

5. Imaging of dopamine transporter with 123I-FP-CIT SPET in movement disorders

Imaging with specific single positron emission computerized tomography ligands for dopamine transporter (FP-CIT) provides a marker for presynaptic neuronal degeneration and could be used for this reason in the assessment of dopamine system disorders. Our experience in this field was focused on the evaluation of the utility of ^{123}I-FP-CIT SPET in clinical settings in the differential diagnosis between Parkinson's disease (PD), atypical parkinsonism (AP) and essential tremor (ET). The preliminary results obtained in twenty-five patients (age range 45-79 years) with movement disorders confirm that the ^{123}I-FP-CIT SPET is a sensitive diagnostic tool for the evaluation of the integrity of the nigro-striatal dopaminergic pathway and to differentiate ET from PD-AP.

6. Efficacy of 99m Tc-depreotide scintigraphy in the evaluation of solitary pulmonary nodules.

^{99m} Tc- depreotide is a peptide analogue of a somatostatin receptor that preferentially binds to somatostatin receptors 2, 3, and 5, recently FDA-approved for use in the evaluation of indeterminate solitary pulmonary nodules. Our experience, including about thirty patients referred for solitary pulmonary nodes and followed after surgery, confirms the effectiveness of this method to in vivo characterization of lung nodes, avoiding unnecessary biopsies.

7. Lymphoscintigraphy in breast, vulvar and colon cancer

The sentinel node (SN) procedure has emerged as an alternative to systematic lymphadenectomy in various cancers, reducing treatment-related morbidity. In melanoma this

procedure is now routinely performed and in other tumors in under evaluation. In our Division we obtained a large experience in a broad spectrum of tumors, including breast, colon, vulvar, penile, head-neck in addition to melanoma with excellent results.

Selected publications 2003

MAINI CL, SCIUTO R, ROMANO L, BERGOMI S.

Radionuclide therapy with bone seeking radionuclides in palliation of painful bone metastases.

J Exp Clin Cancer Res 22 (4 Suppl.): 71-74, 2003

PANZUTO F., FALCONI M., NASONI S., ANGELETTI S., MORETTI A., BEZZI M., GUALDI G., POLETTINI E., SCIUTO R., FESTA A., SCOPINARO F., CORLETO V.D., BORDI C., PEDERZOLI P., DELLE FAVE G.

Staging of digestive endocrine tumors using helical computer tomography and somatostatin receptor scintigraphy.

Annals of Oncology 14: 586-591, 2003

SCIUTO R, FESTA A, PERRI P, MAINI C.L.

Scintigrafia radioreettoriale con 111-In-Octreotide (Octreoscan).

In: I tumori neuroendocrini Ed. Club delle UEC- Torino. 2003. Cap. I, pagg 42-46

Laboratory of Clinical Pathology

DIRECTOR:
FIORELLA GUADAGNI, MD

Fiorella Guadagni received her M.D. degree (summa cum laude) in 1983 at the University of Perugia, then completed a postdoctoral fellowship at the Laboratory of Immunopharmacology, Italian National Council of Research, Rome. Specialized in Oncology (summa cum laude) at Tor Vergata University of Rome in 1987 and in Clinical Pathology (summa cum laude) at La Sapienza University of Rome in 1996. In 1985 she joined the Laboratory of Tumor Immunology & Biology, National Cancer Institute, N.I.H., Bethesda, MD, USA as a Fogarty fellow, and in 1988, was appointed as a visiting scientist. In 1991 she joined the Laboratory of Cellular Metabolism, Regina Elena National Cancer Institute, Rome as a senior staff researcher. From 1993 to 2000 she worked as a senior staff member and from 2000 to date as Director of the Laboratory of Clinical Pathology, Regina Elena National Cancer Institute of Rome.
From 1997 she has also been a Contract Professor in 'Tumor Immunology' at the Oncology School, School of Medicine, Tor Vergata University of Rome, and in 'Biotechnologies in Oncology', at the 'Oncobiopathology School', School of Medicine, University of Palermo.
Her major scientific interest is focused on translational research involving the design of new diagnostic strategies for human cancer. Firstly, developing several types of new immunoassays to better evaluate the presence of circulating tumor antigens potentially useful in monitoring human cancer. Recent research interests have broadened to include the investigation of different pro-inflammatory cytokines involved in cancer. More recently, her scientific interest has been dedicated to studying novel cancer diagnostic strategies, with emphasis on the identification and development of molecular diagnostics tools.
Dr Guadagni has been and is currently the principal investigator and/or coordinator of numerous studies granted by governmental and scientific organizations and a member of several national and international scientific societies and Editorial Boards as well as a reviewer of several Peer-Reviewed Scientific Journals.

Staff:
IOLE CORDONE - M.D., PHD
LAURA CONTI - M.D., PHD
ANNA CIANCIULLI - PHD
ANNAMARIA FRASCA - M.D.
GIOVANNA DIGIESI - M.D.
GABRIELLA D'ALESSANDRO - PHD
CLAUDIA GRECO - PHD
TINA ROSITO - PHD
GAETANO VITELLI - M.D.
GIOVANNI CIGLIANA - PHD
GIOVANNI CATALANI - PHD
RAFFAELE PALMIROTTA - M.D., PHD
CARMINE PARRACINO - M.D.
SPILA ANTONELLA - PHD Fellow
D'ALESSANDRO ROBERTA - PHD Fellow
VERCILLO GIUSEPPE - M.D. Fellow
MEROLA ROBERTA - PHD Fellow
ORLANDI GIULIA - PHD Fellow

Activities 2003

Research efforts of the Laboratory of Clinical Pathology involve the evaluation and development of novel laboratory tools useful in the diagnosis and monitoring of human cancer. The Scientific activities of 2003 include:
Platelet activation, commonly found in human cancer patients, may cause the release of angiogenic factors, such as vascular endothelial growth factor (VEGF-A). Our recent study was designed to investigate whether plasma VEGF-A levels were associated with different stages of non-small cell lung cancer (NSCLC). Moreover, sP-selectin, prothrombin fragment 1+2 (F1+2), thrombin-antithrombin III complex (TATc) and D-dimer levels were

measured to test the hypothesis of an involvement of platelet and coagulation activation in tumor angiogenesis. VEGF-A, sP-selectin, F1+2, TATc and D-dimer levels were elevated in patients with NSCLC, particularly in metastatic patients. sP-selectin ($p < 0.003$) and F1+2 ($p < 0.005$) levels were independently associated with VEGF-A. In addition, patients with positive levels of both sP-selectin and F1+2 had the highest levels of VEGF-A. In conclusion, our findings support the hypothesis that thrombin generation might induce platelet activation and VEGF-A release in NSCLC. We were also interested to analyze the behavior of pre-surgical serum levels of soluble (s)E-selectin and vascular cell adhesion molecule (sVCAM) in patients with colorectal cancer, and to evaluate their possible correlation with carcinoembryonic antigen (CEA), pro-inflammatory cytokines and clinicopathological features with respect to their prognostic value in predicting metastatic disease. Pre-surgical serum levels of sE-selectin, sVCAM, interleukin-6 (IL-6), IL-1beta, tumor necrosis factor-alpha(TNF-alpha) and CEA were measured in patients with colorectal adenocarcinoma and benign colorectal diseases as well as healthy subjects. sE-selectin, sVCAM, TNF-alpha and IL-6 levels were significantly higher in patients with colorectal cancer compared to either healthy subjects or patients with benign disease. Positive rates of sE-selectin, sVCAM and TNF-alpha levels were significantly associated with Dukes' stage D colorectal cancer, and all three variables were independently associated with the presence of distant metastases. Positive sE-selectin, sVCAM and TNF-alpha levels were significantly associated with CEA. TNF-alpha and CEA levels were independently related to the presence of positive levels of sE-selectin and/or sVCAM. Our findings suggest that the host inflammatory response to cancer cells, and/or their released products (*i.e.*, CEA), might be responsible (via cytokine release) for the elevation in circulating adhesion molecules in patients with colorectal cancer. In addition we are also currently investigating the possible correlation(s) of these recent results with innovative laboratory parameters such as methylene tetrahydrofolate reductase (MTHFR) C677T mutation, factor II G20210A mutation, factor V Leiden, S protein level, C protein level, APCR presence (Activated Protein C Resistance), homocysteine and Beta-thromboglobulin levels.

The availability of biological parameters useful for stratifying sub-groups of patients with a different clinical outcome may be of great value in the clinical management of cancer patients.

With this aim, we evaluated the prognostic significance of tumor antigens at tissue level and/or shed into the serum (i.e., CEA, CA 19-9 and CA 72-4) in gastric cancer. A longitudinal study was designed to analyze the presurgical serum and tumor tissue content of CA 72-4, CEA and CA 19-9 in patients at different stages of gastric cancer, and to evaluate the possible correlation with clinicopathological features with respect to prognostic information on relapse-free survival. The results obtained showed that 48.4% of patients with tumor recurrence had positive presurgical CA 72-4 levels compared to approximately 24% of patients who remained free of disease. Furthermore, the median presurgical serum CA 72-4 levels were significantly elevated in relapsing patients. Serosa and lymph node involvement as well as positive presurgical serum CA 72-4 levels had an independent prognostic value in predicting recurrence. A significant association between disease-free survival and lymph node involvement, depth of invasion and tumor tissue content of CA 72-4 was also demonstrated. We may therefore conclude that CA 72-4 antigen can be considered the marker of choice in the follow-up of gastric cancer patients and may be used as a prognostic indicator of relapse.

The presence of the p53 mutant protein at serum level has been evaluated as a potential marker for laboratory management of monoclonal gammapathy. We measured the serum levels of p53 mutant protein (p53M-ELISA) in patients with plasma cell dyscrasia (PCD) and compared them with some conventional laboratory variables. Twenty-three out of 65 patients had monoclonal gammapathy of undetermined significance (MGUS) and 42 suffered from multiple myeloma (MM). MM patients, with no prior chemotherapy consecutively entered this study. They were treated with standard regimens of Melphalan and Prednisone (MP) and were analyzed for serum p53M levels from the time of diagnosis to re-

sponse to therapy or death. A subgroup of nine patients was regularly monitored for changes occurring in p53M levels during MP therapy. Serum levels of p53M were elevated in MM patients compared with MGUS and healthy controls ($p = 0.002$). Significantly higher p53M levels were shown by MM patients refractory to chemotherapy than by responding patients (0.38 ng/ml vs 0.22 ng/ml, $p = 0.05$). The measurement of serum p53M in the nine patients during the course of chemotherapy correlated with disease progression or response to therapy. If confirmed on a larger series of patients, these results suggest a potential role of serum p53 mutant levels in laboratory management of PCD patients.

We also evaluated the potential usefulness of serum metalloproteinase-9 (MMP-9) for laboratory management of plasma cell dyscrasias. Serum levels of matrix metalloproteinase-9 (MMP-9) which agree with progression in solid and haematological tumors were correlated to the risk of disease progression in 62 patients with early (Binet stage A) B-cell chronic lymphocytic leukaemia (CLL). Sera were taken at diagnosis and tested by an enzyme-linked immunosorbent assay. MMP-9 levels positively correlated with haemoglobin levels ($P = 0.03$) and platelet count ($P = 0.03$). No association was found with main clinico-haematological features representative of tumor mass, such as peripheral blood lymphocytosis, bone marrow histology, Rai substages and beta-2 microglobulin (beta-2m). A cut-off of MMP-9 levels corresponding to 33rd percentile (203 ng/mL) or higher identified earlier upstaging and shorter progression-free survival. MMP-9 was a significant prognostic marker in multivariate analysis and partially independent of Rai substages, which suggests its inclusion into such a staging system to better stratify prognostically Rai stages I and II patients. In conclusion MMP-9 serum levels predict disease behavior and help to refine the prognosis of stage A CLL patients.

Recent research interests have been broadened to include the investigation of molecular markers (mithocondrial DNA and the mismatch repair system) and cytogenetic markers with the aim of identifying molecular targets for therapy.

The correlation between HER-2 gene amplification and HER-2 protein overexpression in endometrial carcinoma using fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) has been evaluated. We also analyzed chromosome 17 aneusomy and the association between these biological parameters and conventional clinicopathological variables. FISH analysis was performed on selected paraffin-embedded sections from endometrial carcinomas which previously had HER-2 status determined immunohistochemically using monoclonal antibodies (MoAb) 300G9 and CB11. Using a ratio of more than two oncogene signals/centromere to indicate amplification, a total of 42 out of the 73 endometrial tumors included in this study resulted positive by FISH, whereas protein overexpression was identified in 29 out of 73 with a concordance rate of 74.3%. However, when the mean signals/centromere per nucleus increased (ratio $> 4 <$ or $= 5$) a higher concordance between the two assays was seen ($p = 0.007$). In addition, HER-2 amplification was significantly correlated with tumor stage ($p = 0.021$) and myometrial invasion ($p = 0.010$), whereas chromosome 17 polisomy only showed a positive correlation with myometrial invasion ($p = 0.004$) No significant correlation was found between HER-2 gene amplification, chromosome 17 aneusomy and patient outcome. Nevertheless, the probability of a 5 year overall survival decreased from 70% to 43%, respectively, for ratio $> 2 <$ or $= 4$ and ratio $> 4 <$ or $= 5$ when we grouped the amplified cases on the basis of HER-2:CEP17 ratio. In conclusion, molecular characteristics provide objective data that may be useful in predicting prognosis in patients with endometrial cancer.

Cytogenetic systematic analysis was also performed on bladder cancer. Both, tumors and the surrounding urothelium in superficial bladder cancer were evaluated to better define the mechanism of multifocal tumor development. In this study we investigated chromosome 1, 7, 9, and 17 aneusomy in 25 superficial papillary carcinomas and in 51 tissue samples taken from sites of macroscopically uninvolved urothelium surrounding the tumors, using the fluorescence in situ hybridization method. Our data demonstrated a close genetic relationship between all examined tumors and normal-appearing mucosa. Numeric aberrations of chromosomes 1, 7, 9, and 17 were found to exhibit similar patterns in all an-

alyzed specimens, although with different frequencies.
We were also interested to study the molecular mechanisms of cancer development and progression with the aim to identify new therapeutic targets. O6-alkylguanine-DNA alkyltransferase (OGAT) and the mismatch repair system (MRS) play a crucial role in the susceptibility of tumor cells to the cytotoxic effects of agents that generate O6-methylguanine in DNA, including the triazene compound temozolomide (TMZ). Studies performed with peripheral blood mononuclear cells (MNC) showed that TMZ was scarcely active on lymphocyte functions not dependent on cell proliferation (e.g. NK activity and cytokine-mediated induction of CD1b molecule in adherent MNC). In contrast, TMZ depressed proliferation and lymphokine activated killer (LAK) cell generation in response to IL-2. In this case, a reasonably good inverse relationship was found between OGAT levels of MNC and their susceptibility to TMZ. This study also analyzed the ratio of the toxic effect of TMZ on MNC and on tumor cells (i.e. 'Tumor-Immune Function Toxicity Index', TIFTI). A particularly favorable TIFTI can be obtained when OGAT levels are extremely high in MNC and markedly low in tumor cells. This holds true for MRS-proficient neoplastic cells, but not for MRS-deficient tumors. In conclusion, strategies aimed at modulating OGAT and MRS may improve the clinical response to TMZ. However, the use of OGAT inhibitors to potentiate the antitumor activity of TMZ might result in a concomitant increase of the immunosuppressive effects of the drug, thus reducing the relative TIFTI.
Recent studies, in various cell types, have indicated that NF-Y could serve as a common transcription factor for an increasing number of cell cycle control genes. For instance, the cyclin B1, cyclin B2, cyclin A, cdc25B, cdc25C, and cdk1 genes all contain NF-Y sites in their promoters, which are required for their transcriptional activation at S phase. NF-Y is composed of three subunits, NF-YA, NF-YB, and NF-YC, all required for DNA binding. All subunits are expressed in proliferating skeletal muscle cells, whereas NF-YA alone is undetectable in terminally differentiated cells in vitro. By immunohistochemistry, we showed that the NF-YA protein is not expressed in the nuclei of skeletal and cardiac muscle cells in vivo. By chromatin immunoprecipitation experiments, we demonstrate that NF-Y does not bind to the CCAAT boxes of target promoters in differentiated muscle cells.
Consistent with this, the activity of these promoters is down-regulated in differentiated muscle cells. Finally, forced expression of the NF-YA protein in cells committed to differentiate leads to an impairment in the down-regulation of cyclin A, cyclin B1, and cdk1 expression and is accompanied by a delay in myogenin expression. Thus, our results indicate that the suppression of NF-Y function is of crucial importance for the inhibition of several cell cycle genes and the induction of the early muscle-specific program in postmitotic muscle cells.

Selected publications 2003

Roselli M, Guadagni F, Martini F, Spila A, Mariotti S, D'Alessandro R, Aloe S, Gazzaniga PP, Basili S, Cosimelli M, Ferroni P.

Related Articles, Links Abstract Association between serum carcinoembryonic antigen and endothelial cell adhesion molecules in colorectal cancer.

Oncology. 2003;65(2):132-8.

Cianciulli AM, Guadagni F, Marzano R, Benevolo M, Merola R, Giannarelli D, Marandino F, Vocaturo G, Mariani L, Mottolese M.

Related Articles, Links Abstract HER-2/neu oncogene amplification and chromosome 17 aneusomy in endometrial carcinoma: correlation with oncoprotein expression and conventional pathological parameters.

J Exp Clin Cancer Res. 2003 Jun;22(2):265-71.

Gurtner A, Manni I, Fuschi P, Mantovani R, Guadagni F, Sacchi A, Piaggio G.

Related Articles, Links Free in PMC Requirement for down-regulation of the CCAAT-binding activity of the NF-Y transcription factor during skeletal muscle differentiation.

Mol Biol Cell. 2003 Jul;14(7):2706-15. Epub 2003 Apr 04.

Pagani E, Pepponi R, Fuggetta MP, Prete SP, Turriziani M, Bonmassar L, Lacal PM, Falcinelli S, Passarelli F, Guadagni F, Alvino E, D'Atri S.

Related Articles, Links Abstract DNA repair enzymes and cytotoxic effects of temozolomide: comparative studies between tumor cells and normal cells of the immune system.

J Chemother. 2003 Apr;15(2):173-83.

Aloe S, D'Alessandro R, Spila A, Ferroni P, Basili S, Palmirotta R, Carlini M, Graziano F, Mancini R, Mariotti S, Cosimelli M, Roselli M, Guadagni F.

Related Articles, Links Abstract Prognostic value of serum and tumor tissue CA 72-4 content in gastric cancer.

Int J Biol Markers. 2003 Jan-Mar;18(1):21-7.

Cianciulli AM, Leonardo C, Guadagni F, Marzano R, Iori F, De Nunzio C, Franco G, Merola R, Laurenti C.

Related Articles, Links Abstract Genetic instability in superficial bladder cancer and adjacent mucosa: an interphase cytogenetic study.

Hum Pathol. 2003 Mar;34(3):214-21.

Roselli M, Mineo TC, Basili S, Mariotti S, Martini F, Bellotti A, Ambrogi V, Spila A, D'Alessandro R, Gazzaniga PP, Guadagni F, Ferroni P.

Vascular endothelial growth factor (VEGF-A) plasma levels in non-small cell lung cancer: relationship with coagulation and platelet activation markers.

Thromb Haemost. 2003 Jan;89(1):177-84.

Greco C, Alvino S, Del Monte G, Venturo I, Lopez M.

Potential usefulness of serum p53 for laboratory management of plasma cell dyscrasias.

J Exp Clin Cancer Res. 2003 Dec;22(4):607-12.

Gandolfo GM, Ferri GM, Conti L, Antenucci A, Marrone R, Frasca AM, Vitelli G.

Prevalence of infections by hepatitis A, B, C and E viruses in two different socioeconomic groups of children from Santa Cruz, Bolivia

Med Clin (Barc). 2003 May 24;120(19):725-7.

Pace A, Vidiri A, Galie E, Carosi M, Telera S, Cianciulli AM, Canalini P, Giannarelli D, Jandolo B, Carapella CM.

Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response. Ann Oncol. 2003 Dec;14(12):1722-6.

Comment in: Ann Oncol. 2003 Dec;14(12):1695-6.

Cruciani F, Moramarco A, Curto T, Labate A, Recupero V, Conti L, Gandolfo GM, Balacco Gabrieli C.

MTHFR C677T mutation, factor II G20210A mutation and factor V Leiden as risks factor for youth retinal vein occlusion.

Clin Ter. 2003 Sep-Oct;154(5):299-303.

Pittoni V, Sorice M, Circella A, Cangemi R, Conti L, Ramenghi U, Gandolfo GM, Dianzani U, Valesini G.

Specificity of antinuclear and antiphospholipid antibodies in sera of patients with autoimmune lymphoproliferative disease (ALD).

Clin Exp Rheumatol. 2003 May-Jun;21(3):377-85.

Verginelli F, Donati F, Coia V, Boschi I, Palmirotta R, Battista P, Costantini RM, Destro-Bisol G.

Variation of the hypervariable region-1 of mitochondrial DNA in central-eastern Italy.

J Forensic Sci. 2003 Mar;48(2):443-4.

Division of histology and citopathology

DIRECTOR:
RAFFAELE PERRONE DONNORSO, MD

Professor R. Perrone Donnorso is currently Chief of Dept. of Diagnostic and Oncological Prevention of the Regina Elena Cancer Research Institute in Rome and Chief of Dept. of Surgical Pathology.
Professor Perrone is a member of the Italian Superior Health Council.
He also represents Italy through his involvement in several prestigious organizations.
Professor R. Perrone Donnorso is the author and co-author of more than 200 publications. He is also a Peer Reviewer of Acta Cytologica and Diagnostic Cytopathology and member of the Editorial Board.

Staff:
MARIANTONIA CAROSI - M.D. Assistant
RENATO COVELLO - M.D. Assistant
MARIA DIODORO - M.D. Assistant
FERDINANDO MARANDINO - M.D. Assistant
MIRELLA MARINO - M.D. Assistant
LETIZIA PERRACCHIO - M.D. Assistant
STENO SENTINELLI - M.D. Assistant
PAOLO VISCA - M.D. Assistant
MARIA BENEVOLO - PHD. Assistant
SIMONETTA BUGLIONI - PHD. Assistant
MARCELLA MOTTOLESE - PHD. Assistant
AMINA VOCATURO - PHD. Assistant

Activities 2003

The research activity of the Pathology Division, during 2003, may be divided in two main fields:

1. Study of molecules involved in a. Breast and b. Uterine cervix carcinogenesis
2. Study of molecules involved in the prognosis of: A. Breast, b. Endometrium, c. Colon, d. Bladder carcinomas

1A. BREAST CARCINOMA

Characterization of the biopathological events underlying the early steps of breast carcinogenesis may have a dramatic impact on reducing breast cancer mortality, since it will offer the unprecedented possibility of anticipating therapeutic intervention. Since non-involved peritumoral tissues are the closest environment of the tumor cells, early molecular changes leading to the development of BC may be demonstrated in these tissues before the disease itself clinically appears.
In breast cancer, genetic inheritance accounts for only a small percentage of cancer incidence in the general population. Biomarkers can detect the outcomes of interaction between genetic susceptibility and the environment and they are therefore extremely important for early detection. This is not unexpected since the interactions between cancer cells and their micro- and macroenviroment create a context that promotes tumor growth and protects it from immune attack. Changes in biomarkers during this phase could be very helpful in early detection of malignant cells. Nevertheless, due to the complexity of the tumorigenesis process, no single-marker-based approach is likely to provide reliable information of highly predictive value. To overcome this limitation we focused our study on a multiparametric parallel analysis of different biomarkers performed on the tumor and the autologous normal appearing tissue. Results obtained were compared with normal breast epithelium sampled from mastoplasty.
A number of molecules involved in cell proliferation and apoptosis such as HER-2, p53, bcl-2, have been evaluated. Furthermore, due to their established role in tumorigenesis, analysis of estrogen ?/b and progesterone receptors, were performed.
This novel investigative approach i.e. "morphologically normal" tissue sampled at different

distance (1cm, 2cm, 3cm) from the malignancy also included the analysis of two apoptotic related pathways which have so far undergone limited scrutiny in breast pathology, namely the Fas-FasL system and COX-2. The pattern of expression of the latter molecule appears to be of major interest in view of the accumulating evidence that COX-2 represents a therapeutic molecular target for cancer prevention.
About 5% and 3% of the peritumoral tissues (PTTs) and 4.5% and 6.8% of benign breast tumors (BBTs) showed alterations in HER2 and p53 expression, respectively. Of interest, gene amplification was observed in 50% of HER2 positive PTTs, but not in any HER2 positive BBTs. Fas, highly expressed in and downregulated in BC, maintained its expression in PTTs, whereas FasL, usually negative in BBTs, was upregulated in BC as well as in the PTTs closest (1 cm) to the invasive lesion. Our data suggest that FasL could be a potential novel biomarker of transformation which may identify, along with HER2 and p53, precursor lesions in a genetically altered breast tissue.

1b. Uterine cervix carcinoma

A computer-assisted assay based on the quantitative analysis of DNA methylation in individual interphase nuclei by indirect immunolabelling with anti-5-methylcytosine antibodies was recently developed in our laboratory. In situ analyses were performed on individual nuclei from normal and experimentally hypo- or hypermethylated cultured cells as well as on human peripheral blood B-lymphocytes from normal and chronic lymphoid leukemia (CLL) samples. We present the results obtained on cells from patients affected by different degrees of preneoplastic or neoplastic changes of the uterine cervix as compared to normal controls. The analysis of DNA methylation in individual cells from cytofuge samples was performed as follows: within each nucleus the eu- and heterochromatin methylation levels were quantified in the gray scale range by dedicated software in terms of numbers, areas and optical densities (ODs) of the immunolabeled dense heterochromatic regions (spots), and of the optical density of nuclear background, i.e., of nuclear euchromatin. Analogously, in randomly chosen microscope fields of tissue sections from paraffin-embedded samples, progressive tissue demethylation was observed in dysplastic and cancer cells as compared to normal ones. Both methods showed significant and progressive DNA hypomethylation in dysplastic and cancer cells as compared to control specimens.

2a. Breast carcinoma

We analyzed immunohistochemically the distribution of Fas and FasL in 166 high risk BC patients submitted to anthracycline based adjuvant therapy, evaluating the expression of Fas system also in $CD3^+$ tumor infiltrating lymphocytes (TIL). The tumor expression of receptor and ligand antigens appeared to be inversely related ($p<0.0001$). In addition Fas and FasL were present in 56% and 28% of $CD3^+$ TIL respectively. When these findings were correlated with patient outcome, according to Kaplan-Meier's method, significantly shorter disease-free and overall survival were observed in patients bearing Fas negative and FasL positive tumors. These results were further reinforced when TIL displayed a Fas+/FasL- phenotype. Otherwise, none of the patients harboring Fas+/FasL- carcinomas and Fas-/FasL+ TIL relapsed or died of disease within 5-years of surgery ($p<0.0001$). Of interest we observed an increase of cell death, detected by TUNEL, in Fas positive tumors in which TIL were FasL positive compared to Fas negative carcinomas. In contrast, increased TIL apoptosis was evidenced within FasL-expressing breast tumors. Our data suggests that BC may elude immunological surveillance by inducing, via the Fas/FasL system, the apoptosis of activated lymphocytes.

2b. Endometrium carcinoma

Endometrial carcinoma is the most common invasive malignant tumor of the female genital tract in developed countries and its occurrence, due to increasing longevity in women, has risen worldwide. Although as many as 70% of these patients can be cured by surgery, often in combination with radiotherapy unexpected recurrent disease may also occur in patients with EC limited to the uterus. In this neoplasia malignant peritoneal microdis-

semination is recognized as an adverse prognostic factor, mainly in those patients without extensive myometrial invasion or macroscopic omental and/or peritoneal implants and immunocytochemistry may significantly increase the diagnostic accuracy of peritoneal cytology. It is widely reported that loss of progesterone receptors (PgR) is one of the most reliable independent parameter for predicting survival whereas the clinical value of HER-2 overexpression and/or amplification is still being debated.
With the aim of addressing the prognostic impact of HER2 overexpression and/or amplification with PgR expression or peritoneal cytology, we studied these parameters in a series of 200 EC. A concordance rate of 74.3% (p=0.007) between IHC and FISH assay was found. Univariate analysis (Cox model) identified, along with nuclear grade (P=0006), tumor stage (p<0.0001) and myometrial invasion (p=0.0007), HER2 overexpression (p=0.05), positive PWs and lack of PgR (p=0.0007) as significant predictors of OS. Moreover HER2 overexpression associated to the loss of PgR (p=0.004) or to positive peritoneal cytology (p=0.004), could identify patients at particularly high risk of death. In addition the backward step procedure indicated that tumor grade (p=0.001), stage (p<0.0001), HER2 overexpression (p=0.03) and loss of PgR (p= 0.04) were independent prognostic variables significantly influencing OS. Of interest, HER2 overexpression associated to the loss of PgR represent a powerful independent indicator of reduced survival in this female neoplasm.

2c. Colon carcinoma

About 40% of patients bearing a colorectal carcinoma will develop local or distant tumor recurrences. Integrated analyses of biopathological markers, predictive of tumor aggressiveness, may offer a more rational approach to adjuvant therapy planning.
We analyzed the correlation between p53 accumulation, bcl-2 expression with cell proliferation, DNA ploidy, and conventional histological parameters, by testing the prognostic significance of these variables in a series of 214 patients bearing a colorectal carcinoma.
When these parameters were examined in the univariate analysis, significantly shorter disease free and overall survival were observed in patients bearing p53+ and bcl-2- tumors. In the multivariate analysis p53 accumulation and bcl-2 expression emerged as independent predictors respectively of worse and better clinical outcome also in Dukes' B stage identifying patients at higher risk to develop liver metastases.. These results indicate that in colorectal adenocarcinomas a biological profile, based on the combined evaluation of p53 and bcl-2, can be useful in identifying high risk patients to be enrolled in an adjuvant setting mainly in early stage of the disease.

2d. Bladder carcinoma

Fatty Acid Synthase (FAS) and Human Erythrocyte Glucose Transporter 1 (GLUT1) are new markers involved in the biological activities of cancer cells. FAS is a multifunctional enzyme that synthesizes palmitate from acetyl-CoA and malonyl-CoA. GLUT1 is a transmembrane protein normally expressed in perineurium and erythrocytes. FAS and GLUT1 expression have been recently described in many aggressive tumors. We explored the immunohistochemical expression of FAS and GLUT1 in bladder carcinomas to reveal statistical associations with clinico-pathological features and recurrence. Thirty-one node- and distant metastasis-negative transitional cell carcinomas from patients with a five-year follow-up were evaluated for FAS and GLUT1 expression.

RESULTS: Univariate analysis showed that low-grade, pTa stage and FAS-negative expression were associated with indolent tumors. Multivariate analysis showed that FAS expression (p = 0.006) and pT1-2 stage tumors (p = 0.001) were independent predictors of recurrence. Endogenous fatty acids are an exploitable storage of energy for aggressive human bladder carcinomas. Glucose uptake is not required by bladder tumors.

Publications 2003

Giorda E., Sibilio L., Martayan A., Moretti S., Venturo I., Mottolese M., Ferrara G.B., Cappellacci S., Eibenschutz L., Catricalà C., Grammatico P., and Giacomini P.

The Antigen Processing Machinery of Class I Human Leukocyte Antigens: Linked Patterns of Gene Expression in Neoplastic Cells.

Cancer Research 63: 4119-4127, 2003

De Capoa A., Musolino A., Della Rosa S., Caiafa P., Mariani L., Del Nonno F., Vocaturo A., Perrone Donnorso R., Niveleau A. and Grappelli C.

DNA demethylation is directly related to tumor progression: Evidence in normal, pre-malignant and malignant cells from uterine cervix samplex.

Oncol Rep, 10: 545-549, 2003.

Cianciulli A.M., Guadagni F., Marzano R., Benevolo M., Merola R., Giannarelli D., Marandino F; Vocaturo G., Mariani L., Mottolese M.

HER-2/Neu Oncogene Amplification and Chromosome 17 Aneusomy in Endometrial Carcinoma: Correlation with Oncoprotein Expression and Conventional Pathological Parameters.

J Exp Clin Cancer Res, 22:265-271, 2003

Visca P., Sebastiani V., Pizer E., Botti C., De Carli P., Filippi S., Monaco S., and Alo P.L.

Immunohistochemical Expression and Prognostic Significance of Fas and GLUTI in Bladder Carcinoma.

Anticancer Research 23:335-340, 2003.

Cianciulli A.M., Guadagni F., Marzano R., Benevolo M., Merola R., Giannarelli D., Marandino F., Vocaturo G., Mariani L., Mottolese M.

HER-2/Neu Oncogene Amplification and Chromosome 17 Aneusomy in Endometrial Carcinoma: Correlation with Oncoprotein Expression and Conventional Pathological Parameters.

J Exp Clin Cancer Res, 22:265-271, 2003

Mottolese M., Buglioni S., Piperno G., Sperduti I., Giannarelli C., Cosimelli M.

Bio-Pathological factor of prognostic value in colorectal adenocarcinomas.

J Exp Clin Cancer Res vol. 22 n4 supplement 2003.

Digestive Endoscopy Unit

DIRECTOR:
VINCENZO CASALE, MD

Dr. Casale graduated in Medicine and Surgery at La Sapienza University of Rome in 1970 and went on to specialize in Gastroenterology in 1972 and Oncology in 1978. During 1989 he was in charge of the Department of Digestive Gastroenterology and Endoscopy for the Regina Elena Cancer Institute of Rome. From 1974 to 1991 he acted as Secretary for the Lazio and Umbria sections of the Italian Society of Diagnostic and Therapeutic Prevention of Tumors and during the period 1992/1995, President of the Lazio section the Italian Society of Digestive Endoscopy.
He has also lectured at the Specialization School in Digestive Gastroenterology and Endoscopy for the La Sapienza University of Rome, the Specialization School of Oncology for the La Sapienza University of Rome and the Graduate course for General and Pediatric Nursing for the La Sapienza University of Rome. From 1997 to 2000 he was the Coordinator of the Oncology Commission for the Italian Society of Digestive Endoscopy.
Dr. Casale is an international member of ASGE (the American Society of Gastrointestinal Endoscopy).
He was in charge of the research completed in 1990 for the Ministry of Health entitled "Study of cellular kinetics and gene characteristics of cells in colic mucous in subjects at risk of colon cancer undergoing treatment with retinoids", and of the research completed in 1997 for the Ministry of Health "Evaluation of some tissue and blood biological parameters for selecting subjects at risk of succumbing to cancer of the rectum/colon". He has also been responsible for 10 clinical experiments, Author of 130 scientific papers in the oncology, digestive gastroenterology and endoscopy fields, Referee for the Ministry of Health, granting credits in the national ECM program as well as organizer and presenter at numerous national and international congresses in gastroenterology and oncology.
Dr. Casale has performed over 50.000 diagnostic and/or therapeutic endoscopic examinations.

Departement Staff:
DR. V. CASALE - Department Director
DR. A. GRASSI - M.D.
DR. R. LAPENTA - M.D.
DR. V. STIGLIANO - M.D.
DR. D. ASSISI - M.D.
MR. G. IRTI - Head Nurse
MR. L. MALATESTA - Nurse
MRS. D. CANNONE - Nurse
MRS. P. CAPRA - Nurse
MRS. M. GIORDANO - Nurse
MRS. A. CINTI - Nurse
MRS. P. CAVALLO - Ota
MRS. M. DI STEFANO - Ota
Specialization: 1st Specialization School in Digestive Gastroenterology and Endoscopy La Sapienza University Rome.

Activity 2003

Digestive gastroenterology and endoscopy is important in the management of oncologic patients in general and plays a determining role in the diagnostic/therapeutic course of patients with tumors of the alimentary canal.
For some time now our structure has been actively involved in the definition and use of protocols for screening as well as innovative diagnostic and therapeutic methods. In particular the long experience gained over decades in the prevention of tumors of the digestive tract has led to the introduction of various protocols and cooperative programs of assistance with the most representative national structures.
Included therein, is the present cooperation with A.S.P (Agenzia di Sanità Pubblica Regionale), which foresees the enrollment of 1st degree relatives under 75 years of age suffering from colorectal cancer and due to undergo preventive colonoscopy.

Furthermore, a study is underway to identify and define the risks of colon cancer in breast cancer patients, in accordance with many international studies, acknowledging a class of greater risk for these patients and the necessity for protocols of careful surveillance.
Furthermore, we are participating in an Italian multicenter study, run by Prof. Massimo Crespi, which provides for the SO research on feces v. colonoscopy in subjects at medium risk of colorectal cancer undergoing screening tests. On the national level our center boasts the most frequent use of colonoscopy.
The identification of relatives at risk of colorectal cancer linked to heredity is one of the most successful activities of our facility and has already been in use for 20 years.
For some time now our center has been a reference point for the region in the study of HNPCC and of familial poliposis with a high number of immediate family members being observed in our dedicated outpatients both from the clinical and endoscopic as well as the bio-molecular point of view. The relative data on the whole family have been stored on a data base, which also holds the family tree taken down during genetic counseling.
Should there be any indication, the patients undergo a biomolecular test of the case and a subsequent clinical and endoscopic follow up.
Our structure is an integral part of the Institute's comprehensive project on colo-rectal cancer coordinated by Dr. Maurizio Cosimelli. Particular attention has been paid to the relationship between Barrett's Syndrome and adrenocarcinoma of the esophagus. As to date, no clear guide lines exist on the type of treatment or on the necessity for such in cases of displasia in Barrett's syndrome.
An effort to obtain the best definition and characterization of the pathology and of the neoplastic risk has been done with the identification of the specialized intestinal metaphagia and of Barrett's syndrome displasia.
In this regard a regional multicenter study coordinated by our facility, is underway.
The necessity to develop new strategies of palliative therapy using these procedures in inoperable tumors has been significantly increased and developed. Recourse to endoscopic palliation for the improvement of the quality of life of selected cancer patients has become a regular procedure. As regards the numerous palliative treatments used by our facility for many years now, particular attention is placed on the recent introduction of enteral prostheses, and great experience has quickly been gained in the technique of prosthesiation and in the management of patients also in artificial nutrition.
In this regard our center has been the reference point for some years for the PEG positioning of many facilities in Lazio.
For three years now a multidisciplinary team (doctors, dietitians, pharmacists and nurses) have managed not only the patients and instructed their relatives but also completely overseen the positioning of correct access to guarantee feeding for the patients.
The conviction that the nutritional status is the basis in planning surgical and/or chemoradiotherapy treatment in a valid and efficacious manner, has led us to concentrate our efforts on nutritional support, adjunctive and adjuvant nutrition, assuring the administration of nutrients capable of manipulating the metabolism of the tumoral cells (nutritional manipulation).
There are numerous clinical and experimental fields in which we cooperate with other facilities.
A cooperative project is underway with the clinical pathology facility of IRE for the definition of molecular changes concerning the Ki-ras oncogene and the adhesion molecule (in particular Galectina-3 and CD-44) which interfere in the progression of preneoplastic and neoplastic lesions. Accordingly blood and tissue samples from patients in our facility, have been obtained. In cooperation with some of the IRE and ISG facilities a multidisciplinary clinical study is underway on patients affected by Celiac disease in order to identify the relationship between this pathology and the disease in dermatologic, endocrinologic, and oncologic conditions.
An international multicenter clinical study on the efficiency and use of Celecoxib (inhibitor of Cox-2) in the prevention of sporadic adenomatosis polyposis is underway in co-

operation with a number of endoscopic centers. There is close cooperation with the Radiotherapy facility for the endoscopic evaluation before and after treatment of patients undergoing radiation therapy for prostate cancer.
Great effort has been dedicated to the field of information through involvement in international projects such as the Internet web site of the Organizzazione Mondiale di Endoscopia Digestiva (OMED), the drafting of the Minimal Standard Terminology for digestive endoscopy for the Terminology, Standardization and data Processing Committee of OMED and participation in the OMED/OMGE Education Committee and the maintenance of the Internet web site of the Italian Society of Digestive Endoscopy.
In cooperation with the regional ASP an annual census of the regional Digestive Endoscopy centers is made in order to optimize the regional health programming. There has been significant cooperation with the doctors of General Medicine, who have organized two courses with ECM credit. The quantity and quality of the clinical and endoscopic involvement found in our facility can be favorably compared to the other facilities in Lazio and the center/south of the country.
In 2003, 9,376 services, 82% outpatients and 18% admitted patients, have been carried out. Out of a total of 3,608 endoscopies carried out, 252 have been therapeutic type tests. One hundred and forty malign tumors have been diagnosed with endoscopy and confirmed histologically, 90 of which were colorectal, 30 of the stomach and 10 of the esophagus. One hundred and eighty nine consultations have been made through the dedicated outpatients for nutritional evaluation and 55 for hereditary tumors of the colon.

Publications 2003

Greco C., Cosimelli M., Casale V., Vona R., Assisi D., Matarrese P., Straface E., Scordati P., et al.

The K-ras codon 12 mutation and the CD 44/6 and galectin-3 are relevant events in the adenoma-carcinoma sequence of the colorectal tract.

Proceeding of the American Association for Cancer Research, Vol 44,52,2003

Grassi A.

Minimal Standard in Endoscopy Report in Structure of the Records, Terms, Definitions and Photo Documentation.

World Gastroenterology News 8, Vol.1, 44, 2003.

Lesnoni I., Stigliano V., Canistracci C., Lauria V., Frascione P., Addesso M., Sentinelli S., Cordiali P., D'agoto G., Appetecchia ML., Petti MC., Picardo M., Casale V.

Il Morbo Celiaco dell'adulto: un approccio multidisciplinare

Esperienze Dermatologiche, Vol.5 n.3 191-200, 2003.

Stigliano V., Lesnoni I., Lauria V., Canistracci C., Frascione P., Addesso M., Sentinelli S., Cordiali P., D'agosto G., Appetecchia ML., Petti MC., Casale V.

L'importanza della manifestazione extraintestinale nella diagnosi e gestione dei pazienti celiaci.

Ospedale e Territorio, Vol. 4 N. 1,9-12,2003.

Endocrinology Unit

DIRECTOR:
MARIALUISA APPETECCHIA, MD

Marialuisa Appetecchia received her M.D. degree (summa cum laude) in 1984 at the University of Rome. Specialized in Endocrinology (summa cum laude) at La Sapienza University of Rome in 1987 and in Oncology (summa cum laude) at La Sapienza University of Rome in 1994. In 1987 she joined the Service of Endocrinology, Regina Elena National Cancer Institute, Rome as fellow. From 1993 to 2000 she worked as a senior staff member and from 2001 to present as Director of the Service of Endocrinology, Regina Elena National Cancer Institute of Rome.
From 2003 she has also held the position of Contract Professor in Oncological Endocrinology at the Endocrinology School, School of Medicine, La Sapienza University of Rome.
Her major scientific interest is focused on research involving the etiopathogenetic relationships between endocrine pathways and human cancer and the design of new diagnostic and therapeutic strategies for human endocrine cancers, with emphasis being placed on the identification and development of molecular and biochemical diagnostic tools. Particularly, her scientific interest is dedicated to studying the relationship between insulin metabolic pathways, cytokines, growth factors and human cancers and novel thyroid cancer diagnostic strategies.
Dr Appetecchia has been and is the principal investigator and/or coordinator of several studies, granted by governmental and scientific organizations, focused on the new aspects of cancer development in emerging diseases. She is also a member of several national and international scientific societies.

Staff:
AGNESE BARNABEI - MD
ELISABETTA FERRETTI - MD, Fellow

Activities 2003

The Service of Endocrinology is interested in the evaluation and development of novel biochemical, clinical and pathologic tools useful in the diagnosis, therapy and follow up of human endocrine-related cancers. The Scientific activities of 2003 include:
1. The development of thyroid tumors derives from genetic and/or epigenetic alterations of genes involved with the regulation of cellular growth, differentiation or death. A common alteration found in tumoral cells is the capacity for uncontrolled growth, due to the alteration of the cellular cycle checkpoints. Two different types of genetic alterations have recently been characterized in thyroid tumors. A reduced expression of the PTEN lipidic phosphatase, with subsequent constitutive activation of the Aktl1 protein-kinasi in around 40% of thyroid carcinoma cases. In addition, a reduction or disappearance was observed in the expression of thyroxine phosphatase DEP-1/PTP_ in an even greater number of both human and experimental thyroid carcinomas. The importance of the loss of expression of DEP-1/PTP_ in the process of thyroid carcinogenesis is demonstrated by the observation that the re-expression of DEP-1/PTP_ in transformed thyroid cells blocks growth through the inactivation of the MEK/Erk pathway. It has also recently been demonstrated that the PTEN/Akt pathway is capable of modulating the oncosuppression activity of p53, influencing the function of its most notable negative regulator, the mdm2 oncogene. This observation, together with the fact that p53 is mutated specifically and selectively in the most aggressive and in differentiated forms of thyroid tumors, suggests that in the area of thyroid carcinogenesis, the alteration of the PTEN/Akt/mdm2 intracellular communication axis may represent an initial event capable of determining the precocious inactivation of the p53 oncosuppressor. Other observations have suggested that the inhibitor of the $p27^{kip1}$ kinasi constitutes a crucial downstream target on which these intercellular communication pathways converge (PTEN/P13K/Akt and PTP_/MEK/Erk). $p27^{kip1}$, one of the main regulators of the G1/S checkpoint, is frequently inactive in human tumors, including thyroid tumors. In thyroid tumors, $p27^{kip1}$ is activated through two different mechanisms: expression reduction and delocalisation through capture in the cytoplasm. However, it is not clear if and how the PTEN/P13K/Akt and PTP_/MEK/Erk pathways, which are often constitutionally activated in thyroid tumors, contribute to the shutting off of expression or to the functional inactivation of $p27^{kip1}$. We have

therefore started to study the signal transduction pathways that converge on the cellular cycle regulators and which are constitutional in the development of thyroid tumors. In particular, we are analyzing the effects of the alteration of the PTEN/Akt pathway on the regulatory activity of the mdm2/mdmx genes towards the oncosuppressor p53. We are also characterizing the protein isoforms of the mdm2 oncogene and its homologous mdmx function in thyroid tumors characterized by the alteration or normality of the PTEN/P13K/Akt transductive communication pathway.

2. Obesity represents a multi-factorial pathology in addition to being one of the emerging health problems in industrialized countries, which is complicated by the onset of many other pathologies such as neoplasias, a pathology with a strong social relevance and significant economic impact in terms of management of health services resources. It is well known that obesity is often accompanied by hyperinsulinemia with insulin-resistance, with an increased hepatic production and then an increased availability of growth factors, such as IGF-I, and an increased availability of free sexual hormones, due to a reduced hepatic production of the SHBG. All these factors could be responsible for the increased incidence of neoplasias in obese subjects, particularly of hormone-dependent (breast cancer, prostate cancer) and of colon rectum cancers. Recent acquisitions have demonstrated that the white adipose tissue represents an endocrine organ to all effects, able to produce substances capable of sparking off metabolic, vascular and neoplastic changes, and activating cellular transformation mechanisms. For these reasons, we have decided to study the activity of adipokines in patients affected by prostatic, breast and colon rectum neoplasias both for obese and for normal weight patients, to perform an in vivo control on the effect of insulin, of growth factors and their receptors in these neoplasias in relation to progressive factors and to perform in vivo controls of the mechanisms of neoplastic induction of factors produced by white tissue.

3. In the management of patients affected by malignant tumors it is very important to differentiate patients with different clinical outcome in order to identify the pathological, biochemical and clinical parameters useful for prognostic evaluations. For this reason, we have started a longitudinal study aimed at analyzing these parameters in patients affected by thyroid carcinoma at different stages of disease and their possible correlation with prognostic information and risk factors, with the aim of identifying new diagnostic and therapeutic strategies for this neoplasia.

Publications 2003

Carlini M., Lonardo M.T., Boschetto A., Carboni F., Appetecchia M., Tropea F., Santoro E.
Adrenal glands metastases from malignant melanoma. Laparoscopic bilateral adrenalectomy.
J. Exp. Clin. Cancer Res., 2003 Mar;22(1):141-5. *I.F. 0.703*

Solivetti F.M., Bacaro D., De Majo A., Coscarella G., Franconi M., Appetecchia M.L.
Role of pulsed doppler of the inferior thyroid artery in patients without hyperthyroidism
Chir Ital. 2003 May-Jun;55(3):373-7. Italian. *I.F. 0.1*

Division of neurosurgery

DIRECTOR:
EMANUELE OCCHIPINTI, MD

Prof. Emanuele Occhipinti was born in Ragusa on December 8, 1940.
He achieved his MD degrre in 1965, summa cum laude at La Sapienza University of Rome - School of Medicine and in 1970 he was postgraduated in Neurosurgery, at La Sapienza University of Rome - School of Medicine. In the same period Assistant Neurosurgeon at the Institute of Neurosurgery - La Sapienza University of Rome - School of Medicine.
From 1970 Assistant Neurosurgeon at Division of Neurosurgery - Regina Elena National Cancer Institute - Rome
1976 training stage at Massachusetts General Hospital, Children's Hospital Medical Center and Peter Bent Brigham Hospital, - Boston - MA (US).
From 1985 Professor of Clinical Neurosurgery at the Postgraduate School of Neurosurgery - Tor Vergata University of Rome.
From 1999 Director of the Division of Neurosurgery - Regina Elena National Cancer Institute - Rome.

Research and professional experience:

Active participation in research projects in the field of Neuro-Oncology, sponsored by CNR, AIRC and Ministry of Health.

Staff:

PROF. C.M. CARAPELLA - M.D. Assistant
DOTT. F. CAROLI - M.D. Assistant
DOTT. F. CATTANI - M.D. Assistant
DOTT. E. MORACE - M.D. Assistant
DOTT. P.A. OPPIDO - M.D. Assistant
PROF. A. POMPILI - M.D. Assistant
DOTT. L. RAUS - M.D. Assistant
DOTT. S. TELERA - M.D. Assistant

Postgraduate School Students:

DOTT. CONTI CARLO
DOTT. DE CERCHIO LEONARDO
DOTT. LANETTI ANTONIO
DOTT. MENNITI AGAZIO
DOTT. RUGGERI FRANCESCO
DOTT. STAVROPULOS STAVROS

Research Activities 2003

Research activity of the Division of Neurosurgery is focused on the study of new diagnostic and therapeutic approaches in the integrated treatment of brain glioma. In this field during 2003 a series of cooperative studies with national and international institutions were activated, or have been planned.
During this year the accrual of patients affected with glioma of different malignancy grading, both newly diagnosed, and at the moment of recurrence and/or clinical/radiological progression, has been carried out. The patients have been followed through the different structures of Dept of Neuroscience (Division of Neurosurgery, Ambulatory of Neuro-Oncology, Day Hospital of Neuro-Oncology, Home Care Continuative Assistance Service), and furthermore through a more efficient integration with the Divisions of Medical Oncology and Service of Radiotherapy, inserted in the Neuro-Oncological Group, actively connected with other regional structures.
New therapeutic protocols have been activated, after surgical procedures (biopsy and/or microsurgical removal), radiation treatment and chemotherapy mainly with Temozolomide, and/or according to the PCV schedule (Procarbazine, Vincristine e Lomustine), as first and second line treatment. In addition, the increasing efficacy of new therapeutic strategies (microsurgical resection, with second surgical intervention and intratumoral administration of antiblastic drugs, conformal radiotherapy, with eventual focal boost, adju-

vant and/or concomitant chemotherapy), leading to third line chemotherapy with Fotemustine, or Cisplatin and Etoposide) in selected patients.
Of particular interest, our experience in the treatment of progressive low grade gliomas, observed after surgical treatment at the moment of progression and/or recurrence; these patients were submitted to Temozolomide chemotherapy with relevant results both in terms of clinical benefit, and as impact on quality of life; these data have been published in the Annals of Oncology.
Presently we are trying to correlate the data regarding tumour bio-molecular characteristics with clinical data of these patients. As matter of fact, in this field the definition of predictive markers of potential efficacy of different therapeutic approaches assumes prominent interest, and a more adequate clinical, radiological, pathological, and bio-molecular knowledge could contribute to define more selective and efficient diagnostic-therapeutic strategies, also allowing clear cut stratification of patients accrued in new clinical trials.
In the literature different Authors (including our group) have described a series of prognostic markers, as expression of p53, amplification and over expression of EGFR, 10q LOH in astrocytic gliomas, and, 1p and 19q LOH in oligodendrogliomas, methylation of methyltransferase, determining chemo resistance to methylating and alkylating agents. This research is a part of PF Ministry of Health, coordinating Prof. Felice Giangaspero-Neuromed (group unit; resp. C.M. Carapella).

New protocols for combined treatment of malignant gliomas have been activated, including new modalities for drug delivery, as convection enhanced direct infusion of drugs into peritumoral region.

1. A phase i-ii study of prolonged gemcitabine infusion as radiosensitizer for glioblastoma multiforme (approved by ec and activated)
2. A phase iii multicenter study of intratumoral/interstitial therapy with transmid compared to best standard care in patients with progressive and/or recurrent, non-resectable glioblastoma multiforme (approved by ec and on-going activation)
3. Phase ii study of a recombinant chimeric protein composed of transforming growth factor (tgf)-a and a mutated form of the pseudomonas exotoxin termed pe-38 (tp-38) in patients with recurrent or persistent glioblastoma multiforme after previous resection and radiation therapy (approved by ec and on-going activation)
4. temozolomide chemotherapy in the treatment of anaplastic gliomas and progressive or recurrent low grade gliomas (approved by EC and activated).

A second relevant research activity is directed toward the evaluation of new surgical strategies in the treatment of spinal and vertebral tumors; of pituitary adenomas and tumors of the sellar region; in the treatment of infratentorial secondary tumors; mainly defining the role of new technologies and mini invasive approaches

- brain metastases: conventional surgery, unconventional approaches; new intra-operative technologies
- mini invasive supra orbital approach of sellar and suprasellar region tumours
- unilateral approach in the resection of intradural spinal tumours
- transfenoidal removal of pituitary adenomas with microsurgical and endoscopy-assisted technique

Principally, our clinical research activity is divided in four different fields: advanced studies on integrated treatment of brain gliomas; microneurosurgical and endoscopy-assisted pituitary surgery; new surgical approaches with mini invasive techniques in the resection of brain and spinal tumors; surgical procedures of removal and reconstruction in the treatment of primary and secondary vertebral tumors; this last protocol is under approval of the EC.
In addition didactic activity has been carried out, as in previous years:
Postgraduate School of Neurosurgery-Tor Vergata University of Rome.
Graduate course of Nursing Science, La Sapienza University of Rome.

In this year an advanced Course of Live Surgery was organized on "Tumori vertebrali. Tecniche ablative e ricostruttive"; with national experts in attendance, this course met with considerable success.
An automatic pneumatically activated osteotomy has been patented (patent PCT/IT03/00205)

Publications 2003 (on impacted journals)

Pace A, Vidiri A, Galiè E, Carosi MA, Telera S, Cianciulli AM, Canalini P, Giannarelli D, Jandolo B, and Carapella CM.

Temozolomide chemotherapy for progressive low grade glioma: clinical benefit and radiological response.

Annals of Oncology, Dec 2003

Boccardo M, Telera S, Vitali A

Tanycytic ependymoma of the spinal cord. Case report and review of the literature.

Neurochirurgie, Dec 2003

Neurology unit

DIRECTOR:
BRUNO JANDOLO, MD

Bruno Jandolo was born in Rome in 1942.
He received his MD cum laude in 1966 and specialized in Neurology and Psychiatry cum laude in 1969 at La Sapienza University of Rome.
He also specialized in Clinical Criminology.
From 1970 to 1973 he worked as assistant Neurologist at the Hospital of Viterbo
From 1973 to 1978 he was assistant Neurologist and from 1978 to 1987 fellow Neurologist at the Regina Elena Institute.
Since 1987 he has been Head of Neurology at the same Institution, and from 2001 he has been Head of the Department of Neurosciences and Cervico-Facial Pathology.
He has been Professor of Clinical Neurophysiology since 1986 at the Tor Vergata University and of Electromyography since 1990 at La Sapienza University, in Rome.
Dr. Jandolo spent periods of study at the Universities of Seattle, Basel, Pavia and Milan.
He is member of various Scientific Societies, and he has been Vice-President, President and Past President of the Italian Society of Neurology, between 1997 and 2001.
Dr. Jandolo's research interests regard Neuro-Oncology and Clinical Neurophysiology, with special focus on tumor-related epilepsy, neurotoxicity, and Nervous System paraneoplastic diseases.
Moreover he is referee of the Regione Lazio for Multiple Sclerosis.

Staff:

ALBERTO PIETRANGELI - M.D., Responsible of Neurorehabilitation
ANDREA PACE - M.D., Responsible for brain tumor home assistance
MARTA MASCHIO - M.D Fellow
ALBINA ANGELINI - M.D Fellow
EDVINA GALIÈ - M.D Fellow
GIULIANA. GRAZIANO - Technician of Clinical Neurophysiology
GIANLUCA PETRERI - Technician of Clinical Neurophysiology (Contract)
ANNA. DI CANIO - Technician of Clinical Neurophysiology
ELEONORA BISOZZI - Technician of Clinical Neurophysiology (Student)
DE FULVIIS ANTONIETTA - Physiotherapist Coordinator
GUERRA MARIA LUISA - Physiotherapist Coordinator
ORAZIO PERROTTA - Physiotherapist
MAURIZIO BRECEVICH - Physiotherapist
FABIO MOSCATELLI - Physiotherapist
RITA CASILLO - Physiotherapist
ALESSIA ZIZZARI - Physiotherapist (Contract)

The association between lung tumors and neurological paraneoplastic syndromes is well known, but its exact prevalence is not as defined.
Therefore, we have begun a study with the aim of evaluating the prevalence of damage to the peripheral nervous system and neuromuscular junction in patients affected by lung carcinoma, before any chemotherapy, and the possible correlation between clinical, neurophysiological and serologic data. Twenty eight patients were recruited (23 males, 5 females age 51-80; 4 with microcytoma, 7 with squamous carcinoma, 8 with adenocarcinoma, 9 with large cell carcinoma).
Each patient was submitted to:
Clinical Neurological examination
Neurophysiological examination (motor and sensory nerve conduction; evolution of the amplitude of the sensory and motor action potentials; decrement test at 3 and 20 Hertz) of one ulnar nerve.
Serologic examination:
Antibodies anti-MAG, anti-Hu, anti-Ri, anti-Yo, anti-Myelin, anti-Gangliosides, ANA. In twelve patients (1 microcytoma, 3 squamous, 2 ADK, 6 large cell) the following autoantibodies were found; 4 anti-gagliosides, 3 ANA; 1 anti-MAG and ANA; 1 anti-myelin; 1 anti-Ri and anti-Hu, 2 anti-Hu.

In 2 patients (1 squamous, 1 microcytoma) the motor conduction velocity was altered.
In 4 patients (1 microcytoma, 3 squamous) the amplitude of the sensory potential was low.
In 4 patients (I microcytoma, 3 ADK) we found a myasthenic decrement at 3 Hz.
In conclusion in 7 patients with positivity to autoantibodies there were also neurophysiological alterations.
These data may suggest that there is a prevalence of 25% of sub clinical paraneoplastic neurophysiological syndromes.
However, the number of cases is not sufficient and the antibody-reactivity is dysomogeneous, so we still need to recruit 50-70 patients to get reliable conclusions.

Cisplatin induced neurotoxicity remains the major dose-limiting toxicity.
Clinical, neurophisiological and neuropathological data suggest that such toxicity may derive from dorsal-root ganglia injury.
Dorsal-root ganglia neurons are the primary target of vitamin E deficiency
We found a decrease in plasma levels of vitamin E in patients with severe peripheral neurotoxicity after cisplatin treatment.
Thus, a study was begun to evaluate the neuroprotective effect of antioxidant supplementation with vitamin E in patients treated with cisplatin chemotherapy.
Methods: Between April 1999 and October 2000, forty seven patients were randomly assigned to either group, one, which received vitamin E supplementation during cisplatin chemotherapy, or group two, which received cisplatin chemotherapy alone.
Alpha-tocopherol (vitamin E; 300 mg/d) was administered orally before cisplatin chemotherapy and continued for 3 months after the suspension of treatment.
For preclinical studies, nude mice carrying the human melanoma tumor were treated with cisplatin alone or in combination with vitamin E.
Results: Twenty-seven patients completed six cycles of cisplatin chemotherapy 13, patients in group one and 14 patients in group two. The incidence of neurotoxicity was significantly lower in group one (30.7%) than it was in group two (85.7%; $P < 01$).
The severity of neurotoxicity, measured with a comprehensive neurotoxicity score based on clinical and neurophysiological parameters, was significantly lower in patients who were supplemented with vitamin E than in patients, who were not supplemented with vitamin E (2 v 4.7, $P < .01$).
The results of the preclinical studies showed that when cisplatin was combined with vitamin E, no differences were observed in tumor weight inhibition, tumor growth delay, or life span as compared to treatment with cisplatin alone.
Conclusion, supplementation of patients receiving cisplatin chemotherapy with vitamin E decreases the incidence and severity of peripheral neurotoxicity.

The optimal treatment for low-grade glioma (LGG) is still controversial. Recent data indicate a potential influence of chemotherapy in the natural evolution of these tumors, allowing for the deferral of more aggressive therapies.
Patients and methods. Forty-three patients affected with LGG (29 astrocytoma, four oligodendroglioma and 10 mixed oligo-astrocytoma) were treated with temozolomide (TMZ) at the time of documented clinical and radiological progression. McDonald's response criteria were utilized to evaluate TMZ activity. Thirty patients (69,7%) had previously received radiotherapy; 16 (37.2%) had received prior chemotherapy. Clinical benefit was evaluated measuring seizure control, reduction in steroid dose and modification of Karnofsky performance status and Barthel index. Quality of life was assessed with the QLQ-C30 questionnaire.
Results: We observed a complete response in four patients, 16 partial responses, 17 stable disease (with four minor response) and six progressive disease.
Median duration of response was 10 months [95% confidence interval (CI) 8—12], with a 76% rate of progression free survival (PFS) at 6 months, and a 39% rate of PFS at 12 months.
A relevant clinical benefit was observed particularity in patients presenting epilepsy.

Conclusions: The high response rate of 47% (95% CI 31% to 61%) confirms that TMZ chemotherapy is a valid option in the treatment of progressive LGG. The present preliminary results seem interesting and warrant further evaluation of TMZ clinical activity in a larger series of progressive LGG.

A retrospective study on 405 patients with supratenterial brain tumor was carried out to evaluate these statistical correlations: epilepsy prevalence in brain tumors, the correlation between epilepsy and histology, between epilepsy and tumor site, between epileptic type and histology, and between epileptic type and tumor site.
Results: 68.4% of patients had seizures.
Of the patients without seizures, 70.3% had glioblastoma, 22.7% anaplastie astrocytoma or oligodendroglioma, and 7% low-grade astrocytoma or oligodendroglioma.
Epilepsy was significantly more frequent in patients with fronto-temporal tumors than in parieto-occipital tumors.
In GBM simple partial and generalized seizures were more frequent, whilst in low-grade astrocytoma s partial-complex seizures, with or without generalization, were prevalent.
Simple partial and partial with generalization seizures were prevalent in frontal tumor patients, while in temporal tumor patients complex partial and generalized seizures prevailed.
Conclusions: in our patients epilepsy prevalence was 15% higher than usually reported in international studies.
Moreover, our data show that epilepsy is statistically more frequent in patients with fronto-temporal tumors than with parieto-occipital.

In a global project focusing on the oncologic problems, we must consider the rehabilitation of the patient with neurological defects, aiming to arrive at both, a good therapeutic goal as well as a good quality of life. A multidisciplinary approach gathering many specialists (surgeons, radiotherapists, neurologists, oncologists, rehabilitators, psycologists, nurses) led to total treatment.
This project verifies all the phases of neoplastic disease, to improve the cancer patient's treatment quality, retorting a patient with neurological defects as a result of his disease, to a normal and functional state as soon as possible. In our Institute we apply the following specific rehabilitation procedures: a) Breast cancer; prevention and therapy of brachial plexus lesions following radiotherapy and cancer involvement; b) Colo-rectal cancer and urogenital tumors; sexual and bladder disorders following non-nerve sparing techniques and radiotherapy, lumbosacral plexus lesions; c) Head and neck cancer; rehabilitation of facial and accessory nerve damage: d) Cerebral and spinal cord tumors; rehabilitation of cognitive and motor defects: e) Toxic neuropathies, fatigue following antineoplastic drugs: rehabilitation of stance and gait. f) Rehabilitation of patients suffering from chronic pain with transcutaneous stimulation and other non-destructive procedures. The specific rehabilitation procedures, required in different tumors must be discussed with the patient and other specialists. We emphasize the importance of the assessment to provide rules and methods for the various forms of treatments, which will differ according to the patient's characteristics, the phase of disease and the survival time.

Since 2000, a comprehensive home rehabilitation and palliative care program for the patients with brain tumors discharged from our Neurological Division, has been started. The aims of this model of assistance are to address the patient's need of care during the last stage of disease, to provide home palliative care, to facilitate death at home and to reduce the re-hospitalization rate. In the course of 2003, 108 patients were followed (68 gliomas, 15 cerebral metastases, 25 other tumors). Forty four patients died, 70% at home, 20% in hospital, 10% in hospice). Thirty three patients with neurological deficits were treated with weekly home neurorehabilitation. Barthel index improved in 29% of cases and was stable in 33%.
There were 46.4% of the patients who developed seizures Non-neurological complica-

tions included deep venous thrombosis (8.7%), pulmonary infection (10.8%), adverse effects to medication, chemotherapy, antiepileptic drugs, steroids, (31.7%). Re-hospitalization occurred in 32% of the patients due to epilepsy, pulmonary infection or neuralgic deterioration.
The most frequent symptoms of the terminal phase were lethargy (35.5%), dysphagia (31.8), and headache (12.3). The lack of a control group does not allow to demonstrate the efficacy of our model, but our findings concerning death a home, re-hospitalization rate, quality of life and satisfaction of patients and their relatives, suggest that a continuing home care program has a positive impact.

Another project concerns the evaluation of two fields of the quality of life of patients with cancer: sexuality and fatigue. The evaluation is psychological, neurophysiological, gynecological, endocrinological and oncological.
Neurophysiological evaluation consists in the measurement of conduction velocity of nerves to verify neurotoxicity of intertumoral therapies, and in the evaluation of sacral reflex and sudomotor response in patients operated in the pelvic floor for bladder, prostate and colo-rectal cancer, with sexual dysfunction
To improve these symptoms patients will be treated with neuro-protective therapies and with drugs for impotence.
We have studied about 50 patients with breast and urogenial cancer.

The association between peripheral neuropathies and monoclonal gammopathies of undetermined significance (MGUS) is well-known, whilst the central nervous system involvement has rarely been reported. Case Report 1: a 30 year old man began suffering at 25 of an intention tremor on the left arm and then on the left leg, associated with dysarthria and cerebellar ataxia. The clinical syndrome worsened progressively. At present the patient shows severe intention tremor on the four limbs, prevailing on the left, severe cerebellar ataxia and dysarthria. Repeated MRI showed marked cerebellar vermis atrophy. CSF examination showed oligoclonal bands (IgG ? e IgG k) and link-index 11.6. An lgG ? monoclonal gammopathy was revealed in the serum. Autoantibodies antì-nervous system were not found. Total body CT scan was normal. Biopsy of the crista iliaca exluded myeloma. Biopsy of the rectal mucosa: normal. Plasmatic vit. E was low.
Serologic research for HBV, HCV, HIV, lues, rubella, measles was negative. Genetic analysis for SCAI, SCA2, SCA7 and Friedreich's ataxia was negative.
Nerve conduction velocity studies were normal.
Treatment with high doses of vitamin E was ineffective, treatment with lg iv. and steroids obtained only transitory clinical benefits. Case Report 2: a 57 year old man, over the last five years, has presented ataxic and spastic gait on the right side, a reduction in fine motor movement of the fingers mainly on the right side, superficial right side brachiocrural hypoesthesia and a marked dysarthria associated with internuclear ophthalmplegia. The neurological picture, after an initial progressive worsening which lasted some months, remained relatively stable over the years. Repeated magnetic resonance imaging (MRI) of the brain and spinal cord documented the presence of demyelinating plaques spreading in the white matter of the periventricular region and the semioval centers, and a right side paramedian plaque at the C4-C5 level, none of which were in the active phase. Oligoclonal bands were revealed in the cerebrospinal fluid (CSF). Monoclonal IgM/? gammopathy with anti-myelin and anti-nucleo reactivity, found with serum immunofixation, were confirmed several times in successive annual controls, not associated with myeloproliferative pathology. The lack of progression in the clinical picture would seem to contradict the diagnosis of late multiple sclerosis.
Conclusion: We hypothesize a pathogenetic role of IgM/? at the onset of the demyelinating disease of the second patient (according to the presence of anti-myelin antibodies), and of IgG/? in the cerebellar atrophy of the second patient. (considering the presence of oligoclonal bands in the CSF).

We evaluated the masseteric silent period and reflex in patients affected by progenia. Before and after maxillofacial surgery. In order to determine their clinical utility.
The electrophysiological changes generated by malocclusion secondary to prognatism have been evaluated before and after maxillofacial corrective surgery in 14 patients aged between 18 and 36 years. The masseteric reflex and the silent period (SP) of the masseteric muscles elicited by stimulation of the mental nerve were recorded. A correspondence between the neurophysiologìcal and clinical findings was present in 12 of 14 patients. In particular concerning the latency of SP2. This study demonstrates that the masseteric silent period may be used as diagnostic and prognostic support, before and after surgery for malocclusion.

Selected publications 2003

Jandolo B., Galiè E., Badia D.

Masseteric silent period and reflex

Neurol Sci, 24, 53-56 (2003).

Galiè E., Pietrangeli A., Maschio M., Pace A., Vidiri A., Carosi M., Jandolo B.

Demyelinating Disease in Monoclonal Gammopathy of Undetermined Significance.

J. Exp. Clin. Cancer Res, 22, 337-339, (2003).

Pace A., Savarese A., Jandolo B., Cognetti F., et al.

Neuroprotective Effect of Vitamnin E Supplementation in Patients Treated With Cisplatin Chemotherapy.

Journal of clinical Oncology, 21, 927-931 (2003).

Pace A., Vidiri A., Galiè, E. Jandolo B., et al.

Temozolomide chemotherapy for progressive low-grande glioma: clinical benefits and radiological response.

Annals of Oncology; 14, 1722-1726 (2003).

Leonetti C., Pace A., Cognetti F., Picardo M., et al

Alpha-Tocopherol protects against cisplatin-induced toxicity without interfering with antitumor efficacy.

Inter. J Cancer.; 2, 243-50, (2003).

Division of otolaryngology, head & neck surgery

DIRECTOR:
GIUSEPPE SPRIANO, MD

Prof. Giuseppe Spriano was born in Asti on January 25th 1953.
He received his degree in Medicine in 1978 at the University of Milan School of Medicine. He became a specialist of Otolaryngology, Head & Neck Surgery in 1981 (University of Milan) and Oncology, in 1984 (University of Genoa).
From 1979-1984 he was Assistant professor and Associate professor, 1985-95 of the Department of Otolaryngology-Head & Neck Surgery at Di Circolo Hospital Varese. Then from 1996-2002 he held the position of Chief of the Department of Otolaryngology-Head & Neck Surgery at Di Circolo Hospital Varese. Since 2002 he has been Chief of the Department of Otolaryngology-Head & Neck Surgery of the Regina Elena National Cancer Institute of Rome.
He has been Professor of Otorhinolaryngology in the Schools of Specialization Otorhinolaryngology, Radiology and Oncology at the Universities of Pavia, Pisa and Rome (La Sapienza University).
He is a member of the Italian Societies of Otorhinolaryngology, Head & Neck Surgery; Medical Oncology; Maxillo-Odonto-Stomatology. He is Corresponding Member of the American Academy of Otolaryngology- Head and Neck Surgery, and Founding Member of G.L.O.C.C.-Work Group for Head & Neck Oncology;
He is Member of GLPO (Group of Northern Italy Otolaryngology Chiefs); of the Board of the Italian Society of Otorhinolaryngology, Head & Neck Surgery. He is the Italian Member of the '5th International conference on head and neck cancer', San Francisco (2000) and of the European Union of Otolaryngologists (UEMS).
He is currently one of the Experts of the Italian Ministry of Health.
He is on the editorial boards of Head & Neck and Agorà Otorinolaringoiatria.
He is author of 85 original papers published in international and national journals. He is responsible for the Research Project: Intraoperative radiotherapy (IORT), in mandibular sterilization in oral carcinoma; coordinator and member of the VOCE project, organized by the National Group against Tumors.
He has personally performed more than 11.000 surgical procedures.

Medical Staff:
PAOLO RUSCITO - Assistant
RAUL PELLINI - Assistant
GIOVANNI CRISTALLI - Assistant
DI PAOLO CONSULTANT - Foniatrician
PAOLO MARCHESI - Fellow
BARBARA PICHI - Fellow
MARZIA RUGGIERI - Fellow
URSULA MORESI - Logopedist
FRANCESCO BIANCO - Audiometrist

Activity 2003

Otolaryngological, head and neck oncological surgery is widely performed by the Division staff (about 540 operations per year). Highly specialized surgical protocols and/or procedures are performed and described below.

EXTENDED THYROID SURGERY.
The extent of thyroid surgery performed depends on the specific thyroid condition being treated. The goal of the surgeon is to treat the condition to the best extent possible, while maintaining the highest quality of life possible. Surgery should only be recommended if the condition cannot be adequately treated medically, i.e. if cancer is found or suspected, if the airway is obstructed, or if the patient can not tolerate medication. Depending on the specific condition, a surgeon may recommend removing only a portion or one lobe of the thyroid, or wing of the butterfly-shaped gland (loboistmectomy, total thyroidectomy). If the thyroid is cancerous, the surgeon may remove the entire gland as well as the lymph nodes close to the

thyroid gland (median compartment) or in the lateral neck (lateral neck dissection). When surrounding lymph nodes are removed, the operation is called a modified radical neck dissection. After the operation, this area of the neck is usually numb because the nerves to the skin in this area are purposely severed in order to remove the diseased lymph nodes. More extensive surgery may be associated with higher complication rates and may require extended resections of the larynx, hypopharinx, trachea, esophagus, followed by their reconstruction by flaps.

Mandibular reconstruction

After tumor-related mandibular resection, the question arises as to what procedure (transplant type, time of reconstruction and implantation) will most reliably restore masticatory function depending on the patient's individual situation. By clinical and radiological analysis of our patient population, our aim was to establish the indications for these transplants and to compare the complications of endosseal dental implants. According to our results, the iliac crest transplant enabled optimal reconstruction of areas equivalent to half a mandible, but it is disadvantageous due to the limited length of the vessel pedicle and considerably voluminous skin-fat component. If there are combined bone and oral mucosa defects, the osteocutaneous fibula transplant offers not only an implantable bone but also a thin skin component for intraoral coverage; a vessel pedicle of up to 15 cm can be exposed during distal flap raising. These results show that restoration of masticatory function after tumour-related mandibular resection is one of the most difficult tasks in maxillofacial surgery.

IORT in head and neck carcinoma

Three pilot studies examining the value of IORT in advanced head and neck carcinoma as anticipated boost, as boost in irradiated recurrent tumors and in tumors slightly infiltrating the mandible or close to it, are ongoing.

Minimally invasive video assisted (MIVA) thyroidectomy.

This pilot study analyzes the use of MIVA in the surgical treatment of small thyroid nodules, avoiding open-surgery. Preliminary results seem to evidence better cosmetic results, less postoperative pain and shorter hospitalization, compared to conventional surgery.

Publications 2003

Spriano G., Ruscito P., Morello R., Pellini R.

Tumori del cavo orale dell'orofaringe: nuove tecniche ricostruttive della mandibola.

Tumori, suppl. 2(4): S57-S60, 2003 *I.F. 0.267*

Division of intensive care, pain therapy and palliative care

DIRECTOR:
EDOARDO ARCURI, MD

Edoardo Arcuri received his degree in Medicine in 1967 and the Anaesthesia and Intensive Care Specialization degree in 1970 from the University of Turin, Italy. He worked as an anesthetist at Regina Elena Cancer Institute from 1971 to 1974 and at the General Hospital of Marino (Rome) from 1975 to 1990. He has been Director of the Department of Intensive Care, Pain Therapy and Palliative Care at Regina Elena Cancer Institute of Rome, since 1991. Since 1994 he has taught Pain Therapy at II Specialization School in Oncology of La Sapienza University, Rome. Since 1999 he has been Director of the Training School in Palliative Care for Central Italy. From 2004 he has been teaching Pain Therapy at the Specialization School for Anesthesia and Intensive Care at Campus Biomedico University, Rome. He has been a member of the Pain Therapy Committee (CUF) of the Ministry of Health, and his interest lies in the modification of the Italian law regarding the use of opioid drugs in pain therapy. Moreover he has been involved in many professional committees for the elaboration of clinical guidelines in Chronic Pain Therapy. He was chief of two research projects sponsored by the Italian Ministry of Health, in 1992 and 2002, and by CNR, in 1997 and 1998.

Staff:

M. ANTONINI - M.D.
A. CALAMARO - M.D.
F. CENTULIO - M.D.
F. CIOCCA - M.D.
L. DI EMIDIO - M.D.
G. FUSCO - M.D.
L. LAURENZI - M.D.
S. NATOLI - M.D.
L. PELAGALLI - M.D.
W. TIRELLI - Senior Fellow
P. GINOBBI - Senior Fellow
A. KAPLLANI - Fellow
A. TENORE - Psychologist
R. MILANA - Secretary

Activities 2003

The work of the Department of Intensive Care, Pain Therapy and Palliative Care is centered on three major issues:

Intensive Care of Neoplastic Patient

Recently the Department has been involved in the identification of biological risk factors as a consequence of antineoplastic therapy. In recent years, we have set up ethico-clinical guidelines, regarding the admission of neoplastic patients to the Intensive Care Unit (ICU), with particular attention for those defined not-admissible, due to advanced disease. An agreement with the Sacro Cuore Hospice has been instituted for the admission of patients out of therapy. This agreement is also extended to an area of research in pain therapy and psychosocial problems.

b) Oncologic Pain Therapy

Over the last few years we have elaborated a hypothesis regarding the possible interference of tumors in the efficacy of opioid treatment, based on the observation of thousands of patients treated in the Pain Therapy Unit. This effect is due to the presence of specific receptors on neoplastic cells: the binding of opioid drugs to these receptors may decrease their analgesic activity. This pseudotolerance characterizes many situations of poor opioid responsiveness in the oncologic patient treated with these drugs. We also demonstrated that one of the functional effects of this particular 'trapping' of opiates by the tumor is the release of nitric oxide (NO) [Fimiani C, Arcuri E, et al.] Mu3 opiate receptor expression in lung and lung carcinoma, ligand binding and coupling to nitric oxide release. [Cancer Lett. 1999 Nov 1; 146(1):45-51]. This highly diffuseable gas plays an important role in the development of poor opioid responsiveness condition (opioid tolerance, hyperalgesia and

neuropathic pain). This hypothesis has been verified on experimental models in vivo, in collaboration with the Regina Elena Cancer Institute Experimental Research Center [Arcuri E, et al. Preliminary in vivo experimental evidence on intratumoral morphine uptake. Possible clinical implications in cancer pain and opioid responsiveness. J Pain Symptom Manage. 2002 Jul;24(1):1-3]. Recent clinical data show that the development of pseudotolerance depends on the type of opioid drug used for analgesic therapy: morphine, more than other opioid drugs, seems to be involved in this mechanism.
These data suggest complex interference between opioid drugs and tumors and could inspire new analgesic strategies. Therefore, based on this research we have included, in our pain therapy protocols, diagnostic and therapeutic items to identify and treat the difficult situations of poor opioid responsiveness or pain due to paradoxical response to opioid drugs.
c) Palliative Care
The agreement with the Regina Elena Cancer Institute and the Sacro Cuore Hospice looked into a new model of residential Hospices, very different from the current one (residence exclusively reserved for terminal patients). Now, in the Sacro Cuore Hospice a restricted number of beds is reserved for patients in need of supportive care and pain therapy and able to receive assistance during a few hours (Day Hospice) or, for a longer period, to resolve the prolonged side effects due to antineoplastic treatment (Restorative Care). A research project of the Ministry of Health is evaluating the clinical-psychosocial and economic impact of this new kind of assistance on the quality of life of patients and their families.

Publications 2003

Mercadante S, Arcuri E.

Sympathetic blocks and disease progression modifying pain mechanisms.

Reg Anesth Pain Med. 28(6):586-7; Nov-Dec 2003.

Mercadante S, Catala E, Arcuri E, Casuccio A.

Celiac plexus block for pancreatic cancer pain: factors influencing pain, symptoms and quality of life.

J Pain Symptom Manage.26(6): 1140-7; Dec 2003.

Ambrosio F, Paoletti F, Savoia G, Amantea B, Arcuri E, Avogaro F, Barbati A, Beltrutti D, Branca L, Camaioni D, De Conno F, De Luca A, Di Massa A, Evangelista M, Finco G, Ischia S, Mattia C, Mascaro A, Mercadante S, Orlandini G, Palomba R, Pasetto A, Polati E, Raffaelli W, Varrassi G, Visentin M, Zucco E.

siaarti recommendations on the assessment and treatment of chronic cancer pain.

Minerva Anestesiol.;69(9):697-716, 717-29. English, Italian, Sep 2003.

Mercadante S, Ferrera P, Villari P, Arcuri E.

Hyperalgesia: an emerging iatrogenic syndrome.

J Pain Symptom Manage. 26(2):769-75; Aug 2003.

Mercadante S, Villari P, Ferrera P, Arcuri E.

Local anesthetic switching for intrathecal tachyphylaxis in cancer patients with pain.

Anesth Analg. 97(1):187-9, table of contents; Jul 2003.

Laurenzi L, Natoli S, Pelagalli L, Marcelli ME, Abbattista D, Carpanese L, Arcuri E.

Long-term central venous catheterization via persistent left superior vena cava: a case report.

Support Care Cancer. 2003 Mar;11(3):190-2. Epub Jan 16, 2003

Pulmonary physiopathology unit

DIRECTOR:
VINCENZO CILENTI, MD

Vincenzo Cilenti, graduated in Medicine and surgery (1970) suma cum laude at La Sapienza University, Rome, and specialized in Anesthesiology and Intensive care at the University of Siena, 1974 then in Phthisiology and diseases of the respiratory apparatus at the University of Rome 1981. He was an associate researcher with the Regina Elena IRCCS, and then became Assistant (1973) and later Aid (1981) in the Anesthesia and Intensive care Service, carrying out his work nearly exclusively in the Intensive care Center. From 1990 he has been the Director responsible for the Autonomous Physiopathology Respiratory Service for the Regina Elena Institute (2000) latter called the Struttura Semplice Dipartimentale (S.S.D.). Over the years he has published works on anesthesia, intensive therapy, parenteral nutrition and pain and pneumonolgy therapy. For some years he has dedicated himself to the prevention and treatment of smoking addiction and smoke related lung disease. He is a member of Scientific Associations and regional and national work groups also for drawing up guide lines. He is Vice President of the Ethical Committee ASP Lazio for oncologic screening. Since 2001 he has been a Contract Professor in Pharmacology and Diseases of the Respiratory apparatus for the Graduate Course in Nursing Science at La Sapenza University, Rome.

Staff:
DR. MARIA PAPALE - M.D.
DR. GIORGIO PIPERNO - M.D.
MRS. MARINA BONACCORSI - physiotherapist
MRS. ILARIA LA VALLE - physiotherapist

Clinical-Scientific Activity Of The Service 2003

The Physiopathology Respiratory Service has forwarded its traditional mission addressing and programming its research activity through useful objectives aimed at the prevention, diagnosis, cure and rehabilitation of pulmonary diseases. The directives have been; the primary and secondary prevention in the field of pneumology through education (above all concerning addiction to smoking) and participation and programming of screening, clinical-functional diagnostics, respiratory therapy and rehabilitation for both inpatients and outpatients, participation in research programs and internal and external work groups of the Institute, participation and organization of courses, conferences and congresses both for reports as well as professional updating. During 2003 11,533 services (visits, consultations, instrumental tests and FKT) have been conducted on behalf of the directors of the Institute. Cooperation with the Department of Surgery, above all Thoracic and Abdominal Surgery for a more accurate identification of surgical risks, has been particularly intense. The preoperative evaluation of patients due to undergo major surgery has been the main focus of a monothematic seminary (Nov. 2003) entitled 'Principles of evaluation of surgical risks' carried out by the Institute in cooperation with the Department of Cardiology and Anesthesiology (Department of Critical Areas).
There have been a total of 6,804 services (visits, instrumental tests) conducted for outpatients. These are referred to the Territorial Service for pathologies of pulmonary oncology and others, they are directed to the Center for the treatment of smoke related diseases (Referral Center for the Observation of Smoke, Alcohol and Addiction of the I.S.S) or are in need of respiratory rehabilitation.
Respiratory rehabilitation is offered to inpatients and outpatients, most of the latter have already undergone pulmonary resection for tumors with the objective of improving their quality of life and also to improve our knowledge, in a scientific context, of an area of respiratory rehabilitation, which requires further study. In 2003 626 patients were treated, the equivalent to 2,931 services.
One hundred and eighty nine individuals sought the help of the Center for the treatment of smoking. For the past two years cooperation with the Department of Psychology of the IRE with the aim of evaluating the validity of integrated pharmacologic treatment (sub-

stituted with nicotine or with Bupropion) and behavioral treatment of addiction to smoking, has been fruitful. The preliminary results of this cooperation were presented verbally at the Eighth National Congress of SIPO (Societá Italiana di Psicologia Oncologica, Oct 2003) entitled: 'Integrated Strategy to terminate addiction to smoking'.
As regards the efforts to prevent smoking, the focus has been aimed at educational and didactic intervention for young people in schools. In particular, the Service has represented Italy (along with the Service for Integrated Epidemiology and the Information System of IRE) in coordinating the European Project "Don't start, quit & win" for the second year in a row. Ten countries participated in the project financed by the European Commission (ENYPAT- European Network Young People Against Tobacco) and the idea had the objective of inducing young smokers between 14 and 21 to stop smoking as well as reinforcing the determination of nonsmokers to remain such. The service has elaborated didactic materials, organized educational meetings with teenagers and teachers in high schools, concerning smoking related problems. At the end of the didactic-educational phase a competition to quit smoking for a month was carried out for young smokers from high schools participating in the Lazio Region, and a prize was offered to the participants. The data obtained from the questionnaires handed out to the participants included questions concerning the various aspects of smoking addiction in young people, the results of the questionnaires were subsequently statistically elaborated and will be published.
The Service participated in the work group of the AIPO-ANCO (Associazioni Nadionali degli Pneumologi e dei Cardiologi) to gather data on the incidence of smoking amongst young people in the Lazio Region, the preliminary results of which have already been published (see below). The group has also promoted the project 'Hospital free of smoke' and organized related meetings such as the Breakfast-meeting (October 2003) on 'Passive smoking and safeguarding the health of workers' on behalf of the Institute.
The Service of Respiratory Physiopathology also participates in the Project headed by the Department of Radiology and Imaging Diagnostics for the IRE which intends to validate the methods of screening for pulmonary tumors in asymptomatic smokers by low dose spiral CT. The first results of this study were presented at the Ninth International Conference on screening of pulmonary tumors (Miami, October 2003): 'Screening for lung cancer with low dose spiral CT in asymptomatic smokers: preliminary data'.
Another interesting cooperation was carried out with the Department of Radiotherapy in an observational study on the correlation between the two-dimensional measurement of the quantity of lung comprised in the field of therapy and the volume of irradiated lung in the complementary radiotherapy of operable mammary carcinoma. The functional evaluation of the respiratory apparatus of the patients, before the beginning of treatment and during the subsequent follow-up at a year and a half, is aimed at evaluating the incidence, with relative methodical radiotherapy, of the possible post-actinic pulmonary lesions.
The Service has taken part in a national multicenter study, coordinated by AIPO, on the correct use of inhalers in pneumological clinical practice, the preliminary results of which were presented at the XXXVII National AIPO Congress (October 2003) entitled: "Progetto Geina: uso degli inalatori pressurizzati convenzionali nella pratica clinica degli anni 2000' and two articles have been published in specialized journals.

Publications 2003

V. Cilenti

"Il tabagismo e il medico di famiglia. La nocività del fumo di tabacco".

Il Policlinico, volume 109, num.11, pg.549-558, Nov. 2002 (edited in 2003).

A.S. Melani, M. Pirrelli, V. Cilenti et al.

"GENEBU Project Equipment and drugs used for home nebulizer therapy in Italy"

Monaldi Arch. Chest Dis, 57: 5-6, 231-236, 2002 (edited in 2003)

AIPO AND ANMCO STUDY

"Rilevamento sull'incidenza del tabagismo nei giovani della Regione Lazio"

Rassegna di Patologia dell'Apparato Respiratorio, vol.18, num.5, pag.442, October 2003

C. CINTI, V. MARIANO, V. CAPPIELLO, V. CILENTI ET AL.

"Survey on the modalites of use of aerolizer: preliminary results of a multicenter study in Italy. GEINA Project".

Rassegna di Patologia dell'Apparato Respiratorio, vol.18, n.5, pag.352-357, October 2003.

Division of anesthesiology

DIRECTOR:
LUIGI ALOE, MD

Doctor Aloe graduated in medicine and surgery in 1966 from the University of Siena. In 1968 he specialized in Anesthesiology at the University of Siena and in 1972 he obtained a second specialization in Intensive Care at the University of Verona. In December 1966 he became a Medical Intern in Anesthesiology and Pain Therapy at the Regina Elena Institute, Rome. In 1967 he was granted a scholarship on Cellular Biochemical Modifications in Hypothermic Perfusion from the Ministry of Health.
He became an assistant in Anesthesiology and Intensive Care for Pain Therapy at the Regina Elena Institute, Rome, in 1969. He was an Assistant Intern in Anesthesiology, Intensive Care and Pain Therapy at the Regina Elena Institute, Rome from June 1974 to May 1975.
In May 1975 he became a full time assistant at the above mentioned Institute. In 1985 he was responsible for a project "Terapia Antalgica ed aspetti logistico organizzativi nell'ambito del progetto finalizzato del Ministero della Sanità: Assistenza al malato terminale" of the Regina Elena Institute. In December 1988 he was responsible for the Anesthesiology sector of the Intraoperative Radiotherapy Research Protocol (IORT). Since June 1991 he has been Director of Anesthesiology and the Operating Room of the IRE. From March 2001 he has been the Director of the Department of Critical Areas of the Oncology Group of the Regina Elena, Rome. Doctor Luigi Aloe is the author of various publications and has participated in numerous national and international congresses both as a spokesman as well as for professional retraining.
He has focused his professional and scientific interests on the problems of anesthesia in oncological surgery and during his career has developed detailed studies on acute and chronic pain therapy in neoplastic patients.

Anesthesiology Staff:
DR. ESTER FORASTIERE
DR. PIERA DI ANGELO
DR. M. MADDALENA GIOVANNETTI
DR. FRANCESCA PRINCIPI
DR. M.CARLA SOFRA
DR. PAOLO MORICCA
DR. FILIPPO GIANSANTE
DR. MARCO FIOCCA
DR. MICHELA MARITTI
DR. SABRINA CRECCO
DR. LORETTA TESSITORE
DR. CLAUDIA FRIGERI
DR. LUANA FABRIZI
DR. CRISTINA DANTIMI
DR. SALVATORE SALERNO - Responsible Dept. Day Surgery

2003 Activity

The main activity of the Department of Anesthesiology is carried out in the operating room, daily guaranteeing adequate assistance in anesthesiology to all those patients, undergoing different kinds of surgery.
An always greater complexity of oncologic pathologies and increasingly more aggressive and destructive surgery require constant and qualified research for anesthesia protocols and therapeutic strategies aimed at assuring minimal risk for the patient.
The treatment protocols are constantly up-dated in accordance with the most recent findings in the pharmacological and technological fields and have accorded notable impetus in all the surgical activities at the IRE.
In fact, in 2003 there have been 4,961 routine and major surgeries (23 liver transplants), with an increase of almost 13% compared to 2002.
Furthermore, the Department of Anesthesiology has greatly contributed to the development of pre-hospitalization, begun in 2002 in an experimental manner, and in 2003, carried out 980 examinations on patients from other surgical services of the Institute.

In 2003 we evaluated the hemodynamic effects of two different concentrations of local anesthetics (Robivocaine) in peridural anesthesia for elderly patient with the aim of preventing the hemodynamic effects of the drug, such as hypertension and brachycardia.
Moreover, the P.V.C changes during major hepatic resections have been evaluated taking into consideration the importance of maintaining a low P.V.C. in this sector of surgery in order to prevent significant blood loss.
Our previous work on the use of N2O in neuro-anesthesia has allowed us to standardize a anesthesia technique, TIVA (Total Intravenous Anesthesia), in this delicate sector. This technique allows the production of an adequate anesthesia level for surgical requirements, guaranteeing a rapid reversion of the effects and the possibility of minimizing any hemodynamic and postoperative repercussions attributed to inhaled anesthetics.
This technique has also allowed the optimization and programming of an adequate postoperative analgesia.
The study of the rheologic problems of reconstructive therapy with tumor flaps of the cervical-facial area, started in 2002, has led to the creation of a protocol of anesthesia which includes not only an adequate preparation of the patient in the preoperative phase but also a standardization for behavior in anesthesiology as well as strict postoperative control. The final aim being the prevention of complications or adverse situations which could irreparably impair the life of the flap.
A protocol was drawn up, in cooperation with the Department of O.R.L and Plastic Surgery in patients undergoing highly destructive surgery with reconstruction of microvascular flaps, using pre-deposited blood of the patients, which permits the optimization of anesthesiology treatment and limited the possible and feared complications of this delicate sector of surgery.
The application of this protocol includes the autologous transfusion via reinfusion of ones own blood, as well as an adequate hemo-dilution and a thrombo-embolic prophylaxis.
In terms of survival, increasingly frequent radiotherapy treatment of prostate tumors has proven as effective as surgery. However, this causes severe bladder and rectal complications as a consequence of the inflammation of the mucosa.
With this in mind, we begun a study aimed at proving the efficacy of COX-2 inhibitors in reducing such side effects, compared to conventional treatment with corticosteroids, in cooperation with the Department of Radiotherapy.
Resuming the administration of TNF with the aid of adequate monitoring systems in hypertermic antiblastic perfusion, has stimulated the study and the control of hemodynamic, oxyphoretic and metabolic modifications during treatment.
This has allowed the prevention of all the possible complications and harmful effects following treatment, via adequate anesthesiology and focused therapeutic strategies.
As for the control of postoperative pain, the effort of the entire staff of the Department of Anesthesiology in the research of new and personalized protocols of treatment which take the numerous variables that characterize post operative pain into account, is still ongoing.
Hopefully within the near future, the project "Hospital without Pain" launched by the Ministry of Health will be created, which would significantly contribute to elevating the level of the quality of cure in our Institute.

Publications 2003

Intratecal levobupivacaina for endoscopic urolological surgery.
MARANDOLA M., ERRIQUEZ A., FERRENTI L, FAZIO R., DI ANGELO P.
Delogu G. Glasgow - Euroanesthesia 2003 May 31-June 3, 2003

Cardiology Unit

DIRECTOR:
ITALO SACCHI, MD

Doctor Italo Sacchi was born in Rome, 19/5/1951. He graduated from La Sapienza University, Rome suma cum Laude in Medicine and Surgery. From the fourth year of the course he interned at Dr. Luigi Condorelli's school, under the direction of Professors Turchetti, Sangiorgi, Sciacca, Testoni, Corsi and Diagianti. He specialized summa cum laude in Diseases of the Cardiovascular System in 1980 at La Sapienza University, Rome and in 1986 he obtained a second specialization in Sports Medicine summa cum laude. He has worked in the Department of Cardiology of the Regina Elena Institute IFO, Rome since February 1983, first as an assistant in cardiology and from the 1st July, 1990 as a full time assistant. In 1989 he was appointed Director of Cardiology, and in May 2001 Director of the IFO Oncology Department of Regina Elena as well as the Dermatology Department San Galicano.
His scientific focus has been on instrumental non-invasive applied diagnostics, the study, prevention and cure of cardiac ischemia, cardiac imbalance, artery hypertension, clinical arrhythmology and cardiotoxicity from antitumor drugs.

Directors of Cardiology:
DR. ARMANDO CARPINO
DR. FABIO MARAMAO
DR. NICOLA MORACE
DR. GIUSEPPE TOGLIA

2003 Activity

As in previous years, the Department of Cardiology of IFO has significantly contributed to the current and institutional research of the Institute taking charge of instrumental clinical assistance and consultations for all the oncology patients of the Regina Elena Institute and the dermopathic patients of the San Galicano Institute.
Apart from general cardiac evaluations of oncology patients, undergoing surgery in order to define individual cardiac risk to prevent and control possible complications, the main objective of the Department is the prevention, early diagnosis and cure of the cardiotoxic effects of antitumor drugs, in particular derivatives of anthracyclines, as well as the harm caused by subsequent oncologic radiotherapy.
Current oncologic therapy makes use of new chemotherapeutics, both alone or in association, for primary and/or adjuvant neoplastic pathology (surgery, and marrow transplants), as well as the metastatic phase of solid and hematologic tumors.
A five-year prognosis, often positive in numerous clinical cases (80% average), can lead to the risk of chronic cardiotoxicity due to chemotherapy and the development of cardiomyopathy with a less positive prognosis than the same neoplasia months or years later (50% mortality in 5 years).
Besides anthracyclines, the drugs responsible are Cyclophosphamide in high doses, the monoclonal antibody Trastuzumab and the Taxines, often used in temporal or sequential association with each other, which increase the cumulative toxicity compared to each drug on its own. For example, Trastuzumab used alone can have a 7% cardiotoxicity, but when combined with anthracyclines, it can lead to a 28% risk. Furthermore, a high percentage (21%) of significant cardio- toxicity can occur with the combination of Doxorubicine and Paclitaxel. Moreover, radiotherapy associated with chemotherapy can further increase the risk.
Keeping the anamnestic risk factors in mind (age, sex, diabetes, left ventricular hypertrophy etc.) at the beginning of chemotherapy, there are no clinical indications which accurately predict the current individual risk of cardiomyopathy. Therefore, prospective monitoring remains the only means of identifying early signs of the development of heart difficulties in the preventive phase. This is due to the fact that the preventative strategies used by oncologists to modulate the schemes and doses or the administration times of chemotherapy drugs, do not always lead to a reduction of this risk.
From both the clinical, as well as the enzyopathogenic point of view (calcium overload, toxicity from free radicals, inhibition of the respiratory system, peroxidation of the lipid

membrane, iron chelation and changes in cellular apoptosis), cardiotoxicity is still a little known phenomenon. This might be due to the phenomenon's characteristics which, varied in their manifestations and in their prognostic implications, are often treated in a late phase when already evident, even obvious, highly symptomatic and often irreversible.
A complete evaluation of cardiotoxicity will only be possible when some essential points have been clarified, such as: the definition of screening tests able to identify subjects at risk; the modalities of development of functional myocardial depression from antiblastics; the diagnostic means to intervene in a pre-clinical phase, when cardiac dysfunction in an initial asymptomatic phase, has not yet manifested (sub clinical cardio- toxicity); the drugs used to prevent, interrupt, contain, and reverse the functional cardiac alterations caused by antitumor therapies, and finally, the underlying pathogenic and cellular mechanisms of fairly late or severe developments of cardiotoxicity.
From 2002, an outpatient clinic has been operating in our Institute, aimed at cardio-protection from cardiotoxicity caused by antiblastic drugs, identifying pre-clinical manifestations and setting up monitoring procedures in cooperation with the oncologists of the oncology patients with associated cardiovascular pathologies. Thus, defining the possible compatible therapeutic strategies which foresee variations in dosage, type and mode of administration of chemotherapeutic drugs, as well as fast cardiovascular and chemo protective therapies.
This form of activity employs cardiac diagnostics using imaging via color Doppler echocardiography both at rest or under forced stress, which has become the universally used method of monitoring the left ventricular systolic function (FE%), and, as an alternative and/or in particular cases, through perfusional myocardial tomoschintigraphy.
Based on the now obsolete consensus guidelines of 1992 the absolute value of EF greater than 50% and/or a reduction of no more than 15% compared to the initial value, suggest the exclusion of cardio-toxicity and the continual use of chemotherapy, if necessary.
However, numerous follow-up studies carried out during the past decade show a lack of accuracy, poor sensitivity and specificity of EF in predicting early sub-clinical cardio-toxicity.
This has lead to the need for new, non-invasive, more accurate diagnostic methods, specific for cardiac illnesses and the consequent ventricular dysfunction. This explains why current clinical studies are focused on researching new functional and biochemical markers.
In the first case, the early ventricular myofibril dysfunction, above all in its capacity of diastolic release, more than in its systolic contraction, has already been under analysis for some time, using echocardiography with Doppler analysis. However, ultrasonic tissue Doppler, along with conventional eco-Doppler parameters are mainly being used as a more sensitive and early means of studying the altered anatomic-functional properties of the myocardium caused by chemotherapeutics.
As for the biochemical markers, toponine (TnT and TnI) and the natriuretic cardiac hormones (BNP and NT pro-BNP) are being proposed as specific markers of left ventricular dysfunction in a sub-clinical phase as they are visible long before the pathologic reduction of EF.
The results obtained from recent studies and their use in yearly follow-ups, have shown a more sensitive and accurate variation trend in the parameters of tissue Doppler of the diastolic function and in the pro-BNP, at the end of the administration of the chemotherapeutic cycle, when compared to the conventional eco-Doppler parameters.
Furthermore, by the end of the therapy, the values of tissue Doppler and of pro-BNP in patients who develop class II or III NYHA (from 5% to 10% according to the type of chemotherapy) cardiomyopathy, within the first year follow-up, had undergone a profound change before the appearance of the illness, when the conventional indexes and above all those of the EF were within the norm.
In the interval between the appearance of the early signs of sub- clinical cardio-toxicity and cardio-myopathy, the major advantage will be the possibility of promptly changing the schemes of administration of the chemotherapeutics and of introducing cardio-protective drugs (ace-inhibitors, alfa-betablockers, etc.) able to modify the progression of cardio-my-

opathy and of its negative prognosis, mainly in those individuals who have a long life expectation with good quality of life. Therefore, this major sensitivity and specificity of the diastolic dysfunction, further validated by current studies and measured with the tissue Doppler technique, and of BNP dosage, such as accurate sub-clinical markers of cardiotoxicity, will not lead to an updating of the current guide lines on the toxic effects of chemotherapeutics on the heart.

As stated above, our Service is already oriented toward this new and more secure type of procedure and of monitoring cardio- toxicity, and the preliminary results of this particular activity seem to be in agreement with the above mentioned studies.

Accordingly the research of the various clinical institutional protocols, is carried out in cooperation with the Oncology Departments of the Regina Elena Institute, as specified below.

Besides the general preoperative cardiac evaluation, the other clinical activities of the Service include; cardiology support in intrahospital emergencies, in intraoperative cardiac complications or during the course of other diagnostic and/or therapeutic procedures, in post surgery cardiology assistance in the various departments as well as in intensive care.

In 2003 our cardiology service carried out almost 27,000 visits of which more than 30% were dedicated to outpatients.

The service is involved, along with all its components, in the following study protocols, assuring an ECG and echocardiogram during the cardiologic visit, before and during antiblastic treatment and in follow-up, as well as further stringent tests aimed at obtaining the sub-clinical signs of cardio toxicity and preventing the onset of cardiac disorders:

- With Medical Oncology A on the verification of cardio-toxicity, recently recognized and comparable to that of the anthracycline Trastuzumab (Hera trial, Hercepitin with or without other chemotherapeutics), on the efficacy and toxicity of progressive doses of Epirubicin + Docetaxel and anthracyclines Lipsomial + Gemcitabine, through echocardiographic monitoring, for metastatic mammary carcinoma.
- With Medical Oncology B, on the evaluation of cardiotoxicity due to anthracyclines and liposomial anthracyclines, through angiocardioscintigraphy monitoring (evaluation of the proto-diastolic release) and monitoring of the new biochemical serum markers (Troponine T, NT-proBNP, Myoglobine) in histologically and/or cytologically confirmed malign neoplasias, and of the Celix protocol through ecocadiogram and/or angiocardioscintigraphy, for metastatic mammary carcinoma.
- With Medical Oncology C, on the tolerability of the association between Paclitaxel + Epirubicin for metastatic mammary carcinoma through the uptake of the echocardiography indexes of the diastolic dysfunction and the release of Troponine T and Sieric Myoglobine after every cycle of chemotherapy.
- With the department of hematology on the evaluation and the eligibility of the patients with malign hemopathies who must undergo strict schemes of intensive and particularly aggressive poly-chemotherapy, including those candidated for autologous transplant of staminal cells through medical study and echocardiography monitoring.

Laboratory A of experimental chemotherapy

DIRECTOR:
GABRIELLA ZUPI, PHD

Gabriella Zupi received the degree in Biological Science in 1968 from La Sapienza University of Rome. In 1970 she was visiting Scientist at the Laboratory of Molecular Biology, University of Alabama, Birmingham, USA. From 1978-87 she was Biology Director, Regina Elena Cancer Institute of Rome, Italy. She has been Director of Lab of Experimental Preclinical Chemotherapy at Regina Elena Cancer Institute of Rome, Italy since 1988. Dr. Zupi's research interests are devoted to study the involvement of some oncogenes in tumor progression and in response to chemotherapy of solid tumors.

Staff:

DR. GABRIELLA ZUPI - Director
DR. CARLO LEONETTI - Assistant
DR. DONATELLA DEL BUFALO - Assistant
DR. ANNAMARIA BIROCCIO - Assistant
DR. FRANCESCA DI MODUGNO - Assistant
ANTONIO CANDILORO - Technician
CARMEN D'ANGELO - Technician
DR. BARBARA BENASSI - Fellow
DR. CHIARA GABELLINI - Fellow FIRC
DR. ANGELA RIZZO - Fellow
DR. LUDOVICA CIUFFREDA - Fellow
DR. SIMONA GIORGINI - Fellow
DR. DANIELA TRISCIUOGLIO - Fellow FIRC
DR. ADELE PETRICCA - Fellow
FABRIZIO BONAVENTURA - Technician
RAFFAELE DOCIMO - Technician
MARCO SCARSELLA - Technician
ROBERTA BONIFAZI - Student
VALERIA SPINOLA - Student

The work of our Lab is centered on three major issues.

1 MOLECULAR MECHANISMS INVOLVED IN BCL-2-INDUCED ANGIOGENESIS

Over the last few years we have focused our attention on the role of bcl-2 on angiogenesis at cellular and molecular levels. We demonstrated that bcl-2 overexpression in human breast carcinoma and melanoma cells synergizes with hypoxia to increase angiogenesis through upregulation of vascular endothelial growth factor (VEGF). We also found that bcl-2 overexpression in cancer cells exposed to hypoxia modulates the urokinase plasminogen activator receptor (uPAR) expression through Sp1 transcription factor, and that the extracellular regulated kinase (Erk) pathway plays a role in Sp1 transcriptional activity. In particular, an increase in uPAR protein and mRNA expression, was found in melanoma bcl-2 transfectants grown under hypoxia when compared to control cells, and a decrease of uPAR protein expression was induced by treatment of cells with specific bcl-2 antisense oligonucleotides. Upregulation of uPAR expression was accompanied by increased Sp1 protein expression, stability, serine-phosphorylation and DNA binding activity. Treatment of cells with Mitramycin A, an inhibitor of Sp1 activity, confirmed the role of Sp1 transcriptional activity in uPAR induction by bcl-2. The contribution of the Erk pathway in Sp1 increased transcriptional activity was demonstrated by the use of chemical inhibition. In fact, Erk kinase activation was induced in bcl-2 overexpressing cells exposed to hypoxia, and the Erk kinase inhibitor UO126 was able to down regulate Sp1 phosphorylation and DNA binding activity. Using a human breast carcinoma line, we obtained data supporting our findings with melanoma cells, and identified a link between the induction of Sp1 and uPAR expression as a common bcl-2-controlled phenomenon in human tumors. In conclusions, our results strongly indicate that upregulation of uPAR expression by bcl-2 in hypoxia is modulated by Sp1 DNA binding activity through the Erk signaling pathway.
We also demonstrated that the bcl-2/bcl-xL bispecific antisense oligonucleotide 4625 inhibits bcl-2 expression and angiogenesis in bcl-2 overexpressing clones derived from a human

melanoma cell line. The antiangiogenic effect was determined in *in vitro* and *in vivo* angiogenesis assays. In particular, a reduction of hypoxia-induced-VEGF secretion was observed after 4625 treatment, and the conditioned medium (CM) of bcl-2 overexpressing clones treated with 4625 and exposed to hypoxic conditions resulted in a decrease in endothelial cell proliferation when compared to CM of untreated control cells. In addition, we found that CM of 4625 antisense-treated bcl-2 transfectants inhibited *in vivo* vessel formation in matrigel plugs implanted subcutaneously in C57/Bl6 mice. Our findings confirm that bcl-2 plays a crucial role in melanoma angiogenesis and demonstrate that downregulation of bcl-2 by antisense treatment has the potential to inhibit angiogenesis independent of its effect on cell survival. The use of 4625 in cancer therapy is suggested as an approach to simultaneously facilitate tumor cell apoptosis and inhibit tumor angiogenesis.

Finally, we assessed whether Lonidamine (LND) interferes with some steps in angiogenesis progression. We reported that LND inhibited angiogenic-related endothelial cell function in a dose-dependent manner. In particular, LND decreased proliferation, migration, invasion, morphogenesis on matrigel and secretion of matrix metalloproteinase-2 and -9 of different endothelial cell lines. Vessel formation in a matrigel plug was also reduced by LND. The viability, migration, invasion and matrix metalloproteinases production of different tumor cell lines was not affected by low doses of LND, while the concentration of LND that corresponds to the dose used in clinical management of tumors, triggered apoptosis both in endothelial and tumor cells. Together, these data demonstrate that LND is a compound that interferes with endothelial cell functions, both at low and high doses. Thus, the effect of LND on endothelial cell function, previously undescribed, may be a significant contributor to the antitumor effect of LND observed for clinical management of solid tumors.

2 Combination targeted therapy for human solid tumors

Metastatic cutaneous melanoma is refractory to conventional therapy and current therapies are unable to significantly modify the prognosis of metastatic disease. Given then that, in the last decade the incidence of this malignancy has risen at a rate equal or exceeding the majority of all other human solid tumors, the development of new therapeutic strategies with preventive/therapeutic use is imperative. As increasingly evident, therapies based on the combination of conventional cytotoxic agents and targeted agents able to impair different molecular pathways that regulate tumor cell survival may be particularly advantageous. In this context, we are studying the ability of antisense oligodeoxynucletides complementary to oncogene-encoded mRNAs to reduce the activity of the targeted gene products and to increase the efficacy of chemotherapy.

In particular, we chose to target c-myc and bcl-2 oncogene that are involved in tumor cell growth, apoptotic signaling as well as cancer cell invasiveness and metastatization. C-myc overexpression is an independent negative prognostic marker for both primary and metastatic melanoma. We have demonstrated that the combination of cisplatin with c-myc antisense oligonucleotides, increases the cytotoxic activity of cisplatin by preventing cells from progressing through the cell cycle. Furthermore, in melanoma xenografts this treatment schedule resulted in a significant reduction in tumor mass and increased survival rates. In addition, we have demonstrated that c-myc antisense oligonucleotides are able to overcome cisplatin resistance in a human melanoma cell line intrinsically resistant to this compound. Finally, we have demonstrated that the biological activity and therapeutic efficacy of c-myc antisense therapy may be improved when these agents are administered in lipid-based delivery systems.

Bcl-2 expression in melanoma patients with regional lymphnode metastasis is also associated with a significantly short survival rate. Experimental and clinical data have demonstrated the efficacy of bcl-2 antisense in combination with dacarbazine and this treatment is now in Phase 3 clinical trials. Based on this evidence, in the attempt to further improve the response of human melanoma to the treatment, we have combined c-myc and bcl-2 antisense oligonucleotides with cisplatin. Our results demonstrate that the treatment of

melanoma overexpressing c-myc and bcl-2 protein with the combination produced a significant decrease in bcl-2 and c-Myc protein expression which in turn significantly increase the survival and cure melanoma bearing-animals. Moreover, the presence of targets is a prerequisite for the success of targeted therapy as the growth of melanoma which did not show detectable levels of both proteins were not affected by the combined targeted therapy, the efficacy of cisplatin alone being comparable to that observed treating animals with c-myc and bcl-2 antisense combined with the antineoplastic agent. While experimental and clinical studies are needed to improve the doses and sequences of administration to obtain higher cure rates as well as clinical studies oriented to select patients on the basis of the targets, our results suggest that the combination of different antisense oligonucleotides with anticancer drugs appears to be a promising antitumor strategy and worthwhile exploring clinically.

3 Biochemical and molecular mechanisms involved in the c-Myc-dependent chemosensitivity

This area of research aims at dissecting the mechanisms by which the down-regulation of c-Myc induces programmed cell death in melanoma cells in order to identify new therapeutic targets.

By using array technology, we revealed that down-regulation of c-Myc produced striking changes of gene expression in the section related to metabolism; where the expression of g-glutamyl-cysteine synthetase and GSSG-reductase was found to be significantly reduced. The decrease of both enzymatic activities caused a decrease in the intracellular reduced glutathione content (GSH) and a concomitant accumulation of its oxidized form. Moreover, cytochrome c was released into the cytosol at very early stages of apoptosis induction, long before detectable production of reactive oxygen species and activation of caspase-9 and -3.

We also demonstrated that alkylating agents, Cisplatin and Melphalan, triggered apoptosis in the c-Myc antisense transfectants, but not in the parental line. On the contrary, topoisomerase inhibitors, Adriamycin and Camptothecin, induced apoptosis to the same extent regardless of c-Myc expression. Moreover, in control cells treated with one of the alkylating agents or the other, GSH depletion achieved by BSO pre-incubation opened the apoptotic pathway. Conversely, ester-mediated increase of GSH abrogated apoptosis induced by Cisplatin and Melphalan.

We also found that inhibition of c-Myc caused a proliferative arrest of M14 melanoma cells by inducing a senescence-like phenotype. The c-Myc-induced crisis was associated with decreased telomerase activity and progressive telomere shortening. To test the hypothesis that both oxidative stress and telomerase dysfunction were involved in the c-Myc-dependent crisis, we directly inhibited telomerase function and GSH levels. Inactivation of telomerase by expression of a dominant negative form of reverse transcriptase, reduced the cellular life span by inducing telomere shortening. Treatment of cells with BSO decreased GSH content and accelerated cell crisis. Analysis of telomere status demonstrated that oxidative stress affects c-Myc-induced crisis by increasing telomere dysfunction, indicating that a cooperation between telomerase dysfunction and oxidative stress is involved in the cellular crisis.

The role of telomerase function on the c-Myc-dependent chemo-sensitivity has also been investigated. Reconstitution of telomerase activity in the c-Myc antisense transfectants improved telomere function and reduced the sensitivity to CDDP and ET-743. The decreased sensitivity to CDDP and ET-743 was mainly due to the ability of cells to recover from drug-induced damage, evaluated both in terms of chromosomal lesions and cell survival. The ability of hTERT-reconstituted cells to recover from drug-induced damage was attributable to restoration of cell cycle progression. In fact, the cells without hTERT restoration remained in the G_2/M phase for a prolonged time, and this cell cycle alteration made the drug-induced-S-G_2/M block irreversible and led to the activation of the apoptotic program. On the contrary, the hTERT-reconstituted cells quickly progressed through the cell cycle, thus acquiring the capacity to recover from drug-induced block and to protect themselves from the G_2/M phase specific drug-triggered apoptosis.

All together these results demonstrate that glutathione and telomerase play a key role in the melanoma response to chemotherapy, identifying GSH and telomerase as two important therapeutic targets.

Publications 2003

Tentori L., Portarena I., Barbarino M., Balduzzi A., Levati L., Vergati M., Biroccio A., Gold B., Lombardi M.L., Graziani G.

Inhibition of telomerase increases resistance of melanoma cells to temozolomide, but not to temozolomide combined with poly (adp-ribose) polymerase inhibitor.

Mol. Pharmacol. 63:192-202, 2003. *IF 5.480*

Biroccio A., Gabellini C., Amodei S., Benassi B., Del Bufalo D., Elli R., Antonelli A., D'Incalci M., Zupi G.

Telomere dysfunction increases cisplatin and Ecteinascidin-743 sensitivity of melanoma cells.

Mol. Pharmacol. 63: 632-638, 2003. *IF 5.480*

Leonetti C., Biroccio A., Gabellini C., Scarsella M., Maresca V., Flori E., Bove L., Pace A., Stoppacciaro A., Zupi G., Cognetti F., Picardo M.

Alpha-tocopherol protects against cisplatin-induced toxicity without interfering with antitumor efficacy.

Int. J. Cancer 104: 243-250, 2003. *IF 4.056*

Di Padova M., Bruno T., De Nicola F., Iezzi S., D'Angelo C., Gallo R., Nicosia D., Corbi N., Biroccio A., Floridi A., Passananti C., Fanciulli M.

Che-1 arrests human colon carcinoma cell proliferation by displacing HDAC1 from the p21WAF1/CIP1 promoter.

J. Biol. Chem. 278: 36496-36504, 2003. *IF 6.696*

Pace A., Savarese A., Picardo M., Maresca V., Pacetti U., Del Monte G., Biroccio A., Leonetti C., Jandolo B., Cognetti F., Bove L.

Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy.

J. Clin. Oncol. 21: 927-931, 2003. *IF 9.868*

Biroccio A., Amodei S., Antonelli A., Benassi B., Zupi G.

Inhibition of c-Myc oncoprotein limits the growth of human melanoma cells by inducing cellular crisis.

J. Biol. Chem. 278: 35693-35701, 2003. IF 6.696

Gabellini C., Antonelli A., Petrinelli P., Biroccio A., Marcucci L., Nigro G., Russo G., Zupi G., Elli R.

Telomerase activity, apoptosis and cell cycle progression in ataxia telangiectasia lymphocytes expressing TCL1.

Br. J. Cancer 89: 1091-1095, 2003. *IF 3.639*

Biroccio A., Leonetti C., Zupi G.

The future of antisense therapy: combination with anticancer treatments.

Oncogene 22: 6579-6588, 2003. Review. *IF 5.979*

Tentori L., Leonetti C., Scarsella M., D'Amati G., Vergati M., Portarena I., Xu W., Kalish V., Zupi G., Zhang J., Graziani G.

Systemic Administration of GPI 15427, a Novel Poly(ADP-Ribose) Polymerase-1 Inhibitor, Increases the Antitumor Activity of Temozolomide against Intracranial Melanoma, Glioma, Lymphoma.

Clin. Cancer Res. 9: 5370-5379, 2003. *IF 5.991*

Del Bufalo D., Trisciuoglio D., Scarsella M., Zangemeister-Wittke U., Zupi G.

Treatment of melanoma cells with a bcl-2/bcl-xL antisense oligonucleotide induces antiangiogenic activity.

Oncogene 22: 8441-8447, 2003. *IF 5.979*

Mottolese M., Buglioni S., Piperno G., Sperduti I., Giannarelli D. D'Angelo C., Cosimelli M.

Bio-pathological factors of prognostic value in colorectal adenocarcinomas.

J. Exp. Clin. Cancer Res. 22: 163-166, 2003. Supplement. *IF 0.754*

Chapter book

Del Bufalo D., Trisciuoglio D., Milella M.

Cross-talk between VEGF and Bcl-2 in tumor progression and angiogenesis.

In: VEGF and Cancer, Landes Bioscience, 2003.

Laboratory B of immunology

Director:
Pier Giorgio Natali, MD

Pier Giorgio Natali graduated in Medicine and Surgery in 1966, at La Sapienza University, in Rome. He received his postgraduate training (1968-1972) in the Immunopathology and Allergy-Immunology Dept.s at the Scripps Clinic Res. Found., La Jolla, USA. Certified by ECFMG (1975) and by the American Academy of Microbiology in Medical Lab. Immunology (1987). He has held the position of Visiting Professor in the Dept.s of Tumor Immunology at Scripps Clinic (1977-1978) and Pathology at Columbia University New York (1986-1988) and of Scientific Director of the Regina Elena Cancer Inst. (1995-2001). President of the Italian Cancer Society (1998-2000), Dr. Natali has been cofounder of the Chart of Paris (2000). His main research interest is the immunopathology and biology of human solid tumors with the aim of identifying diagnostic and therapeutic targets of clinical relevance.

Personnel

Staff Scientists:
Patrizio Giacomini - M.D.
Paola Nisticò, - M.D.
Oreste Segatto - M.D.

Post-doctoral Fellows:
Ezio Giorda - Ph.D
Leonardo Sibilio - Ph.D
Aline Martayan - Ph.D
Sergio Anastasi - Ph.D
Gianluca Sala - Ph.D
Duilia Del Bello - Ph.D
Belinda Palermo - Ph.D
Simona Cascioli - Ph.D
Alessandra Gasbarri - Ph.D airc Fellow

Ph.D students:
Giovanna Bronzi - B.Sc.
Eleonora Puggioni - B.Sc.
Jasminka Omerovic - B.Sc.

Marie Curie Training Site Fellows (Dr. Natali Coordinator, Drs F. Guadagni and M.G. Paggi Mentors):
Edit Andrea Nadasi - Ph.D
Fanny De la Iglesia Lopez - Ph.D
Martin Mojzisek - Ph.D
Alvaro Avivar Valderas - Ph.D
Ioana Laura Tuduce - Ph.D
Laurence Havard - Ph.D

Technicians:
Rocco Fraioli
Cynthia Full Reed
Emilio Camilli
Maria Vincenza Sarcone
Alessandra Ranieri

Biology Students:
Andrea Conidi
Elisa Melucci
Francesca Baietti
Fabiana Lucini
Valentina Federici
Elisa Lo Monaco
Gianpaolo Centra

Hosts
Maria Rita Nicotra - Istit. Biologia e Patologia Molecolari, CNR
Maurizio Alimandi - Ph.D Dip. Medicina Sperimentale e Patologia Univ. "La Sapienza"

Activities 2003

Understanding human cancer using Drosophila:

Recessive mutations of the Drosophila gene lethal(2)-tumorous imaginal discs (l(2)tid) cause neoplastic growth of the anlagen of the adult organs, the imaginal discs. We demonstrated that the three proteins encoded by this evolutionarily conserved gene, Tid50, Tid47, and Tid40, identified as members of the DnaJ cochaperone family, are destined for different cellular compartments, may be complex with many proteins in a developmental stage-specific manner, and are likely to be involved in different cellular processes. The cytosolic Tid47 molecule is a novel component of the Hedgehog (Hh)-Patched (Ptc) signaling regulating cell/tissue polarity and spatial patterning during development and is associated with human tumors, i.e. basal cell carcinoma (BCC) and medulloblastoma. We provide functional evidence for its direct in vivo interaction with the Hh-bound Ptc receptor during signal transduction. Because loss of l(2)tid causes neoplastic transformation of Hh-responsive cells, it is likely that Tid47 may at least act as a guardian of the Hh signaling gradient by regulating Ptc homeostasis in the tissue. Finally, we describe that the expression of htid-1, the human counterpart of l(2)tid, is altered in human BCCs. In these malignancies loss of htid expression correlates with loss of differentiation capacity of the neoplastic cells similar to that found in the Drosophila tumor model.
Since preliminary studies have revealed molecular interactions of htid-1 with the APC gene product, we will extend these studies in human colon carcinoma.

Malignant melanoma: biology and experimental therapy

Adhesion between the CD44s receptor and hyaluronic acid plays an important role in cell migration, tumour growth and progression. Although the alternative splicing of CD44 variant exons represents the principal regulatory mechanism of CD44-mediated functions, CD44v spliced variants are scantily expressed in melanoma cells. For this reason, we have investigated the possibility that post-translational modifications of the CD44 standard receptor could play a pivotal role in regulating CD44-mediated functions in melanoma. Using metabolic inhibitors of N- and O-glycosylation, as well as melanoma transfectants expressing CD44s O-glycosylation site-specific mutants, we performed structural and functional analysis of N- and O-deglycosylated CD44s molecules expressed in melanoma cells. We discovered that complete N- and O-glycosylation is not required by CD44s to be correctly expressed on the melanoma cell surface. Indeed, variably glycosylated and functionally different CD44s molecules were constitutively expressed in primary and metastatic lesions. Furthermore, we observed that changes in N- and O-glycosylation of CD44s could modulate its cleavage. In fact, spontaneous CD44s shedding was dependent on the presence of partial or complete O-glycosylation of four serine-glycine motifs localized in the membrane-proximal CD44 ectodomain. Mutation of these serine residues, as well as an extensive metabolic O-deglycosylation, strongly impaired spontaneous CD44 shedding. Furthermore, an O-glycosylation-independent mechanism of CD44 cleavage has been identified. This alternative mechanism of receptor cleavage is phorbol 12-myristate-13-acetate (PMA) inducible, mediated by metalloproteinase and requires the presence of N-linked sugar residues. Our findings demonstrate that the post-translational modification of CD44s represents the principal regulatory mechanism of CD44s-mediated functions in melanoma.
T cells engineered to express hybrid receptors with antibody defined specificity can successfully be targeted to tumor cells. We compared the function of receptors at single-cell level by using a T-cell line that expressed an activation-dependent EGFP-reported gene. The receptors, share the same extracellular antigen-binding part, joined to different intracellular signal transduction units. The antigen binding domain of the receptors was a single-chain fragment of a monoclonal antibody, which recognizes a High Molecular Weight Melanoma-Associated Antigen with high affinity. The intracellular tails were derived from the T-cell receptor zeta chain (TCR-zeta), from the B-cell receptor Ig-alpha molecule and from a mutated Ig-alpha molecule capable of stronger signal transduction. EGFP expres-

sion was induced by contact to melanoma cells in vitro only in T cells that expressed the chimeric receptor that contained the TCR-zeta intracellular tail. In these T cells, the co-expression of chimeric receptors that contain a mutated Ig-alpha tail lowers the threshold of T-cell activation and facilitates tumor recognition in vitro and in vivo. Given their specificity and efficiency, T cells grafted with these type of receptors may represent potential candidates for cancer passive immunotherapy and for the in vivo analysis of the trafficking of tumor specific T lymphocytes. The latter aspect is currently under investigation.

Additional studies in melanoma (gene profile and functional studies) have been conducted in collaboration with the research group of this Institute led by Dr. M.G. Paggi. Please see the dedicated report.

Novel therapeutic targets in neuroblastoma

Coexpression for c-Kit receptor and its ligand stem cell factor (SCF) has been described in neuroblastoma (NB) cell lines and tumors, also by our suggestion of an autocrine loop modulating tumor growth. We have now evaluated c-Kit and SCF expression by immunohistochemistry in a series of 75 primary newly diagnosed neuroblastic tumors. Immunostaining for c-Kit was found in 10/75 and for SCF in 17/75, with 5/10 c-Kit-positive tumors also expressing SCF. For both, c-Kit and SCF staining were predominantly found in the most aggressive subset of tumors, i.e., those amplified for MYCN: c-Kit was detected in 8/14 amplified vs. 2/61 single copy ($p<0.001$), and SCF in 9/14 amplified vs. 8/61 single copy tumors ($p<0.001$). Furthermore, the association of c-Kit expression with advanced stage (3 or 4) ($p=0.001$) and of SCF expression with adrenal primary ($p=0.03$) was substantiated. The in vitro activity of the tyrosine kinase inhibitor STI-571 (imatinib mesylate, Gleevec, Glivec) on NB cell lines positive or negative for c-Kit was also assessed. When cells were grown in 10% fetal calf serum, the 4 c-Kit-positive cell lines tested were sensitive to STI-571 growth inhibition to a different extent (ranging from 30 to 80%); also the c-Kit-negative cell line GI-CA-N was slightly affected, suggesting that other STI-571 targets operate in regulating NB proliferation. In addition, c-Kit-positive cell lines SK-N-BE2(c) and HTLA230, grown in SCF only, remained sensitive (40 and 70% of growth inhibition, respectively), while, in the same conditions, proliferation of the c-Kit-negative cell line GI-CA-N was not affected. Immunoprecipitation of c-Kit from cell lysates of SK-N-BE2(c) and HTLA230 cells grown in SCF and subsequent Western blot analysis of the immunoprecipitates revealed a sharp decrease of c-Kit phosphorylation after STI-571 treatment. These data demonstrate that both c-Kit and SCF are preferentially expressed in vivo in the most aggressive neuroblastic tumors and that their signaling is active in promoting in vitro NB cell proliferation that can be selectively inhibited by treatment with STI-571. These findings will be further validated on a larger cohort of human neuroblastomas which is now under scrutiny.

"Low profile" tumor escape and surveillance in the balance

(Patrizio Giacomini, MD)

The immune system adopts a general strategy for the recognition of altered and missing self, based on a delicate balance of opposing signals delivered by activating and inhibitory immune receptors expressed by cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, macrophages, and dendritic cells. The ultimate outcome of an immune response (escape or surveillance) depends on the expression of target molecules shifting this balance toward either direction. For instance, loss and down-regulation of Human Leukocyte Antigens (HLA) class I molecules may be important for keeping tumors below the T cell detection level, but may at the same time incite recognition by NK cells or other effectors of the adaptive as well as innate immunity. Unfortunately, this emerging concept of 'balanced' immune surveillance is not kept in due account by many tumor immunologists, who postulate HLA loss as the sole or major mechanism of tumor immune evasion. In contrast to this view, we favor the hypothesis that the maintenance of normal levels of expression (or even up-regulation) of HLA class I molecules may be favorable to tumors, at least in certain cases.

In order to systematically describe patterns of immune recognition of oncological relevance, we extensively characterized by Northern and/or Western blotting (e.g. mini-transcriptome/mini-proteome analysis) the expression of HLA-A, -B, -C, b_2m, and the members of the 'antigen processing machinery' of class I molecules (LMP2, LMP7, TAP1, TAP2, tapasin, calreticulin, calnexin, and ERp57) in a selected panel of early-passage tumor cell lines, as well as in paired cultures comprising melanoma cells and normal melanocytes from the same patient. We found that, approximately 97% of the 185 tested gene products were expressed (although often weakly), and in many cases coordinately regulated. Linked expression patterns could be hierarchically arranged by statistical methods, and graphically described as a class I HLA 'coordinome'. Deviations (both down- and up-regulation) from the coordinome expression pattern inherited from the normal, paired melanocyte counterpart, were allowed but limited in magnitude, as if melanoma cells were trying to keep a 'low profile' HLA phenotype (1). We conclude that irreversible HLA loss is a rare event, and HLA class I expression in tumor cells almost invariably results from global, coordinated, linked, to an extent predictable, and almost invariably reversible, gene regulatory (rather than gene disruption) events. In addition, a DNase I hypersensitive region within a putative far upstream regulatory region of the human HLA-DRA gene was identified in tumor cells and transgenic HLA-DRA mice that appears to be involved in the fine tuning of these (tumor) antigen presenting molecules in macrophages but not dendritic cells (2). These results exemplify the resolution power of model organisms (transgenic mice), and of the systematic description of expression profiles of functionally linked gene subsets within the same genetic background ('autologous' approach). They also suggest a novel model of immune surveillance against tumors based on overall HLA antigen recognition patterns. The predictive ability of such a model is being validated in different diagnostic and prognostic settings, in collaboration with the clinical departments of the Regina Elena Institute for Cancer Research, and our twin Dermatological S. Maria and S. Gallicano Institute.

Negative signalling to ErbB receptors: implications to breast cancer pathogenesis and therapeutics

(Oreste Segatto, MD)

Receptor tyrosine kinases (RTKs) control a wide repertoire of cellular programs, including cell survival, cell growth and proliferation, cell motility. While tightly regulated in normal cells, their signaling activity is often aberrant in normal cells. This may be caused by either receptor over-expression or mutational activation. The causal relationship between abnormal RTK activity and cancer pathogenesis has spurred intense research aimed at the discovery and clinical validation of novel drugs capable of interfering with RTK oncogenic signalling.

The erbB-2 RTK is abnormally expressed in 25% of breast carcinomas, most often due to *ERBB-2* gene amplification. This is associated with a more aggressive disease course and worse clinical prognosis. Trastuzumab, a humanized IgG1 against the erbB-2 extracellular domain, has been the first genomic research based drug to gain FDA approval for cancer treatment and is currently used in the adjuvant setting for the treatment of *ERBB-2* amplified breast carcinomas.

We are interested in studying mechanisms involved in negative regulation of erbB-2. Our laboratory has identified RALT/Mig-6 as a transcriptionally controlled feed-back inhibitor of erbB-2 mitogenic and transforming signals. Due to its function RALT is a candidate tumor suppressor gene/protein. We have pursued the mutational analysis of the *RALT* coding sequence in about 100 breast tumors and a dozen breast cancer cell lines. We have found no mutations, thus ruling out that *RALT* may undergo mutational inactivation in a sizable fraction of human breast tumors. Rather, we found that RALT expression is down-regulated in *ERBB-2* amplified breast cancer cell lines due to transcriptional repression of the *RALT* gene. Retrovirus mediated reconstitution of RALT expression in these tumor cells was sufficient to attenuate erbB-2 signaling and reduce cell prolifera-

tion. Furthermore, RALT reconstituted cells were more sensitive to Herceptin and could not be rescued from the cytostatic activity of Herceptin by administration of erbB ligands such as TGF-a or NRG1. Hence, down-regulation of RALT expression contributes to unleashing the oncogenic potential of aberrant erbB-2 signaling and may adversely impact on therapeutic responses to erbB-2 targeted therapeutic agents.

NEW MOLECULAR TARGETS IN BREAST TUMORIGENESIS. ANALYSIS OF THE INTEGRATED IMMUNE RESPONSE IN A LARGE COHORT OF BREAST CANCER PATIENTS.

(Paola Nisticò, MD)

The identification of the repertoire of molecules recognized by the immune system of cancer patients at different stages of the disease, is of major biological and clinical relevance, as the immune system continuously shapes the immunogenic phenotype of the developing tumor, by a complex process recently referred to as 'cancer immunoediting'.

Genetic changes continuously occurring during tumor development and progression lead to a number of mutant and/or aberrantly expressed proteins, which can potentially function as tumor associated antigens and elicit anti-tumor immune responses. However, the dynamics and the consequences of these events have not yet been fully elucidated. The SEREX (serological analysis of cDNA expression libraries) analysis of human tumors has identified a broad spectrum of tumor proteins capable of eliciting a humoral immune response in tumor patients.

We have recently identified through the SEREX approach in breast cancer hMena, as the human ortholog of murine Mena protein belonging to the ENA/VASP family of proteins that controls cell motility and cell-cell adhesion by regulating the actin cytoskeleton. These events are frequently deregulated in tumors. Following cloning and sequencing, three hMena isoforms were identified and we investigated their expression by Western Blot in a large panel of tumor cell lines of different histotypes and in a number of normal cells. We demonstrated that hMena is overexpressed in a high percentage of tumors with respect to the normal cells and that the isoforms are differently modulated in epithelial or mesenchymal cells.

In breast cancer we analyzed hMena expression by immunohistochemistry in a representative panel of benign, preneoplastic and neoplastic lesions. hMena, while undetectable in normal mammary epithelium and in benign lesions, is consistently overexpressed in tumors and in preneoplastic lesions at high risk of transformation, thus suggesting that hMena overexpression is an early event in breast tumorigenesis.

A cancer-restricted antibody response against hMena was demonstrated and we have identified three hMena peptides representing HLA-A2 restricted T cell epitopes recognized by CD8+ T lymphocytes of HLA-A2 breast cancer patients, as evaluated by *ex vivo* IFNg ELISPOT assay. This spontaneous CD8+ T cell response was in some instances concomitant with the antibody response in breast cancer patients, bearing hMena+ tumors. Furthermore, we established hMena specific T cell lines from different HLA-A2 positive patients, and functional studies have demonstrated that, at least one of the hMena peptides identified (hMena-502) is naturally processed in a breast cancer cell line as well as in a melanoma cell line.

We are exploring the biological role of the different hMena isoforms in breast tumorigenesis and we are evaluating the kinetics of the correlated immune response in a large cohort of high risk breast cancer patients, in order to gain insights in breast cancer biology and management.

Publication 2003

LOSCH O.F., R. MULLER, B. MUTSCHLER, D. NERI, P.G. NATALI, M. RETH, R. CARSETTI.

Activation of T cell via tumor antigen specific chimeric receptors: the role of the intracellular signaling domain.

Int J Cancer, 103: 399-407, 2003.

Baldi A., T. Battista, A. De Luca, D. Santini, L. Rossiello, F. Baldi, P.G. Natali, D. Lombardi, M. Picardo, A. Felsani, M.G. Paggi.

Identification of genes down-regulated during melanoma progression: a cDNA array study.

Exp Dermatol, 12 (2): 213-218, 2003.

Rosanò L., F. Spinella, D. Salani, V. Di Castro, A. Venuti, M.R. Nicotra, P.G. Natali, A. Bagnato.

Therapeutic targeting of the endothelin a receptor in human ovarian carcinoma.

Cancer Res., 63(10): 2447-2453, 2003.

Vitali R., V. Cesi, M.R. Nicotra, H.P. McDowell, A. Donfrancesco, O. Mannarino, P.G. Natali, G. Raschella, C. Dominici.

c-Kit is preferentially expressed in MYCN-amplified neuroblastoma and its effect on cell proliferation is inhibited in vitro by STI-571.

Int J Cancer, 106(2):147-152, 2003.

Canamasas I., A. Debes, P.G. Natali, U. Kurzik-Dumke.

Understanding human cancer using drosophila: Tid47, a cytosolic product of the DnaJ-like tumor suppressor gene l(2)tid, is a novel molecular partner of patched related to skin cancer.

J Biol Chem, 278(33):30952- 30960, 2003.

Fonsatti E., Altomonte M., Nicotra M.R., Natali P.G., Maio M.

Endoglin (CD105): a powerful therapeutic target on tumor-associated angiogenetic blood vessels.

Oncogene 22: 6557-6563, 2003.

Spinella F., Rosanò L., Di Castro V., Nicotra M.R., Natali P.G., Bagnato

Endothelin-1 decreases gap junctional intercellular communication by inducing phosphorylation of connexin 43 in human ovarian carcinoma cells.

J Biol Chem. 278:41294-41301, 2003.

Gasbarri A, Del Prete F, Girnita L, Martegani MP, Natali PG, Bartolazzi A.

CD44s adhesive function spontaneous and PMA-inducible CD44 cleavage are regulated at post-translational level in cells of melanocytic lineage.

Melanoma Res. 13:325-337, 2003.

Rosanò L., Spinella F., Di Castro V., Nicotra M.R., Albini A., Natali P.G., Bagnato. A.

Endothelin receptor blockade inhibits molecular effectors of Kaposi's sarcoma cell invasion and tumor growth in vivo.

Am J Pathol. 163:753-762, 2003.

10. Giorda E., Sibilio L., Martayan A., Moretti S., Venturo I., Mottolese M., Ferrara G.B. Cappellacci S., Eibenschutz L., Catricalà C., Grammatico P., Giacomini P.

The antigen processing machinery of class I human leukocyte antigens: linked patterns of gene expression in neoplastic cells.

Cancer Res. 63: 4119-4127, 2003.

Anastasi S., Fiorentino L., Fiorini M., Fraioli R., Sala G., Castellani L., Alema' S., Alimandi M., Segatto O.

Feedback inhibition by RALT controls signal output by the ErbB network.

Oncogene. 22(27): 4221-4234, 2003.

Tomassetti M., Feriotto G., Giacomini P., Giorda E., Bianchi N., Borgatti M., Finotti A., Mischiati C., Gambari R.

Identification of a novel Dbasel Hypersensitive site within the far upstream region of the human HLA-DRA gene.

Int. J. Mol. Med., 12(6): 929-934, 2003.

Mastrandrea F, Nicotra MR, De Vita L, Coradduzza G, Minardi A, Scarcia G, Manelli M, Cadario G, Parmiani S, Natali PG. Mite antigens enhance

ICAM-1 and induce VCAM-1 expression on human umbilical vein endothelium. Allergol.

Immunopathol. (Madr). 31 (5): 259-264, 2003.

Laboratory C of molecular oncogenesis

DIRECTOR:
ADA SACCHI, PHD

Ada Sacchi received her Degree in Biology summa cum laude in 1965 from La Sapienza University of Rome. From 1965 to 1966 was Assistant Professor at the Human Genetics Laboratory of the Catholic University of Rome, and from 1966 to 1969 was Research Scientist at the Laboratory of Animal Radiobiology, of the Atomic Energy Agency in Rome. From 1970 to 1973 was Assistant at the Biophysics Laboratory of the Regina Elena Cancer Institute of Rome, and from 1973 to 1987 was Associated Director of the same laboratory. Since 1987 she has been Director of the Molecular Oncogenesis Laboratory and since 2001 she directed the Experimental Oncology Department at the Regina Elena Cancer Institute.

Staff Molecular Oncogenesis Laboratory:

BLANDINO GIOVANNI - M.D., Senior Scientist
GRADI ALESSANDRA - Fellow
FALCIONI RITA - PHD, Senior Scientist
GRASSELLI ANNALISA - Fellow PHD, Student
PIAGGIO GIULIA - PHD, Senior Scientist
GURTNER AYMONE - Fellow
RIZZO MARIA GIULIA - PHD, Senior Scientist
LAPI ELEONORA - Fellow
SOSSU SILVIA - M.D., Senior Scientist
LAZZARI CHIARA - Fellow
ARMEZZANI ALESSIA - Fellow
MANNI ISABELLA - Fellow
BACCARINI ALESSIA - Fellow
MANCINI FRANCESCA - Fellow
BON GIULIA - Fellow Monti Olimpia Fellow
BOSSI GIANLUCA - Senior Fellow
NANNI SIMONA - Fellow
CECCHINELLI BARBARA - Fellow
PHD, STUDENT IOVINO ALESSANDRA - Fellow
CIUFFINI LAURA - Fellow
PRODOSMO ANDREA - Undergraduate
D'AMALAS ALEXANDER - Fellow
RICCIONI SABRINA - Fellow
DI AGOSTINO SILVIA - Fellow
RINALDO CINZIA - Fellow
DI STEFANO VALERIA - Fellow
STRANO SABRINA - Researcher
EMILIOZZI VELIA - Fellow
TIBURSI GIULIO - Chief Technician
FONTEMAGGI GIULIA - Fellow
D'ANGELO MARCO - Technician
FUSCHI PAOLA - Fellow
GENTILESCHI MARIA PIA - Technician

Activities 2003

The work of our laboratory is historically centered on these major issues:
1. P53 and p53 family members: tumor response and tumor progression
2. Signal control of cell cycle progression
3. Integrin signaling in growth control
4. Hormone regulation of telomere dysfunction in cancer

1. P53 AND P53 FAMILY MEMBERS: TUMOR RESPONSE AND TUMOR PROGRESSION

The p53 tumor suppressor gene is the most frequent target for genetic alterations in human cancers. The p53 gene product is a nuclear protein that exerts several biological activities ranging from growth arrest to apoptosis, differentiation, and senescence. These biological outputs are exploited by wild type p53 (wt-p53), at least in part, through the activation of a large plethora of target genes. Human cancers generally exhibit p53 mutations that abolish the

transacting activity of the wild type protein, but retain high expression of the full-length mutated protein that is localized preferentially in the nucleus. This observation suggested that some mutations of p53 might actively contribute to tumor progression through "gain of function" activities.

Two different explanations for GOF activity of m-p53 proteins have been proposed: 1) mutant proteins can function as transcription factors recognizing DNA binding sites different from those recruited by wt-p53, 2) mutant proteins through specific protein/protein interaction could bind, sequester and inactivate other tumor suppressor proteins. Recently identified p53 homologues, p73 and p63, have been shown to exert a suppressive function which is severely impaired if m-p53 proteins are present because of their specific interactions. Recent reports have, also, shown that in mutant-carrying p53 tumor cells, p63 and p73 are unable to recruit their target genes to induce apoptosis *in vivo*, thus, inducing increased resistance to antineoplastic drug treatments. The mechanism of physical association between p53 mutants and p73, responsible for transactivating activity inhibition, has been investigated in the attempt to define whether the nature of the mutant p53 engaged in this association might be relevant. Using the unique opportunity of the temperature sensitivity of *Xenopus* p53, we have demonstrated that binding of and interference with p73 require a change of conformation in the p53 protein. This interaction occurs through the DNA-binding domain of p53 only when it is in a denatured state. These results reinforced the notion that mutant p53 with a conformational change can act as a down-regulator of the p73 pathway in human cancer and could confer a selective survival advantage to the tumor.

The function of p73 proteins in different cellular and pathophysiological contexts is regulated not only through protein-protein interactions, but also by post-translational modifications. We found that p73 is a physiological target of the p34*cdc2*-cyclin B mitotic kinase complex *in vivo*. Both p73 and its isoforms are hyper-phosphorylated in normal mitotic cells and during mitotic arrest induced by microtubule-targeting drugs and p34*cdc2*-cyclin B phosphorylates and associates with p73 *in vivo*. The association results in a decreased ability of p73 to bind DNA and activate transcription in mitotic cells, thus indicating that M phase-specific phosphorylation of p73 by p34*cdc2*-cyclin B is associated with negative regulation of its transcriptional activating function.

We have, recently, shown that p53-dependent apoptosis is promoted by homeodomain-interacting protein kinase-2 (HIPK2), which is known to bind p53 and induce its phosphorylation in promyelocytic leukemia protein nuclear bodies (PML-NBs). To further investigate the role of this kinase and p53 activation during stress conditions, studies have been undertaken to evaluate whether the stress protein TP53INP1 might be involved in activation of p53 and its phosphorylation. The *TP53INP1* gene encodes two protein isoforms, TP53INP1a and TP53INP1b, located into the nucleus. Their synthesis is increased during cellular stress by p53-mediated activation of transcription. Overexpression of these isoforms induced apoptosis, suggesting an involvement of TP53INP1s in p53-mediated cell death. We found that 1) TP53INP1s localize with p53, PML-IV, and HIPK2 into the PML-NBs, 2) TP53INP1s interact physically with HIPK2 and p53, 3) TP53INP1s, in association with HIPK2, regulate p53 transcriptional activity on *p21*, *mdm2*, *pig3*, and *bax* promoters, 4) TP53INP1s overexpression induces G1 arrest and increases p53-mediated apoptosis. These results indicate that TP53INP1s and HIPK2 could be partners in regulating wt-p53 activity.

2. Signal control of cell cycle progression

Studies on transcription control of the cell cycle progression and differentiation have been particularly focused on understanding how NF-Y transcription factor regulates cell fate, cell proliferation and/or transformation, and cellular functions. The rationale is based on the consideration that the majority of the genes essential for the progression of the cells throughout the cell cycle phases are regulated, at transcription level, by the NF-Y complex. Most of the cell cycle regulatory genes are targets for NF-Y transcription factor, thus this complex could play a key role in the control of the cell cycle progression. Our work allowed the identification, during cell cycle checkpoints and differentiation, of a common mechanism of inactivation of

a class of cell cycle regulatory genes mediated by NF-Y. NF-Y is composed of three subunits, NF-YA, NF-YB, and NF-YC, all required for DNA binding. Recently we have reported that all subunits are expressed in proliferating skeletal muscle cells, whereas NF-YA alone is undetectable in terminally differentiated cells in vitro. By immunohistochemistry, we have shown that the NF-YA protein is not expressed in the nuclei of skeletal and cardiac muscle cells in vivo. By chromatin immunoprecipitation experiments, we demonstrated that NF-Y does not bind to the CCAAT boxes of target promoters in differentiated muscle cells. Consistent with these data, we found that the activity of these promoters is down-regulated in differentiated muscle cells, and forced expression of the NF-YA protein in cells committed to differentiate leads to an impairment in the down-regulation of cyclin A, cyclin B1, and cdk1 expression accompanied by a delay in myogenin expression. Thus, our results indicate that the suppression of NF-Y function is of crucial importance for the inhibition of several cell cycle genes and the induction of the early muscle specific program in post-mitotic muscle cells.

3. Integrin signaling in growth control

The a6b4 integrin was originally identified as a tumor-associated antigen (TSP-180). The integrin a6b4 is essentially expressed by epithelial tissues where it plays an essential role for the formation and the stabilization of the emidesmosomes. We have previously reported that b4-subunit expression correlates with the metastatic phenotype of mouse tumors and increases in human invasive carcinomas suggesting a role for this integrin during tumor progression. With the aim to understand the pathways of interaction between growth factors and integrins we also demonstrated that the laminin receptor a6b4 integrin associates with ErbB-2 tyrosine kinase in human mammary and ovarian carcinoma cell lines. We also found that the association of a6b4 integrin with ErbB-2 generates a strong activation of PI3K that results in a strong increase of invasion. These studies addressed for the first time the identification of a specific signaling pathway, activated by the b4 integrin subunit and ErbB-2 receptor interaction, which modulate the invasion. Both b4 integrin subunit and ErbB-2 receptor lack the consensus motif for p85 binding suggesting that the mechanism by which a6b4 and ErbB-2 cooperate to activate PI3K involves their synergistic activation of signaling intermediates that could represent potential targets for tumor therapy. Recently, by the use of two-hybrid system we found that b4 interacts *in vitro* and *in viv*o with a protein named WSB1 recently cloned in human and mouse. WSB1 is a member of the SOCS family and among this class of proteins its function in unknown. The relevance of b4 and WSB1 protein interaction in physiological and pathological conditions is now under investigation.

4. Hormone regulation of telomere dysfunction in cancer

Studies have been pursued through a close collaboration between the Molecular Oncogenesis Laboratory and Dr. Antonella Farsetti (CNR, Rome). The group has demonstrated that the catalytic subunit of human telomerase (hTERT) is a direct target of estrogen receptor signaling in normal and malignant hormone-dependent tissues, such as ovary, mammary and prostate human epithelium (Misiti et al., Mol. Cell. Biol. 2000 e Nanni et al. J. Clin. Invest. 2002).

The scope of the on-going project is to develop innovative therapeutical strategies for hormone-dependent cancers, in particular prostate cancer (PCa), based on modifications of Estrogen Receptor signaling through the use of Selective Estrogen Receptor Modulators, SERMs. The long-term goal of the research is to provide a rationale for the development of clinical trials aimed at preventing or curing PCa using hormone-based therapeutics capable to inhibit telomerase activity, and hence cancer progression.

To pursue this goal, the group has established a large number of independent populations of epithelial cells freshly explanted from PCa specimens. Using this unique experimental material, she has set out to gather interrelated information directed at the identification of molecular targets and mechanisms which may be relevant to PCa development and progression. In this context great emphasis is given to recently obtained data deriving from gene expression profiles of PCa-derived cells analyzed before and after treatment with a combination of se-

lective estrogen receptor modulators (SERMs) and/or anti-androgens to identify novel hormone-responsive genes. In this regard, the research project has both basic and translational relevance.
Validation of the experimental cellular model for the identification of novel biomarkers potentially useful in predicting biological responses to therapy and eventually disease outcome, has been obtained in pilot experiments in which was analyzed the gene expression profile of 16 independent PCa cell populations. A restricted number (200) of genes resulted significantly regulated across the samples (at least a two-fold difference) and appears to be organized in two clusters by means of an unsupervised two-dimensional cluster analysis. This peculiar distribution among samples suggests that test populations present a characteristic profile that might be correlated with clinical and/or histopathological data.

Selected Publications 2003

GURTNER A, MANNI I, FUSCHI P, MANTOVANI R, GUADAGNI F, SACCHI A, PIAGGIO G.

"Requirement for down-regulation of the CCAAT-binding activity of the NF-Y transcription factor during skeletal muscle differentiation".

Mol. Biol. Cell., 14: 2706-15. 2003

JURCHOTT K, BERGMANN S, STEIN U, WALTHER W, JANZ M, MANNI I, PIAGGIO G, FIETZE E, DIETEL M, ROYER HD.

"YB-1 as a cell cycle-regulated transcription factor facilitating cyclin A and cyclin B1 gene expression".

J Biol Chem., 278: 27988-27996, 2003.

ACOSTA JC, RICHARD C, DELGADO MD, HORITA M, RIZZO MG, FERNANDEZ-LUNA JL, LEON J.

"Amifostine impairs p53-mediated apoptosis of human myeloid leukemia cells".

Mol Cancer Ther., 2: 893-900, 2003.

ILLI B, NANNI S, SCOPECE A, FARSETTI A, BIGLIOLI P, CAPOGROSSI MC, GAETANO C.

"Shear Stress–Mediated Chromatin Remodeling Provides Molecular Basis for Flow-Dependent Regulation of Gene Expression".

Circulation Research, 93:155-161, 2003

PUXEDDU E., MORETTI S., GIANNICO A., MARTINELLI M., MARINO C., AVENIA N., CRISTOFANI R., FARABI R., REBOLDI G., RIBACCHI R., PONTECORVI A, SANTEUSANI F.

"Ret/PTC activation does not influence clinical and pathological features of adult papillary thyroid carcinomas".

Eur J Endocrinol., 148: 505-13, 2003.

ARDITO G., FADDA G., DANESE D., MODUGNO P., GIORDANO A., REVELLI L., ARDITO F., PONTECORVI A.

"Coexistence of a parathyroid adenoma and parathyroid cyst causing primary hyperparathyroidism".

J Endocrinol Invest., 26: 679-682. 2003

TOMASINI R, SAMIR AA, CARRIER A, ISNARDON D, CECCHINELLI B, SODDU S, MALISSEN B, DAGORN JC, IOVANNA JL, DUSETTI NJ.

"TP53INP1s and homeodomain-interacting protein kinase-2 (HIPK2) are partners in regulating p53 activity".

J Biol Chem., 278: 37722-37729, 2003

Fulco M, Costanzo A, Merlo P, Mangiacasale R, Strano S, Blandino G, Balsano C, Lavia P, Levrero M.
"p73 is regulated by phosphorylation at the G2/M transition".
J Biol Chem., 278: 49196-49202. 2003

Strano S, Blandino G.
"p73-mediated chemosensitivity: a preferential target of oncogenic mutant p53".
Cell Cycle., 2: 348-349. 2003.

Bensaad K, Le Bras M, Unsal K, Strano S, Blandino G, Tominaga O, Rouillard D, Soussi T.
"Change of conformation of the DNA-binding domain of p53 is the only key element for binding of and interference with p73".
J Biol Chem., 278: 10546-10555, 2003

Laboratory D of virology

DIRECTOR:
ALDO VENUTI, MD

Aldo Venuti received his MD in 1979 and specialized in Clinical Pathology in 1983 at the "La Sapienza" University of Rome Medical School. He received his PhD in 1986 in Microbiology and Epidemiology at the "La Sapienza" University of Rome. From 1982 to 1983 he was Director of Clinical Pathology Laboratory at BioLab Company, Rome. In 1984 was research associate at the Dept. of Biology, Indiana University (USA) where he was lecturer on molecular cloning techniques. Since 1985 he was Group Leader at the Laboratory of Virology, Regina Elena Cancer Institute, Rome and from 2003 he is responsible of it. He was visiting scientist at the Beatson Institute for Cancer Research, Glasgow, Scotland (1988-1989) and at the Center for Immunology and Cancer Research, University of Queensland, Brisbane, Australia (1998). Since 1999 he is Professor of Clinical Pathology at the Nurse School of the "La Sapienza" University, Rome and from 2003 he is also Professor under contract at the Faculty of Veterinary, "Federico II" University, Naples. He is currently member of the Società Italiana di Virologia (SIV), Società Italiana di Cancerologia (SIC), and International Papillomavirus Society (IPS). Dr's Venuti research interests are focused on DNA tumour viruses; in particular on molecular biology and epidemiology of HPV infections and on the development of new therapeutic strategies against HPV and associated cancers. In this area he holds an International Patent on subunit vaccines.

Researcher staff:
ALDO VENUTI - M.D., PHD
FEDERICO DE MARCO - M.D., PHD
GIANNA BADARACCO - MSC

Technician Staff:
ANTONIO MULLER - Senior Technician
SILVIO FLAMINI - Technician
SABATINO PETRELLI - Technical assistant

Post doc position:
DR. ALESSIA CIRILLI
DR. CONSUELO RIZZO
DR. PAOLA SIMEONE
DR. BARBARA MAFERA

Students:
FABIO DI DOMENICO
FABIO ISIDI
FRANCESCA PAOLINI

Collaborators:
DR. ELENA ILLIANO
DR. FEDERICA POGGIALI
DR. PASQUALINA MARZANO
DR. MAIJLINDA KOTA - Public Health Inst., Tirana
DR. KOZETA KULE - Public Health Inst., Tirana
DR. FATMA HOUISSA - Habib Tameur Hôpital, Tunis
DR. SOPHIE HALLEZ - Bruxelles Univ.
PROF. SAVERIA CAMPO - Glasgow Univ.
DR. MARZIA PERLUIGI - La Sapienza, Univ. Roma
DR. GIUSEPPE BORZACCHIELLO - Federico II, Univ. Napoli
DR. SANTE ROPERTO - Federico II, Univ. Napoli
DR. SILVIA MASSA - ENEA Roma
DR. ROSELLA FRANCONI - ENEA Roma

Scientific Activities

NEW DIAGNOSTIC STRATEGIES FOR HUMAN PAPILLOMAVIRUS (HPV) AND DETERMINATION OF PROGNOSTIC MARKERS.

Growing evidence suggest that some aspects of HPV infection may be used not only for the diagnosis but also for the prognosis of the lesion. The Virology Lab. is developing new

methods to obtain a definition of risk factors associated with different biological features of HPV infection. In particular the following features of viral infection, that may be correlated with the progression of the lesion, have been analysed:

- incidence of HPV, typing and intra-type variants by PCR and sequencing, in the attempt to define the role of the viral sub types;
- mRNA level for the HPV oncogenic proteins that are an index of active viral transcription, in the attempt to distinguish active from latent infection;
- viral load by quantitative PCR methods using dedicated real-time methods, in order to verify inter- and intra-tumour differences during the time;
- episomal or integrated state of viral genome through a dedicated method of PCR for the detection of infections due to evolve into neoplastic lesions.

These characteristics have been studied in a large number of gynaecological samples, mostly collected from patients attending, either the Gynaecology Division of our Institute or other National Medical Institutions. Samples deriving from patients from scientific institutions of other Mediterranean countries (Albania; Tunisia) were also analysed. In every population high risk HPV-16 confirmed to be the most prevalent type. However, there was a sharp difference in frequency from one region to another, as well as from that expected on the basis of global survey data. Striking differences were also observed in other less frequent types. These findings suggest that HPV distribution is far more complex at the regional level than commonly supposed. Regarding the viral genome physical status, available data indicated that a high frequency of integrated forms, both of type 16 and 18, are present in the neoplastic tissue as well as in the adjacent tumour-free area. This phenomenon could be responsible of the disease recurrence after surgery.

Detection of HPV in extra-genital tumours (head/neck and skin cancers) and in other animal species.

Head and neck. Data currently available are in favour of an association of HPV infection with tumours affecting specific subsites of head/neck region. However, present data are fragmentary because it is derived from studies carried out with inconsistent methodologies on heterogeneous populations. Therefore, the prevalence of HPV infection, its association with the clinical-histopathological features and its precise role in the neoplastic progression of head and neck lesions, is far from being established. To address these questions our group is carrying out studies on head/neck tumours collected from Otorhinolaryngology Division of San Carlo di Nancy Hospital (IDI-IRCCS) and from our Institute. In agreement with published results the presence of HPV is consistently observed in these samples, although to a lesser extent compared to the genital area. In particular, tonsil carcinomas are highly associated with HPV 16. The analysis of viral factors involved in neoplastic progression is currently in progress. The results will be correlated to expose other risk factors, to pathological parameters and clinical outcome. Final data are expected to be obtained at the end of the enrolment due in 2005.

Skin. Cutaneous HPVs have been detected in squamous cell carcinoma in EV patients (HPV5b, 21, 17). These results reinforce the hypothesis of an association between viruses and tumour progression. Studies are under way to evaluate the mechanism of cancerogenesis that seems to be linked to an inhibition of apoptosis rather than to an inactivation of oncosuppressor genes.

Animal species. Studies on papillomavirus infection in animals provide precious answers to questions pertaining to virus biology and address aspects of the natural virus history, otherwise almost obtainable in humans. For this reason the research for papillomavirus sequences has been extended to animal species, highly relevant to the human food chain. Our results indicate the PV involvement in bovine pathology such as oesophageal papillomas and urinary bladder carcinomas of cattle.

New therapeutic strategies against HPV infection and associated tumours.

DNA vaccines. The intrinsically poor immune response to natural viral infection is a key factor in anogenital HPV persistence and the consequent cancer development. To assess the

appropriateness of genetic immunisation in order to overcome this drawback a heterologous mouse model has been set up and used. Mice C57BL/6 were vaccinated with several HPV-16 E7 DNA constructs expressing either the unmodified E7 protein or fused to products able to target the fusion protein to the processing pathways of MHC class I or II molecules. Groups of vaccinated animals were challenged with different cancer cell lines engineered to express the HPV16 E7 protein. Each cell line was characterised by different levels of MHC class I on the cell surface. The different preparations elicited poor protection by i.m. administration except for the E7-Invariant Chain fusion protein (E7-Ii) that induced more pronounced inhibition of tumour growth. No differences were associated with the MHC class I status of the challenging cell lines, demonstrating that engineering the intracellular pathway for antigen presentation is able to produce a valid therapeutic response even against tumours with down-regulated MHC class I.

In another attempt to improve the efficacy of anti HPV vaccines the E7 gene has been fused to one of the coat protein (CP) of the vegetal virus PVX and cloned into the pcDNA plasmid. This PVX protein is known to have self assembling activity and it is a primary antigen for humans. In this fused E7/PVX construct the E7-Rb binding domain was mutated by base substitution to obtain an E7 domain with no or very low oncogenic activity and to maintain a correct folding, a Gly-Pro-Gly-Pro linker has been inserted between the E7 and CP protein. This recombinant plasmid proved to be able to induce a strong Th1 and Th2 response in mice, representing a possible therapeutic vaccine without oncogenic activity.

Finally the gene gun delivery system has been introduced in the schedule of vaccination improving the performance of the DNA vaccines that were being administered by i.m..

Plant extract vaccines. In previous works a transient expression of the HPV16 E7 protein has been obtained in tobacco plants by infection with the PVX recombinant virus. From data collected it is evident that PVX is a convenient, rapid and low cost plant expression system. Conclusive results in the mouse model developed in the Virology Lab. have now firmly established that the E7-containing foliar extracts act *per se* as a potent adjuvant. One explanation of this function may be the peculiar ability of the E7 protein in interacting with plant cell components, producing macro-aggregates able to induce strong Th1 immune response.

To increase the quantity of E7 protein into the plant extracts, constructs of the E7 gene have been made with an N-terminal signal sequence for targeting to the endoplasmic reticulum (ER). Protein targeting to the secretory pathway and, possibly, to the apoplast, might facilitate purification procedures, offering a natural way to concentrate foreign proteins. The signal peptide coding sequence of a bean protein, the Polygalacturonase-Inhibiting Protein (PGIP) has been utilised for this purpose. Plants infected the PGIP-E7 construct show a 5-fold increase of the expression levels compared to the cytoplasmic construct. This new PGIP-E7 plant extract has been analysed in our pre-clinical models by i.m. and oral administration. Preliminary results demonstrate an high efficacy for the i.m. administration while the oral delivery, although promising, requires further studies.

Animal models. Animal studies are essential for devising a candidate HPV vaccine to be used in clinical trials. The bovine papillomavirus (BPV) system has been utilised to explore the efficacy of vaccine strategy (particularly therapeutic) during the natural history of the disease. In the South of Italy we have identified a bovine population in which bladder tumours arise in BPV2 infected animals with enzootic hematuria. In these animals the presence of the E5 protein has been detected in both pre-neoplastic and neoplastic lesions but not in normal tissues. This is the first demonstration of E5 expression in naturally occurring BPV-associated urinary bladder tumours and reinforces the hypothesis that BPV remains latent in normal tissue until some factors triggers viral gene expression. Thus, this model is appropriate to check the activity of an anti-E5 vaccine. Moreover, the number of infected animals is quite large, BPV being present in up to 70% of tumours, facilitating the enrolment of a herd for a proposed study on a therapeutic DNA vaccine.

Endothelin-1 receptor antagonists in the treatment of cervix carcinoma. Previous research conducted in the Virology Lab have clearly indicate that:

I) ET-1 participates in the progression of neoplastic growth in HPV associated carcinoma, in which ET_AR are increased;
II) Treatment of mouse xenografts with a selective antagonist of ET_AR (atrasentan) are effective in reducing the number and the size of tumors produced by CaSki cells (HPV16 positive cell line of human cervix carcinoma);
III) This action is associated with a reduced vascularization and an increased apoptosis. Similar results have also been obtained in ovarian carcinoma. Starting from these results we have extended the study to other compounds. B-selective or non-selective ET-1 antagonists that are effective in blocking both type A and B receptors have been analysed. A truly 'balanced' ET_A/ET_B antagonist (A-182086), was the only compound able to affect growth rate. The A-182086 shows a similar potency to atrasentan. In conclusion targeting the ET_AR may be a valid tool in the therapy of cervix carcinoma. To validate this hypothesis the presence of these receptors and the E5 oncogene of HPV16 have been analysed in archival clinical samples by immunohistichemistry and real time RT-PCR. Data collected have indicated that it is possible to quantify precisely the expression levels, but only fresh samples guarantee the collection of the appropriate RNA. Therefore, fresh samples will be required to define the association between progression of displasia and expression of the viral E5 gene and ET-1 receptor type A.

MOLECULAR MECHANISMS OF CANCEROGENESIS:
E5 oncogene and apoptosis. Recent reports suggest that HPV E5 interacts with the cell cycle and concurs to the ability of HPV-positive keratinocytes to retain proliferative competence. HPV-16 E5 has been implicated in protecting cells from apoptosis induced by several stimuli (UV-B irradiation; FAS ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL). The inhibition of apoptosis in human keratinocytes could be a primary function of the HPV-16 E5 protein necessary to prevent apoptosis at early stages of viral infection. To dissect this phenomenon at the molecular level, two established cell lines, HaCaT E5 and E5RxR, and primary human keartinocytes have been employed. HaCaT cells have a mutated p53 and are suitable for the analysis of p53-independent apoptosis, whereas primary keratinocytes would give information on apoptosis in a normal p53 condition. The first cell line expresses the E5 protein under the control of a desamethasone inducible promoter, whereas the second one was established in our laboratory by transfection of HaCat cells with a plasmid carrying the HPV16 E5 sequence under a ponasterone inducible promoter. Primary keratinocytes obtained from human foreskins by standard procedure have been infected with a retrovirus expressing high levels of the E5 protein, the LZRS-16E5. All these cell lines have been treated with paclitaxel to induce apoptosis. Differences have been evaluated in E5 expressing cells by measuring apoptosis by several conventional methods like DNA ladder, FACS analysis, TUNEL assay and enzymatic cell death ELISA. Preliminary data indicate that E5 impairs paclitaxel-induced apoptosis in human keratinocytes.
Oxidative stress in HPV transformed cells. Oxidative Stress (OS) represents the common trait of several physical, chemical and biological toxic stimuli. OS plays a crucial role in several cellular functions, highly relevant for carcinogenesis. The epithelial tissues, the natural target of HPV infection are heavily exposed to oxidative stress that might therefore represent a key factor in viral carcinogenesis and tumour progression. To shed light on this possible connection, studies have been conducted on the role of OS in neoplastic progression, cell proliferation and cell death.
The effect of Reactive Oxygen Species (ROS) generated under sub-lethal UV-B irradiation on HPV-16 mRNA expression has been studied in human keratinocytes transfected with the whole HPV-16 genome (HK-168). This OS has induced a global reduction of viral oncogenes transcription that was followed by growth arrest and moderate apoptosis. HK-168, as well as other HPV transformed cells, appear rather resistant to OS compared with HPV negative cells. This difference in cell response seems to correlate with the activity of the NAD(P)H Quinone Oxidoreductase (NQO-1). This is a cytoplasmic mem-

brane-bound enzyme that, catalysing the two electron reduction of quinones to hydroquinones, prevents the semiquinone radical generation. Preliminary results indicate that this correlation does not depend on the physical interaction of NQO-1 t with the cellular p53, and suggest that the modulation of the viral E2 gene might be involved.
The study of the action of NQO-1 has also been extended to diploid melanocytes and to melanoma cells. In this cell setting the NQO-1 takes part in the generation of melanin precursors, and provides a mechanism for sinking quinones (highly reactive, potentially harmful compounds) into stable inert polymers (the melanins). This scavenging mechanism is also available in diploid keratinocytes where it may be relevant in sinking aldehydes and quinones into the lipo-fuscin pigments. Moreover, preliminary observation suggests that a similar mechanism may also be occurring in non related cell lines, namely neuronal cells where the detoxication of potentially hazardous compounds may fuel the unexplained pigment deposition into deep brain loci.

CONTROL OF KERATINOCYTE GROWTH AND DIFFERENTIATION IN THE PSORIASIS.

HPV5 induces cutaneous lesions in the skin of patients with *Epidermodysplasia Verruciformis* (EV) and the involvement of HPV5 subtype b is associated with the malignant transformation of EV lesions. Recently, patients with psoriasis have been proposed as a reservoir of HPV5. Psoriasis is a T-cell mediated inflammatory disease with release of a number of cytokines that may be the cause of the epidermal proliferation. Preliminary results are suggestive of an involvement of HPV type 5b in psoriasis. According to this view, the replication of HPV5b (in conjunction with a particular genetic background) may cause the epidermal hyperproliferation and antigen stimulation. This chronic antigene stimulation would induce autoimmune phenomena thus priming a vicious circle reinforcing the viral replication. This hypothesis may offer a rationale for therapeutic intervention aimed at eradicating viral replication and suppressing the stimulation of T-cells, inducing keratinocyte hyper-proliferation through cytokine production. Moreover, high levels of ET-1 have been found in psoriatic skin and in the serum of patients. Inflammatory cytokines like IL-1 alfa increase the production of ET-1 that, in turn, may lead to the chronic stimulation of keratinocyte proliferation. Studies are in progress to verify this hypothesis and to evaluate possible new therapies in controlling the skin proliferation of psoriasis by utilising ET-1 antagonists

Clinical outcomes

NEW TESTS FOR HPV TYPING

Validation of hybrid capture II (hcII Digene) as a screening tool for high-risk papillomavirus infection.

Viral integration as possible prognostic marker.

Atrasentan (ET_AR antagonist) as a possible therapeutic tool for cervix carcinoma

Plant (tobacco) production of a therapeutic vaccine against HPV16 (National and International Patent, together with ISS and ENEA).

Publications 2003

BORZACCHIELLO G., AMBROSIO V., ROPERTO S., POGGIALI F., TSIRIMONAKIS E., VENUTI A., CAMPO M.S., ROPERTO F.

Bovine papillomavirus type 4 in oesophageal papillomas of cattle from the South of Italy.

Comp Pathol. 128(2-3): 203-6. 2003

PERLUIGI M., DE MARCO F., FOPPOLI C., COCCIA R., BLARZINO C., MARCANTE M.L. CINI C.

Tyrosinase protects human melanocytes from ROS-generating compounds.

Biochem Biophys Res Commun. 305(2):250-256. 2003.

De Marco F., Hallez S., Brulet J.M., Gesche F., Marzano P., Flamini S, Marcante M. L. Venuti A.

DNA Vaccine against HPV-16 E7-expressing Tumour Cells.

Anticancer Res 23:1449-1454. 2003.

Rosanò L., Spinella F., Salani D., Di Castro V., Venuti A., Nicotra M.R., Natali P.G., Bagnato A.

Therapeutic targeting of the endothelin A receptor in human ovarian carcinoma.

Cancer Res. 63(10): 2447-53. 2003

Borzacchiello G., Iovane G., Marcante M.L., Poggiali F., Roperto F., Roperto S., Venuti A.

Presence of bovine papillomavirus type 2 DNA and expression of the viral oncoprotein E5 in naturally occurring urinary bladder tumors in cows.

J Gen Virol. 84(11): 2921-6. 2003

Laboratory A associated to surgical oncologic departement

DIRECTOR:
PIER GIORGIO NATALI, MD

Pier Giorgio Natali graduated in Medicine and Surgery in 1966, at La Sapienza University, in Rome. He received his postgraduate training (1968-1972) in the Immunopathology and Allergy-Immunology Dept.s at the Scripps Clinic Res. Found., La Jolla, USA. Certified by ECFMG (1975) and by the American Academy of Microbiology in Medical Lab. Immunology (1987). He has held the position of Visiting Professor in the Dept.s of Tumor Immunology at Scripps Clinic (1977-1978) and Pathology at Columbia University New York (1986-1988) and of Scientific Director of the Regina Elena Cancer Inst. (1995-2001). President of the Italian Cancer Society (1998-2000), Dr. Natali has been cofounder of the Chart of Paris (2000). His main research interest is the immunopathology and biology of human solid tumors with the aim of identifying diagnostic and therapeutic targets of clinical relevance.

Personnel

Staff Scientists:
ANNA BAGNATO - PH.D
VALERIANA DI CASTRO - PH.D
STEFANIA MICCADEI - PH.D
POST-DOCTORAL - Fellows
LAURA ROSANÒ - PH.D
FRANCESCA SPINELLA - PH.D FIRC Fellow

Technicians:
ALDO LUPO
GIACOMO ELIA
BIOLOGY STUDENTS
GIULIA GENOVESI
SAMANTHA DECANDIA

Hosts
DONATO CIVITAREALE - Ph.D, Ist. Neurobiologia e Medicina Molecolare, CNR

Activities 2003

ENDOTHELIN –1 RECEPTORS AS NOVEL TARGETS IN TUMOR THERAPY
(Anna Bagnato, Ph.D)

In ovarian carcinoma cells, engagement of the endothelin A receptor (ET_AR) by endothelin-1 (ET-1) triggers activation of multiple signalling pathways that lead to enhanced tumor cell proliferation, angiogenesis, survival and invasiveness. The acquisition of migratory and invasive abilities of tumor cells is also characterized by the loss in the gap junctional intercellular communication (GJIC), that enables tumor cells to overcome microenvironmental control of the host, to invade surrounding tissues and to metastasize. In ovarian carcinoma cell lines, ET-1 leads to a 50-75% inhibition in intercellular communication and to a decrease in the connexin 43 (Cx43)-based gap junction plaques. These mechanisms are due to a transient tyrosine phosphorylation of Cx43 induced by ET_AR-activated Src tyrosine kinase pathway, suggesting that ET_AR blockade may also contribute to the control of ovarian carcinoma cell and progression by preventing the loss of GJIC.

The recent identification of low molecular weight compounds that inhibit ligand-induced activation of the ET_AR now offers the possibility of testing this therapeutic approach in a clinical setting. ABT-627 (atrasentan) a small molecule ET_AR antagonist orally bioavalaible and with suitable pharmacokinetic and toxicity profiles, inhibits cell proliferation and VEGF secretion of ovarian carcinoma cell lines and primary cultures and sensitizes these cells to paclitaxel-induced apoptosis. In ovarian carcinoma xenografts, in which the ET-1/ET_AR autocrine pathway is overexpressed, tumor growth was significantly inhibited in ABT-627-treated mice compared with control. The therapeutic efficacy of ABT-627 was associated with a significant reduction in microvessel density, reduced expression of VEGF, MMP-2, Cx43 phosphorylation and increased percentage of apoptotic tumor cells. Com-

bined treatment of ABT-627 with paclitaxel produced additive antitumor, apoptotic and antiangiogenic effects.
A different approach in targeting the ET-1 receptor in cancer treatment is represented by Kaposi's sarcoma (KS) in which ET-1 acts as an autocrine growth factor through both ET_AR and ET_BR. Binding of ET-1 and ET-3 to both receptors increased the proliferation, migration and invasiveness of the KS derived cell line, KS IMM cells. Treatment of KS IMM xenografts with the small molecule ET_A/ET_B antagonist A182086 produced a tumor growth inhibition. Thus ET-1 receptor antagonists may be effective for treatment of this malignancy, being capable of interfering simultaneously with cell proliferation, invasiveness and angiogenesis.
On the contrary, in melanoma, multiple molecular pathways elicited by ET-1 and ET-3 are triggered by the ET_BR leading to the activation of all the molecular effectors involved in melanoma progression, including integrins, tumor proteases, cell-cell adhesion and communication molecules. The small molecule A-192621, an orally biovailable non peptide ET_BR antagonist, significantly inhibited melanoma growth in nude mice. Therefore, blockade of this receptor results in inhibition of melanoma growth in vitro and in vivo, offering an unprecedented opportunity of targeted therapy in this malignancy.
Nevertheless, aggressive tumor cells are endowed with multiple signaling molecules that could potentially counteract the blockade of the endothelin receptor. In future studies, we propose to expand the therapeutic repertoire of ET-1 receptor antagonists with other integrated protocols targeting multiple molecules to create the rationale to design novel clinical therapeutic approaches in cancer treatment.

Antioxidant and hepatoprotective effects of artichoke extracts

(Stefania Miccadei, Ph.D)

Epidemiological studies have shown that consumption of fruits and vegetables is associated with reduced risk of chronic diseases.. Diets rich in grains, fruits and vegetables are known to reduce cancer risk, implicating edible plants as potential sources of anticancer agents, many of these belong to the flavonoid family.
Extracts from artichokes, *Cynara Scolimus* have been claimed to exert a beneficial action against hepato-biliary disease, some of these effects are due to the antioxidative potential of artichoke extracts or their constituents that are mainly flavones, flavanones, flavonols and phenolic acids.
The therapeutic activity of the extract is probably due to the phenolic structure of these substances, that are responsible for the free radical mediated process inhibition. Free radicals and lipid peroxidation are known to play an important role in a great number of pathological states.
The purpose of this study, was to characterize the antioxidative, hepatoprotective and antiproliferative potential of extracts from the edible part of artichoke and to identify some of the constituents responsible for these effects.

- Extracts from artichoke protect against oxidative stress induced by hydrogen peroxide in cultured rat hepatocytes.
- The artichoke extracts diminished the loss of total cellular glutathione resulting from exposure to hydrogen peroxide and reduced the accumulation of lipid peroxidation induced by the oxidative stress.
- In a rat hepatoma cell line system, the extracts induced cells to undergo apoptosis in a dose-dependent manner. Because isolated human hepatocytes represent a valuable *in vitro* model to investigate the metabolism and cytotoxicity of xenobiotics, we will study the antioxidative and protective potential of artichoke in isolated human hepatocytes induced by oxidative stress. Further studies will be designed to investigate the effects of the artichoke on cell growth, cell cycle and apoptosis induction in human hepatoma cell lines.

We are performing these experiments in collaboration with Dr. G.Maiani (INRAN).

RETINOBLASTOMA PROTEIN AS A CO-ACTIVATOR IN THYROID SPECIFIC TRANSCRIPTION
(Stefania Miccadei, Ph.D)

We are studying the regulation of the tissue-specific gene expression in thyrocytes. We have focused on the role of the transcription factor Pax 8 in the control of the thyroperoxidase (TPO) gene promoter activity and we are interested in the identification of Pax 8 transcriptional co-activator. The retinoblastoma protein (pRB) is an important regulator of the cell cycle and works as a tumor suppressor. Although the exact mechanisms are not fully understood, pRb also plays a positive role in induction of tissue-specific gene expression. Furthermore, pRb enhances the transcriptional activity of several transcription factors including MyoD, MEF2 and C/EBPs

We have obtained experimental data suggesting that pRb cooperates with Pax 8 in the induction of the TPO gene promoter. We have found that Pax 8 and pRb directly interact and, through X-CHIP experiments, that pRb is bound to the same promoter in thyrocytes. Furthermore, utilizing the RNA interference protocol, we have been able to show that the pRb positive role on the TPO gene promoter is mediated by Pax 8.

In order to obtain some in vivo data on the pRb role in thyrocytes we are selecting a mouse strain with the somatic, tissue-specific and inducible pRb gene knock-out.

We are performing these experiments in collaboration with Dr. D. Civitareale(CNR).

Publications 2003

ROSANÒ L., F. SPINELLA, D. SALANI, V. DI CASTRO, A. VENUTI, M.R. NICOTRA, P.G. NATALI, A. BAGNATO.

Therapeutic targeting of the endothelin a receptor in human ovarian carcinoma.

Cancer Res., 63(10): 2447-2453, 2003.

SPINELLA F., ROSANÒ L., DI CASTRO V., NICOTRA M.R., NATALI P.G., BAGNATO A.

Endothelin-1 decreases gap junctional intercellular communication by inducing phosphorylation of connexin 43 in human ovarian carcinoma cells.

J Biol Chem. 278:41294-41301, 2003.

ROSANÒ L., SPINELLA F., DI CASTRO V., NICOTRA M.R., ALBINI A., NATALI P.G., BAGNATO.

A Endothelin receptor blockade inhibits molecular effectors of Kaposi's sarcoma cell invasion and tumor growth in vivo.

Am J Pathol. 163:753-762, 2003.

BAGNATO A. AND SPINELLA F.

Emergine role of endothelin-1 in tumor angiogenesis Trends Endocrinol.

Metab. 14:44-50, 2003

NELSON J., BAGNATO A., BATTISTINI B, NISEN P.

The endothelin axis: emerging role in cancer.

Nature Review Cancer 3:110-116, 2003

BAGNATO A.

Therapies for cancer targeting endothelin receptors.

Drugs of the Future, 28: 983-989, 2003

Laboratory B associated to medical oncology departement

DIRECTOR:
GABRIELLA ZUPI, PHD

Gabriella Zupi received the degree in Biological Science in 1968 from La Sapienza University of Rome. In 1970 she was visiting Scientist at the Laboratory of Molecular Biology, University of Alabama, Birmingham, USA. From 1978-87 she was Biology Director, Regina Elena Cancer Institute of Rome, Italy. She has been Director of Lab of Experimental Preclinical Chemotherapy at Regina Elena Cancer Institute of Rome, Italy since 1988. Dr. Zupi's research interests are devoted to study the involvement of some oncogenes in tumor progression and in response to chemotherapy of solid tumors.

Staff:

DR. MAURIZIO FANCIULLI - Assistant
DR. SIMONA IEZZI - Post-Doctoral Fellow
DR. FRANCESCA DE NICOLA - Post-Doctoral Fellow
CARLO DEL CARLO - Technician
TIZIANA BRUNO - Technician
ALBERTO CIOLFI - Student
ALESSIA VIVANTI - Student

Molecular characterization of Che-1 functions

Control of transcription and chromatin remodeling are the main areas of interest for Laboratory B. In particular, The members of Lab B are characterizing the functions of a novel human nuclear protein, Che-1, identified by a two-hybrid screening using the subunit 11 of RNA polymerase II. Che-1 is an ubiquitously expressed nuclear protein. The studies performed on this protein and its homologues in rat and mice strongly support the idea that Che-1 is involved in the regulation of gene transcription and cell proliferation. Che-1 directly interacts with Rb and the core of RNA pol II, it is down-regulated by TGF-b, and when fused to the GAL4 DNA binding domain transactivates GAL4 target reporters. The knockout of Traube, the murine Che-1, blocks early embryonic development and reduces cell proliferation. Che-1 contains a leucine zipper structure, several potential phosphorylation sites for different kinases, and three nuclear receptor-binding LXXLL consensus sequences. Although Che-1 does not possess a LXCXE motif, one of the two regions of interaction with Rb (aa 305-323) contains features that are conserved among viral Rb-binding proteins and HDAC1-3, with the importance predicted by crystallographic data and supported by peptide competition experiments. We have demonstrated that Che-1 contacts the Rb pocket region and competes with HDAC1 for Rb binding site, removing HDAC1 from the Rb/E2F complex *in vitro* and from the E2F target promoters *in vivo*. Furthermore, in this way we found that Che-1 expression can regulate E2F dependent transcription and cell proliferation, supporting a novel mechanism of Rb inactivation.
Despite the pro-proliferative role of Che-1/Traube, we observed that Che-1 is down-regulated in several tumors compared to matching normal tissue with an incidence of 80% in the colon carcinomas examined. In agreement with these data, Che-1 overexpression caused cell cycle arrest in human colon carcinomas cell lines through induction of the cyclin-dependent kinases inhibitor $p21^{Waf1}$ (p21).
We have investigated the expression of Che-1 in neuronal cells and we showed that Che-1 directly interacts with Tau, which is a microtubule-associated protein involved in the assembly and stabilization of the neuronal microtubule network that plays a crucial role modulating neuronal morphogenesis, axonal shape and transport. In rat cerebellar granule neurons (CGNs) Che-1 partially co-localizes with Tau in the cytoplasm, and we observed that Tau/Che-1 interaction is modulated during neuronal apoptosis.
Moreover, we have characterized the genomic organization of the mouse ortholog for Che-1 and the promoter region together with its activity. The promoter resulted TATA less and presented several potential transcription factor binding motifs. Importantly, we showed that Che-1 expression is regulated by a negative feed-back mechanism in which this protein binds its own promoter and represses its transcription.
Recently, we found that Che-1 is accumulated and phosphorylated in cells responding to

genotoxic agents, such as Doxorubicin and ionizing radiation. The DNA damage-activated checkpoint kinases ATM and Chk2 interact with and phosphorylate Che-1, enhancing its accumulation and stability, and promoting Che-1-mediated transcription of p53-responsive genes and of p53 itself, as evidenced by cDNA microarray analysis.

Publications 2003

De Angelis, R., Iezzi, S., Bruno, T., Corbi, N., Di Padova, M., Floridi, A., Fanciulli, M., Passananti, C.

Functional interaction of the subunit 3 of RNA polymerase II (RPB3) with transcription factor-4 (ATF4).

FEBS Lett., 547, 15-19, 2003. *I.F. 3,6*

Di Padova, M., Bruno, T., De Nicola, F., Iezzi, S., D'Angelo, C., Gallo, R., Nicosia, D., Corbi, N., Biroccio, A., Floridi, A., Passananti, C., Fanciulli, M.

Che-1 arrests human colon carcinoma cell proliferation by displacing HDAC1 from theP21WAF1/CIP1 promoter.

J. Biol. Chem., 278, 36496-504, 2003. *I.F.6,96*

Monaco, L., Passananti, C., Fanciulli, M.

Genomic structure and transcriptional regulation of Che-1, a novel partner of Rb.

Gene, 321,57-63, 2003. *I.F.3,41*

Barbato, C., Corbi, N., Canu, N., Fanciulli,M., Serafino, A., Ciotti, M.T., Libri,V., Bruno, T., Amadoro, G., De Angelis, R., Calissano, P. and Passananti, C.

Rb Binding Protein Che-1 Interacts with Tau in Cerebellar Granule Neurons: Modulation during Neuronal Apoptosis.

Mol.Cell. Neuroscience, 24,1030-1041, 2003. *I.F. 5,4*

Laboratory C associated to prevention and diagnosis department

DIRECTOR:
MARCO GIORGIO PAGGI, MD

Marco Giorgio Paggi graduated in Medicine & Surgery in 1978 at the University of Naples, Italy. He received his post-graduate training in: General Pathology (1981) at La Sapienza University, Roma, Italy; Biological Chemistry (1984) at Johns Hopkins University, School of Medicine, Baltimore, Maryland, USA; and Clinical Pharmacology (1989) at La Sapienza University, Roma, Italy.
Since 1990 he has been Staff Scientist at the Center for Experimental Research, Regina Elena Institute for Cancer Research, Roma, Italy. Since 2001 he has been Adjunct Professor at the Center of Biotechnology, Temple University, Philadelphia, PA, USA.
His main fields of scientific interest are focused on the molecular bases of cellular transformation and tumor progression, with the aim to identify sets of diagnostic, prognostic and therapeutic targets to be used in cancer clinical practice.

Staff Scientists:
ANNA MARIA MILEO - PH.D.
MAURO CASTELLI - PH.D.

Post-Doctoral Fellows:
ANNA SEVERINO - PH.D. (FIRC Fellow)

Ph.D. Students:
GIULIANO COTTONE - B.SC.
LUCREZIA MANENTE - B.SC.
ALESSANDRA TRITARELLI - B.SC.

Technicians:
ANTONIO FEDERICO
FRANCESCO GALLI

Marie Curie Training Site Fellows (Mentor: Marco G. Paggi):
EDIT ANDREA NADASI - PH.D.
ALVARO AVIVAR VALDERAS - PH.D.
IOANA LAURA TUDUCE - PH.D.

Biology Students:
MARA CAMPIONI

Guests:
DANIELA LOMBARDI - Ph.D. Associate professor, University of L'Aquila
EMANUELA PIOMBINO - B.Sc, Ph.D. Student, University of L'Aquila
ALFONSO BALDI - M.D., Assistant professor, 2nd University of Napoli
ANTONIO DE LUCA - M.D., Assistant professor, 2nd University of Napoli

Activities 2003

Our laboratory is essentially involved in studies regarding the molecular bases of cellular transformation and tumor progression, in order to identify sets of diagnostic, prognostic and therapeutic targets of potential interest in cancer clinical practice.

E1A deregulates the centrosome cycle in a Ran GTPase-dependent manner

The small DNA virus proteins E1A and E1B from human Adenovirus, E6 and E7 from human papillomavirus, and large T and small T antigens from SV40, are multifaceted molecular tools that can carry out an impressive number of tasks in the host cell. These viral factors, collectively termed "oncoproteins" for their ability to induce cancer, can be viewed as paradigmatic oncogenic factors which can disrupt checkpoint controls at multiple levels - they interfere with both 'gatekeeper' cellular functions, including major control pathways of cell cycle and apoptosis, and with 'caretaker' functions, thereby inducing mitotic abnormalities and increasing genomic instability.
Exploring the Adenovirus interactome by means of the yeast two-hybrid system, we have discovered a novel physical interaction between the Adenovirus E1A oncoprotein and Ran, a small GTPase which regulates nucleo-cytoplasmic transport, cell cycle progression,

and mitotic spindle organization. Expression of E1A elicits induction of S phase and centrosome amplification in a variety of rodent cell lines. The induction of supernumerary centrosomes requires functional RCC1, the nucleotide exchange factor for Ran and, hence, a functional Ran network. The E1A portion responsible for the interaction with Ran is the ENT (Extreme N-Terminal) region (amino acids 1-36), which is also required for induction of centrosome amplification. In an *in vitro* assay with recombinant proteins, wild-type E1A interferes with nucleotide exchange on Ran, while an E1A mutant, lacking the ENT region/deleted from the ENT region, does not. In addition, we detected an *in vitro* interaction between Ran and HPV-16 E7 and SV40 large T Ag, two oncoproteins functionally related to E1A. These findings suggest a common pathway of these oncoproteins in eliciting virus-induced genomic instability. In essence, we showed that interference with the control of the centrosome number is a novel function of E1A, which places E1A upstream of processes implicated in genomic instability. The finding that both E1A and E7 physically interact with Ran suggests that these oncoproteins - besides their established role in interfering with pRb/E2F-dependent pathways - can also deregulate the centrosome cycle by altering Ran GTPase-dependent control directly. Thus, indicating the Ran GTPase as a novel target of E1A in the pathways controlling centrosome homeostasis, might represent a novel shared function among the viral oncoproteins E1A, E7 and large T Ag. Acute expression of these oncoproteins can thus be viewed as a key event able to uncouple the centrosome cycle from the cell cycle, highlighting a direct link between viral infection and the induction of genomic instability.

Co-expression of Helicobacter Pylori's proteins CagA and HspB induces cell proliferation independently from the bacterial infection

Adenocarcinoma of the stomach is the second most common cause of cancer mortality in the world. The purpose of this study was to evaluate the potential role in carcinogenesis of two secreted *Helicobacter pylori*'s proteins, CagA and HspB, both shown to increase the risk of gastric carcinoma in patients infected with H. pylori-positive strain. The effects of these two proteins on cell kinetics and the ability to selectively affect the expression of cell cycle-related proteins by transfection of a human gastric epithelial cell line (AGS) were analyzed. Using a genomic library of *H. pylori*, we isolated and cloned *CagA* and *HspB* cDNAs. The effects of the overexpression of the respective proteins on cell growth were analyzed in AGS cells by immunoblots, proliferation assay, and flow cytometry. Coexpression of CagA and HspB in AGS cells in the first 48 h caused an increase of the level of E2F transcription factor, Cyclin D3, and phosphorylated retinoblastoma protein, all involved in the G1-S checkpoint of the cell cycle. Consistently, an increase of cell proliferation, corresponding to an augment of the fraction of the cells in the S-G2-M phase of the cell cycle, was also demonstrated. Moreover, an increase of c-jun protein levels, but not of c-fos, was also found after coexpression of CagA and HspB. All these data suggest that, at least in these cells, the development of cancer is not due to a nonspecific accumulation of random mutations, but may be triggered by hyperproliferative effects specifically due to some proteins produced by the pathogenic strains of *H. pylori*. To the best of our knowledge, this is the first report showing a specific hyperproliferative effect on gastric epithelial cells caused by the action of two bacterial protein products, independently from any effect due to the mechanism of infection. This observation further contributes to the elucidation of the molecular mechanisms involved in the effects of *H. pylori* on cell cycle control and provides insights into the roles played by the organism's proteins in gastric carcinogenesis. Nevertheless, it indicates possible molecular targets of diagnosis and therapy for this kind of neoplasm.

Identification of genes down-regulated during melanoma progression: a cDNA array study

Despite the clonal origin of most tumors, their tremendous heterogeneity suggests that cancer progression springs from the combined forces of both genetic and epigenetic events, which produce variant clonal populations, together with the selective pressures of

the microenvironment, which promote growth and, perhaps, dissemination of variants with a specific set of characteristics.

In order to identify genes relevant for melanoma development, we carried out cDNA array experiments employing an *in vitro* model of human melanoma progression, consisting of two cell lines: one, LP, derived from a primary melanoma and the other, LM, from its metastatic supraclavicular lymph node. Basic cDNA array data identified 26 genes as down-regulated in the LM cell line. Northern blot analysis confirmed an effective transcriptional down-regulation for five out of 13 genes analyzed. The products of these five genes belong to different functional protein types, such as transcription and translation regulators (Edg-2, eIF-3 p110, and RNPL/RBM3), extracellular communicators (PRSS11) and members of the major histocompatibility complex (beta2-microglobulin). Some previously described differences in expression patterns, such as loss of HLA I, were confirmed by our array data. In addition, we identified and validated for the first time the reduced expression level of several genes during melanoma progression. In particular, reduced Edg-2 gene product expression was also confirmed in a group of 50 primary melanomas and unrelated metastases. In conclusion, comparative hybridization by means of cDNA arrays assisted in identifying a series of novel progression-associated changes in gene expression, confirming, at the same time, a number of previously described results.

In addition, we reported ferritin light chain (L-ferritin) gene overexpression in the LM metastatic cell line. We are currently demonstrating that artificial L-ferritin down-modulation in the LM cells strongly inhibits proliferation and chemoinvasion *in vitro*, and cell growth *in vivo*. In addition, LM cells with artificially down-modulated L-ferritin levels display enhanced sensitivity to oxidative stress, epitomized as increased superoxide dismutase and decreased catalase activities, and to apoptosis. Immunohistochemical analysis of a human melanoma tissue array is revealing that ferritin expression levels in metastatic lesions (50 cases) is significantly higher ($P<0.0001$) than in primary melanomas. Additionally, ferritin expression results constantly up-regulated in autologous lymph node melanoma metastases, when compared to the primary tumor (11 cases tested). These data suggest that high ferritin expression can enhance cell growth and improve resistance to oxidative stress in metastatic melanoma cells, by interfering with their cellular antioxidant system. The potential significance of these findings deserves to be validated in a clinical setting.

Analysis of APAF-1 Expression in Human Cutaneous Melanoma Progression

APAF-1 plays a pivotal role in mitochondria-dependent apoptosis, binding to cytochrome c and favoring activation of caspase-9. It has been shown that epigenetic silencing of the APAF-1 gene is a common event in several metastatic melanoma cells *in vitro*. We determined, by Western blot, variations in the level of expression of APAF-1 in several human melanoma cell lines and, by immunohistochemistry, in a group of 106 histological samples including benign and malignant melanocytic lesions. We observed APAF-1 down-regulation or loss of expression in two metastatic melanoma cell lines, compared to primary melanoma cell lines. The immunohistochemical analysis revealed a significant difference in APAF-1 staining between nevi and melanomas. In addition, we found a significant negative correlation between APAF-1 expression level and tumor thickness and between primary melanomas and metastases. To the best of our knowledge, this is the first report showing APAF-1 loss of expression as a marker of malignant transformation and tumor progression in human melanoma samples. In particular, the observation that melanomas which have developed metastasis display a lower APAF-1 expression when compared to melanomas that have not developed a metastasis, irrespective of melanoma thickness, strongly suggests a possible prognostic value of APAF-1 expression. However, further studies with a larger number of patients are urgently needed to confirm these observations.

Publications 2003

Full Papers

Baldi, A., Santini, D., De Luca, A., and Paggi, M. G.

cDNA array technology in melanoma: An overview.

J.Cell Physiol, 196: 219-223, 2003.

Baldi A., Battista T., De Luca A., Santini D., Rossiello,L., Baldi F., Natali P. G., Lombardi D., Picard, M., Felsani A., and Paggi M. G.

Identification of genes down-regulated during melanoma progression: a cDNA array study.

Exp. Dermatol., 12: 213-218, 2003.

De Falco M., Sciarrillo R., Capaldo A., Laforgia V.,Varano L., Cottone G., and De Luca A.

Shift from noradrenaline to adrenaline production in the adrenal gland of the lizard, Podarcis sicula, after stimulation with vasoactive intestinal peptide (VIP).

Gen. Comp Endocrinol., 131: 325-337, 2003.

De Luca A., Baldi A., Russo P., Todisco A., Altucci L., Giardullo N., Pasquale L., Iaquinto S., D'Onofrio V., Parodi M. C., Paggi M. G., and Iaquinto G.

Coexpression of Helicobacter Pylori's Proteins CagA and HspB Induces Cell Proliferation in AGS Gastric Epithelial Cells, Independently from the Bacterial Infection.

Cancer Res., 63: 6350-6356, 2003.

De Luca A., De Falco M., Severino A., Campioni M., Santini D., Baldi F., Paggi M. G., and Baldi A.

Distribution of the Serine Protease HtrA1 in Normal Human Tissues.

J. Histochem. Cytochem., 51: 1279-1284, 2003.

De Luca A., De Falco M., Baldi A., and Paggi M. G.

Cyclin T: Three forms for different roles in physiological and pathological functions.

J. Cell Physiol, 194: 101-107, 2003.

De Luca A., Mangiacasale R., Severino A., Malquori L., Baldi A., Palena A., Mileo A. M., Lavia P., and Paggi M. G.

E1A Deregulates the Centrosome Cycle in a Ran GTPase-dependent Manner.

Cancer Res., 63: 1430-1437, 2003.

Lavia P., Mileo A. M., Giordano A., and Paggi M. G.

Emerging roles of DNA tumor viruses in cell proliferation: new insights into genomic instability.

Oncogene, 22: 6508-6516, 2003.

Lombardi D. and Mileo A. M.

Protein interactions provide new insight into Nm23/nucleoside diphosphate kinase functions.

J.Bioenerg. Biomembr., 35: 67-71, 2003.

Macaluso M., Paggi M. G., and Giordano A.

Genetic and epigenetic alterations as hallmarks of the intricate road to cancer.

Oncogene, 22: 6472-6478, 2003.

Paggi M. G., Catricala C., Amantea A., Picardo M., Natali P. G., Baldi F., and Baldi A.
Analysis of APAF-1 Expression in Human Cutaneous Melanoma Progression.
Pigment Cell Res., 16: 589, 2003.

Carboni F., Carlini M., Scardamaglia F., Santoro E., Boschetto A., Castelli M., Marandino F., Santoro E.
Gastrointestinal Stromal Tumors of the Stomach. A Ten Year Surgical Experience.
J.Exp.Clin.Cancer Res. 22:421-426, 2003.

Book Chapters

Paggi M. G., Felsani A., and Giordano A.
Growth control by the retinoblastoma gene family.
Methods Mol.Biol., 222: 3-19, 2003.

Severino A., Felsani A., Giordano A., and Paggi M. G.
Synthetic Oligopeptides as Cancer Cell Cycle Modulators.
In A. Giordano and K. J. Soprano (eds.), Cell Cycle Inhibitors in Cancer Therapy, pp. 297-310. Totowa, NJ: Humana Press Inc, 2003.

Laboratory D associated to Neurosciences, Head and Neck and Facial pathologies department

Director ad interim:
Ada Sacchi, PHD

Staff "D" Laboratory:
Alberto Chersi - PhD
Mattioni Manlio - M.D., Senior Scientist
Galati Alessandra - PhD, Senior Scientist
Verdina Rossella - PhD, Senior Scientist
Falasca Adriana - Technician Senior Scientist

Activities 2003

The work of our laboratory is centered on these major issues:
Peptide Synthesis and antibodies production.
Role of genetic polymorphisms in individual susceptibility of occupationally exposed populations.
Serum p53 antibody as a useful marker in cancer

1. Peptide synthesis and antibodies production.

An important field we investigated is the use of synthetic peptides to produce specific antibodies or to inhibit the functions of target proteins.
The production of specific antibodies against a protein involves a rather thorough study on the structure/function relationship (i.e. conformational, chemical, etc.,) that leads to the identification of the immunogenical regions therefore identifying the amino acid sequence to be used.
The preparation of the antigen can be started only after the peptide characterization (i.e. length, hydrophilicity, side residues). This investigation allows to choose the proper carrier as well as the amino acidic residue to use in the carrier-peptide conjugation reaction. After the completion of these theoretical studies, the peptide synthesis is begun.
These studies allowed to produce several polyclonal antibodies from laboratory animals (rats and rabbits), currently used by researchers from IFO and other institutes.
The characterization of the protein is mandatory in order to use the peptides as specific proteins inhibitors. Furthermore, it is important to decide at which level the inhibition of proteins needs to take place. It is possible to use peptides that impair the protein-receptor binding or peptides that prevent the conformational change (i.e. the passage from monomer to dimmer). This structural study allows the identification of groups of peptides that are synthesized and tested.
In recent years synthetic peptides have been widely used in the treatment of some diseases, however the main problem of these therapeutic trials is the short life of the peptides in the blood; since they are inactivated by exopeptidases that affect the amino-terminus leading to a mix of amino acids and, eventually, a hydrophobic core composed of a few amino residues.
In an attempt to increase peptide resistance towards seric proteases we performed studies on some peptides that we synthesized and modified at the amino-terminal position.
Synthesis and utilization of quenched fluorescent peptides
A new, innovative and inexpensive synthesis strategy has permitted the assembly and 'in synthesis' labeling of quenched fluorescent peptides to be used in several research projects. Such peptides contain a fluorescent group, a quencher, and a scissile bond, which can be cleaved by a protease. The specific trimming of the peptide by exo- or endopeptidases separates the quencher and the fluorescent reporter group, and this results in a 20 to 40-fold increase of fluorescence, which can be measured by a luminescence Spectrometer or even a colorimeter or an ELISA-reader. Such peptides are actually used for the study of antigen processing and modeling in the endoplasmatic reticulum of selected cancer cells during the complex pathways of antigen presentation.
Utilization of quenched fluorescent peptides
a) Studies on HIV
A panel of synthetic peptides selected from the amino acid sequence of HIV gp120, known to inhibit in vitro the binding of the viral protein to CD4 receptors of human lym-

phocytes, are actually being tested in cultures of infected PBMC, and the results are very encouraging. At the same time, for future use in clinical trials, a few of these peptides have been suitably modified at the amino termini in order to increase their resistance to the action of circulating amino peptidases.

b) Antigen presentation

Polystyrene 5 m beads linked to purified HLA-A2 chains and loaded with a single synthetic peptide deduced from a Hepatitis C Virus protein have been able to stimulate an HCV-specific T-cell clone, with a substantial production of g-IFN. The stimulation was peptide-specific and the efficiency was dependent on bead concentration, surface HLA class I density, and peptide-bound amount. Thus, polystyrene beads carrying single peptide-loaded HLA class I molecules might be potentially useful for the induction of T-cell responses in viral infections and in tumors expressing known specific antigens.

2. Role of genetic polymorphisms in individual susceptibility of occupationally exposed populations.

In the context of the joint project with the Istituto Superiore di Sanità-Ministero dell'Ambiente (Health impacts of urban air pollution), we began a study to highlight the possible effects of some metabolic polymorphisms (CYP1A1, CYP2E1, GSTM1, GSTT1, NQO1, MTHFR, MTRR) and of DNA- repair gene polymorphisms (APE1, XRCC1 280, XRCC1 399, XRCC3 241, XPD). We evaluated some biohazard indicators in a human cohort exposed to occupational hazards. Air pollution is in fact one of the major health problems in urban areas. The extensive use of oil derivatives for vehicles, house heating, and energy production involves the release in the air of several substances with a proven mutagenic and carcinogenic potential such as benzene, benzo(a)pyrene as well as gas pollutants and dusts.

The cohort we examined was that of Rome traffic officers. These workers are a model to assess the effects of exposure to air pollutants in urban areas showing a similar hazard potential to that of other workers who are exposed daily to traffic induced pollutants.

The genotyping of these subjects allowed to investigate the effects of some common phase I and II metabolic polymorphisms (CYP1A1, CYP2E1, GSTM1, GSTT1, NQO1) on the excretion rates of two metabolites of benzene: S-phenimercapturic acid (S-PMA), and transmuconic acid (TMA).

The results obtained showed that the TMA/benzene hematic ratio is influenced, in addition to sex, seasonality, smoking habits, also by the metabolic group GSTM 1 or GSTT1 with relatively higher values in individuals with null genotype. The latter group is more likely to be sensitive to the toxic effects of benzene, since TMA is respectively a metabolite of trans-trans-mucon aldeide (highly myelotoxic).

To assess the variable sensitivity to genotoxins we evaluated the individual DNA repair ability, showing that smoking habits and GSTM1 genotype modulate the individual DNA repair ability.

On this population we assessed the potential modulating effect of folic acid, that is deeply involved in DNA methylation and nucleotide synthesis processes. Specifically we evaluated the role of the interaction between gene and environment on chromosomal stability in individuals with different exposure to environmental pollutants.

On this regard, individuals were genotyped for polymorphisms of the methylenetetrahydrofolate reductase (MTHFR) and methionine sinthase reductase (MTRR) loci.

The results observed showed that seric levels of metabolic folic acid markers are influenced by genetic factors and sex: in particular homozygotes for the genetic variant 667T of MTHFR have higher levels of plasmatic omocystine, that is associated with a higher risk of severe pathologies.

3. Serum p53 antibody as a useful marker in cancer

Dysfunctions in the p53 gene are the most common genetic alterations in cancer. They can lead to the expression of a dysfunctional p53 protein with a longer half –life than the func-

tional one, resulting in accumulation of the dysfunctional protein in cancer cells. The accumulated protein may act as antigen and induce an immune response with production of anti-p53 antibodies, detectable in the sera from patients with various types of cancer.
The aim of our work has been to evaluate the presence and the prognostic value of serum anti-p53 antibodies in gastric carcinoma. In collaboration with the Laboratory of Clinical Pathology of our Institute, we analysed anti-p53 antibodies by ELISA in sera from 135 patients with gastric carcinoma and 64 healthy blood donors as a control. The results demonstrated that 14% gastric cancer patients (19 out of 135), but none of the healthy donors, had significant levels of serum anti-p53 antibodies. Our results suggest that a low percentage of the sera from gastric cancer patients have anti-p53 antibodies; however, they are specific, resulting absent in healthy donors. The survival time, over 48 months, for patients with serum positive for anti-p53 antibodies was longer than for those with serum negative for anti-p53 antibodies.
Since it has been previously reported that serum anti-p53 antibodies may be an early marker of lung cancer, preceding clinical and radiological signs of disease, we wondered whether serum anti-p53 antibodies could also be useful in the early diagnosis of gastric carcinoma, where p53 alterations represent an early event in tumorigenesis. We analysed 100 patients with benign gastric diseases and found that 5 % patients resulted positive for the presence of anti-p53 antibodies in their sera; in view of these results a higher number of patients with benign gastric diseases will be studied in order to define the predictive significance of serum anti-p53 antibodies in gastric cancer.
H. Pylori infection can induce p53 mutations and appears to be directly involved in the gastric carcinogenesis. Patients with H. pylori infection and no-ulcer dyspepsia are at risk of developing gastric cancer. To evaluate a possible role for serum anti-p53 antibodies in the diagnosis of gastric carcinoma in these patients, we analysed, in collaboration with the Department of Internal Medicine of the Catholic University of Rome, 287 dyspeptic patients and found high levels of anti-p53 antibodies in 11 (4 %); 4 of them also resulted H. pylori positive. These patients are under investigation with regard to clinicopathologic parameters and clinical examinations.

Selected Publications 2003

Di Somma C., Fiore L., Di Lonardo A., Ridolfi B., Garzillo C., Chersi A., Buono C., Menna T., and Ruffilli A.

Cross-reactivity between the major Parietaria allergen and Rotavirus VP4 protein.

Allergy, 58: 503-510, 2003.

Galati R., Verdina A., Falasca G., and Chersi A.

Increased resistence of peptides to serum proteases by modification of their amino groups.

Z. Naturforsch., 58C: 558-561, 2003.

Marcon F, Andreoli C, Rossi S, Verdina A, Galati R, Crebelli R.

Assessment of individual sensitivity to ionizing radiation and DNA repair efficiency in a healthy population.

Mutation Res., 10: 541:1-8, 2003.

Zijno A, Andreoli C, Leopardi P, Marcon F, Rossi S, Caiola S, Verdina A, Galati R, Cafolla A, Crebelli R.

Folate status, metabolic genotype, and biomarkers of genotoxicity in healthy subjects.

Carcinogenesis., 24: 1097-103, 2003.

Leopardi P, Zijno A, Marcon F, Conti L, Carere A, Verdina A, Galati R, Tomei F, Baccolo TP, Crebelli R.

Analysis of micronuclei in peripheral blood lymphocytes of traffic wardens: effects of exposure, metabolic genotypes, and inhibition of excision repair in vitro by ARA-C.

Environ. Mol. Mutagen., 41:126-30, 2003.

Crebelli R, Zijno A, Leopardi P, Marcon F, Conti L, Andreoli C, Rossi S, Carere A, Caiola S, Tomei F, Martini A, Marcellini L, Verdina A, Galati R, Ghittori S, Imbriani M. (2003).

Monitoraggio biologico dell'esposizione ad inquinanti atmosferici nei vigili urbani del Comune di Roma.

Rapporti ISTISAN, 03(11): 53-79.

Publications in Referenced Journals

(Impact Factor - I.F.: Institute for Scientific Information 2002)

1. Acosta J.C., Richard C., Delgado M.D., Horita M., Rizzo M.G., Fernandez-Luna J.L., Leon J.

Amifostine impairs p53-mediated apoptosis of human myeloid leukemia cells.

Mol. Cancer Ther., 2(9), p.893-900, 2003 I.F. 2.188

2. Agostino A., Invernizzi F., Tiveron C., Fagiolari G., Prelle A., Lamantea E., Giavazzi A., Battaglia G., Tatangelo L., Tiranti V., Zeviani M.

Constitutive knockout of Surf1 is associated with high embryonic lethality, mitochondrial disease and cytochrome coxidase deficiency in mice.

Hum. Mol. Genet., 12(4), p.399-413, 2003 I.F. 8.726

3. Alimonti A., Ferretti G., Di Cosimo S., Cognetti F., Vecchione A.

Can colorectal cancer patients with thymidylate synthase-overexpressing liver metastases have an overall survival advantage with hepatic arterial infusion alone?

J. Clin. Oncol., 15, 21(18), p.3543-4, author reply 3544-5, 2003 I.F. 9.868

4. Alimonti A., Di Cosimo S., Di Stani F., Vecchione A., Di Palma M., Ferretti G.

Subacute motor weakness and left renal mass.

Am. J. Med., 1, 114(8), p.706-8, 2003 I.F. 4.904

5. Alisi A., Giambartolomei S., Cupelli F., Merlo P., Fontemaggi G., Spaziani A., Balsano C.

Physical and functional interaction between HCV core protein and the different p73 isoforms.

Oncogene, 22(17), p.2573-80, 2003 I.F. 5.979

6. Aloe S., D'alessandro R., Spila A., Ferroni P., Basili S., Palmirotta R., Carlini M., Graziano F., Mancini R., Mariotti S., Cosimelli M., Roselli M., Guadagni F.

Prognostic value of serum and tumor tissue CA 72-4 content in gastric cancer.

Int. J. Biol. Markers, 18(1), p.21-7, 2003 I.F. 1.571

7. Anastasi S., Fiorentino L., Fiorini M., Fraioli R., Sala G., Castellani L., Alema S., Alimandi M., Segatto O.

Feedback inhibition by RALT controls signal output by the ErbB network.

Oncogene, 22(27), p.4221-34, 2003 I.F. 5.979

8. Ardito G., Fadda G., Danese D., Modugno P., Giordano A., Revelli L., Ardito F., Pontecorvi A.

Coexistence of a parathyroid adenoma and parathyroid cyst causing primary hyperparathyroidism.

J. Endocrinol. Invest., 26(7), p.679-82, 2003 I.F. 1.476

9. Augustin L.S., Polesel J., Bosetti C., Kendall C.W., La Vecchia C., Parpinel M., Conti E., Montella M., Franceschi S., Jenkins D.J., Dal Maso L.
Dietary glycemic index, glycemic load and ovarian cancer risk: a case-control study in Italy.
Annals Oncology, 14(1), p.78-84, 2003 I.F. 3.114

10. Bagnato A.
Therapies for cancer targeting endothelin receptors.
Drug of the Future, 28, p.983-989, 2003 I.F. 0.386

11. Bagnato A., Spinella F.
Emerging role of endothelin-1 in tumor angiogenesis.
Trends Endocrinol. Metab., 14(1), p.44-50, 2003 I.F. 7.969

12. Baldi A., Battista T., De Luca A., Santini D., Rossiello L., Baldi F., Natali P.G., Lombardi D., Picardo M., Felsani A., Paggi M.G.
Identification of genes down-regulated during melanoma progression: a cDNA array study.
Exp. Dermatol., 12(2), p.213-8, 2003 I.F. 2.303

13. Baldi A., Santini D., De Luca A., Paggi M.G.
DNA array technology in melanoma: an overview.
J. Cell. Physiol., 196(2), p.219-23, 2003 I.F. 4.845

14. Barbato C., Corbi N., Canu N., Fanciulli M., Serafino A., Ciotti M., Libri V., Bruno T., Amadoro G., De Angelis R., Calissano P., Passananti C.
Rb binding protein Che-1 interacts with Tau in cerebellar granule neurons. Modulation during neuronal apoptosis.
Mol. Cell. Neurosci., 24(4), p.1038-50, 2003 I.F. 4.519

15. Bensaad K., Le Bras M., Unsal K., Strano S., Blandino G., Tominaga O., Rouillard D., Soussi T.
Change of conformation of the DNA-binding domain of p53 is the only key element for binding of and interference with p73.
J. Biol. Chem., 278(12), p.10546-55, 2003 I.F. 6.696

16. Biagini R., Casadei R., Boriani S., Erba F., Sturale C., Mascari C., Bortolotti C., Mercuri M.
En bloc vertebrectomy and dural resection for chordoma: a case report.
Spine, 28(18), p.E368-72, 2003 I.F. 2.311

17. Biroccio A., Amodei S., Antonelli A., Benassi B., Zupi G.
Inhibition of c-Myc oncoprotein limits the growth of human melanoma cells by inducing cellular crisis.
J. Biol. Chem., 278(37), p.35693-701, 2003 I.F .6.696

18. Biroccio A., Gabellini C., Amodei S., Benassi B., Del Bufalo D., Elli R., Antonelli A., D'incalci M., Zupi G.
Telomere dysfunction increases cisplatin and ecteinascidin-743 sensitivity of melanoma cells.
Mol. Pharmacol., 63(3), p.632-8, 2003 I.F. 5.480

19. Biroccio A., Leonetti C., Zupi G.

The future of antisense therapy: combination with anticancer treatments.

Oncogene, 22(42), p.6579-88, 2003 I.F. 5.979

20. Boccardo M., Telera S., Vitali A.

Tanycytic ependymoma of the spinal cord. Case report and review of the literature.

Neurochirurgie, 49(6), p.605-10, 2003 I.F. 0.210

21. Boogaerts M., Coiffier B., Kainz C., And The Epoetin b Qol Working Group; (Cognetti F.)

Impact of epoetin b on quality of life in patients with malignant disease.

Br. J. Cancer, 88(7), p.988-95, 2003 I.F. 3.639

22. Borzacchiello G., Ambrosio V., Roperto S., Poggiali F., Tsirimonakis E., Venuti A., Campo M.S., Roperto F.

Bovine papillomavirus type 4 in oesophageal papillomas of cattle from the south of Italy.

J. Comp. Pathol., 128(2-3), p.203-6, 2003 I.F. 1.290

23. Borzacchiello G., Iovane G., Marcante M.L., Poggiali F., Roperto F., Roperto S., Venuti A.

Presence of bovine papillomavirus type 2 DNA and expression of the viral oncoprotein E5 in naturally occurring urinary bladder tumours in cows.

J. Gen. Virol., 84(Pt 11), p.2921-6, 2003 I.F. 3.300

24. Breccia M., Carmosino I., Diverio D., De Santis S., De Propris M.S., Romano A., Petti M.C., Mandelli F., Lo-Coco F.

Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count.

Br. J. Haematol., 120(2), p.266-70, 2003 I.F. 3.052

25. Brusa A., Bentivoglio A.R., Calzetti S., Cammarata S., Congia S., Fasano A., Jandolo B., Lucci B., Primavera A., Stoehr R.

The diagnostic importance of the isolated supranuclear downward gaze ophthalmoplegia in progressive supranuclear palsy.

Neurol. Sci., 24(3), p.161, 2003 I.F. 0.907

26. Cairns L.A., Moroni E., Levantini E., Giorgetti A., Klinger F.G., Ronzoni S., Tatangelo L., Tiveron C., Et Al.

Kit regulatory elements required for expression in developing hematopoietic and germ cell lineages.

Blood, 102(12), p.3954-62, 2003 I.F. 9.631

27. Canamasas I., Debes A., Natali P.G., Kurzik-Dumke U.

Understanding human cancer using Drosophila: Tid47, a cytosolic product of the DnaJ-like tumor suppressor gene l2Tid, is a novel molecular partner of patched related to skin cancer.

J. Biol. Chem., 278(33), p.30952-60, 2003 I.F. 6.696

28. Capocaccia R., Gatta G., Roazzi P., Carrani E., Santaquilani M., De Angelis R., Tavilla A., And The Eurocare Working Group (Conti E.M.S.)

The Eurocare-3 databse: methodology of data collection, standardisation, quality control and statistica analysis.

Annals Oncology, 14(Suppl. 5), p.v14-v27, 2003 I.F. 3.114

29. Carboni F., Carlini M., Boschetto A., Scardamaglia F., Santoro E., Castelli M., Marandino F., And Santoro E.

Gastrointestinal Stromal Tumors of the Stomach. A Ten-Year Surgical Experience.

J. Exp. Clin. Cancer Res., 22(3), p.379-84, 2003 I.F. 0.703

30. Carlini M., Lonardo M.T., Boschetto A., Carboni F., Appetecchia M., Tropea F., Santoro E.

Adrenal glands metastases from malignant melanoma. Laparoscopic bilateral adrenalectomy.

J. Exp. Clin. Cancer Res., 22(1), p.141-5, 2003 I.F. 0.703

31. Carlini P., Ferretti G., Di Cosimo S., Colella E., Tonachella R., Romiti A., Tomao S., Frassoldati A., Papaldo P., Fabi A., Ruggeri E.M., Cognetti F.

Is there a benefit by the sequence anastrozole-formestane for postmenopausal metastatic breast cancer women?

J. Steroid Biochem. Mol. Biol., 86(1), p.107-9, 2003 I.F. 2.637

32. Carlini P., Di Cosimo S., Ferretti G., Papaldo P., Fabi A., Ruggeri E.M., Milella M., Cognetti F.

Alopecia in a premenopausal breast cancer woman treated with letrozole and triptorelin.

Annals Oncology, 14(11), p.1689-90, 2003 I.F. 3.114

33. Cavaliere F., Perri P., Rossi C.R., Pilati P.L., De Simone M., Vaira M., Deraco M., Di Filippo F.

Indications for integrated surgical treatment of peritoneal carcinomatosis of colorectal origin: experience of the Italian Society of Locoregional Integrated Therapy in Oncology.

Tumori, 89(Suppl. 4), p.21-3, 2003 I.F. 0.267

34. Cavaliere F., Perri P., Rossi C.R., Pilati P.L., De Simone M., Vaira M., Deraco M., Aloe S., Di Filippo S. And Di Filippo F.

Sitilo Experience on Peritoneal Carcinomatosis From Colorectal.
Cancer: Clinical Prognostic Features.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003 I.F. 0.703

35. Ceribelli A., Gridelli C., De Marinis F., Fabi A., Gamucci T., Cortesi E., Barduagni M., Antimi M., Maione P., Migliorino M.R., Giannarelli D., Cognetti F.

Prolonged gemcitabine infusion in advanced non-small cell lung carcinoma: a randomized phase II study of two different schedules in combination with cisplatin.

Cancer, 98(2), p.337-43, 2003 I.F. 3.941

36. Cianciulli A.M., Guadagni F., Marzano R., Benevolo M., Merola R., Giannarelli D., Marandino F., Vocaturo G., Mariani L., Mottolese M.

HER-2/neu oncogene amplification and chromosome 17 aneusomy in endometrial carcinoma: correlation with oncoprotein expression and conventional pathological parameters.

J. Exp. Clin. Cancer Res., 22(2), p.265-71, 2003 I.F. 0.703

37. Cianciulli A.M., Leonardo C., Guadagni F., Marzano R., Iori F., De Nunzio C., Franco G., Merola R., Laurenti C.

Genetic instability in superficial bladder cancer and adjacent mucosa: an interphase cytogenetic study.

Hum. Pathol., 34(3), p.214-21, 2003 I.F. 3.049

38. Cippitelli M., Fionda C., Di Bona D., Lupo A., Piccoli M., Frati L., Santoni A.

The cyclopentenone-type prostaglandin 15-deoxy-delta 12,14-prostaglandin J2 inhibits CD95 ligand gene expression in T lymphocytes: interference with promoter activation via peroxisome proliferator-activated receptor-gamma-independent mechanisms.

J. Immunol., 170(9), p.4578-92, 2003 I.F. 7.014

39. Cocconi G., Passalacqua R., Foladore S., Carlini P., Acito L., Maiello E., Marchi M., Gebbia V., Di Sarra S., Beretta M., Bacchi M.

Treatment of metastatic malignant melanoma with dacarbazine plus tamoxifen, or vindesine plus tamoxifen: a prospective randomized study.

Melanoma Res., 13(1), p.73-9, 2003 I.F. 1.773

40. Cocconi G., Carlini P., Gamboni A., Gasperoni S., Rodino C., Zironi S., Bisagni G., Porrozzi S., Cognetti F., Di Costanzo F., Canaletti R., Ruggeri E.M., Camisa R., Pucci F.

Cisplatin, epirubicin, leucovorin and 5-fluorouracil (PELF) is more active than 5-fluorouracil, doxorubicin and methotrexate (FAMTX) in advanced gastric carcinoma.

Annals Oncology, 14(8), p.1258-63, 2003 I.F. 3.114

41. Cognetti G. And Cecere L.

E-Oncology and Health Portals: Instructions and Standards for the Evaluation, Production Organisation and Use.

J. Exp. Clin. Cancer Res., 22(4), p.677-86, 2003 I.F. 0.703

42. Coleman M.P., Gatta G., Verdecchia A., Esteve J., Sant M., Storm H., Allemanic., Ciccolallo L., Santaquilani M., Berrino F., And The Eurocare Working Group (Conti E.M.S.)

Eurocare-3 summary: cancer survival in Europe at the end of the 20th century.

Annals Oncology, 14(Suppl. 5), p.v14-v27, 2003 I.F. 3.114

43. Conti F., Vici P.

Chemotherapy in the treatment of breast carcinoma.

Tumori, 89(Suppl. 4), p.181-2, 2003 I.F. 0.267

44. Dal Maso L., Franceschi S., Polesel J., Braga C., Piselli P., Crocetti E., Falcini F., Guzzinati Zanetti R., Vercelli M., Rezza G.; Cancer And Aids Regisity Linkage Study...(Conti E., Ramazzotti V.)

Risk of cancer in persons with AIDS in Italy, 1985-1998.

Br. J. Cancer, 89(1), p.94-100, 2003 I.F. 3.639

45. Dal Maso L., Polesel J., Serraino D., Franceschi S. For The Cancer And Aids Registry Linkage Study. Cancer And Aids Registry Linkage Study:...(Conti E.)

Lung cancer in persons with AIDS in Italy, 1985-1998.

AIDS, 26,17(14), p.2117-9, 2003 I.F. 5.983

46. De Angelis R., Iezzi S., Bruno T., Corbi N., Di Padova M., Floridi A., Fanciulli M., Passananti C.

Functional interaction of the subunit 3 of RNA polymerase II (RPB3) with transcription factor-4 (ATF4).

FEBS Lett., 547(1-3), p.15-9, 2003 I.F. 3.912

47. De Capoa A., Musolino A., Della Rosa S., Caiafa P., Mariani L., Del Nonno F., Vocaturo A., Perrone Donnorso R., Niveleau A., Grappelli C.

DNA demethylation is directly related to tumour progression: Evidence in normal, pre-malignant and malignant cells from uterine cervix samples.

Oncol. Rep., 10(3), p.545-9, 2003 I.F. 1.171

48. De Falco M., Sciarrillo R., Capaldo A., Laforgia V., Varano L., Cottone G., De Luca A.

Shift from noradrenaline to adrenaline production in the adrenal gland of the lizard, Podarcis sicula, after stimulation with vasoactive intestinal peptide (VIP).

Gen. Comp. Endocrinol., 131(3), p.325-37, 2003 I.F. 1.844

49. De Luca A., Baldi A., Russo P., Todisco A., Altucci L., Giardullo N., Pasquale L., Iaquinto S., D'onofrio V., Parodi M.C., Paggi M.G., Iaquinto G.

Coexpression of Helicobacter Pylori's Proteins CagA and HspB Induces Cell Proliferation in AGS Gastric Epithelial Cells, Independently from the Bacterial Infection.

Cancer Res., 63(19), p.6350-6, 2003 I.F. 8.318

50. De Luca A., De Falco M., Severino A., Campioni M., Santini D., Baldi F., Paggi M.G., Baldi A.

Distribution of the Serine Protease HtrA1 in Normal Human Tissues.

J. Histochem. Cytochem., 51(10), p.1279-84, 2003 I.F. 2.283

51. De Luca A., Severino A., De Paolis P., Cottone G., De Luca L., De Falco M., Porcellini A., Volpe M., Condorelli G.

p300/cAMP-response-element-binding-protein ('CREB')-binding protein (CBP) modulates co-operation between myocyte enhancer factor 2A (MEF2A) and thyroid hormone receptor-retinoid X receptor.

Biochem. J., 369(Pt 3), p.477-84, 2003 I.F. 4.589

52. De Luca A., Mangiacasale R., Severino A., Malquori L., Baldi A., Palena A., Mileo A.M., Lavia P., Paggi M.G.

E1A deregulates the centrosome cycle in a Ran GTPase-dependent manner.

Cancer Res., 63(6), p.1430-7, 2003 I.F. 8.318

53. De Luca A., De Falco M., Baldi A., Paggi M.G.

Cyclin T: three forms for different roles in physiological and pathological functions.

J. Cell. Physiol., 194(2), p.101-7, 2003 I.F. 4.845

54. De Marco F., Hallez S., Brulet J.M., Gesche F., Marzano P., Flamini S., Marcante M.L., Venuti A.

DNA vaccines against HPV-16 E7-expressing tumour cells.

Anticancer Res., 23(2B), p.1449-54, 2003 I.F. 1.447

55. De Sanctis V., Mazzucconi M.G., Spadea A., Alfo M., Mancini M., Bizzoni L., Peraino M., Mandelli F.

Long-term evaluation of 164 patients with essential thrombocythaemia treated with pipobroman: occurrence of leukaemic evolution.

Br. J. Haematol., 123(3), p.517-21, 2003 I.F. 3.052

56. Del Bufalo D., Trisciuoglio D., Scarsella M., Zangemeister-Wittke U., Zupi G.

Treatment of melanoma cells with a bcl-2/bcl-xL antisense oligonucleotide induces antiangiogenic activity.

Oncogene, 22(52), p.8441-7, 2003 I.F. 5.979

57. Deraco M., De Simone M., Rossi C.R., Cavaliere F., Di Filippo F., Vaira M., Piatti P. And Kusamura S.

An Italian Multicentric Phase II Study on Peritonectomy and Intra Peritoneal Hyperthermic Perfusion (IPHP) to treat patients with Pseudomyxoma Peritonei.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003 I.F. 0.703

58. Deraco M, De Simone M., Rossi C.R., Cavaliere F., Difilippo F., Scuderi S., Pilatti P. And Kusamura S.

An Italian Multicentric Phase II Study on Peritonectomy and Intra Peritoneal Hyperthermic Perfusion (IPHP) to Treat Patients with Peritoneal Mesothelioma.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003 I.F. 0.703

59. Di Cosimo S., Ferretti G., Fazio N., Silvestris N., Carlini P., Alimonti A., Gelibter A., Felici A., Papaldo P., Cognetti F.

Docetaxel in advanced gastric cancer-review of the main clinical trials.

Acta Oncol., 42(7), p.693-700, 2003 I.F. 1.909

60. Di Cosimo S., Ferretti G., Papaldo P., Carlini P., Fabi A., Cognetti F.

Lonidamine: Efficacy and safety in clinical trials for the treatment of solid tumors.

Drugs Today (Barc), 39(3), p.157-74, 2003 I.F. 0.258

61. Di Filippo F., Garinei R., Anzà M., Cavaliere F., Giannarelli D., Cagol P.P., Rossi C.R., Santinami M., Deraco M., Botti C., Perri P., Di Filippo S., Piarulli L., Bruno P.

Doxorubicin in isolation limb perfusion in the treatment of advanced limb soft tissue sarcoma.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003 I.F. 0.703

62. Di Filippo F., Garinei R., Giannarelli D., Anzà M., Cavaliere F., Botti C., Perri P., Di Filippo S., Psaila A., Callopoli A., Maialetti R., Sega F., Frezza F., Viticci C.

Hyperthermic antiblastic perfusion in the treatment of loco-regional spreading limb melanoma.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003 I.F. 0.703

63. Di Filippo F., Garinei R., Anza M., Cavaliere F., Botti C., Perri P., Di Filippo S.

Anti-blastic hyperthermic perfusion in the treatment of melanoma of the extremities in the loco-regional diffusion phase.

Tumori, 89(Suppl. 4), p.241-3, 2003 I.F. 0.267

64. Di Filippo F., Rossi C.R., Garinei R., Anzà M., Cavaliere F., Botti C., Perri P., Di Filippo S., Di Angelo P., Principi F., Laurenzi L.

Hyperthermic antiblastic perfusion with TNFα and melphalan in stage III limb melanoma patients: a phase I - II SITILO study

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003 I.F. 0.703

65. Di Maio M., Perrone F., Gallo C., Iaffaioli R.V., Manzione L., Piantedosi F.V., Cigolari S., Illiano A., Barbera S., Robbiati S.F., Piazza E., Ianniello G.P., Frontini L., Veltri E., Castiglione F., Rosetti F., De Maio E., Maione P., Gridelli C., Rossi A., Barletta E., Barzelloni M.L., Signoriello G., Bilancia D., Dinota A., Rosati G., Germano D., Lamberti A., Pontillo V., Brancacio L., Crispino C., Esposito M., Battiloro C., Tufano G., Cioffi A., Guardasole V., Angelini V., Guidetti G., Barbera S., Renda F., Romano F., Volpintesta A., Robbiati S.F., Sannicolo M., Filipazzi V., Esani G., Gambaro A., Ferrario S., Tinessa V., Caprio M.G., Zonato S., Cabiddu M., Raina A., Veltri E., D'aprile M., Pistillucci G., Porcile G., Ostellino O., Vinante O., Azzarello G., Gebbia V., Borsellino N., Testa A., Gasparini G., Morabito A., Gattuso D., Romito S., Carrozza F., Fava S., Calcagno A., Grimi E., Bertetto O., Ciuffreda L., Parello G., Maiorino L., Santoro A., Santoro M., Failla G., Aiello R.A., Bearz A., Sorio R., Scalone S., Clerici M., Bollina R., Belloni P., Sacco C., Sibau A., Adamo V., Altavilla G., Scimone A., Spatafora M., Bellia V., Hopps M.R., Monfardini S., Favaretto A., Stefani M., Corradini G.M., Pavia G., Scagliotti G., Novello S., Selvaggi G., Tonato M., Darwish S., Michetti G., Belometti M.O., Labianca R., Quadri A., De Marinis F., Migliorino M.R., Martelli O., Colucci G., Galetta D., Giotta F., Isa L., Candido P., Rossi N., Calandriello A., Ferrau F., Malaponte E., Barni S., Cazzaniga M., Gebbia N., Valerio M.R., Belli M., Colantuoni G., Capuano M.A., Angiolillo M., Sollitto F., Ardizzoia A., Luporini G., Locatelli M.C., Pari F., Aitini E., Pedicini T., Febbraro A., Zollo C., Di Costanzo F., Bartolucci R., Gasperoni S., Gaion F., Palazzolo G., Galligioni E., Caffo O., Cortesi E., D'auria G., Curcio C., Vasta M., Bumma C., Celano A., Bretti S., Nettis G., Anselmo A., Mattioli R., Nistico C., Aschelter A., Foa P.

Supportive care in patients with advanced non-small-cell lung cancer.

Br. J. Cancer, 89(6), p.1013-21, 2003 I.F. 3.639

66. Di Padova M., Bruno T., De Nicola F., Iezzi S., D'angelo C., Gallo R., Nicosia D., Corbi N., Biroccio A., Floridi A., Passananti C., Fanciulli M.

CHE-1 arrests human colon carcinoma cell proliferation by displacing HDAC1 from theP21WAF1/CIP1 promoter.

J. Biol. Chem., 278(38), p.36496-504, 2003 I.F. 6.696

67. Di Rosa F., Santoni A.

Memory T-cell competition for bone marrow seeding.

Immunology, 108(3), p.296-304, 2003 I.F. 2.729

68. Di Sano F., Fazi B., Citro G., Lovat P.E., Cesareni G., Piacentini M.

Glucosylceramide synthase and its functional interaction with RTN-1C regulate chemotherapeutic-induced apoptosis in neuroepithelioma cells.

Cancer Res., 63(14), p.3860-5, 2003 I.F. 8.318

69. Di Somma C., Fiore L., Di Lonardo A., Ridolfi B., Garzillo C., Chersi A., Buono C., Menna T., Ruffilli A.

Cross-reactivity between the major Parietaria allergen and rotavirus VP4 protein.

Allergy, 58(6), p.503-10, 2003 I.F. 3.666

70. Esposito A., Mancini R., Ettorre G., Garufi C., Saracca E., Arcieri S., Cosimelli M.

A Combined Approach of Neoadjuvant Chemotherapy and Surgery for Colorectal Liver Metastases

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003 I.F. 0.703

71. Ettorre G.M., Vennarecci G., Boschetto A., Giovannelli L., Antonini M., Carboni F., Santoro R., Lepiane P., Cosimelli M., Lonardo M.T., Del Nonno F., Perracchio L., Maritti M., Moricca P., D'offizi G., Narciso P., Noto P., Boumis E., Petrosillo N., Visco G., Santoro E.

Resection and Transplantation: Evaluation of Surgical Perspectives in HIV Positive Patients Affected by End-Stage Liver Disease.

J. Exp. Clin. Cancer Res., 22(Suppl.4), 2003 I.F. 0.703

72. Ettorre G.M., Vennarecci G., Lonardo M.T., Boschetto A., Antonini M., Carboni F., Carlini M., Santoro E.

The modified "hanging maneuver" during orthotopic liver transplantation using a technique for conserving the inferior vena cava.

Tumori, 89, (Suppl.4), p.63-5, 2003 I.F. 0.267

73. Ettorre G.M., Vennarecci G., Santoro R., Antonini M., Lonardo M.T., Carlini M., Santoro E.

Modified liver hanging maneuver during orthotopic liver transplantation with inferior vena cava preservation.

Transplantation, 27, 75(2), p.247-9, 2003 I.F. 3.265

74. Fabi A., Barduagni M., Lauro S., Portalone L., Mauri M., Marinis F., Narduzzi C., Tonini G., Giampaolo M., Pacetti U., Paoloni F., Cognetti F.

Is delayed chemotherapy-induced emesis well managed in oncological clinical practice? An observational study.

Support Care Cancer, 11(3), p.156-61, 2003 I.F. 1.299

75. Facciolo F., Piovanello P., Cerasoli V., Carlini S., Ghini C.

Il tumore del polmone non a piccole cellule i limiti della chirurgia.

Tumori, 4 (Suppl. 2), S95-S96, 2003 I.F. 0.267

76. Foggi P., Amodio A.

Molecular therapy of breast carcinoma in the advanced phase.

Tumori, 89 (Suppl. 4), p.189-91, 2003 I.F. 0.267

77. Fonsatti E., Altomonte M., Nicotra M.R., Natali P.G., Maio M.

Endoglin (CD105): a powerful therapeutic target on tumor-associated angiogenetic blood vessels.

Oncogene, 22(42), p.6557-63, 2003 I.F. 5.979

78. Franceschi S., Dal Maso L., Pezzotti P., Polesel J., Braga C., Piselli P., Serraino D., Tagliabue G., Federico M., Ferretti S., De Lisi V., La Rosa F., Conti E., Budroni M., Vicario G., Piffer S., Pannelli F., Giacomin A., Bellu F., Tumino R., Fusco M., Rezza G.; Cancer And Aids Registry Linkage Study (Ramazzotti V.).

Incidence of AIDS-defining cancers after AIDS diagnosis among people with AIDS in Italy, 1986-1998.

J. Acquir. Immune Defic Syndr., 34(1), p.84-90, 2003 I.F. 3.586

79. Fulco M., Costanzo A., Merlo P., Mangiacasale R., Strano S., Blandino G., Balsano C., Lavia P., Levrero M.

p73 Is Regulated by Phosphorylation at the G2/M Transition.

J. Biol. Chem., 278(49), p.49196-202, 2003 I.F. 6.696

80. Gabellini C., Antonelli A., Petrinelli P., Biroccio A., Marcucci L., Nigro G., Russo G., Zupi G., Elli R.

Telomerase activity, apoptosis and cell cycle progression in ataxia telangiectasia lymphocytes expressing TCL1.

Br. J. Cancer, 89(6), p.1091-5, 2003 I.F. 3.639

81. Galati R., Verdina A., Falasca G., Chersi A.

Increased resistance of peptides to serum proteases by modification of their amino groups.

Z. Naturforsch [C], 58(7-8), p.558-61, 2003 I.F. 0.715

82. Galie E., Pietrangeli A., Maschio M., Pace A., Vidiri A., Carosi M., Jandolo B.

Demyelinating disease in monoclonal gammopathy of undetermined significance.

J. Exp. Clin. Cancer Res., 22(2), p.337-9, 2003 I.F. 0.703

83. Gallus S., Altieri A., Bosetti C., Franceschi S., Levi F., Negri E., Dal Maso L., Conti E., Zambon P., La Vecchia C.

Cigarette tar yield and risk of upper digestive tract cancers: case-control studies from Italy and Switzerland.

Annals Oncology, 14(2), p.209-13, 2003 I.F. 3.114

84. Gallus S., Bosetti C., Negri E., Talamini R., Montella M., Conti E., Franceschi S., La Vecchia C.

Does pizza protect against cancer?

Int. J. Cancer, 107(2), p.283-4, 2003 I.F. 4.056

85. Gandolfo G.M., Ferri G.M., Conti L., Antenucci A., Marrone R., Frasca A.M., Vitelli G.

Prevalence of infections by hepatitis A, B, C and E viruses in two different socioeconomic groups of children from Santa Cruz, Bolivia.

Med. Clin. (Barc), 120(19), p.725-7, 2003 I.F. 0.854

86. Garufi C., Cristaudo A., Vanni B., Bria E., Aschelter A.M., Santucci B., Terzoli E.

Skin testing and hypersensitivity reactions to oxaliplatin.

Annals Oncology, 14(3), p.497-8, 2003 I.F. 3.114

87. Garufi C., Bria E., Vanni B., Zappala A.M., Sperduti I., Terzoli E.

A phase II study of irinotecan plus chronomodulated oxaliplatin, 5-fluorouracil and folinic acid in advanced colorectal cancer patients.

Br. J. Cancer, 89(10), p.1870-5, 2003 I.F. 3.639

88. Gasbarri A., Del Prete F., Girnita L., Martegani M.P., Natali P.G., Bartolazzi A.

CD44s adhesive function spontaneous and PMA-inducible CD44 cleavage are regulated at post-translational level in cells of melanocytic lineage.

Melanoma Res., 13(4), p.325-37, 2003 I.F. 1.773

89. Gatta G., Corazziari I., Magnani C., Peris-Bonet R., Roazzi P., Stiller., And Eurocare Working Group (Conti E.M.S).

Childhood cancer survival in Europe.

Annals Oncology, 14(Suppl. 5), p.v119-v127, 2003 I.F. 3.114

90. Gebbia V., Galetta D., Caruso M., Verderame F., Pezzella G., Valdesi M., Borsellino N., Pandolfo G., Durini E., Rinaldi M., Et Al.; Gruppo Oncologico Italia Meridionale.

Gemcitabine and cisplatin versus vinorelbine and cisplatin versus ifosfamide+gemcitabine followed by vinorelbine and cisplatin versus vinorelbine and cisplatin followed by ifosfamide and gemcitabine in stage IIIB-IV non small cell lung carcinoma: a prospective randomized phase III trial of the Gruppo Oncologico Italia Meridionale.

Lung Cancer, 39(2), p.179-89, 2003 I.F. 2.451

91. Gelibter A., Ceribelli A., Milella M., Mottolese M., Vocaturo A., And Cognetti F.

Clinically Meaningful Response to the EGFR Tyrosine Kinase Inhibitor Gefitinib ('Iressa', ZD1839) in Non Small Cell Lung Cancer.

J. Exp. Clin. Cancer Res., 22(3), p.481-5, 2003 I.F. 0.703

92. Giorda E., Sibilio L., Martayan A., Moretti S., Venturo I., Mottolese M., Ferrara G.B., Cappellacci S., Eibenschutz L., Catricala C., Grammatico P., Giacomini P.

The antigen processing machinery of class I human leukocyte antigens: linked patterns of gene expression in neoplastic cells.

Cancer Res., 63(14), p.4119-27, 2003 I.F. 8.318

93. Girmenia C., Lo Coco F., Breccia M., Latagliata R., Spadea A., D'andrea M., Gentile G., Micozzi A., Alimena G., Martino P., Mandelli F.

Infectious complications in patients with acute promyelocytic leukaemia treated with the AIDA regimen.

BLeukemia, 17(5), p.925-30, 2003 I.F. 4.693

94. Granata F., Potenza R.L., Fiori A., Strom R., Caronti B., Molinari P., Donsante S., Citro G., Iacovelli L., De Blasi A., Ngomba R.T., Palladini G., Passarelli F.

Expression of OP4 (ORL1, NOP(1)) receptors in vascular endothelium.

Eur. J. Pharmacol., 482(1-3), p.17-23, 2003 I.F. 2.342

95. Greco C., Alvino S., Del Monte G., Venturo I. And Lopez M.

Potential Usefulness of Serum p53 for Laboratory Management of Plasma Cell Dyscrasias.

J. Exp. Clin. Cancer Res., 22(4), p.607-12, 2003 I.F. 0.703

96. Gridelli C., Gallo C., Shepherd F.A., Illiano A., Piantedosi F., Robbiati S.F., Manzione L., Barbera S., Frontini L., Veltri E., Et Al., And Gemvin Investigatorrs (Aschelter A.M.).

Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer: a phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group.

J. Clin. Oncol., 21(16), p.3025-34, 2003 I.F. 9.868

97. Guadagni S., Santinami M., Patuzzo R., Pilati P.L., Miotto D., Deraco M., Rossi C.R., Fiorentini G., Di Filippo F., Valenti M., Amicucci G.

Hypoxic pelvic and limb perfusion with melphalan and mitomycin C for recurrent limb melanoma: a pilot study.

Melanoma Res., 13(1), p.51-8, 2003 I.F. 1.773

98. Gurtner A., Manni I., Fuschi P., Mantovani R., Guadagni F., Sacchi A., Piaggio G.

Requirement for down-regulation of the CCAAT-binding activity of the NF-Y transcription factor during skeletal muscle differentiation.

Mol. Biol. Cell., 14(7), p.2706-15, 2003 I.F. 7.599

99. Iacopini F., Consolazio A., Bosco D., Marcheggiano A., Bella A., Pica R., Paoluzi O.A., Crispino P., Rivera M., Mottolese M., Nardi F., Paoluzi P.

Oxidative Damage of the Gastric Mucosa in Helicobacter pylori Positive Chronic Atrophic and Nonatrophic Gastritis, Before and After Eradication.

Helicobacter, 8(5), p.503-12, 2003 I.F. 2.482

100. Illi B., Nanni S., Scopece A., Farsetti A., Biglioli P., Capogrossi M.C., Gaetano C.

Shear stress-mediated chromatin remodeling provides molecular basis for flow-dependent regulation of gene expression.

Circ. Res., 93(2), p.155-61, 2003 I.F. 9.694

101. Jandolo B., Galie E., Badia D.

Masseteric silent period and reflex before and after dentomaxillofacial surgery.

Neurol. Sci., 24(2), p.53-6, 2003 I.F. 0.907

102. Jurchott K., Bergmann S., Stein U., Walther W., Janz M., Manni I., Piaggio G., Fietze E., Dietel M., Royer H.D.

YB-1 as a cell cycle-regulated transcription factor facilitating cyclin A and cyclin B1 gene expression.

J. Biol. Chem., 278(30), p.27988-96, 2003 I.F. 6.696

103. Laurenzi L., Natoli S., Pelagalli L., Marcelli M.E., Abbattista D., Carpanese L., Arcuri E.

Long-term central venous catheterization via persistent left superior vena cava: a case report.

Support Care Cancer, 11(3), p.190-2, 2003 I.F. 1.299

104. Lavia P., Mileo A.M., Giordano A., Paggi M.G.

Emerging roles of DNA tumor viruses in cell proliferation: new insights into genomic instability.

Oncogene, 22(42), p.6508-16, 2003 I.F. 5.979

105. Leonetti C., Biroccio A., Gabellini C., Scarsella M., Maresca V., Flori E., Bove L., Pace A., Stoppacciaro A., Zupi G., Cognetti F., Picardo M.

Alpha-tocopherol protects against cisplatin-induced toxicity without interfering with antitumor efficacy.

Int. J. Cancer, 104(2), p.243-50, 2003 I.F. 4.056

106. Leopardi P., Zijno A., Marcon F., Conti L., Carere A., Verdina A., Galati R., Tomei F., Baccolo T.P., Crebelli R.

Analysis of micronuclei in peripheral blood lymphocytes of traffic wardens: effects of exposure, metabolic genotypes, and inhibition of excision repair in vitro by ARA-C.

Environ. Mol. Mutagen., 41(2), p.126-30, 2003 I.F. 2.546

107. Lo-Coco F., Romano A., Mengarelli A., Diverio D., Iori A.P., Moleti M.L., De Santis S., Cerretti R., Mandelli F., Arcese W.

Allogeneic stem cell transplantation for advanced acute promyelocytic leukemia: results in patients treated in second molecular remission or with molecularly persistent disease.

Leukemia, 17(10), p.1930-3, 2003 I.F. 4.693

108. Lombardi D., Mileo A.M.

Protein interactions provide new insight into Nm23/nucleoside diphosphate kinase functions.

J. Bioenerg. Biomembr., 35(1), p.67-71, 2003 I.F. 2.920

109. Losch F.O., Muller R., Mutschler B., Neri D., Natali P.G., Reth M., Carsetti R.

Activation of T cells via tumor antigen specific chimeric receptors: the role of the intracellular signaling domain.

Int. J. Cancer, 103(3), p.399-407, 2003 I.F. 4.056

110. Macaluso M., Paggi M.G., Giordano A.

Genetic and epigenetic alterations as hallmarks of the intricate road to cancer.

Oncogene, 22(42), p.6472-8, 2003 I.F. 5.979

111. Maini C.L., Sciuto R., Romano L., Bergomi S.

Radionuclide Therapy with Bone Seeking Radionuclides in Palliation of Painful Bone Metastases.

J. Exp. Clin. Cancer Res., 22(Suppl.4), 2003 I.F. 0.703

112. Mancini R., Ettorre G., Vennarecci G., Sperduti I., Garufi C., Esposito A., Cosimelli M.

Personal Experience on Treatment of Colorectal Liver Metastases: a Multidisciplinary Approach.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003 I.F. 0.703

113. Mancini F., Gentiletti F., D'angelo M., Giglio S., Nanni S., D'angelo C., Farsetti A., Citro G., Sacchi A., Pontecorvi A., Moretti F.

MDM4 (MDMX) overexpression enhances stabilization of stress-induced p53 and promotes apoptosis.

J. Biol. Chem., 279(9), p.8169-80, 2003 I.F. 6.696

114. Mancini R., Tedesco M., Garufi C., Filippini A., Arcieri S., Caterino M., Pizzi G., Cortesi E., Spila A., Sperduti I., Cosimelli M.

Hepatic arterial infusion (HAI) of cisplatin and systemic fluorouracil in the treatment of unresectable colorectal liver metastases.

Anticancer Res., 23(2C), p.1837-41, 2003 I.F. 1.447

115. Mandala M., Ferretti G., Cremonesi M., Cazzaniga M., Curigliano G., Barni S.

Venous thromboembolism and cancer: new issues for an old topic.

Crit. Rev. Oncol. Hematol., 48(1), p.65-80, 2003 I.F. 2.758

116. Mandelli F., Latagliata R., Avvisati G., Fazi P., Rodeghiero F., Leoni F., Gobbi M., Nobile F., Gallo E., Fanin R., Amadori S., Vignetti M., Fioritoni G., Ferrara F., Peta A., Giustolisi R., Broccia G., Petti M.C., Lo-Coco F.; Italian Gimema Cooperative Group.

Treatment of elderly patients (> or =60 years) with newly diagnosed acute

promyelocytic leukemia. Results of the Italian multicenter group GIMEMA with ATRA and idarubicin (AIDA) protocols.
Leukemia, 17(6), p.1085-90, 2003 I.F. 4.693

117. Marcon F., Andreoli C., Rossi S., Verdina A., Galati R., Crebelli R.
Assessment of individual sensitivity to ionizing radiation and DNA repair efficiency in a healthy population.
Mutat. Res., 541(1-2), p.1-8, 2003 I.F. 3.795

118. Mastronicola D., Genova M.L., Arese M., Barone M.C., Giuffre A., Bianchi C., Brunori M., Lenaz G., Sarti P.
Control of respiration by nitric oxide in Keilin-Hartree particles, mitochondria and SH-SY5Y neuroblastoma cells.
Cell. Mol. Life Sci., 60(8), p.1752-9, 2003 I.F. 5.259

119. Mercadante S., Ferrera P., Villari P., Arcuri E.
Hyperalgesia: an emerging iatrogenic syndrome.
J. Pain Symptom Manage., 26(2), p.769-75, 2003 I.F. 2.466

120. Mercadante S., Villari P., Ferrera P., Arcuri E.
Local anesthetic switching for intrathecal tachyphylaxis in cancer patients with pain.
Anesth. Analg., 97(1), p.187-9, 2003 I.F. 2.332

121. Mercadante S., Catala E., Arcuri E., Casuccio A.
Celiac plexus block for pancreatic cancer pain: factors influencing pain, symptoms and quality of life.
J. Pain Symptom Manage., 26(6), p.1140-7, 2003 I.F. 2.466

122. Mercadante S., Arcuri E.
Sympathetic blocks and disease progression modifying pain mechanisms.
Reg. Anesth. Pain. Med., 28(6), p.586-7, 2003 I.F. 1.062

123. Milella M.
Relevance of cytoplasmic intermediates (MAPK-PI3K) in signal transduction.
Tumori, 2, (Suppl. 2), p.S35-S36, 2003 I.F.0.267

124. Miligi L., Costantini A.S., Bolejack V., Veraldi A., Benvenuti A., Nanni O., Ramazzotti V., Tumino R., Stagnaro E., Et Al.
Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study.
Am. J. Ind. Med., 44(6), p.627-36, 2003 I.F. 1.670

125. Molica S., Vitelli G., Levato D., Giannarelli D., Vacca A., Cuneo A., Cavazzini F., Squillace R., Mirabelli R., Digiesi G.
Increased serum levels of matrix metalloproteinase-9 predict clinical outcome of patients with early B-cell chronic lymphocytic leukaemia.
Eur. J. Haematol., 70(6), p.373-8, 2003 I.F. 1.807

126. Monaco L., Passananti C., Fanciulli M.
Genomic structure and transcriptional regulation of Che-1, a novel partner of Rb.
Gene, 321, p.57-63, 2003 I.F. 2.778

127. Mottolese M., Buglioni S., Piperno G., Sperduti I., Giannarelli D., D'angelo C., Cosimelli M.

Bio-pathological factors of prognostic value in colorectal adenocarcinomas.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), p.163-166, 2003 I.F. 0.703

128. Mouridsen H., Gershanovich M., Sun Y., Perez-Carrion R., Boni C., Monnier A., (In Addition To Listed Autors) Were As Follows: Italy: P. Carlini Et Al..

Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group.

J. Clin. Oncol., 21(11), p.2101-9, 2003 I.F. 9.868

129. Negri E., Pelucchi C., Franceschi S., Montella M., Conti E., Dal Maso L., Parazzini F., Tavani A., Carbone A., La Vecchia C.

Family history of cancer and risk of ovarian cancer.

Eur. J. Cancer, 39(4), p.505-10, 2003 I.F. 3.562

130. Nelson J., Bagnato A., Battistini B., Nisen P.

The endothelin axis: emerging role in cancer.

Nat. Rev. Cancer, 3(2), p.110-6, 2003 I.F. 13.625

131. Pace A.Vidiri A., Galiè E., Carosi M., Telera S., Cianciulli A.M., Canalini P., Giannarelli D., Jandolo B., Carapella C.M.

Temozolomide chemioterapy for progressive low-grade glioma: clinical benefits and radiological response.

Annals Oncology, 14(12), p.1722-6, 2003 I.F. 3.114

132. Pace A., Savarese A., Picardo M., Maresca V., Pacetti U., Del Monte G., Biroccio A., Leonetti C., Jandolo B., Cognetti F., Bove L.

Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy.

J. Clin. Oncol., 21(5), p.927-31, 2003 I.F. 9.868

133. Pagani E., Pepponi R., Fuggetta M.P., Prete S.P., Turriziani M., Bonmassar L., Lacal P.M., Falcinelli S., Passarelli F., Guadagni F., Alvino E., D'atri S.

DNA repair enzymes and cytotoxic effects of temozolomide: comparative studies between tumor cells and normal cells of the immune system.

J. Chemother., 15(2), p.173-83, 2003 I.F. 0.828

134.Panzuto F., Falconi M., Nasoni S., Angeletti S., Moretti A., Bezzi M., Gualdi G., Polettini E., Sciuto R., Festa A., Scopinaro F., Corleto V.D., Bordi C., Pederzoli P., Delle Fave G.

Staging of digestive endocrine tumours using helical computed tomography and somatostatin receptor scintigraphy.

Annals Oncology, 14(4), p.586-91, 2003 I.F. 3.114

135. Papaldo P., Ferretti G.L., Di Cosimo S.

Indicazioni nella pratica clinica della chemioterapia nelle pazienti con tumore della mammella operato con linfonodi negativi.

Tumori, 2(Suppl. 4), p.S11-S12, 2003 I.F. 0.267

136. Papaldo P., Lopez M., Cortesi E., Cammilluzzi E., Antimi M., Terzoli E., Lepidini G., Vici P., Barone C., Ferretti G., Di Cosimo S., Nistico C., Carlini P., Conti F., Di Lauro L., Botti C., Vitucci C., Fabi A., Giannarelli D., Marolla P.

Addition of either lonidamine or granulocyte colony-stimulating factor does not improve survival in early breast cancer patients treated with high-dose epirubicin and cyclophosphamide.

J. Clin. Oncol., 21(18), p.3462-8, 2003 I.F. 9.868

137. Pelucchi C., Talamini R., Negri E., Levi F., Conti E., Franceschi S., La Vecchia C.

Folate intake and risk of oral and pharyngeal cancer.

Annals Oncology, 14(11), p.1677-81, 2003 I.F. 3.114

138. Perluigi M., De Marco F., Foppoli C., Coccia R., Blarzino C., Marcante M.L., Cini C.

Tyrosinase protects human melanocytes from ROS-generating compounds.

Biochem Biophys Res. Commun., 305(2), p.250-6, 2003 I.F. 2.935

139. Petti M.C., Tafuri A., Latagliata R., Aloe Spiriti M.A., Montefusco E., Mancini M., Meloni G., Petrucci M.T., Spadea A., Redi R., Alimena G., Mandelli F.

High-dose hydroxyurea in the treatment of poor-risk myeloid leukemias.

Ann. Hematol., 82(8), p.476-80, 2003 I.F. 1.416

140. Pittoni V., Sorice M., Circella A., Cangemi R., Conti L., Ramenghi U., Gandolfo G.M., Dianzani U., Valesini G.

Specificity of antinuclear and antiphospholipid antibodies in sera of patients with autoimmune lymphoproliferative disease (ALD).

Clin. Exp. Rheumatol., 21(3), p.377-85, 2003 I.F. 1.284

141. Puxeddu E., Moretti S., Giannico A., Martinelli M., Marino C., Avenia N., Cristofani R., Farabi R., Reboldi G., Ribacchi R., Pontecorvi A., Santeusanio F.

Ret/PTC activation does not influence clinical and pathological features of adult papillary thyroid carcinomas.

Eur. J. Endocrinol., 148(5), p.505-13, 2003 I.F. 2.560

142. Quaglia A., Vercelli M., Puppo A., Casella C., Artioli E., Crocetti E., Falcini F., Ramazzotti V., Tagliabue G.; Prostate Working Group.

Prostate cancer in Italy before and during the 'PSA era': survival trend and prognostic determinants.

Eur. J. Cancer Prev., 12(2), p.145-52, 2003 I.F. 1.685

143. Quattrini M., Del Nonno F., Pacetti U., Visca P., Atlante M., Brenna A., Romagnoli F., Marandino F., Sbiroli C., Mariani L.

Rapid Modification of Aggressiveness of a Primary Non-Hodgkin Lymphoma of Uterine Cervix.

J. Exp. Clin. Cancer Res., 22(4), p.633-5, 2003 I.F. 0.703

144. Roazzi P., Capocaccia R., Santaquilani M., Carrani E., (Eurocare Working Group) (Conti E.M.S.).

Electronic availability of Eurocare-3 data: a tool for further analysis.

Annals Oncology, 14(Suppl. 5), p.v150-v155, 2003 I.F. 3.114

145. Rosano L., Spinella F., Di Castro V., Nicotra M.R., Albini A., Natali P.G., Bagnato A.
Endothelin receptor blockade inhibits molecular effectors of Kaposi's sarcoma cell invasion and tumor growth in vivo.
Am. J. Pathol., 163(2), p.753-62, 2003 I.F. 6.750

146. Rosano L., Spinella F., Salani D., Di Castro V., Venuti A., Nicotra M.R., Natali P.G., Bagnato A.
Therapeutic targeting of the endothelin a receptor in human ovarian carcinoma.
Cancer Res., 63(10), p.2447-53, 2003 I.F. 8.318

147. Rosell R., Scagliotti G., Danenberg K.D., Lord R.V., Bepler G., Novello S., Cooc J., Crino L., Sanchez J.J., Taron M., Boni C., De Marinis F., Tonato M., Marangolo M., Gozzelino F., Di Costanzo F., Rinaldi M., Et Al.
Transcripts in pretreatment biopsies from a three-arm randomized trial in metastatic non-small-cell lung cancer.
Oncogene, 22(23), p.3548-53, 2003 I.F. 5.979

148. Roselli M., Guadagni F., Martini F., Spila A., Mariotti S., D'alessandro R., Aloe S., Gazzaniga P.P., Basili S., Cosimelli M., Ferroni P.
Association between serum carcinoembryonic antigen and endothelial cell adhesion molecules in colorectal cancer.
Oncology, 65(2), p.132-8, 2003 I.F. 2.330

149. Roselli M., Mineo T.C., Basili S., Mariotti S., Martini F., Bellotti A., Ambrogi V., Spila A., D'alessandro R., Gazzaniga P.P., Guadagni F., Ferroni P.
Vascular endothelial growth factor (VEGF-A) plasma levels in non-small cell lung cancer: relationship with coagulation and platelet activation markers.
Thromb. Haemost., 89(1), p.177-84, 2003 I.F. 4.357

150. Sant M., Aareleid T., Berrino F., Bielska Lasota M., Carli P.M., Faivre J., Grosclaude P., Hèdelin G., Matsuda T., Moller H., And The Eurocare Working Group (Conti E.).
Eurocare-3: survival of cancer patients diagnosed 1990-94-result and commentary.
Annals Oncology, 14(Suppl. 5), p.v61-v118, 2003 I.F. 3.114

151. Santoro R., Carlini M., Carboni F., Boschetto A., Lepiane P., Sperduti I., Santoro E.
Gastric cancer in elderly and young patients: a western experience.
Tumori, 89(Suppl. 4), p.138-40, 2003 I.F. 0.267

152. Santoro R., Carlini M., Carboni F., Nicolas C., Santoro E.
Delayed massive arterial hemorrhage after pancreaticoduodenectomy for cancer. Management of a life-threatening complication.
Hepatogastroenterology, 50(54), p.2199-204, 2003 I.F. 0.833

153. Santucci B., Cannistraci C., Lesnoni I., Ferraro C., Rocco M.G., Dell'anna L., Giannarelli D., Cristaudo A.
Cutaneous response to irritants.
Contact Dermatitis, 48(2), p.69-73, 2003 I.F. 0.928

154. Sarti P., Arese M., Bacchi A., Barone M.C., Forte E., Mastronicola D., Brunori M., Giuffre A.
Nitric oxide and mitochondrial complex IV.
IUBMB Life, 55(10-11), p.605-11, 2003 I.F. 1.824

155. Savarese A., Cognetti F.

New drugs in the treatment of recurrent or metastatic cervical cancer.

Crit. Rev. Oncol. Hematol., 48(3), p.323-7, 2003 I.F. 2.758

156. Scagliotti G.V., Fossati R., Torri V., Crino L., Giaccone G., Silvano G., Martelli M., Clerici M., Cognetti F., Tonato M.; Adjuvant Lung Project Italy/European Organisation For Research Treatment Of Cancer-Lung Cancer Cooperative Group Investigators.

Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer.

J. Natl. Cancer Inst., 95(19), p.1453-61, 2003 I.F. 14.500

157. Serra C., Federici M., Buongiorno A., Senni M.I., Morelli S., Segratella E., Pascuccio M., Tiveron C., Mattei E., Tatangelo L., Lauro R., Et Al.

Transgenic mice with dominant negative PKC-theta in skeletal muscle: a new model of insulin resistance and obesity.

J. Cell. Physiol., 196(1), p.89-97, 2003 I.F. 4.845

158. Spinella F., Rosano L., Di Castro V., Nicotra M.R., Natali P.G., Bagnato A.

Endothelin-1 decreases gap-junctional intercellular communication by inducing phosphorylation of connexin 43 in human ovarian carcinoma cells.

J. Biol. Chem., 278(42), p.41294-301, 2003 I.F. 6.696

159. Spriano G., Ruscito P., Morello R., Pellini R.

Tumori del cavo orale dell'orofaringe: nuove tecniche ricostruttive della mandibola.

Tumori, 2(Suppl. 4), p.S57-S60, 2003 I.F. 0.267

160. Spugnini E.P., And Porrello A.

Potentiation of Chemotherapy in Companion Animals with Spontaneous Large Neoplasms by Application of Biphasic Electric Pulses.

J. Exp. Clin. Cancer Res., 22(4), p.571-80, 2003 I.F. 0.703

161. Stasi R., Abriani L., Beccaglia P., Terzoli E., Amadori S.

Cancer-related fatigue: evolving concepts in evaluation and treatment.

Cancer, 98(9), p.1786-801, 2003 I.F. 3.941

162. Sternberg C.N., Pansadoro V., Calabro F., Schnetzer S., Giannarelli D., Emiliozzi P., De Paula F., Scarpone P., De Carli P., Pizzo M., Platania A., Amini M.

Can patient selection for bladder preservation be based on response to chemotherapy?

Cancer, 97(7), p.1644-52, 2003 I.F. 3.941

163. Tentori L., Leonetti C., Scarsella M., D'amati G., Vergati M., Portarena I., Xu W., Kalish V., Zupi G., Zhang J., Graziani G.

Systemic Administration of GPI 15427, a Novel Poly(ADP-Ribose) Polymerase-1 Inhibitor, Increases the Antitumor Activity of Temozolomide against Intracranial Melanoma, Glioma, Lymphoma.

Clin. Cancer Res., 9(14), p.5370-9, 2003 I.F. 5.991

164. Tentori L., Portarena I., Barbarino M., Balduzzi A., Levati L., Vergati M., Biroccio A., Gold B., Lombardi M.L., Graziani G.

Inhibition of telomerase increases resistance of melanoma cells to temozolomide, but not to temozolomide combined with poly (adp-ribose) polymerase inhibitor.

Mol. Pharmacol., 63(1), p.192-202, 2003 I.F. 5.480

165. Tomasini R., Azizi Samir A., Carrier A., Isnardon D., Cecchinelli B., Soddu S., Malissen B., Dagorn J.C., Iovanna J.L., Dusetti N.J.

TP53INP1s and HIPK2 are partners in regulating p53 activity.

J. Biol. Chem., 278(39), p.37722-9, 2003 I.F. 6.696

166. Tomassetti M., Feriotto G., Giacomini P., Giorda E., Bianchi N., Borgatti M., Finotti A., Mischiati C., Gambari R.

Identification of a novel DNase I hypersensitive site within the far upstream region of the human HLA-DRA gene.

Int. J. Mol. Med., 12(6), p.929-34, 2003 I.F. 2.063

167. Tonini G., Vincenzi B., Santini D., La Cesa A., Finolezzi E., Onori N., D'angelillo R., Baldi A. And Trodella L.

Prevention of Radiotherapy-Induced Emesis.

J. Exp. Clin. Cancer Res., 22(1), p.17-22, 2003 I.F. 0.703

168. Tonini G., Vincenzi B., Santini D., Avvisati G., La Cesa A., Baldi A.

Unusual problems in breast cancer and a rare lung cancer case. Case 1. Clinical complete response of breast cancer metastases after trastuzumab-based immunotherapy.

J. Clin. Oncol., 1, 21(11), p.2215-6, 2003 I.F. 9.868

169. Trisciuoglio D., Iervolino A., Candiloro A., Fibbi G., Fanciulli M., Zangemeister-Wittke U., Zupi G., Del Bufalo D.

Bcl-2 induction of urokinase plasminogen activator receptor expression in human cancer cells through Sp1 activation: Involvement of Erk1/Erk2 activity.

J. Biol. Chem., 279(8), p.6737-45, 2003 I.F. 6.696

170. Vennarecci G., Ettorre G.M., Antonini M., Maritti M., Moricca P., D'offizzi G., Narciso P., Lonardo M.T., Boschetto A., Del Nonno F., Perracchio L., Palmieri G.P., Visco G., Santoro E.

Acute liver toxicity of antiretroviral therapy (HAART) after liver transplantation in a patient with HIV-HCV coinfection and associated hepatocarcinoma (HCC)].

Tumori, 89(Suppl. 4), p.159-61, 2003 I.F. 0.267

171. Vineis P., Miligi L., Crosignani P., Davico L., Fontana A., Masala G., Nanni O., Ramazzotti V., Rodella S., Stagnaro E., Tumino R., Vigano C., Vindigni C., Costantini A.S.

Delayed infection, late tonsillectomy or adenoidectomy and adult leukaemia: a case-control study.

Br. J. Cancer, 88(1), p.47-9, 2003 I.F. 3.639

172. Visca P., Sebastiani V., Pizer E.S., Botti C., De Carli P., Filippi S., Monaco S., Alo P.L.

Immunohistochemical expression and prognostic significance of FAS and GLUT1 in bladder carcinoma.

Anticancer Res., 23(1A), p.335-9, 2003 I.F. 1.447

173. Vitali R., Cesi V., Nicotra M.R., Mcdowell H.P., Donfrancesco A., Mannarino O., Natali P.G., Raschella G., Dominici C.

c-Kit is preferentially expressed in MYCN-amplified neuroblastoma and its effect on cell proliferation is inhibited in vitro by STI-571.

Int. J. Cancer, 106(2), p.147-52, 2003 I.F. 4.056

174. Vizza E., Galati G.M., Corrado G., Sbiroli C.

Role of pelvic lymphadenectomy in the management of stage I endometrial cancer: our experience.

Eur. J. Gynaecol. Oncol., 24(2), p.126-8, 2003 I.F. 0.395

175. Zeuli M., Nardoni C., Pino M.S., Gamucci T., Gabriele A., Ferraresi V., Giannarelli D., Cognetti F.

Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer.

Annals Oncology, 14(9), p.1378-82, 2003 I.F. 3.114

176. Zijno A., Andreoli C., Leopardi P., Marcon F., Rossi S., Caiola S., Verdina A., Galati R., Cafolla A., Crebelli R.

Folate status, metabolic genotype, and biomarkers of genotoxicity in healthy subjects.

Carcinogenesis, 24(6), p.1097-103, 2003 I.F. 5.405

Amifostine impairs p53-mediated apoptosis of human myeloid leukemia cells.

ACOSTA J.C., RICHARD C., DELGADO M.D., HORITA M., RIZZO M.G., FERNANDEZ-LUNA J.L., LEON J.

Mol. Cancer Ther., 2(9), p.893-900, 2003

Amifostine is used as a cytoprotective agent in cancer treatments. Amifostine protects from apoptosis in some models and has been used as hematopoiesis stimulator in myeloid malignancies. As the apoptosis induced by many antitumoral agents is mediated by p53, we studied the effect of amifostine on p53-mediated apoptosis. We used human myeloid leukemia K562 and NB4 cells expressing the temperature-conditional p53-Val(135) mutant. Both cell lines undergo apoptosis at 32 degrees C due to the presence of p53 in wild-type conformation. We found that amifostine dramatically reduced apoptosis by p53 in both cell lines, as assessed by cell morphology, annexin V binding, fraction of sub-G(1) cells, and DNA laddering. To explore the mechanism responsible for this apoptosis protection, we tested the effect of amifostine on p53 transcriptional activity. We found that amifostine reduced p53-mediated transactivation of target promoters in NB4 and K562. Macroarray analysis confirmed that several p53 target genes as p21(Waf1), mdm2, gadd45, pig8, and pig3 were down-regulated at the mRNA level by amifostine in NB4 and K562. Also, c-myc was up-regulated by amifostine in K562 in the presence of p53, consistently with the impairment of p53-mediated apoptosis exerted by c-Myc in these cells. We conclude that amifostine impairs p53-dependent apoptosis of myeloid leukemia cells by reducing the activation of apoptosis-related genes. Our results open the possibility that amifostine could reduce the effectiveness of antitumoral treatments when it is dependent on active p53.

Constitutive knockout of Surf1 is associated with high embryonic lethality, mitochondrial disease and cytochrome c oxidase deficiency in mice.

AGOSTINO A., INVERNIZZI F., TIVERON C., FAGIOLARI G., PRELLE A., LAMANTEA E., GIAVAZZI A., BATTAGLIA G., TATANGELO L., TIRANTI V., ZEVIANI M.

Hum. Mol. Genet., 12(4), p.399-413, 2003

We report here the creation of a constitutive knockout mouse for SURF1, a gene encoding one of the assembly proteins involved in the formation of cytochrome c oxidase (COX). Loss-of-function mutations of SURF1 cause Leigh syndrome associated with an isolated and generalized COX deficiency in humans. The murine phenotype is characterized by the following hallmarks: (1) high post-implantation embryonic lethality, affecting approximately 90% of the Surf1(-/-) individuals; (2) early-onset mortality of post-natal individuals; (3) highly significant deficit in muscle strength and motor performance; (4) profound and isolated defect of COX activity in skeletal muscle and liver, and, to a lesser extent, heart and brain; (5) morphological abnormalities of skeletal muscle, characterized by reduced histochemical reaction to COX and mitochondrial proliferation; (6) no obvious abnormalities in brain morphology, reflecting the virtual absence of overt neurological symptoms. These results indicate a function for murine Surf1 protein (Surf1p) specifically related to COX and recapitulate, at least in part, the human phenotype. This is the first mammalian model for a nuclear disease gene of a human mitochondrial disorder. Our model constitutes a useful tool to investigate the function of Surf1p, help understand the pathogenesis of Surf1p deficiency in vivo, and evaluate the efficacy of treatment.

Can colorectal cancer patients with thymidylate synthase-overexpressing liver metastases have an overall survival advantage with hepatic arterial infusion alone?

ALIMONTI A., FERRETTI G., DI COSIMO S., COGNETTI F., VECCHIONE A.

J. Clin. Oncol., 21(18), p.3543-4, 2003

No abstract available

Subacute motor weakness and left renal mass.

ALIMONTI A., DI COSIMO S., DI STANI F., VECCHIONE A., DI PALMA M., FERRETTI G.

Am. J. Med., 114(8), p.706-8, 2003

No abstract available

Physical and functional interaction between HCV core protein and the different p73 isoforms.

ALISI A., GIAMBARTOLOMEI S., CUPELLI F., MERLO P., FONTEMAGGI G., SPAZIANI A., BALSANO C.

Oncogene, 22(17), p.2573-80, 2003

Hepatitis C virus (HCV) core protein is a structural viral protein that packages the viral genomic RNA. In addition to this function, HCV core also modulates a number of cellular regulatory functions. In fact, HCV core protein has been found to modulate the expression of the cyclin-dependent inhibitor p21(WAF1/CIP1) and to promote both apoptosis and cell proliferation through its physical interaction with p53. Here, we studied the ability of HCV core to bind the p53-related p73 protein, its isoforms and its deletion mutants. We found that HCV core co-immunoprecipitated with p73 in HepG2 and SAOS-2 cells. Deletion mutational analysis of p73 indicates that the domain involved in HCV core binding is located between amino-acid residues 321-353. We also demonstrate that p73/core interaction results in the nuclear translocation of HCV core protein either in the presence of the p73 alpha or p73 beta tumor-suppressor proteins. In addition, the interaction with HCV core protein prevents p73 alpha, but not p73 beta dependent cell growth arrest in a p53-dependent manner. Our findings demonstrate that HCV core protein may directly influence the various p73 functions, thus playing a role in HCV pathogenesis.

Prognostic value of serum and tumor tissue CA 72-4 content in gastric cancer.

ALOE S., D'ALESSANDRO R., SPILA A., FERRONI P., BASILI S., PALMIROTTA R., CARLINI M., GRAZIANO F., MANCINI R., MARIOTTI S., COSIMELLI M., ROSELLI M., GUADAGNI F.

Int. J. Biol. Markers, 18(1), p.21-7, 2003

To date no general agreement has been reached regarding the prognostic significance of CEA, CA 19-9 and CA 72-4 as serum markers in gastric cancer, and only scattered information is available on the predictive value of marker expression in tumor tissue. Therefore, a longitudinal study was designed to analyze the presurgical serum and tumor tissue content of CA 72-4, CEA and CA 19-9 in 166 patients at different stages of gastric cancer, and to evaluate the possible correlation with clinicopathological features in respect to prognostic information on relapse-free survival. The results obtained showed that 48.4% of patients with tumor recurrence had positive presurgical CA 72-4 levels compared to approximately 24% of patients who remained free of disease. Furthermore, the median presurgical serum CA 72-4 levels were significantly elevated in relapsing patients. Serosa and lymph node involvement as well as positive presurgical serum CA 72-4 levels had independent prognostic value in predicting recurrence. A significant association between disease-free survival and lymph node involvement, depth of invasion and tumor tissue content of CA 72-4 was also demonstrated. We may therefore conclude that CA 72-4 antigen can be considered the marker of choice in the follow-up of gastric cancer patients and may be used as a prognostic indicator of relapse.

Feedback inhibition by RALT controls signal output by the ErbB network.

Anastasi S., Fiorentino L., Fiorini M., Fraioli R., Sala G., Castellani L., Alema S., Alimandi M., Segatto O.

Oncogene, 22(27), p.4221-34, 2003

The ErbB-2 interacting protein receptor-associated late transducer (RALT) was previously identified as a feedback inhibitor of ErbB-2 mitogenic signals. We now report that RALT binds to ligand-activated epidermal growth factor receptor (EGFR), ErbB-4 and ErbB-2.ErbB-3 dimers. When ectopically expressed in 32D cells reconstituted with the above ErbB receptor tyrosine kinases (RTKs) RALT behaved as a pan-ErbB inhibitor. Importantly, when tested in either cell proliferation assays or biochemical experiments measuring activation of ERK and AKT, RALT affected the signalling activity of distinct ErbB dimers with different relative potencies. RALT deltaEBR, a mutant unable to bind to ErbB RTKs, did not inhibit ErbB-dependent activation of ERK and AKT, consistent with RALT exerting its suppressive activity towards these pathways at a receptor-proximal level. Remarkably, RALT deltaEBR retained the ability to suppress largely the proliferative activity of ErbB-2.ErbB-3 dimers over a wide range of ligand concentrations, indicating that RALT can intercept ErbB-2.ErbB-3 mitogenic signals also at a receptor-distal level. A suppressive function of RALT deltaEBR towards the mitogenic activity of EGFR and ErbB-4 was detected at low levels of receptor occupancy, but was completely overcome by saturating concentrations of ligand. We propose that quantitative and qualitative aspects of RALT signalling concur in defining identity, strength and duration of signals generated by the ErbB network.

Coexistence of a parathyroid adenoma and parathyroid cyst causing primary hyperparathyroidism.

Ardito G., Fadda G., Danese D., Modugno P., Giordano A., Revelli L., Ardito F., Pontecorvi A.

J. Endocrinol. Invest., 26(7), p.679-82, 2003

The association of a functional parathyroid cyst with a parathyroid adenoma is an uncommon finding. In this report we describe the clinical history of a 60-yr-old man, presenting with the following findings: hypercalcemia (18.9 mg/dl), elevated serum parathormone levels (1320 pg/dl), hypercalciuria (228 mg/dl), and hyperphosphaturia (155 mg/dl). Neck ultrasound, magnetic resonance imaging (MRI) and 99Tc Sestamibi scintigraphy led to the identification of a left parathyroid adenoma, located at the lower pole of the left thyroid gland lobe, associated with a parathyroid cyst, located at the upper extremity of the same thyroid lobe. Parathyroidectomy was performed and the histological examination confirmed the diagnosis of a parathyroid adenoma with aspects of cystic degeneration and an upper parathyroid cyst. Analysis of the crystal clear intracystic fluid showed elevated parathyroid hormone (PTH) levels (137.000 pg/ml). The patient is normocalcemic at 2 yr after surgery without signs of recurrent parathyroid enlargements. Aetiology, diagnosis and management of parathyroid cyst will be discussed.

Dietary glycemic index, glycemic load and ovarian cancer risk: a case-control study in Italy.

Augustin L.S., Polesel J., Bosetti C., Kendall C.W., La Vecchia C., Parpinel M., Conti E., Montella M., Franceschi S., Jenkins D.J., Dal Maso L.

Ann. Oncol., 14(1), p.78-84, 2003

Background: Dietary carbohydrates vary in their ability to raise blood glucose and insulin levels, which, in turn, influence levels of sex hormones and insulin-like growth factors. We analyzed the effect of type and amount of carbohydrates on ovarian cancer risk, using the glycemic index (GI) and the glycemic load (GL) measurement in a large case-control study conducted in Italy.

Materials and methods: Cases included 1031 women with incident, histologically confirmed epithelial ovarian cancer, from four Italian regions. Controls included 2411 women admitted to the same hospital networks for acute, non-neoplastic conditions. Average daily GI and GL were calculated from a validated food frequency questionnaire. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were computed using multiple logistic regression.

Results: Ovarian cancer was directly associated with dietary GI (OR for highest versus lowest quartile = 1.7, 95% CI 1.3-2.1) and GL (OR = 1.7, 95% CI 1.3-2.1). The associations were observed in pre- and postmenopausal women, and they remained consistent across strata of major covariates identified. CONCLUSIONS: This study supports the hypothesis of a direct association between GI and GL and ovarian cancer risk and, consequently, of a possible role of hyperinsulinemia/insulin resistance in ovarian cancer development.

Therapies for cancer targeting endothelin receptors.

BAGNATO A.

Drug of the Future, 28, p.983-989, 2003

No abstract available

Emerging role of endothelin-1 in tumor angiogenesis.

BAGNATO A., SPINELLA F.

Trends Endocrinology Metabolism, 14(1), p.44-50, 2003

Tumor vessels express distinct molecular markers that are functionally relevant in the angiogenic process. Although tyrosine kinase receptor agonists are the major mediators of angiogenesis, several G-protein-coupled receptor agonists have also been shown to have a role. Among these, endothelin-1 (ET-1), by acting directly on endothelial cells via the ET(B) receptor, modulates different stages of neovascularization, including proliferation, migration, invasion, protease production and morphogenesis, and also stimulates neovascularization in vivo. ET-1 can also modulate tumor angiogenesis indirectly through the induction of vascular endothelial growth factor (VEGF). Engagement of the ET(A) receptor by ET-1 induces VEGF production by increasing levels of hypoxia-inducible factor 1 alpha. Moreover, tumor cells themselves, predominantly expressing the ET(A) receptor, might form vessel-like channels within the tumors. The role of ET-1 and its signaling network in tumor angiogenesis suggests that new therapeutic strategies using specific ET(A)-receptor antagonists could improve antitumor treatment by inhibiting both neovascularization and tumor cell growth.

Identification of genes down-regulated during melanoma progression: a cDNA array study.

BALDI A., BATTISTA T., DE LUCA A., SANTINI D., ROSSIELLO L., BALDI F., NATALI P.G., LOMBARDI D., PICARDO M., FELSANI A., PAGGI M.G.

Exp. Dermatol., 12(2), p.213-8, 2003

In order to identify genes relevant for melanoma development, we carried out cDNA array experiments employing an in vitro model of human melanoma progression, consisting of two cell lines: one, LP, derived from a primary melanoma and the other, LM, from its metastatic supraclavicular lymph node. Basic cDNA array data identified 26 genes as down-regulated in the LM cell line. Northern blot analysis confirmed an effective transcriptional down-regulation for five out of 13 genes analyzed. The products of these five genes belong to different functional protein types, such as transcription and translation regulators (Edg-2, eIF-3 p110, and RNPL/RBM3), extracellular communicators (PRSS11) and members of the major histocompatibility complex (beta2-microglobulin). Some previously described differences in expression patterns, such as loss of HLA I, were confirmed by our array data. In addition, we identified and validated for the first time the reduced expression level of several genes during melanoma progression. In particular, reduced Edg-2 gene product expression was also confirmed in a group of 50 primary melanomas and unrelated metastases. In conclusion, comparative hybridization by means of cDNA arrays assisted in identifying a series of novel progression-associated changes in gene expression, confirming, at the same time, a number of previously described results.

cDNA array technology in melanoma: an overview.

BALDI A., SANTINI D., DE LUCA A., PAGGI M.G.

J. Cell. Physiol., 196(2), p.219-23, 2003

Genetic aberrations, mostly resulting in changes in gene expression, are critical events in cancer onset and progression. The advent of the cDNA array technology allows the screening and the efficient measurement of expression of thousands genes simultaneously in a wide spectrum of experimental and clinical models. This genomic scale approach is being currently used to obtain global views of human cancer gene expression and to identify genetic markers that might be important for diagnosis, prognosis, and therapy. This review discusses some recent findings obtained by means of cDNA arrays investigating the human melanoma.

Rb binding protein Che-1 interacts with Tau in cerebellar granule neurons. Modulation during neuronal apoptosis.

Barbato C., Corbi N., Canu N., Fanciulli M., Serafino A., Ciotti M., Libri V., Bruno T., Amadoro G., De Angelis R., Calissano P., Passananti C.

Mol. Cell. Neurosci., 24(4), p.1038-50, 2003

Che-1 is a recently identified human Rb binding protein that inhibits the Rb growth-suppressing function and regulates cell proliferation. Che-1 contacts the Rb and competes with HDAC1 for Rb-binding site, removing HDAC1 from the Rb/E2F cell cycle-regulated promoters. We have investigated the expression of Che-1 in neuronal cells and we showed that Che-1 directly interacts with Tau. Tau is a microtubule-associated protein involved in the assembly and stabilization of neuronal microtubules network that plays a crucial role modulating neuronal morphogenesis, axonal shape, and transport. In rat cerebellar granule neurons (CGNs) Che-1 partially colocalizes with Tau in the cytoplasm. Che-1 binds the amino-terminal region of Tau protein, which is not involved in microtubule interactions. Tau and Che-1 endogenous proteins coimmunoprecipitate from CGNs cellular lysates. In addition, Che-1/Tau interaction was demonstrated both in overexpressing COS-7 cells and CGNs by FRET analysis. Finally, we observed that Tau/Che-1 interaction is modulated during neuronal apoptosis.

Change of conformation of the DNA-binding domain of p53 is the only key element for binding of and interference with p73.

Bensaad K., Le Bras M., Unsal K., Strano S., Blandino G., Tominaga O., Rouillard D., Soussi T.

J. Biol. Chem., 278(12), p.10546-55, 2003

Xenopus p53 has biological and biochemical properties similar to those of human p53, except for optimal temperature. The frog protein is fully active at 30 degrees C and inactive at 37 degrees C, leading to a temperature-sensitive behavior similar to that of the human mutant p53Ala(143) and the murine mutant p53Val(135). Using hybrid proteins between human and Xenopus expressed from artificial p53 minigenes, we have been able to demonstrate that change of conformation of the DNA-binding domain is the major determinant of this heat sensitivity. It has been reported that some human tumor-derived p53 mutants can engage in a physical association with p73, thus inhibiting its transactivating properties. The mechanism of this association remains to be elucidated. The nature of the mutant p53 that can engage in this association also remains controversial. Using the unique opportunity of the temperature sensitivity of Xenopus p53, we demonstrate that binding of and interference with p73 require a change of conformation in the p53 protein. This interaction occurs through the DNA-binding domain of p53 only when it is in a denatured state. These results reinforce the notion that mutant p53 with a conformational change can act as a down-regulator of the p73 pathway in human cancer and could confer a selective advantage to the tumor.

En bloc vertebrectomy and dural resection for chordoma: a case report.

Biagini R., Casadei R., Boriani S., Erba F., Sturale C., Mascari C., Bortolotti C., Mercuri M.

Spine, 28(18), p.E368-72, 2003

Study design: Case report.

Objectives: Report a surgical technique for dural reconstruction after vertebrectomy.

Methods: Clinical case analysis: chordoma from T12 to L2 with infiltration of the dura.

Results: Forty-six months after vertebral resection and reconstruction, the patient is disease free.

Conclusions: Wide en bloc resection is required for local control in chordoma. When the tumor permeates the dura, resection not including the dura is intralesional with high risk of local recurrence. Therefore, a proper wide resection consists in vertebrectomy removing the dura infiltrated by the tumor. The two-stage dural reconstruction had strongly limited the leakage of liquor during surgery, and the dural patch provided extra strength anteriorly, where the dural suture is more difficult.

Inhibition of c-Myc oncoprotein limits the growth of human melanoma cells by inducing cellular crisis.

Biroccio A., Amodei S., Antonelli A., Benassi B., Zupi G.

J. Biol. Chem., 278(37), p.35693-701, 2003

Here, we show that inhibition of c-Myc causes a proliferative arrest of M14 melanoma cells through cellular crisis, evident by the increase in size, multiple nuclei, vacuolated cytoplasm, induction of senescence-associated beta-galactosidase activity and massive apoptosis. The c-Myc-induced crisis is associated with decreased human telomerase reverse transcriptase expression, telomerase activity, progressive telomere shortening, glutathione (GSH), depletion and, increased production of reactive oxygen species. Treatment of control cells with L-buthionine sulfoximine decreases GSH to levels of c-Myc low expressing cells, but it does not modify the growth kinetic of the cells. Surprisingly, when GSH is increased in the c-Myc low expressing cells by treatment with N-acetyl-L-cysteine, cells escape crisis. To test the hypothesis that both oxidative stress and telomerase dysfunction are involved in the c-Myc-dependent crisis, we directly inhibited telomerase function and glutathione levels. Inactivation of telomerase, by expression of a catalytically inactive, dominant negative form of reverse transcriptase, reduces cellular lifespan by inducing telomere shortening. Treatment of cells with L-buthionine sulfoximine decreases GSH content and accelerates cell crisis. Analysis of telomere status demonstrated that oxidative stress affects c-Myc-induced crisis by increasing telomere dysfunction. Our results demonstrate that inhibition of c-Myc oncoprotein induces cellular crisis through cooperation between telomerase dysfunction and oxidative stress.

Telomere dysfunction increases cisplatin and ecteinascidin-743 sensitivity of melanoma cells.

Biroccio A., Gabellini C., Amodei S., Benassi B., Del Bufalo D., Elli R., Antonelli A., D'Incalci M., Zupi G.

Mol. Pharmacol., 63(3), p.632-8, 2003

The aim of this study was to investigate the role of telomerase function on the chemosensitivity of melanoma cells. To this end, ecteinascidin-743 (ET-743) and cisplatin [cis-diamminedichloroplatinum(II) (CDDP)], two DNA-interacting drugs that invariably cause an arrest in the G(2)/M phase, and 1-(2,4-dichlorobenzyl)-1H-indazole-3-carboxylic acid (LND), a mitochondria-targeting drug inducing a G(1) block, were used. As experimental model, human melanoma clones showing reduced human telomerase reverse transcriptase (hTERT) expression and telomerase activity and characterized by telomere dysfunction were used. Reconstitution of telomerase activity by exogenous hTERT expression improved telomere function and reduced the sensitivity to CDDP and ET-743 without affecting LND susceptibility. The decreased sensitivity to CDDP and ET-743 was mainly caused by the ability of cells to recover from drug-induced damage, evaluated in terms of both chromosomal lesions and cell survival. The ability of hTERT-reconstituted cells to recover from drug-induced damage was attributable to the restoration of cell cycle progression. In fact, the cells without hTERT restoration remained for a prolonged time in the G(2)/M phase, and this cell cycle alteration made irreversible the drug-induced S-G(2)/M block and led to the activation of apoptotic program. On the contrary, the hTERT-reconstituted cells progressed quickly through the cell cycle, thus acquiring the capacity to recover from drug-induced block and to protect themselves from the G(2)/M phase-specific drug-triggered apoptosis.

The future of antisense therapy: combination with anticancer treatments.

Biroccio A., Leonetti C., Zupi G.

Oncogene, 22(42), p.6579-88, 2003

The current direction in cancer research is rational drug design, which is based on the evidence that transformed cells are characterized by alterations of genes devoted to the regulation of both cell proliferation and apoptosis. A variety of approaches have been carried out to develop new agents selective for cancer cells. Among these, antisense oligonucleotides (ASOs) are one of such class of new agents able to inhibit specifically the synthesis of a particular cancer-associated protein by binding to protein-encoding RNA, thereby preventing RNA function. In the past decade, several ASOs have been developed and tested in preclinical and clinical studies. Many have shown convincing in vitro reduction in target gene expression and promising activity against a wide variety of tumors. However, because of the multigenic alterations of tumors, the use of ASOs as single agents does not seem to be effective in the treatment of malignancies. Antisense therapy that interferes with signaling pathways involved in cell

proliferation and apoptosis are particularly promising in combination with conventional anti-cancer treatment. An overview of the progress of ASOs used in combination therapy is provided.

Tanycytic ependymoma of the spinal cord. Case report and review of the literature.

BOCCARDO M., TELERA S., VITALI A.

Neurochirurgie, 49(6), p.605-10, 2003

Objective and importance: We report a rare case of the tanycytic variant of intramedullary ependymoma. Tanycytes are the common progenitor cells of both ependymal cells and astrocytes. These particular elongate unipolar and bipolar ependymal cells extend from the ventricular lumen to the surface of the nervous system. It is extremely important, in terms of both management and prognosis, to distinguish intramedullary tanycytic ependymomas from intramedullary astrocytomas although a correct histological diagnosis may be difficult since tanycytes resemble astrocytes.

Case report: A 39-year-old woman underwent surgical treatment for a cervical intramedullary tumor in our department. Although pathological examination of frozen sections was suggestive of low-grade astrocytoma, the definitive histological diagnosis was "tanycytic" ependymoma, a tumor characterized by poor cellularity, elongated elements mixed with fibrillary components, rare pseudo-rosettes and mixed astro-ependymal aspects. Since a complete resection was performed at surgery, no further treatment was proposed. After a follow-up period of two years the patient is free from recurrence.

Conclusion: Tanycytic ependymomas should be managed in the same way as "ordinary" ependymomas, since there is no current evidence suggesting that these morphologically distinct tumors differ in terms of biological behavior. Increased awareness of this transitional form of intramedullary ependymoma among neurosurgeons and pathologists may avoid incorrect surgical approaches and postoperative treatment.

Impact of epoetin beta on quality of life in patients with malignant disease.

BOOGAERTS M., COIFFIER B., KAINZ C.; EPOETIN BETA QOL WORKING GROUP (COGNETTI F.)

Br. J. Cancer, 88(7), p.988-95, 2003

This open-label, prospective study was conducted to compare the impact of epoetin beta vs standard care on quality of life (QoL) in anaemic patients with lymphoid or solid tumour malignancies. A total of 262 anaemic patients (haemoglobin [Hb]<or=11 g dl(-1)) were randomised to a 12-week treatment with s.c. epoetin beta (initial dose 150 IU kg(-1) three times weekly) or standard care. Transfusions were recommended for both groups at an Hb threshold of 8.5 g dl(-1). The primary efficacy variables were improvement in QoL as measured using the Short-Form-36 physical component summary (SF-36 PCS) score and the Functional Assessment of Cancer Therapy fatigue and anaemia subscales (FACT-F and FACT-An). A visual analogue scale (VAS) was also used as a global QoL measure. Clinical response was defined as a >or=2 g dl(-1) increase in Hb level without need of transfusion after the initial 4 weeks of treatment. Baseline to final visit changes in SF-36 PCS, FACT-F and VAS scores were significantly greater with epoetin beta than with standard care ($P<0.05$); changes in FACT-An subscale score tended to be greater with epoetin beta ($P=0.076$). Epoetin beta significantly increased Hb concentrations relative to standard care (responders: 47% vs 13%; $P<0.001$). Levels of endogenous erythropoietin <50 mIU ml(-1) were significantly predictive of response (OR 2.496, 95% CI: 1.21-5.13). Epoetin beta therapy significantly improves QoL compared with standard care in anaemic patients with solid tumours and lymphoid malignancies.

Bovine papillomavirus type 4 in oesophageal papillomas of cattle from the south of Italy.

Borzacchiello G., Ambrosio V., Roperto S., Poggiali F., Tsirimonakis E., Venuti A., Campo M.S., Roperto F.

J. Comp. Pathol., 128(2-3), p.203-6, 2003

Oesophageal papillomas are known to occur in cattle infected with bovine papillomavirus type 4 (BPV-4), and BPV-4 papillomas may undergo malignant progression in cattle that feed on bracken fern. In the south of Italy, where bracken fern is common, examination of 1133 slaughterhouse cattle aged 4-12 years revealed oesophageal lesions (single or multiple pedunculated proliferations, or mucosal thickening) in 147 (13%). These two types of lesion were consistent with exophytic and inverted papilloma, respectively. BPV-4 was detected by polymerase chain reaction (PCR) analysis in >60% of the samples in which oesophageal papilloma was diagnosed histopathologically. Nucleotide sequencing of the PCR amplicons confirmed the presence of BPV-4 in the papillomas. This is the first report of such infections in a European country other than Britain.

Presence of bovine papillomavirus type 2 DNA and expression of the viral oncoprotein E5 in naturally occurring urinary bladder tumours in cows.

Borzacchiello G., Iovane G., Marcante M.L., Poggiali F., Roperto F., Roperto S., Venuti A.

J. Gen. Virol., 84(Pt 11), p.2921-6, 2003

Samples of neoplastic and normal urothelium were obtained from cows originating from areas of southern Italy, a region in which chronic enzootic haematuria is endemic and bracken fern infestation is widespread. Specimens were analysed for bovine papillomavirus type 2 (BPV-2) DNA, BPV-2 E5 expression and telomerase activity. A total of 46 of 60 tumours and 17 of 34 normal bladder mucosa samples harboured BPV-2 DNA. Analysis of a subset of samples showed E5 protein expression and telomerase activity in tumour tissue only. No normal samples positive for BPV DNA showed E5 protein expression or telomerase activity, suggesting the presence of DNA in a latent state. Taken together, these data on naturally occurring bovine bladder tumours corroborate the hypothesis of their virus origin.

Early detection of meningeal localization in acute promyelocytic leukaemia patients with high presenting leucocyte count.

Breccia M., Carmosino I., Diverio D., De Santis S., De Propris M.S., Romano A., Petti M.C., Mandelli F., Lo-Coco F.

Br. J. Haematol., 120(2), p.266-70, 2003

Extramedullary relapse occurs infrequently in acute promyelocytic leukaemia (APL) but has been increasingly reported after the advent of all-trans retinoic acid (ATRA) treatment, probably as a consequence of improved patient survival. We describe our single centre experience of six APL patients who had disease localization in the central nervous system (CNS). In three patients, clinical symptoms (headache and/or nausea) that presented during follow-up led to the performance of a lumbar puncture and detection of overt CNS infiltration. Two of these patients had simultaneous haematological relapse and one was in molecular remission when CNS leukaemia was documented. One patient with no local symptoms showed CNS infiltration at the time of molecular relapse. Following the introduction of routine lumbar puncture, carried out after frontline induction in all newly diagnosed patients with white blood cell count (WBC) greater than 10 x 109/l, two additional patients in molecular remission with no local symptoms were found to have initial APL localization in the CNS. Presenting features included in 6/6 patients an elevated WBC count (> 10 x 109/l) and a predominance of the PML/RAR bcr3 type (5/6 patients) and of microgranular morphology (5/6 patients). Our findings highlight the importance of carrying out lumbar puncture in APL patients presenting with high-risk features.

The diagnostic importance of the isolated supranuclear downward gaze ophthalmoplegia in progressive supranuclear palsy.

Brusa A., Bentivoglio A.R., Calzetti S., Cammarata S., Congia S., Fasano A., Jandolo B., Lucci B., Primavera A., Stoehr R.

Neurol. Sci., 24(3), p.161, 2003

No abstract available

Kit regulatory elements required for expression in developing hematopoietic and germ cell lineages.

CAIRNS L.A., MORONI E., LEVANTINI E., GIORGETTI A., KLINGER F.G., RONZONI S., TATANGELO L., TIVERON C., DE FELICI M., DOLCI S., MAGLI M.C., GIGLIONI B., OTTOLENGHI S.

Blood, 102(12), p.3954-62, 2003

The Kit (White) gene encodes the transmembrane receptor of stem cell factor/Kit ligand (KL) and is essential for the normal development/maintenance of pluripotent primordial germ cells (PGCs), hematopoietic stem cells (HSCs), melanoblasts, and some of their descendants. The molecular basis for the transcriptional regulation of Kit during development of these important cell types is unknown. We investigated Kit regulation in hematopoietic cells and PGCs. We identified 6 DNase I hypersensitive sites (HS1-HS6) within the promoter and first intron of the mouse Kit gene and developed mouse lines expressing transgenic green fluorescent protein (GFP) under the control of these regulatory elements. A construct driven by the Kit promoter and including all 6 HS sites is highly expressed during mouse development in Kit+ cells including PGCs and hematopoietic progenitors (erythroid blast-forming units and mixed colony-forming units). In contrast, the Kit promoter alone (comprising HS1) is sufficient to drive low-level GFP expression in PGCs, but unable to function in hematopoietic cells. Hematopoietic expression further requires the addition of the intron-proximal HS2 fragment; HS2 also greatly potentiates the activity in PGCs. Thus, HS2 acts as an enhancer integrating transcriptional signals common to 2 developmentally unrelated stem cell/progenitor lineages. Optimal hematopoietic expression further requires HS3-HS6.

Understanding human cancer using Drosophila: Tid47, a cytosolic product of the DnaJ-like tumor suppressor gene l2Tid, is a novel molecular partner of patched related to skin cancer.

CANAMASAS I., DEBES A., NATALI P.G., KURZIK-DUMKE U.

J. Biol. Chem., 278(33), p.30952-60, 2003

Recessive mutations of the Drosophila gene lethal(2)-tumorous imaginal discs (l(2)tid) cause neoplastic growth of the anlagen of the adult organs, the imaginal discs. Here we report that the three proteins encoded by this evolutionarily conserved gene, Tid50, Tid47, and Tid40, identified as members of the DnaJ cochaperone family, are destined for different cellular compartments, build complexes with many proteins in a developmental stage-specific manner, and are likely to be involved in different cellular processes. We show that the cytosolic Tid47 molecule is a novel component of the Hedgehog (Hh)-Patched (Ptc) signaling regulating cell/tissue polarity and spatial patterning during development and is associated with human tumors such as basal cell carcinoma (BCC) and medulloblastoma. We provide functional evidence for its direct in vivo interaction with the Hh-bound Ptc receptor during signal transmission. Because loss of l(2)tid causes neoplastic transformation of Hh-responsive cells, we suggest that Tid47 may at least act as a guardian of the Hh signaling gradient by regulating Ptc homeostasis in the tissue. Finally, we show that the expression of htid-1, the human counterpart of l(2)tid, is altered in human BCCs. We demonstrate that in BCCs loss of htid expression correlates with loss of differentiation capacity of the neoplastic cells similar to that found in the Drosophila tumor model.

The EUROCARE-3 database: methodology of data collection, standardisation, quality control and statistical analysis.

CAPOCACCIA R., GATTA G., ROAZZI P., CARRANI E., SANTAQUILANI M., DE ANGELIS R., TAVILLA A., THE EUROCARE WORKING GROUP (CONTI E.M.S.).

Ann. Oncol., 14 Suppl 5, p.V14-V27, 2003

No abstract available

Gastrointestinal stromal tumors of the stomach. A ten-year surgical experience.

CARBONI F., CARLINI M., SCARDAMAGLIA F., SANTORO E., BOSCHETTO A., CASTELLI M., MARANDINO F., SANTORO E.

J. Exp. Clin. Cancer Res., 22(3), p.379-84, 2003

Gastrointestinal stromal tumors show an increasing incidence. Immunohistochemistry is mandatory to make differential diagnosis with other mesenchimal tumors. We retrospectively reviewed 15 primary stomach GISTs operated during the last decade. Gastroscopy, Ultrasonography and CT scan were employed to obtain the diagnosis. Tumor size ranged from 1.5 to 30 cm in diameter. Treatment consisted of curative surgical resection without sistematic lymph node dissection. A wedge resection was sufficient in 8 cases. In 2 patients a distal subtotal gastrectomy was required and in 1 a total enlarged gastrectomy with pancreaticosplenectomy was performed. 4 GISTs were incidentally discovered and removed during surgical procedures for other gastrointestinal malignancies. In 4 cases a laparoscopic wedge resection was possible. In all cases postoperative course was uneventful. No adjuvant treatment was administered. Concerning the follow-up, two patients died for local and distant relapse while 13 are still alive (most of them operated during the last three years). GISTs show a very unpredictable clinical course and curative surgery is the only potential effective curative treatment.

Adrenal glands metastases from malignant melanoma. Laparoscopic bilateral drenalectomy.

CARLINI M., LONARDO M.T., BOSCHETTO A., CARBONI F., APPETECCHIA M., TROPEA F., SANTORO E.

J. Exp. Clin. Cancer Res., 22(1), p.141-5, 2003

Adrenal metastases from Malignant Melanoma (MM) represent a debated therapeutical problem particularly in the case of disseminated disease. Surgical treatment, however, seems to be able to provide improvement on survival. Laparoscopic adrenalectomy is considered a gold standard procedure in benign adrenal disease but its value in malignancy, in terms of oncological effectiveness, is not known. A case of bilateral adrenal malignant melanoma metastases is reported. The patient, affected by superficial spreading melanoma of the right foot, eleven years after the primary developed a right adrenal metastasis. The relapse was treated by laparoscopic right adrenalectomy. One year later the patient had a new metastasis in the left adrenal gland and was submitted to laparoscopic left adrenalectomy. The two step laparoscopic bilateral adrenalectomy showed to be quite easy to perform, providing a complete removal of the whole glands, without adrenal tissue crushing and without neoplastic tissue dissemination in abdominal cavity. The postoperative course was excellent and the patient was discharged within about 72 hours after the two procedures. In literature only few reports indicate the feasibility of laparoscopic adrenalectomy for malignancy. In the reported case of malignant melanoma metastasis, minimally invasive adrenalectomy was very satisfactory and the good results obtained suggest its routine use.

Is there a benefit by the sequence anastrozole-formestane for postmenopausal metastatic breast cancer women?

CARLINI P., FERRETTI G., DI COSIMO S., COLELLA E., TONACHELLA R., ROMITI A., TOMAO S., FRASSOLDATI A., PAPALDO P., FABI A., RUGGERI E.M., COGNETTI F.

J. Steroid Biochem. Mol. Biol., 86(1), p.107-9, 2003

To explore the different sequence interactions between reversible non-steroidal (anastrozole, ANZ and letrozole, LTZ) and non-reversible steroidal aromatase inhibitors (formestane, FOR and exemestane, EXE), we evaluated the clinical benefit (CB) in postmenopausal breast cancer patients, who had previously received anastrozole and subsequently formestane. In 19 out of 21 patients (90.5%), a clinical benefit response was achieved by anastrozole, with a median duration of 12 months. Out of the 21 women progressing on anastrozole, 12 achieved stable disease (SD)>/=6 months by formestane only. The overall clinical benefit was 66.5%. The median duration of clinical benefit was 11 months with a time to progression of 6.5 months. The median duration of clinical benefit in our series is similar to that reported in two phase II trials with the sequence aminogluthetimide→formestane and aminogluthetimide→exemestane as third-line hormonal therapy, suggesting a non-cross-resistance between the two classes of inhibitors.

Alopecia in a premenopausal breast cancer woman treated with letrozole and triptorelin.

CARLINI P., DI COSIMO S., FERRETTI G., PAPALDO P., FABI A., RUGGERI E.M., MILELLA M., COGNETTI F.

Ann. Oncol., 14(11), p.1689-90, 2003

No abstract available

Indications for integrated surgical treatment of peritoneal carcinomatosis of colorectal origin: experience of the Italian Society of Locoregional Integrated Therapy in Oncology

CAVALIERE F., PERRI P., ROSSI C.R., PILATI P.L., DE SIMONE M., VAIRA M., DERACO M., DI FILIPPO F.

Tumori, 89(Suppl. 4), p.21-3, 2003

A multicentric prospective study has been carried on 69 patients affected by peritoneal carcinomatosis from colorectal cancer. Patients have been treated by cytoreductive surgery and intraoperative hyperthermic chemoperfusion. CC 0-1 has been achieved in 82%. Major morbidity and mortality was respectively 21.7% and 2.9%. Three years overall survival was 26.7% for all series. Difference in survival evaluating CC 0-1 vs CC 2 patients and PCI < or = 10 vs > 10 was statistically significant. Evaluating only patients CC 0-1 and PCI < or = 10 overall survival rised up to 44.7% at 4 years. A smaller subgroup of patients with a disease-free interval to peritoneal carcinomatosis > or = 2-year showed a 50% disease-free survival at 5 years. In conclusion PCI < or = 10, complete or optimal cytoreduction feasibility and disease-free interval have to be considered for the patients selection to the integrate treatment.

Sitilo Experience on Peritoneal Carcinomatosis From Colorectal Cancer: Clinical Prognostic Features

CAVALIERE F., PERRI P., ROSSI C.R., PILATI P.L., DE SIMONE M., VAIRA M., DERACO M., ALOE S., DI FILIPPO S., AND DI FILIPPO F.

J. Exp. Clin. Cancer Res., 22, (Suppl. 4), 2003

No abstract available

Prolonged gemcitabine infusion in advanced non-small cell lung carcinoma: a randomized phase II study of two different schedules in combination with cisplatin.

CERIBELLI A., GRIDELLI C., DE MARINIS F., FABI A., GAMUCCI T., CORTESI E., BARDUAGNI M., ANTIMI M., MAIONE P., MIGLIORINO M.R., GIANNARELLI D., COGNETTI F.

Cancer, 98(2), p.337-43, 2003

Background: Preclinical and clinical evidence suggests that a fixed infusion rate of 10 mg/m2 per minute may be more effective than the standard 30-minute infusion of gemcitabine. To investigate the activity and toxicity of the cisplatin plus gemcitabine combination with gemcitabine at a fixed infusion rate in patients with advanced non-small cell lung carcinoma (NSCLC), the authors conducted a randomized Phase II trial of cisplatin plus gemcitabine at the 30-minute standard infusion (calibration arm) or cisplatin plus gemcitabine at a fixed infusion rate (experimental arm).

Methods: A total of 112 chemonaive patients with advanced NSCLC entered the study: 57 patients in Arm A and 55 patients in Arm B. The patients were randomly assigned to receive gemcitabine at a dose of 1000 mg/m2 on Days 1, 8, and 15 over 30 minutes (Arm A) or at a rate of 10 mg/m2 per minute (Arm B). In both treatment arms, cisplatin at a dose of 80 mg/m2 was administered on Day 15 every 28 days. RESULTS: The overall response rates in Arms A and B were 26% (95% confidence interval [95% CI], 10-42%) and 34% (95% CI, 17-52%) (intent-to-treat-analysis), respectively. The median time to disease progression was 6 months (range, 1-26 months) and 8 months (range, 2-21 months), respectively, for Arms A and B and the median overall survival was 13 months (range, 2-26 months) for each arm. It is interesting to note that a high response rate (67%) of brain metastases was noted in the experimental arm. Toxicity was tolerable and comparable in the two arms.

Conclusions: The results of this randomized Phase II trial demonstrated that cisplatin plus gemcitabine with gemcitabine at fixed infusion rate (10 mg/m2 per minute) is active and well tolerated in patients with advanced NSCLC.

HER-2/neu oncogene amplification and chromosome 17 aneusomy in endometrial carcinoma: correlation with oncoprotein expression and conventional pathological parameters.

Cianciulli A.M., Guadagni F., Marzano R., Benevolo M., Merola R., Giannarelli D., Marandino F., Vocaturo G., Mariani L., Mottolese M.

J. Exp. Clin. Cancer Res., 22(2), p.265-71, 2003

The objective of the present study was to evaluate the correlation between HER-2 gene amplification and HER-2 protein overexpression in endometrial carcinoma using fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). We also analyzed chromosome 17 aneusomy and the association between these biological parameters and conventional clinicopathological variables. FISH analysis was performed on 73 selected paraffin-embedded sections from endometrial carcinomas which previously had HER-2 status determined immunohistochemically using monoclonal antibodies (MoAb) 300G9 and CB11. Using a ratio of more than two oncogene signals/centromere to indicate amplification, a total of 42 out of the 73 endometrial tumors included in this study resulted positive by FISH where as protein overexpression was identified in 29 out of 73 with a concordance rate of 74.3%. However, when the mean signals/centromere per nucleus increased (ratio > 4 < or = 5) a higher concordance between the two assays was seen ($p = 0.007$). In addition, HER-2 amplification was significantly correlated with tumor stage ($p = 0.021$) and myometrial invasion ($p = 0.010$), whereas chromosome 17 polisomy showed a positive correlation only with myometrial invasion ($p = 0.004$) No significant correlation was found between HER-2 gene amplification, chromosome 17 aneusomy and patient outcome. Nevertheless, the probability of a 5 year overall survival decreased from 70% to 43%, respectively, for ratio > 2 < or = 4 and ratio > 4 < or = 5 when we grouped the amplified cases on the basis of HER-2:CEP17 ratio. In conclusion, molecular characteristics provide objective data that may be useful in predicting prognosis in patients with endometrial cancer.

Genetic instability in superficial bladder cancer and adjacent mucosa: an interphase cytogenetic study.

Cianciulli A.M., Leonardo C., Guadagni F., Marzano R., Iori F., De Nunzio C., Franco G., Merola R., Laurenti C.

Hum. Pathol., 34(3), p.214-21, 2003

A systematic analysis of both tumors and the surrounding urothelium to help identify what lies behind the mechanism of multifocal tumor development has not yet been performed. In this study we investigated chromosome 1, 7, 9, and 17 aneusomy in 25 superficial papillary carcinomas and in 51 tissue samples taken from sites of macroscopically uninvolved urothelium surrounding the tumors, using the fluorescence in situ hybridization method. Our data demonstrated a close genetic relationship between all examined tumors and normal-appearing mucosa. Numeric aberrations of chromosomes 1, 7, 9, and 17 were found to exhibit similar patterns in all analyzed specimens, although with different frequencies.

The cyclopentenone-type prostaglandin 15-deoxy-delta 12,14-prostaglandin J2 inhibits CD95 ligand gene expression in T lymphocytes: interference with promoter activation via peroxisome proliferator-activated receptor-gamma-independent mechanisms.

Cippitelli M., Fionda C., Di Bona D., Lupo A., Piccoli M., Frati L., Santoni A.

J. Immunol., 170(9), p.4578-92, 2003

15-Deoxy-delta(12,14)-PGJ(2) (15d-PGJ(2)) is a cyclopentenone-type PG endowed with anti-inflammatory properties and produced by different cells, including those of the immune system. 15d-PGJ(2) is a natural ligand of the peroxisome proliferator-activated receptor (PPAR)-gamma nuclear receptor, but relevant PPARgamma-independent actions mediated by this prostanoid have been described. Fas (APO-1/CD95) and its ligand (Fas-L) are cell surface proteins whose interaction activates apoptosis of Fas-expressing targets. In T cells, the Fas-Fas-L system regulates activation-induced cell death and has been implicated in diseases in which lymphocyte homeostasis is compromised. Moreover, several studies have described the pathogenic functions of Fas and Fas-L in vivo, particularly in the induction-progression of organ-specific autoimmune diseases. In this study we describe the effect of 15d-PGJ(2) on the activation of the fas-L gene in T lymphocytes. We show that 15d-PGJ(2) inhibits fas-L mRNA expression, activation-induced cell death, and fas-L promoter activity by mechanisms independent of PPARgamma and mediated by its chemically reactive cyclopentenone moiety. Our data indicate that 15d-PGJ(2) may repress fas-L activation by interfering with the expression and/or transcriptional activity of different transcription factors (early growth re-

sponse types 3 and 1, NF-kappaB, AP-1, c-Myc, Nur77) whose altered balancing and transactivation may contribute for overall repression of this gene. In addition, the activation/expression of the heat shock response genes HSF-1 and HSP70 is not directly involved in the repression, and the electrophilic molecule cyclopentenone (2-cyclopenten-1-one) may reproduce the effects mediated by 15d-PGJ(2). These results suggest that modulation of Fas-L by 15d-PGJ(2) in T cells may represent an additional tool to consider for treatment of specific autoimmune and inflammatory disorders.

Treatment of metastatic malignant melanoma with dacarbazine plus tamoxifen, or vindesine plus tamoxifen: a prospective randomized study.

Cocconi G., Passalacqua R., Foladore S., Carlini P., Acito L., Maiello E., Marchi M., Gebbia V., Di Sarra S., Beretta M., Bacchi M.

Melanoma Res., 13(1), p.73-9, 2003

This study aimed to verify whether the advantage in terms of response rate and survival of dacarbazine plus tamoxifen over dacarbazine alone in metastatic malignant melanoma reported in a previous randomized trial was due to a specific interaction of dacarbazine with tamoxifen. A total of 125 patients with locoregional or disseminated malignant melanoma were randomized to receive dacarbazine (250 mg/m(2) days 1-5 every 3 weeks) plus tamoxifen (arm A) or vindesine (3 mg/m(2) every week for 6 weeks, then every 2 weeks) plus tamoxifen (arm B). Of the 125 randomized patients, 57 and 59 were evaluable in arm A and B, respectively. The complete response rates were the same (2% versus 2%) and the complete plus partial response rates were similar (11% versus 14%) in the two groups. There was no significant difference in survival. Neither response or survival correlated with gender. In conclusion, when combined with tamoxifen, dacarbazine does not have a specific effect on response or survival compared with vindesine. The lower response rate to dacarbazine plus tamoxifen (11%) than that reported in the previous trial (28%) might be explained by actual differences in patient and/or participating centre accrual characteristics in the presence of apparently identical eligibility criteria.

Cisplatin, epirubicin, leucovorin and 5-fluorouracil (PELF) is more active than 5-fluorouracil, doxorubicin and methotrexate (FAMTX) in advanced gastric carcinoma.

Cocconi G., Carlini P., Gamboni A., Gasperoni S., Rodino C., Zironi S., Bisagni G., Porrozzi S., Cognetti F., Di Costanzo F., Canaletti R., Ruggeri E.M., Camisa R., Pucci F.; Italian Oncology Group for Clinical Research.

Ann. Oncol., 14(8), p.1258-63, 2003

Background: 5-Fluorouracil (5-FU), doxorubicin and methotrexate (FAMTX) and cisplatin, epirubicin, leucovorin and 5-FU (PELF) have both been reported to be superior to the combination 5-FU, doxorubicin and mitomycin C (FAM) in advanced gastric carcinoma. On the basis of the presence and dose intensity of the included agents, we hypothesised that PELF would be superior to FAMTX.

Patients and methods: Two hundred patients with untreated advanced gastric carcinoma were randomised to receive PELF or FAMTX for a maximum of six cycles or until disease progression.

Results: The complete response (CR) rates to PELF and FAMTX were, respectively, 13% [95% confidence intervals (CI) 6% to 20%] and 2% (95% CI 0% to 5%; P = 0.003), and the objective response rates [CR plus partial response (PR) rates] 39% (95% CI 29% to 49%) and 22% (95% CI 13% to 30%; P = 0.009), thus significantly favouring the PELF combination. The survival rates after 12 months (30.8% versus 22.4%) and 24 months (15.7% versus 9.5%) were also higher among patients receiving PELF, but these differences were not statistically significant. The toxicities were qualitatively different but quantitatively similar. Both regimens seem to be feasible provided that careful patient monitoring is assured.

Conclusions: PELF is significantly more active than FAMTX and deserves further research in the adjuvant setting.

E-oncology and health portals: instructions and standards for the evaluation, production organisation and use.

COGNETTI G., CECERE L.

J. Exp. Clin. Cancer Res., 22(4), p.677-86, 2003

In 2002 the Italian Ministry of Health promoted the institution of a network and a web portal, E-oncology (2), for the seven NHS research institutions specialising in oncology (Istituti di Ricovero e Cura a Carattere Scientifico-IRCCS). One of the aims was to gather and provide information on tumoral pathologies to operators and the public. For an optimum organisation of a health web site it is necessary to comply with the standards internationally used. The World Wide Web Consortium (W3C) has developed guidelines for accessibility and usability of the sites, implemented in Italy through governmental issues. Many international organisations adopt rules and codes of conduct to validate biomedical information and have organised quality portals such as NLM, OMNI, MEDCIRCLE, HON etc. Some terminological standards, such as the MESH thesaurus and UMLS, have been produced by the libraries for a correct management and an effective information retrieval, and are currently used by the most important biomedical web sites. The Dublin Core, metadata standard for the integration of information deriving from heterogeneous archives, has also been developed by the libraries. The easy access to information dims the complex architecture necessary for the construction of a web site. The contribution of different professionals is necessary to guarantee the production of quality medical/health web sites, among them librarians have always been involved with the management of knowledge and their skills are extremely valuable. Furthermore, the libraries' network is essential in order to guarantee universal access to health information, mostly still against payment, and to contribute to overcoming the 'digital divide' and 'second-level digital divide'.

EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century.

COLEMAN M.P., GATTA G., VERDECCHIA A., ESTEVE J., SANT M., STORM H., ALLEMANI C., CICCOLALLO L., SANTAQUILANI M., BERRINO F.; THE EUROCARE WORKING GROUP, (CONTI E.M.S.).

Ann. Oncol., 14(Suppl. 5), p.V128-V149, 2003

No abstract available

Chemotherapy in the treatment of breast carcinoma

CONTI F., VICI P.

Tumori, 89(Suppl. 4), p.181-2, 2003

Breast cancer (BC) is the most common malignancy and the second most common cause of cancer-related death in Western European and North American women. Neoadjuvant chemotherapy may be used in the management of both BC patients with locally advanced disease, and those with earlier stage and operable tumors. Data from recently phase III trials and worldwide consensus conference document the benefit of adjuvant chemotherapy in improving disease free survival and overall survival for patients diagnosed with invasive BC > 1 cm. When BC cells metastasize to distant organs, the disease is incurable, but chemotherapy may offer these patients a significant palliation.

Risk of cancer in persons with AIDS in Italy, 1985-1998.

DAL MASO L., FRANCESCHI S., POLESEL J., BRAGA C., PISELLI P., CROCETTI E., FALCINI F., GUZZINATI S., ZANETTI R., VERCELLI M., REZZA G.; CANCER AND AIDS REGISTY LINKAGE STUDY. (CONTI E.)

Br. J. Cancer, 89(1), p.94-100, 2003

A record linkage was carried out between the Italian Registry of AIDS and 19 Cancer Registries (CRs), which covered 23% of the Italian population, to estimate the overall cancer burden among persons with HIV or AIDS (PWHA) in Italy, according to various characteristics. Observed and expected numbers of cancer and standardised incidence ratios (SIRs) were assessed until 1998 in 12 104 PWHA aged 15-69 years, for a total of 60 421 person-years. Significantly increased SIRs were observed for Kaposi's sarcoma (KS, 1749-fold higher than the general population), non-Hodgkin's lymphomas (NHL, 352), and invasive cervical cancer (22). SIR was significantly elevated also for cancer of the anus (34), lung cancer (2.4), brain tumours (4.4), Hodgkin's dis-

ease (16), and leukaemias (5.3). The majority of lung and brain cancers were not histologically confirmed, and the possibility of misclassification with KS or NHL cannot be ruled out. The SIR for all non-AIDS-defining cancers was 2.2 in men and 2.5 in women. Intravenous drug users showed significantly more elevated SIRs for lung cancer (9.4), and brain tumours (6.7) than other transmission categories (SIR=1.4 and 2.3, respectively). This study confirmed increased SIRs for haemolymphopoietic neoplasms other than NHL in PWHA, although many-fold smaller than for NHL. An association with human papillomavirus-related cancers was also confirmed.

Lung cancer in persons with AIDS in Italy, 1985-1998.

DAL MASO L., POLESEL J., SERRAINO D., FRANCESCHI S.

AIDS, 17(14), p.2117-9, 2003

No abstract available

Functional interaction of the subunit 3 of RNA polymerase II (RPB3) with transcription factor-4 (ATF4).

DE ANGELIS R., IEZZI S., BRUNO T., CORBI N., DI PADOVA M., FLORIDI A., FANCIULLI M., PASSANANTI C.

FEBS Lett., 547(1-3), p.15-9, 2003

RPB3 is a core subunit of RNA polymerase II (pol II) that, together with the RPB11 subunit, forms the heterodimer considered as a functional counterpart of the bacterial alpha subunit homodimer involved in promoter recognition. We previously employed the yeast two-hybrid system and identified an interaction between RPB3 and the myogenic transcription factor myogenin, demonstrating an involvement of this subunit in muscle differentiation. In this paper we report the interaction between RPB3 and another known transcription factor, ATF4. We found that the intensity of the interaction between RPB3 and ATF4 is similar to the one between RPB3 and myogenin. This interaction involves an RPB3 specific region not homologous to the prokaryotic alpha subunit. We demonstrated that RBP3 is able to enhance ATF4 transactivation, whereas the region of RPB3 (Sud) that contacts ATF4, when used as a dominant negative, markedly inhibits ATF4 transactivation activity. Interestingly, ATF4 protein level, as reported for its partner RPB3, increases during C2C7 cell line muscle differentiation.

DNA demethylation is directly related to tumour progression: evidence in normal, pre-malignant and malignant cells from uterine cervix samples.

DE CAPOA A., MUSOLINO A., DELLA ROSA S., CAIAFA P., MARIANI L., DEL NONNO F., VOCATURO A., DONNORSO R.P., NIVELEAU A., GRAPPELLI C.

Oncol. Rep., 10(3), p.545-9, 2003

A computer-assisted assay based on the quantitative analysis of DNA methylation in individual interphase nuclei by indirect immunolabelling with anti-5-methylcytosine antibodies was recently developed in our laboratory. In situ analyses were performed on individual nuclei from normal and experimentally hypo- or hypermethylated cultured cells as well as on human peripheral blood B-lymphocytes from normal and chronic lymphoid leukemia (CLL) samples. We present the results obtained on cells from patients affected by different degrees of preneoplastic or neoplastic changes of the uterine cervix as compared to normal controls. The analysis of DNA methylation in individual cells from cytofuge samples was performed as follows: within each nucleus the eu- and heterochromatin methylation levels were quantified in the grey scale range by dedicated software in terms of numbers, areas and optical densities (ODs) of the immunolabeled dense heterochromatic regions ("spots"), and of the optical density of nuclear background, i.e., of nuclear euchromatin. Analogously, in randomly chosen microscope fields of tissue sections from paraffin-embedded samples, progressive tissue demethylation was observed in dysplastic and cancer cells as compared to normal ones. Both methods showed significant and progressive DNA hypomethylation in dysplastic and cancer cells as compared to control specimens.

Shift from noradrenaline to adrenaline production in the adrenal gland of the lizard, Podarcis sicula, after stimulation with vasoactive intestinal peptide (VIP).

De Falco M., Sciarrillo R., Capaldo A., Laforgia V., Varano L., Cottone G., De Luca A.

Gen. Comp. Endocrinol., 131(3), p.325-37, 2003

The aim of this study was to investigate the distribution and function of VIP in the adrenal gland of the lizard, Podarcis sicula. We have shown by immunohistochemistry that VIP fibers were localized exclusively around clusters of chromaffin cells in the dorsal ribbon of the lizard adrenal gland. Moreover, a strong positivity for this peptide was observed within ganglial cells and within most chromaffin cells of the gland. To investigate the effects of VIP on the adrenal gland, we have treated lizards with several doses of this peptide and we have shown that injections of exogenous VIP increased plasma levels of catecholamines and corticosteroids, but not of ACTH. This probably suggests a direct effect of VIP on the control of adrenal hormone secretion without the involvement of the hypothalamo-hypophyseal axis. Our results also establish that the increased levels of the hormones were modulated in a time- and dose-dependent manner. Therefore, our morphological studies showed a clear increased function of steroidogenic cells. In the medullary region, VIP administration induced not only a functional enhancement of adrenaline release from adrenergic cells, but also a shift of noradrenaline cells to adrenaline ones.

Coexpression of Helicobacter pylori's proteins CagA and HspB induces cell proliferation in AGS gastric epithelial cells, independently from the bacterial infection.

De Luca A., Baldi A., Russo P., Todisco A., Altucci L., Giardullo N., Pasquale L., Iaquinto S., D'Onofrio V., Parodi M.C., Paggi M.G., Iaquinto G.

Cancer Res., 63(19), p.6350-6, 2003

Adenocarcinoma of the stomach is the second most common cause of cancer mortality in the world. The purpose of this study was to evaluate the potential role in carcinogenesis of two secreted Helicobacter pylori's proteins, CagA and HspB, both shown to increase the risk of gastric carcinoma in patients infected with H. pylori-positive strain. The effects of these two proteins on cell kinetics and the ability to selectively affect the expression of cell cycle-related proteins by transfection of a human gastric epithelial cell line (AGS) were analyzed. Using a genomic library of H. pylori, we isolated and cloned CagA and HspB. The effects of the overexpression of these proteins on cell growth were analyzed in AGS cells by immunoblots, proliferation assay, and flow cytometry. Coexpression of CagA and HspB in AGS cells in the first 48 h caused an increase of the level of E2F transcription factor, cyclin D3, and phosphorylated retinoblastoma protein, all involved in the G(1)-S checkpoint of the cell cycle. Consistently, an increase of cell proliferation, corresponding to an augment of the fraction of the cells in the S-G(2)-M phase of the cell cycle, was also demonstrated. Moreover, an increase of c-jun protein levels, but not of c-fos, was also found after coexpression of CagA and HspB. All these data suggest that CagA and HspB, independently from the bacterial infection, have a direct effect on the cell growth of the gastric cells acting on the G(1)-S checkpoint of the cell cycle.

Distribution of the serine protease HtrA1 in normal human tissues.

De Luca A., De Falco M., Severino A., Campioni M., Santini D., Baldi F., Paggi M.G., Baldi A.

J. Histochem. Cytochem., 51(10), p.1279-84, 2003

The human HtrA family of proteases consists of three members: HtrA1, HtrA2, and HtrA3. In bacteria, the chief role of HtrA is recognition and degradation of misfolded proteins in the periplasm, combining a dual activity of chaperone and protease. In humans, the three HtrA homologues appear to be involved in diverse functions such as cell growth, apoptosis, allergic reactions, fertilization, control of blood pressure, and blood clotting. Previous studies using RNA blot hybridization have shown that the expression of HtrA1 is ubiquitous in normal human tissues. Here we show by immunohistochemistry (IHC) that HtrA1 is widely expressed, although different tissue distributions and/or levels of expression were detected in the different tissues examined. In particular, high to medium HtrA1 expression was detected in mature layers of epidermis, in secretory breast epithelium, in liver, and in kidney tubules of cortex, in concordance with its secretory properties. Furthermore, we show a higher protein expression level in the epithelium of proliferative endometrium, in contrast to epithelium of secretory endometrium, which is almost completely negative

for this protein. This suggests a possible role for HtrA1 in the modulation of tissue activity in this organ. The various expression levels in human tissues indicate several possible roles for HtrA1 in different cell types.

p300/cAMP-response-element-binding-protein ('CREB')-binding protein (CBP) modulates co-operation between myocyte enhancer factor 2A (MEF2A) and thyroid hormone receptor-retinoid X receptor.

De Luca A., Severino A., De Paolis P., Cottone G., De Luca L., De Falco M., Porcellini A., Volpe M., Condorelli G.

Biochem. J., 369(Pt 3), p.477-84, 2003

Thyroid hormone receptors (TRs) and members of the myocyte enhancer factor 2 (MEF2) family are involved in the regulation of muscle-specific gene expression during myogenesis. Physical interaction between these two factors is required to synergistically activate gene transcription. p300/cAMP-response-element-binding-protein ('CREB')-binding protein (CBP) interacting with transcription factors is able to increase their activity on target gene promoters. We investigated the role of p300 in regulating the TR-MEF2A complex. To this end, we mapped the regions of these proteins involved in physical interactions and we evaluated the expression of a chloramphenicol acetyltransferase (CAT) reporter gene in U2OS cells under control of the alpha-myosin heavy chain promoter containing the thyroid hormone response element (TRE). Our results suggested a role of p300/CBP in mediating the transactivation effects of the TR-retenoid X receptor (RxR)-MEF2A complex. Our findings showed that the same C-terminal portion of p300 binds the N-terminal domains of both TR and MEF2A, and our in vivo studies demonstrated that TR, MEF2A and p300 form a ternary complex. Moreover, by the use of CAT assays, we demonstrated that adenovirus E1A inhibits activation of transcription by TR-RxR-MEF2A-p300 but not by TR-RxR-MEF2A. Our data suggested that p300 can bind and modulate the activity of TR-RxR-MEF2A at TRE. In addition, it is speculated that p300 might modulate the activity of the TR-RxR-MEF2A complex by recruiting a hypothetical endogenous inhibitor which may act like adenovirus E1A.

E1A deregulates the centrosome cycle in a Ran GTPase-dependent manner.

De Luca A., Mangiacasale R., Severino A., Malquori L., Baldi A., Palena A., Mileo A.M., Lavia P., Paggi M.G.

Cancer Res., 63(6), p.1430-7, 2003

By means of the yeast two-hybrid system, we have discovered a novel physical interaction between the adenovirus E1A oncoprotein and Ran, a small GTPase which regulates nucleocytoplasmic transport, cell cycle progression, and mitotic spindle organization. Expression of E1A elicits induction of S phase and centrosome amplification in a variety of rodent cell lines. The induction of supernumerary centrosomes requires functional RCC1, the nucleotide exchange factor for Ran and, hence, a functional Ran network. The E1A portion responsible for the interaction with Ran is the extreme NH(2)-terminal region (amino acids 1-36), which is also required for the induction of centrosome amplification. In an in vitro assay with recombinant proteins, wild-type E1A interferes with nucleotide exchange on Ran, whereas an E1A mutant, deleted from the extreme NH(2)-terminal region, does not. In addition, we detected an in vitro interaction between Ran and HPV-16 E7 and SV40 large T antigen, two oncoproteins functionally related to E1A. These findings suggest a common pathway of these oncoproteins in eliciting virus-induced genomic instability.

Cyclin T: three forms for different roles in physiological and pathological functions.

De Luca A., De Falco M., Baldi A., Paggi M.G.

J. Cell. Physiol., 194(2), p.101-7, 2003

Cyclins are members of family of proteins involved in the cell cycle regulation. They are regulatory subunits of complexes with proteins called cyclin-dependent kinases (CDKs). There are three forms of cyclin T: cyclin T1, cyclin T2a, and T2b. All cyclin T contain an N-terminal "cyclin homology box," the most conserved region among different members of the cyclin family that serves to bind CDK9. In addition to the N-terminal cyclin domain, cyclin T contains a putative coiled-coil motif, a His-rich motif, and a C-terminal PEST sequence. The CDK9/cyclin T complex is able to activate gene expression in a catalytic-dependent manner, phosphorylating the carboxy-terminal domain (CTD) of RNA polymerase II. In addition, only cyclin T1 supports interactions between Tat and TAR. The interaction of Tat with cyclin T1

alters the conformation of Tat to enhance the affinity and specificity of the Tat:TAR interaction. On the other hand, CDK9/cyclin T2 complexes are involved in the regulation of terminal differentiation in muscle cells.

DNA vaccines against HPV-16 E7-expressing tumour cells.

De Marco F., Hallez S., Brulet J.M., Gesche F., Marzano P., Flamini S., Marcante M.L., Venuti A.

Anticancer Res., 23(2B), p.1449-54, 2003

Background: Genetic immunisation induces the endogenous production of the encoded antigens, which favours their presentation by MHC class I molecules. The E7 protein from "high risk" Human Papillomavirus (HPV) is constitutively expressed in cervical cancer and represents a target for immunotherapy.

Materials and methods: Several E7-encoding DNA vaccines were constructed including unmodified E7 and E7 fused to ubiquitin or to the Invariant chain in order to increase the presentation of E7-derived peptides by MHC class I or II molecules, respectively. These vaccines were administered i.m. to C57BL/6 mice that were subsequently challenged with E7-positive tumour cell lines expressing different levels of MHC class I molecules.

Results: The E7-Ii fusion sequence protected a number of animals from tumour challenging. No differences were associated with the MHC class I status of the challenging cell lines.

Conclusion: Engineering the intracellular pathway for antigen presentation is able to produce a valid therapeutic response even against tumours with down-regulated MHC class I.

Long-term evaluation of 164 patients with essential thrombocythaemia treated with pipobroman: occurrence of leukaemic evolution.

De Sanctis V., Mazzucconi M.G., Spadea A., Alfo M., Mancini M., Bizzoni L., Peraino M., Mandelli F.

Br. J. Haematol., 123(3), p.517-21, 2003

Essential thrombocythaemia (ET) is usually considered an indolent disease, but it may progress during its natural course into acute leukaemia (AL); however, an influence of myelosuppressive agents in the blastic transformation of ET cannot be excluded. We performed a retrospective study to assess the incidence of AL in ET patients treated with pipobroman (PB) as first-line therapy. One hundred and sixty-four patients with ET were managed with PB at a dose of 1 mg/kg/d until a stable platelet count below 400 x 10(9)/l was achieved. Maintenance therapy was given at a planned dose ranging between 0.2 and 1 mg/kg/d according to platelet count, in all cases, with a median daily dose of 25 mg (range 7-75 mg/d). The median treatment time was 100 months (range 25-243 months). The patients were evaluated for the occurrence of AL and/or secondary malignancies and survival end-points. AL was observed in nine patients (5.5%) after a median treatment time of 153 months (range 79-227 months). The overall survival (OS) and the event-free survival (EFS) at 120 months were 95% and 97%, whereas at 180 months, they were 84% and 76% respectively. In conclusion, this retrospective analysis shows a low incidence of AL in a large group of patients consecutively treated with PB as first-line chemotherapy. Therefore, an investigation of the role of myelosuppressive agents in the blastic transformation of ET would be of interest.

Treatment of melanoma cells with a bcl-2/bcl-xL antisense oligonucleotide induces antiangiogenic activity.

Del Bufalo D., Trisciuoglio D., Scarsella M., Zangemeister-Wittke U., Zupi G.

Oncogene, 22(52), p.8441-7, 2003

We have recently reported that bcl-2 overexpression and hypoxia synergistically interact to modulate vascular endothelial growth factor (VEGF) and in vivo angiogenesis in tumour cells through VEGF mRNA stabilization and hypoxia-inducible factor 1-mediated transcriptional activity. Bcl-2 antisense treatment has shown promising clinical results in patients with malignant melanoma. In the present study, we demonstrated that the bcl-2/bcl-xL bispecific antisense oligonucleotide 4625 inhibits bcl-2 expression and angiogenesis in two bcl-2 overexpressing clones derived from the M14 human melanoma cell line. The antiangiogenic effect was determined in in vitro and in vivo angiogenesis assays. In particular, a reduction of hypoxia-induced

VEGF secretion was observed after 4625 treatment, and the conditioned medium (CM) of bcl-2 overexpressing clones treated with 4625 and exposed to hypoxic conditions resulted in decreased endothelial cell proliferation when compared to CM of untreated control cells. In addition, we found that CM of 4625 antisense-treated bcl-2 transfectants inhibited in vivo vessel formation in matrigel plugs implanted subcutaneously in C57/B16 mice. Our findings confirm that bcl-2 plays a crucial role in melanoma angiogenesis and demonstrate for the first time that downregulation of bcl-2 by antisense treatment has potential to inhibit angiogenesis independent of its effect on cell survival. The use of 4625 in cancer therapy is suggested as an approach to facilitate simultaneously tumour cell apoptosis and inhibit tumour angiogenesis.

An Italian Multicentric Phase II Study on Peritonectomy and Intra Peritoneal Hyperthermic Perfusion (IPHP) to treat patients with Pseudomyxoma Peritonei.

Deraco M., De Simone M., Rossi C.R., Cavaliere F., Di Filippo F., Vaira M., Piatti P. and Kusamura S.

J. Exp. Clin. Cancer Res., 22, (Suppl. 4), p.35-39, 2003

No abstract available

An Italian Multicentric Phase II Study on Peritonectomy and Intra Peritoneal Hyperthermic Perfusion (IPHP) to Treat Patients with Peritoneal Mesothelioma.

Deraco M., De Simone M., Rossi C.R., Cavaliere F., Di Filippo F., Vaira M., Piatti P. and Kusamura S.

J. Exp. Clin. Cancer Res., 22, (Suppl. 4), p.41-45, 2003

No abstract available

Docetaxel in advanced gastric cancer-review of the main clinical trials.

Di Cosimo S., Ferretti G., Fazio N., Silvestris N., Carlini P., Almonti A., Gelibter A., Felici A., Papaldo P., Cognetti F.

Acta Oncol., 42(7), p.693-700, 2003

The aim was to investigate the activity of docetaxel in advanced gastric cancer either as single agent or in combination with other drugs. A systematic review was carried out using the databases of Medline, Embase and CancerLit. Results from ASCO and ESMO meetings during 2002 were also included. Eight phase II trials focused on docetaxel as a single agent. Considering collectively the 262 evaluable patients enrolled in these studies, the mean response rate (RR) was 19% (CI 95% 14-24%). Docetaxel was well tolerated with a dose-limiting myelosuppression (grade 3-4 neutropenia in 36-95% of cases). Adding fluorouracil, an RR ranging from 22% to 86% was registered, due to differences in populations studied (young vs elderly) and modalities of drug administration (continuous vs. bolus infusion). RRs for docetaxel-cisplatin combination were 56%, 37% and 36% in three phase II trials and 35% in a phase III trial. The addition of both cisplatin and fluorouracil to docetaxel did not increase toxicity. Randomized trials comparing docetaxel-cisplatin-fluorouracil with ciplatin-fluorouoracil or epirubicin-cisplatin-fluorouracil, the most commonly used regimens, are ongoing. The future results of the above phase III studies could indicate docetaxel as a key drug to improve treatment of patients with advanced gastric cancer.

Lonidamine: efficacy and safety in clinical trials for the treatment of solid tumors.

Di Cosimo S., Ferretti G., Papaldo P., Carlini P., Fabi A., Cognetti F.

Drugs Today (Barc), 39(3), p.157-74, 2003

Lonidamine, a derivate of indazole-3-carboxylic acid, is an antineoplastic drug with a typical mechanism of action. Lonidamine has no function on cellular nucleic acids or protein synthesis, whereas it exerts a powerful inhibitory effect on oxygen consumption, aerobic glycolysis and lactate transport and accumulation of neoplastic cells. Nevertheless, its proven ability to modify the permeability of membranes is consistent with the possible increase of drug uptake, reverse of drug resistance and triggering of apoptotic pathway. Lonidamine has been experimentally shown to potentiate the cytotoxic effects of anthracyclines in human breast cancer cell lines and cisplatin activity in both platinum-sensitive and platinum-resistant human ovarian carcinoma cell lines. Since the specific mechanism of action and side effects are not overlapping with those of standard antineoplastic agents, combination of lonidamine with standard chemotherapy has been widely investigated for the treatment of solid tumors. Additionally, the enhancement of radiotherapy activity by lonidamine has been considered for palliative therapy of lesions from metastatic cancers. The encouraging results of phase II-III trials for the treatment of advanced breast, ovarian and lung cancer must be confirmed by larger studies. Specifically designed studies to address the role of lonidamine in the adjuvant setting are warranted. Lonidamine, a dechlorinate derivative of indazole-3-carboxylic acid, has proved to exert a powerful antiproliferative effect and to impair the energy metabolism of neoplastic cells. Herein we review the current experience on combining lonidamine and chemotherapy and/or radiation therapy in the treatment of solid tumors. Several studies have been published on this topic. The total number of trials reported in literature and length of follow-up are still insufficient to draw a firm conclusion. However, the available data demonstrate a significant role of lonidamine in modulating anthracycline and platinum compound activity.

Doxorubicin in Isolation Limb Perfusion in the Treatment of Advanced Limb Soft Tissue Sarcoma.

Di Filippo F., Garinei R., Anzà M., Cavaliere F., Giannarelli D., Cagol P.P., Rossi C.R., Santinami M., Deraco M., Botti C., Perri P., Di Filippo S., Piarulli L., Bruno P.

J. Exp. Clin. Cancer Res., 22, (Suppl. 4), 2003

No abstract available

Hyperthermic antiblastic perfusion in the treatment of loco-regional spreading limb melanoma.

Di Filippo F., Garinei R., Giannarelli D., Anzà M., Cavaliere F., Botti C., Perri P., Di Filippo S., Psaila A., Callopoli A., Maialetti R., Sega F., Frezza F., Viticci C.

J. Exp. Clin. Cancer Res., 22, (Suppl. 4), 2003

No abstract available

Anti-blastic hyperthermic perfusion in the treatment of melanoma of the extremities in the loco-regional diffusion phase

Di Filippo F., Garinei R., Anza M., Cavaliere F., Botti C. Perri P., Di Filippo S.

Tumori, 89(Suppl. 4), p.241-3, 2003

Primary limb melanoma may recur in terms of satellitosis, in transit metastases and/or regional node involvement. Hyperthermic antiblastic perfusion (HAP) permits the isolation of involved extremity from the systemic circulation and to deliver high doses of antineoplastic drugs. The association of cytostatic drugs to hyperthermia (> or = 41.5 degrees C) results in a synergistic effect with an increased therapeutic effectiveness. The overall 5 and 10-year survival rates in relation to the disease stages are st. II 75% and 67%; st. IIIA 59% and 42%; st. IIIAB 36% and 30% respectively. The results confirm that HAP is considered the treatment of

choice of loco-regional spreading limb melanoma. Recently, the tumor necrosis factor (TNF) has been combined with Melphalan and hyperthermia. This trimodality association seems to be superior to Melphalan and hyperthermia alone only in patient with bulky tumors (i.e., multiple nodules), as a matter of fact the complete tumor response rates observed in these patients have been 67% and 20% respectively. The greater effectiveness of trimodality association has to be confirmed by multicentric randomized trials.

Hyperthermic Antiblastic Perfusion with TNFα and Melphalan in Stage III Limb Melanoma Patients: A Phase I - II SITILO Study.

Di Filippo F., Rossi C.R., Garinei R., Anzà M., Cavaliere F., Botti C., Perri P., Di Filippo S., Di Angelo P., Principi F., Laurenzi L.

J. Exp. Clin. Cancer Res., 22, (Suppl. 4), 2003

No abstract available

Supportive care in patients with advance non-small-cell lung cancer.

Di Maio M., Perrone F., Gallo C., Iaffaioli R.V., Manzione L., Piantedosi F.V., Cigolari S., Illiano A., Barbera S., Robbiati S.F., Piazza E., Ianniello G.P., Frontini L., Veltri E., Castiglione F., Rosetti F., De Maio E., Maione P., Gridelli C., Rossi A., Barletta E., Barzelloni M.L., Signoriello G., Bilancia D., Dinota A., Rosati G., Germano D., Lamberti A., Pontillo V., Brancacio L., Crispino C., Esposito M., Battiloro C., Tufano G., Cioffi A., Guardasole V., Angelini V., Guidetti G., Barbera S., Renda F., Romano F., Volpintesta A., Robbiati S.F., Sannicolo M., Filipazzi V., Esani G., Gambaro A., Ferrario S., Tinessa V., Caprio M..G., Zonato S., Cabiddu M., Raina A., Veltri E., D'Aprile M., Pistillucci G., Porcile G., Ostellino O., Vinante O., Azzarello G., Gebbia V., Borsellino N., Testa A., Gasparini G., Morabito A., Gattuso D., Romito S., Carrozza F., Fava S., Calcagno A., Grimi E., Bertetto O., Ciuffreda L., Parello G., Maiorino L., Santoro A., Santoro M., Failla G., Aiello R.A., Bearz A., Sorio R., Scalone S., Clerici M., Bollina R., Belloni P., Sacco C., Sibau A., Adamo V., Altavilla G., Scimone A., Spatafora M., Bellia V., Hopps M.R., Monfardini S., Favaretto A., Stefani M., Corradini G.M., Pavia G., Scagliotti G., Novello S., Selvaggi G., Tonato M., Darwish S., Michetti G., Belometti M.O., Labianca R., Quadri A., De Marinis F., Migliorino M.R., Martelli O., Colucci G., Galetta D., Giotta F., Isa L., Candido P., Rossi N., Calandriello A., Ferrau F., Malaponte E., Barni S., Cazzaniga M., Gebbia N., Valerio M.R., Belli M., Colantuoni G., Capuano M.A., Angiolillo M., Sollitto F., Ardizzoia A., Luporini G., Locatelli M.C., Pari F., Aitini E., Pedicini T., Febbraro A., Zollo C., Di Costanzo F., Bartolucci R., Gasperoni S., Gaion F., Palazzolo G., Galligioni E., Caffo O., Cortesi E., D'Auria G., Curcio C., Vasta M., Bumma C., Celano A., Bretti S., Nettis G., Anselmo A., Mattioli R., Nistico C., Aschelter A., Foa P.

Br. J. Cancer, 89(6), p.1013-21, 2003

The present study describes supportive care (SC) in patients with advanced non-small-cell lung cancer (NSCLC), evaluating whether it is affected by concomitant chemotherapy, patient's performance status (PS) and age. Data of patients enrolled in three randomised trials of first-line chemotherapy, conducted between 1996 and 2001, were pooled. The analysis was limited to the first three cycles of treatment. Supportive care data were available for 1185 out of 1312 (90%) enrolled patients. Gastrointestinal drugs (45.7%), corticosteroids (33.4%) and analgesics (23.8%) were the most frequently observed categories. The mean number of drugs per patient was 2.43; 538 patients (45.4%) assumed three or more supportive drugs. Vinorelbine does not produce substantial variations in the SC pattern, while cisplatin-based treatment requires an overall higher number of supportive drugs, with higher use of antiemetics (41 vs 27%) and antianaemics (10 vs 4%). Patients with worse PS are more exposed to corticosteroids (42 vs 30%). Elderly patients require drugs against concomitant diseases significantly more than adults (20 vs 7%) and are less frequently exposed to antiemetics (12 vs 27%). In conclusion, polypharmacotherapy is a relevant issue in patients with advanced NSCLC. Chemotherapy does not remarkably affect the pattern of SC, except for some drugs against side effects. Elderly patients assume more drugs for concomitant diseases and receive less antiemetics than adults.

Che-1 arrests human colon carcinoma cell proliferation by displacing HDAC1 from the p21WAF1/CIP1 promoter.

Di Padova M., Bruno T., De Nicola F., Iezzi S., D'Angelo C., Gallo R., Nicosia D., Corbi N., Biroccio A., Floridi A., Passananti C., Fanciulli M.

J. Biol. Chem., 278(38), p.36496-504, 2003

Che-1 is a recently identified human RNA polymerase II binding protein involved in the regulation of gene transcription and cell proliferation. We previously demonstrated that Che-1 inhibits the Rb growth-suppressing function by interfering with Rb-mediated HDAC1 recruitment on E2F target gene promoters. By hybridization of cancer profile arrays, we found that Che-1 expression is strongly down-regulated in several tumors, including colon and kidney carcinomas, compared with the relative normal tissues. Consistent with these data, Che-1 overexpression inhibits proliferation of HCT116 and LoVo human colon carcinoma cell lines by activation of the cyclin-dependent kinase inhibitor p21WAF1/Cip1 in a p53-independent manner and by promoting growth arrest at the G1 phase of the cell cycle. Che-1 activates p21WAF1/Cip1 by displacing histone deacetylase (HDAC)1 from the Sp1 binding sites of the p21WAF1/Cip1 gene promoter and accumulating acetylated histone H3 on these sites. Accordingly, Che-1-specific RNA interference negatively affects p21WAF1/Cip1 transactivation and increases cell proliferation in HCT116 cells. Taken together, our results indicate that Che-1 can be considered a general HDAC1 competitor and its down-regulation is involved in colon carcinoma cell proliferation.

Memory T-cell competition for bone marrow seeding.

Di Rosa F., Santoni A.

Immunology, 108(3), p.296-304, 2003

The presence in the bone marrow of memory CD8 T cells is well recognized. However, it is still largely unclear how T-cell migration from the lymphoid periphery to the bone marrow is regulated. In the present report, we show that antigen-specific CD4 T cells, as well as antigen-specific CD8 T cells, localize to the bone marrow of immunized mice, and are sustained there over long periods of time. To investigate the rules governing T-cell migration to the bone marrow, we generated chimeric mice in which the lymphoid periphery contained two genetically or phenotypically distinct groups of T cells, one of which was identical to the host. We then examined whether a distinct type of T cell had an advantage over the others in the colonization of bone marrow. Our results show that whereas ICAM1 and CD18 molecules are both involved in homing to lymph nodes, neither is crucial for T-cell bone marrow colonization. We also observed that memory-phenotype CD44high T cells, but not virgin-type CD44-/low T cells, preferentially home to the bone marrow upon adoptive transfer to normal young mice, but not to thymectomized old recipients where an existing memory T-cell pool precludes their free access. Thus, T-cell colonization of the bone marrow uses distinct molecules from those implicated in lymph node homing, and is regulated both by the properties of the T cell and by the competitive efficacy of other T cells inhabiting the same, saturable niche. This implies that the homing potential of an individual lymphocyte is not merely an intrinsic property of the cell, but rather a property of the lymphoid system taken as a whole.

Glucosylceramide synthase and its functional interaction with RTN-1C regulate chemotherapeutic-induced apoptosis in neuroepithelioma cells.

Di Sano F., Fazi B., Citro G., Lovat P.E., Cesareni G., Piacentini M.

Cancer Res., 63(14), p.3860-5, 2003

Glucosylceramide synthase (GCS), the key enzyme in the biosynthesis of glycosphingolipids, has been implicated in many biological phenomena, including multidrug resistance. GCS inhibition, by both antisense and the specific inhibitor (D-threo)-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), results in a drastic decrease of apoptosis induced by the p53-independent chemotherapeutic agent N-(4-hydroxyphenyl)retinamide in neuroepithelioma cells. By using the yeast two-hybrid system, we have identified a member of the reticulon (RTN) family (RTN-1C) as the major GCS-protein partner. Interestingly, RTN-1C not only interacts with GCS at Golgi/ER interface but also modulates its catalytic activity in situ. In fact, overexpression of RTN-1C sensitizes CHP-100 cells to fenretinide-induced apoptosis. These findings demonstrate a novel p53-independent pathway of apoptosis regulated by Golgi/endoplasmic reticulum protein interactions, which is relevant for cancer combined therapy.

Cross-reactivity between the major Parietaria allergen and rotavirus VP4 protein.

di Somma C., Fiore L., Di Lonardo A., Ridolfi B., Garzillo C., Chersi A., Buono C., Menna T., Ruffilli A.

Allergy, 58(6), p.503-10, 2003

Background: The present study investigates immunological cross-reactivity between Par o 1, the major pollen allergen of Parietaria, and the VP4 protein of rotavirus, a microorganism that is world-wide the main etiological agent of gastroenteritis in children.

Methods: IgG and IgE cross-reactivity was assessed by direct binding and competitive inhibition assays (ELISA and DARIA), using recombinant VP4 from rhesus infectious rotavirus (RR), synthetic peptides and Par o 1-specific antibodies affinity purified from pooled and individual human sera.

Results: Antibodies specifically binding Par o 1, affinity purified from the sera of 35 individuals with skin test positivity to Parietaria and from 14 pools, were extensively cross-reactive with RRVP4. Cross-reactive binding was specifically inhibited by synthetic peptides derived from the C-terminal sequences of the VP4 proteins from human and rhesus infectious rotavirus.

Conclusions: This study reports the first evidence of cross-reactivity between an allergen and a viral antigen.

A Combined Approach of Neoadjuvant Chemotherapy and Surgery for Colorectal Liver Metastases.

Esposito A., Mancini R., Ettorre G., Garufi C., Saracca E., Arcieri S., Cosimelli M.

J. Exp. Clin. Cancer Res., 22, (Suppl. 4), 2003

No abstract available

Resection and Transplantation: Evaluation of Surgical Perspectives in HIV Positive Patients Affected by End-Stage Liver Disease.

Ettorre G.M., Vennarecci G., Boschetto A., Giovannelli L., Antonini M., Carboni F., Santoro R., Lepiane P., Cosimelli M., Lonardo M.T., Del Nonno F., Perracchio L., Maritti M., Moricca P., D'Offizi G., Narciso P., Noto P., Boumis E., Petrosillo N., Visco G., Santoro E.

J. Exp. Clin. Cancer Res., 22, (Suppl. 4), 2003

No abstract available

The modified "hanging maneuver during orthotopic liver transplantation using a technique for conserving the inferior vena cava

Ettorre G.M., Vennarecci G., Lonardo M.T., Boschetto A., Antonini M., Carboni F., Carlini M., Santoro E.

Tumori, 89(Suppl. 4), p.63-5, 2003

We describe a modification of Belghiti's "liver hanging maneuver" applied to the last phase of hepatectomy during OLT with IVC preservation. The proposed maneuver provides a better exposition of the suprahepatic veins allowing an ortogonal clamping of the suprahepatic confluence and avoiding caval clamping. It allows, moreover, an increase of venous surface available for the anastomosis that results wider and easier to perform. This provides a large outflow anastomotic cloaca and prevents outflow problems of the graft.

Modified liver hanging maneuver during orthotopic liver transplantation with inferior vena cava preservation.

Ettorre G.M., Vennarecci G., Santoro R., Antonini M., Lonardo M.T., Carlini M., Santoro E.

Transplantation, 75(2), p.247-9, 2003

No abstract available

Is delayed chemotherapy-induced emesis well managed in oncological clinical practice? An observational study.

Fabi A., Barduagni M., Lauro S., Portalone L., Mauri M., Marinis F., Narduzzi C., Tonini G., Giampaolo M., Pacetti U., Paoloni F., Cognetti F.

Support Care Cancer, 11(3), p.156-61, 2003

Nausea and vomiting have a negative influence on the quality of life of patients receiving chemotherapy. The Consensus Conference held in 1997 outlined the therapeutic procedure to prevent delayed emesis that might otherwise be induced by chemotherapy. So far, no study has evaluated the correct management of delayed emesis in clinical practice. This study was performed in an attempt to verify the conformity of the delayed emesis therapy administered in some oncological centres with the Consensus Conference guidelines. A total of 149 patients were observed for a minimum of one up to a maximum of four chemotherapy cycles; analysis of the data took account of whether the chemotherapy had a high (HEC), moderate (MEC) or low (LEC) emetogenic potential. Among 42 patients who received HEC, 18 (43%) received antiemetic prophylaxis conforming to standards; 23 (54.7%) of these 42 had delayed emesis, only 8 (34.7%) of whom were treated with adequate antiemetic protection. MEC was administered to 72 patients, 46 (64%) of whom received adequate prophylaxis; delayed emesis was observed in 31 (43%) of the 72 patients, 20 (64.5%) of whom received antiemetic prophylaxis according to established guidelines. Of 35 patients treated with LEC, 22.8% manifested delayed emesis; a high percentage of these patients, 68.5%, received prophylaxis, even though it was unnecessary. Of all patients observed, only 50.3% received correct antiemetic protection. We deduce from the study that antiemetic treatment for delayed emesis in clinical practice needs more attention. Correct prophylaxis is necessary when HEC is given, and antiemetic protection for patients receiving MEC must be improved; among patients treated with LEC those at high risk must be identified so that overtreatment can be avoided.

Il tumore del polmone non a piccole cellule i limiti della chirurgia.

Facciolo F., Piovanello P., Cerasoli V., Carlini S., Ghini C.

Tumori, 2(Suppl. 4), p.S95-S96, 2003

No abstract available

Molecular therapy of breast carcinoma in the advanced phase

Foggi P., Amodio A.

Tumori, 89(Suppl. 4), p.189-91, 2003

Conventional chemotherapy regimens for the treatment of breast cancer have limited efficacy and are associated with significant toxicity, highlighting the need for novel targeted therapies. Increased expression and activation of receptor tyrosine kinases frequently occurs in human breast carcinomas and, therefore, several clinical trials are currently evaluating therapies targeting these receptors. Therapeutic strategies include blockade of individual receptors with monoclonal antibodies (e.g., trastuzumab) and inhibition of tyrosine kinase function (e.g., gefitinib). Trastuzumab is the first agent that has been approved for patients with human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer. Other growth-factor targeted drugs are in clinical development such as STI-571, farnesyl-transferase inhibitors and antibodies directed at the insulin-like growth factor.

Endoglin (CD105): a powerful therapeutic target on tumor-associated angiogenetic blood vessels.

Fonsatti E., Altomonte M., Nicotra M.R., Natali P.G., Maio M.

Oncogene, 22(42), p.6557-63, 2003

Among surface molecules expressed on endothelial cells, endoglin (CD105) is emerging as a prime vascular target for antiangiogenetic cancer therapy. CD105 is a cell membrane glycoprotein mainly expressed on endothelial cells and overexpressed on tumor-associated vascular endothelium, which functions as an accessory component of the transforming growth factor -beta receptor complex and is involved in vascular development and remodelling. Quantification of intratumoral microvessel density by CD105 staining and of circulating soluble CD105 has been suggested to have prognostic significance in selected neoplasias. In addition, the potential usefulness of CD105 in tumor imaging and antiangiogenetic therapy has been well documented utilizing different animal models.

Incidence of AIDS-defining cancers after AIDS diagnosis among people with AIDS in Italy, 1986-1998.

Franceschi S., Dal Maso L., Pezzotti P., Polesel J., Braga C., Piselli P., Serraino D., Tagliabue G., Federico M., Ferretti S., De Lisi V., La Rosa F., Conti E., Budroni M., Vicario G., Piffer S., Pannelli F., Giacomin A., Bellu F., Tumino R., Fusco M., Rezza G.; Cancer and AIDS Registry Linkage Study.

J. Acquir. Immune Defic Syndr., 34(1), p.84-90, 2003

A record linkage was carried out between the Italian National Registry of AIDS and 19 cancer registries. The aim was to evaluate the 1986 through 1998 trends in incidence rate (IR) of AIDS-defining cancers (ADCs) among persons with AIDS (PWA) in Italy overall and according to various characteristics. A steady decrease in IRs was found for Kaposi sarcoma (KS) in men between 1986-1992 (2.5 per 100 person-years [py]) and 1997-1998 (1.0 per 100 py). Conversely, the first decrease in IRs of KS in women (from 0.9 to 0.6 per 100 py) and of non-Hodgkin lymphoma in both genders (from 1.7 to 0.7 per 100 py) was seen between 1993-1996 and 1997-1998, thus pointing to a favorable impact of highly active antiretroviral therapies. The decline was consistent across different age and HIV transmission groups, but it was more marked in PWA with a CD4 count >50 cells/microL than in PWA with more severe immune suppression. As a proportion of AIDS cases, invasive cervical cancer increased from 1.5% in 1993-1996 to 2.4% in 1997-1998, but IRs after AIDS could not be evaluated. On account of the marked decline of KS in men in 1997-1998, the overall burden of ADCs in Italy became similar in both genders.

p73 is regulated by phosphorylation at the G2/M transition.

Fulco M., Costanzo A., Merlo P., Mangiacasale R., Strano S., Blandino G., Balsano C., Lavia P., Levrero M.

J. Biol. Chem., 278(49), p.49196-202, 2003

p73 is a p53 paralog that encodes proapoptotic (transactivation-competent (TA)) and antiapoptotic (dominant negative) isoforms. TAp73 transcription factors mediate cell cycle arrest and/or apoptosis in response to DNA damage and are involved in developmental processes in the central nervous system and the immune system. p73 proteins may also play a role in the regulation of cell growth. Indeed, p73 expression is itself modulated during the cell cycle and TAp73 proteins accumulate in S phase cells. In addition, the function of p73 proteins is also regulated by post-translational modifications and protein-protein interactions in different cellular and pathophysiological contexts. Here we show that p73 is a physiological target of the p34cdc2-cyclin B mitotic kinase complex in vivo. Both p73beta and p73alpha isoforms are hyperphosphorylated in normal mitotic cells and during mitotic arrest induced by microtubule-targeting drugs. p34cdc2-cyclin B phosphorylates and associates with p73 in vivo, which results in a decreased ability of p73 to both bind DNA and activate transcription in mitotic cells. Indeed, p73 is excluded from condensed chromosomes in meta- and anaphase, redistributes throughout the mitotic cytoplasm, and unlike p53, shows no association with centrosomes. Together these results indicate that M phase-specific phosphorylation of p73 by p34cdc2-cyclin B is associated with negative regulation of its transcriptional activating function.

Telomerase activity, apoptosis and cell cycle progression in ataxia telangiectasia lymphocytes expressing TCL1.

Gabellini C., Antonelli A., Petrinelli P., Biroccio A., Marcucci L., Nigro G., Russo G., Zupi G., Elli R.

Br. J. Cancer, 89(6), p.1091-5, 2003

Individuals affected by ataxia telangiectasia (AT) have a marked susceptibility to cancer. Ataxia telangiectasia cells, in addition to defects in cell cycle checkpoints, show dysfunction of apoptosis and of telomeres, which are both thought to have a role in the progression of malignancy. In 1-5% of patients with AT, clonal expansion of T lymphocytes carrying t(14;14) chromosomal translocation, deregulating TCL1 gene(s), has been described. While it is known that these cells can progress with time to a frank leukaemia, the molecular pathway leading to tumorigenesis has not yet been fully investigated. In this study, we compared AT clonal cells, representing 88% of the entire T lymphocytes (AT94-1) and expressing TCL1 oncogene (ATM(-) TCL1(+)), cell cycle progression to T lymphocytes of AT patients without TCL1 expression (ATM(-) TCL1(-)) by analysing their spontaneous apoptosis rate, spontaneous telomerase activity and telomere instability. We show that in ATM(-) TCL1(+) lymphocytes, apoptosis rate and cell cycle progression are restored back to a rate comparable with that observed in normal lymphocytes while telomere dysfunction is maintained.

Increased resistance of peptides to serum proteases by modification of their amino groups.

Galati R., Verdina A., Falasca G., Chersi A.

Z. Naturforsch [C], 58(7-8), p.558-61, 2003

The ability of synthetic protein fragments to survive the degradative action of aminopeptidases and serum proteolytic enzymes can be remarkably enhanced by slight modifications at their N-terminal alpha-amino group. This can be achieved by addition of beta-alanine or amino acids of the D-configuration, amino acids which are seldom found in a living organism. These modifications do scarcely modify the chemical and physical properties of the peptides, and should be preferred, especially for in vivo tests, to drastic alterations of peptides as produced by dinitrophenylation or dansylation of the amino groups.

Demyelinating disease in monoclonal gammopathy of undetermined significance.

Galie E., Pietrangeli A., Maschio M., Pace A., Vidiri A., Carosi M., Jandolo B.

J. Exp. Clin. Cancer Res., 22(2), p.337-9, 2003

We describe herein the case of a 57 year old man who, over the last five years, has presented ataxic and spastic gait on the right side, a reduction in fine motor movement of the fingers mainly on the right side, superficial right side brachiocrural hypoesthesia and a marked dysarthria associated with internuclear ophthalmoplegia. The neurological picture, after an initial progressive worsening which lasted some months, remained relatively stable over the years. Repeated magnetic resonance imaging (MRI) of the brain and spinal cord documented the presence of demyelinating plaques spread in the white matter of the periventricular region and the semioval centres, and a right side paramedian plaque at the C4-C5 level, none of which were in the active phase. Oligoclonal bands were revealed in the cerebrospinal fluid (CSF). Monoclonal IgM/lambda gammopathy with anti-myelin and anti-nucleo reactivity, found with serum immunofixation, were confirmed several times in successive annual controls, not associated to myeloproliferative pathology. The lack of progression in the clinical picture would seem to contradict the diagnosis of late Multiple Sclerosis. The presence of antibody activity against the myelin might support the hypothesis of a pathogenetic role of the immunoglobulins at the onset of the demyelinating disease in this patient. However, in the end, there is the possibility of casual association with a poorly functioning immune system connected to age.

Cigarette tar yield and risk of upper digestive tract cancers: case-control studies from Italy and Switzerland.

Gallus S., Altieri A., Bosetti C., Franceschi S., Levi F., Negri E., Dal Maso L., Conti E., Zambon P., La Vecchia C.

Ann. Oncol., 14(2), p.209-13, 2003

Background: Tobacco smoking is one of the main risk factors for oral, pharyngeal and oesophageal cancers in developed countries. Information on the role of the tar yield of cigarettes in upper digestive tract carcinogenesis is sparse and needs to be updated because the tar yield of cigarettes has steadily decreased over the last few decades.

Patients and methods: We analysed two case-control studies, from Italy and Switzerland, conducted between 1992 and 1999, involving 749 cases of oral and pharyngeal cancer and 1770 controls, and 395 cases of squamous-cell oesophageal carcinoma and 1066 matched controls. Odds ratios (ORs) were estimated by unconditional multiple logistic regression models, including terms for age, sex, study centre, education and alcohol consumption.

Results: Based on the brand of cigarettes smoked for the longest time, the multivariate ORs for current smokers compared with never smokers were 6.1 for <20 mg and 9.8 for >or=20 mg tar for oral and pharyngeal neoplasms, and 4.8 and 5.4 for oesophageal cancer, respectively. For the cigarette brand smoked in the previous six months, the ORs for >or=10 mg compared with <10 mg were 1.9 for cancer of the oral cavity and pharynx and 1.8 for oesophageal cancer, after allowance for number of cigarettes and duration of smoking.

Conclusions: The present study confirms the direct relationship between the tar yield of cigarettes and upper digestive tract neoplasms, and provides innovative information on lower tar cigarettes, which imply reduced risks compared with higher tar ones. However, significant excess risks were observed even in the lower tar category, thus giving unequivocal indications for stopping smoking as a priority for prevention of upper digestive tract neoplasms.

Does pizza protect against cancer?

GALLUS S., BOSETTI C., NEGRI E., TALAMINI R., MONTELLA M., CONTI E., FRANCESCHI S., LA VECCHIA C.

Int. J. Cancer, 107(2), p.283-4, 2004

We analyzed the potential role of pizza on cancer risk, using data from an integrated network of case-control studies conducted in Italy between 1991 and 2000. Cancer sites were: oral cavity and pharynx (598 cases), esophagus (304 cases), larynx (460 cases), colon (1,225 cases) and rectum (728 cases). Controls were 4,999 patients admitted for acute, non-neoplastic conditions to the same hospital network as cases. Odds ratios for regular pizza consumers were 0.66 (95% confidence interval, CI = 0.47-0.93) for oral and pharyngeal cancer, 0.41 (95% CI = 0.25-0.69) for oesophageal, 0.82 (95% CI = 0.56-1.19) for laryngeal, 0.74 (95% CI = 0.61-0.89) for colon and 0.93 (95% CI = 0.75-1.17) for rectal cancer. Pizza appears therefore to be a favorable indicator of risk for digestive tract neoplasms in this population.

Prevalence of infections by hepatitis A, B, C and E viruses in two different socioeconomic groups of children from Santa Cruz, Bolivia.

GANDOLFO G.M., FERRI G.M., CONTI L., ANTENUCCI A., MARRONE R., FRASCA A.M., VITELLI G.

Med. Clin. (Barc), 120(19), p.725-7, 2003

Background and objectives: The epidemiology of hepatitis A, E, B and C was analyzed in 1,393 children living in Santa Cruz de la Sierra, Bolivia. They were distributed in two groups according to the social condition.

Materials and method: 1,393 children were selected from two different schools: one attended by children belonging to a high social class of the town (group A), and the other school attended by children belonging to the poorest social class (group B). Blood samples were drawn by a team of physicians from Rome University La Sapienza. Serum antibodies against hepatitis A, B, C and E virus, and the hepatitis B surface antigen were evaluated by immunometric methods. The significance was evaluated using the ⋆2 test.

Results: Antibodies against hepatitis A virus were detected in 82% of examined children, with a significant difference between the two groups (56.3% vs 94.8%). The incidence of anti-HBc antibodies increased with age, so the infection is acquired prevalently in adolescence with a significant difference between both groups (1.1% vs 3.8%). The same phenomenon was observed with anti-HCV antibodies (4.7% positivity only in group B). Serum antibodies against hepatitis E virus were observed in 1.7% cases.

Conclusions: In Bolivia, as in other developing countries, viral hepatitis represents a serious burden for public health. Spreading of viral hepatitis can be controlled upon improving hygienic conditions and customs. Moreover, a vaccination plan against hepatitis A and B virus is necessary for the population living in endemic areas.

Skin testing and hypersensitivity reactions to oxaliplatin.

Garufi C., Cristaudo A., Vanni B., Bria E., Aschelter A.M., Santucci B., Terzoli E.

Ann. Oncol., 14(3), p.497-8, 2003

No abstract available

A phase II study of irinotecan plus chronomodulated oxaliplatin, 5-fluorouracil and folinic acid in advanced colorectal cancer patients.

Garufi C., Bria E., Vanni B., Zappala A.M., Sperduti I., Terzoli E.

Br. J. Cancer, 89(10), p.1870-5, 2003

The combination of irinotecan (CPT-11), oxaliplatin (L-OHP), 5-fluorouracil (5-FU) and folinic acid (FA) is one of the possibilities to overcome chemoresistance in advanced colorectal cancer (ACRC) patients. The aim of this study was to determine the tolerability and activity of CPT-11 plus chronomodulated infusion of L-OHP, 5-FU and FA in ACRC patients. A total of 35 patients (91% pretreated, 77% with CPT-11, 54% with L-OHP, 42% with both) were treated every 3 weeks with CPT-11, 180 mg m(-2) day 1 i.v., plus L-OHP, 20 mg m(-2) day(-1), 5-FU, 700 mg m(-2) day(-1) and FA, 150 mg m(-2) day(-1), all three drugs from day 2 to day 5 by chronomodulated infusion. The patients' (pt) data were as follows: male/female 21/14; median age 58 years (range: 38-70); PS 0: 26 pts (74%), PS 1: 8 pts (23%), PS 2: 1 pt (3%); primary tumour colon/rectum 26/9; involved organs: 1, 14 pts (40%); 2, 17 pts (48%); >or=3: 4 pts (11%); previous chemotherapy lines 1: 12 pts (34%), 2: 10 pts (28%), >or=3: 10 pts (28%). A total of 221 courses (c) were performed; no grade 4 toxicity was observed with only one grade 3 (G3) neutropenia and thrombocytopenia (3%) in one out of 221 courses (<1%). Maximal toxicity (G3) was nausea and diarrhoea in 10 pts (28%), occurring in 14 out of 221 c (6%) and 12 out of 221 c (5%) respectively. Seven patients achieved a partial response (20%, confidence interval (c.i.) 6.8-33.3) and one patient a complete response (2.9%, c.i. 0-8.4), for a total overall response rate of 22.9% (c.i. 9-36.8); 15 out of 35 (42.9%, c.i. 26.5-59.3) had stable disease and 12 out of 35 (34.3%, c.i. 18.6-50) patients underwent a progression. In conclusion, this four-drug regimen is feasible in advanced pretreated ACRC patients with no significant haematological toxicity and acceptable diarrhoea. The activity of this combination is currently studied in EORTC 05011 study.

CD44s adhesive function spontaneous and PMA-inducible CD44 cleavage are regulated at post-translational level in cells of melanocytic lineage.

Gasbarri A., Del Prete F., Girnita L., Martegani M.P., Natali P.G., Bartolazzi A.

Melanoma Res., 13(4), p.325-37, 2003

Adhesion between the CD44s receptor and hyaluronic acid plays an important role in cell migration, tumour growth and progression. Although the alternative splicing of CD44 variant exons represents the principal regulatory mechanism of CD44-mediated functions, CD44v spliced variants are scantily expressed in melanoma cells. For this reason, we have investigated the possibility that post-translational modifications of the CD44 standard receptor could play a pivotal role in regulating CD44-mediated functions in melanoma. Using metabolic inhibitors of N- and O-glycosylation, as well as melanoma transfectants expressing CD44s O-glycosylation site-specific mutants, we performed structural and functional analysis of N- and O-deglycosylated CD44s molecules expressed in melanoma cells. We discovered that complete N- and O-glycosylation is not required by CD44s to be correctly expressed on the melanoma cell surface. Indeed, variably glycosylated and functionally different CD44s molecules were constitutively expressed in primary and metastatic lesions. Furthermore, we observed that changes in N- and O-glycosylation of CD44s could modulate its cleavage. In fact, spontaneous CD44s shedding was dependent on the presence of partial or complete O-glycosylation of four serine-glycine motifs localized in the membrane-proximal CD44 ectodomain. Mutation of these serine residues, as well as an extensive metabolic O-deglycosylation, strongly impaired spontaneous CD44 shedding. Furthermore, an O-glycosylation-independent mechanism of CD44 cleavage has been identified. This alternative mechanism of receptor cleavage is phorbol 12-myristate-13-acetate (PMA) inducible, mediated by metalloproteinase and requires the presence of N-linked sugar residues. Our findings demonstrate that the post-translational modification of CD44s represents the principal regulatory mechanism of CD44s-mediated functions in melanoma.

Childhood cancer survival in Europe.

GATTA G., CORAZZIARI I., MAGNANI C., PERIS-BONET R., ROAZZI P., STILLER C.; THE EUROCARE WORKING GROUP (CONTI E.M.S)

Ann. Oncol., 14 (Suppl. 5), p.V119-V127, 2003

No abstract available

Gemcitabine and cisplatin versus vinorelbine and cisplatin versus ifosfamide+gemcitabine followed by vinorelbine and cisplatin versus vinorelbine and cisplatin followed by ifosfamide and gemcitabine in stage IIIB-IV non small cell lung carcinoma: a prospective randomized phase III trial of the Gruppo Oncologico Italia Meridionale.

GEBBIA V., GALETTA D., CARUSO M., VERDERAME F., PEZZELLA G., VALDESI M., BORSELLINO N., PANDOLFO G., DURINI E., RINALDI M., ET AL., GRUPPO ONCOLOGICO ITALIA MERIDIONALE.

Lung Cancer, 39(2), p.179-89, 2003

PURPOSE: we carried out a phase III randomized trial to compare vinorelbine-cisplatin regimen to gemcitabine-cisplatin regimen, and to a sequential administration of gemcitabine-ifosfamide followed by vinorelbine-cisplatin or the opposite sequence of vinorelbine-cisplatin followed by ifosfamide-gemcitabine according to the 'worst drug rule' hypothesis in patients with locally advanced unresectable stage IIIB or metastatic stage IV non-small cell lung cancer. The primary endpoint was survival parameters, while secondary endpoints included analysis of response rates and toxicity.

Patients and methods: patients were randomized to receive: (a) gemcitabine 1000 mg/m(2) on days 1, 8 and 15 plus ifosfamide 1500 mg/m(2) on days 8-12 with mesna uroprotection (GI regimen) followed by vinorelbine 25 mg/m(2) on days 1 and 8 plus cisplatin 100 mg/m(2) on day 1 (GI → VC regimen); (b) the opposite sequence (VC → GI); (c) vinorelbine plus cisplatin as above described (VC regimen); or (d) gemcitabine 1400 mg/m(2) on days 1 and 8 plus cisplatin 100 mg/m(2) on day 8 (GC regimen). All regimens were given every 4 weeks. All patients were chemotherapy naive and had a ECOG PS 0-2.

Results: 400 patients were enrolled into the trial. Interim analysis after inclusion of 243 patients showed that ORR were 19% in the GI → VC arm, 32% in the inverse sequence arm (CV → GI), 42% in the VC arm, and 30% in the GC arm. The VC arm was statistically superior over the GI → VC arm ($p = 0.0074$), but not over the other regimens. Median TTP was 3.1 months in the GI → VC arm versus 5.0 months in the VC → GI arm ($p = 0.014$). For these reasons the GI → VC and VC → GI arm were closed since the 'worst drug rule' hypothesis was rejected. Accrual in the VC and GC arms continued up to 140 and 138 patients respectively. Final ORR were 44% for the VC regimen (4 CR), and 34% for the GC regimen (1 CR). This difference was statistically significant ($p = 0.032$). OS was 9.0 and 8.2 months, respectively, with no statistically significant difference. The 1-year survival rate was 24 and 20%, respectively for VC and GC regimens. As expected the incidence of phlebitis was higher in the VC arm, while thrombocytopenia, flu-like syndrome and asthenia were more frequent in the GC arm.

Conclusions: the results of this trial indicate that the combination of vinorelbine and cisplatin and that of gemcitabine and cisplatin are equivalent in terms of median TTP and OS, although the vinorelbine-cisplatin regimen is associated with a higher ORR. Both regimens may be considered as reference treatments for future studies. Moreover, our data reject the 'worst drug rule' hypothesis of sequential treatments in NSCCL at least with the combination used in this study.

Clinically meaningful response to the EGFR tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in non small cell lung cancer.

GELIBTER A., CERIBELLI A., MILELLA M., MOTTOLESE M., VOCATURO A., COGNETTI F.

J. Exp. Clin. Cancer Res., 22(3), p.481-5, 2003

Preclinical research and ongoing clinical trials are validating epidermal growth factor receptor (EGFR) as a suitable molecular target in cancer therapy. Here we report the case of a 39-year-old non-smoking man with heavily pretreated stage IV bronchioloalveolar NSCLC who was treated with gefitinib ('Iressa', ZD1839) at the dose of 250 mg/day, orally. Symptomatic relief was already detectable after 2 weeks of gefitinib therapy, pulmonary function tests readily improved, performance status went from 2 to 0 within 8 weeks, CT scan performed after 10 weeks of

treatment showed nearly complete resolution of the clinical picture, and clinical remission was maintained up to 32 weeks. This case-report illustrates the potential of EGFR tyrosine kinase inhibition to induce clinically meaningful responses in heavily pretreated, advanced NSCLC patients and suggests that participation of such patients into clinical trials of signal transduction inhibitors should be encouraged.

The antigen processing machinery of class I human leukocyte antigens: linked patterns of gene expression in neoplastic cells.

GIORDA E., SIBILIO L., MARTAYAN A., MORETTI S., VENTURO I., MOTTOLESE M., FERRARA G.B., CAPPELLACCI S., EIBENSCHUTZ L., CATRICALA C., GRAMMATICO P., GIACOMINI P.

Cancer Res., 63(14), p.4119-27, 2003

The ultimate outcome of an immune response (escape or surveillance) depends on a delicate balance of opposing signals delivered by activating and inhibitory immune receptors expressed by cytotoxic T lymphocytes and natural killer cells. In this light, loss and down-regulation of human leukocyte antigens (HLA) class I molecules, while important for keeping tumors below the T-cell detection levels, may incite recognition of missing self. Conversely, the maintenance of normal levels of expression (or even up-regulation) may be favorable to tumors, at least in certain cases. In this study, we took advantage of a previously characterized panel of 15 early passage tumor cell lines (mainly from melanoma and lung carcinoma lesions) enriched with class I-low phenotypes. These cells were systematically characterized by Northern and/or Western blotting (e.g., mini-transcriptome/mini-proteome analysis) for the expression of HLA-A, -B, -C, beta(2)-microglobulin, and the members of the "antigen processing machinery" of class I molecules (LMP2, LMP7, TAP1, TAP2, tapasin, calreticulin, calnexin, and ERp57). In addition, we established four pairs of cultures, each comprising melanoma cells and normal melanocytes from the same patient. We found that approximately 97% of the 185 tested gene products are expressed (although often weakly), and in many cases coordinately regulated in 18 of 19 tumor cell lines. Linked expression patterns could be hierarchically arranged by statistical methods and graphically described as a class I HLA "coordinome." Deviations (both down- and up-regulation) from the coordinome expression pattern inherited from the normal, paired melanocyte counterpart, were allowed but limited in magnitude, as if melanoma cells were trying to keep a "low profile" HLA phenotype. We conclude that irreversible HLA loss is a rare event, and class I expression in tumor cells almost invariably results from reversible gene regulatory (rather than gene disruption) events.

Infectious complications in patients with acute promyelocytic leukaemia treated with the AIDA regimen.

GIRMENIA C., LO COCO F., BRECCIA M., LATAGLIATA R., SPADEA A., D'ANDREA M., GENTILE G., MICOZZI A., ALIMENA G., MARTINO P., MANDELLI F.

Leukemia, 17(5), p.925-30, 2003

Infections represent a frequent complication of chemotherapy used for acute myeloid leukaemia (AML) and are associated with important toxicity frequently leading to treatment discontinuation. Acute promyelocytic leukaemia (APL) is a unique AML subset requiring tailored therapy including all-trans retinoic acid and anthracycline-based chemotherapy. We analysed in this study the incidence and type of infections complicating the clinical course of 89 consecutive APL patients receiving the AIDA protocol at a single institution. A total of 179 febrile episodes were registered during induction and consolidation, 52% of which were of unknown origin. Infections were clinically and microbiologically documented in 10.6 and 37.4% of cases, respectively. Coagulase-negative staphylococci represented the major cause of septicaemia (28%) and were more frequently isolated during induction, whereas viridans group streptococci, the second pathogen most frequently isolated from blood (27%), represented the principal pathogen detected during consolidation and were significantly associated with mucositis. Gram-negative bacteria accounted for 33.3% of all blood isolates. Fungal infections were only occasionally observed. Bloodstream infections in APL patients were compared with those documented in 271 consecutive patients affected by other subtypes of AML. The incidence of total septicaemia episodes, of staphylococcal bacteraemias and of fungaemias was significantly higher in patients with other AMLs. Empirical antibiotic therapy with ceftriaxone plus amikacin was effective in 73% of APL cases, most of the remaining cases being successfully managed by the addition of teicoplanin. One single death apparently related to infec-

tious complication was recorded. Overall, infections led to antileukaemic treatment withdrawal in six patients, five of whom currently remain in haematologic remission for 13-106 months. These results indicate that a particular pattern of infections is observed in APL patients receiving ATRA plus anthracycline-based chemotherapy and that these appear to be effectively counteracted by standard management.

Expression of OP4 (ORL1, NOP1) receptors in vascular endothelium.

Granata F., Potenza R.L., Fiori A., Strom R., Caronti B., Molinari P., Donsante S., Citro G., Iacovelli L., De Blasi A., Ngomba R.T., Palladini G., Passarelli F.

Eur. J. Pharmacol., 482(1-3), p.17-23, 2003

Endothelial cells from rat brain microvessels, human aortic artery and human umbilical vein were examined, together with ex vivo rat brain capillaries and rat aortic ring sections, for the expression of opioid receptor-like OP-4 mRNA and protein. High levels of mRNA expression and an immunopositive reaction for the receptor protein were detected in the endothelial cells from primary and from established in vitro cultures, as well as in the intima of ex vivo rat aortic rings, where the signal was limited to the endothelial layer. Interaction of the OP4 receptor with its physiological ligand nociceptin caused, in cultured endothelial cells, the activation of a mitogen-activated protein (MAP) kinase cascade. Taken together, these results show that the OP4 receptor is synthesised and functionally expressed in endothelial cells, presumably as a starting point for some vasoactive mechanism(s).

Potential usefulness of serum p53 for laboratory management of plasma cell dyscrasias.

Greco C., Alvino S., Del Monte G., Venturo I., Lopez M.

J. Exp. Clin. Cancer Res., 22(4), p.607-12, 2003

We measured the serum levels of p53 mutant protein (p53M-ELISA) in 65 patients with plasma cell dyscrasia (PCD) and compared them with some conventional laboratory variables. Our aim was to assess, for the first time, the potential of this parameter as a new marker for laboratory management of PCD. Twenthy-tree out of 65 patients had monoclonal gammapathy of undetermined significance (MGUS) and 42 suffered from multiple myeloma (MM). MM patients, with no prior chemotherapy consecutively entered this study. They were treated with standard regimens of Melphalan and Prednisone (MP) and were analyzed for serum p53M level from the time of diagnosis to response to therapy or death. A subgroup of nine patients was regularly monitored for changes occurring in p53M levels during MP therapy. Serum levels of p53M were elevated in MM patients compared with MGUS and healthy controls ($p = 0.002$). Significantly higher p53M levels were shown by MM patients refractory to chemotherapy than by responding patients (0.38 ng/ml vs 0.22 ng/ml, $p = 0.05$). The measurement of serum p53M in the nine patients during the course of chemotherapy correlated with disease progression or response to therapy. If confirmed on a larger series of patients, these results suggest a potential role of serum p53 mutant levels in laboratory management of PCD patients.

Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small-cell lung cancer: a phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group.

Gridelli C., Gallo C., Shepherd F.A., Illiano A., Piantedosi F., Robbiati S.F., Manzione L., et al. and gemvin investigatorrs (aschelter a.m.)

J. Clin. Oncol., 21(16), p.3025-34, 2003

Purpose: Platinum-containing chemotherapy regimens are the standard treatment for patients with advanced non-small-cell lung cancer (NSCLC), although toxicity is common and may significantly affect the patient's quality of life (QoL). This trial aimed to assess whether a combination of gemcitabine and vinorelbine had benefits in terms of QoL, without influencing negatively on survival, compared with cisplatin-containing regimens.

Patients and methods: Patients with stage IIIB (effusion and supraclavicular nodes) or IV documented NSCLC who were younger than 70 years of age were randomly assigned gemcitabine plus vinorelbine (GemVin) or either gemcitabine plus cisplatin or vinorelbine plus cisplatin (cisplatin-based). European Organization for Research and Treatment of Cancer scales were used for QoL analysis.

Results: Five hundred one patients were randomly assigned to treatment. The median age was 62 years. There were no significant differences in global QoL scores between the two arms after 2 months of treatment. However, worsening scores for appetite, vomiting, and alopecia were significantly more common in the cisplatin-based arm. Median survival was 38 v 32 weeks and median progression-free survival was 23 v 17 weeks in the cisplatin-based versus GemVin arms, respectively. For the GemVin arm the hazard ratio for death was 1.15 (90% confidence interval [CI], 0.96 to 1.37) and the hazard ratio for progression was 1.29 (90% CI, 1.10 to 1.52). Grade 3 or 4 myelosuppression, vomiting, alopecia, and ototoxicity were significantly more frequent with cisplatin-based treatment.

Conclusion: Global QoL is not improved with GemVin, although advantages in some components of QoL were apparent. GemVin is less toxic than standard cisplatin-based chemotherapy. There is a nonsignificant slight survival advantage with cisplatin-based chemotherapy. GemVin could be offered to advanced NSCLC patients who express concern about toxicity.

Hypoxic pelvic and limb perfusion with melphalan and mitomycin C for recurrent limb melanoma: a pilot study.

Guadagni S., Santinami M., Patuzzo R., Pilati P.L., Miotto D., Deraco M., Rossi C.R., Fiorentini G., Di Filippo F.,Valenti M., Amicucci G.

Melanoma Res., 13(1), p.51-8, 2003

Hypoxic pelvic and limb perfusion by means of a balloon occlusion technique was evaluated in patients with recurrent melanoma of the lower limbs who were non-responders to isolated hyperthermic limb perfusion or who were not eligible for this procedure. A pilot study was performed in 17 patients, who underwent hypoxic pelvic and limb perfusion with 50 mg/m(2) of melphalan or 50 mg/m(2) of melphalan and 25 mg/m(2) of mitomycin C. Each procedure was followed by haemofiltration. A leakage monitoring study was performed in five of the 17 patients. The response rate and time to disease progression were the primary endpoints, with overall survival as the secondary endpoint. During the procedures there were no technical, haemodynamic or vascular complications, and no deaths occurred during surgery or in the postoperative period. Significant leakage (median 40%) was measured in the five patients studied. No severe systemic or regional toxicity was observed. After one course of treatment, the objective response rate was 47% (95% confidence interval 22.5-71.5%), the median time to disease progression was 10 months (range 2-40 months), and the 3 year overall survival was 20%. Hypoxic pelvic and limb perfusion seems to be a safe and effective treatment for patients with unresectable recurrent limb melanoma who are not eligible for isolated hyperthermic limb perfusion. Due to the non-homogeneity of the study, with some patients receiving a combination of melphalan and mitomycin C and others receiving only melphalan, it is not possible to make definite conclusions with regard to efficacy. Further studies are necessary to establish whether the response rates can be improved by using different drug regimens.

Requirement For Down-Regulation Of The CCAAT-Binding Activity Of The NF-Y Transcription Factor During Skeletal Muscle Differentiation.

Gurtner A., Manni I., Fuschi P., Mantovani R., Guadagni F., Sacchi A., Piaggio G.

Mol. Biol. Cell., 14(7), p.2706-15, 2003

NF-Y is composed of three subunits, NF-YA, NF-YB, and NF-YC, all required for DNA binding. All subunits are expressed in proliferating skeletal muscle cells, whereas NF-YA alone is undetectable in terminally differentiated cells in vitro. By immunohistochemistry, we show that the NF-YA protein is not expressed in the nuclei of skeletal and cardiac muscle cells in vivo. By chromatin immunoprecipitation experiments, we demonstrate herein that NF-Y does not bind to the CCAAT boxes of target promoters in differentiated muscle cells. Consistent with this, the activity of these promoters is down-regulated in differentiated muscle cells. Finally, forced expression of the NF-YA protein in cells committed to differentiate leads to an impairment in the down-regulation of cyclin A, cyclin B1, and cdk1 expression and is accompanied by a delay in myogenin expression. Thus, our results indicate that the suppression of NF-Y function is of crucial importance for the inhibition of several cell cycle genes and the induction of the early muscle-specific program in postmitotic muscle cells.

Oxidative damage of the gastric mucosa in Helicobacter pylori positive chronic atrophic and nonatrophic gastritis, before and after eradication.

Iacopini F., Consolazio A., Bosco D., Marcheggiano A., Bella A., Pica R., Paoluzi O.A., Crispino P., Rivera M., Mottolese M., Nardi F., Paoluzi P.

Helicobacter, 8(5), p.503-12, 2003

Background: Helicobacter pylori is the main cause of gastritis and a primary carcinogen. The aim of this study was to assess oxidative damage in mucosal compartments of gastric mucosa in H. pylori positive and negative atrophic and nonatrophic gastritis.

Materials and methods: Five groups of 10 patients each were identified according to H. pylori positive or negative chronic atrophic (Hp-CAG and CAG, respectively) and nonatrophic gastritis (Hp-CG and CG, respectively), and H. pylori negative normal mucosa (controls). Oxidative damage was evaluated by nitrotyrosine immunohistochemistry in the whole mucosa and in each compartment at baseline and at 2 and 12 months after eradication. Types of intestinal metaplasia were classified by histochemistry.

Results: Total nitrotyrosine levels appeared significantly higher in H. pylori positive than in negative patients, and in Hp-CAG than in Hp-CG ($p < .001$); no differences were found between H. pylori negative gastritis and normal mucosa. Nitrotyrosine were found in foveolae and intestinal metaplasia only in Hp-CAG. At 12 months after H. pylori eradication, total nitrotyrosine levels showed a trend toward a decrease in Hp-CG and decreased significantly in Hp-CAG ($p = .002$), disappearing from the foveolae ($p = .002$), but remaining unchanged in intestinal metaplasia. Type I and II of intestinal metaplasia were present with the same prevalence in Hp-CAG and CAG, and did not change after H. pylori eradication.

Conclusions: Oxidative damage of the gastric mucosa increases from Hp-CG to Hp-CAG, involving the foveolae and intestinal metaplasia. H. pylori eradication induces a complete healing of foveolae but not of intestinal metaplasia, reducing the overall oxidative damage in the mucosa.

Shear stress-mediated chromatin remodeling provides molecular basis for flow-dependent regulation of gene expression.

Illi B., Nanni S., Scopece A., Farsetti A., Biglioli P., Capogrossi M.C., Gaetano C.

Circ. Res., 93(2), p.155-61, 2003

Shear stress (SS), the tangential component of hemodynamic forces, modulates the expression of several genes in endothelial cells. However, no information is available about its effect on chromatin structure, which plays a key role in gene transcription. In this study, a link between SS and chromatin remodeling was established in human umbilical vein endothelial cells (HUVECs). HUVECs were exposed to SS of 10 dyne/cm2 per second, in the presence or absence of the histone deacetylase inhibitor trichostatin A, and assayed for histone H3 and histone H4 modifications. SS induced histone H3 serine phosphorylation at position 10 (S10) and lysine acetylation at position 14 (K14) but required trichostatin A to induce H3 phosphoacetylation and H4 acetylation. The phosphatidylinositol 3-kinase inhibitor wortmannin and the mitogen-activated protein kinase inhibitor PD98059 decreased SS-dependent histone H3 phosphorylation, without affecting its acetylation; the p38 inhibitor SB203580 reduced both H3 phosphorylation and acetylation, whereas the protein kinase A inhibitor PKI-tide reduced histone H3 acetylation. Remarkably, the abrogation of histone acetylation inhibited SS-dependent c-fos expression. SS also activated ribosomal S6 kinase-2 and mitogen- and stress-activated kinase-1 protein kinases and promoted the formation of a cAMP-responsive element-binding protein (CREB)/CREB-binding protein complex, providing the molecular basis for the increase in histone acetyltransferase activity observed in HUVECs exposed to SS. Finally, the effect of SS on chromatin remodeling was examined. In HUVECs exposed to SS, chromatin within c-fos and c-jun promoters was specifically immunoprecipitated by an antibody against acetylated histone H3 on K14. These results indicate that SS induces posttransduction modifications of histones; this is an early step toward the flow-dependent regulation of gene expression.

Masseteric silent period and reflex before and after dentomaxillofacial surgery.

JANDOLO B., GALIE E., BADIA D.

Neurol. Sci., 24(2), p.53-6, 2003

The aim of this study was to evaluate massetteric silent period and reflex in patients affected by progenia, before and after maxillofacial surgery, in order to determine their clinical utility. The electrophysiological changes generated by malocclusion secondary to prognatism have been evaluated before and after maxillofacial corrective surgery in 14 patients aged between 18 and 36 years. The masseteric reflex and the silent period (SP) of the masseteric muscles elicited by stimulation of the mental nerve were recorded. A correspondence between the neurophysiological and clinical findings was present in 12 of 14 patients, in particular concerning the latency of SP2. This study demonstrates that the masseteric silent period may be used as a diagnostic and prognostic support, before and after surgery for malocclusion.

YB-1 as a cell cycle-regulated transcription factor facilitating cyclin A and cyclin B1 gene expression.

JURCHOTT K., BERGMANN S., STEIN U., WALTHER W., JANZ M., MANNI I., PIAGGIO G., FIETZE E., DIETEL M., ROYER H.D.

J. Biol. Chem., 278(30), p.27988-96, 2003

Expression of the Y-box protein YB-1 is increased in proliferating normal and cancer cells, but its role in cell proliferation and cell cycle progression is unclear. We have identified a cell cycle-dependent relocalization of YB-1 from the cytoplasm to the nucleus at the G1/S phase transition and demonstrate that both the charged zipper and the cold shock domain are involved in regulating this process. Using cell lines that constitutively overexpress YB-1, we show that nuclear accumulation of YB-1 is associated with increased cyclin A and cyclin B1 mRNA and protein expression. We provide evidence that deregulated YB-1 expression is linked to adhesion-independent cell proliferation through the induction of cyclin A. Thus, we have identified YB-1 as a cell cycle stage-specific transcription factor important for cell proliferation.

Long-term central venous catheterization via persistent left superior vena cava: a case report.

LAURENZI L., NATOLI S., PELAGALLI L., MARCELLI M.E., ABBATTISTA D., CARPANESE L., ARCURI E.

Support Care Cancer, 11(3), p.190-2, 2003

We report a case of a cancer patient who displayed a persistent left superior vena cava (PLSVC) after implantation of a central venous catheter (Port-a-Cath), as revealed by angiography. This anomaly is rather rare (0.3% of healthy individuals), and the few studies on the long-term maintenance of an implant in situ are not very informative. Nevertheless, based on the acceptable venous caliber and the patient's serious clinical situation, we decided to leave the catheter in place and perform infusional chemotherapy and supportive therapy with careful and continuous control. The patient died after 8 months of this therapy. No complications attributable to the catheter were observed. We think that the risk is acceptable in similar conditions.

Emerging roles of DNA tumor viruses in cell proliferation: new insights into genomic instability.

LAVIA P., MILEO A.M., GIORDANO A., PAGGI M.G.

Oncogene, 22(42), p.6508-16, 2003

The small DNA virus proteins E1A and E1B from human Adenovirus, E6 and E7 from human papillomavirus, and large T and small T antigens from SV40, are multifaceted molecular tools that can carry out an impressive number of tasks in the host cell. These viral factors, collectively termed 'oncoproteins' for their ability to induce cancer, can be viewed as paradigmatic oncogenic factors which can disrupt checkpoint controls at multiple levels-they interfere with both 'gatekeeper' cellular functions, including major control pathways of cell cycle and apoptosis, and with 'caretaker' functions, thereby inducing mitotic abnormalities and increasing genomic instability. Both E1A and E7 have been recently found to interact physically with the Ran GTPase. This interaction is key in uncoupling the centrosome cycle from the cell cycle, highlighting a direct link between viral infection and the induction of genomic instability. Further expanding our current knowledge in this field will be crucial to elucidate viral strategies leading to cellular transformation and cancer progression, as well as design novel preventive or therapeutic approaches to human cancer.

Alpha-tocopherol protects against cisplatin-induced toxicity without interfering with antitumor efficacy.

Leonetti C., Biroccio A., Gabellini C., Scarsella M., Maresca V., Flori E., Bove L., Pace A., Stoppacciaro A., Zupi G., Cognetti F., Picardo M.

Int. J. Cancer, 104(2), p.243-50, 2003

Our aim was 2-fold: to investigate the role of alpha-tocopherol supplementation on the antitumor activity of DDP and to evaluate the effect of alpha-tocopherol on the survival and neurotoxicity of DDP-treated mice. Experiments performed on the M14 human melanoma line demonstrated that alpha-tocopherol supplementation did not influence the efficacy of DDP; the inhibition of cell survival and of the in vivo tumor growth after treatment with alpha-tocopherol and DDP combination was similar to that observed after DDP alone. Conversely, alpha-tocopherol was also able to increase survival of mice treated with a high dose of DDP. While DDP alone produced death in about 70% of mice, the combination reduced deaths to about 30%. Analysis of oxidative stress markers and peroxidative damage in organs indicated that the protective effect of alpha-tocopherol was mainly related to its antioxidant activity. A significant increase in the concentration of TBARS and decreased PUFAs and catalase activity were observed after DDP treatment, while with alpha-tocopherol the levels of these markers were comparable to those observed in untreated mice. Histologic analysis performed on peripheral nerve revealed that alpha-tocopherol also protected mice from severe neurologic damage induced by DDP treatment. In conclusion, our results demonstrate that alpha-tocopherol protects against the systemic toxicity and neurotoxicity induced by DDP without interfering with its antitumor activity and suggest that this combination is a promising strategy to improve the therapeutic index of DDP-based chemotherapy.

Analysis of micronuclei in peripheral blood lymphocytes of traffic wardens: effects of exposure, metabolic genotypes, and inhibition of excision repair in vitro by ARA-C.

Leopardi P., Zijno A., Marcon F., Conti L., Carere A., Verdina A., Galati R., Tomei F., Baccolo T.P., Crebelli R.

Environ. Mol. Mutagen., 41(2), p.126-30, 2003

The cytokinesis-block micronucleus (MN) assay in peripheral lymphocytes was used to assess the genetic effects of the occupational exposure to traffic fumes in policemen from the Municipality of Rome. The study population consisted of 192 subjects engaged in traffic control (exposed, 134 subjects), or in office work (controls, 58 subjects). Groups were balanced for age, gender, and smoking habits. The average benzene exposure during the workshift was 9.5 and 3.8 microg/m(3) in exposed individuals and controls, respectively. All subjects were genotyped for CYP1A1, CYP2E1, GSTM1, GSTT1, and DT-diaphorase polymorphisms. The incidence of micronuclei and micronucleated cells was recorded in 1,000 binucleated cells harvested 66 hr after mitogen stimulation. Regression analysis of data showed that MN frequency was mainly modulated by the age ($P = 0.001$) and gender ($P = 0.001$) of the study subjects (relatively higher in the elderly and females), whereas it was unaffected by the occupational exposure to traffic fumes and smoking habits. A weak ($P = 0.02$) association between lower MN frequency and the GSTM1 null genotype was also observed. In order to improve the sensitivity of the method to excision-repairable lesions, a modified protocol, with exposure of cells to the repair inhibitor cytosine arabinoside (Ara-C) during the first 16 hr of growth, was applied to 78 subjects (46 exposed and 32 controls). The results confirmed the higher MN frequency in females ($P < 0.05$), but failed to demonstrate any significant effect of chemical exposure (occupational or related to smoking habits). When the frequency of MN induced by Ara-C (i.e., spontaneous values subtracted) was considered, a significant inverse correlation with age was observed ($P = 0.005$), possibly related to the age-dependent decrease in repair proficiency.

Allogeneic stem cell transplantation for advanced acute promyelocytic leukemia: results in patients treated in second molecular remission or with molecularly persistent disease.

Lo-Coco F., Romano A., Mengarelli A., Diverio D., Iori A.P., Moleti M.L., De Santis S., Cerretti R., Mandelli F., Arcese W.

Leukemia, 17(10), p.1930-3, 2003

In all, 17 consecutive patients in hematological complete remission (HCR) of acute promyelocytic leukemia (APL) received allogeneic stem cell transplantation (SCT) from an HLA-identical sibling and were monitored by reverse transcriptase polymerase chain reaction of PML/RARalpha prior and after transplant. Median age was 31 years (range 3-50 years). At 10 years, the actuarial probabilities of nonrelapse mortality, relapse and disease-free survival were 32% (95% CI: 8-56%), 33% (95% CI: 6-60%) and 46% (95% CI: 22-70%). Six patients tested PCR +ve (1st HCR n=2; 2nd HCR n=3; 3rd HCR n=1) and 11 PCR -ve (2nd HCR n=11) pre-SCT. Of the six patients PCR +ve, two showed early persistence of PCR positivity and converted to sustained PCR negativity after CSA withdrawal (one died of secondary tumor in molecular remission and one is alive in relapse), while four converted to PCR -ve rapidly (one died of the underlying disease and three are in molecular remission). Of the 11 patients PCR -ve pre-SCT, six died (four of transplant-related mortality, one of relapse and one after heart transplantation) and five are alive, four in molecular remission and one is in relapse. Allogeneic SCT seems a valid option for advanced APL, particularly for the poor prognostic group of patients with pre-SCT molecularly persistent disease.

Protein interactions provide new insight into Nm23/nucleoside diphosphate kinase functions.

Lombardi D., Mileo A.M.

J. Bioenerg Biomembr., 35(1), p.67-71, 2003

Nm23-NDPKs besides contributing to the maintenance of the cellular nucleoside triphosphate pool, exert regulatory properties in a variety of cellular events including proliferation, invasiveness, development, differentiation, and gene regulation. This review focuses on recently discovered protein-protein interactions involving the Nm23 proteins. The findings herein summarized provide new and intriguing suggestions for a more extensive understanding of the biological functions of the Nm23 proteins.

Activation of T cells via tumor antigen specific chimeric receptors: the role of the intracellular signaling domain.

Losch F.O., Muller R., Mutschler B., Neri D., Natali P.G., Reth M., Carsetti R.

Int. J. Cancer, 103(3), p.399-407, 2003

T cells engineered to express hybrid receptors with antibody defined specificity can successfully be targeted to tumor cells. In order to select intracellular domains of chimeric receptors capable of efficiently activate T cells in vitro and in vivo, we compared the function of receptors, which share the same extracellular antigen-binding part, joined to different intra-cellular signal transduction units. The antigen binding domain of the receptors was a single-chain fragment of a monoclonal antibody, which recognize a High Molecular Weight Melanoma-Associated Antigen with high affinity. The intracellular tails were derived from the T-cell receptor zeta chain (TCR-zeta), from the B-cell receptor Ig-alpha molecule and from a mutated Ig-alpha molecule able of stronger signal transduction. We compared the activity of the different chimeric receptors at a single-cell level by using a T-cell line that expressed an activation-dependent EGFP-reporter gene. Upon cross-linking with immobilized antibodies, all receptors were able to induce EGFP expression in the majority of the T cells. In contrast, EGFP expression was induced by contact to melanoma cells in vitro only in T cells that expressed the chimeric receptor that contained the TCR-zeta intracellular tail. In these T cells, the co-expression of chimeric receptors that contain a mutated Ig-alpha tail lowers the threshold of T-cell activation and facilitates tumor recognition in vitro and in vivo. Given their specificity and efficiency, T cells grafted with these type of receptors may represent potential candidates for cancer passive immunotherapy.

Genetic and epigenetic alterations as hallmarks of the intricate road to cancer.

MACALUSO M., PAGGI M.G., GIORDANO A.

Oncogene, 22(42), p.6472-8, 2003

Despite the clonal origin of most tumors, their tremendous heterogeneity suggests that cancer progression springs from the combined forces of both genetic and epigenetic events, which produce variant clonal populations, together with the selective pressures of the microenvironment, which promote growth and, perhaps, dissemination of variants with a specific set of characteristics. Although the importance of genetic mutations in cancer has long been recognized, the role of epigenetic events has been suggested more recently. This review focuses on the genetic and epigenetic molecular mechanisms involved in cancer onset and progression, and discusses the possibility of new strategies in the development of anticancer treatments.

Radionuclide Therapy with Bone Seeking Radionuclides in Palliation of Painful Bone Metastases

MAINI C.L., SCIUTO R., ROMANO L., BERGOMI S.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003

No abstract available

Personal Experience on Treatment of Colorectal Liver Metastases: a Multidisciplinary Approach

MANCINI R., ETTORRE G., VENNARECCI G., SPERDUTI I., GARUFI C., ESPOSITO A., COSIMELLI M.

J. Exp. Clin. Cancer Res., 22(Suppl. 4), 2003

No abstract available

MDM4 (MDMX) overexpression enhances stabilization of stress-induced p53 and promotes apoptosis.

MANCINI F., GENTILETTI F., D'ANGELO M., GIGLIO S., NANNI S., D'ANGELO C., FARSETTI A., CITRO G., SACCHI A., PONTECORVI A., MORETTI F.

J. Biol. Chem., 279(9), p.8169-80, 2003

Rescue of embryonic lethality in MDM4(-/-) mice through concomitant loss of p53 has revealed a functional partnership between the two proteins. Biochemical studies have suggested that MDM4 may act as a negative regulator of p53 levels and activity. On the other hand, MDM4 overexpression has been reported to stabilize p53 levels and to counteract MDM2-degradative activity. We have investigated the functional role of MDM4 overexpression on cell behavior. In both established and primary cells cultured under stress conditions, overexpression of MDM4 significantly increased p53-dependent cell death, in correlation with enhanced induction of the endogenous p53 protein levels. This phenomenon was associated with induced p53 transcriptional activity and increased levels of the proapoptotic protein, Bax. Further, p53 stabilization was accompanied by decreased association of the protein to its negative regulator, MDM2. These findings reveal a novel role for MDM4 by demonstrating that in non-tumor cells under stress conditions it may act as a positive regulator of p53 activity, mainly by controlling p53 levels. They also indicate a major distinction between the biological consequences of MDM4 and MDM2 overexpression.

Hepatic arterial infusion (HAI) of cisplatin and systemic fluorouracil in the treatment of unresectable colorectal liver metastases.

MANCINI R., TEDESCO M., GARUFI C., FILIPPINI A., ARCIERI S., CATERINO M., PIZZI G., CORTESI E., SPILA A., SPERDUTI I., COSIMELLI M.

Anticancer Res., 23(2C), p.1837-41, 2003

Background: Only 5-10% of colorectal cancer patients (pts) with liver metastases are eligible for surgical resection. Regional and systemic chemotherapy represents the best therapeutic options for unresectable metastases.

Materials and methods: In a randomized phase II trial 123 pts were enrolled with a minimum follow-up of 3 years. In

Arm A 58 pts were submitted to intraarterial continuous infusion of cisplatin (CDDP), 24 mg/m2/day, while the other 65 were included in Arm B (bolus of CDDP, 24 mg/m2/day). All the pts were also given i.v. escalating doses of fluorouracil. Response was evaluated after a minimum of 3 cycles.

Results: Toxicity > or = G3 was lower in Arm B. The objective response rate was 52% in all the series, the complete responses being 17.3% (17.6% vs. 17% in Arms A and B, respectively). The overall median survival was 18 months rising to 28 months in the responders.

Conclusion: CDDP HAI provided similar results as FUdR in terms of response to treatment. Moreover, long-term survivors were unexpectedly observed.

Venous thromboembolism and cancer: new issues for an old topic.

MANDALA M., FERRETTI G., CREMONESI M., CAZZANIGA M., CURIGLIANO G., BARNI S.

Crit. Rev. Oncol. Hematol., 48(1), p.65-80, 2003

Thromboembolic complications represent the second leading cause of death for cancer patients. Even though the correlation between cancer and a hypercoagulable state has been widely recognised, the pathogenesis of thromboembolism during malignancy is not yet entirely understood. The direct or indirect activation of the coagulation cascade favours neoplastic dissemination and metastasis. Disordered coagulation is encountered in up to 90% of cancer patients, although only 15% of them develop a localised acute or chronic deep venous thrombosis or a disseminated intravascular coagulation. This risk is significantly increased by chemotherapy, hormone therapy, surgery and central venous catheters. Therefore, much effort is needed to develop efficient prophylaxis and treatment, to reduce recurrence and bleeding and finally, to improve quality of life. Better knowledge about the biochemical bases of the coagulation process represents a pivotal step in cancer biology comprehension and global therapeutic management.

Treatment of elderly patients (> or =60 years) with newly diagnosed acute promyelocytic leukemia. Results of the Italian multicenter group GIMEMA with ATRA and idarubicin (AIDA) protocols.

MANDELLI F., LATAGLIATA R., AVVISATI G., FAZI P., RODEGHIERO F., LEONI F., GOBBI M., NOBILE F., GALLO E., FANIN R., AMADORI S., VIGNETTI M., FIORITONI G., FERRARA F., PETA A., GIUSTOLISI R., BROCCIA G., PETTI M.C., LO-COCO F.; ITALIAN GIMEMA COOPERATIVE GROUP.

Leukemia, 17(6), p.1085-90, 2003

In all, 134 elderly patients (median age 66 years, range 60-75 years) with newly diagnosed acute promyelocytic leukemia (APL) were enrolled in two successive protocols of the Italian multicenter group GIMEMA. All patients received an identical induction with all-trans retinoic acid and idarubicin; 116 (86%) entered complete remission (CR), two (2%) were resistant and 16 (12%) died during induction. After CR, 106 patients received further therapy whereas 10 did not, because of refusal (n=5) or toxicity (n=5). Consolidation consisted of three chemotherapy courses in the AIDA protocol (AIDA, 67 patients) or, since 1997, of an amended protocol including only the first cycle (amended AIDA, aAIDA, 39 patients). In the AIDA group, 43 patients (64%) completed consolidation, while seven (11%) and 17 (25%) patients were withdrawn after first and second courses, respectively; nine patients (13%) died in CR and 12 (18%) relapsed. In the aAIDA group, all patients received the assigned treatment; two patients (5%) died in CR and six (15%) relapsed. In the AIDA and aAIDA series, the 3-year overall and discase-free survival rates were 81 and 83% (P=NS), 73 and 72% (P=NS), respectively. We highlight here the frequency and severity of complications linked to intensive chemotherapy in this clinical setting and suggest that, in APL of the elderly, less intensive postremission therapy allows significant reduction of severe treatment-related toxicity and may be equally effective.

Assessment of individual sensitivity to ionizing radiation and DNA repair efficiency in a healthy population.

MARCON F., ANDREOLI C., ROSSI S., VERDINA A., GALATI R., CREBELLI R.

Mutat. Res., 541(1-2), p.1-8, 2003

Inter-individual variation in response to exposure to carcinogens has been ascribed to differences in carcinogen metabolism as well as to variability in DNA repair capacity (DRC). In order to investigate the role of inherited and acquired factors on individual variation in DNA repair capacity, a mutagen sensitivity assay was carried out on 31 healthy subjects. Fresh blood samples were irradiated with gamma-rays (2Gy) and the kinetics of DNA repair in leukocytes assessed by the comet assay 0, 15, and 30 min after irradiation. Whole blood cultures were set up to detect spontaneous and induced structural chromosomal aberrations in lymphocytes 48 h after irradiation. The results obtained were evaluated with respect to age, gender, smoking habits, occupational exposure to chemicals and metabolic genotype (NQO1, GSTM1 and GSTT1) of the study subjects. A higher frequency of radiation-induced aberrations was observed in GSTM1-positive individuals compared with GSTM1-null subjects (P=0.025), as well as in non-smokers compared with heavy smokers (P=0.05). Similar results were obtained by measuring residual DNA damage (RD) shortly after irradiation by means of the comet assay, with non-smokers showing a higher amount of RD compared with smokers (P=0.016). Moreover, a significant correlation (P=0.008) was observed between the amount of RD and the frequency of chromosome breaks after irradiation. The results of this pilot study suggest a modulator effect of smoking habits and GSTM1 genotype on the individual DNA repair capacity, possibly related to the higher expression of enzymes involved in the repair of oxidative DNA damage in heavy smokers and GSTM1-null subjects.

Control of respiration by nitric oxide in Keilin-Hartree particles, mitochondria and SH-SY5Y neuroblastoma cells.

MASTRONICOLA D., GENOVA M.L., ARESE M., BARONE M.C., GIUFFRE A., BIANCHI C., BRUNORI M., LENAZ G., SARTI P.

Cell. Mol. Life Sci., 60(8), p.1752-9, 2003

The pattern of cytochrome c oxidase inhibition by nitric oxide (NO) was investigated polarographically using Keilin-Hartree particles, mitochondria and human neuroblastoma cells. NO reacts with purified cytochrome c oxidase forming either a nitrosyl- or a nitrite-inhibited derivative, displaying distinct kinetics and light sensitivity of respiration recovery in the absence of free NO. Keilin-Hartree particles or cells, respiring either on endogenous substrates alone or in the presence of ascorbate, as well as state 3 and state 4 mitochondria respiring on glutamate and malate, displayed the rapid recovery characteristic of the nitrite derivative. All systems, when respiring in the presence of tetramethyl-p-phenylenediamine, were characterised by the slower, light-sensitive recovery typical of the nitrosyl derivative. Together the results suggest that the reaction of NO with cytochrome c oxidase in situ follows two alternative inhibition pathways, depending on the electron flux through the respiratory chain.

Hyperalgesia: an emerging iatrogenic syndrome.

MERCADANTE S., FERRERA P., VILLARI P., ARCURI E.

J. Pain Symptom Manage., 26(2), p.769-75, 2003

Clinical reports suggest that opioids, intended to abolish pain, can unexpectedly produce hyperalgesia. This paradoxical effect may be mechanistically related to tolerance induced by increasing doses of opioids. Two case reports illustrate a syndrome characterized by increasing pain pursued by escalating opioid doses, which results in a worsening of the clinical picture. Several experimental data may help explain the course of this challenging clinical condition. In escalating opioid doses rapidly, a risk of opioid-induced hyperalgesia should be recognized, as higher doses of opioids may stimulate rather than inhibit the central nervous system by different mechanisms. Alternative procedures should be taken into consideration to break this cycle, should it occur. More data are needed to detect this condition, as currently no diagnostic information on specific markers, clinical or biochemical, exists.

Local anesthetic switching for intrathecal tachyphylaxis in cancer patients with pain.

MERCADANTE S., VILLARI P., FERRERA P., ARCURI E.

Anesth. Analg., 97(1), p.187-9, 2003

Implications: Switching from bupivacaine to lidocaine may improve intrathecal morphine analgesia in advanced cancer patients, possibly because of different spinal mechanisms limiting the hyperalgesic processes.

Neurolytic celiac plexus block (NCPB) is claimed to be an effective method of pain control for pancreatic cancer pain. However, the factors that may influence long-term analgesia, adverse effects, and quality of life after performing NCPB have never been determined. In a prospective multicenter study, 22 patients who underwent NCPB were followed until death. Numerous parameters other than pain and symptom intensity were evaluated, including age, gender, initial site of cancer, sites of pain, possible peritoneal involvement, technique, and oncologic interventions. Indices were calculated to determine the opioid consumption ratio (EAS) and the trend of opioid escalation (OEI). NCPB was effective in reducing opioid consumption and gastrointestinal adverse effects for at least 4 weeks. In the last four weeks prior to death, there was the typical trend of increasing symptom intensity common to the terminal cancer population. None of the factors studied influenced the analgesic effectiveness of NPCB. NPCB, performed by skilled clinicians, regardless of the technique chosen, is a safe and useful means that should be considered as an adjuvant to common analgesic regimens at any stage, as it may allow the reduction of the visceral component of pancreatic pain that may prevail in certain phases of the illness. The analgesic and symptomatic effect of NCPB is presumably advantageous for about four weeks. A possible factor interfering with long-term outcome includes the capacity of cancer to involve the celiac axis, which can distort the anatomy and prevent neurolytic spread, or modify the pain mechanisms. Outcomes are strongly based on individual variation.

Sympathetic blocks and disease progression modifying pain mechanisms.

MERCADANTE S., ARCURI E.

Reg. Anesth. Pain Med., 28(6), p.586-7, 2003

No abstract available

Relevance of cytoplasmic intermediates (MAPK-PI3K) in signal transduction.

MILELLA M.

Tumori, 2(Suppl. 2), p.S35-S36, 2003

No abstract available

Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case-control study.

MILIGI L., COSTANTINI A.S., BOLEJACK V., VERALDI A., BENVENUTI A., NANNI O., RAMAZZOTTI V., TUMINO R., STAGNARO E., RODELLA S., FONTANA A., VINDIGNI C., VINEIS P.

Am. J. Ind. Med., 44(6), p.627-36, 2003

Background: The etiology of non-Hodgkin's lymphoma (NHL) and leukemia is still largely unknown, but exposure to chemicals, in particular pesticides, has been suggested to be a risk factor.

Methods: A large population-based case-control study was conducted in Italy with the aim of investigating the associations between pesticide exposure and NHL, and solvents and leukemia. Data presented in this article refer to 1,575 interviewed cases and 1,232 controls in the nine agricultural study areas.

Results: Exposure to nitro-derivatives and phenylimides among fungicides, hydrocarbon derivatives and insecticide oils among insecticides, and the herbicide amides are the chemical classes observed to be associated with the pathologies under investigation.

Conclusions: The results of the case-control study suggest an increased risk for NHL and leukemia, and some chemical classes of pesticides, although few are statistically significant and

some are based on few exposed cases. The results also show that men and women experience both similar and different risks for the same environmental agricultural exposures.

Increased serum levels of matrix metalloproteinase-9 predict clinical outcome of patients with early B-cell chronic lymphocytic leukaemia.

MOLICA S., VITELLI G., LEVATO D., GIANNARELLI D., VACCA A., CUNEO A., CAVAZZINI F., SQUILLACE R., MIRABELLI R., DIGIESI G.

Eur. J. Haematol., 70(6), p.373-8, 2003

Background and methods: Serum levels of matrix metalloproteinase-9 (MMP-9) which agree with progression in solid and haematological tumours were correlated to the risk of disease progression in 62 patients with early (Binet stage A) B-cell chronic lymphocytic leukaemia (CLL). Sera were taken at diagnosis and tested by an enzyme-linked immunosorbent assay.

Results: MMP-9 levels positively correlated with haemoglobin levels (P = 0.03) and platelet count (P = 0.03). No association was found with main clinico-haematological features representative of tumour mass, such as peripheral blood lymphocytosis, bone marrow histology, Rai substages and beta-2 microglobulin (beta-2m). A cut-off of MMP-9 levels corresponding to 33rd percentile (203 ng/mL) or higher identified earlier upstaging and shorter progression-free survival. MMP-9 was a significant prognostic marker in multivariate analysis and partially independent of Rai substages, which suggests its inclusion into such a staging system to better stratify prognostically Rai stages I and II patients.

Conclusions: MMP-9 serum levels predict disease behaviour and help to refine the prognosis of stage A CLL patients.

Genomic structure and transcriptional regulation of Che-1, a novel partner of Rb.

MONACO L., PASSANANTI C., FANCIULLI M.

Gene, 321, p.57-63, 2003

We recently identified and cloned a novel human gene, Che-1, whose product interacts with both RNA polymerase II and the retinoblastoma gene product (Rb). Furthermore, we found that Che-1 overexpression counteracts the growth inhibitory effects of Rb, regulating in such way both transcription and cell proliferation. In this paper, we describe the genomic organization of the mouse orthologous Che-1 gene and its promoter region. The promoter is TATA less and presents several potential transcription factor-binding motifs. Importantly, we showed that Che-1 expression is regulated by a negative feedback mechanism, in which this protein is present on its own promoter repressing transcription.

Bio-pathological factors of prognostic value in colorectal adenocarcinomas.

MOTTOLESE M., BUGLIONI S., PIPERNO G., SPERDUTI I., GIANNARELLI D., D'ANGELO C., COSIMELLI M.

J. Exp. Clin. Cancer Res., (Suppl. 22), p.163-166, 2003

No abstract available

Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group.

MOURIDSEN H., GERSHANOVICH M., SUN Y., PEREZ-CARRION R., BONI C., MONNIER A., APFFELSTAEDT J., SMITH R., SLEEBOOM H.P., JAENICKE F., PLUZANSKA A., DANK M., BECQUART D., BAPSY PP., SALMINEN E., SNYDER R., CHAUDRI-ROSS H., LANG R., WYLD P., BHATNAGAR A.

J. Clin. Oncol., 21(11), p.2101-9, 2003

Purpose: To analyze overall survival (OS) and update efficacy data for letrozole versus tamoxifen as first-line therapy in postmenopausal women with locally advanced or metastatic breast cancer.

Patients and methods: This multicenter phase III trial randomly assigned 916 patients with hormone receptor-positive or unknown tumors letrozole 2.5 mg (n = 458) or tamoxifen 20 mg (n = 458) daily until disease progression. Optional cross-over was permitted at the treating physician's discretion. This report updates efficacy at a median follow-up of 32 months.

Results: The superiority of letrozole to tamoxifen was confirmed for time to progression (median, 9.4 v 6.0 months, respectively; P <.0001), time to treatment failure (median, 9 v 5.7 months, respectively; P <.0001), overall objective response rate (32% v 21%, respectively; P =.0002), and overall clinical benefit. Median OS was slightly prolonged for the randomized letrozole arm (34 v 30 months, respectively). Although this difference in OS is not significant, survival was improved in the randomized letrozole arm over the first 2 years of the study. Approximately one half of the patients in each arm crossed over. Total duration of endocrine therapy ("time to chemotherapy") was significantly longer (P =.005) for patients initially on letrozole (median, 16 months) than for patients initially on tamoxifen (median, 9 months). Time to worsening of Karnofsky performance score was significantly delayed with letrozole compared with tamoxifen (P =.001).

Conclusion: This study documents the superiority of letrozole over tamoxifen in first-line endocrine therapy in postmenopausal women with advanced breast cancer.

Family history of cancer and risk of ovarian cancer.

NEGRI E., PELUCCHI C., FRANCESCHI S., MONTELLA M., CONTI E., DAL MASO L., PARAZZINI F., TAVANI A., CARBONE A., LA VECCHIA C.

Eur. J. Cancer, 39(4), p.505-10, 2003

The aim of this study was to examine the relationship between history of cancer in first-degree relatives and ovarian cancer risk. Between 1992 and 1999, we conducted a case-control study in Italy on 1031 women with epithelial ovarian cancer and 2411 women admitted to hospital for acute non-neoplastic conditions. Odds ratios (OR) were estimated using unconditional logistic regression, adjusted for age and several potential confounders. Overall, 27 cases and nine controls reported a family history of ovarian cancer (OR = 7.0; 95% confidence interval (CI) 3.1-16). The OR was 23 (95% CI 2.6-212) below age 50 years, based on 10 cases and one control only. The risk of ovarian cancer was also increased in women with a family history of cancer of the stomach (OR = 1.5; 95% CI 1.0-2.1), intestine (OR = 1.7; 95% CI 1.2-2.4), lung (OR = 1.3; 95% CI 1.0-1.8), breast (OR = 2.3; 95% CI 1.7-3.1), lymphomas (OR = 2.3; 95% CI 1.0-5.1) and all sites (OR = 1.6; 95% CI 1.4-1.9). Our results confirm the higher ovarian cancer risk in women with a family history of ovarian and breast cancer, and suggest a few associations with other sites.

The endothelin axis: emerging role in cancer.

NELSON J., BAGNATO A., BATTISTINI B., NISEN P.

Nat. Rev. Cancer, 3(2), p.110-6, 2003

Collectively, the endothelins and their receptors—referred to as the endothelin (ET) axis—have key physiological functions in normal tissue, acting as modulators of vasomotor tone, tissue differentiation, development, cell proliferation and hormone production. Based on new data, the ET axis also functions in the growth and progression of various tumours. Preliminary results from clinical trials, such as those with atrasentan—an ET(A)-receptor antagonist—in prostate cancer, are encouraging. The place of ET-receptor antagonists in cancer therapy for a range of malignancies merits further investigation.

Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response.

PACE A., VIDIRI A., GALIE E., CAROSI M., TELERA S., CIANCIULLI A.M., CANALINI P., GIANNARELLI D., JANDOLO B., CARAPELLA C.M.

Ann. Oncol., 14(12), p.1722-6, 2003

Background: The optimal treatment for low-grade glioma (LGG) is still controversial. Recent data indicate a potential influence of chemotherapy on the natural evolution of these tumors, allowing for the deferral of more aggressive therapies.

Patients and methods: Forty-three patients affected with LGG (29 astrocytoma, four oligodendroglioma and 10 mixed oligo-astrocytoma) were treated with temozolomide (TMZ) at the time of documented clinical and radiological progression. McDonald's response criteria were utilized to evaluate TMZ activity. Thirty patients (69.7%) had previously received radiotherapy; 16 (37.2%) had received prior chemotherapy. Clinical benefit was evaluated measuring seizure control, reduction in steroid dose and modification of Karnofsky performance status and Barthel index. Quality of life was assessed with the QLQ-C30 questionnaire.

Results: We observed a complete response in four patients, 16 partial responses, 17 stable disease

(with four minor response) and six progressive disease. Median duration of response was 10 months [95% confidence interval (CI) 8-12], with a 76% rate of progression free survival (PFS) at 6 months, and a 39% rate of PFS at 12 months. A relevant clinical benefit was observed particularly in patients presenting epilepsy.

Conclusions: The high response rate of 47% (95% CI 31% to 61%) confirms that TMZ chemotherapy is a valid option in the treatment of progressive LGG. The present preliminary results seem interesting and warrant further evaluation of TMZ clinical activity in a larger series of progressive LGG.

Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy.

Pace A., Savarese A., Picardo M., Maresca V., Pacetti U., Del Monte G., Biroccio A., Leonetti C., Jandolo B., Cognetti F., Bove L.

J. Clin. Oncol., 21(5), p.927-31, 2003

Purpose: The aim of this study is to evaluate the neuroprotective effect of antioxidant supplementation with vitamin E in patients treated with cisplatin chemotherapy.

Methods: Between April 1999 and October 2000, forty-seven patients were randomly assigned to either group one, which received vitamin E supplementation during cisplatin chemotherapy, or to group two, which received cisplatin chemotherapy alone. Alpha-tocopherol (vitamin E; 300 mg/d) was administered orally before cisplatin chemotherapy and continued for 3 months after the suspension of treatment. For preclinical studies, nude mice carrying the human melanoma tumor were treated with cisplatin alone or in combination with vitamin E.

Results: Twenty-seven patients completed six cycles of cisplatin chemotherapy: 13 patients in group one and 14 patients in group two. The incidence of neurotoxicity was significantly lower in group one (30.7%) than it was in group two (85.7%; P <.01). The severity of neurotoxicity, measured with a comprehensive neurotoxicity score based on clinical and neurophysiological parameters, was significantly lower in patients who were supplemented with vitamin E than in patients who were not supplemented with vitamin E (2 v 4.7, P <.01). The results of the preclinical studies showed that when cisplatin was combined with vitamin E, no differences were observed in tumor weight inhibition, tumor growth delay, or life span as compared with treatment with cisplatin alone.

Conclusion: Supplementation of patients receiving cisplatin chemotherapy with vitamin E decreases the incidence and severity of peripheral neurotoxicity.

DNA repair enzymes and cytotoxic effects of temozolomide: comparative studies between tumor cells and normal cells of the immune system.

Pagani E., Pepponi R., Fuggetta M.P., Prete S.P., Turriziani M., Bonmassar L., Lacal P.M., Falcinelli S., Passarelli F., Guadagni F., Alvino E., D'Atri S.

J. Chemother., 15(2), p.173-83, 2003

O6-alkylguanine-DNA alkyltransferase (OGAT) and the mismatch repair system (MRS) play a crucial role in the susceptibility of tumor cells to the cytotoxic effects of agents that generate O6-methylguanine in DNA, including the triazene compound temozolomide (TMZ). Studies performed with peripheral blood mononuclear cells (MNC) showed that TMZ was scarcely active on lymphocyte functions not dependent on cell proliferation (e.g. NK activity and cytokine-mediated induction of CD1b molecule in adherent MNC). In contrast, TMZ depressed proliferation and lymphokine activated killer (LAK) cell generation in response to IL-2. In this case, a reasonably good inverse relationship was found between OGAT levels of MNC and their susceptibility to TMZ. This study also analyzed the ratio of the toxic effect of TMZ on MNC and on tumor cells (i.e. "Tumor-Immune Function Toxicity Index", TIFTI). A particularly favorable TIFTI can be obtained when OGAT levels are extremely high in MNC and markedly low in tumor cells. This holds true for MRS-proficient neoplastic cells, but not for MRS-deficient tumors. In conclusion, strategies aimed at modulating OGAT and MRS may improve the clinical response to TMZ. However, the use of OGAT inhibitors to potentiate the antitumor activity of TMZ might result in a concomitant increase of the immunosuppressive effects of the drug, thus reducing the relative TIFTI.

Staging of digestive endocrine tumours using helical computed tomography and somatostatin receptor scintigraphy.

Panzuto F., Falconi M., Nasoni S., Angeletti S., Moretti A., Bezzi M., Gualdi G., Polettini E., Sciuto R., Festa A., Scopinaro F., Corleto V.D., Bordi C., Pederzoli P., Delle Fave G.

Ann. Oncol., 14(4), p.586-91, 2003

Background: In patients with digestive endocrine tumours, complete pre-operative staging is essential in planning proper management and evaluating treatment efficacy. To date, somatostatin receptor scintigraphy (SRS) is considered the 'gold standard' imaging procedure, and very few data are available concerning the use of helical computed tomography (hCT). This study aimed to determine the diagnostic accuracy and the ability to modify the surgical management of hCT, alone or combined with SRS.

Patients and methods: Sixty patients were staged before surgery by hCT, SRS and tumour markers, and included in group 1 if suitable for radical surgery, otherwise in group 2. All patients underwent laparotomy followed by subsequent re-staging.

Results: SRS sensitivity was 77%, 48% and 67% for primary, lymph-node and liver lesions, respectively. hCT sensitivity was 94%, 69% and 94% for primary, lymph-node and liver lesions, respectively (P = 0.02 versus SRS, for liver lesions). During pre-operative evaluation, hCT correctly staged 92% and SRS 75% of patients (P = 0.02). hCT provided additional information in 17% of patients.

Conclusions: Since hCT has been shown to be extremely accurate, providing essential information for the planning of surgical treatment compared with that of SRS, both techniques should be used in the pre-operative work-up of digestive endocrine tumours.

Indicazioni nella pratica clinica della chemioterapia nelle pazienti con tumore della mammella operato con linfonodi negativi.

Papaldo P., Ferretti G.L. Di Cosimo.

Tumori, 2(Suppl. 4), p.S11-S12, 2003

No abstract available

Addition of either lonidamine or granulocyte colony-stimulating factor does not improve survival in early breast cancer patients treated with high-dose epirubicin and cyclophosphamide.

Papaldo P., Lopez M., Cortesi E., Cammilluzzi E., Antimi M., Terzoli E., Lepidini G., Vici P., Barone C., Ferretti G., Di Cosimo S., Nistico C., Carlini P., Conti F., Di Lauro L., Botti C., Vitucci C., Fabi A., Giannarelli D., Marolla P.

J. Clin. Oncol., 21(18), p.3462-8, 2003

Purpose: Lonidamine (LND) can enhance the activity of anthracyclines in patients with metastatic breast cancer. A multicenter, prospective, randomized trial was designed to determine whether the association of LND with high-dose epirubicin plus cyclophosphamide (EC) could improve disease-free survival (DFS) in patients with early breast cancer (BC) compared with EC alone. Granulocyte colony-stimulating factor (G-CSF) was added to maintain the EC dose-intensity.

Patients and methods: From October 1991 to April 1994, 506 patients with stage I/II BC were randomly assigned to four groups: (A) epirubicin 120 mg/m2 and cyclophosphamide 600 mg/m2 administered intravenously on day 1 every 21 days for four cycles (124 patients); (B) EC plus LND 450 mg/d administered orally (125 patients); (C) EC plus G-CSF administered subcutaneously (129 patients); (D) EC plus LND plus G-CSF (128 patients). RESULTS: Median follow-up was 55 months. Five-year DFS rate was similar for LND (B+D groups; 69.6%) versus non-LND arms (A+C groups; 70.3%) and G-CSF (C+D groups; 67.2%) versus non-G-CSF arms (A+B groups; 72.9%). Five-year overall survival (OS) was comparable in LND (79.1%) versus non-LND arms (81.3%) and in G-CSF (80.6%) versus non-G-CSF arms (79.6%). DFS and OS distributions in LND and G-CSF arms did not change according to tumor size, node, receptor, and menopausal status. G-CSF dramatically reduced hematologic toxicity without having a significant impact on dose-intensity (98.1% v 95.5% for C+D and A+B groups, respectively).

Conclusion: EC is active and well tolerated in patients with early breast cancer. The addition of LND or G-CSF does not improve DFS or OS.

Folate intake and risk of oral and pharyngeal cancer.

PELUCCHI C., TALAMINI R., NEGRI E., LEVI F., CONTI E., FRANCESCHI S., LA VECCHIA C.

Ann. Oncol., 14(11), p.1677-81, 2003

Background: Diet has been recognised as having a role in the aetiology of oral and pharyngeal cancer, and dietary factors may account for 10-15% of cases in Europe. Folate deficiency has been linked to risk of several cancers, but has not been studied adequately with respect to oral cancer.

Patients and methods: This case-control study, conducted in Italy and French-speaking Switzerland, included 749 patients with incident cancer of the oral cavity and pharynx, and 1772 hospital controls with acute, non-neoplastic conditions. The interviews used a validated food frequency questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multiple logistic regression.

Results: The ORs were 0.68 (95% CI 0.52-0.88) for the intermediate tertile and 0.53 (95% CI 0.40-0.69) for the highest tertile of dietary folate intake, compared with the lowest tertile. No heterogeneity was found in strata of gender, age, methionine intake or alcohol consumption. The combined OR for low-folate and high-alcohol intake versus high-folate and low-alcohol intake was 22.3 (95% CI 13.1-38).

Conclusions: Our study supports a protective role of folate against oral and pharyngeal carcinogenesis. Compared with low folate intake, a consistent reduction in risk was already observed from intermediate levels of intake, suggesting that cancer risk may be related to relative folate deficiency.

Tyrosinase protects human melanocytes from ROS-generating compounds.

PERLUIGI M., DE MARCO F., FOPPOLI C., COCCIA R., BLARZINO C., MARCANTE M.L., CINI C.

Biochem Biophys Res. Commun., 305(2), p.250-6, 2003

The effects of two tetrahydroisoquinolines (TIQs), tetrahydropapaveroline (THP) and salsolinol (SAL), on human primary melanocytes were studied. These compounds are naturally occurring alkaloids deriving from the condensation of dopamine with aldehydes. The effects on the viability were studied by treating the cells with variable concentration of THP or SAL; both TIQs were well tolerated up to roughly 30 micro M. At higher concentrations, THP became overtly toxic while SAL showed no cytotoxic effect up to 100 micro M. TIQs treatment determined an impairment of intracellular activity of antioxidant enzymes, like SOD, DT-diaphorase, and glutathione peroxidase. A decrease of alpha-ketoglutarate dehydrogenase activity was also evidenced following TIQs treatment; a very strong diminution was found in THP-treated cells, whose viability was highly decreased. Both TIQs increased tyrosinase-specific mRNA transcription followed, in the case of SAL, by an activation of tyrosinase. In the presence of tyrosinase inhibitors TIQs treatment resulted in a sharp cytotoxic effect even at concentrations normally well tolerated. Taken together these data suggest that tyrosinase represents an outstanding protective mechanism against ROS-generating compounds, once primary detoxifying mechanisms are impaired or not available.

High-dose hydroxyurea in the treatment of poor-risk myeloid leukemias.

PETTI M.C., TAFURI A., LATAGLIATA R., ALOE SPIRITI M.A., MONTEFUSCO E., MANCINI M., MELONI G., PETRUCCI M.T., SPADEA A., REDI R., ALIMENA G., MANDELLI F.

Ann. Hematol., 82(8), p.476-80, 2003

The aim of the study was to evaluate the antileukemic effectiveness and toxicity of high-dose hydroxyurea (HHY) and to assess its acute toxicity. Between August 1997 and October 1998, 12 consecutive adult patients (>18 years) with high-risk acute myeloid leukemia (AML) (four patients in first early relapse, seven patients with secondary AML, and one patient with de novo AML concomitant to a lymphoproliferative disorder) were enrolled to receive a single course of HY (100 mg/kg per day) until bone marrow aplasia or for a maximum of 30 days. Of the 12 patients, 5 (41.6%) achieved complete remission (CR), 1 achieved partial remission (PR), 4 were resistant to treatment, and 2 died during induction from infection. No patient with relapsed AML achieved CR, while it was

achieved by five of eight patients with secondary AML at diagnosis; five of six MDR1+ patients achieved CR. As concerns follow-up of the CR patients, one did not receive any further treatment and died in CR from pulmonary aspergillosis, and one with a concomitant chronic lymphocytic leukemia (CLL) received two courses of FLAG (fludarabine, cytarabine, granulocyte colony-stimulating factor) regimen with disappearance of the clonal Ig rearrangement, but relapsed after 11 months and died from pneumonia. The remaining three patients were consolidated with two courses of high-dose cytosine arabinoside (AraC), followed by peripheral blood stem cell transplantation (PBSCT) in one patient. One of them relapsed after 3 months, while the other two are still in continuous complete remission (CCR) after 16 and 28 months, respectively. This study has demonstrated the safety and efficacy of HHY in inducing CR in AML patients with unfavorable prognosis. Despite the small number of patients, these encouraging results warrant further studies.

Specificity of antinuclear and antiphospholipid antibodies in sera of patients with autoimmune lymphoproliferative disease (ALD).

PITTONI V., SORICE M., CIRCELLA A., CANGEMI R., CONTI L., RAMENGHI U., GANDOLFO G.M., DIANZANI U., VALESINI G.

Clin. Exp. Rheumatol., 21(3), p.377-85, 2003

Objective: A human lymphoproliferative syndrome characterized by a defect of the Fas-mediated apoptosis pathway in the absence of a fas gene mutation (Autoimmune Lymphoproliferative Disease) has recently been described and characterized by autoimmune phenomena. The aim of this study was to investigate the presence of antinuclear and antiphospholipid antibodies and to define their specificity in 5 pediatric patients with this syndrome.

Methods: Antinuclear antibodies were investigated by Western Blot and IIF performed under standard as well as apoptotic conditions. The fine specificity of antiphospholipid antibodies was dissected by an ELISA for anti-beta 2-glycoprotein I, anti-prothrombin, anti-annexin V and anti-protein S antibodies, and by immunostaining on thin layer chromatography plates for antiphospholipid molecule antibodies.

Results: This study showed that the autoantibodies found in these patients targeted a broad spectrum of nuclear antigens which undergo redistribution from the nucleus to the cytoplasm and plasma membrane during the course of the apoptotic process. This reactivity does not comprise known specificities such as anti-extractable nuclear antigens or anti-dsDNA. Antiphospholipid antibodies were also found in these sera. A further characterization of the antiphospholipid antibodies showed the presence of a heterogeneous response with antibodies directed to negatively-charged phospholipids and antibodies targeting coagulation-related proteins (beta 2-GPI, prothrombin, annexin V) which are considered relevant antigens in the antiphospholipid syndrome.

Conclusions: These results suggest that lack of tolerance due to a defect of Fas-mediated apoptosis allows the survival of B and T clones involved in the antinuclear and antiphospholipid immune responses.

Ret/PTC activation does not influence clinical and pathological features of adult papillary thyroid carcinomas.

PUXEDDU E., MORETTI S., GIANNICO A., MARTINELLI M., MARINO C., AVENIA N., CRISTOFANI R., FARABI R., REBOLDI G., RIBACCHI R., PONTECORVI A., SANTEUSANIO F.

Eur. J. Endocrinol., 148(5), p.505-13, 2003

Objective: RET proto-oncogene rearrangements (ret/PTCs) represent the most common genetic alterations found in papillary thyroid carcinomas (PTCs). Correlation of ret/PTC expression with clinical outcome is controversial. The aim of the present study was to analyze the frequency of RET rearrangements in adult PTCs, and to investigate if ret/PTCs influence biological behavior and clinical features of the cancers.

Design: Ret/PTC rearrangements were looked for in tIssue samples of 48 PTCs collected at our institution. Data about clinical and pathological features of the tumors were also reviewed. Three separate association analyses were carried out on the cohort evaluating the effects of, respectively, ret/PTC positivity, preferential RET tyrosine kinase domain (RET-TK) expression, and ret/PTC plus RET-TK positivity, on age, sex, tumor size, staging, number of neoplastic foci, and histological subtype.

Methods: The genetic study was conducted with the RT-PCR-Southern blot technique. Standard Student's t-test and Fisher exact test were applied for the association analyses. RESULTS: The molecular genetic study demonstrated the positivity of ret/PTC1 and ret/PTC3 in 13 of 48 tumors (27.1%), and an exclusive or preferential RET-TK expression in 17 cases (35.4%). None of the three genetico-clinical analyses showed any significant association between ret/PTC expression and the clinical and pathological features of the cancers.

Conclusions: These data indicate that RET rearrangements may not play any distinctive role in driving histotype development and cancer progression in these neoplasms. Moreover, they weaken the possibility of using ret/PTC as a prognostic marker for papillary thyroid carcinomas.

Prostate cancer in Italy before and during the 'PSA era': survival trend and prognostic determinants.

QUAGLIA A., VERCELLI M., PUPPO A., CASELLA C., ARTIOLI E., CROCETTI E., FALCINI F., RAMAZZOTTI V., TAGLIABUE G.; PROSTATE WORKING GROUP.

Eur. J. Cancer Prev., 12(2), p.145-52, 2003

The aim of the study was to investigate the variations in prostate cancer prognosis during a period of major diagnostic change, such as the introduction of the prostate-specific antigen (PSA) test. Data were provided by 14 Italian cancer registries (CRs). Incidence and follow-up information was collected for patients diagnosed from 1978 to 1994. Relative survival was computed taking into account incidence period, age, tumour stage and grade at diagnosis. A multivariate analysis was carried out to evaluate the independent simultaneous effect on survival of some prognostic determinants. A large geographical variability was observed: in 1993-1994 Italian survival rates ranged from 76% to 52%, with a north-south gradient. A striking prognostic improvement (up to +27 percentage points) between the late 1980s and the early 1990s occurred in almost all CRs, particularly with regard to younger patients. Multivariate analysis showed a strong influence of incidence period on survival, also after correction by tumour stage. The slowdown of metastatic cancers suggests that the survival improvement could be due both to the introduction of an effective opportunistic screening and to a quantitative change in the application of clinical treatment, even if the effect of the lead-time bias phenomenon has to be taken into account.

Rapid modification of aggressiveness of a primary non-Hodgkin lymphoma of uterine cervix.

QUATTRINI M., DEL NONNO F., PACETTI U., VISCA P., ATLANTE M., BRENNA A., ROMAGNOLI F., MARANDINO F., SBIROLI C., MARIANI L.

J. Exp. Clin. Cancer Res., 22(4), p.633-5, 2003

Primary malignant lymphoma of the uterine cervix is an extremely rare condition, with only about 100 cases reported in international literature. The diagnosis can be difficult, as stated by some authors finding only 10 up to 40% of cases of cervical lymphoma diagnosed by positive cytology. We present a case of primary malignant lymphoma of the cervix in a 57 year old woman treated at the Department of Gynecological Oncology at the Regina Elena Cancer Institute in Rome, with a sudden and unfavorable outcome.

Electronic availability of EUROCARE-3 data: a tool for further analysis.

ROAZZI P., CAPOCACCIA R., SANTAQUILANI M., CARRANI E.; THE EUROCARE WORKING GROUP. (CONTI E.M.S.).

Ann. Oncol., 14 (Suppl. 5), p.V150-V155, 2003

No abstract available

Endothelin receptor blockade inhibits molecular effectors of Kaposi's sarcoma cell invasion and tumor growth in vivo.

Rosano L., Spinella F., Di Castro V., Nicotra M.R., Albini A., Natali P.G., Bagnato A.

Am. J. Pathol., 163(2), p.753-62, 2003

Endothelin-1 (ET-1) and its receptors are overexpressed in human Kaposi's sarcoma lesions. Here we show that in human KS IMM cell line ET-1 increased secretion and activation of matrix-metalloproteinase-2 (MMP-2), -3, -7, -9 and -13, as well as of membrane-type 1-MMP (MT1-MMP). ET-1 and ET-3 also enhanced the expression of tissue inhibitor of MMP-2, essential for MT1-MMP-mediated MMP-2 activation. Combined addition of both ET(B) receptor (ET(B)R) and ET(A)R antagonists completely blocked the ET-1-induced MMP activity. By immunohistochemistry, we observed that ET-1 increased MMP-2 and MT1-MMP expression and their localization at the cell surface. Treatment with both antagonists resulted also in the suppression of ET-1-induced phosphorylation of focal adhesion proteins, FAK and paxillin, which are essentials for cell motility. ET-1 induced a dose-dependent enhancement in KS IMM cell migration and MMP-dependent invasiveness that were inhibited by ET-1 receptor antagonists. The small molecule, A-182086, an orally bioavailable ET(A/B)R antagonist, completely inhibited cell proliferation and tumor growth in KS IMM xenografts. These findings demonstrate that ET-1-driven autocrine loop is crucial for enhanced invasiveness of KS IMM cells and promote tumor growth in vivo. Such activities can be blocked by the ET(A/B)R antagonists, which may be effective anti-angiogenic and anti-tumor molecules for the treatment of Kaposi's sarcoma.

Therapeutic targeting of the endothelin a receptor in human ovarian carcinoma.

Rosano L., Spinella F., Salani D., Di Castro V., Venuti A., Nicotra M.R., Natali P.G., Bagnato A.

Cancer Res., 63(10), p.2447-53, 2003

The endothelin A receptor (ET(A)R) autocrine pathway is overexpressed in many malignancies, including ovarian carcinoma. In this tumor, engagement of ET(A)R triggers tumor growth, survival, neoangiogenesis, and invasion. To evaluate whether ET(A)R represents a new target in cancer treatment, we examine in vitro and in vivo the effect of the selective ET(A)R antagonist ABT-627 (atrasentan), a small p.o. bioavailable molecule, in mono- and combination therapy with taxane. ABT-627 effectively inhibits cell proliferation, vascular endothelial growth factor (VEGF) secretion of ovarian carcinoma cell lines, and primary cultures. ET(A)R blockade also results in the sensitization to paclitaxel-induced apoptosis. In ovarian carcinoma xenografts, in which the ET-1/ET(A)R autocrine pathway is overexpressed, tumor growth was significantly inhibited in ABT-627-treated mice compared with control. The therapeutic efficacy of ABT-627 was associated with a significant reduction in microvessel density, expression of VEGF, and matrix metalloproteinase-2, and increased the percentage of apoptotic tumor cells. Combined treatment of ABT-627 with paclitaxel produced additive antitumor, apoptotic, and antiangiogenic effects. These findings demonstrate that the small molecule ABT-627 is a candidate for clinical testing as an antitumor agent in ovarian cancer patients, especially in combination with taxane therapy. Interruption of ET(A)R signaling therefore, represents, a promising therapeutic strategy in ovarian carcinoma.

Transcripts in pretreatment biopsies from a three-arm randomized trial in metastatic non-small-cell lung cancer.

Rosell R., Scagliotti G., Danenberg K.D., Lord R.V., Bepler G., Novello S., Cooc J., Crino L., Sanchez J.J., Taron M., Boni C., De Marinis F., Tonato M., Marangolo M., Gozzelino F., Di Costanzo F., Rinaldi M., et al.

Oncogene, 22(23), p.3548-53, 2003

Non-small-cell lung cancer patients with locally advanced or metastatic disease at the time of diagnosis show marginal response to chemotherapy in terms of tumor shrinkage, time to progression and median survival. The identification and implementation of predictive genetic markers of response-specific cytotoxic drugs is a priority of current research and future trials. In this study, we have used quantitative PCR to analyse expression of beta-tubulin III, stathmin, RRM1, COX-2 and GSTP1 in mRNA isolated from paraffin-embedded tumor biopsies of 75 nonsmall-cell lung cancer patients treated as part of a large randomized trial. In total, 22 patients were treated with gemcitabine/cisplatin, 25 with vinorelbine/cisplatin and 28 with paclitaxel/carboplatin. There were

no differences in clinical characteristics and transcript levels in the pretreatment biopsies according to treatment arm. Patients with low beta-tubulin III levels had better response in the paclitaxel/carboplatin arm (P=0.05), and those with low RRM1 levels showed a tendency to better response in the gemcitabine/cisplatin arm. Time to progression was influenced by beta-tubulin III (P=0.03) and stathmin (P=0.05) levels in the vinorelbine/cisplatin arm, and there was a tendency toward correlation between beta-tubulin III levels and time to progression in the paclitaxel/carboplatin arm. RRM1 levels influenced time to progression (P=0.05) and even more so, survival (P=0.0028) in the gemcitabine/cisplatin arm. The predictive value of beta-tubulin III, stathmin and RRM1 should be tested in prospective customized chemotherapy trials, the results of which will help tailor chemotherapy to improve patient survival.

Association between serum carcinoembryonic antigen and endothelial cell adhesion molecules in colorectal cancer.

ROSELLI M., GUADAGNI F., MARTINI F., SPILA A., MARIOTTI S., D'ALESSANDRO R., ALOE S., GAZZANIGA P.P., BASILI S., COSIMELLI M., FERRONI P.

Oncology, 65(2), p.132-8, 2003

Objectives: To analyse the behaviour of pre-surgical serum levels of soluble (s)E-selectin and vascular cell adhesion molecule (sVCAM) in patients with colorectal cancer, and to evaluate their possible correlation with carcinoembryonic antigen (CEA), pro-inflammatory cytokines and clinico-pathological features with respect to their prognostic value in predicting metastatic disease.

Methods: Pre-surgical serum levels of sE-selectin, sVCAM, interleukin-6 (IL-6), IL-1beta, tumour necrosis factor-alpha (TNF-alpha) and CEA were measured in 194 patients with colorectal adenocarcinoma, 40 patients with benign colorectal diseases and 59 healthy subjects.

Results: sE-selectin, sVCAM, TNF-alpha and IL-6 levels were significantly higher in patients with colorectal cancer compared to either healthy subjects or patients with benign disease. Positive rates of sE-selectin, sVCAM and TNF-alpha levels were significantly associated with Dukes' stage D colorectal cancer, and all three variables were independently associated to the presence of distant metastases. Positive sE-selectin, sVCAM and TNF-alpha levels were significantly associated to CEA. TNF-alpha and CEA levels were independently related to the presence of positive levels of sE-selectin and/or sVCAM.

Conclusions: Our findings suggest that the host inflammatory response to cancer cells, and/or their released products (i.e. CEA), might be responsible (via cytokine release) for the elevation in circulating adhesion molecules in patients with colorectal cancer.

Vascular endothelial growth factor (VEGF-A) plasma levels in non-small cell lung cancer: relationship with coagulation and platelet activation markers.

ROSELLI M., MINEO T.C., BASILI S., MARIOTTI S., MARTINI F., BELLOTTI A., AMBROGI V., SPILA A., D'ALESSANDRO R., GAZZANIGA P.P., GUADAGNI F., FERRONI P.

Thromb. Haemost., 89(1), p.177-84, 2003

Platelet activation, commonly found in lung cancer patients, may cause the release of angiogenic factors, such as vascular endothelial growth factor (VEGF-A). The present study was designed to investigate whether plasma VEGF-A levels were associated to different stages of non-small cell lung cancer (NSCLC). Moreover, sP-selectin, prothrombin fragment 1+2 (F1+2), thrombin-antithrombin III complex (TATc) and D-dimer levels were measured to test the hypothesis of an involvement of platelet and coagulation activation in tumor angiogenesis. VEGF-A, sP-selectin, F1+2, TATc and D-dimer levels were elevated in 65 patients with NSCLC, particularly in metastatic patients. sP-selectin ($p < 0.003$) and F1+2 ($p < 0.005$) levels were independently associated to VEGF-A. In addition, patients with positive levels of both sP-selectin and F1+2 had the highest levels of VEGF-A. In conclusion, our findings support the hypothesis that thrombin generation might induce platelet activation and VEGF-A release in NSCLC

EUROCARE-3: survival of cancer patients diagnosed 1990-94- results and commentary.

SANT M., AARELEID T., BERRINO F., BIELSKA LASOTA M., CARLI P.M., FAIVRE J., GROSCLAUDE P., HEDELIN G., MATSUDA T., MOLLER H., MOLLER T., VERDECCHIA A., CAPOCACCIA R., GATTA G., MICHELI A., SANTAQUILANI M., ROAZZI P., LISI D.; THE EUROCARE WORKING GROUP. (CONTI E.)

Ann. Oncol., 14 (Suppl 5), p.V61-V118, 2003

No abstract available

Gastric cancer in elderly and young patients: a Western experience.

SANTORO R., CARLINI M., CARBONI F., BOSCHETTO A., LEPIANE P., SPERDUTI I., SANTORO E.

Tumori, 89(Suppl. 4), p.138-40, 2003

No abstract available

Delayed massive arterial hemorrhage after pancreaticoduodenectomy for cancer. Management of a life-threatening complication.

SANTORO R., CARLINI M., CARBONI F., NICOLAS C., SANTORO E.

Hepatogastroenterology, 50(54), p.2199-204, 2003

Background/aims: Delayed massive arterial hemorrhage from the operating field occurs in 1-4% of cases after pancreaticoduodenectomy, with a mortality rate up to 50%. The purpose of this study was to define diagnostic and treatment methodologies to maximize survival.

Methodology: Between 1990 and 1999, 84 pancreaticoduodenectomies were performed for periampullary and pancreatic head cancer. After surgery, massive bleeding occurred in two patients (2.3%), 30 and 8 days after resection, respectively.

Results: Pancreatic leak and disruption of the pancreaticojejunostomy were reported in both cases. Bleeding was controlled by suture ligation of the stump of the gastroduodenal artery. Completion pancreatectomy and a new pancreaticojejunostomy were respectively performed. Hemorrhage recurred in both cases from a ruptured pseudoaneurysm of the hepatic artery, requiring re-exploration and surgical ligation. The first patient died of re-bleeding despite completion pancreatectomy, the other survived after oversewing the residual pancreatic stump at re-exploration.

Conclusions: Early diagnosis and management of pancreatic leak represents the only means to prevent a delayed massive arterial hemorrhage. Transarterial embolization or surgical ligation of the hepatic artery proximal to the celiac axis represents the procedure of choice to control the bleeding. Taking down the pancreatic anastomosis and oversewing the pancreatic stump is safe and effective. Extensive drainage of the operating field should always be associated to prevent multisystem organ failure.

Cutaneous response to irritants.

SANTUCCI B., CANNISTRACI C., LESNONI I., FERRARO C., ROCCO M.G., DELL'ANNA L., GIANNARELLI D., CRISTAUDO A.

Contact Dermatitis, 48(2), p.69-73, 2003

We evaluated the role of pre-existing dermatitis in the response to irritants by patch testing the skin of 40 healthy volunteers and the uninvolved skin of 480 subjects for 2 days. These latter were affected by active atopic dermatitis, psoriasis, eczema with positive and negative patch test reactions, urticaria and generalized pruritus. A first panel containing 15 micro L of aq. solutions of disodium laureth sulfosuccinate (NaLSS) 5% and 10%, potassium cocoate (KCC) 5%, potassium oleate (KOL) 5%, zinc coleth sulphate (ZnCS) 5%, sodium mireth sulphate (NaMS) 5%, sodium cocoamphoacetate (NaCCAA) 3% and 5%, was simultaneously applied to 1 site on the upper back. The results, scored by visual assessment, were compared to those observed when testing on the opposite side a second panel containing 15 micro L of aq. solutions of 3 well-known irritants, benzalkonium chloride (BAK) 1%, sodium lau-

ryl sulphate (SLS) 1%, and dimethylsulphoxide (DMSO) 10%. Whilst the substances of the first panel and DMSO gave, on the whole, a scarce number of positive responses in all the tested groups, more evident differences in number, percent and mean intensity of the positive responses to BAK and SLS were found between the different groups. Although some of them seemed statistically significant, when the same values were evaluated by means of chi2 and Student t-test, they did not differ in a statistically significant way from the values found in healthy subjects. The results of this study seem to indicate that the substances of the first panel have a chemical structure that makes them quite safe in real-life conditions. In contrast, BAK and SLS have chemical properties that condition the number and intensity of the responses, making the role exerted by the pre-existing dermatosis quite marginal. In particular, there is no proof that the healthy skin of active atopic subjects is the most susceptible to the irritating effects of the tested substances.

Nitric oxide and mitochondrial complex IV.

Sarti P., Arese M., Bacchi A., Barone M.C., Forte E., Mastronicola D., Brunori M., Giuffre A.

IUBMB Life, 55(10-11), p.605-11, 2003

Micromolar nitric oxide (NO) rapidly (ms) inhibits cytochrome c oxidase in turnover with physiological substrates. Two reaction mechanisms have been identified leading, respectively, to formation of a nitrosyl- [a3(2+) -NO] or a nitrite- [a3(3+) -NO2-] derivative of the enzyme. In the presence of O2, the nitrosyl adduct recovers activity slowly, following NO displacement at k' approximately equal to 0.01 s(-1) (37 degrees C); the recovery of the nitrite adduct is much faster. Relevant to pathophysiology, the enzyme does not degrade NO by following the first mechanism, whereas by following the second one it promotes NO oxidation and disposal as nitrite/nitrate. The reaction between NO and cytochrome c oxidase has been investigated at different integration levels of the enzyme, including the in situ state, such as in mouse liver mitochondria or cultured human SY5Y neuroblastoma cells. The respiratory chain is inhibited by NO, either supplied exogenously or produced endogenously via the NO synthase activation. Inhibition of respiration is reversible, although it remains to be clarified whether reversibility is always full and how it depends on concentration of and time of exposure to NO. Oxygraphic measurements show that cultured cells or isolated state 4 mitochondria exposed to micromolar (or less) NO recover from NO inhibition rapidly, as if the nitrite reaction was predominant. Mitochondria in state 3 display a slightly more persistent inhibition than in state 4, possibly due to a higher accumulation of the nitrosyl adduct. Among a number of parameters that appear to control the switch over between the two mechanisms, the concentration of reductants (reduced cytochrome c) at the cytochrome c oxidase site has been proved to be the most relevant one.

New drugs in the treatment of recurrent or metastatic cervical cancer.

Savarese A., Cognetti F.

Crit. Rev. Oncol. Hematol., 48(3), p.323-7, 2003

Cervical cancer is the second major cause of death in women. In locally-advanced or refractory cervical cancer, cisplatin-based chemotherapy still represents the best chance of cure, although chemotherapy in these patients usually results in excessive toxicity and short duration of response. Newly developed chemotherapy agents, widely used in other cancers, have been employed as single agents and in combination with cisplatin in the treatment of locally advanced or recurrent cervical cancer. Several phase II-studies have been performed in order to assess the effectiveness of gemcitabine, paclitaxel, vinorelbine and camptothecines in cervical cancer. When used as single agents, these compounds have an overall response rate (ORR) of 8-25%. Cisplatin-combined regimens may offer improved efficacy, with a ORR between 41 and 60%. Toxicity remains the more limiting factor in the treatment of irradiated or pretreated patients. New targets must be identified for innovative therapeutic approaches that could improve the response rate and survival of cervical cancer patients.

Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer.

Scagliotti G.V., Fossati R., Torri V., Crino L., Giaccone G., Silvano G., Martelli M., Clerici M., Cognetti F., Tonato M.; Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer-Lung Cancer Cooperative Group Investigators.

J. Natl. Cancer Inst., 95(19), p.1453-61, 2003

Background: Surgery is the primary treatment for patients with stage I, II, or IIIA non-small-cell lung cancer (NSCLC). However, long-term survival of NSCLC patients after surgery alone is largely unsatisfactory, and the role of adjuvant chemotherapy in patient survival has not yet been established.

Methods: Between January 1994 and January 1999, 1209 patients with stage I, II, or IIIA NSCLC were randomly assigned to receive mitomycin C (8 mg/m2 on day 1), vindesine (3 mg/m2 on days 1 and 8), and cisplatin (100 mg/m2 on day 1) every 3 weeks for three cycles (MVP group; n = 606) or no treatment (control group; n = 603) after complete resection. Randomization was stratified by investigational center, tumor size, lymph-node involvement, and the intention to perform radiotherapy. The primary endpoint was overall survival and secondary endpoints were progression-free survival and toxicity associated with adjuvant treatment. Survival curves were analyzed using the log-rank test. All statistical tests were two-sided.

Results: After a median follow-up time of 64.5 months, there was no statistically significant difference between the two patient groups in overall survival (hazard ratio = 0.96, 95% confidence interval = 0.81 to 1.13; P =.589) or progression-free survival (hazard ratio = 0.89, 95% confidence interval = 0.76 to 1.03; P =.128). Only 69% of patients received the three planned cycles of MVP. Grades 3 and 4 neutropenia occurred in 16% and 12%, respectively, of patients in the MVP arm. Radiotherapy was completed by 65% of patients in the MVP arm and by 82% of patients in the control group. In the multivariable analysis, only disease stage and sex were associated with survival.

Conclusion: This randomized trial failed to prospectively confirm a statistically significant role for adjuvant chemotherapy in completely resected NSCLC. Given the poor compliance with the MVP regimen used in this study, future studies should explore more effective treatments.

Transgenic mice with dominant negative PKC-theta in skeletal muscle: a new model of insulin resistance and obesity.

Serra C., Federici M., Buongiorno A., Senni M.I., Morelli S., Segratella E., Pascuccio M., Tiveron C., Mattei E., Tatangelo L., Lauro R., Molinaro M., Giaccari A., Bouche M.

J. Cell. Physiol., 196(1), p.89-97, 2003

Protein kinase C theta (PKC-theta) is the PKC isoform predominantly expressed in skeletal muscle, and it is supposed to mediate many signals necessary for muscle histogenesis and homeostasis, such as TGFbeta, nerve-dependent signals and insulin. To study the role of PKC-theta in these mechanisms we generated transgenic mice expressing a "kinase dead" mutant form of PKC-theta (PKC-thetaK/R), working as "dominant negative," specifically in skeletal muscle. These mice are viable and fertile, however, by the 6-7 months of age, they gain weight, mainly due to visceral fat deposition. Before the onset of obesity (4 months of age), they already show increased fasting and fed insulin levels and reduced insulin-sensitivity, as measured by ipITT, but normal glucose tolerance, as measured by ipGTT. After the 6-7 months of age, transgenic mice develop hyperinsulinemia in the fasting and fed state. The ipGTT revealed in the transgenic mice both hyperglycemia and hyperinsulinemia. At the molecular level, impaired activation of the IR/IRS/PI3K pathway and a significant decrease both in the levels and in insulin-stimulated activation of the serine/threonine kinase Akt were observed. Taken together these data demonstrate that over-expression of dominant negative PKC-theta in skeletal muscle causes obesity associated to insulin resistance, as demonstrated by defective receptor and post-receptorial activation of signaling cascade.

Endothelin-1 decreases gap junctional intercellular communication by inducing phosphorylation of connexin 43 in human ovarian carcinoma cells.

Spinella F., Rosano L., Di Castro V., Nicotra M.R., Natali P.G., Bagnato A.

J. Biol. Chem., 278(42), p.41294-301, 2003

Endothelin-1 (ET-1) is overexpressed in ovarian carcinoma and acts as an autocrine factor selectively through the ETA receptor (ETAR) to promote tumor cell proliferation, survival, neovascularization, and invasiveness. Loss of gap junctional intercellular communication (GJIC) is critical for tumor progression by allowing the cells to escape growth control. Exposure of HEY and OVCA 433 ovarian carcinoma cell lines to

ET-1 led to a 50-75% inhibition in intercellular communication and to a decrease in the connexin 43 (Cx43)-based gap junction plaques. To investigate the phosphorylation state of Cx43, ovarian carcinoma cell lysates were immunoprecipitated and transient tyrosine phosphorylation of Cx43 was detected in ET-1-treated cells. BQ 123, a selective ETAR antagonist, blocked the ET-1-induced Cx43 phosphorylation and cellular uncoupling. Gap junction closure was prevented by tyrphostin 25 and by the selective c-Src inhibitor, PP2. Furthermore, the increased Cx43 tyrosine phosphorylation was correlated with ET-1-induced increase of c-Src activity, and PP2 suppressed the ET-1-induced Cx43 tyrosine phosphorylation, indicating that inhibition of Cx43-based GJIC is mainly mediated by the Src tyrosine kinase pathway. In vivo, the inhibition of human ovarian tumor growth in nude mice induced by the potent ETAR antagonist, ABT-627, was associated with a reduction of Cx43 phosphorylation. These findings indicate that the signaling mechanisms involved in GJIC disruption on ovarian carcinoma cells depend on ETAR activation, which leads to the Cx43 tyrosine phosphorylation mediated by c-Src, suggesting that ETAR blockade may contribute to the control of ovarian carcinoma growth and progression also by preventing the loss of GJIC.

Tumori del cavo orale dell'orofaringe: nuove tecniche ricostruttive della mandibola.

SPRIANO G., RUSCITO P., MORELLO R., PELLINI R.

Tumori, 2(Suppl. 4), p.S57-S60, 2003

No abstract available

Potentiation of chemotherapy in companion animals with spontaneous large neoplasms by application of biphasic electric pulses.

SPUGNINI E.P., AND PORRELLO A.

J. Exp. Clin. Cancer Res., 22(4), p.571-80, 2003

The objectives of this phase I/II study were: i) to determine whether electrochemotherapy (intralesional bleomycin + electric pulses) could be effective in companion animals with different, large neoplasms compared to chemotherapy (conventional intralesional bleomycin); ii) to identify potential toxicities; iii) to preliminarily assess the electric field requirements. Twenty-two patients received intralesional bleomycin + administration of permeabilizing electric pulses. Specifically, after the injection of the drug, sequences of 8 biphasic electric pulses lasting 50 + 50 micros each, with 1 ms interpulse intervals, were delivered in bursts of 1300 V/cm for cutaneous and soft tissue lesions, and of 800 V/cm for oral mucosal and exposed soft tissue neoplasms, using caliper electrodes. The treatment was well tolerated and side effects were infrequent. Nevertheless, two previously unreported toxicities (drug-induced vasculitis and pulmonary thromboembolism) have been identified. A high response rate (complete remission + partial remission: > 80%), often long lasting (> 40%) was obtained. Furthermore, results of this trial were compared to a subset of veterinary cancer patients treated with bleomycin single agent, observing a remarkable superiority of the combined treatment ($p < 0.01$). Altogether, results suggest that electrochemotherapy is a potentially advantageous rescue protocol for bulky, even relapsing neoplasms of companion animals. Further investigations in this field might allow developing improved protocols for the treatment of down-staged relapsing cancer in pets as well as in humans.

Cancer-related fatigue: evolving concepts in evaluation and treatment.

STASI R., ABRIANI L., BECCAGLIA P., TERZOLI E., AMADORI S.

Cancer, 98(9), p.1786-801, 2003

Background: Although fatigue is one of the most common complaints of patients with cancer, it went unrecognized or overlooked for many years, until clinicians achieved better control over the more acute symptoms of nausea, emesis, and pain. A number of treatment-related and disease-related factors may contribute to the development of fatigue, but its physiologic basis remains poorly understood, and many proposed interventions have not been studied systematically. The lack of a standard of care for the assessment or treatment of fatigue in patients with cancer has limited research in this field. A critical appraisal of these issues is presented in this review.

Methods: The published literature was reviewed for definition, prevalence, causes, and means of managing cancer-related fatigue (CRF).

Results: Fatigue was reportedly present at the time of diagnosis in approximately 50-75% of cancer patients. The prevalence of CRF increased to 80-96% in patients undergoing chemotherapy and to 60-93% in patients receiving radiotherapy. Two tested interventions that showed consistent effects to alleviate CRF were treatment of cancer-related anemia with erythropoietin agents (recombinant human erythropoietin and darbepotin alpha) and aerobic exercise.

Conclusions: Several lines of research are needed to bridge the specific gaps in the current knowledge of CRF. These involve the pathophysiology of the symptom, the validation of diagnostic criteria, and specific therapeutic interventions. Current practice guidelines are based on a combination of research and expert clinical judgment and should be used to guide care with the expectation that they will evolve to incorporate the results of studies currently underway.

Can patient selection for bladder preservation be based on response to chemotherapy?

Sternberg C.N., Pansadoro V., Calabro F., Schnetzer S., Giannarelli D., Emiliozzi P., De Paula F., Scarpone P., De Carli P., Pizzo M., et al.

Cancer, 97(7), p.1644-52, 2003

Background: Neoadjuvant chemotherapy for patients with muscle-invasive bladder carcinoma is given to treat micrometastases and to preserve the bladder. The objective of this study was to evaluate the possibility of bladder preservation in patients with muscle-invasive bladder carcinoma who were treated with neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) chemotherapy.

Methods: One hundred four consecutive patients with T2-T4,N0,M0 transitional cell carcinoma of the bladder were treated with 3 cycles of neoadjuvant M-VAC chemotherapy. After clinical restaging, 52 patients underwent transurethral resection of the bladder (TURB) alone, 13 patients underwent partial cystectomy, and 39 patients underwent radical cystectomy.

Results: The median survival for the entire group was 7.49 years (95% confidence interval, 4.86-10.0 years). Forty-nine patients (49%) were T0 at the time of TURB after receiving M-VAC. Thirty-one of 52 patients (60%) who received chemotherapy and underwent TURB alone were alive at a median follow-up of 56 + months (range, 10-160 + months): Twenty-three patients (44%) in that TURB group maintained an intact bladder. Of 13 responding patients with monofocal lesions who underwent partial cystectomy, only 1 patient required salvage cystectomy, and survival generally was good. The 5-year survival rate for this group was 69%. With a long median follow-up of 88 + months (range, 16-158 months), 4 patients (31%) were alive with a functioning bladder. In the radical cystectomy group, the median follow-up was 45 months (range, 4-172 + months), and 15 of 39 patients (38%) patients remained alive. In 77 patients who had their tumors down-staged to T0 or superficial disease, the median follow-up was 63 months (range, 4-172 + months), and the 5-year rate survival was 69%. This is in contrast to a 5-year survival rate of only 26% in 27 patients who failed to respond and had a status >/= T2 after receiving chemotherapy (median follow-up, 31 months; range, 7-156 + months). The median survival for 27 elderly patients (age >/= 70 years; median age, 73 years; range, 70-82 years) was 90 months (7.5 years). For elderly patients who underwent TURB and partial cystectomy, the 5-year survival rate was 67% with a 109-month (9-year) median survival; 47% of patients preserved their bladders intact. The median follow-up of the living elderly patients was 61 months (range, 20-120 + months).

Conclusions: Bladder sparing in selected patients on the basis of response to neoadjuvant chemotherapy is a feasible approach that should be confirmed in prospective, randomized trials. Selected elderly patients are candidates for this approach.

Systemic administration of GPI 15427, a novel poly(ADP-ribose) polymerase-1 inhibitor, increases the antitumor activity of temozolomide against intracranial melanoma, glioma, lymphoma.

Tentori L., Leonetti C., Scarsella M., D'Amati G., Vergati M., Portarena I., Xu W., Kalish V., Zupi G., Zhang J., Graziani G.

Clin. Cancer Res., 9(14), p.5370-9, 2003

Purpose: Temozolomide (TMZ) is a DNA methylating agent that has shown promising antitumor activity in recent clinical trials against high grade gliomas, metastatic melanoma, and brain lymphoma. In this study, we tested whether systemic administration of GPI 15427, a novel poly(ADP-ribose) polymerase (PARP-1) inhibitor capable of crossing the blood-brain barrier, could enhance the efficacy of TMZ against metastatic melanoma, glioblastoma multiforme, and lymphoma growing in the brain.

Experimental design: Murine B16 melanoma or L5178Y lymphoma cells were injected intracranially in syngeneic mice. An orthotopic xenograft of the human SJGBM2 glioblastoma multiforme was implanted in nude mice. Animals were treated with TMZ + GPI 15427 using a schedule of 40 mg/kg/i.v. GPI 15427 + 100 mg/kg/i.p. TMZ for 3 days. The efficacy of drug treatment was assessed by: (a) the increase of mouse survival and life span; and (b) the suppression of melanoma metastases to lung after i.v. injection of B16 cells.

Results: In all models, systemic administration of GPI 15427 shortly before TMZ significantly increased life span of tumor-bearing mice with respect to untreated controls or to groups treated with either GPI 15427 or TMZ only. Moreover, GPI 15427 increased the antimetastatic effect of TMZ.

Conclusions: These data indicate that systemic administration of the poly(ADP-ribose) polymerase-1 inhibitor GPI 15427 significantly enhances TMZ antitumor efficacy against solid or hematological neoplasias even when located at the central nervous system site.

Inhibition of telomerase increases resistance of melanoma cells to temozolomide, but not to temozolomide combined with poly (adp-ribose) polymerase inhibitor.

Tentori L., Portarena I., Barbarino M., Balduzzi A., Levati L., Vergati M., Biroccio A., Gold B., Lombardi M.L., Graziani G.

Mol. Pharmacol., 63(1), p.192-202, 2003

In the present study, we have investigated the influence of telomerase inhibition in chemosensitivity of melanoma cells to temozolomide (TMZ), a methylating agent with promising antitumor activity against metastatic melanoma. In fact, telomerase, a ribonucleoprotein enzyme expressed in the majority of tumors, is presently considered an attractive target for anticancer therapy, with the double aim of reducing tumor growth and increasing chemosensitivity of cancer cells. Susceptibility to TMZ and to other antitumor agents used for treatment of metastatic melanoma was initially assessed in melanoma lines with different basal levels of telomerase activity. Thereafter, chemosensitivity was investigated after inhibition of telomerase by means of stable transfection of a catalytically inactive, dominant-negative mutant of hTERT (DN-hTERT). This study shows for the first time that: a) susceptibility to TMZ of melanoma lines derived from the same patient did not depend on basal telomerase activity; b) inhibition of telomerase by DN-hTERT resulted in reduced growth rate and increased resistance to TMZ and to the chloroethylating agent carmustine, increased sensitivity to cisplatin, and no change in response to tamoxifen or to a selective N3-adenine methylating agent; c) inhibition of poly(ADP-ribose) polymerase (PARP), an enzyme involved in the repair of N-methylpurines, restored sensitivity of DN-hTERT clones to TMZ. These results indicate that a careful selection of the antitumor agent has to be made when antitelomerase therapy is combined with chemotherapy. Moreover, the data presented here suggest that TMZ + PARP inhibitor combination is active against telomerase-suppressed and slowly growing tumors.

TP53INP1s and homeodomain-interacting protein kinase-2 (HIPK2) are partners in regulating p53 activity.

Tomasini R., Samir A.A., Carrier A., Isnardon D., Cecchinelli B., Soddu S., Malissen B., Dagorn J.C., Iovanna J.L., Dusetti N.J.

J. Biol. Chem., 278(39), p.37722-9, 2003

The TP53INP1 gene encodes two protein isoforms, TP53INP1alpha and TP53INP1beta, located into the nucleus. Their synthesis is increased during cellular stress by p53-mediated activation of transcription. Overexpression of these isoforms induces apoptosis, suggesting an involvement of TP53INP1s in p53-mediated cell death. It was recently shown that p53-dependent apoptosis is promoted by home-

odomain-interacting protein kinase-2 (HIPK2), which is known to bind p53 and induce its phosphorylation in promyelocytic leukemia protein nuclear bodies (PML-NBs). In this work we show that TP53INP1s localize with p53, PML-IV, and HIPK2 into the PML-NBs. In addition, we show that TP53INP1s interact physically with HIPK2 and p53. In agreement with these results we demonstrate that TP53INP1s, in association with HIPK2, regulate p53 transcriptional activity on p21, mdm2, pig3, and bax promoters. Furthermore, TP53INP1s overexpression induces G1 arrest and increases p53-mediated apoptosis. Although a TP53INP1s and HIPK2 additive effect was observed on apoptosis, G1 arrest was weaker when HIPK2 was transfected together with TP53INP1. These results indicate that TP53INP1s and HIPK2 could be partners in regulating p53 activity.

Identification of a novel DNase I hypersensitive site within the far upstream region of the human HLA-DRA gene.

Tomassetti M., Feriotto G., Giacomini P., Giorda E., Bianchi N., Borgatti M., Finotti A., Mischiati C., Gambari R.

Int. J. Mol. Med., 12(6), p.929-34, 2003

The class II products of the major histocompatibility complex have a distribution restricted to certain tissues and cells. For instance, they are constitutively expressed by B lymphocytes, but not by resting T lymphocytes. In this study, we report the identification of a novel DNase I hypersensitive site within a putative regulatory region of the human HLA-DRA gene, the so-called far upstream region. This hypersensitive site was present in the genome of the DRalpha-positive human B-lymphoid Raji cell line, and absent in the DRalpha-negative T-lymphoid Jurkat cell line. In addition, this hypersensitive site was also present in transgenic B lymphocytes isolated from the murine transgenic line TG 53, carrying a single integrated copy of the human HLA-DRA gene per haploid genome. The correlation between DRA expression and the presence of this far upstream hypersensitive site suggests novel long distance chromatin remodeling mechanisms possibly shared by human and murine class II genes.

Prevention of radiotherapy-induced emesis.

Tonini G., Vincenzi B., Santini D., La Cesa A., Finolezzi E., Onori N., D'Angelillo R., Baldi A., Trodella L.

J. Exp. Clin. Cancer Res., 22(1), p.17-22, 2003

In this minireview the authors examine and discuss the radioprotective compounds and the new combination therapies for the prophylaxis of radiation-induced emesis. Radiation-induced emesis is an important secondary effect of this anticancer treatment and it represents one of the causes of therapy interruption and decay of life quality before the introduction of optimal control of radiation-induced emesis with new antiemetic drugs which ensure the continuance of radiotherapy and avoid time breaks, that could negatively influence the efficacy of anticancer treatment. The incidence, the severity or the latency of radiotherapy-induced nausea and vomiting are correlated both with the treatment features (fractions, total dose, irradiation site) and with the main clinical characteristics of the patients. In contrast to the very extensive literature on the prevention of chemotherapy-induced emesis, relatively few studies about the prevention of nausea and vomiting in patients submitted to radiotherapy have been published. Among antiemetic drugs for the prevention of emesis, benzamides and in particular metoclopramide, are widely used in clinical practice. The introduction of selective 5-HT3 antagonists in clinical practice produced an important improvement in control of chemotherapy induced emesis, but few published studies were aimed at evaluating the efficacy of these drugs in the prophylaxis of nausea and vomiting due to radiation exposure. We herewith present a brief summary of Clinical practice guidelines for the use of antiemetics in anticancer therapy recently published by ASCO (American Society of Clinical Oncology).

Unusual problems in breast cancer and a rare lung cancer case. Case 1. Clinical complete response of breast cancer metastases after trastuzumab-based immunotherapy.

Tonini G., Vincenzi B., Santini D., Avvisati G., La Cesa A., Baldi A.

J. Clin. Oncol., 21(11), p.2215-6, 2003

No abstract available

Bcl-2 induction of urokinase plasminogen activator receptor expression in human cancer cells through Sp1 activation: involvement of ERK1/ERK2 activity.

Trisciuoglio D., Iervolino A., Candiloro A., Fibbi G., Fanciulli M., Zangemeister-Wittke U., Zupi G., Del Bufalo D.

J. Biol. Chem., 279(8), p.6737-45, 2003

We have previously demonstrated that Bcl-2 overexpression in human breast carcinoma and melanoma cells synergizes with hypoxia to increase angiogenesis through up-regulation of vascular endothelial growth factor. In this work we demonstrated, for the first time, that Bcl-2 overexpression in cancer cells exposed to hypoxia modulates urokinase plasminogen activator receptor (uPAR) expression through Sp1 transcription factor and that the extracellular signal-regulated kinase (ERK) pathway plays a role in Sp1 transcriptional activity. In particular, an increase in uPAR protein and mRNA expression was found in melanoma bcl-2 transfectants grown under hypoxia when compared with control cells, and a decrease of uPAR protein expression was induced by treatment of cells with specific bcl-2 antisense oligonucleotides. Up-regulation of uPAR expression was accompanied by increased Sp1 protein expression, stability, serine phosphorylation, and DNA binding activity. Treatment of cells with mitramycin A, an inhibitor of Sp1 activity, confirmed the role of Sp1 transcriptional activity in uPAR induction by Bcl-2. The contribution of the ERK pathway in Sp1-increased transcriptional activity was demonstrated by the use of chemical inhibition. In fact, ERK kinase activation was induced in Bcl-2-overexpressing cells exposed to hypoxia, and the ERK kinase inhibitor UO126 was able to down-regulate Sp1 phosphorylation and DNA binding activity. Using a human breast carcinoma line, we obtained data supporting our findings with melanoma cells and identified a link between the induction of Sp1 and uPAR expression as a common bcl-2-controlled phenomenon in human tumors. In conclusion, our results strongly indicate that up-regulation of uPAR expression by Bcl-2 in hypoxia is modulated by Sp1 DNA binding activity through the ERK signaling pathway.

Acute liver toxicity of antiretroviral therapy (HAART) after liver transplantation in a patient with HIV-HCVcoinfection and associated hepatocarcinoma (HCC)

Vennarecci G., Ettorre G.M., Antonini M., Maritti M., Moricca P., D'Offizzi G., Narciso P., Lonardo M.T., Boschetto A., Del Nonno F., Perracchio L., Palmieri G.P., Visco G., Santoro E.

Tumori, 89(Suppl. 4), p.159-61, 2003

OLT in HIV infected patients still remains a challenging option requiring a careful monitoring of patients for HCV reinfection, drug interactions and antiretroviral toxicity. Severe adverse events due to HAART have been already reported for post exposure prophylaxis in HIV infected patients. Here we report a case of liver graft toxicity related to HAART in a HIV-HCV co-infected patient (46 yrs-male) with associated a small HCC transplanted with a marginal liver graft. The patient had pre-OLT plasma HIV 1-RNA levels undetectable and CD4+ T-cell count of > 200 cells/microL for 6 months. At day 2 a severe graft dysfunction was observed (AST 1570 U/L, ALT 2180 U/L, BIL tot 8.3 mg/dL, BIL Dir 6.6 mg/dL and PT 35%—INR 2.5). Doppler scan showed hepatic artery always patient. Later the postoperative in-hospital course was complicated by tense ascites and severe cholestasis. Serum bilirubin reached 42 mg/dL in day 12. Hypertransaminasemia ended at day 15 while cholestasis ended after 46 days. Tacrolimus was reintroduced at day 7. A liver biopsy 10 after OLT showed severe intrahepatic cholestasis, centrolobular necrosis and macrovesicular steatosis (30%). The patient was discharged 48 days after OLT with good liver function. After seven months HIV-RNA is still undetectable and HAART has not been restarted. We believe that the early complications we observed may be attributed to a sudden increase in plasma concentration of antiretroviral drugs secondary to drug redistribution from peripheral tissues and hepatic clearance deficiency after OLT. Although a pre-OLT withdrawal of HAART seems unjustified a delayed re-introduction of HAART or the use of less hepatotoxic drugs may be advisable.

Delayed infection, late tonsillectomy or adenoidectomy and adult leukaemia: a case-control study.

VINEIS P., MILIGI L., CROSIGNANI P., DAVICO L., FONTANA A., MASALA G., NANNI O., RAMAZZOTTI V., RODELLA S., STAGNARO E., TUMINO R., VIGANO C., VINDIGNI C., COSTANTINI A.S.

Br. J. Cancer, 88(1), p.47-9, 2003

In a population-based case-control study among adults in Italy, of 261 lymphoid and 313 myeloid leukaemias and 1718 controls, a later age at adenoidectomy and tonsillectomy (after age 10 years) increased considerably the risk of lymphocytic (but not myeloid) leukaemia (odds ratio 4.2, 95% confidence interval 1.1-16.2). We propose that late infection is a proliferative stimulus for B-cells.

Immunohistochemical expression and prognostic significance of FAS and GLUT1 in bladder carcinoma.

VISCA P., SEBASTIANI V., PIZER E.S., BOTTI C., DE CARLI P., FILIPPI S., MONACO S., ALO P.L.

Anticancer Res., 23(1A), p.335-9, 2003

Background: Fatty Acid Synthase (FAS) and Human Erythrocyte Glucose Transporter 1 (GLUT1) are new markers involved in the biological activities of cancer cells. FAS is a multifunctional enzyme that synthesizes palmitate from acetyl-CoA and malonyl-CoA. GLUT1 is a transmembrane protein normally expressed in perineurium and erythrocytes. FAS and GLUT1 expression have been recently described in many aggressive tumors. We explored the immunohistochemical expression of FAS and GLUT1 in bladder carcinomas to reveal statistical associations with clinico-pathological features and recurrence.

Materials and methods: Thirty-one node- and distant metastasis-negative transitional cell carcinomas from patients with a five-year follow-up were evaluated for FAS and GLUT1 expression.

Results: Univariate analysis showed that low-grade, pTa stage and FAS-negative expression were associated with indolent tumors. Multivariate analysis showed that FAS expression ($p = 0.006$) and pT1-2 stage tumors ($p = 0.001$) were independent predictors of recurrence.

Conclusion: Endogenous fatty acids are an exploitable storage of energy for aggressive human bladder carcinomas. Glucose uptake is not required by bladder tumors.

c-Kit is preferentially expressed in MYCN-amplified neuroblastoma and its effect on cell proliferation is inhibited in vitro by STI-571.

VITALI R., CESI V., NICOTRA M.R., MCDOWELL H.P., DONFRANCESCO A., MANNARINO O., NATALI P.G., RASCHELLA G., DOMINICI C.

Int. J. Cancer, 106(2), p.147-52, 2003

Coexpression for c-Kit receptor and its ligand stem cell factor (SCF) has been described in neuroblastoma (NB) cell lines and tumors, suggesting the existence of an autocrine loop modulating tumor growth. We evaluated c-Kit and SCF expression by immunohistochemistry in a series of 75 primary newly diagnosed neuroblastic tumors. Immunostaining for c-Kit was found in 10/75 and for SCF in 17/75, with 5/10 c-Kit-positive tumors also expressing SCF. For both, c-Kit and SCF staining were predominantly found in the most aggressive subset of tumors, i.e., those amplified for MYCN: c-Kit was detected in 8/14 amplified vs. 2/61 single copy ($p<0.001$), and SCF in 9/14 amplified vs. 8/61 single copy tumors ($p<0.001$). Furthermore, the association of c-Kit expression with advanced stage (3 or 4) ($p=0.001$) and of SCF expression with adrenal primary ($p=0.03$) was substantiated. The in vitro activity of the tyrosine kinase inhibitor STI-571 (imatinib mesylate, Gleevec, Glivec) on NB cell lines positive or negative for c-Kit was also assessed. When cells were grown in 10% fetal calf serum, the 4 c-Kit-positive cell lines tested were sensitive to STI-571 growth inhibition to a different extent (ranging from 30 to 80%); also the c-Kit-negative cell line GI-CA-N was slightly affected, suggesting that other STI-571 targets operate in regulating NB proliferation. In addition, c-Kit-positive cell lines SK-N-BE2(c) and HTLA230, grown in SCF only, remained sensitive (40 and 70% of growth inhibition, respectively), while, in the same conditions, proliferation of the c-Kit-negative cell line GI-CA-N was not affected. Immunoprecipitation of c-Kit from cell lysates of SK-N-BE2(c) and HTLA230 cells grown in SCF and subsequent western blot analysis of the immunoprecipitates revealed a sharp decrease of c-Kit phosphorylation after STI-571 treatment. These data demonstrate that both c-Kit and SCF are preferentially expressed in vivo in the most aggressive neuroblastic tumors and that their signaling is active in promoting in vitro NB cell proliferation that can be selectively inhibited by treatment with STI-571.

Role of pelvic lymphadenectomy in the management of stage I endometrial cancer: our experience.

VIZZA E., GALATI G.M., CORRADO G., SBIROLI C.

Eur. J. Gynaecol. Oncol., 24(2), p.126-8, 2003

Objectives: To estimate the prognostic value of pelvic-node removal on survival of patients affected by endometrial carcinoma at presurgical FIGO Stage I.

Methods: A retrospective analysis was performed on a total of 111 patients recruited from 1990 to 1996 at the S. Carlo di Nancy Hospital. Thirty-nine (35%) of them underwent a total hysterectomy and bilateral salpingo-oophorectomy with removal of the vaginal cuff (group 1), while 72 (65%) underwent a total hysterectomy combined with pelvic lymphadenectomy (group 2). Prognostic features including tumor grade, depth of myometrial invasion and histologic subtype. Survival rates were calculated with Cox and Kaplan analyses.

Results: Overall survival rate at five years was 91.2%. The survival rate of group 1 and group 2 was 89% and 92.8%, respectively which is not statistically significant. Stage, grade, histotype, age at diagnosis, and presence of positive lymph nodes did not show any significant prognostic value on survival probability.

Conclusions: The survival rate for patients submitted to lymphadenectomy (group 2) was the same of patients who did not undergo this treatment (group 1). Nevertheless, pelvic lymphadenectomy in endometrial carcinoma at presurgical FIGO stage I was worthwhile as it allowed correct staging to be performed. The prediction of nodal disease based only on preoperative investigations (such as TC, NMR) is often inaccurate.

Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer.

ZEULI M., NARDONI C., PINO M.S., GAMUCCI T., GABRIELE A., FERRARESI V., GIANNARELLI D., COGNETTI F.

Ann. Oncol., 14(9), p.1378-82, 2003

Background: Capecitabine and oxaliplatin are both active anticancer agents in the treatment of patients with advanced colorectal cancer. The aim of this phase II study is to determine the efficacy and tolerability of combining oxaliplatin with capecitabine in the treatment of advanced non-pretreated colorectal cancer.

Patients and methods: Forty-three chemotherapy-naive patients were enrolled. Capecitabine 2500 mg/m(2)/day was administered orally twice a day continuously for 14 days and oxaliplatin 120 mg/m(2) was administered as a 2-h infusion on day 1, repeated every 3 weeks.
Results: Forty-three patients were assessable for toxicity and 39 for clinical activity: the main toxicity was grade 3 or 4 diarrhea, which occurred in 28% of the patients. The response rates were 44% [95% confidence interval (CI), 29.3% to 59.0%] and 48.7% (95% CI 33.0% to 64.4%) (intention-to-treat and per protocol analysis, respectively). The median overall survival was 20 months (95% CI 12-28).

Conclusions: Combining capecitabine and oxaliplatin yields promising activity in advanced colorectal cancer; therefore, the capecitabine dose we utilized is probably too high. The main toxicity is diarrhea, which is manageable with appropriate dose reductions. This combination may be preferable compared to a standard combination with infusional fluorouracil/leucovorin as it is more convenient and practical with similar efficacy. Thus, phase III trials are needed to clarify its role in the treatment of chemotherapy-naive advanced colorectal cancer patients.

Folate status, metabolic genotype, and biomarkers of genotoxicity in healthy subjects.

ZIJNO A., ANDREOLI C., LEOPARDI P., MARCON F., ROSSI S., CAIOLA S., VERDINA A., GALATI R., CAFOLLA A., CREBELLI R.

Carcinogenesis, 24(6), p.1097-103, 2003

Gene-environment interactions play an important role in folate metabolism, with a potential impact on human health. Deficiencies in the uptake of key micronutrients and variant genotypes can affect the folic acid cycle, modulating methyl group transfer in key processes and leading to increased cancer risk and Down syndrome incidence. So far, the significance of folate status and metabolic genotypes on baseline levels of DNA damage in normal individuals has not been fully elucidated. In this study, the possible modulation of SCE, micronuclei and tail moment values in peripheral lymphocytes by plasma levels of folic acid, homocysteine and vitamin B12, and by the methylenetetrahydrofo-

late reductase (MTHFR) C677T and methionine synthase reductase (MTRR) A66G polymorphisms was investigated in 191 healthy subjects. The results obtained show a highly significant (P = 0.001) positive association between plasma levels of vitamin B12 and frequencies of both SCE and high frequency cells (HFC, above 90 degrees percentile) in smokers. No significant effect was observed in non-smokers. Moreover, after correction for age, gender and GSTM1 genotype, a significant association (P = 0.026) between the MTRR 66GG variant genotype and higher micronucleus rates was observed. Tail moment values were not affected by any of the independent variables considered. Overall, the results obtained suggest that both folate status and relevant metabolic genotype can influence background levels of DNA damage in normal subjects. The significant association observed in smokers between plasma vitamin B12 and SCE frequencies may highlight the effect of methylation status on DNA damage and repair, although the role of other, unidentified dietary factors cannot be ruled out. At the same time, micronucleus data indicate that the MTRR 66GG variant may represent another individual trait of relative genomic instability, thus supporting epidemiological data on increased risk of Down syndrome conception in MTRR 66GG subjects.

Publications in Non-Referenced Journals

1. Ambrosio F., Paoletti F., Savoia G., Amantea B., Arcuri E., Avogaro F., Barbati A., Et Al.
SIAARTI recommendations on the assessment and treatment of chronic cancer pain.
Minerva Anestesiol., 69(9), p.697-729, 2003

2. Biagini R., Boriani S., Bandiera S., Casadei R., Favale L., Salducca N., Erba F., Lari S., Gamberini G., Mercuri M.
Substitution in vertebral resections.
Chir. Organi. Mov., 88(2), p.185-91, 2003

3. Cataldi C., Vennarecci G., Tuccimei U., Ballatore S., Mazzarella Farao R.
Trauma of the liver and hepatic pedicle.
Minerva Chir., 58(4), p.615-20, 2003

4. Cilenti V.
Il tabagismo e il medico di famiglia. La nocività del fumo di tabacco.
Il Policlinico, 9(11), p.549-558, 2003

5. Cilenti V. Et Al.
Rilevamento sull'incidenza del tabagismo nei giovani della regione Lazio.
Rassegna di Patologia dell' Apparato Respiratorio, 18(5), p.422, 2003

6. Cinti C., Mariano V., Cappiello V., Cilenti V. Et Al.
Survey on the modalities ofuse of Aerolizer: preliminary results of a multicenter study in Italy. GEINA Project.
Rassegna di Patologia dell' Apparato Respiratorio, 18(5), p.352-357, 2003

7. Grassi A.
Censimento delle Strutture di Endoscopia Digestiva della Regione Lazio-anno 2002
Giornale Italiano di Gastroenterologia, In press 2003

8. Di Cocco B., Calabretta F., Alghisi F., Salesi N., Bossone G.
Tumor markers in epithelial ovarian cancer.
Minerva Ginecol. 55(4), p.327-32, 2003

9. Grassi A.
Minimal Standards in Endoscopy Reporting:Structure of the Records, Terms, Definitions and Photo Documentation
World Gastroenterology news,8(1), p.44, 2003

10. Lesnoni I., Stigliano V., Canistracci C., Lauria V., Frascione P., Addesso M., Sentinelli S., Cordiali P., D'agosto G., Appetecchia M.L., Petti M.C., Picardo M., Casale V.
Il Morbo Celiaco dell'adulto: un approccio multidisciplinare.
Esperienze Dermatologiche, 5(3), p.193-200, 2003

11. Melani A.S., Pirrelli M., Cilenti V. Et Al.
GENEBU Project. Equipment and drugs used for home nebulizer therapy in Italy
Arch. Chest. Dis., 57(5-6), p.231-236,2003

12. Solivetti F.M., Bacaro D., De Majo A., Coscarella G., Franconi M., Appetecchia M.L.
Role of pulsed doppler of the inferior thyroid artery in patients without hyperthyroidism.
Chir. Ital., 55(3), p.373-7, 2003

13. Stigliano V. Lesnoni I.,Lauria V.,Canistracci C., Frascione P., Addesso M., Sentinelli S., Cordiali P., D'agosto G., Appetecchia M.L., Petti M.C., Casale V.
L'importanza delle manifestazioni extraintestinali nella diagnosi e gestione dei pazienti celiaci.
Ospedale e Territorio, 4(1), p.9-12, 2003

14. Strano S., Blandino G.
p73-Mediated Chemosensitivity: A Preferential Target of Oncogenic Mutant p53.
Cell. Cycle, 2(4), p.348-349, 2003

15.Vennarecci G., Ettorre G.M., Boschetto A., Carboni F., Et Al.
Il trapianto epatico nei tumori primitivi e secondari del fegato. Revisione della letteratura e prospettive.
Chir. Ital., 55, p.797-810, 2003

Book - Book Chapters

1. Arcuri E.
Interfaccia tra cure palliative e terapia del dolore
In: Libro Italiano di Cure Palliative. D.Amadori/ De Conno. Casa Editrice-Poletto, Milano, 2003

2. Carlini P., Salesi N., Priolo C., Saracino B., De Carli P., Ruggeri E.M., Cognetti F.
Ruolo dell'ormonoterapia adiuvante nel carcinoma della prostata.
Educazionale, pp.31-35, 2003

3. Caruso A., Condoleo M.F.
Un modello operativo di intervento psicologico in ambito oncologico.
Paoline Editoriale Libri, 2003

4. Cognetti F., Gelibter A.
I tumori delle vie Biliari - Capitolo 8, pp. 209-232.
In: I tumori dell'apparato gastroenterico, Ed. Masson, 2003

5. Congiu M., Romanini M.E., Arduini D., Romanini C.
In: Ginecologia ed Ostetricia - Patologie Maligne dell'apparato genitale femminile.
pp. 89-101 Ed.T.Wierdis-C.Romanini, 2a Edizione, Minerva Medica, 2003

6. Del Bufalo D., Trisciuoglio D., Milella M.
Crosstalk between VEGF and Bcl-2 in tumor progression and angiogenesis.
In: VEGF and Cancer, Landes Bioscience, 2003

7. Di Filippo F., Cavaliere F., Anzà M., Garinei R., Perri P., Botti C., Grassi G.A., Cavaliere R.
L'ipertermia in oncologia.
Trattato di Chirurgia Oncologica, 1,2003

8. Garufi C., Vanni B., Bria E., Zappalà A.R., Aschelter A.M., Terzoli E.
Terapia cronomodulata - Capitolo 26, pp. 413-420.
In: I tumori dell'apparato gastroenterico, A. Zaniboni, L. Gennai, P. Olmi, Ed. Masson, 2003

9. Jandolo B.
Neurofisiologia Normale e Patologica.
Medicina e Mediterraneo, 2003

10. Jandolo B.
Neurotossicità non Platino - Correlata.
CEPI AIM Group, 2003

11. Lopez M., Conti F., Foggi P.
La chemioterapia nella fase avanzata.
In: Neoplasie dell'aziano, V. Lorusso, D. Cova, G. Colucci, et al., Vol. 1°. Ragusa Grafica Moderna, Bari, 2003

12. Mancini R., Aloe S., D'alessandro R., Spila A., Giunta S., Sperduti I., Roselli M., Guadagni F., Cosimelli M.
Significato biologico delle micrometastasi circolanti nel carcinoma colorettale.
In: Atti della Società Italiana di Chirurgia, Centocinquantesimo congresso della società italiana di chirurgia, Vol 1°, pp. 397-401, Editore L. Pozzi, Napoli, 5-8 Ottobre 2003

13. Marandino F.
Quadri clinici delle precancerosi e cenni di anatomia patologica
In: Le lesioni precancerose della cavità orale. Casa Editrice: Frusinate srl. Frosinone, 2003

14. Nisticò C., Bria E., Vanni B., Terzoli E.
Le terapia settimanali.
NPT, Dompè Biotec., 2003

15. Pace. A.
Complicanze Midollari Iatrogene.
Springer-Verlag 2003

16. Petti M.C.
L'impiego dell'eritropoietina nell'anziano
In: La patologia ematologica dell'anziano di A. Zanella e M.D. Cappellini. Il Pensiero Scientifico Editore, 2003

17. Romanini M.E., Congiu M., Arduini D., Romanini C.
In: Ginecologia ed Ostetricia - Patologie Benigne dell'apparato genitale femminile. pp.50-55. Ed. T.Wierdis-C.Romanini, 2a Edizione, Minerva Medica, 2003

18. Sacchi A.
Le proteine che sopprimono la formazione dei tumori.
In: Atti del XXX Seminario sulla Evoluzione Biologica ed i grandi problemi della Biologia, sul tema "Molecole e Malattie".
Accademia Nazionale dei Lincei. Pp. 1- 16, 2003

19. Vizza E., Sbiroli C.
Percorsi Diagnostici in Oncologia Ginecologica
In: Diagnostica Ecografia in Ginecologia. Editors: P. Pirillo e CM Stigliano. Edizioni CIC, 2003

Abstract: International Congresses

1. Acosta J.C., Richard C., Delgrado M.D., Horita M., Rizzo M.G., Fernàndez-Luna J.L., And Lèon J.

Amifostine impairs p53-mediated apoptosisof human myeloid cell AACR-NCI-EORTC.

Boston, 17-21 November 2003

2. Appetecchia M., Baldelli R., Diacono F., Stigliano V., Addesso M., Cannistraci C., Frascione P., Lauria V., Lesnoni I., Petti M.C., Sentinelli S., Casale V.

85th Annual Meeting of the Endocrine Society.

Philadelphia, USA 19-22 June 2003

3. Arcuri E., Di Emidio L., Ginobbi P., Laurenzi L., Marcelli M.E., Tirelli W.

Neurolisi alcolica caudale: una tecnica da salvare.
II International Meeting of Pain Therapy in Abruzzo.

Montesilvano (Pescara), 17-19 September 2003

4. Arcuri E., Di Emidio L., Ginobbi P., Laurenzi L., Marcelli M.E., Tirelli W.

Aspetti peculiari della tolleranza agli oppioidi nella terapia del dolore neoplastico.
II International Meeting of Pain Therapy in Abruzzo.

Montesilvano (Pescara), 17-19 September 2003

5. Arcuri E., Tirelli W., Ginobbi P., Penco I., Marcelli M.E., Ciocca F.

Isues of antalgic therapy in 241 terminal cancer patients adrnitted at "Sacro Cuore" Hospice. ll dolore è un killer?

The International Meeting of Hospices.

Roma, 6-7 November 2003

6. Avvisati G., Petti M.C., Lo Coco F., Testi A.M., Fazi P., Specchia G., Malagola M., Di Bona E., Recchia A., Marrnont F., Buelli M., Et Al.

AIDA: The Italian way of treating Acute Promyelocytic Leukemia (APL). Final act.

45th annual meeting, American Society of Hematology,.

7. Baccarini A., Monti O., Pediconi N., Fontemaggi G., Lorenzon L., Sacchi A., Blandino G., And Strano S.

The trascriptional co-activator yap physically interacts witth p73 and enhances its apoptotic activity in response to DNA damage.
8th Congress on Advances in Oncology.

Greece, 16-18 October 2003

8. Bagnato A., Rosano' L., Spinella F., Di Castro V., Natali P.G.

Endothelin B receptor blockade inhibits dynamics of cell interactions and communications in melanoma cell progression.
AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.

Boston, 16-22 November 2003

9. Bagnato A., Rosanò L., Spinella F., Di Castro V., Nicotra M.R., Natali P.G.

Therapeutic targeting of the endothelin A receptor in human ovarian carcinoma: efficacy of cytotoxic agents is markedly enhanced by coadministration of Atrasentan.
8th International Conference on Endothelin.

Ibaraki, Japan, 23-26 November 2003

10. Bagnato A., Spinella F., Di Castro V., Natali P.G., Rosanò L.

Endothelin B receptor blockade inhibits melanoma-stromal interactions during tumor progression.
8th International Conference on Endothelin.

Ibaraki, Japan, 23-26 November 2003

11. Bagnato A., Rosanò L., Elia G., Di Castro V., Nicotra M.R., Natali P.G., Spinella F.

Endothelin-1 stimulates cycloxygenase-2 expression in ovarian cancer cells through multiple signalling pathways: evidence for involvment of transactivation of the epidermal growth factor receptor.
8th International Conference on Endothelin.

Ibaraki, Japan, 23-26 November 2003

12. Biagini R., Casadei R., Boriani S., Laus M., Parisinni P., Favale L., Salducca N., Erba F., Errani C., Staals E., Picci P., Merciri M.

Surgical treatment for tumors of the cervical spine

II ISG/SSG Meeting, Gothenburg, Sweden, 10-13 June 2003

13. Biroccio A., Benassi B., Zupi G.

Role of glutathione on the c-Myc-dependent chemosensitivity of melanoma cells.
94th Annual Meeting AACR.

Washington, 11-14 July 2003

14. Blandino G.

Interaction of p53 mutants with p63/p73 proteins, Functional consequences of TP53 mutations: Characterization of common and rare p53 mutants and relevance to human cancer.

AIRC, Lyon, 30 June 3 July 2003

15. Blarzino C., Foppoli C., De Marco F., Perluigi M., Coccia R., Cini C.

DT-diaphorase expression in oxidative stress conditions in normal and HPV-transformed human keratinocytes.
Joint Symposia with the British Biochemistry Society and Italian Biochemistry Society.

Ferrara, 15-18 September 2003

16. Borzacchiello G., Poggiali F., Roperto S., Simeone P., Roperto F., Venuti A.

BPV2 and E5 protein expression in urinary bladder carcinoma.
ICGEB DNA Tumour Virus Meeting.

Trieste, 15-20 July 2003

17. Branca M., Giorgi C., Benedetto A., Favalli C., Ciotti M., Piccione E., Sesti F., Sbiroli C., Mariani L., Costa S., Santini D., Agarossi A., Di Carlo A., Di Bonito L., Syrjänen K.

Assessment of risk factors and HPV-related pathogenetic mechanisms of CIN in HIV-positive and HIV-negative women. Implications in screening and patient management*
21° International Papillomavirus Congress.

Mexico City, 20-26 February 2003

18. Bruno T.

Che-1 affects cell growth by interfering with the recruitment of HDAC1 by Rb.
94th Annual Meeting AACR (Americen Association for Cancer Research).

Washington 11-14 July 2003

19. Bruno T., De Angelis R., De Nicola F., Barbato C., Di Padova M., Corbi N., Libri V., Benassi B., Mattei E., Chersi A., Soddu S., Floridi A., Passananti C., And Fanciulli M.

Che-1 affects cell growth by interfering with the recruitment of HDAC1 by Rb.
Chromatin and epigenetics. Alan Wolffe EMBO workshop.

EMBL Heidelberg, 19-22 June 2003

20. Carapella C.M., Pace A., Fabi A., Galiè E., Telera S., Giannarelli D., Vidiri A., Jandolo B., Occhipinti E.

The potential role of temozolomide chemotherapy in the treatment of low grade glioma.
12th European Congress of Neurosurgery - EANS

Lisbona, 7-12 September 2003

21. Caroli F., Raus L., Pompili A., Pasquali Lasagni R., Telera S., Occhipinti E.

Single stage somatectomy and vertebrectomy for removal and stabilization of thoracolumbar metastases

World Spine II, Chicago, 10-13 August 2003

22. Ceribelli A., Milella M., Facciolo F., Salesi N., Cei R., Pellicciotta M., Cognetti F.

Sequential chemotherapy in non-small cell lung cancer (NSCLC): Cisplatin and gemcitabine (P/G) followed by docetaxel (D).
Proc. Am. Soc. Clin. Oncol. 22, p. 690, 2003 (abs 2775)

XXIX Congresso ASCO - Chicago, 29 May 3 June 2003

23. Ceribelli A., Milella M., Facciolo F., Salesi N., Cei R., Pellicciotta M., Cognetti F.

Sequential chemotherapy in non-small cell lung cancer (NSCLC): Cisplatin and gemcitabine (P/G) followed by docetaxel (D).
10th World Conference on Lung Cancer, (abs 541)

Vancouver, Canada 10-14 August 2003

24. Cianciulli A.M. And Galloro P.

The role of the fish in diagnosis and monitoring of urothelial tumors.

4th Joint International Workshop, 30 April 3 May 2003

25. Cianciulli A.M., Corrado G., Merola R., Vizza E., Marzano R., De La Iglesia Lopez F., Vincenzoni C., Galati G.M., Sbiroli C.

Clinical significance of genetic alterations of chromosome 3,7,x and EGFR gene in uterine cervical cancer progression.
5th International Congress of the European Research Organization on Genital Infection and Neoplasia.

Paris, 13 - 16 April 2003

26. Cianciulli A.M., Marzano R., Merola R., De La Iglesia F., Leonardo G., Piperno G., Sperduti I., Mancini R., Cosimelli M.

Evaluation of chromosome 1p, 17 AND 18q status in colorectal cancer and adjacent mucosa. American Association for Cancer Research.

Toronto, Canada, 5-9 April 2003

27. Cini C., Perluigi M., Foppoli C., De Marco F., Marcante M.L., Blarzino C., Coccia R.

Biological response of human keratinocytes to ROS-producing compounds.
Joint Symposia with the British Biochemistry Society and Italian Biochemistry Society.

Ferrara, 15-18 September 2003

28. Cirilli A., Simeone P., Muller A., Bagnato A., Venuti A.

ETAR selective antagonist versus balanced ETAR/ETBR antagonist in the growth inhibition of cervix carcinoma cells.
8th International Conference on Endothelin.

Ibaraki, Japan, 23-26 November 2003

29. Colucci G., Maiello E., Gebbia V., Lopez M., Carteni G., Rosati G., Giuliani F., Misino A., Pezzella G., Gebbia N., Goim.

Preliminary results of a randomized multicenter trial of the Gruppo Oncologico Italia Meridionale (GOIM) comparing FOLFIRI vs FOLFOX in advanced colorectal cancer (ACC) patients.
Proc. Am. Soc. Clin. Oncol. 22, p. 255, 2003 (abs 1021)

XXIX Congresso ASCO - Chicago, 29 May 3 June 2003

30. Corrado G., Mottolese M., Carosi M.A., Bavarese A., Giannarelli D., Vizza E., Zerbini V., Vincenzoni C., Natali P.G., Sbiroli C.

Altered expression of Fas system in ovarian carcinomas: correlation to conventional progno-stic parameters
13th International Meeting of The European Society of Gynecologic Oncology.
Bruxelles, 6–10 April 2003

Int. J. Gynecol. Cancer, 13(S1) p.19, 2003

31. De Marco F., Perluigi M., Flamini S., De Marco C., Cini C., Marcante M.L.

UV modulation of HPV 16 mRNA expression. Role of reactive oxygen species (ROS).
ICGEB DNA Tumour Virus Meeting.

Trieste, 15–20 July 2003

32. Del Bufalo D., Trisciuoglio D., Scarsella M., Zangemeister-Wittke U., Zupi G.

Bcl-2 antisense treatment of melanoma cells induces antiangiogenic activity.
Angiogenesis 2.

Paris, 19-20 June 2003

33. Del Bufalo D., Trisciuoglio D., Scarsella M., Zangemeister-Wittke U., Zupi G.

Treatment of melanoma cells with bcl-2/bcl-xl antisense oligonucleotides antiangiogenic avtivity.
AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.

Boston, 16-22 November 2003

34. Del Rosso M., Margheri F., Fibbi G., D'alessio S., Pucci M., Angelucci A., Festuccia C., Leonetti C., Scarsella M., Zupi G., Tognella S., Monia B., Bologna M.

Anti-tumor, anti-metastatic and anti-angiogenic activity of an antisense oligonucleotide against u-PAR: In vivo and in vitro evidences.
94th Annual Meeting AACR (Americen Association for Cancer Research).

Washington, 11-14 July 2003

35. Di Costanzo F., Gasperoni S., Manzione L., Tonato M., Bisagni G., Bravi S., Cortesi E., Carlini P., Floriani I., Labianca R., For Goirc & Giscad.

Postoperative chemotherapy (CT) in resected gastric cancer (GC): follow-up (FUP) vs pelf. results of an Italian intergroup (GOIRC & GISCAD) study.
XXIX Congresso ASCO, (abs. 1189)

Chicago, 29 May 3 June 2003

36. Farsetti C., Gaetano G., Zaccagnini L., Della Pietra S., Nanni A., Grasselli A., Mangoni R., Benvenuto A., Germani F., Moretti A., Sacchi, A., Pontecorvi S., Capogrossi M.C.

Activation of telomerase through VEGF signaling triggers angiogenesis following hind-limb ischemia.
Institute Juan March de Estudios e Investigationes - Workshop on Telomeres and telomerase: therapeuthical targets for cancer and aging.

Madrid, 16-18 November 2003

37. Felici A., Carlini P., Ruggeri E.M., Gelibter A., Di Cosimo S., Gamucci T., Fariello A.M., De Marco S., Adami E.A., Cognetti F.

A feasibility study of a bi-weekly PELF regimen in advanced gastric cancer (AGC).
Proc. Am. Soc. Clin. Oncol. 22, 2003 (abs. 1402)

XXIX Congresso ASCO - Chicago, 29 May 3 June 2003

38. Franconi R., Benvenuto E., Illiano E., Massa S., Bitti O., Giorgi C., Venuti A.

Crude plant extracts containing the HPV16 E7 protein can act as anti-cancer vaccine with intrinsic adjuvant-like properties.
7th International Congress of Plant Molecular Biology.

Barcellona, 23-28 June 2003

39. Franconi R., Cirilli A., Accardi L., Muller A., Illiano E., Massa S., Bitti O., Giorgi C., Venuti A.

Improving the anticancer activity of a vaccine made by crude Nicotiana benthamiana extracts containing the HPV16 E7 protein. Symposium: HPV Vaccines and Immunotherapies.

Cambridge, U.K., 10-13 July 2003

40. Gallucci M., Leonardo C., Marzano R., Cantiani R., Sentinelli S., Covello R., Ruggeri E., And Cianciulli A.M.

Genetic and molecular alterations in bladder cancer as potential prognostic markers.
13th Congress of the European Association of Urology.

Madrid, 12-15 March 2003

41 Gallucci M., Leonardo C., Marzano R., Ruggeri E., Cantiani R., Sentinelli S., Addesso M., And Cianciulli A.M.

Genetic prognostic marckers in bladder cancer
94th Annual Meeting 2003, AACR (American Association for Cancer Research).

Toronto, 5-9 April 2003

42. Garufi C., Vanni B., Bria E., Aschelter A.M., Casali A., Izzo F., Nistico C., Tropea F., Giannarelli D., Terzoli E.

Long-term survival of advanced colorectal cancer (acr) patients treated with chronotherapy.
Proc. Am. Soc. Clin. Oncol. 22, 2003 (abs 929)

XXIX Congresso ASCO - Chicago, 29 May 3 June 2003

43. Gasparini G., Gion M., Crivellari D., Morabito A., Rocco S., Spada A., Cognetti F., Filippelli G., Silingardi V., Amadori D.

Interim analysis of a randomized phase IIb study of weekly paclitaxel (PCT) with or without trastuzumab (T) as first-line therapy of patients (pts) with HER-2/neu positive metastatic breast cancer (MBC): Clinical and biological results.
Proc. Am. Soc. Clin. Oncol. 22, p. 35, 2003 (abs 138)

XXIX Congresso ASCO - Chicago, 29 May 3 June 2003

44. Gelibter A., Pino M.S., Ceribelli A., Milella M., Pollera C.F., Moscetti L., Di Lauro L., Di Cocco B., Cognetti F.

Results from compassionate use of ZD1839 in pre-treated non small cell lung cancer (NSCLC): Our experience.
Proc. Am. Soc. Clin. Oncol. 22, p. 232, 2003 (abs 929)

XXIX Congresso ASCO-Chicago, 29 May 3 June 2003

45. Gelibter A., Pino M.S., Ceribelli A., Milella M., Pollera C.F., Moscetti L., Di Lauro L., Di Cocco B., Cognetti F.

Results from compassionate use of ZD1839 in pre-treated non small cell lung cancer (NSCLC): Our experience.
10th World Conference on Lung Cancer, (abs 345)

Vancouver, Canada 10-14 August 2003

46. Giunta S., Crecco M., Canitano S., Carlini S., Cerasoli V., Marandino F., Cilenti V., Guadagni F., Pugliese P.

Screening for lung cancer with low-dose: spiral CT in asymptomatic smokers: preliminary data.
9th International Conference on Screening for Lung Cancer.
University of Miami-Jackson Memorial Hospital.

Miami, FL, 24-26 October 2003

47. Greco C., Giannarelli D., Sperduti I., Venturo I. And Alvino S.

Activation of the c-myc proto-oncogene in multiple myeloma: a new tool for clinical management of treated patients.
13th Inter. Conference of Laboratory Medicine & 10th Europ. Conference of Clinical Molecular Biology. Abs. P04, p. 36, 2003

Capri, 27-30 June 2003

48. Gridelli A., Illiano A., Salvagni S., Piantedosi F., Palazzolo G., Caffo O., Tibaldi C., Ceribelli A., Iaffaioli R.V., Perrone F., For The Distal Investigators.

Effect on quality-of-life (QoL) of weekly vs 3-weekly docetaxel (D) in second-line treatment of advanced non-small-cell lung cancer. The DISTAL randomized phase 3 study.
Proc. Am. Soc. Clin. Oncol. 22, p. 625, 2003 (abs 2515)

XXIX Congresso ASCO-Chicago, 29 May 3 June 2003

49. Guadagni F., Ferroni P., Basili S., Facciolo F., Carlini S., Crecco M., Martini F., Spila A., Mineo T.C., Roselli M.

Correlation between Tumor Necrosis Factor-alpha and D-dimer Levels in Non-Small Cell Lung Cancer Patients.

Proceedings ECCO 12. Copenhagen, Denmark, 21-25 September 2003

50. Guadagni F., Ferroni P., Bucher S., Di Filippo F., Ferraresi V., Catricalà C., Roselli M., Cognetti F.

Vascular endothelial growth factor levels in melanoma. Relationship with coagulation and platelet activation markers.

Proceedings ECCO 12 Copenhagen, Denmark, 21-25 September 2003

51. Iervolino A., Trisciuoglio D., Candiloro A., Fibbi G., Del Rosso M., Zupi G., Del Bufalo D.

Bcl-2 Overexpression Induces Urokinase Plasminogen Activator Receptor Expression and Sp1 transcriptional activity.
V Meeting of molecular oncology.

Positano, 12-15 May 2003

52. Illi B., Nanni S., Scopece A., Farsetti A., Biglioli P., Capogrossi M.C., Gaetano C.L.

Shear Stress-Mediated Chromatin Remodeling Provides Molecular Basis for Flow-Dependent Regulation of Gene Expression.
American Heart Association Meeting.
Orlando (USA) 28 October 2003.

Circulation, 108(S17).

53. Iovino A., Fontemaggi G., Kela I., Amariglio N., Rechavi G., Krishnamurthy J., Lorenzon L., Strano S., Sacchi A., Givol D., Blandino G.

Identification of direct p73 target genes combining DNA microarray and chromatin immunoprecipitation analyses
8th World Congress on Advances in Oncology.

Greece, 16-18 October 2003

54. Leonetti C., Scarsella M., D'angelo C., Semple S.C., Zupi G.

Liposome-encapsulated vincristine exhibits significant in vivo anti-tumor activity against vincristine-resistant human solid tumors.
94th Annual Meeting AACR (Americen Association for Cancer Research).

Washington, 11-14 July 2003

55. Marchetti A., Cecchinelli B., D'angelo M., Sacchi A., And Soddu S.

p53 can inhibit cell proloferation through caspase-mediated cleavage of ERK2/MAPK.

Lausanne, Switzerland, 22-25 January 2003

56. Mariani M., Preti L., Micheletti M., Sideri S., Costa L., Mariani F., Bogliatto M., Massobrio M.

Working together: how the cooperative study fails, and how can we find a way out.
World Ccongress of the International Society for the study of vulvovaginal disease.

Salvador, Brazil, 10-16 October, 2003

57. Marucci L., Niemierko A., Liebsch N.J., Aboubaker F., Liu M.C.C., Munzenrider J.E.

Spinal cord tolerance to high dose fractionated 3D conformal proton-photon irradiation as evaluated by equivalent uniform dose and dose volume histogram analysis.

Chester, UK, 14–16 may 2003

58. Milella M., Trisciuoglio D., Bruno T., Mottolese M., Cianciulli A., Ciuffreda L., Fabi A., Cognetti F., Zangemeister-Wittke U., Del Bufalo D., Zupi G.

HER-2 targeting by Trastuzumab (T) modulates Bcl-2 expression and potentiates apoptosis induction by Bcl-2/Bcl-XL bispecific antisense oligonucleotides (AS-4625).

AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.

Boston, 16-22 November 2003

59. Mirri M.A.

A phase II study combining oral Vinorelbine (Navelbine Oral) and cisplatin administered as induction therapy and concurrently with radiotherapy in locally advanced non small cell lung cancer (NSCLC).
Investigator's Meeting.

Paris, 28 February 2003

60. Mottolese M., Nadasi E.A., Buglioni S., Benevolo M., Cianciulli A.M., Merola R., Venturo I., Del Monte G., Giannarelli D., Botti C., Natali P.G.

HER2 expression and/or gene amplification, p53 nuclear accumulation, Fas ligand up-regulation in breast cancer and autologous peritumoral tissues: diagnostic implications.
94th Annual Meeting 2003, AACR (American Association for Cancer Research).

Toronto, 5-9 April 2003

61. Nanni S., Della Pietra L., Grasselli A., Priolo C., Armezzani A., Moretti F., Sacchi A., Pontecorvi A., Farsetti A.

Estrogens, telomerase and prostate cancer progression.
International Symposium "Prostate Cancer: novel strategies for a new disease".

Torino, 16-18 September 2003

62. Nistico C., Bria E., Vanni B., Tropea F., Izzo F., Aschelter A.M., Garufi C., Casali A., Astorre P., Terzoli E.

Weekly epirubicin-paclitaxel as first line chemotherapy in advanced breast cancer patients: A phase II study.

Proceedings ASCO 2003, Abs. 280

63. Novelli F., Vocaturo A., Piperno G., Scordati P., Cianciulli A.M., Merola R., Marandino F., Giannarelli D., Benevolo M., Buglioni S., Mottolese M.

Evaluation of her-2 gene amplification by chromogenic in situ hybridization: correlation with immunohistochemistry and fluorescence in situ hybridization
5th Milan Breast Cancer Conference.

Milan, 11-13 June 2003

64. Occhipinti E., Giovannetti M., Morace E., Oppido P., Vidiri A., Pompili A.

The supraorbital mininvasive approach for the removal of tumors of the sellar area.
12th European Congress of Neurosurgery - EANS

Lisbona, 7-12 September 2003. Abs. 344

65. Pace A., Galiè E., Jandolo B., Carapella C.M.

Temozolomide Chemiotherapy for progressive low grade glioma.
Meeting proceedings of the American Society of Clinical Oncology.

Chicago, 31 May 3 June 2003

66. Palumbo A., Bertola A., Musto P., Nunzi M., De Stefano V., Callea V., Rotoli B., Petti M.C., Caravita T., Lauta V.M., Patti C., Brighenti S., Cavallo F., Et Al.

Oral melphalan, prednisone and thalidomide far newly diagnosed myeloma.
45th annual meeting, American Society of Hematology.

San Diego, California 6-9 December 2003

67. Papaldo P., Fabi A., Pino M.S., Carlini P., Nardoni C., Mottolese M., Cianciulli A.M., Lanzetta G., Giannarelli D., Cognetti F.

Comparison between vinorelbine (V) in HER2-negative and vinorelbine plus trastuzumab (T) in HER2-positive pretreated metastatic breast cancer (MBC) patients (pts).
XXIX Congresso ASCO, (abs. 296)

Chicago, 29 May 3 June 2003

68. Papaldo P., Fabi A., Nardoni C., Pino S., Ferretti G., Carlini P., Mottolese M., Cianciulli A.M., Alimonti A., Sperduti I., Di Cosimo S., Cognetti F.

Trastuzumab improves the prognosis in HER2-positive when compared with HER2-negative patients. Trastuzumab plus vinorelbine in HER2-positive versus vinorelbine alone in HER2- negative metastatic breast cancer patients.

Breast Cancer Res. Treat. 82 (S1), abs.311, S. Antonio - Texas 2003

69. Pinto C., Marino A., De Pangher Manzini V., Benedetti G., Galetta D., Panetta A., Bruschi D., Del Conte G., Lopez M., Martoni A.

Sequential chemotherapy with ciplastin/gemcitabine (CG) followed by mitoxantrone/methotrexate/mitomycin (MMM) in untreated malignant pleural mesothelioma (MPM): a multicentric italian phase II study (SITMP1).
Proc. Am. Soc. Clin. Oncol. 22, p. 650, 2003 (abs 2613)

XXIX Congresso ASCO-Chicago, 29 May 3 June 2003

70. Pino M.S., Ruggeri E.M., Carlini P., Felici A., Ceribelli A., Zeuli M., Pollera C.F., Cognetti F.

Long-term outcome of patients (pts) with metastatic renal cell carcinoma (MRCC) treated with IL-2-based combination. A retrospective analysis.
XXIX Congresso ASCO, (abs. 1748)

Chicago, 29 May 3 June 2003

71. Pompili A., Caroli F., Cattani F., Giovannetti M., Vidiri A., Occhipinti E.

The suboccipital transtentorial approch for cerebellar iuxtatentorial metastases. 12th European Congress of Neurosurgery

Lisbona, 7-12 September 2003. (abs. 206)

72. Pompili A., Caroli F., Giovannetti M., Raus L., Telera S., Vidiri A., Occhipinti E.

Unilateral limited laminectomy for the removal of thoraco-lumbar neurofibromas.
12th European Congress of Neurosurgery

Lisbona, 7-12 September 2003. (abs. 347)

73. Pompili A., Carapella C.M., Raus L., Pace A.

Home care for malignant brain tumor patients.
12th European Congress of Neurosurgery - EANS

Lisbona, 7-12 September 2003

74. Porrello A., Soddu S., Zbilut J.P., Crescenzi M., Giuliani A.

Discrimination of single amino acid mutations of the p53 protein by means of deterministic singularities of recurrence quantification analysis.
International Agency for Research on Cancer.

Lione, Francia, 30 June 3 July 2003

75. Raftopoulos H., Gralla R.J., Nelli F., D'auria G., Bria E.

Can Survival Differences be found among Cisplatin, Carboplatin, and Non-Platinum Regimens?
Results of a Comprehensive Review of Chemotherapy in Advanced Non-Small-Cell-Lung Cancer (NSCLC) Randomized Trials Including 12181 Patients from 1992-2002.
10th World Conference on Lung Cancer (IASLC 2003)

Vancouver, Canada, 10-14 August 2003

76. Roche H.H., Cure H., Bunnell C., Cognetti F., Mauriac F., Perez E., Miller K., Sparano J., Peck R., Yelle L.

A phase II study of epothilone analog BMS-247550 in patients (pts) with metastatic breast cancer (MBC) previously treated with an anthracycline.
Proc. Am. Soc. Clin. Oncol. 22, p. 18, 2003 (abs 69)

XXIX Congresso ASCO-Chicago, 29 May 3 June 2003

77. Rosano' L., Spinella F., Di Castro V., Nicotra M.R., Natali P.G., Bagnato A.

Antitumor activity of atrasentan, a selective endothelin A receptor antagonist, in combination with cytotoxic agents in ovarian carcinoma xenografts.
AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.

Boston, 16-22 November 2003

78. Roselli M., Mineo T.C., Basili S., Martini F., Mariotti S., Aloe S., Bellotti A.M., Ambrogi V., Spila A., D'alessandro R., Davì G., Guadagni F., Ferroni P.

Soluble CD40 ligand (sCD40L) plasma levels in non-small cell lung cancer.
Proceedings XIX Congress of the International Society on Thrombosis and Haemostasis.
J. Thromb. Haemost. 1(S.1) Abs. 1213, 2003

Birmingham, UK, 12-18 July 2003

79. Santoro E., Carlini M., Carboni F.

Lymphatic spread and sentinel node in gastric cancer surgery.
V International Symposium in Advances in Gastric Cancer Management.

Cracovia, 12-14 January 2003

80. Savarese A., Corrado G., Pellicciotta M., Vizza E., Ferretti G., Natali P.G., Sbiroli C., Cognetti F., Mottolese M.

Prognostic Value of FAS and its ligand FAS-L in ovarian carcinoma
Proc. Am. Soc. Clin. Oncol., 22, p.459, 2003 (abs 1845)

XXIX Congresso ASCO - Chicago, 29 May 3 June 2003

81. Selvaggi G., De Marinis F., Maestri A., Foggi P., Aristides M., Stynes G., Et Al.

A patient-level cost comparison of gemcitabine/ciplastin, paclitaxel/carboplatin and vinorelbine/ciplastin regimens in the treatment of advanced non-small cell lung cancer in Italy.
Proc. Am. Soc. Clin. Oncol. 22, p. 646, 2003 (abs 2599)

XXIX Congresso ASCO-Chicago, 29 May 3 June 2003

82. Serrone L., Catricalà C., Zeuli M., Cognetti F.

"Weekly" cisplatin and "decrescendo" interferon-_ schedule in advanced melanoma patients: Preliminary evidence for a new active combination.
Proc. Am. Soc. Clin. Oncol. 22, p.717, 2003 (abs 2884)

XXIX Congresso ASCO-Chicago, 29 May 3 June 2003

83. Sibilio L., Martayan A., Fraioli R., Lo Monaco E., Melucci E., Suchànek M., Giacomini P.

Biochemical characterization of monoclonal antibodies to HLA-E and HLA-G.

Parigi, Tissue Antigens 62:356, 2003

84. Soriani A., Landoni V., Iaccarino G., Marzi S., Benassi M.

La radioterapia intraoperatoria nei tumori della prostata: aspetti operativi e dosimetrici. International Workshop New Trends in Radiotherapy: Novac 7, 5 anni di esperienza clinica utilizzando tecnologia italiana.

Roma, 30 May 2003

85. Soriani A., Iaccarino G., Landoni V., Marzi S., Benassi M., Fantini M., Teodoli S.

Technical features optimization and dosimetric characteristics improvement of a new IORT dedicated accelerator
1st Austrian, Italian, and Slovenian Medical Physics Meeting, "Physics contribution to radiation therapy"

Udine, 7-8 November 2003

86. Spinella F., Rosano' L., Di Castro V., Nicotra M.R., Natali P.G.

Efficacy of cytotoxic agents against ovarian umor xenografts is markedly enhanced by coadministration of Atrasentan, an antagonist of endothelin A receptor.
94th Annual Meeting AACR (Americen Association for Cancer Research).

Washington, 11-14 July 2003

87. Spriano G., Ruscito P., Morello R.

Conservative surgery in the treatment of laryngeal carcinoma.
Scientific Meeting: Preserving organ and functions: new challanges for multidisciplinarity in Oncology.
Organisation of European Cancer Institutes.

Paris, 16-18 May 2003

88. Telera S., Oppido P.A., Pompili A.

Three cases of CSF rhinorrhea due to sellar and sphenoidal pathology.
12th European Congress of Neurosurgery-EANS.

Lisbona, 7-12 September 2003

89. Tentori L., Leonetti C., Scarsella M., D'amati G., Xu W., Kalish V., Zhang J., Zupi G., Graziani G.

Systemic administration of the PARP inhibitor GPI 15427 increases the anti-tumor activity of temozolomide in melanoma, glioma and lymphoma preclinical models in vivo.
94th Annual Meeting AACR (Americen Association for Cancer Research).

Washington, 11-14 July 2003

90. Trisciuoglio D., Del Bufalo D., Scarsella M., Zangemeister-Wittke U., Zupi G.

Downregulation of bcl-2 protein by bcl-2/bcl-xl bispecific antisense oligonucleotide reduces angiogenesis.
V International Congress, Biotherapy of solid tumors.

Forlì, 13-14 November 2003

91. Vennarecci G., Ettorre G.M., Antonini M., D'offizzi G., Narciso P., Moricca P., Maritti M., Del Nonno F., Perracchio L., Visco G., Santoro R., Santoro E.

Liver graft toxicity related to hughly active antiretroviral therapy in a coinfected patient after liver transplantation.
9th Meeting of the International liver transplantation society (ITLS),

Barcelona, 18-21 June 2003

92. Venuti A., Marcante M.L.

Development of new therapeutic strategies against cervix cancer.
8th world Congress on Advances in Oncology and 6th International Symposium on Molecular Medicine.

Crete, 16-18 October 2003

93. Vici P., Foggi P., Conti F., Capomolla E., Cauchi C., Giacinti L., Santiccioli S., Paoletti G., Di Lauro L., Lopez M.

Docetaxel and vinorelbine in anthracycline-resistant breast cancer patients.
Proc. Am. Soc. Clin. Oncol. 22, p. 71, 2003 (abs 285)

XXIX Congresso ASCO-Chicago, 29 May 3 June 2003

94. Vizza E., Corrado G., Galati G.M., Cutillo G., Congiu M.A., Quattrini M., Sbiroli C.

Total laparoscopic radical hysterectomy in cervical and endometrial cancer: our experience
World Meeting on Minimally Invasive Surgery in Gynecology.

Roma, 24-28 June 2003

95. Vizza E., Muglia U.

A new morpho-functional classification of the Fallopian tube based on its myoarchitecture
5th International Malpighi Symposium in memory of Prof. Pietro Motta.

Roma, 11-13 September 2003

96. Vizza E., Mazzon I., Heyn R., Correr S., Motta P.M.

Three-dimensional microanatomy of the leyomyoma
5th International Malpighi Symposium in memory of Prof. Pietro Motta.

Roma, 11-13 September 2003

Abstract: National Congresses

1. Aloe S., Ferroni P., Basili S., Facciolo F., Carlini S., Crecco M., Martini F., Spila A., D'alessandro R., Palmirotta R., Mineo T.C., Mariotti S., Del Monte G., Cerasoli V., Roselli M., Guadagni F.

Correlation between Tumor Necrosis Factor-alpha and D-dimer Levels in Non-Small Cell Lung Cancer Patients.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

2. Ameglio F., Alvino S., Vitelli G., D'agnano I., Greco C.

Coinvolgimento della disregolazione di c-myc nella risposta a Melphalan del mieloma multiplo. Effetto di PDGF-BB.
V Congresso nazionale AfaR.

Roma, 25-27 Settembre 2003

3. Amodei S., Zupi G., Biroccio A.

Chronic inhibition of c-Myc oncoprotein limits the growth of human melanoma cells by inducing cellular crisis. Struttura e funzione del genoma.

Cortona, 10-12 Aprile 2003

4. Appetecchia M., Barnabei A., Ferretti E., Iacovelli P., Paro Vidolin A., Leone G.

Association between thryoid dysfunction and vitiligo.
XXX Congresso Nazionale Società Italiana di Endocrinologia.

Milano, 24-27 Settembre 2003

5. Appetecchia M., Barnabei A., Ferretti E., Diacono F., Carducci M., Izzo F., Terzoli E.

Somatostatin analogs and interferon alfa in the treatment of malignant glucagonoma.
XXX Congresso Nazionale Società Italiana di Endocrinologia.

Milano, 24-27 Settembre 2003

6. Arcangeli G., Saracino B., Bandoni V., Chianese E., Petrongari M.G., Marzi S., Iaccarino G., Soriani A., Benassi M.

Studio dell'effetto degli errori di set up e del movimento degli organi interni nel trattamento del cancro della prostata con tecnica IMRT.
XIII Congresso Nazionale SIUrO.

Ancona, 8-11 Novembre 2003

7. Arcangeli G., Gallucci M., Saracino B., Albino G., De Carli P., Bandoni V., Soriani A., Marzi S.

La IORT dopo prostatectomia nei tumori prostatici
XIII Congresso Nazionale SIUrO.

Ancona, 8-11 Novembre 2003

8. Arcangeli G., Marucci L., Giovinazzo G., Benassi M., Gomellini S., Marzi S., Iaccarino G., Landoni V., Soriani A.

Set-up error for IMRT in the nasopharyngeal carcinoma: effect on dose distribution
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

9. Arcangeli G., Saracino B., Chianese E., Rallo F., Bandoni V., Marzi S., Iaccarino G., Soriani A., Benassi M.

A study of the effect of set up errors and organ motion in IMRT for prostate cancer
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

10. Arcangeli G., Pinnarò P.

Randomized study of delayed VS immediate radiotherapy in patients with mammary carcinoma undergoing conservative surgery and CMF chemotherapy.
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

11. Arcangeli G., D'avenia P.

Novità nella radioterapia dei tumori della prostata
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

12. Arcuri E., Di Emidio D., Pelagalli L., Ginobbi P., Laurenzi L., Marcelli M.E., Tirelli W.

La neurolesione nel terzo millennio.
X Congresso Nazionale della Società Italiana di Cure Palliative.

Milano, 5-8 Marzo 2003

13. Arcuri E.

Il IV gradino nella scala OMS
XXV Congresso Nazionale AISD.

Mestre, 8-10 Maggio 2003

14. Badaracco G., Marcante M.L., Venuti A.

Pattern of HPV16 and HPV18 physical status within genital tumors and adjacent normal mucosa.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

15. Bagnato A.

Endothelin receptor as novel therapeutic targets.
V National Congress of Medical Oncology-AIOM.

Roma, 21-24 Ottobre 2003

16. Bagnato A., Rosanò L., Spinella F., Di Castro V., Nicotra M.R., Natali P.G.

Increased efficacy of cytotoxic agents against ovarian tumor xenografts by endothelin a receptor blockade.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

17. Benassi M., Marzi S., Iaccarino G., Landoni V., Soriani A.

Utilizzo degli indicatori radiobiologici TCP ed NTCP nella valutazione dei trattamenti IMRT
ISE "Metodo per la conformazione della dose in radioterapia".

Villa Gualino (Torino), 12-13 Dicembre 2003

18. Benevolo M., Vocaturo G., Piperno G., Sindico R., Marandino F., Canalini P., Perrone Donnorso R., Mottolese M., Vocaturo A.

P16 overexpression and hpv infection in cervical intraepithelial neoplasias.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9–12 Novembre 2003

19. Biroccio A., Benassi B., Zupi G.

Glutathione dpletion commits M14 human melanoma cells to c-myc-dependent drug-induced apoptosis.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-11 Novembre 2003

20. Biagini R., Boriani S., Casadei R., Favale L., Salducca N., Erba F., Mercuri M.

Reconstruction using stackable cages. Spinal tumor surgery.

Bologna, 9-10 Gennaio 2003

21. Biagini R., Boriani S., Bandiera S., Casadei R., Favale L., Salducca N., Erba F., Lari S., Gamberini G., Mercuri M.

Substitution in vertebral resection.

Chir. Org. Mov., LXXXVIII, p.185-191, 2003

22. Blandino G., Fontemaggi G., Gurther A., Strano S., Higashi Y, Sacchi A., Piaggio G.

p53 family members as trascriptional target of deltaEF1 repressors.
Telethon Scientific Convention.

Riva del Garda, 23-25 Novembre 2003

23. Breccia M., Latagliata R., Mengarelli A., Biondo F., D'Andrea M., Gentilini F., Milano F., Et Al.

Prognostic factors in chronic myelomonocytic leukemia: analysis of 83 patients from a single institution.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs. n. PO 230.

24. Breccia M., Diverio D., Noguera N.I., Latagliata R., Visani G., Santoro A., Locatelli F., Vignetti M., Damiani D., Marmont F., Petti M.C.

Clinico-biological features and outcome of acute promyelocYtic leukemia patients with persistent PCRdetectable disease after the AIDA front-line induction and consolidation therapy.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. PU 117.

25. Breccia M., Mandelli F., Petti M.C., D'andrea M., Gallucci C., Carmosino I., Pescarmona E., Et Al.

Clinico-pathological characteristics of myeloid sarcoma: report of 12 cases from a single institution.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. PU 104.

26. Bruzzaniti V., Strigari L., Benassi M., Maini C. L., Sciuto R., Romano L.

Nuovo approccio per il calcolo della dose assorbita nei trattamenti terapeutici con radiofarmaco.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

27. Caccia B., Marzi S., Benassi M., Pedrini M., Andenna C., Zicari C.

Valutazione della distribuzione di dose nei trattamenti radioterapici con fasci ad intensità modulata
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

28. Carapella C.M., Fabi A., Mirri A., Pace A., Et Al.

Regional Survey of Brain Metastases from Different tumour Types: The Potential Role of Integrated Therapeutical Strategies.
V National Congress of Medical Oncology-AIOM.

Roma, 21-24 Ottobre 2003

29. Carlini P., Salesi N., Priolo C., Saracino B., De Carli P., Ruggeri E.M., Cognetti F.

Ruolo dell'ormonoterapia adiuvante nel carcinoma della prostata
V National Congress of Medical Oncology-AIOM.

Roma, 21–24 Ottobre 2003

30. Carmosino I., Latagliata R., Breccia M., Finolezzi E., D'andrea M., Cimino G., Avvisati G., Lo Coco F., Mandelli F., Petti M.C.

Arsenic trioxide in the treatment of advanced acute promyelocYtic leucemia (APL).
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. PU 115.

31. Carmosino I., Biondo F., Russo E., D'andrea M., Galucci C., Anticoli Borza P., Morano G., Mecarocci S., Latagliata R., Breccia M., Mengarelli A., Et Al.

Risk-based strategy in the management of community acquired febrile neutropenia: a prospective study.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. PO 112.

32. Carmosino I., Latagliata R., Breccia M., D'andrea M., Testi A.M., Gallucci C., Avvisati G., Petti M.C., Et Al.

Incidence of late relapse (>5 years) in patients with acute promyelocYtic leukemia.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. PU 118.

33. Carpitelli G., Podo F., Giannini M., Carosi M.A., Carapella C.M.

Contributo diagnostico di metodiche HR-MAS NMR: esperienze in vitro.
VIII Congresso Corso Residenziale dell'Associazione Italiana di Neuro-Oncologia

Ancona, 2-4 Ottobre 2003

34. Ceribelli A., Milella M., Facciolo F., Salesi N., Cei R., Pellicciotta M., Cognetti F.

Sequential chemotherapy in non-small cell lung cancer (NSCLC): Cisplatin and gemcitabine (P/G) followed by docetaxel (D).
V National Congress of Medical Oncology-AIOM. Roma, 21–24 Ottobre 2003.

Ann. Oncol., 14(S4), abs B 29, 2003

35. Cianciulli A.M., Marzano R., Leonardo C., Merola R., Sentinelli S., Cantiani R., Mattace Raso D., Canalini P., Gallucci M.

Analisi citogenetica dell'instabilità genomica nell'epitelio apparentemente sano in pazienti con tumore muscolo-invasivo della vescica.
X Congresso Nazionale AURO 2003.

Roma, 22-25 Ottobre 2003

36. Cimino G., Lo Coco F., Minucci S., Careddu A., Fiorini R., Finolezzi E., Noguera N., Travaglini L., Gelmetti V., Diverio D., Fenu S., Mancini M., De Propriis S., Aloe M., Spiriti A., Petti M.C, Et Al.

Valproic acid plus retinoic acid induce myeloid differentiation in chemotherapyresistant acute myeloid leukemia patients.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003

37.Cividalli A., Creton G., Ceciarelli F., Strigari L., Tirindelli Danesi D., Benassi M.

Influence of time interval between surgery and radiotherapy on tumor regrowth
SIRR, INFN, FIRR "Radiazioni in Medicina e Biologia: ricerche ed applicazioni cliniche"

Padova, 20-22 Novembre 2003

38. Cognetti G.

Informative first aid: the role of libraries in training and updating.
ICT from the Alps to the Mediterranean.
I Conference and Expo.

Napoli, 5-8 Giugno 2003

39. Cognetti G.

Ruolo delle biblioteche biomediche nel Sistema Sanitario Nazionale-"Conoscere in tempo utile. L'importanza di essere biblioteca medica".
Conoscenza clinica 2003: la gestione nelle Aziende Sanitarie-Azienda Ospedaliera "Santa Maria della Misericordia" di rilievo nazionale di alta specializzazione.

Udine, 19-20 Settembre 2003

40. Condoleo M.F., Pietrangeli A., De Fulviis A., Casillo R., Falcicchio C., Bussoletti F., Pugliese P.

L'impatto del linfedema sulla qualità di vita nelle pazienti con cancro della mammella.
VII Convegno Nazionale Società Italiana di Psico-Oncologia (SIPO).

Acireale, 7-11 Ottobre 2003

41. Consorti R., Petrucci A., Soriani A., Benassi M.

Caratterizzazione di un sistema on-line per dosimetria in vivo con rivelatori mosfet nella IORT
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

42. D'alessandro R., Roselli M., Cosimelli M., Martini F., Spila A., Aloe S., Mariotti S., Del Monte G., Basili S., Ferroni P., Palmirotta R., Guadagni F.

Prognostic Value Of Soluble P-selectin Levels In Colorectal Cancer.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

43. D'Andrea M., Latagliata R., Finolezzi E., Torromeo C., Breccia M., Carmosino I., Biondo F., Gallucci C., Russo E., Cimino G., Petti M.C., Et Al.

Increased risk of thrombotic events in patients with acute promyelocytic leukemia receiving ATRA treatment.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. PO 060.

44. De Marco F., Perluigi M., Flamini S., Cini C., Marcante M.L.

NAD(P)H quinone oxidoreductase 1 expression and activity in HPV-16 transformed human keratinocytes.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

45. De Angelis G., Grande G., Donati G., Cilenti V., Bonaria M.

Progetto GEIna: uso degli inalatori pressurizzati convenzionali nella pratica clinica degli anni 2000.
XXXVII Congresso Nazionale ArPO (Ass. Ita. Pneumologi Ospedalieri).

Napoli, 16-19 Ottobre 2003

46. De Lellis L., Aceto G., Curia M.C., Veschi S., Matera S., Palmirotta R., Catalano T., Verginelli F., Mariani C., Costantini R., Battista P., Cama A.

Geneting testing in familial colorectal cancer.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

47. De Pasquale F., Barone P., Sebastiani G., Stander J., Crecco M., Di Nallo A.M., Gentile F.P.

Analisi bayesiana di immagini RM dinamiche della mammella.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

48. Della Pietra L., Zaccagnini G., Gaetano C., Nanni S., Grasselli A., Mangoni A., Benvenuto R., Germani A., F. Moretti, A. Pontecorvi, A. Sacchi, S. Bacchetti M., Capogrossi C., And Farsetti A.

Activation of telomerase through VEGF signaling promotes neo-angiogenesis.
Convegno annuale Struttura e funzione del genoma.

Cortona, 11-13 Aprile 2003

49. Di Costanzo F., Gasperoni S., Manzione L., Tonato M., Bisagni G., Bravi S., Cortesi E., Carlini P., Rossetti R., Floriani I., Labianca R.

Postoperative chemotherapy (ct) in resected gastric cancer (gc): follow-up (fup) vs pelf. results of an italian intergroup study (Goirc & Giscad).
V National Congress of Medical Oncology-AIOM. Roma, 21–24 Ottobre 2003.

Ann. Oncol., 14(S4), abs. 1, 2003

50. Di Lauro L., Belli F., Arena M.G., Giannarelli D., Santiccioli S., Carpano S.

Epirubicin ciplastin and docetaxel (ECD) for measurable advanced gastric carcinoma (AGC)
V National Congress of Medical Oncology-AIOM. Roma, 21–24 Ottobre 2003.

Ann. Oncol., 14(4), abs D63, 2003

51. Di Padova M., Bruno T., De Nicola F., Iezzi S., D'angelo C., Corbi N., Biroccio A., Floridi A., Passananti C., Fanciulli M.

Che-1 arrests human colon carcinoma cell proliferation by displacing HDAC1 from theP21WAF1/CIP1 promoter. Struttura e Funzione del genoma.

Cortona, 10-12 Aprile 2003

52. Di Padova M., Bruno T., De Nicola F., Iezzi S., D'angelo C., Corbi N., Biroccio A., Floridi A., Passananti C., Fanciulli M.

Che-1 arrests human colon carcinoma cell proliferation by displacing HDAC1 from theP21WAF1/CIP1 promoter.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

53. Di Stefano V., Rinaldo C., Sacchi A., Soddu S., D'orazi G.

Homeodomain-interacting protein kinase-2 activity and p53 phosphorylation are critical events for cisplatin-mediated apoptosis.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

54. Di Stefano V., Rinaldo C., Sacchi A., Soddu S., D'orazi G.

Tumor cell response to cisplatin requires HIPK2 and p53 phosphorylation at ser46.
Gruppo di Studio: Struttura e Funzione del Genoma.

Cortona(AR), 10-12 Aprile 2003

55. Ettorre G.M., Antonini M., Boschetto A., Carboni F., Et Al.

Rischio di esposizione del personale sanitario nella chirurgia trapiantologica del fegato nei pazienti HIV positivi.
XVII Congresso Nazionale AIDS e Sindromi Correlate.

Roma, 28-30 Novembre 2003

56. Ettorre G.M., Vennarecci G., Boschetto A., Giovannelli L., Antonini M., Carboni F., Santoro R., Et Al.

Valutazione delle prospettive resettive e trapiantologiche nell'epatopaziente coinfettato.
IHPBA - Italian Chapter. Congresso Nazionale.

Napoli, 12-14 Giugno 2003

57. Ettorre G.M., Vennarecci G., Boschetto A., Giovannelli L., Antonini M., Carboni F., Santoro R., Et Al.

Valutazione delle prospettive resettive epatiche e del trapianto di fegato nei pazienti HIV positivi.
VI° Congresso nazionale S.I.T.I.L.O.

Roma, 26-28 Novembre 2003

58. Ettorre G.M., Vennarecci G., Lonardo M.T., Boschetto A., Antonini M., Santoro E.

Modified liver hanging maneuver during orthotopic liver transplantation with inferior vena cava preservation.
IHPBA - Italian Chapter. Congresso Nazionale.

Napoli, 12-14 Giugno 2003

59. Ettorre G.M., Vennarecci G., Lonardo M.T., Antonini M., Carboni F., Carlini M., Santoro E.

Manovra di "hanging" modificata durante il trapianto ortotopico di fegato con tecnica di conservazione della vena cava inferiore.
XXVII° Congresso della Società di Chirurgia Oncologica (SICO).

Cagliari, 29-31 Maggio 2003

60. Fabi A., Papaldo P., Ciccarese M., Salesi N., Lo Russo V., Ferretti G., Carlini P., Sacchi I., Cecere F., Cognetti F.

Pegylated liposomal doxorubicin (pld) and gemcitabine (g) in metastatic breast cancer (mbc) patients: a phase II study.
Proc. 1st Mediterranean Conference on Oncology-Treatment of Gastrointestinal Cancer.

Bari, 5-8 Ottobre 2003

61. Fedele F., De Renzis C., Portoriero A., Mirri M.A., Giovinazzo G.

New emollient cream treatment for acute radiation dermatitis: preliminary data from an observational study on 111 women undergoing breast radiotherapy.
XIII Congresso Nazionale A.I.R.O.

Pescara, 5–8 Ottobre 2003

62. Felici A., Carlini P., Ruggeri E.M., Gelibter A., Di Cosimo S., Gamucci T., Fariello A.M., Pollera C.F., Adami E.A., Cognetti F.

A bi-weekly pelf regimen in advanced gastric cancer.
V National Congress of Medical Oncology-AIOM. Roma, 21–24 Ottobre 2003.

Ann. Oncol., 14(4), abs D62, 2003

63. Ferraresi V., Giampaolo M.A., Gabriele A., Mansueto G., Gamucci T.
Oxaliplatin (OXA) and I.V. bolus 5-fluorouracil (5-FU) plus leucovorin (LV) in c.i. 5-FU pretreted advanced colorectal cancer (CRC)".

V National Congress of Medical Oncology-AIOM. Roma, 21-24 Ottobre 2003.

Ann. Oncol., 14(4) abs D4, 2003

64. Franconi R., Cirilli A., Accardi L., Muller A., Illiano E., Massa S., Bitti O., Giorgi C., Venuti A.

Improving the anticancer activity of a vaccine made by crude Nicotiana benthamiana extracts containing the HPV16 E7 protein.
III Congresso Società Italiana di Virologia.

Cortona, 22-24 Settembre 2003

65. Frascione P., Piemonte P., Tomaselli R., Fossati B., Merra V.C.

Un caso di malattia di Grover trattato con tacalcitolo.
78° Congresso Nazionale SIDEV.

Roma, 25-28 Giugno 2003

66. Frascione P., Piemonte P., Tomaselli R., Fossati B., Merra V.C.

Un caso di malattia di Darier trattato con tazarotene.
78° Congresso Nazionale SIDEV.

Roma, 25-28 Giugno 2003

67. Frascione P., Fossati B., Piemonte P., Melchionda G.

Molluschi contagiosi e AIDS.
78° Congresso Nazionale SIDEV.

Roma, 25-28 Giugno 2003

68. Galiè E., Maschio M., Jandolo B.

Cerebellar Atrophy and Monoclonal Gammopathy of Underterminated Significance: a Possible Correlation.
Società Italiana di Neurologia (SIN).

Roma, 24 Ottobre 2003

69. Gallucci M., Marzano R., Leonardo C., Ruggeri E.M., Merola R., Sentinelli S., Addesso M., And Cianciulli A.M.

Alterations of the 9p21,Rb, p53, Her-2 neu genes and chromosomes 3,7,9, in bladder cancer.
V National Congress of Medical Oncology-AIOM.

Roma, 21-24 Ottobre 2003

70. Garufi C.,Vanni B., Calabretta F., Bria E., Campanella C.,Terzoli E.

L'infusione cronomodulata.
Proc. 1st Mediterranean Conference on Oncology-Treatment of Gastrointestinal Cancer.

Bari, 5-8 Ottobre 2003

71. Garufi C.,Vanni B., Calabretta F., Bria E.,Terzoli E.

Il trattamento oncologico del paziente anziano affetto da neoplasie del tratto gastroenterico (stomaco, pancreas, colon e retto). Ruolo della terapia medica.
Proc. I Stage di Oncologia geriatrica.

Roma, 16-19 Settembre 2003

72. Gasparini G.,Gionm.,Crivellari D., Morabito S.R., Spada A., Filippelli G., Silingardi., De Sio L., Cognetti F., Et Al.

Arandomized phase IIB study of weekly paclitaxel (PCT) ± trastuzumab (T) as first-line therapy of patients (PTS) with HER-2/NEU positive metastatic breast cancer (MBC): results of the first interim analysis.
V National Congress of Medical Oncology-AIOM. Roma, 21-24 Ottobre 2003

Ann. Oncol., 14(4), abs A25, 2003

73. Gelibter A., Pino M.S., Ceribelli A., Milella M., Pollera C.F. Moscetti L. Di Cocco B., Cognetti F.

Comassionate use of Gefitinib (IRESSA) in progressive pre-treated non small cell lung cancer (NSCLC): our experience.
V National Congress of Medical Oncology-AIOM. Roma, 21-24 Ottobre 2003

Ann. Oncol., 14(4), abs B37, 2003

74. Gentile F.P., Giunta S., Ordóñez P.L., Pompei E., Crecco M.

Ottimizzazione del Protocollo di Screening, per la Diagnosi Precoce del Cancro del Polmone Mediante TC Spirale a Bassa Dose e Valutazione del Rischio.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

75. Gentile F.P., Ordóñez P.L., Pompei E., Saracca E., Ferranti F.R., Rea F., Rossi G.

Valutazione Dosimetrica Nelle Procedure Stereotassiche di Biopsia Mammaria Guidata con Raggi X.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

76. Giovinazzo G., Benassi M., Gomellini S., Serraino F., Micheli A., Marucci L., Arcangeli G.

Palliative radiotherapy of bone metastases: patterns of practice in a new radiotherapy department: what's the best hypofractionation schedale in terms of pain relief, biological EQ dose, financial gain?
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

77. Giovinazzo G., Benassi M., Gomellini S., Serraino F., Micheli A., Marucci L., Arcangeli G.

The rapid palliation of symptomatic metastatic bone disease: a new approach with high biological equivalent dose.
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

78. Greco C., Ameglio F., Alvino S., Vitelli G., D'agnano I.

C-myc deregulation is involved in response a Melphalan of multiple myeloma: an in vitro-in vivo study.
XXXV Congresso Nazionale SIBiOC.

Firenze, 14-17 Ottobre 2003

79. Gurtner A., Manni I., Fuschi P., Mantovani R., Guadagni F., Sacchi A., Piaggio G.

Requirement for down-regulation of the CCAAT-binding activity of the NF-Y transcription factor during skeletal muscle differentiation.
V meeting of Molecular Oncology.

Positano, 12-15 Maggio 2003

80. Iaccarino G., D'andrea M., Landoni V., Luppino S., Marzi S., Pedrini M., Soriani A., Benassi M.

Dosimetria in vivo mediante il sistema AS500 Portal Vision nell'esecuzione della tecnica IMRT.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

81. Iaccarino G., Landoni V., Marzi S., Pedrini M., Soriani A., Benassi M.

Procedura di verifica parallela del calcolo delle UM per la tecnica IMRT mediante un metodo modificato di integrazione della radiazione diffusa.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

82. Iori A.P., Cerretti R., De Felice L., Screnci M., Mengarelli A., Roveda A., Romano A., Et Al.

Identical, single center policy far unrelated cord blood transplant in young patients with high-risk acute lymphoblastic leukemia: a long-terrn follow-up.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. CO 052.

83. Latagliata R., Breccia M., Carmosino I., Montefusco E., Mancini M., Chistolini A., De Cuia R., Milano F., Morano S., Biondo F., Spadea A., Et Al.

Elderly patients with ph+ chronic myelogenous leukemia (CML): results of Imatinib mesylate treatment.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. PO 265.

84. Latagliata L., Carmosino I., Mengarelli A., Bongarzoni V., Anticoli P., Breccia M., Aloe M.A., Mecarocci S., Russo E., Spadea A., Petti E.C., Et Al.

A simple scoring system to evaluate prognosis of elderly patients with acute myelogenous leukemia (AML) not eligible far intensive chemotherapy.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. PU 114.

85. Lembo O., Pace A., Cei R., Giovannelli M., Guastamacchia P., Parisi C., Salis P., Vita S., Zizzari A., Pompili. A.

Continuative Care or Permanent Assistence in Brain tumor Patients: A Cost/Utility Analisys.
V National Congress of Medical Oncology-AIOM.

Roma, 21-24 Ottobre 2003

86. Lopez M.

GIST.
Proc. 1st Mediterranean Conference on Oncology-Treatment of Gastrointestinal Cancer. pp. 64-66.

Bari, 5-8 Ottobre 2003

87. Maggi G., Savarese A., Sega M.F., Palmirotta R., Gasparro S., Caruso A.

Il paziente oncologico e la sua famiglia: l'impatto emotivo del counselling genetico.
VII Convegno Nazionale Società Italiana di Psico-Oncologia (SIPO).

Acireale, 7-11 Ottobre 2003

88. Maggi G., Cilenti V., Papale M., Piperno G., Busoletti F., Pugliese P.

Strategia integrata per la cessazione dell 'abitudine al fumo.
VII Convegno Nazionale Società Italiana di Psico-Oncologia (SIPO).

Acireale, 7-11 Ottobre 2003

89. Malinverni G., Bonetta A., Bortolus R., Colombo A., Falchi A., Franzone P., Frezza F., Greco C., Lanceni A., Mauro F., Moro G., Nava S., Rossi A., Saracino B., Et Al.

Adjuvant and salvage radiation therapy for prostate carcinoma, final update of the italian survey by the AIRO national working group on prostate cancer
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

90. Mancini F., Gentiletti F., Farsetti A., D'angelo C., Jochemsen A.G., Sacchi A., Pontecorvi A., Moretti F.

MDM4 (MDMX) overexpression positively regulates activated p53 in NIH3T3 cells.
V Meeting of Molecular Oncology.

Positano, 12-15 Maggio 2003

91. Mancini F., Gentiletti F., S. Giglio, Farsetti A., Sacchi A., Moretti F. And Pontecorvi A.

Identificazione e caratterizzazione di una isoforma di MDM4 capace di stabilizzare l'onocgene MDM2 nei carcinomi papilliferi della tiroide.
XXI Giornata italiana della tiroide.

Chieti, 27-29 Novembre 2003

92. Mancini R., Aloe S., D'alessandro R., Spila A, Giunta S., Sperdeuti I., Roselli M., Guadagni F., Cosimelli M.

Significato biologico delle micrometastasi circolanti nel carcinoma colorettale.
105° Congresso della Società Italiana di Chirurgia.

Napoli, 5-8 Ottobre 2003

93. Mansueto G., Fedele F., Sciacca V., Mirri A., Vaccaio A., Gamucci T.

C6 Temozolomide (TMZ) in combination whit radiotherapy (RT) in newly diagnosed glioblastoma multiforme (GBM). A single institution experience.
V National Congress of Medical Oncology-AIOM.

Roma, 21-24 Ottobre 2003

94. Mariani L., Quattrini M., Sindico R., Galati M.

Infezione da HPV: conseguenze cliniche in ginecologia
III Congresso Nazionale Società It. Malattie Sess. Trasmesse (SIMAST)

Roma, 20-22 Marzo 2003

95. Marchetti A., Cecchinelli B., D'angelo M., D'orazi G., Iacovelli S., Sacchi A., Soddu S.

New kinases in the p53 pathway.
V Meeting of Molecular Oncology.

Positano, 12-15 Maggio 2003

96. Marzano R., Cosimelli M., Merola R., Piperno G., Sperduti I., Leonardo G., Mancini R., Cianciulli A.M.

Pathological significance of status of chromosomes 1P, 17P, 18Q and HER-2 gene in colorectal cancer and related normal colonic mucosa.
V National Congress of Medical Oncology-AIOM.

Roma, 21-24 Ottobre 2003

97. Marzi S., Landoni V., Iaccarino G., Soriani A., Benassi M., Saracino B., Arcangeli G.

Uso delle immagini digitali e di tecniche di fusione per l'analisi della riproducibilità del trattamento IMRT del tumore della prostata.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

98. Maschio M., Jandolo B.

A Case of Pregnancy in Patient With Levetiracetam.
Società Italiana di Neurologia (SIN).

Roma, 24 Ottobre 2003

99. Maschio M., Galiè E., Angelini A., Pietrangeli A., Jandolo B., Et Al.

Polineuroradicolopatia Cronica Motoria dei Nervi Mediani Post- Morbillosa: Un caso Atipico di CIDP?

S.N.O. Vibo Valentia, 28-31 Maggio 2003

100. Massa S., Simeone P., Illiano E., Benvenuto E.,Venuti A., Franconi R.

Plant-derived sequences and plant viral genes fused with a modified HPV16 E7 gene for the development of new DNA therapeutic vaccines against HPV-related tumors.
XLVII Convegno Annuale Società Italiana di Genetica Agraria.

Verona, 24-27 Settembre 2003

101. Mattiucci G. C., Pompei L., Fortuna G, Immaturo M.V., Et Al.

Acute toxicity associated with the treatment of prostate cancer with external beam radiotherapy in the elderly.
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

102. Mengarelli A., Romano A., Marcacci G.P., Pisani F., Marino M., Spadea A., Giunta S., Toglia G., Pinto A., Petti M.C.

Treatment of newly diagnosed diffuse large b.cell lymphoma in young adult patients with a combination regimen based on macop-b and rituximab.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs 027

103. Milella M., Gelibter A., Di Cosimo S., Carlini P., Ruggeri E.M., Ceribelli A., Daddiego G., Lifrieri M., Carboni F.,Vennarecci G., Ettorre G.M., Cognetti F.

Fixed dose-rate gemcitabine (gem) infusion in advanced pancreatic (p) and biliary tree (b) carcinoma.
V National Congress of Medical Oncology-AIOM. Roma, 21–24 Ottobre 2003.

Ann. Oncol., 14(4), Abs D54, 2003

104. Mojzisek M., Miccadei S., Natali P.G., Civitareale D.

Retinoblastoma protein role in the thyroid-specific activity of PAX 8.
V Meeting of Molecular Oncology.

Positano, 12-15 Maggio 2003

105. Mottolese M., Novelli F., Scordati P., Piperno G., Buglioni S., Benevolo M., Marandino F., Natali P.G., Botti C.

Espressione del recettore beta degli estrogeni in neoplasie benigne e maligne della mammella: correlazione con la fase del ciclo mestruale".
VI congresso Nazionale S.I.Ci

Montegrotto Terme (PD), 26-27 Settembre 2003

106. Mottolese M., Nádasi E.A., Botti C., Cianciulli A.M., Merola R., Buglioni S., Benevolo M., Giannarelli D., Marandino F., Del Monte G.,Venturo I., Natali P.G.

Increased expression of Fas ligand in normal peritumoral breast tissue: a potential novel risk biomarker.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

107. Nanni S., Della Pietra L., Grasselli A., Priolo C., Moretti F., Sacchi A., Pontecorvi A. And Farsetti A.

Steroid Receptor signaling and telomerase activation in the initiation and progression of human prostate cancer.
V Meeting of Molecular Oncology.

Positano, 12-15 Maggio 2003

108. Narciso P., D'offizi G., Ettorre G.M., Vennarecci G., Antonini M., Et Al.

Il trapianto epatico nei pazienti con malattia da HIV: l'esperienza italiana.
XVII Congresso Nazionale AIDS e Sindromi Correlate.

Roma, 28-30 Novembre 2003

109. Natali P.G., Rosanò L., Spinella F., Di Castro V., Bagnato A.

Leaving the neighborhood: molecular mechanisms activated by endothelin B receptor during melanoma progression.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

110. Novelli F., Botti C., Scordati P., Piperno G., Buglioni S., Benevolo M., Marandino F., Natali P.G., Mottolese M.

Estrogen receptors a and b in breast cancer and peritumoral tissues of premenopausal women: correlation with the menstrual phase.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

111. Occhipinti E.

Le metastasi cerebrali
Chirurgia estrema: quando e come.
III Seminario Internazionale di Chirurgia Digestiva Oncologica.

Roma, 6-8 Novembre 2003

112. Oppido P.A., Cattani F., Morace E., Occhipinti E.

Endoscopic recanalization of aqueduct of Sylvius

Castel dell'Ovo, Napoli, 11-13 Settembre 2003

113. Ordonez Valverde P.L., Gentile F.P., Pompei E., Benassi M., Crecco M.

Modello Entità Relazione per la Garanzia della Qualità.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

114. Pace A., Galie E., Et Al.

The Potential Role of Temozolomide Chemiotherapy in the Treatment of Progressive Low-Grade Glioma.
National Congress of Medical Oncology-AIOM. Roma, 21-24 Ottobre 2003

Ann. Oncol., 14(4), sbs C10, 2003

115. Palmirotta R., Guadagni F., Crognale S., Aceto G., Vanni C., Verginelli F., Matera S., Cama A., Battista P., Mariani-Costantini R.

Valutazione della progressione neoplastica ed eterogeneità intratumorale in neoplasie colorettali HNPCC mediante analisi della instabilità genomica.
II Congresso Nazionale A.I.F.E.G.

Chieti, 19-20 Novembre 2003

116. Papaldo P., Fabi A., Pino M.S., Carlini P., Ferretti G., Nardoni C., Mottolese M., Cianciulli A.M., Lanzetta G., Sperduti I., Di Cosimo S., Cognetti F.

Two parallel studies comparing trastuzumab (T) plus vinorelbine (V) in her2-positive with vinorelbine alone in her2-negative metastatic breast cancer (MBC) patients (PTS).
V National Congress of Medical Oncology-AIOM. Roma, 21-24 Ottobre 2003

Ann. Oncol., 14(4), abs A56, 2003

117. Pellini R., Marvaso V., Marchesi P., Morello R., Ruscito P., Pezzuto R.W., Spriano G.

La laringectomia sovracricoidea come chirurgia di recupero dopo fallimento della radioterapia. 90° Congresso Nazionale Società Italiana di Otorinolaringologia e Chirurgia Cervico-Facciale.

Roma, 28-31 Maggio 2003

118. Perrone M., Garufi C., Terzoli E., Falcicchio C., Pugliese P.

Il distress emotivo durante trattamento medico nel paziente oncologico in fase avanzata di malattia.
VII Convegno Nazionale Società Italiana di Psico-Oncologia (SIPO).

Acireale, 7-11 Ottobre 2003

119. Petrella P.P., Tomao S.,Colloca M.L., Spalletta B., Rossi R., Pericola F., Rosati M.S., Trapuzzano C., Ricciardi S.,Di Seri M.

Novel adjuvant chemotherapy in high risk breast cancer patients.
V National Congress of Medical Oncology-AIOM.

Roma, 21-24 Ottobre 2003

120. Petti M.C., Niscola P., Cortelezzi A., Francesconi M., Ferrari D., Et Al.

Effect of a new dosing regimen of epoietin alfa on anemia and quality of life in low risk myelodysplastic syndrome patients.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003

121. Pietrangeli A., De Fulviis A., Guerra M.L., Brecevich M., Casillo R., Moscatelli F., Perrotta O., Jandolo B.

Neurorehabilation of the Oncologic Patient.
Società Italiana di Neurologia (SIN)

Roma, 24 Ottobre 2003

122. Pisani F., Spadea A., Mengarelli A., Romano A., Marino M., Carpanese L., Petti M.C.

Outcome of patients with diffuse large BcelI lymphoma (DLBCL) of the breast.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs n. 028

123. Pompei E., Ordóñez P.L., D'auria L., Rossi G., Crecco M., Gentile F.P.

Progetto "QUARIS": Sviluppo, sperimentazione ed applicazione di un sistema integrato RIS.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

124. Pompili A., Occhipinti E.

Chirurgia tradizionale - approccio suboccipitale per metastasi cerebrali.
XLIII Congresso Nazionale SNO.

Vibo Valentia, 28-31 Maggio 2003

125. Pompili A., Caroli F., Cattani F., Raus L., Telera S., Occhipinti E.

Approccio mininvasivo per la rimozione dei neurinomi spinali dorsolombari.
XXVI Congresso Nazionale G.I.S.

Roma, 6-7 Giugno 2003

126. Pugliese P., Perrone M., Mariani L., Pietrangeli A., Appetecchia M.L., Sbiroli C.

Impatto della menopausa indotta dai trattamenti medici sulle aree della qualità di vita.
VII Convegno Nazionale Società Italiana di Psico-Oncologia (SIPO).

Acireale, 7-11 Ottobre 2003

127. Reni M., Pace A., Et Al.

A Phase II Trial of Salvage Temozolomide in primary CNS Lymphomas (PCNSL): an Interemi Analysis.
V National Congress of Medical Oncology-AIOM.

Roma, 21-24 Ottobre 2003.

128. Rizzo C., Kule K., De Marco F., Celiku S., Kota M., Marzano P., Muller A. Marcante M.L.

Human Papillomavirus Presence in Genital Pre-Neoplastic Lesions of Albanian Women.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

129. Rosanò L., Spinella F., Di Castro V., Ricci R., Natali P.G., Bagnato A.

Endothelin B receptor blockade inhibits molecular effectors of melanoma cell invasion and tumor growth in vivo.
Meccanismi di trasduzione del segnale in adesione e differenziamento cellulare, ABCD.

Roma, 21-22 Marzo 2003

130. Rosanò L., Spinella F., Di Castro V., Ricci R., Natali P.G., Bagnato A.

Endothelin B receptor signaling and invasive phenotype of melanoma cells.
V Meeting of Molecular Oncology.

Positano, 12-15 Maggio 2003

131. Rosanò L., Spinella F., Genovesi G., Di Castro V., Natali P.G., Bagnato A.

ET-1-induced epithelial-mesenchymal transition in human ovarian carcinoma cells.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

132. Ruscito P., Morello R., Pellini R., Pezzuto R.W., Marchesi P., Marvaso V., Spriano G.

La recidiva del cancro della laringe: definizione e classificazione.
90° Congresso Nazionale Società Italiana di Otorinolaringologia e Chirurgia Cervico-Facciale.

Roma, 28-31 Maggio 2003

133. Salis P., Pace A., Maggi G., Giovannelli M., Zizzari A., Parisi R., Lembo O. Guastamacchia P., Vita S., Pompili A.

The impact of the Brain Tumor Patients' Care Needs o their Care Givers.
V National Congress of Medical Oncology-AIOM.

Roma, 21–24 Ottobre 2003

134. Salis P., Pace A., Giovannelli M., Guastamacchia G., Maggi G., Lembo O., Parisi C., Vita S., Zizzari A., Pompili A.

The impact of the Brain Tumor Patients' Care Needs o their Care Givers.
VII Convegno Nazionale Società Italiana di Psico-Oncologia (SIPO).

Acireale, 7-11 Ottobre 2003

135. Salis P., Pace A., Giovannelli M., Gustamacchia P., Maggi G., Lembo O., Parisi C., Vita S., Zizzari A., Pompili A.

Care giver's impact of brain tumor management.
VII Convegno Nazionale Società Italiana di Psico-Oncologia (SIPO).

Acireale, 7-11 Ottobre 2003

136. Saracino B., Albino G., De Carli P., Soriani A., Landon V., Marzi S., Gallucci M., Arcangeli G.

A dose-finding study of IORT after radical prostatectomy in prostate cancer.
XIII Congresso Nazionale A.I.R.O.

Pescara, 5-8 Ottobre 2003

137. Savarese A., Corrado G., Felici A., Vizza E., Di Cocco B., Carosi M.A., Sbiroli C., Cognetti F., Mottolese M.

Expression of FAS and FAS Ligand in patients with ovarian cancer
V National Congress of Medical Oncology-AIOM. Roma, 21–24 Ottobre 2003

Ann. Oncol., 14(S4) p.73, 2003

138. Sbiroli C., Corrado G., Merola R., Vizza E., Marzano R., Vincenzoni C., Galati G.M., Cianciulli A.M.

Genetic alterations accumulate during cervical tumorigenesis
V National Congress of Medical Oncology-AIOM. Roma, 21–24 Ottobre 2003

Ann. Oncol., 14(S4) p.73, 2003

139. Simeone P., Cirilli A., Illiano E., Massa S., Giorgi C., Franconi R., Marcante M.L., Venuti A.

From plants to therapeutic vaccines against HPV-associated tumors.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

140. Soriani A., De Angelis C., Onori S., Iaccarino G., Marzi S., Landoni V., Benassi M.

Sistemi a stato solido per la dosimetria di fasci di elettroni ad alto rateo di dose
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

141. Soriani A., Iaccarino G., Landoni V., Marzi S., Benassi M., Et Al.

Soluzioni tecniche e innovazioni dosimetriche per un acceleratore dedicato alla IORT
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

142. Soriani A., Iaccarino G., Landoni V., Marzi S., Benassi M.

Dosimetria in vivo mediante MOSFET nella Radioterapia Intraoperatoria (IORT) della mammella.
III Congresso Nazionale dell'Associazione Italiana di Fisica in Medicina (AIFM).

Agrigento, 24-28 Giugno 2003

143. Spadea A., Pisani F., Romano A., Marino M., Minutilli E., Berardesca E.

Primary cutaneous natural killer celI lymphomas: a description oftwo cases.
XXXIX Congress of the Italian Society of Hematology.

Roma, 26-29 Ottobre 2003. Abs. n. PU 040.

144. Spila A., Roselli M., Martini F., Mariotti S., D'alessandro R., Aloe S., Basili S., Cosimelli M., Palmirotta R., Ferroni P., Guadagni F.

Association between serum carcinoembryonic antigen and endothelial cell adhesion molecules in colorectal cancer.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

145. Spinella F., Rosanò L., Di Castro V., Nicotra M.R., Natali P.G.

Endothelin-1 downregulates connexin43-mediated gap junctional intercellular communication in ovarian carcinoma cells.
V Meeting of Molecular Oncology.

Positano, 12-15 Maggio 2003

146. Spinella F., Rosanò L., Elia G., Di Castro V., Nicotra M.R., Natali P.G., Bagnato A.

Endothelin-1 stimulates cycloxygenase-1 and -2 expression in ovarian cancer cells
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

147. Tomacelli G., Appetecchia M.

Livelli sierologici di citocheratine nei carcinomi della tiroide.
90° Congresso Nazionale Società Italiana di Otorinolaringologia e Chirurgia Cervico-Facciale.

Roma, 28-31 Maggio 2003

148. Trisciuoglio D., Iervolino A., Candiloro A., Fibbi G., Fanciulli M., Zangemeister-Wittke U., Zupi G., Del Bufalo D.

Induction of urokinase plasminogen activator receptor in cancer cells through SP1 activation by bcl-2 overexpression.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

149. Trisciuoglio D., Scarsella M., D'amati G., Candiloro A., Iervolino A., Leonetti C., Zupi G., Del Bufalo D.

Inhibition of angiogenesis by lonidamine.
XLV Congresso Nazionale della Società Italiana di Cancerologia (SIC).

Bergamo, 9-12 Novembre 2003

150. Tomao S., Di Seri M., Romiti A., Mezi S., Caprio G., Primi F., Sarcina I., Spinelli G.P., Spalletta B., Colloca M.L.

Gemcitabine and Paclitaxel in advanced breast cancer pretreated with antracyclines.
V National Congress of Medical Oncology-AIOM.

Roma, 21–24 Ottobre 2003

151. Vennarecci G., Ettorre G.M., Antonini M., Et Al.

Liver graft toxicity related to highly active antiretroviral therapy in a HIV-HCV coinfected patient after liver transplantation.
IHPBA - Italian Chapter. Congresso Nazionale.

Napoli, 12-14 Giugno 2003

152. Vennarecci G., Ettorre G.M., Antonini M., Maritti M., Moricca P., D'offizzi G., Narciso P., Lonardo M.T., Boschetto A., Del Nonno F., Perracchio L., Palmieri G.P., Visco G., Santoro E.

Tossicità acuta da terapia antiretrovirale (HAART) dopo trapianto di fegato in un paziente con coinfezione da HIV-HCV ed associato epatocarcinoma (HCC).
XXVII° Congresso della Società di Chirurgia Oncologica (SICO).

Cagliari, 29-31 Maggio 2003

153. Vocaturo A., Novelli F., Benevolo M., Scordati P., Piperno G., Marandino F., Mottolese M.

Ibridazione in situ cromogenica:impiego su agoaspiranti mammari.
VI congresso Nazionale S.I.Ci

Montegrotto Terme (PD), 26-27 Settembre 2003

154. Vocaturo A., Piperno G., Marandino F., Canalini P., Perrone Donnorso R., Mottolese M., Vocaturo G., Sindico R., Benevolo M.

P16INK4A immunohistochemical overexpression as a biomarker of active HPV oncogene infection.
VI congresso Nazionale S.I.Ci

Montegrotto Terme (PD), 26-27 Settembre 2003

155. Vocaturo A., Novelli F., Piperno G., Scordati P., Cianciulli A.M., Merola R., Marandino F., Giannarelli D., Benevolo M., Buglioni S., Mottolese M.

Chromogenic in situ hybridization (cish): a novel method to determine her-2 amplification in histological routine sections and cytological samples.
V National Congress of Medical Oncology-AIOM.

Roma, 21–24 Ottobre 2003

156. Vocaturo G.

2003P16INK4A Immunohistochemical Overespression As A Biomarker Of Active HPV Oncogene Infection.
VI Congresso Nazionale S.I.Ci

Montegrotto Terme (PD), 26-27 Settembre 2003

157. Zarivi O., Bonfigli A., Colafarina S., Ragnetti A.M., Aimola P., Amicarelli F., Cimini A., Full C., Natali P.G., Cerù M.P., Miranda M.

Tyrosinase expression in non melanocytic tissues.
49° Convegno Gruppo Embriologico Italiano.

Pisa, 3-6 Giugno 2003

Hosted Lectures

13 Febbraio — Roberto Mantovani, Università Di Milano

Approcci strutturali e gnomici allo studio di NF-Y, l'attivazione trascrizionale che lega il CCAAT box

Organizzato: Dr.ssa Piaggio Giulia

14 Febbraio — Perez A. Edith, Division Of Hemathology/Oncology Mayo Clinic Jacksonville, Fl

Recent Advances in Breast Cancer Treatment

Organizzato: Prof. Cognetti Francesco

4 Marzo — Carlo Garufi, Oncologia Medica C, Istituto Regina Elena

Crono-terapia dei tumori solidi

Organizzato: Dr. Garufi Carlo

17 Marzo — Arthur Mercurio, Beth Israel Deaconess Medical Center

Progression to invasive carcinoma: EMT, integrins and VEGF

Organizzato: Dr.ssa Falcioni Rita

18 Marzo — Claudio Doglioni, U.O. Anatomia Patologica Ospedale "San Martino", Belluno

Identificazioni di lesioni metastatiche di origine ignota

Organizzato: Prof. Cognetti Francesco

28 Marzo — Fabrizio Loreni, Universita' Tor Vergata, Roma

Growth signaling to the translational apparatus:regulation of TOP mRNAs

Organizzato: Dr.ssa Piaggio Giulia

14 Aprile — Oskana R. Bereshchenko, Dept. Pathology Of Columbia

Regulation of BCL6 transcriptional repressor function by p300-mediated acetylation

Organizzato: Dr. Milella Michele

29 Aprile — David Givol, Dept. Molecular Cell Biology, Weizmann

DNA microarray analysis of p53 induced apoptosis and cancer related problems

Organizzato: Dr. Blandino Giovanni

5 Maggio — Paul Fisher, Columbia University - N.Y. Usa

Defining the Molecular Basis of Cancer Aggressiver

Organizzato: Dr. Giacomini Patrizio

21 Maggio — Massimo Loda, Dana Farber Cancer Institute Harvard Medical School - Boston

Diagnosi molecolare nei tumori solidi

Organizzato: Prof. Cognetti Francesco

23 Maggio — Massimo Santoro, Dept. Medical Sciences, University Of Eastern Piedmont "A. Avogadro"

The MSP receptor regulates alfa6beta4 and alfa3beta1 integrins via 14-3-3 proteins in keratinocyte re-epithelization

Organizzato: Dr.ssa Falcioni Rita

27 Maggio — Pasquale De Luca, Biogem, Napoli

Organizzazione del Gene Expression Core Lab del BioGeM

Organizzato: Dr.ssa Piaggio Giulia

29 Maggio — Iatin Shah, Memorial Hospital-New York

Nuances in the multidisciplinary treatment of differentiated carcinoma of the thyroid gland

Organizzato: Prof. Cognetti Francesco

13 Giugno — Musarò Antonio, Dipartimento Istologia Ed Embriologia Medica, Universita' Degli Studi "La Sapienza", Roma

Strategie sperimentali di terapia cellulare e genica per attenuare il "muscle wasting": ruolo dell'igf-1

Organizzato: Dr.ssa Piaggio Giulia

24 Giugno — Guy Storme, Reparto Di Radioterapia Centro Oncologico Az-Vub

Extra-cranial radiosurgery: what are the possibilities and expectations

Organizzato: Prof. Cognetti Francesco

25 Giugno — Ulrich Pfeffer, Lab. Oncologia Molecolare, Istituto Nazionale Per La Ricerca Sul Cancro, Genova

Il profilo di espressione genica rivela l'interferenza degli anti-ossidanti N-acetylcysteine e (-)-epigallocatechin-3-gallate con la risposta infiammatoria dipendente da TNF-alpha in cellule endoteliali

Organizzato: Dr.ssa Piaggio Giulia

1 Luglio — Anna Tramontano, Dipartimento Scienze Biochimiche "Rossi Fanelli", Università Degli Studi La Sapienza, Roma

"Raffaele Tecce Memorial Lecture":

Dalla conoscenza alla comprensione dei genomi: il ruolo della biologia computazionale

Organizzato: Dr.ssa Bagnato Anna, Dr.ssa Nisticò Paola, Dr. Segatto Oreste

29 Settembre — Giannino Del Sal, Lab. Nazionale Cib, Università Trieste

More about p53 family: how common interactors help explaining their specific factors

Organizzato: Dr. Blandino Giovanni

8 Ottobre — Joseph Costello, Cancer Center University California

Integrating genomic and epigenomic views of human tumors

Organizzato: Dr. Segatto Oreste

29 Ottobre — Michele Brada, The Institute Of Cancer Research And The Royal Marsden Nhs Trust Sutton, Surrey - Uk

Advances in Radiotherapy as Applied to Malignant Brain Tumours

Organizzato: Prof. Cognetti Francesco

4 Novembre — Roberto Guerrieri, Centro Eccellenza Sui Sistemi Elettronici (Arces), Università Di Bologna

Nuove biomolecole e nanotecnologie per lo sviluppo di farmaci antitumorali: chimere PNA-DNA e Lab-on-a-chip

Organizzato: Dr. Giacomini Patrizio

19 Novembre — Renato Baserga, Kimmel Cancer Center, Jefferson University - Philadelphia, Usa

Controllo della crescita cellulare da parte dell'IGF-I

Organizzato: Dr.ssa Sacchi Ada

19 Dicembre — Vittorio Sartorelli, National Institutes Healt, Bethesda

Manipulating skeletal myogenesis with deacetylases inhibito

Organizzato: Dr. Fanciulli Maurizio

Intramural Seminars c.r.s.

29 Gennaio — "La ferritina partecipa alla progressione del melanoma umano modulando la crescita cellulare e la sensibilità allo stress ossidativo"
A. Baldi

12 Febbraio — "Purging del midollo da cellule tumorali mediante trasferimento non specifico del gene p53"
S. Soddu

26 Febbraio — "Ruolo della subunita' catalitica della telomerasi nella rigenerazione tissutale in un modello sperimentale in vivo di ischemia periferica"
A. Farsetti

12 Marzo — "Ruolo biologico del fattore trascrizionale NF-Y in cellule normali e trasformate"
G. Piaggio

26 marzo — "Meccanismi di regolazione negativa di recettori ErbB"
O. Segatto

9 Aprile — "La subunità polimerasica RPB3 è coinvolta nel differenziamento muscolare trasmite il legame con miogenina"
M. Fanciulli

6 Ottobre — "RAD-51 come marcatore della progressione meiotica"
A. La Volpe

8 Ottobre — "p73 isoforms and Acute Myeloid Leukemias"
M.G. Rizzo

22 Ottobre — "Ruolo del loop regolativo MDM2/MDMX sull'attività dell'oncosoppressore p53"
F. Moretti

5 Novembre — "Topi transgenici per HLA-DRA: come esprimere differenzialmente un gene utilizzando segmenti diversi di un promotore modulare"
E. Giorda

19 Novembre — "hMena un nuovo antigene overespresso nei tumori: analisi della risposta immunitaria in pazienti affette da neoplasia della mammella"
P. Nisticò

3 Dicembre "Ruolo della chinasi HIPK2 nella regolazione dell'oncosoppressore p53"
B. Cecchinelli

17 Dicembre "Potenziale attività oncosoppressoria di RALT in neoplasie dipendenti dall'attività trasformante di recettori ErbB"
G. Sala

Multidisciplinary Seminary

14 Gennaio — Moderatore: F. Cognetti

Studi di fase I

A. Felici - D. Giannarelli

4 Febbraio — Moderatore: A. Sacchi

Apoptosi basi sperimentali ed implicazioni

G. Ferretti-G. Blandino

4 Marzo — Moderatore: F. Di Filippo

Tumori della mammella (trattamento integrato delle forme loco-regionali)

P. Papaldo-P.Vici– P. Carlini

1 Aprile — Moderatore: G. Spriano

Tumori della testa e del collo (trattamento integrato dei tumori operabili)

E.M. Ruggeri– B. Saracino

6 Maggio — Moderatore: F. Facciolo

Tumori del polmone non microcitoma (trattamento integrato dei tumori a diffusione loco-regionali)

A. Ceribelli-M.A. Mirri

3 Giugno — Moderatore: M. Gallucci

Tumori renali: aspetti biologici e clinici

P. Nisticò-M. Lopez

7 Ottobre — Moderatore: M. L. Marcante

Papillomaviruses e cancro: dalla ricerca di base alle applicazioni cliniche

F. De Marco - A.Venuti - G. Cutillo

4 Novembre — Moderatore: I. Sacchi

Principi di valutazione del rischio operatorio

V. Cilenti - F. Maramao - F. Principi

2 Dicembre — Moderatore: E. Occhipinti

Neurochirurgia Mininvasiva

E. Occhipinti - E. Morace - A. Pompili

Breakfast-Meetings

16 Gennaio — Ricostruzione mammaria
Chairman: R. De Vita
A. Varanese: Tessuto autologo
M. Pozzi: Materiali protesici

23 Gennaio — Sindromi linfoproliferative croniche
Chairman: M.C. Petti
I. Cordone: Inquadramento diagnostico
F. Pisani: Approccio Terapeutico

30 Gennaio — Carcinoma della mammella avanzato
Chairman: E. Terzoli
C. Nisticò: Epirubicina e Paclitaxel: risultati e tossicità
A. Carpino: Valutazione della cardiotossicità

6 Febbraio — Qualità della vita in Neuro-oncologia
Chairman: B. Jandolo
A. Pace: Il progetto di continuità assistenziale Ire-Regione Lazio
M. Maschio: Il trattamento antiepilettico

13 Febbraio — Melanoma dell'infanzia
Chairman: C. Catricalà
M. C. Cercato: Uno studio di sopravvivenza di popolazione in Europa dal 1978

20 Febbraio — Carcinoma della Tiroide
Chairman: M.L. Appetecchia
F. Moretti: Ruolo del loop regolativo M2/MDMX/p53 nei tumori tiroidei
A. Pontecorvi: Genetica molecolare dei tumori della Tiroide

27 Febbraio — Resezione epatica e trapianto
Chairman: G. M. Ettorre
M. Antonini: Aspetti anestesiologici e rianimatori
G. Vennarecci: Indicazione, tecnica e risultati

6 Marzo — Tumori della cervice uterina
Chairman: I. Venturo
E. Vizza: Gestione del Pap test anomalo e trattamento delle displasie della cervice uterina
A. Vocaturo: HPV nello screening del carcinoma della cervice

13 Marzo — Case Report
Tumori Neuroendocrini
M.L. Appetecchia: Glucagonoma metastatico
Discussant: E. Terzoli

20 Marzo

GIST

CHAIRMAN: M. CARLINI
V. FERRARESI: Approccio terapeutico
M. MILELLA: Gestione clinica

27 Marzo

Ginecologia Oncologica

CHAIRMAN: C. SBIROLI
L. MARIANI: Terapia ormonale sostitutiva nelle pazienti oncologiche

3 Aprile

Discrasie Plasmacellulari

CHAIRMAN: F. GUADAGNI
C. GRECO: Individuazione di potenziali nuovi markers
A. SPADEA: Gammopatie monoclonali e mieloma multiplo: dal laboratorio alla clinica

10 Aprile

La palliazione nel Carcinoma Rettale

CHAIRMAN: V. CASALE
R. LAPENTA: Endoscopia digestiva
R. MANCINI: La chirurgia nei pazienti ultrasettantenni

17 Aprile

Distress emotivo in oncologia

CHAIRMAN: P. PUGLIESE
M. PERRONE: Prevenzione e cura nel percorso terapeutico
A. PIETRANGELI: Supporto Psicofarmacologico

8 Maggio

La qualità di vita

CHAIRMAN: E. TERZOLI
A. FABI - P. PUGLIESE: Qualità di vita e cancro della mammella in fase adiuvante

15 Maggio

Colon retto avanzato

CHAIRMAN: M. LOPEZ
M. ZEULI: Ruolo e sviluppo delle fluoropirimidine orali
C. GARUFI: Risultati della chemioterapia cronomodulata

22 Maggio

Leucemia acuta promielocitica

Article Review
A. SPADEA: Passato, presente e futuro della terapia
DISCUSSANT: M.C. Petti

29 Maggio

Mesotelioma pleurico

CHAIRMAN: F. FACCIOLO
E. CONTI: Epidemiologia
M. RINALDI: Trattamento medico

5 Giugno

Neoplasie e Trombosi

CHAIRMAN: M. RINALDI
L. CONTI: Inquadramento diagnostico
R. PISTOLESE: Trattamento clinico

12 Giugno

Endocrinoterapia del carcinoma della mammella

Article review
G. FERRETTI: Fulvestrant e sequenza endocrina in post menopausa
DISCUSSANT: P. Carlini

19 Giugno — Trapianto di Mandibola

Chairman: R. De Vita

Dr. R. Pellini: Report clinici

26 Giugno — Terapia intensiva in oncologia

Chairman: E. Arcuri

F. Centulio: Nuova classificazione

L. Laurenzi: Riflessi clinici-etici ed economici in oncologia

18 Settembre — Neoplasie d'interesse neurochirurgico

Chairman: E. Occhipinti

F. Caroli: Procedure chirurgiche e tecniche di stabilizzazione delle neoplasie vertebrali

A. Pompili: Tumori della regione ipofisaria e fistole liquorali

24 Settembre — Carcinoma Mammario

Chairman: R. De Vita

C. Botti: Chirurgia conservativa oggi: rivalutazione critica

M. Pozzi: Il rimodellamento immediato della mammella dopo quadrantectomia

2 Ottobre — Carcinoma della vulva

Chairman: C. Sbiroli

M. Mottolese: Valutazione di p53, Ki-67 e Cox-2

L. Mariani: Correlazione sull'outcome

9 Ottobre — Carcinoma Rettale

Chairman: M. Cosimelli

R. Mancini: Avanzamenti diagnostici e terapeutici

G. Piperno: Fattori patologici non convenzionali

14 Ottobre — Sistemi impiantabili

Chairman: C. Garufi

L. Laurenzi - A. Calamaro: Considerazioni su selezione dei pazienti - complicanze-economia

16 Ottobre — Ospedalizzazione Domiciliare

Chairman: E. Terzoli

F. Izzo - P. Pugliese: Il futuro negli Istituti a carattere Scientifico

30 Ottobre — Fumo passivo e tutela della salute nei posti di lavoro

Chairman: V. Cilenti

F. Facciolo: Storia naturale e nosografismo del tumore polmonare

R. Marchini: Progetto ospedale senza fumo

6 Novembre — Terapia del dolore

Chairman: E. Arcuri

L. Di Emidio - L. Laurenzi: La scarsa risposta agli oppioidi nel paziente neoplastico: aspetti clinici e sperimentali

13 Novembre

Neoplasie Colorettali

CHAIRMAN: F. GUADAGNI

C. GARUFI: Implicazioni cliniche delle acquisizioni in campo biomolecolare

C. GRECO: Alterazioni geniche, apoptosi, e molecole di adesione nel corso della progressione neoplastica

20 Novembre

Tumori della prostata

CHAIRMAN: M. GALLUCCI

P. CARLINI: Il trattamento integrato del carcinoma della prostata localizzato

S. SENTINELLI: La diagnosi dell'adenocarcinoma della prostata post-terapia neoadiuvante

25 Novembre

Neoplasie Vescicali

CHAIRMAN: E. RUGGERI

A. M. CIANCIULLI: Marcatori Genetici e Molecolari: significato Prognostico e/o di Risposta a Terapia"

E. RUGGERI: Stato di avanzamento sulla terapia adiuvante del carcinoma della vescica. Studio nazionale

4 Dicembre

Carcinoma della Mammella

CHAIRMAN: P. CARLINI

G. FERRETTI: Fulvestrant e sequenza endocrina nel carcinoma della mammella

M. MOTTOLESE: Ruolo del recettore Beta nel carcinoma della mammella

11 Dicembre

Tumori tiroidei

CHAIRMAN: C.L. MAINI

P. RUSCITO: Il trattamento di N chirurgico dei tumori della tiroide

R. SCIUTO: Terapia radiometabolica dei tumori della tiroide

18 Dicembre

Carcinoma gastrico

CHAIRMAN: V. CASALE

D. ASSISI: Trattamento Nutrizionale nei pazienti gastrectomizzati

F. PISANI: Trattamento ematologico

Organization of Seminars and Meetings

Bari, 23-24 Gennaio	Corso teorico-pratico AICC sulle "Metodologie di studio dell'angiogenesi" (Dr. Leonetti C. in collaborazione con l'Università degli Studi di Bari)
Alghero, 30 marzo-1 aprile	VI Conferenza Nazionale AIOM: "Bersagli molecolari e nuove terapie biologiche in oncologia" (Prof. Cognetti F.)
Cortona, 10-12 Aprile	Convegno SIBBM 2003-"Struttura e Funzione del Genoma" (Dr. Piaggio G.)
Roma, 5-7 Maggio	Convegno su: "Il malato oncologico. Dal curare al prendersi cura: aspetti biologici e aspetti relazionali" (Dr.ssa Caruso A.)
Fabriano, 8 maggio	V Congresso interregionale AIOM: "La qualità della vita in oncologia: un obiettivo possibile" (Prof. Cognetti F.)
Taormina, 11-14 maggio	VII Conferenza Nazionale AIOM: "Le terapie integrate in oncologia - dall'empirismo alla realtà clinica, dove stiamo andando?" (Prof. Cognetti F.)
Vibo Valentia 28-31 Maggio	Congresso S.N.O. (Prof. Jandolo. B.)
Roma, 21 Giugno	Convegno su: "Malattia tromboembolica" (Prof. Terzoli E.)
Brescia, 23 Giugno	Corso teorico-pratico AICC sull'"Utilizzo di cellule in terapie sperimentali" (Dr. Leonetti C. in collaborazione Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna)
Rionero in Vulture, 26-28 Giugno	Convegno "Approccio multidisciplinare in Oncologia" (Dr. Carlini P.)
Roma, 26-27 Giugno	Convegno: "Qualità di Vita ed equipe multidisciplinare: la nuova frontiera dell'oncologia" (Prof. Cognetti F.)
Viterbo, 5 luglio	II Incontro regionale giovani oncologi AIOM. (Prof. Cognetti F.)

Roma, 5 Settembre	Convegno-Riunione di aggiornamento: "Farmaci antiepilettici e chemioterapici: quali interazioni farmacologiche? (Prof. Jandolo B., Dr.ssa Maschio M.)
L'Aquila, 19 settembre	Riunione annuale GIM: "Trattamento adiuvante del carcinoma mammario: stato dell'arte e prospettive future" (Prof. Cognetti F.)
Roma, 2 Ottobre	Giornata di studio: "Il mesotelioma pleurico" (Prof. Cognetti F.)
Tunisi, 9 ottobre	Seminario di Oncologia (Prof. Cognetti F.)
Rimini, 11 Ottobre	V Convegno FISV - Minisimposio: "Regolazione della trascrizione" (Dr. Piaggio G.)
Roma, 11-15 Ottobre	Gruppo di Studio di Neuro-Oncologia Congresso S.I.N. (Prof. Jandolo B.)
Roma, 21-24 Ottobre	V Convegno Nazionale AIOM (Prof. Cognetti F.)
Roma, 29 Ottobre	Convegno nell'ambito di Bibliocom 2003 "La Buona informazione è la migliore medicina 2003 - Dalla tecnologia dell'informazione e comunicazione (ICT) alla gestione integrata delle conoscenze biomediche: i progetti" (Dr.ssa Cognetti G.)
Brescia, 10-12 Novembre	Corso teorico-pratico AICC sulle "Cellule staminali da tessuto adulto" (Dr. Leonetti C. in collaborazione con l'Istituto Zooprofilattico Sperimentale di Brescia e con l'Università degli Studi di Milano)
Roma, 6-8 Novembre	III Seminario Internazionali di Chirurgia Digestiva Oncologica. "Chirurgia Estrema: quando e come" (Prof. Santoro E.)
Roma, 12 Novembre	Convegno AIOM - CNR "Le Terapie orali in Oncologia" (Dr. Carlini P.)
Roma, 15 Novembre	Workshop-Incontri FIMMG-AIGO Lazio: "Gastroenterologia basata sull'evidenza" (Dr.ssa Stigliano V.)
Modena, 1-2 Dicembre	Convegno Annuale AICC 2003 (Dr. Leonetti C. in collaborazione con l'Università degli Studi di Modena "Biologia Postgenomica" -Università degli Studi di Modena)
Roma, 12 Dicembre	Convegno "Innovazioni diagnostiche e terapeutiche nel carcinoma mammario". (Dr. Carlini P.)

Teaching Courses

Corso per volontari A.R.V.A.S, anno 2003

55° Corso di formazione per Assistenti Volontari A.M.S.O., anno 2003

II Simposio internazionale sullo stato dell'arte nell'impiego clinico dei laser e della luce pulsata
(Corso di aggiornamento tecnologico e strumentale)
(Prof. De Vita R.)
Roma, 17-18 Gennaio

VI corso biennale in psicologia oncologica
(Dr.ssa Caruso A.)
Roma, Febbraio - Novembre

Corso di formazione per il personale di comparto del Servizio Farmacia
(Dr. Musicco F.)
Roma, Febbraio

Corso di aggiornamento AIOM-AIRO
"Il trattamento multidisciplinare delle neoplasie del distretto cervico-facciale"
(Prof. Arcangeli G.)
Roma, 21 Febbraio

Corso su: "Diagnostica molecolare: principi di base ed applicazioni"
(Dr.ssa Guadagni F.)
Roma, 27-28 Marzo

Corso della Mediterranean School of Oncology.
"Somministrazione continua di farmaci in oncologia: strumenti e procedure"
(Prof. Terzoli E., Dr. Garufi C.)
Roma, 28-29 Marzo

Corso di Chirurgia in oncologia medica
(Prof. Sbiroli C.)
Roma, Marzo-Settembre

Corso di aggiornamento AIRO-AIOM.
"L'integrazione terapeutica nel tumore della prostata: cosa è standard e cosa è da definire"
(Prof. Arcangeli G.)
Roma, 4 Aprile

Corso teorico-pratico di urologia
(Prof. Gallucci M.)
Roma, 17 Aprile

XV Corso Internazionale Tumore Gastrico
(Prof. Santoro E.)
Roma, 4-7 Maggio

Giornata di studio: "I tumori Borderline epiteliali dell'ovaio"
(Dr. Vizza E.)
Roma, 9 Maggio

Corso Residenziale Accademia Nazionale di Medicina su: "Problematiche ed evoluzioni terapeutiche in neuro-oncologia"
(Dr. Carapella C.M.)
Milano, 9 Maggio

Simposio Monotematico: "Il carcinoma della mammella biologia molecolare e terapie innovative"
(Prof. Lopez M.)
Roma, 16 Maggio

Corso teorico-pratico "Diagnostica molecolare: principi di base ed applicazioni"
(Dr.ssa Guadagni F.)
Roma, 27-28 Maggio

Corso di formazione: "Trattamento delle lesioni ossee dolorose mediante RF", "Evoluzione e prospettive delle tecniche radiologiche topografiche (TC e RM)"
(Prof. Crecco M., Dr. Carpanese L.)
Roma, 23 Giugno

Master di chirurgia Cervico-facciale
(Prof. Spriano G.)
Roma, 9-13 Giugno

Corso su: "Advances in biology and treatment of malignant glial tumors"
(Dr. Carapella C.M.)
Roma, 23-24 Giugno

Corso teorico-pratico per il trattamento del carcinoma vescicale superficiale
Scuola Superiore di Oncologia-Scienze Biomediche
(Prof. Gallucci M.)
Roma, 27-28 Giugno

Corso di Chirurgia dal vivo: "tumori vertebrali: tecniche ablative e ricostruttive"
(Prof. Occhipinti E.-Dr. Caroli F.)
Roma, 19-20 Settembre

Corso di aggiornamento AIRO/SIE: "Trattamento multidiscipplinare dei linfomi extra-nodali"
(Prof. Arcangeli G.)
Roma, 25 Settembre

Corso permanente per i medici di medicina generale da parte della U.O. di gastroenterologia ed endoscopia digestiva.
(Dr. Casale V.)
Roma, 25 Settembre

Corso Residenziale Dolore e le Cure Palliative.
(Prof. Arcuri E.)
Firenze, 29-30 Settembre

Giornata di studio: "Mesotelioma Pleurico"
(Prof. Facciolo F.-Prof. Cognetti F.)
Roma, 2 Ottobre

VIII Corso Residenziale dell'Associazione Italiana di Neuro-Oncologia. "Trattamento integrato dei gliomi maligni"
(Dr. Carapella C.M.)
Ancona, 2-4 Ottobre

Corso di formazione ed aggiornamento per medici e fisici: "Protezione di operatori e pazienti in medicina nucleare"
(Prof. Maini M.)
Roma, 5-13-20 Novembre

Corso teorico-pratico di urologia.
(Prof. Gallucci M.)
Roma, 13-14 Novembre

Corso teorico-pratico: "Le Terapie settimanali nelle principali neoplasie"
(Prof. Terzoli E., Dr.ssa Nisticò C.)
Roma, 20 Novembre

Convivium MOLTENI "Nuove conoscenze sul dolore oncologico ed implicazioni cliniche nella Terapia con Oppioidi"
(Prof. Arcuri E.)
Roma, 21-22 Novembre

Roma, 26-28 Novembre
VI Congresso nazionale SITILO (Società Italiana di Terapie integrate locoregionali in oncologia)
(Prof. Di Filippo F.)

Corso della Mediterranean School of Oncology
(Prof. Terzoli E.)
Roma, 28-29 Novembre

Corso di aggiornamento AIRO/AINO: "Integrazione terapeutica nei tumori preventivi del sistema nervoso centrale dell'adulto: cosa è standard e cosa è da definire"
(Prof. Arcangeli G.)
Roma, 12 Dicembre

Post Graduate Specialization Courses and Venues

Anatomia Patologica

Pathology

Università degli Studi "Tor Vergata", Roma

Insegnamenti: Tecnica e Diagnostica delle Autopsie, Anatomia Patologica del Tratto Gastro-Digerente, Statistica, Istocitodiagnostica in Ematologia

Anestesia e Rianimazione

Anaesthesiology and Intensive Care

Università "Campus Biomedico", Roma

Insegnamenti: Terapia del dolore

Chirurgia Generale

General Surgery

Università degli Studi "La Sapienza", Roma.

Insegnamenti: Patologia Mammaria e Melanomi, Chirurgia Oncologica, Terapie Parachirurgiche, Chirurgia Toracica

Università degli Studi "Tor Vergata", Roma

Insegnamenti: Chirurgia Oncologica

Chirurgia Plastica

Plastic and reconstructive Surgery

Università degli Studi "La Sapienza", Roma

Insegnamenti: Chirurgia Oncologica

Chirurgia Toracica

Thoracic Surgery

Università degli Studi "La Sapienza", Roma

Insegnamenti: Endoscopia Toracica

Chirurgia Vascolare

Vascular Surgery

Università degli Studi "La Sapienza", Roma

Insegnamenti: Accessi vascolari in Chirurgia Oncologica

Dermatologia e Venereologia

Dermathology

Università degli Studi "Tor Vergata" Roma

Insegnamenti: Dermatologia Clinica

Ematologia

Emathology

Università degli Studi "La Sapienza", Roma

Insegnamenti: Manifestazioni cliniche delle emopatie

Endocrinologia e malattie metaboliche

Endocrinology and Metabolic Diseases

Università degli Studi "La Sapienza", Roma

Insegnamenti: Endocrinologia, Andrologia, Malattie del Ricambio

Fisica Sanitaria

Medical Physics

Università degli Studi "Tor Vergata", Roma

Insegnamenti: Strumentazione Ospedaliera II, Risonanza Magnetica, Brachiterapia, Garanzia della qualità in Radiodiagnostica, Aspetti operativi dei controlli di qualità

Gastroenterologia

Gastroenterology

Università degli Studi "La Sapienza", Roma

Insegnamenti: Endoscopia digestiva, Ematologia

Geriatria

Geriatric

Università degli Studi "La Sapienza", Roma

Insegnamenti: Terapia del dolore, La patologia oncoematologica dell'anziano

Medicina Nucleare

Nuclear Medicine

Università degli Studi "La Sapienza", Roma

Insegnamenti: Indagini medico-nucleari in oncologia

Università Cattolica del Sacro Cuore, Roma

Insegnamenti: Struttura ed organizzazione dei Servizi di Medicina Nucleare

Neurochirurgia

Neurosurgery

Università degli Studi "Tor Vergata", Roma

Insegnamenti: Neurochirurgia III, Neurochirurgia Stereotassica e Funzionale, Neurofisiologia

Neurologia

Neurology

Università degli Studi "La Sapienza", Roma

Insegnamenti: Patologia Elettromiografica ed Elettroneurografica

Oncologia

Oncology

Università degli Studi "La Sapienza", Roma

Insegnamenti: Endoscopia digestiva, Epidemiologia, Biologia Molecolare, Terapia del dolore, Oncologia Medica, Chirurgia toracica oncologica, Determinazioni dei Recettori e loro Implicazione Terapeutica, Immunologia, Biologia Molecolare

Università degli Studi "Tor Vergata", Roma

Insegnamenti: Oncologia Medica, Anticorpi monoclonali in Oncologia: Nuove Prospettive, Chirurgia dei tumori del sistema endocrino, Chirurgia Generale I, Farmacoresistenza, Ruolo della terapia radiante nel carcinoma rettale

Università Cattolica del S. Cuore, Roma

Insegnamenti: Immunologia

Università degli studi, L'Aquila

Insegnamenti: Patologia Molecolare

Ostetricia e Ginecologia

Obstetries and gynecology

Università degli studi, Palermo

Insegnamenti: Tecnica chirurgica in Ginecologia Oncologica

Università degli studi G. D'Annunzio, Chieti

Insegnamenti: Storia naturale di principali tumori umani, terapie integrate (trial clinici)

Patologia Clinica

Clinical Pathology

Università degli Studi "La Sapienza", Roma.

Insegnamenti: Elementi di Indagini Citodiagnostiche, Patologia Generale, Tecniche analitiche II

Tisiologia e malattie apparato respiratorio

Pulmonary diseases

Università degli Studi "La Sapienza", Roma

Insegnamenti: Chirurgia Toracica

Urologia

Urology

Università degli Studi "La Sapienza", Roma

Insegnamenti: Urologia d'urgenza, Endourologia

Teaching Courses

Corso di Perfezionamento in Oncobiologia
Università degli Studi, Palermo

Insegnamenti: Biotecnologie nella diagnostica oncologica di laboratorio, Controllo di qualità in oncobiopatologia

Corso di Laurea breve per Tecnici di Neurofisiopatologia
Università degli Studi "Tor Vergata", Roma

Insegnamenti: Tecniche di Registrazione Elettromiografiche

Corso integrato di Batteriologia e Virologia
Università degli Studi "La Sapienza", Roma

Insegnamenti: Patologia Clinica

Corso di Laurea in Medicina Veterinaria
Università "Federico II", Napoli

Insegnamenti: Malattie infettive

Corso di Laurea in Medicina e Chirurgia
Università degli Studi "La Sapienza", Roma

Insegnamenti: Oncologia Medica

Corso di Laurea in terapisti della Riabilitazione
Università di Bologna

Insegnamenti: Servizi sociali e relazioni umane

Corso di Laurea in terapisti dell'età evolutiva
Università degli Studi "La Sapienza", Roma

Insegnamenti: Biologia applicata

Scuola Medica Ospedaliera di Roma e della Regione Lazio.
Insegnamenti: Prevenzione, diagnosi e terapia chirurgica dei tumori del colon-retto.

Corso di Laurea in Scienze motorie
Università Cattolica del Sacro Cuore, Milano

Insegnamenti: Endocrinologia

Corso di Laurea in Scienze Motorie
Facoltà di Scienze Motorie, Cassino

Insegnamenti: Farmacologia

Corso di specialista in Biotecnologie applicabili alle malattie oncologiche
DIMOTECH, Università degli studi di Bari

Insegnamenti: HLA e Tumori: un approccio biotecnologico, Impiego di anticorpi monoclonali in diagnostica in vivo

Istituto di Patologia Medica
Università Cattolica del Sacro Cuore, Milano
Insegnamenti: Endocrinologia

Corso di II livello in traduzione specializzata
Università degli Studi "La Sapienza", Roma
Insegnamenti: Thesauri e terminologia per la documentazione biomedica

Corso su Ricerca/Intervento su percorsi formativi finalizzati alla sperimentazione di moduli professionalizzati nelle nuove lauree delle università abruzzesi
Università degli studi di L'Aquila
Insegnamenti: Terminologie tecnico scientifiche e traduzione

Corso di Laurea in Ingegneria dei Sistemi
Università degli Studi "Tor Vergata", Roma
Insegnamenti: Ultrasuoni, Risonanza Magnetica

Corso integrato di Medicina e Chirurgia Specialistica
Università degli Studi "La Sapienza", Roma
Insegnamenti: Malattie dell'Apparato Cardiovascolare

Corso integrato di Medicina e Chirurgia d'urgenza e Terapia Intensiva
Università degli Studi "La Sapienza", Roma
Insegnamenti: Medicina Interna

Overseas Training and Experience

Dr.Ssa Alessia Baccarini - Laboratorio "C" Oncogenesi Molecolare
(30 Maggio - 31 Dicembre 2003)
Dana Farber Cancer Institute, Harvard University, Boston, USA.

Dr.Ssa Di Cosimo Serena - S.C. Oncologia Medica "A"
(giugno 2003 - ottobre 2004)
Hospital Universitari Vall d'Hebron, Psg. Vall d'Hebron 119-129, 08035, Barcelona, Spain.

Dr. Alain Gelibter - S.C. Oncologia Medica "A"
(agosto 2002-gennaio 2003)
Department of Medical Oncology and Laboratory of Molecular Cytogenetic, Sheba Medical Center (Tel Aviv, Israel).

Dr.Ssa Laura Marucci - S.C. Radioterapia
(1 - 13 dicembre 2003)
University of Texas M.D. and Anderson Cancer Center Houston (Texas)

Dr.Ssa Giulia Piaggio - Laboratorio "C" Oncogenesi Molecolare
(8 luglio - 3 agosto 2003)
Laboratory of Molecular Growth Regulation - National Institute of Child Health and Human Development - National Institutes of Health, (NIH), Bethesda USA

Dr.Ssa Maria Simona Pino - S.C. Oncologia Medica A
(giugno 2003 - ottobre 2004)
University of Texas M.D. and Anderson Cancer Center Houston (Texas)

Dr. Luca Paoluzzi - S.C. Oncologia Medica A
(settembre 2003 - settembre 2004)
Department of Pharmacology and Molecolar Biology - National Institute of Child Health and Human Development - National Institutes of Health, (NIH), Bethesda USA

Participation to Definition of Guidelines

Progetto congiunto Istituto Superiore di Sanità- Ministero dell'Ambiente: "Effetti sulla salute dell'inquinamento atmosferico nelle aree urbane". Vedi rapporti dell'Istituto Superiore della Sanità 2003.
Dr.ssa Verdina A., Dr.ssa Galati R.

Progetto congiunto Istituto Superiore di Sanità -: ISTISAN 03/1 IT
Linee guida per la garanzia di qualità nella radioterapia intraoperatoria.
Dr.ssa Soriani A.

Gruppo di Studio "Proteine". Metodologia di studio delle componenti monoclonali nei liquidi biologici. Università di Pavia
Dr.ssa Greco C.

Research Projects

Finanziamenti Aeroporti di Roma-Enel-Telecom Italia

Screening sul tumore del polmone. La TC-spirale "low-dose" nella diagnosi precoce del cancro del polmone in soggetti a rischio.

Responsabile: Salvatore Giunta

Finanziamenti Associazione Italiana per la Ricerca sul Cancro (A.I.R.C.)

Endothelin-1 receptor blockade as terapeutical target in ovarian carcinoma.

Responsabile: Anna Bagnato

P53 family interactions as determinants for tumor response to anti-neoplastic treatment.

Responsabile: Giovanni Blandino

Impact of Biological Profile, Chemoradiation and Surgery of Rectal Cancer on Downstaging and Quality of Life.

Responsabile: Maurizio Cosimelli

Study of the mechanisms by which bcl-2 modulates angiogenesis.

Responsabile: Donatella Del Bufalo

Mechanisms that regulate the function of alpha6beta4 integrin during tumor progression.

Responsabile: Rita Falcioni

Molecular characterization of the mechanisms by which Che-1 affects Rb activity.

Responsabile: Maurizio Fanciulli

Altered HLA phenotypes in tumors and their correction.

Responsabile: Patrizio Giacomini

Molecular changes in peritumoral non-involved breast tissue: implications for early diagnosis of cancer.

Responsabile: Marcella Mottolese

SEREX-defined antigens in breast cancer: characterization of their immunogenicity in breast cancer patients.

Responsabile: Paola Nisticò

Peptides interfering with the cell cycle machinery. A hypothesis for targeted cancer therapy.

Responsabile: Marco Giorgio Paggi

Biological role of the transcription factor NF-Y in cell growth and transformation.
Responsabile: Giulia Piaggio

Identification of genes activated/repressed by p53 family members using microarrays: implications for prognosis and therapy.
Responsabile: Ada Sacchi

Negative regulation of signals propagated by Erb-B receptors.
Responsabile: Oreste Segatto

Role of the p53 onco-suppressor in the differentiation of normal and tumor cells: dissection of moleculare mechanisms (N.U.S.U.G.).
Responsabile: Silvia Soddu

New therapeutic strategies against cervix carcinoma: ET-1 receptor antagonist and vaccines against the HPV.
Responsabile: Aldo Venuti

Study of intracellular redox-state and telomerase involvement in c-Myc mediated apoptosis to design effective therapeutic strategies in melanoma.
Responsabile: Gabriella Zupi

Finanziamenti C.E.E.

Artificial regulation of cell cycle in cancer cells and its potential clinical applications.
Responsabile: Pier Giorgio Natali

Quality of Life and Managment of Living Resources "Mutant p53 Gain of Function Activities as Determinants for Tumor Prognosis and Therapy".
Responsabile: Ada Sacchi

Finanziamenti CNR-MIUR

Ruolo dell'endotelina-1 nella progressione del carcinoma ovarico: nuove prospettive terapeutiche.
Responsabile: Anna Bagnato

Studio del ruolo di p73 nel differenziamento attraverso la caratterizzazione della sua regolazione trascrizionale e l'identificazione di nuovi geni bersaglio.
Responsabile: Giovanni Blandino

Monitoraggio biochimico del marker di attività angiogenica VEGF: Implicazioni prognostiche e terapeutiche nel melanoma cutaneo.
Responsabile: Francesco Cognetti

Terapie adiuvanti basate sul profilo biologico del carcinoma colorettale curabile.
Responsabile: Maurizio Cosimelli

Comportamento alle coapplicazioni delle metodologie statistico matematiche alla diagnostica clinica per immagini con particolare riferimento alla RM nella patologia mammaria.

Responsabile: Marcello Crecco

Studio multicentrico di fase II volto a testare in modo formale l'attività del regime TNF/adriamicina in termini di risposte patologiche complete in pazienti affetti da sarcoma delle parti molli localmente avanzato.

Responsabile: Franco Di Filippo

Indicatori biologici di risposta ai trattamenti clinici in oncologia. Studio delle alterazioni del sistema FAS/FASL nel carcinoma della mammella.

Responsabile: Marcella Mottolese

Identificazioni di nuovi antigeni nel carcinoma della mammella: definizione di nuovi protocolli immunoterapeutici e ruolo della risposta immune nell'andamento clinico della malattia.

Responsabile: Paola Nisticò

Ruolo biologico del complesso trascrizionale legante le CCAAT, NF-Y nell'arresto in G2.

Responsabile: Giulia Piaggio

Differenziazione p53 e p73 - Dipendente nella terapia del cancro.

Responsabile: Ada Sacchi

Modulazione del trattamento antineoplastico in relazione all'espressione di alcuni geni coinvolti nel processo apoptotico e nella farmacoresistenza.

Responsabile: Gabriella Zupi

Finanziamenti Compagnia di San Paolo

Tumori Testa-Collo: Identificazione di Targets Molecolari per Diagnosi Precoce e Terapia.

Responsabili: Maria Luisa Marcante, Aldo Venuti

Finanziamenti Istituto Superiore di Sanità

Meccanismi di resistenza e terapie innovative del melanoma umano.

Responsabile: Francesco Cavaliere

Il valore predittivo del test "estreme drug resistance" in pazienti con carcinoma ovarico refrattario sottoposti a chemioterapia test-selezionata confrontata con chemioterapia non-test selezionata.

Responsabile: Francesco Cognetti

Sviluppo di nuove strategie di immunoterapia e terapie combinate contro i tumori: studio clinico dei parametri ematologici in pazienti affetti dal melanoma e trattati con immunoterapia.

Responsabile: Virginia Ferraresi

Sviluppo di nuove strategie di immunoterapia e terapie combinate contro i tumori: istituzione di una banca biologica.

Responsabile: Fiorella Guadagni

Carcinoma del colon-retto: bersagli molecolari rilevanti per il processo tumorigenico e per l'immunoterapia.

Responsabile: Fiorella Guadagni

Studio caso-controllo sui tumori dell'encefalo, della testa e del collo in relazione all'uso di telefoni cellulari.

Responsabile: Bruno Jandolo, Emanuele Occhipinti

Studio dell'efficacia di nuove modalita' di "delivery" di molecole antitumorali per migliorare il trattamento dei tumori solidi umani

Responsabile: Carlo Leonetti

Sviluppo di nuove strategie antitumorali: identificazione dei target subcellulari mediante l'applicazione di metodologie avanzate.

Responsabile: Carlo Leonetti

Sviluppo di nuove strategie di immunoterapia e terapie combinate contro i tumori: monitoraggio immunologico di pazienti vaccinati con dc e peptidi contro il melanoma.

Responsabile: Pier Giorgio Natali

Carcinoma del colon-retto: bersagli molecolari rilevanti per il processo tumorigenico e per l'immunoterapia.

Responsabile: Pier Giorgio Natali

Definizione di nuovi criteri per la selezione di pazienti da arruolare in studi chimici di immunoterapia

Responsabile: Paola Nisticò

Controllo della stabilità del genoma: bersagli molecolari rilevanti nella prevenzione e nel controllo del processo neoplastico.

Responsabile: Ada Sacchi

Differentiation defects and transformation potential of myelodiplastic syndroms: underlyng mechanisms and averriding strategies.

Responsabile: Silvia Soddu

Approccio proteomico allo studio della malattia neoplastica.

Responsabile: Silvia Soddu

Finanziamenti Lega Italiana per la Lotta contro i Tumori

La relazione d'aiuto nella pratica clinica infermieristica.

Responsabile: Anita Caruso

Validazione di strategie di diagnosi clinica e molecolare per la valutazione del rischio per la diagnosi e per la prevenzione del tumore mammario ad incidenza familiare.
Responsabile: Francesco Cognetti

Studio delle alterazioni fenotipiche e molecolari nel tessuto peritumorale morfologicamente indenne del carcinoma mammario: implicazioni diagnostiche.
Responsabile: Marcella Mottolese

Progetto Voce.
Responsabile: Giuseppe Spriano

Progetto pilota integrato di informazione, educazione sanitaria e formazione oncologica per il personale docente delle Scuole Medie Superiori.
Responsabile: Silverio Tomao

Finanziamenti Ministero della Salute

Caratterizzazione biologica delle neoplasie polmonari: (NSCLC): integrazioni diagnostiche ed implicazioni terapeutiche.
Resonsabile: Sandro Carlini

Studio dei meccanismi molecolari attraverso cui bcl-2 modula la risposta a trattamenti antitumorali.
Responsabile: Donatella Del Bufalo

Impatto clinico delle micrometastasi nel linfonodo sentinella e nel sangue in pazienti con melanoma.
Responsabile: Franco Di Filippo

Guadagno di funzione delle proteine p53 mutate come indicatore della prognosi e terapia dei tumori.
Responsabile: Ada Sacchi

Uptake intratumorale come causa di scarsa risposta alla morfina nella terapia del dolore da cancro.
Responsabile: Edoardo Arcuri

Programma di sorveglianza per l'identificazione e prevenzione di tumori mammari ad alto rischio genetico.
Responsabile: Francesco Cognetti

Caratterizzazione del ruolo di Che-1 nel fenotipo neoplastico e nell'apoptosi.
Responsabile: Maurizio Fanciulli

Profili di espressione genica e immunoevasione: dal melanocita al melanoma metastatico.
Responsabile: Pier Giorgio Natali

Ruolo di nuovi indicatori biomolecolari dell'epatocarcinoma su cirrosi in relazione all'efficacia dei diversi approcci terapeutici.
Responsabile: Eugenio Santoro

Identificazione di molecole coinvolte nello stress ossidativo quali bersagli per la terapia antitumorale.

Responsabile: Gabriella Zupi

Profili di espressione dei geni p53-relati p73/p63 in cellule normali e trasformate: identificazione di nuovi bersagli terapeutici.

Responsabile: Giovanni Blandino

Sviluppo di modelli animali transgenici per gli oncogeni c-Myc, Ret ed il gene oncosoppressore Fhit.

Responsabile: Gennaro Citro

Controllo neuroendocrino della crescita a modulazione immunitaria nei tumori epiteliali del timo.

Responsabile: Franco Facciolo

Ruolo del microambiente e ricerca di nuovi target terapeutici nel carcinoma prostatico.

Responsabile: Michele Gallucci

Caratterizzazione funzionale e molecolare degli effetti di farmaci interferenti con la trasduzione del segnale e la trascrizione.

Responsabile: Michele Milella

Identificazione e caratterizzazione funzionale di nuovi antigeni nel carcinoma della mammella.

Responsabile: Paola Nisticò

Il blocco del recettore a dell'endotelina come nuovo approccio terapeutico antitumorale.

Responsabile: Anna Bagnato

Alterazioni fenotipiche e molecolari associate alla risposta a terapie ormonali in pazienti affette da carcinoma mammario.

Responsabile: Marcella Mottolese

Espressione di geni proinfiammatori nel ca mammario umano come indicatore di prognosi e come individuazione di bersagli molecolari.

Responsabile: Raffaele Perrone Donnorso

Studio e manipolazione dell'attivita' apoptotica del complesso p53/hipk2 per il miglioramento della terapia antitumorale.

Responsabile: Silvia Soddu

Studio delle interazioni tra oncogeni e oncosoppressori per identificare nuove strategie terapeutiche.

Responsabile: Gabriella Zupi

Meccanismi molecolari dell'apoptosi ed applicazioni in terapia oncologica.

Responsabile: Giovanni Blandino, Capofila: G. Melino, I.D.I.-Roma

Caratterizzazione clinica, istologica, biochimica e genetica del melanoma cutaneo familiare.

Responsabile: Patrizio Giacomini, Capofila: C. Catricala', I.S.G.-Roma

Sviluppo di un protocollo preclinico di immunizzazione genetica verso un antigene tumore-associato del colon.

Responsabile: Fiorella Guadagni, Capofila:V. M. Fazio, Casa Sollievo Della Sofferenza - S. G. Rotondo

Protocollo di vaccinazione con cellule dendritiche autologhe in pazienti con melanoma metastatico.

Responsabile: Pier Giorgio Natali, Capofila: M. De Lena, Ist. Oncologico-Bari

Tumori neuroendocrini dell'apparato digerente: caratterizzazione clinico-patologica molecolare ed ottimizzazione terapeutica.

Responsabile: Pasquale Perri, Capofila: R. Canizzaro, C.R.O.-Aviano

Ruolo biologico del complesso trascrizionale legante le CCAAT, NF-Y nella malattia dell'Alzheimer.

Responsabile: Giulia Piaggio, Capofila: M. C. Capogrossi, I.D.I. Roma

Determinanti molecolari della proliferazione cellulare e farmacoresistenza in tumori del tessuto nervoso centrale.

Responsabile: Silvia Soddu, Capofila: L. Frati, Neuromed - Isernia

Meccanismi di leucemogenesi: generazione di modelli murini per la leucemia acuta promielocitica (LAP).

Responsabile: Silvia Soddu, Capofila: S. Minucci, I.E.O.-Milano

Psoriasi: analisi delle basi genetiche e molecolari in correlazione con l'espressione clinica della malattia.

Responsabile: Aldo Venuti, Capofila: M. Carducci, I.S.G.-Roma

Ruolo ed alterazioni della regolazione di proliferazione. Ciclo cellulare ed apoptosi nella chemiosensibilità.

Responsabile: Gabriella Zupi, Capofila: F. Zunino, Int-Milano

Trattamento del ca muscolo-invasivo della vescica. Fattori prognostici e predittivi della risposta della chemioterapia adiuvante.

Responsabile: Anna Maria Cianciulli, Capofila: F. M. Boccardo, Ist-Genova

Caratterizzazione della risposta a diversi trattamenti antineoplastici (sensibilità e apoptosi).

Responsabile: Donatella Del Bufalo, Capofila: G. Ragona, Neuromed-Isernia

Controllo Qualità nel laboratorio oncologico: concerted action nazionale, definizione interventi prioritari, metodologie e realizzazione.

Responsabile: Marcella Mottolese, Capofila: A.V. Paradiso, Ist. Oncologico-Bari

Vitiligine: studio sui meccanismi patogenetici e sulle modalità di approccio terapeutico.
Responsabile: Marco Giorgio Paggi, Capofila: M. Piccardo, I.S.G.-Roma

Trattamento del ca muscolo-invasivo della vescica. Fattori prognostici e predittivi della risposta della chemioterapia adiuvante.
Responsabile: Enzo Maria Ruggeri, Capofila: F. M. Boccardo, Ist-Genova

L'instabilità genetica nei tumori: studio dei meccanismi molecolari e apllicazioni in oncologia predittiva e terapia.
Responsabile: Silvia Soddu, Capofila: A.Viel, C.R.O.-Aviano

Alterazioni delle vie di trasduzione del segnale nei tumori tiroidei: effetti su proliferazione, differenziamento ed apoptosi.
Responsabile: Maria Luisa Appetecchia, N. Mozzillo, Int Pascale-Napoli

Determinants of prognosis and treatment response.
Responsabile: Anna Biroccio, Capofila: M. G. Daidone, Int-Milano

Marcatori molecolari ed immunoterapia genica per la diagnosi ed il trattamento dei gliomi diffusi.
Responsabile: Carmine Carapella, Capofila: G. Felice, Neuromed-Isernia

Studio dei meccanismi di controllo del sistema Redox intracellulare come possibile target di terapie innovative nel melanoma.
Responsabile:Virginia Ferraresi, Capofila:V. Maresca, I.S.G.-Roma

Sviluppo di protocolli preclinici di vaccinazioni a DNA antitumorale ed immunomodulazione orientati al trasferimento clinico.
Responsabile: Fiorella Guadagni, Capofila:V. M. Fazio, Casa Sollievo Della Sofferenza-S. G. Rotondo

Strategie di immunoterapia contro genotipi di HPV oncogeni e non oncogeni.
Responsabile: Luciano Mariani; Capofila: A. Di Carlo, I.S.G.-Roma

Nuove strategie terapeutiche di combinazione: ipometilazione del DNA e bioimmunoterapia.
Responsabile: Marcella Mottolese, Capofila: M. Maio, C.R.O.-Aviano

Studio dei meccanismi di controllo del sistema Redox intracellulare come possibile target di terapie innovative nel melanoma.
Responsabile: Marco Giorgio Paggi, Capofila:V. Maresca, I.S.G.-Roma

Apoptosis in tumor growth and treatment: identification and characterization of novel regulatory mechanism.
Responsabile: Silvia Soddu, Capofila: K. Helin, I.E.O.-Milano

Strategie di immunoterapia contro genotipi di HPV oncogeni e non oncogeni.
Responsabile: Aldo Venuti, Capofila: A. Di Carlo, I.S.G.-Roma

Lead molecules inibitrici di alcune signaling proteins affette da eccesso/deregulazione di funzione.
Responsabile: Gennaro Citro, Capofila: S. Parodi, Ist - Genova

Gli I.R.C.C.S. oncologici come modello di Centro di eccellenza: implementazione di servizi gestionali innovativi per la ricerca.

Responsabile: Tommaso Coppola, Capofila: M. De Lena, Ist. Oncologico - Bari

Vaccino con cellule dendritiche pulsate con linea cellulare tumorale o tumore autologo in pazienti con carcinoma renale.

Responsabile: Pier Giorgio Natali, Capofila: D. Casamassima, Ist. Oncologico - Bari

Caratterizzazione di potenziali bersagli biomolecolari nella terapia antitumorale delle neoplasie del sistema nervoso centrale.

Responsabile: Paola Nisticò, Capofila: Neuromed - Isernia

Studio delle varianti alleliche del gene MC1-R ed associazione con il melanoma cutaneo.

Responsabile: Marco Giorgio Paggi, Capofila: C. Catricalà, I.S.G. - Roma

Espressione e ruolo funzionale del sistema ligando/recettore CRIPTO-1 (CR-1) nella emopoiesi umana normale e neoplastica.

Responsabile: Maria Giulia Rizzo, Capofila: A. Pinto, Int Pascale - Napoli

Co-regolatori di p53 ed E2F nelle risposte cellulari al danno del DNA indotto da agenti antineoplastici.

Responsabile: Silvia Soddu, Capofila: B. Amati, I.E.O.-Milano

Biomarcatori tumorali (BT) ed il medico di medicina generale (MMG): efficienza ed appropriatezza di utilizzo clinico.

Responsabile: Silverio Tomao, Capofila: A. Paradiso, Ist. Oncologico - Bari

Cofinanziamento Ministero della Salute-Dompé S.p.A

Identificazione e caratterizzazione di inibitori potenti e selettivi di fattori chemiotattici per il trattamento di neoplasie e di patologie infiammatorie acute e croniche.

Responsabile: Donatella Del Bufalo

Finanziamenti Ministero Affari Esteri

Prevenzione del tumore della cervice uterina.

Responsabili: Maria Luisa Marcante, Federico De Marco

Finanziamenti MIUR-FIRB

Modulazione razionale dell'attività antitumorale di farmaci "classici" tramite intervento selettivo su specifiche cascate regolatorie.

Responsabile: Ada Sacchi

Meccanismi di trasduzione del segnale e funzione sinaptica: sviluppo di modelli molecolari, cellulari e animali.

Responsabile: Oreste Segatto

Finanziamenti Provincia di Roma

Programma di prevenzione dei tumori della cute nei bambini delle scuole materne della Regione Lazio.

Responsabile: Maria Cecilia Cercato

Finanziamenti Regione Lazio

Catalogazione del fondo di pubblicazioni monografiche posseduto dalla biblioteca dell'IRE di Roma e riversamento dei record bibliografici nel catalogo collettivo del servizio Bibliotecario Nazionale.

Responsabile: Gaetana Cognetti

Programma di prevenzione dei tumori della cute nei bambini delle scuole materne della Regione Lazio.

Responsabili: Ettore M. Conti, M. Cecilia Cercato

Proposta di un programma di screening del tumore polmonare per la Regione Lazio.

Responsabile: Fiorella Guadagni

Assistenza continuativa integrata e neuroriabilitazione a domicilio per pazienti affetti da tumori cerebrali.

Responsabili: Andrea Pace, Alfredo Pompili

Valutazione dell'impatto clinico, psicologico e socio-sanitario del ricovero temporaneo in Hospice di pazienti in Cure Palliative.

Responsabile: Edmondo Terzoli

Studio della valutazione dell'obesità come fattore per patologie cardiovascolari e neoplasie.

Responsabile: Maria Luisa Appetecchia, Capofila: E. Brunetti, A.Fa.R. - Roma

Identificazione e caratterizzazione di geni di suscettibilità alle malattie dermatologiche a patogenesi autoimmune/infiammatoria.

Responsabile: Giovanni Blandino, Capofila: S. Chimenti, Univ. Tor Vergata - Roma

Finanziamenti Telethon

Functional role of the HIPK2/p53 interaction in differentiation and development.

Responsabile: Silvia Soddu

Transgenic Mice Service Center.

Responsabile: Cecilia Tiveron

Finanziamenti Alleanza Contro il Cancro

Studio multicentrico cooperativo finalizzato alla verifica della fattibilità della metodica di radioterapia con intensità modulata del fascio anche con tecnica stereotassica, con particolare enfasi alla sicurezza, adeguatezza della dose erogata ed alla ricaduta nel Servizio Sanitario Nazionale, anche attraverso interscambio e condivisione dei parametri di trattamento tra i vari centri.

RESPONSABILE: GIORGIO ARCANGELI

Progetto AZALEA biblioteca virtuale in oncologia

RESPONSABILE: GAETANA COGNETTI

Il controllo di qualità nel laboratorio oncologico: e-oncology per lo sviluppo di linee guida di appropriatezza di utilizzo clinico e di CQ dei biomarcatori.

RESPONSABILI: MARCELLA MOTTOLESE, FIORELLA GUADAGNI

Standardizzazione della tecnica di biopsia del linfonodo sentinella nel carcinoma mammario.

RESPONSABILI: FRANCO DI FILIPPO, CARLO LUDOVICO MAINI

Organizzazione di un servizio di proteomica per la diagnosi molecolare dei tumori.

RESPONSABILI: ADA SACCHI, FIORELLA GUADAGNI

TESEO (Telepatologia a Scannerizzazione degli Enti Oncologici Italiani) – Progetto per un collegamento via telematica fra dipartimenti di patologia degli IRCCS oncologici a scopo di consulenza diagnostica, attività didattica, controllo di qualità e riunioni di consenso.

RESPONSABILE: RAFFAELE PERRONE DONNORSO

L'epidemiologia per l'informazione e l'educazione sanitaria. Progetto "I TUMORI IN ITALIA", un sito di Epidemiologia in e-oncology.it.

RESPONSABILE: VALERIO RAMAZZOTTI

START – Stato dell'arte in oncologia.

RESPONSABILE: CARLO GARUFI

Rete Italiana Tumori Rari.

RESPONSABILE: VIRGINIA FERRARESI

Allestimento di una unità GLP/GMP per la produzione di sostanze biologicamente attive per trials clinici.

RESPONSABILE: FIORELLA GUADAGNI

Classificazione molecolare per migliorare la diagnosi, prognosi e cura dei tumori epiteliali *(genomica)*.

RESPONSABILE: ADA SACCHI

SOS Tumori – Numero verde telefonico e sito Internet.

RESPONSABILE: PATRIZIA PUGLIESE

Progetto OMERO (*Oncotipo Mammario ER2 Overesprimente)*: studio su carcinomi mammari HER2 positivi indirizzato alla impostazione di un percorso diagnostico terapeutico specifico per questo tipo di tumore.

Responsabili: Marcella Mottolese, Michele Milella

Progetto globale per la valutazione ed il miglioramento della QoL nei pazienti oncologici a lunga aspettativa di vita.

Responsabili: Patrizia Pugliese, Alessandra Fabi, Alberto Pietrangeli, Carlo Garufi

Network per l'analisi epidemiologica, etiopatogenica ed economico-sanitaria della popolazione con tumore della tiroide e patologia tiroidea d'interesse neoplasico afferente agli IRCCS.

Responsabile: Valerio Ramazzotti

Studio osservazionale sui pazienti oncologici anziani.

Responsabile: Cecilia Nisticò

Fellowships

FIRC

Amodei Sarah (S.C. Lab. "A" Chemioterapia Sperimentale)

Ruolo della telomerasi nella risposta ai farmaci antineoplastici in linee di melanoma umano.

Fontemaggi Giulia (S.C. Lab. "C" Oncogenesi Molecolare)

Espressione di p73: meccanismi regolativi e possibili applicazioni per una terapia differenziativi.

Gasbarri Alessandra (S.C. Lab. "B" Immunologia)

Dall'alterazione genetica specifica del sarcoma sinoviale alla ricerca di potenziali nuovi marcatori diagnostico-terapeutici per le neoplasie umane.

Iervolino Angela (S.C. Lab. "A" Chemioterapia Sperimentale)

Studio del ruolo di bcl-2 nel fenotipo angiogenico di diversi istotipi tumorali.

Nanni Simona (S.C. Lab. "C" Oncogenesi Molecolare)

Modulazione dell'attività telomerasica attraverso la segnalazione dei recettori estrogenaci: prospettive terapeutiche nel cancro della prostata.

Porrello Alessandro (S.C. Lab. "C" Oncogenesi Molecolare)

Studio delle attività di mutazioni del gene TP53: analisi in vivo, in vitro ed attraverso modelli matematici.

Severino Anna (S.C. Lab. "C" Aggregato)

Identificazione e caratterizzazione di nuovi partner cellulari delle oncoproteine virali EE1A di Adenovirus e E7 di HPV-16.

Spinella Francesca (S.C. Lab. "A" Aggregato)

Ruolo dell'endotelina-1 nei meccanismi che regolano le comunicazioni intercellulari coinvolte nella migrazione e nell'invasione cellulare del carcinoma ovarico.

Trisciuoglio Daniela (S.C. Lab. "A" Chemioterapia Sperimentale)

Ruolo di Bcl2 c-myc e hTERT nel senotipo angiogenico del melanoma.

Scholarship FIRC

De Luca Antonio (S.C. Lab. "C" Aggregato)

The effects of pRb2/p130 and E1a-associated protein on cell cycle e regulation and neoplastic transformation.

Borse di Studio C.E.-Marie Curie Training Site Fellowships

Artificial regulation of cell cycle in cancer cells and its potential clinical applications.

Funny De La Iglesia Lopez (S.C. Lab. "B" Immunologia)

Laurence Havard (S.C. Lab. "B" Immunologia)

Martin Mojzisek (S.C. Lab. "B" Immunologia)

Edit Andrea Nadasi (S.C. Lab. "B" Immunologia)

Ioana Laura Tuduce (S.C. Lab. "B" Immunologia)

Alvaro Avivar Valderas (S.C. Lab. "B" Immunologia)

Fondazione "Telethon"

Tiveron Cecilia (Safu)

Produzione di animali transgenici e "Knock-out".

Lega Italiana per la Lotta contro i tumori

Intercettazione, anticipazione diagnostica, studio prognostico attraverso lo studio sui nuclei in interfasi delle alterazioni genetiche dei cromosomi 3p, 9p e 17p mediante la tecnica FISH, follow up delle lesioni precancerose e dei tumori del cavo orale nella popolazione a rischio.

Pichi Barbara (S.C. Otorinolaringoiatra)

Ruggieri Marzia (S.C. Otorinolaringoiatra)

Cerulli Giulio (S.C. Otorinolaringoiatra)

Consultants

Dr. Mauro Boldrini
Direzione Scientifica Ire

Ing.Vincenzo Giusti
S.C. Laboratorio "C" Oncogenesi Molecolare

Dr.Ssa Elena Illiano
S.C. Laboratorio "D"Virologia

Dr.Ssa Pasqualina Marzano
S.C. Laboratorio "D"Virologia

Sig.Ra Sonia Minelli
S.A.F.U.

Dr.Ssa Federica Poggiali
S.C. Laboratorio "D"Virologia

Dr.Ssa Laura Pozzi
S.A.F.U.

Dr. Enrico Spugnini
S.C. Laboratorio "C" Oncogenesi Molecolare

S.A.F.U.
Dr.Ssa Laura Tatangelo

Research Contracts

Personale laureato
Post-graduate Contract Researchers

Nominativi *Name*	Ente Erogatore *Fund granted by:*	Strutture Complesse/SSD/SSO *Assignement*
Acquadro Francesco	MIN. SALUTE	Chemioterapia Sperimentale
Aloe Simona	REGIONE LAZIO	Patologia Clinica
Anastasi Sergio	AIRC	Immunologia
Baccarini Alessia	MIN. SALUTE	Oncogenesi Molecolare
Bacchetti Silvia	AIRC	Oncogenesi Molecolare
Battisti Francesca	CNR-MIUR	Chemioterapia Sperimentale
Benassi Barbara	MIN. SALUTE	Chemioterapia Sperimentale
Bernardi Roberto	RIC. CORRENTE	Oncogenesi Molecolare
Bon Giulia	CNR MIUR	Oncogenesi Molecolare
Bona Daniela	RIC. CORRENTE	Oncogenesi Molecolare
Bossi Gianluca	AIRC	Oncogenesi Molecolare
Bria Emilio	RIC. CORRENTE	Oncologia Medica "C"
Bussoletti Federico	RIC. CORRENTE	Oncologia Medica "C"
Campioni Mara	FIRC	Lab. "C" Aggregato
Capomolla Elisabetta	Contr. Aventis Pharma	Oncologia Medica "B"
Cascioli Simona	CNR-MIUR	Immunologia
Cecchinelli Barbara	ISS	Oncogenesi Molecolare
Cecere Lucia	RIC. CORRENTE	Biblioteca IRE
Cerrone Antonella	RIC. CORRENTE	Patologia Clinica
Cervini Federica	RIC. CORRENTE	Direzione Scientifica IRE
Cirilli Alessia	AIRC	Virologia
Ciuffini Laura	MIN. SALUTE	Oncogenesi Molecolare
Chicherchia Giuseppina	MIN. SALUTE	Anatomia Patologica
Cottone Giuliano	FIRC	Lab. "C" Aggregato
Ciuffreda Federica	MIN. SALUTE	Oncologia Medica "A"
Cocco Roberta	RIC. CORRENTE	Patologia Clinica
Coletta Angela M.	MIN. SALUTE	Patologia Clinica
D'Alessandro Roberta	REGIONE LAZIO	Patologia Clinica
D'Amalas Alexander	MIN. SALUTE	Oncogenesi Molecolare
D'Andrea Marco	MIUR	Fisica Medica
D'Avenia Paola	RIC. CORRENTE	Radioterapia
D'Eletto Manuela	Mc Master University	Oncogenesi Molecolare
Del Bello Duilia	ISS	Immunologia
Del Bravo Jessica	MIN. SALUTE	Chemioterapia Sperimentale
Del Monte Girolamo	RIC. CORRENTE	Patologia Clinica
Di Agostino Silvia	AIRC	Oncogenesi Molecolare
Di Benedetto Anna	MIN. SALUTE	Anatomia Patologica

Di Segni Susanna	RIC. CORRENTE	Farmacocinetica IRE
Di Stefano Valeria	AIRC	Oncogenesi Molecolare
Felici Alessandra	RIC. CORRENTE	SAFU
Fonsi M. Assunta	MIN. SALUTE	Anatomia Patologica
Forte Eleonora	RIC. CORRENTE	Oncologia Medica "A"
Fuschi Paola	MIN. SALUTE	Oncogenesi Molecolare
Gasparro M. Simona	MIN. SALUTE	Oncologia Medica "A"
Ginobbi Patrizia	Contri. Pfizer	Rianimazione
Giorda Ezio	AIRC	Immunologia
Giovanelli Morena	REGIONE LAZIO	Neurochirurgia/Neurologia
Gradi Alessandra	AIRC	Oncogenesi Molecolare
Gurtner Aymone	MIN. SALUTE	Oncogenesi Molecolare
Iezzi Simona	AIRC	Lab. "B" Aggregato
Illiano Elena	AIRC	Virologia
Iovino Alessandra	AIRC	Oncogenesi Molecolare
Lapi Eleonora	AIRC	Oncogenesi Molecolare
Lauria Valentina	RIC. CORRENTE	Gastroenterologia
Lazzari Chiara	AIRC	Oncogenesi Molecolare
Loda Massimo	MIN. SALUTE	Oncologia Medica "A"
Lonardo M. Teresa	MIN. SALUTE	Chirurgia Generale "B"
Mafera Barbara	Compagnia S. Paolo	Virologia
Maggini Alda	MIN. SALUTE	Patologia Clinica
Malaguti Paola	MIN. SALUTE	Oncologia Medica "A"
Mancini Raffaello	AIRC	Chirurgia Generale "B"
Mancini Milo	RIC. CORRENTE	Patologia Clinica
Manente Lucrezia	MIN. SALUTE	Lab. "C" Aggregato
Manni Isabella	MIN. SALUTE	Oncogenesi Molecolare
Martayan Aline	MIN. SALUTE	Immunologia
Mastronicola Daniela	MIN. SALUTE	S.A.F.U.
Mattace Raso Daniele	MIN. SALUTE	Urologia
Mazzieri Marinella	RIC. CORRENTE	Biblioteca IRE
Miele Paola	MIN. SALURE	Oncogenesi Molecolare
Minghi Enrico	MIUR	Fisica Medica
Monti Olimpia	MIN. SALUTE	Oncogenesi Molecolare
Novelli Flavia	CNR- RIC. CORRENTE	Anatomia Patologia
Orlandi Giulia	MIN. SALUTE	Patologia Clinica
Palermo Blinda	MIN. SALUTE	Immunologia
Pellicciotta Mario	Contr. Eli Lilly - Roche	Direzione Scientifica IRE
Petricca Adele	AIRC	Chemioterapia Sperimentale
Pierluigi Marzia	Ministero Affari E.	Virologia
Piperno Giulia	RIC. CORRENTE	Anatomia Patologica
Precupanu Cristina	RIC. CORRENTE	Oncologia Medica "A"
Riccioni Sabrina	AIRC	Oncogenesi Molecolare
Rinaldo Cinzia	ISS	Oncogenesi Molecolare
Rizzo Angela	AIRC	Chemioterapia Sperimentale
Rizzo Consuelo	Compagnia S. Paolo	Virologia
Rosanò Laura	CNR-MIUR	Lab. "A" Aggregato

Ruscio Giusy	MIN. SALUTE	Oncogenesi Molecolare
Sala Gianluca	AIRC	Immunologia
Salis Patrizia	REGIONE LAZIO	Neuochirurgia/Neurologia
Santiccioli Silvia	Contr. Rhone Poulenc Rore	Oncologia Medica "B"
Sessa Anna	RIC. CORRENTE-REG. LAZIO	SINTESI
Sibilio Leonardo	MIN. SALUTE	Immunologia
Simeone Paola	MIN. SALUTE	Virologia
Sperduti Isabelli	Contr. Eli Lilly	Direzione Scientifica IRE
Spila Antonella	MIN. SALUTE	Patologia Clinica
Strano Sabrina	MIN. SALUTE	Oncogenesi Molecolare
Tatangelo Laura	MIN. SALUTE	SAFU
Tirelli Walter	RIC. CORRENTE	Rianimazione
Tritarelli Alessandra	MIN. SALUTE	Lab. "C" Aggregato
Vallati Ilaria	AIRC	Direzione Scientifica IRE
Vanni Barbara	RIC. CORRENTE	Oncologia Medica "C"
Venturini Cristina	AIRC –Aeroporti RM- ENEL	Dir. Generale IFO - Radiologia
Vercillo Giuseppe	LEGA IT. TUMORI	Patologia Clinica

Personale non laureato
Non Graduated Contract Researchers

Nominativi *Names*	Ente Erogatore *Funds Granted by:*	Strutture Complesse/SSD/SSO *Assignement*
Antonucci Alessia	MIUR 00	Fisica Medica
Armezzani Alessia	MIN. SALUTE	Oncogenesi Molecolare
Bernardi Roberto	MIN. SALUTE	Oncogenesi Molecolare
Bona Daniela	MIN. SALUTE	Oncogenesi Molecolare
Bonaventura Fabrizio	ISS 03	Chemioterapia Sperimentale
Bruno Teresa	Aeroporti RM-ENEL	Radiologia
Bruno Tiziana	MIN. SALUTE	Lab. "B" Aggregato
Buongiorno Santa L.	LEGA IT. TUMORI	Psicologia
Calvo Adab Ana I.	REGIONE LAZIO	SINTESI
Canfora Marco	REGIONE LAZIO	SINTESI
Careddu Angela	MIN. SALUTE	Patologia Clinica
Cassani Stefania	MIN. SALUTE	Chirurgia Toracica
Chiarenza Andrea	MIN. SALUTE	Anatomia Patologica
D'Angelo Marco	MIN. SALUTE	Oncogenesi Molecolare
Di Chio Chiara	REGIONE LAZIO	SINTESI
Di Giorgi Silvia	Contr. Aventis Pharma	Oncologia Medica "B"
Di Lelio Maurizio	REGIONE LAZIO	Neurochirurgia/Neurologia
Edlisca Anna M.	Contr. Aventis Pharma	Oncologia Medica "B"
Fagioli Cecilia	REGIONE LAZIO	SINTESI
Farinacci Raffaella	RIC. CORRENTE	S.A.R
Gabrielli Francesca	REGIONE LAZIO	SINTESI
Giacomo Elia	AIRC	Lab. "A" Aggregato
Ginnetti Alessia	RIC. CORRENTE	Oncologia Medica "A"
Gioffrè Giuseppina	AIRC	Chirurgia Generale "B"
Guerriera Paolo	MIN. SALUTE	S.A.F.U.

Harris Deborah	Aeroporti RM-ENEL	Radiologia
Iacovelli Stefano	AIRC	Oncogenesi Molecolare
Matrascia Barbara	Cont. Eli Lilly REG. LAZIO	Oncologia Medica "A"
Merola Roberta	MIN. SALUTE	Patologia Clinica
Milana Rossella	RIC. CORRENTE	Rianimazione
Monori Annalisa	MIN. SALUTE	Lab. "B" Aggregato
Parasecoli Cristina	Contr. Rhone Poulenc Rorer	Oncologia Medica "B"
Parisi Cristiniano	REGIONE LAZIO	Neurochirurgia/Neurologia
Pascucci Anna Lisa	RIC. CORRENTE	Patologia Clinica
Pecci Andrea	INEX Pharm.	Chemioterapia Sperimentale
Perretta Flavia	LEGA IT. TUMORI	Patologia Clinica
Perrotta Gioia	MIN. SALUTE	Patologia Clinica
Petrungaro Silvia	RIC. CORRENTE	Patologia Clinica
Piccoli Marzia	REGIONE LAZIO	Neurochirurgia/Neurologia
Piccolo Tiziana	MIN. SALUTE	Chirurgia Generale "A"
Ranieri Alessandra	ISS	Immunologia
Riccioni Sabrina	RIC. CORRENTE	Oncogenesi Molecolare
Ripanucci Daniele	RIC. CORRENTE	Patologia Clinica
Rondanini Federica	RIC. CORRENTE	Anatomia Patologica
Rossi Sabrina	MIN. SALUTE	Medicina Nucleare
Sarcone Vincenza	AIRC	Immunologia
Sbraga Simona	REGIONE LAZIO	SINTESI
Scarsella Marco	AIRC	Chemioterapia Sperimentale
Scordati Patrizia	AIRC - CNR	Anatomia Patologia
Travaglini Claudia	MIN. SALUTE	Urologia
Valentini Emanuela	AIRC	S.A.R.
Vitolo Donatella	MIN. SALUTE	Oncogenesi Molecolare
Zerbini Valentina	AIRC-MIN. SALUTE	Anatomia Patologia
Zizzari Alessia	REGIONE LAZIO	Neurochirurgia

Visiting Researchers

Aggiornamento professionale
Professional Updating

Personale laureato – *Visiting Post-graduate Researchers*

Nominativi	Strutture Complesse/SSD
Aliotta Nicoletta	Oncogenesi Molecolare
Benassi Michela	Radioterapia
Bianciardi Federico	Radioterapia
Caponetti Rosita	Oncologia Medica "B"
Cervo Emanuele	Radioterapia
Chierichetti Walter	Oncologia Medica "C"
Corrado Giacomo	Ginecologia Oncologica
Cusumano Giuliana	Neurologia
Damalas Alexander	Neurologia
D'Angelo Annelisa	Fisica Medica
Della Pietra Linda	Oncogenesi Molecolare
Fattorusso Silvia	Oncologia Medica "B"
Gallo Gaia	Lab. "C" Aggregato
Gentiletti Francesca	Oncogenesi Molecolare
Giglio Simona	Oncogenesi Molecolare
Giordano Carolina	Radioterapia
Grandinetti Paolo	Otorinolaringoiatra
Grasselli Annalisa	Oncogenesi Molecolare
Guaglianone Salvatore	Urologia
Kchouk Huissa Fatma	Virologia
Lanzinotta Graziella	Servizi Aziendali
Mancini Francesca	Oncogenesi Molecolare
Marcelli Maria Elena	Rianimazione
Massaro Rosalba	Endocrinologia
Mastroianni Santo	Neurologia
Merra Valeria	Dermatologia
Messina Mauro	Radioterapia
Pasca Raymondo Federica	Dir. Sanitaria Presidio
Prodosmo Andrea	Oncogenesi Molecolare
Roma Carmine Luigi	Oncologia Medica "B"
Russo Andrea	Anatomia Patologica
Salerno Manuela	Patologia Clinica
Soliera Angela Rachele	Oncogenesi Molecolare
Velia Emiliozzi	Oncogenesi Molecolare
Viola Giuditta	Oncologia Medica "B"

Personale non laureato – *Non-graduated Visiting Researchers*

Nominativi	Strutture Complesse/SSD
Coccia Margherita	Oncogenesi Molecolare
Giglio Simona	Oncogenesi Molecolare
Guerriera Paolo	S.A.F.U.
Mainardi Sara	Oncogenesi Molecolare

Svolgimento tesi di laurea
Degree Thesis

Nominativi	Strutture Complesse/SSD
Baietti M. Francesca	Immunologia
Bonifazi Roberta	Chemioterapia Sperimentale
Carlino Claudia	Dip. Oncologia Sperimentale
Centra Gianpaolo	Immunologia
Cicchetti Alessia	Oncologia Medica "C"
Ciolfi Alberto	Lab. "B" Aggregato
Conidi Andrea	Immunologia
Decandia Samantha	Lab. "A" Aggregato
Federici Valentina	Immunologia
Folgiero Valentina	Oncogenesi Molecolare
Fragomeli Caterina	Chemioterapia Sperimentale
Genovesi Giulia	Lab. "A" Aggregato
Inzillo Simone	Chemioterapia Sperimentale
Lo Monaco Elisa	Immunologia
Lucini Fabiana	Immunologia
Melucci Elisa	Immunologia
Pensieroso Simone	Dip. Oncologia Sperimentale
Priolo Carmen	Oncogenesi Molecolare

Dottorati
Doctorates

Nominativi	Strutture Complesse/SSD
Bronzi Giovanna	Immunologia
De Nicola Francesca	Lab. "B" Aggregato

Collaborazione scientifica
Scientific Cooperation

Nominativi	Strutture Complesse/SSD
Alimandi Maurizio	Immunologia
Belloni Laura	Dip. Oncologia Sperimentale
Campo Saveria	Virologia
Chiara Romano	Oncogenesi Molecolare
Cippitelli Marco	Dip. Oncologia Sperimentale

Civitareale Donato	Lab. "A" Aggregato
Cristiano Simone	Dip. Oncologia Sperimentale
Farsetti Antonella	Oncogenesi Molecolare
Fionda Cinzia	Dip. Oncologia Sperimentale
Forcales Fernandez Sonia V.	Dip. Oncologia Sperimentale
Giorgini Angela	Oncogenesi Molecolare
Guerrieri Francesca	Dip. Oncologia Sperimentale
Hallez Sophie	Virologia
Latella Lucia	Chemioterapia Sperimentale
Levrero Massimo	Dip. Oncologia Sperimentale
Lombardi Daniela	Lab. "C" Aggregato
Napoletano Silvia	Immunologia
Nicotra Rita	Immunologia
Omerovic Jasminka	Immunologia
Palesandolo Emanuele	Dip. Oncologia Sperimentale
Pediconi Natalia	Dip. Oncologia Sperimentale
Piombino Emanuela	Dip. Onocologia Sperimentale
Pollicino Teresa	Dip. Oncologia Sperimentale
Pontecorvi Alfredo	Oncogenesi Molecolare
Puggioni Eleonora	Immunologia
Santoni Angela	Dip. Oncologia Sperimentale
Serra Carlo	Dip. Oncologia Sperimentale
Velotti Francesca	Dip. Oncologia Sperimentale
Vossio Stefania	Dip. Oncologia Sperimentale

Specializzandi
Postgraduate student

Nominativi	Strutture Complesse/SSD
Akpan Grace P.	Urologia
Alessandrini Grabiele	Chirurgia Toracica
Alimonti Andrea	Oncologia Medica "A"
Boschetto Arianna	Chirurgia Generale "B"
Buscaglia Francesco	Chirurgia Generale "B"
Cacciotti Gugliemo	Neurochirurgia
Camapanella Carla	Oncologia Medica "C"
Cauchi Carolina	Oncologia Medica "B"
Ceccatelli Alessia	Fisica Medica
Cecere Fabiana	Oncologia Medica "A"
Cerrone Antonella	Patologia Clinica
Condorelli Alessia	Oncologia Medica "B"
Conti Barbara	Patologia Clinica
Conti Carlo	Neurochirurgia
Corazza Valerio	Chirurgia Generale "B"
Credendino Angelo	Anatomia Patologica
Cuiuli Giuseppe	Otorinolaringoiatra
Cuppone Federica	Oncologia Medica "C"

De Cerchio Leonardo	Neurochirurgia
Di Cocco Barbara	Oncologia Medica "A"
Di Cosimo Serena	Oncologia Medica "A"
Esposito Alessandro	Chirurgia Generale "B"
Fraioli Mario Francesco	Neurochirurgia
Ghini Cristian	Chirurgia Toracica
Giacinti Laura	Oncologia Medica "B"
Irakli nadashvli	Chirurgia Generale "A"
Lanetti Antonio	Neurochirurgia
Leonardo Costantino	Urologia
Lo Russo Riccardo	Chirurgia Generale "B"
Maggini Aldo	Patologia Clinica
Magnapera Agesilao	Patologia Clinica
Mancini Pietro	Chirurgia Generale "B"
Marchetti Gabriele	Chirurgia Toracica
Marvaso Vincenzo	Otorinolaringoiatra
Marzano Raffaella	Patologia Clinica
Mascelli Alberto	Otorinolaringoiatra
Masi Maria Claudia	Oncologia Medica "B"
Masini Andrea	Serv. Endosc. Digestiva
Menniti Agazio	Neurochirurgia
Miceli Mario	Chirurgia Toracica
Pascazio Carola	Chirurgia Toracica
Patrizi Vanessa	Chirurgia Generale "A"
Pino Maria Simona	Oncologia Medica "A"
Polistena Andrea	Chirurgia Toracica
Pozza Mariangela	Urologia
Quattrini Marco	Ginecologia Oncologica
Romano Emanuela	Oncologia Medica "A"
Ruggeri Marzia	Neurochirurgia
Salesi Nello	Oncologia Medica "A"
Zennaro Stefano	Fisica Medica

Ospitalità a ricercatori esterni
Hosted foreign researchers

Nominativi

Nhili Ahed
Provenienza Borsista nell'ambito del progetto del Ministero degli Esteri Cooperazione Italia - Tunisia
Periodo: 7 Febbraio - 2 Marzo 2003

Silvia Bacchetti
Mc Master University, Hamilton, Canada
Periodo: 2003

Guido Bongioannini
Primario ORL Ospedale Mauriziano Torino
Periodo: 2003

Angelo Caroggio
Primario Div. ORL Ospedale di Reggio Emilia
Periodo: 2003

Marco Devincentiis
Direttore Clinica ORL Università "La Sapienza" Roma
Periodo: 2003

Quertani Latifa
Provenienza Borsista nell'ambito del progetto del Ministero degli Esteri Cooperazione Italia - Tunisia
Periodo: 7 Febbraio - 2 Marzo 2003

Francesco Lunghi
Primario ORL Ospedale di Monselice Padova
Periodo: 2003

Edit Nadasi
Dipartimento di Medicina Preventiva, Università di Pécs, Ungheria
Periodo: 2 - 31 Maggio 2003
Periodo: 18 Novembre - 15 Dicembre 2003

Giuseppe Rizzotto
Primario ORL Ospedale di Vittorio Veneto
Periodo: 2003

Samia Hanachi Sassi
Provenienza Borsista nell'ambito del progetto del Ministero degli Esteri Cooperazione Italia - Tunisia
Periodo: 17 Marzo - 8 Aprile 2003

Jatin P. Shah
Chief Dept. Of Otolaryngology Head and Neck Surgery. Memorial Sloan Kettering Cancer Center New York
Periodo: 2003

Maurizio Vigili
Primario ORL Ospedale S. Carlo di Nancy Roma
Periodo: 2003

Reviewing and Editorial Board Membership in indexed journal

- Acta Cytologica (Perrone Donnorso R.)
- Annals of Oncology (Cognetti F.)
- American Journal of Clinical Oncology (Arcangeli G.)
- Anticancer Research (Guadagni F.)
- Biochimica et Biophysica Acta (Blandino G.)
- Cancer Detection and Prevention (Mottolese M.)
- Cancer Research (Blandino G., Farsetti A., Segatto O.)
- Cell Death and Differentiation (Blandino G., Soddu S.)
- Cell Proliferation (Zupi G.)
- Chirurgia Italiana (Santoro E.)
- Clinica Terapeutica (Arcangeli G., Guadagni F.)
- Diagnostic Cytopathology (Perrone Donnorso R.)
- EMBO Journal (Soddu S.)
- Endoscopy (Grassi A.)
- European Journal of Cancer (Zupi G., Falcioni R.)
- European Journal of Clinical Oncology (Guadagni F.)
- European Journal of Immunology (Falcioni R.)
- Europen Journal of Biochemistry (Blandino G.)
- Experimental and Clinical Cancer Research (Carlini M., Falcioni R.)
- Experimental Cell Research (Falcioni R.)
- FEBS letters (Blandino G.)
- Gastric Cancer (Santoro E.)
- General Surgery (Santoro E.)
- Gastroenterologia (Grassi A.)
- Head and Neck (Spriano G.)
- Hepatogastroenterology (Santoro E.)
- Hepatologie (Santoro E.)
- Hystology and Histopathology (Natali P.G.)
- In vivo (Guadagni F.)
- International Journal of Biological Markers (Guadagni F., Natali P.G.)
- International Journal of Cancer (Natali P.G., Zupi G.)
- International Journal of Hyperthermia (Arcangeli G.)
- International Journal of Radiation Oncology Biology and Physics (Arcangeli G.)
- Journal Medicine Virology (Badaracco G.)
- Journal Immunotherapy (Nisticò P.)
- Journal Traslational Medicine (Natali P.G.)
- Journal Biological Chemistry (Soddu S.)
- Journal de Celiochirurgie (Santoro E.)
- Journal of Experimental & Clinical Cancer Research (Arcangeli G.,Benassi M., Blandino G., Jandolo B.,Leonetti C., Mariani L., Mottolese M., Natali P.G., Santoro E.,Sega F.M.,Venuti A., Zupi G.)
- Journal of Medical Education (Grassi A.)

- Journal of Nuclear Medicine (Sciuto R.)
- Laparoscopic Surgery (Santoro E.)
- Lung Cancer (Natali P.G.)
- Melanoma Research (Natali P.G.)
- Molecular and Cellular Biology (Falcioni R.)
- Molecular Carcinogenesis (Blandino G.)
- Mutation Research (Del Bufalo D.)
- Neurological sciences (Jandolo B.)
- Oncogene (Blandino G., Farsetti A., Piaggio G., Soddu S.)
- Oncogyn (Mariani L.)
- Oncology (Zupi G.)
- Tumor Biology (Guadagni F.)
- Tumori (Natali P.G., Zupi G.)

Research Project Review

- A.I.R.C. (Sacchi A., Soddu S., Zupi G.)
- C.N.R. (Zupi G.)
- Dutch Cancer Society (Falcioni R.)
- F.I.R.C. (Biroccio A., Del Bufalo D., Leonetti C., Zupi G.)
- M.U.R.S.T. (Zupi G.)
- Referee Nazionale EMC (Santoro E.)
- World Cancer Research Fund Programme (Venuti A.)

Appointments to Foundations, Societies, Associations

Arcangeli G.

- Associazione Italiana di Radioterapia Oncologica (AIRO) Sezione Lazio/Abruzzo: Presidente
- Società Italiana di Urologia Oncologica (SIUrO): Vicepresidente

Arcuri E.

- Associazione Italiana per lo Studio del Dolore (AISD): Vicepresidente
- Centro di Ascolto "Gigi Ghirotti" Associazione ONLUS: Consulente Scientifico per la Terapia del Dolore e Assistenza Domiciliare
- Fondazione Federico Calabresi: Membro del Comitato Scientifico

Carapella C.M.

- Associazione Italiana di Neuro-Oncologia-AINO: Segretario
- European Association of Neuro-Oncology-Executive Committee: President
- EORTC-Brain Tumor Group: Membro
- FECS - Board Member

Carlini M.

- Lap Group Roma-Gruppo Laparoscopico Romano: Segretario

Carlini P.

- Sezione Regione –Lazio AIOM: Tesoriere

Castelli M.

- Associazione Promozione Studi Immunologia dei Tumori-APSIT: Presidente

Cavaliere F.

- Consiglio Direttivo della Società Polispecialistica Italiana dei Giovani Chirurghi: (S.P.I.G.C.): Consigliere
- International Society Regional Cancer Treatment (I.S.R.C.T.): Membro
- Società Italiana di Chirurgia Oncologica (S.I.C.O.): Tesoriere Nazionale

Cilenti V.

- ANAAO-ASSOMED: Consigliere nazionale

Cognetti F.

- AIOM - Associazione Italiana di Oncologia Medica: Presidente
- AIOM - Associazione Italiana di Oncologia Medica: Chairman della Commissione Educazionale
- American Society of Clinical Oncology (ASCO): Membro
- Associazione Alleanza Contro il Cancro: Segretario - Tesoriere
- Collegio Sindacale di "Galileo 2001-Associazione per la libertà e la dignità della scienza": Socio Fondatore e Sindaco Effettivo
- Comitato operativo Progetto Italia-USA: Membro
- Commissione Oncologica Nazionale: Membro
- Commissione Oncologica Regione Lazio: Vice Presidente

- Consiglio Superiore della Sanità: Membro
- EORTC-Head and Neck cooperative group: Membro
- ESMO-European Society of Medical Oncology: Membro executive and steering committee, National Representative for Italy
- FECS-Federation of the European Cancer Societies: Membro del Membership Committee
- Fondazione per la Ricerca Oncologica FO.R.O. ONLUS: Presidente
- GOL-Gruppo Oncologico del Lazio: Presidente
- Scuola Superiore di Oncologia: Presidente consiglio scientifico

Cosimelli M.

- Consiglio Direttivo S.I.T.I.L.O.-Società Italiana di Terapie Integrate Locoregionali in Oncologia: Consigliere

Di Filippo F.

- Forza Operativa Nazionale sul Carcinoma Mammario (F.O.N.Ca.M): Membro
- Italian Sarcoma Group: Responsabile del trattamento delle forme avanzate degli arti
- Italian Melanoma Intergroup: Membro del Comitato Scientifico
- International Society of Regional Cancer Treatment: Chairman of Membership Committee
- European Society of Surgical Oncology: Membro
- Società Italiana Terapie Loco-Regionali in Oncologia (S.I.T.I.L.O.): Presidente

Società Italiana di Chirurgia Oncologica (S.I.C.O.): Coordinatore regionale per il Lazio
Società Italiana di Prevenzione Diagnosi e Terapia dei Tumori: Membro
WHO Melanoma Programme: Membro

Farsetti A.

- Commissione Didattica di base in Endocrinologia Molecolare della Società Italiana di Endocrinologia: Membro

Garufi C.

- AIOM Lazio: Consigliere Regionale
- Board dell'EORTC Chronotherapy Group: Membro

Grassi A.

- Comitato Education and Training OMGE/OMED: Membro
- Comitato Terminology and Data Processing dell' OMED: Membro

Guadagni F.

- Comitato Scientifico del Gruppo per l'Applicazione delle Biotecnologie in Oncologia (ABO): Membro
- Comitato Scientifico Internazionale "Institute for Anticancer Research", Atene, Grecia: Membro
- Comitato Direttivo del Gruppo Italiano per lo Studio della Chirurgia Radioimmunoguidata e della Immunoscintigrafia (G.I.S.C.R.I.S.):Vice-Presidente
- Direttivo dell'"European Group of Tumor Marker" (E.G.T.M.): Membro

Jandolo B.

- Comitato dei Probi-Viri della Società Italiana di Neurologia (SIN): Membro
- Consiglio Direttivo della SNO (Scienze Neurologiche Ospedaliere): Membro in qualità di segretario del Comitato di redazione della Rivista di Neurobiologia
- Gruppo di Studio di Neuro-oncologia della SIN: Coordinatore

Leonetti C.

- AICC-Associazione Italiana Colture Cellulari: Segretario

Marino M.

- SIAPEC (Società Italiana di Anatomia Patologica e Citopatologia Diagnostica): Consigliere Regione Lazio

Mottolese M.

- Hungarian Society of Molecular and Preventive Epidemiology: Membro Fondatore

Natali P.G.

- American Academy of Microbiology: Proctor
- AACR: Membro
- Comitato AIRC Lazio: Membro Scientifico
- Comitato Premio G.Venosta, FIRC: Membro
- Commissione Scientifica Int. Conf. Anti Cancer Treatment (ICAT), Parigi: Membro
- Hungarian Society of Molecular and Preventive Epidemiology: Socio Fondatore
- Progetto Marie Curie Training Site: Coordinatore
- SIC- Società Italiana di Cancerologia: Past Presidente
- World Alliance of Cancer Research Organization: Membro International Steering Commitee

Paggi M.G.

- American Association for Cancer Research: Active Member

Perri P.

- European Society of Surgical Oncology (E.S.S.O.): Membro
- European network for Endocrine Tumors (E.N.E.T.): Membro
- Società Italiana di Chirurgia Oncologica (S.I.C.O.): Tesoriere Nazionale
- Scientific Advisory Board of the International Institute of Anticancer Research: Membro.

Perrone M.

- SIPO-Lazio: Consigliere

Perrone Donnorso R.

- Società Italiana di Citologia Clinica e Sociale (S.I.C.C.S): Presidente

Pugliese P.

- SIPO-Lazio: Segretario regionale

Sacchi A.

- Comitato Tecnico Scientifico A.I.R.C.: Membro

Santoro E.

- Accademia Romana di Chirurgia: Accademico Reggente
- Federchir: Presidente
- IGCA: Presidente Eletto
- Lega Italiana Lotta contro i tumori: Membro Consiglio Direttivo
- Società Italiana di Chirurgia: Presidente Emerito

Sega F. M.
- Roswell Park Surgical Society: Membro
- Associazione Promozione Studi Immunologia Tumori (A.P.S.I.T.): Vicepresidente

Stigliano V.
- AIGO: Consigliere Regionale

Terzoli E.
- Lega Italiana Tumori-Sez. Provincia di Roma: Vicepresidente
- Presidente Associazione Coordinamento Primari Regina Elena.

Tomao S.
- Consiglio direttivo della Associazione Italiana di Oncologia Medica-Sezione Lazio: Membro
- Consiglio direttivo della Società Italiana tumori- Sezione Lazio: Membro

Vizza E.
- Gruppo Italiano di Studio sull'Endometriosi (G.I.S.E.): Membro

Zupi G.
- AICC-Associazione Italiana Colture Cellulari: Socio Onorario
- FIRC-Fondazione Italiana Ricerca sul Cancro: Membro del Comitato Scientifico
- Fondazione Federico Calabresi: Membro del Consiglio Direttivo
- SICCAB-Società Italiana Cinetica Cellulare Applicata e di Base: Consigliere
- SIC-Società Italiana di Cancerologia: Consigliere
- Temple University, College of Science and Technology, Centre for Biotechnology: Adjunct Professor

AWARDS

DR. ENRICO BERSANI, DR. ALBERTO BERSANI E DR. ALESSANDRO PORRELLO

"Virtual celll building by bio-mathematical models and intracellular biochemical experiments".
Selezionato tra i 40 migliori progetti di modellistica matematica dal CERN di Ginevra e presentato al SIS-FORUM di Ginevra, 9-13 dicembre 2003

DR.SSA GABRIELLA ZUPI

Socio Onorario AICC-Associazione Italiana Colture Cellulari. 2003

DR. DANIELA TRISCIUOGLIO

Premio per il miglior poster selezionato per presentazione orale al V International Congress Biotherapy of solid tumors tenutosi a Forlì il 13-14 novembre 2003

Bilateral Agreements

Italia - Albania (2002-2003)

La prevenzione del tumore della cervice uterina.

The Prevention Uterine Cancer.

Project Co-ordinators:

Prof.ssa Maria Luisa Marcante S.C. Lab. D di Virologia, Istituto Regina Elena, Roma, Italia.
"Institute of Public Health" di Tirana.

Italia-Canada (2000-2004)

Regolazione dell' attività telomerasica e dell' espressione della subunità catalitica della telomerasi umana (hTERT) in cellule epiteliali umane provenienti da espianti di prostata normale e tumorale.

Regulation of Telomerase Activity and Expression of Catalytic Telomerase Subunit (hTERT) in Human Epithelial Cells Derived from Normal and Tumoral Prostate Explants.

Project Co-ordinators:

Dr.ssa Ada Sacchi - Dr.ssa Antonella Farsetti, S.C. Lab. C Oncogenesi Molecolare, Istituto Regina Elena, Roma, Italia.

Prof.ssa Silvia Bacchetti, McMaster University Dept. of Pathology and Molecular Medicine, Hamilton ON, Canada.

Costruzione di nuovi vettori adenovirali per terapia genica.

Construction of New Adenoviral Vectors for Gene Therapy.

Project Co-ordinators:

Dr.ssa Ada Sacchi, S.C. Lab. C Oncogenesi Molecolare, Istituto Regina Elena, Roma, Italia.

Dr. Frank Graham, McMaster University, Department of Biology, Hamilton ON, Canada.

Sperimentazione dell'efficacia antitumorale di oligo antisenso c-myc in combinazione con il cisplatino nel melanoma umano su linee in vitro e su tumori impiantati in animali immunodepressi.

Pre-Clinical Evaluation of the Antitumoral Efficacy of C-myc Antisense Oligodeoxymucleotides in combination with Cisplatin in Human Melanoma Lines in vitro and in vivo.

Project Co-ordinators:

Dr.Ssa Gabriella Zupi, S.c. Lab. A Chemioterapia Sperimentale, Istituto Regina Elena, Roma, Italia.

Dr. Sean Semple, INEX Pharmaceuticals Corp., Burnaby, Canada.

Italia - Finlandia (2000-2005)

Valutazione di nuovi parametri diagnostici e prognostici nei pazienti affetti da cancro, con enfasi particolare alla potenziale applicazione di biotecnologie in ambiente di laboratorio, per una migliore definizione dei sotto gruppi di soggetti ad alto rischio.

Evaluation of New Diagnostic and Prognostic Parameters in Cancer Patients, with Special Emphasis on the Potential Application of Biotechnologies in the Laboratory Setting for a Better Definition of High-Risk Subgroups of Subject.

Project Co-ordinators:

Dr.ssa Fiorella Guadagni, S.C. Patologia Clinica, Istituto Regina Elena, Roma, Italia.

Prof. Grènman Reidar, Department of Medical Biochemistry, University of Turku, Finland.

Molecole espresse da tumori umani di utilizzo clinico diagnostico terapeutico. Sviluppo di misure metodologiche in vitro e in vivo.

Molecules Expressed by Human Tumours for Clinical, Diagnostic and Therapeutic Use. Development of New in vitro and in vivo Methodologies.

Project Co-ordinators:

Dr. Pier Giorgio Natali, S.C. Lab. B Immunologia, Istituto Regina Elena, Roma, Italia.

Dr. Michele Maio, Advanced Immunotherapy Unit-CRO Aviano, Italia.
Dr. Kalevi Kairemo, Department of Nuclear Medicine-Helsinki University Central Hospital, Finland.

Italia-Tunisia (2000-2003)

Programma integrato di assistenza tecnica, formazione e ricerca con l'Ospedale Habib Thameur di Tunisi.

Integrated Programme for the Improvement of Hospice Habib Thameur and Tunisia.

Project Co-ordinator:

Prof. Massimo Crespi, Responsabile Rapporti Internazionali, Istituto Regina Elena, Roma, Italia.
Convenzione tra il M.AA.EE.-DGCS/Università La Sapienza-CIRPS e L'Istituto Regina Elena, di Roma in prosecuzione del precedente programma.

Chirurgia plastica e ricostruttiva per pazienti oncologici con patologia del distretto testa-collo.

Plastic and Reconstructive Surgery for Oncological Patients with Head and Neck Pathologies.

Project Co-ordinator:
Dr. Lorenzo Palma, S.C. Otorinolaringoiatria, Istituto Regina Elena, Roma, Italia
PROF. BEN AVED, Istituto Oncologico Salaz Azaiz, Tunisi, Tunisia

Danno cutaneo e tumorigenesi da luce occupazionale: diagnosi e prevenzione del cancro cutaneo, esteso anche all' età scolare.

Skin Damage and Tumorigenesis caused by Occupational Light: Skin Cancer Diagnosis and Prevention, extended to School-Age Children.

Project Co-ordinator:
Dr. Ettore M.S. Conti, Sintesi (Servizio Integrato di Epidemiologia e Sistemi Informativi), Istituto Regina Elena, Roma, Italia
Prof. Zahaf Abdel Majid, Facoltà di Medicina, Università di Sfax, Tunisia

Trials Approved By The Ethic Committee

Stato A= aperto
Stato C= chiuso

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	Colon-retto						
	Casale						
Stato A	Studio di fattibilità di screening per cancro colorettale: FOBT annuale vs RSCS "once in a lifetime"	Gastro	No	Sì	06/09/2002	59	59
	Stigliano						
Stato A	Valutazione del rischio del cancro del colon in pazienti operate per cancro della mammella	Gastro	No	No	17/11/2003	-	0
	Zeuli						
Stato A	Studio di fase II di ZD1839 (IRESSA) in combinazione con oxaliplatino e capecitabina nel trattamento di prima linea di pazienti con carcinoma del colon-retto in stadio avanzato	OMA	No	Sì	28/06/2002	4	13
	Cognetti/ Zeuli						
Stato A	Studio di fase III randomizzato, in aperto, multicentrico, con Irinotecan e Cetuximab in confronto ad Irinotecan nel trattamento di seconda-linea in pazienti con carcinoma del colon-retto metastatico, esprimente il recettore per l'epidermal growth factor (EGFr)	OMA	Sì	Sì	30/10/2003	-	-
	Milella						
Stato A	Studio esplorativo di fase II con Capecitabina e Celecoxib in pazienti affetti da neoplasie avanzate del pancreas/vie biliari (CapCel-01), del distretto cervico-facciale (CapCel-02), del colon-retto (CapCel-03) e della mammella (CapCel-04).	OMA	No	No	30/10/2003	-	1
	Zeuli						
Stato C	Studio di fase III randomizzato, in doppio cieco, controllato verso placebo: oxaliplatino/5-fluorouracile/leucoverin e PTK787/ZK222584 o placebo, per il trattamento di prima linea di pazienti affetti da adenocarcinoma del colon o del retto metastatico	OMA	Sì	Sì	19/05/2003	4	7

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	LOPEZ						
STATO C	Studio randomizzato di fase III che compara capecitabina (RO 09-1978) con fluorouracile (5-FU) endovena bolo combinato con bassi dosaggi di leucovorin come terapia adiuvante in pazienti sottoposti ad intervento chirurgico per carcinoma del colon in stadio C di Dukes	OMB	Sì	Sì	05/07/1999	-	0
	PAOLETTI						
STATO A	Folfiri vs folfiri+celecoxib nel trattamento del carcinoma colorettale in fase avanzata	OMB	Sì	Sì	16/12/2003	0	0
	PAOLETTI						
STATO A	A dose-finding study followed by a phase II trial of oral UFT and LV (Leucovorin) plus I.V. mitomycin in metastatic colorectal cancer	OMB	No	Sì	20/06/2001	1	4
	GARUFI						
STATO A	Valutazione dell'acetil-l-carnitina (ST 200) nel ridurre l'intensità della neuropatia periferica sensoriale indotta da oxaliplatino. Studio di fase II randomizzato, esplorativo	OMC	Sì	Sì	10/04/2003	0	0
	GARUFI						
STATO A	Time finding study of chronomodulated irinotecan, 5-Fluoraucil, leucoverin and oxaliplatin as first line against metastatic colorectal cancer	OMC	Sì	Sì	20/03/2002	17	30
	DISFUNZIONE ERETTILE						
	JANDOLO						
STATO C	Studio randomizzato, crossover, in aperto con IC351 (LY450190) somministrato in pazienti con disfunzione erettile, per valutare la preferenza dei pazienti per uno schema di assunzione "a richiesta" o "predefinito"	Neuro	Sì	Sì	07/10/2002	0	10
	FEGATO						
	SANTORO/VENNARECCI						
STATO A	Protocollo per la selezione, per il trattamento immunosoppressivo e antiretrovirale ed il monitoraggio post-trapianto. Trapianto di fegato nei soggetti con infezione da HIV: valutazione osservazionale di fattibilità	CHB	No	Sì	10/04/2003	6	6
	MILELLA						
STATO C	Peg-interferon Alfa-2b nell'epatocarcinoma HCV-correlato dopo resezione completa o necrosi completa. Studio multicentrico randomizzato di fase III	OMA	Sì	Sì	10/04/2003	-	-

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	GIST ZEULI						
STATO C	STI571 (Glivec) in KIT-expressing gastrointestinal stromal tumors (GIST): a prospective, open-label, multicenter study on best clinical use in advanced disease	OMA	No	Sì	20/03/2002	0	5
	GLIOBLASTOMA CARAPELLA						
STATO A	Studio multicentrico di fase III sulla terapia intratumorale/interstiziale con TransMID in confronto alla migliore terapia disponibile in pazienti affetti da glioblastoma multiforme progressivo e/o ricorrente non asportabile chirurgicamente	NCH	No	Sì	30/10/2003	-	-
	HPV MARIANI						
STATO C	Immunogenicità e sicurezza del vaccino tetravalente HPV L1 (tipo 6,11,16,18) costituito da particelle virus simili (VLP) in lotti differenti in donne di età tra i 16 ed i 23 anni ed immunogenicità del vaccino HPV 16 (VLP) e studio x valutare l'efficacia del vaccino HPV L1 tetravalente (tipo 6,11,16,18) costituito da particelle virus simili (VLP) nel ridurre CIN e VaIN correlati a HOV 6,11,16 e 18 e di lesioni verrucose genitali esterne e vin correlate a HPV 6,11,16 e 18 in donne di età compresa tra i 16 ed i 23 anni.	Gine	Sì	Sì	20/03/2002	-	2
	LEUCEMIA PIASANI						
STATO A	Studio osservazionale di pazienti con leucemia mieloide cronica di nuova diagnosi trattati con Imatinib.	Emat	No	Sì	30/10/2003	-	1
	PIASANI						
STATO A	Studio di fase III: Imatinib a dose standard (400mg/al dì) vs Imatinib ad alte dosi (800mg/al dì) per il trattamento di pazienti ad alto rischio con leucemia mieloide cronica in fase cronica di nuova diagnosi	Emat	Sì	Sì	30/10/2003	-	0
	PIASANI						
STATO A	Imatinib ad alte dosi (800mg/al dì) nel trattamento di pazienti di nuova diagnosi con leucemia mieloide cronica in fase cronica con rischio intermedio. Studio esplorativo di fase II.	Emat	No	Sì	30/10/2003	-	1

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	PETTI						
STATO A	Il valore delle alte dosi standard di ARA-C durante l'induzione e dell'IL-2 dopo consolidamento intensivo/trapianto autologo di cellule staminali in pazienti (età 15-60 anni) con leucemia mieloide acuta	Emat	Sì	Sì	13/02/2003	1	1
	LNH LINFOMA NON-HODGKIN						
	PETTI /MAINI						
STATO A	Valutazione dell'efficacia e tollerabilità del trattamento con 90Y-ibritumomab tiuxetano a confronto con nessuna terapia, in pazienti con linfoma non-Hodgkin follicolare in stadio III e IV, che hanno ottenuto una remissione completa o parziale dopo un trattamento chemioterapico di prima linea. Studio clinico di fase III prospettico, multicentrico, randomizzato	Emat	No	Sì	19/05/2003	1	1
	PETTI						
STATO A	Terapia con ciclofosfamide-fludarabina-rituximab verso il miglior trattamento convenzionale in pazienti con Linfoma non-Hodgkin follicolare ricaduti: valutazione della risposta clinica e della predittività dei test di chemio-sensibilità	Emat	Sì	Sì	13/03/2003	1	1
	PETTI						
STATO A	Studio prospettico randomizzato nei linfonomi non-Hodgkin (LNH) aggressivi - NHLCSG: 1) VACOP-B e high dose sequential therapy (HDS) nei LNH in stadio avanzato; 2) anti-CD 20 nei linfonomi b/CD 20 + in prima remissione completa	Emat	Sì	Sì	14/11/2001	2	4
	MAMMELLA						
	DI FILIPPO						
STATO A	Studio multicentrico, prospettico, randomizzato di fase III: linfonodo sentinella +- linoadenectomia ascellare nel carcinoma della mammella allo stadio iniziale	CHA	Sì	Sì	11/11/1999	5	99
	MARIANI						
STATO A	Studio internazionale, multicentrico, randomizzato, in doppio cieco, a gruppi paralleli, controllato verso placebo, per valutare efficacia e sicurezza del tibolone (Org OD14) in donne con sintomi climaterici e storia di cancro della mammella	Gine	Sì	Sì	07/10/2002	2	4
	COGNETTI/MILELLA						
STATO C	Studio di fase II, randomizzato, in aperto con CI-1033 come singolo agente in pazienti con carcinoma mammario metastatico	OMA	Sì	Sì	10/04/2003	1	1

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	CARLINI						
STATO A	Studio di fase II, multicentrico, in aperto, in due stadi, di Anastrozolo (Arimidex™) in combinazione con ZD1839 (IRESSA™) nel trattamento di donne in postmenopausa affette da carcinoma della mammella metastatico che hanno precedentemente fallito un trattamento con Tamoxifen.	OMA	No	Sì	10/04/2003	-	1
	CARLINI						
STATO C	Terapia di mantenimento con anastrozolo (Arimidex) verso controllo in pazienti affetti da neoplasia mammaria metastatica, responsivi o in stabilità di malattia dopo chemioterapia antiblastica	OMA	Sì	Sì	25/09/2000	0	1
	CARLINI						
STATO A	Exemestane (Aromasin): ormonoterapia di mantenimento dopo chemioterapia di I linea nel trattamento del carcinoma mammario metastatico	OMA	No	Sì	17/01/2001	1	4
	CARLINI						
STATO A	Studio osservazionale sulle modalità di trattamento adiuvante e sui pattern di ricaduta delle pazienti con carcinoma mammario operato (Studio NORA).	OMA	No	Sì	16/01/2003	46	46
	CARLINI						
STATO C	Valutazione dei livelli sierici di VGEF (Vascular Endothelial Growth Factor) in pazienti affette da carcinoma della mammella metastatico trattate con ormonoterapia	OMA	No	Sì	14/11/2001	0	0
	CARLINI						
STATO C	Studio osservazionale sull'attività dell'inibitore non-steroideo Anastrozole (Arimidex) in pazienti Tamoxifen refrattari-resistenti con carcinoma della mammella metastatico (CMM) in post-menopausa	OMA	Sì	Sì	12/06/2001	0	5
	SAVARESE/SEGA						
STATO A	Consulenza integrata oncologica-genetica-psicooncologica (counselling genetico) nelle neoplasie mammarie ad incidenza familiare. Programma di sorveglianza per la identificazione e prevenzione dei tumori mammari in soggetti ad alto rischio genetico	OMA	No	No	10/10/2001	80	233

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	PAPALDO						
STATO A	Studio randomizzato di fase III con EC seguito da Paclitaxel verso FEC seguito da Paclitaxel, cicli somministrati ogni 3 settimane o 2 settimane con supporto di Pegfilgrastim, per pazienti con carcinoma della mammella con linfonodi ascellari positivi (Studio randomizzato di fase III con EC seguito da Paclitaxolo versus FEC seguito da Paclitaxolo in pazienti con neoplasia mammaria con linfonodi positivi)	OMA	Sì	Sì	07/10/2002	13	33
	FABI						
STATO A	Associazione di doxorubicina liposomiale (caelix) e gemcitabine (gemzar) nel trattamento della neoplasia mammaria avanzata: studio di fase II	OMA	No	Sì	11/12/2002	25	35
	PAPALDO						
STATO A	Confronto randomizzato, multicentrico a tre bracci tra il trattamento con Herceptin per 1 anno e 2 anni rispetto a nessun trattamento aggiuntivo nelle pazienti con carcinoma primario della mammella HER2 positivo dopo chemioterapia adiuvante	OMA	No	Sì	06/09/2002	9	9
	CARLINI						
STATO C	An open, randomized sequential study of endocrine therapy in postmenopausal patients with advanced breast cancer with estrogen and/or progesteron positive tumors	OMA	Sì	Sì	30/05/2001	0	0
	FABI /PUGLIESE						
STATO A	La qualità di vita durante il trattamento chemioterapico e/o ormonoterapico adiuvante delle pazienti affette da neoplasia mammaria operata	OMA	No	No	18/09/2003	30	33
	SAVARESE						
STATO C	Progetto Artemide: campagna di informazione sul cancro al seno	OMA	No	Sì	18/09/2003	10	10
	MILELLA						
STATO A	Studio esplorativo di fase II con Capecitabina e Celecoxib in pazienti affetti da neoplasie avanzate del pancreas/vie biliari (CapCel-01), del distretto cervicofacciale (CapCel-02), del colon-retto (CapCel-03) e della mammella (CapCel-04).	OMA	No	No	30/10/2003	-	9

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	PAPALDO						
STATO A	An open label randomized phase 2 study of Trastuzumab (Herceptin) given with weekly Paclitaxel (Taxol) versus weekly Paclitaxel as single agent in first-line therapy metastatic breast cancer (MBC) patients with HER-2/neu overexpression	OMA	Sì	Sì	15/11/2000	5	14
	PAPALDO						
STATO C	Studio di fase II, aperto, multicentrico con MAC-321 somministrato per via intravenosa come agente singolo per il trattamento di soggetti affetti da cancro metastatico della mammella con patologia resistente ai taxani	OMA	No	Sì	30/10/2003	-	-
	SAVARESE						
STATO A	Studio multicentrico in doppio cieco, placebo vs Exemestane (Aromasin) per la prevenzione del carcinoma della mammella in donne in menopausa portatrici di mutazione predisponente dei geni BRCA1 o BRCA2. Aromasin Prevention Study (A.Pre.S.).	OMA	No	Sì	18/09/2003	-	-
	CARLINI						
STATO A	Studio in aperto, randomizzato, multicentrico per valutare l'utilizzo dell'acido zoledronico nella prevenzione della perdita ossea correlata al trattamento del tumore in donne postmenopausa, con carcinoma mammario positivo per i recettori degli estrogeni e/o progesterone, in trattamento adiuvante con letrozolo	OMA	Sì	No	17/11/2003	-	-
	LOPEZ						
STATO A	Epirubicina e vinorelbina verso doxorubicina liposomiale pegilata e vinorelbina nel trattamento di I linea del carcinoma mammario metastatizzato. Studio multicentrico randomizzato di fase II (GOIM 2304)	OMB	Sì	Sì	19/05/2003	10	10
	LOPEZ						
STATO A	Docetaxel e gemcitabina verso docetaxel e capecitabina nel trattamento di I linea del carcinoma mammario metastatizzato. Studio multicentrico randomizzato di fase II (GOIM 2305)	OMB	Sì	Sì	19/05/2003	6	6
	VICI						
STATO A	An open label randomized phase III study of Capecitabine in combination with exemestane compared with exemestane alone as maintaining therapy for metastatic hormonereceptor positive breast cancer patients	OMB	Sì	Sì	30/05/2001	-	0

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	VICI						
STATO A	Epirubicina e ciclosfamide vs taxotere seguito da epirubicina e ciclosfamide nel trattamento adiuvante del carcinoma mammario con linfonodi ascellari positivi. Studio multicentrico randomizzato	OMB	Sì	Sì	07/06/1999	18	120
	VICI						
STATO C	An open, randomized sequential study of endocrine therapy in postmenopausal patients with advanced breast cancer with estrogen and/or progesteron positive tumors	OMB	Sì	Sì	30/05/2001	0	0
	VICI						
STATO A	Gemcitabina e docetaxel come terapia di prima linea nel carcinoma mammario metastatizzato. Studio multicentrico di fase II	OMB	No	Sì	20/06/2001	3	15
	Izzo						
STATO C	Studio clinico in aperto per valutare l'efficacia e la tollerabilità dello zometa (Zolendronato) 4mg somministrato per via endovenosa a pazienti affetti da carcinoma mammario metastatico, in cui sia indicato il trattamento con bifosfonati	OMC	No	Sì	19/12/2001	-	0
	TERZOLI						
STATO C	An open, randomized sequential study of endocrine therapy in postmenopausal patients with advanced breast cancer.	OMC	Sì	Sì	30/05/2001	0	0
	NISTICÒ						
STATO A	Studio randomizzato di fase III con EC seguito da Paclitaxel verso FEC seguito da Paclitaxel, cicli somministrati ogni 3 settimane o 2 settimane con supporto di Pegfilgrastim, per pazienti con carcinoma della mammella con linfonodi ascellari positivi	OMC	Sì	Sì	17/11/2003	-	5
	TONACHELLA						
STATO A	Studio osservazionale sulle modalità di trattamento adiuvante e sui pattern di ricaduta delle pazienti con carcinoma mammario operato (Studio NORA).	OnGer	No	Sì	10/04/2003	0	0
	PINNARÒ						
STATO A	Studio osservazionale sulla correlazione tra misura bidimensionale della quantità di polmone compresa nel campo di terapia e volume di polmone irradiato nel trattamento radiante complementare del carcinoma mammario operato	Radio	No	No	10/06/2003	66	66

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	PINNARÒ						
STATO C	Studio prospettico e randomizzato di fase III: RT dilazionata vs RT immediata in pazienti affette da ca mammrio sottoposte a chirurgia conservativa, CMF adiuvante e RT complementare	Radio	Sì	No	01/01/1998	-	256
	PINNARÒ						
STATO A	Studio prospettico e randomizzato di confronto tra quadrantectomia seguita da radioterapia esterna complementare e quadrantectomia associata a radioterapia intraoperatoria in pazienti affette da carcinoma mammario di piccole dimensioni e di età > a 48 anni in postmenopausa	Radio	Sì	Sì	16/01/2002	12	40
	MELANOMA						
	FERRARESI						
STATO C	Adjuvant PEG-Intron treatment in stage III melanoma (Trattamento adiuvante con PEG-Intron vs osservazione dopo linfoadenectomia regionale in pazienti affetti da melanoma stadio III: studio randomizzato di fase III)	OMA	Sì	Sì	14/03/2001	2	5
	FERRARESI						
STATO A	Studio clinico di fase II, multicentrico, randomizzato, in aperto, per valutare l'efficacia del farmaco ST1472 in una terapia di combinazione con basse dosi di IFN+DTIC paragonata alla terapia ST1472+DTIC e alla terapia DTIC+IFN a basse dosi in pazienti affetti da melanoma maligno avanzato	OMA	Sì	Sì	28/06/2002	8	13
	FERRARESI						
STATO A	Studio multicentrico, in aperto, non comparativo per valutare l'efficacia e la tollerablità della fotemustina, in associazione alla bio-chemioterapia, in pazienti con melanoma avanzato	OMA	No	Sì	13/03/2003	-	0
	FERRARESI						
STATO A	Monitoraggio biochimico del marker di attività angiogenica VEGF: implicazioni prognostiche e terapeutiche nel melanoma cutaneo	OMA	No	No	07/10/2002	14	23
	ZEULI						
STATO C	Studio multicentrico per la valutazione dell'attività di Temozolomide preceduta da radioterapia in pazienti affetti da metastasi cerebrali da melanoma maligno	OMA	No	Sì	13/09/2000	2	3

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	FERRARESI						
STATO A	Post-operative adjuvant ganglioside GM2-KLH/QS-21 vaccinacion treatment vs observation after resection of primary cutaneous melanoma (AJCC Stage II, T3-T4N0M0)	OMA	Sì	Sì	12/06/2002	3	3
	FERRARESI						
STATO A	Studio clinico di fase II per la valutazione delle interazioni tra chemioterapia e immunoterapia di pazienti affetti da melanoma	OMA	No	Sì	16/12/2003	-	0
	MESOTELIOMA						
	COGNETTI/CERIBELLI						
STATO A	Studio in aperto sulla sicurezza di Alimta (pemetrexed) come singolo farmaco o in combinazione con Cisplatino o Carboplatino in pazienti con Mesotelioma Maligno	OMA	No	Sì	10/06/2003	6	11
	LOPEZ						
STATO A	Studio in aperto sulla sicurezza di Alimta (pemetrexed) come singolo farmaco o in combinazione con Cisplatino o Carboplatino in pazienti con Mesotelioma Maligno	OMB	No	Sì	10/06/2003	1	1
	MIELOMA MULTLIPO						
	PETTI						
STATO A	Trattamento del mieloma multiplo alla diagnosi: confronto prospettico randomizzato di chemioterapia intensificata con supporto di progenitori emopoietici e melphalan alla dose di 100 mg/mq verso lo stesso tipo di trattamento con melphalan alla dose di 200 mg/mq	Emat	Sì	Sì	11/12/2002	7	7
	MORBO CELIACO						
	CASALE						
STATO A	Studio multidisciplinare sull'associazione tra Morbo Celiaco e Malattie autoimmuni endocrinologiche e dermatologiche	Gastro	No	No	16/01/2003	31	31
	NEUROENDOCRINO						
	PERRI						
STATO A	Studio osservazionale per la valutazione della Cromogranina A come marker per la diagnosi ed il follow-up della terapia dei NET: CROMANET	CHA	No	Sì	18/09/2003	-	0
	NEUROENDOCRINO NET						
	ZEULI						
STATO C	Studio clinico biologico multicentrico, randomizzato, in aperto, di fase III, per valutare l'equivalenza clinica di due formulazioni di lanreotide (SR 60 mg ed ATG 120 mg) in pazienti affetti da tumore neuroendocrino ben differenziato	OMA	Sì	Sì	28/06/2002	-	0

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	Ovaio						
	Ferretti						
Stato A	Confronto tra chemioterapia standard e chemioterapia Estreme Drug Resistance-test selezionata dopo chirurgia citoriduttiva di prima istanza nel carcinoma ovarico avanzato: studio randomizzato di fase III	OMA	No	Sì	18/09/2003	-	-
	Savarese						
Stato A	Carboplatino/Paclitaxel vs Carboplatino/doxorubicina liposomiale stealth in pazienti con carcinoma ovarico: studio multicentrico randomizzato	OMA	Sì	Sì	10/06/2003	7	10
	Savarese						
Stato A	Studio Randomizzato di Fase III di comparazione fra Gemcitabina, Topotecan e Doxorubicina Liposomiale nel trattamento del carcinoma ovarico recidivante	OMA	No	Sì	18/09/2003	2	3
	Pancreas						
	Milella						
Stato A	Infusione Prolungata di Gemcitabina (Dose-Rate Fisso: 10 mg/m2/min) nei Tumori Pancreatici e delle Vie Biliari Localmente Avanzati (Inoperabili) e/o Metastatici: Studio Osservazionale.	OMA	No	No	10/06/2003	21	24
	Milella						
Stato A	Studio esplorativo di fase II con Capecitabina e Celecoxib in pazienti affetti da neoplasie avanzate del pancreas/vie biliari (CapCel-01), del distretto cervicofacciale (CapCel-02), del colon-retto (CapCel-03) e della mammella (CapCel-04).	OMA	No	No	30/10/2003	-	-
	Carlini						
Stato A	Gemcitabina vs gemcitabina + cisplatino nel trattamento del carcinoma del pancreas avanzato	OMA	Sì	Sì	12/06/2002	3	3
	Lopez						
Stato A	Gemcitabina vs gemcitabina + cisplatino nel trattamento del carcinoma del pancreeas avanzato	OMB	Sì	Sì	06/09/2002	1	1
	Izzo						
Stato C	A phase III trial of Alimta plus gemzar versus gemzar in patients with unresectable or metastatic cancer of the pancreas	OMC	Sì	Sì	19/12/2001	2	12
	Pi patologie						
	Cavaliere						
Stato A	Trattamento integrato dello pseudomixoma peritonei da carcinoma appendicolare colorettale ed ovarico	CHA	No	No	11/12/1999	2	4

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	ZEULI						
STATO A	Trapianto allogenico non mieloablativo (mini-allotrapianto) di cellule staminali emopoietiche come terapia di salvataggio nei tumori solidi refrattari ai trattamenti convenzionali	OMA	No	Sì	06/09/2002	-	2
	GIOVINAZZO						
STATO A	Studio prospettico e randomizzato tra due diversi schemi di radioterapia, in associazione o meno con Zolendronato, in pazienti affetti da metastasi ossee sintomatiche da carcinoma mammario e prostatico	Radio	Sì	Sì	20/02/2002	32	45
	POLMONE						
	JANDOLO						
STATO A	Prevalenza di sindromi paraneoplastiche del Sistema Nervoso Periferico e della Placca Neuromuscolare in pazienti affetti da neoplasia polmonare	Neuro	No	No	19/05/2003	21	21
	CERIBELLI						
STATO C	Studio di fase III con LY900003 più Gemcitabina e Cisplatino versus Gemcitabina e Cisplatino in Pazienti con Carcinoma Polmonare Non a Piccole Cellule in fase avanzata non precedentemente trattato	OMA	No	Sì	20/02/2002	5	5
	CERIBELLI						
STATO C	Studio multicentrico randomizzato di fase II di ZD1839 in combinazione con gemcitabina e ZD1839 in combinazione con Vinorelbina nel trattamento di prima linea di pazienti anziani con carcinoma del polmone non a piccole cellule in stadio avanzato	OMA	Sì	Sì	20/03/2002	-	-
	CERIBELLI						
STATO A	Aggiunta del rofecoxib alla polichemioterapia con cisplatino e Gemcitabina e infusione costante prolungata di gemcitabina in associazione con il cisplatino, nel trattamento del carcinoma polmonare NSCLC in fase avanzata. Studio multicentrico di valutazione della tollerabilità e dell'efficacia (fase II-III)	OMA	Sì	Sì	16/01/2003	16	22
	CERIBELLI						
STATO A	Programma clinico internazionale A di accesso a ZD1839 (IRESSA) per i pazienti affetti da carcinoma del polmone non a piccole cellule (NSCLC)	OMA	No	Sì	16/12/2003	-	-

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	CERIBELLI						
STATO A	Studio di fase III, randomizzato, doppio cieco, di confronto tra ZD1839 (IRESSA) verso placebo come terapia di mantenimento in soggetti con tumore polmonare non a piccole cellule (NSCLC) localmente avanzato dopo terapia a modalità combinata	OMA	No	Sì	16/12/2003	-	-
	CERIBELLI						
STATO C	Studio multicentrico di fase II di Gemcitabina-oxaliplatino come prima linea di trattamento in pazienti con tumore polmonare non microcitoma (NSCLC) in stadio avanzato	OMA	No	Sì	20/02/2002	-	5
	SAVARESE						
STATO C	Chemioterapia seguita da radioterapia standard vs chemioterapia seguita da radio+chemioterapia concomitante nel trattamento del NSCLC inoperabile in stadio III	OMA	Sì	Sì	12/04/2000	-	4
	CERIBELLI						
STATO A	A randomized phase III of surgery alone or surgery plus gemcitabine - cisplatin in clinical early stages (T2N0, T1, T3 N0 and T3N1) non small cell lung cancer (NSCLC)	OMA	Sì	Sì	13/09/2001	8	20
	CERIBELLI						
STATO A	Associazione bisettimanale di Paclitaxel e Gemcitabina, seguita da Paclitaxel settimanale, nella terapia di I linea del carcinoma del polmone Non a Piccole Cellule Localmente avanzato e metastatico (stadio IIIB-IV) in pazienti con età superiore a 65 anni e/o PS2	OMA	No	Sì	13/02/2003	1	4
	LOPEZ						
STATO C	Chemioterapia seguita da radioterapia standard vs chemioterapia seguita da radio+chemioterapia concomitante nel trattamento del NSCLC inoperabile in stadio III	OMB	No	Sì	12/04/2000	-	-
	LOPEZ						
STATO A	Efficacia clinica sulla sopravvivenza del trattamento con chemioterapia standard vs chemioterapia standard + modulo di attivazione linfocitaria con interleuchina-2 (IL-2) Tumore polmonare non-microcitoma non resecabile	OMB	Sì	Sì	01/01/2000	-	12

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	RINALDI						
STATO C	Studio multicentrico randomizzato di fase II di ZD1839 in combinazione con gemcitabina e ZD1839 in combinazione con Vinorelbina nel trattamento di prima linea di pazienti anziani con carcinoma del polmone non a piccole cellule in stadio avanzato	OMB	Sì	Sì	20/03/2002	-	-
	RINALDI						
STATO A	A randomized phase III of surgery alone or surgery plus gemcitabine - cisplatin in clinical early stages (T2N0, T1, T3 N0 and T3N1) non small cell lung cancer (NSCLC)	OMB	Sì	Sì	13/09/2000	-	2
	RINALDI						
STATO A	Studio clinico di fase II nel carcinoma polmonare non a piccole cellule localmente avanzato relativo alla combinazione di vinorelbine orale (Navelbine) e cisplatino, somministrata come terapia d'induzione e contemporaneamente alla radioterapia	OMB	No	Sì	12/06/2002	1	2
	RINALDI						
STATO A	Chemioterapia con gemcitabina in infusione prolungata o con schemi contenenti cisplatino nel trattamento del carcinoma polmonare non a piccole cellule avanzato in pazienti anziani	OMB	No	Sì	16/12/2003	-	-
	RINALDI						
STATO A	Studio multicentrico di fase II che valuta la fattibilità e l'attività di due diverse combinazioni di Docetaxel e Gemcitabina e del trattamento Gemcitabina Cisplatino seguito da Docetaxel in pz con carcinoma del polmone NSCLC localmente avanzato o metastatico che non abbiano ricevuto precedentemente trattamento chemioterapico	OMB	Sì	Sì	20/02/2002	8	10
	TERZOLI						
STATO A	Aggiunta del rofecoxib alla polichemioterapia con cisplatino e Gemcitabina e infusione costante prolungata di gemcitabina in associazione con il cisplatino, nel trattamento del carcinoma polmonare NSCLC in fase avanzata. Studio multicentrico di valutazione della tollerabilità e dell'efficacia (fase II-III)	OMC	Sì	Sì	10/04/2003	-	1
	GIUNTA						
STATO A	La TAC spirale "low-dose" nella diagnosi precoce del cancro del polmone nei soggetti a rischio	RX	No	No	03/07/2000	221	671

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	POLMONE MICRO						
	CERIBELLI						
STATO A	Valutazione dell'attività e della tossicità della polichemioterapia con schemi a due farmaci contenenti Gemcitabina nel microcitoma polmonare esteso in pazienti anziani	OMA	No	Sì	16/01/2002	3	4
	LOPEZ						
STATO A	Studio randomizzato, in doppio cieco, con controllo plcebo in soggetti non pretrattati con microcitoma polmonare in stadio esteso trattati con chemioterapia a base di platino e etoposide con o senza darbepoetin alfa	OMB	Sì	Sì	16/01/2003	1	1
	PROCTITE						
	CASALE						
STATO C	Butirrato di sodio per via topica nella prevenzione della proctite acuta da radiazioni. Studio multicentrico controllato a doppia cecità contro placebo	Gastro	No	Sì	18/04/2000	-	27
	PROSTATA						
	CARLINI						
STATO A	Studio prospettico multicentrico randomizzato di fase II con Docetaxel ed Estramusina in due diverse schedules nel trattamento del carcinoma prostatico ormono-refrattario (HRPC)	OMA	Sì	Sì	30/10/2003	-	-
	CARLINI						
STATO C	Studio osservazionale multicentrico e multinazionale per documentare il trattamento e lo standard di cura dei pazienti affetti da carcinoma metastatico della prostata refrattario al trattamento ormonale (W01-381)	OMA	No	Sì	07/10/2002	-	5
	CARLINI						
STATO C	Studio di fase II multicentrico, randomizzato, in doppio cieco, controllato con placebo, per valutare la sicurezza e l'attività di ZD1839 (IRESSA) nel migliorare il controllo del PSA e il decorso clinico del tumore alla prostata refrattario agli ormoni	OMA	Sì	Sì	06/09/2002	1	1
	GIOVINAZZO						
STATO C	Three dimensional conformal radiotherapy alone vs three dimensional conformal therapy plus adjuvant hormonal therapy in localized T1b-c, T2a, M0 prostatic carcinoma. A phaseIII randomized study	Radio	Sì	Sì	11/07/2001	-	-

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	ARCANGELI						
STATO A	Studi paralleli di fase II con assegnazione randomizzata tra frazionamento convenzionale standard e ipofrazionamento nell'irradiamento del carcinoma prostatico a prognosi sfavorevole, in associazione a soppressione androgenica totale	Radio	Sì	Sì	11/12/2002	32	49
	SARACINO						
STATO A	Impiego della radioterapia intraoperatoria (IORT) dopo prostatectomia radicale nell'adenocarcinoma prostatico, studio di fase finding	Radio	No	No	16/01/2002	9	28
	SARACINO						
STATO A	Studio osservazionale sulla valutazione dell'accuratezza e della riproducibilità di Radioterapia ad Intensità Modulabile (IMRT) nel trattamento del tumore prostatico	Radio	No	No	10/04/2003	18	18
	ARCANGELI/TESSITORE						
STATO A	Studio di fase II, randomizzato, per il confronto tra trattamento convenzionale versus trattamento con inibitore delle COX-2 delle complicanze della radioterapia per carcinoma della prostata	Radio	No	Sì	18/09/2003	-	10
	GALLUCCI/DE CARLI						
STATO A	Studio in doppio cieco, randomizzato, placebo-controllato, multicentrico per valutare l'effetto del rofecoxib nel ridurre il rischio di carcinoma prostatico	URO	No	Sì	18/09/2003	-	-
	GALLUCCI						
STATO A	Ruolo del microambiente e ricerca di nuovi target terapeutici	URO	No	Sì	19/05/2003	-	-
	RENE						
	COGNETTI/RUGGERI						
STATO A	Studio randomizzato di fase III di BAY 43-9006 in pazienti affetti da carcinoma delle cellule renali metastatico e/o non operabile	OMA	Sì	Sì	17/11/2003	-	-
	RUGGERI						
STATO A	Studio aperto di fase III, randomizzato a tre bracci con Alfa Interferone in monoterapia, CCI-779 in monoterapia e l'associazione di Alfa Interferone e CCI-779 somministrati come trattamenti di prima linea in soggetti affetti da carcinoma a cellule renali avanzato con prognosi severa	OMA	Sì	No	16/12/2003	-	2

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	RETTO						
	COSIMELLI						
STATO A	Retrostadiazione preoperatoria nel carcinoma rettale extraperitoneale T3: Raltitrexed + Oxaliplatino + radioterapia (Tomoxrt) versus cisplatino + 5 Fluorouracile + radioterapia (Plafur). Studio randomizzato multicentrico.	CHB	Sì	Sì	16/01/2003	12	13
	COSIMELLI						
STATO A	Valutazione dell'impatto che i profili biologici, il trattamento combinato radio-chemioterapico e la chirurgia esercitano nella sottostadiazione del carcinoma del retto e sulla qualità della vita dei pazienti	CHB	No	Sì	20/03/2002	17	36
	S.N.C. (SISTEMA NERVOSO)						
	CARAPELLA/FABI						
STATO A	Radioterapia concomitante ad infusione prolungata di gemcitabine nel trattamento del glioblastoma multiforme: studio di fase I-II	NCH	No	No	02/07/2003	1	7
	PACE						
STATO A	Progetto di assistenza continuativa integrata e neuroriabilitazione a domicilio per pazienti affetti da tumori cerebrali	Neuro	No	No	11/11/2002	67	149
	PACE						
STATO A	Studio osservazionale sul trattamento chemioterapico con Temozolomide in pazienti affetti da astrocitoma grado 2 (WHO) in fase di progressione o recidiva	Neuro	No	Sì	16/01/2003	9	9
	SARCOMA						
	FERRARESI						
STATO A	Gemcitabina in infusione prolungata di 100' (rate costante 10/mg/m2/min) in pazienti con sarcomi dei tessuti molli avanzati: studio di fase II	OMA	No	No	18/09/2003	6	7
	SCLEROSI MULTIPLA						
	JANDOLO						
STATO A	Studio osservazionale Beta-intergeron in Early RR-MS Surveillance Trial (BEST)	Neuro	No	Sì	02/07/2003	-	-
	JANDOLO						
STATO A	Monitoraggio degli aspetti cognitivi e affettivi in pazienti affetti da sclerosi multipla recidivante-remittente in trattamento con farmaci immunomodulatori	Neuro	No	Sì	10/06/2003	2	2

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	TESTA-COLLO						
	MILELLA						
STATO A	Studio esplorativo di fase II con Capecitabina e Celecoxib in pazienti affetti da neoplasie avanzate del pancreas/vie biliari (CapCel-01), del distretto cervico-facciale (CapCel-02), del colon-retto (CapCel-03) e della mammella (CapCel-04).	OMA	No	No	30/10/2003	-	-
	RUSCITO/MARUCCI						
STATO A	Studio pilota sulla fattibilità dell'uso della radioterapia intraoperatoria (IORT) nei carcinomi del cavo orale come boost di dose sulla mandibola incaso di sospetta o minima infiltrazione	ORL	No	No	17/11/2003	-	-
	MARUCCI						
STATO A	Studio pilota sulla fattibilità dell'uso della radioterapia intraoperatoria (IORT) come "boost anticipato" nei tumori localmente avanzati del distretto cervico-cefalico	Radio	No	No	16/01/2003	-	-
	MIRRI						
STATO C	Studio multicentrico (doppio cieco) comparativo su efficacia e tollerabilità del fluoconazolo versus placebo in pazienti sottoposti a radioterapia per tumore di testa e collo	Radio	Sì	Sì	15/12/1999	-	20
	ARCANGELI/ MARUCCI						
STATO A	Studio sulla fattibilità dell'uso integrato della chirurgia di salvataggio, della radioterapia intraoperatoria (IORT) e della radioterapia a fasci esterni (EBRT) nei tumori del distretto cervico-cefalico recidivi dopo trattameno radiante	Radio	No	No	16/12/2003	-	-
	VARIE						
	SANTORO						
STATO C	Studio prospettico, multicentrico, in aperto, randomizzato, comparatico per valutare l'efficacia, la sicurezza e la tollerabilità di ertapenem (MK-826) verso ceftriaxone/metronidazolo nel trattamento delle infezioni intra-addominali negli adulti	CHB	Sì	Sì	28/06/2002	-	-
	PETTI						
STATO A	Valutazione clinica dell'effetto del mantenimento dei livelli di emoglobina con dosaggi settimanali di eprex/erypo (epoetina alfa) nei soggetti affetti da tumori linoidi maligni (malattia di hodgkin, linfonoma non-hodgkin, leucemia linfocitica cronica e mieloma multiplo	Emat	No	Sì	12/06/2002	7	7

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	APPETECCHIA						
STATO A	Valutazione dell'efficacia del trattamento con lanreotide negli adenomi ipofisari non funzionanti	Endo	No	Sì	17/11/2003	-	-
	MUSICCO						
STATO A	Misurazione della qualità della vita in pazienti con tumore della mammella metastatico sottoposta a trattamento con trastuzumab: studio osservazionale multicentrico	Farmacia	No	Sì	13/03/2003	3	3
	GRASSI						
STATO A	Studio policentrico sulla prevalenza della metaplasia intestinale e displasia sulla giunzione esofagogastrica nei pazienti che si sottopongono a gastroscopia	Gastro	No	Sì	14/11/2001	35	84
	MARIANI						
STATO A	Infezione della cervice uterina da Virus del Papilloma Umano (HPV), valutazione di test molecolari aggiuntivi di screening (HCII e PCR), identificazione di genotipi HPV ad alto rischio e sviluppo di test immunologici anti-HPV utilizzanti virus Like Particles (HPV-Pathogene ISS)	Gine	No	Sì	13/02/2003	90	90
	PACE						
STATO A	Ruolo della vitamina E nella neuroprotezione della neurotossicità e della ototossicità indotte da cisplatino	Neuro	Sì	Sì	16/12/2003	-	-
	COGNETTI						
STATO A	Progetto globale per l'identificazione ed il miglioramento della Qualità di vita nei pazienti oncologici a lunga aspettativa di vita	OMA	No	Sì	11/12/2002	6	91
	FABI						
STATO C	Studio randomizzato in doppio cieco, di confronto tra la dose standard di carico di darbepoetina alfa e la somministrazione standard settimanale per il trattamento dell'anemia in soggetti affetti da neoplasia non-mieloide che ricevono cicli multipli di chemioterapia	OMA	Sì	Sì	16/01/2003	1	1
	SAVARESE						
STATO A	Studio di fase II randomizzato di due diverse schedule di ondansteron nella terapia di salvataggio dell'emesi indotta da chemioterapia ad alto e moderato potere emetogeno	OMA	Sì	Sì	28/06/2002	59	94
	SAVARESE/FABI						
STATO A	Trattamento d'induzione con epoetina alfa nell'anemia del paziente oncologico sottoposto a chemioterapia	OMA	Sì	Sì	12/02/2003	4	4

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	SAVARESE /JANDOLO						
STATO A	Valutazione dell'efficacia e tollerabilità di L-acetilcarnitina nel prevenire o ridurre la polineuropatia indotta da trattamento con Taxolo in monoterapia o in associazione ad altri farmaci neurotossici e non. Studio multicentrico, randomizzato in doppio cieco controllato verso placebo	OMA	Sì	Sì	20/06/2001	9	14
	COGNETTI/FERRETTI						
STATO A	Prevenzione del tromboembolismo venoso ed arterioso con l'eparina a basso peso molecolare nadroparina calcica in pazieni in trattamento chemioterapico. Studio randomizzato, placebo-controllato, in doppio-cieco, multicentrico di fase III	OMA	Sì	Sì	18/09/2003	-	1
	FABI						
STATO A	Studio multicentrico per la valutazione della tollerabilità e dell'efficacia della somministrazione di 30000 U.I. di Eritropoietina beta sottocute in pazienti anemici in trattamento chemioterapico per tumore della mammella	OMA	No	Sì	16/12/2003	-	3
	FABI/FERRETTI						
STATO A	Il profilo sierico di fattori angiogenetici, citochine e metalloproteinasi durante l'utilizzo di acido zoledronico in pazienti con tumore della mammella o della prostata con metastasi ossee	OMA	No	Sì	11/12/2002	18	18
	DELLA GIULIA						
STATO C	Studio randomizzato in doppio cieco, di confronto tra la dose standard di carico di darbepoetina alfa e la somministrazione standard settimanale per il trattamento dell'anemia in soggetti affetti da neoplasia non-mieloide che ricevono cicli multipli di chemioterapia	OMB	Sì	Sì	16/01/2003	-	-
	TERZOLI						
STATO A	Trattamento d'induzione con epoetina alfa nell'anemia del paziente oncologico sottoposto a chemioterapia	OMC	Sì	Sì	12/02/2003	2	2
	TERZOLI						
STATO C	A randomized study to evaluate the effect of maintaining haemoglobin levels with epotin alfa, on anemia quality of life in breast cancer subjects receiving myelotoxic chemotherapy	OMC	Sì	Sì	14/03/2001	-	-

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	GIOVINAZZO						
STATO A	Studio osservazionale sugli effetti del medrossiprogesterone acetato sul peso e qualità della vita dei pazienti con neoplasie polmonari, cervicofacciali e gastro intestinali sottoposti a radioterapia	Radio	No	No	10/04/2003	23	25
	ARCURI						
STATO A	Studio clinico multicentrico in aperto per valutare il periodo di tempo con dolore controllato nella fase di inizio del trattamento in pazienti con dolore oncologico di grado moderato-severo trattati con morfina orale a rapido rilascio (Oramorph). - Studio M.E.R.I.T.O., Morfina (AD) Efficacia Rapida nell'Inizio del Trattamento in Oncologia -	Rian	No	Sì	19/05/2003	4	7
	ARCURI						
STATO C	Studio clinico policentrico sull'utilizzo del tramadolo nel trattamento del dolore oncologico. Confronto tra due vie di somministrazione	Rian	Sì	Sì	17/01/2001	2	24
	VESCICA						
	RUGGERI						
STATO A	Chemioterapia adiuvante con Cisplatino/Gemcitabine in pz con carcinoma transizionale della vescica ad elevato rischio di recidiva dopo cistectomia radicale vs chemioterapia differita alla ripresa di malattia	OMA	Sì	Sì	30/05/2001	12	38
	GALLUCCI						
STATO A	Somministrazione endovescicale di gemcitabina nelle neoplasie superficiali della vescica: studio di fase II	URO	No	Sì	11/12/2002	7	7

Finito di stampare nel mese di dicembre 2004
presso Euroteam - Nuvolera (Bs)