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

SCIENTIFIC REPORT 2004

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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

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Scientific Director's Report

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:

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Giovanna Santuccio
Antonio De Paolis

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International Affairs Bureau:
Ilaria Vallati

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Piera Brugnoli
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Giovanni Cavallotti
Giuseppe Filardo
Antonio Verbicaro

Photographers - Tecnical Service:
Ivana Zardin
Mauro Di Giovanni

During the year 2004 there was a significant general increase of the clinical activity, with about 14,000 hospitalizations and 869,000 outpatient services, thus allowing an important growth of the clinical trials (186 running in the year and the total number of patients enrolled for the same trials equals to 1763). The Institute reached, therefore, a 2nd national position among the centers and facilities involved into clinical trials as scored by the periodic report produced by the Minister of Health. At the same time, we had an increase of the clinical trials coordinated by the Institute and the number of the no-profit studies in comparison to those sponsored by the pharmaceutical companies. Of considerable relevance the contribution given by the Institute in the role of the coordinating center to the GIM Cooperative Group (Gruppo Italiano Mammella) in conducting clinical trials in adjuvant setting in breast cancer and to a national cooperative group on adjuvant chemotherapy in bladder carcinoma. The Institute run trials on about twenty new antitumoral agents. As in previous years we have been successful in 2004 in obtaining grant support from many different sources: out of a grand total of 9.701.637, where 6.715.470 from the Ministry of Health (significantly decreased on a national basis of a funding for both Current and Targeted Research) when compared with previous years; 1.350.000 from AIRC and FIRC; 1.231.867 from the European Community and 404.300 from other sources. The Institute published a total number of 171 scientific papers for a rough impact factor equals to 656.9. In December 2004 we had a site visit of a committee of scientists and directors of the Ministry of Health which confirmed our recognition as National Scientific Institute. The clinical activity was reorganized through the establishing of the Disease Management Team – DMT – working groups for single tumors, in total 21, aiming at the formulation of diagnostic and therapeutic guidelines, the discussion of clinical cases, the planning of research activities and the standardization of clinical trials pro-

tocols among the different services and divisions, also in cooperation with other institutions or cooperative groups. The DMT groups started to meet regularly every week to discuss clinical cases, and research issues for the single neoplastic pathologies. The international scientific cooperation with foreign countries started with the aim to support the exchange of experiences in the specific fields of education, exchange of researchers and professors, organizations of seminars and bilateral workshops and have already started with Tunisia, Israel and China. The educational and training activity has had a significant increase with 117 intramural events (breakfast-meetings, panels, lectures) organized for a total no. of 1085 credits, double the number of the previous year. On a translational and experimental research's point of view, the Institute, leading of a network, mainly of the city of Rome's research institutions, won an AIRC competition for the oncogenomic technological platform (Rome Oncogenomic Center ROC) foreseeing the organization of a central CORE FACILITY of 700 square meters with 12 module labs including technologies of high complexity. The basic research Core Program is organized into three research work packages: a) integrated approaches for targeted gene identifications; b) MI-RNA and diagnostic and therapeutic tools to fight cancer; c) cancer and cancer stem-cells. The Institute was also awarded as coordinating center a EC funding within the VI Framework Research Program for a cooperative international research study on P53 protein in which other 20 important European research Institutions are partecipating. The Research activity of the Experimental Oncology Department has mainly been focused on new molecular indicators useful in the diagnosis and prevention for tumors, on preclinical approaches to best new drugs, on the genetics of tumors, immunotherapy, vaccines and gene therapy. The use of animal models (transgenic mice and nude mice with human tumor transplants) has permitted the production of specific antibodies for functional domains of oncoproteins. An integrated database system (Tissue and Serum Bank, Clinical Data) was created with the aim to define a proper and clear pattern of biological material for research and related clinical info for the interest of institutions, researchers and patients. The Institute has actively participated into two Italy-USA research programmes (micro RNA gene and Oncoproteomics for early diagnosis and target therapy). We are very grateful to all the granting Institutions which supported a good number of fellows who are involved in Basic and Clinical Research also in other Institutions abroad. Moreover, we should extend our gratitude to the General Director, prof. Luigi Giusto Spagnoli, to the members of the Ethical Committee, the Board of Directors all those in charge of clinical and experimental research, all the Administration Staff for their continuous support and all the personnel for their active service carried out during the course of the year 2004. My thanks also go to Diana Giannarelli as well as the staff of the Scientific Director for the invaluable contribution with the editing. The Research Activity present in this volume has been made possible also thanks to the contributions of the Ministry of Health, the Italian Association for Cancer Research, and the National Institute of Health as well as the other authorities, corporations and private companies.

Francesco Cognetti
Scientific Director

Scientific Activity

N° of Publications by Departments

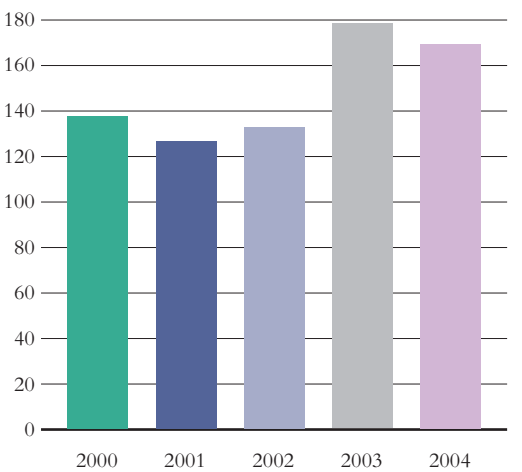
Departments	2000	2001	2002	2003	2004
Central Facilities	17	25	21	41	36
Surgical Oncology	28	34	23	36	27
Medical Oncology	30	29	33	47	62
Prevention and Diagnosis	39	32	41	35	43
Neuroscience & Head - Neck Pathologies	8	4	5	9	5
Critical Area	7	15	2	13	11
Experimental Oncology	47	35	43	46	49
Therapeutic Programs Development	31	30	26	31	26

Impact Factor *

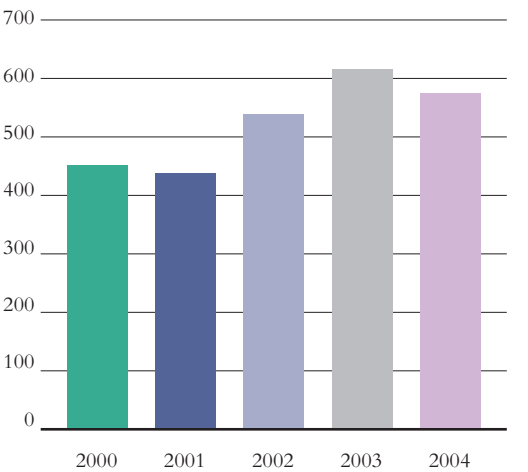
Departments	2000	2001	2002	2003	2004
Central Facilities	36,14	62,62	49,30	60,12	51,32
Surgical Oncology	22,87	21,13	26,80	34,02	31,98
Medical Oncology	45,62	46,11	106,10	124,65	131,47
Prevention and Diagnosis	60,53	65,20	71,30	44,05	82,30
Neuroscience & Head - Neck Pathologies	9,49	2,83	13,00	15,08	12,52
Critical Area	6,95	0,00	2,50	25,37	23,91
Experimental Oncology	170,02	141,23	188,42	158,24	163,22
Therapeutic Programs Development	100,51	101,84	85,58	155,32	79,98
Total	**452,1**	**441,0**	**543,0**	**616,9**	**576,7**

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

Publications



Impact Factor*



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

Publications 2002-2004

	2002	2003	2004
Full Papers			
Journals with Impact Factor	134	179	171
Total Impact Factor (*)	542,96	616,85	576,70
Full Papers			
Journals without Impact Factor	28	15	20
Total Full Papers	162	194	191
- Abstract: International Congresses	74	96	137
- Abstract: National Congresses	75	157	126
- Books, chapters	20	19	18
Total publications	**331**	**466**	**472**

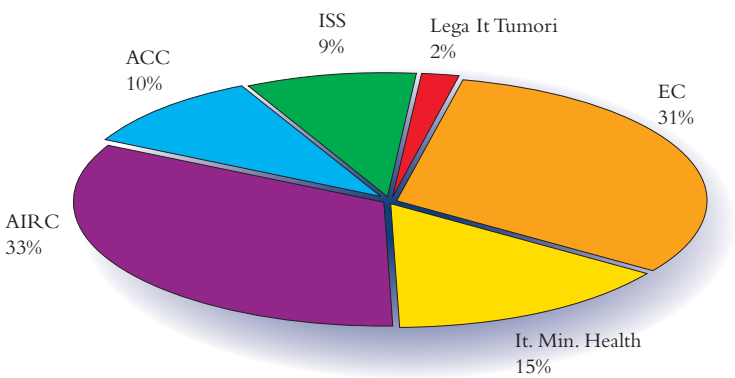
* Normalized according to the Italian Ministry of Health's indications

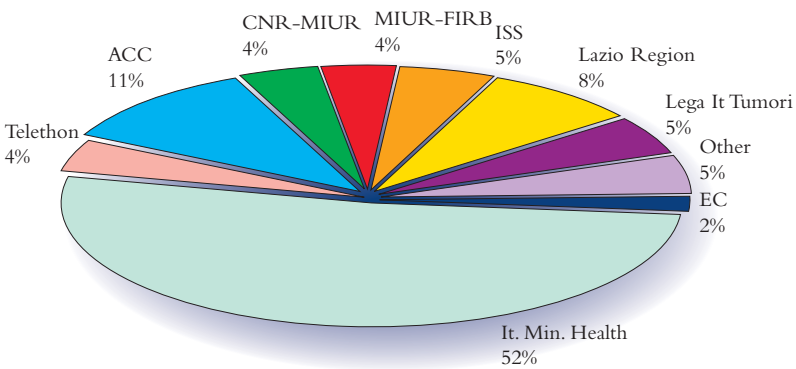
Educational activity (CME) 2002-2004

Intramural educational activity	2002		2003		2004	
Events	N°	Total credits	N°	Total credits	N°	Total credits
Breakfast meetings	33		36		31	
Multidisciplinary panels	9		9		10	
Lectures	2		7		11	
Experimental research seminars	15		13		14	
Meetings, courses	43		46		51	
Total	**102**	**321**	**111**	**531**	**117**	**1.078**

Institutional Grants Started in 2004

Institution	Project No.	Financial support
Italian Ministry of Health	7	€ 585.750,00
AIRC	14	€ 1.350.000,00
ACC	18	€ 415.720,16
ISS	7	€ 339.651,00
Lega It Tumori	1	€ 64.649,06
EC	2	€ 1.231.867,00
Total	**49**	**€ 3.987.637,22**





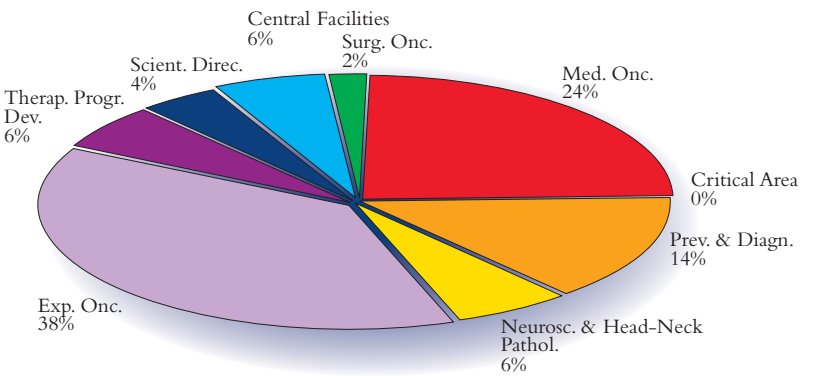
Institutional Grants Started before 2004 Ongoing

Institution	Project No.	Financial support
Italian Ministry of Health	43	€ 4.727.482,42
ACC	18	€ 957.000,00
CNR-MIUR	8	€ 364.099,13
MIUR-FIRB	3	€ 399.200,00
ISS	8	€ 433.600,00
Lazio Region	6	€ 729.818,48
Lega It Tumori	5	€ 474.051,30
Telethon	2	€ 364.102,01
EC	1	€ 180.000,00
Other	5	€ 420.137,06
Total	**99**	**€ 9.049.490,40**

Founded Projects Started in 2004

Departments	P.I.*	External Units P.I.*	Total
Central Facilities	2	1	3
Surgical Oncology	0	1	1
Medical Oncology	5	7	12
Prevention and Diagnosis	1	5	6
Neuroscience & Head - Neck Pathologies	1	2	3
Critical Area	0	0	0
Experimental Oncology	17	2	19
Therapeutic Programs Development	3	0	3
Scientific Direction	1	1	2
Total	**30**	**19**	**49**

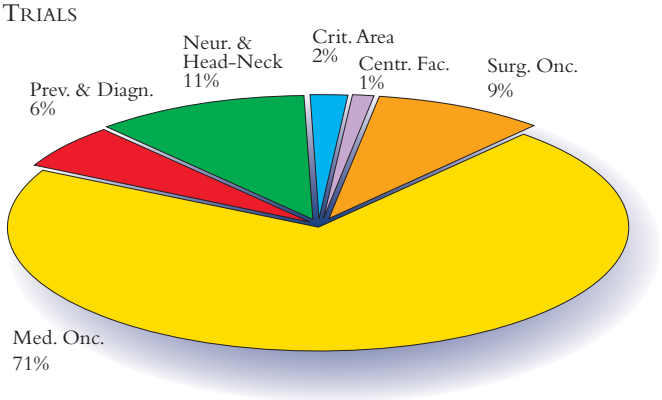
*Principal investigator



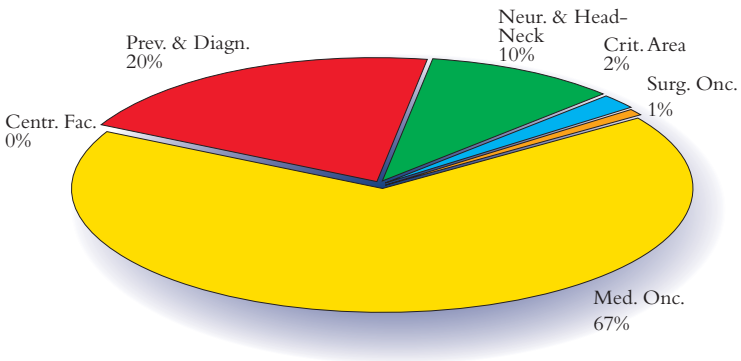
Active Clinical trials (2004)

Department	Trial No.	Patient No.
Central Facilities	1	0
Surgical Oncology	16	20
Medical Oncology	134	1.004
Prevention and Diagnosis	11	299
Neuroscience & Head - Neck Pathologies	20	144
Critical Area	4	26
Total	**186**	**1.493**

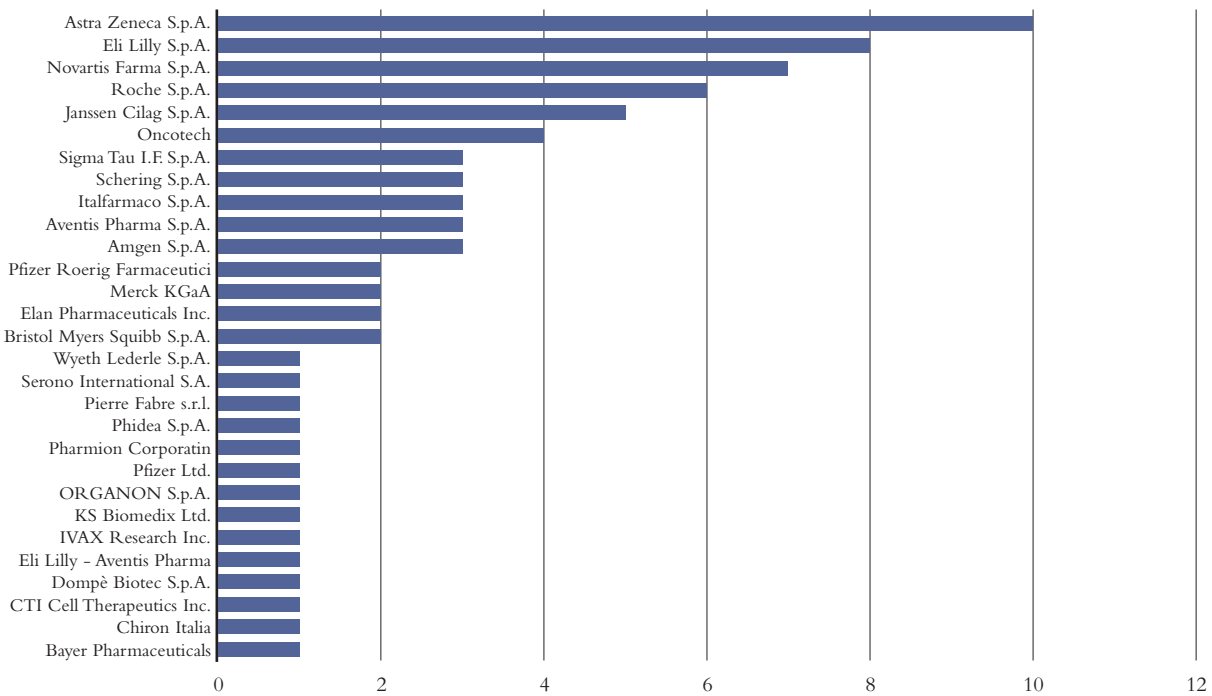
Trials



Patients



Number of supported clinical trials (2004)



Clinical Activity

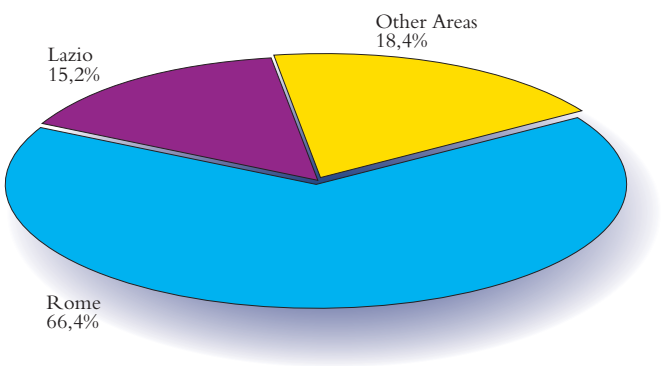
In patients

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Inpatient admissions	7220	7755	8627	8374	8083	6673	6721	8080	9478	10191
Inpatient Days	79022	75933	76092	73510	67728	55064	54832	65706	72314	74754
Alos	11	10	8,82	8,78	8,38	8,25	8,16	8,13	7,63	7,34
Surgical index %	52	55	52	53	51	50	51	51	51	48
Day Surgery Admissions						752	828	1079	1305	1620
Day Hospital Cycles						1674	2003	2084	2335	2236
Day Hospital Treatments						16634	16626	17865	17059	16672
Average n. of Treatments/Cycle						9,9	8,3	8,6	7,3	7,5
Total Admissions	**7220**	**7755**	**8627**	**8374**	**8083**	**9099**	**9552**	**11243**	**13119**	**14047**

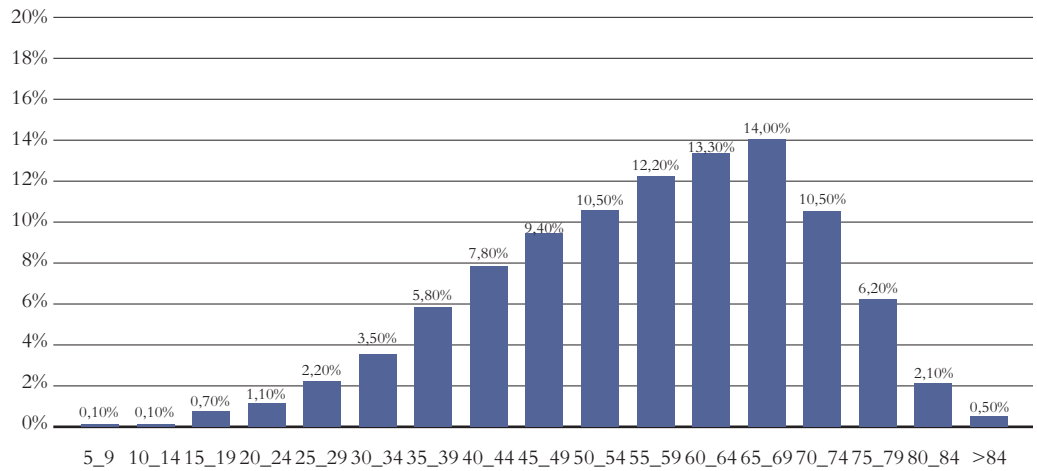
Case-mix by speciality (2004)

	Beds	Admissions	Days	ALOS	Surgical Index	Average Weight
General & Mammary Surgery	22	1032	6613	6,41	93,4	1,318
Abdominal Surgery	37	903	12641	14,00	63,5	3,003
Chest Surgery	22	796	5808	7,30	68,5	2,245
Plastic Surgery	8	508	2287	4,50	93,9	1,033
Neurosurgery	16	428	4992	11,66	67,1	2,253
Gynecology	22	822	5953	7,24	80,3	1,287
Otorhinolaryngology	18	526	5349	10,17	80,6	1,863
Urology	22	865	6496	7,51	87,9	1,849
Intensive Care	8	65	1210	18,62	50,8	6,286
Nuclear Medicine	8	616	2404	3,90	0	0,929
Medicine Oncology and Ematology	75	3630	21001	5,79	3,6	1,250
Day Hospital	33	2236	16672	7,5		0,81
Day Surgery	7	1620	6059	3,7		0,90

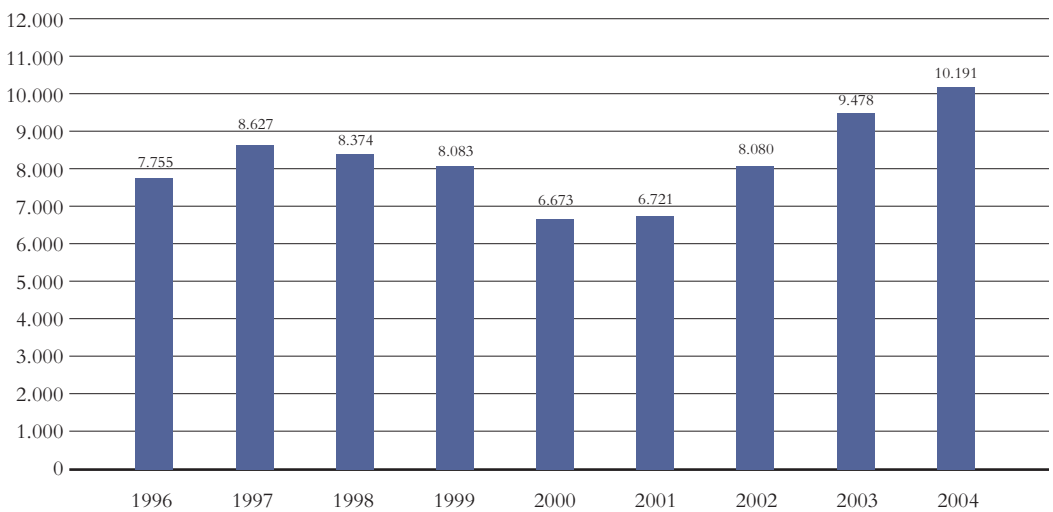
Inpatient Admissions by Geographical Area (2004)



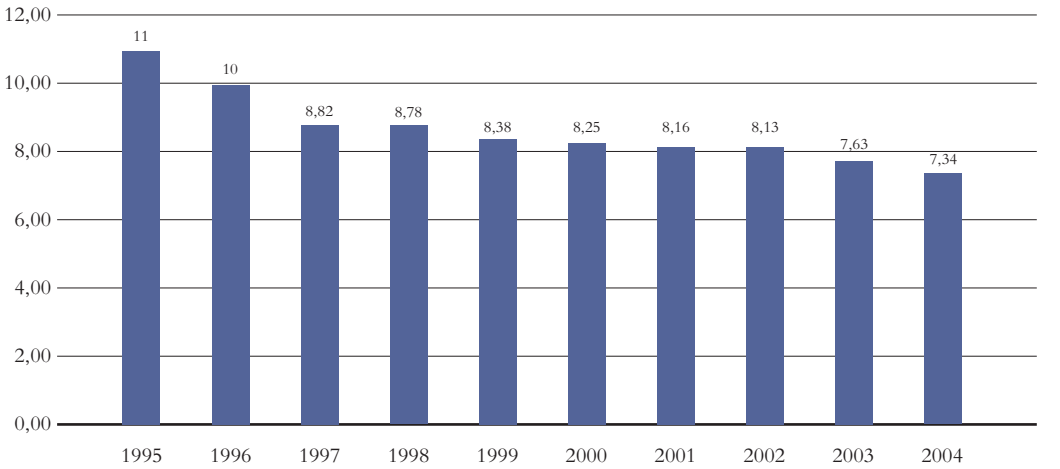
Inpatient Admissions by age (2004)



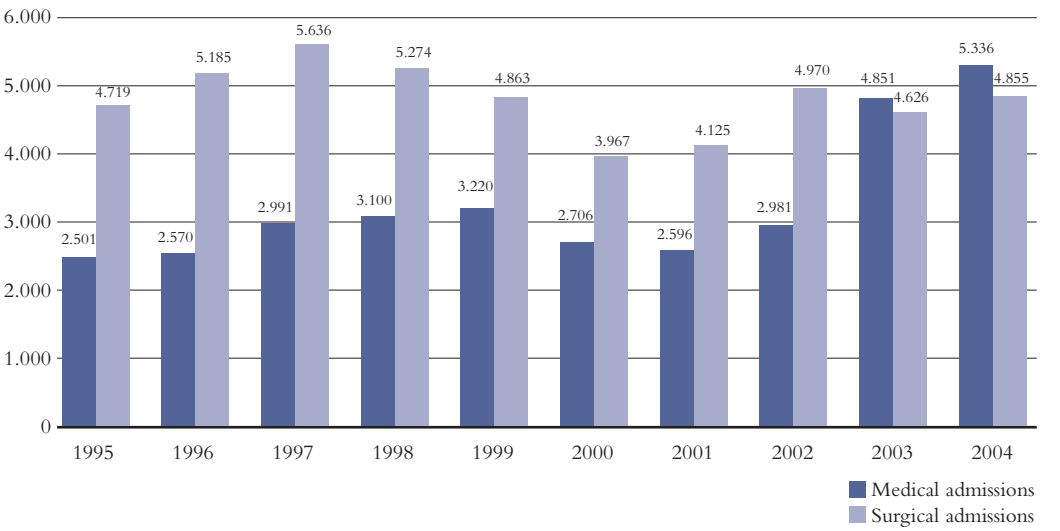
Inpatient Admissions



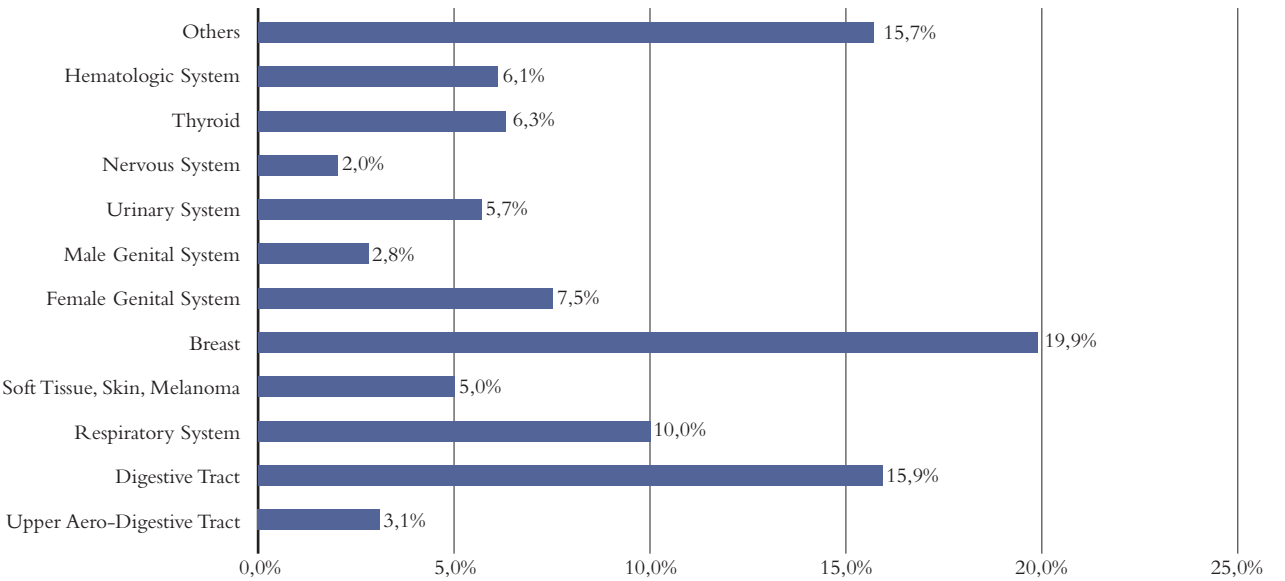
Average Length of Stay



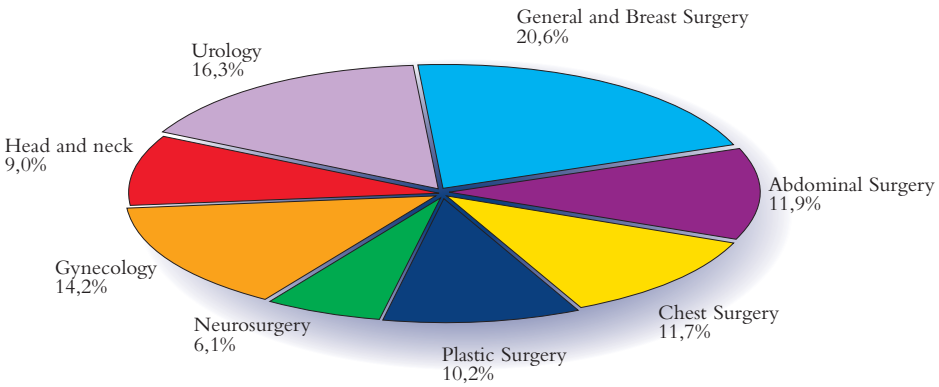
Hospital Admissions



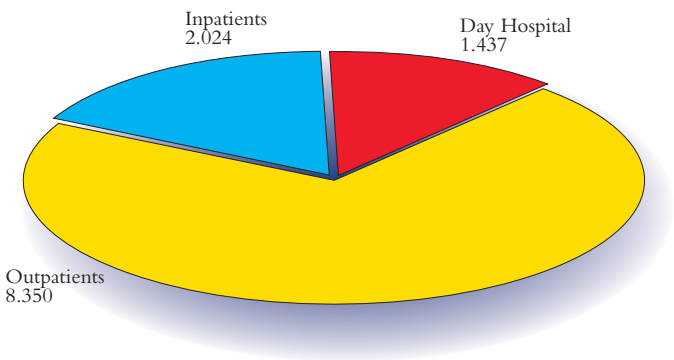
Neoplastic Pathology (140-208, ICD9CM) distribution by site of 10.446 (74% of the total No. of 2004 hospitalizations)



Surgical Interventions (2004)



Systemic Treatments (2004)



	Outpatients (visits and performances 2004)
Breast surgery	7.617
Abdominal surgery	3.900
Thoracic surgery	1.149
Plastic and reconstructive surgery	3.806
Gynaecology	15.534
Urology	6.249
Medical Oncology	45.488
Hematology Oncology	3.802
Radiotherapy	140.636
Radiology and diagnostic imaging	37.362
Nuclear medicine	20.600
Clinical pathology	489.716
Histo and cytopathology	18.292
Digestive endoscopy	6.836
Endocrinology	5.832
Oncologic dermatology	6.520
Neurosurgery	1.033
Neurology	17.616
Head&Neck surgery	11.116
Intensive care, pain therapy and palliative care	1.211
Pulmonary physiopathology	7.768
Cardiology	7.290
Psychology	1.840
Cancer Prev. Inst. And External Affairs and Educat. Programs	7.861
Total	**869.074**

Departments s.c. • s.s.d.

Clinical Research Area

Services
Marcello Benassi (ad interim)

- Cancer Prevention Institutional and External Affairs and Educational Programs *(Silverio Tomao)*
- Integrated Service of Epidemiology and Information Systems *(vacant)*
- 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
(*vacant*)

- 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
Manlio Moretti

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 Dimiziani*)
- BioInformatics and Telemedicine Center
- Technical Photography Service
- Unity for the Management of Clinical and Scientific Activities (*Italo Lorenzon*)

Administrative Director
Angelo Massimiani

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, Manlio Moretti, Felice Musicco
Secretary:	Anna Maria D'Ambrosio

Scientific reports

Cancer prevention institutional and external affairs and educational programs

Director:
Silverio Tomao, MD

Silverio Tomao graduated in Medicine and Surgery in 1978 and subsequently specialized in Obstetrics and Gynecological Clinic (1982) and Clinical Oncology (1986). After having served as a Public Health Physician from 1980 to1986, he then went on to conduct his clinical and scientific activity in the National Institute for Cancer Research of Genoa and in the Department of Experimental Medicine and Pathology at La Sapienza University, Rome, as Deputy Head of medical oncology (from 1986 to 1992) and Head of Medical Oncology from 1993 todate. Since September 2003 he has been the Director of the Service for the promotion of prevention activities, of institutional activities, of foreign relationships and of didactic and educational activities of the Regina Elena Institute, Rome. In this role he coordinates and directs the initiatives of primary and secondary prevention of the institute as well as the programs of training and updating, in rigorous collaboration with the Scientific Direction. He is a member of numerous commissions and technical-scientific work-groups and Head of the teaaching courses for the Universities of Rome, Genoa and Cassino. Author of around 200 scientific articles published in national and international papers he has been the chairman and moderator of several scientific conferences, many of which he personally organized.

Medical Staff:
Oreste Aronadio - MD (Epidemiology of Hereditary cancer)
Maurizio de Santis - MD (Preventive Oncologic Center of V. le Trastevere in a joint venture with the Center of Preventive Medicine of migrations, of tourism and of tropical Dermatology)
Giuseppe La Ferla - MD (Unit of preventive senology)
Giacomo Carlo Rispoli MD (Unit of General Oncologic Prevention)

Aims of the Service

The mission of the Service is the improvement of education, training and preventive strategies in oncology.
In the year 2004, the clinical and scientific activity of the Service was organized through the integrated development of different institutional initiatives. Our aims are; the promotion and implementation of interventions devoted to oncological prevention, foreign relations to promote the activities of the institution, the development of training and educational initiatives in the oncological field.

Educational Activity

The service is countersigned as a Provider of educational and didactic activities of the ECM-Commission of the Ministry of Health using the scientific and clinical patrimony of the National Cancer Institute of Rome as well as the availability of a polyvalent high level Convention Center (Raffaele Bastianelli Convention Center). This Center is devoted not only to institutional and didactic-formative activities but also to other scientific initiatives in partnership with other institutions and scientific societies.
Through such initiatives the Service has organized and developed various training events, in co-operation with the Scientific Direction of the Regina Elena National Cancer Institute, Rome. For many years the Institute has been devoted to the scientific investigation and the promotion of clinical activities in the oncological field, from early diagnosis to screening programs. Based on such planning, several educational initiatives have been organized, such as courses, seminars, workshop, round tables, etc., directed at the staff of the Institute and external sanitary operators, privileging certain professional categories (physicians, nurses, psychologists), extensively involved in the oncological field. In recent years the Training Center of IRCCS Regina

Elena has become a center of regional reference in the organization of oncological didactic-educational activities, guaranteeing a diversified and high quality training. This extensive and growing activity counts on short weekly meetings, monthly seminars and training sessions carried out throughout the year.

Preventive Oncology

The activity of the Preventive Cancer Center has always been characterized as a point of regional reference for the prevention of neoplastic pathologies being able to offer a complete and qualified service thanks to the high level of human and structural resources supported by the Institute.
The center continues in its mission to offer services of high-level primary and secondary prevention to the public as well as institutional and territorial initiatives for healthcare information and education. This approach enables responsible prevention and moreover, a satisfactory improvement in healthcare.

Scientific and clinical activities

In 2004 the clinical and scientific activities of the Service have expanded in terms of quality and the number of medical examination performed. The Center is organized on two levels:
• the first, a multidisciplinary strategy for the early diagnosis of tumors and precancerous lesions;
• the second, a strategy of formative and educational intervention for primary prevention and healthcare.
Furthermore, the Center addresses the initiatives for territorial intervention, promoting preventive services for Corporations, Institutions and Factories, in cooperation with other health Institutions with common strategic objectives for public health.
The clinical activity of the Service for Prevention is as follows:
• Clinical examinations for general oncological prevention
• Clinical follow up of oncological patients
• First level examinations for mammary prevention
• Dosing PSA and urinary cytology
• Specialized examinations in oncological gynecology and dermatology
• Early diagnosis of lung cancer
• Diagnosis and follow up of hereditary tumors
• Service for oncological chemoprevention
• Service of Psycho-oncology

Scientific and clinical activities

In 2004 around 10.000 diagnostic services including general examinations and check-ups, breast examinations, diagnostic tests and follow-ups have been effected.
The senology outpatients performed 4,713 breast examinations and detected numerous cases of breast cancer. This service implements protocols set up by the joint Italy-USA program and the protocol Service for the study of hereditary breast-ovarian cancer syndrome of the Institute.
In the general preventive oncology outpatients around 6,000 clinical consultations with diagnostic scheduling were performed, in the clinic of the Center and that of the S. Gallicano Dermatology Center of Viale Trastevere.
Through the activity of scientific research, impulse was given to some priority topics such as;
• early diagnosis of lung cancer with spiral CT (ELCAP project)
• prevalence and incidence of genital infection from HPV
• study of the hereditary predisposition to breast and ovarian tumors
• familiarity and hereditary of melanoma and colorectal cancer.
The medical staff of the center has participated in research projects in collaboration with re-

search Institutes of national level (Ministry of Health, l'Istituto Superiore di Sanità and have developed projects concerning the correlation between different lifestyle and cancer risk (feeding, smoking, environmental pollution).
The Center has also developed training and sanitary education initiatives throughout the territory, organizing events and activating projects in collaboration with educational Institutions, i.e. junior and senior schools for healthcare training of students and teachers. Dr. Rispoli and Dr La Ferla in particular have been involved in a project in schools and cultural associations, offering the experience and competence of the Regina Elena Institute. Prof. Tomao, Dr. La Ferla and Dr.Rispoli are actively involved in the services of the Disease Management Team of the Institute.
Dr. Rispoli graduated in Space and aeronautic medicine at the School of Specialization in La Sapienza University of Rome.
In 2004 the physicians of the Center have forwarded the internal and external training initiatives of the institute. Dr. Rispoli, Dr. La Ferla, Dr. De Santis and Dr.Aronadio have achieved a high number of educational credits participating in numerous internal and external meetings, according to the directives of the National Continuous Educational Committee of the Ministry of Health.
Prof. Tomao, Director of the Center, received his Degree of Managerial Training from the Regione Liguria. He has taken part in numerous groups of study and research as well as on the boards of scientific societies (the Italian Society of Tumors, the Italian Association of Medical Oncology-Section of Lazio). He has run and organized training events and congresses in which he has covered the role of chairman and moderator. He is in charge of the Operative Unit for Epidemiological, biological and clinic evaluation of occupational risk after exposure to chemotherapic drugs in hospitals through the project financed by the Ministry of Health on the evaluation of the risks in the manipulation of chemotherapic drugs in sanitary environment. He is an Expert of the Ministry of Health on the National Commission for the Continuous Medical Training, and Vice President of the Ethical Committee of the Istituti Fisioterapici Ospitalieri of Rome, Oncological Consultant in the Cancer Prevention Center of La Sapienza University, Palazzo Baleani, Rome.
He is responsible for the project of research financed by the Lega Italiana per la Lotta contro i Tumori, entitled Integrated Pilot Project of information, health education and oncological formation for teachers of high school. He is also in charge of the Operative Unit in the Project financed by the Ministry of Health on Tumor markers and the general practitioner efficacy and adequacy of prescription.

Teaching activities

- Ottimizzazione dei marcatori tumorali nella diagnosi e nel follow-up in oncologia Breakfast Meeting I semester 2004- 3 March 2004 - I.R.E. - G. La Ferla
- Cycles of conferences in the Educational teaching program in different schools of Rome (Casal del Marmo, Peano) January-December 2004 - Dr.La Ferla, Dr.Rispoli, Prof.Tomao
- Prof.Tomao is professor of Oncology at the University of Rome (Courses of Specialization in Oncology, Occupational Medicine and Obstetrics and Gynecology) and the University of Genoa in the Specialization School of Oncology. Moreover Prof. Tomao is professor of Pharmacology in the University of Cassino (College of Sport Medicine).

Publications 2004

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Alteration of E-Cadherin Expression in Gastric Mucosa: Role of Intestinal Metaplasia and Helicobater pylori Infection.

Anticancer Res 2004, 24(3.a): 1603-1607

Integrated service of epidemiology and information systems

DIRECTOR:
VACANT

Staff:
VALERIO RAMAZZOTTI - MD Epidemiologist
MARIA CECILIA CERCATO - MD Epidemiologist
MARCO CAPERLE - MD Epidemiologist

Epidemiology activities:
MINA LOMUSCIO - Administrative Assistant

Research Staff under contract:
ANNA SESSA - Graduate
CARMELINA DE STEFANO - 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 - MD Post-graduate under Contract

Activities 2004

ACTIVITIES OF S.I.O. AND S.I.A.S.

During 2004, S.I.O. (Sistema Informativo Ospedaliero) the database on inpatient hospital admissions and S.I.A.S. the database on outpatient hospital procedures, have assured the institutional link with national and regional authorities and gave their support to the internal decision-making process in medical as well as administrative management.

Epidemiology Activities

CANCER REGISTRY

The registration of the oncological cases at the Regina Elena Institute has been carried out according to the S.I.O. database. This will allow us to update acquired data concerning the previous period.
The Population-based Cancer Registry of Latina Province at 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 2004, the Cancer Registry was involved in co-operative activities with other Italian and European Cancer Registries.

EUROCARE WORKING GROUP.

The working group analyzed the relative survival for gastric cancer derived from the EUROCARE-2 database for 47 cancer registries in 17 European countries. The evidences demonstrated a variability in survival from gastric cancer in Europe. Sixty percent of this variability was explained by differences in age, sex, period of diagnosis, subsite, histologic type and stage at diagnosis. Treatment is expected to play some role in the remaining differences, such as that observed for England with respect to Italy and France.

EUROPREVAL WORKING GROUP.

The aim of the working group is to estimate cancer prevalence, the proportion of people in a population with a diagnosis of cancer. In 2004, the original article *Colon cancer prevalence and estimation of differing care needs of colon cancer patients* was published. Prevalence by year since diagnosis was estimated from incidence and vital status data on 243,471 colon cancer cases collected by EUROPREVAL from 36 European population-based cancer

registries and concluded that; in 1992, 660,000 people with a diagnoses of colon cancer were living in Europe. The proportions of this prevalence requiring particular kinds of health care in the years following diagnosis were estimated, providing useful data for planning the allocation of health-care resources.

Network of italian cancer registries

In 2004 this working group published the article *Population-based incidence and mortality cancer trends (1986-1997) from the network of Italian cancer registries*. The aim of the study was to estimate the incidence and mortality of cancer trends in the Italian areas covered by the network of cancer registries with a population of about 8,000,000 inhabitants during the time period 1986-1997. The study included 525,645 incident cases of cancer and 269,902 cancer deaths (age over 14 years). The results pointed out that overall cancer incidence increased in both sexes and cancer mortality significantly decreased (since 1991 among men). Results by specific cancer site, such as lung with significantly decreasing incidence and mortality among men, can be related to the changes in smoking habits or, as for other cancer sites, as a consequence of expansion of secondary prevention activities.

Skin cancer prevention program in school-age children.

A Skin Cancer Prevention program was carried out in children from the primary school of Valencia (Spain) and of Pecs (Hungary). The program undertook to make personalized guidelines for sun exposure available for each child, based on a questionnaire to be completed on skin photosensitivity, which was carried out in the school. The analysis of data resulting from the questionnaires, allowed us to process and send personalized guidelines to all children involved in the project and then send the results of the analysis of the sample to those responsible in the foreign countries involved.
We have also carried out a new project in a sample of children from a nursery school in Rome, previously involved by the prevention program during the school year 2002-2003. With the support of the Administration of the Province of Rome, at the beginning of the school year 2004-05, the sample of children received a dermatological evaluation in the presence of their parents in order to investigate the appropriateness of sun exposure behavior during the last summer. The children's parents were also asked for an interview, by trained interviewers, in order to evaluate the extent of the message received with the letter containing the personalized guidelines for sun exposure. Data analysis is still ongoing.

Alliance against cancer

Project n° 15: Network for the economic-health, etiopathogenetic and epidemiological analysis of the population with thyroid tumor and thyroid oncological pathology under the auspices of IRCCS.
For this project S.Int.E.S.I. held the role of coordination center together with the National Cancer Institute of Milan. The main purpose is to establish a network among the participating Institutions (national IRCCS), which will enable us to share a database of the cases concerning thyroid cancer at each center.
S.Int.E.S.I. submitted the structure of a shared database to other involved centers, which will enable the setting up of a common database for all the Institutes involved.
The database links information from inpatients (SIO database), outpatients (SIAS database), and data from clinical departments. These links provide an integration of the available data for each patient, thus allowing to overcome the lack of a single database, such as the lack of histological data in the SIO database, as well as the lack of information concerning the economic data, typical of the clinical database.
Project n° 7: *Epidemiology for healthy education and information*. Project *Tumours in Italy* a site of Epidemiology in E- oncology.
S.Int.E.S.I. participated as a co-operative centre in the project based on the Alleanza contro il Cancro portal, E-Oncology, set up with the aim of making oncological information for an acquainted and specific health education available on the web.

The project *Tumours in Italy* (www.tumori.net), supported by Alleanza contro il Cancro in co-operation with E-Oncology has the goal to produce the Epidemiology portal of Italian Oncology.
The activities involve IRCCS, experts and oncological networks divided in Gruppi Obiettivo (GO).
GO *Stime Epidemiologiche* resulted from the collaboration between the National Cancer Institute of Milan and Istituto Superiore di Sanità of Rome with the aim of producing estimates of epidemiological indicators at both a regional and national level. It benefited from the cooperation of the Cancer Registries, among them the Cancer Registry of Latina Province connected to S.Int.E.S.I.
GO *Sud Italia*: Latina Cancer Registry is involved, together with the Italian Association of Medical Oncology, IRCCS of Naples and Bari, and with Ragusa Cancer Registry. The main purpose 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 2004:
• the multicentre case-control study on *Non Hodgkin's lymphoma and type of tobacco smoke* that pointed out a statistically significant association for blond tobacco exposure and Non Hodgkin's lymphoma, especially follicolar lymphoma.
• the multicentre case-control study on *Fibre intake and prostate cancer risk* that suggests a favourable association of vegetable fibres with prostate cancer risk, comparing the highest quintile of total fibre intake to the lowest quintile.
• the multicentre case-control study on *Food groups and risk of prostate cancer in Italy*. This unique large study on prostate cancer and diet in a southern European population confirms that no strong association exists between any specific foods and prostate cancer, apart from an uncreased risk for milk and dairy products and a possible protective effect of vegetables.
• the multicentre case-control study on *Retinol, carotenoids and the risk of prostate cancer: a case control study from Italy*, that supports the hypothesis of a weak protective effect of carotene, particularly beta carotene, on the risk of prostate cancer, while it indicates that other carotenoids, including lycopene, and retinol are not appreciably related to the risk of this neoplasm.
• the multicentre case-control study on *Glycemic index, glycemic load and risk of prostate cancer*. The study pointed out the direct relationship between the dietary glycemic index and glycemic load and prostate cancer risk. Correcting for potential confounding factors did not substantially modify these associations.
• the multicentre case-control study *Prostate cancer and body size at different ages: an Italian multicentre case control study*, that supports the possible relationship between high body mass in young adulthood, and a tendency to high weight throughout adult life, and the risk of prostate cancer.

As to the activities of epidemiology, S.Int.E.S.I. is involved in other studies with Clinical Departments of the Institute:
• Pulmonary Physiopathology Unit: statistical analysis of data from *European Competition Quit & Win! 2003*, a project with the aim of helping young smokers (aged 14-21) to quit smoking through a competition held in the High Schools of Rome and province.
• Digestive Endoscopy Unit: statistical analysis of data from a survey of quality of information on endoscopic examinations in outpatients and inpatients of the Endoscopy Unit.

Publications 2004

Augustin L.S., Galeone C., Dal Maso L., Pelucchi C., Ramazzotti V., Jenkins D.J., Montella M., Talamini R., Negri E., Franceschi S., La Vecchia C.

Glycemic index, glycemic load and risk of prostate cancer.

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Food groups and risk of prostate cancer in Italy.

Int J Cancer. 2004 Jun 20;110(3):424-8. *I.F. 4.375*

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Prostate cancer and body size at different ages: an Italian multicentre case-control study.

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Gatta G., Capocaccia R., Berrino F., Ruzza M.R., Contiero P.; Europreval Working Group.(Ramazzotti V., Conti Ems)

Colon cancer prevalence and estimation of differing care needs of colon cancer patients.

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Fibre intake and prostate cancer risk.

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Stagnaro E., Tumino R., Parodi S., Crosignani P., Fontana A., Masala G., Miligi L., Nanni O, Ramazzotti V., Rodella S., Senoiri Constantini A., Vigano C., Vindigni C., Vineis P.

Non-Hodgkin's Lymphoma and Type of Tobacco Smoke.

Cancer Epidemiol Biomarkers Prev. 2004 Mar;13(3):431-7. *I.F. 4.720*

Verdecchia A., Corazziari I., Gatta G., Lisi D., Faivre J., Forman D. And The Eurocare Working Group. Members Of The Eurocare Working Group For This Study Are As Follows: Italy: Conti E. (Latina Cancer Registry).

Explaining gastric cancer survival differences among european countries.

Int. J. Cancer. 109. 737-741. 2004 *I.F. 4.375*

Laboratory of Medical Physics and Expert Systems

DIRECTOR:
MARCELLO BENASSI, PhD

Study: Marcello Benassi received his PhD at La Sapienza University, Rome. He became a member of the 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 Cancer Institute, Rome, Italy and since 1979 he has been the Director of the Laboratory. He also served as Scientific Consultant on Radioprotection and Security for the Tor Vergata University, Rome and the Istituto Superiore Sanità Rome.

From 1985 he has also been a Professor at the Specialization School of Medical Physics at Tor Vergata University, Rome.

Scientific Societies: He served as the President of AIFB, Associazione Italiana di Fisica Biomedica (1992 - 1996); and has been a member of ESTRO, the European Society for Therapeutic Radiology and Oncology, ESHO, the 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 Italina 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 - PhD
ANNA DI NALLO - PhD
GIUSEPPE IACCARINO - PhD
VALERIA BANDONI - PhD
SIMONA MARZI - PhD
LUIS PEDRO ORDONEZ - PhD
ANTONELLA SORIANI - PhD
LIDIA STRIGARI - PhD

Post graduate contract researcher:
MARCO D'ANDREA - PhD

On training:
ANNELISA D'ANGELO - Physicist
ORNELLA ORTENZIA - Physicist
STEFANO ZENNARO - Physicist
ALESSIA BECCATELLI - Physicist
STEFANIA TEODOLI - Physicist
DANIELA D'ALESSIO - Physicist
PATRIZIA FERRO - Engineer
ELISABETTA GENOVESE - Physicist
CARMELINA SALIERNO - Engineer

Activities 2004

INTRAOPERATIVE RADIOTHERAPY

Intraoperative radiotherapy (IORT) is becoming an increasingly common procedure for treating tumors, 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 recent years there has been an increasing interest in IORT techniques, 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 end goal of IORT is enhanced locoregional tumor control. IORT is feasible for various intra-abdominal, 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 cancers of the stomach, pancreas, colon-rectum and soft tissue sarcoma.

Widespread application of IORT at various disease sites is feasible thanks to improvements in the technology. By increasing the maximum energy of the linear IORT accelerators and the total radiation dose it is possible to improve the therapeutic ratio and the local control of tumor without any increase in 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, experienced in clinical practice, in order to develop guidelines on quality assurance for the IORT technique. In this context, new requirements have been established, to meet the need for more specific clinical applications and more widespread and less complex accelerator usage.

IORT STUDIES:

Prostate cancer: a dose-finding study in patients with intermediate risk prostate cancer, who have undergone radical prostatectomy. Patients 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 or conventional EBRT on the tumor bed. 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 larinx 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, recurring after radiation therapy. IORT is used at the end of the resection with intent to deliver 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 patient 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 necessity for biological criterion and correlating it with the clinical outcome becomes urgent. 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 an inhomogeneous dose distribution, which is difficult to interpret and a greater awareness of the radiobiologic properties of tissues is required. IMRT has also induced new dose escalation protocols, urging the definition of 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 doses to the target with a better sparing of organs at risk, such as the parotids. The goal of our study is to evaluate subjectively, through a patient filled questionnaire, and objectively, with the collection of the saliva before the treatment and then for a further 12 months thereafter, the real efficacy of this technique in reducing xerostomia and improving patients comfort. 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 effects 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 the 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 complication probability of normal tissue for the organs at risk by means of mathematical models.

Prostate Cancer

An institutional, multidisciplinary project with the participation of the Radiation Oncology, Urology, Radiology, Pathology, Physics, and Gastroenterology Divisions, 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 objective of this study is the evaluation of the biochemical control and 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 acute and late side effects of radiation therapy 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 thereafter. The aim of the study is to evaluate the eventual reduction of acute and late side effects on the rectal and vescical mucosa.

Nuclear medicine

Patient specific dosimetry refers to the estimation of dose to tissue of a specific patient based on the individual body habitus and radio-pharmaceutical 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 cannot be used to calculate the dose released by low energy Auger electrons emitted by radiopeptide internalized within the tumor, which is the most important component of accumulated dose at the intracellular lev-

el. To overcome the 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 non uniform macroscopic dose distributions, primarily because of the demanding computational requirements of the Monte Carlo simulations. This calculation approach is mainly designed for internal dosimetry in patients with solid tumors. The Biodistribution is taken from measurements of 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 the dose point kernel, derived from the Monte Carlo simulations using the EGSnrc code, to calculate 3D dose distributions. Dose released by, β γ-radiation and low energy Auger electrons is provided by activity distribution obtained from SPECT and sequential planar images.
Co-registered or matched CT/ SPECT images permit the identification of the volumes of tumor and organ at risk, based on both morphologic and functional images. The volumes of interest tumor and organ at risk (liver, kidneys) 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 was derived from DVHs applying the linear quadratic model. We also derived the TCP taking into account the dose rate variability between voxels.

Magnetic resonance physics

The activity essentially concerns:

- The tools for the procedure and analysis of MRI quality assurance, control and protection. Guidelines and recommendations for MRI users, related to the acceptance test for systems used in clinical practice, have been proposed to verify the performances;
- The study of functional and spectroscopic imaging techniques, implemented in strong field MRI. The possibility to integrate morphologic patient data of conventional Magnetic Resonance with metabolic-functional data and with spectroscopic analysis of the nucleotides present in the tissues, enable diagnosis implementation;
- Bayesian analysis of dynamic Magnetic Resonance breast images 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 a lack of suitable guidelines. Therefore, a specific quantitative quality assurance program has been proposed for optimizing diagnosis;
- The applications of color and power Doppler ultrasound are in progress to visualize hypervascularization areas for morphologic-functional diagnoses.

Radiation imaging

The Medical Physics Laboratory cooperates with the Radiology Department on the maintenance and constant actualization and optimization of a quality assurance (QA) program concerning the technical and physical aspects of medical imaging with ionizing and non-ionizing radiation.
This means that in order to achieve and maintain high standards in medical imaging 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 cooperates in the evaluation and optimization of the computer network of the Radiology Department.

Publications 2004

Squillaci E., Manenti G., Di Stefano F., Miano R., Strigari L., Simonetti G.

Diffusion-weighted MR imaging in the evaluation of renal tumours.

J Exp Clin Cancer Res. 2004 Mar;23(1):39-45. *I.F. 0.574*

Strigari L., Soriani A., Landoni V., Teodoli S., Bruzzaniti V., Benassi M.

Radiation exposure of personnel during intraoperative radiotherapy (IORT): radiation protection aspects.

J Exp Clin Cancer Res. 2004 Sep;23(3):489-94. *I.F. 0.574*

Psychology Unit

DIRECTOR:
PATRIZIA PUGLIESE, MD

Patrizia Pugliese graduated in 1984 at the University of Rome and specialised 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 the 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 PhD:
DR. PAOLA TORTI

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

Time-limited contract:

DR. ALESSANDRO BONUCCI
DR. CHIARA FALCICCHIO
DR. FEDERICO BUSSOLETTI

Fellow PhD in training:

DR. SANTINA TRAVO
DR. ROBERTA DI FILIPPO

Student:
CLAUDIO DIODATI

Activities 2004

Oncology is a field which connects both medical and psychological cultures. This confrontation should result in a shared clinical practice in order to guarantee global care for both patients and their families. This new approach to oncological disease consists of a multi-dimensional team who work in the clinical and research process, with the following objectives in mind: prevention, cure and rehabilitation.

All activities in 2004 were based on our interest in the multidisciplinary approach centred on the integration between clinical, research and formative areas. This new approach has determined the regular integration of the psychologist within a core multi-disciplinary team. This has led to the need to prepare clinical practice guidelines in conjunction with medical guidelines.

Following a multidisciplinary approach, research activities in 2004 were based prevalently on Quality of Life (QoL) longitudinal studies, early diagnosis and early prevention studies and studies focused on rehabilitation.

The assessment strategy was multi-dimensional and consisted of structured and semi-structured interviews (to evaluate personality and social variables, distress, sexuality, fatigue, menopause, sterility/infertility, lymphedema, and quality of care) and psychometric instruments (to evaluate personality, QoL, anxiety and depression). All the instruments were administered before, during, after the treatment and in the follow-up.

During 2004, 1,042 new patients (287 in patient and 755 out patient) were accepted and 3,130 activities (psychotherapy, clinical interview and tests) were carried out for IRE.

The clinical activity of our Service provides for different psychological strategy (counselling, integrated physician-psychologist intervention, individual and group psychotherapy).

The results of the retrospective study *Lymphedema and QoL* concerning the lymphedema impact on QoL, in collaboration with the Department of Neurology, showed a negative impact of lymphedema on all QoL areas, particularly distress and body image. These data motivated a longitudinal study on evaluation and improvement of lymphedema in agree-

ment with the importance of prevention and management of treatment sequelaes. The study *QoL and lymphedema in patients with breast cancer after surgery: effectiveness of an integrated phisician-psychologist intervention* aimed at evaluating the impact of lymphedema on QoL and distress and the effectiveness of integrated intervention both on symptoms and on QoL. The lymphedema is classified in four levels according to severity. The psychological evaluation performed at baseline and after every three cycles of medical treatment consisted of a semistructured interview for the psychosocial and distress variables evaluation, of EORTC QLQ C30 and QLQ BR23 questionnaires for QoL evaluation, of HADs for anxiety and depression evaluation. The cognitive-behavioural intervention consisted of 12 bi-monthly group sessions. The retrospective study gave rise to an abstract which was presented at 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 women with breast and gynaecological cancers during follow-up, was carried out in collaboration 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 psychological evaluation regarded 61 patients with a median age of 50 years and a median follow-up of 36 months. Early menopause determined the worsening of couple relationship (18%), of sexuality (a worsening of desire (35%), of pleasure (45%), of sexual satisfaction (48%) and the presence of dispareunia (19%) and high levels of distress (61%).

The high percentage (36%) of patients who requested psychological therapy underlines the subjective significance of menopause negative impact on QoL.

Emotional distress is an important area of QoL related to disease adaptation and treatment compliance. The study *Emotional distress in advanced cancer patients treated with chronomodulated chemotherapy* has shown that improvement of emotional distress is related to the supportive function of the integrated team or to the natural development of adaptation in a crisis situation. This study gave rise to an abstract which was presented at the 7th World Congress of Psycho-Oncology.

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. The benefits of early breast cancer adjuvant chemotherapy in terms of disease free intervals and survival is well known, while little is known regarding the impact of chemotherapy and its sequelae (early menopause and sterility) on QoL. The aim of this study was to evaluate QoL, anxiety, depression and patient perception of treatment sequelae during adjuvant chemotherapy. This longitudinal study on QoL provided the opportunity to carry-out QoL preventative improvement strategies. Patients were followed by a team which included both psychologists and oncologists. 45 patients were enrolled and 22 patients were evaluated after a six-month and one year follow-up. At the end of chemotherapy and in follow-up the most affected QoL domains were anxiety (48% - 70%), depression (57% - 59%), sexuality (33% - 23%). Fatigue improved in follow-up (mean=36 vs mean=42). The results showed 62% patients experienced the information as good and 71% were compliant to treatment.

According to Kajat (2002), the psychological symptoms experienced by patients were the worst. At the start of treatment the worst symptom was distress (27%), at the end of chemotherapy, fatigue (24%) in the follow-up depression (35%).

The study gave rise to an abstract which was presented at the 7th World Congress of Psycho-Oncology. Our study received much interest as few longitudinal studies on QoL of breast cancer patients submitted to adjuvant chemotherapy have been carried out.

The results of retrospective studies led to the carrying out of the *Global Project for QoL evaluation and improvement in oncological long-survivors*. The aim of this project was to work out and circulate guidelines 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 forma-

tive training facilitates adequate communication skills and thus good quality of care.
The guidelines arise from previous experience at the Regina Elena Cancer Institute and from the collaboration with other oncological IRCCS.
In 2004 the project was centered on the execution of the third and fourth phase that regard the enrollment of patients and the improvement of QoL variables.
The psychological evaluation regarded a total sample of 156 patients, 77 for sexuality (M =34; F= 43 median age 46) and 79 for fatigue (M=22; F=55 median age 47). The whole sample was evaluated for distress. As regards fatigue or sexuality, the highest percentage was breast cancer patients, with 12 non eligible patients. Before treatment the results for fatigue showed mean scores equal 8 in the anxiety scale and mean scores equal 7 in the depression scale with psychological anxiety problems in 50% of patients and psychological depression problems in 58% of patients. The fatigue evaluation questionnaire (FACT-an) showed mild fatigue levels (mean= 35) and a negative correlation between hemoglobin levels and fatigue and between depression and fatigue. During treatment 69% of patients referred fatigue, and the worst symptoms experienced by patients were fatigue (45%) and distress (67%).
At baseline, the results of sexuality variables showed a negative impact of disease diagnosis in all areas (no desire = 53%, no pleasure = 57%; decrease of sexual satisfaction = 52%, decrease of intercourse = 64%). In addition, surgery deterred the entire sexuality area (no desire = 76%, no pleasure = 76%; decrease of sexual satisfaction = 69%, decrease of intercourse = 38%). The worsening of sexuality after surgery was associated with the worsening of body image (65%) and the presence of distress (76%). Distress is the psychological response to crisis represented by different phases of oncologic therapy. The presence of high levels of distress has an impact on compliance to treatment and on the quality of life during the treatment and in the follow-up.
Most patients referred significant need for information and for participation in the treatment decision making process. The response to these needs consists of ongoing formative training which facilitates adequate communication skills and thus good quality of care. In this project the meetings of team members are the basis of QoL improvement. After the multidisciplinary diagnostic meeting 24 patients were submitted to psychological interventions (12 for distress, 7 for sexuality and 5 for fatigue).
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 utilized 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 the participation in the screening program and the motivation to smoking cessation.
The evaluation of lung cancer screening psychological issues involved 536 individuals.
The presence of psychologists within the I-ELCAP team was finalized in order to carry out interventions for subject's crisis with positive diagnosis and to improve information and program quality through counseling of health professionals.
The trait anxiety inventory showed normal mean scores(mean=37). The state anxiety inventory administered before and after CT results showed mean scores comparable to trait anxiety mean scores (mean=38). The state mean scores are higher in the patients with positive CT scan results (mean=45). These are reduced to baseline again after 1 year in the false-positive findings.
This underlines the necessity of monitoring the moment when CT findings are communicated. The aim of this is to prevent long-term distress. Moderate distress does not deter from participation in the screening and the false-positive findings in screening may even increase adherence to recommended screening. Nevertheless as some reports show, negative screening experienced may reduce re-attendance, screening organizers should put ef-

fort into reducing unnecessary distress whenever possible.
The evaluation of QoL was carried out with the SF-36 questionnaire. The scores of SF-36 range from 0 to 100. The higher the scores, the greater the quality of life.
During screening program the whole sample showed means scores comparable to normative data. The lower mean scores regard Mental Health. This could be a link to a higher involvement of this variable in the cancer worry related to the screening program. The analysis of two groups of subjects those who were recalled after three months for lung cancer risk and those with normal findings, who were recalled after 1 year showed lower mean scores of this variable in the first group after 1 year.
The interview on quality of screening showed a high number of subjects who had a positive experience of the screening program organization and of the relationship with health professionals centered on good information quality and quantity.
The more frequent referred motivation for screening participation is cancer worry, which is also the same motivation associated with smoking cessation. In a sample of subjects submitted to annual repeat screening, it emerged that 25% of subjects had quit for more than 6 months. Smoking cessation was higher in the risk subjects (29% vs 26%). Younger smokers, who were found to have an abnormal CT scan and female subjects were most likely to report smoking cessation or smoking reduction.
It is known that cancer specific distress such as worry about cancer and different levels of anxiety and depression can be acted upon by providing information and counseling in the course of screening. Specific crisis moment as the communication of positive CT scan results that underline a high level of health risk situation, should guide efforts at communication. Good quality and quantity of information achieved with counseling for health professionals should increase screening re-attendance and motivation to smoking cessation.
Smoking cessation intervention through health-care providers in clinical settings is a promising strategy for motivating and assisting smokers to quit.
In the integrated pharmacological and psychological approach with the Service of Pneumology the psychological intervention is based on a cognitive-behavioral approach, with the aim of increasing or maintaining the motivation to smoking cessation. The results regard 322 patients. With regard to the stage of change as described by Prochaska (1991), 41% of the sample was in the "contemplative" stage, 47% in the "precontemplative" stage and the remaining 12% in the "action" one. Most of the individuals underlined a psychological dependence to smoking: 34% considered cigarettes as a pleasure, 21% as a way to control anxiety, 27% as an habit, and the remaining 18% as able to give self-confidence. After six months 34% of the sample still maintain smoking abstinence.
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 at the 7th World Congress of Psycho-Oncology. This study received interest because there were few studies on life styles and none following an integrated approach.

Future perspectives:

Our key point is the multidisciplinary approach based on the integration between clinical, research and formative areas.

Patients with cancer often have complex needs that can not be addressed by a single specialty or discipline. This has led to the development of a disease management team (DMT) to ensure a consistent and equitable approach to planning and managing care. It is now recognized that the clinical psychologist should be an integral part of this network. In our Institute the integration of the psychologist within a core multidisciplinary team and the psychological scientific activity determined the drawing-up of clinical guidelines for psychological care of cancer patients and their families. The psychological guidelines should be extended to all neoplasms. This strategy will assure that all patients coming to the Institute for the first time would receive a psychological diagnostic and therapeutic intervention.

The evaluation in the I-ELCAP project underlines the presence of preventive behavior in subjects submitted to the screening program: of the subjects that refer a smoking behavior change, 87% had maintained the quitting for more than 6 months. This underlines the necessity of a formal integration between early diagnosis and early prevention. This integration should provide formal smoking cessation advice or interventions. The usefulness of psychological intervention in smoking cessation is well established. On-going efforts are aimed at establishing the best smoking cessation strategy extending the research to effectiveness trials.

Publications 2004

Pugliese P., Perrone M., Garufi C., Maggi G., Condoleo M.F.

The desire for motherhood and fatherhood.

Tumori 3(3):10-13,2004 *I.F. 0.348*

Terzoli E, Garufi C, Zappala Ar, Vanni B, Pugliese P, Cappellini Ga, Aschelter Am, Perrone M, Giannarelli D.

High-dose chronomodulated infusion of 5-fluorouracil (5-FU) and folinic acid (FA) (FF(5-16)) in advanced colorectal cancer patients.

J Cancer Res Clin Oncol. 2004 Aug;130(8):445-52. *I.F. 2.162*

Laboratory animal center (S.AF.U.)

DIRECTOR:
GENNARO CITRO, PhD

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

Teaching Experience

1985-86 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; In charge 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) 2002/2004 Project Coordinator, Ministry of Health; G) the Operative Unit, Ministry of Health Project; H) 2003/05 the Operative Unit AIRC project; I) 2004/2006 Project Coordinator, Ministry of Health.

Staff:
DR. GIANCARLO CORTESE - BIOL.
DR. ENRICO SPUGNINI - VETERINARY CONSULTANT
MR. GIUSEPPE BERTINI - TECNICIAN
MR. PIERINO PICCOLI - TECNICIAN
MR. DEMETRIO SPOSATO - TECNICIAN

Activies 2004

The work carried out for S.A.F.U. has mainly been in support of the clinical and 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;
• 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 with other agents.
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, is experimentally evaluated. In particular, synthetic peptides are produced, the amino-acid sequence of which is able to inhibit the links with oncogene products and other functional proteins. Moreover, an experimental evaluation is made of the possibility of using reagents as drugs in new therapeutic strategies from the peptides produced.

Current Research Projects

• (2002/04)Transgenic Mouse Models) Coordinator in charge of End Project Ministry of Health); of the Operative Unit, Ministry of Health Project;

• (2003/05) Lead Molecules inhibitors of some Signaling Proteins affected by excess/deregulation of function.

• (2003/05)of the Operative Unit, AIRC Project;

• (2004/06) Coordinator 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 2004

Catena R., Tiveron C., Ronchi A, Porta S., Ferri Al, Tatangelo L., Cavallaro M., Favaro R., Ottolenghi S., Reinbold R., Scholer H., Nicolis S.K.

Conserved POU-binding DNA sites in the Sox2 upstream enhancer regulate gene expression in embryonic and neural stem cells.

J Biol Chem. 2004 Oct 1;279(40):41846-57I.F. 6.696 *I.F. 6.482*

Contino G., Amati F., Pucci S., Pontieri E., Pichiorri F., Novelli A., Botta A., Mango R., Nardone A.M., Sangiuolo F.C., Citro G., Spagnoli L.G., Novelli G.

Expression analysis of the gene encoding for the U-box-type ubiquitin ligase UBE4A in human tissues.

Gene. 2004 Mar 17;328:69-74. *I.F. 2.754*

Mancini F., Gentiletti F., D'angelo M., Giglio S., Nanni S., D'angelo C., Farsetti A., Citro G., Sacchi A., Pontecorvi A., Moretti F.

High-dose chronomodulated infusion of 5-fluorouracil (5-FU) and folinic acid (FA) (FF(5-16)) in advanced colorectal cancer patients.

J Cancer Res Clin Oncol. 2004 Aug;130(8):445-52. *I.F. 2.162*

Mastronicola D., Arcuri E., Arese M., Bacchi A., Mercadante S., Cardelli P., Citro G., Sarti P.

Morphine but not fentanyl and methadone affects mitochondrial membrane potential by inducing nitric oxide release in glioma cells. Cell Mol Life Sci.

2004 Dec;61(23):2991-7. *I.F. 4.995*

Porrello A., Cardelli P., Spugnini E.P.

Pet models in cancer research: general principles.

J Exp Clin Cancer Res. 2004 Jun;23(2):181-93. *I.F. 0.574*

Saran A., Spinola M., Pazzaglia S., Peissel B., Tiveron C., Tatangelo L., Mancuso M., Covelli V., Giovannelli L., Pitozzi V., Pignatiello C., Milani S., Dolara P., Dragani T.A.

Loss of tyrosinase activity confers increased skin tumor susceptibility in mice.

Oncogene. 2004 May 20;23(23):4130-5. *I.F. 6.495*

Sarti P., Fiori P.L., Forte E., Rappelli P., Teixeira M., Mastronicola D., Sanciu G., Giuffre A., Brunori M.

Trichomonas vaginalis degrades nitric oxide and expresses a flavorubredoxin-like protein: a new pathogenic mechanism?

Cell Mol Life Sci. 2004 Mar;61(5):618-23. *I.F. 4.995*

Vigliotta G., Miele C., Santopietro S., Portella G., Perfetti A., Maitan M.A., Cassese A., Oriente F., Trencia A., Fiory F., Romano C., Tiveron C., Tatangelo L., Troncone G., Formisano P., Beguinot F.

Overexpression of the ped/pea-15 gene causes diabetes by impairing glucose-stimulated insulin secretion in addition to insulin action.

Mol Cell Biol. 2004 Jun;24(11):5005-15. *I.F. 8.142*

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 at the University of Naples.
From March to September 1983 he worked as fellow 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.
Since 1999 he has been teaching in the school of General Surgery, Plastic Surgery - Medical Oncology at the University of Rome, and since March 1999 he has been the Director of the Department of Surgical Oncology of the National Cancer Institute of Rome.
He is a member of the Italian Society of Surgery, the 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 - MD
CLAUDIO BOTTI - MD
PIETRO BRUNO - MD
ALFREDO CALLOPOLI - MD
FRANCESCO CAVALIERE - MD
FABRIZIO FREZZA - MD
ROSA GARINEI - MD
ROBERTO MAIALETTI - MD
LOREDANA PIARULLI - MD
ANGELO PSAILA - MD
PASQUALE PERRI - MD
FABIO MASSIMO SEGA - MD
CARLO VITICCI - MD
VANESSA PATRIZI - MD Student
FRANCESCO PRIORE - MD Student
GIUSEPPE CURINGA - MD Student
IRAKLI NADASHVILI - MD STUDENT
UMBERTO FAMA - MD 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 2004

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

Breast cancers

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 and T<3cm. During the operation, frozen sections of tissue underlying the NAC are always carried out to exclude the infiltration of subareolar ducts. The results are evaluated in terms of feasibility, rate of complication (skin or NAC necrosis) cosmetic and oncological results (recurrence).

To date 50 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, as well as oncological results (no recurrences have been recorded thus far).

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 <2.5 cm, age >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 are also evaluated.

Characterization of intermediate markers of breast carcinoma

Background

Characterization of the biopathological events underlying the early steps of breast carcinogenesis may have a dramatic impact on reducing breast cancer mortality, since it offers 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 outcome of the interaction between genetic susceptibility and the environment and they are therefore extremely important for early detection. This is not unexpected since the interaction 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.

Methods and Results

To overcome this limitation we focused our study on a multiparametric parallel analysis of dif-

ferent 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, along with HER2 and p53,
More recently we extended our investigation to hMena protein, 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.While undetectable in normal mammary epithelium and in benign lesions, hMena 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 retrospective study is currently under way to evaluate hMena as predictor of interval breast cancer in patients previously submitted to excisional biopsy for benign disease.

EVALUATION OF PROGNOSTIC FACTORS IN YOUNG WOMEN AFFECTED WITH BREAST CANCER.
Background
Breast cancer is quite rare in very young women. It is a disease that usually occur in older women, with 75% of cases in women over 50 years of age. Only 6.5% of cases occur in women under 20 years of age. Breast tumor in women under 30 years of age is a rare event accounting for 0.6% of cases.
Usually breast cancer in young patients is more aggressive, the median tumor size is generally greater and also the stage is more advanced (st. II - III), with positive nodes.
Cancers are more poorly differentiated, more likely to be receptor negative, and more often aneuploid with high phase percentage.

Methods and Results
We have analyzed our database of 3,000 breast cancer treated at Regina Elena Cancer Institute from 1999 to 2003 and 390 patients (66 with age<40 years and 324>40 years) with a median follow-up of 57 months have been selected.
The analysis of histological prognostic factors showed that in patients <40 years there has been a higher proportion of N+, T2 and G2-G3 cancers.
The analysis of biomolecolar prognostic parameters demonstrated that in young patients there was a higher proportion of negative hormone receptors (ER, PgR), high p53, Her-2 and Ki67.
The 5-year disease-free survival rate was higher in patients >40 year than in patients <40 year, being 33% and 71.9%, respectively.
The multivariate analysis showed that the prognostic parameters with independent value were: age (0.04); N (p<.0001);T (p=0.03) and Ki67 (p<.0001). (tab 1)
Young breast cancer patients deserve more aggressive treatment. Margin-free conservative surgery associated with tailored radiotherapy and systemic chemotherapy should be the standard of care.
Tab. 1

Disease-free survival: multivariate analysis

PARAMETERS	H.R	CI 95%	P
AGE	1.73	1.02-2.91	0.04
N	2.98	1.85-4.80	<.0001
T	1.64	1.04-2.61	0.03
Ki-67	2.28	1.44-3.61	<.0001

Melanoma

Evaluation of prognostic factors influencing tumor response of stage III limb melanoma patients treated with TNFα-based isolation limb perfusion.

Background

There are two major arguments concerning the use of TNFα in the treatment of advanced limb melanoma patients with isolation limb perfusion: the TNFα dosage and identification of patients who will really benefit from this drug.

Methods and Results

We have collected 113 patients affected with stage IIIA - IIIAB treated in three Centers (Rome - Milan - Padua) belonging to SITILO Society.

The median age was 60 years (range 23-82), 37 were male and 76 were female.

Metastatic nodules were located in upper and lower limbs in 14 and 99 patients respectively, in 42.5% of the patients the disease was bulky (>10 nodules) or unresectable in 33% of the cases, the median follow-up was 27 months (range 3-123)

All the patients were treated with hyperthermic perfusion with L-PAM and TNFα at two dosages: <1 mg or >1 mg.

The complete response rates were 75% and 85% in patients treated with TNFα <1 mg or >1 mg respectively, the difference is not statistically significant.

Tumor temperature seems to influence the rate of CR (61.3% with a temperature <41°C and 65% with a temperature >41°C) even if the difference is not statistically significant. Only the type of disease strongly influences the OR that were 74.1% and 89.1% for bulky and non bulky disease (p=.05).

This data was confirmed with a multivariate analysis that evaluated 8 parameters.

Only bulky disease maintained its independent value (p=.02; RR 4.1) tab 1

TNFα limb prefusion for stage III melanoma

MULTIVARIATE ANALYSIS FOR TUMOR RESPONSE		
PARAMETER	P	RR
age	ns	
Sex	ns	
Stage	ns	
Bulky	.02	4.1
Temperature	ns	
TNF	ns	
Duration	ns	
Toxicity	ns	

These results obtained in a large series of patients highlight two important issues for the oncological community:

- The dosage of 1 mg of TNFα is equivalent to 3-4 mg (the cost of 1 mg is 2.800 E. vs. 9.200 E. for 4 mg)
- The patients who really benefit from TNFα are those with bulky or unresectable disease.

EVALUATION OF PROGNOSTIC FACTORS ON LOCOREGIONAL CONTROL AND SURVIVAL IN 113 STAGE IIIA - IIIAB LIMB MELANOMA PATIENTS TREATED WITH TNFα - BASED ISOLATION LIMB PERFUSION.

Background

Stage IIIA - IIIAB in limb melanoma patients represent a treatment challenge for the oncological community. At the present time TNFα- based isolation perfusion is considered the treatment of choice. Since the locoregional control and survival may be influenced by some treatment parameters we have analyzed 113 patients in order to identify the prognostic factors that have an impact on patients outcome.

Methods and Results

One hundred and thirteen patients affected with stage IIIA - IIIAB were treated with hyperthermic antiblastic perfusion with L-PAM and TNFα.

Thirty-seven were male and 76 female, the median age was 60 years (range 23-82), with a median follow-up of 27 months (range 3-123).

The 5-year locoregional control was 42.7%.

Tumor temperature seems to influence the 5 year locoregional control, as a matter of fact the figures were 44.7% and 37.6% for patients treated with a tumor temperature >41°C and <41°C, respectively. This data was confirmed also in the subset of complete responders with a 5-year locoregional control of 41.2% and 26.9% for patients treated with a tumor temperature >41°C and <41°C, respectively.

The 5-year overall survival was 49%, at univariate analysis only stage and tumor response maintained the independent value. (tab 1)

TNFα LIMB PREFUSION FOR STAGE III MELANOMA

UNIVARIATE ANALYSIS FOR OVERALL SURVIVAL		
PARAMETER	P	RR
Age	ns	1.5
Sex	ns	1.3
Stage	.04	2.3
Bulky	.02	1.1
Temperature	ns	1.1
TNF	ns	1.2
Duration	ns	1.6
Toxicity	ns	1.1
Response	.005	3.9

In conclusion our results demonstrate that optimization of treatment parameters can lead to obtain the highest proportion of CR rate that, in turn, positively affect locoregional control and survival.

Soft tissue sarcoma

HYPERTHERMIC ANTIBLASTIC PERFUSION WITH DOXORUBICIN AND TNFα (1 MG) IN THE MULTI DISCIPLINARY TREATMENT OF 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 Adryamicin and TNFα. The results were: CR 25%, PR 55%, with an OR of 80%. Moreover, limb sparing surgery was carried out in 77% of patients candidate to amputation.

No correlation has been found between tumor response and TNFα dosage, and our conclusion was that 1 mg of TNFα is the optimal dosage to employ during perfusion.

Methods and Results

We have conducted a prospective phase II study employing 1 mg of TNFα in association with Adryamicin in the treatment of advanced soft tissue limb sarcoma.

Fifty-eight patients have been enrolled thus far, with a median age of 53 years. Twenty-nine patients were male and 29 female; the tumor localization was mainly in the lower limb (74%), most of the patients were high grade (G2-G3 in 90% of the cases).

The grade of limb reaction, according to Wieberdink classification was mild-moderate (G1-3) in 80% of the patients, a grade IV was observed in 18% of the patients and a grade V was only recorded in 2 patients.

Systemic toxicity was only observed in 10% of the patients and was generally mild. Complete pathological response was obtained in 34% of the patients, partial response in 48%, with an objective response of 82%. Limb sparing surgery was carried out in 84.5% of the patients, only 9 were amputated.

At a median follow-up of 26 months local recurrence occurred in 22% of the cases.

The 5-year disease-free survival was 41.6% whereas 5-year overall survival was 72.4%.

The results of the study can be regarded as satisfactory for three reasons:

- It has been demonstrated that the trimodality (TNFα-Adryamicin-hyperthermia), carried out by isolation perfusion is superior to every kind of chemotherapy (systemic or regional) with a complete and objective response rate of 34% and 82%, respectively.
- Hyperthermic antiblastic perfusion carried out as neoadjuvant chemotherapy permitted to carry out conservative instead of demolite surgery in 84% of the patients.
- The utilization of 1 mg vs 3-4 mg implies two advantages: a) the use of 1 mg of TNFα results in less systemic complications, because even if with a 10% leakage, the MTD (300 mcg) is not reached: b) the cost of 1 mg is 2,300 Euro vs 9,200 when 4 mg. are employed.

Hyperthermic antiblastic perfusion with liposomal adryamicin and tnfα in the 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 Liposomal Doxorubicin.

The results of the study have demonstrated that MTD is 16 mg/Liter of limb volume; up to this dosage the grade of limb reaction was always between I and II. The treatment efficacy was quite good with a tumor necrosis >50% recorded in 7 out of 15 patients.

Experimental and clinical data have demonstrated that TNFα is able to improve the efficacy of Doxorubicin, therefore we have initiated a phase II study associating Liposomal Doxorubicin and TNFα.

Methods and Results

Two patients have been enrolled in the study thus far, 1 male and 1 female.

The tumor localizations were in the upper and lower limb respectively, the tumor was high grade (G3)in both the patients; histologically the tumors were MFH and angiosarcoma.

The two patients have been treated by isolation limb perfusion with Liposomal Doxorubicin (16 mg of limb volume) and TNFα (1 mg)

During regional perfusion drug leakage was carefully monitored, recording the radioactivity in the cardiac area, after the injection of albumin labeled with Tecknetium 99 in the perfusional circuit

A grade I limb reaction was observed in both patients. Systemic toxicity was very mild and mainly characterized by moderate increase of blood pressure and heart rate.

The tumor necrosis rate was 60% and 80% respectively, in both the patients a conservative surgery was carried out.

Role of the Fas/Fas-L system in the response to neoadjuvant treatment with hyperthermic perfusion (HP) associated to doxorubicin and rTNFα (DT) in locally advanced soft tissue sarcomas (STS)

The interaction between Fas/APO-1 (Fas-R) with its ligand (Fas-L), members of the TNF family proteins, plays a key role in a number of physiological mechanisms and, in particular, is able to activate apoptotic processes in various cell type. Alterations in the Fas-R/Fas-L system could represent one of the mechanism by which the tumor may succeed in evading the host immuno-surveillance. Recent studies demonstrated in fact that several human tumors of epithelial origin such as liver, lung, esophagus, breast carcinomas may unexpectedly overexpress Fas-L loosing contemporary Fas-R. In breast cancer the altered Fas-Fas-L system is correlated with adverse clinical parameters (positive node, high tumor grade, larger tumor size) and with a poorer prognosis also in BC patients treated with anthracycline based chemotherapy. These observations suggest that Fas-R could play a pivotal role in the apoptotic processes which are under regulation of tumor infiltrating lymphocytes (TIL). This data is of particular clinical relevance taking into account that in breast carcinoma, as in other solid tumors, the immune system is unable to control tumor growth (Menard S. 1997).

Because the mechanism of the antitumor effects of hyperthermia combined with chemotherapy is still poorly understood in STSs and studies suggest that chemotherapeutic drugs in general inhibit proliferation by generating cell cycle arrest and subsequently apoptosis, in this study we analyzed, using immunohistochemical (IHC) methods, the expression of Fas-R and Fas-L in STSs together with other genes involved in the apoptosis (Bcl2, Bax, Bclx) and proliferation (Ki-67) in order to:

- evaluate whether the treatment response and clinical outcome of STSs bearing patients submitted to hyperthermic perfusion associated to antracyclines and rTNFα is correlated with apoptosis Fas-R/FasL regulated in tumor specimens obtained before and after therapy
- investigate the influence of hyperthermic treatment on these parameters
- study the Fas-R/Fas-L phenotype of TIL before and after the above described schedule of treatment

At present we have enrolled in this study 10 patients bearing different types of sarcomas submitted to neoadjuvant therapy as described before. The histological diagnosis was made on H&E-stained paraffin sections of incisional biopsies. All cases were classified according to Enzinger and Weiss in order to accurately characterize the sarcoma histotype. The STSs was graded according to the grading system of Coindre et al. in which points are assigned to differentiation level, mitotic index and necrosis. In the resection specimens, after therapy, the amount of necrosis was estimated on gross examination. For histology at least one section per centimeter of the largest tumor diameter has been analyzed determining the presence of necrosis, viable tumor and fibrosis.

- Preliminary results, summarized in table 1, seem to suggest that patients bearing Fas positive /Fas-L negative tumor both before and after therapy presented a complete response (CR), whereas patients with alteration in the Fas system before and/or after therapy presented only a partial response (PR). Only in 1 case we found a CR although the Fas system was impaired.
- Studies of the Fas system in combination with other molecules involved in apoptotic processes or in proliferation, performed on a larger cohort of patients, could be useful to understand the role of Fas and Fas-L in response to neoadjuvant treatment with hyperthermic perfusion (HP) associated to Doxorubicin and rTNFα (DT) in locally advanced soft tissue sarcomas.

Fas system expression in 10 sarcomas pre and post hyperthermic treatment

PRE-THERAPY			POST-THERAPY		
N° of cases	Fas	Fas-L	Fas	Fas-L	Response
3	+	-	+	-	CR
2	+	-	-	+	PR
4	-	+	-	+	PR
1	-	+	-	+	CR

Peritoneal carcinomatosis

Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-istitutional study.

Background

Three studies have demonstrated that patients affected with peritoneal carcinomatosis from colorectal cancer have a median survival ranging between 6 and 8 months. Many phase II studies and a multicenter randomized study showed that cytoreductive surgery and perioperative intraperitoneal chemotherapy is able to improve patient survival.
We have participated in a retrospective multicenter international study aimed at evaluating the effectiveness of the combined treatment and at identifying the most relevant prognostic factors.

Methods and Results

Five hundred and six patients from 28 institutions have been enrolled in this study. All patients were treated with cytoreductive surgery, intraperitoneal chemohyperthermia and/or immediate postoperative intraperitoneal chemotherapy.
Peritoneal carcinomatosis from appendiceal cancer were excluded.
The median follow-up was 53 months. There were 273 female patients and 233 male patients. The lymph node status of the primary tumors was ascertained in 450 patients and was positive in 322 patients and negative in 128 patients.
The extent of carcinomatosis was limited in 171 patients, extensive in 329 patients, and unknown in six patients. Two hundred seventy-five patients were previously treated with systemic chemotherapy. Two hundred seventy-one were considered CCR-0 resection, 106 patients were considered a CCR-1, and 129 patients a CCR-2. Sixty-one patients were submitted to a simultaneous resection of liver metastases.
The morbidity and the mortality rates were22.9% and 4%, respectively, the overall survival was 19.2 months.
For CCR-0 patients, the 1-year, 3 year and 5-year survival rates were 87%, 47% and 31%, respectively, with a median survival of 32.4 months. For CCR-1 patients, the 1-year, 3-year, and 5-year survival rates were 79%, 29% and 15% respectively with a median survival of 24 months. For CCR-2 patients, the 1-year and 3-year survival rates were 38% and 6%, respectively ($p<.0001$).
Positive independent prognostic factors by multivariate analysis were complete cytoreduction, treatment by a second procedure, limited extent of peritoneal carcinomatosis, age less than 65 years, and use of adjuvant chemotherapy. Neoadjuvant chemotherapy, lymph node involvement, presence of liver metastasis, and poor histologic differentiation were shown to be negative independent prognostic parameters.

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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 the 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 the 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 the Lega Italiana Lotta ai Tumori, the commission for medical devices of the 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 a board member 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 - MD PhD Assistant
MAURIZIO COSIMELLI - MD Assistant
MARCO D'ANNIBALE - MD Assistant
GIUSEPPE ETTORRE - MD Assistant
FRANCO GRAZIANO - MD Assistant
PASQUALE LEPIANE - MD Assistant
ROBERTO SANTORO - MD PhD Assistant
GIOVANNI VENNARECCI - MD Assistant
VALERIO CORAZZA - MD Fellow
ALESSANDRO ESPOSITO - MD Fellow
RICCARDO LORUSSO - MD Fellow
PIETRO MANCINI - MD Fellow
FRANCESCO BUSCAGLIA - MD Fellow
DAMIANO CAPUTO - MD Fellow
CARLO BRUGIOTTI - MD Fellow

Clinical 2004 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 2004, 959 patients were admitted and 575 underwent surgery. This year we recorded an increment of 10% of our total activity in comparison to 2003. 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 2004 the division performed 63 gastrectomies, 130 colectomies, 24 pancreasectomies, 83 hepatectomies and 36 liver transplantations. With respect to the transplant activity this year we recorded an increment of 50% of liver transplants performed.
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 throughout 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 ontological 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 2004 accounts for over 3,200 out-patient visits.

Research Activity

Research on liver cancer

In 2004, 83 patients with liver neoplasms have been submitted to surgery: 30 for HCC, 42 for liver metastases, 7 for cholangiocarcinoma including gallbladder cancer, and 4 for other pathologies. Furthermore, 36 liver transplantations have been performed in the Department for liver cirrhosis, 13 of them with associated HCC, and 23 other patients underwent surgery for post viral liver cirrhosis.
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) (25), percutaneous Ethanol injection (PEI) (8), and radiointerstitial thermal ablation (RITA) (12).
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.** Since 2002 we have included in the current study 25 patients with HCC who underwent liver transplantation and other 25 patients affected by liver cirrhosis post-hepatitis were also transplanted and included in the study. Furthermore another 25 patients with HCC grown on liver cirrhosis have been included in the study as a control group. The results of the current study are under evaluation.
- **Chemotherapy and liver surgery in the treatment of colorectal metastasis.** The current study started last year has reached the inclusion of 44 pts with liver metastasis that have been resected during the study period 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 current study is under development and so far 47 patients have been included. 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 ongoing.

Research on colo-rectal cancer

In 2004, 116 patients affected by primary, resectable colorectal cancer were admitted and underwent surgery at our department (+4% if compared to the 2003 series). Moreover, another 15 cancer patients, affected with abdominal (lymph nodes) or pelvic recurrence after primary removal elsewhere, were operated on. In 2004, 777 patients were examined for clinical follow-up (+4.4% if compared to the 2003 activity).

All the translational and clinical research on colorectal cancer was carried out by the Colorectal Disease Management Team. In particular, the sections of activity were the following:

• **Neoadjuvant pelvic chemoradiation in extraperitoneal, resectable T3 rectal cancer**: from 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 2004, 26 pts. were enrolled and randomized (12 tomox, 14 plafur) at our institute. By December 2004 the overall study accrual was 150: preliminary results are under evaluation by the study coordinator (Prof. V. Valentini, Catholic University of Rome), since all the pathological diagnoses are being reviewed to confirm the tumor regression grade (TRG) of each patient.

• **Ultraconservative sphincter-saving surgery in very low rectal cancer responding to neoadjuvant chemoradiation**: to date, 15 patients have undergone a transanal, full-thickness rectal excision of the microscopic, residual rectal cancer or fibrotic scar tissue after neoadjuvant chemoradiation. Selection criteria were old age (72 as a median) and 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 yet. To date, 4 locoregional (3 local, 1 mesorectal) relapses were observed after a median time of 7 months. No distant events were recorded. As this particular surgical approach is regarded, our Institute was one of the first ones to start in the world, considering the very high chances of cure that a rectal cancer patient has after a clinically complete response following preoperative chemoradiation. However, potential discrepancies between clinical and pathological responses have to be taken into account.

• **Sentinel lymph node study in rectal cancer (within the 2003 AIRC project: Impact of biological profile, chemoradiation and surgery of rectal cancer on downstaging and quality of life)**: this promising and original clinico-pathological study of staging mesorectal lymph nodes during the preoperative, immediately post-surgical and pathological phases has virtually stopped for problems related to our Nuclear Medicine availability, despite the low number of cases each month (2-3).

• **Project C.N.R.-MIUR ONCOLOGIA SP5: Adjuvant therapy based on biological profile in curable colorectal cancer**: a new section to study the independent prognostic role of the tumor regression grade (TRG) in rectal cancer patients, who have

undergone preoperative chemoradiation and surgery has enriched the results of this project, virtually closed in 2004. Univariate and multivariate analyses for survival were carried out on all the TRG groups together as well as in each of them respectively: a correlation between TRG groups and risk of relapse was found, independently from pT. Furthermore, correlations between TRG and the most important clinical and pathological variables were also found. Submitted to the Annals of Surgical Oncology for final publication.

• **Project Italian Minister of Health Global Project for evaluation and improvement of QoL in oncological patients with long-term life expectancy**: the study enrollment is continuing, no data are yet available.

• **Project Italy- USA**: 62 patients I to III TNM stages were prospectively enrolled in this study. Data are not yet available.

• **Phase II clinical trial on treatment of unresectable, colorectal liver metastases non responding to FOLFOX or FOLFIRI chemotherapy by selective, intra-arterial hepatic radiotherapy with microspheres containing Ittrium-90**: in the last 4 months of 2004, after several preliminary meetings, 5 principle Italian centers engaged in the field of colorectal liver metastases (Naples, Udine, Bologna and Massa Carrara, as well as our Institute) and belonging to the Italian Society of Locoregional Therapy in Oncology (SITILO) participated in this common project. Prof. Maurizio Cosimelli was appointed as study coordinator. The study protocol has recently been approved by our Ethical Committee

Research on gastric cancer

In 2004, 63 patients affected by primary gastric cancer were operated on at our department. Of these, 11 underwent an exploratory laparotomy or palliative procedures and 52 surgical resections. Moreover, about 200 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 will be 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 4 more operated patients, the number of harvested lymphnodes and operation time were comparable to those of traditional open surgery as early clinical results show, 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 the 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 other 4 patients were comparable to those of traditional open surgery, but several advantages have been confirmed 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. Preliminary results showed that 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 2004, 43 patients affected with peri-ampullary and pancreatic neoplasms were admitted and studied in our Department. Of these, 11 were submitted to conservative treatment only, 9 underwent an exploratory laparotomy or palliative procedures and 22 surgical resec-

tion. Moreover, regular follow-up for operated patients in an outpatient setting was carried out. 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 results seem to confirm the high 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. During this year, we admitted 6 patients with these lesions. Of these, 3 were operated for cystic tumors, 1 for a non functioning endocrine tumor and 2 other were observed only. All the resected 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 clinical, functional and oncological results are promising.

Selected publications 2004

Antonini M., Ettorre G.M., Vennarecci G., D'offizi G., Narciso P., Del Nonno F., Perracchio L., Visco G., Santoro E.

Anti-retrovirals and immunosuppressive drug interactions in a HIV-positive patient after liver transplantation.

Hepatogastroenterology. 2004 May-Jun;51(57):646-8. *I.F. 0.837*

Carboni F., Graziano F., Lonardo M.T., Lepiane P., Santoro R., Lorusso R., Mancini P., Santoro E.

Pancreaticoduodenectomy for pancreatic metastatic melanoma.

J Exp Clin Cancer Res. 2004 Sep;23(3):539-43. *I.F. 0.574*

Cianciulli A., Cosimelli M., Marzano R., Merola R., Piperno G., Sperduti I., De La Iglesia F., Leonardo G., Graziano F., Mancini R., Guadagni F.

Genetic and pathologic significance of 1p, 17p, and 18q aneusomy and the ERBB2 gene in colorectal cancer and related normal colonic mucosa.

Cancer Genet Cytogenet. 2004 May;151(1):52-9. *I.F. 1.542*

Ettorre G.M., Vennarecci G., Boschetto A., Douard R., Santoro E.

Feasibility of hanging maneuvers in orthotopic liver transplantation with inferior vena cava preservation and in liver surgery.

J Hepatobiliary Pancreat Surg. 2004;11(3):155-8. *I.F. 0.1*

Ferroni P., Roselli M., Martini F., D'alessandro R., Mariotti S., Basili S., Spila A., Aloe S., Palmirotta R., Maggini A., Del Monte G., Mancini R., Graziano F., Cosimelli M., Guadagni F.

Prognostic value of soluble P-selectin levels in colorectal cancer.

Int J Cancer. 2004 Sep 1;111(3):404-8. *I.F. 4.375*

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

Cell surface overexpression of Galectin-3 and the presence of its ligand 90k in the blood plasma as determinants in colon neoplastic lesions.

Glycobiology. 2004 May 12 *I.F. 3.490*

Piperno G., Cosimelli M., Perrone D.R., Mancini R., Buglioni S;, Novelli F., Sperduti I., Zerbini V., Garufi C., Mottolese M.

Role of P53 and Bcl-2 in advanced rectal carcinomas treated with adjuvant therapy.

J Chemother. 2004 Nov;16 Suppl 5:11-4. *I.F. 1.088*

Santoro R., Santoro E., Ettorre G.M., Nicolas C., Santoro E.

Benign hilar stenosis mimicking Klatskin tumor

Ann Chir. 2004 Jun;129(5):297-300. French. *I.F. 0.487*

Vidiri A., Carpanese L., Annibale MD, Caterino M., Cosimelli M., Zeuli M., David V., Crecco M.

Evaluation of hepatic metastases from colorectal carcinoma with MR-superparamagnetic iron oxide.

J Exp Clin Cancer Res. 2004 Mar;23(1):53-60. *IF 0.574*

Division of thoracic surgery

DIRECTOR:
FRANCESCO FACCIOLO, MD

Francesco Facciolo, MD was born in 1953. He received his Degree in Medicine 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 La Sapienza University of Rome, first as a student and then as an assistant. In 1993 he became First Assistant at the Division of Thoracic Surgery of S. Camillo Forlanini Hospital were he worked until 2001. He then became Chief of Thoracic Surgery for the Department of Surgical Oncology of the Regina Elena Cancer Institute of Rome and Professor at the Post Degree Specialization Schools of Thoracic Surgery, General Surgery, Thysiology and Respiratory diseases at La Sapienza University of Rome. He is a member of the European Association for Cardio-Thoracic Surgery, the European Association for Endoscopic Surgery, the Italian Society for Thoracic Surgery, the Italian Society for Endcoscopic Surgery and the Italian Association for Hospital Surgeons.

Staff:
SANDRO CARLINI - MD: Assistant
MASSIMO FILIPPETTI - MD: Assistant
FELICITA CORZANI - MD: Assistant
VIRNA CERASOLI - MD: Assistant
ENRICO MELIS - MD: Assistant
LUIGI IONI - MD: Fellow
GABRIELE ALESSANDRINI - MD: Fellow
MARIO MICELI - MD: 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 with autoimmune diseases. A good diagnostic approach to these lesions requires a multidisciplinary team and multistep decisions.
Over the years, Thymoma classification has been a controversial field in pathology, as these are rare significantly heterogeneous tumors in their microscopical features. In 1999, the World Health Organization published a proposal for a Thymic Epithelial Tumors (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 for our understanding of biological/immunological thymoma features of relevant interest for therapeutic options.
A multicenter, multidisciplinary collaborative thymoma study has been recently undertaken by thoracic surgeons, pathologists, neurologists, oncologists and immunologists from three large Institutions (the Regina Elena Cancer Institute of Rome, the Catholic University of Rome and the Federico II University of Naples) particular interested in mediastinal and thymic pathology in Italy. We are now evaluating the clinicopathological, biological, immunological and oncological characteristics of thymoma patients over recent years in a preliminary phase of a retrospective study. In 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 carried out 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. Af-

ter a sufficiently long follow-up of the diagnosed cases it will be possible to assess the curability of the screen-diagnosed lung cancers. To date, about 27,000 participants have been screened, including over 16,000 repeat screenings and more than 400 cases of lung cancer have been diagnosed. To date we have enrolled 790 patients and 18 (2.27%) NSCLC, 15 (83%) of whom were diagnosed at stage I.

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 eligible. 700 patients in total will be randomized to arm A (chemotherapy plus surgery) and arm B (surgery).

Serum-proteomic project (ITALY-USA project).

The behavior 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 tumor behavior, such as pathological stage, response to chemotherapy and site of relapse are very important in clinical practice. To date, none of the hundreds of single markers evaluated have been of significant clinical use, but by surveying thousands of genes, using both microarrays and proteomic technologies it is now possible to read the molecular signature of an individual tumor.

Proteomic-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 close connection between apoptosis and cancer has lead to an explosion of research about 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.

The Italy-USA serum-proteomic project for lung cancer enrolls smokers and non-smokers with NSCLC divided in four groups.

P1: smokers and non-smokers with NSCLC histologically proved (100 patients);

P2: smokers and non-smokers with negative spiral CT scan (300 patients);

P3: people with spiral CT scan suspicion of lung cancer followed by negative histologic findings (20 patients);

P4: people with spiral CT scan suspicion of lung cancer and positive histologic findings (100 patients);

NEW APPROACH TO MALIGNANT PLEURAL MESOTHELIOMA.

This study will start in 2005 with the aim of assessing 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).

Selected Publications 2004

FABI A., BARDUAGNI M., FERRARESI V., CORTESI E., GAMUCCI T., DE MARINIS F., SALTARELLI R., GABRIELE A., PELLICCIOTTA M., CERIBELLI A., DE MARCO S., FACCIOLO F., COGNETTI F.

The combination of carboplatin and weekly paclitaxel: a safe and active regimen in advanced non small-cell lung cancer patients. A phase I-II study.

J Exp Clin Cancer Res. 2004 Mar;23(1):25-32 *IF 0.574*

GUADAGNI F., FERRONI P., BASILI S., FACCIOLO F., CARLINI S., CRECCO M., MARTINI F., SPILA A., D'ALESSANDRO R., ALOE S., CERASOLI V., DEL MONTE G., MARIOTTI S., MINEO T.C., ROSELLI M.

Correlation between tumor necrosis factor-alpha and D-dimer levels in non-small cell lung cancer patients.

Lung Cancer. 2004 Jun;44(3):303-10. *IF 1.798*

Clinical Activity

Our activity enrolls all the general thoracic surgery procedures with special interest in surgery for malignant pleural mesothelioma and extended chest wall resections for lung cancer. In 2004, we referred 900 patients and we performed 610 surgical interventions. We also performed 420 diagnostic endoscopic procedures.

Division of gynecology

Director:
Carlo Sbiroli, PhD

Carlo Sbiroli graduated in Medicine in 1964, completed the Specialization School in Obstetrics & Gynecology in 1980, and since1969 has been a Lec-turer on Obstetrics & Gynecology. Between 1970-72 he was an Assistant Professor in the Department of Obstetrics & Gynecology, La Sapienza Uni-versity of Rome. From 1972 to 1977 he held the post of Senior Registrar in the Division of Obstetrics & Gynecology, S. Giovanni Calibita - Fatebene-fratelli hospital, Rome. From 1977 to 2001 he was the Director of the Divi-sion of Gynecology, S.Carlo di Nancy-IDI Hospital, Rome. Since June 2001 he has been the Director of the Division of Gynecologic Oncology at the Regina Elena National Cancer Institute. From 1968-70, Prof. Sbiroli was involved in the study of ovarian steroids at the Chelsea Hospital for Woman in London and from 1974-78 he was at the Department of Urology, the University of California, Los Angeles doing research in the field of uro- gynecology. He completed his preparation on pelvic and oncologic surgery, attending European as well as American institutions. He is currently the Professor of Gynecologic Oncology at the Specialization School on Oncol-ogy, La Sapienza University of Rome.
Dr Sbiroli has published three books on gynecology and 186 papers. Be-tween 1983-89 he 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 the President of the Italian Association of Obstetrics and Gynecology.

Staff:
Enrico Vizza - M.D, PhD: Deputy Director, Chief of Minimally Invasive Surgery Unit.
Mario Antonio Congiu - MD
Giuseppe Cutillo - MD
Fabio F. Diotallevi - MD
Luciano Mariani - MD
Domenica Mazza - MD
Roberto Sindico - MD
Cristina Vincenzoni - MD
Giuseppe Vocaturo - MD
Giacomo Corrado - PhD
Gregorio Marco Galati - PhD Fellow
Marco Atlante - MD Fellow

The Division of Gynecologic Oncology is mainly dedicated to the screen-ing, diagnosis, treatment and follow-up of gynecologic cancer. It is com-posed of 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 also includes a Minimally Invasive Surgery Unit mainly dedicated to the application of new minimally invasive technologies in the field of Gynecologic Oncology Surgery. The surgical activity, both conventional and mini-invasive, implies the most advanced technologies, a highly specialized interdisciplinary team and integrated treatment for the advanced stages. During 2003, various clinical research protocols as well as studies in the field of the biology of tumors have been conducted.

Activities in progress

Evaluation of efficacy of diagnostic tests in a population at risk for endo-metrial cancer

This study evaluates the efficacy (sensitivity and specificity) of immunocy-tology in the liquid phase to detect endometrial cancer and their precursors in a population at risk for endometrial cancer (BMI>30, Tamoxifen-users, familiarity for breast, colorectal, ovarian and endometrial cancer. In the next two years the study intends to enroll 500 women at risk of endometrial can-cer in which an endometrial immunocytology will be performed. The posi-tive or suspicious endometrial cytology are referred to hysteroscopy and bi-opsy for histologic diagnosis.

Clinical significance of genetic alterations of chromosome 3,7,X e EGFR gene in uter-

INE CERVICAL CANCER PROGRESSION

The primary objective of the study is to identify the genetic alterations of chromosome 3,7,X e EGFR gene expressed by squamous cells during trans-formation and progression from L-SIL and H-SIL to invasive cervical car-cinoma. Aberrations of chromosomes 3,7,X and EGFR gene status is as-sessed by FISH in samples coming from patients affected by L-SIL, H-SIL and invasive squamous cells carcinoma. Data obtained from a first set of 60 patients revealed a strong correlation between the 3,7 and X chromosomes polysomia and development and progression of H-SIL to invasive carci-noma. Therefore, the present observations seem to suggest an emerging role of the status of chromosomes 3,7 and X as predictive markers of H-SIL progression to invasive cancer.

METALLOPROTEINASE(MMP) AND C-KIT PROTEIN EXPRESSION IN MESENCHIMAL TU-MORS 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 - arises 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 possible genomic instability. The aim of the present study is: 1) to evaluate the expression of Metalloproteinase (MMP) and c-Kit protein in mesenchimal 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 Metalloprote-inase (MMP) and c-Kit protein with the stages of the new classification of Soft Tissue Tumors proposed by the French Federation of Anticancer Cen-ters. The immunohistochemical expression of Metalloproteinase (MMP) and c-Kit protein is assessed in 25 cases of mesenchimal 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 mesenchimal tu-mor of the uterus as has been demonstrated to occur 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 CHEMOTHER-APY VERSUS EXTREME DRUG RESISTANCE ASSAY-SORTED CHEMOTHERAPY FOLLOWING UP-FRONT DEBULKING SURGERY IN ADVANCED EPITHELIAL OVARIAN CANCER

The Division of Gynecologic Oncology participates together with the Divi-sion of Oncology "A" in a prospective international multicenter phase III study. After surgical debulking, the results of in vitro assays for drug resis-tance are 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/m2 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 → open to discussion). Stratification factors will include the treating institution and 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-GENOMICS

This study is structured in two parts: 1) determination of the alterations of the serum protein pattern correlated with pathogenesis, prognosis using proteomic spectra generated by mass spectroscopy. 2) identification of spe-cific clusters of proteins predictive of early diagnosis and on which treat-ment using Phosphoproteomic is tailored. In this prospective study, the al-terations of the serum protein pattern of 200 patients collected at the time of first diagnosis of ovarian cancer is analyzed, comparing the proteomic spec-tra with that obtained from the serum protein coming from 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 trasmembrane proteins be-longing to the family of tumor necrosis factor and tumor necrosis factor re-ceptor. 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 determine if there is any correlation be-tween the expression of Fas and Fas-L and the other clinicopathologic pa-rameters (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 further develop into invasive cervical cancer. The division of Gynecologic Oncology participates 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 16-23 years of age are enrolled in this study and immunized against HPV6, 11, 16, 18.

LAPAROSCOPIC STAGING AND RESTAGING OF GYNECOLOGIC TUMORS

Continuing worldwide interest clearly demonstrates that laparoscopic tech-niques are now part of the armamentarium of the gynecological oncologist. Therefore, great effort has been made to introduce laparoscopic and related mini-invasive techniques in staging and surgery of gynecologic tumors. The main fields of exploration and application are; pelvic and lomboartic ex-traperitoneal and transperitoneal lymphadenectomy as a staging or a restag-ing procedure; differential diagnosis in carcinosis; selection of patients can-didate to primary cytoriductive surgery in advance ovarian cancer; intensive surgical staging of cervical and endometrial cancer totally laparoscopic; re-staging of borderline ovarian tumors after incomplete primary surgery.

Publications 2004

MARZANO R., CORRADO G., MEROLA R., SBIROLI C., GUADAGNI F., VIZZA E., DEL NONNO F., CAROSI M., GALATI M.M., SPERDUTI I., CIANCIULLI A.M.

Analysis of chromosomes 3, 7, X and the EGFR gene in uterine cervical cancer progression.

Eur J Cancer. 2004 Jul;40(10):1624-9. *IF 3.694*

SEBASTIANI V., VISCA P., BOTTI C., SANTEUSANIO G., GALATI G.M., PICCINI V., CA-PEZZONE DE JOANNON B., DI TONDO U., ALO P.L.

Fatty acid synthase is a marker of increased risk of recurrence in endometrial carcinoma.

Gynecol Oncol. 2004 Jan;92(1):101-5. *IF 2.341*

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., SYRJANEN K.

Assessment of risk factors and human papillomavirus (HPV) related patho-genetic mechanisms of CIN in HIV-positive and HIV-negative women. Study design and baseline data of the HPV-Pathogen ISS study.

Eur J Gynaecol Oncol. 2004;25(6):689-98. *IF 0.547*

Marzano R., Orlandi G., Corrado G.

ERBB2 amplification is superior to protein expression status in predicting patient outcome in serous ovarian carcinoma. (92:31-39) by Lassus H et al.

Gynecol Oncol: 2004; vol. 95 (2): 416-417

Vincenzoni C., Diotallevi F., Carpanese L., Corrado G., Vizza E., Congiu M.A., Cutillo G., Galati G.M., Sbiroli C.

Use of ureteral stents in the treatment of hydroureteronephrosis from locally advanced or recurrent cervical carcinoma.

Int J Gynecol Cancer 2004, 14 (S1): 120.

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

Total laparoscopic radical hysterectomy (TLRH) in endometrial adenocar-cinoma (EA): our experience.

Int J Gynecol Cancer 2004, 14 (S1): 183.

Vizza E., Sbiroli C.

Advantages of laparoscopy in staging and management of cervical cancer. Preceedings13th Annual Congress of The European Society for Gyneco-logical Endoscopy (ESGE) Cagliari 14-17 October 2004.

Journal Gynecological Surgery, 26 (5):187 2004.

Vizza E., Corrado G., Sbiroli C.

Gestione delle complicanze emorragiche in chirurgia ginecologica. In.: Pro-blematiche coagulative ed emorragiche in Ostetricia e Ginecologia.

L. Falasca. Arti Grafiche Editore, Agnone. pp.65-73, 2004.

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 Assistant Professor of the Department 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 the 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 of the Regina Elena Cancer Institute Rome.

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

Activities 2004

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 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-circulatory 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 abdominal 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 Level 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 invasiveness 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, laboratory 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 intra-caval 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. *The identification of patients at increased risk of progression is an important goal in bladder cancer research because such patients will be candidates for newer treatments and follow up strategies*. In our study, we analyzed deletions of 9p21 (p16), 17p13.1 (p53), and 13q14 (RB1) in 48 bladder cancer specimens and the adjacent normal mucosa. In the same specimens, the status of the 3, 7, 9, and 17 chromosomes and of the HER-2 gene was examined. The genetic evaluation was determined using fluorescence in situ hybridization (FISH). The preliminary part of our investigation analyzed the frequency of chromosomal alterations, gene amplification, and deletion in bladder cancer and the surrounding mucosa to evaluate general genetic instability in the entire transitional epithelium. In the second part of our study, we concentrated on patients with advanced disease to evaluate the role of molecular markers that could potentially have important prognostic implications by complementing the standard histopathological staging system. The identification of patients at increased risk of progression is an important goal in bladder cancer research because such patients will be candidates for newer treatments and follow up strategies.

FISH analysis

Touch preparations were reviewed by a pathologist to verify the adequacy of the cellular components. The FISH analysis procedure has been described previously labeled probes for FISH assay, specific for the centromeric region of three chromosomes (D3Z1), 7 (D7Z1), 9 (D9Z5), and 17 (D17Z1) (Vysis Inc, Downers Grove, Illinois, USA) were used for specific ploidy detection. We also used specific probes for p16 (9p21), p53 (17p13.1), and RB1 (13q14) (Vysis) to assess the deletion (not mutation) of these loci. The status of the HER-2 gene was evaluated by the HER-2 DNA probe kit (Vysis). We also applied chromosome enumeration probes (CEP) 9 and 17 to adjust for the effects of aneuploidy and to establish the presence of amplification and/or deletion of HER-2, p53, and 9p21. Copy numbers for centromeres and specific gene regions were counted in at least 100 non overlapping cells. Some samples were not evaluated for all variables for technical reasons. Statistical analysis.

Results

Chromosome 3, 7, 9, and 17 and LSI (17q11.2, 9p21, 17p13.1, and 13q14) status in normal and neoplastic bladder tissue. In this first evaluation, we performed a control FISH assay to establish the hybridization patterns in bladder samples from 15 patients undergoing prostatectomy.

Tumors and distal epithelial samples were determined to be monosomic and/or polysomic for chromosomes 3, 7, 9, and 17 and deleted for the RB1 gene when the dominant population exceeded the mean +3 SD of any of the signal categories seen in the control group. In addition, we used the locus specific identifier (LSI) 13 probe (Vysis) to distinguish between failure of hybridization and deletion of the RB1 sequence. Homozygous deletion of the RB1 gene was present

when no RB1 and two LSI 13 signals were seen, whereas heterozygous deletion was present when one RB1 and two LSI 13 signals were seen. The control for aneuploidy of chromosome 17, where the HER-2 and p53 genes are located, was an a satellite centromere

probe, which was co-hybridized with the HER-2 and p53 genes. The probes for chromosome 9 (CEP 9 and LSI 9p21) were chosen to detect monosomy/polysomy and losses of the p16 gene, respectively. We used a ratio of more than two oncogene signals/centromere to define HER-2 gene amplification. We used ratios of 17p13.1: CEP 17 and 9p21: CEP 9 lower than 0.5 as a measure of homozygous deletion, whereas heterozygous deletion was determined for ratios between 0.5 and compares tumor and normal adjacent mucosa for all examined genetic markers, based on established criteria. Monosomy and polysomy of the evaluated chromosomes ranged from 20.8% (chromosome 9 polysomy) to 68.7% (chromosome 9 monosomy) in the tumors and from 5.0% (chromosome 7 and 17 monosomy and chromosome 9 polysomy) to 55.0% (chromosome 9 monosomy) in the adjacent mucosa. A significant difference was seen only for chromosomes 7 and 17. Most of the tumors and adjacent mucosa (68.7% and 55.0%, respectively) showed monosomy of chromosome 9. As illustrated in table 2, FISH analysis performed using LSI probes revealed no differences in the frequency of deletions between tumor samples and the surrounding mucosa. The highest percentage of homozygous deletion of neoplastic informative cases was found at the 13q14 (RB1) locus (12.5%). Homozygous deletion of the 9p21 (p16) and 17p13 (p53) loci was present in 8.6% of the patients. Heterozygous deletion was more frequent than homozygous deletion in cancer samples, ranging from 56.2% (17p13) to 81.2% (13q14). Even though the difference is not significant, HER-2 amplification was found in seven tumor specimens (14.5%), whereas the adjacent mucosa did not show amplification. Five HER-2 amplified tumors had concomitant chromosome 17 polysomy (fig 1. Association between genetic alterations and pathological characteristics. In the second part of our study, contingency table 3 and the x2 tests were used to evaluate the association between the pathological characteristics and genetic alterations in the 48 samples. In this part of the study, the discriminative power of heterozygous deletion and chromosomal aberrations was considered to be the median value of the percentage alteration. With regard to homozygous deletion, the discriminative power was its presence or absence. Chromosome 3, 7, and 17 monosomy and RB heterozygous deletions were significantly associated with T3–4 stage ($p = 0.03$, $p = 0.04$, $p = 0.04$, and $p = 0.03$, respectively).

In some cases, when chromosomal and gene characteristics were compared with T3–4 stage and lymph nodal involvement, a positive trend was found even though the results were not significant.

Discussion

Our evaluation of chromosomes 3, 7, 9, and 17 and the p53, p16, RB, and HER-2 genes in human bladder neoplasia focused on specific issues, namely: (1) the detection and comparison of multiple genetic alterations identified in bladder cancer and in normal urothelium, and (2) the association of genetic alterations with clinicopathological characteristics. We found chromosomal numerical aberrations in all specimens analyzed. Nevertheless, when malignant and non-malignant cells were compared, significant differences were seen only for chromosomes 7 and 17. These results, show that the T3–4 stages are significantly associated with chromosome 3, 7, and 17 monosomy.

Most tumors and normal urothelium showed chromosome 9 monosomy, with mean percentages of 71.2% and 55.0%, respectively. These data, according to a recent study performed by our group on superficial bladder cancer, indicate that this alteration is ubiquitous, and is not related to specific pathogenetic subsets, histological grade, or invasive phenotype. In addition, no significant differences in 9p21 deletion were found between malignant and nonmalignant cells.

The clinical relevance of p53 suppressor gene mutation is a controversial issue in bladder cancer. Alterations in the p53 and RB tumor suppressor genes are an important component in the development of bladder cancer, but the downstream pathways that contribute to urothelial transformation are not completely defined. We found no significant difference between cancer specimens and the distal mucosa with regard to p53 deletion. The pres-

ence of allelic losses of the TP53 markers in cystectomy specimens and in areas of urothelium that are considered benign has been demonstrated by conventional histology. These data, together with the results of our study, support the hypothesis that many normal appearing areas of the bladder are genetically altered in patients with bladder cancer. Our study strongly confirms the importance of chromosome 17 polysomy in HER-2 amplification detection. Inactivation of the RB1 gene is a common event in bladder cancer and it has been associated to higher grade, invasive stage tumors, and decreased survival. We found that the histopathological stage was significantly associated with RB1 heterozygous deletion. In addition, a higher proportion of neoplastic samples had RB1 deletion, both for homozygous (11.0%) and for heterozygous (86.0%) deletion.
Emerging data on the use of HER-2 amplification as a prognostic marker and/or therapeutic target (Trastuzumab) in breast cancer stimulated our interest in assessing the rate of HER-2 amplification in these specimens, and we were also encouraged by the cancer and leukemia group B, which has started a trial of single agent Trastuzumab in patients with previously treated advanced bladder disease. Studies of HER-2 overexpression and amplification have shown varying results in bladder cancer, as a result of the application of different laboratory techniquesSauter et al found amplification in 10 of 141 bladder tumors, but only in those with aneusomy of chromosome 17. Chromosome 17 polysomy was detected in five of seven of our amplified tumors. Polysomy of chromosome 17 in bladder cancer occurs independently of tumor polyploidy. Our study strongly confirms the importance of chromosome 17 polysomy in HER-2 amplification detection.
The results of our investigation highlight: (1) the presence of general genetic instability in the entire transitional epithelium and a close genetic relation between tumors and the adjacent mucosa; and (2) that the status of chromosomes 7 and 17 and the RB1 gene could be useful
genetic markers to complement the standard histopathological staging system and to identify patients at risk of progression. Because bladder cancer progression is undoubtedly associated with particular somatic genetic alterations, individual patients could be characterized by defining any significant genetic aberrations in the tumor obtained during cystectomy. We propose that chromosome 3, 7, and 17 monosomy and RB1 heterozygous deletion should be considered potentially useful intermediate biomarkers to detect patients at high risk of progression who may benefit from particular and innovative therapeutic interventions. Each of these parameters individually and together could improve the understanding of this disease and contribute to categorizing patients with advanced bladder cancer. Only larger studies with long term follow up will determine the usefulness of this observation.

Clinical Activities

For patients at risk a protocol for intraoperative adjuvant radiotherapy (IORT), an agreement with the 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 - MD
Simona Marzi - PhD
Michele Gallucci - MD

Maria G. Petrongari - MD
Enrico Chianese - MD
Michela Benassi - MD
Giuseppe Iaccarino - PhD
Antonella Soriani - PhD
Giorgio Arcangeli - MD

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 Activities

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 mo-

lecular prognostic markers in phase II and III trials to define their role in the clinical outcome.

Publications 2004

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Urology. 2004 Aug;64(2):405 *IF 2.782*

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. Since June that year, he has been the Director of the Plastic Reconstructive Surgery Department at the 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 2004

BREAST RECONSTRUCTIVE SURGERY

Immediate and delayed breast reconstructive surgery is performed in the Department using highly specialized 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 2004 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 have begun 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 compared to traditional surgery treatment, NSM does not have an increase of local recurrence.
Methods - We divided our study in two parts. The first included 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 sub-

cutaneous 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 is 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. Moreover, 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 - MD Assistant
ANNA CERIBELLI - MD Assistant
ALESSANDRA FABI - MD Assistant
VIRGINIA FERRARESI - MD Assistant
GIANLUIGI FERRETTI - MD Assistant
MICHELE MILELLA - MD Assistant
PAOLA PAPALDO - MD Assistant
ENZO MARIA RUGGERI - MD Assistant
ANTONELLA BAVARESE - MD Assistant
MASSIMO ZEULI - MD Assistant
ALESSANDRA FELICI - MD Senior Fellow
ALAIN GELIBTER - MD Senior Fellow
CHIARA NARDONI - MD Senior Fellow
MARIANGELA CICCARESE - MD Fellow
FABIANA CECERE - MD Fellow
BARBARA DI COCCO - MD Fellow
NELLO SALESI - MD Fellow
ANDREA ALIMENTI - MD Fellow
SERENA DI COSIMO - MD Fellow
SIMONA PINO - MD Fellow
SUSANNA DI SEGNI - Pharmacist Fellow
LUCA PAOLUZZI - MD Fellow
EMANUELA ROMANO - MD Fellow
CARMEN NUZZO - MD Fellow

Activities 2004

The Division of Medical oncology A has a long-standing commitment to improving the detection and treatment of solid cancer. More than 1,875 new patients with solid cancer came to our Division in 2004, which has one of the largest referral programs for this disease.
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 medical oncology (e.g. gonadal or extragonadal germinal cell tumors and soft tissue sarcomas). Team members provide state-of-the-art diagnosis and treatment to patients with solid cancers, adding continually to a database that tracks the history of the patient. One important advantage of this database is the knowledge gained to help each patient avoid unnecessary surgery, chemotherapy, and radiation therapy, and help predict outcome.
In 2004, 2,053 new patients have been accepted and 18,958 activities (visits and treatments) have been carried out. There have been 17,464 in-patient admissions and 1,494 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 28 indexed publications (total impact factor: 167,34).

Non Small Cell Lung Cancer

A randomized phase III study of surgery alone or surgery plus Gemcitabine - Cisplatin in clinical early stages (T2N0, T1, T3 N0 and T3N1) non small cell lung cancer (NSCLC) has been recently closed and 24 patients were accrued.
A multicenter phase III study investigating the role of prolonged infusion of Gemcitabine in association with Cisplatin is underway in the Division of Medical Oncology A, and 31 patients have been accrued.
Two multicenter phase III studies with Iressa vs placebo as maintenance therapy in patients with locally advanced NSCLC, and Iressa vs Taxotere (INTEREST-Study) as second line therapy have been recently opened.
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 and accrual is continuing.

Breast Cancer

Adjuvant

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. Three 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 dosedensity. 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 the EC combination followed by Taxol and a dose-dense schedule (every 2 weeks) will improve disease-free and overall survival. Our department contributed to the success of this study with 62 patients.
The second study (GIM 1) regards patients with node-negative breast cancer, that received either EC or FEC all given either every 3 weeks or 2 weeks, as adjuvant therapy. The study will determine how 5-Fluorouracil addition 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) has recently been closed, 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 2004, 251 subjects belonging to 160 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 has recently closed in our Division, after 37 patients were accrued. 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 large randomized phase III studies has been recently activated in metastatic colorectal cancer with the introduction of two new molecules: Irinotecan + Cetuximab vs. Irinotecan alone after failure of first-line chemotherapy in patients with metastatic colorectal cancer expressing EGFR, and ABX + best supportive care vs. best supportive care in patients with colorectal cancer, who have received at least two lines of chemotherapy.
Two multicenter trials, both coordinated by the Division of Medical Oncology A, finished the accrual in 2004. 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 and continued until 2004 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 started in 2004. Patients were treated with Capecitabine and Celecoxib after the failure of first line chemotherapy. (Cap-cel study)

A phase II study for advanced pancreatic and biliary tree carcinoma was concluded in 2004. Patients were treated with Gemcitabine 1,000 mg/m2 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 active and accrual is continuing.

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 2004. An EORTC phase III study evaluating the role of Pegylated Interferon (PEG-Intron) in an adjuvant setting and a phase II study. e 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.

Renal cancer

Innovative research efforts are currently under way involving improvements in treatment of this disease. Newer treatment options, available in clinical trials, include biologic therapy for advanced and recurrent disease. Three phase III randomized trials start the accrual in 2004. In such badly prognosis disease, use of new approach is mandatory, so all four trials are designed using new smart molecules (CCi-779, SU011248, and Bay 439006.

Ovarian Carcinoma

The extreme drug resistance assay sorted chemotherapy (EDRA) randomised trial has been activated in 2004 in collaboration with ISS and University of Brescia, after the recent final approval obtained by the local ethical committee.

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.

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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 specialized in medical oncology and internal medicine at the same University. From 1969 to 1986 he worked at the 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 the G. Porfiri Oncologic Center, Latina, as Director of the Division of Medical Oncology. He left Latina and went to the Regina Elena Institute for Cancer Research in 1990 to work as Director of the Division of Medical Oncology B. During recent years, his research interests have been 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), the European Society for Medical Oncology (ESMO), and the 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 - MD Assistant
SILVIA CARPANO - MD Assistant
FRANCESCA CONTI - MD Assistant
MARINA DELLA GIULIA - MD Assistant
LUIGI DI LAURO - MD Assistant
PAOLO FOGGI - MD Assistant
GIANCARLO PALETTI - MD Assistant
MASSIMO RINALDI - MD Assistant
IRENE VENTURO - MD Assistant
PATRIZIA VICI - MD Assistant
ROSITA CAPONETTI - MD Senior Yellow
CAROLINA CAUCHI - MD Fellow
SONJA CONDORELLI - MD Yellow
MARIA CLAUDIA MASI - MD Fellow
DOMENICO SERGI - MD Yellow
GIUDITTA VIOLA - MD Yellow
SERENA CORSETTI - MD Yellow
SIMONA APICELLA - Student
LUIGI CARMINE ROMA - Student
WALTER CHIERICHETTI - Student
SILVIA ILEANA SARA FATTORUSO - Student

Activities 2004

Among the fields of interest of the Division of Medical Oncology B (MOB) is to create and maintain liaisons with other oncological associations, universities, and to cooperate with the pharmaceutical industry in areas of mutual interest.
During 2004 several clinical trials concerning many oncologic fields have been carried out. In particular, the Division of MOB served as coordinating center of various breast cancer clinical trials in adjuvant, neoadjuvant and advanced settings, in collaboration with other Italian oncologic centers.
In the adjuvant setting we are currently investigating the efficacy of 4 cycles of an Epirubicin/Cyclophosphamide regimen versus the same regimen preceded by 4 cycles of Docetaxel in node positive breast cancer patients in a phase III multicenter randomized trial. In 2004 we continued the enrollment of the patients; the accrual will be completed at the beginning of 2005 and final data will be analyzed.
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 a hormonal treatment at the end of chemotherapy. The enrollment continued during 2004.

In one of our most recent articles on treatment of advanced breast cancer (J Clin Oncol 20 (11) 2689-2694, 2002, Vici P 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. On the basis of the results of this study, in 2003 we designed and activated a new 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. During 2004 the patients enrollment has almost been completed.

During 2004, we completed the analysis of final data of a sequential trial of Docetaxel followed by Epirubicin and Vinorelbine as first line treatment in metastatic breast cancer. This manuscript related to this trial has been accepted by Anticancer Research, and will be published in 2005.

We are also very interested in the clinical evaluation of new drugs and new combinations, and we have designed and activated several clinical trials, nearly all multicenter, in advanced breast cancer patients. The first one was a combination of Docetaxel 80 mg/m^2 d 8 and Gemcitabine, 1000 mg/m2 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. The second trial is a 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. In 39 patients, we observed a 45% response, a TTP of 9 months, an OS of 21 months, with very mild toxicity. These data are very encouraging and supported by a synergistic activity between the two drugs, as demonstrated by the results of in vitro and in vivo studies carried out at the Department of Preclinical Pharmacology of our Institute. The paper has been submitted for publication. The excellent results of this trial prompted us to design and activate another clinical trial, with the biweekly combination of infusional Gemcitabine with Paclitaxel, in anthracycline-pretreated advanced breast cancer.

In 2004 we also continued and concluded the enrollment of two phase II multicenter clinical trials Docetaxel and Gemcitabine, as first-line chemotherapy in patients treated with adjuvant anthracyclines, and Docetaxel and Vinorelbine as 2nd line treatment in metastatic breast cancer. We are now evaluating the final data of both studies.

In 2004 we continued the enrollment in 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/m2 d 1 and Capecitabine 1,250 bid d 1→4, with cycles repeated every 3 weeks, as first-line treatment for advanced disease, in patients previously treated with adjuvant anthracyclines.

Several studies have been devoted, during 2004, to the development of new combinations in molecularly targeted treatment of a number of cancers, mostly breast cancer. In this disease in particular, attention has been focused on DNA methyltransferase and histone deacetylase inhibitors.

Another important field of interest of the Division of Medical Oncology B is the early diagnosis and prevention of cardiotoxicity. A review of the role of the cardiotoprotectant Dexrazoxane in anthracycline treatment has been published (see selected publications), and a prospective trial has been designed to evaluate cardiotoxicity in patients treated with cardiotoxic drugs by several laboratory tests.

The Division of OMB is also involved in several other trials in lung cancer, gastric cancer, colorectal cancer, melanoma, and soft tissue sarcomas. Among these sarcomas, gastrointestinal stromal tumors, (GIST) have received particular attention and their clinical and therapeutic aspects have been summarized in a forthcoming book (Massimo Lopez: GIST. Tumori stromali gastrointestinali, società Editrice Universo, Roma, 2005)

In 2004, a new edition of the following book has been published: Cugini P., Fiorelli G., Guarini G., Lopez M., Violi F., Volpe M.: Teodori Trattato Italiano di Medicina Interna, Società Editrice Universo, Roma, 2004.

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Clin Cancer Res. 2004 Feb 15;10(4):1360-5. *I.F. 6.511*

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Rinaldi M.

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Suppl Tumori. 2004 Mar-Apr;3(2):S45-6. *I.F. 0.348*

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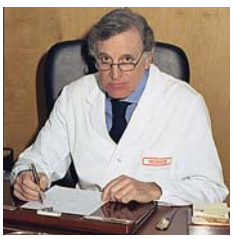
J Cancer Res Clin Oncol. 2004 Jan;130(1):1-7. *I.F. 2.162*

Division of medical oncology C

DIRECTOR:
EDMONDO TERZOLI, MD



Prof. Edmondo Terzoli, MD graduated in Medicine & Surgery in 1969 at La Sapienza University of Rome. He received Hematology, Medical Oncology and Pulmonary Fellowships in 1972, 1974 and 1976, respectively, at the same university. From 1970 to 1979 he worked at the Regina Elena National Cancer Institute of Rome as Attending MD; in 1979, he became Head of Division, and in 1991 Head of the Complementary Medical Oncology Division. Since 2000, he has been the Director of the Medical Oncology "C" Division, and in 2003 he was appointed Head Director of the Department of Medical Oncology of the Regina Elena National Cancer Institute, Rome. During these years, Prof. Terzoli has held several roles in the Italian Association of Medical Oncology (AIOM). Since 2004, he has been a member of the "AIOM Servizi" board.

Staff:

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

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

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

Activities 2004

During 2004 the Division of Medical Oncology "C" focused its major scientific activity on breast and colorectal cancer. Moreover, a methodological field of research regarding pooled-analysis and meta-analysis has been successfully approached.
In particular, the development of weekly chemotherapy and the chronomodulated infusion of chemotherapy in breast and colorectal cancer respectively, have been an ongoing experience of the Division directed by Prof. Terzoli for more than 12 years, as well as a cultural and scientific heritage for the Regina Elena National Cancer Institute of Rome. Like old drugs, new chemotherapeutic and molecular targeted agents are being developed for weekly and chronomodulated application. Both research lines have been enriched by several international peer-reviewed publications and by meetings in which national and international leaders of opinion were present.
In order to follow the rapidly growing need to update knowledge and research as required by medical oncology, our division has also distinguished itself for the organization of several skilled courses strictly focused on weekly schedules, in which doctors coming from around the country partook in a discussion where issues regarding the most recent clinical studies and their application to real clinical cases were raised. Based on the criteria set out therein, an ideal skilled training scheme of research and clinical practice has been followed. The international consensus about weekly chemotherapy for breast cancer, was recently reached at the last American Society of Clinical Oncology Meeting (ASCO 2004), where a phase III trial showed the benefit in activity and efficacy of such approaches when compared to conventional 3-weekly chemotherapy. Thanks to these important results, the experience and the numbers in terms of enrolled breast cancer patients undergoing weekly chemotherapy of our Division, have to be considered as one of the most skilled and largest 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 has to be considered a national and international reference center. 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.

Breast Cancer.
Until few years ago, 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 comorbidities.
Conversely, today it is recognized as a new administration option for chemotherapeutics, 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 increased number of dead cells for each cycle; anyway, the re-growing effect between 2 courses, as described by the Gompertzian model, should explain the failure of all strategies based only on dose-augmentation. Furthermore, the endothelial cells of the new born vessels can re-start to proliferate, favoring the neoplastic cells growing through neoangiogenesis enpowerment.
More recently, as hematopoietic growth factors have become 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 effect of the re-growth of cancer cells between cycles, increasing the efficacy of such drugs, for which cytotoxicity does not follow a linear dose-response curve either. Besides, the prolonged exposure of cancer cells to agents which interfere with mechanisms of cellular proliferation could permanently damage the re-growth potential, even in the absence of chemotherapy. This approach offers pharmacokinetic advantages too, allowing for a reduction of the drug-concentration peak, which is often toxicity-related, while maintaining overall AUC.
In conclusion, the weekly administration of chemotherapeutics theoretically increases the frequency of the 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. Toxicities of such an approach seem to be lower than 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 the 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 is likely to happen in a metastatic setting. All these theories have recently been supported and finally assessed by 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.
Since 1990, our Division has been working on the development of a weekly schedule in metastatic breast cancer; during 2004 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 ancillar studies have also been conducted to evaluate cardio- and neuro-toxicity of such schedules from a clinical, serological and instrumental perspective.
Two studies started in 2000, a phase I-II study with weekly Docetaxel without a rest period in pre-treated patients with advanced breast cancer and a phase II study with weekly Epirubicin plus Vinorelbine in locally advanced breast cancer, have been accepted for publication.

Anthracycline-resistant or refractory patients were enrolled in a phase II study with weekly Gemcitabine and Paclitaxel; Gemcitabine was also administered as fixed dose rate (FDR) of 10 mg/m2/min, owing to the extremely recent pharmacokinetic and clinical news about such drugs.
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 did partake in both trials coordinated by the Gruppo Italiano Mammella (GIM); node-positive patients after surgery for early stage breast cancer have continued to be randomized in the GIM 2 protocol and node-negative patients in the GIM 1 trial.

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 is an effort to synchronize medical therapies with endogenous physiologic rhythms to increase the therapeutic index of the drugs administered. 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 vary in a regular and predictable periodical way in the function of time. Some more common rhythms of the human species are ultradian (circadian rhythm that go on through 24 h, such as the sleep-waking rhythm and cortisole rhythm), infradian (> 24 h, as menstrual cycle in woman) and seasonal rhythms. The suprachiasmatic nucleus of the anterior hypothalamus (SCN) coordinates circadian rhythms and, through connections with the retinal epithelium, is responsible of melatonin synthesis, a pineal hormone involved in circadian sleep-waking 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 skin, with a time lag of 4-6 hours with respect to the SCN rhythm. Recent studies have demonstrated that the expression of hundreds of genes is under control of the clock-gene. 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 cytotoxicity of antiballistic drugs, for example enzymatic activities responsible of 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 the circadian function both in experimental models and in patients, so it would seem that the cortisole, 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 are still in course, about metastatic colorectal cancer. Strategic lines developed within the studies effected in single institutions and in a cooperative way were the following: a) the 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 FFL schedule, obtaining an intensification of treatment; b) the introduction of a neoadjuvant chemotherapy concept for patients with liver metastases, unresectable at time of diagnosis; c) the development of models of new psychological interventions for patients with metastasis; d) the evaluation of the role of circadian rhythms as an independent prognostic factor in patients with advanced disease. Currently the activity of the chronotherapy centers has been institutionalized within the EORTC Cronotherapy Group that include more than 40 centers in Europe, Canada and Israel. was based on Participation in the European multicenter study EORTC 05011 (of which our Division is the coordinating center), centered on the treatment of colorectal cancer as first line that consists of the chronomodulated infusion of 4 drugs, CPT-11, 5-FU, FA and L-OHP in patients randomized

to receive Irinotecan according to 6 different peaks of infusion to evaluate the time of better tolerability of this drug. More than 166 patients have been randomized up to now in Europe. The development of this study arose from our previous experience in animals and in humans, published on BJC on 2002 and 2003. In the first of these two studies, run in collaboration with Villejuif (France), the synergism between CPT-11 and L-OHP was evaluated in animals having a transplanted tumor with sensitivity to both drugs. In the second study pre-treated patients received L-OHP, 5-FU and FA in chronomodulated infusion and CPT-11 in i.v. 90 minute infusions showing tolerability of the triplet combination. The development of the triplet combination, all three active drugs 5-Fluorouracil, Oxaliplatin and Irinotecan, given concomitantly represents one the ways to increase activity and allows more resections for liver metastases from colorectal cancer after neoadjuvant chemotherapy.
Highly pretreated patients are the objective of a phase II experience with Mytomicin C plus chronomodulated oral Capecitabine given in a chronomodulated way (20% of total dose in the morning and 80% of dose in the evening). Regarding adjuvant chemotherapy of colorectal cancer, the protocol of our Institute for patients with Dukes B2/C stage of colorectal cancer based on the biological determination of tumor aggressiveness was closed to patient entry.
Patients with extraperitoneal locally advanced T 3-4, anyN, M0 rectal cancer are candidate for a protocol of neoadjuvant radio-chemotherapy (Plafur vs Tomox plus RT) in collaboration with the Radiotherapy and Surgical Divisions. Moreover we 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 a chemotherapic regimen with L-OHP in the presence of G3 neuropathy.
A new study on the use of Low-weight- molecular Eparine is starting with the primary objective to reduce the incidence of deep venous thrombosis.

Other diseases.

The international randomized phase III trial started in 2002, in which patients affected by advanced untreated pancreatic carcinoma underwent standard Gemcitabine chemotherapy versus the experimental combination of Gemcitabine plus Pemetrexed, has been successfully presented at the American Society of Clinical Oncology Annual Meeting held in New Orleans (USA). Our center enrolled the largest number of patients in Italy. A paper is being prepared by the scientific writing board. During 2004, patients affected by advanced untreated pancreatic carcinoma were enrolled in a Institutional phase II trial designed and coordinated by the Medical Oncology "A" Division, in which Gemcitabine FDR (10 mg/m2/min) was delivered in patients affected by advanced untreated pancreatic carcinoma. Furthermore, the pilot study with 5-fluoruracil in continuous infusion in combination with the selective COX-2 inhibitor Celecoxib in pretreated patients (designed and coordinated by the Medical Oncology "A" Division), has recently been published.
Given the fact that in today's evidence-based medicine, the greatest contribution to healthcare changes is provided by recommendations from large randomized clinical trials (RCTs) or meta-analyses, our Division has started a research plan in this methodological field. The experience developed by our investigators in collaboration with Columbia University of New York 3 years ago, has become a clinical project in our Institution, involving a panel of medical doctors and statisticians coming from the Divisions of Medical Oncology "C" and "A" as well as the Biostatistic Unit. A method to pool results from conflicting and controversial data from randomized clinical trials, has been developed. The issues involved were: the use of taxanes in first line chemotherapy for metastatic breast cancer and their role in the neoadjuvant approach and adjuvant chemotherapy for non small cell lung cancer. The results of such analyses have been successfully presented at major meetings (the American Society of Clinical Oncology and the European Society for Medical Oncology), and the first paper has been accepted for publication.

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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 the same university, where she was an 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 chemotherapy, Hopital S. Louis, Paris,
Dr Petti is Professor at La Sapienza University and the Biomedico Campus, 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.

Staff:
ANDREA MENGARELLI - MD
FRANCESCO PISANI - MD
ATELDA ROMANO - MD
ANTONIO SPADEA - MD
PAOLA ANTICOLI BORGIA - MD Fellow
FRANCESCA PALOMBI - MD Fellow

Areas of Research Interest:

Biology of acute leukemias, myeloproliferative disorders and myelodysplastic syndromes.
Clinical trials on the role of chemothrapies, BRM's, differentiative agents and growth factors in leukemias, lymphoproliferative and myeloproliferative disorders, myelodysplastic syndromes.

Activities 2004

The efforts of our Unit (S.C. Ematologia) in 2004 was aimed at carrying out clinical trials of primary relevance in different hematological malignancies working in cooperation with other hematological institutions. In particular, our Unit is member of the following cooperative group:

- Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA)
- The European Organization for Research and Treatment of Cancer (EORTC)
- Italian Cooperative Study Group on Chronic Myeloid Leukemia (ICSG on CML)
- Non-Hodgkin Lymphoma Cooperative Study Group (NHLCSG)
- Intergruppo Italiano Linfomi (ILL)
- Italian Multiple Myeloma Study Group (IMMSG)

As a consequence, we report here data on the most relevant studies in which our Unit is involved.
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 the identification, in collaboration with the Spanish PETHEMA group, of distinct prognostic categories among APL patients receiving AIDA-like therapies, the GIMEMA cooperative group designed a new protocol named AIDA 2000 in which the intensity of post-remission treatment was adapted to 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 schedule, 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.
The results of this trial have been presented at the 2004 ASH meeting in San Diego, California (December 4-7, 2004): in line with recent PETHEMA results, our data confirm that anthracycline-based consolidation is equally effective as Cytarabine-containing regimens for patients with low and intermediate-risk and suggest that a risk-adapted strategy including ATRA for consolidation provides an outcome improvement in newly diagnosed APL. In addition, our results suggest a benefit in terms of relapse rate reduction using Cytarabine coupled to anthracyclines and ATRA during consolidation in the high-risk group.
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 (Carmosino I et al., Haematologica 89 (5):613-7,2004) 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 from 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.
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 achievable by 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 detect a superior arm.

All patients with an identical HLA 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 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 response) 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 plan of investigation; however, clinical data on both of the protocols are not yet available.

In newly diagnosed multiple myeloma (MM) patients, the combination Melphalan, Prednisone and Thalidomide (MPT) induces a fast tumor response with a high complete remission rate. In a prospective randomized trial the Italian Multiple Myeloma Study Group (IMMSG) compare the efficacy and toxicity of oral MPT and MP: an interim analysis was conducted after the first 200 patients, median age 72 years (range 56-85), and was presented at the 2004 ASH meeting held in San Diego, California on December 4-7, 2004.

The response rate among patients who received MPT was: 25.9% CR, 5.5% near-CR, 48.2% PR, 9.3% SD and 11.1% PD; the response rate after MP was 4.2% CR, 0% near-CR, 43.6% PR, 23% SD and 29.2% PD. Response was followed by significant improvement of performance status, skeletal pain, anemia and transfusion requirement. The Event Free Survival (EFS) at 26 months was 67.8% for MPT and 32.4% for MP; the median Overall Survival has not been reached. These preliminary data allow us to conclude that MPT significantly improves response rate and EFS in elderly myeloma patients with a median age of 2 years.

Radiolabeled antibodies may be particularly effective in treating non-Hodgkin's lymphomas (NHL) for the following reasons: lymphocytes and lymphoma cells are inherently sensitive to radiotherapy; the local emission of ionizing radiation by radiolabeled antibodies can kill cells with or without the target antigen being in close proximity to the bound antibody; and penetrating radiation may obviate the problem of limited access in bulky or poorly vascularized tumors.

The immunoglobulin Ibritumomab is the murine parent IgG, kappa monoclonal antibody of Rituximab which also target the CD20 antigen. Ibritumomab is covalently linked to the Tiuxetan chelate and radiolabeled with 90Yttrium. To optimize bio-distribution, Rituximab is given prior to the radiolabeled antibody in order to deplete all normal circulating B-cells and thereby avoid non-targeted radiation.

A phase I dose-escalation study of 90Y-ibritumomab Tiuxetan was performed in 17 patients with refractory low- or intermediate-grade B-cell lymphoma. Tumor response was seen at all dose levels with an overall response rate of 64%.

One hundred and forty three patients with relapsed or refractory, low-grade, follicular, or transformed CD20+ B-cell NHL were enrolled in a prospective randomized trial comparing 90Y-Ibritumomab Tiuxetan to a standard course of Rituximab. The overall response rate was 80% in the 90Y-Ibritumomab Tiuxetan group and 44% in the Rituximab group, while the complete response rates were 21% and 7%, respectively. These results prompted

us to participate in a prospective, multicenter, multinational, randomized phase III clinical trial aimed at determining the efficacy and safety of subsequent treatment with a single course of 90Y-Ibritumomab Tiuxetan given at a dose of 0.4 mCi/kg versus no further treatment in patients with stage III or IV follicular NHL who are in PR or CR after first line remission induction chemotherapy. The study (350 patients planned to be enrolled) is now closed to enrollment: data on safety and efficacy are not yet available.

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Impact of a new dosing regimen of epoietin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome.

Ann.Hematol. 2004 Nov.30 *I.F. 1.241*

Division of radiotherapy

DIRECTOR:
GIORGIO ARCANGELI, MD

Prof. G. Arcangeli received his MD degree in 1965. He specialized in Gastroenterology in 1967, at the 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. Medical and Scientific Research in Rome and from 1985 to 1996 of the Department of Radiotherapy Ospedale S. Maria Goretti in Latina. Since 1996 he has been the head of the Department of Radiation Oncology of the 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: The American Society of Clinical Oncology (ASCO); The American Society of Therapeutic Radiology and Oncology (ASTRO); The American Radium Society (ARS); The European Society for Hyperthermic Oncology (ESHO); The European Society for Therapeutic Radiology and Oncology (ESTRO); Soc. Italiana per le Ricerche sulle radiazioni (SIRR); EORTC Radiotherapy Group; The New York Academy of Sciences; Ass. Italiana di Oncologia Medica (AIOM); Soc. Medica per il Lazio; Ass. Italiana di Radioterapia Oncologica.

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.

Staff:

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

Time limited contract physician:
SARA GOMELLINI - MD

Physicians in training:
BENASSI MICHAELA
CERVO EMANUELE
FARELLA ANTONIO
GIORDANO CAROLINA
MESSINA MAURO
PARRETTA TERESA
VACCARO CATERINA

Activities 2004

The recent installation of high technology equipment in our division allowed us to start several clinical studies to implement and validate new radiation therapy techniques in the treatment of various cancer sites.

IORT STUDIES: this technique was implemented thanks to a dedicated movable 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 prostatic cancer who have undergone 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 ob-

served, 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 coordination 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 objectives of this study are to evaluate the local recurrence rate and secondary ipsilateral tumors, as well as the local recurrence free interval. Seventy five patients have been accrued in this studies (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 allows 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 thanks to the limited dose penetrance of typical electrons.
The goal of our study is to evaluate the feasibility and eventual side effects of this modality used to boost the dose on the tumor bed in patients with locally advanced tumors (>T3 or >N2) of the oral cavity, oropharynx, hypopharynx and larinx, who undergo resection with curative intent. Standard post operative 3D wide radiation field therapy will follow for all the patients.
The protocol has been 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 recurring 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 external beam cannot be used with curative doses because of the limiting tolerance of the organ at risk.
Similarly to the previous protocol, IORT is used at the end of the resection with intent 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. Six patients have been enrolled in the study and 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 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, through a patient filled questionnaire, and objectively, with the collection of the saliva before and up to 12 months after the end of the treatment, 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.

Twelve 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 Divisions, has already been conducted in our institution 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 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 objectives of this study are the evaluations 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 antiCox 2 vs standard treatment to reduce acute and late side effects of radiation therapy 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 thereafter. The aim of the study is to evaluate the eventual reduction of acute and late rectal and genital/urinary side effects.

The ethical committee approved the protocol and patients accrual started in 2004.

BREAST CANCER:

Prospective phase III randomized study of immediate versus delayed radiotherapy in patients who have undergone 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 and ended in December 2003, after the accrual of 207 patients and 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 measurements of the irradiated lung in the postoperative treatment of breast cancer

The objectives of the study are to look for 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. 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 multi-center 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 down-staging ability of the chemo-radiotherapy combinations. Eighteen patients have been 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 metastases 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 using the VAS score and the Barthel index which fraction is more effective in decreasing or eliminating the symptom.

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 is 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/day. 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 with that schedule of treatment there have been no major toxicities, in the last three patients the 175 mg/mq dose was extended for 6 weeks. The study is ongoing.

Publications 2004

Danesi D.T., Arcangeli G., Cruciani E., Altavista P., Mecozzi A., Saracino B., Orefici F.

Conservative treatment of invasive bladder carcinoma by transurethral resection, protracted intravenous infusion chemotherapy, and hyperfractionated radiotherapy: long term results.

Cancer. 2004 Dec 1;101(11):2540-8. *I.F. 4.017*

Fabi A., Vidiri A., Carapella C., Pace A., Occhipinti E., Caroli F., Mirri A., Carlini P., Cognetti F.

Bone metastasis from glioblastoma multiforme without central nervous system relapse: a case report.

Anticancer Res. 2004 Jul-Aug;24(4):2563-5. *I.F. 1.347*

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 held the rank of Second Lieutenant MedicaI 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 was given the position of Senior Radiologist, and then in November 1999 he took on a five year appointment as Consultant Radiologist. He specialized in Radiology (Diagnostic, Radiotherapy, Nuclear Medicine) in 1981 and in Oncology in 1988 at La Sapienza University, Rome. He lectured in Diagnostic Radiology at Tor Vergata University from 1990-91, 1991-92, 1993-94. He has participated in many professional refresher courses, congresses and seminars and was responsible for the CNR ACRO research project in Instrumental Diagnosis *Clinical applications of oncological research*. He is the author of numerous publications.

Staff:
LAURA ANGELONE - MD
STEFANO CANITANO - MD
LIVIO CARPANESE - MD
MAURO CATERINO - MD
CARLO DE MUTIIS - MD
FRANCESCA ROMANA FERRANTI - MD
SALVATORE GIUNTA - MD
MARCELLO GRECO - MD
RAMY KYAL - MD
ANNELISA MARSELLA - MD
ANTONIETTA MAZZONE - MD
GIUSEPPE PIZZI - MD
ELENA SARACCA - MD
MIRELLA TERAMO - MD
GIULIO VALLATI - MD
ANTONELLO VIDIRI - MD

Activities 2004

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 2004 approximately 65,000 radiological examination were carried out.

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 spiraI 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 measurements (in particular in lesions with irregular edges). Since November 2003, our Radiology Service has been taking part in an Italian multicenter study promoted by SIRM (the Italian Society of Medical Radiology), aimed at identifying hepatic metastasis through echothomographic contrast medium, conducted on 18 groups, selected from 50 university and hospital centers.

Specific studies on hepatic metastases in colorectal disease are being carried out on patients treated with different chemotherapeutics agents, concerning the drugs used and the administration method, such as bolus, or 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. San toro.
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. Prof. Franceso Cognetti was the Scientific Director of the project and Dr Marcello Crecco was in charge of the Operative Unit Service. The project was initiated by the Ministry for Health and was concluded during 2004.
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 85 procedures with stereotassic biopsies with Mammotome.

Neuroradiology - Head and Neck Imaging

The study on the evaluation of early-MR of the glial tumors (GBM and anaplastic astrocitomas) is drawing to a close. The purpose of this study has been to compare the results obtained with early-MR and those of Progression Free Survival (PFS) and Survival time (S) in order to define the role of early-MR in the evaluation of surgical resection in patients affected by malignant gliomas. Forty seven patients have been enrolled in the study. The present data has shown a good correlation between early-MR findings, PFS and S. Early-MR can reduce the mistakes of post-surgical treatment and represents a good baseline for the evaluation of radio-chemotherapy treatment, and may be considered an accurate technique for monitoring the surgical resection of malignant gliomas.
In collaboration with the Department of Neurosurgery, Radiotherapy, Neurology Clinical Oncology A and Histology two studies are underway regarding the evaluation of CT-Perfusion in the evaluation of malignant glial tumors and metastases; CT-perfusion has been utilized to evaluate microvascular characteristics of brain tumors, with the aim of contributing to the non-invasive assessment of tumor malignancy grading, and the effects of monitoring treatment, particularly radiation necrosis. In this study, 5 patients have been enrolled for glial tumors as well as 19 patients for metastases. The results have been compared to FDG PET and SPECT scans and subsequent surgical specimens in patients have undergone surgery.
A study is underway in collaboration with the Department of Neurosurgery, Radiotherapy, Neurology and Clinical Oncology A regarding the evaluation with MR in patients treated with combined radiotherapy and extended infusion of Gemcitabine in the treatment of GBM.
A study in collaboration with the Department of Radiotherapy is underway regarding

the fusion of MR and CT stereotactic imaging in glial brain tumors with the aim of obtaining more precise and limited irradiation fields and 36 patients have been enrolled in the study. Another study of the fusion of MR and CT stereotactic imaging is underway to evaluate nasopharynx tumors.
A study in collaboration with the Department of Maxillo-Facial Surgery and Histology is underway regarding the comparative evaluation of the clinical, MR and pathological data regarding T Stage tumors of the oral cavity and base of the tongue and 26 patients have been enrolled in the study. Another study regarding the correlation between clinical, CT, MR and pathological data in the evaluation of the involvement of the mandible is underway and 15 patients have been enrolled.

Angiography Imaging and Interventional Radiology

Percutaneous tumor ablation with radio frequency.

In 2004, following current trends and technological and material developments, patients with inoperable lung and renal tumors were enrolled in a 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 c stents were routinely performed, such as treatment with self expandable metallic stents in malignant bilary obstruction in patients with contraindications for surgery
During the last year in cooperation with the Urology Department, a new therapeutic approach to kidney neoplasms of small dimensions and detected in the periferic portion has been achieved Videolaparoscopic treatment of these neoplasms, which were previously embolized through trans-arterial (OK) supereselective catheterism, was performed in a selected group of patients.
Angiographic trans-arterial embolization of small kidney hypervascularized tumors, allows the ischemic treatment of neoplasia, associated with a devascularization of the surrounding parenchyma.
Subsequent reduction of hemorrhagic complications and reduced operative time, encouraged intervention such as this to be performed, in single kidney patients with conservative postoperative clear renal function.
Thanks to this surgical intervention a 100% technical success was achieved in 30 pts total, average age 69 years.
In 21 cases with renal cell carcinoma no recurrence was reported during mean follow up (6 months).
Further prolongation of follow up, looks necessary to validate this kind of technique, which is no longer routinely performed in other clinical centers around the world.

Urologic and Gynecologic Imaging

In 2004 the interdisciplinary prostate work group coordinated by Prof. Arcangeli as already mentioned in 2003 has continued to optimize radiotherapy for prostate carcinoma with conformation techniques. Diagnostic radiology in the detection of nodules and grading use a multicore method with transrectal echothomography, which allows for a large number of prostatic biopsy samples (up to 20) with a greater accuracy.
With CDUS we are evaluating the vascularization of the prostate and the rectal wall before and after radiotherapy in order to study its modifications.
A trial regarding the study of the T stage of bladder tumors with spiral CT with air instillation (forse!) was concluded. Another study for the evaluation of cervical tumors before and after chemo-radiation therapy with MR is ongoing.
A new study has begun in patients affected by endometrial cancer. These patients undergo careful RM and TVUS study in order to perform more conservative surgery.
We are monitoring active protocols to study different therapies in patients affected by advanced renal cell carcinoma.

Thoracic Imaging

To date a study *Low dose spiraI CT in the early diagnosis of lung cancer in patients at risk* has enrolled 804 patients; 307 patients have undergone first annual repeat screening and 108 have undergone second annual repeat screening, moreover 257 follow-up (not annual repeat) examinations have been done in this year.

Eighteen NSCLC (2.2 %) were detected, 17 of these at baseline (2.1%) and 1 (0.36%) at annual repeat screening. Ten of the cancers detected were at stage I A, some at IB, two at II B, two at III A, two al III B and one at IV.

The study is part of I-ELCAP (International Lung Cancer Action Program).

In an additional CAD study of pulmonary nodules, 87 cases evaluated with a Siemens prototype system, showed a 50% sensitivity of radiological reading alone, while radiological reading + CAD had a 97% sensitivity. Recently a comparative study between endoscopic colonoscopy and virtual colonoscopy with Low-dose spiral CT has been initiated. This method can be suggested in incomplete colonoscopy, insurmountable narrowing lesion and in the staging the colorectal cancer.

The method showed an high specificity (95%), for polyps > 1 cm.

Publications 2004

Fabi A., Vidiri A., Carapella C., Pace A., Occhipinti E., Caroli F., Mirri A., Carlini P., Cognetti F.

Bone metastasis from glioblastoma multiforme without central nervous system relapse: a case report.

Anticancer Res. 2004 Jul-Aug;24(4):2563-5. *I.F. 1.347*

Guadagni F., Ferroni P., Basili S., Facciolo F., Carlini S., Crecco M., Martini F., Spila A., D'alessandro R., Aloe S., Cerasoli V., Del Monte G., Mariotti S., Mineo T.C., Roselli M.

Correlation between tumor necrosis factor-alpha and d-dimer levels in non-small cell lung cancer patients.

Lung Cancer. 2004 Jun;44(3):303-10. *I.F. 1.798*

Pompili A., Caroli F., Cattani F., Crecco M., Giovannetti M., Raus L., Telera S., Vidiri A., Occhipinti E.

Unilateral limited laminectomy as the approach of choice for the removal of thoracolumbar neurofibromas.

Spine. 2004 Aug 1;29(15):1698-702. *I.F. 2.676*

Salesi N., Fabi A., Di Cocco B., Marandino F., Pizzi G., Vecchione A., Cognetti F.

Testis metastasis as an initial manifestation of an occult gastrointestinal cancer.

Anticancer Res. 2004 Mar-Apr;24(2C):1093-6. *I.F. 1.347*

Vidiri A., Carpanese L., Annibale MD, Caterino M., Cosimelli M., Zeuli M., David V., Crecco M.

Evaluation of hepatic metastases from colorectal carcinoma with MR-superparamagnetic iron oxide.

J Exp Clin Cancer Res. 2004 Mar;23(1):53-60. *I.F. 0.574*

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 has led to over 350 publications with over 95 published in international peer-reviewed journals.
From 1992 he developed and organized the Nuclear Medicine Division of the Regina Elena 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 clinical practice.

Staff:
ROSA SCIUTO - MD Deputy Director and Head of Radiometabolic Therapy Unit
SERENELLA BERGOMI - MD Assistant
ANNA FESTA - MD Assistant
ROSELLA PASQUALONI - MD Assistant
GERMANA A. PETRILLI - MD Assistant
SANDRA REA - MD Assistant
ALESSANDRO SEMPREBENE - MD Assistant
ANNA TOFANI - MD Assistant
LUISA ROMANO - MD Assistant
GIANLUCA LOPES - Chief Technician
NICOLA CANNIZZO - Head Nurse

Activities 2004

The activities of Nuclear Medicine Division are focused on clinical research oriented to therapy and diagnostics. Therapy includes radionuclide treatment of thyroid carcinoma, neuroblastoma, pain from bone metastase, neuroendocrine tumors and lymphoma. Diagnostics includes, besides routine oncological studies, radioreceptorial scintigraphy with 111In-octreotide and 99mTc-depreotide, sentinel node mapping, cardiac gated-SPET and neurological DAT scanning. In 2004 a total of 21,000 therapeutic and diagnostic procedure were performed with more than 470 cancer radionuclide treatments.

1. ROLE OF ADJUVANT RADIOIODINE THERAPY IN DIFFERENTIATED THYROID CANCER: A RETROSPECTIVE ANALYSIS ON A SERIES OF 1,500 PATIENTS

Our main clinical and research interest from 1992 until today has been focused on thyroid cancer management and the role of radioiodine therapy role. 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 1,500 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 under treatment.
- radioiodine therapy improves recurrence rate and specific cancer mortality in both low-risk and high risk patients.

These data, partially published, are currently submitted to publication in a more extensive

analysis. In addition our personal experience has been formalized in the *I.R.E. Guidelines for differentiated thyroid cancer management*.

2. Valuation of the cost-effectiveness of recombinant human TSH in thyroid cancer follow-up

The wide experience in the use of recombinant human TSH obtained in over 450 patients followed at our Institution for differentiated thyroid cancer has 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 from late 1992 for bone metastases performed with all three available bone seeking radioisotopes (89Sr; 186Re; 153Sm) 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 to clarify clinical indications using standard procedures and explore innovative strategies by a series of clinical trials. In particular, in 2004 the results published were, a review of on 153Sm-EDTMP use in breast cancer and a radiation protection plan for national guideline purposes.

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 to be 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 computed tomography (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 in 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 90Y-DOTATOC.

Our Division is 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. Radioreceptorial therapy of neuro-endocrine tumours (NET) using 111-In-OCT

Radioreceptprial therapy with 111-In-OCT has been performed in a selected numbers of neurodocrine tumors (medullar thyroid carcinoma and Merkel tumors). Preliminary results and dosimetric evaluations demonstrated that this innovative therapy is safe and feasible while efficacy is currently under evaluation.

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

Imaging with specific single photon positron emission computerized tomography (SPET) 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 setting 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 to evaluate the integrity of the nigro-striatal dopaminergic pathway and to differentiate ET from PD-AP.

7. Efficacy of ^{99}m Tc-depreotide scintigraphy in the evaluation of solitary pulmonary nodules

^{99}m 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 methods to in vivo characterization of lung nodes avoiding unnecessary biopsies.

8. 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 is 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 2004

Maini C.L., Bergomi S., Romano L., Sciuto R.

153Sm-EDTMP for bone pain palliation in skeletal metastases.

Eur J Nucl Med Mol Imaging. 2004 Jun;31 Suppl 1:S171-8 *I.F.3.324*

Laboratory of Clinical Pathology

DIRECTOR:
FIORELLA GUADAGNI, MD

Fiorella Guadagni received her MD 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 - MD, PhD
LAURA CONTI - MD, PhD
ANNA CIANCIULLI - PhD
ANNAMARIA FRASCA - MD
GIOVANNA DIGIESI - MD
GABRIELLA D'ALESSANDRO - PhD
CLAUDIA GRECO - PhD
IMMACOLATA CONCETTA ROSITO - PhD
GAETANO VITELLI - MD
GIOVANNI CIGLIANA - PhD
GIOVANNI CATALANI - PhD
RAFFAELE PALMIROTTA - MD, PhD
CARMINE PARRACINO - MD
SPILA ANTONELLA - PhD Fellow
D'ALESSANDRO ROBERTA - PhD Fellow
VERCILLO GIUSEPPE - MD Fellow
MEROLA ROBERTA - PhD Fellow
ORLANDI GIULIA - PhD Fellow

Activities 2004

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 2004 include:
The evaluation of haemostatic abnormalities in cancer patients. In fact, haemostatic abnormalities can be found in more than 90% of cancer patients, regardless of the presence or absence of clinical evidence for thromboembolic disease, and there is reason to believe that these abnormalities contribute substantially to solid tumor organization, demarcation

of tumor from normal host tissues, regulation of inflammatory cell accumulation, tumor angiogenesis and tumor stroma generation.

Tumor-induced platelet activation may cause the release of various cytokines, including CD40 ligand (CD40L). Activation of the CD40/CD40L pathway in human tumors may result in thrombin generation, which is known to be involved in angiogenesis. Thus, we investigated whether soluble (s)CD40L levels are increased in patients with lung cancer as a result of platelet and/or coagulation activation. Despite recent evidence that activation of the CD40/CD40L pathway may enhance the procoagulant activity of certain tumor cells, no clinical evidence is yet available linking platelet and/or coagulation to sCD40L production *in vivo*. The study below reported is the first to demonstrate that elevated sCD40L levels can be found in patients with lung cancer compared with control subjects of similar age and gender. Citrated plasma samples were obtained from 120 patients with different stages and histotypes of lung cancer and 60 age- and sex-matched control subjects. sCD40L, sP-selectin (marker of platelet activation), prothrombin fragment 1 + 2, and thrombin-antithrombin III complex levels (both markers of coagulative activation) were measured in all samples. The results obtained demonstrated that patients with lung cancer had median sCD40L levels higher than in control subjects (0.46 *versus* 0.13 ng/ml; $P < 0.0001$), although correlation with the stage of disease was not evident. Nonetheless, sCD40L levels were significantly higher in squamous cancer compared with adenocarcinoma (0.75 *versus* 0.27 ng/ml; $P < 0.05$). Moreover, median sCD40L levels were higher in stage IV compared with non-metastatic squamous lung cancer (1.02 *versus* 0.61 ng/ ml; $P < 0.05$). sCD40L levels significantly correlated with sP-selectin ($P < 0.001$), prothrombin fragment 1 + 2 ($P < 0.001$), or thrombin-antithrombin III complex ($P < 0.05$) in squamous lung cancer, but only sP-selectin ($P = 0.011$) was independently related to sCD40L. In conclusion, these findings indicate that elevated sCD40L levels can be preferentially found in patients with advanced squamous cancer and provide evidence that increased levels of this cytokine are associated to the occurrence of *in vivo* platelet activation. Better knowledge of CD40/CD40L activation in human cancer will help to improve our understanding of the pathophysiological significance of tumor-induced coagulopathies and may prompt investigators to develop novel strategies against blood-born metastasis.

Although a number of studies have found an association between fibrinolysis and non-small cell lung cancer (NSCLC), this relationship is by no means completely understood. Indeed, significant elevation in the blood concentrations of the split product from cross-linked fibrin, d-dimer, was found in lung cancer patients, with either extensive or limited disease, suggesting that a sub-clinical activation of blood coagulation and fibrinolysis can occur in NSCLC from the early clinical stages of disease. Despite these studies, the origin of the activation of fibrinolysis in NSCLC is still unclear. Moreover, it is well known that tumor cells may produce inflammatory cytokines such as IL-6 and TNF-a and that the release of inflammatory cytokines is involved in activation of the fibrinolitic/coagulative system**.** Thus, we analyzed the possible association between TNF-a, IL-6 and coagulation (Thrombin—antithrombin, TATc) or fibrinolysis (D-dimer) activation in NSCLC patients. One hundred thirty patients with NSCLC ($n = 65$; adenocarcinoma $n = 32$, squamous cancer $n = 33$) or chronic obstructive pulmonary disease (COPD) ($n = 65$) were studied. As control group 65 healthy donors were also evaluated. The results obtained showed that median D-dimer levels were higher in NSCLC patients (3.0 mg/ml) compared either to COPD patients (1.1mg/ml, $P < 0.05$) or controls (0.3mg/ml, $P < 0.0001$). Positive TNF-a levels (>10 pg/ml) were found in 26% of NSCLC compared to 3% of COPD ($P < 0.002$) and 5% of controls ($P < 0.0005$). On the other hand, positive (>8.5 pg/ml) IL-6 levels were found in 53% of NSCLC and 21% of COPD patients, compared to 5% of control subjects ($P < 0.001$). Median TATc levels were elevated in either NSCLC (6.9 mg/l) or COPD (5.7mg/l) patients compared to controls (1.8mg/l, $P < 0.0001$). Elevated D-dimer levels were significantly associated to positive TNF-a levels in patients without distant metastasis ($F = 4.3$, $P < 0.05$). Moreover, TNF-a levels ($P < 0.01$) were independently related to the presence of positive D-dimer levels in patients with non-

metastatic NSCLC. These results suggest that increased levels of TNF-a might be responsible for the activation of fibrinolysis in patients with NSCLC.
In conclusion, the present study confirms previously published observation that NSCLC causes a profound alteration in fibrinolysis and suggests that TNF-a could be, at least in part, responsible for the increased d-dimer levels found in this malignant disease. There have been no other reports of such an association between TNF-a and D-dimer levels in NSCLC, but our results suggest that the increases D-dimer levels might account for a primary activation of fibrinolysis by TNF-a in the early stages of NSCLC. Better knowledge of the biologic effects of TNF-a in human cancer will help to improve our understanding of the pathophysiological significance of tumor-induced coagulopathies.
Human angiogenin was the first angiogenic protein to be isolated from a human tumor and was characterized on the basis of its ability to induce neovascularization. The association between angiogenin and cancer progression and poor outcome in solid tumors has been documented, but its significance in leukemia has not been evaluated.
Moreover results of several recent studies have suggested that increased angiogenesis might be important in the pathophysiology of a number of hematological malignancies. Angiogenesis is also involved in the pathogenesis of B-cell chronic lymphocytic leukemia (CLL), and its clinico-prognostic relevance has been demonstrated in patients with early disease. As a matter of fact, low cellular and high serum levels of the angiogenic vascular endothelial growth factor (VEGF) agree with poor clinical outcome and elevated pre-treatment cellular levels of the angiogenic basic fibroblast growth factor (FGF-2) correlate with a more advanced clinical stage and resistance to Fludarabine.
The clinical significance of angiogenin was mainly evaluated in acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). Higher angiogenin levels were found in AML and MDS patients and such a finding correlated with a prolonged survival period.
Our study is the first to address the clinical significance of angiogenin in B-cell chronic lymphocytic leukemia (CLL). We measured serum angiogenin levels in patients previously untreated Binet stage A B-cell CLL patients. In addition, we explored whether changes of circulating levels of angiogenin reflect features of increased angiogenesis such as bone marrow (BM) microvessel area and serum levels of the VEGF and the FGF-2. Finally, angiogenin was investigated as an indicator of disease progression (DP) of stage A patients.
No difference in angiogenin serum levels could be found between patients and sex-matched healthy controls. In addition angiogenin did not reflect the extent of bone marrow(BM) angiogenesis as evaluated by microvessel area, circulating levels of VEGF and FGF-2.
The finding of a correlation between high angiogenin levels and prolonged progression-free survival (PFS) times is in agreement with the results obtained in AML, but contrasts with those obtained in solid tumors. Angiogenin in addition to its potent angiogenic activity has weak Rnase activity, which shows a 35% homology with pancreatic Rnase. It is speculated that high serum levels of angiogenin might influence clinical outcome of AML by higher Rnase activity, which causes inhibition of protein synthesis in circulating malignant cells. In contrast, in solid tumors the concentration of angiogenin present at the level of tumor environment is lower than in the blood thus losing its significance in terms of Rnase activity.
In conclusion, our study demonstrated that serum angiogenin levels although not increased in comparison with healthy controls, may predict clinical outcome of patients with early CLL and help to refine Rai's stratification. Given the absence of standardized methods for its measurement and reliable cut-off, the evaluation of angiogenin serum levels should not be considered standard practice in CLL but, as shown in the present paper, might be used for the assessment of prognosis of individual patients with early disease.
Recent research interests have been broadened to include the investigation of molecular markers such as, the mismatch repair system (MMR) and cytogenetic markers with the aim of identifying molecular targets of therapy.
Hereditary non polyposis colorectal cancer (HNPCC) is the most frequent autosomal

dominant form of predisposition to colorectal cancer and is widely considered a syndrome of deficient mismatch repair (MMR). A limiting factor in the identification of pathogenic mutations is the heterogeneous genetics of HNPCC, which involves at least six different genes implicated in MMR. Furthermore, additional genes (related or unrelated to MMR) might be involved in the pathogenesis of HNPCC. Thus, identification of phenotypic criteria predictive for germline mutations in MMR genes (*e.g.*, Amsterdam criteria I and II, or Bethesda criteria) may be helpful in efficient HNPCC genetic testing. Using a complementary approach based on tumor microsatellite instability (MSI) analysis, we confirmed that the Amsterdam criteria perform significantly better than the Bethesda criteria in predicting families with MSI-H tumors (P=0.0227). Our results also suggested that a cut off at <50 year's mean age at diagnosis of HNPCC-related cancers (especially colorectal and endometrial cancer) may be an additional tool for the identification of families with defective MMR. In particular, when we stratified our HNPCC families according to a mean age cut off of 50 years at cancer diagnosis, nearly all families with mean age at colorectal cancer diagnosis < 50 years had MSI-H (MSI High) tumors while most families with mean age ‡ 50 years displayed MSS (Microsatellite Stability) tumors (P=0.0201). When mean ages at endometrial and colorectal cancer diagnosis were considered together, we observed similar findings at a higher level of significance (P=0.0023). These results indicate that clinical selection criteria based upon a mean age at colorectal or endometrial and colorectal cancer diagnosis < 50 years identify families with MSI-H tumors significantly better than at a mean age > 50. Furthermore, in our study we observed that all MSI-H families and half of the families with MSS phenotype met the Amsterdam criteria, whereas the families fulfilling the Bethesda criteria in our series had MSS tumors (P=0.0227). This result also confirms that the Amsterdam criteria perform significantly better than the Bethesda criteria in predicting families with MSI-H tumors. Based on our results, the Amsterdam criteria appear to be more sensitive, but less specific than a mean age cut off at 50 years for identifying families with MSI-H tumors. In this perspective, a mean age cut off at 50 years may be an additional clinical selection tool to complement the Amsterdam criteria.

Our results indicate that fulfillment of the Amsterdam criteria and young mean age at colorectal cancer diagnosis correlate with MSI-H molecular phenotype in HNPCC. We conclude that identification of phenotypic characteristics and molecular markers predictive of genotype should significantly improve the efficiency and utility of mutational analysis. Moreover, these clinical and molecular tools might help to identify series of candidate families in the search for novel HNPCC-related genes.

Among chromosome defects in colon cancer, deletions in 1p, 17p, and 18q have been reported as frequent events. Therefore, 1p, 17p, and 18q aneusomy in 60 colorectal cancers and their surrounding mucosa by means of fluorescence in situ hybridization (FISH) have been analyzed. We also evaluated *ERBB2* gene (alias *HER-2/neu*) amplification in a subset of tumors. The genetic picture in tumors was correlated with chromosomal alterations in normal colonic mucosa, as well as with clinicopathologic variables. A population of cells in morphologically normal epithelium possesses genetic aberrations common to those in colon cancer, although in different percentages. No significant differences emerged in terms of fraction of nuclei with 17p monosomy between primary tumors and distal normal mucosal samples. Of tumor samples aneusomic for the three chromosomes, 58.3% also showed aneusomy in related normal colonic mucosa. In neoplastic samples, significant correlation existed between 1p aneusomy and mucosal component ($P = 0.007$), between 17p aneusomy and increased depth of invasion (T3–T4) (P _ 0.05), and between 18q aneusomy and tumor site ($P = 0.03$). None of the evaluated samples, neoplastic or normal, showed *ERBB2* gene amplification. In conclusion, the data obtained in our study suggest that general genetic instability is already present in the colonic epithelium at the time of tumor occurrence and that clinical application of molecular genetics can be expected to help the clinician in stratifying patients and to supplement standard clinicopathological staging.

Converging points of evidence implicate infection by high-risk HPV types as a critical aetiological factor in cervical tumorigenesis. However, epidemiological and experimental data show that only a small fraction of HPV-infected squamous intraepithelial lesions progress to invasive cervical carcinoma. However, the positive predictive value of HPV testing is limited, especially in young sexually active women, among whom transient innocuous infections are very common. These findings suggest that somatic genetic mutations play a critical role in the initiation and progression of cervical carcinoma. Delineation of these genetic changes is crucial in obtaining an understanding of the molecular basis of cervical carcinoma. Premalignant lesions of the uterine cervix represent a pathological continuum of mild to severe epithelial dysplasias. In order to identify characteristic chromosomal changes related to different stages of cervical tumor progression, a number of preinvasive cervical lesions, as well as invasive cervical carcinomas were analyzed. The 3, 7, X aneusomy of chromosomes and the status of the epidermal growth factor receptor (EGFR) gene by fluorescence in situ hybridisation (FISH) analysis were evaluated. Polysomy of chromosomes 3 and X defined the transition from high-grade squamous intraepithelium lesions (HSIL) to cervical carcinoma. Chromosome 7 monosomy and polysomy did not show any statistical significant differences between the groups examined. When we compared the chromosomal aneusomies in all of the specimens using the Kruskal–Wallis test, significant differences ($P = 0{:}0001$, $P = 0{:}0001$ for chromosomes 3 and X, respectively) were observed. Using a ratio of the EGFR gene signals and chromosome 7 centromeric signals, no samples showed gene amplification. Our results demonstrate the importance of chromosomal 3 and X aneusomies in the development and progression from HSIL to cervical carcinoma, highlighting their usefulness as genetic markers for identifying SILs at high-risk of progression.

Our data highlight: (I) the importance of increased DNA copy number of chromosomes 3 and X in the development and progression from HSIL to cervical carcinoma; (II) that the status of chromosomes 3 and X could be a useful genetic marker for identifying SILs at high risk of progression; (III) alterations of chromosome 7 seems to be an early event in oncogenesis. Recently, the development of assays with high-specificity for detecting cancer precursors, as well as with excellent sensitivity, represent attractive alternatives as primary screening tests or as tests to complement cytology, HPV-typing or other assays. We may therefore conclude that the FISH assay, with probes specific for the chromosomes involved in cervical carcinogenesis, is a valuable tool to identify women with LSIL who harbor undetected HSIL or are destined to progress and may help determine their risk of progression.

The availability of new diagnostics tools useful to improve clinical staging at time of diagnosis of primary tumors or to identify sub-groups of patients with different clinical outcome, may be of great value in the clinical management of cancer patients.

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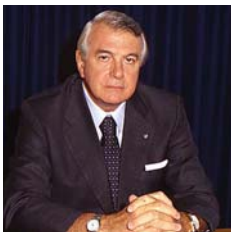
Division of histology and citopathology

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 Consiglio Superiore di Sanità. 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 - MD Assistant
Renato Covello - MD Assistant
Maria Diodoro - MD Assistant
Franca Del Nonno - MD Assistant
Ferdinando Marandino - MD Assistant
Mirella Marino - MD Assistant
Letizia Perracchio - MD Assistant
Steno Sentinelli - MD Assistant
Paolo Visca - MD Assistant
Maria Benevolo - PhD Assistant
Simonetta Buglioni - PhD Assistant
Marcella Mottolese - PhD Assistant
Amina Vocaturo - PhD Assistant
Paola Canalini - Chief Technician
Antonio Cione - Chief Technician
Angela Lattanzi - Technician
Mario Moauro - Technician
Patrizia Palmarelli - Technician
Francesca Romagnoli - Technician
Patrizia Scordati - Technician
Stefania Sperduti - Technician
Vincenzo Veltri - Technician
Roberto Paone - Administrative
Claudio Cuppone - Auxiliary
Leonardo Rocco Valenti - Auxiliary

Time limited contract:
Vera Chiari - Technician
Alessandro Ferrara - Technician
Eliana Pallottini - Technician
Arianna Papadantonakis - Technician
Marta Stefanelli - Technician

Fellows:
Anna Di Benedetto - PhD
Giuseppina Chichierchia - PhD
Flavia Novelli - PhD
Giulia Piperno - MD
Barbara Antoniani - Technician
Andrea Chiarenza - Technician
Francesca Rollo - Technician
Ilaria Targa - Technician
Valentina Zerbini - Technician
Maria Assunta Fonsi - Dr.Administrative

Activities 2004

The major effort in research activity, during 2004, have been focused on five main pathologies:

1. Breast carcinomas
2. Colon carcinomas
3. Cervical carcinoma
4. Thymic epithelial neoplasms (thymoma)
5. Non hodgkin lymphomas: Results obtained are described in the following paragraphs:

1. Breast carcinoma

A. Modulation of Estrogen Receptor ≤ In Breast Carcinoma and Autologous Peritumoral Tissues during the Menstrual Cycle: Correlation with Estrogen Receptor α.

The importance of estrogen receptor a (ER) in the development and progression of breast cancer (BC) has been widely recognized. Recently a second ER, ER*β*, showing a similar affinity in estrogen binding, has been identified. ER*β* might modulate ERα action contrasting the mitogenic activity of estrogens in mammary premalignant lesions. In young women, normal breast shows a cyclic modulation of ERα, whereas limited studies evaluated ER*β* expression during the menstrual cycle. In this study we analyzed, by immunohistochemistry (IHC), the ERα and ER*β* modulation in 40 benign lesions (BL) and in 90 invasive BC sampled from premenopausal patients whose menstrual phase was determined through multiple serum progesterone analysis. In parallel we evaluated by IHC the autologous adjacent non-involved epithelium. Results obtained showed that ERα percentage was higher in BC than PTT (30% vs 17.5%, $p<0.0001$). In contrast ER*β* decreased in BC with respect to PTT (22% vs 35% $p=0.05$). When patients were stratified according to the menstrual phase, BL showed a physiological downregulation of ERα, but not of ER*β*, in the luteal phase with respect to the follicular one ($p=0.03$). Otherwise BC as well as PTT did not show any significant variation in ERα and ER*β* during the menstrual cycle. In conclusion in normal breast ER*β*, in contrast to ERα, did not display any cyclic modulation indicating that ER*β* regulation is different from that of ERα. On the other hand a lack of modulation during the menstrual cycle in BC and PTT was demonstrated for the two ERs. These findings, although preliminary, indicating that ERα and ER*β* could play a distinct role in the regulation of hormone responsiveness in the mammary gland of premenopausal women and might be helpful in rationalizing antiestrogen preventive therapy in high risk BC patients.

B. Phenotypic Changes of p53, HER2 and FAS system in multiple normal tissues surrounding Breast Cancer

The molecular identification of high risk breast lesions could improve the efficacy of current preventive strategies and the application of selected therapeutic interventions. According to the field cancerization hypothesis it is likely that benign breast tumors (BBTs), precursors for invasive cancer, and the normal appearing peritumoral tissue (PTT), may harbor molecular changes heralding early stages of cancer The frequency of chromosomal abnormalities found in BBTs, although lower than in BC, correlates with the corresponding risk of developing invasive carcinoma. Moreover, the benign parenchyma of cancer-containing breasts and the contralateral normal epithelium in patients who experienced cancer in one breast, can share the same pattern of chromosomal abnormalities with invasive carcinoma. Furthermore, it has been reported that altered expression of p53 and HER2 can be detected in BBTs as well as in normal breast epithelium adjacent to excised tumors suggesting that perturbations in tumor suppressor genes and oncogenes may occur in breast tissue before morphological changes are apparent. Although somatic p53 mutations in the majority of cases may be silent, such alterations could still serve as an index of accumulating genetic damage and/or defects in DNA repair. It is widely recognized that HER2 overexpression is an early event in breast carcinogenesis and HER2 gene amplification and protein overexpression has been reported in benign proliferative lesions such as

usual (UDH) and atypical ductal hyperplasia (ADH) and in morphologically normal appearing mammary epithelium adjacent to invasive cancer cell cycle control is a highly complex, finely tuned process in which genes modulating cell proliferation are balanced by gene products, such as Fas/Fas ligand (FasL), controlling apoptosis We have recently reported that in BC the loss of Fas receptor accompanied by FasL upregulation is associated with a worse clinical outcome. In contrast, no data are available on Fas system expression in preneoplastic lesions. To determine whether phenotypic field changes occur in tissues adjacent to carcinoma, we assayed, by immunohistochemistry, the expression of HER-2, p53, Fas and FasL in 72 breast cancers (BC) and multiple autologous peritumoral tissues (PTTs) sampled up to 5 cm distance and in 44 benign breast tumors (BBTs). About 5% and 3% of the PTTs and 4.5% and 6.8% of 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 BBTs 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.

C. Altered expression of FAS-system is related to adverse clinical outcome in stage I-II Breast Cancer patients treated with adjuvant anthracycline-based chemotherapy

To determine the prognostic value of Fas receptor and Fas ligand (FasL) as apoptosis-related biomarkers in the context of chemoresponsiveness in breast cancer (BC) patients submitted to anthracycline-based adjuvant therapy. The two molecules were investigated by immunohistochemistry in surgical samples collected from 167 stage I-IIa-b BC patients enrolled in a prospective clinical trial using Epirubicin plus Cyclophosphamide (EC) in the adjuvant setting. Fas and FasL were significantly associated to tumor stage ($p<0.0001$). Multivariate analysis indicated that stage, loss of Fas (relative risk, 8.5 and 9.12 $p<0.0001$) and FasL upregulation (relative risk, 2.38 and 2.88 $p=0.01$) were independent prognostic variables influencing both disease free (DFS) and overall survival (OS). A Cox analysis using a four category Fas/FasL phenotype (+/- +/+, -/+, -/-) as a stratification factor evidenced a highly positive association between Fas /FasL phenotype and the cumulative hazard of relapse and death in the entire series of patients. We also estimated the DFS and OS for different combinations of the p-TNM stage and Fas/FasL by using the K sample log-rank exact test, demonstrating that significantly shorter DFS and OS were observed in Fas negative and FasL positive patients both in stage I-IIa and IIb.

Data presented herein demonstrated that, according to a number of in vitro studies, prognosis of BC patients receiving adjuvant anthracycline-based CT strongly depends on the Fas/FasL status. Therefore a concomitant altered pattern of Fas/FasL expression seems to configure an aggressive tumor phenotype linked to disease progression.

D. Chromogenic in situ hybridization (CISH): a novel method to determine her-2 amplification in histological routine sections and cytological samples.

The application of Trastuzumab needs a correct and accurate evaluation of HER2 status. Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) are the two major methods for evaluating gene amplification and protein overexpression. Although a strong correlation has been demonstrated between the two methods, FISH does not allow to accurately evaluate tumor morphology. Recently an in situ hybridization based on a chromogenic detection system (CISH; Zymed, USA) has been developed. In order to compare CISH with FISH (Vysis) and IHC we tested by Herceptest and CB11 monoclonal antibody a series of 64 paraffin embedded breast carcinomas. Immunoreactivity was scored on 0 to 3+ scale and a high concordance between CB11 vs Herceptest ($K=0.78$, $p<0.0001$) was found. Gene copies were recognized by CISH as intranuclear brown spots. Results obtained demonstrated a good concordance between FISH vs CISH ($K=0.56$, $p<0.0001$) and IHC vs CISH ($K=0.41$, $p<0.0001$ and $K=0.53$, $p<0.0001$ with Herceptest and CB11 respectively). The latter concordance is comparable to that observed between

IHC and FISH (K=0.44, p<0.0001 and K=0.47, p<0.0001 with Herceptest and CB11 respectively). By permitting observation of morphology, thus distinguishing in situ from invasive carcinoma, CISH is a promising approach to screen HER2 status in breast cancers and may also be a good method to calibrate, as a quality control test, IHC procedures.

2. Colon carcinoma

A. Role of P53 and Bcl-2 in Advanced Rectal Carcinomas Treated with Adjuvant Therapy

Tumors occurring in the rectum, which account for more than 30% of large bowel cancers, present a higher incidence of locoregional lymph nodes and distant metastases and a poorer outcome than colon cancers with a 5-year survival rate of less than 40%. Adjuvant chemotherapy, alone or in combination with radiotherapy, represents the standard treatment for locally advanced rectal cancer.

At present a limited number of studies have defined the biopathological factors associated with tumor progression in stage III-IV rectal cancer. The evaluation of biological parameters related to proliferation and apoptosis, i.e p53 and Bcl-2, may be useful in identifying patients at higher risk of progression. Wild type p53, involved in cell cycle regulation and apoptosis in response to DNA damage is frequently mutated in colorectal cancer and these mutations may affect response to radiochemotherapy. In contrast to its anti-apoptotic role, Bcl-2 is usually related to a more favorable clinical outcome in human colorectal cancer.

Limited data are available so far in advanced rectal cancer, therefore this study aimed at comparing the impact of p53 and Bcl-2 on overall survival in a cohort of 126 patients surgically treated for advanced rectal cancer (Stage III and IV, UICC, 2002) and submitted to 5 Fluorouracil based (5FU) adjuvant therapy.

To this end we analyzed the impact on overall survival of p53 and Bcl-2, evaluated by immunohistochemical techniques, in 126 advanced rectal cancer patients submitted to 5 Fluorouracil based adjuvant therapy. Shorter overall survival was observed in patients bearing p53 positive and Bcl-2 negative tumors, although in multivariate analysis only p53 emerged as independent predictor of a worse outcome.

These results seem to indicate that, in stage III-IV rectal cancer, p53 alterations may identify high risk patients for enrollment in more aggressive and/or innovative adjuvant/neoadjuvant treatments.

3 Cervical carcinoma

A. Overexpression of p16ink4a in cervical intraepithelial neoplasias as possible marker of HPV infection

Immunohistochemical (IHC) studies demonstrated that p16, a cyclin-dependent kinase inhibitor, is overexpressed in preneoplastic and neoplastic lesions of the uterine cervix and this overexpression is induced, in the majority of cases, by human papillomavirus (HPV) oncogenes. In order to verify whether p16 expression may be a biomarker useful in identifying dysplastic lesions at higher risk of progression, we investigated in two different studies: (**1. cervical biopsies and 2. liquid based citological cervico-vaginal samples**) the potential association between p16 expression and infection with different HPV types.

Histological cervical samples. 77 formalin fixed cervical biopsies were considered in the study: 13 normal tissues and 64 neoplasias (48 CIN1, 10 CIN2 and 5 CIN3, and 1 invasive squamous cancers). 5°-sections were IHC evaluated by the means of p16 kit (DakoCytomation, Milan, Italy). The presence of HPV DNA was detected by the polymerase chain reaction (PCR) using HPV Star Blot kit (DiaTech, Iesi, Italy) that enables amplification and detection of HPV DNA by reverse dot blot hybridization with sequence-specific oligonucleotide probes. Results obtained showed that all the 13 normal cervical tissues were p16 negative whereas 9 out of 10 CIN2 (90%) and the CIN3 lesions as well as the invasive cancers displayed p16 expression. In the 48 CIN1 lesions we found p16 immunostaining in 15 cases (31%). High risk HPV genotypes were found in all high grade lesions and in squamous cancer. Of interest, 14 out of the 15 p16 positive CIN1 lesions (93%) showed high risk HPV genotypes. These data suggest that there is a significant potential association between p16

overexpression, infection with high risk HPV and the presence of HPV-induced dysplastic or neoplastic lesions. Therefore p16 appears to be a useful biomarker for identifying cervical intraepithelial lesions which could progress because they harbor high risk HPV.
Liquid based cytological cervico-vaginal samples (LBC):. On 282 LBC (Thin-prep Cytic), diagnosed as 230 negative, 30 ASC-US, 16 LSIL and 6 HSIL, we performed p16 immunocytochemical analysis (DakoCytomation) and HR-HPV hybrid capture 2 (HC2 Digene. p16 was immunocytochemically positive in 77 of 282 (27.3%) women (24% of the negative, 30% of the ASC-US, 50% of the LSIL and 66% of the HSIL cases). HC2 test was positive in 62 out of 282 (22%) women (12% of the negative, 53% of the ASC-US, 81% of the LSIL and 100% of the HSIL cases). When the p16 expression in combination with HR-HPV infection was taken into account, we found 70% concordance between the two assays; in fact 28 out of 62 HR HC2 positive patients (45%) showed p16 immunoreactivity, whereas 170 out of 220 HC2 negative patients (77.3%) were p16 negative. Therefore, while the p16 Positive Predictive Value (PPV) for HR-HPV was only 36%, the Negative Predictive Value (NPV) was 83%. In addition, excluding the ASC-US cases from our series, the p16 PPV for LSIL/HSIL was 18% and the NPV for LSIL/HSIL was 95%. These findings suggest that p16, used as an adjunct to LBC in cervical screening, may be a particularly useful biomarker in discriminating negative from LSIL/HSIL specimens. Broader additional studies are required to confirm our data

4. Thymic epithelial neoplasms (thymoma)

Growth Factor and neuroendocrine hormone receptors in Thymoma

Among epithelial tumors, Thymic Epithelial Tumors (TET), also called Thymomas, are rare diseases; however, because the neoplastic thymic epithelium maintains its "educational" activity in T- lymphocyte maturation, a variety of immune derangements/autoimmune diseases are associated to TET. Previously considered a morphological continuum, several Thymoma morphological/biological entities have been recently defined by the World Health Organization and the histological features are now considered an independent prognostic factor in evaluating patient prognosis and treatment. In addition to the main morphological/biological diagnostic categories, new thymoma variants have now been identified and recently included in the WHO classification. The Department of Pathology of the Regina Elena Cancer Institute has contributed to the definition of a peculiar variant of TET, the Micronodular Thymoma (MNT) (1) a unique example of TET which is able to attract and to maintain a relevant B-cell population and immature T cells in the tumor stroma. In collaboration with the Institute of Pathology of the University of Wuerzburg, we further characterized in a recent study (2) this peculiar thymoma entity and we showed that a high percentage of MNT contains intra-tumorous monoclonal B cell populations or even low grade lymhomas with a VDJ usage similar to MALT lymphoma. Moreover, MNT showed abnormal overexpression of various chemoattractants for T cells, dendritic cells and B cells. We concluded that MNT might provide a high risk environment for the development of mediastinal lymphomas. Furthermore, the expression by thymoma epithelial cells of growth factor receptors and neuroendocrine hormone receptors (Somatostatin Receptors- SSTRs) involved in the epithelial proliferative activity is currently being investigated. Preliminary correlative data with treatment and clinical responses have been obtained (3-4).

5. Non Hodgkin Lymphomas

B. Prognostic factors in non-Hodgkin lymphomas

Lymphoproliferative diseases, particularly non-Hodgkin Lymphomas (NHL), are currently been investigated by a variety of immunohistochemical markers, in situ Hybridization to viral mRNA (EBER-ISH for Epstein Barr Virus) and Fluorescent in situ Hybridization (FISH) in order to characterize, at the diagnosis, biological or cytogenetic features of diagnostic/prognostic relevance (5-6-7).

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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. Since 1989 he has been 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 as President of the Lazio section the Italian Society of Digestive Endoscopy.
He has lectured at the Specialization School of Oncology as well as the Graduate course for General and Pediatric Nursing for La Sapienza University, Rome. From 1997 to 2000 he was the Coordinator of the Oncology Commission for the Italian Society of Digestive Endoscopy. He currently lectures at the Specialization School in Digestive Gastroenterology and Endoscopy for La Sapienza University, Rome.
Dr. Casale is an international member of ASGE (the American Society of Gastrointestinal Endoscopy) and a member of the National Oncologic Commission of the Italian Association of Gastroenterologists.
He was in charge of the research entitled "Study of cellular kinetics and gene characteristics of cells in colic mucous in subjects at risk of colon cancer undergoing treatment with retinoids" completed in 1990 for the Ministry of Health, and the "Evaluation of some tissue and blood biological parameters for selecting subjects at risk of succumbing to cancer of the rectum colon" completed in 1997 for the Ministry of Health. 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 - MD
DR. R. LAPENTA - MD
DR.V. STIGLIANO - MD
DR. D. ASSISI - MD
DR.V. LAURIA - MD, Research Contract
DR. T. FEDERICI - MD, Consultant

Specialization: 1st Specialization School in Digestive Gastroenterology and Endoscopy La Sapienza University, Rome: F. Liguori, M.G. Mancino, G. Nicolini, L. Kondili.

Activity 2004

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 Division 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 operation 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 polyposis 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 colorectal cancer coordinated by Dr. Maurizio Cosimelli. Particular attention has been paid to the relationship between Barrett's Syndrome and adrenocarcinoma of the esophagus. 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 neoplastic risk has been done with the identification of the specific intestinal metaplasia (OK) and 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 increased significantly and been 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 rapidly 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 conducted by 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).
We cooperate with other facilities on numerous clinical and experimental fields: 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, we obtain blood and tissue samples from patients in our facility; 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 cooperation 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 inter-

national 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 as well as 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 that of other facilities in Lazio and the center/south of the country.
In recent years, radial instruments in endoscopic exams for the study of mucous and submucous lesions of the digestive tract and for the pathology of the bilio-pancreatic region have begun to be used.
As part of the study "Italia - USA program on Cancer Pharmacogenomics" under the control of the Italian Ministry of Health and of the Higher Institute of Health. The operative unit of gastroenterology has the task of enrolling for the pathology of the colon, patients with adenomas and subjects with negative results following colonscopies.
In 2004, 7,915 services, 81% outpatients and 19% admitted patients, have been carried out. Out of a total of 3,400 endoscopies carried out, 247 have been therapeutic type tests. One hundred and forty malign tumors have been diagnosed with endoscopy and confirmed histologically, 88 of which were colorectal, 32 of the stomach and 12 of the esophagus. Two hundred and fifteen consultations have been made through the dedicated outpatients for nutritional evaluation and 87 for hereditary tumors of the colon.

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Endocrinology Unit

DIRECTOR:
MARIALUISA APPETECCHIA, MD

Marialuisa Appetecchia received her MD 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 Department 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 date as Director of the Department of Endocrinology, Regina Elena National Cancer Institute of Rome.
Since 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, focusing 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 2004

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 2004 include:
1. The development of thyroid tumors deriving from genetic and/or epigenetic alterations of genes involved in the regulation of cell 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-kinase 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 p27kip1 kinase constitutes a crucial downstream target on which these intercellular communication pathways converge (PTEN/P13K/Akt and PTP_/MEK/Erk). p27kip1, one of the main regulators of the G1/S checkpoint, is frequently inactive in human tumors, including thyroid tumors. In thyroid tumors, p27kip1 is activated through two different mechanisms: expression reduction and delocalization 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, con-

tribute to the shutting off of expression or to the functional inactivation of p27kip1. 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 on the management of the resources of health services. 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 also of free sexual hormones, due to a reduced hepatic production of the SHBG. All these factors could be responsible for an 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 white adipose tissue is an endocrine organ to all effects, able to produce substances capable of sparking off metabolic, vascular and neoplastic changes, and activate 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 a different clinical outcome in order to identify the pathological, biochemical and clinical parameters useful for prognostic evaluations. For this reason, we have started a long term 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 2004

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Division of Dermatological Oncology

DIRECTOR:
PASQUALE FRASCIONE, MD

Professor Pasquale Frascione is currently the Director of the Dermatological Oncology Division of the Regina Elena Cancer Institute in Rome.
He represents Italy through his involvement in several prestigious organizations; as the Scientific Adviser of ADIPSO (Association of Psoriatic Patients), the Regional Director of ISPLAD (the Italian Society of Plastic, Aesthetic and Oncologic Dermatology). He is also a member of the teaching staff for the degree course in Dermatology and Venereology and Master of Plastic Dermatology promoted by the Tor Vergata University, Rome. Prof. Frascione is the Dermatology Adviser of Contagious Disease for the Lazzaro Spallanzani Institute and for the Rebibbia prison in Rome and Medical member of F.I. G.C.
Paolo Piemonte MD is a teacher for the degree course of Urology as well as the Masters in Plastic Dermatology at the Tor Vergata University. He belonged to the scientific committee in the III International Congress of Psoriasis.

Staff
PASQUALE FRASCIONE - MD Director
PAOLO PIEMONTE - MD Assistant
MARCELLO CASALE - Hospital Attendant.

Activities 2004

The clinical activity performed by the Dermatological Oncology Division guarantees diagnosis of skin cancers by clinical evidence and digital technology and their treatment by surgery or systemic and topic therapies.
The Division participates in drawing up the guide lines for melanoma and also follows non-melanoma-skin cancers management. Other fields of interest include psoriasis treatment: the staff of the Devision are involved in a multicenter study of sub-cutaneously administered Efalizumab in the treatment of adult patients with moderate to severe chronic claque psoriasis, who have failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapies including Ciclosporin, Methotrexate and PUVA.
Professor Frascione and Dr. Piemonte are the Authors and Co-authors of publications and conferences.

Publications 2004

FARGNOLI MC, PERIS K, FRASCIONE P, BARBATI R, ANEMONA L, UCCINI S, FRANCESCONI F, CHIMENTI S.

Psoriasis, Kaposi's Sarcoma and Hodgkin's Disease in a Patient with Down's Syndrome.

Dermatology. 2004;209(2):158-159. *I.F. 1.190*

Division of neurosurgery

DIRECTOR:
EMANUELE OCCHIPINTI, MD

Prof. Emanuele Occhipinti was born in Ragusa December 8, 1940.
He achieved his MD degree in 1965, summa cum laude at La Sapienza University of Rome - School of Medicine and in 1970 he obtained his Postgraduate Degree in Neurosurgery, at La Sapienza University School of Medicine of Rome. In the same period he was Assistant Neurosurgeon at the Institute of Neurosurgery - La Sapienza University of Rome - School of Medicine and from 1970 Assistant Neurosurgeon at the Neurosurgery Division - Regina Elena National Cancer Institute - Rome.
1976 he attended a training stage at Massachusetts General Hospital, Children's Hospital Medical Center and Peter Bent Brigham Hospital, - Boston - MA (US).
From 1985 he was Professor of Clinical Neurosurgery at the Postgraduate School of Neurosurgery - Tor Vergata University of Rome and from 1999 the Director of the Neurosurgery Division - 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 - MD Associate Neurosurgeon
DOTT. F. CAROLI - MD Associate Neurosurgeon
DOTT. F. CATTANI - MD Associate Neurosurgeon
DOTT. E. MORACE - MD Associate Neurosurgeon
DOTT. P.A.OPPIDO - MD Associate Neurosurgeon
PROF. A. POMPILI - MD Associate Neurosurgeon
DOTT. L. RAUS - MD Associate Neurosurgeon
DOTT. S. TELERA - MD Associate Neurosurgeon

Postgraduate School Students:

DOTT. CONTI CARLO
DOTT. DE CERCHIO LEONARDO
DOTT. LANETTI ANTONIO
DOTT. MENNITI AGAZIO
DOTT. RUGGERI FRANCESCO
DOTT. FRAIOLI MARIO FRANCESCO
DOTT. CACCIOTTI GUGLIELMO

Research Activities 2004

The research activity of the Neurosurgery Division is focused on the study of new diagnostic and therapeutic approaches in the integrated treatment of brain glioma. In this field during 2004 a series of cooperative studies with national and international institutions were pursued, activated, or are on going.
During this year the accrual of patients affected with glioma of different malignancy grading was continued, considering both new diagnosed tumors, and at the moment of recurrence and/or clinical/radiological progression. The patients have been followed through the different structures of Dept. of Neuroscience (Divisione di Neurochirurgia, Ambulatorio Neuro-Oncologico, Day Hospital Neuro-Oncologico, Servizio di Assistenza Continuativa Domiciliare), and furthermore, through a more efficient integration with the Medical Oncology Division and with Radiotherapy Service, inserted in a Neuro-Oncologic Group favorably connected with other regional structures; actually these structures actively cooperate in the DMT on brain tumors.
New therapeutic protocols have been activated, considering after surgical procedures (biopsy and/or microsurgical removal), radiation treatment and chemotherapy with different therapeutic schedules, both as first (mainly Temozolomide), and as second line treatment. In addition, the increasing efficacy of new therapeutic strategies (microsurgical resection, with second surgical look and intratumoral antiblastic treatment, conformal ra-

diotherapy, with eventual focal boost, adjuvant and/or concomitant chemotherapy), indicated third line chemotherapy (mainly with Fotemustine) for selected patients.
Presently we are trying to correlate the data regarding tumor bio-molecular characteristics with the 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, histological, immuno-histochemical and bio-molecular knowledge could contribute in the definition of more selective and efficient diagnostic-therapeutic strategies, also allowing a more clear cut stratification of patients accrued in new clinical trials.
In the literature different Authors (and our group too) 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 the Ministry of Health, coordinating Prof. Felice Giangaspero - Neuromed (pooled: Resp. C.M. Carapella, that has obtained new funding for 2005).

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

1. A phase I-II study of prolonged gemcitabine infusion as radiosensitizer for glioblastoma multiforme (approved by the 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 the ec and activated)
3. Phase II study of a recombinant chimeric protein composed of transforming growth factor (tgf)-α 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 the ec and activated)
4. Unconventional temozolomide chemotherapy, with increased dose-intensity, in the treatment of anaplastic gliomas and progressive or recurrent low grade gliomas (approved by the ec and activated).

As an active member of the EORTC Brain Tumour Group (C.M. Carapella) a new randomized phase III study on post-operative residual meningiomas has been approved by the EC and activated: observation versus conventional- fractionated radiotherapy or radiosurgery after non-radical surgery for benign intracranial meningiomas.
With regard to this trial our center will act as the Italian Coordinating Center.
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 tumors
- unilateral approach in the resction of intradural spinal tumors
- transphenoidal removal of pituitary adenomas with microsurgical and endoscopy-assisted technique

Basically, our clinical research activity is divided into 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.

Publications 2004

Fabi A., Vidiri A., Carapella C., Pace A., Occhipinti E., Caroli F., Mirri A., Carlini P., Cognetti F.

Bone metastasis from glioblastoma multiforme without central nervous system relapse: a case report.

Anticancer Res. 2004 Jul-Aug;24(4):2563-5. *I.F. 1.347*

Pompili A., Caroli F., Cattani F., Crecco M., Giovannetti M., Raus L., Telera S., Vidiri A., Occhipinti E.

Unilateral limited laminectomy as the approach of choice for the removal of thoracolumbar neurofibromas.

Spine. 2004 Aug 1;29(15):1698-702. *I.F. 2.676*

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, Rome.
He also specialized in Clinical Criminology.
From 1970 to 1973 he worked as Assistant Neurologist at the Hospital of Viterbo. Then from 1973 to 1978 he was Assistant Neurologist and from 1978 to 1987 he was the Vice Director of Neurology for the Regina Elena Cancer Institute. In 1987 he was appointed Head of Neurology at the same Institution, and from 2001 he has been Head of the Department of Neurosciences and Cervico-Facial Pathology.
Since 1986 he has been a Professor of Clinical Neurophysiology at Tor Vergata University and of Electromyography at La Sapienza University in Rome since 1990.
Dr. Jandolo spent periods of study at the Universities of Seattle, Basel, Pavia and Milan.
He is member of various Scientific Societies, and he was 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 paraneoplastic diseases of the nervous system.
He serves on the Editorial Board of some scientific journals. Moreover he is Referee of Multiple Sclerosis for the Lazio Region Administration.
He is author or co-author of 120 original papers and 100 abstracts.

Staff:
ALBERTO PIETRANGELI - MD, Responsible of Neurorehabilitation
ANDREA PACE - MD, Responsible for brain tumor home assistance.
MARTA MASCHIO - MD Assistant
ALBINA ANGELINI - MD Assistant
EDVINA GALIÈ - MD Assistant
ETTORE DI SCIPIO - Fellow (Contract)
ANNA DE SENA NURSE - Nurse Coordinator
ANTONELLA GAGLIARDO - Nurse
ANTONIA SORRENTINO - Nurse
PATRIZIA SPECCHIO - O.T.A.
VALERIA VENEZIANO - Secretary
GIULIANA. GRAZIANO - Technician of Clinical Neurophysiology
GIANLUCA PETRERI - Technician of Clinical Neurophysiology (Contract)
ANGELA. DI CANIO - Technician of Clinical Neurophysiology
ELEONORA BISOZZI - Technician of Clinical Neurophysiology (Contract)
ANTONIETTA DE FULVIIS - Physiotherapist Coordinator
MARIA LUISA GUERRA - Physiotherapist Coordinator
ORAZIO PERROTTA - Physiotherapist
MAURIZIO BRECEVICH, - Physiotherapist
FABIO MOSCATELLI - Physiotherapist
RITA CASILLO - Physiotherapist
ALESSIA ZIZZARI - Physiotherapist (Contract)
ANDREA MINNETTI - Physiotherapist (Contract)

Activities 2004

The role of chemotherapy (CT) in the treatment of malignant gliomas is still debated. Different chemotherapeutic agents are currently used with modest impact on survival. At the moment there are no clear-cut data indicating more effective or better tolerated treatments. Furthermore, the evaluation of response to CT should also include clinical benefit and quality of life.

We retrospectively analyzed our experience in chemotherapy of malignant gliomas with the aim of evaluating time to tumor progression, clinical benefit, quality of life (EORTC QLQ-C30), and toxicity. Two hundred and fifty five recurrent malignant glioma patients

have been treated with chemotherapy (PCV or Temozolomide) in our institution since 1997. The histology was as follows: glioblastoma (GB) in 123; anaplastic astrocytoma (AA) 56; mixed anaplastic oligo-astrocytoma (AO) 43; progressive low grade astrocytoma (LGA) 42; anaplastic oligos (0) 28. The overall response rate (RR) by histology was: CR+PR in GB 7.4%; AA26.8%; AO 51.6%; LGA 484%; 044.4%. Treatment schedule was PCV in 193 patients and Temozolomide (TMZ) standard schedule in 129. RR was not significantly different for the two treatments. Sixty nine patients received two lines of chemotherapy (44 first line PCV and 25 first line TMZ). In the present series, tumors which respond to first line CT are more likely to respond to second line treatment. In 13.5% of patients treated with PCV the treatment was interrupted for toxicity. During TMZ treatment 10.9% of patients presented myelotoxicity grade 3-4 (WHO), leading to treatment interruption in 4.6% of cases. Considering the modest influence of CT on overall survival in malignant gliomas, less toxic drugs should be preferred for first line treatment.

The association between Lung Tumors and Neurological Paraneoplastic Syndromes is well known, but its exact prevalence is not well defined.

So 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. Fifty one (51) patients were recruited (43 males, 8 females age 42-80; 8 with microcitoma, 15 with squamous carcinoma, 16 with adenocarcinoma, 12 with large cells carcinoma).

Each patients was submitted to:

- Clinical Neurological examination
- Neurophysiological examination (motor and sensory nerve conduction; evaluation of the amplitude of the sensory and motor action potentials; decrement test at 3 and 20 Hertz) of one ulnar nerve.

Serologic examination:

Antibody anti-MAC, anti- Hu, Anti-Ri, anti-Yo, anti-Myelin, anti gagliosides, ANA.

The data collected till now may suggest that there is a prevalence of 25% of sub-clinical paraneoplastic neurophysiological syndromes.

However the number of cases is not enough and the antibody-reactivity is dishomogeneous, so we still need to recruit 80-100 patients to obtain reliable conclusions.

Naturopathic pain has been defined by the International Association for the Study of Pain as pain "initiated or caused by a primary lesion or dysfunction in the nervous system". Peripheral nervous system toxicity is a major dose-limiting factor for chemotherapic agents as vinca alkaloids, platinum derivates, taxanes. Peripheral neurophaties have different clinical presentation, but sensory symptoms, like distal paresthesias and burning pain, are often present. The activities of daily life are impaired by these troubles. In the Regina Elena Institute about 1,100 neurological consultations per year are performed, 10% of which regard patients with neuropathic pain due to chemotherapy. In our experience Gabapentin (1800-2400 mg/die) has proven to be very effective. Tricyclic antidepressants are useful too, but they need caution if co-administered with cardiotoxic chemotherapy. Moreover, they may interfere with the metabolism of some chemotherapeutic drugs, owing to their interaction with cytochrome P450. In conclusion, we feel that a careful evaluation of neuropathic pain due to chemotherapy must be a priority and that a prompt therapeutic decision may improve the quality of life of oncologic patients.

In a retrospective study on 405 patients with supratentorial brain tumors we found that epilepsy prevalence was 13% higher than usually reported in international studies Moreover, we showed that in neuro-oncology it is important to select groups of high-risk patients, in which an antiepileptic prophylaxis may be necessary. With this aim, we are starting a prospective study in melanoma patients with brain metastasis.

Temozolomide is a well tolerated alkylating agent, that is able to permeate the blood brain barrier (BBB), and has additive cytotoxicity when given with radiotherapy (RT). We participated in a phase II trial assessing Temozolomide 150 mg/m2/day, for 5 days every 28

days in primary central nervous system (CNS) lymphoma (PCNSL) patients with negative human immunodeficient virus (HIV) serology, Eastern Cooperative Oncology Group (BCOG) performance status (PS)<4, previously treated with high-dose methotrexate-containing (HD-MTX) chemotherapy and/or RT. Twenty three patients were enrolled and median age was 60 years. Five complete remissions (median duration 6+ months; range 2 - 36 months), one partial response, four stable disease (median duration 7.2 months, range 2 - 16.5 months), and 13 progressions were observed. No major toxicity was observed, apart grade 3 vomiting in a single cycle. Main grade 1 - 2 toxicities were: 15% nausea, 6% vomiting, 9% fatigue and 9% neurological symptoms. This is the first prospective trial assessing single-agent activity in PCNSL at failure. Although some patients had a poor PS and had been heavily pre-treated, Temozolomide yielded 26% objective responses and was well tolerated without any major toxicity.

The extraneural diffusion of malignant gliomas is not frequent and some authors have reported single or multiple bone metastases from glioblastoma contemporary to the time of primary, cerebral tumor or accompanying relapse on the brain. We have reported the case of a man affected by a gliobastoma who had a lumbar spine metastases without any brain relapse after excision of cerebral glioblastoma multiforme and brain radiotherapy.

Low-grade gliomas represent a heterogeneous group of tumors with variable natural histories, in which the relative risks and benefits of aggressive treatment must be balanced for each individual patient. We performed a retrospective analysis of 86 patients treated in the neuro-oncological day hospital of the Regina Elena Cancer Institute in the last five years. Histology was grade 11 (WHO) astrocytoma in 43 cases, mixed oligo-astrocytoma in 20, and oligodendroglioma in 23. Median age was 41 years (range 17-71). The median interval between diagnosis and anaplastic progression was 53 months (range 5-144). Median survival was 75 months (range 25-156): 74 months in low-grade astrocytoma, 84 in mixed oligo-astrocytoma, and 114 months in oligodendroglioma. Epilepsy at the onset was present in 82% of patients. Surgery was the first line treatment in 70 patients (86.5%) with partial removal in 44 (61.9%); biopsy was performed in 16 (18.6%). 68% of patients were treated with radiotherapy (RT). Time to progression in patients not treated with RT after surgery was 58 months; in patients treated with RT it was 46 months (not significant). Chemotherapy (CT) was utilized in adjuvant setting, or at the moment of clinical and histological progression. Patients were treated with PCV in 45 cases, with TMZ in 59 cases; 31 patients received 2 lines of CT. An objective response was achieved in 36 patients (40.4%; 8 complete response and 28 partial response). 37 patients (43%) presented epilepsy resistant to antiepileptic treatment with more than one drug.

In order to evaluate trend and clinical behavior of patients (pts) affected by brain metastases (BM), the Latium Neuro-Oncology Group members (Neurology, Neurosurgery, Oncology and Radiotherapy Units) applied a multi-institutional survey to clarify the community employed therapeutic strategies and indicate the most effective approach arising from a multidisciplinary experience. Primary outcomes have been identified in overall survival (OS) and overall survival after BM appearance (BM-OS). The outcome monitoring was accomplished through a questionnaire with items regarding patients and treatment characteristics. From March 2003 to March 2004, 152 patients were registered for the study, from different primary tumor sites: NSCLC 65 (42,8%), breast 27 (17.8%), colorectal 19 (12.5%), melanoma 13 (8.6%), SCLC 6 (3.9%), unknown primary tumor 4 (2.6%), kidney 4 (2.6%), others 14 (9.2%). Neurological symptoms were present in 89 pts (58.6%), and RPA-RTOG scale was I in 50 pts, II in 83 pts, II in 12 pts, unknown in 7 pts.

One single lesion was observed in 67 pts (47.2%), and more than 3 lesion in 48 pts (33.8%). Surgery was 1st and 2nd line treatment in 37 and 3 pts; chemotherapy in 30 and 28; whole brain radiation (WBRT) in 75 and 27; radiosurgery in 5 and 4. With a median follow-up of 16 months, median overall survival (OS) was 27 months and median OS from BM diagnosis was 9 months (lung: 13 mths, breast: 11 mths, melanoma: 7 mths, colorectal: 3 mths). Patients with 1 and >2 lesions had a median CS of 14 and 8 mths respectively (p=0.02). Aggressive local treatment (surgery and radiosurgery) has determined superior

median OS compared with CT and WBRT (19 and 9 mths, p=0.01). In the present series, no significant differences were seen in OS from BM, diagnosis between patients affected by either lung or breast cancer. Patients with colorectal BM have the worst prognosis. Numbers of lesions and aggressive local treatment are predictive for OS.

In a global project focusing at the oncologic problems, we must consider the rehabilitation of the patient with neurological defects with the aim to reach both a good therapeutic goal and a good quality of life. A multidisciplinary approach gathering many specialists (surgeons, radiotherapists, neurologists, oncologists, rehabilitators, psychologists, nurses) led to a "total treatment".

This project verifies all the phases of neoplastic disease, to improve the cancer patient's quality treatment, with the restoration of a patient with neurological defects as a result of his disease, to as normal and functional state 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 nerves damage: d) Cerebral and spinal cord tumors; rehabilitation of cognitive and motor defects: e) toxic neuropathies a "fatigue" following antineoplastic drugs: rehabilitation of stance and gait. f) rehabilitation of patients suffering from chronic pain with transcutaneous stimulations 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.

Another project regards the evaluation of two fields of quality of life of patients with cancer: sexuality and fatigue. The evaluation is psychological, neurophysiological, gynecological, endocrinological and oncological.

Neurophysiological evaluation consists of measurement of conduction velocity of nerves to verify neurotoxicity of antitumorale therapies, and in the evaluation of sacral reflex and psudomotor 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 160 patients with breast and urgenital cancer.

Since October 2000 in the I.R.E., we have introduced a palliative home- care program for patients affected by malignant brain tumor discharged from our Neurosurgical Division, with financial support from the Lazio Region Administration. The aims of this model of assistance are to meet the patient's care needs in the last stages of disease, to provide home palliative care and to facilitate death at home. In the first 3 years of our program, 215 patients have been assisted at home and 131 have died. The complications in the last phase of disease was: pulmonary infections (10.6%), deep venous thrombosis (9.7%) with embolic complicance in six cases, diabetes due to chronic steroid treatment (8.4%), psychiatric syndromes (5.7%). 70 patients (37%) presented epilepsy in spite of anticonvulsant treatment; 24% presented adverse reactions to medication (chemotherapy, antiepileptic drugs, steroids). Sixty-nine per cent (90/131) of the patients were able to die at home.

Among the 131 patients who died, the most frequent symptoms of the terminal phase were lethargy (35.5%), dysphagia (31.8), and headache (12.3%). Brain tumor patients present peculiar symptoms and complicances that require specific treatment in the course of the disease. Although there is a lack of guidelines for support therapy, clinical evidence and literature data indicate the need for better definition of antiepileptic, antiedema, psychiatric and antithrombotic prophylactic treatment.

Selected publications 2004

Fabi A., Vidiri A., Carapella C., Pace A., Occhipinti E,. Caroli F., Mirri A., Carlini P., Cognetti F.

Bone metastasis from glioblastoma multiforme without central nervous system relapse: a case report.

Anticancer Res. 2004 Jul-Aug;24(4):2563-5. *I.F. 1.347*

Reni M., Mason W., Zaja F;, Perry J., Franceschi E., Bernardi D., Dell'oro S., Stelitano C, Candela M., Abbadessa A,. Pace A., Bordonaro R., Latte G.,Villa E., Ferreri A.J.

Salvage chemotherapy with temozolomide in primary CNS lymphomas: preliminary results of a phase II trial.

Eur J Cancer. 2004 Jul;40(11):1682-8. *I.F. 3.694*

Division of otolaryngology, head & neck surgery

DIRECTOR:
GIUSEPPE SPRIANO, MD

Prof. Giuseppe Spriano was born in Asti 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 was appointed Chief of the Department of Otolaryngology-Head & Neck Surgery. Since 2002 he has been Chief of the Department of Otolaryngology-Head & Neck Surgery of the Regina Elena National Cancer Institute, Rome.
He has been Professor of Otorhinolaryngology in the Specialization Schools of 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 and Maxillo-Odonto-Stomatology. He is a 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;
Dr. Spriano is a member of GLPO (Group of Northern Italy Otolaryngology Chiefs); of the Board of the Italian Society of Otorhinolaryngology, Head & Neck Surgery. He was 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 and serves on the Editorial Boards of Head & Neck and Agorà Otorinolaringoiatria.
He is the Author of 85 original papers published in national and international 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
PAOLO RUSCITO - Assistant
RAUL PELLINI - Assistant
GIOVANNI CRISTALLI - Assistant
DEGANELLO ALBERTO - Piece-work assistant
MANCIOCCO VALENTINA - Piece-work assistant
DORA DI PAOLO - Phoniatrician
PAOLO MARCHESI - Fellow
BARBARA PICHI - Fellow
MARZIA RUGGIERI - Fellow
URSULA MORESI - Logopedist
FRANCESCO BIANCO - Audiometrist

Activity 2004

Otolaryngologic, head and neck oncological surgery is widely performed by the Division staff (more than 540 operations per year), and the highly specialized surgical protocols and/or procedures performed are 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 cannot 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, we aimed at establishing the indications for these transplants and 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 tumor-related mandibular resection is one of the most difficult tasks in maxillofacial surgery.

IORT in head and neck carcinoma

Intra-operative radiotherapy (IORT) is already used to treat different kinds of tumors (such as liver, breast, colon-rectal carcinoma, etc.), in order to deliver a preliminary or an extra-dose of radiation limited to high-risk-of-recurrence structures, as soon as the excision is completed.
IORT is performed by mean of a mobile linear accelerator, which produces 7-9 Mev electron beam, characterized by a low-penetration index (up to 2.5cm).
At the end of the tumor excision, the IORT is focused on the operatory surgical field, preserving the skin and the other structures lying over the oncologic target from irradiation.
Two pilot-studies are on-going at the moment.

- Anticipated boost of 12-18Gy directly to the high-risk zone (primary tumor and/or nodal metastases) in case of R1 or post-operative radiation planned tumors;
- Extra boost of 12-18Gy in case of recurrent irradiated tumors.

Twenty-seven cases have been treated till now; oral cavity tumors in 9 cases, neck space in 7, skull base tumor in 3, pharyngeal tumor in 7, intratemporal space in one case.
No direct short-time complications have been observed, neither has an increase of the surgical-complication rate been evidenced. Follow-up examinations for oncological results are ongoing.

Skull base surgery

Diseases of the skull base are rare but potentially life threatening disorders. Treatment is challenging due to the complex anatomy of the cranial base. Diseases in this area include benign and malignant tumors (cancers).
Diseases can effect the function of the brain or complex senses such as hearing, vision, hearing and balance. Due to the complex nature of the skull base disease, multidisciplinary treatment offers the most up-to-date diagnostic/treatment modalities.
The Division of Otolaryngology Head and Neck Surgery uses a multi-disciplinary approach which combines the skills of Neurosurgery, Otolaryngology and Head and Neck Surgery, Neuroradiology, Radiation Oncology and Intensive Care Medicine. Specialists in these fields collaborate to develop treatment protocols that leverage the resources of the medical research center to provide the safest and most comprehensive care possible. Specially trained and highly qualified staff have the expertise and experience of the latest treatment and care of a wide

variety of lesions. For patients requiring physical rehabilitation after surgery, on-site neuro-rehabilitation therapists are available.

FUNCTIONAL LARYNGEAL SURGERY

When the tumor involves part of the larynx above the vocal cords, surgeons can use techniques to remove the affected part of the larynx only using a technique called Partial Laryngectomy or Supracricoid Laryngectomy, thereby preserving voice.
Even with advanced tumors that involve the vocal cords, and a significant part of the larynx, it is still possible to preserve or restore the voice using a procedure called a Supracricoid Laryngectomy.

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 post-operative pain and shorter hospitalization, compared to conventional surgery.

Publications 2004

ROSELLI R., MUSCATELLO L., VALDATTA L., PAVAN G., SPRIANO G.

Mandibular reconstruction with frozen autologous mandibular bone and radial periosteal fasciocutaneous free flap: preliminary report.

Ann Otol Rhinol Laryngol. 2004 Dec;113(12):956-60. *I.F. 1.085*

Division of intensive care, pain therapy and palliative care

DIRECTOR:
EDOARDO ARCURI, MD

Edoardo Arcuri received his Degree in Medicine in 1967 and the Specialization Degree in Anesthesia and Intensive Care in 1970 from the University of Turin, Italy. He worked as an anesthetist at the 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 the Regina Elena Cancer Institute of Rome, Italy since 1991. Since 1994 he has taught pain therapy at II Specialization School in Oncology at La Sapienza University of Rome. Since 1999 he has been the Director of the Training School in Palliative Care for Central Italy. Since 2004 he has taught pain therapy at the Anaesthesia and Intensive Care Specialization School at the Biomedico University Campus, Rome, Italy. He has been a member of the Pain Therapy Committee (CUF) at the Ministry of Health, interested in the modification of the Italian laws on the use of opioid drugs in pain therapy. Moreover he has been involved in many professional committees for the elaboration of clinical guidelines for chronic pain therapy. Since 1999 he has been the Scientific Consultant for pain therapy at the Sacro Cuore Hospice. He was in charge 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 - MD
A.CALAMARO - MD
F.CENTULIO - MD
F.CIOCCA - MD
L. DI EMIDIO - MD
G.FUSCO - MD
L. LAURENZI - MD
S. NATOLI - MD
L. PELAGALLI - MD
W. TIRELLI - Senior Fellow
P. GINOBBI - Senior Fellow
A. KAPLLANI - Fellow
A. TENORE - Psychologist
R. MILANA - Secretary

Activities 2004

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

a) Intensive Care of Neoplastic Patients

Recently the Department has turned its attention the identification of biological risk factors as a consequence of antineoplastic therapy. In recent years, we have drawn up our ethic-clinical guidelines, regarding the admission of neoplastic patients to the Intensive Care Unit (ICU), with particular attention to those defined as not admissible because of advanced disease.

An agreement with the Sacro Cuore Hospice has been instituted for the admission of patients "out of therapy". This agreement has also been extended to an area of research in pain therapy and psychosocial problems.

b) Oncologic Pain Therapy

Over the last few years we have elaborated an hypothesis regarding a possible tumor interference on the efficacy of opioid treatment, based on the observation of thousands of patients treated by the Pain Therapy Unit. This effect is due to the presence of specific opioid receptors on neoplastic cells: the binding of opioid drugs to these receptors may decrease their analgesic activity. This pseudo-tolerance characterizes many situations in clinical setting of oncologic pain therapy of poor opioid responsiveness. We also demonstrated that one of the functional effects of this particular "trapping" of opiate by the tumor is the release of nitric oxide (NO) [Fimiani C, Arcuri E, et al. Mu3 opiate receptor expres-

sion in lung and lung carcinoma: ligand binding and coupling to nitric oxide release. Cancer Lett. 1999 Nov 1; 146(1):45-51]. This highly diffused gas plays an important role in the development of poor opioid responsiveness conditions (opioid tolerance, hyperalgesia and neuropathic pain). This hypothesis has been verified on experimental models in vivo, in collaboration with the Experimental Research Center of the Regina Elena Cancer Institute [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 any other opioid drug, seems to be involved in this mechanism. (Mastronicola D, Arcuri E, et al. Morphine but not Fentanyl and Methadone affects the mitochondrial membrane potential by inducing nitric oxide release in glioma cells. Cell Mol Life Sci.;61(23):2991-7. 2004 Dec)
These data suggest a complex interference between opioid drugs and tumors and could inspire new analgesic strategies. Therefore, based on this research we have included diagnostic and therapeutic items in our pain therapy protocol to identify and treat the difficulties of poor opioid responsiveness or pain due to paradoxical response to opioid drugs.
c) Palliative Care
The Regina Elena Cancer Institute and the Sacro Cuore Hospice have made an agreement to look into a new model of residential Hospice very different from the current one (residence exclusively reserved for terminal patients). Now, in the Sacro Cuore Hospice a restricted number of beds have been reserved for patients needing supportive care and pain therapy and able to receive assistance for a few hours (Day Hospice) or, over a longer period, to deal with 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 2004

Antonini M., Ettorre G.M., Vennarecci G., D'offizi G., Narciso P., Del Nonno F., Perracchio L., Visco G., Santoro E.

Anti-retrovirals and immunosuppressive drug interactions in a HIV-positive patient after liver transplantation.

Hepatogastroenterology. 2004 May-Jun;51(57):646-8. *I.F. 0.837*

Caraceni A., Zecca E., Bonezzi C., Arcuri E., Tur R.Y., Maltoni M., Visentin M., Gorni G., Martini C., Tirelli W., Barbieri M., De Conno F.

Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group.

J Clin Oncol. 2004 Jul 15;22(14):2909-17. *I.F. 10.864*

Laurenzi L., Natoli S., Di Filippo F., Calamaro A., Centulio F., Anza M., Cavaliere F., Marcelli M.E., Garinei R., Arcuri E.

Systemic and haemodynamic toxicity after isolated limb perfusion (ILP) with TNF-alpha.

J Exp Clin Cancer Res. 2004 Jun;23(2):225-31. *F. 0.574*

Laurenzi L., Natoli S., Benedetti C., Marcelli M.E., Tirelli W., Di Emidio L., Arcuri E.

Cutaneous bacterial colonization, modalities of chemotherapeutic infusion, and catheter-related bloodstream infection in totally implanted venous access devices.

Support Care Cancer. 2004 Sep 15 *I.F. 1.367*

Mastronicola D., Arcuri E., Arese M., Bacchi A., Mercadante S., Cardelli P., Citro G., Sarti P.

Morphine but not fentanyl and methadone affects mitochondrial membrane potential by inducing nitric oxide release in glioma cells.

Cell Mol Life Sci. 2004 Dec;61(23):2991-7. *I.F. 4.995*

Mercadante S., Arcuri E.

Opioids and renal function.

J Pain. 2004 Feb;5(1):2-19. *I.F.2.264*

Mercadante S., Villari P., Ferrera P., Arcuri E.

Prolonged uncontrolled pain, psychological distress, and opioid escalation.

Pain Symptom Manage. 2004 Jul;28(1):1-3. *I.F.1.885*

Niscola P., Arcuri E., Giovannini M., Scaramucci L., Romani C., Palombi F., Trape G., Morabito F.

Pain syndromes in haematological malignancies: an overview.

Hematol J. 2004;5(4):293-303. *I.F. 0.1*

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 has been an associate researcher with the Regina Elena IRCCS, and then became Assistant (1973) and later Aid (1981) in the Anesthesia and Intensive Care Unit, carrying out his work nearly exclusively in the Intensive Care Unit. From 1990 he has been the Director responsible for the Physiopathology Respiratory Unit (2000) latter renamed the Struttura Semplice Dipartimentale (SSD). Over the years he has published works on anesthesia, intensive therapy, parenteral nutrition, pain and pneumology therapy. For some years he has dedicated himself the prevention and treatment of smoking addition and smoke related diseases. He is a member of a number of scientific associations and regional and national working groups also involved in drawing up guide lines. He is Vice President of the Ethical Committee ASP Lazio for oncology screening. Since 2001 he has been Professor in Pharmacology and Diseases of the Respiratory apparatus for the Graduate Course in Nursing Science at La Sapienza University, Rome.

Staff:
DR MARIA PAPALE - MD
DR. ELIUCCIA MASTROPASQUA - MD
DR. GIORGIO PIPERNO - MD
MRS. MARINA BONACCORSI - physiotherapist
DR. ANTONIO SCAPPATICCI, - (for the project "Hospital free of smoke")

Clinical-Scientific Activity Of The Unit 2004

The Physiopathology Respiratory Unit has forwarded its traditional mission through useful objectives, addressing and programming research activities 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 working groups of the Institute; participation and organization of courses, conferences and congresses both for reports as well as professional updating. During 2004, 12.043 services (visits, consultations, instrumental tests and FKT) have been conducted on patients coming from different Departments 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.

There have been a total of 7672 services (visits, instrumental tests) conducted for outpatients, who have come for treatment of pulmonary oncology and other diseases or for the treatment of smoking, as well as those in need of respiratory rehabilitation.
Respiratory rehabilitation is offered to patients who either have to undergo major thoracic or abdominal surgery or have already undergone pulmonary resection for cancer. The objectives are to improve the quality of life and increase our knowledge of an area of respiratory rehabilitation which require further study. In 2004, 699 patients were treated, the equivalent to 2831 services.
About 200 individuals have sought the help of the Center for the treatment of smoking (referral Center for the Observation of Smoke, Alcohol and Addiction of the I.S.S.). Cooperation with the Unit of Psychology of the I.R.E. continues with the aim of evaluating the validity of integrated pharmacologic treatment (substituted with nicotine or with Bupropione) and behavioral treatment of addiction to smoking. The results of this activity have been presented verbally at courses and congresses (Experience of the Center for treatment of smoking of the Regina Elena Institute at the 6th Interregional Congress of AIPO-Lazio; Research on smoking and screening behaviour at the 11th Inter-

national Conference on screening for lung cancer; Prophylaxis and treatment of tabagism at the 6th Interregional Congress of AIPO-Lazio; COPD-prevention: atmospheric pollutants and cigarette smoke at the Pneumology course Focus on COPD), and abstracts (Treatment of tobacco addiction at 5th National Congress on Pneumology; The out-patients' department treatment for tabagism treatment in oncology at the 6th National Congress on Oncology).

As regards the efforts to prevent smoking, the focus has been aimed at educational and didactic intervention for young people in schools (4th Project Education in health care of the Liceo Scientifico G. Peano, Rome: lecture on Respiratory diseases: environmental influences and life style). A resume on the results of a two-year participation in the European Project Don't start, quit and win was written in cooperation with the Epidemiology Unit of the IRE.

The Hospital free smoke project goes on with didactic initiatives and monitoring activities.

The Respiratory Physiopathology Unit also participates in the ELCAP Project headed by the Unit of Radiology and Imaging Diagnostics of the IRE which intends to validate the methods of screening for the early diagnosis of lung cancer in asymptomatic smokers by low-dose spiral CT. The results of this study were presented in the Journal of European Radiology (supplement to Volume 14/February 2004).

The cooperation with the Unit of Radiotherapy of the IRE continues with an observational study on the correlation between the two-dimensional measurements of the quantity of lung comprised in the field of therapy and 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 half, is aimed at evaluating the incidence, with relative methodical radiotherapy, of the possible post-actinic pulmonary lesions. The study is in an advanced stage.

The Unit of Respiratory Physiopathology is part of the Operative Unit International stage III Randomized Multicenter Study conducted in the open on parallel groups, comparing ZD1839 (IRESSA) by mouth vs Docetaxel (Taxotere) intravenous in patients previously treated with chemotherapy with Platinum and suffering from relapsing metastasis or locally advanced non small cell pulmonary cancer.

The Unit is also taking part in a USA-Italian project. Participating in this project our Unit will enroll smokers and nonsmokers with negative spiral CT scan. From each participant will be collected a 10ml sample of blood then which will be examined to identify the proteomic profile and to discover novel molecular targets and potential cell-specific biomarkers for increasing rates of early stage lung cancer detection.

Division of anesthesiology

DIRECTOR:
LUIGI ALOE, MD

Dr. Luigi Aloe graduated in medicine and surgery in 1966 from the University of Studies of Siena and went on to specialize in Anesthesiology at the same university in 1968, and Intensive care at the University of Verona in 1972. In December 1966 he did an internship in the Department of Anesthesiology and Pain Therapy at the Regina Elena Institute of Rome. In 1967 he won a scholarship from the Ministry of Health on Cellular Biochemical Modifications during Hyperthermic Perfusion.
In May 1969 he was a Permanent Assistant in the Department of Anesthesiology, Intensive Care and Pain Therapy at the Regina Elena Institute of Rome, and then from June 1974 to May 1975 he was an Assistant Intern. He became a Full-time Assistant in the same Institute in May 1975. In September 1985 he was in charge of the Regina Elena Institute's project Terapia Antalgica ed aspetti logistico organizzativi nell'ambito del progetto finalizzato del Ministero della Sanità: Assistenza al malato terminale. In December 1988 he was put in charge of the Anesthesiology sector of the Research Protocol on Intraoperative Radiotherapy (IORT). Since 1991 he has held the position as Head of Anesthesiology and the Operating Theater at the Regina Elena Institute and has become the Head of the Department of Critical Areas of Oncology.
Dr. Aloe is the Author of various publications and has participated in many national and international congresses as a speaker and moreover, as a means to update professionally. He has focused his professional and scientific interests on the problems of anesthesia in oncologic 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 for Department of Day Surgery)
DR. EDVINA GALIÈ (student)

Activity 2004

The department of Anesthesiology and the Operating Theater along with the Department of Surgery assure daily surgical activity for patients suffering from complex neoplastic pathologies, in need of highly destructive surgery.

Apart from major surgery, for which all the members of staff require the help of assistants and nurses, there was a significant increase in liver transplants, more than 50% (36 in 2004 against 23 in 2003) in the year 2004.
The Anesthesiology Department also offers a consulting activity in different wards in order to provide the patients with complete and detailed information on surgical risks.
The organization and function of the prehospitalization activity has been left up to the Anesthesiology Department, which has allowed for the complete planning of procedures and processes, resulting in patient satisfaction. This has contributed to a reduction of the waiting lists and has almost eliminated unnecessary admissions.
Furthermore, a correct anesthetic assistance is assured for all patients who use our structure daily in order to undergo various types of diagnostic and therapeutic exams, for example: CAT,

MRI, digital angiographs, gastroenterology endoscopies.

Scientific Activity

The scientific activity of the Anesthesiology and Operating Theater Department which had to be reduced during the past few years due to the prevalence of routine activity and to the chronic lack of staff, has returned to normality since 2003.

The construction of the DMT's, which was eagerly awaited and unanimously shared, has stimulated all the sections of the entire Anesthesiology structure in finding fields of interest in different sectors of various surgical disciplines for the development of anesthesiology protocols, ever more adequate for the needs of our patients.

The study on Conventional treatment with cortico-steroids for treatment with COX-2 inhibitors of the complications of radiotherapy in prostate cancer, which was started in 2003 and lasted 3 years, has enrolled 25 random patients in collaboration with the Department of Radiotherapy. Dr. Tessitore, who is responsible for the Anesthesiology sector intends the preliminary data to confirm the rational of the study, which will be published within the year. Dr. Forastiere has found different interesting lines of research within the field of Surgical Urology, amongst which, we can find the Factors of renal protection in patients undergoing nephrectomies. The study, which took a lead from a critical revision of the literature regarding oncologic patients suffering renal neoplasia and undergoing surgical nephrectomy and evolve towards chronic renal failure at a rate of 15%. This occurs above all in those patients who have manifested acute renal failure that regressed in the period immediately following surgery.

The study foresees a retrospective analysis on the rate of acute renal failures in patients undergoing total nephrectomy for renal neoplasia, the evaluation of the effects of Fenoldopan (renal protector of the antihypertensive type) on the renal function of these patients and the detection of renal protection factors, comparing the use of low dose Dopamine to Fenoldopam.

The natural reduction of the functional reserves of the organs in elderly patients, who ever more frequently undergo surgery due to an extended middle age, necessitates a careful preoperative evaluation, which must take into consideration the vascular reserves and the physiologic and pathologic modifications of the respiratory system. These are conditions that predispose for hypoxemia and hypercapnia, leading to postoperative complications.

The prevention of the onset of these complications which negatively condition the functional postoperative recovery of the elderly patient, is of fundamental importance, and one of the problems the Anesthesiologist has to consider is the choice of the most adequate anesthetic treatment for the various surgical procedures.

There have been studies based on these assumptions, aimed at evaluating General anesthesia vs peridural anesthesia in elderly patients undergoing radical prostatectomy; the Hemodinamic modifications in elderly patients undergoing peridural anesthesia with Repivocaine and the Problems of anesthesiology in elderly patients undergoing laparoscopic surgery.

The numerous variables which characterize postoperative pain and the need for a constant updating of the treatment protocols, using new molecules and new procedures (presidi) have lead us to study the best way to address this problem in order to obtain pain relief without side effects.

Multimodal analgesia proposed by Kehlet et al. in 1989 is currently universally used and finds it rational by exploiting its synergic effect and boost for other analgesics, with a concomitant reduction of side effects.

It is possible to boost synergy by taking advantage of the effects of different drugs on different levels of pain. The local anesthetics, the non steroid anti-inflammatory the opioids and the Alpha 2 agonist have an effect on the peripheral level

The infiltration with local anesthetic in the area of surgical incision reduces the need for systemic analgesics, although, there are currently no studies aimed at evaluating the efficacy of the post surgery administration of a local anesthetic on the lesion.

The data published refer to the intermittent administration of local anesthetics which act for a limited duration, with modest impact on pain control.

For years, the international literature has provided data in agreement on the efficacy of multi-

modal analgesics created by associating intravenous or peridural analgesic drugs. On the other hand, there are very few studies on the combination of agents with a central or peripheral action that act specifically on the surgery site.
The following studies were carried out on this basis, by various surgical specializations and are aimed at evaluating the efficacy of a new procedure ON Q System, which has a continuous flow of local anesthetic in the surgical area for 48 hours:
• Multimodal approach to the treatment of postoperative pain in oncologic surgery. Evaluation of the ON Q Pain Management System / In charge Dr. Ester Forastiere.
• Controlling postoperative pain in thoracic surgery via ON Q Pain Management System / In charge, Dr. Michela Maritti.
• Controlling postoperative pain in patients undergoing total intravenous anesthesia (TIVA) through ON Q Pain Management System / In charge, Dr. Loretta Tessitore.

The surgical risk in patients affected by cervico-facial neoplasia is usually evaluated by using anesthetic risk scales, which take the cardio circulatory, pulmonary, hepatic and renal functions of the patients into account.
None of the scales used shows a specific application for highly destructive surgery of the cervico-facial area and generally they all have limits, due to the fact that they do not take into account other parameters, such as the patients age, type of surgery, type of anesthesia, length of the operation, use of steroids, preoperators, broncodialators, opioid nitrates of postoperative chemo and radiotherapy.
In order to verify the influence these factors have on increasing surgical risk, Dr. Maria Sofra has created a study on; A multivariate analysis on the prognostic role of some anesthetic risk scales in patients operated for cervico-facial neoplasia.
Highly destructive surgery of the cervico-facial tract (or area) which consider reconstruction with microvascular flaps foresee hematic leakage, elevated tissue loss, an elevated thrombotic risk secondary to a ischemia-reperfusion syndrome and a increased thrombotic risk due to the high number of smokers and drinkers among the patients.
The study carried out by Dr. M.C. Sofra in 2003 on the Possible benefits of hemodilution in highly destructive surgery with reconstruction of microvascular flaps in patients with tumors in the cervico-facial area, has evidenced a significantly reduced incidence of thrombo-embolic complications and has allowed for the layout of a standardized treatment protocol in which the essential conditions are hemoglobin values of 10-11gr and hematocrit values which should never exceed 30%.
There is hope that during the course of 2005, the different specializations can individuate other fields of interest in order to stimulate an increasingly fruitful research activity in every section of the Anesthesiology Department, in accordance with the institutional aims of the Institute.

Scientific Publications 2004

Di Filippo F., Cavaliere F., Anza M., Garinei R., Botti C., Perri P., Di Angelo P., Patrizi V., Di Filippo S., Visca P.

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

J Chemother. 2004 Nov;16 Suppl 5:66-9. *I.F. 1.088*

Di Filippo F., Cavaliere F., Garinei R., Anza M., Di Angelo P., Psaila A., Piarulli L., Callopoli A., Bruno P., Di Filippo S., Priore F.

TNFa-based isolated hyperthermic limb perfusion (HILP) in the treatment of limb recurrent melanoma: update 16 years after its first clinical application.

J Chemother. 2004 Nov;16 Suppl 5:62-5. *I.F. 1.088*

Cardiology Unit

DIRECTOR:
ITALO SACCHI, MD

Dr. Italo Sacchi, was born in Rome 19/5/1951. He graduated suma cum laude in medicine and surgery from La Sapienza University in Rome in 1976. From the forth year of the course he attended the school of Prof. Luigi Condorelli, under the direction of Professors Turchetti, Sangiorgi, Sciacca, Testoni, Corsi and Dagianti. In 1980 he specialized (summa cum laude) in Cardiovascular Diseases at La Sapienza University of Rome and in 1986 in Sports medicine (summa cum laude). From February 1983 he has been a member of the Cardiology Department of the Regina Elena Institute I.F.O in Rome, initially as an assistant cardiologist and from the 1st July 1990 as permanent assistant. In 1989 he qualified as a consultant of cardiology and since May 2001 he has been in charge of the Department of Cardiology of the Oncology Center of the Regina Elena and the Dermatology Center of San Gallicano I.F.O.
His main area of scientific interest has been directed towards non invasive instrumental diagnostics, applied to the study, the prevention and cure of ischemic cardiopathy, cardiac decompensation, arterial hypertension, clinical arrhythmology and cardiotoxicity from antitumoral drugs.

Directors of Cardiology:
DR. ARMANDO CARPINO - MD
DR. FABIO MARAMAO - MD
DR. NICOLA MORACE - MD
DR. GIUSEPPE TOGLIA - MD

Activity 2004

During 2004, the assisted and specialized consultations which were carried out by the Department of Cardiology of I.F.O. numbered 27,142, divided as follows: 16,622 clinical and instrumental tests for patients of the Department and the day hospital of the Regina Elena Institute (+ 11% compared to 2003), 3,308 for patients of the Department and day hospital of the San Gallicano Institute (+ 0.25% compared to 2003), 7,212 for outpatients (- 17% compared to 2003).

In 2004, the internal institutional activity of the IRE has also increased significantly, reflecting the on going progress since 2002 after the development and increased potential of the Institute, when the two I.R.C.C.S were transferred to the new structure in Mostacciano in November 2000. Within the last three years the Institute has managed to establish the following. Liver transplant center, the third division of Medical
Oncology, a new division of Hematology and Oncological Ortopedics, a service for prehospitalization, full use of all the beds along with a high level of assistance and performance as well as scientific activity.
Furthermore, this considerable increase of the internal activity has influenced in no small way the development of the outpatient departments of the region, given the extensive area for which our Institute is responsible there has been a notable request for cardiac visits
As usual, besides the general presurgery cardiac evaluation of oncologic patients aimed at defining individual cardiac risk and post surgery cardiac assistance in complications from surgery and intrahospital emergencies, the primary institutional aim of the Department of Cardiology has been the prevention, early diagnosis and cure of cardiotoxic effects of antitumoral drugs, in particular the derivatives of anthracyclines as well as damage due to oncological radiotherapy treatment.
Besides anthracyclines, current oncologic therapy avails itself of chemotherapic drugs, already in common use, such as Trastuzumab and Taxanes These are often used in temporal or sequential association, as has been widely shown, can hold some risk, even chronic, after months or even years of cardiotoxicity, enough to bring on an unfavorable prognosis of cardiomyopathy at 5 years in nearly 50% of the cases.
The outpatients attached to our Department is dedicated to cardioprotection against cardiotoxicity of antiblastic drugs. The aims are, on the one hand, to gather information on the preclinical manifestations and its prevalent signs in the early and still asymptomatic

phase (subclinical cardiotoxicity). On the other, in cooperation with oncologists, to conduct monitoring procedures,
reserved in particular for oncologic patients with associated cardiovascular pathology, and aimed at defining compatible therapeutic strategies. This
involves variation of dose, type and modality of administration of chemotherapeutics and early chemioprotective cardiologic therapy, for those patients who may benefit in some way from favorable expectations and quality of life after chemotherapy for their oncologic disease.
Apart from a cardiac visit with ECG this service makes use of echocardiograph color Doppler. This is the most important and qualifying diagnostic activity of our Department with 3,000 internal and external exams annually, thanks to the peculiar diagnostic usefulness of echocardiographs both in the evaluation of oncologic patients for surgery as well as the monitoring of cardiotoxicity from antiblastics.
Of note, echocardiograms color Doppler both at rest and under induced stress is universally the most common method of monitoring the study of the left ventricular systolic function (ejection murmurs) and in particular for the study of diastolic relaxation through Color flow Doppler analysis.
The results obtained by some recent studies and their projected follow-up at one year have in fact demonstrated the early dysfunction of the ventricular myofibrilation, above all its diastolic relaxation properties (analyzed with precision with the tissular Doppler technique), rather than systolic contractions, represents a more sensitive and accurate early marker of subclinical cardiotoxicity.
In these studies, along with the diastolic dysfunction some biochemical markers such as troponine (TnT and TnI) as well as the cardiac natriuretic hormones, in particular the cerebral (BNP and NT pro-BNP) have been suggested as early and specific markers of left ventricular dysfunction in the subclinical stage, to be seen even before the pathological reduction of the F.E.
In fact, values of tissular echo Doppler and NT pro-BNP at the end of therapy were highly altered before the disappearance of the disease when the same conventional Doppler indicators and above all the ejection murmurs were still in normal limits, can be observed in the follow-up at one year, in subjects who develop a II or III class clinical cardiomiopathy NYHA (of 5 to 10%, according to the type of chemotherapy).
Our Department has also adopted new and safer methods for the procedures and monitoring of subclinical cardiotoxicity and associated preliminary results are in agreement with those of studies to be found in literature.
During 2004, in our outpatients for cardioprotection, out of 850 breast cancer patients under observation 190 have been monitored, undergoing potentially cardiotoxic chemotherapy with anthracycline derivatives (also Liposomial) used alone or in combination, with Trastuzumab, Taxanes, Vinorelbine and Gemcitabine. Of these 5 have been identified as presenting functional and or biochemical markers of subclinical cardiotoxicity, limiting the dose of biochemical markers to only those patients (13) at high risk because of the coexistence of associated cardiac pathology.
More than 450 echocardiograms have been carried out on patients undergoing high dose chemotherapy, and not with one of the more common antiblastic drugs which might lead to cardiac compromise (Cyclosphosphamide, Cisplatin, 5-fluorouracile, Interleukin).
The research activity of the Department on various current and finalized institutional clinical research protocol which involves all the heads of department is generally carried out in close cooperation with the three oncological divisions as well as the hematology division of the Regina Elena Institute.
In 2004 the Cardiology Department of IRE has been involved in the following studies:
- monitoring of cardiotoxicity related to antiblastic chemotherapy. Anthracycline derivatives used alone or in association, in cooperation with the A, B and C divisions of Medical Oncology.
- in breast cancer (in the metastatic phase or not) with Doxorubicin,

Epiribicin, Trastuzumab, Paclitaxel, Docetaxel and Gemcitabine in primary or adjuvant chemotherapy programs.

• in solid tumors treated with high dose chemotherapy schedules cardiac visits are carried out before, during and in the follow up of chemotherapy with ECG and echocardiograms intended to highlight subclinical cardiotoxicity signs and to prevent the onset of dilated cardiomiopathy.

• clinical-instrumental cardiac monitoring, in cooperation with the Hematology division, for patients affected by hemopoietic tumors due to both the therapeutic regimes (chemo-radiotheraputic), often aggressive and intensive which may cause acute or chronic cardiac events, or due to the involvement of the heart provoked by the tumors because of direct infiltration or compressive mechanisms or alteration of the hemorrheologic characteristics of the blood.

• in the active phase, a prospective observational study in cooperation with the Medical B Oncology and Nuclear Medicine Division to evaluate the cardiotoxicity of anthracyclines and Liposomial anthracyclines in 150 patients, to evaluate the clinical, instrumental (basal scintigraph and myocardial - echocardiogram under stress for the evaluation of F.E. and the proto-diastolic relaxation) and serous (biochemical markers: Troponine Mioglobin, NT-proBNP)

• echocardiograph monitoring of the clinical evolution of pericardiac effusion of the paracardiac masses and of tumors of the heart.

Publications 2004

Fabi A., Papaldo P., Pino M.S., Ferretti G., Carlini P., Pacetti U., Di Cosimo S., Nardoni C., Giannarelli D., Sacchi I., Cognetti F.

Epirubicin plus docetaxel in metastatic breast cancer: escalating dose does not improve efficacy. A phase II study.

Anticancer Res. 2004 May-Jun;24(3b):1963-7. *I.F. 1.347*

Laboratory A of experimental chemotherapy

DIRECTOR:
GABRIELLA ZUPI, PhD

Gabriella Zupi received her degree in Biological Science in 1968 from La Sapienza University of Rome. In 1970 she was a visiting Scientist at the Laboratory of Molecular Biology, the University of Alabama, Birmingham, USA. From 1978-87 she was the Biology Director at the Regina Elena Cancer Institute of Rome, Italy and since 1988 she has been the Director of the Lab of Experimental Preclinical Chemotherapy at the same institue.
Dr. Zupi's research interests are devoted to the study of the involvement of some oncogenes in tumor progression and in response to chemotherapy of solid tumors.

Staff:
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
DR. ANGELA RIZZO - Fellow
DR. ERICA SALVATI - Fellow
DR. LUDOVICA CIUFFREDA - Fellow
DR. SIMONA GIORGINI - Fellow
DR. DANIELA TRISCIUOGLIO - Fellow FIRC
DR. LAURA CASTELLINI - Fellow
DR. MARIANNA DESIDERI - Fellow
DR. ADELE PETRICCA - Fellow
ROBERTO BOSI - Technician
ANDREA PECCI - Technician
FABRIZIO BONAVENTURA - Technician
RAFFAELE DOCIMO - Technician
MARCO SCARSELLA - Technician
ROBERTA BONIFAZI - Student
VALERIA SPINOLA - Student

Activity 2004

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 demonstrated that bcl-2 overexpression in human breast carcinoma and melanoma cells exposed to hypoxia increases the expression of vascular endothelial growth factor (VEGF) gene through the hypoxia-inducible factor-1 (HIF-1), and modulates the urokinase plasminogen activator receptor (uPAR) expression through extracellular regulated kinase (Erk)-dependent Sp1 transcription factor activity.
During 2004 we performed experiments to evaluate signaling pathways involved in bcl-2-induced VEGF and HIF-1α expression. We demonstrated that exposure of bcl-2 overexpressing melanoma cells to hypoxia induces phosphorylation of AKT and activation and consequent redistribution of ERK1/2 proteins into subcellular compartments. Pharmacological inhibition of MAPK and phosphatidylinositol 3-kinase (PI3K) signaling pathways reduced the induction of VEGF and HIF-1 in response to bcl-2 overexpression in hypoxia. In particular, treatment of bcl-2 overexpressing cells with specific inhibitors of MAPK (UO126, PD98059) and PI3K (LY29402, Wortmannin) reduced VEGF protein, mRNA expression and VEGF promoter activity and this reduction was paralleled by a decrease in HIF-1α protein expression, DNA binding and transcriptional activity. We also demonstrated that RNA interference-mediated down-regulation of bcl-2 expression results in a decrease in the ERK1/2 phosphorylation and VEGF secretion. These results indicate that activity of multiple signal transduction pathways is required for the HIF-1-mediated induction of VEGF by bcl-2 overexpression in melanoma cells exposed to hypoxia, and that PI3K and MAPK pathways play an important role in bcl-2-induced angiogenesis in this experimental model.

We also found that bcl-2 overexpression in human melanoma cells consistently induces the activity of multiple metastasis-related proteinases and enhances in vitro cell invasion. In particular, by using the M14 parental cell line and bcl-2 overexpressing derivatives, we found that bcl-2 overexpressing cells exposed to hypoxia, when compared to parental cells, express higher level of several metalloproteases (MMPs) such as MMP-2, MMP-7, MT1-MMP, and tissue inhibitors of metalloproteases-1 and -2. We also demonstrated an increase in urokinase plasminogen activator receptor expression, and a cell surface preferential partitioning of urokinase plasminogen activator in bcl-2 transfectants when compared to parental cells. Moreover, an in vitro assay evidenced that bcl-2 overexpression in melanoma cells increases invasion in matrigel. Finally, experiments performed using nude mice demonstrated the ability of bcl-2 to increase in vivo tumor growth. These data indicate that bcl-2 plays a significant role in the regulation of molecules involved in tumor progression, and that, through this mechanism, bcl-2 in cooperation with hypoxia may contribute to malignant progression.

We are also evaluating whether different inhibitors of CXCR1 and CXCR2 IL-8 receptors (furnished by Dompè) are able to modulate in vitro and in vivo growth and angiogenesis of several human melanoma lines expressing different levels of the receptors. In particular, we are focusing our attention on M20 and A375 SM human melanoma lines, which are metastatic and express different but considerable levels of both IL-8 receptors. We have observed a consistent decrease in in vitro cell proliferation and migration and in vivo tumor growth after exposure of melanoma cells to several inhibitors. In parallel, we are studying whether IL-8 receptor inhibitors induce the inhibition of angiogenesis-related endothelial cell functions, such as proliferation, differentiation and migration. We have preliminary evidence that IL-8 receptor inhibitors decrease some endothelial cell functions crucial to angiogenesis.

Finally, in collaboration with Dr Milella we investigated the possible existence of an anti-apoptotic cross-talk between HER-2 and anti-apoptotic Bcl-2 family members, and assessed whether the Mammalian Target of Rapamycin Inhibitor, Temsirolimus (CCI-779), is able to modulate angiogenesis. We demonstrated that trastuzumab downregulates bcl-2 expression and potentiates apoptosis induction by bcl-2/bcl-XL bispecific antisense oligonucleotides in HER-2 gene amplified BT474 breast cancer cells, and that CCI-779 interferes with some steps in angiogenesis progression.

2 Role of c-Myc in cellular response to stress

Beside the well-established role of c-Myc in regulating cell growth, a novel picture is beginning to emerge identifying new functions of c-Myc in multiple metabolic pathways.

We defined a functional role for the c-Myc oncoprotein in determining cellular redox balance and response to oxidative stress. We demonstrated that c-Myc regulates γ-glutamyl-cysteine synthetase (γ-GCS), the enzyme responsible for catalyzing the rate-limiting step in the bio-synthesis of glutathione, the most important low molecular thiol involved in cellular detoxification, maintaining redox homeostasis and determining response to oxidative stress. Specifically, c-Myc protein directly bound and activated promoters of both heavy and light γ-GCS subunits. Deletion of c-Myc boxes on both regulator regions significantly reduced the promoter transcriptional rate. The mechanism underlying γ-GCS regulation by c-Myc has also been defined. The regulation of γ-GCS genes by c-Myc strictly depends on the intracellular redox state. Exposure to H2O2 led to a fast reactive oxygen species production, concomitantly to a higher γ-GCSH and γ-GCSL promoter activity and mRNA expression. The stress-triggered GSH neo-synthesis enhanced c-Myc recruitment to γ-GCS promoters that was completely abolished by loading cells with exogenous GSH ethyl ester. H2O2 treatment did not affect c-Myc protein expression levels but triggered phosphorylation at Ser62/Thr58 residues. Stress-induced post-translational modification of c-Myc protein was mediated by ERK and drove c-Myc to γ-GCS promoters. Phosphorylation at the Thr58 site was required for c-Myc recruitment to γ-GCS promoters, since the mutant c-MycT58A protein was unable to bind to either of the γ-GCS regulator regions. Finally, over-expression of both exogenous c-Mycwildtype and c-MycS62A protected cells from H2O2-induced damage, whereas mutant c-MycT58A and c-MycT58A/S62A did not, thus demonstrating the key role of c-

Myc phosphorylation at a specific residue in determining the cellular response to oxidative stress.

3 pRb2/p130 role in drug-induced apoptosis

pRb2/p130, together with pRB/p105 and p107, is a member of the retinoblastoma family and is known to play an important role as a negative regulator of cell proliferation.
In addition to their original function as cell cycle regulators, the Retinoblastoma (Rb) family members were recently reported to modulate the sensitivity of cancer cells to apoptosis induced by different chemotherapeutic agents. Several studies highlight an anti-apoptotic function of pRb/p105 but little is known about the role of the other two Rb family members, pRb2/p130 and p107, in apoptosis. We have investigated the possible role of pRb2/p130 in the sensitivity of ovarian cancer to Camptothecin, Doxorubicin and Taxol. Through adenoviral trasduction, the pRb2/p130 protein was overexpressed in the CAOV-3 ovarian cancer cell line and its effect on sensitivity to apoptosis trigged by IC50 doses of different drugs was evaluated by various methods, including MTT assay, flow cytometry and Western blot analyses. We evaluated the effect of pRb2/p130 expression on the sensitivity of an ovarian cancer cell line to treatment with three drugs with different mechanism of action: Camptothecin, Doxorubicin and Taxol. The results support the conclusion that overexpression of pRb2/p130 in the CAOV-3 ovarian cancer cell line is able to inhibit apoptosis triggered by Camptothecin and Doxorubicin through the c-Jun N-terminal kinase (JNK) signaling transduction pathway, whereas Taxol-induced apoptosis does not seem to be influenced by pRb2/p130. Specifically, with Camptothecin and Doxorubicin treatments, pRb2/p130 inhibits the NH2-terminal phosphorylation of the c-Jun induced by the drugs, which is crucial since it inactivates the c-Jun transactivation ability, leading to an arrest of the downstream apoptotic pathway. We found that pRb2/p130 inhibits the autophosphorylation activity of JNK in the Camptothecin-treated cells, therefore inactivating its ability to phosphorylate c-Jun. This does not appear to happen with Doxorubicin treatment, which led us to the conclusion that different pathways, other than JNK, act as upstream effectors for c-Jun phosphorylation and are, indeed, influenced by pRb2/p130 overexpression.
Overall, these data suggest a significant impact of pRb2/p130 in inhibiting Camptothecin- and Doxorubicin-induced apoptosis.

4 Telomere maintenance mechanisms in cancer therapy

Activation of the enzyme telomerase is the major mechanism by which cancer cells maintain their telomeres. The proposal that the upregulation of telomerase expression is a critical step in the process of malignant transformation of cells has made this enzyme a potentially useful new target for cancer therapy. However, the therapeutic outcome, resulting from this strategy, strictly depends on telomere shortening, which would require a long treatment duration. While telomerase may not be the universal target for cancer therapy, targeting the telomere maintenance mechanisms will be important in future research aimed toward a successful strategy for curing cancer.
We demonstrated that pharmacological targeting of telomeres by using a new G-quadruplex ligand, the pentacyclic acridine, 3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]acridinium methosulfate (RHPS4), is effective on human melanoma lines, possessing long telomeres. We also elucidated the relationship between G-quadruplex-based telomerase inhibitor-induced cellular effects and telomere length/dysfunction. The cellular pharmacological effects of RHPS4 have been evaluated by treating melanoma lines with increasing concentrations of RHPS4. A dose-dependent inhibition of cell proliferation was observed in all the lines during short-term treatment. Flow cytometric analysis demonstrated that RHPS4 induced a dose-dependent accumulation of cells in the S-G2/M phase of the cell cycle. The RHPS4-induced cell cycle alteration was irreversible even at low doses, and the cells died from apoptosis. At high RHPS4 concentration, apoptosis was accompanied by the induction of a senescence phenotype: large cell size, vacuolated cytoplasm and ≤-galactosidase activity. The short-term biological activity of RHPS4 was not due to telomere shortening, but it was associated

with telomere dysfunction, in terms of presence of telomeric fusions, polynucleated cells, and typical images of telophase bridge. In conclusion, our results demonstrate that the G-quadruplex ligand RHPS4 can function in a telomere length-independent manner through its ability to cause telomere-capping alterations. On the basis of the promising in vitro results, the antitumoral effect of RHPS4 will be studied in vivo alone or in combination with antineoplastic drugs.

We also demonstrated that upregulation of telomerase can be an additional mechanism by which bcl-2 oncogene exerts its antiapoptotic effect. In this study, the 4625 Bcl-2/Bcl-xL bispecific antisense oligonucleotide and the HA14-1 Bcl-2 inhibitor were used. We found that apoptosis induced by 4625 oligonucleotide was associated with decreased Bcl-2 protein expression and telomerase activity, while HA14-1 triggered apoptosis without affecting both Bcl-2 and telomerase levels. Interestingly, HA14-1 treatment resulted in a profound change from predominantly nuclear to a predominantly cytoplasmatic localization of hTERT. Upregulation of telomerase by Bcl-2 or hTERT overexpression blocked both 4625 and HA14-1-induced apoptosis. The mutant biologically inactive hTERT-HA showed a similar behavior as the wild-type form, indicating that hTERT inhibited the Bcl-2-dependent apoptosis regardless of its ability to lengthening telomeres. Finally, both hTERT and Bcl-2 protected from 4625 and HA14-1-induced mitochondrial dysfunction and inhibited nuclear export of hTERT. In conclusion, our results demonstrate that hTERT is involved in mitochondrial apoptosis induced by interference with Bcl-2 expression and function. Therefore, inhibitors of telomerase can be effective in tumor cells expressing high bcl-2 levels.

5 Combination targeted therapy for human solid tumors

We have previously demonstrated that combination of antisense oligonucleotides and cytotoxic drugs is a promising approach in cancer treatment. In this context we have also demonstrated that the combination of two antisense oligonucleotides targeted to bcl-2 mRNA (ODN bcl-2) and c-myc mRNA (ODN c-myc) in some human melanoma lines are more effective combined with cisplatinum (DDP) than the combination of a single antisense oligonucleotides with DDP. We have demonstrated that the efficacy of the combination is sequence dependent and this is consistent with previous data which demonstrate that the use of ODN bcl-2 as the first drug sensitizes to chemotherapy and that ODN c-myc administered after DDP prevents cells from progressing through the cell cycle, demonstrating the relevance of the sequence of administration in improving the antitumor efficacy. In addition we have proved that the efficacy of the antisense oligonucleotides treatment correlates with the level of expression of the two target genes in melanoma cells; in fact, the treatment was ineffective in a tumor which lacks detectable levels of c-Myc and Bcl-2 proteins. On the contrary, the combination treatment was effective in two tumors which express high levels of c-Myc and Bcl-2. We have also explained that the efficacy of the combination is due to a significant increase in the apoptotic index and proliferative index ratio and a significant reduction in tumor vessel density. The combination of these effects, including Bcl-2 and c-Myc down regulation, together with reduced vessel formation, decreased proliferation index and increased apoptosis, results in an increase of life span of treated mice. Studies are in progress to validate these results on other melanoma tumors and in prostate tumors.

Data reported over the last few years have demonstrated that the nitric-oxide donating non-steroidal antiinflammatory drugs (NO-NSAIDs) maintain the chemopreventive properties of classical NSAIDs against the risk of colorectal cancer and exert a protective effect on gastric mucosa damage, due to long-term treatment with NSAIDs. We are studying a new NO-NSAID compound (NCX-4040) and we have proved that it is effective in reducing the proliferation and inducing apoptosis in human colon cancer cell lines. Apoptotic death was induced by mitochondrial-dependent signaling pathways, as demonstrated by the concomitant activation of caspases-9 and -3 a few hours after NCX 4040 exposure. The lack of efficacy of aspirin and the denitrated NCX 4042 indicates a pivotal role of the -NO2 group in the NCX-4040 induced an antiproliferative effect. The long-term in vivo administration of NCX-4040 demonstrates that this drug was well tolerated by mice and it was able to inhibit

the growth of human colon cancer xenografts.
Based on this evidence we have evaluated the antitumor activity of NCX 4040, in combination with antineoplastic drugs on a panel of human colon cancer lines in vitro and on xenografted immunosuppressed mice in an attempt to improve the response of human colon cancer to chemotherapy. The cytotoxic activity of the NCX 4040 and oxaliplatin combination was evaluated in vitro following simultaneous exposure or different drug sequences. Simultaneous exposure to both drugs or a 24-h exposure to Oxaliplatin followed by a 24-h treatment with NCX 4040 did not significantly increase cell death induced by a single drug. Conversely, a synergistic interaction was produced in all cell lines, in a sequential administration of the drugs. Similarly, in xenografted colon cancer-bearing mice, a combination of the two agents produced a 60% tumor weight reduction which was significantly higher than that induced by Oxaliplatin 20% ($p< 0.01$) or NCX 4040 40% ($p<0.05$) used alone. These data demonstrate the ability of NCX 4040 to sensitize human colon cancer to the effect of chemotherapeutic agents, both in vitro and in vivo, and suggest that the combination of this novel NO-NSAID with antineoplastic drugs could be potentially useful for the clinical management of this tumor.

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Laboratory B of immunology

DIRECTOR:
PIER GIORGIO NATALI, MD

Pier Giorgio Natali, MD graduated in Medicine and Surgery in 1966, La Sapienza University in Rome. 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 Academy of Microbiology in Medical Lab. Immunology, USA (1987). Held the position of Visiting Professor in the Dept.s of Tumor Immunology at Scripps Clinic (1977-1978) and Pathology at the 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 is a co-founder of the Chart of Paris (2000). He is presently serving in a number of committees of the American Association for Cancer Research and on the Editorial board of J. Translational Medicine. 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. (Citation Index 2003)

Staff Scientists:
PATRIZIO GIACOBINI - MD
PAOLA NISTICÒ - MD
ORESTE SEGATTO - MD

Post-doctoral Fellows:
EZIO GIORDA - PhD
LEONARDO SIBILIO - PhD
ALINE MARTAYAN - PhD
SERGIO INASTASI - PhD
GIANLUCA SALA - PhD
DUILIA DEL BELLO - PhD
BELINDA PALERMO - PhD

Ph.D students
ELEONORA PUGGIONI - B.SC.
JASMINKA OMEROVIC - B.SC

Marie Curie Training Site Fellows (Dr. Natali Coordinator, Drs F. Guadagni and M.G. Paggi Mentors)
LAURENCE HAVARD - PhD, Liegi Univ. Hospital

Master Dimotech - Biotechnologies in Oncology (MUIR)

VALERIA SFRECOLA - PhD
ANTONELLA MARZIA DE MATEIS - PhD

Technicians
ROCCO FRAIOLI
GIULIANA FALASCA
CYNTHIA FULL RED
EMILIO CAMILLI
MARIA VINCENZA SARCONE
ALESSANDRA RANIERI

Biology Students
ANDREA CONIDI
ELISA MELUCCI
FRANCESCA BAIETTI
VALENTINA FEDERICI
ELISA LO MONACO
STEFANO LUCIOLI
GIANPAOLO CENTRA
MICHELE BALSAMO
PAMELA ROSSI
FROSI YURI

Hosts
MARIA RITA NICOTRA - Istit. Biologia e Patologia Molecolari, CNR
MAURIZIO ALIMANDI - PhD Dip. Medicina Sperimentale e Patologia La Sapienza Univ.

FLAVONOIDS INHIBIT MELANOMA LUNG METASTASIS BY IMPAIRING TUMOR CELLS ENDOTHELIUM INTERACTIONS (IN COLLABORATION WITH DEPT. ONCOLOGY AND NEUROSCIENCES, CHIETI UNIV.) *(Pier Giorgio Natali, MD)*

We have previously shown that flavonoids are capable of impairing tumor growth and metastasis in murine melanoma. To gain insights into the mechanisms underlaying metastasis inhibition, we have employed the B16-BL6 murine melanoma lung metastasis model. B57BL/6N mice were injected i.v. with tumor cells and Apigenin, Quercetin, or Tamoxifen, each at 50 mg/Kg given i.p., and lung tumor cell colonies counted 14-16 days thereafter. Three different injection schedules were used for each drug: a) daily injection, starting 24 hrs before injection of the tumor cells; b) single dose, 24 hrs preceding tumor challenge; c) daily injection, starting 24 hrs after the injection of the tumor cells. All three compounds significantly reduced tumor lung deposits (Apigen=Quercetin>Tamoxifen). However, when treatment was delayed by 24 hrs after tumor cells (schedule c), multiple daily doses of Apigenin or Quercetin were less effective than a single dose of the same compound given 24 hrs before tumor challenge (schedule b). These findings led us to hypothesize that flavonoids may reduce, metastatization by interfering with host microenviromental "factors". To test this hypothesis we will now evaluate whether flavonoids impair the early attachment of tumor cells to the endothelium.

PHENOTYPIC AND FUNCTIONAL CHANGES OF HUMAN MELANOMA XENOGRAFTS INDUCED BY DNA HYPOMETHYLATION: IMMUNOTHERAPEUTIC IMPLICATIONS (IN COLLABORATION WITH DIV. MEDICAL ONCOLOGY, IMMUNOTHERAPY, SIENA UNIV.) *(Pier Giorgio Natali, MD)*
In vitro evidences have raised the possibility that DNA hypomethylating drugs may have immunomodulatory activity. We investigated the potential of 5-aza-2'-Deoxycytidine (5-AZA-CdR) to modulate the expression of components of the tumor recognition complex by human melanoma xenografts, resulting in improved immune recognition and immunogenicity of neoplastic cells. In this regard we have used three primary cultures of melanoma cells, with distinct immune phenotype and growth rate which, were grafted into BALB/c nu/nu mice receiving different dose- and time-schedules of 5-AZA-CdR. We have been able to demonstrate a de novo, long-lasting expression of the Cancer Testis Antigens (CTA) MAGE-1, -2, -3, -4, -A10, GAGE 1-6, NY-ESO-1, and the up-regulation of MAGE-1, MAGE-3 and NY-ESO-1 levels tumors of 5-AZA-CdR-treated mice. Concomitant and persistent up-regulation of HLA class I antigens and of HLA-A1 and -A2 alleles was also documented. We are now evaluating whether 5-AZA-CdR enhances the immunogenicity of melanoma cells i.e. stimulators of autologous PBMC in mixed lymphocyte-tumor cultures.

LAMININ □2 ISOFORM AND EGF IN VESSEL NEOPLASTIC INVASION AND METASTASIS IN SCLC (IN COLLABORATION WITH DEPT EXP. MEDICINE, LA SAPIENZA UNIV., ROME). *(Pier Giorgio Natali, MD)*
The kinetic of Laminin □2 chain expression in endothelial cells strongly suggests that, this molecule is an early marker of neoangiogenesis. We investigated whether and how laminin □2 chain expression may favor transendothelial migration of neoplastic cells and metastasis during angiogenesis. Expression of laminin □2 was documented in vivo with high frequency in pulmonary vessels of small and large cell neuroendocrine carcinomas, suggesting a relationship between laminin □2 chain positive vessels and the high metastatic rate of these tumors. To address this issue we used the AE-2 lung neuroendocrine carcinoma cell line for in vitro studies which costitutively expresses □□/ß1 and □/ß1 integrins. We can demonstrate that EGF a known stimulator of these heterodimeric receptors is capable of increasing migration of AE-2 cells through laminin □2 than through laminin 1 coated filters. We will now extend these experiments using monolayers of endothelial cells.

C-KIT AND STEM CELL FACTOR EXPRESSION IDENTIFIES A SUBSET OF NEUROBLASTOMAS WITH MORE AGGRESSIVE MOLECULAR AND CLINICAL FEATURES (MULTICENTER STUDY: LA SAPIENZA UNIV, BAMBIN GESÙ HOSPITAL, ENEA, CNR, ROME. DEPT. PATHOLOGY SURGERY, UNIV. LIVERPOOL., DEPT. PATHOLOGY UNIV. KIEL). *(Pier Giorgio Natali, MD)*
Stem celI factor (SCF) and its receptor c-kit play a key role in the differentiation of progenitors cells. With the aim of investigating the prognostic relevance of c-kit and SCF expression in neuroblastic tumors (NTs), were analyzed 168 NTs for c-kit and SCF expression using immunohistochemistry and Northern blot analysis. Mutational status of c-kit was evaluated using PCR on DNA extracted from paraffin sections. Correlation between c-kit and SCF expression and histological, clinical and molecular features were analyzed using X2 test, univariate and multivariate regression analyses. C-kit protein expression was detected in 21 of 168 NTs (13%) and was present in neoplastic neuroblasts. c-kit mRNA was detected in 23 out of 106 NTs (22%). SCF protein was documented in 30 out of 106 NTs (28%) by immunohistochemistry and its mRNA in 33 out of 106 NTs (31%). Mutations in exon 11 of the c-kit gene could not be demonstrated in 9 c-kit positive and 9 c-kit negative matched NTs. The presence of c-kit and SCF expression correlated by univariate analysis with advanced stage (3 and 4), MYCN amplification and 1p36 allelic loss. Cox simple regression analysis demonstrated that overall survival was 17% in patients with c-kit positive tumors and 68% in c-kit negative cases (p<O.OOl). Likewise, survival probability was 43% in SCF positive cases compared to 78% in SCF negative patients (p<0.001). These results demonstrate that c-kit and SCF expression identifies a subset of NTs with unfavorable clinical and molecular features. This manuscript is being submitted for publication.

NEGATIVE SIGNALLING TO ERBB RECEPTORS: IMPLICATIONS TO BREAST CANCER PATHOGENESIS AND THERAPEUTICS *(Oreste Segatto, MD)*
An emerging paradigm holds that loss of negative signaling to receptor tyrosine kinases (RTKs) is permissive for their oncogenic activity. We have addressed tumor suppression by RALT/MIG-6, a transcriptionally-controlled feed-back inhibitor of erbB RTKs discovered in our laboratory, in breast cancer cells. Knock-down of RALT expression by RNAi enhanced the EGF-dependent proliferation of normal breast epithelial cells, indicating that loss of RALT signaling in breast epithelium may represent an advantageous condition during erbB-driven tumorigenesis. Although we did not detect mutational inactivation of the RALT gene in human breast carcinomas, RALT mRNA and protein expression was strongly and selectively reduced in ERBB-2-amplified breast cancer cell lines. Reconstitution of RALT expression in ERBB-2-amplified SKBr-3 and BT474 cells inhibited erbB-2-dependent mitogenic signaling and counteracted the ability of erbB ligands to promote resistance to the erbB-2 targeting drug Herceptin. Thus, loss of RALT expression cooperates with ERBB-2 gene amplification to drive full oncogenic signaling by the erbB-2 receptor. Moreover, loss of RALT signaling may adversely affect tumor responses to erbB-2 targeting agents.

NEW MOLECULAR TARGETS IN BREAST TUMORIGENESIS. ANALYSIS OF THE INTEGRATED IMMUNE RESPONSE IN A LARGE COHORT OF BREAST CANCER PATIENTS. *(Paola Nisticò, MD)*
On the trail toward new tumor antigens potentially able to elicit a protective immune response, we screened by SEREX a cDNA expression library obtained from the primary breast tumor of a long-surviving patient using the autologous serum. The primary tumor was selected on the basis of a dense intratumoral CD3+ T-cell infiltrate, a phenotypic feature which is known to correlate with the expression of HLA class I antigens. By following this experimental approach we have identified a novel gene, human Mena, that maps on chromosome 1 and encodes a protein belonging to the ENA/VASP family implicated in the regulation of actin cytoskeleton dynamics. When hMena protein expression was analyzed by Western blot and immunohistochemistry, the antigen was overexpressed in the majority of breast cancer cell lines and in 75% of primary breast tumor lesions evaluated.

A cancer-restricted antibody response against hMena was demonstrated, since 18/93 cancer patient sera, the majority (10/52) from breast cancer, showed anti-hMena-specific IgG, while no antibodies were present in healthy donors. The persistence of this specific IgG response is tumor-dependent, since no IgG reactivity was found in the serum of the patient collected 2, 3 or 5 years after the surgical removal of the tumor. Furthermore, when HLA-A2 restricted peptides from the hMena sequence were used to stimulate CD8+ T cells, an hMena specific response was found in 9 out of 12 HLA-A2+ breast cancer patients. Of note, in 4 patients this cell-mediated immune response was concomitant with the antibody response to hMena. Furthermore, and hMena-specific T cell line was established from an HLA-A2+ breast cancer patient whose primary tumor lesion overexpressed the hMena protein.
To our knowledge this is the first report describing a concomitant antibody and T cell response directed against a cytoskeleton regulatory protein. The present findings highlight the emerging role that overexpression of cytoskeleton regulatory components may have in the induction of a specific anti-tumor immune response. Studies in progress suggest that hMena is overexpressed in preneoplastic lesions at high risk of transformation, in primary tumors and in metastatic lesions. This is in agreement with the first proteomic analysis in breast cancer, showing a significant divergence between in situ breast cancer and matched normal tissue in the expression of a cluster of proteins controlling cytoskeleton dynamics. Thus, hMena is an attractive model for exploring breast tumor progression and the kinetics of the correlated immune response, providing new insights in breast cancer biology management.

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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, Rome. From 1965 to 1966 she was an Assistant Professor at the Human Genetics Laboratory of the Catholic University of Rome, and from 1966 to 1969 was a Research Scientist at the Laboratory of Animal Radiobiology of Atomic Energy Agency in Rome. From 1970 to 1973 she was an Assistant at the Biophysics Laboratory of the Regina Elena Cancer Institute of Rome, and from 1973 to 1987 was an Associated Director of the same laboratory. Since 1987 she has been the Director of the Molecular Oncogenesis Laboratory and since 2001 she has directed the Experimental Oncology Department at the Regina Elena Cancer Institute.

Staff Molecular Oncogenesis Laboratory:
BLANDINO GIOVANNI - MD, Senior Scientist
GURTNER AYMONE - Fellow
FALCIONI RITA - PhD, Senior Scientist
IOVINO ALESSANDRA - Fellow
PIAGGIO GIULIA - PhD, Senior Scientist
IACOVELLI STEFANO - Fellow
RIZZO MARIA GIULIA - PhD, Senior Scientist
LAPI ELEONORA - Fellow
SODDU SILVIA - MD, Senior Scientist
LAZZARI CHIARA - Fellow
ARMEZZANI ALESSIA - Yellow
MANNI ISABELLA - Fellow
BON GIULIA - Yellow
MANCINI FRANCESCA - Fellow
BOSSI GIANLUCA - Senior Fellow
MONGIOVÌ ADRIANA - Fellow
BOSSI GIANLUCA - Senior Fellow
MONTI OLIMPIA - Fellow
CIUFFINI LAURA - Yellow
NANNI SIMONA - Fellow
D'AMALAS ALEXANDER - Fellow
PORRELLO ALESSANDRO - Fellow
DI AGOSTINO SILVIA - Yellow
PRODOSMO ANDREA - Fellow
DI STEFANO VALERIA - Fellow
RINALDO CINZIA - Fellow
EMILIOZZI VELIA - Yellow
SOLIERA ANGELA RACHELE - Fellow
FONTEMAGGI GIULIA - Yellow
STRANO SABRINA - Researcher
FUSCHI PAOLA - Yellow
TIBURSI GIULIO - Chief Technician
GRADI ALESSANDRA - Yellow
D'ANGELO MARCO - Technician
GRASSELLI ANNALISA - Fellow PhD, student
GENTILESCHI MARIA PIA - Technician
GIOMBINI EMANUELA - Fellow PhD, student

Activities 2004

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. The p53 is strictly maintained in an inactive form under normal conditions, while it is post-translationally activated by a variety of stresses, enacting different protective biological functions. Since one critical issue in cancer gene therapy is tumor specificity, we asked whether the tight p53 regulation applies also to exogenously transferred p53. In principle, this type of regulation could allow p53 gene transfer in both normal and tumor cells to produce detrimental effects only in the latter ones. We report that primary bone marrow cells infected with a p53 recombinant retrovirus and transplanted into irradiated mice reconstitute the haematopoietic system, with no detectable alterations in any of its compartments. Furthermore, simultaneous infection of leukaemia and bone marrow cells depleted the neoplastic contamination, allowing lifelong, disease-free survival of 65% of the transplanted animals. These results show that exogenous p53 is controlled as tightly as the endogenous one, and opens the way to p53 gene therapy, without requiring tumor targeting. It has been reported that stimulation of the Ras/MAPK cascade can either activate p53 and promote replicative senescence and apoptosis, or degrade p53 and promote cell survival. Now, we report that p53 can directly counteract the Ras/MAPK signaling by inactivating ERK2/MAPK. This inactivation is due to a caspase cleavage of the ERK2 protein and contributes to p53-mediated growth arrest. We found that in Ras-transformed cells, growth arrest induced by p53, but not p21Waf1, is associated with a strong reduction in ERK2 activity, phosphorylation, and protein half-life, and with the appearance of caspase activity. Likewise, DNA damage-induced cell cycle arrest correlates with p53-dependent ERK2 down regulation and caspase activation. Furthermore, caspase inhibitors or expression of a caspase-resistant ERK2 mutant interfere with ERK2 cleavage and restore proliferation in the presence of p53 activation, indicating that caspase-mediated ERK2 degradation contributes to p53-induced growth arrest. These findings strongly point to ERK2 as a novel p53 target in growth suppression. To define the modulation of p53 tumor suppressor activity in non-tumor cells, we studied whether MDM4 (MDMX) act only as a negative regulator of p53 levels and activity. To address this issue, the functional role of MDM4 overexpression in both established and primary cells cultured under stress conditions was investigated. We found that 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 pro-apoptotic protein, Bax. Further, decreased association of the protein to its negative regulator, MDM2, accompanied p53 stabilization. These findings revealed a novel role for MDM4, demonstrating that in non-tumor cells under stress conditions it may act as a positive regulator of p53 activity, mainly by controlling p53 levels.

We have, previously, 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, we studied its involvement in cisplatin-induced death. We demonstrate that the chemotherapeutic drug cisplatin increases HIPK2 protein expression and its kinase activity, and that HIPK2 is involved in cisplatin dependent apoptosis. Indeed, induction of HIPK2 and cell death by cisplatin is efficiently inhibited by the serine-threonine kinase inhibitor SB203580 or the transduction of HIPK2-specific RNA-interfering molecules. HIPK2 gene silencing efficiently reduces the p53-mediated transcriptional activation of apoptotic gene promoters as well as apoptotic cell death after treatment with cisplatin. These findings, along with the involvement of p53 phosphorylation at serine 46 (Ser46) in the transcriptional activation of apoptotic gene promoters, suggest a critical role for HIPK2 in triggering p53-dependent apoptosis in response to the antineoplastic drug cisplatin.

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. Structural, biochemical, and functional studies have reported that the different p53 mutants possess a broad range of behaviors that include the elimination of the tumor-suppression function of wild-type protein, the acquisition of dominant-negative function over the wild-type form, and the establishment of gain-of-function activities. The contribution of each of these types of mutations to tumor progression, grade of malignancy, and response to anticancer treatments has so far been analyzed only for a few "hotspots". In an attempt to identify new approaches to systematically characterize the complete spectrum of p53 mutations, we applied recurrence quantification analysis (RQA), a non-linear signal analysis technique, to p53 primary structure. Moving from the study of the p53 hydrophobicity pattern, which revealed important similarities with the singular deterministic structuring of prions, we could statistically discriminate, on a pure amino acid sequence basis, between experimentally characterized DNA-contact defective and conformational p53 mutants with a very high percentage of success. This result indicates that RQA is a particularly advantageous mathematical tool for the development of a database of p53 mutations that integrates epidemiological data with structural and functional categorizations.
Recently identified p53 homologues, p73 and p63, have been shown to exert a suppressive function. Unlike p53, which is mutated in half of human cancers, p73 is rarely mutated. However, altered expression of the p73 gene has been reported in neuroblastoma, lung cancer, prostate cancer and renal cell carcinoma. The potential involvement of an altered expression of p73 in acute myeloid leukemias (AMLs) have been analyzed in samples of AML patients. We detected p73 gene expression in AML irrespective of FAB subtypes, but analysis of DN-p73 expression, which has been reported to inactivate both p53 and p73 antitumor effects, revealed that it was detectable in 27/28 (96.4%) cases of M0, M1, M2, M4, M5 and M6 AML and only in 13/41 (31.7%) cases of PML-RAR_ positive M3 AML. It is known that activation of p73 triggers apoptosis of tumor cells lacking functional p53 and involves the activities of c-Abl and p300. In collaboration with other groups we demonstrated that upon treatment with chemotherapeutic drugs c-Abl enhances the phosphorylation-dependent interaction between Pin1 and p73, and this in turn promotes p73 acetylation by p300. Thus, the ability of c-Abl and p300 to increase p73 stability and transcriptional activity requires Pin1. As a consequence, Pin1 appears to be essential for activation of the apoptotic response by endogenous p73.

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 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 the 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. Our previous results have indicated that the suppression of NF-Y function is of crucial importance for the inhibition of several cell cycle genes and that P53 also represses genes with no target site, such as Cdc2 and Cyclin B. These genes are key regulators of the G2/M transition and their promoters display multiple CCAAT-boxes activated by NF-Y, whose binding to DNA is timely regulated during the cell cycle. Studies in the laboratory have demonstrated that NFY associates with p53 in vitro and in vivo, through the _C helix of NFYC and a region close to the tetramerization domain of p53. ChIPs (chromatin immunoprecipitation experiments) indicate that p53 is associated to Cyclin B2, CDC25C and Cdc2 promoters in vivo before and after DNA damage, requiring a DNA-bound NFY. Following DNA damage, p53 is rapidly acetylated at K320

and K373/382 and histones are deacetylated. HDACs recruitment requires intact NFY binding sites and a non-acetylable p53 mutant shows a complete loss of repression potential, despite its ability to bind NFY and be recruited on G2/M promoters. For the first time our results detail a strategy of direct p53 repression through the association with multiple NFYs, independent from sequence-specific binding of p53, and requiring C terminal acetylations. Moreover, results also point to p53 as a DNA-damage sentinel of the G2/M transition and delineate a new role of PCAF in cell cycle control.

3. Integrin signaling in growth control

The α6β4 integrin was originally identified as a tumor-associated antigen (TSP-180). The integrin α6β4 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 β4-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 □6□4 integrin associates with ErbB-2 tyrosine kinase in human mammary and ovarian carcinoma cell lines. We also found that the association of α6β4 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 □4 integrin subunit and ErbB-2 receptor interaction, which modulate the invasion. Both □4 integrin subunit and ErbB-2 receptor lack the consensus motif for p85 binding suggesting that the mechanism by which □6□4 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 β4 interacts in vitro and in vivo 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 β4 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. 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 selective 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 analysed 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 2004

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Mol Biol Cell. 2004 Aug;15(8):3751-7 *I.F. 7.454*

Laboratory D of virology

DIRECTOR:
ALDO VENUTI, MD

Aldo Venuti received his MD in 1979 and specialized in Clinical Pathology in 1983 at La Sapienza University of Rome Medical School. He received his PhD in 1986 in Microbiology and Epidemiology at La Sapienza University of Rome. From 1982 to 1983 he was the 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 a lecturer on molecular cloning techniques. In 1985 he became the Group Leader at the Laboratory of Virology, Regina Elena Cancer Institute, Rome and he was put in charge in 2003. He was a 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 has been Professor of Clinical Pathology at the Nursing School of La Sapienza University, Rome and from 2003 he has also been Professor under contract at the Veterinary Faculty, Federico II University, Naples. He is currently a member of the Società Italiana di Virologia (SIV), Società Italiana di Cancerologia (SIC), and International Papillomavirus Society (IPS). Dr. Venuti's research interests are focused on DNA tumor 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 - MD, PhD
FEDERICO DE MARCO - MD, 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. ROSELLA FRANCONI - ENEA Roma
DR. SILVIA MASSA - ENEA Roma - ENEA Roma
DR. ELENA ILLIANO
PROF. FRANCO ROPERTO - Univ. Federico II, Napoli
DR. SANTE ROPERTO - Univ. Federico II, Napoli
DR. GIUSEPPE BORZACCHIELLO - Univ. Federico II, Napoli
DR. KOZETA KULE - Inst. Public Health Tirana
DR. MAIJLINDA KOTA - Inst. Public Health Tirana
PROF SILVA BINO - Inst. Public Health Tirana
PROF. DELLA SALDE - Univ. Teramo
PROF. G. DI GUARDO - Univ. Teramo
DR. MARZIA PERLUIGI - Univ La Sapienza, Roma
PROF. CHIARA CINI - Univ La Sapienza, Roma
PROF. RAFFAELLA COCCIA - Univ La Sapienza, Roma
PROF. SAVERIA CAMPO - Univ. Glasgow
DR. FATMA HOUISSA - Hôpital Habib Tameur, Tunis

Scientific Activities

Bio-molecular characteristics of HPV infection with potential prognostic relevance.

Carcinogenesis by human papillomavirus (HPV) is driven by specific viral factors that seem to significantly affect the progression of the disease. Numerous studies have evidenced that the specific HPV type and intra-type variant present as single or multiple infection, the number of viral copies, the physical status, the mRNA expression level of the E5, E6 and E7 oncogenes, may be considered indicators of prognostic relevance. These characteristics were studied in samples from patients affected by various lesions of the genital area by updated PCR-based techniques. HPV detection was implemented by combined PCR assays, including different consensus and type-specific primers, to achieve higher sensitivity and specificity levels. In particular, the Hybrid Capture type II (HC II, Digene) method was validated in comparison with other assays, routinely utilized in this Laboratory, in a group of gynecological samples derived from patients attending the Gynecology Division of our Institute and the San Gallicano Institute. Good concordance of the HPV prevalence data was achieved by the different tests utilized. High-risk HPV prevalence was higher in pre-neoplastic lesion and a perfect HPV type matching was found between samples of women and those of their partners. For the male sampling, the cellular scraping by non-invasive techniques failed to demonstrate the HPV presence even in clinically evident lesions, while the analysis of the sperm revealed the presence of HPV sequences. These data reinforce the hypothesis that the sperm is a possible reservoir of HPV infection and indicate that more invasive methods should be utilized for male screening (i.e. scraping by emery paper).

The HPV16 and HPV18 physical status was compared among samples from different areas within the tumor, and from tumor and paired non-lesional adjacent epithelium in a group of HPV positive gynecological lesions, by using dedicated PCR assays for the detection of specific viral subgenomic fragments. In intra-tumor samples a complete uniformity (HPV18) or a low variability (HPV16) of the detection and viral physical status were found, suggesting a constant pathway of virus-host interaction, as expected from a clonal origin of the neoplastic cells. HPV integration was detected in almost all tumors, especially in those infected by the HPV18, confirming its higher aggressiveness. The occurrence of high-risk HPV integrated forms in morphological tumor-free adjacent mucosa, especially in HPV18-positive cases, indicated that the research of viral integration in the adjacent tumor tissues may be a valuable tool in assessing risk factors for local recurrences after therapy.

HPV infection within the Mediterranean area.

Considering the promising role of HPV typing in the patient's care and the growing evidence of interregional variation of high risk (HR) HPV prevalence we undertook a study of HR-HPV types circulating within some countries of the Mediterranean area. This region is particularly suitable for these studies because it is densely populated by different people with sharply different social, economical and cultural conditions and intense migratory exchanges have taken place in the recent years. Samples deriving from patients referring to scientific institutions of Mediterranean countries (Albania; Tunisia) and from patients participating in international screening programs (WHO UNOPS-PASARP) were analyzed and compared with data from Italian patients examined in our previous studies. In every geographic area assayed the high risk HPV16 was the most prevalent type. This finding qualitatively confirmed the world global pattern. However, in quantitative terms HPV16 prevalence sharply changed from one region to another, ranging from less then 50% up to nearly 90%, with a worldwide value of nearly 60%. Similar fluctuations were also seen in the prevalence of HPV18 (the second most common viral type according global data) and of related types. Finally, also the so called "rare types" showed a large variability, being much more abundant than supposed in some areas. As a whole, these findings suggest that HPV distribution is far more complex at the regional level than expected and that larger studies are needed for a precise description of the viral types circulation in different regions.

HPV IN EXTRA-GENITAL TUMORS.

Head and neck.

HPV seems to be involved in head and neck carcinogenesis. Results of a study conducted on a group of patients with invasive squamous cell carcinomas of different localization, stage and histotype attending the Otorhinolaryngology Division of San Carlo di Nancy Hospital (IDI-IRCCS) have confirmed the association of HPV infection with tumors affecting specific anatomical sites of this region. The tonsil area was the location with the highest HPV positivity, significantly different with respect to all other sites. Moreover, the detection of viral transcripts for the major oncogenes present in all HPV16 tumors suggest that the HPV16 is actively involved in the genesis of a subset of the head and neck cancers and that the tonsillar localization may be considered a hot spot for viral transformation. Although HPV status does not seem to be related to the main clinical-pathological parameters and use of alcohol and/or tobacco, preliminary follow up data seem to evidence a direct correlation between the presence of the virus and favorable clinical outcome in a subset of these tumors.

Skin. The presence of HPV in cutaneous tumors was ascertained in patients suffering from a rare hereditary disease, the Epidermoyisplasia Verruciformis and in immune-compromised patients (i.e. renal transplant patient). During an observational study the cutaneous HPVs, mostly the E.V. types, were detected even in squamous cell carcinoma of immune-competent patients, indicating a possible direct role of these viruses in skin carcinogenesis

In a patient with aggressive recurrent benign lesions, a new type of HPV was detected for the first time, the SIBX1. This type was isolated only once from the eyebrows of a healthy Slovenian male. This finding stress the need of more complex strategies for the HPV detection in skin lesions. In another patient the presence of HPV 21 and HPV 17 was linked with the development of SCC after treatment with Chlorambucil that it reported to induce DNA damages/apoptosis, and immune-suppression. Taken together, these data indicate that the inhibition of apoptosis plays a role in the genesis of HPV-associated skin cancers.

INNOVATIVE STRATEGIES IN THE TREATMENT OF HPV INFECTION AND ASSOCIATED TUMORS.

Endothelin-1 receptor antagonists

A number of pre-clinical studies conducted in the Lab of Virology have evidenced that antagonists of ET-1 are effective in reducing the growth of cervix carcinoma cells by blocking the ETA receptor. This action is associated with a reduced vascularization and an increased apoptosis. Two compounds, the ABT627 and the A-182086, possessing equal affinity for the ETA receptor, showed similar efficacy in controlling the growth of experimental-induced tumors. In a previous study we demonstrated that HPV infection leads to an up-regulation in the ET-1 autocrine loop and in particular the oncogene E5 of HPV16 seems to play a central role. Thus E5 expression and up-regulation of ET-1 might take place in the progressive lesions of the cervix. To validate this hypothesis the presence of these receptors and the E5 oncogene of HPV16 was analyzed in archival clinical samples by immunohistochemistry and PCR. Data collected until now are too preliminary to draw any firm conclusion, but there are promising indications for a possible discrimination between progressive and regressive lesions.

DNA vaccines.

The E7 protein of the "high risk" types of HPV is a tumor-specific antigen, central to cervical cancer progression. DNA vaccination, based on the E7 gene is an attractive approach for a selective anti-cancer immunotherapy. However, the limited ability of DNA plasmids to amplify and to spread the antigen in vivo together with the general poor immunogenicity of the E7 protein, may affect vaccine efficacy. Our previous research demonstrated that engineering the intracellular pathway for antigen presentation, a valid therapeutic response was evident even against tumors with down-regulated MHC class I molecules.

Therefore, we analyzed plant potentialities in increasing the "visibility" to the immune system of an E7-based DNA vaccine, by providing sequences that are primary antigens in humans. We evidenced the ability of a plant-derived signal peptide, the signal sequence (ss) of the "Polygalacturonase-inhibiting protein" (PGIP) from P. vulgaris (PGIPss), to target the

model antigen to the human secretory pathway providing a unique approach for triggering intracellular processing/presentation of the HPV16-E7 tumor antigen. Exploiting the ability of the PGIPss to drive the HPV16-E7 protein in the secretory compartment of mammalian cells, we fused it with a harmless version of the model antigen, E7GGG (three point mutations abolishing the transformation potential). We cloned the E7GGG gene alone or the PGIPss-E7GGG fusion gene into a mammalian expression vector. Cell transfection experiments demonstrated that the E7 gene alone was expressed but not secreted while the fused gene was efficiently secreted into the conditioned medium. This is one of the first demonstrations that plant secretory signals are active in mammalian cells. We are now producing the secretory version of the E7GGG-CP fusion. All the new constructs bearing the plant-derived sequences will be analyzed in mouse pre-clinical DNA vaccination experiments to check if they represents improved and safer vaccines able to enhance tumor protection.

Plant extract vaccines.

Previous results obtained in the Lab of Virology firmly established that the E7-containing foliar extract acts 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 macroaggregates able to induce a strong Th1 immune response. With this cytoplasmic construct the E7 protein expression levels were 20-fold lower than that known to prevent tumor growth. Hence, it was reasonable to assume that the activity of the E7 "in planta" formulation as immunogen might be further improved by increasing the amount of E7 protein expressed in the plant extract. To achieve this the production of the HPV16-E7 protein in N. benthamiana plants was enhanced at least five-fold by its expression in the secretory pathway by means of the signal sequence of the PGIP. Indeed the biological efficacy of this vaccine was improved with more than 80% of animals being protected from tumor challenge and mounting a strong Th1 response. We believe that a further enhancement of anti-tumor immunity could be achieved by combination of E7- containing extracts with immune-stimulatory gene(s) and/or by application of heterologous boosts.

Taken together these data represent a significant step toward the formulation of a HPV-associated cancer vaccine that is effective, temperature-stable, easy to administer in a poor resource setting and amenable to large scale manufacturing.

Animal models for pre-clinical studies.

Based on previous results we have proposed the bovine bladder tumors as a model to study the efficacy of vaccinal strategy (particularly the therapeutic one) during the natural history of the disease. In this model the infection by bovine papillomavirus (BPV) is one of the key features of carcinogenesis, and, in particular the E5 oncogene seems to play a pivotal role (see previous paragraphs). Thus, this model is appropriate to check the activity of an anti-E5 vaccine. Scheduling and follow up design were set up and the animal will be enrolled according to the following procedures. At time zero (T0) a recombinant BPV2/E5-encoding plasmid DNA will be delivered i.d. in the hip of calves by gene gun. At the same time, other animals will be immunized with CP or PGIP- E5 fused constructs under the same conditions. Fifteen days after T0 each animal will receive a booster in the most caudal part of the vulval mucosa (i.v.m.) with four gene gun shots. Hip and vulval boosters will be performed alternatively until six months after T0 and, at this point, each animal will undergo ultrasound examination of the urinary bladder and cystoscopy.

MOLECULAR MECHANISMS OF VIRAL CARCINOGENESIS.

E5 oncogene and apoptosis.

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. The triggering of apoptotic cell death by different stimuli, such as death ligands, ionizing irradiation or chemotherapeutic drugs, leads to the activation of a family of cysteine proteases called caspases. Paclitaxel, a chemotherapeutic compound, induces apoptosis in a death receptor- and p53-independent way. This requires a complete activation of the mitochondrial pathway with an amplification loop based on caspase-3 and caspase-8 activation.

We studied the E5 activity against paclitaxel-induced apoptosis in HaCaT cells in which the p53 is inactivated by mutation and, therefore, only the p53-independent pathway of apoptosis is available.
In these cells Paclitaxel was able to induce a dose-dependent growth inhibition that was associated with a corresponding increase of the apoptosis. The presence of actively transcribed HPV16 E5 protein had dramatic effects on the apoptosis by decreasing the percentage of apoptotic cells 8-fold, this percentage was below the value of the control indicating that E5 may affect the basal apoptosis too. The Paclitaxel-induced apoptosis correlated with an activation of caspase-3 and caspase-8 in absence of death specific receptor activation. This result has been already reported for other cell lines and allows to speculate that caspase-3/caspase-8 loop is a primarily active circuit in the p53- and death-receptor-independent activation of apoptosis.
E5 caused a decrease in the activation of both caspases even after a long exposure to Paclitaxel. Based on this result we propose that one of the primary function of E5 in blocking Paclitaxel-induced apoptosis is the inhibition of the caspase-3/caspase-8 loop suggesting a direct or indirect interaction with these caspases. Further studies are needed to confirm this hypothesis.
Oxidative stress and HPV expression in epithelial cell transformation.
Oxidative Stress (OS) represents the common final mechanism of most physical, chemical and biological toxic stimuli and plays crucial roles in several cellular functions highly relevant for carcinogenesis. The epithelial tissues being the physiological target of HPV infection and at the same time being heavily exposed to all known source of oxidative stress may represent an ideal environment to study the possible interaction between these two carcinogens. Therefore the Lab of Virology started a research aimed to shed light on the possible connection between viral expression and OS in epithelial cells. Initial activities were carried out in continuous cell lines, as well as on primary cells transformed by HPV-16 and focused on the role of OS in cell proliferation, cell death. and tumor progression..
Considering that OS is the final process of most noxious agents, we decided to use UV-B as OS inducer because of its highly reproducible and finely tuning dosage. The effect of Reactive Oxygen Species (ROS) generated under sub-lethal UV-B irradiation on HPV-16 mRNA expression was studied in human keratinocytes transfected with the whole HPV-16 genome (HK-168). This OS induced a global reduction of viral oncogenes transcription that was followed by a growth arrest and moderate apoptosis. HK-168, as well as other HPV transformed cells, appeared rather resistant to OS compared with HPV negative cells. This difference in cell response correlated with the activity of the NAD(P)H Quinone Oxidoreductase (NQO-1). This is a cytoplasmic membrane-bound enzyme that, catalyzing the two electron reduction of quinones to hydroquinones, prevents the semiquinone radical generation. Preliminary results indicate that this correlation did not depend on the physical interaction of NQO-1 with the cellular p53, and suggest that the modulation of the OS responsive viral E2 gene might be involved.
The study of the action of NQO-1 was also extended to diploid melanocytes and to melanoma cells. In these cells 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 working in diploid keratinocytes, where it may be relevant in sinking aldehydes and quinines into senile pigments as, for instance, the lipo-fuscins. Moreover, preliminary observations suggest that a similar mechanism may also be active in non related cell lines, namely locus ceruleous and substantia nigra neuronal cells, where the detoxication of potentially hazardous compounds (such as dopamine) may take place through the accumulation of the, so far unexplained, neuromelanine.
Papillomavirus carcinogenesis in animal species.
It has recently been suggested that animal papillomaviruses studies are useful in providing models for human papillomavirus infection, as well as for the development of anti-viral vaccines.

We demonstrated, in collaboration with the Veterinary Faculties of the Federico II University of Naples and of the University of Teramo, the association of bovine bladder carcinoma with the infection by BPV2, and the presence of a new papillomavirus in caprine tumors. In the bovine model we demonstrated that a physical interaction between the viral oncogene E5 and the PDGF β receptor occurred during the natural history of bovine urinary bladder tumors. In addition, the PDGF β receptor was highly phosphorylated in the BPV2 positive tumors suggesting its activation upon E5 interaction and indicating that that this molecular pathway was active in E5-mediated carcinogenesis.
Our data about E5 functions in naturally occurring animal cancer gain new insights into pathogenetic mechanisms underlying bladder carcinogenesis. Moreover, it was recently shown that mouse vaccination with HPV-16 E5 can elicit cytotoxic T lymphocytes inhibiting the growth of murine tumor cells, indicating that the E5 proteins may represent a target for therapeutic intervention. Therefore, the bovine bladder cancer could represent a model to develop therapeutic tools for comparable human pathologies and will be utilized to validate the potential for E5 vaccination in naturally occurring animal papillomavirus tumors.

HPV AND ET-1 IN THE PSORIASIS.

The replication of HPV5b in conjunction with a particular genetic background may cause the epidermal hyperproliferation and antigen stimulation in the psoriatic skin. The activation of the virus seems to be independent of a stimulation by cytokines because specific viral transcripts were detected in keratinocytes cultures. This chronic antigen stimulation would induce autoimmune phenomena, thus priming a vicious circle reinforcing the viral replication and producing large quantities of inflammatory cytokines. Many growth factors and cytokines can regulate the homeostasis of epidermal differentiation and proliferation, and we demonstrated that endothelin 1 (ET-1) seems to play an important role in these processes. In an attempt to evaluate possible new therapies in controlling the skin proliferation of psoriasis, ET-1 antagonists have been administered to primary keratinocytes isolated from psoriatic patients. Keratinocytes were treated with the ET-1 antagonist, ABT-627, already registered as Atrasentan (Abbott Laboratories, Abbott Park, IL, USA). This compound is a non-peptide selective antagonist of ETA receptor working by a competitive inhibition of the ET-1 binding. The keratinocytes obtained from all the psoriatic lesions were very responsive to the treatment with the ABT-627. It is known that the ET-1 is able to induce proliferation of serum-starved keratinocytes through the binding to the ETA receptor. When ET-1 was added to the cell cultures in amounts that may mimic the quantities found in the lesional skin, a proliferative effect was detected. This proliferation was dramatically reduced by the antagonist in the keratinocyte cultures from psoriatic lesions whereas the keratinocytes from control and from normal-appearing psoriatic skin were less sensitive to the ABT-627 treatment.
This result indicates that the psoriatic keratinocytes would respond to a treatment with this compound that is expected to be very active particularly in conditions of hyper-stimulation of the keratinocytes. Moreover, it was recently described that ET-1 stimulates angiogenesis via vascular endothelial growth factor (VEGF) upregulation and, therefore, the ET-1 blocking might also influence the keratinocyte hyperproliferation and the angiogenesis by this VEGF-mediated pathway. Our data stress the need to develop new therapeutic strategies in psoriatic patients by altering the biological response of the keratinocytes to the ET-1 proliferative stimuli.

MAJOR TRANSLATIONAL ACHIEVEMENTS.

- Hybrid Capture II (HC II Digene) as screening tool for high-risk HPV infection.
- Viral integration as possible prognostic marker.
- Xinlay (Atrasentan,ETAR antagonist, Abbott) as possible therapeutic tool for the cervix carcinoma.
- Xinlay (Atrasentan,ETAR antagonist, Abbott) in the local control of psoriasis lesions.
- Plant production of a therapeutic vaccine against HPV16.

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Laboratory A associated to surgical oncologic departement

DIRECTOR:
PIER GIORGIO NATALI, MD

Pier Giorgio Natali, MD graduated in Medicine and Surgery in 1966, La Sapienza University in Rome. 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 Academy of Microbiology in Medical Lab. Immunology, USA (1987). Has held the position of Visiting Professor in the Dept.s of Tumor Immunology at Scripps Clinic (1977-1978) and Pathology at the 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 co-founder of the Chart of Paris (2000). Is presently serving on a number of Committees of the American Association for Cancer Research and in the Editorial board of J. Translational Medicine. 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. (Citation Index 2003)

Staff Scientists:
ANNA BAGNATO - PhD
VALERIANA DI CASTRO - PhD
STEFANIA MICCADEI - PhD

Post-doctoral - Fellows
LAURA ROSANÒ - PhD
FRANCESCA SPINELLA - PhD FIRC Fellow

Technicians:
ALDO LUPO
GIACOMO ELIA

Biology Students
GIULIA GENOVESI
SAMANTHA DECANDIA

Hosts
DONATO CIVITAREALE - PhD, Ist. Neurobiologia e Medicina Molecolare, CNR

Activities 2004

ENDOTHELIN -1 RECEPTORS AS NOVEL TARGETS IN TUMOR THERAPY
(Anna Bagnato, PhD)

The endotelin (ET) axis, that includes ET-1, ET-2, ET-3, and the ETA receptor (ETAR) and ETBR, represents a novel and promising target in tumor treatment. ET-1 may directly contribute to tumor growth and indirectly by modulating tumor-host interactions in a variety of tumors. Upon being activated, ET-1 receptors mediate multiple steps of cancer progression including cell proliferation, inhibition of apoptosis, invasiveness, angiogenesis, and metastatization.

• Endothelin-1 induces prostaglandin E2- and their rate-limiting enzymes cyclooxygenase-1 and -2 to regulate vascular endothelial growth factor production and ovarian carcinoma cell invasion

Prostaglandins (PG) are involved in the onset and progression of a variety of malignancies. Moreover high COX-1 and -2 have been reported in association with elevated levels of proangiogenic factors in ovarian cancer. In ovarian carcinoma cells, ET-1 significantly increases the expression of COX-1 and -2, at mRNA and protein level, the COX-2 promoter activity and PGE2 production. These effects depend on the ETAR activation and involve multiple MAPK signal pathways, including p42/44 MAPK, p38 MAPK and the transactivation of EGFR.

There is increasing evidence that PGE2 contributes to tumor progression also by promoting tumor angiogenesis and that this effect is mediated by VEGF. COX-2 and-1 inhibitors blocked ET-1-induced PGE2 and VEGF release demonstrating that both enzymes, although to a different extent, participate in PGE2 and VEGF production. These results in-

dicate that impairing COX-1 and -2 and their downstream effect by targeting ETAR can be therapeutically advantageous also in view of the fact that elevated COX-2 levels are associated with tumor progression and chemoresistance.
Moreover, we demonstrated that ET-1 through the binding with ETA receptor (ETAR) induces prostaglandin E2 (PGE2) production, as the more represented PG types, and increases the expression of PGE2 receptor type 2 (EP2) and type 4 (EP4). The use of pharmacological EP agonists and antagonists indicates that ET-1 and PGE2 stimulate VEGF production principally through EP2 and EP4 receptors. At the mechanistic level, we have proved that the induction of PGE2 and VEGF by ET-1 involves Src-mediated EGFR transactivation. Finally, we demonstrate that ETAR-mediated activation of PGE2-dependent signaling participates in the regulation of the invasive behavior of ovarian carcinoma cells by activating tumor-associated matrix-metalloproteinase. These results implicate EP2 and EP4 receptors in the induction of VEGF expression and cell invasiveness by ET-1, and provide a mechanism by which ETAR/ET-1 can promote and interact with PGE2-dependent machinery to amplifying its proangiogenic and invasive phenotype in ovarian carcinoma cells. Pharmacological blockade of ETAR can therefore represent an additional strategy to control PGE2 signaling, which has been associated with ovarian carcinoma progression.

• Therapeutic targeting of the endothelin A receptor in human ovarian carcinoma: efficacy of cytotoxic agents is markedly enhanced by blockade of endothelin A receptor with atrasentan.

The recent identification of high-selective small molecules that inhibit ligand-induced activation of ETAR now offers the possibility of testing this therapeutic approach in a clinical setting. Among various ETAR antagonists, ABT-627 (atrasentan, Abbott Laboratories, Abbott Park, IL) is an orally bioavailable endothelin antagonist that potently (Ki = 34 pM) and selectively binds to the ETAR, blocking signal transduction pathways implicated in cancer cell proliferation and other host-dependent processes promoting cancer growth.
We explored the efficacy of Atrasentan (ABT-627), a small orally active ETAR antagonist, in mono and combination therapy on HEY ovarian carcinoma xenografts. Atrasentan (2mg/Kg/24h i. p. for 21 days) induced similar inhibition of tumor growth as Paclitaxel (20mg/Kg i.v. for three times every four days) with a reduction of 65% compared to control. The coadministration of Atrasentan enhanced the efficacy of cytotoxic agents, such as taxanes or platinum compounds. Administration of Atrasentan in combination with Paclitaxel caused a strong antitumor effect. Remarkably, 4 out of 10 mice bearing HEY xenografts had no histological evidence of tumors. Tumor growth inhibition was accompanied by a significant decrease of molecular effectors involved in angiogenesis and invasion and by enhanced tumor cell apoptosis. Moreover, although Cisplatin as a single agent (5mg/kg i.p. on day 1) markedly inhibited HEY tumors, Atrasentan was very effective in potentiating this effect with partial or complete tumor regression. Immunohistochemical analysis of the xenografts following combined treatment of ABT-627 with cytotoxic agent revealed an almost complete reduction in the percentage of COX-2, VEGF and MMP-2 in treated mice. Tumor-induced vascularization, quantified as MVD was directly proportional to the expression of VEGF. The antitumor, antiangiogenic, and apoptotic activities obtained with Atrasentan and the enhanced efficacy of cytotoxic agents provide a rationale for its clinical evaluation in ovarian carcinoma.

• The endothelin B receptor is a relevant therapeutic target in human cutaneous melanoma.

Gene expression profiling and immunophenotyping of human cutaneous melanoma have recently identified ETBR as critical in the progression of this malignancy. Through the same receptor, ET-1 acts as antiapoptotic factor for melanoma cells and melanocytes. While these early studies defined a relevant role of the ET-1/ETBR pathway in the biology of melanocytic tumors, the molecular events underlying this activity are now being identified. Early melanoma growth is the result of disrupted intercellular homeostatic regulation. Once this balance is lost and malignant transformation has occurred, microenviromental

factors such as cell adherence to extracellular matrix, host-tumor interactions, degradation of matrix components, migration and invasion became essential for the tumor progression to the metastatic phenotype. Changes in cadherins, gap junctions and matrix metalloproteinases expression have emerged as key factors in melanoma progression. In this regards ET-1 and ET-3 by ETBR signaling induce the inactivation of the gap junctions through the phosphorylation of the Cx43, which are responsible for contact mediated regulatory control of keratinocytes. In addition, activation of ETBR pathway by ET-1 and ET-3 contributes to the disruption of normal host-tumor interaction by downregulating the expression of E-cadherin and associated β-catenin adhesion proteins. Significant mRNA expression of the transcription factor Snail, which has been identified as a potent inhibitor of E-cadherin expression in melanoma, closely correlates with downregulation of E-cadherin. ETs also causes a tyrosine phosphorylation of β-catenin which contributes to the loss of E-cadherin function, with a concomitant upregulation of N-cadherin. This latter change can mediate homotypic adhesive interaction as well as heterotypic melanoma cell-cell interaction. Concurrently ETs increase αvβ3 and α2β1 integrin expression and MMP-2, -9, and membrane type-1-MMP activation. These effects were associated with ETBR-mediated enhancement of cell adhesion, migration and invasiveness. Due to the resistance of melanoma to current therapies, the identification of molecular mechanisms underlying local and metastatic growth is mandatory for the development of novel treatments. The small molecule A-192621, an orally biovailable non peptide ETBR antagonist, significantly inhibited melanoma growth in nude mice.
In conclusion, because multiple molecular pathways, such as FAK and MAPK, elicited by ET-1 and ET-3 are triggered by the ETBR leading to the activation of all the molecular effectors involved in melanoma progression, including integrins, tumor proteases, cell-cell adhesion and communication molecules, blockade of this receptor by small molecules results in the inhibition of melanoma growth in vitro and in vivo, thus offering an unprecedented opportunity of targeted therapy in this malignancy.

Antioxidant and hepatoprotective effects of artichoke extracts

(Stefania Miccadei PhD)

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 purpose of our recent studies was to investigate the antioxidative and hepatoprotective action of three different extracts from the edible part of the artichoke, and to evaluate a relationship between hepatoprotective properties of the different preparations and their constituents. We determined in each extract the amount of chlorogenic acid and di-caffeoylquinic acids. The results show that the antioxidative action, measured as inhibition of loss of glutathione and prevention of accumulation of malondialdehyde following the oxidative damage in rat hepatocytes, was mainly related to the highest amount of chlorogenic acid in the extracts.
Further studies will be designed to investigate the effects of these three different extracts on cell growth, cell cycle and apoptosis in human hepatoma cell lines. We are performing these experiments in collaboration with Dr.G.Maiani (INRAN)

Gene expression of alfa-MSH-receptor in melanocytes

(Stefania Miccadei, PhD)

We are studying the regulation of the gene expression, in particular we are interested in tissue-specific gene expression. As a model system we use thyrocytes and melanocytes. In melanocytes, we intend to decipher the biochemical pathways that restrict the melanocortin receptor (MSHr) gene expression to this cell type. Therefore, we have cloned, from a human library the genomic sequences flanking the MSHr gene. In order to identify the minimal gene promoter, able to direct the melanocyte-specific gene expression, we have cloned such sequences in respect to the luciferase reporter gene and have generated several deletion mutants. These constructs have been used in transfection experiments in melanocytes (MeWo cells) and in non-melanocytes (HeLa cells). In this way we have identified the MSHr gene promoter. We are now studying DNA-protein interaction that take place on the promoter.

We are performing these experiments in collaboration with Dr. D.Civitareale (INMM-CNR).

Role of the transcription factor pax8 in the control of thyroperoxidase activity

(Stefania Miccadei PhD)

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 Pax8 transcriptional co-activator. Recently, we have found that YAP65, known to act as transcriptional co-activator, interacts with Pax 8 and we are studying the role of this interaction in the regulation of thyroid-specific gene expression.

We are performing these experiments in collaboration with Dr. D. Civitareale (INMM-CNR).

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Endothelin-1 stimulates cyclooxygenase-2 expression in ovarian cancer cells through multiple signaling pathways: evidence for involvement of transactivation of the epidermal growth factor receptor.

J. Cardiovasc. Pharmacology 44 (1): S140-S143, 2004. *I.F. 1.905*

Laboratory B associated to medical oncology departement

DIRECTOR:
GABRIELLA ZUPI, PhD

Gabriella Zupi received the degree in Biological Science in 1968 from the La Sapienza University of Rome. In 1970 she was a visiting Scientist at the Laboratory of Molecular Biology, University of Alabama, Birmingham, USA. From 1978-87 she was Biology Director for the Regina Elena Cancer Institute of Rome, Italy. She has been Director of Lab of Experimental Preclinical Chemotherapy at this Institute since 1988. Dr. Zupi's research interests are devoted to the study of the involvement of some oncogenes in tumor progression and the response to chemotherapy of solid tumors.

Staff Interni Lab. B:
DR. MAURIZIO FANCIULLI - Staff scientist
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

Activity 2004

Control of transcription and chromatin remodeling are the main areas of interest for LabThe product of the TP53 gene is a tumor suppressor mainly involved in the transcriptional regulation of a large number of growth arrest- and apoptosis-related genes. Upon genotoxic damage, p53 contributes to cell cycle arrest at the G1/S or G2/M checkpoints through diverse mechanisms. To exert this function, the p53 protein, constitutively expressed at very low levels and in an inactive conformation, must be induced and activated. These events are thought to depend mainly on post-translational modifications of the p53 protein, including phosphorylation by ATM/ATR and Chk2 kinases, at least upon certain stress stimuli. However, there is increasing evidence supporting a role also for p53 regulation at the transcription level in response to genotoxic stress.
Che-1 is a human RNA polymerase II (Pol II) binding protein involved in the regulation of gene transcription and cell proliferation that is highly conserved during evolution. We showed that Che-1 interacts with Rb and affects its growth suppression activity by interfering with the Rb-mediated recruitment of histone deacetylase I on the promoters of E2F1-responsive genes. Furthermore, Traube, the mouse homologue of Che-1 was shown to be essential for proliferation of pre-implantation embryos. Despite this 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 p21Waf1 (p21).
The latter finding prompted us to investigate Che-1 regulation in response to DNA damaging agents. In this study, we show that DNA damage by different genotoxic agents is associated with Che-1 phosphorylation and extended half-life. These posttranslational modifications were induced by ATM and Chk2 which phosphorylated Che-1 on specific residues and were functionally linked to DNA damage-induced G2/M checkpoint.
Microarray analysis showed that Che-1 overexpression produces upregulation of several important genes involved in cellular response to DNA damage, such as p53, p21, BRCA1, NBS1, MDM2 and XPF. Finally, chromatin immunoprecipitation and Western blot analyses showed that Che-1 activates the transcription of p53 and, consequently of several p53 target genes, identifying a new pathway by which ATM and Chk2 modulate p53 levels.

Publications 2004

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The artificial zinc finger protein "Blues" binds the enhancer of the fibroblast growth factor 4 and represses transcription.

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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.

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Deacetylase inhibitors increase muscle cell size by promoting myoblast recruitment and fusion through induction of follistatin.

Dev Cell. 6, 673-84, 2004. *I.F. 14.8.*

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 Napoli, Italy. He received his post-graduated training in: General Pathology (1981) at the La Sapienza University, Rome, Italy; Biological Chemistry (1984) at the Johns Hopkins University, School of Medicine, Baltimore, Maryland, USA; and Clinical Pharmacology (1989) at the La Sapienza University, Rome, Italy.
Since 1990 he has been Staff Scientist at the Center for Experimental Research, Regina Elena Institute for Cancer Research, Rome, 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, aimed at identifying sets of diagnostic, prognostic and therapeutic targets to be used in cancer clinical practice.

Staff Scientists:
ANNA MARIA MILEO - PhD
MAURO CASTELLI - PhD

Post-Doctoral Fellows
ANNA SEVERINO - PhD (FIRC FELLOW)
PhD STUDENTS
LUCREZIA MANENTE - B.SC.
ALESSANDRA TRITARELLI - B.SC.

Technicians
ANTONIO FEDERICO
FRANCESCO GALLI

Biology Students
PAOLA PISANO
STEFANO DELLA BIANCA

Guests
DANIELA LOMBARDI, PhD Associate professor, University of L'Aquila
EMANUELA PIOMBINO, B.SC, PhD Student, University of L'Aquila
ALFONSO BALDI, MD, Assistant professor, 2nd University of Napoli
ANTONIO DE LUCA, MD, Assistant professor, 2nd University of Napoli

Activities 2004

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. Cellular targets of the viral oncoproteins from small DNA tumor viruses. The adenoviral E1A proteins have been implicated in the promotion of proliferation and transformation, inhibition of differentiation, induction of apoptosis, regulation of transcription, and suppression of tumor growth. The ability of E1A to override the fundamental controls of host cells is based on its ability to physically interact with several cellular proteins. We recently characterized RACK1 as a new E1A-interacting protein (Sang, N. et al. RACK1 Interacts with E1A and Rescues E1A-induced Yeast Growth Inhibition and Mammalian Cell Apoptosis. J. Biol. Chem., 276: 27026-27033, 2001). Later we showed that the extreme N-terminal region of E1A, spanning from aminoacids 1-36, and the conserved WD regions of RACK1 are responsible for this interaction. We also demonstrated that E1A and RACK1 co-localize at the level of the perinuclear membrane in the cells. Furthermore, we proved that E1A is able to antagonize the inhibitory effects of RACK1 on Src activity. These results suggest that RACK1 signaling pathway may be a functional target of E1A, contributing to E1A oncogenic effect in the host cells.
Studies on genes detected as down-regulated during melanoma progression: A) Expression of HtrA1, the gene product of PRSS11, in human placenta during pregnancy.
Differential gene expression of cell lines derived from a malignant melanoma or its autologous lymph node metastasis using cDNA arrays indicated down-regulation of PRSS11,

a gene encoding the serine protease HtrA1, a homolog of the Escherichia coli protease HtrA, in the metastatic line. Stable PRSS11 overexpression in the metastatic cell line strongly inhibited proliferation, chemoinvasion and Nm23-H1 protein expression *in vitro*, as well as cell growth *in vivo* in nu/nu mice. The use of a polyclonal anti-HtrA1 serum revealed a significantly higher expression in primary melanomas when compared to unrelated metastatic lesions in a human melanoma tissue array, and down-modulation of HtrA1 expression in autologous lymph node melanoma metastases in seven out of 11 cases examined. Our results suggest that down-regulation of PRSS11 and HtrA1 expression may represent an indicator of melanoma progression (Baldi, A. et al. The HtrA1 serine protease is down-regulated during human melanoma progression and represses growth of metastatic melanoma cells. Oncogene, 21: 6684-6688, 2002).

To investigate the molecular functions of HtrA1 we analyzed its expression during some physiological processes.

1. Expression of HtrA1 in human placenta. The placenta has dynamic and continuous self-renewal ability. The molecular mechanisms responsible for controlling trophoblast proliferation are still unclear. It is generally accepted that the simultaneous activity of proteins involved in cell proliferation, apoptosis, and extracellular matrix degradation plays an important role in correct placental development. We investigated in depth the expression of the serine protease HtrA1 during pregnancy in human placenta by *in situ* hybridization and IHC, demonstrating that HtrA1 displayed a low level of expression in the first trimester of gestation and a strong increase of HtrA1 expression in the third trimester. Finally, by electron microscopy, we demonstrated that HtrA1 was localized either in the cytoplasm of placental cells, especially close to microvilli that characterized the plasma membrane of syncytiotrophoblast cells, or in the extracytoplasmic space of the stroma of placental villi, particularly in the spaces between collagen fibers and on collagen fibers themselves. The expression pattern of HtrA1 in human placentas strongly suggests a role for this protein in placental development and function. Moreover, on the basis of its subcellular distribution it can be postulated that HtrA1 acts on different targets, such as intracellular growth factors or extracellular matrix proteins, to favor the correct formation/function of the placenta.

2. Expression of HtrA1 during mouse embryo development. In previous studies we showed that the expression of HtrA1 was ubiquitous in normal adult human tissues. Then we examined the expression of HtrA1 protein and its corresponding mRNA during mouse embryogenesis using Northern blotting hybridization, RT-PCR, and immunohistochemical staining analyses. Our results indicate that HtrA1 is expressed in a variety of tissues in mouse embryos. Furthermore, this expression is regulated in a spatial and temporal manner. Relatively low levels of HtrA1 mRNA are detected in embryos at the beginning of organogenesis (E8), and the levels of expression increase during late organogenesis (E14-E19). Our results show that HtrA1 was expressed during embryonic development in specific areas where signaling by the TGF□ family proteins plays an important regulatory role. HtrA1 expression in the developing nervous system, documented both at mRNA and protein levels by RT-PCR and immunohistochemistry, is consistent with a possible role of this protein in both dividing and post-mitotic neurons, possibly via its documented inhibitory effects on TGF□ proteins. An exhaustive knowledge of the different cell- and tissue-specific patterns of expression of HtrA1 in normal mouse embryos is essential for a critical evaluation of the exact role played by this protein during development.

APAF-1 Expression and 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, variation 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-regula-

tion 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 that 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.

Identification of genes up-regulated during melanoma progression: Ferritin contributes to melanoma progression by modulating cell growth and sensitivity to oxidative stress

Employing an *in vitro* model system of human melanoma progression, we previously reported ferritin light chain (L-ferritin) gene overexpression in the metastatic phenotype. Thus we attempted to characterize the role of ferritin in the biology of human melanoma and in the progression of this disease. Starting from the LM human metastatic melanoma cell line, we engineered cell clones in which L-ferritin gene expression was down-regulated by means of the stable expression of a specific antisense construct. These cells were then assayed for their growth capabilities, chemoinvasive properties and sensitivity to oxidative stress. Additionally, ferritin protein content in primary and metastatic human melanomas was determined by means of immunohistochemistry.

Artificial L-ferritin down-regulation in the LM cells strongly inhibited proliferation and chemoinvasion in vitro, and cell growth in vivo. In addition, L-ferritin down-regulated cells displayed enhanced sensitivity to oxidative stress and to apoptosis. Concurrently, immunohistochemical analysis of a human melanoma tissue array revealed that the ferritin expression level in metastatic lesions was significantly higher ($P<0.0001$) than in primary melanomas. Furthermore, ferritin expression constantly resulted up-regulated in autologous lymph node melanoma metastases, when compared to the respective primary tumors, in a cohort of 11 patients (manuscript in preparation).

These results 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.

Therapeutic targets in melanoma: *In vitro* and *in vivo* tumor growth inhibition by a p16-mimicking peptide in $p16^{INK4A}$-defective, pRb-positive human melanoma cells.

In higher eukaryotes, many important biological processes are closely related to the cell cycle. In the past decade, the basic knowledge on the machinery controlling the cell cycle has been unquestionably improved. Many genes involved in cell cycle regulation have been recognized, and their importance has been carefully evaluated. This created a strong impulse to investigate diseases in which the cell cycle is known to play a pivotal role, such as cancer. Physical interaction among specific factors is a crucial mechanism in cell cycle homeostasis, so that its regulation can be achieved by artificially modulating such protein-protein interactions. Synthetic oligopeptides mimicking small epitopes of pivotal cell cycle regulators have been employed in order to manipulate pathological cell cycle conditions.

The cell cycle regulatory pathway responsible for the control of the late-G1 checkpoint is found recurrently altered in human malignant melanoma, often due to lack of functional p16 or pRb (pRb-1) proteins. We examined the ability of p16-derived peptides to mimic p16 function in two exemplary human melanoma cell lines: the p16-defective, pRb-positive A375M cells and p16-positive, pRb-defective A2058 cells. The synthetic p16-mimicking peptides strongly induced apoptosis in p16-, pRb+ A375M cells *in vitro*, while they had significantly less activity on p16+, pRb- A2058 cells. The most active p16-mimicking peptide, p16-AP9, also potently inhibited *in vivo* growth of the A375M melanoma. Treat-

ed tumors showed a 3-fold smaller volume (P<0.025) and a significant reduction of the mitotic index and of PCNA expression. Growth of A2058 cells *in vivo* was not affected by treatment with the p16-mimicking peptide. Our results demonstrate that p16-mimicking peptides can induce apoptosis *in vitro* and that can inhibit tumor growth *in vivo* in p16-defective, pRb-expressing human melanoma cells, suggesting that p16-mimicking peptides can represent a promising tool for targeted therapy in selected cancer phenotypes (manuscript in press).

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Exp Dermatol. 2004 Feb;13(2):93-7. *I.F. 2.040*

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De Falco M., Fedele V., Cobellis L., Mastrogiacomo A., Giraldi D., Leone S., De Luca L., Laforgia V., De Luca A.

Pattern of expression of cyclin D1/CDK4 complex in human placenta during gestation.
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The serine protease HtrA1 is upregulated in the human placenta during pregnancy.
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Expression of 60 kDa heat shock protein (Hsp60) on plasma membrane of Daudi cells.

Mol Cell Biochem. 2004 Apr;259(1-2):1-7 *I.F. 1.763*

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Paggi M.G., And Felsani A.

Synthetic oligopeptides as G1 checkpoint modulators in cancer

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RACK1 is a functional target of the E1A oncoprotein.

J Cell Physiol. 2004 Apr;199(1):134-9. *I.F. 5.463*

Laboratory D associated to Neurosciences, Head and Neck and Facial pathologies department

DIRECTOR AD INTERIM:
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 she was an Assistant Professor at the Human Genetics Laboratory of Catholic University of Rome, and from 1966 to 1969 was Research Scientist at the Laboratory of Animal Radiobiology, of Atomic Energy Agency in Rome. From 1970 to 1973 she was an Assistant at the Biophysics Laboratory at the Regina Elena Cancer Institute of Rome, and from 1973 to 1987 was Associated Director of the same laboratory. Since 1987 she has been the Director of Molecular Oncogenesis Laboratory and since 2001 she has directed the Experimental Oncology Department at the Regina Elena Cancer Institute.

Staff "D" Laboratory:
CHERSI PhD, Senior Scientist
MATTIONI MANLIO MD, Senior Scientist
GALATI ALESSANDRA PhD, Senior Scientist
VERDINA ROSSELLA PhD, Senior Scientist
FALASCA ADRIANA Technician

Activities 2004

The work of the 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
COX-2 in the pathogenesis and therapy of human mesothelioma

1. PEPTIDE SYNTHESIS AND ANTIBODIES PRODUCTION.

The laboratory serves as a facility to synthesize peptides upon the request of internal and external institutional researchers. These peptides have been used as inhibitors of target protein activities or to generate specific antibodies. The production of specific antibodies against a protein requires an in-deep study to underscore the structure/function relationship (i.e. conformational, chemical, etc,) that leads to the identification of the immunogenical regions and the amino acid sequence (peptide) adequate to the scope. The preparation of the antigen can be started only after the peptide characterization (i.e. length, hydrophilicity, side residues). This investigation allows the proper carrier as well as the amino acidic residue to be used in the carrier-peptide conjugation reaction, to be chosen. After the completion of these theoretical studies, the peptide synthesis is begun. The characterization of the protein is mandatory in order to use the peptides as specific protein inhibitors. Furthermore, it is important to decide at which level the proteins' inhibition 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 the last 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.
During the year several sequences have been studied and 16 successful peptides synthesized. Some peptides and antibodies have been tested for their biological activity and then proposed for patent. In particular, peptides to 73 and polyclonal antibodies specific for different isoforms of p73 were generated.

2. Role of DNA-repair polymorphisms in individual susceptibility of occupationally exposed populations.

Levels of genotoxic damage measured in human peripheral lymphocytes are associated with increased risk of cancer incidence and mortality. Because this association is independent of external exposure (occupational or tobacco related) to genotoxic agents, both unidentified exposure and genetic traits are claimed to explain this association. Among genetic determinants able to modify the individual levels of DNA damage, xenobiotics metabolizing genes and DNA repair genes, both polymorphic in human population, may play a central role. In the context of the joint project with the Istituto Superiore di Sanità-Ministero dell'Ambiente (Health impacts of urban air pollution), we have analyzed different DNA-repair polymorphisms in a human cohort of Rome traffic officers.

In particular, the following polymorphisms were investigated: the apurinic endonuclease 1 (APE1) involved in basic excision repair (BER), the x-ray cross complementation group 1 (XRCC1) a scaffold protein also involved in BER, the x-ray cross complementation group 3 (XRCC3) involved in the repair of double strand breaks by homologous recombination (HR) and the excision repair cross complementation group 2 (ERCC2/XPD) a helicase belonging to the THFII factor of nucleotide excision repair (NER). Different genotypes were compared with DNA damage levels in order to display a possible correlation. In the general population an increase of SCEs was observed in relation to the XPD genotype. This value reached statistical significance in the Gln/Gln group compared to the Lys/Lys group and a slight increase was observed also in the heterozygous, suggesting a slight gene dosage. With regard to the APE genotype, a small significant increase was observed.

No effects of the two XRCC1 and the XRCC3 polymorphisms on SCE were observed.

3. Serum p53 antibody as a useful marker in cancer

Dysfunction in the *TP53* tumor suppressor gene is 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 functional one, resulting in the 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 (p53-Abs), detectable in the sera of patients with various types of cancer. There is a close correlation between the presence of p53-Abs and the increased expression of p53 protein in the corresponding tumor, thus the detection of p53-Abs can be used as a marker for the occurrence of p53 gene alterations. These antibodies show high specificity, since healthy controls rarely result positive, and there is a sensitivity up to 30 % in most tumor types.

In lung cancer, p53 protein accumulation and production of p53-Abs represent early events in neoplastic process, indeed p53-Abs were found in patients at high risk of lung cancer, such as heavy smokers with chronic obstructive pulmonary disease (COPD), months before any clinical evidence of cancer. However, clinical implications of p53-Abs in lung cancer resulted controversial: in non-small cell lung cancer, p53-Abs were predominantly related to short survival, but were also predictors of better survival, after radiotherapy, or showed absence of prognostic relevance. However, in small cell lung cancer, studies were very divergent. The aim of our work, as far as far as pulmonary disease is concerned, was to evaluate the role of the detection of p53-Abs in the early diagnosis of patients at high risk of lung cancer and to investigate the actual prognostic significance of these antibodies in lung cancer patients. In collaboration with clinical departments of our Institute, we started a large prospective study to analyze, by a specific ELISA, p53-Abs in sera of non-neoplastic people, including patients at high risk of lung cancer, and of patients with histological diagnosed lung cancer. Preliminary results indicate that 10 out 170 non-neoplastic people were positive, 6 with a diagnosis of COPD, whereas 9 out 46 lung cancer patients showed significant levels of p53-Abs; in particular, 6 positive patients of the latter group had very high levels of p53-Abs and 3 of them derived from a group of 4 patients with non-small cell lung cancer.

4. COX-2 AND PATHOGENESIS AND THERAPY OF HUMAN MESOTHELIOMA

Malignant mesothelioma (MM) is a rare, highly aggressive tumor, accounting for less than 1% of all cancer deaths in the world. Although the association between exposure to asbestos and the development of MM is commonly accepted, the exact mechanism whereby asbestos induces MM is unknown. MM has proved resistant to classical chemotherapeutic and radiation regimens and the natural history has not been influenced by standard therapy so far. Moreover, it has been recently demonstrated *in vitro* that COX-2 is implicated in MM pathogenesis. In this view and in strict collaboration with Dr. Alfonso Baldi professor at Napoli University, we started to analyze *in vitro* and *in vivo* the effects of COX-2 inhibitors in MM pathogenesis and progression in order to define the molecular pathways activated or down-regulated by this treatment and understand the molecular mechanisms responsive to the antitumoral activity of specific COX-2 inhibitors. Mesothelioma cells (MSTO-211H) have been exposed to a specific COX-2 inhibitor (NS-398) and the effects on cell proliferation have been studied. Moreover, *in vivo* studies looking at the effects of COX-2 inhibition on mesothelioma cell growth on nude mice have also been undertaken. Nude mice have been inoculated subcutaneously with human mesothelioma cells (MSTO) and randomized to receive either vehicle (control) or COX-2 inhibitor (NS-398) alone or in combination with Cis-platinum.

Publications 2004

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J Immunol Methods. 2004 Aug;291(1-2):79-91. *I.F. 2.744*

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Scientific activities

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J. Exp. Clin. Cancer Res., Sep;23(3):469-75, 2004 I.F. 0.574

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Int. J. Oncology, 25: 0-00, 2004 I.F. 2.536

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Endothelin receptors as novel targets in tumor therapy.

J. Transl. Med., May 27;2(1):16, 2004 I.F. 0.1

8. Bagnato A., Natali P.G.

Targeting endothelin axis in cancer.

Cancer Treat. Res., 119:293-314, 2004 I.F. 0.1

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Fatty Acid Synthase (FAS) is a marker of increased risk of recurrence in lung carcinoma.

Anticancer Research, 24(6) 4169, 2004 I.F. 1.347

New approaches to prevent intestinal toxicity of irinotecan-based regimens.

ALIMONTI A., GELIBTER A., PAVESE I., SATTA F., COGNETTI F., FERRETTI G., RASIO D., VECCHIONE A., DI PALMA M.

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Background: Irinotecan is a selective inhibitor of topoisomerase I, an enzyme part of the replication and transcription system of DNA. Irinotecan is employed, with different modalities, in the treatment of metastatic colorectal cancer, and recently it has been officially approved in association with fluorouracil (FU) and leucovorin (LV) as a first-line option in metastatic colorectal cancer.

Results: One of the problems linked to the administration of this drug is the high intestinal toxicity, which constitutes its dose limiting toxicity (DLT). In routine practice, loperamide is employed as symptomatic drug for the treatment of CPT-11-induced diarrhoea, but is not completely adequate to control the problem. The role of the intestinal bacterial microflora in the pathogenesis of CPT-11-induced intestinal toxicity has been recently discovered. The active metabolite of CPT-11, SN38, is generated from CPT-11 by sieric carboxylesterase, and subsequently conjugated to SN38-G by hepatic UDP-glucuronyltransferase. SN38-G is the inactive metabolite of CPT-11 and is excreted into the small intestine, from which it is eliminated in the faeces. Some studies have shown the ability of intestinal bacterial beta-glucoronidases to transform SN38-G into SN38, causing direct damage to the intestinal mucosa. Thus, alternative strategies such as intestinal alkalinization and anti-cyclooxygenase 2 (COX-2) therapy have been explored.

Conclusions: In this review, we will illustrate the mechanisms which cause the CPT-11-induced diarrhoea and the potential measures available to prevent it.

Anti-retrovirals and immunosuppressive drug interactions in a HIV-positive patient after liver transplantation.

ANTONINI M., ETTORRE G.M., VENNARECCI G., D'OFFIZI G., NARCISO P., DEL NONNO F., PERRACCHIO L., VISCO G., SANTORO E.

Hepatogastroenterology, May-Jun;51(57):646-8, 2004

We report a case of drug-related toxicity after liver transplantation for hepatocellular carcinoma in a HIV-HCV co-infected patient. Before transplant the patient was on a triple antiretroviral therapy (zidovudine and lamivudine and efavirenz) with a stable CD4+ cell count >500 cells/microL. Liver transplantation was performed with a liver graft showing a 10% of macrosteatosis and with a graft-to-recipient body weight ratio of 1.3. Immunosuppression was achieved with tacrolimus, azathioprine and steroids. The antiretroviral therapy was resumed in the first postoperative day as the early graft function was in the normal range. After a few hours the patient showed myoglobinuria, rhabdomyolysis and a fast-deteriorating graft function. All drugs were withdrawn except steroids and an empiric therapy with riboflavin and glutathione was maintained for five days until myoglobinuria ended. Nevertheless the serum levels of tacrolimus remained in the therapeutic range for six days when it was reintroduced at a reduced dosage (0.01 mg/kg/die). The postoperative course was complicated by tense ascites and severe hyperbilirubinemia without any rejection episodes. The patient was discharged 48 days post-transplantation with a good liver function. During the following year no signs of aggressive HCV-HIV recurrences were observed and the patient is maintaining a CD4+ cells count >400 without antiretroviral therapy.

Sertoli-Leydig cell androgens-estrogens secreting tumor of the ovary: ultra-conservative surgery.

Appetecchia M., Cela V., Bernardi F., Burelli A., Cionini R., Pucci E.

Eur. J. Obstet. Gynecol. Reprod. Biol., Sep 10;116(1):113-6, 2004

No abstract available

C-MYB, serum P-53M, genetic instability, labeling index and endoscopic findings in patients with adenoma or colorectal cancer.

Assisi D., Grassi A., La Penta R., Stigliano V., Greco C., Cianciulli A.M., Giannarelli D., Casale V.

J. Exp. Clin. Cancer Res., Sep;23(3):469-75, 2004

Structural alterations of c-myb proto-oncogenes and serum p53 mutant level, Mitomycin C-induced chromosomal aberrations and sister chromatid exchanges and proliferative activity of mucosa (H3-thymidine -labeling index LI) are often determined to obtain more information about the diagnosis and prognosis of neoplastic and preneoplastic lesions of the colon. The aim of this study was to evaluate the endoscopic findings of a 5 year follow-up in three groups of subjects (normal, adenoma or cancer patients) and to correlate these findings with the biological alterations in the same subjects between 1990 and 1993. We analyzed 200 subjects (118 Male and 82 Female), 78 normal subjects (group A), 60 patients with adenoma (group B) and 62 with carcinoma (group C). Data regarding endoscopic lesions was collected from June 1998 to December 2000 after a 5 year follow-up and correlated with the biological alterations in the same subjects between 1990—1993. We obtained endoscopic findings from 23/137 subjects (16.8%), 6/137 (4.4%) died from other causes and 108/137 (78.8 %) were negative for lesions. The percentage of disease after 5 years is not statistically different among the three groups (groups A, B and C). There was no statistically significant association between values of the labeling index, structural alterations of c-myb, p-53-M serum levels and chromosomal aberrations and endoscopic findings in the 5 year follow-up. We conclude that the biological markers considered are not able to stratify patients in terms of risk of progression to malignant disease.

Glycemic index, glycemic load and risk of prostate cancer.

Augustin L.S., Galeone C., Dal Maso L., Pelucchi C., Ramazzotti V., Jenkins D.J., Montella M., Talamini R., Negri E., Franceschi S., La Vecchia C.

Int. J. Cancer, Nov 10;112(3):446-50, 2004

Dietary carbohydrates have different glycemic and insulinemic potentials depending on type (glycemic index, GI) and amount (glycemic load, GL) of carbohydrate consumed or both. Insulin in turn has been implicated as a risk factor for several cancers, including that of the prostate. We assessed the relationship of GI and GL with prostate cancer risk in a multicenter case-control study. Cases and controls were recruited between 1991 and 2002 in the network of major teaching and general hospitals in 4 Italian areas. Cases were 1,204 men (age range 46-74 years) admitted for incident, histologically confirmed prostate cancer. Controls were 1,352 men (age range 46-74 years) admitted for acute, nonmalignant conditions unrelated to long-term modifications of diet. ORs of prostate cancer and the corresponding 95% CIs were derived using unconditional multiple logistic regression, including terms for age, study center, education, family history of prostate cancer, smoking, body mass index, physical activity, alcohol consumption, intake of energy, fiber and lycopenes. Compared to the lowest quintile of GI, the ORs were 1.23, 1.24, 1.47 and 1.57 for subsequent levels of GI. The corresponding values for GL were 0.91, 1.00, 1.20 and 1.41. No heterogeneity was found among strata of selected covariates. We found direct relations between dietary GI and GL and prostate cancer risk. Correcting for potential confounding factors did not substantially modify these associations.

Physical status of HPV types 16 and 18 in topographically different areas of genital tumours and in paired tumour-free mucosa.

BADARACCO G., VENUTI A.

Int. J. Oncology, 25: 0-00, 2004

No abstract available

Endothelin receptors as novel targets in tumor therapy.

BAGNATO A., NATALI P.G.

J. Transl. Med., May 27;2(1):16, 2004

The endotelin (ET) axis, that includes ET-1, ET-2, ET-3, and the ET receptors, ETA and ETB, plays an important physiological role, as modulator of vasomotor tone, tissue differentiation and development, cell proliferation, and hormone production. Recently, investigations into the role of the ET axis in mitogenesis, apoptosis inhibition, invasiveness, angiogenesis and bone remodeling have provided evidence of the importance of the ET-1 axis in cancer. Data suggest that ET-1 participates in the growth and progression of a variety of tumors such as prostatic, ovarian, renal, pulmonary, colorectal, cervical, breast carcinoma, Kaposi's sarcoma, brain tumors, melanoma, and bone metastases. ET-1 receptor antagonists beside providing ideal tools for dissecting the ET axis at molecular level have demonstrated their potential in developing novel therapeutic opportunity. The major relevance of ETA receptor in tumor development has led to an extensive search of highly selective antagonists. Atrasentan, one of such antagonists, is orally bioavailable, has suitable pharmacokinetic and toxicity profiles for clinical use. Preliminary data from clinical trials investigating atrasentan in patients with prostate cancer are encouraging. This large body of evidence demonstrates the antitumor activity of endothelin receptor antagonists and provides a rationale for the clinical evaluation of these molecules alone and in combination with cytotoxic drugs or molecular inhibitors leading to a new generation of anticancer therapies targeting endothelin receptors.

Targeting endothelin axis in cancer.

BAGNATO A., NATALI P.G.

Cancer Treat. Res., 119:293-314, 2004

No abstract available

Endothelin B receptor blockade inhibits dynamics of cell interactions and communications in melanoma cell progression.

BAGNATO A., ROSANO L., SPINELLA F., DI CASTRO V., TECCE R., NATALI P.G.

Cancer Res., Feb 15;64(4):1436-43, 2004

Phenotypic and genotypic analyses of cutaneous melanoma have identified the endothelin B receptor (ET(B)R) as tumor progression marker, thus representing a potential therapeutic target. Here, we demonstrate that activation of ET(B)R by endothelin-1 (ET-1) and ET-3 leads to loss of expression of the cell adhesion molecule E-cadherin and associated catenin proteins and gain of N-cadherin expression. Exposure of melanoma cells to ET-1 leads to a 60% inhibition in intercellular communication by inducing phosphorylation of gap junctional protein connexin 43. Additionally, activation of the ET(B)R pathway increases alpha(v)beta(3) and alpha(2)beta(1) integrin expression and matrix metalloproteinase (MMP)-2 and MMP-9, membrane type-1-MMP activation, and tissue inhibitor MMP-2 secretion. The ET(B)R pathway results into the downstream activation of focal adhesion kinase and extracellular signal-regulated kinase 1/2 signaling pathways, which lead to enhanced cell proliferation, adhesion, migration, and MMP-dependent invasion. The small molecule A-192621, an orally bioavailable nonpeptide ET(B)R antagonist, significantly inhibits melanoma growth in nude mice. These findings demonstrate that ET-1 and ET-3 through ET(B)R activation trigger signaling pathways involved in events associated with disruption of normal host-tumor interactions and progression of cutaneous melanoma. Pharmacological interruption of ET(B)R signaling may represent a novel therapeutic strategy in the treatment of this malignancy.

Analysis of APAF-1 expression in human cutaneous melanoma progression.

Baldi A., Santini D., Russo P., Catricala C., Amantea A., Picardo M., Tatangelo F., Botti G., Dragonetti E., Murace R., Tonini G., Natali P.G., Baldi F., Paggi M.G.

Exp. Dermatol., Feb;13(2):93-7, 2004

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, variation 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. We conclude that loss of APAF-1 expression can be considered as an indicator of malignant transformation in melanoma.

Characterization of tissue specific expression of Notch-1 in human tissues.

Baldi A., De Falco M., De Luca L., Cottone G., Paggi M.G., Nickoloff B.J., Miele L., De Luca A.

Biol. Cell., May;96(4):303-11, 2004

Signaling through the Notch cell surface receptors is a highly conserved mechanism of cell fate specification. Notch signaling regulates proliferation, differentiation and cell death. In vertebrates, putative gene duplication has originated four Notch genes, Notch-1, -2, -3 and -4. They have been implicated in neurogenesis, hematopoiesis, T-cell development, vasculogenesis and brain cortical growth. We have investigated Notch-1 distribution in normal human tissues by immunohistochemistry and immunoblot. We detected widespread expression of Notch-1 cytoplasmatic staining, with different tissue distributions in the different organs examined. In particular, high expression of Notch-1 was detected in the intermediate suprabasal layers, but not in the dead cells at the extreme periphery of stratified epithelia. Moreover, a low/intermediate level of Notch-1 was observed in lymphocytes in several peripheral lymphoid tissues; in particular the germinal centers of lymph nodes showed the most abundant number of positive cells, which appeared to be centroblasts/immunoblasts based on nuclear morphology. Notch-1 participates in keratinocytes differentiation. We showed by Western blot analysis that Notch-1 level was clearly increased in HaCaT cells after Ca(++) addition and remained substantially elevated until late differentiation stages. These results suggest that Notch-1 may function in numerous cell types in processes beyond cell fate determination, such as neuronal plasticity, muscle hypertrophy, liver regeneration, and germinal center lymphopoiesis during the immune response.

Modulation of retrovirally driven therapeutic genes by mutant TP53 in anaplastic thyroid carcinoma.

Barzon L., Gnatta E., Castagliuolo I., Trevisan M., Moretti F., Pontecorvi A., Boscaro M. And Palù G.

Cancer Gene. Therapy, 2004

We previously demonstrated that restoration of TP53 activity in anaplastic thyroid carcinoma inhibits cell growth and induces expression of thyroid differentiation markers. Here, we investigated whether TP53 status may condition the expression of therapeutic genes driven by retroviral LTR or tissue-specific enhancer elements. The TP53-defective ARO anaplastic thyroid carcinoma cells were transfected with TP53(Val135), which exhibits wild-type activity at 32 degrees C, and transduced with retroviral vectors, in which therapeutic genes were driven either by wild-type LTR or by a reshuffled LTR containing thyroglobulin (TG) enhancer. Both at 37 and 32 degrees C, expression of transgenes driven by TG enhancer was 10-fold lower than that obtained with wild-type LTR retroviral vector. TP53(Val135) transfer into ARO cells repressed transcription from wild-type LTR but increased expression of TG-driven therapeutic genes. This effect was markedly enhanced by cell culture at 32 degrees C and by TSH treatment. Cytotoxic effects shown after ganciclovir treatment paralleled therapeutic gene expression levels. In conclusion, TP53 status in the tumor cell can influence expression of therapeutic genes. When using retroviral-vector-based gene therapy, wild-type LTR vectors should be employed to target TP53-defective tumors, whereas thyroid-specific promoters should be used for transcriptional targeting of thyroid carcinomas carrying wild-type TP53.

Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer.

Bernier J., Domenge C., Ozsahin M., Matuszewska K., Lefebvre J.L., Greiner R.H., Giralt J., Maingon P., Rolland F., Bolla M., Cognetti F., European Organization For Research And Treatment Of Cancer Trial 22931.

N. Engl. J. Med., May 6;350(19):1945-52, 2004

Background: We compared concomitant cisplatin and irradiation with radiotherapy alone as adjuvant treatment for stage III or IV head and neck cancer.

Methods: After undergoing surgery with curative intent, 167 patients were randomly assigned to receive radiotherapy alone (66 Gy over a period of 6 1/2 weeks) and 167 to receive the same radiotherapy regimen combined with 100 mg of cisplatin per square meter of body-surface area on days 1, 22, and 43 of the radiotherapy regimen.

Results: After a median follow-up of 60 months, the rate of progression-free survival was significantly higher in the combined-therapy group than in the group given radiotherapy alone (P=0.04 by the log-rank test; hazard ratio for disease progression, 0.75; 95 percent confidence interval, 0.56 to 0.99), with 5-year Kaplan-Meier estimates of progression-free survival of 47 percent and 36 percent, respectively. The overall survival rate was also significantly higher in the combined-therapy group than in the radiotherapy group (P=0.02 by the log-rank test; hazard ratio for death, 0.70; 95 percent confidence interval, 0.52 to 0.95), with five-year Kaplan-Meier estimates of overall survival of 53 percent and 40 percent, respectively. The cumulative incidence of local or regional relapses was significantly lower in the combined-therapy group (P=0.007). The estimated five-year cumulative incidence of local or regional relapses (considering death from other causes as a competing risk) was 31 percent after radiotherapy and 18 percent after combined therapy. Severe (grade 3 or higher) adverse effects were more frequent after combined therapy (41 percent) than after radiotherapy (21 percent, P=0.001); the types of severe mucosal adverse effects were similar in the two groups, as was the incidence of late adverse effects.

Conclusions: Postoperative concurrent administration of high-dose cisplatin with radiotherapy is more efficacious than radiotherapy alone in patients with locally advanced head and neck cancer and does not cause an undue number of late complications.

Glutathione depletion induced by c-Myc downregulation triggers apoptosis on treatment with alkylating agents.

Biroccio A., Benassi B., Fiorentino F., Zupi G.

Neoplasia, May-Jun;6(3):195-206, 2004

Here we investigate the mechanism(s) involved in the c-Myc-dependent drug response of melanoma cells. By using three M14-derived c-Myc low-expressing clones, we demonstrate that alkylating agents, cisplatin and melphalan, trigger apoptosis in the c-Myc antisense transfectants, but not in the parental line. On the contrary, topoisomerase inhibitors, adriamycin and camptothecin, induce apoptosis to the same extent regardless of c-Myc expression. Because we previously demonstrated that c-Myc downregulation decreases glutathione (GSH) content, we evaluated the role of GSH in the apoptosis induced by the different drugs. In control cells treated with one of the alkylating agents or the others, GSH depletion achieved by L-buthionine-sulfoximine preincubation opens the apoptotic pathway. The apoptosis proceeded through early Bax relocalization, cytochrome c release, and concomitant caspase-9 activation, whereas reactive oxygen species production and alteration of mitochondria membrane potential were late events. That GSH was determining in the c-Myc-dependent drug-induced apoptosis was demonstrated by altering the intracellular GSH content of the c-Myc low-expressing cells up to the level of controls. Indeed, GSH ethyl ester-mediated increase of GSH abrogated apoptosis induced by cisplatin and melphalan by inhibition of Bax/cytochrome c redistribution. The relationship among c-Myc, GSH content, and the response to alkylating agent has been also evaluated in the M14 Myc overexpressing clones as well as in the melanoma JR8 c-Myc antisense transfectants. All together, these results demonstrate that GSH plays a key role in governing c-Myc-dependent drug-induced apoptosis.

Telomerase as a new target for the treatment of hormone-refractory prostate cancer.

Biroccio A., Leonetti C.

Endocr. Relat. Cancer, Sep;11(3):407-21, 2004

Prostate cancer is the leading cause of cancer-related deaths in men. Androgen ablation is the mainstay of treatment for advanced prostate cancer. This therapy is very effective in androgen-dependent cancer; however, these cancers eventually become androgen independent, rendering anti-androgen therapy ineffective. The exploration of novel modalities of treatment is therefore essential to improve the prognosis of this neoplasia. Telomeres are specialized heterochromatin structures that act as protective caps at the ends of chromosomes. Telomere maintenance in the majority of tumor cells is achieved by telomerase, a reverse transcriptase enzyme that catalyzes the synthesis of further telomeric DNA. Telomerase is detected in the majority of prostate cancers, but not in normal or benign prostatic hyperplasia tissue. Moreover, the human telomerase reverse transcriptase (hTERT) gene, the catalytic subunit of telomerase, is regulated by androgens as well as by different oncogenes including Her-2, Ras, c-Myc and Bcl-2, which seem to play an important role in prostate cancer progression. Thus, telomerase may represent a very good candidate for targeted therapy in prostate tumors. To inhibit telomere maintenance by telomerase, approaches that directly target either telomerase and telomeres or the telomerase regulatory mechanisms have been used. Moreover, strategies targeting telomerase-positive cells as a means to directly kill the tumor cells have been tested. This review summarizes the most promising results achieved by anti-telomerase strategy in different solid tumors. Most of the telomerase-associated therapies described here have proved very promising for the treatment of prostate cancer. On the basis of the good results obtained and considering the multigenic defects of human tumors, including prostate cancer, the combination of anti-telomerase strategies with conventional drugs and/or molecules capable of interfering with oncogenic pathways could efficiently improve the response of this neoplasia.

p73 and p63: Why Do We Still Need Them?

Blandino G., Dobbelstein M.

Cell. Cycle., Jul 2;3(7), 2004

When p73 and p63 were initially described as homologues of the tumor suppressor p53, the three family members seemed almost exchangeable, raising the question why all three were retained during evolution. It later turned out that the corresponding genes, TP63 and TP73, appear phylogenetically older than TP53, and that their targeted deletion causes severe developmental defects, in contrast to a deletion of TP53. Hence, p63 and p73 are responsible for biological effects that cannot be elicited by p53 alone. Here, we provide an overview of properties ascribed to p63 and p73 that distinguish them from p53. Differences occur at the following levels: (i) protein structure, especially with regard to the aminoterminal transactivation domains and the carboxyterminal portions unique to p63 and p73; (ii) regulation, affecting mRNA levels, posttranslational modifications and interaction with other cellular proteins; (iii) activities, resulting in the regulation of gene expression, the programming of development, and the emergence of tumors. We speculate that, during the course of evolution, p63 and p73 have first pursued a broader range of activities, whereas p53 later specialized on genome maintenance.

Food groups and risk of prostate cancer in Italy.

Bosetti C., Micelotta S., Dal Maso L., Talamini R., Montella M., Negri E., Conti E., Franceschi S., La Vecchia C.

Int. J. Cancer, Jun 20;110(3):424-8, 2004

Although several studies have been conducted, the relation between diet and prostate cancer remains unclear. The role of a wide range of foods on the risk of prostate cancer has thus been analyzed in a case-control study conducted in Italy between 1991 and 2002. Cases were 1,294 patients below age 75 years with incident, histologically confirmed carcinoma of the prostate; controls were 1,451 subjects below age 75 years admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic conditions. Multivariate odds ratios (ORs) were obtained after allowance for major potential confounding factors, including calorie intake. Among the 19 food groups considered, 4 showed some significant association with prostate cancer risk. A significant trend of increasing risk with more frequent consumption was found for milk and dairy products (OR = 1.2 for highest vs. lowest quintile, p = 0.03) as well as bread (OR = 1.4, p = 0.01), whereas inverse associations were observed for soups (OR = 0.8, p =

0.02) and cooked vegetables (OR = 0.7, p = 0.01). This uniquely large study on prostate cancer and diet in a southern European population confirms that no strong association exists between any specific foods and prostate cancer, apart from an increased risk for milk and dairy products and a possible protective effect of vegetables.

Retinol, carotenoids and the risk of prostate cancer: a case-control study from Italy.

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

Int. J. Cancer, Nov 20;112(4):689-92, 2004

Several studies have evaluated the possible association between intakes of retinoids and carotenoids and the risk of prostate cancer, but the evidence is still inconsistent. Further, only a few studies have investigated the role of specific carotenoids other than beta-carotene. We have thus considered the association between retinol and various carotenoids using data from a multicentric case-control study conducted in Italy between 1991 and 2002. This included 1,294 incident, histologically confirmed prostate cancer cases below age 75 years admitted to major teaching and general hospitals in the areas under study, and 1,451 controls below age 75 years selected among patients admitted to the same hospitals as cases for a wide spectrum of acute nonneoplastic conditions not related to long-term modifications of diet. Subjects' usual diet was investigated by means of a validated food-frequency questionnaire. Multivariate odds ratios and the corresponding 95% confidence intervals were estimated using unconditional logistic regression models. The risk of prostate cancer tended to decrease with increasing intake of retinol (OR=0.79 for the highest versus the lowest quintile of intake), carotene (OR=0.70), alpha-carotene (OR=0.85) and beta-carotene (OR=0.72), although the estimates were significant for carotene and beta-carotene only. No meaningful associations emerged for nonprovitamin A carotenoids, such as lycopene (OR=0.94) and lutein/zeaxanthin (OR=0.91). No systematic heterogeneity was observed across strata of age, education and body mass index. Thus, our study supports the hypothesis of a weak protective effect of carotene, particularly beta-carotene, on the risk of prostate cancer, while it indicates that other carotenoids, including lycopene, and retinol are not appreciably related to the risk of this neoplasm.

Wild-type p53 gene transfer is not detrimental to normal cells in vivo: implications for tumor gene therapy.

Bossi G., Mazzaro G., Porrello A., Crescenzi M., Soddu S., Sacchi A.

Oncogene, Jan 15;23(2):418-25, 2004

The p53 oncosuppressor is strictly maintained in an inactive form under normal conditions, while it is post-translationally activated by a variety of stresses, enacting different protective biological functions. Since one critical issue in cancer gene therapy is tumor specificity, we asked whether the tight p53 regulation applies also to exogenously transferred p53. In principle, this type of regulation could allow p53 gene transfer in both normal and tumor cells to produce detrimental effects only in the latter ones. Here, we report that primary bone marrow cells infected with a p53 recombinant retrovirus and transplanted into irradiated mice reconstitute the hematopoietic system, with no detectable alterations in any of its compartments. Furthermore, simultaneous infection of leukemia and bone marrow cells depleted the neoplastic contamination, allowing lifelong, disease-free survival of 65% of the transplanted animals. These results show that exogenous p53 is controlled as tightly as the endogenous one, and opens the way to p53 gene therapy, without requiring tumor targeting.

Altered expression of FAS system is related to adverse clinical outcome in stage I-II breast cancer patients treated with adjuvant anthracycline-based chemotherapy.

Botti C., Buglioni S., Benevolo M., Giannarelli D., Papaldo P., Cognetti F., Vici P., Di Filippo F., Del Nonno F., Venanzi F.M., Natali P.G., Mottolese M.

Clin. Cancer Res., Feb 15;10(4):1360-5, 2004

Purpose: To determine the prognostic value of Fas receptor and Fas ligand (FasL) as apoptosis-related biomarkers in the context of chemoresponsiveness in breast cancer (BC) patients submitted to anthracycline-based adjuvant therapy.

Experimental design: Fas and FasL were investigated by immunohistochemistry in surgical samples collected from 167 stage I-IIa-b BC patients enrolled in a prospective clinical trial using epirubicin plus cyclophosphamide in the adjuvant setting.

Results: Fas and FasL were significantly associated with tumor stage ($P < 0.0001$). Multivariate analysis indicated that stage, loss of Fas (relative risk, 8.5 and 9.12; $P < 0.0001$) and FasL up-regulation (relative risk, 2.38 and 2.88; $P = 0.01$) were independent prognostic variables influencing both disease-free survival (DFS) and overall survival (OS). A Cox analysis using a four-category Fas/FasL phenotype (+/-, +/+, -/+, -/-) as a stratification factor evidenced a highly positive association between Fas/FasL phenotype and the cumulative hazard of relapse and death in the entire series of patients. We also estimated the DFS and OS for different combinations of the pathological-tumor-node-metastasis (TNM) stage and Fas/FasL by using the K sample log-rank exact test demonstrating that significantly shorter DFS and OS were observed in Fas-negative and FasL-positive patients in both stage I-IIa and IIb.

Conclusions: Data presented herein demonstrated that, according to a number of in vitro studies, the prognosis for BC patients receiving adjuvant anthracycline-based chemotherapy strongly depends on the Fas/FasL status. Therefore, a concomitant altered pattern of Fas/FasL expression seems to configure an aggressive tumor phenotype linked to disease progression.

Assessment of risk factors and human papillomavirus (HPV) related pathogenetic mechanisms of CIN in HIV-positive and HIV-negative women. Study design and baseline data of the HPV-Pathogen ISS study.

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., Et Al.

Eur. J. Gynaecol. Oncol., 25(6):689-98, 2004

Objectives: In women with HIV-associated immunosuppression, HPV infections have an increased risk of progression to high-grade cervical intraepithelial neoplasia (CIN). With the HAART-induced prolonged survival and more protracted clinical course of AIDS, progression of CIN to cervical cancer (CC) has become a clinically relevant issue, and the mechanisms responsible for HIV-HPV interactions need further elucidation. The study design and analysis of the baseline data of our new project are presented.

Material and methods: This project is a combination of a prospective cohort study of HIV- and HIV+ women, and a retrospective analysis of CIN lesions and cervical cancer. Up to the present, 244 women have been enrolled (17 HIV+) and subjected to epidemiological interview, colposcopic examination, sampling for HPV testing and typing (PCR, InnoLiPA), and HPV serology. The retrospective series of biopsies were analysed for 13 biomarkers (monitoring key molecular events) using immunohistochemistry and tested for HPV by PCR and TaqMan.

Results: HIV- and HIV+ women differ in their exposure status to many of the key epidemiological risk factors of cervical cancer, the most significant ones being number of sexual partners ($p = 0.0001$), age at onset of sexual activity ($p = 0.002$), and contraception (yes-no) ($p = 0.009$). The differences in the baseline clinical observations are less dramatic; HIV-positive women had more frequent HSIL PAP tests ($p = 0.040$), CIN2 or higher in cervical biopsy ($p = 0.049$), and external genital warts ($p = 0.019$). The factors predicting intermediate endpoint markers of cervical cancer, i.e., HSIL PAP smear, ATZ2 in colposcopy, and high-grade CIN in biopsy were analysed in univariate and multivariate regression models. All factors significant in univariate analysis were entered in the multivariate model; HIV-status and Pap smear history maintained their independent predictive power of the HSIL Pap test. The most powerful predictor of ATZ2 colposcopy was HSIL in Pap test. Only the HSIL Pap test and ATZ2 colposcopy remained significant independent predictors of high-grade CIN ($p = 0.0001$ and $p = 0.008$, respectively) in the multivariate model.

Conclusions: The three intermediate endpoint markers are closely interrelated, but predicted in part by different covariantes in the causal pathway to cervical cancer. To elucidate whether the increased risk of HIV-positive women to high-grade CIN is due a) to their different exposure status to the risk factors, b) to the direct effects of HIV, or c) to molecular interactions between HIV and HPV, we need to complete these analyses separately in HIV+ and HIV- women.

Novel association with gemcitabine and docetaxel as salvage chemotherapy in metastatic breast cancer previously treated with anthracyclines: results of a multicenter phase II study.

Brandi M., Vici P., Lopez M., Valerio M.R., Giotta F., Gebbia N., Schittulli F., Colucci G.; Gruppo Oncologico Italia Meridionale.

Semin. Oncol., Apr;31(2 Suppl 5):13-9, 2004

The goals of this study were to evaluate the efficacy and toxicity of the gemcitabine/docetaxel combination in metastatic breast cancer previously treated with anthracyclines. Fifty-three patients with metastatic breast cancer who had failed or relapsed after anthracycline-based chemotherapy entered the study and were evaluable. Patients received gemcitabine (1,000 mg/m(2) days 1 and 8) and docetaxel (80 mg/m(2) day 8), every 3 weeks. The regimen was generally well tolerated with good feasibility. A complete response occurred in six patients (9.4%) and partial response in 23 (43.4%) for an overall response rate of 53% (95% confidence interval, 38.9% to 66.7%). Median survival rate was 70%; and the duration of response, time to progression, and overall survival were 6, 7.5, and 16.5 months, respectively. We conclude that the gemcitabine/docetaxel combination constitutes a manageable and tolerable combination as salvage chemotherapy in metastatic breast cancer and may represent a valid treatment option in patients previously treated with anthracyclines.

Acute myeloid leukemia secondary to a myelodysplastic syndrome with t(3;3) (q21;q26) in an HIV patient treated with chemotherapy and highly active antiretroviral therapy.

Breccia M., Gentile G., Martino P., Petti M.C., Russo E., Mancini M., Alimena G.

Acta Haematol., 111(3):160-2, 2004

We describe the first case of secondary acute myeloid leukemia (AML) with t(3;3) (q21;q26) occurring in a human immunodeficiency virus (HIV)-infected patient sequentially treated with chemotherapy and highly active antiretroviral therapy (HAART). The t(3;3) is a nonrandom abnormality found in a small percentage of patients with myelodysplastic syndrome, secondary AML or chronic myeloid leukemia and is strongly associated with abnormal thrombopoiesis and a particularly poor prognosis. So far, it has never been observed in HIV-positive patients. Sporadic cases of AML have been reported in HIV patients and the feasibility of chemotherapy in association with HAART and disease outcome are still not clearly defined. Despite the poor response to chemotherapy in our case, which might also be related to the unfavorable karyotype, the secondary nature of the disease and the HIV positivity, the patient had a relatively long period of survival that could be due to the use of HAART. The association of chemotherapy with HAART appeared to be feasible and tolerable and could be suggested as a choice treatment in this peculiar subset of HIV/AML patients.

Clinico-biological features and outcome of acute promyelocytic leukemia patients with persistent polymerase chain reaction-detectable disease after the AIDA front-line induction and consolidation therapy.

Breccia M., Diverio D., Noguera N.I., Visani G., Santoro A., Locatelli F., Damiani D., Marmont F., Vignetti M., Petti M.C., Lo Coco F.

Haematologica, Jan;89(1):29-33, 2004

Background and objectives: Front line treatment of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA) and chemotherapy (CHT) results in molecular remission in approximately 95% of patients tested after consolidation. The small fraction of patients with persistence of molecular disease (i.e. those in whom polymerase chain reaction (PCR) is positive for PML/RARalpha) after such therapy are thought to have a dismal prognosis but has not yet been investigated in detail.

Design and methods: We analyzed the clinico-biological features at presentation of APL patients who showed PCR-detectable residual disease and compared them to those of patients achieving molecular remission after AIDA induction and consolidation. Furthermore, we report the outcome of patients with molecularly persistent disease treated with salvage therapy.

Results: Patients attaining molecular remission (n=650) and patients who tested PCR+ve at the end of consolidation (n=23) were not statistically significantly different as regards median age, white cell and platelet counts, morphologic subtype (M3 or M3v), fibrinogen levels or PML/RARalpha transcript type. As to treatment outcome after salvage therapy, 7 patients were treated before morphologic relapse [3 with chemotherapy and autologous stem cell transplantation (SCT) and 4 with allogeneic SCT], and are alive after 64-118 months. Of 16 pa-

tients treated at the time of morphologic relapse, only 2 patients are alive, both of whom received an allogeneic SCT.

Interpretation and conclusions: Our findings indicate that APL patients who are molecularly resistant to the AIDA protocol have no distinguishing features at presentation. Their outcome suggests the need for early therapeutic intervention with aggressive treatment prior to the occurrence of hematologic relapse.

Prognostic factors in myelodysplastic and myeloproliferative types of chronic myelomonocytic leukemia: a retrospective analysis of 83 patients from a single institution.

BRECCIA M., LATAGLIATA R., MENGARELLI A., BIONDO F., MANDELLI F., ALIMENA G.

Haematologica, Jul;89(7):866-8, 2004

We analyzed independent prognostic factors associated with survival and risk of evolution to acute leukemia in our series of 83 patients with previously untreated chronic myelomonocytic leukemia (CMML), with the aim of testing the validity of the stratification based on white blood cell (WBC) count, in myeloproliferative and myelodysplastic types of the revisited WHO classification.

Clinico-pathological characteristics of myeloid sarcoma at diagnosis and during follow-up: report of 12 cases from a single institution.

BRECCIA M., MANDELLI F., PETTI M.C., D'ANDREA M., PESCARMONA E., PILERI S.A., CARMOSINO I., RUSSO E., DE FABRITIIS P., ALIMENA G.

Leuk. Res., Nov;28(11):1165-9, 2004

The aim of this study was to describe the presenting features, the frequency and outcome of myeloid sarcoma (MS) diagnosed in our Institution from January 1995 to December 2000. Twelve MS were seen and the frequency account for only 2% of all acute myeloid leukemia (AML) patients observed in our department in the same period. Median age was 45 years (range: 4-84). All had been initially misdiagnosed as malignant lymphoma (ML) and a median of 2.9 months (range: 1-6) elapsed between the misdiagnosis and the correct of MS, effectuated in our department. At that time, a bone marrow examination revealed a myelodysplastic condition in seven patients, an infiltration by blast cells >30% in two patients, and normal features in the other three. In the non-leukemic patients a median of 5 months (range: 2-44 months) elapsed between the diagnosis of MS and acute leukemia. In all, 10 patients received intensive treatment. A total of seven patients (70%) achieved MS complete remission (CR). Patients who presented isolated skin localization and received only radiotherapy, obtained a MS-CR, but subsequently developed AML. Only in patients who were treated within 4 months from the initial ML diagnosis we achieved complete remission of both MS and leukemia, whereas in patients who were treated after this time, we obtained a complete disappearance of MS without response at the bone-marrow level, irrespectively of the specific therapy regimen. Median survival time from MS diagnosis was 7 months (range: 1-49 months), and only one patient is still alive, 49 months after bone marrow transplantation. Our data stress the importance of an accurate and prompt identification of this rare form of AML, and suggest that, even in patients with isolated MS, the early administration of AML-like intensive chemotherapy followed by bone marrow transplantation might reduce the risk of subsequently developing systemic disease.

Metastatic breast cancer: is global survival increase a realistic endpoint in phase III clinical trials? Studies on taxanes; studies on trastuzumab.

BRIA E., VANNI B., CUPPONE F., CALABRETTA F., CAMPANELLA C., TORSELLO A., TERZOLI E.

Suppl. Tumori, Jul-Aug;3(4):S65-6, 2004

No abstract available

Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group.

Caraceni A., Zecca E., Bonezzi C., Arcuri E., Tur R.Y., Maltoni M., Visentin M., Gorni G., Martini C., Tirelli W., Barbieri M., De Conno F.

J. Clin. Oncol., Jul 15;22(14):2909-17, 2004

Purpose: To determine the analgesic effect of the addition of gabapentin to opioids in the management of neuropathic cancer pain.

Patients and Methods: One hundred twenty-one consecutive patients with neuropathic pain due to cancer, partially controlled with systemic opioids, participated in a multicenter, randomized, double-blind, placebo-controlled, parallel-design, 10-day trial from August 1999 to May 2002. Gabapentin was titrated from 600 mg/d to 1,800 mg/d in addition to stable opioid dose. Extra opioid doses were available as needed. Zero to 10 numerical scale was used to rate average daily pain. The average pain score over the whole follow-up period was used as main outcome measure. Secondary outcome measures were: intensity of burning pain, shooting/lancinating pain, dysesthesias (also scored on 0 to 10 numerical scale), number of daily episodes of lancinating pain, presence of allodynia, and daily extra doses of opioid analgesics.

Results: Overall, 79 patients received gabapentin and 58 (73%) completed the study; 41 patients received placebo and 31 (76%) completed the study. Analysis of covariance (ANCOVA) on the intent-to-treat population showed a significant difference of average pain intensity between gabapentin (pain score, 4.6) and placebo group (pain score, 5.4; P =.0250). Among secondary outcome measures, dysesthesia score showed a statistically significant difference (P =.0077; ANCOVA on modified intent-to-treat population = 115 patients with at least 3 days of pain assessments). Reasons for withdrawing patients from the trial were adverse events in six patients (7.6%) receiving gabapentin and in three patients receiving placebo (7.3%).

Conclusion: Gabapentin is effective in improving analgesia in patients with neuropathic cancer pain already treated with opioids.

Pancreaticoduodenectomy for pancreatic metastatic melanoma.

Carboni F., Graziano F., Lonardo M.T., Lepiane P., Santoro R., Lorusso R., Mancini P., Santoro E.

J. Exp. Clin. Cancer Res., Sep;23(3):539-43, 2004

Isolated pancreatic metastatic melanoma is a rare occurrence. Even more rare is the surgical treatment of this lesion. However, considering the lack of effective systemic treatment and the decreasing morbidity and mortality rates of pancreatic resections in specialized centers, selected patients, especially if symptomatic, may be considered for surgical resection to achieve good palliation or improve survival. We performed a pancreaticoduodenectomy in a patient with a bleeding pancreatic metastasis from cutaneous melanoma excised 10 years before and reviewed the recent literature.

Arsenic trioxide in the treatment of advanced acute promyelocytic leukemia.

Carmosino I., Latagliata R., Avvisati G., Breccia M., Finolezzi E., Lo Coco F., Petti M.C.

Haematologica, May;89(5):615-617, 2004

Eleven patients with advanced APL were treated with ATO (0.15 mg/Kg daily). Eight (73%) achieved molecular CR, but 5 relapsed, 1 died in molecular CR, 1 was lost to follow-up and 1 is still alive in CR after allogeneic transplantation. We suggest that ATO may be effective also in advanced APL, but given the short CR, it seems indicated only in patients eligible for transplant procedures.

5-lipoxygenase antagonizes genotoxic stress-induced apoptosis by altering p53 nuclear trafficking.

Catalano A., Caprari P., Soddu S., Procopio A., Romano M.

FASEB J., Nov;18(14):1740-2, 2004

5-lipoxygenase (5-LO) promotes cancer cell proliferation and survival by unclear mechanisms. Here, we show that 5-LO expression and activity were induced by genotoxic agents in a p53-independent manner and antagonized p53- or genotoxic drug-induced apoptosis in a variety of cancer cells. 5-LO inhibited p53-governed transactivation of the pro-apoptotic genes bax and pig3 but not of p21(WAF1/CIP1) or mdm2. This may be explained by 5-LO capability to inhibit the binding of p53 to promyelocytic leukemia protein (PML) and p53 subnuclear relocalization into PML-nuclear bodies in response to ge-

notoxic stress. Interestingly, 5-LO activity appears to be involved in nuclear retention and inactivation of wild-type p53 in malignant mesothelioma cells. In these cells, genetic or pharmacological inhibition of 5-LO enabled suppression of in vitro tumorigenicity by low doses of chemotherapeutic drugs. Together, these results uncover novel functions of 5-LO and contribute to the understanding of 5-LO involvement in tumor progression. Moreover, they provide a rationale to the therapeutic use of 5-LO inhibitors to enhance cancer chemosensitivity in selected tumors.

Conserved POU-binding DNA sites in the Sox2 upstream enhancer regulate gene expression in embryonic and neural stem cells.

Catena R., Tiveron C., Ronchi A., Porta S., Ferri A.L., Tatangelo L., Cavallaro M., Favaro R., Ottolenghi S., Reinbold R., Scholer H., Nicolis S.K.

J. Biol. Chem., Oct 1;279(40):41846-57, 2004

The Sox2 transcription factor is expressed early in the stem cells of the blastocyst inner cell mass and, later, in neural stem cells. We previously identified a Sox2 5'-regulatory region directing transgene expression to the inner cell mass and, later, to neural stem cells and precursors of the forebrain. Here, we identify a core enhancer element able to specify transgene expression in forebrain neural precursors of mouse embryos, and we show that the same core element efficiently activates transcription in inner cell mass-derived embryonic stem (ES) cells. Mutation of POU factor binding sites, able to recognize the neural factors Brn1 and Brn2, shows that these sites contribute to transgene activity in neural cells. The same sites are also essential for activity in ES cells, where they bind different members of the POU family, including Oct4, as shown by gel shift assays and chromatin immunoprecipitation with anti-Oct4 antibodies. Our findings indicate a role for the same POU binding motifs in Sox2 transgene regulation in both ES and neural precursor cells. Oct4 might play a role in the regulation of Sox2 in ES (inner cell mass) cells and, possibly, at the transition between inner cell mass and neural cells, before recruitment of neural POU factors such as Brn1 and Brn2.

N(6)-Methyldeoxyadenosine, a nucleoside commonly found in prokaryotes, induces C2C12 myogenic differentiation.

Charles M.P., Ravanat J.L., Adamski D., D'orazi G., Cadet J., Favier A., Berger F., Wion D.

Biochem. Biophys. Res. Commun., Feb 6;314(2):476-82, 2004

N(6)-methyl-2(')-deoxyadenosine (MedAdo) is a nucleoside naturally found in prokaryotic DNA. Interestingly, the N(6)-methylation of adenine in DNA seems to have been counter-selected during the course of evolution since MedAdo has not been detected in mammalian DNA until now. We show here that treatment with MedAdo induces myogenesis in C2C12 myoblasts. The presence of MedAdo in C2C12 DNA was investigated using a method based on HPLC coupled to electrospray ionization tandem mass spectrometry which is several thousand fold more sensitive than assays used previously. By this procedure, MedAdo is detected in the DNA from MedAdo-treated cells but remains undetectable in the DNA from control cells. Furthermore, MedAdo regulates the expression of p21, myogenin, mTOR, and MHC. Interestingly, in the pluripotent C2C12 cell line, MedAdo drives the differentiation towards myogenesis only. Thus, the biological effect of MedAdo is suppressed in the presence of BMP-2 which transdifferentiates C2C12 from myogenic into osteogenic lineage cells. Taken together these results point to MedAdo as a novel inducer of myogenesis and further extends the differentiation potentialities of this methylated nucleoside. Furthermore, these data raise the intriguing possibility that the biological effects of MedAdo on cell differentiation may have led to its counter-selection in eukaryotes.

Responses of peptide-specific T cells to stimulation with polystyrene beads carrying HLA class I molecules loaded with single peptides.

Chersi A., Galati R., Accapezzato D., Francavilla V., Barnaba V., Butler R.H., Tanigaki N.

J. Immunol. Methods, Aug;291(1-2):79-91, 2004

Cell-sized microbeads carrying single peptide-loaded HLA class I molecules were prepared for HLA-A2 and HLA-B7 by a simple procedure which transfers single peptide-loaded HLA class I molecules from cultured cells to polystyrene beads using anti-peptide antibodies directed to an intracellular segment of HLA-A alpha chains. The surface density of peptide-loaded HLA class I molecules on beads was comparable to that on the peptide-loaded cells. HLA-A2 beads loa-

ded with an HCV peptide HCV1073 were tested for stimulation activity on an HCV1073-specific CD8+ T cell clone NS3-1. A substantial level of gamma-IFN production was induced. The stimulation was peptide-specific. The efficiency was dependent on the bead concentration and the surface HLA class I density on beads and enhanced significantly by co-coupling of anti-CD28 to peptide-loaded beads. The peptide-loading efficiency on HLA class I molecules and the transfer efficiency of HLA class I molecules to polystyrene beads were reasonably high for HLA-A2 and HLA-B7. Thus, polystyrene beads carrying these single peptide-loaded HLA class I molecules are potentially useful in further analysis of the co-stimulatory or inhibitory factors involved in CD8+ T cell responses and eventually in detection of cytotoxic T cells in PBLs.

A biochemical approach for detecting interactions between peptides from the HIV gp120 glycoprotein and a CD4 sequence.

CHERSI A., FALASCA G., MALORNI W.

Z Naturforsch [C], Sep-Oct;59(9-10):734-8, 2004

Peptides selected from the HIV viral protein gp120 bind to a synthetic peptide mimicking sequence 78-89 of the human lymphocyte CD4 molecule, linked to activated Sepharose. The binding of viral fragments to the CD4 peptide-Sepharose beads was ascertained either by aid of a ninhydrin reagent or by fluorescence microscopy. A suitable alignment of these HIV peptides with the CD4 fragment showed that multiple interactions might occur between hydrophobic or charged groups of the two molecules. Although this experiment does not demonstrate that these two amino acid stretches are involved in the primary binding of gp120 to CD4 receptors, the present data suggest that the two sequences might have some kind of interaction during subsequent steps of viral infection.

Intramyocyte Detection of Epstein-Barr Virus Genome by Laser Capture Microdissection in Patients With Inflammatory Cardiomyopathy.

CHIMENTI C., RUSSO A., PIERONI M., CALABRESE F., VERARDO R., THIENE G., RUSSO M.A., MASERI A., FRUSTACI A.

Circulation, Nov 22, 2004

Background: The causal role of Epstein-Barr virus (EBV) in inflammatory cardiomyopathy (IC) is still unclear, because this virus is present in latently infected circulating B lymphocytes in 90% of adults. Laser capture microdissection (LCM) has been applied on endomyocardial biopsy samples from patients with IC to assess the presence of EBV genome in separately dissected lymphocytes and myocytes.

Methods and results: Among 142 patients with cardiac dilation and dysfunction and a histological and immunohistochemical diagnosis of myocarditis, 44 had a myocardial viral infection detected by polymerase chain reaction on frozen endomyocardial biopsy samples. In 9 of them, the virus detected was EBV. LCM was performed on 5-microm-thick paraffin sections of EBV-infected hearts. Lymphocytes and myocytes were microdissected and analyzed separately by polymerase chain reaction analysis on DNA extracted from the collected cells. Blood and myocardial samples from patients with positive and negative serology for EBV were used as controls. EBV genome was detected in myocytes but not in infiltrating lymphocytes of patients, nor in myocardial samples from controls. Despite full conventional antifailure therapy, a progressive cardiac dilation and dysfunction was documented in patients with EBV-related IC at a mean of 31+/-14 months of follow-up.

Conclusions: Intramyocyte detection of EBV can be obtained by LCM in up to 6.3% of patients with IC. This supports a cytopathic EBV role and suggests the opportunity for an antiviral/immunomodulatory therapy.

Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy.

CHIMENTI C., PIERONI M., MORGANTE E., ANTUZZI D., RUSSO A., RUSSO M.A., MASERI A., FRUSTACI A.

Circulation, Aug 31;110(9):1047-53, 2004

Background: Fabry disease (FD) has been recognized as the cause of left ventricular hypertrophy in 6% of men with late-onset hypertrophic cardiomyopathy (HCM). Although FD is considered a recessive X-linked disorder, affected women are increasingly reported. The aim of our study was to determine the prevalence of FD in female patients with HCM.

Methods and Results: Thirty-four consecutive women (mean age, 50+/-13.6 years) who received an ECG and echocardiographic diagnosis of HCM were submitted to an invasive car-

diac study that included a biventricular endomyocardial biopsy. Tissue samples were analyzed for histology and electron microscopy. Peripheral blood activity of alpha-galactosidase (alpha-Gal) A was assessed in all patients. None of them had a family history of FD. Histology and electron microscopy showed in 4 patients (12%; mean age, 51.5+/-3.9 years) the presence of cell vacuoles characterized by the accumulation of glycolipid material organized in concentric lamellar structures, diagnostic for FD. In the remaining patients, histology was consistent with HCM. In all the female carriers, the heart was the only organ clinically involved in the disease, showing concentric hypertrophy in 2 patients, asymmetric hypertrophy in 1, and apical hypertrophy in 1. The alpha-Gal A enzymatic activity was 44+/-14% of control values. Genetic analysis showed the presence of alpha-Gal A gene mutation in all 4 cases.

Conclusions: FD may account for up to 12% of females with late-onset HCM. Those heterozygous for FD with left ventricular hypertrophy are potential candidates for enzyme enhancement/replacement therapy.

Genetic and pathologic significance of 1p, 17p, and 18q aneusomy and the ERBB2 gene in colorectal cancer and related normal colonic mucosa.

Cianciulli A., Cosimelli M., Marzano R., Merola R., Piperno G., Sperduti I., De La Iglesia F., Leonardo G., Graziano F., Mancini R., Guadagni F.

Cancer Genet. Cytogenet., May;151(1):52-9, 2004

Among chromosome defects in colon cancer, deletions in 1p, 17p, and 18q have been reported as frequent events. To verify this, we investigated 1p, 17p, and 18q aneusomy in 60 colorectal cancers and their surrounding mucosa by means of fluorescence in situ hybridization (FISH). We also evaluated ERBB2 gene (alias HER-2/neu) amplification in a subset of tumors. The genetic picture in tumors was correlated with chromosomal alterations in normal colonic mucosae, as well with clinicopathologic variables. A population of cells in morphologically normal epithelium possesses genetic aberrations common to those in colon cancer, although in different percentages. No significant difference emerged in terms of fraction of nuclei with 17p monosomy between primary tumors and distal mucosal samples. Of tumor samples aneusomic for the three chromosomes, 58.3% also showed aneusomy in related normal colonic mucosa. In neoplastic samples, significant correlation existed between 1p aneusomy and mucosal component ($P<0.007$), between 17p aneusomy and increased depth of invasion (T3-T4) ($P<0.05$), and between 18q aneusomy and tumor site ($P<0.03$). None of the evaluated samples, neoplastic or normal, showed ERBB2 gene amplification.

Complex variant philadelphia translocation involving the short arm of chromosome 9 in a case of chronic myeloid leukemia.

Cianciulli A.M., Marzano R., Merola R., Orlandi G., Petti M.C., Guadagni F., Pisani F.

Haematologica, Sep;89(9):ECR37, 2004

Here we describe how we detected the BCR/ABL fusion gene on the short arm of der(9) combining classical GTG banding and Fluorescence In Situ Hybridization (FISH) in a case of chronic myeloid leukemia (CML). To our knowledge, variant translocations involving the short arm of chromosome 9, in literature, are almost rare in chronic myeloid leukemia. It is not clear if this complex genetic translocation represents clonal evolution or a unique, initial presentation variant of the Philadelphia chromosome (Ph).

Expression of 60 kDa heat shock protein (Hsp60) on plasma membrane of Daudi cells.

Cicconi R., Delpino A., Piselli P., Castelli M., Vismara D.

Mol. Cell. Biochem., Apr;259(1-2):1-7, 2004

In Daudi cells, a fraction of the 60 kDa heat shock protein (Hsp60), which is typically a mitochondrial protein, is located on cell membrane. This was demonstrated by the recovery of biotinylated Hsp60 in the anti-Hsp60 immunoprecipitate obtained from cells in which surface-exposed proteins were selectively labeled with biotin. In further experiments, isolated membrane proteins (obtained by two different biochemical methods) were probed in Western blot with two antibodies (N-20 and K-19) directed against different epitopes located, respectively, at the amino- and at the carboxyl-terminus of the Hsp60. Both these antibodies reco-

gnized, among the isolated membrane proteins, a unique band with an electrophoretic mobility identical to that of the cytoplasmic Hsp60, thus demonstrating that Hsp60 is present on cell surface as an intact, full-length, protein. FACS analysis, performed with the same two highly specific anti-Hsp60 antibodies, confirmed that both the N-terminus and the C-terminus of the Hsp60 are exposed outside the cell and are accessible for recognition by the corresponding antibody. Moreover, quantitative analysis of the data showed that constitutive cell surface expression of the Hsp60 is limited to a small fraction (about 10%) of the whole cell population.

Targeting endothelin receptor type A in human cervical Carcinoma Cells.

CIRILLI A., SIMEONE P., MULLER A., BAGNATO A.VENUTI A.

J. Cardiovasc. Pharmacology, 44 (1): S72-S75, 2004

No abstract available

Expression analysis of the gene encoding for the U-box-type ubiquitin ligase UBE4A in human tissues.

CONTINO G., AMATI F., PUCCI S., PONTIERI E., PICHIORRI F., NOVELLI A., BOTTA A., MANGO R., NARDONE A.M., SANGIUOLO F.C., CITRO G., SPAGNOLI L.G., NOVELLI G.

Gene, Mar 17;328:69-74, 2004

The Ubiquitination Factor E4A gene (UBE4A) encodes for a U-box-type ubiquitin ligase, originally described as an E4 ubiquitination factor. UBE4A is a mammalian homolog of Saccharomyces cerevisiae Ufd2. The UBE4A gene has been mapped on the human chromosome region 11q23.3, a critical region involved in some specific cancers such as neuroblastoma. Northern blots analysis on foetal and adult human tissues revealed a single band of approximately 7.5 kb transcript most abundant in the heart, skeletal muscle and kidney. We generated a polyclonal antibody to UBE4A and performed immunoblot and immunohistochemical analysis. The UBE4A protein appeared as a single band of approximately 125 kDa. UBE4A was present in the skeletal muscle, kidney and liver; a faint band was visible in peripheral blood leukocytes and spleen. We did not reveal expression of UBE4A in whole brain, colon, lung and heart. At the cellular level, UBE4A results predominantly expressed in the nucleus and the cytoplasm of cortical neurons and liver and in the nucleus of tubular kidney cells. In the liver, the nucleus of similar cells appeared to be unstained or stained at different levels suggesting that UBE4A may have a cell cycle dependent expression or a role of in cell cycle control. In conclusion, our results show that UBE4A is expressed in different tissues in a pattern that seems to be dependent from cell type and cell cycle and that UBE4A might have a specific role in different biochemical processes other than ubiquitination, including growth or differentiation.

A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.

COOMBES R.C., HALL E., GIBSON L.J., PARIDAENS R., JASSEM J., DELOZIER T., JONES S.E., ALVAREZ I., BERTELLI G., ORTMANN O., COATES A.S., BAJETTA E., DODWELL D., ET AL.; INTERGROUP EXEMESTANE STUDY. (COGNETTI F.)

N. Engl. J. Med., Dec 2;351(23):2461, 2004

Background: Tamoxifen, taken for five years, is the standard adjuvant treatment for postmenopausal women with primary, estrogen-receptor-positive breast cancer. Despite this treatment, however, some patients have a relapse. METHODS: We conducted a double-blind, randomized trial to test whether, after two to three years of tamoxifen therapy, switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the five years of treatment. The primary end point was disease-free survival.

Results: Of the 4742 patients enrolled, 2362 were randomly assigned to switch to exemestane, and 2380 to continue to receive tamoxifen. After a median follow-up of 30.6 months, 449 first events (local or metastatic recurrence, contralateral breast cancer, or death) were reported—183 in the exemestane group and 266 in the tamoxifen group. The unadjusted hazard ratio in the exemestane group as compared with the tamoxifen group was 0.68 (95 percent confidence interval, 0.56 to 0.82; P<0.001 by the log-rank test), representing a 32 percent reduction in risk and corresponding

to an absolute benefit in terms of disease-free survival of 4.7 percent (95 percent confidence interval, 2.6 to 6.8) at three years after randomization. Overall survival was not significantly different in the two groups, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group. Severe toxic effects of exemestane were rare. Contralateral breast cancer occurred in 20 patients in the tamoxifen group and 9 in the exemestane group (P=0.04).

Conclusions: Exemestane therapy after two to three years of tamoxifen therapy significantly improved disease-free survival as compared with the standard five years of tamoxifen treatment.

A randomized phase II study of combination, alternating and sequential regimens of doxorubicin and docetaxel as first-line chemotherapy for women with metastatic breast cancer.

Cresta S., Grasselli G., Mansutti M., Martoni A., Lelli G., Capri G., Buzzi F., Robustelli Della Cuna G., Jirillo A., Terzoli E., Frevola L., Tarenzi E., Et Al.

Ann. Oncol., Mar;15(3):433-9, 2004

Background: This randomized phase II study was conducted to evaluate the efficacy of doxorubicin and docetaxel (DOC) administered either as a combination, an alternating or a sequential regimen in women with metastatic breast cancer. Secondary objectives included overall response, time to progression, survival and safety.

Patients and methods: Patients with breast cancer (n=123) were randomized to receive doxorubicin and DOC either in combination (60 mg/m2 of each drug), or by alternated or sequential schedule (100 mg/m2 DOC and 75 mg/m2 doxorubicin) every 3 weeks for a maximum of eight cycles as first chemotherapy for stage IV disease. A second randomization allocated patients from each arm to receive prophylactic oral ciprofloxacin or no therapy to prevent febrile neutropenia.

Results: Patients received a median of eight cycles. In an intention-to-treat analysis, the overall response was 63%, 52% and 61% in the combination, alternating and sequential schedules, respectively. Corresponding rates of complete response were 15%, 14% and 11%. Grade 4 neutropenia was common in all arms (81%) and, together with febrile neutropenia, was significantly more frequent with the combination. Prophylaxis with ciprofloxacin did not reduce the incidence of febrile neutropenia or infection. Other frequent non-hematological adverse events included alopecia, nausea, vomiting, stomatitis and asthenia. Congestive heart failure only occurred in the combination arm (10%).

Conclusion: All three schedules are feasible and endowed of good therapeutic activity. In view of the more pronounced toxicity and the risk of cardiac events because of the higher exposure to doxorubicin, the combination should be least favored when treating women with metastatic breast cancer. Prophylaxis with ciprofloxacin was ineffective and is not recommended.

Population-based incidence and mortality cancer trends (1986-1997) from the network of Italian cancer registries.

Crocetti E., Capocaccia R., Casella C., Guzzinati S., Ferretti S., Rosso S., Sacchettini C., Spitale A., Stracci F., Tumino R.; Network Of The Italian Cancer Registries (Airt). (Cercato M.C.)

Eur. J. Cancer Prev., Aug;13(4):287-95, 2004

The objective of this study was to analyse incidence and mortality cancer trends in the Italian Network of Cancer Registries (about 8,000,000 inhabitants) during the period 1986-1997. Included were 525,645 newly diagnosed cancers and 269,902 cancer deaths (subjects > 14 years). Joinpoints (points in time where trend significantly changes from linearity) were found and estimated annual percentage changes (EAPC) used to summarize tendencies. Overall cancer incidence increased in both sexes and cancer mortality significantly decreased (since 1991 among men). Lung cancer showed significantly decreasing incidence (EAPC = -1.4%) and mortality (EAPC = -1.6%) among men and increasing trends among women. In women, breast cancer incidence significantly increased (EAPC= +1.7%) and mortality decreased since 1989 (EAPC= -2.0%). Stomach cancer incidence and mortality decreased in both sexes. Prostate incidence sharply increased since 1991 and mortality decreased. Colon cancer incidence increased and rectum mortality decreased significantly in both sexes. Significant increases in incidence were also found for kidney (up to 1991 among men), urinary bladder, skin epithelioma, melanoma, liver (up to 1993 among men), pancreas, mesothelioma, Kaposi's sarcoma (up to 1995 among men), testis, thyroid, non-

Hodgkin's lymphomas and multiple myeloma. Mortality significantly decreased for cancers of the oral cavity and pharynx, oesophagus, liver (women), larynx (men), bone, cervix (since 1990), central nervous system, urinary bladder, thyroid, Hodgkin's lymphomas and leukaemias (men). Non-Hodgkin's lymphoma mortality increased in both sexes. In conclusion, most of the changes seen can be explained as the effect of changes in smoking habits and of the extension of secondary prevention activities. The Italian health care system will also have to cope with growing cancer diagnostic and therapeutic needs due to population ageing.

Antisense oligodeoxynucleotides for urokinase-plasminogen activator receptor have anti-invasive and anti-proliferative effects in vitro and inhibit spontaneous metastases of human melanoma in mice.

D'Alessio S., Margheri F., Pucci M., Del Rosso A., Monia B.P., Bologna M., Leonetti C., Scarsella M., Zupi G., Fibbi G., Del Rosso M.

Int. J. Cancer, May 20;110(1):125-33, 2004

We have targeted the urokinase-type plasminogen activator receptor (uPAR) with phosphorothioate antisense oligonucleotides (aODN) in vitro to evaluate the anti-invasive and anti-proliferative effects of uPAR down-regulation, as well as in vivo to evaluate anti-tumor and anti-metastatic activity. aODN-dependent uPAR downregulation in vitro was induced in cells of human melanoma, mammary carcinoma, ovarian carcinoma and SV-40-transformed embryonic lung fibroblasts. uPAR was determined by an antibody-based assay and by semiquantitative polymerase chain reaction. Cell invasion was evaluated by Matrigel invasion assay and cell proliferation by direct cell counting. aODN reduced uPAR, invasion and proliferation in all the treated cell lines. Following aODN treatment, human melanoma cells exhibited a strong decrease of uPAR-dependent ERK1/2 activation and were used in vivo to control metastasis in CD-1 male nude (nu/nu) mice by uPAR aODN injection. 60 mice were injected in the hind leg muscles with a suspension of 10(6) melanoma cells. After 4 days, when a tumor mass of about 350 mg was evident in all the mice injected, 20 mice were treated i.v. with aODN and 20 with dODN at 0.5 mg/day for 5 consecutive days. Twenty control mice were not treated. A second and third cycle of treatment was administered at 2-day intervals. Treatment with aODN resulted into a 78% reduction of lung metastases and 45% reduction of the primary tumor mass with no loss of body weight. Our results suggest to evaluate the utility of uPAR aODN in controlling the metastatic spreading of human melanoma.

Conservative treatment of invasive bladder carcinoma by transurethral resection, protracted intravenous infusion chemotherapy, and hyperfractionated radiotherapy: long term results.

Danesi D.T., Arcangeli G., Cruciani E., Altavista P., Mecozzi A., Saracino B., Orefici F.

Cancer, Dec 1;101(11):2540-8, 2004

Background: Organ preservation has been investigated in patients with muscle-invasive bladder carcinoma over the past decades as an alternative to radical cystectomy. The majority of studies reported that trimodal schedules, including transurethral resection of bladder tumor (TURB), radiotherapy (RT), and chemotherapy, are a feasible and safe organ-sparing approach without deferring the survival probability. However, to the authors' knowledge the best combination of RT and chemotherapy has yet to be well defined. The current study evaluated the long-term results of a schedule of concurrent cisplatin and 5-fluorouracil (5-FU) administered as protracted intravenous infusions (PVI) during hyperfractionated radiotherapy (HFRT) with organ-sparing intent in patients with infiltrating transitional cell carcinoma of the bladder (TCCB).

Methods: Seventy-seven patients with a classification of T2-T4aN0M0 TCCB were enrolled in the current study. After a complete TURB and bladder mapping, 42 of 77 patients underwent 2 cycles of induction chemotherapy. All 77 patients underwent HFRT and a schedule of cisplatin (4-6 mg/m(2) per day) and 5-FU (180-220 mg/m(2) per day) as concomitant PVI (radiochemotherapy [RCT]). Six to 8 weeks after RCT, patient response was evaluated by computed tomography scan, urine cytology, and TURB. Patients who achieved a complete response (CR) were followed at regular intervals. For patients with residual or recurrent invasive tumor, salvage cystectomy was recommended.

Results: Seventy-two patients were evaluable for response: 65 achieved a CR (90.3%) and 7 (9.7%) achieved a partial response. No significant difference was observed for the different pro-

gnostic factors with the exception of stage of disease (T2 [95.7%] vs. T3-T4a [80.0%]; P = 0.04). The observed toxicity, mainly hematologic, was higher among the patients who received induction chemotherapy compared with the patients who did not receive induction chemotherapy, even though the difference was not statistically significant. After a median follow-up of 82.2 months (range, 30-138 months), 44 of 65 (57.1%) patients who achieved a CR were alive. Of these 44 patients, 33 had tumor-free bladders. The 5-year overall, bladder-intact, tumor-specific, disease-free, and cystectomy-free survival rates for all 77 patients were 58.5%, 46.6%, 75.0%, 53.5%, and 76.1%, respectively. No associations were observed in overall and tumor-specific survival with different prognostic factors.

Conclusions: Combined treatment appeared to provide high response rates and can be offered as an alternative option to radical cystectomy in selected patients who refuse or are unsuitable for surgery.

Immunohistochemical distribution of proteins belonging to the receptor-mediated and the mitochondrial apoptotic pathways in human placenta during gestation.

De Falco M., Fedele V., Cobellis L., Mastrogiacomo A., Leone S., Giraldi D., De Luca B., Laforgia V., De Luca A.

Cell. Tissue Res., Dec;318(3):599-608, 2004

The balance between cell death and cell proliferation and its regulation are essential features of many physiological processes and are particularly important in fetal morphogenesis and adult tissue homeostasis. Apoptosis is a type of cell suicide that is activated in two main ways: through a receptor-mediated pathway or through a mitochondrial pathway. We have investigated the immunohistochemical distribution of proteins belonging to these two pathways in human placenta during gestation by comparing their expression levels between the first and third trimester of gestation. In the first trimester, the receptor-mediated pathway prevails over the mitochondrial pathway with a moderate/intense expression of its three components, viz., Fas ligand (FasL), Fas, and caspase-8, and weak positivity of anti-apoptotic FLIP, these proteins being mainly localized in the cytotrophoblast compartment. In the third trimester of gestation, there is an increased expression of mitochondrial pathway proteins, viz., Apaf-1 and caspase-9. We have also investigated the expression level of caspase-3, the primary effector caspase of both pathways, and have observed that it is moderately expressed during gestation, being mainly localized in the cytotrophoblast during the first trimester and in both placental compartments during the third trimester of gestation. Thus, both pathways actively function in human placenta to execute cell death. By means of immunoelectron microscopy, we have further shown that, in human placenta, the two proteins of the mitochondrial pathway together with caspase-3 are localized both in the cytoplasm and in the nucleus. In particular, Apaf-1 and caspase-9 are distributed near to the nuclear envelope suggesting an important role for these two proteins in disrupting the nuclear-cytoplasmic barrier.

Evaluation of cyclin D1 expression and its subcellular distribution in mouse tissues.

De Falco M., Fedele V., De Luca L., Penta R., Cottone G., Cavallotti I., Laforgia V., De Luca A.

J. Anat., Nov;205(5):405-12, 2004

Cyclin D1 is a key cell-cycle regulatory protein required for the cell to progress through G1 to S phase. We have shown by Western blot analysis that cyclin D1 has a wide distribution in adult mouse tissues, with its level of expression being tissue-dependent. Immunohistochemistry has also shown that cyclin D1 may be present in the cytoplasm, in the nucleus or in both these cell compartments: cytoplasmic staining was observed in both proliferating cells (e.g. kidney, intestine, stomach and salivary gland) and in the non-dividing cells (the mature neurons of adult brain), while nuclear staining was seen in the neurons of the embryonic nervous system. Immunoelectron microscopy results indicate that, in tissues where cyclin D1 is present in both compartments (e.g. intestinal enterocytes), it may move via nuclear pores from the nucleus to the cytoplasm, and vice versa. The findings as a whole suggest that cyclin D1 may play multiple roles within specific tissues, probably by interacting with different substrates, and that its transit between nuclear and cytoplasmic compartments may help maintain cell homeostasis.

Distribution of apelin, the endogenous ligand of the APJ receptor, in the lizard Podarcis sicula.

De Falco M., Fedele V., Russo T., Virgilio F., Sciarrillo R., Leone S., Laforgia V., De Luca A.

J. Mol. Histol., Jun;35(5):521-7, 2004

Apelin is a novel bioactive peptide that has been isolated from bovine stomach extracts and identified as the endogenous ligand for the APJ receptor. Although the main physiological functions of apelin have not yet been clarified, it is known that apelin is involved in the regulation of blood pressure, central control of body fluid homeostasis and the modulation of immune response. In order to investigate the distribution of apelin in reptiles, we have performed an immunohistochemical analysis on tissues of the lizard Podarcis sicula. The peptide was found to be widely distributed, although its cellular localization differed in the various organs examined. A strong immunopositivity was found in the heart, stomach and intestine. In the spleen, an intense apelin immunopositivity was restricted to a discrete number of cells scattered throughout the red pulp and co-localized with immunoglobulin kappa and lambda chains, suggesting an analogous function of this peptide in immune responses also in reptiles. Intriguingly, apelin immunoreactivity was discretely localized in endothelial cells in the lung and thyroid gland. In the light of these data, we conclude that apelin may have multiple functions in reptiles.

Pattern of expression of cyclin D1/CDK4 complex in human placenta during gestation.

De Falco M., Fedele V., Cobellis L., Mastrogiacomo A., Giraldi D., Leone S., De Luca L., Laforgia V., De Luca A.

Cell. Tissue Res., Aug;317(2):187-94, 2004

Progression through the cell cycle in eukaryotic cells is controlled by a family of protein kinases, termed cyclin-dependent kinases (CDKs), and their specific partners, the cyclins. In particular, the control of mammalian cell proliferation occurs largely during the G1 phase of the cell cycle. Five mammalian G1 cyclins have been enumerated to date: cyclins D1, D2, and D3 (D-type cyclins), and cyclins E and E2. By the use of immunohistochemistry and immunoelectron microscopy, we observed that in the first trimester of gestation of human placenta, cyclin D1 was distributed in the nuclei of the cytotrophoblast compartment together with a weak positivity of endothelial cells surrounding blood vessels. The endothelial positivity of cyclin D1 strongly increased in the third trimester of gestation. Moreover, we observed the subcellular localization of cyclin D1 that was present both in the stroma of placental villi and in the nuclei of syncytiotrophoblast cells. Therefore, we observed that CDK4 was localized in the nuclei of the cytotrophoblast compartment during the first and third trimesters and it also had a nuclear positivity in the endothelial cells of blood vessels at the end of the third trimester of gestation. In conclusion we may hypothesize that cyclin D1/CDK4 complex functions to regulate the cell cycle progression in the proliferative compartment of human placenta, the cytotrophoblast, during the first trimester through interaction with p107 and p130. Therefore, cyclin D1 and CDK4 seem to be involved in the control of placental angiogenesis during the third trimester of gestation.

The serine protease HtrA1 is upregulated in the human placenta during pregnancy.

De Luca A., De Falco M., Fedele V., Cobellis L., Mastrogiacomo A., Laforgia V., Tuduce I.L., Campioni M., Giraldi D., Paggi M.G., Baldi A.

J. Histochem. Cytochem., Jul;52(7):885-92, 2004

The placenta has a dynamic and continuous capacity for self-renewal. The molecular mechanisms responsible for controlling trophoblast proliferation are still unclear. It is generally accepted that the simultaneous activity of proteins involved in cell proliferation, apoptosis, and extracellular matrix degradation plays an important role in correct placental development. We investigated in depth the expression of the serine protease HtrA1 during pregnancy in human placenta by in situ hybridization and immunohistochemistry, we demonstrated that HtrA1 displayed a low level of expression in the first trimester of gestation and a strong increase of HtrA1 expression in the third trimester. Finally, by electron microscopy, we demonstrated that HtrA1 was localized either in the cytoplasm of placental cells, especially close to microvilli that characterized the plasma membrane of syncytiotrophoblast cells, or in the extracytoplasmic space of the stroma of placental villi, particularly in the spaces between collagen fibers and on collagen fibers themselves. The expression pattern of HtrA1 in human placentas strongly suggests a role for this protein in placental development and function. Moreover, on the basis of its subcellular distribu-

tion it can be postulated that HtrA1 acts on different targets, such as intracellular growth factors or extracellular matrix proteins, to favor the correct formation/function of the placenta.

Pattern of expression of HtrA1 during mouse development.

De Luca A., De Falco M., De Luca L., Penta R., Shridhar V., Baldi F., Campioni M., Paggi M.G., Baldi A.

J. Histochem. Cytochem., Dec;52(12):1609-17, 2004

The human HtrA family of proteases consists of four members: HtrA1, HtrA2, HtrA3, and HtrA4. In humans the four HtrA homologues appear to be involved in several important functions such as cell growth, apoptosis, and inflammatory reactions, and they control cell fate via regulated protein metabolism. In previous studies it was shown that the expression of HtrA1 was ubiquitous in normal adult human tissues. Here we examined the expression of HtrA1 protein and its corresponding mRNA during mouse embryogenesis using Northern blotting hybridization, RT-PCR, and immunohistochemical staining analyses. Our results indicate that HtrA1 is expressed in a variety of tissues in mouse embryos. Furthermore, this expression is regulated in a spatial and temporal manner. Relatively low levels of HtrA1 mRNA are detected in embryos at the beginning of organogenesis (E8), and the levels of expression increase during late organogenesis (E14–E19). Our results show that HtrA1 was expressed during embryonic development in specific areas where signaling by TGFbeta family proteins plays important regulatory roles. The expression of HtrA1, documented both at mRNA and protein levels by RT-PCR and immunohistochemistry in the developing nervous system, is consistent with a possible role of this protein both in dividing and postmitotic neurons, possibly via its documented inhibitory effects on TGFbeta proteins. An exhaustive knowledge of the different cell- and tissue-specific patterns of expression of HtrA1 in normal mouse embryos is essential for a critical evaluation of the exact role played by this protein during development.

Ectopic deposition of melanin pigments as detoxifying mechanism: a paradigm for basal nuclei pigmentation.

De Marco F., Foppoli C., Coccia R., Blarzino C., Perluigi M., Cini C., Marcante M.L.

Biochem. Biophys. Res. Commun., Feb 6;314(2):631-7, 2004

Melanins are UV shielding pigments found in skin and other light exposed tissues. However, a kind of melanin, named neuromelanin (NM), is found in those deep brain loci that degenerate in Parkinson's disease (PD), where no such a function may be imagined. The NM synthetic pathway, different from the one of eumelanin based on tyrosinase, is still obscure as well as its physiological function. Here we show that under conditions of excess of toxic quinone concentration, nonmelanocytic cell strains (i.e., primary keratinocytes) may accumulate a dark cytoplasmatic pigment that proved to be a melanin. The ability of pigment deposition, possibly driven by peroxidases, is restricted to diploid cells and increases cell survival acting as a sink for potentially hazardous quinones. We suggest that in the basal nuclei, exposed to high level of catecholaminergic neurotransmitters, NM deposition is a relevant antioxidant mechanism by trapping quinones and semiquinones, thus protecting neurons from accumulating damage over many years. In this perspective, just as a hypothesis, we may imagine that PD neuron degeneration is the consequence of a reduced/abrogated ability to produce neuromelanin.

Prostate cancer and body size at different ages: an Italian multicentre case-control study.

Dal Maso L., Zucchetto A., La Vecchia C., Montella M., Conti E., Canzonieri V., Talamini R., Tavani A., Negri E., Garbeglio A., Franceschi S.

Br. J. Cancer, Jun 1;90(11):2176-80, 2004

We investigated the influence of anthropometric measures at diagnosis and at different ages on prostate cancer risk using an Italian multicentre case-control study conducted between 1991 and 2002 of 1294 histologically confirmed cases and 1451 controls admitted to the same network of hospitals for acute non-neoplastic conditions. Height, weight, body mass index (BMI), waist-to-hip ratio, lean body mass 1 year before diagnosis/interview were not significantly associated with risk. However, a positive association with high BMI at age 30 years was found (odds ratio=1.2 for BMI> or =24.7 vs <22.7) and: for less differentiated prostate cancer, with BMI 1 year before diagnosis/interview. This study supports possible relationships between high body mass in young adulthood, and a tendency to high weight throughout adult life, and the risk of prostate cancer.

Lonidamine causes inhibition of angiogenesis-related endothelial cell functions.

Del Bufalo D., Trisciuoglio D., Scarsella M., D'amati G., Candiloro A., Iervolino A., Leonetti C., Zupi G.

Neoplasia, Sep-Oct;6(5):513-22, 2004

The aim of this study was to assess whether lonidamine (LND) interferes with some steps in angiogenesis progression. We report here, for the first time, that LND inhibited angiogenic-related endothelial cell functions in a dose-dependent manner (1-50 microg/ml). In particular, LND decreased proliferation, migration, invasion, and morphogenesis on matrigel of different endothelial cell lines. Zymographic and Western blot analysis assays showed that LND treatment produced a reduction in the secretion of matrix metalloproteinase-2 and metalloproteinase-9 by endothelial cells. Vessel formation in a matrigel plug was also reduced by LND. The viability, migration, invasion, and matrix metalloproteinase production of different tumor cell lines were not affected by low doses of LND (1-10 microg/ml), whereas 50 microg/ml LND, which 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 functions, previously undescribed, may be a significant contributor to the antitumor effect of LND observed for clinical management of solid tumors.

Alfa-epoietin and anaemia in gynaecological cancer.

Di Cocco B., Salesi N., Fabi A., Nardoni C., Ferretti G., Bossone G., Ciccarese M., Savarese A., Vecchione A., Cognetti F.

Anticancer Res., Mar-Apr;24(2C):1287-92, 2004

The incidence and severity of anaemia in gynaecological cancer patients depends on several factors including age, histology and tumor stage, site of neoplasm and treatment. At present, two principal opinions are available for the management of chronic anaemia in cancer patients: blood transfusions and treatment with recombinant human Erythropoietin (rHuEPO). Clinical studies showed that rHuEPO can ameliorate chronic and chemotherapy-induced anaemia and reduce transfusions in patients with various malignant diseases. In this review we discuss the role of alfa-epoetin in the management of gynaecological and breast cancers.

Incidence of chemotherapy-induced amenorrhea depending on the timing of treatment by menstrual cycle phase in women with early breast cancer.

Di Cosimo S., Alimonti A., Ferretti G., Sperduti I., Carlini P., Papaldo P., Fabi A., Gelibter A., Ciccarese M., Giannarelli D., Mandala M., Milella M., Ruggeri E.M., Cognetti F.

Ann. Oncol., Jul;15(7):1065-71, 2004

Background: The aim of this study was to characterize the factors associated with chemotherapy-induced amenorrhea (CIA) and to examine whether the phase of the menstrual cycle at chemotherapy start could affect the rate of CIA in premenopausal women with early breast cancer.

Methods: CIA was defined as the cessation of menses for at least 3 months during or after chemotherapy. Menstrual phase was defined as days 1-6, follicular phase as days 7-14, luteal phase as days 15-20 and premenstrual phase as days 21-28. Univariate and multivariate predictors of CIA were examined.

Results: Among 111 premenopausal women, univariate analysis showed a higher incidence of CIA in patients treated in the follicular phase rather than in other menstrual cycle phases (67.6% compared with 45.5%; P=0.03). The rate of CIA increased with age: 65.2% and 45.8% in patients aged >42 and </=42 years, respectively (P=0.05). Upon multivariate analysis these differences remained statistically significant and duration of chemotherapy of more than six cycles correlated significantly with the incidence of CIA (P=0.03).

Conclusions: The major implication of this analysis is that the timing of treatment within the menstrual cycle may potentially modulate the onset of CIA. This work and its future confirmation using prospective randomized trials would be useful in predicting the likelihood of CIA and in counseling breast cancer patients, especially those with a good prognosis who benefit less from chemical castration.

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

Di Filippo F., Cavaliere F., Anza M., Garinei R., Botti C., Perri P., Di Angelo P., Patrizi V., Di Filippo S., Visca P.

J. Chemother., Nov;16 Suppl. 5:66-9, 2004

Liposome-containing doxorubicin has been employed in the treatment of advanced soft tissue limb sarcoma during hyperthermic perfusion. A phase I-II study was carried out starting with a standard dose of 10 mg//L of limb volume, the dosage was escalated with 2 mg for each triplet of patients. The maximum tolerable (MTD) dose was established as the amount able to cause a grade IV limb reaction at least in two out of three patients, the temperature level remained unchanged (41.5 degrees C). The grade of limb reaction ranged between I-II (mild edema and erythema). Only in two patients treated with 18 mg/L of limb volume was a grade IV limb reaction observed, therefore MTD at a temperature of 41.5 degrees C is 16 mg. A good tumor response was observed in 29% of the patients, partial response in 71%. The tumor shrinkage after perfusion permitted conservative surgery in 91% of the cases.

TNFa-based isolated hyperthermic limb perfusion (HILP) in the treatment of limb recurrent melanoma: update 16 years after its first clinical application.

Di Filippo F., Cavaliere F., Garinei R., Anza M., Di Angelo P., Psaila A., Piarulli L., Callopoli A., Bruno P., Di Filippo S., Priore F.

J. Chemother., Nov;16 Suppl. 5:62-5, 2004

Hyperthermic Limb Perfusion (HILP) with Tumor Necrosis Factor alpha (TNFalpha) and interferon gamma (IFNgamma) was pioneered by Lienard and Lejeune in 1988. TNFalpha was empirically employed at a dosage of 3-4 mg that is ten times the systemic maximum tolerated dose (MTD). Sixteen years after its first clinical application more than 300 patients have been treated and some clarifications can be made regarding three major questions: the real role of IFNgamma, the TNFalpha dose and eligibility criteria for patient selection. A randomized phase II study has demonstrated that IFNgamma does not increase significantly the efficacy but does increase side-effects. Experimental and clinical results seem to indicate that patients with bulky melanoma disease can really benefit from TNFalpha HILP carried out with only 1 mg.

Loco-regional treatment of young age breast cancer.

Di Filippo F., Botti C., Cavaliere F., Perri P., Psaila A., Di Filippo S.

Tumori, 3(3):129-31, 2004

No abstract available

Human Mena protein, a serex-defined antigen overexpressed in breast cancer eliciting both humoral and CD8+ T-cell immune response.

Di Modugno F., Bronzi G., Scanlan M.J., Del Bello D., Cascioli S., Venturo I., Botti C., Nicotra M.R., Mottolese M., Natali P.G., Santoni A., Jager E., Nistico P.

Int. J. Cancer, May 10;109(6):909-18, 2004

Screening of a cDNA expression library from a primary breast tumor with the autologous patient serum led to the isolation of 6 cDNA clones corresponding to 3 different genes, including a novel gene that maps to chromosome 1 and encodes the human homologue of mouse Mena (hMena, cDNA clone RMNY-BR-55), a protein of the Ena/VASP family involved in the regulation of cell motility and adhesion. A cancer-restricted antibody response against hMena was demonstrated, since 18/93 cancer patient sera, the majority (10/52) from breast cancer, showed anti-hMena-specific IgG, while no antibodies were present in healthy donors. When hMena protein expression was analyzed by Western blot and immunohistochemistry, the antigen was overexpressed in the majority of breast cancer cell lines and in 75% of primary breast tumor lesions evaluated. Furthermore, when HLA-A2-restricted peptides from the hMena sequence were used to stimulate CD8+ T cells, an hMena-specific response was found in 9 out of 12 HLA-A2+ breast cancer patients. In 4 patients, this cell-mediated immune response was concomitant with antibody response to hMena. Furthermore, an hMena-specific T-cell line was established from an HLA-A2+ breast cancer patient whose primary tumor lesion overexpressed the hMena protein. The present findings highlight the emerging role that overexpression of cytoskeleton regulatory components may have in the induction of a specific antitumor immune response.

Homeodomain-interacting protein kinase-2 activity and p53 phosphorylation are critical events for cisplatin-mediated apoptosis.

Di Stefano V., Rinaldo C., Sacchi A., Soddu S., D'orazi G.

Exp. Cell. Res., Feb 15;293(2):311-20, 2004

HIPK2 is a member of a novel family of nuclear serine-threonine kinases identified through their ability to interact with the Nkx-1.2 homeoprotein. The physiological role of these kinases is largely unknown, but we have recently reported on the involvement of HIPK2 in the induction of apoptosis of tumor cells after UV stress through p53 phosphorylation and transcriptional activation. Here, we demonstrate that the chemotherapeutic drug cisplatin increases HIPK2 protein expression and its kinase activity, and that HIPK2 is involved in cisplatin-dependent apoptosis. Indeed, induction of HIPK2 and of cell death by cisplatin are efficiently inhibited by the serine-threonine kinase inhibitor SB203580 or the transduction of HIPK2-specific RNA-interfering molecules. HIPK2 gene silencing efficiently reduces the p53-mediated transcriptional activation of apoptotic gene promoters as well as apoptotic cell death after treatment with cisplatin. These findings, along with the involvement of p53 phosphorylation at serine 46 (Ser46) in the transcriptional activation of apoptotic gene promoters, suggest a critical role for HIPK2 in triggering p53-dependent apoptosis in response to the antineoplastic drug cisplatin.

HIPK2 neutralizes MDM2 inhibition rescuing p53 transcriptional activity and apoptotic function.

Di Stefano V., Blandino G., Sacchi A., Soddu S., D'orazi G.

Oncogene, Jul 1;23(30):5185-92, 2004

The p53 oncosuppressor protein is subject to negative regulation by MDM2, which efficiently inhibits its activity through an autoregulatory loop. In response to stress, however, p53 undergoes post-translational modifications that allow the protein to escape MDM2 control, accumulate, and become active. Recent studies have shown that, following DNA damage, the HIPK2 serine/threonine kinase binds and phosphorylates p53, inducing p53 transcriptional activity and apoptotic function. Here, we investigated the role of HIPK2 in the activation of p53 in the presence of MDM2. We found that HIPK2 rescues p53 transcriptional activity overcoming MDM2 inhibition, and that restoration of this p53 function induces apoptosis. Recovery of p53-dependent apoptosis is achieved by preventing p53 nuclear export and ubiquitination mediated by MDM2 in vitro and in vivo following genotoxic stress. These results shed new light on the mechanisms by which the HIPK2/p53 pathway promotes apoptosis and suppression of tumorigenesis.

Feasibility of hanging maneuvers in orthotopic liver transplantation with inferior vena cava preservation and in liver surgery.

Ettorre G.M., Vennarecci G., Boschetto A., Douard R., Santoro E.

J. Hepatobiliary Pancreat. Surg., 11(3):155-8, 2004

Background/purpose: The aim of this work was to study the feasibility and complication rates of liver hanging maneuvers: the Belghiti liver hanging maneuver (BLHM) in liver resection and the modified liver hanging maneuver (MLHM) in orthotopic liver transplantation (OLT) with inferior vena cava (IVC) preservation.

Methods: From January 2001 to August 2003, BLHM was planned in 26 consecutive right hepatectomies and MLHM in 28 consecutive OLTs with IVC preservation.

Results: BLHM was performed in 24/26 patients (92%). In the 2 remaining patients, chronic biliary infection (n = 1) and intraparenchymal hemorrhagic hepatocellular carcinoma (n = 1) did not allow BLHM to be achieved. Bleeding during the BLHM procedure occurred in 1 patient (4%), with no need for interruption. MLHM was performed in all 28 patients, and in none of them was bleeding observed during the maneuver.

Conclusions: BLHM and MLHM are important technical refinements with several advantages. Feasibility rates were 92% and 100%, respectively. Bleeding risk remained low (4%) for BLHM and was 0% for MLHM. The rate of BLHM failure suggests that the feasibility rate may be higher in normal liver parenchyma.

Bone metastasis from glioblastoma multiforme without central nervous system relapse: a case report.

Fabi A., Vidiri A., Carapella C., Pace A., Occhipinti E., Caroli F., Mirri A., Carlini P., Cognetti F.

Anticancer Res., Jul-Aug;24(4):2563-5, 2004

The extraneural diffusion of malignant gliomas is not frequent and some authors have reported single or multiple bone metastases from glioblastoma contemporary to the time of primary cerebral tumor or accompanying relapse on the brain. We report the case of a man affected by a glioblastoma who had a lumbar spine metastases without any brain relapse after excision of cerebral glioblastoma multiforme and brain radiotherapy.

Epirubicin plus docetaxel in metastatic breast cancer: escalating dose does not improve efficacy. A phase II study.

Fabi A., Papaldo P., Pino M.S., Ferretti G., Carlini P., Pacetti U., Di Cosimo S., Nardoni C., Giannarelli D., Sacchi I., Cognetti F.

Anticancer Res., May-Jun;24(3b):1963-7, 2004

Background: The combination of anthracyclines and docetaxel have demonstrated a significant activity in metastatic breast cancer (MBC) as first-line chemotherapy. In a previous multicenter phase I study, we recommended two schedules of epirubicin-docetaxel combination for MBC: 1) epirubicin 75 mg/m2, docetaxel 80 mg/m2 every 3 weeks without G-CSF; 2) epirubicin 90 mg/m2 plus docetaxel 90 mg/m2 every 3 weeks, with G-CSF support.

Patients and Methods: Twenty-five advanced breast cancer patients were treated with epirubicin 90 mg/m2 plus docetaxel 90 mg/m2 every 3 weeks, with prophylactic G-CSF.

Results: The main toxicity was grade 3-4 neutropenia (41% of cycles) despite the use of G-CSF; febrile neutropenia was observed in 14% of cycles necessitating a dose reduction of both drugs in 30% of patients. Response was observed in 79% of patients: 21% complete responses and 58% partial responses. The median response duration was 10 months (range: 3-16). The median time to progression was 11 months. The overall 3-year survival was 49.7%.

Conclusion: The antitumor activity observed in this series was comparable with that seen in other studies of taxane/anthracycline combinations. The degree of myelosuppression was severe, even though G-CSF was administered as a prophylactic. We recommend a lower dose of both drugs as reported by other authors.

The combination of carboplatin and weekly paclitaxel: a safe and active regimen in advanced non small-cell lung cancer patients. A phase I-II study.

Fabi A., Barduagni M., Ferraresi V., Cortesi E., Gamucci T., De Marinis F., Saltarelli R., Gabriele A., Pellicciotta M., Ceribelli A., De Marco S., Facciolo F., Cognetti F.

J. Exp. Clin. Cancer Res., Mar;23(1):25-32, 2004

The combination of carboplatin and paclitaxel given every three weeks is a tolerated and reasonably active regimen in advanced non-small cell lung cancer (NSCLC). This study was designed to evaluate the maximum tolerated dose (MTD) of a fixed dose of carboplatin with an area under the curve (AUC) of 6 and escalating doses of weekly paclitaxel with an initial dose of 50 mg/m2 with 10 mg/m2 increments at each level in untreated NSCLC patients (phase I study). The study continued with a phase II study. Thirty patients entered the phase I study. The MTD was: carboplatin AUC = 6 on days 1 and 28 plus paclitaxel 100 mg/m2 (1 hour) on days 1, 8,15, 28. The dose-limiting toxicity (DLT) was severe neutropenia and cardiological toxicity. Subsequently, 42 patients entered the phase II study with the same treatment schedule. The 2-drug combination was globally well tolerated. The overall response rate (RR) was 42% [CI 95%: 26.3-57.7], stable disease (SD) 29% and progression (PD) 29%. The median duration of response was 8.0 mos (range: 1.0-19.0). The median time to progression was 8.0 mos (range: 7.0-19.0) and the median survival was 14.0 months (range: 9.0-19.0). The association of carboplatin AUC = 6 and weekly paclitaxel 100 mg/m2 proved to be manageable, active and extremely safe even in elderly patients (one third of all patients in our cohort). The survival results were interesting: the median survival time was 14 months (9-19 months) and the 1- and 2-year survival was 59% and 16%, respectively.

Psoriasis, Kaposi's Sarcoma and Hodgkin's Disease in a Patient with Down's Syndrome.

Fargnoli M.C., Peris K., Frascione P., Barbati R., Anemona L., Uccini S., Francesconi F., Chimenti S.

Dermatology, 209(2):158-159, 2004

No abstract available

HER2/neu expression and hormonal therapy in early breast cancer: can muddy waters become clear?.

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

J. Clin. Oncol., Feb 1;22(3):568-9, 2004

No abstract available

Zoledronic acid-associated thrombotic thrombocytopenic purpura.

Ferretti G., Petti M.C., Carlini P., Zeuli M., Picardi A., Meloni G., Bria E., Papaldo P., Fabi A., Cognetti F.

Ann. Oncol., Dec;15(12):1847-1848, 2004

No abstract available

Prognostic value of soluble P-selectin levels in colorectal cancer.

Ferroni P., Roselli M., Martini F., D'alessandro R., Mariotti S., Basili S., Spila A., Aloe S., Palmirotta R., Maggini A., Del Monte G., Mancini R., Graziano F., Cosimelli M., Guadagni F.

Int. J. Cancer, Sep 1;111(3):404-8, 2004

Measurement of soluble (s) P-selectin levels has been proposed as a diagnostic tool for monitoring the clinical course of human neoplasms. Thus, our study was aimed at analyzing the role of sP-selectin in association with clinicopathological variables in 181 patients with primary (n =149) or metastatic (n = 32) colorectal cancer (CRC), 34 patients with benign diseases and 181 control subjects. The results obtained showed that sP-selectin levels were higher in patients with CRC compared either to patients with benign disease ($p = 0.006$) or controls ($p = 0.003$). No differences were observed between the latter and patients with benign diseases. Increased median sP-selectin levels were significantly associated with the presence of distant metastasis (68.2 ng/ml vs. 48.6 ng/ml, $p = 0.002$). Of interest, carcinoembryonic antigen (CEA) levels were independently associated to sP-selectin (regression coefficient = 0.28, $p < 0.002$). Cox's proportional hazards survival analysis of primary CRC patients demonstrated that beside the stage of disease sP-selectin levels had an independent prognostic role in predicting recurrent disease (HR = 2.22, $p = 0.019$) and mortality from CRC (HR = 3.44, $p= 0.017$). These results suggest that measurement of plasma sP-selectin might represent a prognostic indicator in the management of patients with CRC.

Cell cycle regulation of NF-YC nuclear localization.

Frontini M., Imbriano C., Manni I., Mantovani R.

Cell. Cycle, Feb;3(2):217-22, 2004

NF-Y is a trimeric activator with histone fold, HFM, subunits that binds to the CCAAT-box and is required for a majority of cell cycle promoters, often in conjunction with E2Fs. In vivo binding of NF-Y is dynamic during the cell cycle and correlates with gene activation. We performed immunofluorescence studies on endogenous, GFP- and Flag-tagged overexpressed NF-Y subunits. NF-YA, NF-YB are nuclear proteins. Unexpectedly, NF-YC localizes both in cytoplamatic and nuclear compartments and its nuclear localization is determined by the interaction with its heterodimerization partner NF-YB. Most importantly, compartmentalization is regulated during the cell cycle of serum restimulated NIH3T3 cells, accumulating in

the nucleus at the onset of S phase. These data point to the control of HFM heterodimerization as an important layer of NF-Y regulation during cell cycle progression.

Liver harvesting surgical technique for the treatment of retro-hepatic caval thrombosis concomitant to renal cell carcinoma: perioperative and long-term results in 15 patients without mortality.

GALLUCCI M., BORZOMATI D., FLAMMIA G., ALCINI A., ALBINO G., CARICATO M., ESPOSITO A., VINCENZI B., ROSSI M., COPPOLA R., BERLOCO P.

Eur. Urol., Feb;45(2):194-202, 2004

Objective: Radical surgical treatment improves the prognosis of patients affected by Inferior Vena Cava (IVC) thrombosis concomitant to renal carcinoma. However, thrombus extension above the infrahepatic IVC represents a major technical topic for surgeons because of the possible occurrence of uncontrollable haemorrhages and tumor fragmentation. We report the results of an innovative surgical approach to caval thrombosis including the isolation of the IVC from the liver as routinely performed during liver harvesting. In the presence of retro-hepatic IVC thrombosis, this technique improves vascular control and allows to perform a large cavotomy with an en-bloc removal of the thrombus and the tumor.

Methods: From January 1995 through June 2003, 15 patients with renal cancer and caval thrombosis were treated at our Institution. Four, ten and one patients were respectively affected by an infrahepatic (Level I), retro-hepatic (Level II) and atrial (Level III) IVC thrombosis.

Results: All patients underwent radical surgical treatment. In presence of Level II caval thrombosis, the patients underwent the above reported surgical technique. Perioperative mortality was absent; major morbidity occurred in one patient (6.7%). The thrombus was radically removed in all cases. After a mean follow-up of 53.9 months (5-100 months) all patients but one are still alive. One patient died 9 months after surgery with multiple bilateral pulmonary metastases.

Conclusions: Isolation of the retro-hepatic IVC is a safe and effective manoeuvre to significantly reduce perioperative mortality and morbidity in patients affected by Level II caval thrombosis concomitant to renal carcinoma.

Hypersensitivity reactions to Oxaliplatin: Incidence and Management. Editorial.

GARUFI C., VANNI B.

Oncology (Huntington) 18(13):1680-1684, 2004

No abstract available

Colon cancer prevalence and estimation of differing care needs of colon cancer patients.

GATTA G., CAPOCACCIA R., BERRINO F., RUZZA M.R., CONTIERO P.; EUROPREVAL WORKING GROUP. (RAMAZZOTTI V., CONTI E.M.S.)

Ann. Oncol., Jul;15(7):1136-42, 2004

Background: Cancer prevalence-the proportion of people in a population with a diagnosis of cancer-includes groups with widely differing cancer care needs. We estimated the proportions of the prevalent colon cancer cases requiring initial care, terminal care and follow-up.

Patients and methods: Prevalence by year since diagnosis was estimated from incidence and vital status data on 243,471 colon cancer cases collected by EUROPREVAL from 36 European population-based cancer registries. The proportions of cured and fatal cases were estimated by applying 'cure' survival models to the dataset. The proportion of recurrence-free cases was estimated by analysis of a representative sample of 278 colon cancer patients from the Lombardy Cancer Registry (LCR), northern Italy.

Results: The proportions of total prevalence requiring initial care was estimated at 12% in the LCR and 10% in Italy and Europe. Recurrence-free patients formed 89% of the total prevalence in the LCR and 91% in Italy and Europe. Eleven per cent (LCR) and 9% (Italy, Europe) of the total prevalence had recurred and consisted of patients in the terminal phase of their illness.

Conclusions: In 1992, 660,000 people were living with a diagnosis of colon cancer in Europe. We have estimated the proportions of this prevalence requiring particular types health care in the years following diagnosis, providing data useful for planning the allocation of health-care resources.

PET scanning evaluation of response to imatinib mesylate therapy in gastrointestinal stromal tumor (GIST) patients.

GELIBTER A., MILELLA M., CERIBELLI A., ZEULI M., FERRARESI V., VECCHIONE A., COGNETTI F.

Anticancer Res., Sep-Oct;24(5B):3147-51, 2004

Background: Unresectable or metastatic gastrointestinal stromal tumors (GISTs) exhibit a dynamic clinical course, with no evidence of benefit from any standard cytotoxic chemotherapy and an inevitably fatal outcome. With the introduction of Imatinib, an oral drug able to inhibit the KIT receptor tyrosine kinase, new questions arise regarding our ability to monitor treatment response with conventional methods and optimally manage such patients on treatment with new agents.

Materials and methods: Herein we report two cases of patients with a history of GIST in treatment with Imatinib.

Results: After 4 weeks from treatment start, CT scan evaluation demonstrated a massive increase in the size of metastatic lesions, but a confirmatory PET excluded, in both patients, the presence of any metabolic activity in the previously known metastatic sites. Imatinib therapy was continued with subjective clinical benefit for 12 further months before a PET scan-confirmed disease progression had occurred in one patient and is still ongoing after 15 months in the other.

Conclusion: These cases open the obvious question of whether conventional imaging techniques are adequate to assess the response to Imatinib treatment in GIST patients.

45th annual meeting of the Italian Cancer Society. Bergamo, 9-12 November 2003.

GIAVAZZI R., AGLIETTA M., ASTOLFI A., FALANGA A., FUSCO A., LABIANCA R., LOLLINI P.L., LOMBARDO C., NATALI P.G., PIEROTTI M.A., PRESTA M., SANTORO M., TARABOLETTI G., ZUPI G., VECCHIO G.

Tumori, May-Jun;90(3):356-62, 2004

The 45th Annual Meeting of the Italian Cancer Society (SIC), held at the Centro Congressi Giovanni XXIII in Bergamo, Italy on 9-12 November, 2003, attracted almost 400 participants. The Scientific Committee chaired by R. Giavazzi (Mario Negri Institute, Bergamo) and the board of the Italian Cancer Society produced a packed and varied program. Plenary sessions with keynote speakers (24 lectures) were combined with oral proffered papers (20 selected presentations), providing a platform from laboratory science to clinical interventions. Two hundred and sixty-one abstracts were submitted to the conference and presented in poster and poster discussion sessions, providing a stimulating ground for discussion and a network of interactive collaboration among young investigators. The venue of Bergamo offered exceptional hospitality with social events in the beautiful old town and at the Modern Art Museum. We hope that the following report gives an idea of the event and will encourage the reader to attend the 46th meeting of the SIC, 24-26 October, 2004 in Pisa.

Cyclolignans as inhibitors of the insulin-like growth factor-1 receptor and malignant cell growth.

GIRNITA A., GIRNITA L., DEL PRETE F., BARTOLAZZI A., LARSSON O., AXELSON M.

Cancer Res., Jan 1;64(1):236-42, 2004

The insulin-like growth factor-1 receptor (IGF-1R) plays a pivotal role in transformation, growth, and survival of malignant cells, and has emerged as a general and promising target for cancer treatment. However, no fully selective IGF-1R inhibitors have thus far been found. This is explained by the fact that IGF-1R is highly homologous to the insulin receptor, coinhibition of which may cause diabetic response. The receptors are both tyrosine kinases, and their ATP binding sites are identical, implying that ATP inhibitors cannot discriminate between them. Therefore, the current strategy has been to identify compounds interfering with receptor autophosphorylation at the substrate level. In this study we investigated the effects of cyclolignans and related molecules on IGF-1R activity. We report that certain cyclolignans are potent and selective inhibitors of tyrosine phosphorylation of the IGF-1R. Of particular interest was picropodophyl-

lin (PPP), which is almost nontoxic (LD(50) >500 mg/kg in rodents). PPP efficiently blocked IGF-1R activity, reduced pAkt and phosphorylated extracellular signal regulated kinase 1 and 2 (pErk1/2), induced apoptosis in cultured IGF-1R-positive tumor cells, and caused complete tumor regression in xenografted and allografted mice. PPP did not affect the insulin receptor or compete with ATP in an in vitro kinase assay, suggesting that it may inhibit IGF-1R autophosphorylation at the substrate level. This is also in agreement with our molecular model of how the cyclolignans may act on the IGF-1R kinase. Our results open the possibility to use PPP or related compounds with inhibitory effects on IGF-1R as lead compounds in development of anticancer agents.

Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study.

GLEHEN O., KWIATKOWSKI F., SUGARBAKER P.H., ELIAS D., LEVINE E.A., DE SIMONE M., BARONE R., YONEMURA Y., CAVALIERE F., QUENET F., GUTMAN M., TENTES A.A., ET AL.

J. Clin. Oncol., Aug 15;22(16):3284-92, 2004

Purpose: The three principal studies dedicated to the natural history of peritoneal carcinomatosis (PC) from colorectal cancer consistently showed median survival ranging between 6 and 8 months. New approaches combining cytoreductive surgery and perioperative intraperitoneal chemotherapy suggest improved survival.

Patients and methods: A retrospective multicenter study was performed to evaluate the international experience with this combined treatment and to identify the principal prognostic indicators. All patients had cytoreductive surgery and perioperative intraperitoneal chemotherapy (intraperitoneal chemohyperthermia and/or immediate postoperative intraperitoneal chemotherapy). PC from appendiceal origin was excluded.

Results: The study included 506 patients from 28 institutions operated between May 1987 and December 2002. Their median age was 51 years. The median follow-up was 53 months. The morbidity and mortality rates were 22.9% and 4%, respectively. The overall median survival was 19.2 months. Patients in whom cytoreductive surgery was complete had a median survival of 32.4 months, compared with 8.4 months for patients in whom complete cytoreductive surgery was not possible (P <.001). Positive independent prognostic indicators by multivariate analysis were complete cytoreduction, treatment by a second procedure, limited extent of PC, age less than 65 years, and use of adjuvant chemotherapy. The use of neoadjuvant chemotherapy, lymph node involvement, presence of liver metastasis, and poor histologic differentiation were negative independent prognostic indicators.

Conclusion: The therapeutic approach combining cytoreductive surgery with perioperative intraperitoneal chemotherapy achieved long-term survival in a selected group of patients with PC from colorectal origin with acceptable morbidity and mortality. The complete cytoreductive surgery was the most important prognostic indicator.

Cell surface overexpression of Galectin-3 and the presence of its ligand 90k in the blood plasma as determinants in colon neoplastic lesions.

GRECO C., VONA R., COSIMELLI M., MATARRESE P., STRAFACE E., SCORDATI P., GIANNARELLI D., CASALE V., ASSISI D., MOTTOLESE M., MOLES A., MALORNI W.

Glycobiology, May 12, 2004

Galectins are a family of beta-galactoside binding molecules involved in cell—extracellular matrix adhesion processes. Specifically, Galectin-3 (Gal-3), one of the members of this family of molecules plays a role in cell adhesion processes as well as in cell survival or apoptosis. Gal-3 was also hypothesized to represent a useful tool in tumor characterization, for example, in thyroid tumors. We report herein the results obtained by evaluating Gal-3 expression of colon cells from human adenomas and adenocarcinomas with two different methodologies: immunohistochemistry and flow cytometry of living dispersed cells. We found that (1) the expression of Gal-3 was significantly increased on the surface of cells from adenomas with respect to normal mucosa from the same patient; (2) Gal-3 ligand, 90k molecule, was increased in the blood plasma from patients with both adenomatous and adenocarcinomatous lesions; and (3) Gal-3 overexpression was not related with the presence of K-ras mutation. Altogether these results clearly indicate that the evaluation of Gal-3 expression (and of its ligand, 90k) can be of interest in the characterization of nonmalignant and malignant colon cancers.

A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study.

Gridelli C., Gallo C., Di Maio M., Barletta E., Illiano A., Maione P., Salvagni S., Piantedosi F.V., Palazzolo G., Caffo O., Ceribelli A., Falcone A., Et Al.

Br. J. Cancer, Dec 13;91(12):1996-2004, 2004

Docetaxel (75 mg m(-2) 3-weekly) is standard second-line treatment in advanced non-small-cell lung cancer (NSCLC) with significant toxicity. To verify whether a weekly schedule (33.3 mg m(-2) for 6 weeks) improved quality of life (QoL), a phase III study was performed with 220 advanced NSCLC patients, < or =75 years, ECOG PS < or =2. QoL was assessed by EORTC questionnaires and the Daily Diary Card (DDC). No difference was found in global QoL scores at 3 weeks. Pain, cough and hair loss significantly favoured the weekly schedule, while diarrhoea was worse. DDC analysis showed that loss of appetite and overall condition were significantly worse in the 3-week arm in the first week, while nausea and loss of appetite were more severe in the weekly arm in the third week. Response rate and survival were similar, hazard ratio of death in the weekly arm being 1.04 (95% CI 0.77-1.39). A 3-weekly docetaxel was more toxic for leukopenia, neutropenia, febrile neutropenia and hair loss; any grade 3-4 haematologic toxicity was significantly more frequent in the standard arm (25 vs 6%). The weekly schedule could be preferred for patients candidate to receive docetaxel as second-line treatment for advanced NSCLC, because of some QoL advantages, lower toxicity and no evidence of strikingly different effect on survival.

Correlation between tumor necrosis factor-alpha and d-dimer levels in non-small cell lung cancer patients.

Guadagni F., Ferroni P., Basili S., Facciolo F., Carlini S., Crecco M., Martini F., Spila A., D'alessandro R., Aloe S., Cerasoli V., Del Monte G., Mariotti S., Mineo T.C., Roselli M.

Lung Cancer, Jun;44(3):303-10, 2004

The present study was designed to investigate whether a correlation exists between IL-6, TNF-alpha and coagulation (Thrombin-antithrombin, TATc) or fibrinolysis (D-dimer) activation in non-small cell lung cancer (NSCLC) patients. One hundred thirty patients with NSCLC (n=65, 53 males, mean age 65 +/- 8, adenocarcinoma n=32, squamous cancer n=33) or chronic obstructive pulmonary disease (COPD) (n=65, 51 males, mean age 67 +/- 9) were studied. As control group 65 healthy donors (51 males, mean age 61 +/- 14) were also evaluated. The results obtained showed that median D-dimer levels were higher in NSCLC patients (3.0 microg/ml) compared either to COPD patients (1.1 microg/ml, P<0.05) or controls (0.3 microg/ml, P<0.0001). Positive TNF-alpha levels (>10 pg/ml) were found in 26% of NSCLC compared to 3% of COPD (P<0.002) and 5% of controls (P<0.0005). On the other hand, positive (>8.5 pg/ml) IL-6 levels were found in 53% of NSCLC and 21% of COPD patients, compared to 5% of control subjects (P<0.001). Median TATc levels were elevated in either NSCLC (6.9 microg/l) or COPD (5.7 microg/l) patients compared to controls (1.8 microg/l, P<0.0001). Elevated D-dimer levels were significantly associated to positive TNF-alpha levels in patients without distant metastasis (F=4.3, P<0.05). Moreover, TNF-alpha levels (P<0.01) were independently related to the presence of positive D-dimer levels in patients with non-metastatic NSCLC. These results suggest that increased levels of TNF-alpha might be responsible for an activation of fibrinolysis in patients with NSCLC.

Determination of chromosome 13 status in bone marrow cells of patients with multiple myeloma using combined morphologic and fluorescence in situ hybridization analysis.

Hardan I., Rothman R., Gelibter A., Cohen N., Shimoni A., Sokolovsky M., Reichart M., Ishoev G., Amariglio N., Rechavi G., Nagler A., Trakhtenbrot L.

Exp. Hematol., Mar;32(3):254-60, 2004

Deletion of chromosome 13q is believed to be an adverse prognostic marker in patients with multiple myeloma (MM). Interphase fluorescence in situ hybridization (I-FISH) is the method of choice for detection of chromosome 13q deletion (del13q). However, I-FISH has high false-positive rates attributed to a low percentage of plasma cells (PC), which are responsible for MM, in bone marrow (BM) samples from MM patients. In an attempt to overcome this problem, combined morphologic and I-FISH analyses were performed by a unique system that allows rapid automatic scanning of a large number of cells with simultaneous determination of the lineage of specific cells carrying del13q. The percentage of PC with del13q in BM samples from 40 MM patients was calculated. In addition, we established a useful prognostic ratio defined as the number of PC with

del13q divided by the number of non-PC with del13q (PDP/PDNP), which may help to precisely define the putative role of del13q in prediction response of MM patients to new therapeutic compounds. We suggest this technique as a novel sensitive and specific method for detection of del13q in a minor PC population of MM patients.

Pre-transplant prognostic factors for patients with high-risk leukemia undergoing an unrelated cord blood transplantation.

Iori A.P., Cerretti R., De Felice L., Screnci M., Mengarelli A., Romano A., Caniglia M., Cerilli L., Gentile G., Moleti M.L., Giona F., Agostini F., Pasqua I., Perrone M.P., Et Al.

Bone Marrow Transplant., Jun;33(11):1097-105, 2004

From July 1995 to December 2001, 42 patients with leukemia aged 1-42 years underwent cord blood transplant (CBT) from unrelated, < or = 2 antigen HLA mismatched donors. In all, 26 patients were in < or = 2nd complete remission and 16 in more advanced phase. Conditioning regimens, graft-versus-host disease (GVHD) prophylaxis and supportive policy were uniform for all patients. The cumulative incidence of engraftment was 90% (95% CI: 0.78-0.91). The cumulative incidence of III-IV grade acute- and chronic-GVHD was 9% (95% CI: 0.04-0.24) and 35% (95% CI: 0.21-0.60), respectively. The 4-year cumulative incidence of transplant-related mortality (TRM) and relapse was 28% (95% CI: 0.17-0.47) and 25% (95% CI: 0.14-0.45), respectively. The 4-year overall survival (OS), leukemia-free survival (LFS) and event-free survival (EFS) were 45% (95% CI: 0.27-0.63), 47% (95% CI: 0.30-0.64) and 46% (95% CI: 0.30-0.62), respectively. In multivariate analysis, the most important factor affecting outcomes was the CFU-GM dose, associated with CMV serology (P=0.003 and 0.04, respectively) in influencing OS and with patient sex (P=0.008 and 0.03, respectively) in influencing LFS. Finally, CFU-GM dose was the only factor that affected EFS significantly (P=0.02). In conclusion, the infused cell dose expressed as in vitro progenitor cell growth is highly predictive of outcomes after an unrelated CBT and should be considered the main parameter in selecting cord blood units for transplant.

Cancer patients submitted to innovative chemotherapeutic agents of intermediate emetogenic potential: antiemetic prescriptions and incidence of emesis.

Italian Group For Antiemetic Research (Cognetti F., Fabi A., Savarese A., Pacetti U.)

Tumori, 90:103-106, 2004

No abstract available

Interobserver reproducibility of immunohistochemical HER-2/neu evaluation in human breast cancer: the real-world experience.

Italian Network For Quality Assurance Of Tumor Biomarkers (Inqat) Group (Mottolese M.)

Int. J. Biol. Markers, 19(2):147-154, 2004

No abstract available

Systemic and haemodynamic toxicity after isolated limb perfusion (ILP) with TNF-alpha.

Laurenzi L., Natoli S., Di Filippo F., Calamaro A., Centulio F., Anza M., Cavaliere F., Marcelli M.E., Garinei R., Arcuri E.

J. Exp. Clin. Cancer Res., Jun;23(2):225-31, 2004

The aim of this study was to evaluate the systemic and haemodynamic postoperative effects of ILP with medium-low dose of TNF alpha in patients diagnosed with primary or recurrent limb melanoma or sarcoma, and to compare the resulting toxicity with Systemic Inflammatory Response Syndrome (SIRS). A prospective study on 17 consecutive patients with primary or recurrent limb tumor (melanoma or sarcoma) subjected to ILP with escalating doses of TNF alpha (0.5-2.0mg) was carried out. Seventeen patients with primary or recurrent limb melanoma or sarcoma were subjected to ILP with escalating doses of TNF alpha. ILP was carried out with the standard techniques, blood

being warmed at 42 degrees C for an hour. Serial serum TNF alpha determinations were performed before, during and after limb perfusion in nine patients. Systemic and pulmonary haemodynamics, by a radial and pulmonary artery catheter inserted before the induction of anesthesia, were monitored at 5 different times: before the induction of anesthesia (T0), and 6, 12, 24 and 48 hours after treatment (T1-4). Complete isolation of the limb was not always achieved, therefore leakage of TNF alpha occurred frequently during the perfusion in all patients with maximum systemic TNF alpha concentrations ranging from 431 to 111000 pg/ml. After perfusion only two patients showed detectable TNF alpha levels in peripheral blood which returned to baseline values within nine hours. These two patients had serious systemic toxicity: shock and respiratory failure secondary to pulmonary edema. Acute pulmonary edema was also observed in another patient. All three cases required supportive therapy provided by means of mechanical ventilation. In the remaining 14 patients a sepsis-like syndrome was observed. The most significant haemodynamic changes were due to the CO, which rose by 35%, and the SVR, which remained consistently low throughout. A reduction in Hb was observed in all patients (with an average decrease of 4 g/dl), while DO2 and VO2 levels rose, though not to statistically significant levels. Hypoxia occurred in all 14 patients. In three of the remaining 14 cases bilateral pulmonary leaks were noted, however the use of mechanical ventilation was not required. No perioperative death occurred and the aforementioned side effects were all reversible resulting in a patient's mean postoperative ICU permanence of 4 days (range 3 to 7 days). In conclusion, ILP with TNF alpha induces cardiovascular, respiratory and hematological toxicity with haemodynamic parameters being similar to those noted in SIRS probably due to leakage of TNF alpha in the systemic circulation during the perfusion. Nevertheless, this systemic toxicity was short-lived resulting in an acute reaction following a single application.

Cutaneous bacterial colonization, modalities of chemotherapeutic infusion, and catheter-related bloodstream infection in totally implanted venous access devices.

Laurenzi L., Natoli S., Benedetti C., Marcelli M.E., Tirelli W., Di Emidio L., Arcuri E.

Support. Care Cancer, 12(11):805-809, 2004

Goals of work: Prospective clinical study to evaluate patients suffering from solid tumor using a totally implanted venous access device (TIVAD) to determine: (1) if there is a relationship between cutaneous contamination at port insertion site and catheter-related bloodstream infection (CRBI); (2) development modalities of CRBI; (3) if there is a relationship between chemotherapy administration modalities by push/ bolus versus continuous infusion and CRBI.

Patients and methods: We studied 41 consecutive patients who needed a TIVAD positioned for chemotherapy administration by bolus/ push or continuous infusion. In every patient, we performed blood cultures from blood samples from port catheters and cutaneous cultures from cutaneous tampons of the skin surrounding the implant area on the first (T0) and eight day (T1) postoperatively, after 1 month (T2), and after 3 months (T3) from insertion.

Main results: The study was completed on 40 patients; in one case, the port was removed at T2 for septic complications. We obtained four positive blood cultures (two, 5%), two in the same patient, all caused by staphylococcus. Positive cutaneous tampons were 21 (13%) in 11 patients (27%); the four CRBI occurred in this group of patients with none in the remaining 30 patients (73%) for a total number of 120 tampons ($p<0.01$). In two cases, the same germ was isolated from both the skin and blood. None of the patients presented a local infection of the subcutaneous pocket. Positive cutaneous cultures decrease over time: T0-T2; 24-5%; T1-T3, 20-5% ($p<0.04$). There were no differences in CRBI incidence and positive cutaneous tampons between the two chemotherapy administration modalities.

Conclusions: Cutaneous microbial flora has a primary role in CRBI development within TIVADs; there is a relationship between cutaneous colonization and CRBI; colonization reaches its maximum during the first days after catheterization in which the use of the system is at high risk; colonization occurs both via extraluminal and endoluminal routes; there is no difference in CRBI incidence between bolus and continuous infusion administration.

Analysis of genetic alterations in normal bladder urothelium.

Leonardo C., Gallucci M., Cianciulli A.M.

Urology, Aug;64(2):405, 2004

No abstract available

Biological Activity of the G-quadruplex Ligand RHPS4 is Associated with Telomere Capping Alteration.

Leonetti C., Amodei S., D'angelo C., Rizzo A., Benassi B., Antonelli A., Elli R., Stevens M., D'incalci M., Zupi G., Biroccio A.

Mol. Pharmacol., Nov;66(5):1138-46, 2004

This study had two goals: 1) to evaluate the biological effect of the novel pentacyclic acridine 3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]acridinium methosulfate (RHPS4) on human melanoma lines possessing long telomeres, and 2) to elucidate the relationship between G-quadruplex-based telomerase inhibitor-induced cellular effects and telomere length/dysfunction. The cellular pharmacological effects of RHPS4 have been evaluated by treating melanoma lines with increasing concentrations of RHPS4. A dose-dependent inhibition of cell proliferation was observed in all the lines during short-term treatment. Flow cytometric analysis demonstrated that RHPS4 induced a dose-dependent accumulation of cells in the S-G(2)/M phase of cell cycle. The RHPS4-induced cell cycle alteration was irreversible even at low doses, and the cells died from apoptosis. At high RHPS4 concentration, apoptosis was accompanied by the induction of a senescence phenotype: large cell size, vacuolated cytoplasm, and beta-galactosidase activity. The short-term biological activity of RHPS4 was not caused by telomere shortening, but it was associated with telomere dysfunction, in terms of presence of telomeric fusions, polynucleated cells, and typical images of telophase bridge. In conclusion, our results demonstrate that the G-quadruplex ligand RHPS4 can function in a telomere length-independent manner through its ability to cause telomere-capping alteration.

In vivo administration of liposomal vincristine sensitizes drug-resistant human solid tumors.

Leonetti C., Scarsella M., Semple S.C., Molinari A., D'angelo C., Stoppacciaro A., Biroccio A., Zupi G.

Int. J. Cancer, Jul 10;110(5):767-74, 2004

Here we evaluated the antitumor efficacy of vincristine (VCR) encapsulated in sphingomyelin/cholesterol liposomes (SM/Chol) on drug-resistant human solid tumors. We firstly used the M14 human melanoma line and the counterpart resistant derivative, M14/R. The M14/R, selected after doxorubicin exposure, was cross resistant to VCR: the in vitro treatment with free VCR reduced the survival of M14, while M14/R line was completely resistant to VCR. Encapsulation in liposomes improved the efficacy of VCR in M14 cells and sensitized the M14/R line to the drug. Experiments in vivo confirmed these results. The treatment of M14 bearing mice with VCR resulted in marked reduction of tumor growth, while no antitumoral effect was observed in M14/R tumors. The administration of VCR encapsulated in liposomes was able to sensitize M14/R tumors to the drug, the antitumoral effect being comparable to that observed in M14 tumors after the same treatment. By injecting animals with the same dose of liposomal VCR fractionated into 3 daily injections and administering repeated cycles of treatment, to a marked improvement of the antitumor activity of liposomal VCR was observed. TUNEL assay in tumor sections indicated that the improved efficacy of liposomal VCR was related to the induction of massive necrosis and apoptosis. To confirm the efficacy of liposomal VCR on drug-resistant tumors, MCF7 breast and LoVo colon carcinomas, sensitive and resistant to VCR treatment, were also employed. The results showed that the treatment with liposomal VCR of mice bearing breast or colon resistant tumors reduced the tumor mass and delayed the tumor regrowth to the same extent observed in the sensitive counterpart. Together, these results demonstrate the ability of VCR encapsulated in liposomes in sensitizing drug resistant tumors of different histotypes.

The artificial zinc finger protein 'Blues' binds the enhancer of the fibroblast growth factor 4 and represses transcription.

LIBRI V., ONORI A., FANCIULLI M., PASSANANTI C., CORBI N.

FEBS Lett., Feb 27;560(1-3):75-80, 2004

The design of novel genes encoding artificial transcription factors represents a powerful tool in biotechnology and medicine. We have engineered a new zinc finger-based transcription factor, named Blues, able to bind and possibly to modify the expression of fibroblast growth factor 4 (FGF-4, K-fgf), originally identified as an oncogene. Blues encodes a three zinc finger peptide and was constructed to target the 9 bp DNA sequence: 5'-GTT-TGG-ATG-3', internal to the murine FGF-4 enhancer, in proximity of Sox-2 and Oct-3 DNA binding sites. Our final aim is to generate a model system based on artificial zinc finger genes to study the biological role of FGF-4 during development and tumorigenesis.

Gangliosides link the acidic sphingomyelinase-mediated induction of ceramide to 12-lipoxygenase-dependent apoptosis of neuroblastoma in response to fenretinide.

LOVAT P.E., DI SANO F., CORAZZARI M., FAZI B., DONNORSO R.P., PEARSON A.D., HALL A.G., REDFERN C.P., PIACENTINI M.

J. Natl. Cancer Inst., Sep 1;96(17):1288-99, 2004

Background: The lipid second messenger ceramide, which is generated by acidic and neutral sphingomyelinases or ceramide synthases, is a common intermediate of many apoptotic pathways. Metabolism of ceramide involves several enzymes, including glucosylceramide synthase and GD3 synthase, and results in the formation of gangliosides (GM3, GD3, and GT3), which in turn promote the generation of reactive oxygen species (ROS) and apoptosis. Fenretinide, a retinoic acid derivative, is thought to induce apoptosis via increases in ceramide levels, but the link between ceramide and subsequent apoptosis in neuroblastoma cells is unclear.

Methods: SH-SY5Y and HTLA230 neuroblastoma cells were treated with fenretinide in the presence or absence of inhibitors of enzymes important in ceramide metabolism (fumonisin B1, inhibitor of ceramide synthase; desipramine, inhibitor of acidic and neutral sphingomyelinases; and PDMP, inhibitor of glucosylceramide). Small interfering RNAs were used to specifically block acidic sphingomyelinase or GD3 synthase activities. Apoptosis, ROS, and GD3 expression were measured by flow cytometry.

Results: In neuroblastoma cells, ROS generation and apoptosis were associated with fenretinide-induced increased levels of ceramide, glucosylceramide synthase activity, GD3 synthase activity, and GD3. Fenretinide also induced increased levels of GD2, a ganglioside derived from GD3. Inhibition of acidic sphingomyelinase but not of neutral sphingomyelinase or ceramide synthase, blocked fenretinide-induced increases in ceramide, ROS, and apoptosis. Exogenous GD3 induced ROS and apoptosis in SH-SY5Y cells but not in SH-SY5Y cells treated with baicalein, a specific 12-lipoxygenase inhibitor. Exogenous GD2 did not induce apoptosis.

Conclusions: A novel pathway of fenretinide-induced apoptosis is mediated by acidic sphingomyelinase, glucosylceramide synthase, and GD3 synthase, which may represent targets for future drug development. GD3 may be a key signaling intermediate leading to apoptosis via the activation of 12-lipoxygenase

153Sm-EDTMP for bone pain palliation in skeletal metastases.

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

Eur. J. Nucl. Med. Mol. Imaging, Jun;31 Suppl. 1:S171-8, 2004

153Sm-ethylene diamine tetramethylene phosphonate (EDTMP) is a widely available and extensively tested radiopharmaceutical for systemic radionuclide therapy in patients with symptomatic multiple skeletal metastases. Its use is approved for any secondary bone lesion which has been shown to accumulate (99m)Tc-methylene diphosphonate, including breast carcinoma. The molecule is stable in vitro and upon injection more than 50% of the dose is avidly fixed by lesional and non-lesional bone, with the rest being rapidly eliminated unchanged via the urine. The short half-life (46.3 h), the relatively low-energy beta emissions (E(ave)=233 keV) and the gamma emission (103 keV) make (153)Sm a very attractive radionuclide, allowing therapeutic delivery of short-range electrons at relatively high dose rates with external imaging to corroborate biodistribution and possible dosimetric estimates. For a stan-

dard dose of 2,590 MBq/70 kg, the estimated radiation dose to metastases is 86.5 Gy. Critical organs are the bladder wall (2.5 Gy/2,590 MBq) and red marrow (4 Gy/2,590 MBq), with the latter being the critical factor in clinical practice as the dose-limiting factor is marrow radiotoxicity. The therapy has, however, proved safe provided that the platelet count exceeds 100 x 10(9)/l and the white blood cell count exceeds 3.5 x 10(9)/l. Clinical data obtained in fewer than 250 patients, within several studies, lead to the following conclusions: a dose of 37 MBq/kg has a better therapeutic ratio than a dose of 18.5 MBq/kg; the mean pain palliation rate after a single treatment in breast cancer is about 80%; toxicity is generally mild and transitory; and re-treatments are effective and safe provided that haematological values have fully recovered.

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., Feb 27;279(9):8169-80, 2004

No abstract available

Oxaliplatin in Colon Cancer.

MANDALA M., FERRETTI G., BARNI S.

N. Engl. J. Med., Oct 14;351(16):1691-2, 2004

No abstract available

Pin1 links the activities of c-Abl and p300 in regulating p73 function.

MANTOVANI F., PIAZZA S., GOSTISSA M., STRANO S., ZACCHI P., MANTOVANI R., BLANDINO G., DEL SAL G.

Mol. Cell., Jun 4;14(5):625-36, 2004

Activation of p73 upon genotoxic treatment triggers apoptosis of tumor cells lacking functional p53 and involves the activities of c-Abl and p300. Here, we demonstrate that conformational changes of p73 catalyzed by the prolyl isomerase Pin1 are crucial in this pathway. Lack of Pin1 reduces p73 stability, hampering its accumulation upon genotoxic stress. Indeed, we show that upon treatment with chemotherapeutic drugs c-Abl enhances the phosphorylation-dependent interaction between Pin1 and p73, and this in turn promotes p73 acetylation by p300. Consistently, the ability of c-Abl and p300 to increase p73 stability and transcriptional activity requires Pin1. As a consequence, Pin1 appears to be essential for activation of the apoptotic response by endogenous p73.

p53 can inhibit cell proliferation through caspase-mediated cleavage of ERK2/MAPK.

MARCHETTI A., CECCHINELLI B., D'ANGELO M., D'ORAZI G., CRESCENZI M., SACCHI A., SODDU S.

Cell. Death Differ., Jun;11(6):596-607, 2004

Stimulation of the Ras/MAPK cascade can either activate p53 and promote replicative senescence and apoptosis, or degrade p53 and promote cell survival. Here we show that p53 can directly counteract the Ras/MAPK signaling by inactivating ERK2/MAPK. This inactivation is due to a caspase cleavage of the ERK2 protein and contributes to p53-mediated growth arrest. We found that in Ras-transformed cells, growth arrest induced by p53, but not p21(Waf1), is associated with a strong reduction in ERK2 activity, phosphorylation, and protein half-life, and with the appearance of caspase activity. Likewise, DNA damage-induced cell cycle arrest correlates with p53-dependent ERK2 downregulation and caspase activation. Furthermore, caspase inhibitors or expression of a caspase-resistant ERK2 mutant interfere with ERK2 cleavage and restore proliferation in the presence of p53 activation, indicating that caspase-mediated ERK2 degradation contributes to p53-induced growth arrest. These findings strongly point to ERK2 as a novel p53 target in growth suppression.

Analysis of chromosomes 3, 7, X and the EGFR gene in uterine cervical cancer progression.

Marzano R., Corrado G., Merola R., Sbiroli C., Guadagni F., Vizza E., Del Nonno F., Carosi M., Galati M. M., Sperduti I., Cianciulli A.M.

Eur. J. Cancer, Jul;40(10):1624-9, 2004

The aim of this study was to investigate the possible role of genetic alterations in the genesis and progression of cervical carcinomas. We analysed the 3, 7, X aneusomy of chromosomes and the status of the epidermal growth factor receptor (EGFR) gene by fluorescence in situ hybridisation (FISH) analysis. Polysomy of chromosomes 3 and X defined the transition from high-grade squamous intraepithelium lesions (HSIL) to cervical carcinoma. Chromosome 7 monosomy and polysomy did not show any statistical significant differences between the groups examined. When we compared the chromosomal aneusomies in all of the specimens using the Kruskal-Wallis test, significant differences ($P = 0.0001$, $P = 0.0001$ for chromosomes 3 and X, respectively) were observed. Using a ratio of the EGFR gene signals and chromosome 7 centromeric signals, no samples showed gene amplification. Our results demonstrate the importance of chromosomal 3 and X aneusomies in the development and progression from HSIL to cervical carcinoma, highlighting their usefulness as genetic markers for identifying SILs at high-risk of progression.

Morphine but not fentanyl and methadone affects mitochondrial membrane potential by inducing nitric oxide release in glioma cells.

Mastronicola D., Arcuri E., Arese M., Bacchi A., Mercadante S., Cardelli P., Citro G., Sarti P.

Cell. Mol. Life Sci., Dec;61(23):2991-7, 2004

We have observed that treatment of human glioma cells with morphine in the nanomolar range of concentration affects the mitochondrial membrane potential. The effect is specific to morphine and is mediated by naloxone-sensitive receptors, and is thus better observed on glioma cells treated with desipramine; moreover, the mitochondrial impairment is not inducible by fentanyl or methadone treatment and is prevented by the nitric oxide (NO) synthase inhibitor L-NAME. We conclude that in cultured glioma cells, the morphine-induced NO release decreases the mitochondrial membrane potential, as one might expect based on the rapid inhibition of the respiratory chain by NO. The identification of new intra-cellular pathways involved in the mechanism of action of morphine opens additional hypotheses, providing a novel rationale relevant to the therapy and toxicology of opioids.

Combined epidermal growth factor receptor targeting with the tyrosine kinase inhibitor gefitinib (ZD1839) and the monoclonal antibody cetuximab (IMC-C225): superiority over single-agent receptor targeting.

Matar P., Rojo F., Cassia R., Moreno-Bueno G., Di Cosimo S., Tabernero J., Guzman M., Rodriguez S., Arribas J., Palacios J., Baselga J.

Clin. Cancer Res., Oct 1;10(19):6487-501, 2004

Purpose: The epidermal growth factor receptor (EGFR) is abnormally activated in cancer and two classes of anti-EGFR agents, monoclonal antibodies and low-molecular-weight tyrosine kinase inhibitors, have shown antitumor activity in patients. Because these two classes of antireceptor agents target the EGFR at different sites, we decided to explore whether the combined administration of gefitinib, a tyrosine kinase inhibitor, and cetuximab, a monoclonal antibody, had superior antitumor activity than either agent given alone.

Experimental design: We studied the effects of the combination of gefitinib and cetuximab in a panel of human cancer cell lines and in an EGFR-dependent human tumor xenograft model (A431). The effects of these two agents on EGFR signaling, proliferation, apoptosis, and vascularization were evaluated. In addition, we analyzed, with cDNA arrays, changes in gene expression profiles induced by both agents.

Results: The combined treatment with gefitinib and cetuximab resulted in a synergistic effect on cell proliferation and in superior inhibition of EGFR-dependent signaling and induction of apoptosis. In a series of in vivo experiments, single-agent gefitinib or cetuximab resulted in transient complete tumor remission only at the highest doses. In contrast, suboptimal doses of gefitinib and cetuximab given together resulted in a complete and permanent regression of large tumors. In the combination-treated tumors, there was a superior inhibition of EGFR, mitogen-activated protein kinase, and Akt phosphorylation, as well as greater inhibition of cell proliferation and vascularization and enhanced apoptosis. Using cDNA arrays, we found 59 genes that were coregulated and 45 genes differentially regulated, including genes related to cell

proliferation and differentiation, transcription, DNA synthesis and repair, angiogenesis, signaling molecules, cytoskeleton organization, and tumor invasion and metastasis.

Conclusions: Our findings suggest both shared and complementary mechanisms of action with gefitinib and cetuximab and support combined EGFR targeting as a clinically exploitable strategy.

Opioids and renal function.

MERCADANTE S., ARCURI E.

J. Pain, Feb;5(1):2-19, 2004

Opioids, both endogenous and exogenous, have a strong influence on the renal function through different mechanisms, producing changes in the renal excretion of water and sodium. Several studies have demonstrated that opioids influence renal function, according to the agonist profile used. Mu, kappa, and delta agonists produce different renal effects, although the mechanisms remain unclear. Experimental data have given the input for a possible therapeutic role of kappa agonists for some specific conditions, for example, in treating water retention or hyponatremia occurring in patients who have hepatic cirrhosis with ascites. On the other hand, changes in renal function might strongly condition the use of opioids in the clinical setting, and the knowledge of the relationship between opioids and renal function is mandatory for a tailored approach to accommodate the individual responses in terms of pain intensity, tolerance, and adverse effects experienced by these groups of patients. The influence of renal function when using different opioids in the clinical setting is reviewed, as well as problems related to transplantation, renal damage induced by opioid addiction, and problems related to the use of opioid antagonists in such conditions.

Perspective: Endogenous opioids exert physiologic effects on renal function, and the use of opioids may have an influence on renal activity. Renal impairment has a serious impact on the clearance of most opioids used in the clinical setting. Biochemical and clinical monitoring is mandatory to prevent serious complications.

Prolonged uncontrolled pain, psychological distress, and opioid escalation.

MERCADANTE S., VILLARI P., FERRERA P., ARCURI E.

J. Pain Symptom Manage., Jul;28(1):1-3, 2004

No abstract available

Ras inhibition amplifies cisplatin sensitivity of human glioblastoma.

MESSINA S., LEONETTI C., DE GREGORIO G., AFFATIGATO V., RAGONA G., FRATI L., ZUPI G., SANTONI A., PORCELLINI A.

Biochem. Biophys. Res. Commun., Jul 23;320(2):493-500, 2004

Resistance to chemotherapy is a common feature of malignant gliomas. This resistance is mediated by receptor tyrosine kinase (RTK)-regulated signaling. p21-Ras protein is pivotal in the propagation of the signal originated from many RTKs. Our aim was to investigate whether inhibition of Ras pathway affects the response to cisplatin in malignant gliomas. We found an enhanced sensitivity to cisplatin of two glioblastoma cell lines expressing dominant negative Ras. Moreover, DN-Ras expressing cells, implanted in nude mice, resulted in being extremely sensitive to cisplatin. The growth of all the tumors was significantly inhibited by combining DN-Ras adenovirus infection with cisplatin treatment. The majority of glioma cells expressing DN-Ras underwent apoptosis in response to cisplatin. In vivo, DN-Ras alone did not influence the growth of tumors, suggesting that the effects of Ras-inhibition observed in vitro could not be extrapolated in vivo. The survival signal pathway transduced by Ras was essentially mediated by inhibition of caspase-9 cleavage via PI3K/Akt.

Pilot study of celecoxib and infusional 5-fluorouracil as second-line treatment for advanced pancreatic carcinoma.

Milella M., Gelibter A., Di Cosimo S., Bria E., Ruggeri E.M., Carlini P., Malaguti P., Pellicciotta M., Terzoli E., Cognetti F.

Cancer, Jul 1;101(1):133-8, 2004

Background: Cyclooxygenase-2 (COX-2) is up-regulated frequently and may constitute a promising therapeutic target in patients with pancreatic ductal adenocarcinoma (PDAC). **Methods**: Patients with advanced PDAC who had progressive disease after gemcitabine-based chemotherapy were eligible for this pilot study. Treatment was comprised of oral celecoxib (400 mg twice daily) and protracted intravenous (i.v.) infusion 5-fluorouracil (5-FU) (200 mg/m(2) per day), both given continuously for a maximum of 9 treatment months, in the absence of disease progression or unacceptable toxicity. Patients were examined weekly for toxicity and were restaged every 6-8 weeks for tumor assessment.

Results: Seventeen patients entered the study. Asymptomatic transaminase elevation was the most common toxicity and reached NCI-CTC (version 3.0) Grade 3-4 in 4 of 133 treatment weeks. No other hematologic or nonhematologic toxicity > Grade 2 was observed. Four patients discontinued celecoxib due to upper gastrointestinal tract toxicity. Two confirmed partial responses (durations of 23 weeks and 68 weeks, respectively) and 2 patients with stable disease (durations of 10 weeks and 13 weeks, respectively) were observed for an overall response rate of 12% (95% confidence interval, 0-27%) in the intent-to-treat population. A significant decrease (> or = 50%) in serum CA 19.9 levels was observed in 3 of 9 evaluable patients. The median time to disease progression was 8 weeks, and the median overall survival was 15 weeks.

Conclusions: The combination of oral celecoxib and 5-FU by protracted i.v. infusion was found to be feasible and well tolerated, and was capable of inducing durable objective responses, even in patients with far advanced, gemcitabine-resistant/refractory PDAC. Further exploration of COX-2 inhibitor/fluropyrimidine combinations is warranted.

Trastuzumab down-regulates Bcl-2 expression and potentiates apoptosis induction by Bcl-2/Bcl-XL bispecific antisense oligonucleotides in HER-2 gene—amplified breast cancer cells.

Milella M., Trisciuoglio D., Bruno T., Ciuffreda L., Mottolese M., Cianciulli A., Cognetti F., Zangemeister-Wittke U., Del Bufalo D., Zupi G.

Clin. Cancer Res., Nov 15;10(22):7747-56, 2004

Purpose: To investigate the possible existence of an antiapoptotic cross-talk between HER-2 and antiapoptotic Bcl-2 family members.

Experimental Design: Bcl-2 and Bcl-XL expression and apoptosis induction were analyzed in HER-2 gene-amplified (BT474) and nonamplified (ZR 75-1) breast cancer cell lines exposed to trastuzumab, alone or in combination with either Bcl-2/Bcl-XL bispecific antisense oligonucleotides (AS-4625) or the small-molecule Bcl-2 antagonist HA14-1.

Results: In addition to HER-2 and epidermal growth factor receptor, trastuzumab down-regulated Bcl-2, but not Bcl-XL, protein, and mRNA expression in BT474 cells. Interestingly, trastuzumab-induced down-regulation of HER-2 and Bcl-2 was also observed in three of five and two of three breast cancer patients undergoing trastuzumab treatment, respectively. Despite Bcl-2 down-regulation, however, trastuzumab only marginally increased the rate of apoptosis (7.3 +/- 3.5%). We therefore investigated whether a combination of AS-4625 and trastuzumab might increase proapoptotic efficiency. AS-4625 treatment of BT474 cells decreased both Bcl-2 and Bcl-XL expression, resulting in a 21 +/- 7% net apoptosis induction; the combination of AS-4625 followed by trastuzumab resulted in a significantly stronger induction of apoptosis (37 +/- 6%, P <0.01) that was not observed with the reverse treatment sequence (trastuzumab followed by AS-4625). Similar results were obtained with the Bcl-2 antagonist HA14-1; indeed, exposure of BT474 cells to HA14-1 followed by trastuzumab resulted in a striking proapoptotic synergism (combination index=0.58 +/- 0.18), as assessed by isobologram analysis.

Conclusions: Altogether our findings suggest that combined targeting of HER-2 and Bcl-2 may represent a novel, rational approach to more effective breast cancer therapy.

Serum angiogenin is not elevated in patients with early B-cell chronic lymphocytic leukemia but is prognostic factor for disease progression.

Molica S., Vitelli G., Levato D., Giannarelli D., Vacca A., Cuneo A., Ribatti D., Digiesi G.

Eur. J. Haematol., Jul;73(1):36-42, 2004

The association between angiogenin and cancer progression and poor outcome in solid tumors has been documented, but its significance in leukemias has not been evaluated. Using an ELISA technique (Quantikine Human Angiogenin Immunoassay; R&D Systems), we measured serum angiogenin levels in 77 previously untreated Binet stage A B-cell chronic lymphocytic leukemia (CLL) patients. No difference in angiogenin serum levels could be found between patients (median: 295 ng/mL; range: 74-1700) and 15 age- and sex-matched healthy controls (median: 264 ng/mL; range: 29-1835) (P = NS; Mann-Whitney test). Increased angiogenin serum level was associated with higher LDH (P = 0.03) and beta2-m (P = 0.007) concentrations. However, angiogenin did not reflect the extent of bone marrow (BM) angiogenesis as evaluated by microvessel area (P = 0.611), circulating levels of vascular endothelial growth factor (VEGF) (P = 0.873) and basic fibroblastic growth factor (FGF-2) (P = 0.421). When the 25 patients with available data were stratified into the four major cytogenetic categories (normal karyotype, 13q as a sole aberration, 12q trisomy, 11q or 17p deletion) and aberrations were compared with angiogenin serum levels, no correlation was found (P = 0.651; Kruskall-Wallis test). A cut-off of angiogenin serum level corresponding to median (i.e. 330 ng/mL) or higher identified later upstaging and longer progression-free survival (PFS). The 5-yr PFS was 51.5% for patients with angiogenin levels lower than median and 85% for patients with higher values [P = 0.03; hazard ratio (HR) = 2.86; 95% CI: 1.08-6.72]. Although in multivariate analysis only Rai substages (P = 0.00001) and peripheral blood lymphocytosis (P = 0.009) retained their prognostic significance, angiogenin could be incorporated into the Rai substages thus leading to the identification of the following risk categories: (i) stage 0 (angionenin >330 ng/mL); (ii) stage 0 (angiogenin <330 ng/mL) + stage I-II (angiogenin >330 ng/mL); and (iii) stage I-II (angiogenin <330 ng/mL). The 40-month PFS were as follows: 85%, 65%, 25% (chi(2) for trend = 6.33; d.f. = 1; P = 0.01). In conclusion, serum angiogenin levels although not increased in comparison with healthy controls, may predict clinical outcome of patients with early CLL and help to refine Rai's stratification.

Phenotypic changes of p53, HER2, and FAS system in multiple normal tissues surrounding breast cancer.

Mottolese M., Nadasi E.A., Botti C., Cianciulli A.M., Merola R., Buglioni S., Benevolo M., Giannarelli D., Marandino F., Donnorso R.P., Venturo I., Natali P.G.

J. Cell. Physiol., Dec 27, 2004

To determine whether phenotypic field changes occur in tissues adjacent to carcinoma, we assayed, by immunohistochemistry, the expression of HER-2, p53, Fas, and FasL in 72 breast cancers (BC) and multiple autologous peritumoral tissues (PTTs) sampled up to 5 cm distance and in 44 benign breast tumors (BBTs). About 5% and 3% of the PTTs and 4.5% and 6.8% of 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 BBTs 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.

Pain syndromes in haematological malignancies: an overview.

Niscola P., Arcuri E., Giovannini M., Scaramucci L., Romani C., Palombi F., Trape G., Morabito F.

Hematol. J., 5(4):293-303, 2004

Several pain syndromes, which may be related to the diagnostic procedures, to the treatments, or to disease itself, may be recorded during the disease course of most haematological malignancies. So far, the painful complication occurring in this setting has been poorly investigated. Pain arising from skeletal and bone marrow (BM) involvement represents the most frequent disease-related painful states observed in this setting, while patients undergoing treatments with curative intent, such as BM transplantation, usually experienced painful stomatitis. Additionally, more than one pathologic process may coexist simultaneously in one patient and the pathophysiology of pain and hypersensitivity may

change over time. An accurate diagnostic assessment and the identification of the underlying pathogenetic mechanism may dictate the treatment approach. For most patients in pain, the World Health Organisation's three-step analgesic scale provides adequate relief with oral options. Pain left unrelieved may induce an aberrant peripheral activity and central functional alterations, generating chronic neuropathic pain. In the aim to summarize the current knowledge on this topic, the pertinent literature and the current guidelines for the pain management were reviewed by a group of haematologists, experienced in palliative care and by a skilled algologist, involved as consultant in this clinical setting.

New Schedules With Taxanes: Experiences Comparison.

NISTICÒ C., BRIA E., CUPPONE F., TERZOLI E.

Suppl. Tumori, Sept-Oct; 90(5):S56-7, 2004

No abstract available

In vitro and in vivo tumor growth inhibition by a p16-mimicking peptide in p16(INK4A)-defective, pRb- positive human melanoma cells.

NOONAN D.M., SEVERINO A., MORINI M., TRITARELLI A., MANENTE L., D'AGNANO I., STARACE G., BALDI A., LOMBARDI D., ALBINI A., FELSANI A., AND PAGGI M.G.

J. Cell. Physiol. DOI 10.1002/jcp.20182, 2004

The cell cycle regulatory pathway responsible for the control of the late-G1 checkpoint is found recurrently altered in human malignant melanoma, often due to lack of functional p16 or pRb (pRb-1) proteins. Here we examined the ability of p16-derived peptides to mimic p16 function in two exemplary human melanoma cell lines: the p16-defective, pRb-positive A375M cells and p16-positive, pRb-defective A2058 cells. The synthetic p16-mimicking peptides strongly induced apoptosis in p16-, pRb+ A375M cells in vitro, while they had significantly less activity on p16+, pRb- A2058 cells. The most active p16-mimicking peptide, p16-AP9, also potently inhibited in vivo growth of the A375M melanoma. Treated tumors showed a threefold smaller volume ($P < 0.025$) and a significant reduction of the mitotic index and of PCNA expression. Growth of A2058 cells in vivo was not affected by treatment with the p16-mimicking peptide. Our results demonstrate that p16-mimicking peptides can induce apoptosis in vitro and that can inhibit tumor growth in vivo in p16-defective, pRb-expressing human melanoma cells, suggesting that p16-mimicking peptides can represent a promising tool for targeted therapy in selected cancer phenotypes.

Ligand-regulated association of ErbB-4 to the transcriptional co-activator YAP65 controls transcription at the nuclear level.

OMEROVIC J., PUGGIONI E.M., NAPOLETANO S., VISCO V., FRAIOLI R., FRATI L., GULINO A., ALIMANDI M.

Exp. Cell. Res., Apr 1;294(2):469-79, 2004

It has been proposed that ligand-dependent Regulated Intramembrane Proteolysis (RIP) of ErbB-4 receptors generates 80 kDa Intra-Cellular Domains (E4.ICDs) that relocate to the nuclear compartments where they implement the signaling abilities of the ErbB-4 receptors. The E4.ICD may directly regulate gene transcription or, in an alternative scenario, the tyrosine kinase activity of E4.ICDs may target proteins involved in transcriptional regulation upon its relocation into the nucleus. We have identified the transcriptional coactivator YAP65, here referred as YAP (Yes Associated Protein), as binding partner of ErbB-4 in a two hybrid screening in yeast. Interaction between YAP and ErbB-4 occurs via the WW domain of YAP and the PPPPY at positions 1297-1301 and the PPPAY at positions 1052-1056 of the amino acid sequence of the Cyt-1 isoform of ErbB-4. Stechiometry of binding is regulated by the ligand-dependent phosphorylation of Tyr 1056 in the PPPAYTPM module that function as "biochemical switch" to decrease the association of YAP to ErbB-4. In principle, this novel interaction highlights new mechanisms of signaling propagation from the ErbB-4 receptors, offering supporting evidences that the E4.ICDs forms released following ligand-receptor engagement may recruit YAP and relocate to the nucleus to implement or regulate transcription.

Synthetic oligopeptides as G1 checkpoint modulators in cancer.

Paggi M.G., And Gelsani A.

Logical Biology, 4(1):68-74, 2004

No abstract available

The involvement of oxidative stress in bovine herpesvirus type 4-mediated apoptosis.

Pagnini U., Montagnaro S., Pacelli F., De Martino L., Florio S., Rocco D., Iovane G., Pacilio M., Gabellini C., Marsili S., Giordano A.

Front. Biosci., Sep 01;9:2106-14, 2004

Bovine herpesvirus type 4 (BHV-4) belongs to the gamma-2-herpesviruses of the Gammaherpesvirinae subfamily. BHV-4 has a worldwide distribution and has been isolated in a variety of clinical diseases as well as from healthy cattle. In this report we demonstrate that BHV-4 induces apoptosis in MDBK cells. In the early phases of apoptosis, cells show an increase in the intracellular level of reactive oxygen species, which is indicative of oxidative stress. This precedes DNA fragmentation, a hallmark typical of apoptosis. Cells were protected from apoptosis only by certain antioxidants (butylated hydroxyanisole and ebselen), whereas N-acetylcysteine turned out to be ineffective. Antioxidants that protected cells from apoptosis prevented oxidative stress but failed to block virus growth. These observations suggest that oxidative stress may be a crucial event in the sequence leading to apoptotic cell death but apoptosis is not required for the multiplication of BHV-4.

Correlations between Phenotype and Microsatellite Instability in HNPCC: Implications for Genetic Testing.

Palmirotta R., Matera S., Curia M.C., Aceto G., El Zhobi B., Verginelli F., Guadagni F., Casale V., Stigliano V., Messerini L., Mariani-Costantini R., Battista P., Cama A.

Fam. Cancer., 3(2):117-21, 2004

Hereditary nonpolyposis colorectal cancer (HNPCC) is widely considered to be a syndrome of defective mismatch repair (MMR). A major concern with genetic diagnosis of HNPCC is the variable, often low, percentage of pathogenic germline mutations that can be detected in MMR genes using common screening methods. The variable percentage of mutation detected is in part related to the sensitivity of conventional screening methods and may also depend on the heterogeneous genetics of HNPCC. Thus, identification of phenotypic criteria predictive of germline mutations in MMR genes may be helpful in efficient HNPCC genetic testing. Clinical diagnostic criteria, initially developed for HNPCC (e.g., Amsterdam I and II, or Bethesda criteria), can be used to clinically select patient candidates that carry germline mutations in MMR genes. More useful criteria were previously developed by analyzing families with germline MMR mutations. Using a complementary approach based on tumor microsatellite instability analysis, we confirm that the Amsterdam criteria are significantly better than the Bethesda criteria in predicting families with MSI-H tumors ($P = 0.0227$). Our results also suggest that a cutoff at < 50 years' mean age at diagnosis of HNPCC-related cancers (especially colorectal and endometrial cancer) may be an additional tool for the identification of families with defective MMR. Recent advances in MMR mutation screening are expected to improve detection of pathogenic MMR mutations in these families. Conversely, the high proportion of MSS tumors observed in our series of families with advanced age at cancer diagnosis is consistent with the low percentage of MMR mutations detected by previous studies in families with this phenotype. These families probably carry mutations in other genes that may or may not be related to MMR. Additional studies are necessary to clarify the molecular basis for HNPCC in families with MSS tumors.

Histone Deacetylase Inhibitors are Potent Radiation Protectants.

Paoluzzi L., Figg W.D.

Cancer Biol. Ther., Jul;3(7):612-3, 2004

Radiation-induced acute and late injuries often represent a limit to the optimal delivery of radiotherapy in cancer patients. Chung et al. reported that histone deacetylase (HDAC) inhibitors, a novel class compound of gene modulators, might have a role in controlling different adverse effects from radiotherapy in preclinical models. They also showed how protection of normal tissues and inhibition of tumor growth might be possible at the same time.

Influence of genetic variants in UGT1A1 and UGT1A9 on the in vivo glucuronidation of SN-38.

Paoluzzi L., Singh A.S., Price D.K., Danesi R., Mathijssen R.H., Verweij J., Figg W.D., Sparreboom A.

J. Clin. Pharmacol., Aug;44(8):854-60, 2004

The uridine diphosphate glucuronosyltransferase (UGT) 1A1 and 1A9 isoforms are involved in the phase II biotransformation of the irinotecan metabolite, SN-38. Recently, several variants in the UGT1A1 and UGT1A9 genes have been described with altered functionality in vitro. The aim of this study was to evaluate the functional consequence of the UGT1A1(TA)(7)TAA (UGT1A1(*)28), UGT1A9 766G>A (D256N; UGT1A9(*)5), and UGT1A9 98T>C (M33T; UGT1A9(*)3) variants in Caucasian patients treated with irinotecan. Pharmacokinetic studies were performed after the first course of irinotecan in 47 males and 47 females. The mean (SD) area under the curves (AUCs) of irinotecan and SN-38 were 20,348 +/- 6466 ng x h/mL and 629 +/- 370 ng x h/mL, respectively, which is in line with earlier findings. For UGT1A9(*)5,novariant alleles were observed, whereas for UGT1A9(*)3, 1 patient with the variant allele was found (allele frequency, 0.633%). The distribution of the UGT1A1(*)28 variant showed 44 wild-type patients (Wt), 37 heterozygotes (Het), and 5 homozygotes (Var). The median AUC ratio of SN-38G to SN-38 was significantly reduced in carriers of the variant UGT1A1(*)28 allele (7.00 [Wt] vs. 6.26 [Het] vs. 2.51 [Var]; p =.022). It is concluded that UGT1A9 functional variants are rare in Caucasians and likely to be clinically insignificant in irinotecan regimens. Screening for the UGT1A1(*)28 polymorphism may identify patients with altered SN-38 pharmacokinetics.

Effect of filgrastim on serum lactate dehydrogenase and alkaline phosphatase values in early breast cancer patients.

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

Cancer Invest., 22(4):650-3, 2004

To improve chemotherapy dose intensity and to optimize the use of granulocyte-colony stimulating factor, 506 patients with early breast cancer were randomly assigned to high dose epirubicin and cyclophospamide (EC) with or without prophylactic subcutaneously filgrastim, according to 5 different schedules: 480 microg or 300 microg daily or every other day, on day 8 through day 14, and 300 microg daily on days 8 and 12 of each chemotherapy course, Serum levels of lactate dehydrogenase (LDH) and alkaline phosphatase (AP) were significantly higher in patients given EC plus filgrastim than EC alone (P = 0.0001), the rate of G1-3 toxicity being 33.4% and 13.1% vs. 1.6% and 1%, respectively. No clinical evidence of filgrastim-related hepatic damage or significant difference in transaminase and gamma-GT elevation was seen between the two groups. LDH and AP closely resembled peripheral blood leukocytes count and increased with increasing leucocytosis, throughout the 5 schedules. Although no patient continued treatment for filgrastim-related side effects, and LDH and AP rises resolved spontaneously within 3 weeks following the chemotherapy course, physicians should be aware of the transient and innocuous change in serum chemistry associated to leucocytosis, since it could be misinterpreted as expression of disease activity.

Variations of telomerase activity in cultured mouse fibroblasts upon proliferation of polyomavirus.

Pastore D., Iacoangeli A., Galati G., Izzo L., Fiori E., Giuliani A., Castelli M., Risuleo G.

Anticancer Res., Mar-Apr;24(2B):791-4, 2004

Telomerase plays a central role in various biological phenomena such as cell differentiation and proliferation, apoptosis, malignant transformation and virus infection, for instance HIV and papillomavirus. In addition, it has recently been shown that, in human fibroblasts transformed by monkey polyomavirus SV40, telomeres became stabilized as a consequence of telomerase activation. However, no information exists on the effects of acute infection by murine polyomavirus on the telomeres maintenance and telomerase activity in the host cell. In this paper we report on a differential activity of telomerase in productively infected cells. The results showed a decreased activity of the enzyme as assessed by the TRAP assay. The decrease had already occurred at a non-lytic time of infection and was observed both after infection and naked DNA transfection. Therefore nuclear decapsidation is not involved in the determination of the phenomenon that is attributed to the proliferation of the virus.

Effects of media information on cancer patients' opinions, feelings, decision-making process and physician-patient communication.

Passalacqua R., Caminiti C., Salvagni S., Barni S., Beretta G.D., Carlini P., Contu A., Di Costanzo F., Toscano L., Campione F.

Cancer, Mar 1;100(5):1077-84, 2004

Background: The objective of the current study was to determine the influence of media information on the opinions and feelings of patients with cancer and to measure the factors that affected the decision-making process and physician-patient communication.

Methods: The study consisted of a sequence of 2 nationwide surveys across the same dynamic target population of 2600 unselected patients with cancer who attended 1 of 13 centers throughout Italy. The authors measured the changes in patients' opinions and attitudes at the peak of a media campaign promoting the Di Bella therapy, an unproven cancer treatment method, and after the publicized demonstration of its ineffectiveness. An identical 10-item questionnaire was used.

Results: Opinions and feelings changed in the two surveys according to the way the media described the efficacy of the treatment, but physician-patient communication and the decision-making process remained unchanged. Multivariate analysis confirmed the enormous influence of the media on patient opinions (odds ratio [OR], 4.67; $P < 0.0001$), feelings of hope (OR, 3.63; $P < 0.0001$), and confusion (OR, 0.51; $P < 0.0001$), but not on physician-patient communication or the decision-making process. Educational level influenced almost all of the studied factors, and communication and decision-making also were influenced by the patients' gender and place of residence. There was no significant correlation with patient age.

Conclusions: The media play a powerful role in affecting patients' opinions and feelings; the physician-patient communication and the decision-making process are not subject to media influence but are related primarily to level of education. The power of the media should be directed toward improving the spread of scientific knowledge to encourage behavioral changes, particularly among individuals with lower levels of education.

Fibre intake and prostate cancer risk.

Pelucchi C., Talamini R., Galeone C., Negri E., Franceschi S., Dal Maso L., Montella M., Conti E., La Vecchia C.

Int. J. Cancer, Mar 20;109(2):278-80, 2004

Dietary fibre has been reported to protect from several neoplasms, but the issue remains controversial. No previous study considered in depth the topic of fibres and prostate cancer. A multicentre case-control study was conducted in Italy from 1991 to 2002, including 1,294 men with incident, histologically confirmed prostate cancer and 1,451 controls admitted to the same network of hospitals as cases with acute nonmalignant conditions. Multivariate odds ratios (OR) and 95% confidence intervals (CI) were obtained after allowance for major identified confounding factors, including total energy intake. Compared to the lowest quintile, the OR of prostate cancer for the highest quintile of total fibre intake was 0.93 (95% CI 0.71-1.22). The risk was inversely related with soluble fibre (OR = 0.89, 95% CI 0.78-1.02, for a difference between 80th and 20th percentile), cellulose (OR = 0.88, 95% CI 0.78-1.01) and vegetable fibre (OR = 0.82, 95% CI 0.73-0.93). These relationships were consistent across strata of age, family history of prostate cancer, body mass index and education. Vegetable fibres appear, therefore, to have a favourable association with prostate cancer risk.

Tissue Doppler imaging in Fabry disease.

Pieroni M., Chimenti C., Russo A., Russo M.A., Maseri A., Frustaci A.

Curr. Opin. Cardiol., Sep;19(5):452-457, 2004

Purpose of review: The development of effective enzyme replacement/enhancement therapy makes of clinical relevance considering Fabry disease in the differential diagnosis of patients with hypertrophic cardiomyopathy. In particular the opportunity to significantly modify the clinical progression of the disease has reinforced the need for early diagnosis of Fabry cardiomyopathy.

Recent findings: The study with tissue Doppler of Fabry patients with endomyocardial biopsy-proven cardiac involvement showed a reduction of both diastolic and systolic myocardial velocities recorded at septal and lateral corners of mitral annulus. Tissue Doppler abnormalities were present not only in patients with left ventricular hypertrophy but also in youn-

ger patients with normal cardiac wall thickness and represent the first sign of myocardial damage. Furthermore tissue Doppler studies have been shown useful in detecting cardiac involvement in female carriers with no systemic manifestations of Fabry disease. In patients already submitted to enzyme-replacement therapy tissue Doppler and strain rate imaging represent useful noninvasive tools in assessing treatment efficacy.

Summary: Tissue Doppler imaging can provide early detection of cardiac involvement in Fabry disease and represents the most accurate and sensitive noninvasive tool for the diagnosis of myocardial dysfunction and for the assessment of cardiac improvement during enzyme replacement therapy. The detection of tissue Doppler abnormalities in female carriers may represent a hint for an invasive assessment of cardiac involvement.

Role of P53 and Bcl-2 in advanced rectal carcinomas treated with adjuvant therapy.

PIPERNO G., COSIMELLI M., PERRONE D.R., MANCINI R., BUGLIONI S., NOVELLI F., SPERDUTI I., ZERBINI V., GARUFI C., MOTTOLESE M.

J. Chemother., Nov;16 Suppl 5:11-4, 2004

Rectal adenocarcinomas is usually associated to a poorer outcome than colon cancers. In this study we analyzed the impact on overall survival of p53 and Bcl-2, evaluated by immunohistochemical techniques, in 126 advanced rectal cancer patients submitted to 5 fluorouracil based adjuvant therapy. Shorter overall survival was observed in patients bearing p53 positive and Bcl-2 negative tumors, although in multivariate analysis only p53 emerged as independent predictor of a worse outcome. These results seem to indicate that, in stage III-IV rectal cancer, p53 alterations may identify high risk patients to be enrolled in more aggressive and/or innovative adjuvant/neoadjuvant treatments.

Unilateral limited laminectomy as the approach of choice for the removal of thoracolumbar neurofibromas.

POMPILI A., CAROLI F., CATTANI F., CRECCO M., GIOVANNETTI M., RAUS L., TELERA S., VIDIRI A., OCCHIPINTI E.

Spine, Aug 1;29(15):1698-702, 2004

Study design: The paper reports a minimally invasive approach to the dorsolumbar spine for the removal of neurofibromas.

Objectives: Demonstrating that a limited unilateral approach is the one of choice for this kind of tumors.

Summary of Background Data: Spinal intradural extramedullary tumors are generally removed by single-level or multilevel laminectomy with midline dural incision. Cases of delayed postoperative kyphosis and spinal instability (6%) may be reduced by unilateral microsurgery, causing minimum damage to ligaments and joints.

Methods: Ten patients with dorsolumbar neurofibroma were operated on between June 2000 and June 2002. There were 5 males (all with lumbar) and 5 females (2 with lumbar and 3 with inferior dorsal neurofibromas). One female had 3 lumbar tumors and required two operations. Surgery was performed in the prone position with a unilateral approach, sparing the joint and the ligamentum interspinosum. The dura was opened paramedially and the tumor dissected from the root and removed in one piece when possible. Water-tight dural closure was done with 5-0 or 6-0 stitches.

Results: All the patients were mobilized on day 2 and discharged on day 4 or day 5. No complications resulting from the technique were observed. Static and dynamic plain radiograph films showed that none of them had kyphosis and/or instability 6 months postoperatively. Neurologic results were good.

Conclusions: Hospital stay may be reduced and stability may be preserved with an appropriate microsurgical technique. The technique reported in the paper should thus become the one of choice and extended to other spinal intradural extramedullary tumors.

Discrimination of single amino acid mutations of the p53 protein by means of deterministic singularities of recurrence quantification analysis.

PORRELLO A., SODDU S., ZBILUT J.P., CRESCENZI M., GIULIANI A.

Proteins, May 15;55(3):743-55, 2004

p53 is mutated in roughly 50% of all human tumors, predominantly in the DNA-binding domain codons. Structural, biochemical, and functional studies have reported that the different p53 mutants possess a broad range of behaviors that include the elimination of the tumor-suppression function of wild-type protein, the acquisition of dominant-negative function over the wild-type form, and the establishment of gain-of-function activities. The contribution of each of these types of mutations to tumor progression, grade of malignancy, and response to anticancer treatments has been so far analyzed only for a few "hot-spots." In an attempt to identify new approaches to systematically characterize the complete spectrum of p53 mutations, we applied recurrence quantification analysis (RQA), a non-linear signal analysis technique, to p53 primary structure. Moving from the study of the p53 hydrophobicity pattern, which revealed important similarities with the singular deterministic structuring of prions, we could statistically discriminate, on a pure amino acid sequence basis, between experimentally characterized DNA-contact defective and conformational p53 mutants with a very high percentage of success. This result indicates that RQA is a mathematical tool particularly advantageous for the development of a database of p53 mutations that integrates epidemiological data with structural and functional categorizations.

Pet models in cancer research: general principles.

PORRELLO A., CARDELLI P., SPUGNINI E.P.

J. Exp. Clin. Cancer Res., Jun;23(2):181-93, 2004

Oncology has made great advancements in the past 50 years, moving from preliminary to complex studies and developing in the process numerous models. An important function in this development has been played by animal investigations that have displayed many aspects of cancer and led to the discovery of new therapies. Nevertheless, the debate about preclinical "tools" suited to predict efficacy as well as side effects of anticancer compounds and treatments is open. In this review we focus on the role of pet models in cancer research, whose continuously increasing importance is due to the disclosure of striking histopathological, anatomical, genetical, and biomolecular similarities among feline, canine, and human tumors. Remarkably, the improvement of clinical condition of companion animals, obtained by their enrolment in cancer trials, is generally perceived as an added value for the whole society. In the first paragraphs we examine crucial ethical, clinical, and financial issues that make up the framework of this area of translational research. Then we illustrate the new figures of researchers, namely experts in laboratory-clinic interface, who are needed in this field, and describe the relevant potentialities of pet cancer registries and genome projects. In the conclusions are summarized the principal arguments that support the adoption of pet models in tumor studies.

The desidere for motherhood and fatherhood.

PUGLIESE P., PERRONE M., GARUFI C., MAGGI G., CONDOLEO M.F.

Tumori, 3(3):10-13,2004

No abstract available

Survival of elderly patients with acute myeloid leukemia.

PULSONI A., PAGANO L., LATAGLIATA R., CASINI M., CERRI R., CRUGNOLA M., DE PAOLI L., DI BONA E., INVERNIZZI R., MARMONT F., PETTI M.C., RIGOLIN G., RONCO F., ET AL.

Haematologica, Mar;89(3):296-302, 2004

Background and objectives: The prognosis of elderly patients with acute myelogenous leukemia (AML) is usually dismal, while the true survival of older patients not included in clinical trials is not known. We retrospectively evaluated the impact on survival of an aggressive versus a non-aggressive approach in 1005 patients aged >60 years registered in the database of the GIMEMA cooperative group.

Design and methods: Group A patients (n=621) received aggressive treatment, while group B patients (n=384) underwent non-aggressive therapy. The groups were different for risk factor distribution: the patients in group B had a higher median age, worse performance status (PS) and a higher proportion of previous myelodysplastic disease.

Results: The overall median survival was 7 and 5 months in groups A and B, respectively (p min of 0.0001). At multivariate analysis the following factors were associated with a significantly shorter survival: age >71 years (RR=1.27; 95% CI=1.07-1.50), PS=2-4 (RR=1.44; 95% CI=1.24-1.68), white cell count > 10,000 mL (RR=1.37; 95% CI=1.06-1.75), and heart dysfunction requiring treatment (RR=1.26; 95% CI=1.05-1.50). No difference in survival was associated with aggressive or non-aggressive treatment (RR=1.1; 95% CI=0.94-1.32). Patients aged min of 70 years, with no heart disease, but a white cell count > 10,000/mL showed a significantly better survival when treated aggressively (median survival 7 vs 3 months, p = 0.011).

Interpretation and conclusions: Despite an obvious selection of patients with a worse prognosis in group B, the difference in survival between the two groups was marginal. Multivariate analysis failed to demonstrate a significant survival benefit in aggressively treated patients. All these considerations indicate that elderly patients with AML are overall unlikely to benefit from aggressive treatment, so that this should be offered only to selected patients.

Salvage chemotherapy with temozolomide in primary CNS lymphomas: preliminary results of a phase II trial.

Reni M., Mason W., Zaja F., Perry J., Franceschi E., Bernardi D., Dell'oro S., Stelitano C., Candela M., Abbadessa A., Pace A., Bordonaro R., Latte G.,Villa E., Ferreri A.J.

Eur. J. Cancer, Jul;40(11):1682-8, 2004

Background: This study evaluates the maximum tolerated dose (MTD) and activity of mitomycin, docetaxel, and irinotecan (MDI) regimen on metastatic pancreatic adenocarcinoma, previously treated with gemcitabine-containing chemotherapy.

Patients and methods: Patients with less than 76 years, Karnofsky performance status > or = 60, and adequate bone marrow, kidney, and liver function were eligible for this trial. Treatment consisted of mitomycin 6 mg/m2 day 1, docetaxel and irinotecan on days 2 and 8 with escalating doses, every 4 weeks. Dose levels were level 1:30 and 70 mg/m2; level 2:30 and 100 mg/m2; level 3:30 and 85 mg/m2; and level 4:35 and 85 mg/m2. Dose-limiting toxicity (DLT) was defined as grade 4 neutropenia > 7 days, febrile neutropenia, grade 4 thrombocytopenia, nausea and vomiting, or diarrhea, grade > or = 3 non-hematological toxicity, or failure to recover to grade < or = 1 toxicity by day 43, occurring during the first cycle of chemotherapy.

Results: Between September 2001 and October 2002, 15 eligible patients, three of whom had been previously treated with two lines of chemotherapy, received 33 cycles of MDI. Toxicity consisted of grade 3 to 4 neutropenia in 23% of cycles, fatigue, diarrhea, and vomiting in 10% of cycles, and one toxic death. DLT was observed in 2 of 6 level 2 patients (one toxic death and one grade 3 fatigue), and 2 of 3 level 4 patients (one neutropenic fever and one grade 3 fatigue). Thirteen patients were assessable for response. No objective response was observed among patients treated with MTD or higher doses. Three patients had stable disease; all other patients had progressive disease. The median time to tumor progression and median survival was 1.7 and 6.1 months, respectively.

Conclusion: The MTD was mitomycin 6 mg/m2 day one, and docetaxel 30 and irinotecan 85 mg/m2 days 2 and 8. This regimen is inactive in metastatic pancreatic cancer.

Apoptosis susceptibility and cell-cycle distribution in cells from myelodysplastic syndrome patients: modulatory in-vitro effects of G-CSF and interferon-alpha.

Ricciardi M.R., Petrucci M.T., Gregorj C., Martini V., Levi A., De Cuia M.R., Latagliata R., Petti M.C., Mandelli F., Foa R., Tafuri A.

Leuk. Lymphoma, Jul;45(7):1437-43, 2004

Susceptibility to apoptosis varies in different forms of myelodysplastic syndromes (MDS). Our in vitro study aimed at better defining the cell kinetic profile by investigating whether G-CSF and interferon-alpha (IFNalpha) were capable of controling apoptotic/proliferative mechanisms in RAEB as well as in RAEB-t forms. Apoptosis and cell-cycle distribution were measured in mononuclear and in CD34+ cells from bone marrow samples of 27 MDS patients with RAEB (n = 15) and RAEB-t (n = 12). In selected samples, the in vitro influence of G-CSF and lymphoblastoid (Ly)-IFNalpha on the apoptotic susceptibility and on the cell kinetics of the above MDS populations was evaluated.

RAEB samples showed a significantly greater apoptosis than RAEB-t ones, both in mononuclear cells (14.76%+/-8.73 vs. 5.95%+/-3.88, P= 0.0058) and in CD34+ cells (24.66%+/-16.08 vs. 3.96%+/-2.57, P = 0.0007). Short-term cell culture in the presence of G-CSF reduced apoptosis in CD34+ cells in all 4 RAEB samples tested (39.1%+/-40.7 vs. 21.0%+/-23.5, P = n.s.); the percentage of cells in S-phase significantly increased in 3/4 samples (19.90%+/-4.40 vs. 32.40%+/-7.85, P = 0.03). Ly-IFNalpha protected CD34+ cells from apoptosis in 3/4 RAEB samples (25.7%+/-8.06 vs. 10.9%+/-8.8, P = n.s.), but did not modulate cell-cycle distribution. G-CSF and Ly-IFNalpha failed to affect apoptosis and proliferation in RAEB-t. These observations indicate that in RAEB forms increased apoptosis can be efficiently counteracted in most of the samples by both G-CSF and Ly-IFNalpha, suggesting that only in these forms a retained regulatory mechanism on the apoptotic/ proliferative balance may allow therapeutic intervention with apoptotic regulators.

Adjuvant medical therapy in NSCLC.

RINALDI M.

Suppl. Tumori, Mar-Apr;3(2):S45-6, 2004

No abstract available

Analysis of p73 expression pattern in acute myeloid leukemias: lack of DeltaN-p73 expression is a frequent feature of acute promyelocytic leukaemia.

RIZZO M.G., GIOMBINI E., DIVERIO D., VIGNETTI M., SACCHI A., TESTA U., LO-COCO F., BLANDINO G.

Leukemia, Nov;18(11):1804-9, 2004

p73, the homologue of p53, is a nuclear protein whose ectopic expression, in p53+/+ and p53-/- cells, recapitulates the most well-characterized p53 effects, such as growth arrest, apoptosis and differentiation. Unlike p53, which is mutated in half of human cancers, p73 is rarely mutated. However, altered expression of the p73 gene has been reported in neuroblastoma, lung cancer, prostate cancer and renal cell carcinoma. To investigate the potential involvement of p73 in acute myeloid leukemias (AMLs), we analyzed 71 samples from AML patients for the expression pattern of N-terminal transactivation-p73alpha (TA-p73alpha), its spliced isoforms and N-terminal-deleted-p73 transcripts (DeltaN-p73). We detected p73 gene expression in AML irrespective of FAB (French-American-British) subtypes. Notably, the analysis of DeltaN-p73 expression, which has been reported to inactivate both p53 and p73 antitumor effects, revealed a rather peculiar pattern. In fact, DeltaN-p73 transcript and protein were detectable in 27/28 (96.4%) cases of M0, M1, M2, M4, M5 and M6 AML and in 13/41 (31.7%) cases of PML-RARalpha-positive M3 AML (P<0.01). Thus, the distinct gene expression profile of p73 further supports the notion that acute promyelocytic leukemia is a biologically different subset of AML.

Transferring scientific evidence to oncological practice: a trial on the impact of three different implementation strategies on antiemetic prescriptions.

ROILA F., AND THE ITALIAN GROUP FOR ANTIEMETIC RESEARCH (FABI A.)

Support. Care Cancer, Jun;12(6):446-53, 2004

Goals: In 1996, a gap between the literature evidence for the prevention of chemotherapy-induced emesis and the prescription pattern in clinical practice was demonstrated in a drug utilization study. This study, carried out in 103 Italian oncological centers (77 new; 26 old that participated in the previous study) evaluates three different intervention strategies to implement these guidelines.

Patients and methods: In cancer patients submitted to chemotherapy, prescriptions of antiemetics were prospectively monitored for 2 consecutive weeks in 1999. Simple diffusion of guidelines was evaluated in an observational study in the 77 new centers, while the double combination of simple diffusion and "audit and feedback" strategy was randomly compared in the old centers with the triple combination of the same two strategies plus an "educational outreach visit".

Main Results: Simple diffusion of guidelines improved the prescription but only for acute and delayed emesis induced by high-moderate emetogenic chemotherapy. No significant difference was detected in the prescriptions against cisplatin-induced emesis. The inappropriate use of

5-HT(3) antagonists for prophylaxis of low emetogenic chemotherapy was found most frequently. Similar poor results were achieved by the audit and feedback strategy, while the educational outreach visit significantly increased the prescription of the optimal prophylaxis for cisplatin-induced acute and delayed emesis.

Conclusions: A combination of interventions, including an educational outreach visit, seems to be a good strategy for transferring the results of antiemetic research to oncological practice.

Therapeutic targeting of the endothelin-A receptor in human ovarian cancinoma: efficacy of cytotoxic agents is markedly enhanced by co-administration with Atrasentan.

ROSANÒ L., SPINELLA F., DI CASTRO V., NATALI P.G., BAGNATO A.

J. Cardiovasc. Pharmacology 44(1):S132-S135, 2004

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.

Endothelin-B receptor blockade inhibits molecular effectors of melanoma cell progression.

ROSANÒ L., SPINELLA F., GENOVESI G., DI CASTRO V., NATALI P.G., BAGNATO A.

J. Cardiovasc. Pharmacology 44 (1): S136-S139, 2004

Phenotypic and genotypic analyses of cutaneous melanoma have identified the endothelin B receptor (ET(B)R) as tumor progression marker, thus representing a potential therapeutic target. Here, we demonstrate that activation of ET(B)R by endothelin-1 (ET-1) and ET-3 leads to loss of expression of the cell adhesion molecule E-cadherin and associated catenin proteins and gain of N-cadherin expression. Exposure of melanoma cells to ET-1 leads to a 60% inhibition in intercellular communication by inducing phosphorylation of gap junctional protein connexin 43. Additionally, activation of the ET(B)R pathway increases alpha(v)beta(3) and alpha(2)beta(1) integrin expression and matrix metalloproteinase (MMP)-2 and MMP-9, membrane type-1-MMP activation, and tissue inhibitor MMP-2 secretion. The ET(B)R pathway results into the downstream activation of focal adhesion kinase and extracellular signal-regulated kinase 1/2 signaling pathways, which lead to enhanced cell proliferation, adhesion, migration, and MMP-dependent invasion. The small molecule A-192621, an orally bioavailable nonpeptide ET(B)R antagonist, significantly inhibits melanoma growth in nude mice. These findings demonstrate that ET-1 and ET-3 through ET(B)R activation trigger signaling pathways involved in events associated with disruption of normal host-tumor interactions and progression of cutaneous melanoma. Pharmacological interruption of ET(B)R signaling may represent a novel therapeutic strategy in the treatment of this malignancy.

Soluble CD40 ligand plasma levels in lung cancer.

ROSELLI M., MINEO T.C., BASILI S., MARTINI F., MARIOTTI S., ALOE S., DEL MONTE G., AMBROGI V., SPILA A., PALMIROTTA R., D'ALESSANDRO R., DAVI G., GUADAGNI F., FERRONI P.

Clin. Cancer Res., Jan 15;10(2):610-4, 2004

Purpose: Tumor-induced platelet activation may cause the release of various cytokines, including CD40 ligand (CD40L). Activation of the CD40/CD40L pathway in human tumors may result in thrombin generation, which is known to be involved in angiogenesis. Thus, we investigated whether soluble (s)CD40L levels are increased in patients with lung cancer as a result of platelet and/or coagulation activation.

Experimental design: Citrated plasma samples were obtained from 120 patients with different stages and histotypes of lung cancer and 60 age- and sex-matched control subjects. sCD40L, sP-selectin (marker of platelet activation), prothrombin fragment 1 + 2, and thrombin-antithrombin III complex levels (both markers of coagulative activation) were measured in all samples.

Results: Patients with lung cancer had median sCD40L levels higher than in control subjects (0.46 versus 0.13 ng/ml; $P < 0.0001$), although correlation with the stage of disease was not evident. Nonetheless, sCD40L levels were significantly higher in squamous cancer compared with adenocarcinoma (0.75 versus 0.27 ng/ml; $P < 0.05$). Moreover, median sCD40L levels were higher in stage IV compared with nonmetastatic squamous lung cancer (1.02 versus 0.61 ng/ml; $P < 0.05$). sCD40L levels significantly correlated with sP-selectin ($P < 0.001$), prothrombin fragment 1 + 2 ($P < 0.001$), or thrombin-antithrombin III complex ($P < 0.05$) in squamous lung cancer, but only sP-selectin ($P = 0.011$) was independently related to sCD40L.

Conclusions: These findings indicate that elevated sCD40L levels can be preferentially found in patients with advanced squamous cancer and provide evidence that increased levels of this cytokine are associated to the occurrence of in vivo platelet activation.

Mandibular reconstruction with frozen autologous mandibular bone and radial periosteal fasciocutaneous free flap: preliminary report.

ROSELLI R., MUSCATELLO L., VALDATTA L., PAVAN G., SPRIANO G.

Ann. Otol. Rhinol. Laryngol., Dec;113(12):956-60, 2004

The authors present a new method of mandibular reconstruction with frozen autologous mandibular bone. Vascular supply to the neomandible is ensured by the periosteal layer of a microvascular radial periosteal fasciocutaneous free flap, placed so as to envelop the bone and cover the surgical defect. The use of the periosteal layer of the radius to provide new blood vessels to the frozen mandible is an original technical feature that we describe. We describe 2 cases of oral carcinoma involving the mandible, treated with mandibular resection and reconstruction. This technique allows good functional and aesthetic results, avoiding more serious complications related to the use of composite free flaps harvested from distant anatomic donor sites.

Hyperthermic intraperitoneal intraoperative chemotherapy after cytoreductive surgery for the treatment of abdominal sarcomatosis: clinical outcome and prognostic factors in 60 consecutive patients.

ROSSI C.R., DERACO M., DE SIMONE M., MOCELLIN S., PILATI P., FOLETTO M., CAVALIERE F., KUSAMURA S., GRONCHI A., LISE M.

Cancer, May 1;100(9):1943-50, 2004

Background: Abdominal sarcomatosis is a rare nosologic entity with a poor prognosis. After a Phase I study on cytoreductive surgery combined with hyperthermic intraperitoneal intraoperative chemotherapy (HIIC), the authors reported the results of the treatment of 60 patients using this novel multimodal approach.

Methods: Twenty-nine patients had multifocal primary disease and 31 patients had recurrent abdominal sarcoma. Tumor histology was represented by visceral (n = 26 [43%]) and retroperitoneal (n = 34 [57%]) sarcoma. All patients underwent cytoreductive surgery (with no or minimal residual disease) and 90-minute HIIC with doxorubicin (15.25 mg/L of perfusate) and cisplatin (43 mg/L). The clinical outcome and the prognostic value of 11 clinicopathologic variables were analyzed.

Results: No postoperative deaths occurred. The morbidity rate was 33% and the moderate to severe locoregional toxicity rate was 15%. The median time to local disease progression and the median overall survival were 22 months and 34 months, respectively. Using multivariate analysis, histologic grading and completeness of surgical cytoreduction predicted patient prognosis,

indicating that both local progression-free and overall survival were affected significantly by tumor aggressiveness and local disease control.

Conclusions: Although these results were encouraging, there was no definitive conclusion reached regarding the therapeutic activity of this locoregional treatment. In addition, the toxicity rate was substantial. In the absence of effective systemic agents, the therapeutic potential of cytoreductive surgery plus HIIC should be explored further in comparative trials.

Meta-analysis of neoadjuvant chemotherapy in locally advanced bladder cancer.

RUGGERI E.M.

Suppl. Tumori, Jul-Aug;3(4):S55-6, 2004

No abstract available

Testis Metastasis As An Initial Manifestation Of An Occult Gastrointestinal Cancer.

SALESI N., FABI A., DI COCCO B., MARANDINO F., PIZZI G., VECCHIONE A., COGNETTI F.

Anticancer Res. 2004 Mar-Apr;24(2C):1093-6.

Metastatic epithelial malignant tumor involving the spermatic cord and epididymis is rare and the prognosis of these patients is poor. Usually gastrointestinal cancers show diffusion to liver, lung and bone. Several routes by which a colorectal cancer can metastasize to the testis have been reported in literature. Herein we report a case of an occult gastrointestinal cancer with an intrascrotal metastasis in an adult patient with possible spread through the spermatic veins due to primary intestinal carcinoma. In the case of a testicular mass or hydrocele evidence in a patient with an unusual age for primary testis tumor, a diagnosis of metastatic cancer should be considered.

Benign hilar stenosis mimicking Klatskin tumor.

SANTORO R., SANTORO E., ETTORRE G.M., NICOLAS C., SANTORO E.

Ann. Chir., Jun;129(5):297-300, 2004

Preoperative diagnosis of hilar carcinoma (Klatskin tumor) is usually done according to the only clinical and imaging findings. However, in 5-15% of patients operated with this diagnosis, hilar stenosis is an inflammatory pseudo-tumoral benign one. We reported the case of a patient who underwent resection of common bile duct for suspicion of hilar carcinoma in whom, despite clinical and imaging findings highly suggestive of malignancy, pathologic examination revealed aspecific cholangitis. After a review of the literature, we conclude that resection of common bile duct is mandatory to exclude malignancy and allows excellent biliary drainage. Associated major hepatectomy should ideally be indicated, due to its higher risks, after pathological confirmation of cholangiocarcinoma, if necessary by frozen section.

Loss of tyrosinase activity confers increased skin tumor susceptibility in mice.

SARAN A., SPINOLA M., PAZZAGLIA S., PEISSEL B., TIVERON C., TATANGELO L., MANCUSO M., COVELLI V., GIOVANNELLI L., PITOZZI V., PIGNATIELLO C., MILANI S., DOLARA P., DRAGANI T.A.

Oncogene, May 20;23(23):4130-5, 2004

The tyrosinase (Tyr) gene encodes the enzyme tyrosinase that catalyses the conversion of L-tyrosine into DOPA (3,4-dihydroxyphenylalanine)-quinone. The albino mutation abrogates functional activity of tyrosinase resulting in deficiency of melanin pigment production in skin and retina. Tyr maps to a region in the central position of Chromosome 7 that contains a skin tumor-modifier locus. We rescued the albino mutation in transgenic mice to assess a possible role of Tyr gene in two-stage skin carcinogenesis. Transgenic expression of the functional Tyr(Cys) allele in albino mice (Tyr(Ser)) caused a reduction in skin papilloma multiplicity, in four independent experiments and at three dose levels of DMBA (9,10-dimethyl-1,2-benzanthracene). In vitro mechanistic studies demonstrated that transfection of the Tyr(Cys) allele in a human squamous cell carcinoma cell line (NCI-H520) increases tyrosinase enzyme activity and confers resistance to hydrogen peroxide-induced oxidative DNA damage. These results provide direct evidence that the Tyr gene can act as a skin cancer-modifier gene, whose mechanism of action may involve modulation of oxidative DNA damage.

Trichomonas vaginalis degrades nitric oxide and expresses a flavorubredoxin-like protein: a new pathogenic mechanism?

SARTI P., FIORI P.L., FORTE E., RAPPELLI P., TEIXEIRA M., MASTRONICOLA D., SANCIU G., GIUFFRE A., BRUNORI M.

Cell. Mol. Life Sci., Mar;61(5):618-23, 2004

Besides possessing many physiological roles, nitric oxide (NO) produced by the immune system in infectious diseases has antimicrobial effects. Trichomoniasis, the most widespread non-viral sexually transmitted disease caused by the microaerophilic protist Trichomonas vaginalis, often evolves into a chronic infection, with the parasite able to survive in the microaerobic, NO-enriched vaginal environment. We relate this property to the finding that T. vaginalis degrades NO under anaerobic conditions, as assessed amperometrically. This activity, which is maximal (133 +/- 41 nmol NO/10(8) cells per minute at 20 degrees C) at low NO concentrations (< or = 1.2 microM), was found to be: (i) NADH dependent, (ii) cyanide insensitive and (iii) inhibited by O(2). These features are consistent with those of the Escherichia coli A-type flavoprotein (ATF), recently discovered to be endowed with NO reductase activity. Using antibodies against the ATF from E. coli, a protein band was immunodetected in the parasite grown in a standard medium. If confirmed, the expression of an ATF in eukaryotes suggests that the genes coding for ATFs were transferred during evolution from anaerobic Prokarya to pathogenic protists, to increase their fitness for the microaerobic, parasitic life style. Thus the demonstration of an ATF in T. vaginalis would appear relevant to both pathology and evolutionary biology. Interestingly, genomic analysis has recently demonstrated that Giardia intestinalis and other pathogenic protists have genes coding for ATFs.

The interruption of a study following an "ad interim" analysis. The example of the NSABP-P1 study.

SAVARESE A.

Suppl. Tumori, Jul-Aug;3(4):S23-4, 2004

No abstract available

Fatty acid synthase is a marker of increased risk of recurrence in endometrial carcinoma.

SEBASTIANI V., VISCA P., BOTTI C., SANTEUSANIO G., GALATI G.M., PICCINI V., CAPEZZONE DE JOANNON B., DI TONDO U., ALO P.L.

Gynecol. Oncol., Jan;92(1):101-5, 2004

Background: We explored the expression of Fatty Acid Synthase (FAS) in lung carcinomas and its association with clinico-pathological features and prognosis. FAS is a recently discovered molecule involved in the energy supply of normal cells. FAS is also overexpressed in neoplastic tissues because of their increased necessity for energy.

Patients and methods: One hundred and six patients with non-small cell lung carcinoma were followed-up for an average period of 5 years. FAS expression was detected immunohistochemically.

Results: FAS staining was observed in 61 out of 106 cases (57.54%). Statistical analysis revealed that FAS had an overall low prognostic value ($p = 0.14$), while FAS-negative expression in stage I patients showed a trend for better survival ($p = 0.10$). PTNM stage ($p < 0.0001$) was the only significant prognostic marker for overall survival.

Conclusion: FAS is a reliable marker of low-stage clinically aggressive lung carcinomas. The determination of FAS expression in lung carcinomas may stratify patients and determine therapeutic approaches for their care.

RACK1 is a functional target of the E1A oncoprotein.

SEVERINO A., BALDI A., COTTONE G., HAN M., SANG N., GIORDANO A., MILEO A.M, PAGGI M.G., DE LUCA A.

J. Cell. Physiol., Apr;199(1):134-9, 2004

The adenoviral E1A proteins have been implicated in promotion of proliferation and transformation, inhibition of differentiation, induction of apoptosis, regulation of transcription, and suppression of tumor growth. The ability of E1A to override the fundamental controls of host cells is based on its ability to physically interact with several cellular proteins. We recently characterized RACK1 as a new E1A-interacting protein. In this report, we show that the extreme N-terminal region of E1A, spanning from ami-

noacids 1-36, and the conserved WD regions of RACK1 are responsible for this interaction. We also demonstrate that E1A and RACK1 colocalize at the perinuclear membrane in the cells. Furthermore, we provide evidence that E1A is able to antagonize the inhibitory effects of RACK1 on Src activity. These results suggest that RACK1 signaling pathway may be a functional target of E1A, contributing to E1A oncogenic effect in the host cells.

Endothelin-1 could be one of the targets of psoriasis therapy.

SIMEONE P., TESON M., LATINI A., CARDUCCI M., VENUTI A.

Br. J. Dermatol., Dec;151(6):1273-5, 2004

No abstract available

Vaccination with a synthetic nonapeptide expressed in human tumors prevents colorectal cancer liver metastases in syngeneic rats.

SINIBALDI VALLEBONA P., RASI G., PIERIMARCHI P., BERNARD P., GUARINO E., GUADAGNI F., GARACI E.

Int. J. Cancer, May 20;110(1):70-5, 2004

In previous studies, the antigen CSH-275 (RTNKEASIC) was found expressed in tissue specimens from colorectal cancer but not in normal colonic mucosa. It was also naturally expressed in the DHD-K12 experimental colorectal cancer in BDIX rats. In this study, we describe the effect of vaccination with the synthetic nonapeptide CSH-275 in preventing tumor growth in a model closely mimicking the clinical situation of liver metastases, after surgical resection of primary colorectal cancer. A vaccination protocol using CSH-275, conjugated with complete or incomplete Freund's adjuvant, was carried out to determine the effect in preventing the progression of liver metastases induced by DHD-K12 cells injected in the splenic vein (preventive vaccine). An additional vaccination procedure was carried out to determine the effect on s.c. tumor growth (therapeutic vaccine). A significant improvement in survival along with the prevention of liver metastases formation and reduced growth of s.c. tumor were observed. CSH-275 vaccination resulted in a significant increase in CTL activity against autologous DHD-K12 cells in DHD-K12 tumor-bearing rats and the generation of a CTL response against DHD-K12 cells in DHD-K12 naive rats. Vaccination also induced massive infiltration of CD8(+) cells in tumor. These results demonstrate that CSH-275 is a new molecular target for colorectal cancer immunotherapy; it is also an excellent candidate for preclinical studies because it is naturally expressed on tumors in a fully competent syngeneic animal, which reproduces the clinical pattern of cancer progression.

Small hyperechogenic nodules in thyroiditis: usefulness of cytological characterization.

SOLIVETTI F.M., BACARO D., CECCONI P., BALDELLI R., MARANDINO F.

J. Exp. Clin. Cancer Res., Sep;23(3):433-5, 2004

Small hyperechogenic nodules occurring in thyroiditis frequently raise the question of their nature requiring additional evaluation. Given the scarcity of the studies addressing this issue, we have investigated whether cytopathological analysis of fine needle aspirates (FNA) of these lesions may be of diagnostic relevance. In this preliminary study, we submitted to cytopathological analysis 10 nodular lesions as well as the normal counter-lateral tissue. In none but one of the cases analyzed, the cytopathology was able to detect differences between the hyperechogenic models and the hypoechogenic parenchyma suggesting that these lesions bear no-clinical relevance. Therefore, FNA of these nodules is not advisable and should be limited to those with defined at risk clinical features.

Endothelin-1-induced prostaglandin E2-EP2,EP4-signaling regulates vascular endothelial growth factor production and ovarian carcinoma cell invasion.

SPINELLA F., ROSANO L., DI CASTRO V., NATALI P.G., BAGNATO A.

J. Biol. Chem., Nov 5;279(45):46700-5, 2004

Cyclooxygenase (COX)-1- and COX-2-derived prostaglandins are implicated in the development and progression of several malignancies. We have recently demonstrated that treatment of ovarian carcinoma cells with endothelin-1 (ET-1) induces expression of both COX-1 and COX-2, which contributes to vascular endothelial growth factor (VEGF) production. In this study, we show that in HEY and OVCA 433 ova-

rian carcinoma cells, ET-1, through the binding with ETA receptor (ETAR), induces prostaglandin E2 (PGE2) production, as the more represented PG types, and increases the expression of PGE2 receptor type 2 (EP2) and type 4 (EP4). The use of pharmacological EP agonists and antagonists indicates that ET-1 and PGE2 stimulate VEGF production principally through EP2 and EP4 receptors. At the mechanistic level, we prove that the induction of PGE2 and VEGF by ET-1 involves Src-mediated epidermal growth factor receptor transactivation. Finally, we demonstrate that ETAR-mediated activation of PGE2-dependent signaling participates in the regulation of the invasive behavior of ovarian carcinoma cells by activating tumor-associated matrix metalloproteinase. These results implicate EP2 and EP4 receptors in the induction of VEGF expression and cell invasiveness by ET-1 and provide a mechanism by which ETAR/ET-1 can promote and interact with PGE2-dependent machinery to amplify its proangiogenic and invasive phenotype in ovarian carcinoma cells. Pharmacological blockade of ETAR can therefore represent an additional strategy to control PGE2 signaling, which has been associated with ovarian carcinoma progression.

Inhibition of cyclooxygenase-1 and -2 expression by targeting the endothelin a receptor in human ovarian carcinoma cells.

Spinella F., Rosano L., Di Castro V., Nicotra M.R., Natali P.G., Bagnato A.

Clin. Cancer Res., Jul 15;10(14):4670-9, 2004

Purpose and experimental design: New therapies against cancer are based on targeting cyclooxygenase (COX)-2. Activation of the endothelin A receptor (ET(A)R) by endothelin (ET)-1 is biologically relevant in several malignancies, including ovarian carcinoma. In this tumor, the ET-1/ET(A)R autocrine pathway promotes mitogenesis, apoptosis protection, invasion, and neoangiogenesis. Because COX-1 and COX-2 are involved in ovarian carcinoma progression, we investigated whether ET-1 induced COX-1 and COX-2 expression through the ET(A)R at the mRNA and protein level in HEY and OVCA 433 ovarian carcinoma cell lines by Northern blot, reverse transcription-PCR, Western blot, and immunohistochemistry; we also investigated the activity of the COX-2 promoter by luciferase assay and the release of prostaglandin (PG) E(2) by ELISA.

Results: ET-1 significantly increases the expression of COX-1 and COX-2, COX-2 promoter activity, and PGE(2) production. These effects depend on ET(A)R activation and involve multiple mitogen-activated protein kinase (MAPK) signaling pathways, including p42/44 MAPK, p38 MAPK, and transactivation of the epidermal growth factor receptor. COX-2 inhibitors and, in part, COX-1 inhibitor blocked ET-1-induced PGE(2) and vascular endothelial growth factor release, indicating that both enzymes participate in PGE(2) production to a different extent. Moreover, inhibition of human ovarian tumor growth in nude mice after treatment with the potent ET(A)R-selective antagonist ABT-627 is associated with reduced COX-2 and vascular endothelial growth factor expression.

Conclusions: These results indicate that impairing COX-1 and COX-2 and their downstream effect by targeting ET(A)R can be therapeutically advantageous in ovarian carcinoma treatment. Pharmacological blockade of the ET(A)R is an attractive strategy to control COX-2 induction, which has been associated with ovarian carcinoma progression and chemoresistance.

Endothelin-1 stimulates cyclooxygenase-2 expression in ovarian cancer cells through multiple signaling pathways: evidence for involvement of transactivation of the epidermal growth factor receptor.

Spinella F., Rosanò L., Elia G., Di Castro V., Natali P.G., Bagnato A.

J. Cardiovasc. Pharmacology, 44(1):S140-S143, 2004

No abstract available

Impact of a new dosing regimen of epoietin alfa on quality of life and anemia in patients with low-risk myelodysplastic sindrome.

Spiriti M.A., Latagliata R., Niscola P., Cortelezzi A., Francesconi M., Ferrari D., Volpe E., Clavio M., Grossi A., Reyes M.T., Musto P., Mitra M.E., Azzara A., Pagnini D., D'arena G., Spadano A., Balleari E., Pecorari P., Capochiani E., Debiasi E., Perego D., Monarca B., Pisani F., Scaramella G., Petti M.C.

Ann. Hematol., Nov.30, 2004

This study evaluated the impact of a new epoetin alfa dosing regimen on quality of life (QOL), transfusion requirements, and hemoglobin (Hb) levels in 133 patients with low-risk myelodysplastic syndrome (MDS) and Hb </=10 g/dl. Epoetin alfa 40,000 IU was given subcutaneously twice weekly; after 4 weeks, the dose could be reduced to 40,000 IU weekly in patients achieving erythroid response. QOL was assessed using the functional assessment of cancer therapy-anemia (FACT-An) questionnaire. FACT-An scores increased on average by 7.5 after 4 weeks and by 8.8 after 8 weeks compared with baseline. FACT-An scores were positively associated with Hb values (r=0.53, P<0.01). The mean FACT-An score increase at week 8 was 10.2 in responders and 5.6 in nonresponders. The overall erythroid response rate at week 8 was 68%: 74% in transfusion-independent patients and 59% in transfusion-dependent patients. Of all responders at week 8, response was maintained in 86% at week 12, 71% at week 16, 65% at week 20, and 54% at week 24. Treatment was generally well tolerated. Our data provide new and encouraging results regarding the benefits of 40,000 IU biweekly induction doses followed by 40,000 IU weekly in improving QOL, correcting anemia, and reducing transfusion requirements in low-risk MDS patients.

Diffusion-weighted MR imaging in the evaluation of renal tumours.

Squillaci E., Manenti G., Di Stefano F., Miano R., Strigari L., Simonetti G.

J. Exp. Clin. Cancer Res., Mar;23(1):39-45, 2004

The aim of this study was to evaluate the capability and the reliability of diffusion-weighted MR imaging to differentiate benign from malignant renal lesions. Twenty healthy volunteers and 48 patients with known renal lesions underwent MR of the kidneys by using a 1.5 T superconductive magnet. Diffusion-weighted images (DWI) were obtained on the axial plane during breathhold (17 s) with a SE EPI single shot sequence using a b value of 500 s/mm2. One region of interest (ROI) (lesions < than 3 cm) or 3 ROI (lesions > than 3 cm) were placed within the lesion for the measurement of apparent diffusion coefficient (ADC). ADC map was obtained at each slice position. Mean ADC value in normal renal parenchyma was 2.2 +/- 0.20 x 10(-3) mm2/s, while ADC values in simple cysts (n = 20) were higher (mean ADC values 3.65 +/- 0.09 x 10(-3) mm2/s). Solid benign and malignant renal tumors (n = 19) showed a mean ADC value of 1.7 +/- 0.48 x 10(-3) mm2/sec. The comparison between ADC values in normal parenchyma group and tumour group were found to be statistically significant (p < 0.0001). ADC values of cystic renal cell carcinomas were higher than those of clear cell carcinomas (p < 0.001). In conclusion, DW MRI of the kidney seems to be a reliable means for differentiating normal renal parenchyma from different renal tumors.

Non-Hodgkin's Lymphoma and Type of Tobacco Smoke.

Stagnaro E., Tumino R., Parodi S., Crosignani P., Fontana A., Masala G., Miligi L., Nanni O., Ramazzotti V., Rodella S., Senoiri Constantini A., Vigano C., Vindigni C., Vineis P.

Cancer Epidemiol. Biomarkers Prev., Mar;13(3):431-7, 2004

Background: In recent decades, the incidence of non-Hodgkin's lymphoma (NHL) has increased in all industrialized countries. Tobacco smoke contains several recognized or putative carcinogenic compounds that differ in concentration depending on which of the two main types, blond or black, is consumed. This investigation sought to evaluate the association between NHL and type of tobacco smoked (blond, black, or mixed), focusing on the Working Formulation (WF) subgroups.

Methods: Reanalysis of Italian data from a recent multicenter population-based case-control study. The 1450 cases of NHL and 1779 healthy controls from 11 Italian areas with different demographic and productive characteristics were included in the study, corresponding to approximately 7 million residents. Odds ratios (ORs) adjusted for age, gender, residence area, educational level, and type of interview were estimated by unconditional logistic regression model.

Results: A statistically significant association [OR = 1.4, 95% confidence interval (CI) 1.1-1.7]

was found for blond tobacco exposure and NHL risk. A dose-response relationship was limited to men younger than 52 years (chi(2) for trend = 9.95, P < 0.001). Subjects starting smoking at an early age showed a higher risk in men younger than 65 years, whereas no clear trend was evident for the other age and gender subgroups. The analysis by WF categories showed the highest risks for follicular lymphoma in blond (OR = 2.1, 95% CI 1.4-3.2) and mixed (OR = 1.8, 95% CI 1.1-3.0) tobacco smokers and for large cell within the other WF group (OR = 1.6, 95% CI 1.1-2.4) only for blond tobacco.

Conclusions: Smoking blond tobacco could be a risk factor for NHL, especially follicular lymphoma.

Once-weekly dosing of recombinant human erythropoietin alpha in patients with myelodysplastic syndromes unresponsive to conventional dosing.

STASI R., BRUNETTI M., TERZOLI E., ABRUZZESE E., AMADORI S.

Ann. Oncol., Nov;15(11):1684-90, 2004

Background: Once-weekly dosing of recombinant human erythropoietin (rhEPO) in patients with myelodysplastic syndromes (MDS) has not been investigated thoroughly. We performed a clinical trial to evaluate the effects of this new dosing regimen in patients with MDS who were unresponsive to the conventional three-times-weekly schedule.

Patients and methods: Forty-eight patients with low- or intermediate-risk MDS were enrolled in a 12-week study. rhEPO alpha (rhEPOalpha) was administered once-weekly by subcutaneous injection with a starting dose of 40,000 U fixed dose. The drug dosage was increased to 60,000 U fixed dose if after 6 weeks there was no or suboptimal erythroid response.

Results: Clinically significant responses were seen in 13 (27%) patients, with 11 improving their response after dose escalation of rhEPOalpha. Only one patient (case 23) maintains a response after a follow-up period of 14 months. All other patients had responses lasting between 10 and 43 weeks, with a median time to relapse of 20 weeks. Treatment was well tolerated, with no relevant adverse events. Response to therapy was associated with significantly higher concentrations of circulating erythroid blast-forming units and a decrease of the bone marrow fraction of apoptic CD34+ cells.

Conclusions: Once-weekly rhEPOalpha therapy results in an improvement of erythropoiesis in a subset of MDS patients who are unresponsive to conventional dosing, and may act by inhibiting apoptosis of erythroid precursors. These results warrant further investigation of this dosing regimen either alone or in combination with other agents.

Radiation exposure of personnel during intraoperative radiotherapy (IORT): radiation protection aspects.

STRIGARI L., SORIANI A., LANDONI V., TEODOLI S., BRUZZANITI V., BENASSI M.

J. Exp. Clin. Cancer Res., Sep;23(3):489-94, 2004

Intraoperative radiotherapy (IORT) is a multidisciplinary procedure which combines two conventional methods of cancer treatment surgery and radiation therapy. The purpose is to deliver a large single dose to the surgically exposed tumor bed while minimizing doses to normal tissues. Intraoperative radiation therapy (IORT) is a technique which allows irradiating the patient directly after the surgical operation using a linear accelerator that can be situated in the operating room. For medical accelerators with energy over 10MeV the need to characterize the neutron spectra for this particular situation arises from the fact that, when neutron spectra is not fully known, it becomes necessary to be more cautious introducing a weight factor wR of 20 (maximum value). This leads to overesteem the equivalent dose due to neutrons and it indicates to introduce additional (mobile) shields for photon and neutrons radiation not easily achievable in an operating room.

The current and future role of dexrazoxane as a cardioprotectant in anthracycline treatment: expert panel review.

Swain S.M., Vici P.

J. Cancer Res. Clin. Oncol., Jan;130(1):1-7, 2004

This article summarizes the views of an expert meeting of cardiologists and oncologists on the use of dexrazoxane in anthracycline-based chemotherapy. Anthracycline-induced cardiotoxicity remains a major concern and new trends in treatment (e.g., combination of an anthracycline with other agents) will ensure that it remains a problem. Dexrazoxane reduces this cardiotoxicity in adults and children with a range of tumor types. Further research may help to identify those patients who are at particular risk of cardiotoxicity and who would benefit the most from dexrazoxane. There are also numerous possibilities for dexrazoxane in other clinical situations, which must be addressed in future trials.

High-dose chronomodulated infusion of 5-fluorouracil (5-FU) and folinic acid (FA) (FF(5-16)) in advanced colorectal cancer patients.

Terzoli E., Garufi C., Zappala A.R., Vanni B., Pugliese P., Cappellini G.A., Aschelter A.M., Perrone M., Giannarelli D.

J. Cancer Res. Clin. Oncol., Aug;130(8):445-52, 2004

Purpose: The best way to deliver infusional 5-fluorouracil (5-FU) and folinic acid (FA) has yet to be determined. The aim of this prospective phase II trial was to verify the tolerability, activity and efficacy of chronomodulated 5-FU-FA (FF(5-16)) every 3 weeks in 48 untreated patients (group A), and 28 pretreated and four non-measurable, advanced colorectal cancer (ACC) patients (group B).

Methods: The sinusoidal delivery of both drugs started at 10.00 p.m. and ended at 10.00 a.m., with peak flow at 4.00 a.m. for 5 consecutive days. The initial 5-FU dose was 900 mg/m(2)/day with intra-patient dose increase at 1,000 and 1,100 mg/m(2)/day, at the second and third course, respectively; FA was injected at a fixed dose of 150 mg/m(2)/day (Garufi et al.1997).

Results: Neither death from toxicity nor hematological toxicities were encountered. Maximal toxicity consisted of Grade 3 oral mucositis in 41% of patients, in only 8% of 535 courses. It was possible to achieve objective responses in 31% of untreated patients, with a progression free survival (PFS) of 7 months, median survival of 14 months and a 2-year survival rate of 28%. Similar results for PFS and survival were obtained in pretreated patients as well. Univariate analysis and multivariate analysis showed that response was related to the occurrence of mucositis and diarrhea (p=0.03 and p=0.0007) and to performance status (PS) (p=0.01). Quality of life, measured with the EORTC QLQ-C30+3 questionnaire, was unaffected by treatment and was better in patients with good PS and responsiveness.

Conclusions: In this chronomodulated FF(5-16) phase II study, the probability of obtaining a relevant tumor reduction was significantly correlated with a patient variable such as PS, and toxicity variables such as mucositis and diarrhea. This observation and the validation of predictive factors for QoL deserve further investigation in ACC patients.

Single-agent vinorelbine in pretreated breast cancer patients: comparison of two different schedules.

Terzoli E., Nistico C., Fabi A., Milella M., Bria E., D'ottavio A.M., Vaccaro A., Vanni B., Garufi C., Ferraresi V., Giannarelli D., Papaldo P., Carlini P., Izzo F., Cognetti F.

J. Exp. Clin. Cancer Res., Jun;23(2):207-13, 2004

This retrospective study compared toxicity and activity of vinorelbine according to two schedules with different projected dose intensities in heavily pretreated breast cancer patients. Forty patients were assessable for toxicity and activity in each group; group A received vinorelbine 25 mg/m2 week + lenograstim (150 microg/m2 s.c. on day 3); group B received 25 mg/m2 on days 1 and 8 every 3 weeks. The projected dose intensity was 25 mg/m2/week and 16.6 mg/m2/week, and delivered dose intensity 95.2% and 94.5% in group A and B, respectively. Grade 3-4 afebrile neutropenia was recorded in 25% and 37.5% of patients in A and B, respectively. Overall response rate, 52.5% and 35%; no change, 35% and 40%; progression of disease, 12.5% and 25% in A and B, respectively. Median duration of the response was 10 months for group A and 7 months for B. Median time to progression: 9.0 months and 4.0 months for A and B, respectively. At a median follow-up of 45 months for group A and 19 months for group B, median overall survival was 19 months and 16, respectively. In conclusion

the results of the study showed that dose intensity of vinorelbine could have an improvement in terms of time to progression in pretreated advanced breast cancer.

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., Feb 20;279(8):6737-45, 2004

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.

p53 localization at centrosomes during mitosis and postmitotic checkpoint are ATM-dependent and require serine 15 phosphorylation.

Tritarelli A., Oricchio E., Ciciarello M., Mangiacasale R., Palena A., Lavia P., Soddu S., Cundari E.

Mol. Biol. Cell., Aug;15(8):3751-7, 2004

We recently demonstrated that the p53 oncosuppressor associates to centrosomes in mitosis and this association is disrupted by treatments with microtubule-depolymerizing agents. Here, we show that ATM, an upstream activator of p53 after DNA damage, is essential for p53 centrosomal localization and is required for the activation of the postmitotic checkpoint after spindle disruption. In mitosis, p53 failed to associate with centrosomes in two ATM-deficient, ataxiatelangiectasia-derived cell lines. Wild-type ATM gene transfer reestablished the centrosomal localization of p53 in these cells. Furthermore, wild-type p53 protein, but not the p53-S15A mutant, not phosphorylatable by ATM, localized at centrosomes when expressed in p53-null K562 cells. Finally, Ser15 phosphorylation of endogenous p53 was detected at centrosomes upon treatment with phosphatase inhibitors, suggesting that a p53 dephosphorylation step at centrosome contributes to sustain the cell cycle program in cells with normal mitotic spindles. When dissociated from centrosomes by treatments with spindle inhibitors, p53 remained phosphorylated at Ser15. AT cells, which are unable to phosphorylate p53, did not undergo postmitotic proliferation arrest after nocodazole block and release. These data demonstrate that ATM is required for p53 localization at centrosome and support the existence of a surveillance mechanism for inhibiting DNA reduplication downstream of the spindle assembly checkpoint.

pRb2/p130 decreases sensitivity to apoptosis induced by camptothecin and doxorubicin but not by taxol.

TONINI T., GABELLINI C., BAGELLA L., D'ANDRILLI G., MASCIULLO V., ROMANO G., SCAMBIA G., ZUPI G., GIORDANO A.

Clin. Cancer Res., Dec 1;10(23):8085-93, 2004

Purpose: In addition to their original function as cell cycle regulators, retinoblastoma (Rb) family members were recently reported to modulate the sensitivity of cancer cells to chemotherapeutic agents. The purpose of this study is to investigate the possible role of pRb2/p130 in the sensitivity of ovarian cancer to camptothecin, doxorubicin, and taxol.

Experimental design: pRb2/p130 was overexpressed in the CAOV-3 ovarian cancer cell line, and the effect of pRb2/p130 overexpression on sensitivity to apoptosis trigged by IC(50) doses of different drugs was evaluated by various methods, including 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, flow cytometry, and Western blot analyses.

Results: The results reported in this study support the conclusion that overexpression of pRb2/p130 in the CAOV-3 ovarian cancer cell line lacking wild-type p53 is able to inhibit apoptosis triggered by camptothecin and doxorubicin through the c-Jun NH(2)-terminal kinase signaling transduction pathway. Conversely, taxol-induced cell death is not influenced by the pRb2/p130 protein level.

Conclusions: A careful analysis of pRb2/p130 expression in tumor specimens could help to identify the best clinical protocol to be used for each patient, improving efficacy and tolerance and therefore offering additional progress in the treatment of advanced ovarian cancer.

Presence of HPV in head and neck tumours: high prevalence in tonsillar localization.

VENUTI A., BADARACCO G., RIZZO C., MAFERA B., RAHIMI S., VIGILI M.

J. Exp. Clin. Cancer Res., 23(4):561-566, 2004

Human papillomavirus (HPV) seems to be involved in head and neck carcinogenesis. To investigate this association, viral presence and expression were analysed by polymerase chain reaction (PCR)-based methods and correlated to tumour localization, clinical-pathological aspects, and alcohol and tobacco exposure in 65 patients. HPV DNA was found in 16 cases (24.6%); the HPV types detected were: HPV16 (10 cases), HPV 6 (3 cases) HPV 33, 35, and 58 (one case each). The tonsil was the location with the highest HPV positivity (6/8, 75%). This percentage was significantly higher than that found in tumours from any other site ($P<0.01$). Viral transcripts of early regions were detected in all HPV16 positive tumours. HPV status was not related to age, gender, tumour stage or grade, and use of alcohol and/or tobacco. The results suggest that HPV16 is actively involved in the genesis of a subset of head and neck cancers and that the tonsillar localization may be considered a hot spot for viral transformation.

Explaining gastric cancer survival differences among european countries.

VERDECCHIA A., CORAZZIARI I., GATTA G., LISI D., FAIVRE J., FORMAN D., AND THE EUROCARE WORKING GROUP. MEMBERS OF THE EUROCARE WORKING GROUP FOR THIS STUDY ARE AS FOLLOWS: ITALY: (CONTI E.) (LATINA CANCER REGISTRY).

Int. J. Cancer, 109: 737-741, 2004

Wide geographic variability in incidence and mortality rates for gastric cancer exists throughout the world despite persistent decreases over several decades. Variability in survival from gastric cancer is also evident and countries with higher incidence rates of gastric cancer show better survival rates than countries with lower incidence. The aim of this study was to identify reasons for the association between incidence and survival and to obtain survival estimates and differences corrected for this variation, thus facilitating further interpretation by clinical factors such as stage and treatment. Relative survival rates for gastric cancer derived from the EUROCARE-2 database for 47 cancer registries in 17 European countries were analyzed with regression methods to adjust differences by age, sex, period of diagnosis, subsite of the stomach, histologic type and stage at diagnosis. Overall, nearly 60% of the variability in gastric cancer relative survival was explained by differences in these variables. Factors are related to treatment and general management of patients is expected to explain the residual variability in gastric cancer survival between European countries. There is a need to improve completeness and standardization of detailed information collected on gastric cancer patients to allow detailed comparative analyses and interpretation.

Evaluation of hepatic metastases from colorectal carcinoma with MR-superparamagnetic iron oxide.

VIDIRI A., CARPANESE L., ANNIBALE M.D., CATERINO M., COSIMELLI M., ZEULI M., DAVID V., CRECCO M.

J. Exp. Clin. Cancer Res., Mar;23(1):53-60, 2004

The purpose of this study was to compare the results obtained with superparamagnetic iron oxide-enhanced and unenhanced Magnetic Resonance at 1.5 T with that of spiral-computed tomography (CT) in order to select those patients suitable for liver resection; the intraoperative US (IOUS) comprised the gold standard. Thirty five candidates for liver resection with known colorectal neoplasm were studied; 26 patients underwent surgery, one patient underwent RF ablation and 8 of them were submitted to follow-up. MR examination was performed using a 1.5 T superconductive instrument, CT examination was performed on a Somatom-Plus (Siemens) scanner. Dimensions and number of the lesions were defined in all patients as well as the sensitivity of spiral CT and MR imaging, using either the plain technique or after Ferumoxides c.m.. In those patients submitted to surgery, results have been correlated to those of IOUS. From 26 patients, a total of 48 lesions were removed surgically. With CT, 34 lesions with 3 false positive cases were detected; 32 with plain MR imaging, while MR imaging with Ferumoxides detected 41 lesions. In the patients not submitted to surgery, MR iron-oxide imaging identified 15 lesions, while both plain MR imaging and CT showed 8 lesions. The smallest lesion was 6 mm. as shown by MR imaging with Ferumoxides. In the cases submitted to surgery, the CT sensitivity was 71%, plain MR imaging 66% and MR imaging with Ferumoxides 85%. In our experience, Ferumoxides-enhanced MR imaging of the liver shows increased sensitivity compared to plain and spiral-CT in the evaluation of hepatic metastases. We think that MR superparamagnetic iron oxide should be used in all patients selected for liver resection.

Overexpression of the ped/pea-15 gene causes diabetes by impairing glucose-stimulated insulin secretion in addition to insulin action.

VIGLIOTTA G., MIELE C., SANTOPIETRO S., PORTELLA G., PERFETTI A., MAITAN M.A., CASSESE A., ORIENTE F., TRENCIA A., FIORY F., ROMANO C., TIVERON C., TATANGELO L., ET AL.

Mol. Cell. Biol., Jun;24(11):5005-15, 2004

Overexpression of the ped/pea-15 gene is a common feature of type 2 diabetes. In the present work, we show that transgenic mice ubiquitously overexpressing ped/pea-15 exhibited mildly elevated random-fed blood glucose levels and decreased glucose tolerance. Treatment with a 60% fat diet led ped/pea-15 transgenic mice to develop diabetes. Consistent with insulin resistance in these mice, insulin administration reduced glucose levels by only 35% after 45 min, compared to 70% in control mice. In vivo, insulin-stimulated glucose uptake was decreased by almost 50% in fat and muscle tissues of the ped/pea-15 transgenic mice, accompanied by protein kinase Calpha activation and block of insulin induction of protein kinase Czeta. These changes persisted in isolated adipocytes from the transgenic mice and were rescued by the protein kinase C inhibitor bisindolylmaleimide. In addition to insulin resistance, ped/pea-15 transgenic mice showed a 70% reduction in insulin response to glucose loading. Stable overexpression of ped/pea-15 in the glucose-responsive MIN6 beta-cell line also caused protein kinase Calpha activation and a marked decline in glucose-stimulated insulin secretion. Antisense block of endogenous ped/pea-15 increased glucose sensitivity by 2.5-fold in these cells. Thus, in vivo, overexpression of ped/pea-15 may lead to diabetes by impairing insulin secretion in addition to insulin action.

Fatty Acid Synthase (FAS) is a marker of increased risk of recurrence in lung carcinoma.

VISCA P., SEBASTIANI V., BOTTI C., DIODORO M.G., LASAGNI R.P., ROMAGNOLI F., BRENNA A., CAPEZZONE DE JOANNON B., PERRONE DONNORSO R., LOMBARDI G., ALO P.L.

Anticancer Research, 24(6) 4169, 2004

Background: We explored the expression of Fatty Acid Synthase (FAS) in lung carcinomas and its association with clinico-pathological features and prognosis. FAS is a recently discovered molecule involved in the energy supply of normal cells. FAS is also overexpressed in neoplastic tissues because of their increased necessity for energy.

Patients And Methods: One hundred and six patients with non-small cell lung carcinoma were followed-up for an average period of 5 years. FAS expression was detected immunohistochemically.

Results: FAS staining was observed in 61 out of 106 cases (57.54%). Statistical analysis revea-

led that FAS had an overall low prognostic value ($p = 0.14$), while FAS-negative expression in stage I patients showed a trend for better survival ($p = 0.10$). PTNM stage ($p < 0.0001$) was the only significant prognostic marker for overall survival.

Conclusion: FAS is a reliable marker of low-stage clinically aggressive lung carcinomas. The determination of FAS expression in lung carcinomas may stratify patients and determine therapeutic approaches for their care.

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Nipple sparing mastectomy. A preliminary review in conservative surgery of breast cancer.

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Journal of Clinical Oncology Vol 22 Suppl. 15, 2004 (abs 4007)
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Concomitant chemo-radiotherapy with continuous infusion cisplatin and 5-fluoruracil in locally advanced cervical carcinoma (LACC) : a single institution experience.

Journal of Clinical Oncology Vol 22 Suppl. 15, 2004 (abs 5073)
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6th Convegno FISV. Riva del Garda, 30 Settembre 3 Ottobre 2004

67. Iervolino A., Trisciuoglio D., Ciuffreda L., Zupi G., Del Bufalo D.

Bcl-2 upregulation of vascular endothelial growth factor expression in melanoma cells exposed to hypoxia is mediated by map and PI3 kinase-dependent pathways.

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

68. Leonetti C., Scarsella M., Lopez M., Zupi G.

Antitumoral efficacy of different pharmacological combinations in an experimental model of breast cancer.

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

69. Leonetti C., Scarsella M., Lopez M., Et Al.

Antitumoral efficacy of different pharmacological combinations in an experimental model of breast cancer.

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

70. Lopez M.

Evoluzione della terapia dei tumori. Dall'empirismo iniziale al razionalismo post-genomico.

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

71. Macaluso M., Montanari M., Giacinti L., Russo A., Lopez M., Et Al.

Is it possibile to convert estrogen-negative breast cancer cells into estrogen-positive breast cancer cells?

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

72. Mara' M., Di Guardo G., Marruchella G., De Rugeriis M., Simeone P., Venuti A., Della Salda L.

Multiple Spontaneous Neoplasms In Two Twin Goats: Morphological, Aetiological And Pathogenetic Investigations.

Convegno Nazionale S.I.P.A.O.C.. Siena, 29 Settembre - 2 Ottobre 2004

73. Marandino F., Vocaturo A., Benevolo M., Piperno G., Canalini P., Mottolese M., Vocaturo G., Sindico R., Ciancaglini G., Perrone Donnorso R.

Overexpression of p16ink4a in cervical intraepithelial neoplasias as possible marker of HPV infection.

3rd Congresso Nazionale SIAPEC –IAP. Firenze, 26-30 Settembre 2004

74. Marino M., Carosi M., Del Nonno F., Visca P., Mottolese M., Buglioli S., Chichierchia G., Piperno G., Canalini P., Pisani F., Spriano G., Pezzuto W., Centra G., Giacomini P., Perrone Donnorso R.

Nodal/Extranodal T-citotoxic lymphomas: from the pathological diagnosis back to the clinical settino. Report of 2 cases.

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

75. Marino M., Chichierchia G., Del Nonno F., Mottolese M., Malandino F., Perracchio L., Benevolo M., Lattanti A., Lapenta R., Romano A., Anticoli Borza P., Perrone Donnorso R.

Prognostic and therapeutical implications of morphophenotypical and cytogenetical extranodal lymphoma characterization.

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

76. Maschio M., Pietrangeli A., Pace A., Jandolo B., Et Al.

Il dolore neuropatico da chemioterapici: quale trattamento?

CNR Roma, 8-9 Marzo 2004

77. Maschio M., Pietrangeli A., Jandolo B., Et Al.

Tumori cerebrali ed epilessia: uno studio retrospettivo su 405 pazienti.

XLIV Congresso Nazionale S.N.O. Vicenza, 26-29 Maggio 2004

78. Maschio M., Jandolo B.

Profilassi antiepilettica in pazienti con tumore cerebrale? Un caso in discussione.

LICE. Milano, 19–22 Settembre 2004

79. Massa S., Simeone P., Venuti A., Franconi R.

Plant-derived signal peptide drives the HPV16 E7 oncoprotein to the secretory pathway of mammalian cells- Implications for the improvement of a DNA vaccine.

48th Annual Congress Società' Italiana di Genetica Agraria. Lecce, 15-18 Settembre 2004

80. Minutilli E., Mastroianni A. D'urso D., Venuti A., Rizzo C., Visca P., Pisani F., Petti M.C., Berardesca E.

Sindrome simil–epidermodisplasia verruciforme in paziente immunocompromesso per terapia con clorambucil.

79° SIDeMaST National Congress. Castellaneta Marina (Taranto), 26-29 Maggio 2004

81. Minutilli E., Carrera M., Canistracci C., Lesnoni I., Donati P., Ceribelli A., Milella M., Berardesca E.

Metastasi cutanea solitaria da carcinoma polmonare.

79° SIDeMaST National Congress. Castellaneta Marina (Taranto), 26-29 Maggio 2004

82. Minutilli E., Mastroianni A., Pittarello A., Cardinali G., Donati P., Carosi M., Spadea A., Petti M.C., Berardesca E.

Un caso di xantogranuloma necrobiotico da paraproteinemia.

79° SIDeMaST National Congress. Castellaneta Marina (Taranto), 26-29 Maggio 2004

83. Minutilli E., Mastroianni A., D'urso D., Cristaudo A., Di Lella M., Pisani F., Petti M.C., Berardesca E.

Un caso di reazione cutanea allergica di tipo ritardato al clorambucil.

79° SIDeMaST National Congress. Castellaneta Marina (Taranto), 26-29 Maggio 2004

84. Morace E., Oppido P.A., Cattani F.

Cisti colloidi del III ventricolo: asportazione endoscopica.

53° Congresso Nazionale della Società Italiana di Neurochirurgia - SINch. Milano, 21-24 Novembre 2004

85. Nanni S., Priolo C., Grasselli A., D'eletto M., Della Pietra L., Moretti F., Gallucci M., Sentinelli S., Cianciulli A.M., Mottolese M., Carlini P., Arcelli D., Pontecorvi A., Bacchetti S., Sacchi A., Farsetti A.

Crescita, caratterizzazione e profilo genico di cellule primarie di tumore della prostata quale utile strumento per nuove strategie terapeutiche ormonali mirate al singolo paziente.

Convegno annuale "Struttura e funzione del genoma". Cortona, 22-24 Aprile 2004

86. Nanni S., Priolo C., Grasselli A., D'eletto M., Della Pietra L., Moretti F., Gallucci M., Sentinelli S., Cianciulli A.M., Mottolese M., Carlini P., Arcelli D., Pontecorvi A., Bacchetti S., Sacchi A., Farsetti A.

Establishment, characterization and gene profiling of prostate cancer primary cultures: a model for development of novel patient-tailored hormonal therapeutic strategies. (abs 162)

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

87. Nisticò C., Bria E., Vanni B., Cuppone F., Campanella C., Calabretta F., Garufi C., Giannarelli D., Terzoli E.

Regina Elena National Cancer Institute experience of 1st line weekly chemotherapy for advanced breast cancer (ABC) patients (pts): survival outcome of 171 patients enrolled in 3 phase II trials.

6th National Congress of Medical Oncology (AIOM). Bologna, 21-24 Settembre 2004

88. Oppido P.A., Cattani F., Morace E., Carapella C.M., Occhipinti E.

Il ruolo della neuroendoscopia nella diagnosi e nel trattamento dei tumori del III ventricolo: case report.

IX Congresso Nazionale AINO (Associazione Italiana di Neuro-Oncologia). Varese, 28-30 Ottobre 2004

89. Oppido P.A.

Meccanismi emodinamici e relativi targets cerebrali del danno secondario in neurotraumatologia.

53° Congresso Nazionale della Società Italiana di Neurochirurgia - SINch. Milano, 21-24 Novembre 2004

90. Pace A.

Peripheral Neurotoxicity Induced by Anticancer drugs and Neuroprotction.

IX Congresso Nazionale AINO (Associazione Italiana di Neuro-Oncologia). Varese, 28-30 Ottobre 2004

91. Pace A., Galiè E., Telera S., Mirri A., Vidiri A., Jandolo B., Carapella C.M.

Natural history, prognostic factors and treatment in 86 low grade glioma.

IX Congresso Nazionale AINO (Associazione Italiana di Neuro-Oncologia). Varese, 28-30 Ottobre 2004

92. Pace A., Jandolo B., Et Al.

Neuroprotective Effect Of Vitamin E Supplementation In Patients Treated With Cisplatin Chemotherapy.

Società Italiana di Neurologia (S.I.N.). Genova, 25 Settembre 2004

93. Pace A., Calabretta P., Giovanelli M., Guastamacchia P., Lembo O., Parisi C., Rosi F., Salis P., Vita S., Pompili A., Et Al.

Assistenza Continuativa Domiciliare Neuro-oncologica. L'esperienza del Progetto dell'Istituto Regina Elena.

S.I.C.P. (Società Italiana di Cure Palliative). Roma, 2004

94. Pace A., Fabi A., Pompili A., Telera S., Jandolo B., Occhipinti E., Carapella C.M.

PCV and/or tmz chemotherapy in 253 gliomas. analysis of the neuro-oncology database of Regina Elena Cancer Institute.

Ann Oncol. 15 (suppl. 2), abs H34, p. ii90, 2004
6th National Congress of Medical Oncology (AIOM). Bologna, 21-24 Settembre 2004

95. Paggi M.G., Severino A., Manente L., Pisano P., Federico A., Lavia P., Mileo A.M.

Novel cellular targets of small DNA virus oncoproteins: unraveling their functional significance.

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

96. Perluigi M., Venuti A., Flamini S., Cini C., Blarzino A., Coccia R., De Marco F.

Oxidative Stress, Cell Proliferation and Viral Oncogenes Expression in HPV-16 Transformed Epithelial Cells.

3rd Forum SIViM Virus e Tumori nell'Uomo. Roma, 18-19 Novembre 2004

97. Piemonte P., Merra V.C., Frascione P.

Adjournment day in Clinic Dermatology and new therapeutic and diagnostic approaches.

SIDEMAST-ADOI Congress. Roma, Marzo 2004

98. Piemonte P., Merra V.C., Fossati B., Covello R., Frascione P.

Atypical clinical expression of squamous cell carcinoma.

XIX SIDCO Congress. Siderno (RC), Aprile 2004

99. Pompili A., Occhipinti E.

L'approccio mininvasivo sopraorbitario per la rimozione delle neoplasie della fossa cranica anteriore. Una procedura utile o un esercizio chirurgico?

VIII Congresso Nazionale della Società Italiana del Basicranio - SIB. Parma, 3-4 Dicembre 2004

100. Porrello A., Giansanti A., Latora V., Pizzitutti F.

Hidrophobicity signal and inner networks of proteins: from universal scale laws to clustering methods.

4th Edition Acta Biophysica Romana, Roma, 17-18 Giugno 2004

101. Pugliese P., Garufi C., Perrone M., Bussolotti F., Falcicchio C., Vanni B., Calabretta F., Terzoli E.

Quality of life (QoL) and quality of care (QoC) in advanced colorectal cancer patients. (Abs N1)

6th National Congress of Medical Oncology (AIOM). Bologna, 21-24 Settembre 2004

102. Riccioni S., Folgiero V., Bon G., Falcioni R.

WSB1 protein is a negative regulator of the 64 signaling. Associazione di Biologia Cellulare e del Differenziamento Meccanismi di trasduzione del segnale in adesione e differenziamento cellulare.

Roma, 19-20 Marzo 2004

103. Rinaldo C., Cecchinelli B., Iacovelli S., Soddu S.

p53 negatively regulates its pro-apoptotic activator HIPK2.

1st IEO-IFOM meeting on cancer. Milano, 11-14 Marzo 2004

104. Rosanò L., Spinella F., Genovesi G., Di Castro V., Nicotra M.R., Natali P.G., Bagnato A.

Endothelin-1 regulates molecular effectors of epithelial to-mesenchymal transition in ovarian carcinoma cells. ABCD, "Meccanismi di trasduzione del segnale in adesione e differenziamento cellulare".

Roma, 19-20 Marzo 2004

105. Rosanò L., Spinella F., Genovesi G., Di Castro V., Nicotra M.R., Natali P.G., Bagnato A.

Activation of endothelin A receptor signaling promotes epithelial to mesenchymal transition in human ovarian carcinoma cells.

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

106. Ruscito P., Cristalli G., Marchesi P., Pellini R., Pichi B., Ruggieri M., Marucci L., Arcangeli G., Spriano G.

Radioterapia intraoperatoria (IORT) in ORL: indicazioni e tecnica.

91° Congresso Nazionale Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale. Torino, 26-29 Maggio 2004

107. Ruscito P., Cristalli G., Marchesi P., Pellini R., Telera S., Occhipinti E.

Asportazione di tumore orbitarlo per la via della fossa cranica anteriore.

91° Congresso Nazionale Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale. Torino, 26-29 Maggio 2004

108. Saracino B., Soriani A., De Carli P., Petrongari M.G., Farella A., Marzi S., Landoni V., Albino G., Gallucci M., Arcangeli G., Benassi M.

Radioterapia Intraoperatoria (IORT) dopo prostatectomia radicale nell'adenocarcinoma prostatico.

XIV Congresso Nazionale AIRO. Torino, 17–20 Ottobre 2004

109. Sarti P., Giuffrè A., Forte E., Arese M., Mastronicola D., Bacchi A., Sacandurra F.M., Brunori M.

Nitric Oxide and Cytochrome c Oxidase.

X Convegno Nazionale "Aspetti Biologici dell'Ossido di Azoto". Urbino, 23-24 Ottobre 2004

110. Savarese A., Felici A., Micheli A., Gasparro S., Magnani E., Carosi M., Vizza E., Mariani L., Sbiroli G., Gamucci T., Arcangeli G., Cognetti F.

L35 concomitant chemo-radiotherapy in ib-IIB cervical carcinoma: a single institution experience.

6th National Congress of Medical Oncology (AIOM). Bologna, 21-24 Settembre 2004

111. Sciuto R., Pasqualoni R., Festa A., Bergomi S., Romano L., Maini C.L.

Adjuvant radioiodine therapy significantly improves survival and decrease morbidity of both high and low risk differeentiated thyroid cancer: a reterospectives analysis on a series of 1350 patients.

Q. J. Nucl. Med., 48 (Suppl. 3): 66, 2004
VII Congresso Nazionale AIMN. Palermo, 15-19 Ottobre 2004

112. Soddu S., Cecchinelli B., Ulivieri A., Rinaldo C., Bartolazzi A., Salvatore S.

HIPK2: a new pro-apoptotic oncosuppressor?

8th Annual Symposium. Siena, 21-24 Maggio 2004

113. Spinella F., Rosanò L., Decandia S., Di Castro V., Natali P.G., Bagnato A.

Endothelin-1-mediated prostaglandin E2-EP2,EP4-signaling regulates vascular endothelial growth factor production and ovarian carcinoma cell invasion.

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

114. Spinella F., Rosanò L., Decandia S., Di Castro V., Albini A., Natali P.G., Bagnato A.

The green tea polyphenol epigallocatechin-3-gallate inhibits the endothelin axis in ovarian carcinoma cells.

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

115. Stigliano V., Lauria V., Lesnono I., Canistacci C., Sentinelli S., Cordiali P., Appetecchia M.L., Frascione P., Petti M.C., Casale V.

Coeliac Disease :multidisciplinary approach.

X Congresso Nazionale delle Malattie digestive. Torino, 27-31 Marzo 2004

116. Strigari L., Maini C.L., Sciuto R., D'andrea M., Bruzzaniti V., Romano L., Benassi M.

Radiobiological models and dose calculation in radionuclide direct therapy.

Q. J. Nucl. Med. 48 (Suppl. 3): 182, 2004.
VII Congresso Nazionale AIMN. Palermo, 15-19 Ottobre 2004

117. Terzoli E., Bria E., Vanni B., Nisticò C., Cuppone F., Campanella C., Calabretta F., Garufi C., Aschelter A.M., Izzo F., Casali C., Sperduti I., Tropea F.

Three-step sequential up-front chemotherapy (SC) for advanced non-small-cell lung cancer (NSCLC): a pilot and feasibility study.

6th National Congress of Medical Oncology (AIOM). Bologna, 21-24 Settembre 2004

118. Tirelli W., Ginobbi P., Di Emidio L., Kapplani L., Arcuri E.

L'importanza del riferimento a morfina per os (titrazione) nello switch tra oppioidi in terapia antalgica. protocolli del servizio di terapia del dolore ire.

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

119. Vici P., Foggi P., Conti F., Di Lauro L., Amodio A., Sergi D., Masi M.C., Cauchi C., Giotta E., Gebbia V., Colucci G., Lopez M.

Docetaxel e vinorelbina nel carcinoma mammario metastatizzato pretrattato con antracicline - studio multicentrico di fase II.

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

120. Vici P., Giotta F., Gebbia V., Colucci G., Lorusso V., Di Lullo L., Paoletti G., Conti F., Foggi P., Mancarella S., Lopez M.

Gemcitabina e docetaxel nel trattamento di prima linea del carcinoma mammario metastatizzato - studio multicentrico di fase II.

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

121. Vici P.

Taxani e gemcitabina nella terapia del carcinoma mammario metastatico.

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

122. Vici P., Foggi P., Conti F., Di Lauro L., Et Al.

Docetaxel e vinorelbina nel carcinoma mammario metastatizzato pretrattato con antracicline - studio multicentrico di fase II.

VII Congresso Nazionale GOIM. Roma, 23-25 Giugno 2004

123. Vidiri A., Mirri A., Fabi A., Telera A., Pace A., Carosi Ma., Portieri F., Carapella C.M., Crecco M.

Preliminary experience with ct- perfusion in primari and secondary brain tumours.

IX Congresso Nazionale AINO (Associazione Italiana di Neuro-Oncologia). Varese, 28-30 Ottobre 2004

124. Visca P., Chichierchia G., Buglioni S., Marandino F., Perrone Donnorso R., Pisani F., Romano A., Gasbarra R., Lattanzi A., Centra G., Giacomini P., Marino M.

Morphological, citogenetical and molecular biological findings in extranodal lymphoma. Report of 3 cases.

3rd Congresso Nazionale SIAPEC-IAP. Firenze, 26-30 Settembre 2004

125. Visca P., Diodoro M.G., Novelli F., Zerbini V., Pasquali Lasagni R., Perrone Donnorso R., Botti C., Mottolese M.

Cytoplasmic expression of Survivin is associated to shorter overall survival in non small cell lung carcinomas.

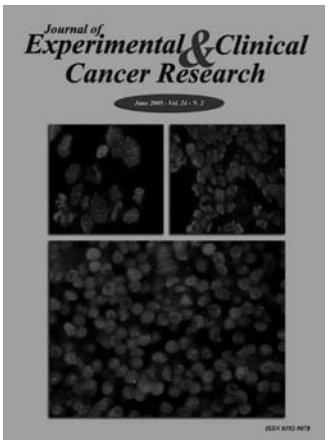
3rd Congresso Nazionale SIAPEC –IAP. Firenze, 26-30 Settembre 2004

126. Visca P., Diodoro M.G., Novelli F., Zerbini V., Pasquali Lasagni R., Perrone Donnorso R., Botti C., Mottolese M.

Cytoplasmic expression of survivin is associated to shorter overall survival in early stages of non small cell lung carcinomas.

46th Congresso Nazionale della Società Italiana di Cancerologia (SIC). Pisa, 24–27 Ottobre 2004

Journal of Experimental and Clinical Cancer Research



The Journal of Experimental and Clinical Cancer Research publishes quarterly original contributions dealing with basic and applied research in the field of experimental and clinical oncology.

The deep convincement that cancer control could be successful only by wide collaborative efforts and information made the National Cancer Institute start the publication of the Journal in 1982, ISI Impact Factor was granted in 1996 with a score of 0.153 which has reached 0.574 in 2003.

Listed in Index Medicus and Medline - Current Contents/Clinical Medicine and abstracted by EMBASE/Excerpta Medica and Chemical Abstracts Service it is participating Journal of the International Committee of Medical Journal Editors.

All manuscripts received by JECCR are subject to editorial review and two substantial reviews are always obtained according to the working schedule established by the Editor and Regional Editors (Europe, Asia-Pacific, America).

Five hundred copies of the Journal are mailed to subscribers of the Japanese Society of Gastroenterological Carcinogenesis (JSGC). Other 500 complimentary copies are made available to libraries, oncological institutes, researchers, etc.

The JECCR is on-line, free-of-charge (http://www.ifo.it) - link to Journal of Experimental and Clinical Cancer Research.

In 2004 one-hundred-thirty-four manuscripts were received for publication, only 92 were accepted by Referees. Their place of origin is as follows: Europe 59 - Asia–Pacific 28 USA America 5.

Hosted Lectures

5 Febbraio — Mark Urken. Derald H. Ruttenberg Cancer Center, New York
Functional Reconstruction of the Maxilla

24 Febbraio — Stefano Piccolo, Universita' Di Padova
Regolazione del segnale TGF-beta

27 Febbraio — Steven M. Kornblau, M.D., University Of Texas
Survivor cells as prognostic factors and guides to the use of targeted therapy in AML

5 Marzo — Alessandro Quattrone. Casa Sollievo Della Sofferenza,San Giovanni Rotondo Di Foggia
Una segnature metastatica per il carcinoma del colonretto

10 Marzo — Cora Sternberg. Ospedale S. Camillo Forlanini Roma
Tumori del Rene: stato dell'arte

22 Marzo — Eric Gilson, Ecole Normale Superieure De Lione-Francia
Telomeric regulations in normal and cancer cells

14 Aprile — Paola Muti. University Of Buffalo State University Of New York.
Endocrine and metabolic pattern and risk of breast cancer and Breast Cancer recurrence

20 Aprile — Caterina Missero, Tigem - Telethon Institute Of Genetics And Medicine Di Napoli
Meccanismi trascrizionali che regolano l'omeostasi cutanea: ruolo di Foxe1 e di p63

12 Maggio — Andre Sentenac, Cea-Centre D'etudes De Saclay, Gif-Sur-Yvette, France
Eukaryotic RNA polymerases

20 Maggio — Matti S. Aapro Multidisciplinary Oncology Institute, Genolier, Ginevra
Supportive Care in Cancer: State of Art

3 Giugno — Xin Lu, St. Mary's Campus Di Londra
Regulating apoptosis by the ASPP family of proteins

11 Giugno — Carol J. Thiele, Nci, Nih Di Bethesda
TrkB and neuroblastoma: novel therapeutics from an understanding of tumor biology

25 Giugno — Mariano Barbacid, Centro Nacional De Investigacion Oncologicas (Cnio), Di Madrid

4th Raffaele Tecce Memorial Lecture - A new generation of animal models for cancer

1 Luglio — Francesco Di Costanzo. A. O. Careggi Di Firenze

Il Trattamento adiuvante nei tumori del colon: stato dell'arte e prospettive della ricerca

9 Settembre — Monica Fornier. Memorial Sloan-Kettering Cancer Center - New York

Attività ricerca clinica dei Trials Clinici del Memorial Sloan-Kettering Cancer Center nei Tumori della Mammella

21 Settembre — Hans Konrad Mueller-Hermelink. University Of Wuerzburg

The role of genetic studies in malignant lymphomas

6 Ottobre — Frauke Goeman, Genetic Institute, Liebig, Germany

Ing tumour suppressors induce cellular senescence and recruit chromatin modifying activity

11 Ottobre — J. Andrew Mccubrey. School Of Medicine,East Carolina University, Usa

Identification of Anchilles heel in drug resistance and cell transformation, interactions between the PI3K/PTEN/Akt and Raf/MEK/ERK

26 Ottobre — Sergio Pecorelli. University Of Brescia

Tumori ginecologici: stato dell'arte

5 Novembre — Uwe Zangemeister-Wittke. University Of Zurigo

Inducible drug resistance in small cell lung carcinoma by akt and surviving activation

30 Novembre — Jose' Baselga.Vall D'hebron University Hospital- Barcelona - Spain

New Targets in anticancer therapy

17 Dicembre — Jan Vermorken. University Hospital Antwerp, Edegem- Belgium

New Development in the Ovarian Cancer

Intramural Seminars c.r.s.

11 Febbraio — L'ubiquitinazione come meccanismo implicato nello spegnimento delle vie di segnalazione mediate dal recettore ad alta affinità per le IgE.
Rossella Paolini, Prof. II Fascia, Dipartimento Patologia Generale, Università Roma

25 Febbraio — Telomere polymorphisms and genome instability in humans
J. Arturo Londono-Vallejo, Ricercatore I livello CNRS, Parigi

10 Marzo — Function of the c-Myc oncoprotein in chromatin remodeling and transcription
Bruno Amati, Direttore di Divisione IEO, Milano

24 Marzo — Che-1 arrests human colon carcinoma cell proliferation by displacing HDAC1 from the p21WAF1/CIP1 promoter
Maurizio Fanciulli

7 Aprile — HPV-16 E7 oncoprotein targets the Nm23 proteins: a novel transforming mechanism?
Anna Maria Mileo

5 Maggio — Geni KRAB/zinc finger: aspetti genomici e molecolari di una famiglia di repressori trascrizionali dei mammiferi
Giovanna Grimaldi, I Ricercatore IGB-CNR, Napoli

11 Maggio — Bcl-2 inducion of urokinase plasminogen activator receptor expression in human cancer cells through Sp1 activation: involvement of Erk1/Erk2 activity
Daniela Trisciuoglio

9 Giugno — Requirement for down-regulation of the CCAAT-binding activity of the NF-Y transcription factor during skeletal muscle differentiation
Aymone Gurtner

8 Novembre — In vivo imaging of transcriptionally active estrogen receptors
Adriana Maggi, Direttore Centro Eccellenza Malattie Neurodegenerative, Università Milano

10 Novembre — Molecular imaging of immunological network in cancer
Alberto Signore, Dirigente I livello Policlinico Umberto I, Roma

17 Novembre — Certificazione di qualità in un laboratorio di patologia clinica all'interno di un IRCCS
Fiorella Guadagni

24 Novembre — Il ruolo del recettore dell'IGF-I nel cancro
Renato Baserga, Direttore, Kimmel Cancer Center, Jefferson University, Philadelphia USA

1 Dicembre

Controllo della trascrizione del gene CCND1 e del ciclo cellulare da ormoni estrogeni nel cancro della mammella

ALESSANDRO WEISZ, Prof. Ordinario Dipartimento Patologia Generale, II Università Napoli

15 Dicembre

Rimodellamento della cromatina e basi molecolari delle malattie degenerative cardiovascolari

CARLO GAETANO, Senior Scientist Lab. Patologia Vascolare, Istituto Dermopatico dell'Immacolata di Roma

Multidisciplinary Seminary

6 Febbraio

Aspetti clinico-terapeutici diversi delle Neoplasie Polmonari

Moderatori: F. Facciolo - F. De Marinis

Approccio Chirurgico al Mesotelioma Pleurico, S. Carlini
Aspetti di Imaging nel Mesotelioma Pleurico, M. Caterino
Trattamento con Iressa nei pazienti con NSCLC chemiorefrattari, A. Gelibter
Ruolo della chemioterapia adiuvante nel NSCLC, M. Rinaldi
Nuovi Schemi di Frazionamento Radioterapico, A. Mirri
Nuove prospettive terapeutiche nel NSCLC, F. De Marinis (A.O. S. Camillo Forlanini - Roma)

27 Febbraio

Il Carcinoma del Retto localmente avanzato o con malattia metastatica minima: strategie terapeutiche e risultati

Moderatori: M. Cosimelli - C. Garufi

Stato dell'arte, R. La Bianca (Osp. Riuniti di Bergamo)
Profili biologici di interesse clinico, F. Guadagni
Biomarcatori tessutali ad impatto prognostico, M. Mottolese
Staging, downstaging, restaging: elementi di interesse terapeutico, M. Caterino
Stadiazione e palliazione: il contributo dell'endoscopia, V. Stigliano
Il trattamento chirurgico: timing, opzioni, risultati, M. Cosimelli
Rationale clinico e potenzialità terapeutiche della radioterapia pelvica, F. Ambesi Impiombato
La chemioterapia sistemica: ottimizzazione dei risultati clinici, M. Zeuli
Un punto decisivo: la qualità della vita, P. Pugliese
Prospettive, A. Zaniboni (Casa di Cura Poliambulanza di Brescia)

23 Marzo

Novità ed alcune Esperienze nel Carcinoma della mammella

Moderatori: F. Di Filippo - M. Lopez

Nipple sparing Mastectomy e tecniche di ricostruzione, G. Psaila– M. Pozzi
Studio di Fase III Chemioterapia-Radioterapia concomitante alla vs Chemioterapia-Radioterapia Sequenziale, P. Pinnarò
Esperienza IRE con Mammotome, E. Saracca
Esperienze sulla chemioterapia settimanale, C. Nisticò
Trattamento Adiuvante:Vecchi e Nuovi Approcci, P. Papaldo- P.Vici
Nuove acquisizioni in terapia ormonale adiuvante, P. Carlini

23 Aprile

Il trattamento integrato del carcinoma tiroideo localmente avanzato

Moderatori: G. Spriano - C.L. Maini

Definizione, G. Spriano
Aspetti istopatologici, F. Marandino
I fattori prognostici, M.L. Appetecchia
Il ruolo dell' Imaging, A.Vidiri
Il Trattamento Chirurgico del T, R. Pellini

Il Trattamento Chirurgico di N, P. Ruscito
La Terapia Radiometabolica, R. Sciuto
Il ruolo della radioterapia transcutanea, G. Arcangeli
Il ruolo della chemioterapia, F. Cognetti
Novità e controversie, C.L. Maini
Lettura: Il carcinoma midollare della tiroide, M. Piemonte (A.O. S.Maria della Misericordia - Udine)

25 Maggio

Nuove integrazioni terapeutiche nel Carcinoma della Prostata

Moderatori: G. Arcangeli - M. Gallucci

Epidemiologia e Screening del carcinoma prostatico, M. Caperle
Approccio Diagnostico per Immagini (Ecografia TransRettale), S. Canitano
Casistica Chirurgica IRE della Prostatectomia, P. De Carli
Nuove Tecniche di Radioterapia: Esperienze IRE con la IORT, IMRT, Nuovi Frazionamenti, B. Saracino
Terapia radiometabolica delle metastasi ossee da Carcinoma Prostatico, R. Sciuto
Novità in terapia ormonale, F. Boccardo (Univ. degli Studi di Genova - Ist. Tumori)

15 Giugno

Ricerca Traslazionale e Nuovi Targets Molecolari

Moderatori: F. Cognetti - G. Scambia

Nuove Strategie Terapeutiche Nel Trattamento Dei Tumori Solidi Umani, C. Leonetti
Monitoraggio Della Risposta Immunitaria Nel Trattamento e Nel Follow Up dei Pazienti Oncologici, P. Nisticò
Blocco del Recettore A per l'Endotelina Come Nuova Strategia Terapeutica nel Carcinoma Ovario, A. Bagnato
Gene Expression Profiling nel Carcinoma Prostatico Umano, A. Farsetti
Studi Preclinici e Clinici con Nuovi Farmaci A Bersaglio Molecolare, M. Milella
Nuovi fattori prognostici ed implicazioni cliniche nei tumori della cervice uterina
G. Scambia (Univ. Cattolica Sacro Cuore - Policlinico Gemelli - Roma)

16 Settembre

Il Melanoma

Moderatori: Caterina Catricalà - Franco Di Filippo

Epidemiologia del melanoma, C. La Vecchia (Ist. Mario Negri di Milano)
Melanoma familiare e primitivo multiplo, P. De Simone
Fattori di rischio biologici, V. Maresca
Recettore B dell'endotelina nella progressione del melanoma cutaneo, A. Bagnato
Diagnosi precoce, C. Catricalà
Diagnosi differenziale con i simulatori del melanoma, A. Amantea
Fattori prognostici istopatologici, F. Marandino
Nuove frontiere terapeutiche, G. Parmiani (Ist. Nazionale Tumori di Milano)
Trattamento chirurgico del melanoma primitivo, S. Bucher
Tecnica e risultati del linfonodo sentinella, R. Garinei
Trattamento medico, V. Ferraresi
Per fusione ipertermia antiblastica, M. Anzà

22 Ottobre

Evoluzione della diagnostica per immagini nei tumori

MODERATORI: F. COGNETTI - M. CRECCO

Nuove tecniche di imaging nello studio delle neoplasie endocraniche e del distretto testa collo, A. VIDIRI

TC spirale: nuove applicazioni nello studio di neoplasie pleuriche e polmonari M. CATERINO

La colonscopia con TC spirale multistrato nel rilevamentodelle lesioni colorettali S. GIUNTA

RM 3 Tesla : applicazioni cliniche in campo neuroradiologico, T. SCARABINO (CASA SOLLIEVO DELLA SOFFERENZA SAN GIOVANNI ROTONDO - FOGGIA)

RM 3 Tesla : prospettive nei distretti extraneurologici, P. TORRICELLI (UNIV. DI MODENA E REGGIO EMILIA)

Radiologia Interventistica e TC angiografia nell'epatocarcinoma e nel trapianto di fegato, L. CARPANESE

I mezzi di contrasto in Ecografia: una evoluzione della Diagnostica per Immagini, G. PIZZI

Contributo della Diagnostica per immagini nel trattamento radioterapico nei tumori della prostata, A. MARSELLA

26 Novembre

Tumori Cerebrali

MODERATORI: B. JANDOLO- G. ARCANGELI

Update sulle metodiche di neuro-imaging, A. VIDIRI

La chirurgia guidata dalle immagini e le terapie loco-regionali, C. M. CARAPELLA

Le nuove metodiche radioterapiche, A. M. MIRRI

Radiosurgery e Ciberknife, L. FARISELLI (IST. CARLO BESTA DI MILANO)

Il ruolo della chemioterapia nei gliomi maligni, A. FABI

Il ruolo della chemioterapia nei gliomi a lenta evoluzione, A. PACE

Le prospettive delle terapie integrate e dei nuovi trials terapeutici, R. SOFFIETTI (UNIV. DI TORINO)

3 Dicembre

Tumori della cervice uterina

MODERATORI: C. SBIROLI-A. VECCHIONE

Epidemiologia, V. RAMAZZOTTI

Fattori Prognostici Istopatologici, F. MARANDINO

Diagnostica Ambulatoriale, L. MARIANI

Approccio Laparoscopico Nella Stadizione e nel Trattamento del Carcinoma Ovarico E. VIZZA

Modulazione Della Radicalita' Chirurgica, P.L. BENEDETTI PANICI (UNIV. DEGLI STUDI DI ROMA "LA SAPIENZA")

Integrazione Chemio-Radioterapica, R. MAURIZI ENRICI (UNIV. DEGLI STUDI DI ROMA "LA SAPIENZA")

Terapia Medica Della Malattia Avanzata, T. GAMUCCI (OSP. UMBERTO I DI FROSINONE)

Trattamenti Innovativi, G. SCAMBIA (UNIV. CATTOLICA SACRO CUORE - POLICLINICO GEMELLI - ROMA)

Breakfast-Meetings

29 Gennaio — Protocolli di screening nel carcinoma del polmone: rapporto del progetto finalizzato Ministero Sanità e dello studio ELCAP
Chairman: F. Facciolo
F. Guadagni, S. Giunta

5 Febbraio — Qualità di vita e trapianto di fegato per HCC: rapporto finale progetto
Chairman: E. Santoro
G. Vennarecci, G. Ettorre

12 Febbraio — Approccio adiuvante e neo adiuvante nei tumori della mammella
Chairman: F. Cognetti
P. Papaldo, F. Conti

19 Febbraio — Linfomi a cellule B del mediastino
Chairman: M.C. Petti
M. Marino, F. Pisani

26 Febbraio — Trattamento del carcinoma muscolo- invasivo della vescica fattori prognostici e predittivi della risposta alla chemioterapia adiuvante
Chairman: M. Gallucci
E.M. Ruggeri, A.M. Cianciulli

4 Marzo — Ottimizzazione dei marcatori tumorali nella diagnosi e nel follow up in oncologia: proposte di linee guida
Chairman: L. Di Lauro
F. Guadagni, G. La Ferla

11 Marzo — Interventi riabilitativi in oncologia
Chairman: B. Jandolo
M. Condoleo, A. Pietrangeli

18 Marzo — Chemio-prevenzione delle neoplasie della mammella e del colon
Chairman: S. Tomao
A. Savarese, V. Stigliano

25 Marzo — Il trastuzumab nel trattamento del carcinoma mammario-Problemi aperti
Chairman: M. Lopez
P. Vici, C. Nisticò

1 Aprile — Infezioni da patogeni emergenti: stato attuale e prospettive future
Chairman: A. Casali
G.P. Testore (Univ. Di Roma "Tor Vergata", M.T Galli (Univ. Di Milano)

15 Aprile — Protocolli di vaccinazione nel Melanoma Maligno Metastatico
Chairman: P.G. Natali
V. Ferraresi, F. Cavaliere

22 Aprile — Screening del carcinoma colorettale
Chairman: V. Casale
A. Grassi, V. Ramazzotti

29 Aprile — Interazioni tra oncogenesi e oncosoppressori per identificare nuove strategie terapeutiche
Chairman: G. Zupi
M. Milella, A. Biroccio

6 Maggio — Test predittivi della sensibilità o resistenza ai farmaci citotossici: studi di fase III sul carcinoma ovarico
Chairman: C. Sbiroli
G. Zupi, G. Ferretti

13 Maggio — Ruolo dei taxani nella prima prima linea metastatica del carcinoma mammario
Chairman: E. Terzoli
E. Bria, D. Giannarelli

20 Maggio — Neoplasie gliali: fattori prognostici e biomolecolari
Chairman: F. Marandino
M. Carosi, A. Cianciulli

27 Maggio — IORT versus radioterapia convenzionale nel carcinoma della mammella
Chairman: G. Arcangeli
P. Pinnarò, C. Botti

3 Giugno — Il linfonodo sentinella nel carcinoma gastrico
Chairman: E. Santoro
P. Lepiane, P. Visca

10 Giugno — Opzioni terapeutiche nel trattamento integrato delle neoplasie del pancreas
Chairman: G. Arcangeli
M. Milella, F. Carboni

17 Giugno — Espressione di geni proinfiammatori nel carcinoma mammario umano come indicatore di prognosi e come individuazione di bersagli molecolari
Chairman: R. Perrone Donnorso
M. Russo, F. Marandino

30 Settembre — Prolonged Gemcitabine Infusion In Advanced Non-Small Cell Lung Carcinoma: A Randomized Phase Ii Study of Two Different Schedules in Combination With Cisplatin. Cancer, JUL 15;98(2): 337-343, 2003
Chairman: M. Rinaldi
Ceribelli, F. De Marinis (Osp. Forlanini - Roma)

7 Ottobre — Venous Thromboembolism Nd Cancer :New Issues For An Old Topic. Crit Rev Oncol Hematol 2003 Oct, 48(1):65-80.
Chairman: L. Conti
G.L. Ferretti, G. Gandolfo (Univ. La Sapienza - Roma)

14 Ottobre — A Phase II Study Of Irinotecan Plus Chronomodulated Oxaliplatin, 5 Fu And Folinic Acid In Advanced Colorectal Cancer Patients. Br. J. Cancer 2003, nov 17;89(10),1870-5
CHAIRMAN: E. TERZOLI
C. GARUFI, A. ALBERTI (OSP. PERTINI - ROMA)

21 Ottobre — The Future Of Antisense Therapy:Combination With Anticancer Treatments.Oncogene 2003, SEP 29;22(42):6579-6588
CHAIRMAN: G. ZUPI
C. LEONETTI, A. RUGHETTI (UNIV. LA SAPIENZA - ROMA)

28 Ottobre — Altered Expression Of Fas System Is Related To Adverse Clinical Outcome In Stage I-Ii Breast Cancer Patients Treated With Adjuvant Antracycline-Based Chemotherapy. Clin. Cancer Res. 2004 feb. 15, 10(4):136O-5
CHAIRMAN: M. MOTTOLESE
C. BOTTI, E. RICEVUTO (UNIV. L'AQUILA)

4 Novembre — Temozolomide Chemotherapy For Progressive Low-Grade Glioma:Clinical Benefits And Radiological Response. Ann Oncol 2003, Dec.,14(12):1722-1726.
CHAIRMAN: B. JANDOLO
A. PACE, M. BARDUAGNI (AZ. OSP. ANZIO - NETTUNO)

11 Novembre — Elective Treatment Of The Neck in Squamous Cell Carcinoma of the Larynx: Clinical Experience Head Neck 2003, Feb 25(2), 97-102
CHAIRMAN: G. SPRIANO
R. PELLINI, A. GALLO (UNIV. LA SAPIENZA - ROMA)

18 Novembre — 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-August, 89(4 Suppl) 21-23.
CHAIRMAN: F. DI FILIPPO
F. CAVALIERE, C.R. ROSSI (UNIV. DI PADOVA)

25 Novembre — Genetic Instability in Superficial Bladder Cancer and Adjacent Mucosa: an Interphase Cytogenetic Study. Hum Pathol 2003 Mar,34(3),214-221.
CHAIRMAN: M. GALLUCCI
A.M. CIANCIULLI, F. MARANDINO

2 Dicembre — The Endothelin Axis: Emerging Role in Cancer Nat. Rev. Cancer, Feb. 3(2), 110-6, 2003.
CHAIRMAN: P.G. NATALI
A. BAGNATO, G. SCAMBIA (UNIV. CATTOLICA SACRO CUORE - ROMA)

9 Dicembre — Is Delayed Chemotherapy-Induced Emesisi Well Managed in Oncological Clinical Practice? An Bservational Study. Support. Care Cancer. MAR 11(3), 156-61, 2003
CHAIRMAN: F. POLLERA
A. FABI, G. LANZETTA (INI - GROTTAFERRATA - ROMA)

Organization of Seminars and Meetings

Roma, 30-31 Gennaio	Convivium "Nuove conoscenze sul dolore Oncologico ed implicazioni cliniche nella Terapia con Oppioidi" (Prof. Arcuri E.)
Roma, 17 Febbraio	Genetic complexity of an inherited disease: splicing factor genes involved in retinis pigmentosa (Prof. Rivolta C.)
Roma, 17 Febbraio	Expression of a new NF-kb inhibitor in thymocytes during negative selection (Prof.ssa Fiorini E.)
Viterbo, 11 Marzo	Progressi nella diagnosi e nella terapia dei tumori ovarici. Incontri della Ricerca (AIRC) (Prof. Natali P.G.)
Roma, 12 Marzo	Corso su: Neoplasie gastriche e pancreatiche. (Prof. Arcangeli G.)
Cremona, 22-23 Aprile	Corso di formazione per infermieri: "Informazione e comunicazione col malato oncologico/Creazione e gestione di una biblioteca per pazienti e dei Punti di Informazione supporto (PIS) nei reparti oncologici". (Dr.ssa Cognetti G.)
Roma, 22 Aprile	Accademia Medica. Progressi in Patologia Oncologica Ovarica (Prof. Natali P.G.)
Cortona, 22-24 Aprile	Convegno SIBBM 2004 - "Struttura e Funzione del Genoma". (Dr. Blandino G.)
Napoli, 26 Aprile	Corso teorico-pratico in Economia e Gestione Aziendale per Dirigenti Amministrativi, Tecnici e Professionali. (Fonti informative in Internet per la gestione Sanitaria) (Dr.ssa Cognetti G.)
Brescia, 3 Maggio	Corso di Ingegneria tissutale " Cellule staminali e progenitori in applicazioni cliniche di ingegneria tissutale", organizzato dall'AICC in collaborazione con la Fondazione Iniziative Zooprofilattiche e Zootecniche. (Dr. Leonetti C.)

Palermo, 26-27 Maggio	Convivium "Nuove conoscenze sul dolore Oncologico ed implicazioni cliniche nella Terapia con Oppioidi" (Prof. Arcuri E.)
Vicenza, 26 - 29 Maggio	Congresso S.N.O. (Prof. Jandolo B.)
La Ciotat, France, 28 Maggio	One Day Meeting "Tyrosine Kinase". (Dr. Segatto O.)
Roma, 3-5 Giugno	Corso su: Evolving Strategies in Radiation Oncology. (Prof. Arcangeli G.)
Dogliani (TO), 18-19 Giugno	Convivium "Nuove conoscenze sul dolore Oncologico ed implicazioni cliniche nella Terapia con Oppioidi" (Prof. Arcuri E.)
Roma, 23-25 Giugno	VII Congresso Nazionale GOIM. (Prof. Lopez M.)
Bologna, 28-30 Giugno	Corso di citogenetica molecolare e microarrays: aspetti metodologici e applicativi, organizzato dall'AICC in collaborazione con gli Istituti Ortopedici Rizzoli (IOR). (Dr. Leonetti C.)
Roma, 7 Settembre	Corso teorico pratico su "EGFR e target therapy: Il ruolo sinergico tra oncologo e anatomo-patologo" Merck. EGFR: Meccanismo Molecolare. (Dr.ssa Mottolese M.)
Genova, 25-29 Settembre	Congresso S.I.N. 2004. (Prof. Jandolo B.)
Roma, 28 Settembre	Meeting: "Protocollo ST1472-DM-01-012 - Timosina alfa 1 - Melanoma" (Dr.ssa Ferraresi V.)
Riva del Garda, 30 Settembre	6° Convegno Nazionale FISV -: "Ciclo cellulare ed organizzazione del genoma, bioinformatica e molecular modelling". (Dr. Segatto O.)
Roma, 2-3 Ottobre	II Convegno Nazionale " Nuove prospettive terapeutiche del carcinoma mammario" Roche. Ibridazione In Situ Cromogenica. (Dr.ssa Mottolese M.)
Roma, 22-24 Ottobre	Corso teorico pratico in Citopatologia Cervico–vaginale e biologia molecolare applicata assistito da docenti–tutor. (Dr.ssa Vocaturo A.)
Roma, 25 Ottobre	Il trapianto di cellule staminali. (Prof.ssa Petti M.C.)

Roma, 28 Ottobre	4° progetto "Educazione alla salute".Prevenzione Tumori & Alimentazione e Salute (Prof. Natali P.G.)
Brescia, 15-16 Novembre	II Corso di formazione teorico pratico "Tecniche di base per la coltura di cellule in vitro", organizzato dall'AICC in collaborazione con il Centro Substrati Cellulari, Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna (Dr. Leonetti C.)
Verona, 19-20 Novembre	Convivium "Nuove conoscenze sul dolore Oncologico ed implicazioni cliniche nella Terapia con Oppioidi" (Prof. Arcuri E.)
Napoli, 9-10 Dicembre	Convegno Annuale ONLUS-AICC: "Apoptosi tra fisiologia e patologia" (Dr. Leonetti C.)
Roma, 17-19 Dicembre	Corso teorico pratico in Citopatologia Cervico–vaginale e biologia molecolare applicata assistito da docenti–tutor (Dr.ssa Vocaturo A.)

Certified Courses

56° Corso di Formazione per volontari AMSO, anno 2004

Corso di formazione per volontari ARVAS, anno 2004

III Corso di formazione: Azalea
Riunione di formazione e operativa del gruppo di ricerca
Il coordinamento e l'armonizzazione dei progetti di informazione ai pazienti
(Dr.ssa Cognetti G.)
Roma, 2-3 Febbraio

Convegno: "L'AIOM incontra la SIOG - innovazione e problemi aperti in oncologia ginecologica"
(Prof. Tomao S.)
Roma, 12 Marzo

Corso: "Chirurgia in oncologia ginecologica"
(Prof. Arcangeli G.)
Roma, 15-16 Marzo, 19-20 Aprile, 17-18 Maggio, 21-22 Giugno

Workshop: "La prevenzione oncologica: prassi ed etica"
(Dr. Cilenti V.)
Roma, 22 Marzo

Convegno: "The 2nd p73/p63 International Workshop"
(Dr. Blandino G.)
Roma, 25-27Marzo

Convegno: "II giornata di Gastroenterologia Oncologica IRE"
(Dr.Casale V.)
Roma, 17 Aprile

Corso: "Tumori cerebrali maligni: dal trattamento terapeutico alle cure palliative"
(Dr. Carapella C. - Dr. Pace A.)
Roma, 7 Maggio

Convegno: "La moderna radioterapia: aspetti scientifici, tecnici e psicologici"

AITRO/IRE Vincenzo Lunghi - Federazione Nazionale Collegi Professionali - Tecnici Sanitari di Radiologia Medica)

Roma, 28 Maggio

Corso di Formazione: "Seminario teorico-pratico per gli operatori addetti alla manipolazione dei citostatici

(Dr. Musicco F.)

Roma, 23-24 Giugno

"Il dolore e le cure palliative in oncologia"

(Prof. Cognetti F. - Prof. Di Costanzo)

Roma, 2 Luglio

Workshop: "Promise Study - International Study on Prostate Cancer"

(Prof.ssa Muti P.)

Roma, 1 Settembre

Workshop: "Le procedure di qualità nell'assistenza farmaceutica orientata al paziente oncologico"

(Dr. Musicco F.)

Roma, 28 Ottobre

Stage Teorico-pratico: "Chemioterapie settimanali nelle principali neoplasie" (n. 5 giornate 2004)

(Dr.ssa Nisticò C.)

"4° Seminario internazionale di chirurgia digestiva oncologica"

(Prof. Santoro E.)

Roma, 4-6 Novembre

Corso: "I Corso teorico-pratico di formazione-informazione riservato agli infermieri professionali che allestiscono le terapie citotossiche"

(Dr. Ascani A.)

Roma, 11 Novembre

"Docetaxel nel NSCLC: il paziente al centro della terapia"

(Prof. Cognetti F.)

Roma, 26 Novembre

Convegno: "Meeting Europeo p53 mutata"

(Dr.ssa Sacchi A.)

Roma, 26-28 Novembre

Convegno: "L'AIOM incontra la SIOG - innovazione e problemi aperti in oncologia ginecologica"

(Prof. Tomao S.)

Roma, 29 Novembre

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, Citopatologia, Istocitodiagnostica in Ematologia, Istocitodiagnostica Giencologica.

Anestesia e Rianimazione

Anaesthesiology and Intensive Care

Università "Campus Biomedico", Roma

Insegnamenti: Terapia del dolore

Università Di Palermo

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

Università "Campus Bio-Medico", Roma

InsegnamentI: Chirurgia Generale: colon, retto e ano: Anatomia chirurgica, patologia chirurgica e tecnica chirurgica.

Chirurgia Toracica

Thoracic Surgery

Università Degli Studi "La Sapienza", Roma

Insegnamenti: : Endoscopia Toracica

Chirurgia Vascolare

Vascular Surgery

Università Degli Studi "La Sapienza", Roma

Insegnamento: Accessi vascolari in Chirurgia Oncologica

Dermatologia e Venereologia

Dermathology

Università Degli Studi "Tor Vergata" Roma

Insegnamenti: Dermatologia Clinica

Endocrinologia e malattie metaboliche

Endocrinology and Metabolic Diseases

Università Degli Studi "La Sapienza", Roma

Insegnamenti: Endocrinologia, Andrologia, Malattie del Ricambio

Ematologia

Emathology

Università Degli Studi "La Sapienza", Roma

Insegnamenti: Manifestazioni cliniche delle emopatie

Università Campus Biomedico, Roma

Insegnamenti: Principi e metodiche per lo studio delle emopatie maligne

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, Produzione di radiofarmaci PET mediante ciclotrone

Università Della Calabria

Master di II livello: Formazione Esperto in Radioprotezione e Dos

Insegnamento: Sistemi gestione qualità

Gastroenterologia

Gastroenterology

Università Degli Studi "La Sapienza", Roma

Insegnamenti: Endoscopia digestiva, Ematologia

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

Università "La Sapienza", Roma

Insegnamento: Master II° livello in: "Terapia radio-metabolica

Neurologia

Neurology

Università degli Studi "La Sapienza", Roma

Insegnamenti: Patologia Elettromiografica ed Elettroneurografica

Neurochirurgia

Neurosurgery

Università degli Studi "Tor Vergata", Roma

Insegnamenti: Neurochirurgia III e V, Neurochirurgia Stereotassica e Funzionale, Neurofisiologia

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, Carcinoma della mammella, Ormonoterapia nel trattamento del carcinoma, Chirurgia oncologica

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. Chirurgia Ricostruttiva.Nuove Strategie Terapeutiche Integrate del Tratto Gastroenterico.

Università Cattolica Del S. Cuore, Roma

Insegnamenti: Immunologia

Università Degli Studi, L'aquila

Insegnamenti: Patologia Molecolare, Patologia Genetica

Università Degli Studi Di Chieti

Insegnamenti: Oncologia Medica

Patologia Clinica

Clinical Pathology

Università Degli Studi "La Sapienza", Roma

Insegnamenti:Virologia - Corso integrato di batteriologia e Virologia, Patologia Generale, Fisiopatologia Generale.

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 laurea per Tecnici di Neurofisiopatologia.

Università Degli Studi "La Sapienza", Roma

Insegnamenti: Tecniche di Registrazione Elettromiografiche.

Corso di Laurea per Infermiere Professionale e Pediatrico.

Università Degli Studi "La Sapienza", Roma

Insegnamenti: Neurologia Clinica, Psichiatria e Igiene Mentale, Fisiopatologia e Patologia Clinica, Malattie dell'apparato respiratorio, Chirurgia Generale II anno, Chirurgia d'urgenza III anno, Medicina Interna, Eondocrinologia, Malattie Infettive, Neurochirurgia, Statistica Medica, Chimica, Fisiologia Umana, Genetica Medica, Patologia Clinica, Informatica e Scienza dell'informazione, Statistica Medica, Fisica Applicata, Informatica e Scienza dell'informazione

Corso biennale in Psicologia Oncologica

Insegnamenti: Tumori ereditari e counselling genetico. Un modello integro: aspetti medici". Fattori diagnostici, prognostici, e possibili interventi terapeutici

Corso di Laurea in Medicina e Chirurgia

Università Degli Studi "La Sapienza", Roma

Insegnamento: Immunologia

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

Corso di Laurea in Medicina e Chirurgia

Università "G. D'Annunzio", Chieti

Insegnamento: Patologia e Fisiopatologia Generale

Università Degli Studi "Tor Vergata", Roma

Insegnamento: Radioterapia

Universita'" Cattolica S. Cuore", Roma

Insegnamento: Immunologia

Università Degli Studi Di Palermo

Insegnamenti: Biotecnologie nella diagnostica oncologica di laboratorio, Controllo di qualità in oncobiopatologia

Corso di Laurea in Dietista

Università "G. D'Annunzio", Chieti

Insegnamenti: Patologia Generale, Patologia Clinica

Corso di Laurea in Fisioterapista

UNIVERSITÀ "G. D'ANNUNZIO", CHIETI

Insegnamento: Patologia Generale

Corso di Laurea in Farmacia

UNIVERSITÀ "G. D'ANNUNZIO", CHIETI

Insegnamenti: Patologia Generale

Overseas Training and Experience

Dr. Alimonti Andrea - S.C. Oncologia Medica "A"

(giugno 2004 - dicembre 2005)

Molecular and development biology. Memorial Sloan Cattering New York (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.Ssa Maria Simona Pino - S.C. Oncologia Medica "A"

(giugno 2003 - settembre 2005)

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

Dr.Ssa Carmen Priolo - Lab. Di Oncogenesi Molecolare, S.C. Oncologia Medica "A"

(maggio 2004 - maggio 2006)

Molecular Pathology Laboratory, Molecular and Cellular Oncology Division, Medical Oncology Department, Dana Farber Cancer Institute, Boston, MA, (USA).

Dr.Ssa Valentina Folgiero - Lab. Di Oncogenesi Molecolare

(30 giugno 2004 - settembre 2004)

Department of Pathology Beth Israel Deaconess Medical Center Harvard Medical School.

Participation to Definition of Guidelines

Gruppo di studio sulla radioterapia con adroni implementazione di una rete di centri clinici sul territorio nazionale. Associazione Italiana Radioterapia Oncologica (AIRO)
Dr. Benassi M.

Garanzia di qualità in radioterapia: la pianificazione del trattamento. Istituto Superiore di Sanità - Rapporto ISTISAN 04/7, ISSN 1123-3117
Dr. Benassi M.

Gruppo di lavoro operante presso l'ASP (Agenzia di Sanità Pubblica) regionale per l'approfondimento delle condizioni clinico-organizzative di erogabilità a domicilio di prestazioni pneumologiche di particolare complessità e relative linee guida
Dr. Cilenti V.

"Linee guida per una corretta informazione dei pazienti con cancro, dei loro familiari ed amici, all'interno delle strutture sanitarie." - Associazione Italiana Oncologia Medica.
Dr.Ssa Cognetti G.

"Raccomandazioni per una corretta informazione dei pazienti con cancro, dei loro familiari e amici, all'interno delle strutture sanitarie." - Associazione Italiana Oncologia Medica.
Dr.Ssa Cognetti G.

Protocollo italiano per il controllo di qualità degli aspetti fisici e tecnici in mammografia. Associazione Italiana Fisica in Medicina (AIFM)
Dr. Gentile P.F.

Raccomandazioni per l'assicurazione di qualità in Risonanza Magnetica. Associazione Italiana Fisica in Medicina (AIFM)
Dr. Di Nallo A.

Indicatori generali di valutazione per radioterapia alla luce di un primo audit clinico. Istituto Superiore di Sanità - Rapporto ISTISAN 04/27, ISSN 1123-3117
Dr.Ssa Soriani A.

Research Projects

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 (€ 154.937,06)

Italian Association for Cancer Research (A.I.R.C.)

Expanding the therapeutic repertoire of endothelin a reception blockade in ovarian cancer.

Responsabile: Anna Bagnato (€ 60.000,00)

Role of telomere maintenance on melanoma malignant behavior in order to identify new therapeutic strategies.

Responsabile: Anna Maria Biroccio (€ 50.000,00)

Linking cancer transcriptome to proteome: functional oncogenomics for diagnosis and treatment of human cancers (Rome Oncogenomic Center - ROC).

Responsabile: Giovanni Blandino (€ 650.000,00)

Studies of the mechanisms by which bcl-2 over expression increases angiogenic activity.

Responsabile: Donatella Del Bufalo (€ 80.000,00)

Characterization of Che-1 activation in response to DNA damage.

Responsabile: Maurizio Fanciulli (€ 40.000,00)

Altered HLA phenotypes in tumors and their correction.

Responsabile: Patrizio Giacomini (€ 35.000,00)

Preclinical development of MEK inhibition-based therapeutic strategies for acute leukemias.

Responsabile: Michele Milella (€ 50.000,00)

Cluster of molecular prognostic indicators in the big, subtle killers: breast, prostate, and colon cancers.

Responsabile: Pier Giorgio Natali (€ 50.000,00)

Novel cellular targets of the Human Papillomavirus-16 oncoproteins: unraveling their functional significance.

Responsabile: Marco Giorgio Paggi (€ 60.000,00)

Dissecting NF-Y activity and its role in cell cycle control and apoptosis.

Responsabile: Giulia Piaggio (€ 30.000,00)

Identification of genes activated/repressed by mutant p53 and p53 family members using micro arrays.

Responsabile: Ada Sacchi (€ 80.000,00)

Novel mechanisms of tumor suppression in human breast cancer.

Responsabile: Oreste Segatto (€ 25.000,00)

HIPK2, a potent inductor of apoptosis: characterization of molecular pathways and role in tumorgenesis.

Responsabile: Silvia Soddu (€ 90.000,00)

p53 family interactions as determinants for tumor response to anti-neoplastic treatment.

Responsabile: Sabrina Strano (€ 50.000,00)

E.C.

Manipulating tumor suppression: a key to improve cancer treatment.

Responsabile: Giovanni Blandino (€ 750.000,00)

Artificial regulation of cell cycle in cancer cells and its potential clinical applications.

Responsabile: Pier Giorgio Natali (€ 180.000,00)

Mutant p53 as a target for improved cancer treatment

Responsabile: Ada Sacchi (€ 481.867,00)

CNR-MIUR

Ruolo dell'endotelina-1 nella progressione del carcinoma ovarico: nuove prospettive terapeutiche.

Responsabile: Anna Bagnato (€ 51.645,68)

Monitoraggio biochimico del marker di attività angiogenica VEGF: Implicazioni prognostiche e terapeutiche nel melanoma cutaneo.

Responsabile: Francesco Cognetti (€ 33.568,71)

Terapie adiuvanti basate sul profilo biologico del carcinoma colorettale curabile.

Responsabile: Maurizio Cosimelli (€ 41.315,56)

Comportamento alle coapplicazioni delle metodologie statistico matematiche alla diagnostica clinica per immagini con particolare riferimento alla RM nella patologia mammaria.

Responsabile: Marcello Crecco (€ 12.911,42)

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 (€ 38.733,28)

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 (€ 41.316,56)

Differenziazione p53 e p73 - Dipendente nella terapia del cancro.

Responsabile: Ada Sacchi (€ 61.974,82)

Modulazione del trattamento antineoplastico in relazione all'espressione di alcuni geni coinvolti nel processo apoptotico e nella farmacoresistenza.

Responsabile: Gabriella Zupi (€ 82.633,10)

MIUR-FIRB

Exploring direct target genes of p53 and p73 proteins in vivo

Responsabile: Giulia Piaggio (€ 145.000,00)

Modulazione razionale dell'attività antitumorale di farmaci "classici" tramite intervento selettivo su specifiche cascate regolatorie.

Responsabile: Ada Sacchi (€ 53.194,00)

Meccanismi di trasduzione del segnale e funzione sinaptica: sviluppo di modelli molecolari, cellulari e animali.

Responsabile: Oreste Segatto (€ 93.000,00)

Compagnia di San Paolo

Tumori Testa-Collo: Identificazione di Targets Molecolari per Diagnosi Precoce e Terapia.

Responsabile: Aldo Venuti (€ 118.000,00)

Italian Institute of Health

Meccanismi di resistenza e terapie innovative del melanoma umano.

Responsabile: Francesco Cavaliere (€ 28.000,00)

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 (€ 96.000,00)

Le basi metodologiche per una chemioterapia anti-tumorale mirata: il saggio dell'EDR nel carcinoma ovarico ed in altre neoplasie (Programma Oncotecnologico).

Responsabile: Francesco Cognetti (€ 50.000,00)

Contributo clinico-scientifico allo studio del carcinoma della mammella, del colon, dell'ovaio e del polmone (programma Italia-USA "Farmacogenomica Oncologica - Oncoproteomica").

Responsabile: Francesco Cognetti (€ 198.000,00)

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 (€ 61.000,00)

Sviluppo di nuove strategie di immunoterapia e terapie combinate contro i tumori: istituzione di una banca biologica.

Responsabile: Fiorella Guadagni (€ 54.000,00)

Marcatori prognostici e strategie terapeutiche su base immunologica.

Responsabile: Fiorella Guadagni (€ 31.800,00)

Studio dell'efficacia di nuove modalita' di "delivery" di molecole antitumorali per migliorare il trattamento dei tumori solidi umani.

Responsabile: Carlo Leonetti (€ 36.000,00)

Uso di nuove metodiche di delivery di agenti neoplastici allo scopo di migliorare la risposta al trattamento di tumori solidi umani impiantati in topi immunodepressi.

Responsabile: Carlo Leonetti (€ 16.753,00)

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 (€ 61.000,00)

Carcinoma del colon-retto: bersagli molecolari rilevanti per il processo tumorigenico e per l'immunoterapia.

Responsabile: Pier Giorgio Natali (€ 31.800,00)

Definizione di nuovi criteri per la selezione di pazienti da arruolare in studi clinici di immunoterapia ed identificazione di nuovi antigeni tumorali nel carcinoma della mammella mediante tecnologia SEREX.

Responsabile: Paola Nisticò (€ 45.000,00)

Controllo della stabilità del genoma: bersagli molecolari rilevanti nella prevenzione e nel controllo del processo neoplastico: p53 mutata e modulazione risposta ai farmaci antineoplastici.

Responsabile: Ada Sacchi (€ 39.298,00)

Identification of si RNA of p53 family members to develop new antineoplastic drug.

Responsabile: Ada Sacchi (€ 110.000,00)

Differentiation defects and transformation potential of myelodiplastic syndroms: underlyng mechanisms and averriding strategies.

Responsabile: Silvia Soddu (€ 41.000,00)

Approccio proteomico allo studio della malattia neoplastica.

Responsabile: Silvia Soddu (€ 47.600,00)

Italian League against Cancer

La relazione d'aiuto nella pratica clinica infermieristica.

Responsabile: Anita Caruso (€ 87.797,68)

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 (€ 196.253,62)

Studio delle alterazioni fenotipiche e molecolari nel tessuto peritumorale morfologicamente indenne del carcinoma mammario: implicazioni diagnostiche.

Responsabile: Marcella Mottolese (€ 90.000,00)

Profilo biologico del carcinoma della mammella associato a malattia linfoproliferativa cronica: valutazione immunofenotipica e citogenetica per una migliore definizione della prognosi nell'ipotesi di una eziologia comune.

Responsabile: Maria Concetta Petti (€ 64.649,00)

Progetto Voce.

Responsabile: Giuseppe Spriano (€ 50.000,00)

Progetto pilota integrato di informazione, educazione sanitaria e formazione oncologica per il personale docente delle Scuole Medie Superiori.

Responsabile: Silverio Tomao (€ 50.000,00)

Ministry of Health

Uptake intratumorale come causa di scarsa risposta alla morfina nella terapia del dolore da cancro.

Responsabile: Edoardo Arcuri (€ 150.805,42)

Programma di sorveglianza per l'identificazione e prevenzione di tumori mammari ad alto rischio genetico.

Responsabile: Francesco Cognetti (€ 150.805,42)

Caratterizzazione del ruolo di Che-1 nel fenotipo neoplastico e nell'apoptosi.

Responsabile: Maurizio Fanciulli (€ 201.418,19)

Profili di espressione genica e immunoevasione: dal melanocita al melanoma metastatico.

Responsabile: Pier Giorgio Natali (€ 201.418,19)

Ruolo di nuovi indicatori biomolecolari dell'epatocarcinoma su cirrosi in relazione all'efficacia dei diversi approcci terapeutici.

Responsabile: Eugenio Santoro (€175.595,35)

Identificazione di molecole coinvolte nello stress ossidativo quali bersagli per la terapia antitumorale.

Responsabile: Gabriella Zupi (€ 377.529,99)

Profili di espressione dei geni p53-relati p73/p63 in cellule normali e trasformate: identificazione di nuovi bersagli terapeutici.

Responsabile: Giovanni Blandino (€ 294.000,00)

Sviluppo di modelli animali transgenici per gli oncogeni c-Myc, Ret ed il gene oncosoppressore Fhit.

Responsabile: Gennaro Citro (€ 294.000,00)

Controllo neuroendocrino della crescita a modulazione immunitaria nei tumori epiteliali del timo.

Responsabile: Franco Facciolo (€ 245.000,00)

Ruolo del microambiente e ricerca di nuovi target terapeutici nel carcinoma prostatico.

Responsabile: Michele Gallucci (€ 147.000,00)

Caratterizzazione funzionale e molecolare degli effetti di farmaci interferenti con la trasduzione del segnale e la trascrizione.

Responsabile: Michele Milella (€ 372.000,00)

Identificazione e caratterizzazione funzionale di nuovi antigeni nel carcinoma della mammella.

Responsabile: Paola Nisticò (€ 294.000,00)

Il blocco del recettore a dell'endotelina come nuovo approccio terapeutico antitumorale.

Responsabile: Anna Bagnato (€ 132.800,00)

Alterazioni fenotipiche e molecolari associate alla risposta a terapie ormonali in pazienti affette da carcinoma mammario.

Responsabile: Marcella Mottolese (€ 88.600,00)

Espressione di geni proinfiammatori nel ca mammario umano come indicatore di prognosi e come individuazione di bersagli molecolari.

Responsabile: Raffaele Perrone Donnorso (€ 256.000,00)

Studio e manipolazione dell'attivita' apoptotica del complesso p53/hipk2 per il miglioramento della terapia antitumorale.

Responsabile: Silvia Soddu (€ 132.800,00)

Studio delle interazioni tra oncogeni e oncosoppressori per identificare nuove strategie terapeutiche.

Responsabile: Gabriella Zupi (€ 380.800,00)

Monitoraggio terapeutico dei farmaci antineoplastici e farmacocinetica clinica.

Responsabile: Gennaro Citro (€ 230.000,00)

Meccanismi molecolari implicati nella generazione di resistenza al trattamento con Herceptin in carcinomi della mammella.

Responsabile: Francesco Cognetti (€ 230.000,00)

Tumori neuroendocrini dell'apparato digerente: caratterizzazione clinico-patologica molecolare ed ottimizzazione terapeutica.

Responsabile: Pasquale Perri; Capofila: R. Canizzaro, C.R.O. - Aviano (€ 51.000,00)

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 (€ 35.635,53)

Caratterizzazione della risposta a diversi trattamenti antineoplastici (sensibilità e apoptosi).

Responsabile: Donatella Del Bufalo; Capofila: G. Ragona, Neuromed - Isernia (€ 20.658,28)

Controllo Qualità nel laboratorio oncologico: concerted action nazionale, definizione interventi prioritari, metodologie e realizzazione.

Responsabile: Marcella Mottolese; Capofila: A.V. Paradiso, Ist. Oncologico - Bari (€ 18.075,99)

Vitiligine: studio sui meccanismi patogenetici e sulle modalità di approccio terapeutico.

Responsabile: Marco Giorgio Paggi; Capofila: M. Piccardo, I.S.G. - Roma (€ 34.086,16)

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 (€ 36.668,44)

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 (€ 60.425,46)

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 (€ 65.000,00)

Sviluppo e validazione di strategie terapeutiche innovative indirizzate a contrastare meccanismi di sopravvivenza cellulare.

Responsabile: Anna Biroccio; Capofila: M. G. Daidone, Int - Milano (€ 45.000,00)

Marcatori molecolari ed immunoterapia genica per la diagnosi ed il trattamento dei gliomi diffusi.

Responsabile: Carmine Carapella; Capofila: G. Felice, Neuromed - Isernia (€ 10.625,00)

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 (€ 22.000,00)

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 (€ 59.000,00)

Strategie di immunoterapia contro genotipi di HPV oncogeni e non oncogeni.

Responsabile: Luciano Mariani; Capofila: A. Di Carlo, I.S.G. - Roma (€ 23.000,00)

Nuove strategie terapeutiche di combinazione: ipometilazione del DNA e bioimmunoterapia.

Responsabile: Marcella Mottolese; Capofila: M. Maio, C.R.O. - Aviano (€ 27.000,00)

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 (€33.300,00)

I sistemi EGFR e VEGF delle cellule stremali emopoietiche: un bersaglio terapeutico innovativo per le neoplasie ematologiche.

Responsabile: Maria Concetta Petti; Capofila: Int Pascale - Napoli (€ 20.000,00)

L'apoptosi nella crescita tumorale e in terapia: identificazione e caratterizzazione di nuovi meccanismi di regolazione.

Responsabile: Silvia Soddu; Capofila: K. Helin, I.E.O. - Milano (€ 37.200,00)

Strategie di immunoterapia contro genotipi di HPV oncogeni e non oncogeni.

Responsabile: Aldo Venuti; Capofila: A. Di Carlo, I.S.G. - Roma (€ 43.500,00)

Lead molecules inibitrici di alcune signaling proteins affette da eccesso/deregulazione di funzione.

Responsabile: Gennaro Citro; Capofila: S. Parodi, Ist - Genova (€ 21.200,00)

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 (€ 21.200,00)

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 (€ 16.335,00)

Caratterizzazione di potenziali bersagli biomolecolari nella terapia antitumorale delle neoplasie del sistema nervoso centrale.

Responsabile: Paola Nisticò; Capofila: Neuromed - Isernia (€ 31.000,00)

Studio delle varianti alleliche del gene MC1-R ed associazione con il melanoma cutaneo.

Responsabile: Marco Giorgio Paggi; Capofila: C. Catricala', I.S.G. - Roma (€ 30.500,00)

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 (€ 16.500,00)

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 (€ 50.000,00)

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 (€ 4.000,00)

Studio del ruolo di CC-779 nell'angiogenesi tumorale.

Responsabile: Donatella Del Bufalo; Capofila: A. Albini, Ist - Genova (€ 28.750,00)

Nuove strategie integrate per l'ottimizzazione del trattamento del cancro colorettale.

Responsabile: Carlo Leonetti; Capofila: A. Budillon, Int Pascale - Napoli (€ 29.000,00)

EGFR, ErB-2 e COX-2 nel carcinoma della mammella: correlazioni funzionali e applicazioni terapeutiche.

Responsabile: Michele Milella; Capofila: N. Normanno, Int Pascale - Napoli (€ 28.000,00)

Network virtuale per una Bio Banca Oncologica Nazionale.

Responsabile: Marcella Mottolese; Capofila: A. Paradiso, Ist. Oncologico - Bari (€ 20.000,00)

Identificazione dei profili molecolari dei tumori cerebrali primitivi

Responsabile: Carmine Maria Carapella; Capofila: F. Giangaspero, Neuromed - Isernia (€ 20.000,00)

Ministry of Health - Dompé S.p.A, Co-funded

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 (€ 101.200,00)

Ministry of Foreign Affairs

Prevenzione del tumore della cervice uterina.

Responsabile: Federico De Marco (€ 35.000,00)

Province of Rome

Programma di prevenzione dei tumori della cute nei bambini delle scuole materne della Regione Lazio.

Responsabile: Maria Cecilia Cercato (€ 11.000,00)

Lazio Region

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 (€ 10.000,00)

Proposta di un programma di screening del tumore polmonare per la Regione Lazio.

Responsabile: Fiorella Guadagni (€ 323.818,48)

Assistenza continuativa integrata e neuroriabilitazione a domicilio per pazienti affetti da tumori cerebrali.

Responsabili: Andrea Pace, Alfredo Pompili (€ 200.000,00)

Valutazione dell'impatto clinico, psicologico e socio-sanitario del ricovero temporaneo in Hospice di pazienti in Cure Palliative.

Responsabile: Edmondo Terzoli (€ 147.000,00)

Studio della valutazione dell'obesità come fattore per patologie cardiovascolari e neoplasie.

Responsabile: Maria Luisa Appetecchia; Capofila: E. Brunetti, A.Fa.R. - Roma (€ 31.000,00)

Identificazione e caratterizzazione di geni di suscettibilità alle malattie dermatologiche a patogenesi autoimmune/infiammatoria.

Responsabile: Giovanni Blandino; Capofila: S. Chimenti, Univ. Tor Vergata - Roma (€ 18.000,00)

Telethon

Functional role of the HIPK2/p53 interaction in differentiation and development.

Responsabile: Silvia Soddu (€ 139.443,36)

Transgenic Mice Service Center.

Responsabile: Cecilia Tiveron (€ 224.658,65)

Alliance against Cancer

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 (€ 30.000,00)

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 (€ 6.000,00)

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 (€ 67.720,16)

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 (€ 30.000,00)

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 (€ 8.000,00)

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 (€ 225.000,00)

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 (€ 41.000,00)

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 (€ 8.000,00)

Studio osservazionale sui pazienti oncologici anziani.

Responsabile: Cecilia Nisticò

GIOTTO (GIST Optimal Treatment and Therapy Outcome): studio osservazionale multicentrico sui GIST in tutte le fasi di malattia.

Responsabile: Virignia Ferraresi

Progetto ARPA. (Progetto di Armonizzazione delle Procedure di Autorizzazione della sperimentazione clinica).

Responsabile: Diana Giannarelli

Banca virtuale dei tessuti tumorali.

Responsabile: Marcella Mottolese

Fellowships

FIRC

Nanni Simona (S.C. Lab. "C" Oncogenesi Molecolare)

Modulazione dell'attività telomerasica attraverso la segnalazione dei recettori estrogenaci: prospettive terapeutiche nel cancro della prostata.

Rinaldo Cinzia (S.C. Lab. "C" Oncogenesi Molecolare)

L'oncosoppressore p53 regola la proteina chinasi HIPK2: caratterizzazione biochimica e funzionale di un nuovo circuito a feedback negativo

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

Laurence Havard (S.C. Lab. "B" Immunologia)

Artificial Regulation of Cell Cycle in Cancer Cells and its potential Clinical Applications

Fondazione "Telethon"

Tiveron Cecilia (Safu)

Produzione di animali transgenici e "Knock-out"

Consultants

Dr. Mauro Boldrini
Direzione Scientifica IRE

Dr. Enrico Spugnini
S.A.F.U.

Ing. Vincenzo Giusti
S.C. Laboratorio "C" Oncogenesi Molecolare

Research Contracts

Post-graduate Contract Researchers

Nominativi *Name*	Ente Erogatore *Fund granted by:*	Strutture Complesse/SSD/SSO *Assignement*
Anastasi Sergio	AIRC	Immunologia
Anticoli Borza	Ric. Corrente	Ematologia
Ascione Alessandro	FIRB	Oncogenesi Molecolare
Atlante Marco	Ric. Finalizzata	Ginecologia
Baccarini Alessia	Ric. Corrente	Oncogenesi Molecolare
Balsamo Michele	Min. Salute	Immunologia
Benassi Barbara	Ric. Corrente	Chemioterapia Sperimentale
Bisozzi Eleonora	Ric. Corrente	Neurologia
Bon Giulia	AIRC	Oncogenesi Molecolare
Bonucci Alessandro	Ric. Corrente	Psicologia
Bossi Gianluca	AIRC	Oncogenesi Molecolare
Bria Emilio	Ric. Corrente	Oncologia Medica "C"
Bussoletti Federico	Ric. Corrente	Psicologia
Campioni Mara	FIRC	Lab. "C" Aggregato
Caponetti Rosita	Sperimentazione	Oncologia Medica "B"
Carbone Ilaria	Ric. Corrente	Direzione Scientifica IRE
Careddu Angela	Ric. Finalizzata	Patologia Clinica
Castellini Laura	Min. Salute	Chemioterapia Sperimentale
Cecchinelli Barbara	ISS	Oncogenesi Molecolare
Cecere Lucia	Ric. Corrente	Biblioteca IRE
Centra Gianpaolo	Min. Salute	Immunologia
Cervini Federica	Ric. Corrente	Direzione Scientifica IRE
Chichierchia Giuseppina	Ric. Finalizzata	Anat. Istol. Patologica e Citod.
Cirilli Alessia	AIRC	Virologia
Ciuffini Laura	AIRC	Oncogenesi Molecolare
Ciuffreda Ludovica	Ric. Finalizzata	Oncologia Medica "A"
Cottone Giuliano	FIRC	Lab. "C" Aggregato
D'Angelo Annelisa	Ric. Corrente	Fisica Medica
D'Eletto Manuela	Mc Master University	Oncogenesi Molecolare
Damalas Alexander	Min. Salute	Oncogenesi Molecolare
Del Bello Duilia	ISS	Immunologia
Desideri Marianna	FIRB-MIUR	Chemioterapia Sperimentale
Di Agostino Silvia	AIRC	Oncogenesi Molecolare
Di Benedetto Anna	Ric. Finalizzata	Anat. Istol. Patologica e Citod.
Di Lelio Maurizio	Regione Lazio	Neurologia
Di Segni Susanna	Ric. Corrente	S.A.F.U.
Di Stefano Valeria	AIRC	Oncogenesi Molecolare
Emiliozzi Velia	AIRC	Oncogenesi Molecolare

Falcicchio Chiara	Ric. Corrente	Psicologia
Felici Alessandra	Ric. Corrente	SAFU
Ferretti Elisabetta	Ric. Finalizzata	Endocrinologia
Fontemaggi Giulia	AIRC	Oncogenesi Molecolare
Fuschi Paola	FIRB	Oncogenesi Molecolare
Gabellini Chiara	Min. Salute	Chemioterapia Sperimentale
Gelibter Alain	Ric. Corrente	Oncologia Medica "A"
Ginobbi Patrizia	Ric. Corrente	Rianimazione Terapia del Dolore
Giorda Ezio	Min. Salute	Immunologia
Giorgini Simona	Min. Salute	Chemioterapia Sperimentale
Giovannelli Morena	Regione Lazio	Neurologia
Gomellini Sara	Ric. Corrente	Radioterapia
Gradi Alessandra	AIRC	Oncogenesi Molecolare
Guastella Fabio	Regione Lazio	Neurologia
Gurtner Aymone	MIUR	Oncogenesi Molecolare
Haoui Mustapha	Ric. Corrente	SAFU
Introna Marianna	Ric. Corrente	Direzione Scientifica IRE
Iovino Alessandra	AIRC	Oncogenesi Molecolare
Kapllani Adelina	Ric. Finalizzata	Rianimazione Terapia del Dolore
Lapi Eleonora	AIRC	Oncogenesi Molecolare
Lauria Valentina	Ric. Corrente	Endoscopia Digestiva
Lazzari Chiara	AIRC	Oncogenesi Molecolare
Macchione Daniela	Ric. Corrente	Biblioteca
Mafera Barbara	Compagnia San Paolo	Virologia
Magnifico Antonia	Ric. Corrente	SAR
Malaguti Paola	Ric. Finalizzata	Oncologia Medica "A"
Mancini Raffaello	Ric. Finalizzata	Chirurgia Generale "B"
Manente Lucrezia	Ric. Corrente	Lab. "C" Aggregato
Mangiacasale Rosamaria	AIRC	Lab. "C" Aggregato
Manni Isabella	Ric. Corrente	Oncogenesi Molecolare
Mariotti Simona	Ric. Corrente	Direzione Scientifica IRE
Merola Roberta	Ric. Finalizzata	Patologia Clinica
Martayan Aline	Min. Salute	Immunologia
Mastronicola Daniela	Ric. Finalizzata	SAFU
Mazzola Alessia	AIRC	Oncogenesi Molecolare
Mazzacuva Amelia	Ric. Corrente	Biblioteca
Mazzieri Marinella	Ric. Corrente	Biblioteca
Mongiovì Adriana	ISS	Oncogenesi Molecolare
Monti Olimpia	Min. Salute	Oncogenesi Molecolare
Novelli Flavia	Ric. Corrente	Anat. Istol. Patologica e Citod.
Orlandi Giulia	Ric. Finalizzata	Anat. Istol. Patologica e Citod.
Ortenzia Ornella	Ric. Corrente	Fisica Medica
Palermo Belinda	Min. Salute	Immunologia
Palombi Francesca	Ric. Corrente	Ematologia
Parisi Cristiano	Ric. Finalizzata	Neurologia
Pellicciotta Mario	Ric. Finalizzata	Direzione Scientifica IRE
Petricca Adele	AIRC	Chemioterapia Sperimentale
Pino Simona	Ric. Corrente	Direzione Scientifica

Piperno Giulia	Ric. Corrente	Anat. Istol. Patologica e Citod.
Pisano Claudio	AIRC	Oncogenesi Molecolare
Porrello Alessandro	AIRC	Oncogenesi Molecolare
Prodosmo Andrea	AIRC	Oncogenesi Molecolare
Riccioni Sabrina	Ric. Corrente	Oncogenesi Molecolare
Rizzo Angela	AIRC	Chemioterapia Sperimentale
Rizzo Consuelo	Compagnia San Paolo	Virologia
Rollo Francesca	Ric. Finalizzata	Anat. Istol. Patologica e Citod.
Rosanò Laura	AIRC	Lab. "A" Aggregato
Rossi Sabrina	Ric. Corrente	Medicina Nucleare
Sala Gianluca	AIRC	Immunologia
Salis Patrizia	Regione Lazio	Neurologia
Salvati Erica	AIRC	Chemioterapia Sperimentale
Santulli Alberta Giulia	Ric. Corrente	Biblioteca
Sessa Anna	Ric. Finalizzata	SINTESI
Sibilio Leonardo	Polymed	Immunologia
Simeone Paola	Min. Salute	Virologia
Sperduti Isabella	Sperimentazione	Direzione Scientifica IRE
Strano Sabrina	Ric. Corrente	Oncogenesi Molecolare
Tirelli Walter	Ric. Corrente	Rianimazione Terapia del Dolore
Travaglini Claudia	Ric. Finalizzata	Anat. Istol. Patologica e Citod.
Tritarelli Alessandra	Min. Salute	Lab. "C" Aggregato
Vallati Ilaria	Ric. Finalizzata	Direzione Scientifica IRE
Vanni Barbara	Ric. Corrente	Oncologia Medica "C"
Varone Fortunato	Ric. Corrente	SAR
Venturini Cristina	Ric. Finalizzata	Direzione Generale IFO

Non Graduated Contract Researchers

Nominativi *Names*	Ente Erogatore *Funds Granted by:*	Strutture Complesse/SSD/SSO *Assignement*
Antoniani Barbara	Ric. Corrente	Anat. Istol. Patologica e Citod.
Bernardi Roberto	Ric. Corrente	Oncogenesi Molecolare
Bona Daniela	Ric. Corrente	Oncogenesi Molecolare
Bonaventura Fabrizio	ISS	Chemioterapia Sperimentale
Bosi Roberto	MIUR	Oncogenesi Molecolare
Bruno Tiziana	AIRC	Lab. "B" Aggregato
Calvo Abad Ana Isabel	Ric. Corrente	SINTESI
Capogna Sveva	AIRC	Lab. "C" Aggregato
Capnist Lavinia	Ric. Corrente	Urologia
Carpino Laura	Ric. Corrente	Radioterapia
Cassani Stefania	Ric. Finalizzata	Chirurgia Toracica
Chiarenza Andrea	Ric. Finalizzata	Anat. Istol. Patologica e Citod
D'Angelo Marco	Ric. Corrente	Oncogenesi Molecolare
D'Orsogna Fabio	Ric. Finalizzata	Biblioteca IRE
Di Giorgi Silvia	Sperimentazione	Oncologia Medica "B"
Dalla Casa Laura	Sperimentazione	Radiologia e Diagnost. Immagini

Docimo Raffaele	FIRB	Oncogenesi Molecolare
Edlisca Ana Maria	Sperimentazione	Oncologia Medica "B"
Elia Giacomo	AIRC	Lab. "A" Aggregato
Fagioli Cecilia	Ric. Corrente	SINTESI
Folgiero Valentina	FIRB	Oncogenesi Molecolare
Full Red Cynthia	Ric. Corrente	Immunologia
Gallo Daniela	AIRC	Lab. "C" Aggregato
Giammarioli Patrizia	Ric. Corrente	Gastroenterologia
Gioffrè Giuseppina	Ric. Finalizzata	Chirurgia Generale "B"
Guerriera Paolo	Min. Salute	S.A.F.U.
Harris Deborah	Sperimetnazione	Radiologia e Diagnost. Immagini
Iezzi Alessio	Ric. Finalizzata	Oncologia Medica "A"
Lucioli Stefano	AIRC	Immunologia
Martelletti Letizia	AIRC	Lab. "C" Aggregato
Matrascia Barbara	Ric. Corr./Reg. Lazio	Dir. Scientifica IRE/Neurologia
Milana Rossella	Ric. Corrente	Rianimazione Terapia del Dolore
Pandolfi Rita	Min. Salute	S.A.F.U.
Parasecoli Cristina	Sperimentazione	Oncologia Medica "B"
Ranieri Alessandra	Ric. Corrente	Immunologia
Sarcone M. Vincenza	Min. Salute	Immunologia
Scarsella Marco	Min. Salute	Chemioterapia Sperimentale
Soliera Angela Rachele	FIRB	Oncogenesi Molecolare
Vitolo Donatella	Ric. Corrente	Oncogenesi Molecolare
Zerbini Valentina	Ric. Finalizzata	Anat. Istol. Patologica e Citod.

Visiting Researchers

Professional Updating

Visiting Post-graduate Researchers

Nominativi	Strutture Complesse/SSD
Apicella Simona	Oncologia Medica "B"
Armezzani Alessia	Oncogenesi Molecolare
Benvenuti Valentina	Oncogenesi Molecolare
Bianciardi Federico	Radioterapia
Biancone Silvia	Patologia Clinica
Bonessa Gianluigi	Chirurgia Plastica
Caponetti Rosita	Oncologia Medica "B"
Carnì Marco	Fisica Medica e Sistemi Esperti
Corrado Giacomo	Ginecologia
Corsetti Serena	Oncologia Medica "B"
D'Alessio Daniela	Fisica Medica e Sistemi Esperti
Francasso Luca	Chirurgia Plastica
Genovese Elisabetta	Fisica Medica e Sistemi Esperti
Gentiletti Francesca	Oncogenesi Molecolare
Giglio Simona	Oncogenesi Molecolare
Gomellini Sara	Radioterapia
Grasselli Annalisa	Oncogenesi Molecolare
Guaglianone Salvatore	Urologia
Kapllani Adelina	Rianimazione e Terapia del Dolore
Iacovelli Stefano	Oncogenesi Molecolare
Infante Costanza	Ginecologia
Izzo Adriano	Chirurgia Plastica
Liquori Silvio	Ginecologia
Ludovici Giorgia	Patologia Clinica
Macchione Daniela	Biblioteca IRE
Macicone Annamaria	Patologia Clinica
Malagutti Nicola	Otorinolaringoiatra
Mancini Francesca	Oncogenesi Molecolare
Mancuso Alessandra	S.A.F.U.
Mandoj Chiara	Patologia Clinica
Mecarelli Alessio	Patologia Clinica
Minutilli Ettore	Chirurgia Generale
Parisi Elisabetta	Oncologia Medica "A"
Pizzigallo Angelo	Otorinolaringoiatra
Ruscio Giusy	Oncogenesi Molecolare
Salierno Carmelina	Fisica Medica e Sistemi Esperti
Saralessandri Claudia	Psicologia

Non-graduated Visiting Researchers

Nominativi	Strutture Complesse/SSD
Savarino Gianluca	Oncologia Medica "A"
Sergi Domenico	Oncologia Medica "B"
Serrain Filiberto	Radioterapia
Serrone Letizia	Oncologia Medica "A"
Stukart Gaelle C.	Oncogenesi Molecolare
Torsello Angela	Oncologia Medica "C"
Vico Erika	Patologia Clinica
Vigna Cristina	Psicologia
Docimo Raffaele	Chemioterapia Sperimentale
Fanelli Eleonora	Neurologia
Rollo Francesca	Anatomia ed Ist. Patol. e Citodiagnostica
Virtuoso Maria	Neurologia

Degree Thesis

Nominativi	Strutture Complesse/SSD
Baietti M. Francesca	Immunologia
Bonifazi Roberta	Chemioterapia Sperimentale
Ciolfi Alberto	Lab. "B" Aggregato
Coccia Margherita	Oncogenesi Molecolare
Conidi Andrea	Immunologia
Decandia Samantha	Lab. "A" Aggregato
Della Bianca Stefano	Lab. "C" Aggregato
Di Domenico Fabio	Virologia
Falciani Veronica	Oncogenesi Molecolare
Federici Valentina	Immunologia
Fragomeli Caterina	Chemioterapia Sperimentale
Frosi Yuri	Immunologia
Genovesi Giulia	Lab. "A" Aggregato
Isidi Fabio	Virologia
Leoni Daniela	Chemioterapia Sperimentale
Lo Monaco Elisa	Immunologia
Lucini Fabiana	Immunologia
Mainardi Sara	Oncogenesi Molecolare
Mattiussi Marina	Oncogenesi Molecolare
Melucci Elisa	Immunologia
Minella Daniela	Oncogenesi Molecolare
Paolini Francesca	Virologia
Pisano Paola	Lab. "C" Aggregato
Santangelo Laura	Immunologia
Sparaco Giorgia	Oncogenesi Molecolare
Spinola Valeria	Chemioterapia Sperimentale
Sturabotti Gianpiero	Oncogenesi Molecolare

Doctorates

Nominativi	Strutture Complesse/SSD
De Nicola Francesca	Lab. "B" Aggregato
Iezzi Simona	Lab. "B" Aggregato

Scientific Cooperation

Nominativi	Strutture Complesse/SSD
Alimandi Maurizio	Immunologia
Appodia Rita	Dip. Oncologia Sperimentale
Belloni Laura	Dip. Oncologia Sperimentale
Cimino Letizia	Dip. Oncologia Sperimentale
Civitareale Donato	Lab. "A" Aggregato
Farsetti Antonella	Oncogenesi Molecolare
Guerrieri Francesca	Dip. Oncologia Sperimentale
Levrero Massimo	Dip. Oncologia Sperimentale
Lombardi Daniela	Lab. "C" Aggregato
Merlo Paola	Dip. Oncologia Sperimentale
Moretti Francesca	Oncogenesi Molecolare
Nicotra Rita	Immunologia
Omerovic Jasminka	Immunologia
Palescandolo Emanuele	Dip. Oncologia Sperimentale
Pediconi Natalia	Dip. Oncologia Sperimentale
Pollicino Teresa	Dip. Oncologia Sperimentale
Pontecorvi Alfredo	Oncogenesi Molecolare
Puggioni Eleonora	Immunologia
Vossio Stefania	Dip. Oncologia Sperimentale

Reviewing and Editorial Board Membership in indexed journal

- Acta Cytologica (Perrone Donnorso R.)
- Acta Otorinolaringol. Ital. (Spriano G.)
- Advances in Molecular Medicine (Guadagni F.)
- American Society for Biochemistry and Molecular Biology (Fanciulli M.)
- Annals of Oncology (Cognetti F.)
- Anticancer Research (Guadagni F.)
- Biochimica et Biophysica Acta (Blandino G. Segatto O.)
- Biochemical Journal (Bagnato A.)
- Biochemistry and Cell Biology (Biroccio A.)
- British Journal of Cancer (Bagnato A., Del Bufalo D.)
- British Journal of Dermatology (Venuti A.)
- Canadian Journal of Physiology and Pharmacology (Gabellini C., Zupi G.)
- Cancer Chemotherapy Pharmacology (Milella M.)
- Cancer Detection and Prevention (Mottolese M.)
- Cancer Research (Bagnato A., Blandino G., Farsetti A., Paggi M.G.)
- Carcinogenesis (Bagnato A., Soddu S., Zupi G.)
- Cell Death and Differentiation (Blandino G., Soddu S.)
- Cell Proliferation (Zupi G.)
- Cell Tissue and Research (Blandino G.)
- Chirurgia Italiana (Santoro E.)
- Clin. Exp. Dermatology (Venuti A.)
- Clinica Terapeutica (Arcangeli G., Guadagni F.)
- Clinical Cancer Res. (Bagnato A.)
- Diagnostic Cytopathology (Perrone Donnorso R.)
- Drugs (Lopez M.)
- EMBO Journal (Soddu S.)
- European Journal of Cancer (Blandino G., Biroccio A., Falcioni R., Zupi G.,)
- European Journal of Oncology (Lopez M.)
- European Journal of Clinical Oncology (Guadagni F.)
- Experimental Cell Research (Soddu S.)
- Expert. Opinion on Invest. Drugs (Bagnato A.)
- Expert. Review of Anticancer Therapy (Benassi B., Zupi G.)
- Faseb Journal (Del Bufalo D.)
- FEBS Letters (Blandino G. Farsetti A. Piaggio G.)
- Gastric Cancer (Santoro E.)
- General Surgery (Santoro E.)
- Head & Neck (Spriano G.)
- Hepatogastroenterology (Santoro E.)
- Hepatologie (Santoro E.)
- Histology and Histopathology (Natali P.G.)
- In vivo (Guadagni F.)
- International Journal of Biochem. Cell. Biol. (Blandino G.)

- International Journal of Biological Markers (Castelli M., Guadagni F., Natali P.G.)
- International Journal of Cancer (Guadagni F., Natali P.G., Segatto O.)
- International Journal of Hyperthermia (Arcangeli G.)
- International Journal of Radiation Oncology Biology and Physics. (Arcangeli G.)
- Journal de Celiochirurgie (Santoro E.)
- Journal Cellular Biochemistry (Paggi M.G.)
- Journal Cellular Physiology (Paggi M.G.)
- Journal Clinical Pathology (Cianciulli A.M.)
- Journal of Experimental & Clinical Cancer Research (Arcangeli G., Benassi M., Castelli M., Falcioni R., Jandolo B., Leonetti C., Mottolese M., Natali P.G., Paggi M.G., Porrello A., Rizzo M.G., Santoro E., Sega M., Soddu S., Trisciuoglio D., Venuti A., Zupi G.)
- Journal Immunotherapy (Nisticò P.)
- Journal Med. Virol. (Badaracco G.)
- Journal Nuclear Medicine (Sciuto R.)
- Journal Traslational Medicine (Natali P.G.)
- Laparoscopic Surgery (Santoro E.)
- Leukemia & Lymphoma (Milella M., Rizzo M.G.)
- Medicinal Chemistry (Biroccio A.)
- Melanoma Research (Paggi M.G.)
- Molecular Carcinogenesis (Blandino G.)
- Molecular and Cellular Biology (Falcioni R.)
- Neurological Sciences (Jandolo B.)
- Neoplasia (Bagnato A.)
- Oncogene (Bagnato A., Benassi B., Blandino G., Farsetti A., Paggi M.G., Segatto O., Zupi G.)
- Oncology (Zupi G.)
- Oncology Care Today and Tomorrow (Lopez M.)
- Physics Letters A (Porrello A.)
- Proc. Nat. Acad. Sci. USA (Segatto O.)
- Tumor Biology (Guadagni F.)
- Tumori (Natali P.G., Zupi G.)
- Virus Research (Venuti A.)

Research Project Review

- A.I.R.C. (Del Bufalo D., Milella M., Sacchi A., Soddu S., Zupi G.)
- C.N.R. (Zupi G.)
- Dutch Cancer Society (Blandino G., Falcioni R.)
- F.I.R.B. (Sacchi A.)
- F.I.R.C. (Biroccio A., Del Bufalo D., Leonetti C., Zupi G.)
- M.I.U.R. (Citro G., Sacchi A., Soddu S., Zupi G.)
- Neuroblastoma (Sacchi A.)
- U.I.C.C. (Venuti A.)

Appointments to Foundations, Societies, Associations

Arcangeli G.

- Commissione Oncologica della Regione Lazio: membro

Arcuri E.

- Associazione Italiana per lo Studio del Dolore (AISD): Vicepresidente
- Fondazione Federico Calabresi: Membro del Comitato Scientifico

Benassi M.

- Comitato Tecnico-Scientifico dell'Agenzia provinciale per la protonterapia (ATreP) di Trento: Membro

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 P.

- Sezione Regione –Lazio AIOM: Tesoriere

Casale V.

- Commissione Oncologica Nazionale dell'Associazione Italiana Gastroenterologi Ospedal.: Membri

Castelli M.

- Associazione Promozione Studi Immunologia dei Tumori - APSIT: Presidente

Cavaliere F.

- Associazione Chirurghi Ospedalieri Italiani (A.C.O.I.): Membro
- 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
- Società Italiana Terapie Loco-Regionali in Oncologia (S.I.T.I.L.O.) : Membro

Cilenti V.

- AMCI (Associazione Medici Cattolici Italiana): Presidente Regionale
- ANAAO-ASSOMED: Consigliere Nazionale

Citro G.

- AACR - American Association for Cancer Research: Membro
- Esperto Scientifico di supporto alla Commissione del Ministero Economia e Finanza: Membro
- Fondo Integrativo Speciale Ricerca: Membro

COGNETTI F.

- AIOM - Associazione Italiana di Oncologia Medica: Past-President
- American Society of Clinical Oncology (ASCO): Membro
- Associazione Alleanza Contro il Cancro: Segretario - Tesoriere
- Associazione "Galileo 2001 - Associazione per la libertà e la dignità della scienza":Socio Fondatore, Sindaco Effettivo e Membro del Consiglio Direttivo
- 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 Rapresentative 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

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

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.

- Consiglio Direttivo della SNO (Scienze Neurologiche Ospedaliere)
- Gruppo di Studio di Neuro-oncologia della SIN: Coordinatore

Leonetti C:

- AICC - Associazione Italiana Colture Cellulari: Segretario

Lopez M.

- Comitato Tecnico Scientifico della Società Italiana Tumori: Presidente
- Consiglio Direttivo e del Consiglio Scientifico del Gruppo Oncologico dell'Italia Meridionale (GOIM): Membro

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 - American Association for Cancer Research: 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
- International Affaire Commitee AACR: chairperson for Europe
- Membro della Commissione AACR per:
  – The AACR G.H.A. Clowes Memorial Award
  – The AACR Award for Outstanding Achievement in Cancer Research

Paggi M.G.

- American Association for Cancer Research: Membro attivo
- Società Italiana di Cancerologia: Membro
- Associazione Italiana Colture Cellulari: Membro

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 Donnorso R.

- Società Italiana di Citologia Clinica e Sociale (S.I.C.C.S): Presidente

Perrone M.

- SIPO - Lazio: Consigliere

Pugliese P.

- SIPO - Lazio: Segretario regionale

Sacchi A.

- Comitato Tecnico Scientifico A.I.R.C. : Membro
- Comitato Scientifico della Fondazione per la lotta al Neuroblastoma: Presidente

Santoro E.

- Accademia Romana di Chirurgia: Accademico Reggente
- Federchir: Presidente
- IGCA (International Association for Gastric Cancer and Gastric Disease): 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.

- Consiglio Direttivo Regionale Associazione Italiana Gastroenterologi Ospedalieri: Membro

Terzoli E.

- Comitato Etico dell'Ospedale "Regina Apostolorum" ad Albano Laziale (RM): Membro
- Lega Italiana Tumori - Sez. Provincia di Roma: Vicepresidente
- Associazione Coordinamento Primari Regina Elena: Presidente
- Componente Gruppo di Lavoro Interdisciplinare per il Coordinamento degli Interventi nel Settore Oncologico.

Vizza E.

- Gruppo Italiano di Studio sull'Endometriosi (G.I.S.E.) : Membro

Vocaturo A.

- SICi (Società Italiana di Citologia): Revisore dei Conti

Zupi G:

- AIRC - Associazione Italiana Ricerca sul Cancro: Membro del Comitato Scientifico
- AICC - Associazione Italiana Colture Cellulari: Socio Onorario
- FIRC - Fondazione Italiana Ricerca sul Cancro: Membro del Comitato Scientifico
- SICCAB - Società Italiana Cinetica Cellulare Applicata e di Base: Consigliere
- SIC - Società Italiana di Cancerologia: Consigliere
- Fondazione Federico Calabresi: Membro del Consiglio Direttivo
- Temple University, College of Science and Technology, Centre for Biotechnology: Adjunct Professor

AWARDS

DR.SSA BARBARA BENASSI

2° Premio Senior AICC 2004 "Studio del ruolo dell'oncogene c-myc nella risposta ai farmaci antineoplastici di linee di melanoma umano"

DR.SSA ANNAMARIA BIROCCIO

EACR Young Cancer Researcher Award 2004

DR. EMILIO BRIA

Award 2004 "Federico Calabresi Fondation" for young oncologist (<40 years) author (first name) of the best international publication with the highest impact factor. Dicember 10, 2004.

FELICI A., FABI A., MIRRI A., BRIA E., SERRAINO F., LANZETTA G., MANSUETO G., MOSCHETTI L., PACE A., TELERA S., CARAPELLA C.M., AND THE LATIUM NEURO-ONCOLOGY GROUP.

Award for best paper presented at AINO Congress (Neuro Oncology Italian Association) "Brain metastases from different tumour types: a survay analisys from multidisciplinary experience"
28-30 ottobre, Varese

ROSANÒ L., SPINELLA F., DI CASTRO V., NICOTRA M.R., DEDHAR S., DE HERREROS A.G., NATALI P.G. AND BAGNATO A.

Nature Review Cancer Poster Prize
"Epithelial to mesenchymal transition: emerging role of endothelin-1 in the progression of ovarian carcinoma". CNIO Cancer conference, Cadherins, Catenins and Cancer, Madrid, November 19-December 1, 2004.

Bilateral Agreements

Italia - Albania (2001-2005)

La prevenzione del tumore della cervice uterina.

The Prevention Uterine Cancer.

Project Co-ordinators:

Dr. Federico De Marco - S.C. Lab. D Di Virologia, Istituto Regina Elena, Roma, Italia.
Dr. Kozeta Filipi Kule "Institute Of Public Health" Di Tirana, Albania.

Italia-Canada (2000-2005)

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 Tebmetase Subunit (hTERT) in Human Epithelial Cells Derived from Normal and Tumoral Prostate Explatns.

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.

ITALIA-TUNISIA (2000-2003) (IN FASE DI RINNOVO)

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.

Protocols List According To Pathology Approved By The Ethic Committee

Stato A= aperto
Stato C= chiuso

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2004*	*TOT Pazienti arruolati*
	Colon-retto						
	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	3	7
	Zeuli						
Stato A	Studio clinico in aperto, multicentrico, a braccio singolo, per determinare la sicurezza di una terapia continuata con ABX-EGF in soggetti con tumore del colon metastatico	OMA	No	Sì	28/04/2004		
	Casale						
Stato A	Consulenza genetica gastroenterologica per i tumori familiari ereditari del colon	Gastro	No	No	06/02/2004	22	25
	Zeuli						
Stato C	Studio clinico di fase III, randomizzato in aperto, sull'associazione di ABX-EGF alla miglior terapia di supporto verso la migliore terapia di supporto in soggetti con tumore al colon retto metastatico	OMA	Sì	Sì	28/04/2004	6	7
	Paoletti						
Stato C	Folfiri vs folfiri+celecoxib nel trattamento del carcinoma colorettale in fase avanzata	OMB	Sì	Sì	16/12/2003	4	4
	Stigliano						
Stato A	Valutazione del rischio del cancro del colon in pazienti operate per cancro della mammella	Gastro	No	No	17/11/2003	5	7
	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	3	3

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	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		1
	GARUFI						
STATO C	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 AP	Trattamento di I linea con Bevacizumab e Chemioterapia del Carcinoma del colon e del retto metastatico	OMC	No	Sì	27/10/2004	0	0
	ZEULI						
STATO C	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	5	15
	ZEULI						
STATO A	Time finding study of chronomodulated irinotecan, 5-Fluoraucil, leucoverin and oxaliplatin as first line against metastatic colorectal cancer	OMA	Sì	Sì	09/12/2004		
	CAVALIERE						
STATO C	Trattamento integrato dello pseudomixoma peritonei da carcinoma appendicolare colorettale ed ovarico	CHA	No	Sì	11/12/1999		44
	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	15	47
	CASALE						
STATO C	Studio di fattibilità di screening per cancro colorettale: FOBT annuale vs RSCS "once in a lifetime"	Gastro	No	Sì	06/09/2002		59
	ZEULI						
STATO A	Trattamento di I linea con Bevacizumab e Chemioterapia del Carcinoma del colon e del retto metastatico	OMA	No	Sì	27/10/2004		
	PAOLETTI						
STATO C	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		4

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	CORDOMA						
	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	131	318
	FERRARESI						
STATO A	Studio di fase II sull'utilizzo di Imatinib mesilato nel trattamento del cordoma	OMA	No	Sì	13/09/2004	1	2
	ENDEMETRIO						
	VOCATURO						
STATO A	Valutazione degli indici di efficienza di test diagnostici in popolazioni a rischio per il carcinoma dell'endometrio	Gine	No	No	28/04/2004		0
	FEGATO						
	MILELLLA						
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		
	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	2	8
	ETTORRE						
STATO A	Studio multicentrico sulla prevenzione primaria e secondaria dell'epatocarcinoma (HCC). Analisi su di un campione di popolazione a rischio	CHB	No	Sì	20/05/2004	6	16
	GIST						
	FERRARESI						
STATO A	I tumori stromali gastroenterici (GIST): studio multicentrico osservazionale	OMA	No	Sì	22/01/2004	2	2
	LEUCEMIA						
	PISANI						
STATO A	Studio osservazionale di pazienti con leucemia mieloide cronica di nuova diagnosi trattati con Imatinib	Emat	No	Sì	30/10/2003	1	1
	PISANI						
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	2

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	PISANI						
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	0
	PETTI/ROMANO						
STATO A	Gemtuzumab ozogamicin (GO) in associazione con chemioterapia intensiva standard verso solo chemioterapia intensiva standard come induzione/consolidamento per pazienti di età 64-75 anni addetti da leucemia mieloide acuta all'esordio: studio randomizzato di fase III (AML17) dell'EORTC-LG	Emat	No	Sì	24/06/2004	0	1
	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	4
	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	3	4
	PETTI						
STATO A	Studio di fase III, randomizzato, in aperto, controllato, per confrontare Pixantrone (BBR.2778) verso altri agenti chemioterapici nel trattamento di pazienti con Linfoma Non-Hodgkin's aggressivo, recidivato, in terza linea	Emat	Sì	Sì	27/10/2004		
	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	3

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	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	0	4
	MAMMELLA						
	CARLINI						
STATO C	Exemestane (Aromasin): ormonoterapia di mantenimento dopo chemioterapia di I linea nel trattamento del carcinoma mammario metastatico	OMA	No	Sì	17/01/2001		4
	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	11/12/2002	18	30
	CARLINI						
STATO C	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	1
	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
	TONACHELLA						
STATO C	Studio osservazionale sulle modalità di trattamento adiuvante e sui pattern di ricaduta delle pazienti con carcinoma mammario operato (Studio NORA).	OMC	No	Sì	10/04/2003		50
	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	0	6

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	CARLINI						
STATO A	Prevenzione della menopausa chemio-indotta attraverso soppressione ovarica temporanea con Triptorelin verso controllo in pazienti giovani affette da carcinoma della mammella. Studio multicentrico randomizzato di fase III	OMA	Sì	Sì	26/02/2004	3	3
	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	115	183
	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	11	21
	PINNARÒ						
STATO A	Studio di fattibilità di un regime di radioterapia ipofrazionata nelle pazienti sottoposte a chirurgia conservativa per cancro della mammella	Radio	No	No	13/09/2004	5	6
	VICI						
STATO A	Gemcitabina in infusione costante prolungata in combinazione con paclitaxel nel carcinoma mammario metastatizzato pretrattato con antracicline	OMB	No	No	18/11/2004		
	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	13	21
	CARLINI						
STATO C	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	0	0

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	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	21	24
	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	0	0
	PIETRANGELI/PUGLIESE						
STATO A	Qualità di vita e linfedema nelle pazienti con neoplasia mammaria operata. Utilità di un intervento integrato medico-psicologo	Neuro	No	No	27/10/2004		5
	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	3	35
	PAPALDO						
STATO A	Studio di fase III con BMS-247550 in associazione con Capecitabina verso Capecitabina in monoterapia, in pazienti con carcinoma avanzato della mammella precedentemente trattate con Antraciclina e con Taxani	OMA	Sì	Sì	06/02/2004	4	5
	FABI						
STATO A	Studio di fase II, randomizzato, in doppio cieco, di AG-013736 in combinazione con Docetaxel versus Docetaxel e placebo, preceduto da una valutazione di fase I della combinazione in pazienti con carcinoma mammario metastatico	OMA	No	Sì	12/07/2004	2	2
	FABI						
STATO A	Gemcitabina in infusione costante prolungata in combinazione con paclitaxel nel carcinoma mammario metastatizzato pretrattato con antracicline	OMA	No	No	18/11/2004	0	5
	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	OMA	Sì	Sì	07/10/2002	46	70

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	PAPALDO						
STATO C	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	8	18
	FABI						
STATO C	Associazione di doxorubicina liposomiale (caelix) e gemcitabine (gemzar) nel trattamento della neoplasia mammaria avanzata: studio di fase II	OMA	No	Sì	11/12/2002	12	37
	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	19	139
	NISTICÒ						
STATO A	Studio clinico randomizzato di fase III di terapia sequenziale con Epidoxorubicina e Ciclofosfamide (EC) seguito da Docetaxel versus la combinazione 5-Fluorouracile, Epidoxorubicina e Ciclofosfamide (FEC) come trattamento adiuvante nelle pazienti con carcinoma della mammella con lindonodi negativi	OMC	Sì	Sì	28/04/2004	2	3
	MARIANI						
STATO C	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		4
	PAPALDO						
STATO A	Studio clinico randomizzato di fase III di terapia sequenziale con Epidoxorubicina e Ciclofosfamide (EC) seguito da Docetaxel versus la combinazione 5-Fluorouracile, Epidoxorubicina e Ciclofosfamide (FEC) come trattamento adiuvante nelle pazienti con carcinoma della mammella con lindonodi negativi	OMA	Sì	Sì	28/04/2004	18	25
	PAPALDO						
STATO C	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	2	11

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	NISTICÒ						
STATO A	Prevenzione della menopausa chemio-indotta attraverso soppressione ovarica temporanea con Triptorelin verso controllo in pazienti giovani affette da carcinoma della mammella. Studio multicentrico randomizzato di fase III	OMC	Sì	Sì	26/02/2004	0	0
	CARLINI						
STATO C	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	4	50
	VICI						
STATO C	Gemcitabina e docetaxel come terapia di prima linea nel carcinoma mammario metastatizzato. Studio multicentrico di fase II	OMB	No	Sì	20/06/2001	8	23
	MELANOMA						
	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	0	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	4	4
	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	6	16
	FERRARESI						
STATO C	Monitoraggio biochimico del marker di attività angiogenica VEGF: implicazioni prognostiche e terapeutiche nel melanoma cutaneo	OMA	No	No	07/10/2002		23
	FERRARESI						
STATO C	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	Sì	Sì	13/03/2003		0

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	Mesotelioma						
	Facciolo						
Stato A	Studio di fase II neoadiuvante di ALIMTA più Cisplatino seguiti da chirurgia e radiazione nel trattamento del mesotelioma pleurico	CHTor	No	Sì	09/12/2004		
	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	12	18
	Rinaldi						
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	3	4
	Mieloma multiplo						
	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	11	20
	Morbo celiaco						
	Casale						
Stato A	Studio multidisciplinare sull'associazione tra Morbo Celiaco e Malattie autoimmuni endocrinologiche e dermatologiche	Gastro	No	No	16/01/2003	16	47
	Neuroendocrino net						
	Perri						
Stato C	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	0
	Ovaio						
	Savarese						
Stato A	Carboplatino/Paclitaxel vs Carboplatino/doxorubicina liposomiale stealth in pazienti con carcinoma ovarico: studio multicentrico randomizzato	OMA	Sì	Sì	10/06/2003	13	24
	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		

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	SAVARESE						
STATO A	Studio Randomizzato di Fase III di comparazione fra Gemcitabina, Topotecan e Doxorubicina Liposomiale nel trattamento del carcinoma ovarico recidivante	OMA	Sì	Sì	18/09/2003	4	6
	SAVARESE						
STATO A	Studio clinico randomizzato di confronto tra epiadriamicina, ifosfamide vs topotecan nel trattamento delle pazienti affette da neoplasia epiteliale ovarica recidiva o persistente	OMA	Sì	Sì	06/02/2004		0
	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	23	44
	PAOLETTI						
STATO A	Gemcitabina vs gemcitabina + cisplatino nel trattamento del carcinoma del pancreeas avanzato	OMB	Sì	Sì	06/09/2002	2	2
	CARLINI						
STATO A	Gemcitabina vs gemcitabina + cisplatino nel trattamento del carcinoma del pancreas avanzato	OMA	Sì	Sì	12/06/2002		3
	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	7	9
	PIÙ PATOLOGIE						
	FABI						
STATO A	Studio randomizzato in aperto di valutazione dell'efficacia del supporto marziale endovenoso (complesso gluconato ferrico sodio, 458mg in infusione endovenosa settimanale per 6 settimane) in pazienti affetti da tumore solido primitivo (mammella, polmone, colon-retto e ginecologia) in trattamento con Darbepoetin alfa (150 una volta alla settimana sottocute per 12 settimane) per anemia correlata alla neoplasia e/o alla chemioterapia	OMA	Sì	Sì	18/11/2004		1
	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

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	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	21	54
	MENGARELLI						
STATO A	Trapianto allogenico di cellule staminali emopoietiche basato su un regime di condizionamento mieloablativo e sulla fotoferesi extracorporea	Emat	No	No	15/04/2004	0	0
	MILELLA						
STATO A	Studio di farmacocinetica in pazienti in trattamento con gemcitabina 1000mg/m2 in infusione di 10 mg/m2/min con normale o alterata funzionalità epatica o renale	OMA	No	No	28/04/2004	4	4
	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	1	19
	POLMONE						
	CERIBELLI						
STATO A	Studio di fase III randomizzato con Alimta (MTA) e Cisplatino oppure Gemzar (Gemcitabina) e Cisplatino in pazienti affetti da carcinoma polmonare non a piccole cellule localmente avanzato o metastatico	OMA	Sì	Sì	13/09/2004		
	LOPEZ						
STATO C	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	15/11/2000		12
	RINALDI						
STATO A	Programma clinico internazionale Adi accesso a ZD1839 (IRESSA) per i pazienti affetti da carcinoma del polmone non a piccole cellule (NSCLC)	OMB	No	Sì	15/01/2004	11	15
	TERZOLI						
STATO A	Programma clinico internazionale Adi accesso a ZD1839 (IRESSA) per i pazienti affetti da carcinoma del polmone non a piccole cellule (NSCLC)	OMC	No	Sì	15/01/2004	29	30

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	CERIBELLI						
STATO A	Studio internazionale di Fase III randomizzato, condotto in aperto, a gruppi paralleli, multicentrico di confronto tra ZD1839(IRESSA®) somministrato per via orale verso Docetaxel (Taxotere®) somministrato per via endovenosa in pazienti precedentemente trattati con chemioterapia a base di platino ed affetti da tumore del polmone non a piccole cellule recidivante metastatico o localmente avanzato	OMA	Sì	Sì	24/06/2004	2	3
	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	5	16
	RINALDI						
STATO C	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		2
	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	15	31
	RINALDI						
STATO A	Studio internazionale di Fase III randomizzato, condotto in aperto, a gruppi paralleli, multicentrico di confronto tra ZD1839(IRESSA®) somministrato per via orale verso Docetaxel (Taxotere®) somministrato per via endovenosa in pazienti precedentemente trattati con chemioterapia a base di platino ed affetti da tumore del polmone non a piccole cellule recidivante metastatico o localmente avanzato	OMB	Sì	Sì	28/04/2004	0	0

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	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	4	7
	FACCIOLO						
STATO C	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)	CHTor	Sì	Sì	13/09/2001	6	28
	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	0	1
	ASCHELTER						
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	5	6
	RINALDI						
STATO C	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	1	3
	CERIBELLI						
STATO A	Programma clinico internazionale di accesso a ZD1839 (IRESSA) per i pazienti affetti da carcinoma del polmone non a piccole cellule (NSCLC)	OMA	No	Sì	16/12/2003	36	36
	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	265	870
	CERIBELLI						
STATO C	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	5	25

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	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	1	1
	POLMONE MICRO						
	LOPEZ/RINALDI						
STATO A	Studio clinico di fase III, in aperto, randomizzato, con irinotecan idrocloruro (Campto) e cisplatino verso etoposide e cisplatino in chemioterapia di prima linea in pazienti con carcinoma polmonare a piccole cellule - malattia estesa	OMB	No	Sì	20/05/2004		0
	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		4
	FACCIOLO						
STATO A	Studio multicentrico pilota di fase II: chemioterapia di induzione seguita da chirurgia (con o senza radioterapia) per pazienti con microcitoma "very limited" (stadio I, II e IIIa operabile)	CHTor	No	Sì	09/12/2004		
	RINALDI						
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	0	1
	PROSTATA						
	ARCANGELI/LANDONI						
STATO A	Studio policentrico di fase II sull'ipofrazionamento nell'irradiazione del carcinoma della prostata	Radio	No	Sì	15/04/2004	0	0
	SARACINO						
STATO C	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	0	18
	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	0	0

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	GALLUCCI						
STATO A	Metastasi ossee nel carcinoma della prostata: studio osservazionale per la valutazione dei pattern di presentazione, di evoluzione clinica e di modalità di trattamento	URO	No	Sì	27/10/2004		
	SARACINO						
STATO A	Impiego della radioterapia intraoperatoria (IORT) dopo prostatectomia radicale nell'adenocarcinoma prostatico, studio di fase finding	Radio	No	No	16/01/2002	7	34
	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	No	18/09/2003	28	37
	SARACINO/PETRONGARI						
STATO A	Studio pilota sulla fattibilità dell'incremento della dose con Radioterapia a Modulazione di Intensità (IMRT) nel carcinoma prostatico a prognosi intermedia	Radio	No	No	18/11/2004	0	0
	GALLUCCI						
STATO A	Ruolo del microambiente e ricerca di nuovi target terapeutici	URO	No	No	19/05/2003		0
	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	35	78
	GALLUCCI						
STATO A	Studio in aperto, randomizzato, a gruppi paralleli, multicentrico, di fase III che confronta l'efficacia di due differenti dosaggi e regimi terapeutici di Nolvadex (20mg al giorno verso 20mg al giorno per 8 settimane e successivamente 20mg alla settimana) nella prevenzione dello sviluppo della ginecomastia indotta dalla monoterapia orale con Casodex 150mg al giorno in pazienti con carcinoma prostatico	URO	Sì	Sì	26/02/2004	4	4

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	PSORIASI						
	FRASCIONE						
STATO A	Studio multicentrico in aprto di fase IIIb/IV con efalizumab somministrato per via sottocutanea in pazienti adulti affetti da psoriasi cronica a placche da moderata a severa, che non rispondono o per i quali vi è una controindicazione o che sono intolleranti ad altre terapie sistemiche che includono ciclosporina, metotressato e puva	Derm	No	Sì	09/12/2004		
	RENE						
	COGNETTI/RUGGERI						
STATO C	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	1	2
	RUGGERI						
STATO C	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	4	4
	RUGGERI						
STATO A	Studio randomizzato di fase III con l'-SU011248 versus l'Interferone-alfa come terapia sistemica di prima linea nei pazienti affetti da carcinoma a cellule renali metastatico	OMA	Sì	Sì	13/09/2004		2
	RUGGERI						
STATO A	Studio randomizzato, in doppio cieco, di fase III per valutare l'efficacia e la sicurezza di bevacizumab in associazione con interferone alfa-2a (Roferon) verso interferone alfa-2a e placebo come prima linea di trattamento da somministrare a pazienti nefrectomizzati affetti da carcinoma renale metastatico a cellule chiare.	OMA	Sì	Sì	24/06/2004		
	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	9	20

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	COSIMELLI						
STATO C	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	No	20/03/2002	1	36
	SNC SISTEMA NERVOSO CENTRALE						
	MASCHIO						
STATO A	Studio pilota per la valutazione della qualità di vita, del controllo delle crisi e degli effetti collaterali in pazienti con tumori cerebrali ed epilessia trattati con levetiracetam in monoterapia	Neuro	No	No	18/11/2004		
	CARAPELLA						
STATO A	Osservazione versus radioterapia frazionata convenzionale (stereotassica) o radiochirurgia dopo asportazione non radicale per meningiomi intracranici benigni: studio di fase III	NCH	Sì	Sì	09/12/2004		0
	VIDIRI						
STATO A	Valutazione con CT-Perfusion delle neoplasie cerebrali nella diagnosi e nel follow-up. Studio osservazionale	RX	No	No	20/05/2004	4	5
	CAROLI						
STATO A	Studio osservazionale di pazienti sottoposti a somatectomia e vertebrectomia, effettuate in un solo tempo, per il trattamento di asportazione e ricostruzione, con stabilizzazione, delle metastasi vertebrali	NCH	No	No	26/02/2004	9	9
	PACE						
STATO A	Studio osservazionale sull'efficacia del trattamento chemioterapico con Temozolomide in pazienti affetti da astrocitoma grado 2 (WHO) in fase di progressione o recidiva	Neuro	No	No	16/01/2003	16	25
	CAROLI						
STATO A	Studio osservazionale del trattamento chirurgico di ablazione e ricostruzione con stabilizzazione, dei tumori primitivi vertebrali	NCH	No	No	26/02/2004	4	4
	CARAPELLA						
STATO A	Studio multicentrico di fase II sull'agente antitumorale TP-38 in pazienti con glioblastoma multiforme ricorrente o progressivo, previa resezione e radioterapia sottoposti a resezione totale	NCH	No	Sì	27/10/2004		0
	POMPILI						
STATO A	Metastasi cerebrali: chirurgia tradizionale, approcci innovativi, utilizzazione di nuove tecnologie di sala operatoria	NCH	No	No	26/02/2004	30	59

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	VIDIRI						
STATO A	Valutazione con CT-Perfusion delle metastasi cerebrali prima e dopo trattamento radioterapico. Studio osservazionale	RX	No	No	20/05/2004	18	18
	POMPILI						
STATO A	Asportazione degli adenomi ipofisari per via transfenoidale microneurochirurgica-endoscopio assistita. Studio osservazionale e di valutazione precoce del risultato con RM	NCH	No	No	26/02/2004	20	42
	RAUS						
STATO A	Studio osservazionale sull'utilizzo delle più avanzate tecniche e tecnologie chirurgiche nel campo delle neoplasie spinali	NCH	No	No	28/04/2004	28	28
	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	10	11
	PACE						
STATO A	Progetto di assistenza continuativa integrata e neuroriabilitazione a domicilio per pazienti affetti da tumori cerebrali	Neuro	No	No	11/11/2002	49	198
	CAROLI						
STATO A	Vertebroplastica e chifoplastica nel trattamento percutaneo dei cedimenti strutturali somatici di natura metastatica, non suscettibili di rimozione chirurgica - studio clinico osservazionale	NCH	No	No	28/04/2004		
	POMPILI						
STATO A	Approccio mininvasivo sopraorbitario per l'asportazione delle neoplasie della regione sellare	NCH	No	No	26/02/2004	3	7
	PACE						
STATO A	Ruolo della vitamina E nella neuroprotezione della neurotossicità e della ototossicità indotte da cisplatino	Neuro	Sì	Sì	16/12/2003	14	18
	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	0	0
	POMPILI						
STATO A	Approccio mininvasivo unilaterale per la rimozione delle neoplasie spinali intradurali. Studio ossevazionale	NCH	No	No	26/02/2004	4	13

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	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	5	11
	FERRARESI						
STATO A	Ifosfamide ad alte dosi in infusione continua prolungata mediante sistema infusorio portatile nei sarcomi dei tessuti molli tipici dell'adulto in fase avanzata in seconda/ulteriore linea chemioterapica	OMA	No	Sì	12/07/2004	1	1
	SCLEROSI MULTIPLA						
	JANDOLO						
STATO A	Studio osservazionale Beta-interferon in Early RR-MS Surveillance Trial (BEST)	Neuro	No	Sì	02/07/2003	0	1
	JANDOLO						
STATO C	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	1	3
	TESTA-COLLO						
	RUGGERI						
STATO A	Studio di fase III randomizzato, stratificato, a gruppi paralleli, multicentrico, di confronto tra (Iressa) 250mg e 500mg verso metotrexato in pazienti precedentemente trattati per carcinoma a cellule squamose di testa e collo	OMA	No	Sì	22/01/2004	6	6
	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	Radio	No	No	17/11/2003	0	0
	RUGGERI						
STATO A	Cetuximab (Erbitux®) in combinazione con cisplatino o con carboplatino e 5-fluorouracile nel trattamento di prima linea di soggetti con carcinoma squamocellulare della testa e del collo recidivante e/o metastatico	OMA	No	Sì	09/12/2004		
	ARCANGELI/MARUCCI						
STATO A	Studio osservazionaledi rilevazione e monitorizzazione della xerostomia nei pazienti con tumori del cavo orale e del faringe sottoposti a radioterapia ad intensità modulata (IMRT)	Radio	No	No	15/04/2004	5	15

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	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	0	0
	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	8	10
	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	12	13
	MARUCCI						
STATO A	Studi paralleli di Fase II sull'impiego della Radioterapia 3D con Amifostina o della RadioTerapia a Modulazione di Intensità (IMRT) per valutare la riduzione della xerostomia nei pazienti con tumori del distretto cervico-cefalico trattati in modo definitivo o adiuvante	Radio	No	No	09/12/2004		
	TIROIDE						
	RUSCITO						
STATO A	Studio pilota sulla fattibilità dell'uso della Chirurgia Endoscopica Video-assistita Mininvasiva (MIVA) nel trattamento dei noduli tiroidei di piccole dimensioni	ORL	No	No	15/04/2004	2	2
	VARIE						
	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	2	3
	FABI						
STATO A	Modalità di gestione terapeutica dell'anemia indotta da chemioterapia: studio osservazionale multicentrico	OMA	No	No	12/07/2004	0	20
	APPETECCHIA						
STATO A	Valutazione dell'efficacia del trattamento con lanreotide negli adenomi ipofisari non funzionanti	Endo	No	Sì	17/11/2003	1	1

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	PETTI						
STATO A	Studio di fase III multicentrico, randomizzato, in aperto, a gruppi paralleli, con azacitidina sottocutanea più terapia di supporto verso chemioterapia convenzionale più terapia di supporto, per il trattamento delle Sindromi Mielodisplastiche (SMD)	Emat	Sì	Sì	13/09/2004	0	0
	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	12	35
	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	5	5
	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	40	123
	TERZOLI/GARUFI						
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	OMC	No	Sì	24/06/2004		3
	FABI						
STATO A	Studio osservazionale sull'impatto delle diverse epoetine (eritropoietina-alfa, beta, e darbopoetina-alfa) nel trattamento dell'anemia in pazienti sottoposti a chemioterapia	OMA	No	Sì	18/11/2004	2	4
	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	16	20

	Protocolli	Divisione	Random	Multicentrico	Attiv.	Pazienti arruolati nel 2003	TOT Pazienti arruolati
	MARIANI						
STATO C	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	0	90
	FABI						
STATO C	Indagine sulla prevalenza e sulla gestione del dolore nelle strutture oncologiche italiane. Studio osservazionale. Progetto DOMA.IN (Dolore in Oncologia Medica e Analgesia)	OMA	No	Sì	28/04/2004	66	66
	TERZOLI						
STATO C	Trattamento d'induzione con epoetina alfa nell'anemia del paziente oncologico sottoposto a chemioterapia	OMC	Sì	Sì	12/02/2003	0	2
	TERZOLI						
STATO C	Indagine sulla prevalenza e sulla gestione del dolore nelle strutture oncologiche italiane. Studio osservazionale. Progetto DOMA.IN (Dolore in Oncologia Medica e Analgesia)	OMC	No	Sì	28/04/2004	25	25
	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	2	14
	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
	PETTI						
STATO C	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	0	7
	APPETECCHIA						
STATO A	Ricerca osservazionale sul controllo e le complicanze della terapia sostitutiva con ormone della crescita in pazienti ipopituitarici (HypoCCS)	Endo	No	Sì	18/11/2004		

	Protocolli	*Divisione*	*Random*	*Multicentrico*	*Attiv.*	*Pazienti arruolati nel 2003*	*TOT Pazienti arruolati*
	LAURENZI						
STATO A	Studio clinico osservazionale sullo stato di ipercoaguabilità e sulla efficacia della profilassi antitrombotica di breve durata e di lunga durata con eparine a basso peso molecolare in pazienti oncologici portatori di catetere venoso centrale a permanenza (CVC)	Rian	Sì	No	02/02/2004	15	23
	LAURENZI						
STATO C	Uno studio in aperto, a lungo termine, multicentrico, dello Ziconotide (PRIALT) somministrato per via intratecale	Rian	No	Sì	06/02/2004		
	LAURENZI						
STATO C	Uno studio in aperto, multicentrico, a lungo termine, di tre settimane con fase di estensione sulla sicurezza ed efficacia dello Ziconotide (PRIALT) somministrato per via intratecale nei dolori cronici acuti tramite pompetta esterna	Rian	No	Sì	06/02/2004		
	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	No	11/12/2002	143	153
	COLELLA						
STATO A	Studio osservazionale sull'emesi ritardata	OMC	No	Sì	12/07/2004	15	15
	GRASSI						
STATO C	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	0	84
	SAVARESE						
STATO C	Trattamento d'induzione con epoetina alfa nell'anemia del paziente oncologico sottoposto a chemioterapia	OMA	Sì	Sì	12/02/2003		4
	VESCICA						
	GALLUCCI						
STATO C	Somministrazione endovescicale di gemcitabina nelle neoplasie superficiali della vescica: studio di fase II	URO	No	No	11/12/2002	0	7
	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	43

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