IRE ISTITUTO NAZIONALE TUMORI REGINA ELENA ISG ISTITUTO DERMATOLOGICO SAN GALLICANO
ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

UOC Acquisizione Beni e Servizi

Il dirigente della UOC Acquisizione Beni e Servizi

in virtù della delega conferita con deliberazione N°327/2025

HA ASSUNTO LA PRESENTE DETERMINAZIONE

N. 421 del 16/04/2025

OGGETTO: Autorizzazione alla liquidazione fatture per la pubblicazione di articoli scientifici alle Società: MDPI AG(Invoice Nr.3473938 - Invoice Nr. 3543065), Springer Nature Group (Invoice nr.2936344117), Elsevier B.V. (Invoice nr. OAD0000556075). Fondo PNRR cod. IFO 24/01/G/33 CUP H53C24000230001, responsabile Dr.ssa Barbara Bellei. Fondo ENEA cod. IFO 22/18/R/40 NOCUP, responsabile Dr.ssa Antonella Soriani. Fondo Ricerca Corrente IRE 2025 CUP H53C25000130001, responsabile Direttore Scientifico IRE f.f. Fondo Ricerca Corrente ISG 2025 CUP H53C25000030001 responsabile Direttore Scientifico ISG.

Esercizi/o e conto 2025-502020196-502020197-502020198 Centri/o di costo 3041050-3050450-1100050-3010250

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Servizio Risorse Economiche: **Giovanna Evangelista**

UOC Acquisizione Beni e Servizi Proposta n° DT-445-2025

L'estensore

Daniela Kolziu

Il Responsabile del Procedimento

Barbara Filipponi

Il Dirigente della UOC Acquisizione Beni e Servizi

Giuseppe Navanteri

La presente determinazione si compone di n° 6 pagine e dei seguenti allegati che ne formano parte integrante e sostanziale:
Allegati nr. 19;nota protocollata e fattura da pagare del articolo scientifico pubblicato.

Il Dirigente della UOC Acquisizione Beni e Servizi

Visto il Decreto Legislativo 30 dicembre 1992, n. 502 e ss.mm.ii.;

Visto il Decreto Legislativo 16 ottobre 2003, n. 288 e ss.mm.ii.;

Vista la Legge Regionale 23 gennaio 2006, n. 2;

Visto il Decreto Legislativo 31 marzo 2023, n. 36 ed integrato e modificato con Decreto Legislativo del 31 dicembre 2024, n.209;

Visto l'Atto Aziendale adottato con deliberazione IFO n.153 del 19.02.2019, ed approvato dalla Regione Lazio con DCA n. U00248 del 02.07.2019, modificato e integrato con deliberazioni n. 1254 del 02.12.2020, n. 46 del 21/01/2021 e n. 380 del 25.03.2021, approvate dalla Direzione Salute ed Integrazione Sociosanitaria della Regione Lazio, con Determinazione n. G03488 del 30.03.2021;

Visto il Decreto del Presidente della Regione Lazio n. T00015 del 12 febbraio 2025 avente ad oggetto "Nomina del Direttore Generale dell'Azienda Sanitaria Locale dell'IRCCS Istituti Fisioterapici Ospitalieri (Art. 8, comma 7 bis, della legge regionale 16 giugno 1994, n. 18 e s.m.i.)";

Vista la deliberazione n. 160 del 18.02.2025 di presa d'atto dell'insediamento del Direttore Generale dell'IRCCS Istituti Fisioterapici Ospitalieri Dott. Livio De Angelis;

Viste le deliberazioni n.367 del 23 aprile 2024 e n. 263 del 18 marzo 2025 con le quali sono stati nominati rispettivamente la Dott.ssa Costanza Cavuto quale Direttore Sanitario f.f. e la Dott.ssa Giovanna Evangelista quale Direttore Amministrativo f.f.;

Visto il D.M. del Ministero della Salute del 20 giugno 2024 di conferma del riconoscimento del carattere scientifico dell'IRCCS di diritto pubblico a Istituti Fisioterapici Ospitalieri (IFO) relativamente alla disciplina di "oncologia" per l'Istituto Nazionale Tumori Regina Elena (IRE) e alla disciplina di "dermatologia" per l'Istituto Santa Maria e San Gallicano (ISG);

Vista la deliberazione n.171 del 28.02.2025 avente ad oggetto: “Nomina del Prof. Giovanni Blandino, Direttore della UOC Ricerca Traslazionale Oncologica, quale Direttore Scientifico IRE facente funzioni, a decorrere dal 01.03.2025.”;

Vista la deliberazione n. 327 del 3 aprile 2025 di attribuzione delle deleghe ai Dirigenti del Ruolo Professionale, Tecnico e Amministrativo da parte del Direttore Generale degli IFO;

Premesso che con nota protocollo n.930 del 21 gennaio 2025 del Direttore Scientifico IRE e Nulla Osta del Commissario Straordinario IFO, è stato autorizzato l’appostamento della Ricerca Corrente 2025 IRE per un importo pari a € 3.462.944,05 responsabile Direttore Scientifico IRE;

con protocollo n. 16070 del 15 dicembre 2023 del Direttore Scientifico ff. ISG, munito di Nulla Osta del Direttore Generale f.f. IFO, è stato autorizzato l'appostamento della Ricerca Corrente 2024 ISG per un importo pari a € 966.909,34 responsabile Direttore Scientifico ISG;

che con deliberazione n. 86 del 09/02/2022 ha avuto oggetto la stipula dell'accordo per incarico di ricerca commissionata da ENEA a IFO-IRCCS IRE ed accettazione dell'importo di euro 39.400,00 per l'esecuzione di attivita' relative al progetto dal titolo: "Techea-technologies for health", cod. IFO 22/18/R/40, da svolgersi sotto la supervisione della Dr.ssa Antonella Soriani;

con deliberazione nr.517 del 18/06/2024 è stato accettato il finanziamento pari a 948.000,00 per realizzazione del progetto PNRR-MCNT2-2023- 12377707, dal titolo: “Targheting skin metabolic activity to correct depigmentation in vitiligo:focus on IGF/insulin signaling and glucose mateabolism to prevent inflammation and immune system activation”, cod. Ifo 24/01/G/33 responsabile Dr.ssa Barbara Bellei;

Considerato che la dr.ssa Annamaria Biroccio con nota protocollo 5774 del 10/04/2025 ha chiesto la liquidazione della seguente fattura:

-Fattura nr. 2936344117 del 13/03//2025 di € 4.934,90 Iva compresa della società Springer Nature Group relativa alla pubblicazione del manoscritto dal titolo “TRF2 interaction with nuclear envelope is required for cell polarization and metastasis in triple negative breast cancer “alla Rivista Scientifica: Cell Death & Disease;

la dr.ssa Emilia Migliano con nota protocollo n. 5628 del 09/04/2025, ha richiesto la liquidazione della seguente fattura:

- Fattura nr. 3473938 del 03/04/2025 di € 3.327,70 Iva compresa della società MDPI AG relativa alla pubblicazione del manoscritto dal titolo "Hard palate graft combined with fricke flap: Satisfactory option for reconstruction on extensive lower eyelid defects- a case series" sulla Rivista Scientifica: Journal of Clinical Medicine;

la dr.ssa Antonella Soriani con nota protocollo 5035 del 28/03/2025 ha richiesto la liquidazione della seguente fattura:

- Fattura nr. OAD0000556075 del 21/03/2025 di € 3.001,20 Iva compresa della società Elsevier B.V. relativa alla pubblicazione del manoscritto dal titolo "6- years results from a prospective phase II trial of ten fraction hypofractionated radiotherapy in locally adcanced breast cancer" sulla Rivista Scientifica: Pratical Radiation Oncology;

la dr.ssa Barbara Bellei con nota protocollo 5623 del 09/04/2025 ha richiesto la liquidazione della seguente fattura:

-Fattura nr.3543065 del 05/04/2025 di € 1.727,90 Iva compresa della società MDPI AG relativa alla pubblicazione del manoscritto dal titolo "Defective intracellular insulting/ IGF-1 Signalng Elucidates the link between metabolik defect and autoimmunity in vitiligo" sulla Rivista Cells;

Acquisito il parere favorevole del Direttore Scientifico f.f. dell'Istituto Regina Elena e Direttore Scientifico dell'Istituto di San Gallicano, apposto in calce alle richieste sopra citate;

Accertata la disponibilità sui Fondi citati in premessa;

Esperiti i controlli sulle richieste presentate dai responsabili dei progetti;

Attestato che il presente provvedimento, a seguito dell'istruttoria effettuata, nella forma e nella sostanza è totalmente legittimo e utile per il servizio pubblico, ai sensi dell'art.1 della legge 20/94 e successive modifiche, nonché alla stregua dei criteri di economicità e di efficacia di cui all'art.1, primo comma, della legge 241/90, come modificata dalla legge 15/2005;

DETERMINA

per i motivi di cui in narrativa che si intendono integralmente confermati di:

1-autorizzare il pagamento della seguente fatture:

-Fattura nr. 2936344117 del 13/03//2025 di € 4.934,90 Iva compresa della società Springer Nature Group relativa alla pubblicazione del manoscritto dal titolo "TRF2 interaction with nuclear envelope is required for cell polarization and metastasis in triple negative breast cancer "alla Rivista Scientifica: Cell Death & Disease;

-Fattura nr. 3473938 del 03/04/2025 di € 3.327,70 Iva compresa della società MDPI AG relativa alla pubblicazione del manoscritto dal titolo "Hard palate graft combined with fricke flap: Satisfactory option for reconstruction on extensive lower eyelid defects- a case series" sulla Rivista Scientifica: Journal of Clinical Medicine;

- Fattura nr. OAD0000556075 del 21/03/2025 di € 3.001,20 Iva compresa della società Elsevier B.V. relativa alla pubblicazione del manoscritto dal titolo "6- years results from a prospective phase II trial of ten fraction hypofractionated radiotherapy in locally adcanced breast cancer" sulla Rivista Scientifica: Pratical Radiation Oncology;

-Fattura nr.3543065 del 05/04/2025 di € 1.727,90 Iva compresa della società MDPI AG relativa alla pubblicazione del manoscritto dal titolo "Defective intracellular insulting/ IGF-1 Signalng Elucidates the link between metabolik defect and autoimmunity in vitiligo" sulla Rivista Cells;

2 - far gravare la spesa complessiva di € 12.991,70 sui Fondi: Fondo Ricerca Corrente IRE 2025 per €4.934,90, responsabile Direttore Scientifico IRE f.f. Fondo Ricerca Corrente ISG 2025 per € 3.327,70, responsabile Direttore Scientifico ISG, Fondo ENEA cod. IFO 22/18/R/40 per € 3.001,20, responsabile dr.ssa Antonella Soriani, Fondo PNRR cod. IFO 24/01/G/33 per € 1.727,90 responsabile dr.ssa Barbara Bellei.

Ricerca Corrente IRE 2025

- assegnato:	€	3.461.944,05
- utilizzato:	€	988.750,14
- presente atto:	€	4.934,90
- residuo:	€	2.469.259,01

Ricerca Corrente ISG 2025

- assegnato:	€	968.139,82
- utilizzato:	€	329.757,89
- presente atto:	€	3.327,70
- residuo:	€	638.054,23

Cod. IFO 22/18/R/40

- assegnato:	€	39.400,00
- utilizzato:	€	6.128,79
- presente atto:	€	3.001,20
- residuo:	€	30.270,01

Cod. IFO 24/01/G/33

- assegnato:	€	346.000,00
- utilizzato:	€	58.042,37
- presente atto:	€	1.727,90
- residuo:	€	287.957,63

- dare atto che il relativo impegno di spesa andrà a gravare come di seguito meglio precisato:

  - € 3.001,20 Conto 502020196
  - € 1.727,90 Conto 502020197
  - € 8.262,60 Conto 502020198

  - Centro di Costo 3041050-3050450-1100050-3010250.

La UOC Acquisizione Beni e Servizi curerà tutti gli adempimenti per l'esecuzione della presente determinazione.

Il Dirigente della UOC Acquisizione Beni e Servizi

Giuseppe Navanteri

Documento firmato digitalmente ai sensi del D.Lgs 82/2005 s.m.i. e norme collegate

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SAN GALLICANO
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

Al Direttore ABS – SAR
SEDE

OGGETTO: RICHIESTA PAGAMENTO ARTICOLO SCIENTIFICO

Con la presente si richiede il pagamento dell'articolo dal titolo "Hard Palate Graft Combined with Fricke Flap: Satisfactory Option for Reconstruction of Extensive Lower Eyelid Defects—A Case Series", autori Paola Parisi, Flavio Andrea Govoni, Tiziano Pallara, Antonio Bonadies, Marinella Tedesco, Elena Govoni e Emilia Migliano e accettato dalla rivista "Journal of Clinical Medicine". La rivista ha un IF grezzo di IF pari a 3 (Normalizzato 6).

Il costo di euro EUR 2. 727.60 dovrà gravare sul Fondo Ricerca Corrente ISG 2025.

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Dr.ssa Emilia Migliano
UOSD Chirurgia Plastica ISG
Istituto Dermatologico San Gallicano IRCCS

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Chirurgo Plastico

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Article

Hard Palate Graft Combined with Fricke Flap: Satisfactory Option for Reconstruction of Extensive Lower Eyelid Defects—A Case Series

Paola Parisi [1], Flavio Andrea Govoni [2], Tiziano Pallara [1,*], Antonio Bonadies [1], Marinella Tedesco [1], Elena Rita Govoni [3] and Emilia Migliano [1]

[1] Department of Plastic and Regenerative Surgery, San Gallicano Dermatological Institute IRCCS, Rome, Italy; paola.parisi@ifo.it (P.P.);tiziano.pallarafo.it antonio.bonadies@ifo.it (A.B.); marinella.tedesco@ifo.it (M.T.); emilia.migliano@ifo.it (E.M.)
[2] Department of Maxillo-Facial Surgery, San Camillo Forlanini Hospital, Rome, Italy; flaviogovoni@gmail.com
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Abstract: Background: The reconstruction of extensive full-thickness lower eyelid defects constitutes a challenge for plastic surgeons. Various techniques have been described to cater to patients' specific defect needs, with the aim of achieving the best results. **Materials and Methods:** We performed a retrospective observational study assessing our experience with a combination of a single-stage procedure consisting of a hard palate graft and a Fricke flap for patients with complex lower lid resections undergoing immediate total reconstruction at our institution. Clinical data, histological type and results, size of tumor, recurrences, and post-operative complications were collected to evaluate outcomes. A Visual Analogue 10-point scale was administered to all patients to assess esthetic and functional outcomes. **Results:** Seven lower lid reconstructions were performed, with all patients receiving immediate reconstruction. The age of the patients ranged from 55 to 82. Five skin cancers were located on the right side and three on the left side. In all cases, histological diagnoses were non-melanoma skin cancers. The mean size of the tumor was 1.7 × 1.7. In all patients, negative surgical margins were obtained. All patients performed a 24-month follow up. No immediate complication from surgery was recorded within the first 30 days. During follow-up, lower lid ectropion was observed in one patient due to the development of a retracting scar. No local cancer recurrence or nodal metastasis were detected until 2 years follow-up. In only one case, adjuvant therapy was required. The esthetic results were deemed satisfactory by all patients. **Conclusions:** According to our experience, the combination of a Fricke flap and hard palate graft is an excellent option for total lower eyelid reconstruction, with low morbidity and favorable outcomes, even in elderly and frail patients where satisfactory results were achieved in a single-stage procedure and short operative times.

Keywords: extensive lower eyelid defect; eyelid reconstruction; hard palate graft; Fricke flap; skin cancer

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Roma, 04/04/2025

Prot.n. RTO2-29/25-AB

Alla Direzione Scientifica IRE

Al Servizio Amm.vo per la Ricerca

Oggetto: richiesta pagamento pubblicazione

La sottoscritta Dr.ssa Annamaria Biroccio, dirigente biologo afferente alla UOC Ricerca Traslazionale Oncologica, chiede il pagamento della fattura N. 2936344117 del 13/03/2025 (Springer Nature Group) relativa alla pubblicazione del manoscritto dal titolo ***TRF2 interaction with nuclear envelope is required for cell polarization and metastasis in triple negative breast cancer*** di Petti *et al.* sulla rivista scientifica *Cell Death & Disease* (IF 8.1).

Cell Death & Disease è una rivista peer-reviewed nel campo della morte cellulare traslazionale. Cerca di promuovere aree diverse e integrate di medicina sperimentale e interna con le sue specialità, tra cui cancro, metabolismo del cancro, immunità e neuroscienze.

La somma di € 4.045,00 potrà gravare sui fondi della Direzione Scientifica, come concesso.

Si allega:

- fattura N. 2936344117 del 13/03/2025 (Springer Nature Group)
- prima pagina del manoscritto
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Il Direttore
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Cordiali saluti

Dr.ssa Annamaria Biroccio

IL DIRETTORE SCIENTIFICO f.f.
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ARTICLE OPEN

TRF2 interaction with nuclear envelope is required for cell polarization and metastasis in triple negative breast cancer

Eleonora Petti[1,12], Serena Di Vito[1,2,12], Roberto Dinami[1,12], Manuela Porru[1], Stefano Marchesi[3,4], Jeroen Lohuis[5], Pasquale Zizza[1], Sara Iachettini[1], Erica Salvati[6], Carmen D'Angelo[1], Angela Rizzo[1], Carmen Maresca[1], Flora Ascione[3], Anna Di Benedetto[7], Simonetta Buglioni[7], Andrea Sacconi[8], Paola Ostano[9], Qingsen Li[3], Antonella Stoppacciaro[10], Carlo Leonetti[1], Jacco van Rheenen[5], Paolo Maiuri[3,11], Giorgio Scita[3,4] and Annamaria Biroccio[1]✉

The Telomere Repeat-Binding factor 2 (TRF2) contributes to cancer progression by both telomere-dependent and independent mechanisms, including immune escape and angiogenesis. Here, we found that TRF2, through its Basic domain, directly interacts with Emerin forming a complex, including Lamin A/C, Lamin B1, SUN1, and SUN2. Importantly, TRF2 association with the inner nuclear membrane is functional to the proper establishment of cell polarity, finally promoting productive 1D and 3D migration in triple negative breast cancer cells (TNBC). In line with this, a spontaneous model of TNBC metastasis, combined with intravital imaging, allowed us to demonstrate that TRF2 promotes cell migration at the primary tumor site and is required for the early steps of the metastatic cascade. In human breast cancers, aberrantly elevated TRF2 expression positively correlates with cancer progression, metastasis, and poor prognosis, identifying TRF2 as a potential target for novel therapeutic strategies against TNBC.

Cell Death and Disease (2025)16:224 ; https://doi.org/10.1038/s41419-025-07415-4

INTRODUCTION

Telomeres are nucleoprotein structures located at the physical ends of eukaryotic chromosomes. In human, they are composed of TTAGGG DNA tandem repeats bound by a multi-protein complex named Shelterin that prevents natural chromosome ends from being recognized as DNA breaks [1]. Among Shelterin components, Telomere Repeat Binding Factors 1 and 2 (TRF1 and TRF2) specifically bind to telomeric double stranded DNA, while Protection Of Telomeres 1 (POT1) associates with the single-stranded TTAGGG repeats at the telomeric 3'-overhang. The other three shelterin proteins, TIN2, TPP1, and RAP1, are indirectly associated to telomeric DNA through protein-protein interactions with TRF1 and/or TRF2 and/or POT1 [1].

TRF2, the central member of Shelterin complex, acts as a master regulator of telomere integrity by favoring the folding of the 3' single-stranded G overhang into the T-loop and by suppressing ATM-mediated DNA damage response and non-homologous end joining repair pathway [1]. TRF2 is composed by four domains: the N-terminal Basic domain binds branched DNA in a sequence-independent manner; the Homodimerization (TRFH) and the HINGE domains are involved in protein-protein interactions, while the C-terminal Myb domain specifically binds telomeric double stranded DNA [1–3]. TRF2 is not frequently mutated in cancers, but it results up-regulated in a large panel of tumors [4–6], including breast cancer where accumulation of TRF2 has been reported to occur during transformation and progression ensuring telomere protection and indefinite life-span maintenance [7, 8]. However, TRF2 contributes to tumorigenesis also through telomere-independent mechanisms, such as immune escape and angiogenesis [6, 9–11]. Till now, its extra-telomeric functions have been ascribed to its ability to bind to interstitial telomeric sequences (ITS) dispersed throughout the human genome, eventually regulating gene expression in cooperation with other chromatin remodeling factors [6, 10–12]. In addition to telomeres and ITS, TRF2 has been reported to be important for the stability of other heterochromatic regions, such as pericentromeres [13].

TRF2 has also been reported to interact with many different classes of proteins, including telomeric accessories factors (e.g., Apollo) [14, 15], components of DNA damage response/repair pathways (e.g., PARP1, BRCA1) [16, 17], chromatin factors [18], proteins involved in DNA replication (e.g., ORC, RTEL) [19–21] and components of the nuclear lamina [22, 23]. In particular, Lamin A/C and Lamin B1 have been included in the plethora of TRF2 interactors and their role has been investigated in the stability of ITS and telomeres, respectively [22–24].

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AUTHOR CONTRIBUTIONS

EP and AB conceived the study and designed the experiments; EP, SDV, RD, PZ, SI, ES, CDA, AR, and CM performed in vitro experiments; EP, SM, PM, and GS performed and analyzed single cell migration experiments; FA and QL performed and analyzed AFM experiments; MP carried out in vivo experiments; JL and JVR performed and analyzed intravital experiments; SDV and AS performed and analyzed immunoistochemistry experiments on mouse tissues; ADB and SB carried out immunoistochemistry analysis on human patients; AS and PO performed bioinformatic analysis; EP and AB wrote the paper; RD, CL, JVR, PM, and GS reviewed the manuscript.

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The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. Animal procedures were compliant with the national and international directives (D.L. 4 March 2014, no. 26; directive 2010/63/EU of the European Parliament and of the council; Guide for the Care and Use of Laboratory Animals, United States National Research Council, 2011 Animal Research guidelines Reporting of In Vivo Experiments (ARRIVE) guidelines) and approved by the Italian Ministry of the health (authorization n. 607/2019-PR issued on date 07-08-2019). Study on human patients surgically treated at the Regina Elena National Cancer Institute was reviewed and approved by the Local Ethic Committee of the same Institute (del. n. 1201/19). Informed consent was obtained from all participants. No identifiable images from the participants are presented in this study.

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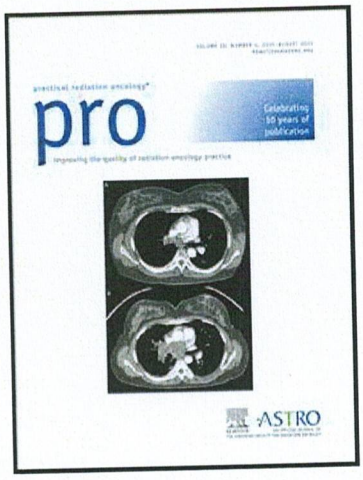

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Author Contributions: P.P. designed the study and selected patients. S.T. and P.P. carried out clinical analysis and follow up. F.S. and D.G. developed the statistical analysis and supervised the findings of this work.

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ABSTRACT

PURPOSE

We report the 6-year results of a phase II study on hypofractionated radiotherapy (HFRT) targeting the primary and regional lymph nodes in ten fractions (fxs).

MATERIALS AND METHODS

A schedule of 34 Gy/10 fxs/2 wks to the whole breast/chest wall and to the draining lymph nodes was used. Both acute and late toxicities were collected. All pts but those who underwent mastectomy without reconstruction or with temporary expander were asked to rate their cosmetic outcome according to the Harvard scale. Toxicity was assessed weekly during RT and then at each follow-up (fup) examination. Cancer related endpoints were evaluated from the date of RT start to the diagnosis of local relapse/distant metastases or the last fup respectively.

RESULTS

From February 2015 to March 2019, 59 women (median age 60 yrs, IQR: 48.3-68.8 yrs) with stage II to IIIA breast cancer who underwent axillary dissection and conservative surgery (83%) or mastectomy (17%) were accrued. One patient was lost to fup immediately after the end of RT. At the median fup of 77.11 months (range: 24-102 months), the cumulative incidence of any grade loco-regional late toxicity estimated with the Kaplan-Meier method is 43.4% (95%CI) (30.0% and 46.1% for patients undergone mastectomy and lumpectomy, respectively). Peak- 2 events have been observed for fibrosis (1 pt, 1.7%), telangiectasia (1 pts, 1.7%) and lymphoedema (1 patient, 1.7%).

One patient (1.7%) experienced grade 3 breast retraction at 36 month fup. The cosmetic outcome resulted to be excellent, good, fair and poor in 61.7%, 25%, 7.6% and 5.7%, respectively.

At 72 months the specific-disease free survival was 96.5%; distant metastasis-free survival (DMFS) and OS rates were 88% and 94.4% respectively.

CONCLUSIONS

Our results support the activity of a 10-fxs Hypo-RT schedule targeting the primary site as well as the draining lymph node stations after surgery for locally advanced BC.

INTRODUCTION

Postoperative radiation therapy (RT) represents an essential component in the multidisciplinary management of breast cancer (BC) patients after lumpectomy and, in selected cases, after mastectomy, reducing both locoregional relapses and breast cancer-related mortality[1]. After breast conserving surgery, conventionally fractionated RT (CFRT) of the breast to 50 Gy in 25 fractions (fxs) over 5 weeks has been considered the standard of care for a long time. In the last two decades CFRT has been replaced by hypofractionated RT (HFRT), which allows to decrease the overall treatment duration by reducing the total number of fractions[2] in patients treated with conservative surgery, as supported by several clinical trials[3-6].

Recent reviews and metanalyses[7,8] always support the use of moderate hypofractionation (40–42.5 Gy in 15–16 fractions) regardless the treated volumes, including the whole breast, the chest wall and the regional nodes. However, in patients treating a larger volume than the residual breast as in the case of regional nodal irradiation (RNI), the use of HFRT still remains debatable[9], since the number and the quality of studies supporting it is limited[6,11-12].

Indeed, international guidelines[13,14] still consider HFRT not to be the standard of care in patients undergoing immediate breast reconstruction.

At our Institution a 10 fraction-accelerated hypofractionated whole breast (WB) schedule (AH-WBRT), followed by 8 Gy single fraction on the tumor bed boost, has

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Defective Intracellular Insulin/IGF-1 Signaling Elucidates the Link Between Metabolic Defect and Autoimmunity in Vitiligo

Silvia Caputo [1], Federica Papaccio [1], Ramona Marrapodi [1], Gianluca Lopez [1], Paolo Iacovelli [2], Alessia Pacifico [2], Emilia Migliano [3], Carlo Cota [4], Anna Di Nardo [1], Mauro Picardo [5] and Barbara Bellei [1,*]

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Abstract: Background: Vitiligo is featured by the manifestation of white maculae and primarily results from inflammatory/immune-selective aggression to melanocytes. The trigger mechanism leading to the activation of resident immune cells in the skin still lacks a molecular description. There is growing evidence linking altered mitochondrial metabolism to vitiligo, suggesting that an underlying metabolic defect may enable a direct activation of the immune system. Recent evidence demonstrated the association of vitiligo with disorders related to systemic metabolism, including insulin resistance (IR) and lipid disarrangements. However, IR, defined as a cellular defect in the insulin-mediated control of glucose metabolism, and its possible role in vitiligo pathogenesis has not been proven yet. **Methods:** In this study, we compared the Ins/IGF-1 intracellular signaling of dermal and epidermal cells isolated from non-lesional vitiligo skin to that belonging to cells obtained from healthy donors. **Results:** We demonstrated that due to the intensified glucose uptake, S6, and insulin receptor substrate 1 (IRS1) chronic phosphorylation, their inducibilities were downsized, a condition that coincides with the definition of insulin resistance at the cellular level. Correspondingly, the mitogenic and metabolic activities normally provoked by Ins/IGF-1 exposure resulted in significantly compromised vitiligo cells ($p \leq 0.05$). Besides all the vitiligo-derived skin cells manifesting an energetic disequilibrium consisting of a low ATP, catabolic processes activation, and chronic oxidative stress, the functional consequences of this state appear amplified in the keratinocyte lineage. **Conclusion:** The presented data argue for insulin and IGF-1 resistance collocating dysfunctional glucose metabolism in the mechanisms of vitiligo pathogenesis. In vitiligo keratinocytes, the intrinsic impairment of intracellular metabolic activities, particularly when associated with stimulation with Ins/IGF-1, converges into an aberrant pro-inflammatory phenotype that may initiate immune cell recruitment.

Keywords: vitiligo; metabolism; insulin; IGF-1; inflammation

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