UNIVERSITY OF TRENTO - Italy
Department of Physics

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

Aifm
Associazione Italiana di Fisica Medica

Physics&Medicine

Toward a future of integration

Trento, November 6th – 8th, 2014

Abstract book

Editors:

Renzo Antolini
Department of Physics
University of Trento

Aldo Valentini
Medical Physics Department
Azienda Provinciale
per i Servizi Sanitari of Trento

UNIVERSITY OF TRENTO - Italy
Department of Physics

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

Aifm
Associazione Italiana di Fisica Medica

Physics & Medicine
Toward a future of integration

Trento, November 6th – 8th, 2014

Abstract book

Editors:

Renzo Antolini
Department of Physics
University of Trento

Aldo Valentini
Medical Physics Department
Azienda Provinciale
per i Servizi Sanitari of Trento

Trento
Università degli Studi di Trento

Physics & Medicine: towards a future of integration: Trento, November 6th- 8th, 2014: abstract book / editors Renzo Antolini, Aldo Valentini. - Trento: Università degli Studi di Trento, 2014. - 72 p.: ill. - ISBN: 978-88-8443-575-0.

CONFERENCE PRESENTATION

On behalf of the Organizing Committee, we would like to welcome you to the Conference "**Physics & Medicine. Toward a future of integration**" in Trento.

The relationship between physics and medicine has ancient roots that sink to the dawn of medicine with the use of physical techniques, like heat and light, to diagnose and treat diseases. In the 17th century, with the advent of the experimental method, the mechanistic description of nature was soon extended to living creatures. At the University of Padua, when Galileo was still there to teach, started the school of iatro-mechanics that was concerned with fundamental questions about the function of the human body and the nature of life itself. Along these lines, physics contributed both to the establishment of new medical disciplines such as biomechanics, electrophysiology and ophthalmology and supported many other clinical practices and medical researches through the development of a huge number of physics-based devices for clinical measurement, diagnosis and treatment. However, medical physics, as we usually understand the term, emerged as a distinct discipline in the 20th century in response to the growing use of ionizing radiation in both diagnosis and treatment. The urgent need to associate to the team of health professionals dealing with ionizing radiation a physicist with the central role of warrantor of the safe and effective use of radiation became soon evident and led to a new health-care profession: medical physics.

In Italy, the Conference "Conversations on the Relations between Physics and Medicine" held in Levico Roncegno Terme (Trento) from September 14th to 19th 1964, was of paramount importance to the activation of the Medical Physics services in the healthcare facilities. Moreover that Conference emphasized the need for basic training in physics for future physicians thus contributing to the establishment of Chairs in Medical Physics at the Schools of Medicine.

The actual Conference "Physics & Medicine. Toward a future of integration" has been organized by the University of Trento, the Azienda Provinciale per i Servizi Sanitari of Trento and the Associazione Italiana di Fisica Medica, on the 50th anniversary of the Levico Roncegno Terme event. Since then the life sciences experienced a true scientific and technological revolution with significant clinical implications demanding to physics and medicine effective patterns of integration . Therefore the goals of the meeting are:

- to review the current status of main topics of medical physics and give a vision of coming developments;
- to consider the profession and the role of the medical physicist projected in the new organizational models of health services;
- to analyze patterns of training and retraining of medical physicists as well as the basic training programs for future physicians;
- to discuss the contribution of research in physics as applied to medicine as an engine for innovation in health care;

The event is organized in conjunction with the **International Day of Medical Physics**, proposed by the International Organization of Medical Physics (IOMP) for the day November 7th, in which it celebrates the anniversary of the birth of Marie Sklodowska-Curie. In this year IOMP proposes the theme "Looking into the Body: Advancement in Imaging through Medical Physics.

The Conference Program also includes two joint sessions with the event "Giornate di Studio sul Piano Triennale 2015-2017" of INFN (National Institute of Nuclear Physics).

We wish you a wonderful experience in this scientific event, and we also hope that you will be

able to find time before or after the Conference to enjoy the many exciting experiences that the Trentino Province has to offer.

Renzo Antolini
Department of Physics
University of Trento
renzo.antolini@unitn.it

Aldo Valentini
Department of Health Physics
Azienda Provinciale per I Servizi Sanitari - APSS, Trento
aldo.valentini@apss.tn.it

ORGANIZING COMMITTEE

University of Trento
Renzo Antolini
Roberto Battiston
Lorenzo Pavesi

Azienda Provinciale per i Servizi Sanitari of Trento
Maurizio Amichetti
Mattia Barbareschi
Roberto Bonmassari
Patrizio Caciagli
Giorgio Camin
Franca Chierichetti
Franco Chioffi
Giovanni de Pretis
Maurizio Del Greco
Enzo Galligioni
Angelo Graffigna
Giovanni Maria Guarrera
Loris Menegotti
Paolo Peterlongo
Luigi Tomio
Aldo Valentini
Roberta Visentin

Azienda Sanitaria of Alto Adige
Markus Haller

INFN, Istituto Nazionale di Fisica Nucleare
Graziano Fortuna

FBK, Fondazione Bruno Kessler, Trento
Giandomenico Nollo

SCIENTIFIC COMMITTEE

Renzo Antolini,	University of Trento
Giovanni Berlucchi,	University of Verona
Carlo Cavedon,	Azienda Ospedaliera Universitaria Integrata, Verona
Roberto Cirio,	University of Torino
Giacomo Cuttone,	INFN, Laboratori Nazionali del Sud, Catania
Alberto Del Guerra,	University of Pisa
Maria Carla Gilardi,	Ospedale San Raffaele, Milano
Peter Lukas,	Medizinische Universitaet Innsbruck
Marta Paiusco,	Istituto Oncologico Veneto, Padova
Cristiana Peroni,	University of Torino
Alessandro Quattrone,	University of Trento
Daniele Regge,	IRCC, Candiolo, Torino
Marco Schwarz,	Azienda Provinciale per i Servizi Sanitari of Trento
Michele Stasi,	A.O. Ordine Mauriziano of Torino
Alberto Torresin,	Ospedale Niguarda Ca' Granda, Milano
Giampaolo Tortora,	University of Verona
Aldo Valentini,	Azienda Provinciale per i Servizi Sanitari of Trento
Vincenzo Valentini,	Università Cattolica, Roma

PROGRAM

Thursday, Novembre 6th

MUSE, Science Museum
corso del Lavoro e della Scienza 3, Trento

16.30 Registration
18.00 Conference opening and greetings from Authorities and Scientific Associations
19.00 Guided tour at the Museum
20.30 Welcome aperitif

Friday, November 7th

Federazione Trentina della Cooperazione
via Segantini 10, Trento
Joint scientific sessions with the Istituto Nazionale di Fisica Nucleare

08.30 Session 1: Physics of Cancer
Chairs: **Luigi Tomio** (Azienda Provinciale per i Servizi Sanitari, Trento), **Marta Paiusco** (Istituto Oncologico Veneto, Padova)

08.30 ***Transport oncophysics***
Mauro Ferrari (Houston Methodist Research Institute, Houston, USA)
(in videoconferenza)

09.00 ***Hitting genomic stability: from cancer cause to cancer cure***
Antonio Giordano (Sbarro Institute for Cancer Research and Molecular Medicine, Temple University, Philadelphia, USA)

09.30 ***Perspectives in particle radiobiology***
Marco Durante (GSI Helmholtz Centre for Heavy Ion Research e Technical University, Darmstadt, Germany)

10.00 ***Physical aspects in the evolving models of cancer treatment with radiations***
Alessio Morganti (Università Cattolica del Sacro Cuore, Roma)

10.30 Coffee break

11.00 Session 2: Physics in Medical Imaging
Chairs: **Carlo Cavedon** (Azienda Ospedaliera Universitaria Integrata, Verona), **Peter Lukas** (Medizinische Universitaet Innsbruck, Austria)

11.00 ***100 years of imaging in radiotherapy – and what's next?***
Frank Lohr (University Medical Center Mannheim, Universitaetsmedizin Mannheim, Germany)

11.30 ***Development of in-vivo imaging techniques for charged particle therapy***
Giuseppe Battistoni (Istituto Nazionale di Fisica Nucleare, Sezione di Milano)

12.00 ***Technologies for dose reduction and monitoring in diagnostic radiology***
Davide Caramella (University of Pisa)

12.30 ***PET/CT and molecular imaging***
Stefano Fanti (University of Bologna)

Faculty of Giurisprudenza
via Rosmini 27, Trento

13.30 Lunch & poster session

14.30 Session 3: Physics in Precision Medicine
Chairs: **Enzo Galligioni** (Azienda Provinciale per i Servizi Sanitari, Trento), **Alessandro Quattrone** (University of Trento)

14.30 ***Lecture title pending***
Gerhardt Attard (Institute of Cancer Research e Royal Marsden Hospital, London, UK)

15.30 Session 4: Physics of Brain
Chairs: **Franco Chioffi** (Azienda Provinciale per i Servizi Sanitari, Trento), **Nathan Weisz** (University of Trento)

15.30 ***Cracking the neural code using tools and concepts from statistical physics***
Stefano Panzeri (Istituto Italiano di Tecnologia, Center for Neuroscience and Cognitive Systems, Rovereto)

16.00 ***Functional imaging of the human brain using MEG and fMRI***
Gian Luca Romani (Università "G. d'Annunzio", Chieti)

16.30 ***Diffusion tensor imaging and modern neurosurgery: toward a connectomic approach to brain surgery***
Silvio Sarubbo (Azienda Provinciale per i Servizi Sanitari, Trento)

17.00 Coffee break & poster session

17.30 Oral presentation of selected posters
Chair: **Otello Nibale** (Associazione Italiana di Fisica Medica, Triveneto)

19.30 Departure by bus to the social dinner (via Petrarca, Trento)
20.00 Social dinner, Cantine "Rotari" of Mezzocorona, Trento
(joint social event with the Istituto Nazionale di Fisica Nucleare)

Saturday, November 8th

Faculty of Giurisprudenza
via Rosmini 27, Trento

08.30 Round Table 1: ***The future role of the Medical Physics Departments in the new organizational models of health services***

Danilo Aragno	(Azienda Ospedaliera San Camillo Forlanini of Roma)
Luisa Begnozzi	(President of Associazione Italiana di Fisica Medica)
Pier Paolo Benetollo	(Direttore Sanitario Azienda Ospedaliera Integrata Unitaria of Verona)
Onelio Geatti	(President of Associazione Italiana di Medicina Nucleare)
Michele Stasi	(IRCC, Istituto per la Ricerca e la Cura del Cancro di Candiolo e Azienda Sanitaria Ospedaliera Ordine Mauriziano, Torino)
Franco Vimercati	(President of FISM, Federazione delle Società Medico-Scientifiche Italiane)

09.30 Round Table 2: ***Patterns of training and retraining of medical physicists***

Marta Bucciolini	(University of Firenze)
Marco Ferdeghini	(University of Verona)
Pier Giorgio Montarolo	(University of Torino)
Cristiana Peroni	(University of Torino)
Gian Luca Romani	(Università "G. d'Annunzio", Chieti)

10.30 Coffee break & poster session

11.00 Round Table 3: ***The research in physics as applied to medicine as an engine for innovation in health care***

Silvio Aime	(Università di Torino e Presidente di 2i3T, Incubatore d'Imprese dell'Università di Torino)
Renzo Antolini	(University of Trento)
Luciano Flor	(Direttore Generale dell'Azienda Provinciale per i Servizi Sanitari, Trento)
Cino Matacotta	(INFN, Comitato Nazionale per il Trasferimento Tecnologico)

12.00 Oral presentation of selected posters
Chair: **Aldo Valentini** (Azienda Provinciale per i Servizi Sanitari, Trento)

13.00 Conference closing

Azienda Provinciale per i Servizi Sanitari di Trento
Proton Therapy Facility
via Al Desert 17, Trento

15.00 Guided tour
(Warning: minors and pregnant women are not allowed in risk areas)

RELATIONS

#	Speaker	Title
1	***Mauro Ferrari***	**Transport oncophysics**
2	***Antonio Giordano***	**Hitting genomic stability: from cancer *cause* to cancer *cure***
3	***Marco Durante***	**Perspectives in particle radiobiology**
4	***Alessio G. Morganti***	**Physical aspects in the evolving models of cancer treatment with radiations.**
5	***Frank Lohr***	**100 years of Imaging in Radiotherapy – and what's next?**
6	***Giuseppe Battistoni***	**Development of in-vivo imaging techniques for charged particle therapy**
7	***Davide Caramella***	**Technologies for dose reduction and monitoring in diagnostic radiology**
8	***Stefano Fanti***	**PET/CT and molecular imaging**
9	***Gerhardt Attard***	**Lecture title pending**
10	***Stefano Panzeri***	**Cracking the neural code using tools and concepts from statistical physics**
11	***Gian Luca Romani***	**Functional Imaging of the Human Brain using MEG and fMRI**
12	***Silvio Sarubbo***	**Diffusion Tensor Imaging and modern neurosurgery: toward a connectomic approach to brain surgery.**

Transport oncophysics

Mauro Ferrari, Ph. D.

Ernest Cockrell Jr. Presidential Distinguished Chair
President and CEO, Houston Methodist Research Institute
Director, Institute for Academic Medicine at Houston Methodist Hospital
Executive Vice President, Houston Methodist Hospital System
www.tmhri.org
6670 Bertner St., M.S. R2-216, Houston, TX 77030
e-mail: mferrari@tmhs.org
Tel (713) 441 8439

Senior Associate Dean and Professor of Medicine
Weill Cornell Medical College
New York, NY

Transport Oncophysics studies cancer as a proliferative disease of mass transport dysregulation at multiple scales, from the molecular to the cell-, tissue-, organ-, and organism-level.

The fundamental characteristics of the mass transport differentials in cancer are associated with the pathological modifications of biological barriers that accompany carcinogenesis. Examples of these are the hyper-permeabilization of vascular endothelia; the flow patterns in highly anastomotic angiogenic vasculature; stromal hypertrophy; and overexpression of ionic and molecular efflux pumps in tumor-initiating and therapy-resistant cells.

Employing methods of Transport Oncophysics it is not only possible to develop novel biomarkers of disease and therapeutic response, but also to envision novel modalities of treatment, especially in the context of metastatic disease, and with the use of therapeutic carriers optimally designed to address the mass transport challenges that pertain to cancer, and its pathological modification of biological barriers.

In this presentation I will review the fundamentals of Transport Oncophysics, review some recent advances in its clinical application to cancer diagnostic and prognostics; and present some nanotechnology-based transport solutions and application in preclinical models of metastatic disease.

Hitting genomic stability: from cancer *cause* to cancer *cure*.

F. Pentimalli[1] and A. Giordano[1,2,3]

(1) Oncology Research Center of Mercogliano (CROM); Istituto Nazionale Per Lo Studio E La Cura Dei Tumori "Fondazione Giovanni Pascale"; IRCCS; Naples, Italy

(2) Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

(3) Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia PA, USA

The association between cancer and the environment dates back to the 18th century, long before the birth of modern epidemiology. Among the environmental factors associated with cancer, physical agents, X rays in particular, were early recognized as capable of increasing cancer rates, inducing tumors that developed at sites of irradiation [1]. Although not all carcinogens are mutagenic to DNA, many chemical and physical agents act directly or indirectly on DNA, challenging genome stability. Whereas ionizing radiations induce DNA double strand breaks, UV rays induce the formation of cyclobutane pyrimidine dimers (CPDs), highly mutagenic species that hamper the DNA replication process.

The ability of many chemotherapy drugs and of ionizing radiations to damage the DNA of the highly proliferating cancer cells has been the mainstay of antitumoral treatments in the clinical setting. However, during the past decades we have moved from a one-size-fits-all approach, typical of cytotoxic chemotherapy, to a personalized medicine strategy that aims to develop molecularly targeted drugs able to exploit particular genetic addictions, dependencies and weaknesses of cancer cells.

Unfortunately, however, cancer cells are highly heterogeneous at the molecular level and tumours continuously evolve managing to escape therapeutic treatments. The main cause of such heterogeneity is the underlying genomic instability, which has been recently defined as one of the key hallmarks enabling cancer development and progression [2]. Recently, many molecular mechanisms that drive the complex cell response to DNA damage have been identified, which, not only helped to shed light on the events triggering tumour development and progression, but also provided new targets for more specific anticancer therapeutic approaches, the best example being the use of PARP inhibitors for the treatment of breast and ovarian cancer owed to faulty BRCA genes, with PARP and BRCA both involved in DNA repair pathways [3]. In our lab we study the mechanisms that regulate cell cycle, which are strictly connected to the cell response to DNA damaging agents, and test new strategies that could function as synthetic lethal approaches to sensitize cancer cells to DNA damaging agents, including radiations and chemotherapy drugs [4,5].

References:

[1] RA Weinberg. The biology of cancer. Garland SCIENCE, Taylor and Francis Group, LLC 2007.

[2] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. Mar 4;144(5):646-74 (2011).

[3] Turner N, Tutt A, Ashworth A. Targeting the DNA repair defect of BRCA tumours. Curr Opin Pharmacol. Aug;5(4):388-93 (2005).

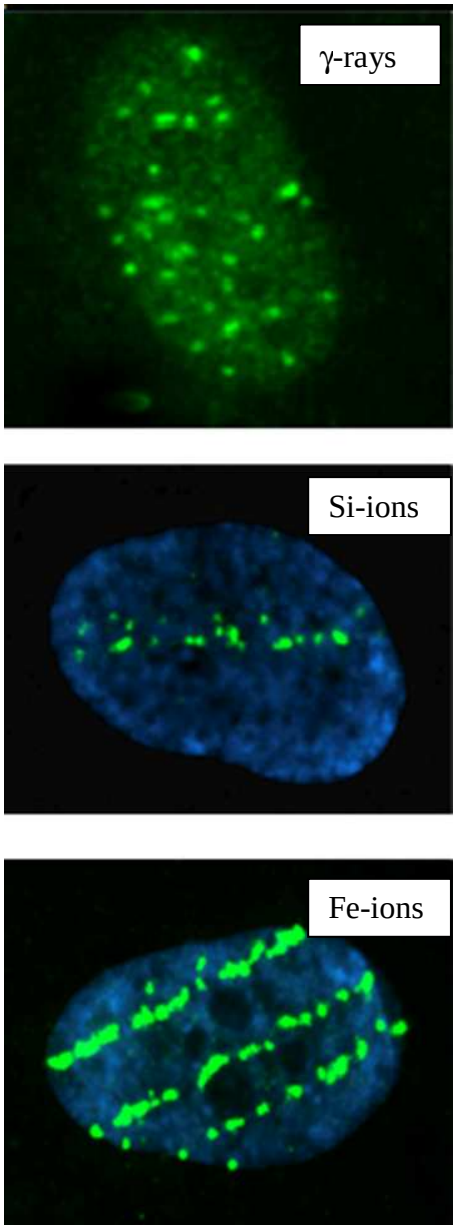
[4] Indovina P, Marcelli E, Di Marzo D, Casini N, Forte IM, Giorgi F, Alfano L, Pentimalli F, Giordano A. Abrogating G_2/M checkpoint through WEE1 inhibition in combination with chemotherapy as a promising therapeutic approach for mesothelioma. Cancer Biol Ther. 15(4):380-8 (2014).

[5] Di Marzo D, Forte IM, Indovina P, Di Gennaro E, Rizzo V, Giorgi F, Mattioli E, Iannuzzi CA, Budillon A, Giordano A, Pentimalli F. Pharmacological targeting of p53 through RITA is an effective antitumoral strategy for malignant pleural mesothelioma. Cell Cycle 15;13(4):652-65 (2014).

Perspectives in particle radiobiology

Marco Durante

Department of Biophysics – GSI Helmholtz Center – Darmstadt, Germany.
Department of Condensed Matter Physics - University of Darmstadt – Darmstadt, Germany



Radiotherapy is an essential tool for curing cancer. Over 50% of all patients with localized malignant tumors receive radiotherapy as part of their initial therapy, either alone or, more frequently, in combination with surgery and chemotherapy. Ionizing radiation effectively kills human cells, and sufficiently high doses of radiation can sterilize any tumor and achieve nearly 100% tumor control probability. However, in external-beam therapy healthy tissue is unavoidably exposed to radiation, therefore increasing the normal tissue complication probability. Over 90% of the patients worldwide are treated with high-energy X-rays produced by electrons accelerated to several MeV in linear accelerators (linacs). Controlling tumors non-invasively using high-energy charged particles (protons or carbon ions) offers advantages over conventional X-ray therapy, since a lower radiation dose is delivered to healthy tissues. Protons and heavy ions deposit energy far more selectively than X-rays, allowing a higher local control of the tumor, a lower probability of damage to healthy tissue, low risk of complications and the chance for a rapid recovery after therapy. Charged particles are also useful for treating tumors located in areas with radiosensitive surrounding tissues, such as the brain, spinal cord and kidney and in anatomical sites where surgical access is limited. Current trial outcomes indicate that accelerated ions may be capable of replacing surgery for radical cancer treatments, which may be beneficial as the success of surgical cancer treatments are largely dependent on the expertise and experience of the surgeon and the location of the tumor. However, only a small number of controlled trials to date have made comparisons between particle therapy and X-rays, making comparisons difficult. Research in medical physics and radiobiology is concentrating on reducing the costs and increasing the benefits of this treatment.

Radiation biology is a potential breakthrough in radiotherapy. DNA damage induced by charged particles is quite distinct from the damage induced by X-rays, as it can be seen using markers of DNA damage (such as the histone γH2AX – see figure) and high-resolution microscopy. We will present recent results showing that charged particles elicit a distinct dmage response signal cascade, which can be used for optimizing the treatment in combination with specific drugs. Particularly important are drugs targeting the DNA resection pathway and immunotherapy drugs, which enhance the immunogenic response caused by localized high doses of heavy ions. Physics and biology are entangled in particle therapy, and this interaction may lead to major breakthroughs in treatment of several lethal cancers.

References:

[1] J.S. Loeffler and M. Durante, Charged particle therapy--optimization, challenges and future directions. *Nat Rev Clin Oncol*. 2013;**10**:411-24.

[2] M. Durante, N. Reppingen and K.D. Held, Immunologically augmented cancer treatment using modern radiotherapy. *Trends Mol Med*. 2013;**19**:565-82

Physical aspects in the evolving models of cancer treatment with radiations.

Alessio G. Morganti (1, 4), Savino Cilla (2), Gabriella Macchia (1), Francesco Deodato (1), Milly Buwenge (1), Angelo Piermattei (3), Vincenzo Valentini (4).

Radiotherapy Unit (1), Medical Physics Unit (2), Università Cattolica del S. Cuore, Campobasso, Italy; Medical Physics Department (3), Radiation Oncology Department (4), Università Cattolica del S. Cuore, Roma, Italy.

Radiation therapy is an important therapeutic resource in treating cancer. Over the past decades there has been a gradual evolution in the interpretation models of the effect of radiation.

Initially, particular attention was paid to the physical and chemical mechanisms underlying the DNA damage. This interest stimulated the research in the field of therapy with hadrons, in some cases with higher biological effectiveness, and a series of studies on the so-called “oxygen effect”, namely on the radioresistance of tissues (especially cancer) in the absence of O_2. In fact, more and more evidences have identified chronic hypoxia as one of the main factors responsible for the lack of success of treatment with radiations. These studies have focused on the possible use of blood transfusions or erythropoietin for the treatment of anaemia and on the possible use of hyperbaric chambers. Another line of research focused on the time-effect, meaning both total duration and fractionation of radiotherapy. As part of this trend several trials on the use of accelerated (to increase the chance of cure) and hyperfractionated (to reduce the risk of late side effects) regimens can be included.

More recently, interest has shifted mainly on biological-genetic factors able to provide an interpretation of the radiotherapy antineoplastic effect and in particular of the radioresistance of cancer cells. This interest stimulated the search for genetic therapies capable of reversing radioresistance mechanisms in order to increase the probability of cure. At the same time, the introduction of the models of Tumor Control Probability (TCP) and Normal Tissues Complication Probability (NTCP) allowed to deepen the knowledge of the so-called “volume-effect”. This knowledge, in turn, allowed the testing of treatment techniques aimed at reducing the NTCP (especially in tissues with “parallel” functional organization), thanks to a reduction of the irradiated volume, and the increase of the TCP due to dose escalation. The result of these investigations is represented by the rapid acceleration in the evolution of treatment techniques, aimed at an increased dose conformation (conformal radiotherapy, intensity modulated radiotherapy, image guided radiotherapy, stereotactic radiotherapy or radiosurgery).

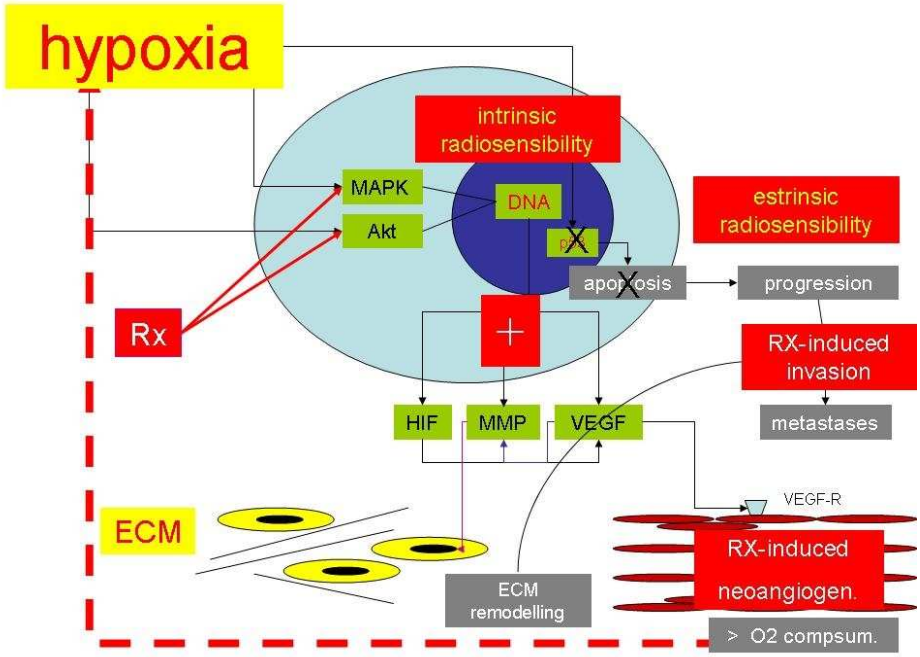
Even more recently, interest has shifted outside of the cellular environment and in particular to the "microenvironment" [1]. In fact, the extracellular space is considered today as the home of several phenomena related to the progression of cancer and to the anti-tumor effect of radiations. Together with the so-called "acute hypoxia", due to short increments of intratumoral pressure, it was observed that the same condition of hypoxia is able to change the plasticity of the extracellular matrix, promoting ultimately both tumor progression and the same hypoxia. Furthermore, it was observed that radiations are able to act on the same mechanisms stimulated by hypoxia, thus favouring phenomena such as radio-induced tumor invasion and radiation-induced hypoxia (Figure 1). From these observations, new lines of research emerged aimed at identifying and inactivating several targets responsible for this somewhat paradoxical phenomenon.

In conclusion, the evolution of models addressing the antitumor effect of radiation allowed, over time, the definition of new therapeutic strategies for the treatment of cancer.

References

1. Hanahan D, Weinberg RA, Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674.

Figure 1.



100 years of Imaging in Radiotherapy – and what's next?

Frank Lohr, M.D.

Dept. of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Germany

Radiotherapy established itself as a significant tool in oncology surprisingly fast after the discovery of X-rays. With an almost simultaneous inception, diagnostic and therapeutic radiology remained closely linked and in the same hands for the better part of the last century and only in the late 1980s the field divided into two specialties.

Imaging related to radiotherapy is of supreme importance in two main areas:

- Diagnostic radiological images provide essential information for target (tumor) identification, the assessment of tumor spread into neighbouring and distant tissues as well as providing information about localization and mobility of normal structures that have to be spared from therapeutic radiation doses. While planar X-ray imaging has fulfilled these functions in some situations, volume imaging based on Ultrasound, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) have dramatically changed the radiotherapy workflow. While initially only morphological information was provided even by cross-sectional/volume imaging, increasingly functional information can be obtained from both CT (with dual source CT as a fundamentally new modality) and MRI and, more recently and with a plethora of possibilities, Positron Emission Tomography (PET). Finally, quantification of tumor response with imaging provides more objective data than clinical exams, an absolute necessity within the framework of clinical trials.

- Imaging innovations at the treatment device such as stereoscopic X-ray-imaging and particularly Cone Beam CT (CBCT) have dramatically increased patient and tumor positioning accuracy. Real time tumor tracking or fast image guided breathhold treatments have become clinically feasible and hold the potential to further improve clinical results.

Despite all these advances, the development of imaging for and during radiotherapy has not lost its dynamics:

- Online Imaging during treatment with Ultrasound and MRI is currently becoming a clinical reality providing 4D-imaing information during dose delivery. While established only for photon radiotherapy, it is a necessity to fully unlock the potential of radiotherapy with charged particles. Based on the constant refinement of detector technology, imaging modalities such as Cherenkov imaging that have been a theoretical possibility for decades are now becoming technically feasible.

- In vivo imaging is venturing into dimensions closer to the cellular level. This will first provide further insight into tumor biology and systems biology in general (supremely important for immunological interventions) in animal models but will gradually also improve the imaging armamentarium in human subjects.

Development of in-vivo imaging techniques for charged particle therapy

G. Battistoni[1]

(1) INFN, Sezione di Milano

Purpose: Charged particle therapy (hadron therapy) is a highly advanced technique of cancer radiotherapy that uses beams of charged hadrons (protons or light ions) to destroy tumour cells. While conventional X-rays traverse the human body depositing radiation as they pass through, ions deliver most of their energy at one point. Hadron therapy is most advantageous once the position of the tumour is accurately known, so that healthy tissues can be protected. Accurate positioning is a crucial challenge for targeting moving organs, as in lung cancer, and for adapting the irradiation as the tumour shrinks with treatment. Therefore, quality assurance becomes one of the most relevant issues for an effective outcome of the cancer treatment. In order to improve the quality assurance tools for hadron therapy, the scientific community is studying specific imaging approaches for real-time non invasive monitoring, quantitative imaging and precise determination of delivered dose, fast feedback for optimal treatment planning and real-time response to moving organs. Some of recent results will be reviewed.

Methods and materials: Several research institutions are active in research and development of imaging for particle therapy. The main activities concern Time-of-Flight In Beam PET, In-beam single particle tomography, in-vivo dosimetry for particle therapy and moving target volumes, combination of in-vivo dosimetry, treatment planning and Monte Carlo simulation of in-vivo dosimetry.
In the last years, the topic received a boost in Europe also thanks to ENVISION (European NoVel Imaging Systems for ION therapy**)** project. funded by European Commission in the framework of the VII Framework Program for Research in the period 2010-2014.

Results: Many have been the outcomes of these projects. At present, the main preferred directions remain the detection of annihilation photons from induced beta+ activity and prompt gamma imaging. This last solution received a particular attention within ENVISION project in terms of valorisation and development of industrial devices ready for clinical evaluation. New ideas are also emerging, although at a very early stage, like the proposal of detecting secondary charged particles.

Conclusion: Many achievements have been obtained in recent years in the field of imaging of charged particle therapy. However more work is still needed to bring the proposed techniques to a mature level for clinical application. Centers for hadrontherapy and Physics research institutes are establishing cooperation agreement to test and develop prototypes and new approaches.

References:

[1] Information and brochures on ENVISION are available on its website http://cern.ch/ENVISION.
[2] J. Smeets, F. Roellinghoff, D. Prieels, F. Stichelbaut, A. Benilov, P. Busca, C. Fiorini, R. Peloso, M. Basilavecchia, T. Frizzi, J. C. Dehaes and A. Dubus: *Prompt gamma imaging with a slit camera for real-time range control in proton therapy*, Phys. Med. Biol. 57 (2012) 3371–3405
[3] M. Testa, M. Bajard, M. Chevallier, D. Dauvergne, N. Freud, P. Henriquet, S. Karkar, F. Le Foulher, J.M. Létang, R. Plescak, C. Ray, M.-H. Richard, D. Schardt, E. Testa: *Real-time monitoring of the Bragg-peak position in ion therapy by means of single photon detection*, Radiation and Environmental Biophysics, 49:3(337-343)
[4] C. Robert, G. Dedes, G. Battistoni, T.T. Böhlen, I. Buvat, F. Cerutti, MPW Chin, A. Ferrari, P. Gueth, C. Kurz, L. Lestand, A. Mairani, G. Montarou, R. Nicolini, P.G. Ortega, K. Parodi, Y. Prezado, P.R. Sala, D. Sarrut, E. Testa: *Distributions of secondary particles in proton and carbon-ion therapy: a comparison between GATE/Geant4 and FLUKA Monte Carlo codes*, Phys. Med. Biol. 58: 2879-2899, 2013.
[5] V. Rosso, G. Battistoni. N. Belcari, N. Camarlinghi, A. Ferrari, S. Ferretti, A. Kraan, A. Mairani, N. Marino, J.E. Ortuno, M. Pullia, P. Sala, A. Santos, G. Sportelli, K. Straub, A. Del Guerra: *A new PET prototype for proton therapy: comparison of data and Monte Carlo simulations*, JINST, 2013, Volume:8,

Article Number: C03021
[6] C. Gianoli, R. Ricotti, E. De Bernardi, M. Riboldi, J. Bauer, J. Debus, G. Baroni, K. Parodi: *Clinical Investigations of a 4D ML Reconstruction Strategy for PET-Based Treatment Verification In Ion Beam Therapy,* IEEE NSS-MIC 2014
[7] T.T. B¨ohlen, F. Cerutti, M.P.W. Chin, A. Fass`o, A. Ferrari, P.G. Ortega, A. Mairani, P.R. Sala, G. Smirnov, and V. Vlachoudis: *The FLUKA Code: Developments and Challenges for High Energy and Medical Applications,* Nuclear Data Sheets 120:211-214, 2014

Technologies for dose reduction and monitoring in diagnostic radiology

Davide Caramella
Diagnostic and Interventional Radiology, University of Pisa

Purpose: In the last decades there has been a significant growth of the number of radiological examinations, resulting in an increase of radiation dose per capita. Multidetector computed tomography (MDCT) nowadays makes the largest contribution among X-ray imaging techniques to the collective dose of a population. Data from literature indicate that multiple imaging procedures are frequently performed, with patients receiving CT scans corresponding to an effective cumulative dose of tens of mSv. For this reason, it is important to reduce the radiation dose given to patients in every MDCT examination without impairing its diagnostic quality, following the strict guidelines contained in the new European Directive 2013/59/EURATOM of 5 December 2013, that gives challenging targets to all stakeholders in terms of justification, optimization and patient information.

Methods and materials: Despite the evidence that MDCT provides invaluable information for diagnosis and patient management, the cancer risk associated with the radiation dose in MDCT is not zero and it is clear that reducing radiation dose must continue to be one of the top challenges in radiology. There are some technical strategies that are commonly used for radiation dose reduction in MDTC. One common method is to adjust the x-ray tube current using the Automatic Exposure Control (AEC), which aims to automatically modulate the tube current to accommodate differences in attenuation due to patient anatomy, shape and size. The tube current may be modulated as a function of projection angle (angular modulation), longitudinal location along the patients (z-modulation) or both. It is also possible to minimize radiation dose by using lower tube potentials (kV) in MDCT imaging.

Recently, iterative reconstruction has introduced relevant changes in the practice of MDCT. In comparison with the conventional filtered back projection techniques, by using iterative reconstruction the number of projection views can be significantly reduced without sacrificing image quality. Therefore, iterative reconstruction algorithms have significant potential to reduce radiation dose in MDCT.

In the last few years, there is also wide interest in patient exposure tracking. Constant and systematic monitoring of radiation dose is indispensable in order to increase the quality of radiological services. Radiation exposure tracking can be either for an individual patient or for quality assurance and benchmarking purposes. Many vendors already provide means to track patient exposure history with new software tools that can automatically retrieve, store and analyze dosimetric data stored in a Picture Archiving and Communication System (PACS). This activity can lead to performance control, protocol optimization and rapid correction of wrong practices. The principal aim of the dose tracking is to minimize the dose variability in radiological procedures, which is clinically not justified.

Results: New technologies for dose reduction and patient exposure tracking are crucial elements in order to reduce radiation dose in diagnostic radiology and to improve the radiologic quality management.

References:

[1] T. Klink, V. Obmann, J. Heverhagen, A. Stork, G. Adamc, P. Begemann. *Reducing CT radiation dose with iterative reconstruction algorithms: The influence of scan and reconstruction parameters on image quality and CTDIvol*. European Journal of Radiology (2014) 1645–1654.

[2] M. Rehani, T. Berris. *Templates and existing elements and models for implementation of patient exposure tracking.* Radiation Protection Dosimetry (2014) 36-42.

PET/CT and molecular imaging

Ghedini P [1], Svirydenka H [1], Tabacchi E [1], Fanti S [1]
[1] Nuclear Medicine Department, Policlinico S.Orsola, University of Bologna.

Radionuclide imaging is the most popular form of imaging used for oncological molecular imaging (MI). MI can be broadly defined as in vivo characterization and measurement of biologic processes at the cellular and molecular level. Molecular imaging techniques such as PET (positron emission tomography) have been introduced in the clinical practice to study the molecular pathophysiology and to assess treatment responses. Molecular imaging rapidly developed in the early 90's, due to parallel evolution and integration of many different disciplines, including medical imaging, molecular biology, pharmacology, and medical physics.

PET is a functional imaging technique of Nuclear Medicine that produces 3d images allowing the visualization and quantification of complex pathophysiological and biochemical processes presenting in a living system [1]. PET uses specific radionuclides labelled to molecular probes in order to generate in vivo images of physiological processes but also to identify and characterize many kind of disease, including cancer, endocrine, gastrointestinal, neurological disorders, heart disease, infections and inflammatory disease that could be anticipated of macroscopically evident changes. PET can also be an ideal tool for the development of new drugs, by characterizing their behaviour in the human body, acting as a bridge between preclinical and clinical research.
Combination of PET with CT or MRI provides the capability of acquiring simultaneously anatomical and functional images for any part of the human body. Modern PET/CT scanners integrate high-end multi-detector-row CT scanners with Time-of-Flight (TOF) PET scanners[2].

The tracer most widely used in PET imaging is 18F-Fluorodeoxyglucose (FDG), that has indeed revolutionized the imaging evaluation of patients with tumour and has been used for about 25 years, with more than 1.5 millions scans performed annually worldwide. FDG, a glucose analogue, becomes trapped in the human cells after injection, through uptake and phosphorylation: FDG-PET resulted a specific, sensitive and reproducible imaging techniques for studying cancer. [3]

18F-FDG was originally proposed in the 70's for basic investigations of cerebral glucose metabolic rate and thereafter it was discovered useful for cancer imaging [4]. The link between glucose metabolism and tumoral cells derived from Nobel prize laureate, Otto Warburg who hypothesized that glucose metabolism would increase in the tissues affected by cancer in correlation with the malignancy. Tumour hypoxia could switch the metabolic pathway to glycolysis from oxidative phosphorylation, and glycolysis guarantees cancer cells growth with a faster energy production. This aspect remains, today, a major indicators of tumour proliferation [5-6-7].

PET radionuclides are unstable nuclides that decay by the emission of a positron. The subsequent annihilation produces two anti-parallel gamma photons, both with energy of 511 keV. PET scanner detects the coincidence of these gamma photons. PET radiopharmaceuticals are usually administered, before the scanning procedure, as bolus in vivo injections; generally there is a delay before scanning to allow the tracer to accumulate in the target. [8]

Limitation of FDG-PET for cancer imaging include:

- Limited reconstructed spatial resolution (about 4-5 mm in recent scanners), subsequently a negative scan cannot exclude the existence of a very small cancer;
- Some tumours (such as mucinous carcinomas) may have a low FDG uptake and may not be detected using such tracer;
- Inflammation and other conditions can show moderate or high glucose uptake. Discriminate cancer from inflammation/other conditions could sometime be difficult [8-9]

In the recent years various other tracers (non-FDG) have been developed and used in PET molecular imaging. An example of a cancer specific, non-FDG, PET tracer is the carbon-11 labelled form of Choline (11C-Choline), a precursors for the synthesis of phospholipids that can marking out membrane metabolism. The clinical value of 11C-Choline is relevant in prostate cancer relapse in previously treated patients [10].
11C-Methionine is an other example of tracer useful to evaluate protein metabolism, significantly increased in malignant tumour, especially in brain (main clinical application) and head and neck tumours [11]. 18F-Dihydroxyphenylalanine (18F-DOPA) [12], originally introduced for studying of movement disorders, was successfully used in the study of neuroendocrine tumours (NET).
68Ga-DOTA-peptides (such as TOC and NOC) take advantage from overexpression of somatostatin receptors in NET, are therefore are excellent tracers in the evaluation of NET, either for staging, and other clinical applications [13-14].
18F-fluorothymidine (18F-FLT) is a marker of cellular proliferation and correlates with DNA synthesis and cellular growth. 18F-FLT has been suggested in several malignancies, such as lymphomas, sarcomas, lung or gastrointestinal tumours [15].
The list of new potential PET tracers is continuously increasing and new applications of PET/CT are rapidly growing, in the study of cancer and other disease: they are likely to be introduced in the clinical practice in the next future.

References

1. Cherry SR. Fundamentals of positron emission tomography and applications in preclinical drug development. J Clin Pharmacol. 2001 May;41(5):482-91.

2. Beyer T, Townsend DW, Brun T et al (2000) A combined PET/CT
scanner for clinical oncology. J Nucl Med 41(8):1369–1379

3. Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. J Nucl Med. 2001 May;42(5 Suppl):1S-93S

4. Som P, Atkins HL, Bandoypadhyay D, et al. A fluorinated glucose analog, 2-fluoro-2-deoxy-D-glucose (F-18): nontoxic tracer for rapid tumor detection. J Nucl Med. 1980 Jul;21(7):670-5.

5. Jaeschke A, Dennis PB, Thomas G. mTOR: a mediator of intracellular homeostasis. Curr Top Microbiol Immunol. 2004;279:283-98.

6. Smith TA. Facilitative glucose transporter expression in human cancer tissue. Br J Biomed Sci. 1999;56(4):285-92.

7. Coleman CN, Mitchell JB, Camphausen K. Tumor hypoxia: chicken, egg, or a piece of the farm? J Clin Oncol. 2002 Feb;20(3):610-5.

8. Schöder H, Erdi YE, Chao K, Gonen M, Larson SM, Yeung HW. Clinical implications of different image reconstruction parameters for interpretation of whole-body PET studies in cancer patients. J Nucl Med. 2004 Apr;45(4):559-66.

9. Zhuang H, Pourdehnad M, Lambright ES, et al. Dual time point 18F-FDG PET imaging for differentiating malignant from inflammatory processes. J Nucl Med. 2001 Sep;42(9):1412-7.

10. Schiavina R, Scattoni V, Castellucci P et al (2008) 11C-choline positron emission tomography/computerized tomography for preoperative lymph-node staging in intermediate-risk and

highrisk prostate cancer: comparison with clinical staging nomograms. Eur Urol 54(2):392–401.

11. Huang MC, Shih MH, Chung WY et al (2005) Malignancy of intracerebral lesions evaluated with 11C-methionine-PET. J Clin Neurosci 12:775–780

12. Imani F, Agopian VG, Auerbach MS et al (2009) 18F-FDOPA PET and PET/CT accurately localize pheochromocytomas. J Nucl Med 50(4):513–519.

13. Campana D, Ambrosini V, Pezzilli R et al (2010) Standardized uptake values of (68)Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. J Nucl Med 51:353–359.

14. Bombardieri E, Maccauro M, De Deckere E et al (2001) Nuclear medicine imaging of neuroendocrine tumours. Ann Oncol 12 (Suppl 2):S51–S61.

15. Shields AF, Grierson JR, Dohmen BM et al (1998) Imaging proliferation in vivo with [18F]FLT and positron emission tomography. Nat Med 4:1334–1336

Lecture title pending

Gerhardt Attard

Cracking the neural code using tools and concepts from statistical physics

Stefano Panzeri
Istituto Italiano di Tecnologia
Center for Neuroscience and Cognitive Systems, Rovereto (TN)

In this talk, I will give an overview of our research line that uses some of the concepts from statistical physics (such as entropy and mutual information) to crack the code used by neurons in the cerebral cortex to transmit and exchange information about important events in the sensory world.

Functional Imaging of the Human Brain using MEG and fMRI

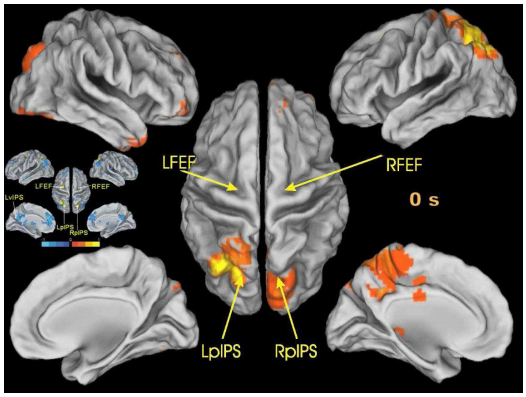
Gian Luca Romani[1,2]

(1) Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University, Chieti;
(2) Institute for Advanced Biomedical Technologies (ITAB), "G. D'Annunzio" University, Chieti.

Purpose: the use of non invasive techniques such as functional Magnetic Resonance Imaging (fMRI) or MagnetoEncephaloGraphy (MEG) permits powerful investigation of brain functions, specifically providing an accurate identification of active areas as well as a precise description of the timing of brain response. Recently, a combined approach of both modalities and successive integration of the results has proved to be extremely useful for the understanding of more complex mechanisms, namely "resting state networks", that have been supposed to likely account for a large part of the basic energy consumption of the brain. In this presentation some basic concepts of the two methodologies will be briefly described with the aim at pointing out respective advantages and limitations and the possible benefits provided by their integration. Then some recent results obtained applying the two techniques in basic neuroscience will be illustrated.

Methods and materials: fMRI, uses the Blood-Oxygen-Level-Dependent (BOLD) contrast method to identify - with high spatial resolution - neural pools where the energy consumption has increased during sensory stimulation or execution of a task. However, since this technique relies on the hemodynamic response, its temporal resolution is in general of the order of 1s. On the other hand, MEG measures the tiny electric fields associated with bioelectric activity of groups of neurons and, with respect to ElectroEncephaloGraphy (EEG), offers the important advantage of permitting identification of the actual sources of the signals with no- or minimum interference by the medium surrounding the sources themselves. However, the unavoidable need of solving the inverse problem reduces the spatial resolution to a few mm at the best and only in the case of sharply localized sources. Additionally, the extreme weakness of signals requires the use of superconducting magnetometers, namely SQUIDs, and that of a magnetically shielded room to perform the measurement. Since the recording bandwidth of these devices is relatively large, it is possible to record neural activity with a time resolution of 1ms or less. This makes MEG technique the ideal complement of fMRI to track brain activity in time and space.

Results: two examples will be provided. The first will illustrate how integration between fMRI and MEG permits to follow neural current density distribution during a time span of about 500ms, as a consequence of a picture-naming test. The second will show how Resting State Networks (RSNs) are identified using fMRI and MEG and the different kind of information that can be obtained with the two approaches. In particular the dynamic activity of RSNs, as measured by MEG only, will be shown, as a result of analyzing in specific bandwidths the spontaneous activity of the brain.



Conclusions: fMRI and MEG represent two unique tools to investigate brain activity. Their combined approach is proving to provide a synergic effect, in simple source identification, in understanding of hierarchical processing of information, and in the investigation of the dynamic correlation between different brain RSNs that - with their relation to spontaneous activity - likely account for a large part of energy consumption in the brain.

Modified from de Pasquale et al., PNAS 2010.

Diffusion Tensor Imaging and modern neurosurgery: toward a connectomic approach to brain surgery.

Silvio Sarubbo[1,2], Monica Dallabona[1], Giuseppe Pulcrano[1,2], Enzo Colarusso[1,2], Francesco Corsini[1,2], Giovanna Faraca[1,2], Umberto Rozzanigo[3], Mattia Barbareschi[4], Franco Chioffi[1,2]
[1]Division of Neurosurgery, [2]Structural and Functional Connectivity Lab (SFC Lab), [3]Department of Radiology, [4]Unit of Surgical Pathology, "S. Chiara" Hospital, Trento APSS, 9 Largo Medaglie d'Oro, 38122 Trento, Italy

Purpose Technical and methodological advancements in physics provided new insights in neurosciences and neurosurgery. Particularly, introduction and improvements in diffusion tensor imaging (DTI) opened a new door in the study of human white matter (WM)[1]. The fascinating tractographic reconstructions renewed the interest for structural connectivity and its role in the models of organization of brain functions, moving on the connectome era[2]. Every brain function is the result of complex and large-scale integrations of multimodal analyses, subserved by parallel and distributed networks connected by different long and short bundles. Even if highly sensitive and continuously improved, the DTI has different technical limitations. It produced a renewed interest for WM anatomical dissection and these data were extensively integrated[3,4]. However, both these techniques do not provide functional informations. Direct electrical stimulation (DES) during awake surgery for cerebral gliomas is a unique opportunity and a validated technique to obtain on-line and reliable functional informations regarding the subcortical connectivity. The challenge is now the integration of functional and structural data in order to understand the role of the different bundles and the anatomical connections subserving the different networks.
Materials and Methods For DTI we adopted a 60 directions diffusion-weighted imaging brain tractography with 1.5-T MRI scanner (GE Healthcare, UK) and an eight-channel head coil. It is performed using a single-shot multislice spin echo–echo planar sequence with the following attributes: 40 slices; slice thickness: 2.4 mm; matrix 256 x 256; TR: 10,000; TE: 92,7; flip angle: 90. Pre-processing, diffusion tensor calculation and tracking are performed with FMRIB Software Library (FSL; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), Diffusion Toolkit and TrackVis (http://trackvis.org), respectively. Specimens for dissection were fixed in a formalin 10% solution and then frozen at -80° C. Intraoperative DES during asleep-awake-asleep surgery for resection of brain tumors provided the functional data. All patients underwent to extensive pre-operative neuropsychological assessments integrated with DTI imaging.
Results DTI reconstructions of the peri-sylvian WM showed two main streams. A dorsal pathway composed of three main bundles: the anterior and posterior indirect components of the superior longitudinal fascicle (SLF) and the arcuate fascicle (AF). The dissection confirmed these data demonstrating terminations of the indirect anterior SLF within the ventral pre-motor cortex (VPMC) and posterior third of the middle frontal gyrus (MFG). The AF directly connects the VPMC, the pars opercularis and the MFG to the posterior thirds of the superior and middle temporal gyri and the middle third of the inferior temporal gyrus. The DES demonstrated the role of the AF as the main phonological stream. The indirect anterior SLF is involved in the articulatory loop for language production. The indirect posterior portion was proposed as a possible semantic retrieval bundle. AF and the anterior and posterior indirect components of the SLF constitute the most long associative bundles of the lateral white matter of the frontal, temporal and parietal lobe and provide a horizontal connection between the main language territories. The inferior-fronto-occipital fascicle (IFOF) constitutes the ventral pathway. Recent dissection evidences demonstrated new terminations of IFOF within the parietal lobe and a deeper and more ventral component directed to the dorso-lateral pre-frontal cortex. DTI confirmed these structural data and DES supported the role of this tract in the semantic network.
Conclusions DTI and recent advancements in brain imaging encouraged and supported the structural and functional study of the human WM from both a conceptual a practical point of view. Tractography joined the clinical practice and it is now a valid and reliable tool for surgical treatment of lesions harboring

eloquent regions. The integration of DTI with structural data of dissections and with functional evidences of DES improved our comprehension of brain networks organization.

REFERENCES

1 Thiebaut de Schotten M, Ffytche DH, Bizzi A, Dell'Acqua F, Allin M, Walshe M, Murray R, Williams SC, Murphy DG, Catani M (2011) Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. Neuroimage 54(1):49-59

2 Sporns O (2013) The human connectome: origins and challenges. Neuroimage 80:53-61

3 Sarubbo S, De Benedictis A, Maldonado IL, Basso G, Duffau H (2013) Frontal terminations for the inferior fronto-occipital fascicle: anatomical dissection, DTI study and functional considerations on a multi-component bundle. Brain Struct Funct 218(1):21-37

4 De Benedictis A, Duffau H, Paradiso B, Grandi E, Balbi S, Granieri E, Colarusso E, Chioffi F, Marras CE, Sarubbo S (2014) Anatomo-functional study of the temporo-parieto-occipital region: dissection, tractographic and brain mapping evidence from a neurosurgical perspective. J Anat 225:132-51

UNIVERSITÀ DEGLI STUDI DI TRENTO

Azienda Provinciale per i Servizi Sanitari
Provincia Autonoma di Trento

Aifm
Associazione Italiana di Fisica Medica

POSTERS

#	Title	Autors
1	**Hepatic Radioembolization Treatment: estimate of the linear-quadratic model α parameter.**	M. Piccinno[1], C. Avigo[2], Dr. A. Traino[3]. (1) Dipartimento di Fisica "E.Fermi"- Università di Pisa; (2) Scuola di Specializzazione in Fisica Medica- Università di Pisa; (3) U.O.Fisica Sanitaria, Azienda Ospedaliero-Universitaria Pisana, Pisa.
2	**Non linear response of TLD-100 irradiate by an Intra Operative Radiation Therapy linear accelerator: preliminary results.**	F. Savino[1], M. Pugliese[2], V. D'Avino[1], L. Cella[1], R. Liuzzi[1] (1) Istituto di Biostrutture e Bioimmagini - CNR - Napoli; (2) Department of Physics - University of Napoli "Federico II".
3	**Dose Tracking Software: the experience of Pisa University Hospital**	C. Sottocornola[1], I. Creonti[2], E. Del Dò[2], F. Paolicchi[2], G. Imbarlina[2], D. Caramella[2] (1) Department of Physics - University of Pisa; (2) Diagnostic and Interventional Radiology, University of Pisa.
4	**Feasibility of small animal irradiation by using TomoTherapy**	A. Miranti[1], M. Poli[1], G. Cattari[2], C. Cutaia[1], E. Garibaldi[2], A. D'Ambrosio[3], F. De Bacco[3], C. Boccaccio[3], P. Gabriele[2], M. Stasi[1] (1) Medical Physiscs Department - IRCCS-FPO, Candiolo Cancer Center, Candiolo (TO); (2) Radiotherapy Department - IRCCS-FPO, Candiolo Cancer Center, Candiolo (TO); (3) Experimental Clinical Molecular Oncology Department - IRCCS-FPO, Candiolo Cancer Center, Candiolo (TO).
5	**FUNCTIONAL MAGNETIC RESONANCE IMAGING REVEALS BRAIN CORTEX REMODELING IN A RAT MODEL OF CHRONIC MULTIPLE SCLEROSIS.**	S. Tambalo[1,2], L. Peruzzotti-Jametti[3], R. Rigolio[4], S. Fiorini[1], P. Bontempi[5], G. Mallucci[3,6], P. Marmiroli[4], G. Cavaletti[4], S. Pluchino[3] and P. Marzola[2,5] (1) Dept of Neurological and Movement Sciences, University of Verona, Italy; (2) INSTM, Firenze, Italy; (3) Dept of Clinical Neurosciences, John van Geest Centre for Brain Repair, Wellcome Trust-MRC Stem Cell Institute and NIHR Biomedical Research Centre, University of Cambridge, CB2 0PY, UK; (4) Dept of Surgery and Translational Medicine, University of Milano-Bicocca, Monza, Italy;

		(5) Dept of Computer Science, University of Verona, Verona, Italy; (6) Dept of Brain and Behavioural sciences, University of Pavia, Pavia, Italy.
6	**Inhibition of tumor growth in a xenograft model of glioblastoma treated with MSR-1 Magnetosomes and Alternating Magnetic Field.**	S. Tambalo[1,2], S. Mannucci[2,3], G. Conti[1], L. Ghin[4], A. Milanese[3], A. Carboncino[1], E. Nicolato[1], M.R. Marinozzi[1], P. Bernardi[1], D. Benati[1], R. Bassi[4], A. Sbarbati[1,2] ,P. Marzola[2,3] (1) Dep. of Neurological and Movement Sciences, University of Verona, Verona, Italy; (2) Consorzio INSTM, Firenze, Italy; (3) Dep. of Computer Science, University of Verona, Verona, Italy; (4) Dep.of Biotechnology, University of Verona, Verona, Italy.
7	**Multiphoton Optical Biopsy of Human Skin: Benefit-risks assessment.**	Giulia Zanini[1], Luca Dalbosco[2], Elvira D'Amato[1], Sebastiana Boi[3], Paolo Bauer[4], Albrecht Haase[1], Renzo Antolini[1] (1) Department of Physics - University of Trento; (2) BIOtech center and Department of Industrial Engineering - University of Trento; (3) Department of Pathology - S. Chiara Hospital, Azienda Provinciale per i Servizi Sanitari, Trento; (4) Department of Dermatology - S. Chiara Hospital, Azienda Provinciale per i Servizi Sanitari, Trento.
8	**Machine Learning Techniques Implemented on Structural MR Images of Children with Autism Spectrum Disorder at Different Dimensional Scales**	Alessia Giuliano[a,b], Ilaria Gori[a,c], Filippo Muratori[d,e], Irene Saviozzi[e], Raffaella Tancredi[d], Angela Cosenza[d], Michela Tosetti[d], Sara Calderoni[d], Alessandra Retico[a] (a) Istituto Nazionale di Fisica Nucleare, Sezione di Pisa, Italy; (b) Dipartimento di Fisica, Università di Pisa, Italy; (c) Dipartimento di Chimica e Farmacia, Università di Sassari, Italy; (d) IRCCS Fondazione Stella Maris, Calambrone (PI), Italy; (e) Dipartimento di Medicina Clinica e Sperimentale, Università of Pisa, Italy.
9	**New semi-automatic tool for 3D quantification and 3D volumetric visualization of left atrium fibrosis based on integration of LGE-MRI and MRA images.**	Daniele Ravanelli[1], Elena Costanza dal Piaz[2], Maurizio Centonze[3], Giulia Casagranda[3], Massimiliano Marini[2], Maurizio Del Greco[2], Rashed Karim[4], Kawal Rhode[4], Aldo Valentini[1] (1) Department of Health Physics - Azienda Provinciale per i Servizi Sanitari - APSS, Trento; (2) Department of Cardiology - Azienda Provinciale per i Servizi Sanitari - APSS, Trento; (3) Department of Radiology - Azienda Provinciale per i Servizi Sanitari - APSS, Trento; (4) Imaging Sciences and Biomedical Engineering, King's College London, London.

10	**Quantifying radiographic contrast of polymeric orthopedic implants with osseointegrative coating by a tissue-equivalent phantom**	N. Pace [1], F. Tessarolo[1,2], G. Miori[3], G. Zappini[4], G. Nollo[1,2], M. Recla[5], A. Valentini[6] (1) Healthcare Research and Innovation Program (IRCS), Bruno Kessler Foundation, Trento, Italy; (2) Department of Industrial Engineering, University of Trento, Trento, Italy; (3) School of Medical Physics, University of Roma Tor Vergata, Rome, Italy; (4) Eurocoating S.p.A., Trento, Italy; (5) Diagnostic Radiology Unit, S. Chiara Hospital, Trento, Italy; (6) Department of Health Physics, Azienda Provinciale per i Servizi Sanitari, Trento, Italy.
11	**New real time evaluation of overranging in modern helical computed tomography.**	Diego Trevisan[1], Faustino Bonutti[2], Daniele Ravanelli[1], Aldo Valentini[1] (1) Department of Health Physics - Azienda Provinciale per i Servizi Sanitari - APSS, Trento; (2) Department of Health Physics - S.M. della Misericordia Hospital, Udine.
12	**INSIDE: INnovative Solutions for In-beam DosimEtry in Hadrontherapy**	G. Pirrone on behalf of the INSIDE collaboration Department of Physics, University of Pisa and INFN sezione di Pisa, Italy.
13	**ESR dosimetry with alanine added with Gadolinium in TRIGA reactor of Mainz**	M. Marrale[1], T. Schmitz[2], G. Hampel[2], M. Brai[1], S. Gallo[1], A. Longo[1], S. Panzeca[1], L Tranchina[3] (1) Dip. di Fisica e Chimica, Viale delle Scienze, Ed.18, I-90128 Palermo, Italy and Gruppo V, INFN, Sezione di Catania, Catania, Italy; (2) Institut für Kernchemie, Fritz Strassmann Weg 2, D-55128 Mainz, Germany; (3) Laboratorio di Fisica e Tecnologie Relative - UniNetLab – Università degli Studi di Palermo – Viale delle Scienze, Ed. 18, 90128 Palermo.
14	**ADVANCED TECHNIQUES IN MAGNETIC RESONANCE IMAGING: CHARACTERIZATION OF NON-GAUSSIAN WATER DIFFUSION USING DIFFUSION KURTOSIS IMAGING (DKI)**	G.Collura[a], M.Marrale[a], C.Gagliardo[b], S.Gallo[a], A.Longo[a], S.Nici[a], S.Panzeca[a], M.Midiri[b], M.Brai[a] (a) Dip. di Fisica e Chimica, Università di Palermo, Viale delle Scienze, Edificio 18, 90128 Palermo, Italy and INFN sez. di Catania, Via Santa Sofia, 64, 951; (b) Dip. di Biopatologia e Biotecnologie Mediche e Forensi – Sezione di Scienze Radiologiche, Università di Palermo, Via del Vespro, 129 - 90127 Palermo.
15	**Resting state fMRI as a tool to investigate brain functional connectivity**	M.Marrale[1], S.Nici[1], G.Collura[1], S.Gallo[1], A.Longo[1], S.Panzeca[1], T.Piccoli[2], C.Gagliardo[3], M.Brai[1] (1) Dipartimento di Fisica e Chimica, Università degli Studi di Palermo; (2) Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Università degli Studi di Palermo; (3) Dipartimento di Biopatologia e Biotecnologie Mediche e Forensi, Università degli Studi di Palermo.

16	**Neutron Electron Spin Resonance dosimetry with phenol compounds**	M.Marrale[1], M.Brai[1], S.Gallo[1,2], A.Longo[1], S.Panzeca[1], A.Buttafava[3], D.Dondi[3], A.Zeffiro[3] (1) Dipartimento di Fisica, Viale delle Scienze, Ed.18, I-90128 Palermo and Gruppo V, INFN, Sez. di Catania, Italy; (2) PH3DRA Laboratory, Dipartimento di Fisica e Astronomia, Università di Catania, Italy; (3) Università di Pavia e INFN, Sezione di Pavia, Pavia, Italia.
17	**Characterization of Fricke gel dosimeters exposed to clinical photons beams and of MRI dosimetrical applications**	M. Marrale[1], M. Brai[1], C. Gagliardo[2], S. Gallo[1,3], A. Longo[1], L. Tranchina[4], G. Collura[1], G. Iacoviello[5], S. Panzeca[1], F. d'Errico[6] (1) Dip. di Fisica e Chimica , Università di Palermo, and INFN, Sez. di Catania, Italy; (2)Dip. di Biopatologia e Biotecnologie Mediche e Forensi , Università di Palermo, Italy; (3) Laboratorio PH3DRA, Dipartimento di Fisica e Astronomia, Università di Catania, Italy; (4) Laboratorio UNINETLAB, Viale delle Scienze, Edificio 18, 90128 Palermo, Italy; (5) U.O.C. di Radioterapia A.R.N.A.S. CIVICO, Palermo, Italy; (6) Dip. di Ingegneria Civile e Industriale, Università di Pisa, Italy and Yale University School of Medicine, New Haven.
18	**Development of Gold/Iron Oxide Hybrid Nanoparticles for Advanced Radiotherapy**	Filippo Benetti[a], Devid Maniglio[a], Giorgio Speranza[b], Claudio Migliaresi[a] (a) Department of Industrial Engineering and Biotech Center, University of Trento, Italy; (b) Fondazione Bruno Kessler, Trento, Italy.
19	**An Improved Method for Hepato-Renal Ratio Assessment: a Feasibility Study**	Sboarina A[1], Perandini S[2], Fenzi A[1] (1) Department of Surgery, University of Verona; (2) Department of Radiology, AOUI Verona.
20	**Intraoperative microelectrode recording does not increase hemorrhagic complications in deep brain stimulation surgery: data from a large series of patients**	A. Romagnolo, M.G. Rizzone, M. Zibetti, A. Merola, F. Dematteis, S. Angrisano, C.A. Artusi, M. Sarchioto, A. Bernardini, E. Crobeddu, R. Fornaro, L. Lopiano, M. Lanotte Department of Neuroscience, University of Turin.
21	**Novel Applications of Cerenkov and Radioluminescence Imaging**	F. Boschi[1], AE. Spinelli[2], A. Fenzi[3]. (1) Department of Computer Science, University of Verona; (2) Medical Physics Department and Center for Experimental Imaging, San Raffaele Scientific Institute, Milan; (3) Department of Surgery, University of Verona.

22	**Damaging effects due to neutrons produced by a VARIAN CLINAC 2100C on pacemakers and defibrillators**	Anna Baratto Roldan[1], E. Sergi[1], L. Toscano[1], F. Bragato[1,2], M. Usikalu[1,2], G.Giannini[1,3], M. Severgnini[4], V. Milan[5], M. Zecchin[6], G.Morea[6], L. Salvatore[6], A. Zorzin Fantasia[6], G. Sinagra[6]. (1) Physics Department, University of Trieste, Italy; (2) Department of Physics Covenant University, Ota, Nigeria and TRIL ICTP, Trieste, Italy; (3) INFN, section of Trieste, Italy; (4) SC di Fisica Sanitaria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Trieste, Italy; (5) Radiotherapy Department "Ospedali Riuniti" and University, Trieste, Italy; (6) Cardiovascular Department, “Ospedali Riuniti” and University, Trieste, Italy.
23	**“Quick Boron”: a new boron carbide based shielding material for neutrons**	Licia Toscano[1], F. Bragato[1,2], E. Sergi[1], M. Usikalu[1,3], A. Baratto R.[1], G. Giannini[1,2], M. Severgnini[4] (1) Physics Department, University of Trieste, Italy; (2) INFN, section of Trieste, Italy; (3) Department of Physics, Covenant University, Ota, Nigeria and TRIL ICTP, Trieste, Italy; (4) SC di Fisica Sanitaria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Trieste, Italy.
24	**Ryan: a new anthropomorphic phantom for neutron dosimetry**	Elisabetta Sergi[1], L. Toscano[1], F. Bragato[1,2], A. Baratto R.[1], M. Usikalu[1,3], G.Giannini[1,2], M. Severgnini[4] (1) Physics Department, University of Trieste, Italy; (2) INFN, section of Trieste, Italy; (3) Department of Physics Covenant University, Ota, Nigeria and TRIL ICTP, Trieste, Italy.
25	**NONO regulates the cell response to UV-induced DNA damage and is a potential therapeutic target in cancer.**	F. Pentimalli[1], L. Alfano[1], C. Costa[1], A. Caporaso[2], A. Altieri[1], P. Indovina[3], A. Giordano[1,2,3] (1) Oncology Research Center of Mercogliano (CROM); Istituto Nazionale Per Lo Studio E La Cura Dei Tumori “Fondazione Giovanni Pascale”; IRCCS; Naples, Italy; (2) Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy; (3) Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia PA, USA.
26	**Shedding light on the workings of the social brain: a fNIRS study on newborns**	Elisa Frasnelli[1], Andrea Vitale[1], Daniela Tosoni[1], Carlo Polloni[2], Giuseppe Menna[2], Ermanno Baldo[2], Marco Ioppi[3], & Giorgio Vallortigara[1] (1) Center for Mind/Brain Sciences (CIMeC), University of Trento, Corso Bettini 31, I-38068 Rovereto (TN), Italy (2) Unità Operativa di Pediatria, Ospedale S. Maria del Carmine, Corso Verona 4, 38068 Rovereto (TN), Italy (3) Unità Operativa di Ostetricia e Ginecologia,

		Ospedale S. Maria del Carmine, Corso Verona 4, 38068 Rovereto (TN), Italy
27	**A time-resolved analysis to evaluate the intra-fraction dose delivered with the modulated scanning ion beam radiotherapy**	S. Giordanengo[1], G. Russo[1], R. Cirio[1,2], M. Donetti[1,3], M. A. Garella[1,3], M. A. Hosseini[1,2], F. Marchetto[1], S. Molinelli[3], V. Monaco[1,2], R.Sacchi[1,2], M. Varasteh Anvar[1,2] and A. Attili[1] *(1) Istituto Nazionale di Fisica Nucleare, Section of Torino, Torino;* *(2) University of Turin, Experimental Physics, Torino;* *(3) Centro Nazionale di Adroterapia Oncologica (CNAO), Pavia.*
28	**Impact of uncertainties in ion beam therapy on the optimality of irradiation condition and fractionation schedule**	*A. Attili[1], F. Bourhaleb[2], A. Svanetti[3], M. Casale[3], D. Bottigliengo[3], S. Giordanengo[1], F. M. Milian[1,4], G. Russo[1], A. C. Kraan[5], F. Marchetto[1], R. Cirio[1,3].* *(1) INFN, Istituto Nazionale di Fisica Nucleare, Sez. di Torino, Italy* *(2) I-See, Internet Simulation Evaluation Evision Ltd, Torino, Italy* *(3) Università degli Studi di Torino, Italy* *(4) UESC, Universidade Estadual de Santa Cruz, Ilhéus Brazil* *(5) INFN, Istituto Nazionale di Fisica Nucleare, Sez. di Pisa, Italy*

Hepatic Radioembolization Treatment: estimate of the linear-quadratic model α parameter.

M. Piccinno[1], C. Avigo[2], Dr. A. Traino[3].
(1)Dipartimento di Fisica "E.Fermi"- Università di Pisa.
(2)Scuola di Specializzazione in Fisica Medica-Università di Pisa.
(3)U.O.Fisica Sanitaria, Azienda Ospedaliero-Universitaria Pisana, Pisa.

Purpose: Some kind of hepatocarcinomas (HCC) can be treated with a recent radiotherapy technique: hepatic radioembolization (TARE). In order to increase the treatment efficacy, an improvement of the 3D dose calculation methods is crucial, for both neoplastic and healthy tissues. The aim of this work is to estimate the α radiobiological parameter of the linear quadratic model in order to perform a personalized calculation of the activity to be injected to the patient.

Material and Methods: The radioembolization involves an activity administration, through an intra-arterial injection of biocompatible microspheres ^{90}Y loaded. ^{90}Y is mainly a β^- emitter, therefore the electron short range is suitable to release high dose to a small region of neoplastic tissue. The radionuclide spatial distribution is not uniform, for this reason a 3D dose calculation is needed. For this calculation CT-SPECT images, obtained injecting the patient before the treatment with Technetium ^{99m}Tc albumin aggregated (^{99m}Tc-MAA) in the same site where microspheres are going to be injected, were used to obtain the activity distribution, this procedure makes sense assuming that ^{99m}Tc-MAA behave as microspheres. The counts obtained are assumed to be proportional to the dose for each voxel, with a proportionality constant calculated as described in [1]. After the treatment the evaluation of the cell survival fraction was performed by using the linear quadratic (LQ) model, which is the radiobiological reference model in radiotherapy. The main parameter of this model, in linear approximation, is α which describes the radiobiological response to a deterministic fatal damage due to ionizing radiations. In order to estimate α, a group of 16 patients (3 cholangiocarcinoma and 13 HCC) was followed after the treatment for a period of time up to 9 months: the mass of the tumor was measured every 3 months and the minimum value was considered; the voxel-by-voxel formulation of the LQ model was employed with the 3D dose and the final mass.

Results: The value obtained for α is 0.22 ± 0.22 Gy^{-1} and 0.20 ± 0.23 Gy^{-1} for HCC and cholangiocarcinoma patients respectively. These values are the mean and the standard deviation of the values calculated for each patient and agree with the order of magnitude of the same parameter proposed by AAPM [2].

Conclusions: The hepatic radioembolization with ^{90}Y microspheres is a recent and promising technique. The estimate of the α radiobiological parameter is crucial for the personalized calculation of the activity to be injected, which is fundamental for improving the efficacy of the treatment.

Refereces:

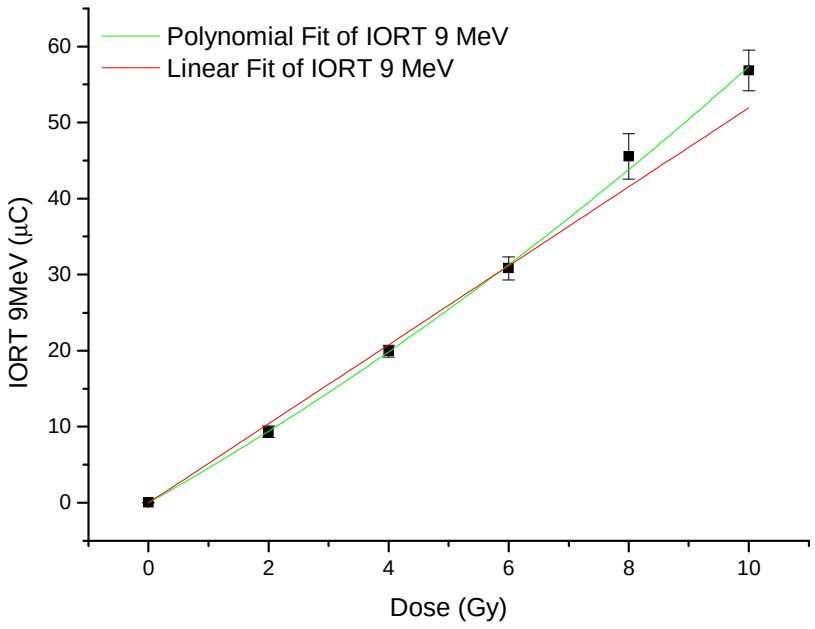
[1] Traino AC, Marcatili S, Avigo C, Sollini M, Erba PA, Mariani G., "Dosimetry for nonuniform activity distributions: a method for the calculation of 3D absorbed-dose distribution without the use of voxel S-values, point kernels, or Monte Carlo simulations", Med Phys. 2013 Apr;40(4):042505. doi: 10.1118/1.4794473.
[2] AAPM REPORT NO. 166, "The Use and QA of Biologically Related Models for Treatment Planning", Report of AAPM TaskGroup 166 of the Therapy Physics Committee, March2012.

Non linear response of TLD-100 irradiate by an Intra Operative Radiation Therapy linear accelerator: preliminary results.

F. Savino[1], M. Pugliese[2], V. D'Avino[1], L. Cella[1], R. Liuzzi[1]
(1) Istituto di Biostrutture e Bioimmagini - CNR - Napoli.
(2) Department of Physics - University of Napoli "Federico II".

Purpose: Thermoluminescence dosimetry is one of the most widely used and cheap techniques of radiation dosimetry. Thermoluminescence dosimeters (TLD) features many advantages such as small detector size and close tissue equivalence that make it useful for application in radiotherapy *in vivo* dosimetry. Due to their small size, TLDs are convenient for point dose measurements in phantoms as well as for *in vivo* dosimetry on patients during radiotherapy treatment [1]. The response of TLDs is energy and dose-per-pulse rate dependent. Intra Operative Radiation Therapy (IORT) is a treatment modality where a large single radiation dose is delivered during a surgery, either with or without a resection of a neoplastic mass. Accelerators specifically designed for IORT are characterized by dose-per-pulse rate (about 3–12cGy/pulse) several times higher than conventional accelerators (0.1–0.6cGy/pulse) [2]. The behaviour of TLD dosimeters when irradiated by high dose-per-pulse beam was not been fully investigated. In the present study, a characterization of TLD's response to high dose-per-pulse electron beam from an IORT device was carried out.

Methods and materials: Of the many types of TLDs available, the lithium fluoride doped with magnesium and titanium LiF:Mg,Ti (TLD-100) is the most widely used dosimeters in routine personal dosimetry, environmental monitoring and space dosimetry. This popularity is due to its approximate tissue equivalence (effective atomic number of 8.2, similar to 7.4 for tissue) which is an important factor in personal dosimetry and in medical application, low signal fading (5 - 10% per year), wide linear response range and high sensitivity for very low dose measurements. In particular, it is known that the thermoluminescence response of TLD-100 at conventional radiotherapy photon beams is linear for doses <10 Gy [3]. Forty-five TLD-100 (Harshaw Chemical Company) chips with nominal dimensions of 3.2 × 3.2 × 0.89 mm were irradiated with an electron beam produced by an IORT specific accelerator (nominal energy 9MeV). The dose dependence of TLD-100 was studied in the range 0-10 Gy, i.e. the range of interest in IORT technique. Regression analyses was performed to establish the response variation of thermoluminescence signal with dose and energy.



Statistical analysis: For each point of measurements (0-10 Gy in step of 2 Gy) the mean and standard error of the response of 9 TLD's was calculated. A linear and a no-linear (quadratic) regression was performed between TLD response and doses; the goodness of the fit was evaluated by the R^2 coefficient. The better performance of the two models was assessed by F test.

Results: The linear model has an R^2= 0.994 while the quadratic model has an R^2 = 0.999. The result of F test was approving the quadratic model ($p<0.0045$).

Conclusion: The thermoluminescence response of TLD-100 is energy and dose-per-pulse rate dependent: when irradiated with a conventional radiotherapy photon beams this response is linear for low doses. In this preliminary work we found that to describe the dependence of thermoluminescent signal of TLD with the absorbed dose when irradiated by a IORT dedicated accelerator a quadratic model performs better than a linear model.

References:

[1] Kron T. *Applications of thermoluminescence dosimetry in medicine.* Radiation Protection Dosimetry, 85:333-340, 1999.

[2] Cella L, Liuzzi R, Salvatore M. *The Italian affair: The employment of parallel-plate ionization chambers for dose measurements in high dose-per-pulse IORT electron beams.* Med. Phys. 37(6): 2918-2924, 2010.

[3] Massillon G, Gamboa-deBuen I, Brandan M.E. *Onset of supralinear response in TLD-100 exposed to ^{60}Co gamma rays.* J. Phys. D:Appl. Phys. 39:262-268, 2006.

Dose Tracking Software: the experience of Pisa University Hospital

C. Sottocornola[1], I. Creonti[2], E. Del Dò[2], F. Paolicchi[2], G. Imbarlina[2], D. Caramella[2]
(1) Department of Physics - University of Pisa
(2) Diagnostic and Interventional Radiology, University of Pisa

Purpose: Medical imaging with ionizing radiation is the non-invasive technique most widely used to identify internal injuries and lesions and effective doses given in a single medical imaging exposure are universally within the low-dose range (<100 mSv). Risks associated to ionizing radiation from medical imaging techniques have focused the attention of medical society and general population and some recent epidemiological studies showed an increased incidence of cancer in patients who underwent to radiological examinations [1]. Therefore, it is necessary to balance the benefit/detriment relationship of such examinations in order to establish the conditions under which its use is justified. Constant and systematic monitoring of radiation dose is indispensable in order to increase the quality of radiological services to patients.

Methods and materials: The purpose of dose tracking is to strengthen the process of justification and optimization with the intent to achieve better protection of patient [2]. Constant and systematic monitoring of radiation dose is indispensable in order to reduce the dose given to patients in every examination without impairing its diagnostic quality, according to the ALARA (As Low As Reasonably Achievable) principle. Dose monitoring can lead to performance control, protocol optimization and rapid correction of wrong practices. Lawmakers are interested in monitoring and reducing radiation doses, as shown by the newly published European Directive EURATOM/59/2013 that contains more stringent radiation protection rules, especially concerning patients' protection. In particular, the European Directive requires that patients are informed about the risk associated with ionizing radiation, and that detailed information about radiation dose is included in every procedure's report. EU Member States must transpose the requirements of this Directive in their national laws by 6th February 2018.

In the last few years, most vendors already provide means to track patient exposure history with new software tools that can automatically retrieve, store and analyze dosimetric data stored in a Picture Archiving and Communication System (PACS). These software can be installed on hospital networks, and are in most cases web-based, ensuring easy access to all authorized users.

In Pisa University Hospital we established a multidisciplinary dose team composed of radiologists, technologists, engineers and physicists, and recently started to evaluate some commercially available dose management systems. Thanks to dose monitoring software, our dose team recovered and analyzed from 1st January 2014 up to now more than 130,000 TC scans, about 7,000 mammography procedures and nearly 123,000 traditional radiography exams. Our analysis showed relevant dosimetric differences between examinations performed on similarly-sized patients and auditing, training and protocol optimization were used to ensure a better homogeneity of dosimetric values. The principal aim of the dose team is to minimize the variability which is clinically not justified.

Results: Dose monitoring software represents an essential part of radiologic quality management by allowing the systematic control of dose performances, by contributing to the reduction of wrong practices, and by supporting protocol optimization.

References:

[1] C. Candela-Juan, A. Montoro, E. Ruiz-Martinez, J. I. Villaescusa, L. Marti-Bonmatì. *Current knowledge on tumor induction by computed tomography should be carefully used.* Eur Radiol (2014) 24:649-656.

[2] M. Rehani, T. Berris. *Templates and existing elements and models for implementation of patient exposure tracking.* Radiation Protection Dosimetry (2014) Vol. 158, No. 1, pp. 36-42.

Feasibility of small animal irradiation by using TomoTherapy

A. Miranti[1], M. Poli[1], G. Cattari[2], C. Cutaia[1], E. Garibaldi[2], A. D'Ambrosio[3], F. De Bacco[3], C. Boccaccio[3], P. Gabriele[2], M. Stasi[1]

(1) Medical Physiscs Department - IRCCS-FPO, Candiolo Cancer Center, Candiolo (TO)

(2) Radiotherapy Department - IRCCS-FPO, Candiolo Cancer Center, Candiolo (TO)

(3) Experimental Clinical Molecular Oncology Department - IRCCS-FPO, Candiolo Cancer Center, Candiolo (TO)

Purpose: Preclinical studies are critical steps in the medical research process. Small animal external beam irradiation is one of the delicate fields in which the different anatomical scale impact the most and the technique may do the difference. For those centers in which both preclinical and clinical researches are conducted, the possibility of exploiting clinical devices for preclinical purposes may be of economical and scientific interest, besides a technical challenge. Small subcutaneous volumes coverage and short irradiation times are the main demands. In the present work the feasibility of using TomoTherapy for preclinical irradiation and the optimal setup have been analyzed.

Methods and materials: Six groups of immunocompromized NOD SCID Xenografts have been irradiated during the period February-June 2014; mice were anesthetized and placed in a Plexiglas cage pie (2BiologicalInstruments). All of the irradiated mice were subcutaneously inoculated with human xenograft glioblastoma multiforme cells.

High-resolution CT scans were acquired and reconstructed with a slice thickness equal to 3 mm for treatment planning purposes. Gross Tumor Volume (GTV) was delineated in between the low-abdomen region and the upper leg, where tumor cells were implanted. A Planning Target Volume (PTV) margin of 2 mm was used. In order to confirm the location of the tumor, lead markers were applied on the skin of the mice. Prescribed total dose to lesions was 6 Gy in 3 fractions delivered with 6 MV TomoTherapy Hi-Art and TomoTherapy HD (Accuray, Inc., Sunnyvale, CA). The two systems do not differ substantially in hardware or software implementations.

TomoDirect Intensity Modulated Radiation Therapy (TD-IMRT) technique was applied with gantry fixed at 0° and 180°. Field width and Pitch were settled equal to 1.05 cm and 0.1.

During 3 irradiations, in order to obtain a better coverage, a bolus layer has been placed upon mice's body to deposit radiation also in the superficial layer. The mean number of mice per cage pie irradiated without bolus (WOB) and with bolus (WB) were 5 and 7, respectively, for a total amount of 15 mice irradiated WOB and 20 mice irradiated WB. Treatment planning and dosimetric results of the two setups have been compared in order to determine the importance of this espedient.

Before the delivery of each RT fraction, a MegaVoltage Computed Tomography (MVCT) image has been acquired in order to correct irradiation setup.

Results: The average body volume of a single irradiated mouse was (19±2) cm^3 and PTV volume was (5±4) cm^3 and (2±1) cm^3 for WOB and WB, respectively. On average, the total delivery time was (377±22) s and (360±27) s for WOB and WB, respectively. In particular, the average time of irradiation of a single mouse (total time/number of mice) was 75 s and 54 s, for WOB and WB, respectively. The average modulation factors (MFs) used for the optimization were 2 for WOB and 1.5 for WB.

The average dose to PTV was 6 Gy for both groups with a maximum dose to the target equal to 6.7 Gy (112%) for WOB and 6.4 Gy (107%) for WB.

Discussion and Conclusions: the good PTV coverage results show that it is possible to irradiate small animals by using Tomotherapy. Moreover, by adopting specific expedients it is possible to reduce irradiation time while achieving equivalent PTV coverage and higher dose homogeneity. Nevertheless, the time which can be dedicated to preclinical studies is limited by patients' treatments and clinical imaging devices do not allow a precise contouring of the target nor of the OARs.

Tomotherapy systems may be a useful mean for small animals irradiation. Nevertheless, clinical-to-preclinical adaptation is not easy to implement and further work is needed.

Preclinical results are still under investigation.

Acknowledgments: The present work was financially supported by the Italian 5 per Mille, 2008 Ministero della Salute - FPRC Onlus.

FUNCTIONAL MAGNETIC RESONANCE IMAGING REVEALS BRAIN CORTEX REMODELING IN A RAT MODEL OF CHRONIC MULTIPLE SCLEROSIS.

S. Tambalo[1,2], L. Peruzzotti-Jametti[3], R. Rigolio[4], S. Fiorini[1], P. Bontempi[5], G. Mallucci[3,6], P. Marmiroli[4], G. Cavaletti[4], S. Pluchino[3] and P. Marzola[2,5]

(1) Dept of Neurological and Movement Sciences, University of Verona, Italy
(2) INSTM, Firenze, Italy;
(3) Dept of Clinical Neurosciences, John van Geest Centre for Brain Repair, Wellcome Trust-MRC Stem Cell Institute and NIHR Biomedical Research Centre, University of Cambridge, CB2 0PY, UK;
(4) Dept of Surgery and Translational Medicine, University of Milano-Bicocca, Monza, Italy,
(5) Dept of Computer Science, University of Verona, Verona,Italy
(6) Dept of Brain and Behavioural sciences, University of Pavia, Pavia, Italy

Introduction: Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system. During the last years functional Magnetic Resonance Imaging (fMRI) studies have shown that cortical reorganization consistently occurs both in acute and clinically stable MS patients [1].
Experimental Autoimmune Encephalomyelitis (EAE) is considered a good model of MS both in rodents and non-human primates. In the present work we have investigated through fMRI and Voxel-Based-Morphometry (VBM) the functional and morphological alteration in rats with induced chronic EAE.

Materials and Methods: EAE was induced as described in the literature [2]. Rats were investigated prior to EAE induction, 30 and 60 days post induction (dpi). To increase the sensitivity of the fMRI experiment, a SPIO contrast agent was administered. Electrical stimulation was delivered through needle electrodes inserted in the right forepaw. T2 weighted RARE images, acquired at high resolution, were analysed by VBM in order to investigate voxel-wise differences in local Grey Matter (GM) volume.

Results: In healthy DA rats, fMRI revealed that most of the activated volume (AV) was observed in the controlateral hemisphere and specifically in the S1 cortex with a relevant percentage in the motor cortex (fig.1A). On 30 and 60 dpi, the activation pattern was substantially altered compared to the pre-induction stage and heterogeneous among different EAE rats. Activation was also detected in the ipsilateral right cortex and in some extra-cortical areas (Fig.1B-C). The qualitative comparison of fMRI maps showed an increased AV after EAE induction in all investigated rats. The total AV increased by about 80% ($p<0.01$) on 60 dpi vs. 30 dpi. The Laterality Index (LI) is an index of hemispheric dominance in functional response. In our MS model, LI strongly decreased on 30 dpi (0.02 ± 0.16) compared to the pre-induction value (0.97 ± 0.09) ($p<0.05$) while on 60 dpi it showed a tendency toward recovery (0.12 ± 0.19) remaining definitely lower than in healthy animals. Statistical maps ($p<0.01$) relative to VBM analysis showed a widespread reduction of GM volume in the cortex at 30 dpi vs. pre-induction stage. This further progressed at 60 dpi. A statistical significant decrease ($p<0.01$) of the whole brain GM volume was found at 30 dpi ($818.3\ mm3 \pm 4.6$) and 60 dpi ($816.8\ mm^3 \pm 2.5$) vs. pre-induction stage ($850.2\ mm^3 \pm 4.3$).

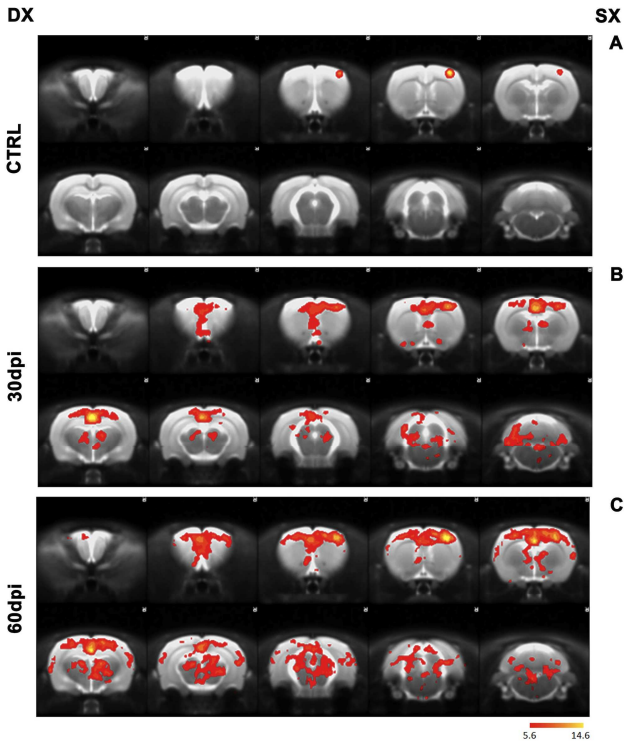


Figure 1: Functional activation maps in EAE rats before (A), 30 (B) and 60 (C) dpi.

Conclusion: The present work is the first attempt to define a reliable model to dissect brain plasticity phenomenon occurring in MS patients. Such a tool could also be used as a sensitive indicator of therapeutic intervention in preclinical studies. This work was supported by Fondazione Italiana Sclerosi Multipla (FISM), grant support (FISM 10/12/F14 /2011).

References:

[1] Filippi, M., Rocca, M.A. 2004. J Neurol Neurosurg Psychiatry. 75(8), 1087-1089.
[2] Giatti S. et al., J Neuroimmune Pharmacol 8:238-250.

Inhibition of tumor growth in a xenograft model of glioblastoma treated with MSR-1 Magnetosomes and Alternating Magnetic Field.

S. Tambalo[1,2], S. Mannucci[2,3], G. Conti[1], L. Ghin[4], A. Milanese[3], A. Carboncino[1], E. Nicolato[1], M.R. Marinozzi[1], P. Bernardi[1], D. Benati[1], R. Bassi[4], A. Sbarbati[1,2], P. Marzola[2,3].

(1) Dep. of Neurological and Movement Sciences, University of Verona, Verona, Italy

(2) Consorzio INSTM, Firenze, Italy

(3) Dep. of Computer Science, University of Verona, Verona, Italy

(4) Dep.of Biotechnology, University of Verona, Verona, Italy

Introduction: Magnetic Fluid Hyperthermia (MFH) involves the use of iron-based magnetic nanoparticles injected into the tumor mass [1, 2] to selectively heat malignant tissues. In 1963 the Italian scientist Salvatore Bellini reported the first description of magnetotactic bacteria (MTB), which naturally produce iron-nanoparticles named magnetosomes (MNs). Recently it has been reported that magnetosomes extracted from bacteria could have a new potential role in cancer treatment of MNs as "theranostics" agents [3,4,5].

Material and Methods: Magnetosomes were extracted from a bacterial strain, *Magnetospirillum griphiswaldense. In vivo* studies were performed on subcutaneous tumors obtained by injecting Human Glioblastoma cells (U87 MG) in mice. MNs (1.5 mg) were injected in the tumor tissue. Animals treated with MNs were exposed three times in a week for 20 minutes to an alternating magnetic field (AMF) with 23 mT strenght and 110 kHz frequency. The efficacy of the treatment was assessed measuring tumor volumes *in vivo* by magnetic resonance imaging (MRI) (Figure 2) and *ex vivo* by histology. MRI was used to map the injection site and distribution of MNs in the neoplastic mass.

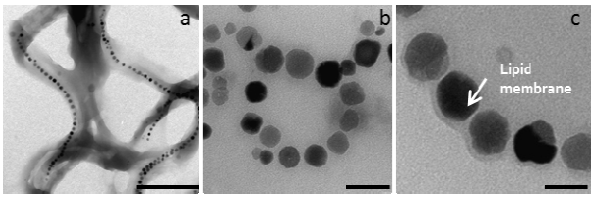


Figure 1: a shows the organization of MNs in chains in the bacteria (scale bar, 500 nm). Panels b-c show that the typical conformation of chains is maintained after isolation of MNs. Scale bars: b > 200 nm,

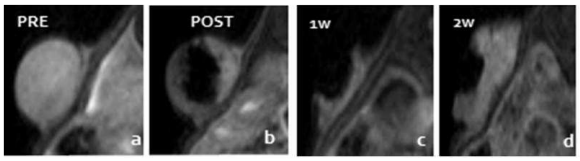


Figure 2: MRI animal treated with MNs injection with AMF images acquired before MNs injection (a), 24 h (b), one week (c) and two weeks (d) after MNs injection.

Results: Transmission Electron Microscopy (TEM) shows the cuboctahedral structure of magnetosomes and their organization in chains (Figure 1a-c). Alterations in signal intensity of tumor tissues were visible in MRI images due to the presence of iron nanoparticles (Figure2). At histological examination, tumors treated with MNs and AMF were characterized by degenerating unclustered cells intruded by extracellular matrix with evidence of edematous and necrotic phenomena. A mild inhibition of the tumor growth was observed in animals treated with MNs and exposed to AMF, compared to controls. In a small number of animals an almost complete reduction of tumor mass was observed soon after MFH treatment.

Conclusion: Magnetic Fluid Hyperthermia mediated by iron-based nanoparticles naturally produced by magnetotactic bacteria has been applied in an experimental model of glioblastoma. Although preliminary, our results show a mild inhibition of tumor growth. In addition, our results demonstrate that MRI detects both the injection site of MNs and the dynamics of tumor size evolution. Theranostic is a combination of diagnosis and therapy; although further investigations are necessary, our data confirms that MNs exhibit some core characteristics of the so called "theranostic agents".

References:

[1] Johannsen M, Eur. Urol. 52(6):1653-61(2007)

[2] Jordan A, J. Neurooncol 78: 7-14 (2006)

[3] Alphandery E, Int. J. Pharm 434: 444-452 (2012)

[4] Alphandery E, ACS Nano 23;5(8):6279-96 (2011)

[5] Mannucci S et al, PLoSOne e108959 (2014)

Multiphoton Optical Biopsy of Human Skin: Benefit-risks assessment.

Giulia Zanini[1], Luca Dalbosco[2], Elvira D'Amato[1], Sebastiana Boi[3], Paolo Bauer[4], Albrecht Haase[1], and Renzo Antolini[1]

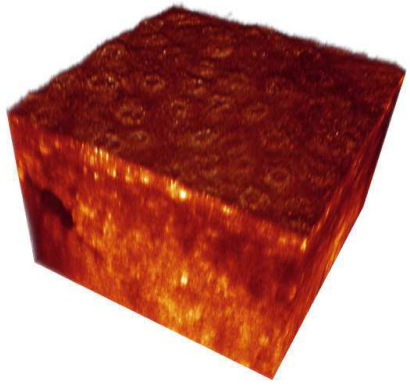
(1) Department of Physics - University of Trento

(2) BIOtech center and Department of Industrial Engineering - University of Trento

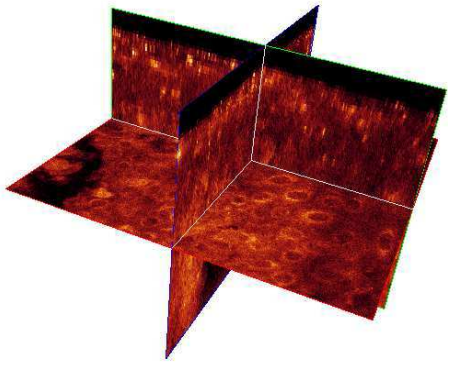
(3) Department of Pathology - S. Chiara Hospital, Azienda Provinciale per i Servizi Sanitari, Trento

(4) Department of Dermatology - S. Chiara Hospital, Azienda Provinciale per i Servizi Sanitari, Trento

Purpose: The feasibility of a noninvasive analysis of human skin tissue samples with nonlinear microscopy techniques, like two-photon-excited autofluorescence and second harmonic generation imaging, was evaluated in a preclinical study. Central points were the resolution of subcellular structures allowing for a noninvasive tumor diagnostics and the extension of the maximum imaging depth by power compensation without inducing tissue damage.



Methods and materials: Fixed biopsy tissue samples (healthy skin and neoplastic lesions) were used to study optical parameters which could allow to identify malignant lesions.
Results were compared with subsequent histological analysis. Different exposure protocols were applied to test possible photodamage mechanisms induced by femtosecond laser radiation and their dependency on laser power, imaging depth, and number of exposures.



Results: Combining autofluorescence and second harmonic generation data allowed to discriminate subcellular structures and their distribution within skin layers [1]. Different damage mechanisms like photobleaching, photoionization, and thermomechanical damage were characterized, and depth and power limits could be determined.
Based on these limits a damage-free power compensation scheme was defined, allowing for deep tissue optical biopsies [2].

References:

[1] G. Zanini, "Towards Optical Biopsy of Human Skin Lesions: A Two-photon Microscopy Feasibility Study" Master thesis, University of Trento (2014).

[2] L. Dalbosco, G. Zanini, E. D'Amato, F. Tessarolo, S. Boi, P. Bauer, A. Haase, and R. Antolini "Photodamage in deep tissue two-photon optical biopsy of human skin" J. Biophotonics *accepted* (2014).

Machine Learning Techniques Implemented on Structural MR Images of Children with Autism Spectrum Disorder at Different Dimensional Scales

Alessia Giuliano[a,b], Ilaria Gori[a,c], Filippo Muratori[d,e], Irene Saviozzi[e], Raffaella Tancredi[d], Angela Cosenza[d], Michela Tosetti[d], Sara Calderoni[d], Alessandra Retico[a]

[a] *Istituto Nazionale di Fisica Nucleare, Sezione di Pisa, Italy*
[b] *Dipartimento di Fisica, Università di Pisa, Italy*
[c] *Dipartimento di Chimica e Farmacia, Università di Sassari, Italy*
[d] *IRCCS Fondazione Stella Maris, Calambrone (PI), Italy*
[e] *Dipartimento di Medicina Clinica e Sperimentale, Università of Pisa, Italy*

The use of pattern classification methods is taking place as alternative approach to standard univariate analyses of structural brain Magnetic Resonance Imaging (sMRI) data. The machine learning technique has the advantage of intrinsically taking into account inter-regional correlations and it allows exploring the predictive power of sMRI. Despite these methods are potentially suitable to infer a large variety of neurological and neuropsychiatric disorders, in the present study we have implemented Support Vector Machines (SVM) to detect structural brain alterations in children with Autism Spectrum Disorder (ASD), a widespread neurodevelopmental disorder whose relevant impact on the neuroanatomy is still poorly investigated.

The sMRI data of 41 male children (2-6 years, 21 ASD matched to 20 control subjects for age and Non-Verbal Intelligence Quotient (NVIQ)) were preprocessed according to two different analysis protocols to finally extract brain features at different spatial scales. In the first place, the standard voxel-based morphometry (VBM) image preprocessing using SPM8 package was applied to analyze images and to extract whole-brain features (gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) segmented tissue volumes) and GM voxel-based features. In the second place, the Freesurfer image analysis suite version 5.1.0 was used to obtain Region-of-Interest (ROI)-based features. It allows the cortical parcellation of each sMRI scan in 62 structures, according to the Desikan-Killiany-Tourville (DTK) atlas and it computes five surface based features for each DTK structure. To investigate which are the most relevant brain features to distinguish ASD from control subjects, we classified the three different sets according to the classification protocol based on linear kernel Support Vector Machine (SVM) classifiers. The classification capability of SVM is evaluated in terms of the Receiver Operating Characteristic (ROC) curve, computing the global performance index of the area under the ROC curve. The leave-pair-out cross-validation protocol has been adopted to reach the classifier performance without undesired bias, and the nested cross-validation was implemented to optimize free model parameters. The most discriminant brain regions in a case-control study have been visualized in discrimination maps with statistical significance ($p<0.05$) obtained through permutation tests.

The relevance of ASD features in a binary discrimination problem emerges at the intermediate scale of GM subregions. The best classification performance is achieved in the classification of regional features, reaching the AUC of 74%. This value is enhanced to 80% when considering only subjects without developmental delay (NVIQ $\geq$ 70). By contrast, when the number of features becomes large with respect to the number of training cases (voxels-based features) or too poor (whole brain features), the classifiers lack sufficient power. The discrimination maps resulting from the permutation tests implemented at voxel and at ROI levels identify cortical regions that belong mainly to frontal, temporal and parietal lobes.

In conclusion, the application of the machine learning technique to sMRI data leaded to highlight the salient features in the ASD-control classification tasks and to identify abnormalities in the neuroanatomy of young ASD children consistently at voxel and at ROI dimensional scales. The morphological abnormalities detected in this analysis involve the cortical networks linked to the common deficits of ASD subjects.

New semi-automatic tool for 3D quantification and 3D volumetric visualization of left atrium fibrosis based on integration of LGE-MRI and MRA images.

Daniele Ravanelli[1], Elena Costanza dal Piaz[2], Maurizio Centonze[3], Giulia Casagranda[3], Massimiliano Marini[2], Maurizio Del Greco[2], Rashed Karim[4], Kawal Rhode[4], Aldo Valentini[1]

(1) Department of Health Physics - Azienda Provinciale per i Servizi Sanitari - APSS, Trento.

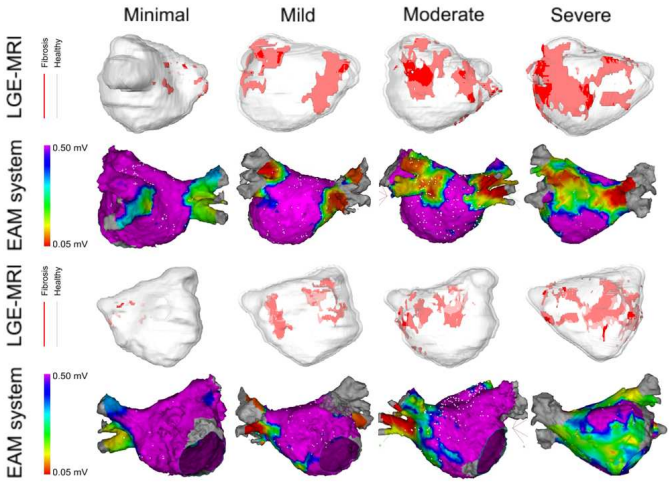
(2) Department of Cardiology - Azienda Provinciale per i Servizi Sanitari - APSS, Trento.

(3) Department of Radiology - Azienda Provinciale per i Servizi Sanitari - APSS, Trento.

(4) Imaging Sciences and Biomedical Engineering, King's College London, London,

Purpose: This work presents a new semi-automatic tool for 3D segmentation, quantification and visualization of cardiac left atrium fibrosis, based on two type of image data: late gadolinium enhancement magnetic resonance imaging (LGE-MRI) images and magnetic resonance angiography (MRA) images. A comparison with the quantification and 3D visualization obtained from 3D bipolar voltage maps, the clinical reference standard technique for atrial substrate characterization was reported. The aim is to develop a non-invasive, semi-automatic and robust 3D segmentation, quantification and visualization of LA fibrosis tool, allowing fast availability, accuracy of results and possibility to stratify patients with atrial fibrillation (AF) that are candidates for radiofrequency catheter ablation (RFCA).

Methods and materials: In this study 10 consecutive patients suffering AF with different grades of atrial fibrosis candidates for RFCA were considered at the Electrophysiology Laboratory of Cardiology Department of the S. Chiara Hospital in Trento, Italy. Using a 3D bipolar voltage map registered with the EAM system before RFCA, patients suffering AF were divided into four stages, based on the percentage of LA fibrosis extent (FE): Minimal (FE<5%), Mild (5%≤FE<20%), Moderate (20%≤FE<35%$20\% \leq FE < 35\%$) and Severe ($FE \geq 35\%$). LGE-MRI and MRA images were used to detect and quantify fibrosis of the left atrium using a threshold and 2D skeleton based approach. Quantification and 3D volumetric views of atrial fibrosis were compared with quantification and 3D bipolar voltage maps measured with EAM considering these voltage maps as surrogate for fibrosis.



Results: Bland-Altman plot of the measurements of fibrosis extent based on the EAM system and on LGE-MRI was generated. Mean difference between the two method measurements (0.2%) confirms that there is no substantial bias of the LGE-MRI based fibrosis quantification (discrepancies in fibrosis quantification less than 4% from EAM results). The figure shows the 3D LA wall in white with segmented fibrosis in red for the antero-posterior and postero-anterior views, in comparison with 3D bipolar voltage maps of the EAM system for all the four fibrosis classes, selected as example. Bipolar voltage maps are reported with a color bar that is violet for potentials upper 0.5 mV (healthy myocardium) and reaches red for potentials lower 0.05 mV (fibrosis). Very good agreement in the localization of fibrosis areas is achieved.

Conclusion: The novel 3D visualization and quantification tool based on LGE-MRI allows detection of cardiac left atrium fibrosis areas. This non invasive method provides a clinical alternative to EAM systems for quantification and localization of atrial fibrosis, proving to be clinically reliable among all different fibrosis stages and yielding accurate 3D volumetric views.

References:

[2] D. Ravanelli, E. C. dal Piaz, M. Centonze, G. Casagranda, M. Marini, M. Del Greco, R. Karim, K. Rhode, and A. Valentini, "A novel skeleton based quantification and 3-D volumetric visualization of left atrium fibrosis using late gadolinium enhancement magnetic resonance imaging," *IEEE Trans. Med. Imaging*, vol. 33, no. 2, pp. 566–576, Feb. 2014.

Quantifying radiographic contrast of polymeric orthopedic implants with osseointegrative coating by a tissue-equivalent phantom

N. Pace [1], F. Tessarolo[1,2], G. Miori[3], G. Zappini[4], G. Nollo[1,2], M. Recla[5], A. Valentini[6]

(1) Healthcare Research and Innovation Program (IRCS), Bruno Kessler Foundation, Trento, Italy
(2) Department of Industrial Engineering, University of Trento, Trento, Italy
(3) School of Medical Physics, University of Roma Tor Vergata, Rome, Italy
(4) Eurocoating S.p.A., Trento, Italy
(5) Diagnostic Radiology Unit, S. Chiara Hospital, Trento, Italy
(6) Department of Health Physics, Azienda Provinciale per i Servizi Sanitari, Trento, Italy.

Purpose: orthopedic implants can nowadays be realized with high performance polymers such as polyether-ether-ketone (PEEK) and its carbon-fiber reinforced composite (CFR-PEEK) in addition to the most routinely used ultra-high molecular weight polyethylene (UHMWPE) [1]. These materials can be coated by plasma-spray or thermal-press techniques with titanium (Ti) or hydroxyapatite (HA) powders to improve osseointegration of the polymeric component. Polymers are radiolucent to X-rays and coatings may allow the visualization of the implanted device in clinical X-ray imaging without the addition of metallic markers. This work aimed at developing a synthetic tissue equivalent phantom and checking its suitability in estimating the radiological contrast of different polymeric substrates coated with Ti or HA powders for orthopedic implant applications.

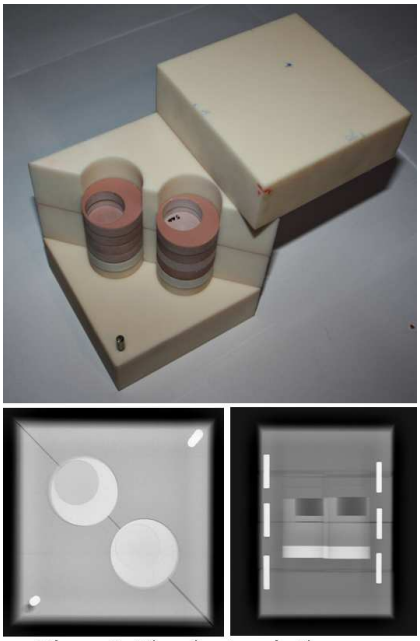


Figure 1: The phantom in the open configuration (top) and its AP and LL projections obtained with the Axiom Aristos FX Plus, Siemens

Methods and materials: an X-ray tissue-equivalent modular phantom was designed to simulate the anatomical tissue dimensions of the human hip (Figure 1). Soft tissues, trabecular bone and cortical bone were differentiated within the phantom by using three tissue-equivalent synthetic materials. Seven different substrate-coating combinations were considered. For each of them the substrate thickness was also varied (6, 8, 10, 12 mm) thus resulting in 28 tested coupons. Radiographic contrast of the coupons was assessed into the phantom using a clinical antero-posterior pelvis image acquisition protocol by a state-of-the-art clinical digital radiography apparatus. Contrast (ΔPI) values were than compared to a minimum contrast threshold for detectability (ΔPI_T=0.05) in compliance with ASTM 640-07 [2].

Results: contrast values (ΔPI) of tested coupons ranged from 0.02 to about 0.27. Both the polymeric substrate and the coating contributed to the measured contrast of the coupons, depending on the combination of polymer type, substrate thickness, coating material, coating thickness and porosity. A sufficient radiographic contrast was found in 18 out of the 28 tested coupons. Thin titanium coatings resulted in a sufficient contrast when deposited on PEEK or CFR-PEEK thicker than 10 mm. Medium thickness coatings with little porosity and thick coatings with higher porosity were above the threshold when associated to 8 mm or more of CFR-PEEK. Differently, titanium alloy pre-sintered grid was clearly distinguished even when attached to 6 mm thin UHMWPE.

Conclusion: the proposed phantom represent a valid tool to assess detectability of polymeric coated implants by X-ray plain radiography. Considering the wide range of coatings and polymers nowadays available, information obtained from the tissue-equivalent phantom are essential in optimizing micro and macro design of polymeric coated implants.

Acknowledgment: This study has been financially supported by Eurocoating S.p.A. through a grant of Provincia Autonoma of Trento (project “Inspired”).

References:

[1] S.M. Kurtz, J.N. Devine, PEEK biomaterials in trauma, orthopedic and spinal implants, Biomaterials (2007), 28 (32),4845-4869;

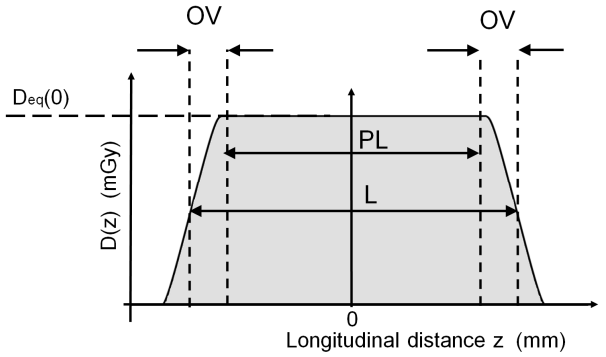
[2] ASTM F 640-07, Standard Test Methods for Determining Radiopacity for Medical Use (2007).

New real time evaluation of overranging in modern helical computed tomography.

Diego Trevisan[1], Faustino Bonutti[2], Daniele Ravanelli[1], Aldo Valentini[1]

(1) Department of Health Physics - Azienda Provinciale per i Servizi Sanitari - APSS, Trento.
(2) Department of Health Physics - S.M. della Misericordia Hospital, Udine.

Purpose: Overranging (OV) increases the dose delivered to patients undergoing helical Computed Tomography (CT) examinations. This side effect of multislice helical CT is due to X-ray data interpolation along the craniocaudal direction z. With reference to figure, the delivered dose to patient is described by the accumulated total dose profile D(z), its equilibrium value $D_{eq}(0)$ at the scan centre z=0, and Dose Line Integral (DLI), represented as the gray area. The ratio $DLI/D_{eq}(0)$ defines the scan length L. OV is given by subtraction of the imaged Planned Length (PL), indicated on the operator's console, from the L value. OV leads to some concerns, especially when radiosensitive organs are in close proximity to the scan extremes. This work proposes and evaluates an alternative new method of estimating the OV in helical CT, using a real-time dosimetry based on a standard pencil chamber (PC). The OV values (OV_{r-t}) are compared with those obtained from measurements with film (OV_{film}), considered the benchmark technique. The new method is suitable for modern scanners equipped with adaptive collimation (AC) (i.e. the dynamic closure of the X-ray collimators at the scan extremes). This method extends the dose-slope method proposed by van der Molen [1], in which OV is quantified without films only on CT scanners without AC.



Methods and materials: The OV_{film} was measured direct from the dose profile, by subtracting PL from L_{film} using Gafchromic films (GF type XR-QA2 ISP). The OV_{eff} was evaluated by means of a PC coupled to an electrometer (10X5-3CT Radcal Corporation) with a charge-collection-length of 100 mm. Two different PC settings were alternatively selected: the Dose Rate mode (DR), providing one reading per second (measurement denoted as R_{DR} and expressed in mGy.cm/min units) and the Dose Accumulate mode (DA), providing an integral reading (R_{DA} in mGy.cm units). The OV_{r-t} was then quantified as: $OV_{r-t} = L_{r-t} - PL = v\cdot(R_{DA}/R_{DR}) - PL$, with the scan speed v calculated as: nominal collimation·pitch / rotation time. The OV_{r-t} evaluation method was tested on three CT scanners. They were a Philips Brilliance 16S installed at the S. Chiara Hospital of Trento (Tomograph A) not equipped with AC, a Siemens Somatom Definition AS 128S operating in the same hospital (Tomograph B), and a General Electric Discovery TM CT750 HD 64S installed at the S.M. della Misericordia Hospital, Udine (Tomograph C). In an attempt to evaluate a wide range of OV values, very different CT scans were considered.

Results: OV_{r-t} and OV_{film} have a good overlap for all Tomographs with absolute discrepancies always less than 2.1 mm. This means that all discrepancies are less than 10% of the measured absolute values. These results are in agreement with other OV evaluations based on van der Molen method. Moreover the new real-time OV evaluation approach proposed in this work can be used also for modern CT scanners with AC.

Conclusions: The present study proposes an uniform approach in OV evaluation, i.e. not depending on the presence or not of AC. The real-time PC based approach described is satisfactory as regards accuracy as well as precision. Advantages of the new method are its simplicity of implementation, because only a standard PC is required, the cost and time saving and the elimination of tedious procedures required by films.

References:

[1] A. J. van der Molen, J. Geleijns, "Overranging in multisection CT. Quantification and relative contribution to dose-comparison of four 16-section CT scanners," *Radiology,* 2007, 242:208-16.

[2] D. Trevisan, F. Bonutti, D. Ravanelli, and A. Valentini, "Real time evaluation of overranging in helical computed tomography," *Physica Medica* 2014, http://dx.doi.org/10.1016/j.ejmp.2014.06.041.

INSIDE: INnovative Solutions for In-beam DosimEtry in Hadrontherapy

G. Pirrone[1] on behalf of the INSIDE collaboration
[1]*Department of Physics, University of Pisa and INFN sezione di Pisa, Italy*

Hadrontherapy is a promising radiotherapy technique, expecially for tumors that are in proximity of critical organs, because it offers the possibility to deliver high dose in well-defined volumes. Its effectiveness is relies on the knowledge of the position of the Bragg peak within the patient, that can be calculated from the well known Bethe-Bloch equation. The precision of the treatment could be impaired if the range during the treatment varies from the calculated one, due to the temporary physiological modifications of organs and tissues. Positron Emission Tomography (PET) is one of the techniques which allows to control the Bragg peak location during the treatment.

The INSIDE project aims to develop a dedicated in-beam PET scanner (Figure 1) for head and neck region able to reconstruct the Bragg peak position after a fraction of the dose delivered to the patient and capable of handling the expected count rate during the treatment.

The PET scanner will be made by two planar heads, each 10 cm (axially) x 25 cm (transaxially), with a gantry aperture of about 55 cm. Each head is composed of 2 x 5 pixelated LFS scintillator matrices of 5 x 5 cm^2, with 16 x 16 pixels (3 x 3 x 20 mm^3) of 3.2 mm picth. Each scintillator is coupled to a matrix of 16 x 16 Multi-Pixel Photon Counters (MPPC) arrays from Hamamatsu with a one-to-one crystal-detector coupling.

Every detector is connected to a 4 custom-designed 64-channels TOF-PET ASIC [1]. Its read-out channels are composed of an analougue front-end that amplifies the input signal and delivers two digital signals to a mixed-mode TDC, which output is a data set containing information on the time of the trigger and the time-over-threshold of the processed input signal.

Each front-end is controlled by a FPGA-based board that calibrates the data and prepares the event data-packet for its transmission to a central processing board (mainboard). The mainboard manages the overall data streaming, the system status and configuration, and performs real-time coincidence detection by timestamp comparison. All the coincident events are then transmitted to the host PC via USB connection and are used for image reconstruction.

The detected coincidences are used to measure the activation line integrals across the target. Each line integral is used to reconstruct the spatial activity distribution map through a MLEM reconstruction algorithm.

An important part of this project is the extension of the in-beam PET technique to Carbon therapy. In fact, the projectile fragmentation at the end of the Carbon range could produce an undesired dose deposition beyond the biological target volume. To measure the fragments produced by therapeutic Carbon beams a dedicated dose profiler will be build. It will make possible the measure of the distal fall-off dose distribution derived from the additional fragments. The traker will be made by 6 planes with 2 cm spacing and a position sensitive calorimeter for the measurement of the proton energy. Each plane is composed by 2 stereo layers of 192 0.5x0.5 mm^2 scintillator fibers read out by 96 1 mm^2 MPPC. The calorimeter is composed of 4x4 LYSO pixellated crystals of 50x50x16 mm^3 each one read out by 64 channel Hamamatsu MultiAnode.

The treatment outcome is verified by comparing the activity image to the simulated one. The tool used for the calculations of particle transport and interaction with matter is FLUKA [2]. Comprehensive geometry and measurements model has been developed by the collaboration, including PET heads, dose profiler, beam pipe and nozzle, target (phantom or patient CT), treatment plan and custom post-processing tools for PET data analysis.

In this work we show the results obtained in the beam tests at the CNAO facility of Pavia.

[1] M. D. Rolo, et al. TOFPET ASIC fot PET applications. Journal of Instrumentation, 8(02):C02050, February 2013.

[2] G. Battistoni, et al. The FLUKA code: description and benchmarking. Proocedings of the “Hadronic shower simulation workshop 2006”, Fermilab (2006), AIP proceedings 896 (2007).

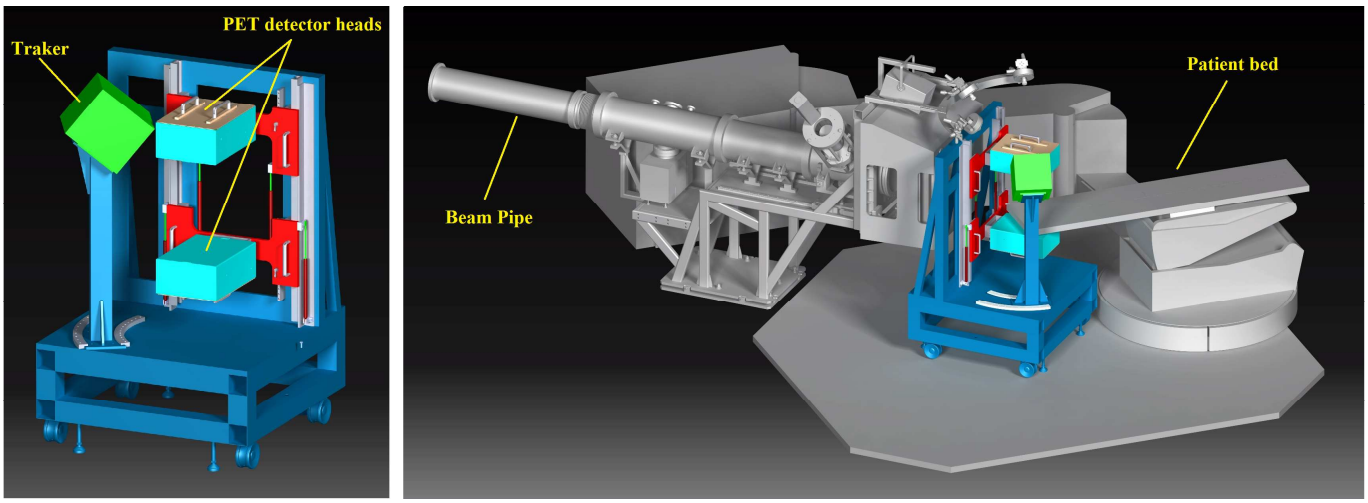


Figure 1: Sketch of the mechanical structure of the scanner (on the left) and its placement in a treatment room of the CNAO facility of Pavia (on the right).

ESR dosimetry with alanine added with Gadolinium in TRIGA reactor of Mainz

M. Marrale[1], T. Schmitz[2], G. Hampel[2], M. Brai[1], S. Gallo[1], A. Longo[1], S. Panzeca[1], L Tranchina[3]

[1]*Dip. di Fisica e Chimica, Viale delle Scienze, Ed.18, I-90128 Palermo, Italy and Gruppo V, INFN, Sezione di Catania, Catania, Italy*
[2]*Institut für Kernchemie, Fritz Strassmann Weg 2, D-55128 Mainz, Germany*
[3]*Laboratorio di Fisica e Tecnologie Relative - UniNetLab – Università degli Studi di Palermo – Viale delle Scienze, Ed. 18, 90128 Palermo*

email: maurizio.marrale@unipa.it
mailto:maurizio.marrale@unipa.it

The development of Neutron Capture Therapy (**NCT**) for cancer treatments has stimulated the research for beam characterization in order to optimize the therapy procedures. The NCT has found to be promising for treatments of tumours which hardly can be treated with other techniques such as gliomas. Alongside with the improvements of this technique, the development of techniques for the beam characterization arouses great interest in order to optimize the therapy procedures by reliably determining the various (*neutronic and photonic*) components of the mixed beam usually employed for therapy.
In the last years there is a large interest in alanine Electron Spin Resonance (ESR) dosimetry for electron and photon beams. Furthermore, recently the applications of ESR dosimetry for high LET radiation beams such as carbon ions and neutrons are continuously increasing. This is because of the very good dosimetric features of alanine EPR detectors such as: tissue equivalence, linearity of its dose-response over a wide range, high stability of radiation induced free radicals, no destructive read-out procedure, no sample treatment before EPR signal measurement and low cost of the dosimeters [1]. Moreover, in order to improve the sensitivity to thermal neutrons of alanine dosimeters the addition of additive nuclei such as Gd_2O_3 was previously studied [2].
The choice of Gd as additive nucleus is due to its very high capture cross section to thermal neutrons and to the possibility for secondary particles produced after interaction with thermal neutrons of releasing their energy in the neighbourhood of the reaction site. In particular, it was found that low concentration (i.e. 5% by weight) of gadolinium oxide brings about an neutron sensitivity enhancement of more than 10 times without heavily reducing tissue equivalence [3].

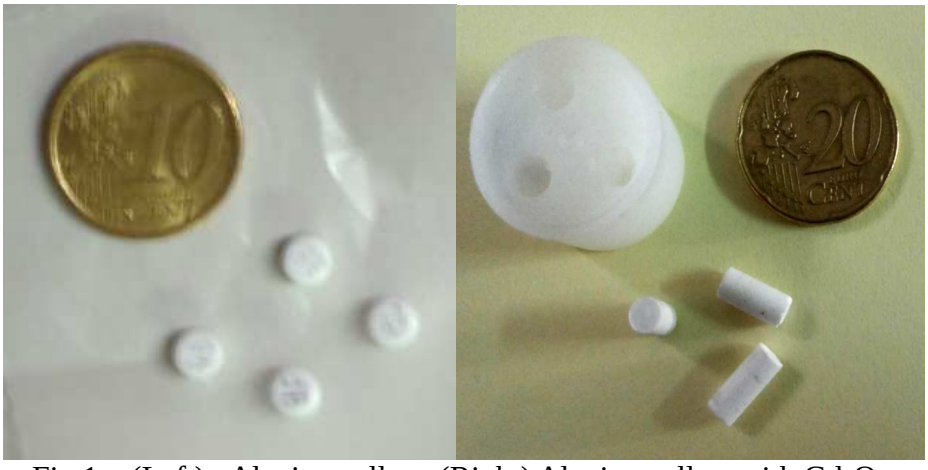


Fig.1 – (Left) Alanine pellets; (Right) Alanine pellets with Gd_2O_3.

In this work we have studied the response of alanine pellets with and without gadolinium exposed to the thermal column of the Mainz reactor. Pure alanine dosimeters (Fig.1 - left) used were produced by Synergy Health (Germany) whereas the Gd-added dosimeters were produced at the University of Palermo (Fig.1 - right). The irradiations were performed inside polyethylene holders to guarantee charged particles equilibrium conditions. ESR measurements were carried out through Bruker ECS106 spectrometer equipped with a TE_{102} rectangular cavity.

The results of ESR experiments are compared to Monte Carlo (MC) simulations [4] aimed at obtaining information about the contribution of the various (neutronic and photonic) components to the total dose measured by means of ESR dosimeters (Fig.2). For alanine dosimeters a good agreement between experimental data and MC simulation have been achieved.

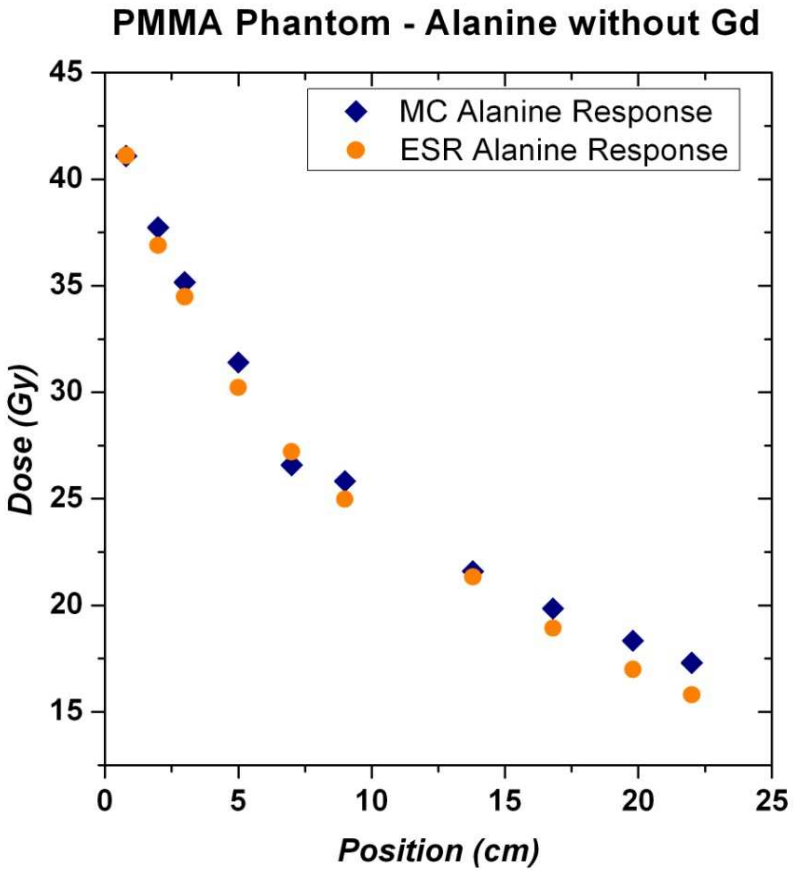


Fig.2 –Measured and calculated (through MC simulation) dose values of alanine pellets in PMMA.

[1] M. Marrale, M. Brai,A. Longo,S. Panzeca, A. Carlino, et al., EPR/ALANINE PELLETS WITH LOW Gd CONTENT FOR NEUTRON DOSIMETRY. Radiation Protection Dosimetry ((2013) - doi: 10.1093/rpd/nct290.

[2] M. Marrale, M. Brai, A. Longo, S. Panzeca, L. Tranchina, E. Tomarchio, A. Parlato, A. Buttafava and D. Dondi, NEUTRON ESR DOSIMETRY THROUGH AMMONIUM TARTRATE WITH LOW Gd CONTENT. Radiation Protection Dosimetry (2014) - doi: 10.1093/rpd/ncu135.

[3] M. Marrale, A. Longo, S. Panzeca, S. Gallo, F. Principato, E. Tomarchio, A. Parlato, A. Buttafava, D. Dondi, A.Zeffiro. ESR response of phenol compounds for dosimetry of gamma photon beams. NIMB (2014). Doi: 10.1016/j.nimb.2014.08.015

[4] T. Schmitz, M. Blaickner, C. Schütz, N. Wiehl et al., Dose calculation in biological samples in a mixed neutron-gamma field at the TRIGA reactor of the University of Mainz. Acta Oncologica (49), 1165–1169 (2010) – doi: 10.3109/0284186X.2010.500306.

ADVANCED TECHNIQUES IN MAGNETIC RESONANCE IMAGING: CHARACTERIZATION OF NON-GAUSSIAN WATER DIFFUSION USING DIFFUSION KURTOSIS IMAGING (DKI)

G.Collura[a], M.Marrale[a,] C.Gagliardo[b], S.Gallo[a], A.Longo[a], S.Nici[a], S.Panzeca[a], M.Midiri[b], M.Brai[a]

[a]*Dip. di Fisica e Chimica, Università di Palermo, Viale delle Scienze, Edificio 18, 90128 Palermo, Italy and INFN sez. di Catania, Via Santa Sofia, 64, 95123 Catania*

[b]*Dip. di Biopatologia e Biotecnologie Mediche e Forensi – Sezione di Scienze Radiologiche, Università di Palermo, Via del Vespro, 129 - 90127 Palermo*

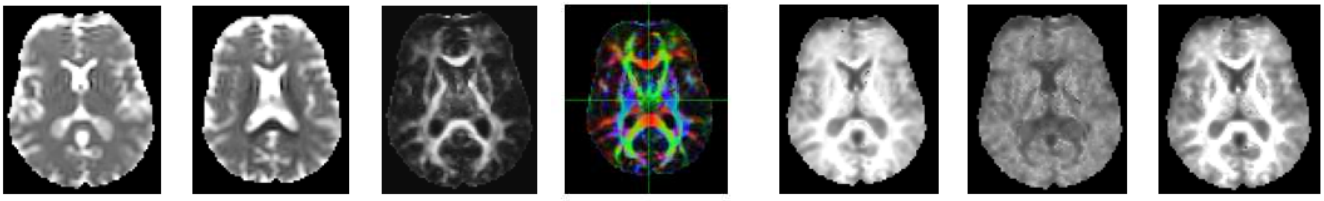
e-mail: giorgio.collura01@unipa.it

The analysis of diffusion tensor imaging (DTI) allows to evaluate in vivo and in a non-invasive way the process of diffusion of water molecules in biological tissues. The peculiar organization of some biological tissues influences this phenomenon making it anisotropic and therefore well evaluable with these techniques. Changes in tissue anisotropy can also be found in many diseases without any signal intensity variation on conventional MR pulse sequences since they are intimately related to intrinsic micro-structural changes.

Despite all these important applications, DTI fails to fully utilize the MR diffusion measurements that are inherent to tissue microstructure. DTI implicitly assumes that water molecule diffusion occurs with a Gaussian distribution of diffusion displacement. This assumption has been experimentally demonstrated to be not always suitable in both white matter and gray matter.

In biological tissue, complex underlying cellular components and structures hinder and restrict the diffusion of water molecules. Moreover, the simplified description of the diffusion process in vivo by a 2nd-order 3D diffusion tensor prevents DTI from being truly effective in characterizing relatively isotropic tissue such as GM. Even in WM, the DTI model can fail if the tissue contains substantial crossing or diverging fibers.

Jensen et al. [1] introduced diffusion kurtosis imaging (DKI), a higher order diffusion model that is a straightforward extension of the DTI model. DKI is an approximation of the logarithmic expansion of the DWI signal decay up to the b^2 term and neglects the b^3 terms. DKI give an dimensionless measure that quantifies the deviation of the water diffusion displacement profile from the Gaussian distribution of unrestricted diffusion, providing a measure of the degree of diffusion hindrance or restriction.



a **b** **c** **d** **e** **f** **g**

Fig.1 – (**a**) mean diffusivity (MD); (**b**) radial diffusivity (RD); (**c**) fractional anisotropy (FA); (**d**); color encoded fractional anisotropy (decFA); (**e**) mean kurtosis (MK); (**f**) assial kurtosis (AK); (**g**) radial kurtosis (RK).

The extensive application of DKI in a clinical routine must deal with several difficulties. The most important is the long acquisition time (much more time than that required for the DTI).

In clinical applications the real issues is to find a good compromise between acquisition time and robustness of the fit [2]. Another major problem of DKI is that these DWI images are usually acquired with an echo planar imaging (EPI) sequence and also require high b-values, resulting in a low SNR of acquired diffusion weighted images. Distortion correction so is an important step in DKI. However, in

order to become a routine procedure, DKI still needs to be improved in terms of robustness, reliability, and reproducibility. The lack of standard procedures for post-processing, especially for noise correction, might become a significant issue for the use of DKI in clinical routine.
The aim of this work is the description of the theory of Diffusion Kurtosis Imaging (DKI), the MRI protocol that we used for DKI acquisitions at 1.5T clinical scanner. Some examples of DKI maps obtained by us are shown in Fig.1.

Acknowledgments
Studies presented in this work are supported by PON Smart Cities PON04a2C “SMART HEALTH – CLUSTER OSDH – SMART FSE - STAYWELL”, Scientific supervisor: Dr. P.Corso.

[1] Jensen JH, Helpern JA, Ramani A, Lu H, and Kaczynski K. *Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging*. Magn Reson Med., (53):1432–40, 2005.

[2] Collura G., Marrale M., Toschi N., Gagliardo C., Midiri M., Brai M. *SVILUPPO DI UN SOFTWARE PER L'ANALISI DI IMMAGINI DI DIFFUSION KURTOSIS IMAGING*. Atti Convegno AIRP-2013 Palermo.

Resting state fMRI as a tool to investigate brain functional connectivity

M.Marrale[1], S.Nici[1], G.Collura[1], S.Gallo[1], A.Longo[1], S.Panzeca[1], T.Piccoli[2], C.Gagliardo[3], M.Brai[1]

[1]*Dipartimento di Fisica e Chimica, Università degli Studi di Palermo*
[2]*Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Università degli Studi di Palermo*
[3]*Dipartimento di Biopatologia e Biotecnologie Mediche e Forensi, Università degli Studi di Palermo*

email: maurizio.marrale@unipa.it

Functional magnetic resonance imaging (fMRI) is a safe, noninvasive and repeatable MRI technique, used to estimate and localize neuronal activation in the gray matter of the brain, with high spatial (millimeters) and temporal resolution (in the order of seconds).
This technique is based on the principle of neurovascular coupling, which implies that an increase in neuronal activity will cause a rise in blood oxygen consumption and a concomitant rise in local cerebral perfusion. This increased blood flow to the activated region alters the ratio between the deoxyhemoglobin and oxyhemoglobin. Deoxyhemoglobin is paramagnetic and, therefore, influences the signal registered in the MRI. This is the so called *blood oxygenation level dependent* (BOLD). The BOLD response reflects the degree of oxygenation of the blood in capillaries supplying brain tissue, and its neurophysiological basis lies in changes to blood flow and level of oxygenation in response to neuronal activity. That changes in the BOLD signal indirectly reflect neuronal activity.
During fMRI experiments, the brain of the subjects is scanned repeatedly, usually using the fast imaging technique of echo planar imaging (EPI).
In the fMRI experiment the subject is required to carry out some task consisting of periods of activity and periods of rest or rest quietly in the scanner without any task (resting-state fMRI).
Resting state fMRI focuses on spontaneous low frequency fluctuations (< 0.1 Hz) in the BOLD signal; investigates synchronous activations between regions that are spatially distinct (functional connectivity), occurring in the absence of a task or stimulus [1].
Functional connectivity is essentially a statistical concept. Unlike anatomical connectivity, which describes physical pathways of information exchange (and which can be obtained by means of MR tractography), functional connectivity describes the correlation of spatially remote areas in the temporal domain. Dependence is calculated between all elements of a system, whether these elements are connected by direct or indirect structural links. Functional connectivity relies primarily on traditional fMRI techniques, but takes advantage of low BOLD frequency fluctuations to examine intrinsic activity in the brain. Functional networks generated using this method have been termed 'resting-state networks' (RSNs).
The target of this work is to investigate the connectivity variation during time, after a particular external stimulus or after drugs administration.
The method used to explore changes or modulations of the functional architecture of brain networks is the group PICA analysis (probabilistic independent component analysis), a statistical technique that separates a set of signals into independent uncorrelated components. The result is a set of ICs (Independent Components) some of which are clearly related to neuronal networks and others linked to physiological processes or artifacts.

References

[1] Lee et al., *Resting-State fMRI: A Review of Methods and Clinical Applications,* AJNR Am J Neuroradiol (2012).

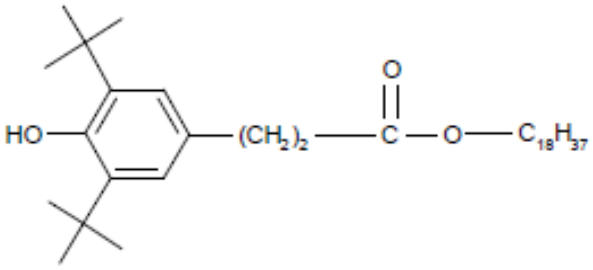
Neutron Electron Spin Resonance dosimetry with phenol compounds

M.Marrale[1], M.Brai[1], S.Gallo[1,2], A.Longo[1], S.Panzeca[1], A.Buttafava[3], D.Dondi[3], A.Zeffiro[3]

[1]*Dipartimento di Fisica, Viale delle Scienze, Ed.18, I-90128 Palermo and Gruppo V, INFN, Sez. di Catania, Italy.*
[2]*PH3DRA Laboratory, Dipartimento di Fisica e Astronomia, Università di Catania, Italy.*
[3]*Università di Pavia e INFN, Sezione di Pavia, Pavia, Italia*

email: maurizio.marrale@unipa.it

In the last years, the development of Neutron Capture Therapy (NCT) [1] for cancer treatments has stimulated the research for beam characterization in order to optimize the therapy procedures. The success of radiation therapy in treating cancer depends on the delivery of lethal radiation dose to the tumour, with as little as possible harm to surrounding tissues.
Several research laboratories have shown an increasing interest aimed at extending the applicability of Electron Spin Resonance (ESR) dosimetry to radiotherapy with different types of radiation beams. In particular, ESR spectrometry provides absorbed dose measurements through the detection of the stable free radicals produced by ionizing radiations. The ESR dosimetric method has many advantages such as simple and rapid dose evaluation, the readout procedure is non-destructive, linear response of many organic and inorganic compounds [2]. ESR detectors show a behavior that suggest possible applications for various kinds of beams used for radiation therapy. Nowadays, the most widely used organic compound as a dosimeter is the alanine [3]. However, many researches are in progress with the aim at improving sensitivity of ESR dosimetry for doses much smaller than 1 Gy.
These works are focused on the investigations of new materials or new mixtures of organic and/or inorganic compounds with suitable features, such as high efficiency of radiation-matter energy transfer and radical stability at room temperature.
Our research group has started an investigation of the ESR response of some phenols compounds for possible dosimetric applications. The aim of this work is to investigate the dosimetric features of some phenols for applications in ESR dosimetry. Phenols are compounds possessing a benzene ring attached to a OH group. After irradiation the final product is a stable phenoxy radical. The stability of such radical can be improved by adding other alkyl chains which can be attached to the benzene ring.
In particular, the phenol *octadecyl-3-(3,5-di-tert.butyl-4-hydroxyphenyl)-propionate* (IRGANOX 1076® phenols) gave interesting results [4]. Moreover, its high molecular weight, the low volatility and the compatibility with the dosimeter binding material (wax) are advantages with respect to lower molecular weight phenols.



In this work we report the ESR investigation of on IRGANOX® 1076 phenols with and without Gd_2O_3 (5% by weight) exposed to neutron beam. The choice of Gd as the additive nucleus has been made because we are interested in applications for mixed field (neutrons/photons) Gd-ESR dosimetry has an high neutron capture cross section and, furthermore, the high Linear Energy Transfer secondary particles release their energy entirely in the dosimeter. The low content of gadolinium guarantees a good tradeoff between the sensitivity to thermal neutrons and the reduction of tissue equivalence. The dosimetric features of these ESR dosimeters (dependence on microwave power and modulation amplitude, their

response after gamma and neutron irradiations, the detection limits for both beam typologies, signal stability after irradiation) have been investigated and the results are reported.

[1] C. Salt, et al., BORON AND GADOLINIUM NEUTRON CAPTURE THERAPY, Russian chemical bulletin (2004).

[2] Baffa O., Kinoshita A., CLINICAL APPLICATIONS OF ALANINE/ELECTRON SPIN RESONANCE DOSIMETRY. Rad. and env. Bioph. (2014) – doi: 10.1007/s00411-013-0509-2.

[3] M. Marrale, M. Brai, A. Longo, S. Panzeca, et al., EPR/ALANINE PELLETS WITH LOW Gd CONTENT FOR NEUTRON DOSIMETRY. Radiation Protection Dosimetry (2013) - doi: 10.1093/rpd/nct290.

[4] M. Marrale, A. Longo, S. Panzeca, S. Gallo, F. Principato, E. Tomarchio, A. Parlato, A. Buttafava, D. Dondi, A.Zeffiro. ESR RESPONSE OF PHENOL COMPOUNDS FOR DOSIMETRY OF GAMMA PHOTON BEAMS. NIMB (2014). doi: 10.1016/j.nimb.2014.08.015.

Characterization of Fricke gel dosimeters exposed to clinical photons beams and of MRI dosimetrical applications

M. Marrale[1], M. Brai[1], C. Gagliardo[2], S. Gallo[1,3,] A. Longo[1], L. Tranchina[4], G. Collura[1], G. Iacoviello[5], S. Panzeca[1], F. d'Errico[6]

[1)]*Dip. di Fisica e Chimica , Università di Palermo, and INFN, Sez. di Catania, Italy*
[2)]*Dip. di Biopatologia e Biotecnologie Mediche e Forensi , Università di Palermo, Italy*
[3)]*Laboratorio PH3DRA, Dipartimento di Fisica e Astronomia, Università di Catania, Italy*
[4)]*Laboratorio UNINETLAB, Viale delle Scienze, Edificio 18, 90128 Palermo, Italy*
[5)] *U.O.C. di Radioterapia A.R.N.A.S. CIVICO, Palermo, Italy*
[6)]*Dip. di Ingegneria Civile e Industriale, Università di Pisa, Italy and Yale University School of Medicine, New Haven*

email: salvatore.gallo05@unipa.it

The Fricke Xylenol Gel (FXG) dosimetric system is based on the radiation induced oxidation of ferrous (Fe^{2+}) to ferric (Fe^{3+}) ions [1].
The application of Fricke type gels for ionizing radiation dosimetry is continuously increasing worldwide due to their many favorable properties. However, one of their shortcomings is that ferrous and ferric ions diffuse in the gel matrix. To maintain the spatial integrity of the dose distribution, Fricke gels must be analyzed within a few hours of their irradiation, so that ferric ions remain close to their point of production. Thus, the spatial integrity of the dose distribution in the Fricke gel is maintained.
The gel matrix also contributes to the oxidation of ferrous ions during irradiation, increasing the chemical yield of ferric ions in aqueous solution and increasing the sensitivity of the dosimeter.
The oxidation of ferrous ions also causes a reduction of the longitudinal nuclear magnetic relaxation time T_1 which can be measured by means of nuclear magnetic resonance (NMR) relaxometry and magnetic resonance imaging (MRI) [2].
In this work the results of our analyses of FXG dosimeters are reported. We performed NMR relaxometry investigations which allow for direct measurements of the relaxation times in samples exposed to clinical photon beams. The main dosimetric features of the NMR signal were investigated. The gels were irradiated in the clinical dose range between 0 and 20 Gy. In order to assess the photon sensitivity we analyzed the dependence of NMR relaxation time on radiation dose with varying ferrous ammonium sulfate content (from 0.5 mM to 5 mM) inside FXGs (Fig.1). Furthermore, signal stability was followed for several days after irradiation [3].

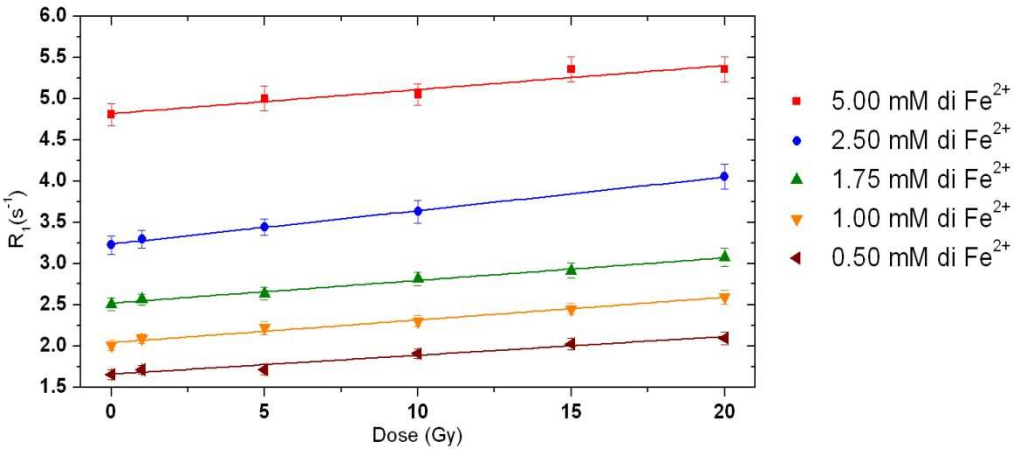


Fig.1 - FXG dose response curve for various concentrations of ferrous sulphate.

These measurements were also aided by acquisitions of magnetic resonance imaging (MRI) which can permit 3D dose mapping [4]. In order to maximize the MRI response a systematic study was performed to

optimize acquisition sequences and parameters. In particular, we analyzed for inversion recovery sequences the dependence of MRI signal on the repetition time T_R and on the inversion time T_I [3].

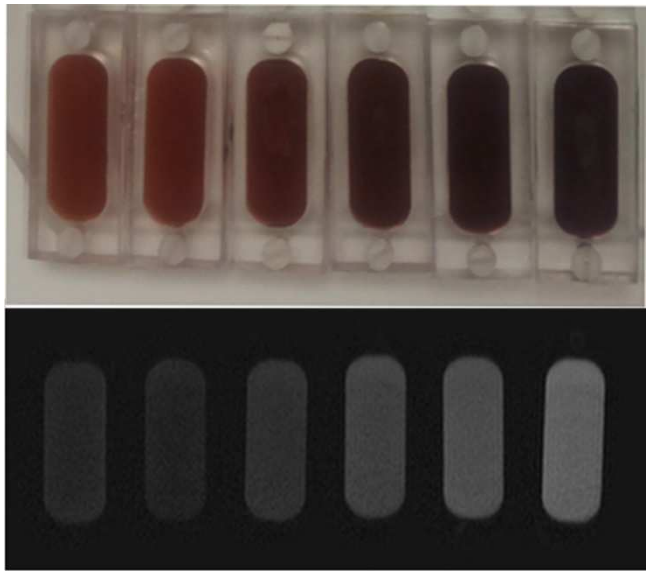


Fig.2 – (**above**) Picture of FXG irradiated in the clinical range (1.75 mM); (**below**) MRI image obtained with IR sequence (T_R=400ms and T_I=2500ms). Dose increases from left to right.

The dose calibration curves are reported and discussed from the point of view of the dosimeter use in clinical radiotherapy (Fig.2). This work has highlighted that the optimization of additives inside gel matrix is fundamental for optimizing photon sensitivity of these detectors. We can conclude that FXG dosimeters with optimal ferrous ammonium sulfate content can be regarded as a valuable dosimetric tool to achieve fast information on spatial dose distribution.

[1] M. DAY, G. STEIN, Chemical effects of ionizing radiation in some gels. Nature (1990) DOI:10.1038/166146a0.

[2] M. MARRALE, M. BRAI, A. LONGO, S. GALLO, E. TOMARCHIO, ET AL., NMR relaxometry measurements of Fricke gel dosimeters exposed to neutrons. Rad. Ph. and Ch. (2014) DOI: 10.1016/j.radphyschem.2014.05.049.

[3] M. MARRALE, M. BRAI, C. GAGLIARDO, S. GALLO, A. LONGO, L. TRANCHINA, B. ABBATE, G. COLLURA, ET AL., Correlation between ferrous ammonium sulfate concentration, sensitivity and stability of Fricke gel dosimeters exposed to clinical X-ray beams. NIM B (2014) DOI: 10.1016/j.nimb.2014.05.012.

[4] A. GALANTE, ET AL., MRI study of radiation effect on Fricke gel solutions. Rad. Meas. (2008) DOI: 10.1016/j.radmeas.2007.12.011.

Development of Gold/Iron Oxide Hybrid Nanoparticles for Advanced Radiotherapy

Filippo Benetti[a], Devid Maniglio[a], Giorgio Speranza[b], Claudio Migliaresi[a]
[a]*Department of Industrial Engineering and Biotech Center, University of Trento, Italy*
[b]*Fondazione Bruno Kessler, Trento, Italy*

The key challenge in radiotherapy regards the achievement of an effective cancer treatment minimizing the dose released to the healthy tissues. In fact, the delivery of dose to healthy organs could provoke severe adverse events even long time after the treatment. A strategy to reduce the overall dose to the patient concerns the employment of radiosensitizing drug able to enhance the cytotoxic effects of radiations in the cancer region. In the last decades, several drugs have been tested for this purpose but, till now, the main limitation that hinders the wide diffusion of radiosensitizing drugs involves the difficulty to monitor the biodistribution of drugs after administration. Gold/iron oxide hybrid nanoparticles (H-NPs) may overcome this obstacle thanks to their biphasic structure. The radiosensitizing activity of H-NPs is ensured by the gold part as gold is a high atomic number element with a large cross-section for gamma-ray scattering. Moreover, the iron oxide part allows the imaging of NPs by Magnetic Resonance Imaging thanks to the magnetic properties of magnetite.

In this work, H-NPs have been synthetized and their feasibility for radiotherapy has been tested in vitro. The synthesis of H-NPs involved the thermal decomposition of gold and iron precursors in the organic phase. During the process, gold seeds are firstly created providing nucleation sites for the iron oxide growth. At the end, hydrophobic H-NPs with an average diameter of 25 nm are obtained, as shown by TEM and SAED investigations (Fig. 1). The H-NPs have been transferred in the aqueous phase using polysorbate, a non-toxic surfactant, which provides a hydrophilic behavior to H-NPs. The chemical composition of the H-NPs have been characterized using an ion-coupled-plasma optical emission spectrometer to evaluate the mass ratio between gold and iron.

In vitro tests were performed to assess the cytotoxicity of H-NPs using osteosarcoma MG63 cells. In particular, the membrane integrity after 48h of incubation with nanoparticles was investigated revealing no significant difference between the H-NPs-exposed samples and the non-exposed ones. Furthermore, the effects over viability and proliferation of H-NPs were studied along 9 days and the results did not show any significant evidence of cytotoxicity related to H-NPs.

The next stages of this work will include the study of the magnetic properties and the radiotherapy enhancement effects of H-NPs in vitro.

The results about morphology, stability in physiological conditions and cytotoxicity are extremely encouraging and H-NPs promise to provide effective tool for advanced radiotherapy.

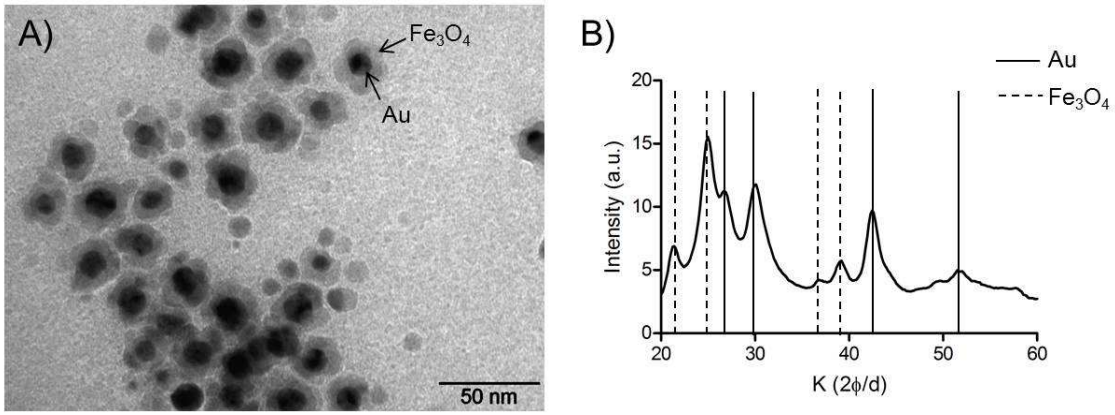


Fig. 1 Transmission Electron Microscopy (A) and Selected Area Electron Diffraction (B) analysis of H-NPs.

An Improved Method for Hepato-Renal Ratio Assessment: a Feasibility Study

Sboarina A[1], Perandini S[2], Fenzi A[1]
[1]*Department of Surgery, University of Verona*
[2]*Department of Radiology, AOUI Verona*

Purpose

Hepato-Renal Ratio (HRR) is a method for the quantitative assessment of liver steatosis based on the processing of ultrasound images.
Its reliability has been validated in literature through biopsy and ^{1}H magnetic resonance spectroscopy.
This paper describes a new method for ROI segmentation and HRR assessment, designed to minimize both inter-observer and inter-scan variability.

Materials and Methods

98 images of 32 patients were analyzed (for 23 patients multiple scans were performed).
HRR is defined as the ratio of the gray scale mean value of the pixels within two given ROIs of the liver and kidney.
Our method comprises three steps.
In the first, the operator selects two “freehand” areas: one for the liver parenchyma and one for the renal cortex. The two ROIs should be as large as possible and positioned approximately at the same depth.
In the second step, the two ROIs are "normalized" (Fig.1) as follows

- the image is divided into sets of pixels which have the same distance from the probe(cluster)
- for every cluster, two groups of pixels were identified, belonging to the liver ROI and kidney ROI respectively. The outermost pixels belonging to the largest group were deleted providing two groups with the same number of pixels, as closely as possible.

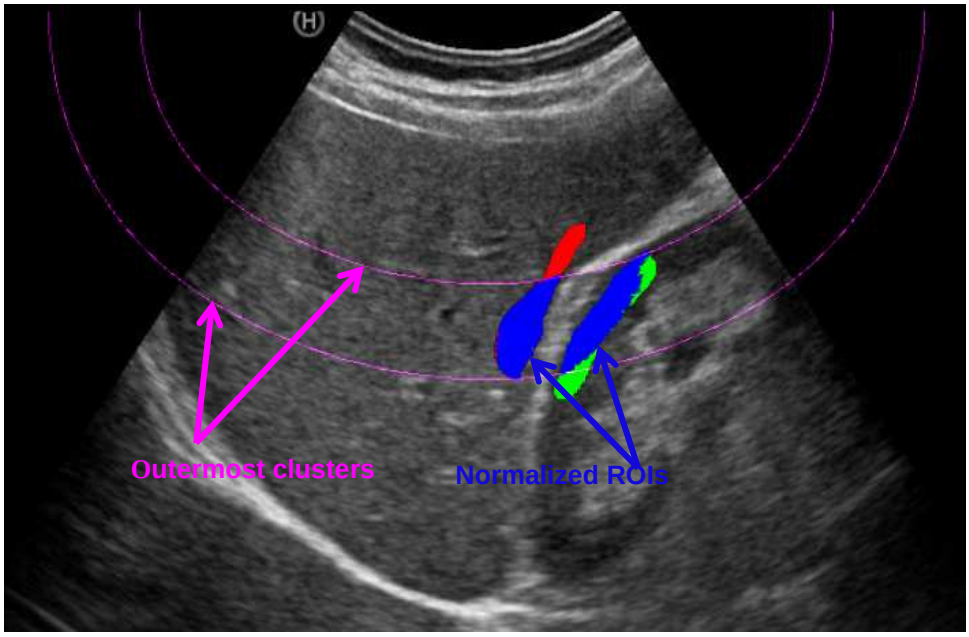


Fig.1 Normalization of freehand ROIs

Finally, the software smoothes out the normalized histograms of the normalized ROIs. HRR is assessed on the basis of these smoothed histograms.
We call this procedure the Irregular method (IM).
To assess inter-observer variability, ROI segmentation was repeated by a second operator using ellipsoidal/circular ROIs. The two ROIs were as large as possible and positioned approximately at the same depth. The ROIs were normalized. HRR was calculated based on the smoothed normalized histograms of the two normalized ROIs. We call this procedure the Ellipse method (EM).

The effectiveness of IM was tested by comparison with a method analogous to the one presented in[1].In particular, two square ROIs were selected: one for the hepatic parenchyma, about 1cm^2, and one for the renal cortex, about 0.25cm^2; the centers of the two ROIs needed to be at the same y-coordinate. HRR was calculated based on the normalized histograms of the two ROIs. We call this procedure the Square method(SM).
For each method, the ROIs should be as homogeneous as possible and positioned as near as possible to the image center. In this study only scans with all the normalized ROIs above 211 pixels were taken into account.
In order to evaluate the inter-scan variability of a specific method, the maximum absolute HRR difference between the scans for each patient (MIS) was calculated.
The effectiveness of our method, the inter-operator and inter-scan variability were assessed by Wilcoxon signed-rank test.

Results

In the experiment we encountered numerous difficulties using SM and EM, often obliging the operator to repeat the ROI segmentation. The freehand selection method facilitated this task, enabling larger areas to be analyzed (e.g. the mean pixel numbers were: 718 for liver Square ROIs and 1324 for normalized freehand ROIs).
The differences between the HRRs obtained by our and the reference method are not statistically significant (IM vs.SM: P-Value=0.52 and EM vs. SM: P-Value=0.14).
Similar results are obtained in the assessment of reproducibility (EM vs. IM: P-Value=0.46).
In the inter-scan analysis, IM produced smaller MISs than SM (respectively: 0.19+-0.14 and 0.37+-0.23, P-Value<0.001). This is probably due to the large ROIs provided by IM. It is reasonable to assume that the larger the ROIs, the better the representation of the pathology.

Conclusions

The method presented is more user-friendly than the reference method, speeding up the procedure. It gave low inter-scan variability. Preliminary results seem to confirm its reproducibility and a diagnostic efficacy comparable to the reference method. Verification of its true effectiveness (and reproducibility) requires further investigation by correlation studies using histological findings.

Reference

[1] Mancini M et al.(2009) Sonographic hepatic-renal ratio as indicator of hepatic steatosis: comparison with ^{1}H magnetic resonance spectroscopy. Metabolism 58: 1724-30

Intraoperative microelectrode recording does not increase hemorrhagic complications in deep brain stimulation surgery: data from a large series of patients.

A. Romagnolo, M.G. Rizzone, M. Zibetti, A. Merola, F. Dematteis, S. Angrisano, C.A. Artusi, M. Sarchioto, A. Bernardini, E. Crobeddu, R. Fornaro, L. Lopiano, M. Lanotte

Department of Neuroscience, University of Turin

Objective

The aim of our retrospective study was to assess the incidence of hemorrhagic complications in a large series of patients who underwent deep brain stimulation (DBS) surgery.

Background

DBS is an effective option for the treatment of movement disorders refractory to medication, and during the last two decades it has became a widespread technique of proven efficacy. Despite its demonstrated safety, rare adverse events (AE) could result in potentially disabling outcomes, leading to further neurological impairment. Among them, hemorrhagic complications are the most dreaded and health-threatening. Age and hypertension were reported to be the most significant patient-related features associated to an increased risk of bleeding, while intraoperative microelectrode recording (MER) and number of MER penetration represent the most important risk factors resulting from the surgical technique [1,2]. Finally, the coexistence of hypertension and MER was associated to an additional rise of bleeding incidence [3].

Methods

Data of all patients submitted to DBS at our Center between 1998 and 2013 were collected. MRI and stereotactic CT scans were performed in all patients prior to surgery for the procedure planning. To minimize hemorrhagic complications, a trajectory avoiding sulci and ventricles was plotted. During all procedures a single-track MER approach to the target was performed, followed by an intraoperative microelectrode stimulation (MS) to evaluate both beneficial and side effects. When the MER did not show typical neuronal activity and/or MS highlighted low-threshold sustained side effects, a second or even third track was sequentially performed. A DBS chronic stimulation electrode was than placed along the best trajectory and a monopolar cathodic stimulation was finally evaluated. To rule out surgical complications, patients underwent an immediate postoperative CT scan and an MRI 7 days after surgery. A single primary surgeon executed all procedures.

Results

All procedures consisted of a single-session bilateral implantation; 221 patients received a total of 442 definitive electrodes. 216 subjects (130 males, 86 females) were affected by Parkinson's Disease , 3 (all males) by Essential Tremor, 2 by Dystonia (1m, 1f). Mean age at surgery was 60.7±6.9 years (males 60.8±6.9; females 60.5±6.9). A total of 590 MER tracks were performed (1.33 MER per lead). 42 (19%) patients suffered from hypertension. Neither intraventricular nor intracerebral hemorrage occurred during both intraoperative and postoperative period

Conclusions

Hemorrhage is probably the most serious AE in functional neurosurgery, reported to have an overall incidence of 5% [1]. In our large series of patients we did not observe hemorrhagic complications, even though the population characteristics – age and hypertension percentage - were similar or even higher to those reported in literature [2,3]. Moreover, we routinely performed MER, considered a significant bleeding risk factor [1], especially if associated with hypertension [3]. These consideration rise the question whether other factors could contribute to the increase of HC risk; according to our results, a careful patient selection, a thorough trajectory planning, a single- rather than a multiple-track MER performing and the application of standardized procedures of an experienced team could prevent high rate of hemorrhagic events.

References

1) Zrinzo L, et al. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J Neurosurg 2012;116:84-94.
2) Xiaowu H, et al. Risks of intracranial hemorrhage in patients with Parkinson's disease receiving deep brain stimulation and ablation. Parkinsonism Relat Disord 2010;16:96–100.
3) Gorgulho A, et al. Incidence of hemorrhage associated with electrophysiological studies performed using macroelectrodes and microelectrodes in functional neurosurgery. J Neurosurg 2005;102:888-96.

Novel Applications of Cerenkov and Radioluminescence Imaging

F. Boschi[1], AE. Spinelli[2], A. Fenzi[3].
(1) Department of Computer Science, University of Verona.
(2) Medical Physics Department and Center for Experimental Imaging, San Raffaele Scientific Institute, Milan.
(3) Department of Surgery, University of Verona.

Purpose: There has been a rapid and growing interest in using small animal optical imaging systems to image *in vitro* and *in vivo* several radiopharmaceuticals[1]. The purpose of this contribution attention is to present the work by our group on Cerenkov luminescence imaging (CLI) and radioluminescece imaging (RLI).

Methods and materials: CLI is based on the detection of Cerenkov radiation (CR) due to the beta particles travelling in the tissues with energy greater than the Cerenkov threshold. For a beta particle in water the energy threshold such that $\beta > 1/n$ is only 260 keV and, thus, most of the isotopes used in nuclear medicine satisfy this condition.
In order to investigate the possibility of detecting in vivo CR we used a small animal optical imaging system composed by a back-thinned, back-illuminated CCD camera, several filters and lens. The instrument was used in bioluminescence mode and, thus, without using any excitation lamp.

Results: We performed a comparison between micro-PET and CLI using an experimental model of mammary carcinoma (BB1). The tumours were obtained by subcutaneous injection of BB1 cells, which are epithelial cells, from spontaneous mammary carcinomas and we found a good agreement between PET and CLI[2].
We also investigated a multispectral 3D approach called multi spectral Cerenkov luminescence tomography[3] (msCLT). The msCLT approach has been tested by using *ex vivo* tissue phantom and by injecting nude mice with [^{32}P]ATP. The results obtained with phantom data showed that for a line source placed 6 mm below the surface the spatial resolution is 1.5 mm, this is an encouraging result considering that we are dealing with an optical imaging method.
With regard to RLI we focused our attention on investigating *in vitro* and *in vivo* the more weaker luminescence signals induced by ^{99m}Tc. In particular *in vivo* imaging was performed by using nude mice models in order to allow the detection of a smaller number of optical photons.
We showed that *ex vivo* and *in vivo* results further confirms the findings obtained by imaging [^{99m}Tc]MDP in a water solution[4].

Conclusion: In this contribution we presented an overview of the most recent results on the use of optical techniques to image radiotracers for small animal pre-clinical imaging. This novel research area has rapidly gain attention of several research groups and this provided a significant boost in the development of this field. Optical imaging offers the advantages of studying more animals at once and it is possible to acquire whole body planar images of small animals within few minutes.
We also showed that dynamic CLI can be easily performed in order to study the whole body biodistribution of the radiopharmaceuticals.

References:

[1] A. E. Spinelli, *et al* Optical imaging using radioisotopes a novel multimodal approach to molecular imaging, Q. Jour. Nuc. Med. (2012), 56, 279-289.
[2] F. Boschi, *et al* In vivo (18)F-FDG tumour uptake measurements in small animals using Cerenkov radiation. Eur. J. Nucl. Med. 2011; 38(1): 120–127.
[3] A.E. Spinelli, *et al* Multispectral Cerenkov luminescence tomography for small animal optical imaging. Opt. Express (2011), 19, 12605–12618.
[4] A.E. Spinelli, *et al* Optical Imaging of Tc-99m based tracers, in vitro and in vivo results. J. Biomed. Opt. (2011), 16(11).

Damaging effects due to neutrons produced by a VARIAN CLINAC 2100C on pacemakers and defibrillators

Anna Baratto Roldan[1], E. Sergi[1], L. Toscano[1], F. Bragato[1,2], M. Usikalu[1,2], G.Giannini[1,3], M. Severgnini[4], V. Milan[5], M. Zecchin[6], G.Morea[6], L. Salvatore[6], A. Zorzin Fantasia[6], G. Sinagra[6]

(1) Physics Department, University of Trieste, Italy;

(2) Department of Physics Covenant University, Ota, Nigeria and TRIL ICTP, Trieste, Italy;

(3) INFN, section of Trieste, Italy;

(4) SC di Fisica Sanitaria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Trieste, Italy;

(5) Radiotherapy Department "Ospedali Riuniti" and University, Trieste, Italy;

(6) Cardiovascular Department, "Ospedali Riuniti" and University, Trieste, Italy;

Introduction: There is evidence[1] that high energy radiotherapy may damage Cardiac Implantable Electronic Devices (CIEDs) placed outside the field of view of direct beam γ irradiation and well away from it. Fast neutrons produced by linear accelerators during high energy ($E_{threshold}$>7MeV) radiation treatments are likely to be the cause of these malfunctioning.

Purposes: The aim of this work is to assess the risk and causes of failure of CIEDs in patients undergoing high energy radiation treatments for prostate cancer.

Materials and Methods: Four prostate-like radiotherapy irradiations were performed with a 15 MV VARIAN CLINAC 2100C linear accelerator, to evaluate thorax neutron dose and the behaviour of a sample of CIEDs.

Three types of dosimeters were used, with two different anthropomorphic phantoms and different models of CIEDs, both Pacemakers (PMs) and Implantable Cardiac Defibrillators (ICDs), previously explanted for different reasons except malfunctions.

First of all both fast and thermal neutron doses were evaluated placing bubble dosimeters inside the phantoms. The first one, called Jimmy, was built for neutron dosimetry by the Turin INFN section in collaboration with the Ispra Joint Research Center. It represents the upper body of an average-male and it has 16 cavities in correspondence to critical organs. The second one, called Ryan, was designed and assembled in the Physics Department of the University of Trieste especially to perform these measurements. It represents the whole body of an average-man and has 42 cavities, some of them in correspondence to critical organs. The larger amount of thermalizing mass of the second phantom appeared to be better for evaluating CIEDs malfunctioning caused by thermal neutrons.

Secondly a total of 59 devices, 34 PMs and 25 ICDs were analyzed and then irradiated. No malfunctions were detected before the treatment, simulating a course of typical radiotherapy (70 Gy) for prostate cancer, according to existing protocols. During the irradiation the total thermal neutron dose was evaluated with CR-39 track detectors. Photon dose to the devices was measured to be lower than 1Gy, as required by the manufacturers[2], and electromagnetic field was measured to be negligible.

The four standard prostate treatments were carried out as follows: two treatments to the Jimmy

phantom, one of which with all collimators closed and two to the Ryan phantom, one of which with a fast neutron shield.

Results: As a consequence of the treatments, a malfunction (memory reset, generator failure, magnet deactivation, VVI back-up) was found in 18 (52%) ICDs and 6 (18%) PMs. The mean measured total neutron dose in the CIED region was 18.9±3.8 mSv, while the dose measured with shield was 7.7±1.5 mSv.

Evidence of neutron capture reactions inside the CIEDs emerged by the study of the weak activation signal in the devices, with a High Purity Germanium Detector for γ spectroscopy. Doses from activation were negligible from the point of view of radioprotection. The shield shows to be effective in both reducing neutron dose and neutron capture induced activity.

Conclusions: High energy radiotherapy treatments may determine malfunctioning of CIEDs due to the production of neutrons and following capture reactions. Failures are more frequent in ICDs than in PMs.

References:

[1] J. Elders et al. *High incidence of implantable cardioverter defibrillator malfunctions during radiation therapy: neutrons as a probable cause of soft errors*. Europace 2013; 15:60-65.

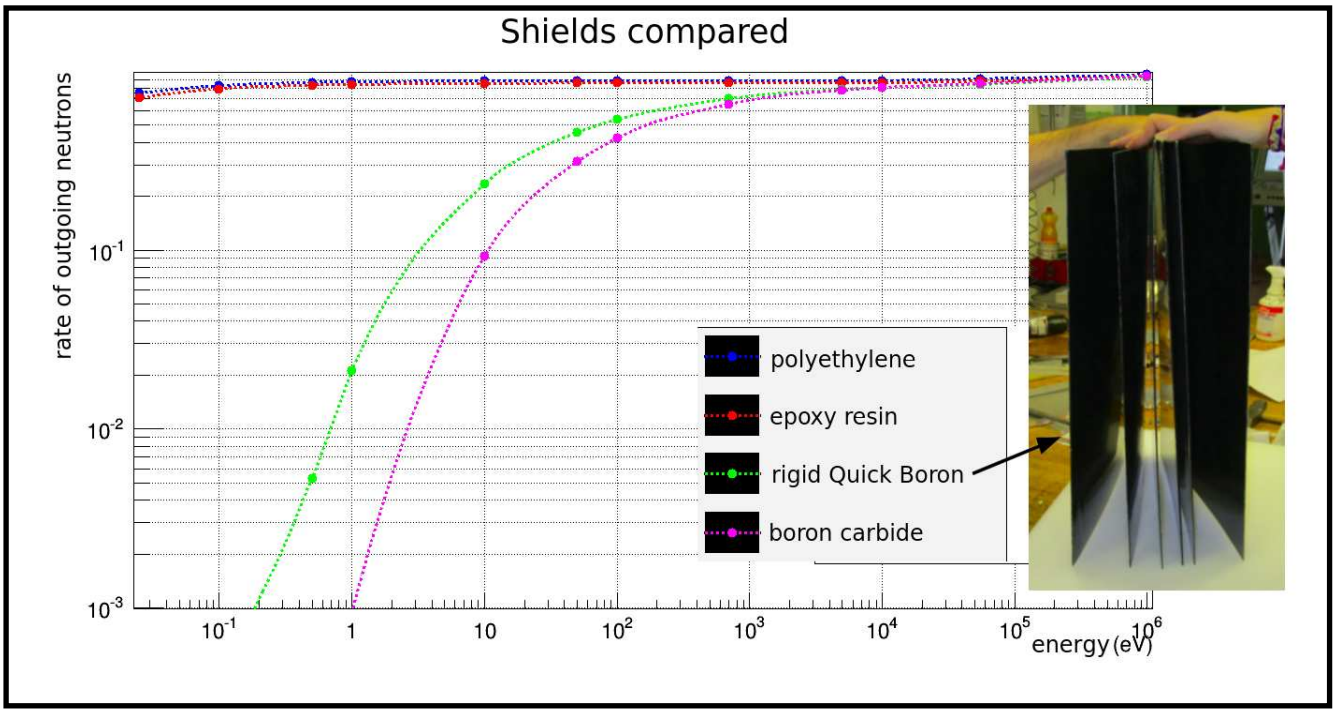
[2] Colleen J. Fox. *Radiation Treatment Planning and Therapy of Patients with Implanted Cardiac Devices.* 2013.

“Quick Boron”: a new boron carbide based shielding material for neutrons

Licia Toscano[1], F. Bragato[1,2], E. Sergi[1], M. Usikalu[1,3], A. Baratto R.[1], G. Giannini[1,2], M. Severgnini[4]
(1) Physics Department, University of Trieste, Italy;
(2) INFN, section of Trieste, Italy;
(3) Department of Physics, Covenant University, Ota, Nigeria and TRIL ICTP, Trieste, Italy;
(4) SC di Fisica Sanitaria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Trieste, Italy

Introduction: New frontiers of medicine take into account the use of different kinds of radiations, including neutron beams for Boron Neutron Capture Therapy (BNCT). It is well known that high-energy radiotherapy beams contain contaminant neutrons that are able to damage electronic devices. This scenario highlights the necessity to have specific and well-working neutron shielding. A new chemical composition was studied in order to improve shields already available on the market.

Purpose: The aim of this work is to build, simulate and test a neutron shield. It can be used whenever there is a neutron field that can both damage electronic devices and give an unwanted dose to individuals.



Materials and Methods: Neutrons interact with matter in a different way with respect to charged particles and their behaviour is strongly dependent on the energy. One way to shield neutrons is to employ their capture reactions, which have an inverse square root energy dependence. For this reason it is not difficult to shield thermal neutrons (E<0.1 eV), while fast (E>10 keV) and epithermal (in between energy region) neutrons spectra have to be degraded to the thermal one with an heterogeneous shield. It is important to shield fast neutrons because their contribution to the effective dose is huge compared to the thermal one. The conversion fluence-to-dose factor is indeed non-linear in energy and presents a peak for E>1 MeV. In designing a shield, it is also important not to produce radioactive nuclei and γ-dose as reaction products and to use safe and cheap materials.

Many shields for thermal neutrons -e.g. Flex Boron[1]- contain boron, which has a high neutron capture cross section. At the Physics Department of the University of Trieste, it has been designed, simulated and built Quick Boron (QB)[2], a shield containing boron carbide (B_4C). It is available in a carbon fiber based rigid version (50% B_4C mass percentage) and a flexible one (57% B_4C mass percentage). The first one was tested both with simulations and experimental measurements.

Simulations were performed with Geant4, a toolkit developed by an international collaboration including CERN. The QB shield was compared to polyethylene, epoxy resin and pure boron carbide shields. The QB attenuation law was also studied. Moreover a heterogeneous shield composed by polyethylene and QB was studied for non-thermal neutrons.

Experimental verifications were performed using neutrons from a medical linear accelerator VARIAN CLINAC 2100C[3]. Neutron doses beyond gradually increasing QB thickness and the heterogeneous shield were evaluated using CR-39 track detectors and bubble dosimeters.

Results: Simulations highlight the B_4C effectiveness as a shielding material. QB indeed seems to be a better solution compared with other materials. A neutron attenuation law well fits simulated data for thermal energies. Half Value Length (HVL) obtained is ≅7.5 times shorter than for Flex Boron.

Neutrons flux attenuation factors at 10 eV are ≅0.24 for the homogeneous and ≅0.98 for the heterogeneous shield.

Experimental thermal and fast neutrons doses decrease by about 36% and 49% respectively using the heterogeneous shield. Data taken with various QB thickness confirmed its good shielding property.

Conclusions: Quick Boron shield is a good choice in all studied situations. Furthermore it's cheap, transportable, safe, it presents some features even better than other commercial solutions and appears suitable for medical environments.

References:

[1] Thermo Electron Corporation, *Catalogue 26, Shielding solutions for the 21st century*: 7

[2] Quick Batten, Trieste, info@quickbatten.com

[3] Howell, Rebecca M., et al. *Secondary neutron spectra from modern Varian, Siemens, and Elekta linacs with multileaf collimators*, Medical physics 36.9 (2009): 4027-4038.

Ryan: a new anthropomorphic phantom for neutron dosimetry

Elisabetta Sergi[1], L. Toscano[1], F. Bragato[1,2], A. Baratto R.[1], M. Usikalu[1,3], G.Giannini[1,2], M. Severgnini[4]

(1) Physics Department, University of Trieste, Italy;

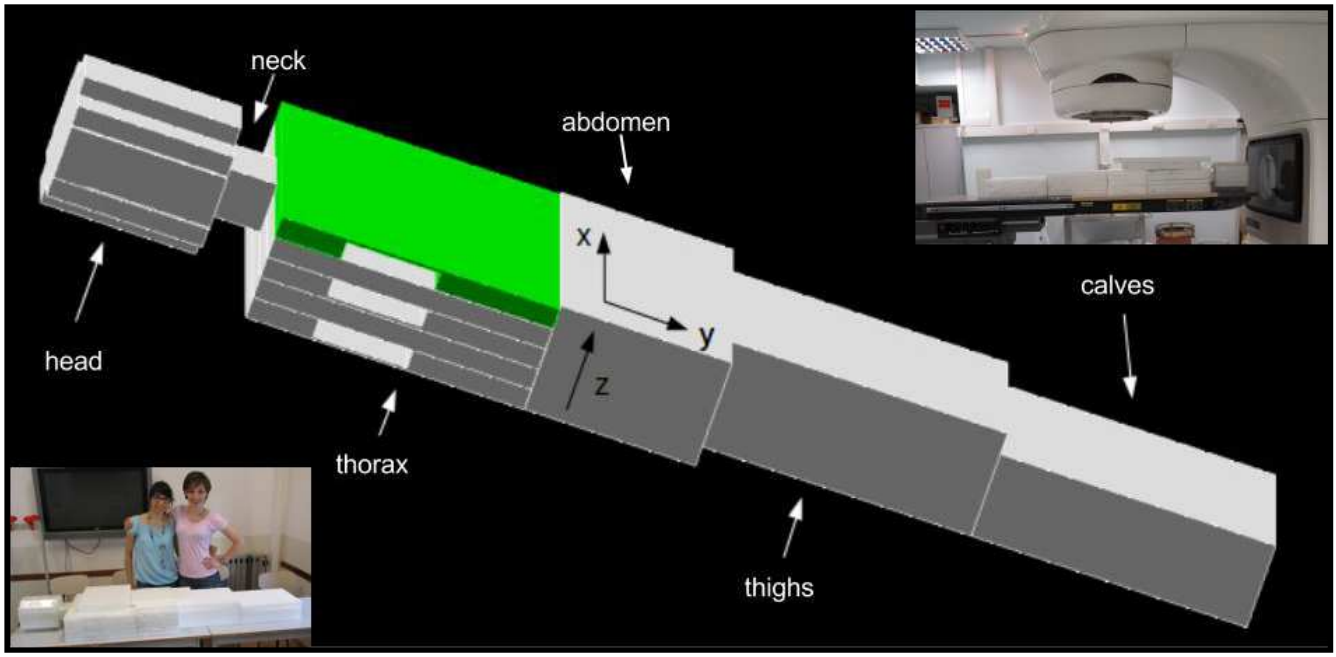
(2) INFN, section of Trieste, Italy;

(3) Department of Physics Covenant University, Ota, Nigeria and TRIL ICTP, Trieste, Italy;

(4) SC di Fisica Sanitaria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Trieste, Italy;

Introduction: Whenever a radiation field is used in therapy it is appropriate to perform dosimetric evaluations for radiation protection and phantoms are widely use to this scope. The evidence of neutron contamination of the radiation fields during high energy radiation therapy requires a neutron interaction specific anthropomorphic phantom. The lack of such phantoms in literature lead us to design and build Ryan: a new man-like full-size phantom.

Purpose: The aim of this work is to reproduce neutrons interactions in the patients, by means of a phantom with average male-body dimensions and proportions.



Materials and Methods: Scattering with nuclei is the main interaction to take into account for the purpose of this work. During elastic scattering the fractional kinetic energy lost by neutrons is highest for lowest mass target nuclei. For this reason scattering on hydrogen atoms is the most relevant for neutron thermalization inside the human body.

Looking to the mean human body composition, in particular for the upper part, hydrogen (H) is present for 0.10 mass fraction. For this reason polyethylene (0.14 H mass fraction) is a good choice for the construction of a neutron phantom. Neutrons in the thorax region are likely to come from every direction, even from the lower part of the body, because of scattering. So, designing a neutron phantom, it is important to take into account also lower limbs. Finally, a phantom must present cavities for dosimeters, especially at critical organs positions.

Taking into account all the previous considerations, our group at the Physics Department of University of Trieste built Ryan, an anthropomorphic phantom suitable for evaluating neutron doses.

The phantom Ryan is entirely composed by polyethylene; it has 42 cavities for the positioning of bubble dosimeters, CR-39 track detectors and biological samples. The thorax is composed by several square slabs that can be rotated one with respect to the other, in order to arrange the dosimeters allocations as necessary. Moreover the phantom Ryan represents the whole human male body. During construction particular attention was devoted to respect male body proportions as described in

literature[1].

The phantom Ryan is made by separable blocks so that it is easy to move, transport and store it. Each block is proportioned to its equivalent human body anatomic structure. These features allow the phantom to be also arranged in a sitting position.

For future developments and uses of Ryan, its geometry was also implemented in Geant4, a toolkit for the simulation of the passage of particles through matter.

In order to test the properties of the phantom Ryan, measurements were performed in the neutron field produced by a 15 MV VARIAN CLINAC 2100C medical linear accelerator. Neutron dose was evaluated with both bubble dosimeters and CR-39 track detectors. Results were then compared to those obtained with the well-known phantom Jimmy[2], in the same experimental conditions.

Results: Phantom Ryan has a height of 1.73 m and weighs 71.0 kg; its mean density is 0.96 g/cm3. Neutron doses evaluated in phantoms Ryan and Jimmy are in good agreement with each other.

Conclusion: Looking at results, anthropomorphic phantom Ryan is suitable for a good evaluation of neutron doses inside human body. Furthermore it is inexpensive, handy, well proportioned and it is perfect for routine measurements both in sitting and supine position. In conclusion Ryan can be considered a good phantom for neutron dosimetry.

References:

[1] Fryar, Cheryl D., Qiuping Gu, and Cynthia L. Ogden. *Anthropometric reference data for children and adults: United States, 2007–2010.* National Center for Health Statistics Vital and Health Statistics 11 (2012): 1-40.

[2] INFN Section of Turin. *Jimmy: un fantoccio antropomorfo per dosimetria neutronica*, Scientific Poster

NONO regulates the cell response to UV-induced DNA damage and is a potential therapeutic target in cancer.

F. Pentimalli[1], L. Alfano[1], C. Costa[1], A. Caporaso[2], A. Altieri[1], P. Indovina[3] and A. Giordano[1,2,3]

(1) Oncology Research Center of Mercogliano (CROM); Istituto Nazionale Per Lo Studio E La Cura Dei Tumori "Fondazione Giovanni Pascale"; IRCCS; Naples, Italy

(2) Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

(3) Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia PA, USA

Purpose: Genomic instability has been recently defined as one of the key hallmarks enabling cancer development and progression [1]. Indeed DNA damage and mutability endow cancer cells with genetic alterations that represent the driving force of tumour progression and account for the high molecular heterogeneity which characterizes a tumour and its ability to escape therapeutic treatments. Physical agents, such as UV and ionizing radiations, are an important environmental challenge to genome stability and a recognized cause of human cancer. However, the ability of ionizing radiations to damage DNA is also exploited to kill cancer cells and is the underlying principle of radiotherapy. In our lab we study both the biology of the cell response to DNA damaging agents and also explore possible strategies to sensitize cancer cells to DNA damaging agents [2,3]. Here we focused in particular on dissecting the role of NONO, a multifunctional protein that is overexpressed in melanoma, compared with normal melanocites, in the cell response to UV radiations, which represent the main risk factor for skin cancer.

Methods and materials: We generated NONO-silenced HeLa cell clones, through shRNA, and analyzed their ability to grow and activate the intra-S phase checkpoint that functions to prevent replication fork collapse, late origin firing and to stabilize fragile sites following UV exposure [4]. We analyzed through immunofluorescence whether NONO localizes to the sites of UV-induced RAD9 foci and, to position NONO in the complex cascade triggered by UV exposure, we analyzed the chromatin loading of various factors involved in the DNA damage response in the absence of NONO.

Results: We first found that lack of NONO decreased HeLa cell growth, likely through a delay in the G1/S cell cycle transition. Then, we challenged NONO-silenced cells with exposure to UV radiations and found that NONO-silenced cells, compared with controls, continued to synthesize DNA, failed to block new origin firing, and impaired S345 phosphorylation of the checkpoint kinase 1 (CHK1) showing a defective checkpoint activation. Consistently, we found that NONO localizes at the sites of UV-induced DNA damage RAD9 foci. Then, we analyzed the loading onto chromatin of various intra-S-phase checkpoint mediators and found that NONO favours the loading of TOPBP1, a crucial activator of the kinase activity of ATR, the main trigger of the UV-induced DNA damage response. Strikingly, re-expression of NONO, through a sh-resistant mRNA, rescued CHK1 S345 phosphorylation in NONO-silenced cells.

Conclusion: Overall, our data uncover a new role for NONO in mediating the cellular response to UV-induced DNA damage and pave the way for future avenues of investigation addressing the potential therapeutic use of NONO targeting as a synthetic lethal approach with DNA damaging agents in tumours such as melanomas in which NONO underlies both cancer development and progression.

References:

[1] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. Mar 4;144(5):646-74 (2011).

[2] Indovina P, Marcelli E, Di Marzo D, Casini N, Forte IM, Giorgi F, Alfano L, Pentimalli F, Giordano A. Abrogating G_2/M checkpoint through WEE1 inhibition in combination with chemotherapy as a promising therapeutic approach for mesothelioma. Cancer Biol Ther. 15(4):380-8 (2014).

[3] Di Marzo D, Forte IM, Indovina P, Di Gennaro E, Rizzo V, Giorgi F, Mattioli E, Iannuzzi CA, Budillon A, Giordano A, Pentimalli F. Pharmacological targeting of p53 through RITA is an effective antitumoral strategy for malignant pleural mesothelioma. Cell Cycle 15;13(4):652-65 (2014).

[4] Branzei D, Foiani M. The checkpoint response to replication stress. *DNA Repair (Amst)* 8: 1038-46 (2009).

Shedding light on the workings of the social brain: a fNIRS study on newborns

Elisa Frasnelli[1], Andrea Vitale[1], Daniela Tosoni[1], Carlo Polloni[2], Giuseppe Menna[2], Ermanno Baldo[2], Marco Ioppi[3], & Giorgio Vallortigara[1]

[1] *Center for Mind/Brain Sciences (CIMeC), University of Trento, Corso Bettini 31, I-38068 Rovereto (TN), Italy*
[2] *Unità Operativa di Pediatria, Ospedale S. Maria del Carmine, Corso Verona 4, 38068 Rovereto (TN), Italy*
[3] *Unità Operativa di Ostetricia e Ginecologia, Ospedale S. Maria del Carmine, Corso Verona 4, 38068 Rovereto (TN), Italy*

Human newborns have been widely shown to exhibit predispositions to attend to and preferentially learn about conspecifics. Such predispositions have been argued to be of vital biological importance. However, little is known as to the extent to which these mechanisms are in place at birth and about the possible role of experience in influencing them. Studying them, and their physiological and neural bases, is crucial for an understanding of typical and atypical human development. This study is part of a wider project that has the originality of investigating for the first time whether (and the extent to which) the mechanisms that preferentially orient the attention of neonates to social stimuli are really inborn. Specifically, the current study exploits the advantages of near infrared spectroscopy (NIRS) to investigate the neural bases of these biological predispositions to attend to biological motion in human newborns. NIRS is a completely non-invasive technique that measures changes in the concentration of oxy- and deoxy-haemoglobin thanks to the different optical properties of these chromophores. In this way, NIRS allows us to detect the brain structures activated in human newborns as they view social stimuli.

A time-resolved analysis to evaluate the intra-fraction dose delivered with the modulated scanning ion beam radiotherapy

S. Giordanengo[1], G. Russo[1], R. Cirio[1,2], M. Donetti[1,3], M. A. Garella[1,3], M. A. Hosseini[1,2], F. Marchetto[1], S. Molinelli[3], V. Monaco[1,2], R.Sacchi[1,2], M. Varasteh Anvar[1,2] and A. Attili[1]
(1) Istituto Nazionale di Fisica Nucleare, Section of Torino, Torino;
(2) University of Turin, Experimental Physics, Torino;
(3) Centro Nazionale di Adroterapia Oncologica (CNAO), Pavia.

Purpose: Modulated scanned beam interplay with the intra-fraction target motion may result in dose deterioration in ion beam therapy. The magnitude of this effect was investigated with a new tool based on forward planning (FP) computation using the data collected at the Italian National Center of Oncological Hadrontherapy (CNAO) for single fields, single fractions and total treatments.

Methods and materials: A forward planning tool has been developed which starting from the patient 4DCT and using both the spot properties measurements and the corresponding prescriptions, evaluates the doses into the target volume and performs comparisons based on gamma index, isodose curves and Dose Volume Histograms (DVH).
A time-resolved approach to the off-line reconstruction of the dose delivered during a treatment is used. A method has been developed which exploits the data collected in real-time by the beam monitor chambers and a forward planning tool in order to determine the accuracy achieved in the full treatment delivery as well as in predefined partial irradiations.

Results: The sensitivity of the method on the deviations of the measured values from the planned beam positions and planned number of particles is presented. The thorough analysis of the data collected at the Italian National Center of Oncological Hadrontherapy (CNAO) is shown both for partial fields, single fields and total treatments. As a result, the negligible effects on the total dose distributions due only to the beam delivery uncertainties were verified for both protons and carbon ions and the results are shown.
Based on a 4DCT, the tool can reproduce the deviations due to the organ motion simulating the treatment delivery (i.e. spot sequence as a function of time) and selecting the portion of the plan for the FP computation on the base of the respiratory phases.
On-line applications of the method with the integration of intra-fraction target movements and using fast forward planning computation are also discussed.

Conclusion: A novel approach to the off-line verification of the dose delivered with the modulated scanning ion beam radiotherapy has been developed and applied to study the treatment delivery performance. The developed tool is a step towards adaptive ion-therapy simulating possible on-line analysis of partial delivered dose distributions. Additionally, it is also expected to help the delivery optimization through comparisons among different motion models as well as different mitigation techniques.

Impact of uncertainties in ion beam therapy on the optimality of irradiation condition and fractionation schedule

A. Attili[1], F. Bourhaleb[2], A. Svanetti[3], M. Casale[3], D. Bottigliengo[3], S. Giordanengo[1], F. M. Milian[1,4], G. Russo[1], A. C. Kraan[5], F. Marchetto[1], R. Cirio[1,3].

1. *INFN, Istituto Nazionale di Fisica Nucleare, Sez. di Torino, Italy*
2. *I-See, Internet Simulation Evaluation Evision Ltd, Torino, Italy*
3. *Università degli Studi di Torino, Italy*
4. *UESC, Universidade Estadual de Santa Cruz, Ilhéus Brazil*
5. *INFN, Istituto Nazionale di Fisica Nucleare, Sez. di Pisa, Italy*

Keywords: Patient setup, Ion Beam Therapy, Treatment Planning

Purpose: The well-defined range of ions, enabling precise dose localization, makes them favorable for highly conformal treatments but also sensitive to uncertainties during planning and delivery. Standard approaches to manage these uncertainties include methods based on safety margins and worst-case optimizations [1], or, alternatively, on probabilistic algorithms [2]. However, all these methods are limited to finding optimal conditions for a single fraction, i.e. the overall effect in terms of tumor control has not been evaluated. In this work, a general probabilistic method to evaluate the optimality for the full fractionation schedule, by means of TPC/NTCP evaluations, was presented. The method was used to evaluate the effects of patient setup errors and CT stochastic noise, in the case of pediatric brain tumor.

Materials/methods: The method reproduced a realistic workflow of treatment planning and delivery. Two kinds of uncertainties were included: 1) in planning, due to erroneous input data such as noisy CT, resulting in a systematic error; and 2) in delivery, due to patient setup errors, in which the effects for each fraction are mostly statistically independent. We performed a Monte Carlo/bootstrap sampling over treatment fraction simulations (400, with protons and carbon ions), aimed to model the full PDF of the treatment outcome. Patient setup errors were included by applying random isocenter shifts, sampled from a Gaussian distribution with σ = 1, 2, 3 and 4 mm (PTV margin = 3 mm). CT spatially correlated noise was generated from a measured noise power spectrum.

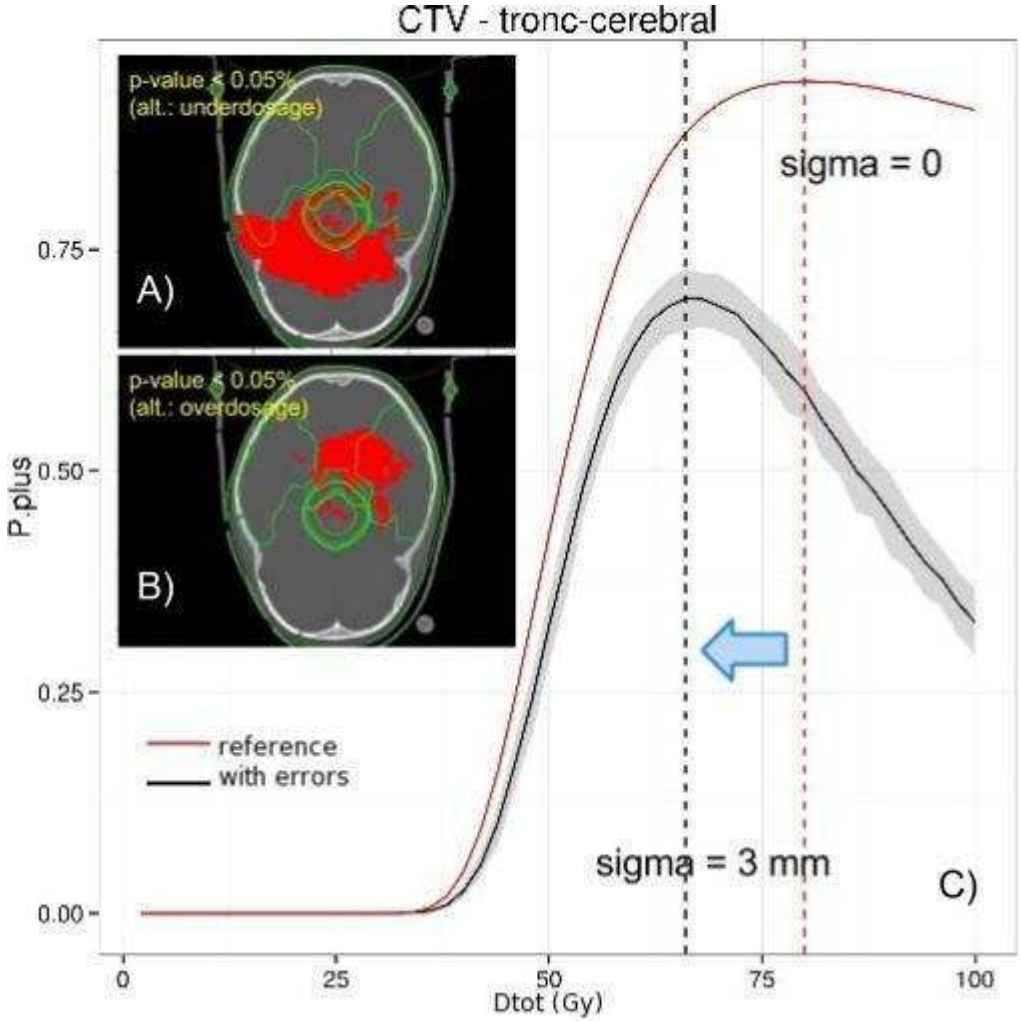
The PDFs of several quality indexes, such as conformity, homogeneity, and DVHs, were evaluated. P-value 3D maps for over/underdosage probabilities were also derived (see fig.A-B). A generalization of the TCP/NTCP models was introduced to estimate the full treatment effect as a function of number of fractions and dose per fraction, accounting for interfraction dose and RBE fluctuations.

Results: We found that treatments with σ>2 mm produce a TCP reduced by 15% or more with respect to the treatment without errors. Also, the optimality of the treatment, quantified by the maximization of the probability of local control without complications (P+), is shifted towards different fractionation schedules (see fig.C). A systematic overestimation of the range of particles (1-2 mm), due to the noise in CT images, was also found. Interestingly, this deviation had the same order of magnitude, but different sign, as the RBE correction to the proton range.

Conclusions: A method was implemented to estimate the effects of stochastic uncertainties on treatment optimality for the full fractionation schedule in ion beam therapy. The method could be used in a treatment procedure to perform robust planning, including also the optimization in fractionation schedule.

References:

[1] Pflugfelder D et al., *Phys Med Biol*, 53 (2008)
[2] Unkelbach J et al., *Med Phys*, 36 (2009)



IMG CREDITS:
from the left historical unit of telecobalt therapy, Ospedale S. Lorenzo, Borgo Valsugana, 1953
(source: AECL and MSD Nordio - Canada)
Protontherapy Facility, APSS - Trento (photo Matteo Visintainer - www.geo360.it)

EDITED BY COMMUNICATION SERVICE UNITRENTO, TRENTO (ITALY), NOVEMBER 2014

The Conference has been organized from the University of Trento, the Azienda Provinciale per i Servizi Sanitari of Trento and the Associazione Italiana di Fisica Medica, on the 50th anniversary of the event “Colloqui sui rapporti tra fisica e medicina” which left an important mark in our Country due to its significant contribution to both the establishment of the Medical Physics Departments in the Hospitals and the introduction of Chairs of Physics at the Schools of Medicine.

“Physics & Medicine. Toward a future of integration” has been organized in conjunction with the International Day of Medical Physics, proposed by the International Organization of Medical Physics (IOMP) for the day November 7th, in which it celebrates the anniversary of the birth of Marie Sklodowska-Curie.

The program did also include some joint sessions with the event of INFN (Italian Istituto Nazionale di Fisica Nucleare) “Giornate di Studio sul Piano Triennale INFN 2015-2017”.

http://events.unitn.it/en/fisica-medicina2014

With the institutional support of

With the contribution of

Under the patronage of

With thanks for the valuable collaboration to

ISBN 978-88-8443-575-0