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SYRA3 COST Action – Microbeam radiation therapy: Roots and prospects

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ABSTRACT

Microbeam radiation therapy (MRT) is an irradiation modality for therapeutic purposes which uses arrays of collimated quasi parallel microbeams, each up to 100 μm wide, to deliver high radiation doses. Several studies have reported the extraordinary tolerance of normal tissues to MRT irradiation; conversely, MRT has been shown to be highly efficient on tumor growth control. The original and most widely developed application of MRT, yet in the preclinical phase, consists in using spatially fractionated X-ray beams issued from a synchrotron radiation source in the treatment of brain tumors. More recently, MRT has been tested in successful pioneering assays to reduce or interrupt seizures in preclinical models of epilepsy. The MRT concept has also been extended to proton therapy. The development of MRT towards its clinical implementation is presently driven by an EU-supported consortium of laboratories from 16 countries within the COST Action TD1205 (SYRA3). The results of the first SYRA3 workshop on "Radiation Therapy with Synchrotron Radiation: Achievements and Challenges" held in Krakow (Poland) during March 25–26 2014 are summarized in this issue with an overview presented in this paper. The papers reflect the multidisciplinary international activities of SYRA3. The topics covered in this focus issue include medical physics aspects, pre-clinical studies, clinical applications, and an industrial perspective; finally an outlook towards future prospects of compact sources and proton microbeams.

To build an international interdisciplinary platform for collaborative research in synchrotron radiation therapy, the COST Action "*Innovative Methods in Radiotherapy and Radiosurgery using Synchrotron Radiation* (SYRA3)" of the European Cooperation in Science and Technology (COST) was launched in May 2013 (http://www.syra3.eu). SYRA3 includes the preparation of clinical trials using orthovoltage X-ray microbeam radiotherapy (MRT) at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France.

MRT, a concept developed about 25 years ago at the National Synchrotron Light Source at Brookhaven National Laboratory (BNL) on Long Island (New York, USA), is based on irradiation for therapeutic purposes by orthovoltage synchrotron X-rays that are spatially fractionated by a collimator into an array of parallel microbeams, each up to 100 μm wide. With its highly collimated microbeams and the characteristically high skin entrance doses it can be considered as a special type of radiosurgery.

The MRT concept was first explored with reference to experiments that had been carried out by Howard J. Curtis and his colleagues at BNL during the 1950s to simulate the biological effects of cosmic ray primaries [1]. They had shown that a single cylindrical, 25 μm wide, cyclotron-generated 22.5 MeV deuteron beam imparting absorbed doses of over 10,000 Gy to a microcylinder of mouse brain tissue during a single exposure resulted in loss of most targeted nuclei with neither loss of neuropil along the first 1.5 mm of its path through the superficial visual cortex of the mouse, nor obvious changes of the animal's behavior. Thus around 1990, Per O. Spanne, a radiation physicist and microtomography researcher, and Daniel N. Slatkin, an anatomic pathologist and boron neutron-capture therapy (BNCT) researcher, both at BNL, informed of those studies, decided to deliver a dose of about 200 Gy to the head of a normal mouse using Spanne's pencil microtomography beam at BNL's National Synchrotron Light Source (NSLS) (unpublished). The mouse recovered normally from anesthesia and was

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euthanized after its otherwise unremarkable life one month later; no histopathological evidence of brain damage in the region of the single beam's path was detected by light-microscopy. But 4 mm high, 25 μm wide, "microplanar" beamlets of 50–150 keV synchrotron X-rays at the NSLS were shown to cause microscopically detectable brain lesions in rats similar to those described by Curtis and his colleagues. Brain tissue tolerance experiments at BNL revealed that normal Mongolian gerbils (unpublished) and normal rats withstood absorbed doses of hundreds, even thousands of gray from such beamlets delivered to noncontiguous, quasi parallel microscopic slices of their CNS tissues [2,3]. The theoretical possibility of radiosurgery by irradiating parallel arrays of such microslices spaced 50–200 μm apart, crossfiring the array through the tumors from several ports, was then investigated and tested for a malignant rat brain tumor at BNL with encouraging results [4]. Astonishingly, it was noticed that some tumors were ablated in rats irradiated unidirectionally. However, despite these exciting pioneering results, the MRT program was not further supported by the BNL. Accordingly, a Swiss-based research group for MRT (Hans Blattmann, Jan-Olaf Gebbers, Jean A. Laissue, Daniel N. Slatkin, Per O. Spanne, Hans Peter Wagner) presented the MRT concept on June 12, 1992 to Professors Haensel, Altarelli and Brändén, then directors of the ESRF, which was under construction in Grenoble, France. Spanne began developing MRT at the ESRF in September 1994 using a single-slit collimator. The first dimensionally adjustable multislit microcollimator (MSC) [5], was manufactured in Canada by David W. Archer (US Patent 5,771,270; 1998), then moved to the ESRF's ID17 biomedical beamline. It was used for irradiations of intracerebral 9L rat gliosarcomas, of the hindbrains of normal suckling rats and of weanling piglets, thus avoiding the time-consuming translation of anesthetized animals back and forth across a single microbeam. Despite its dimensional irregularities, experimental and theoretical studies proved the Archer MSC very useful for in vivo preclinical MRT studies and Monte Carlo therapy planning. Spanne's tragic death in an airplane crash on September 2, 1998 determined significant changes in the microbeam research program at the ESRF.

MRT has attracted the attention of several research groups internationally; it has been investigated in many experiments, with modifications of a host of parameters such as geometry of the beamlets, number of ports, dose, microdosimetry; adjuvants and radiation enhancers have been added. Normal tissue tolerance, bystander effects, basic radiobiological developments in several species, therapeutic ratios for a range of experimental tumors of small laboratory animals, postirradiation memory and other aspects have been tested, mainly in rodents. Collimators and detectors have been developed specifically for MRT. New mathematical models have been designed and investigated using Monte Carlo dose simulations. A therapy planning system adapted from commercial therapy planning software, specifically geared to the technical parameters and requirements of synchrotron based MRT, is currently being developed. The ESRF now has an MRT facility for animal and clinical studies, including an elaborate patient safety system. To bridge the gap between MRT research on small animals and human patients, a pet animal patient trial based in Switzerland and France has been initiated. Pet animals such as cats and some breeds of dogs develop spontaneous malignant tumors very similar to those seen in human patients. Radiation therapy for animal tumors has become an established part of veterinary medicine in several countries for more than a decade. Some canine tumors are so similar to their human counterparts both in their histological signature and in the dynamics of their growth that they are considered excellent platforms to answer one of the key questions about safety and efficacy of MRT before a clinical trial would be initiated: Will such spontaneous tumors in larger animals respond to MRT as well as the much smaller, orthotopically implanted malignancies in rodents? Answering this question is a major logistic challenge because of the sporadic occurrence and the diversity of spontaneous tumors in dogs and cats, not to mention the restricted availability for post-therapy follow-up by pet owners.

A significantly shorter hospitalization time for tumor patients is a major advantage of radiosurgery over temporally fractionated radiotherapy. The quality of life, particularly in very young children with tumors of the brain or the spinal cord, might be improved if the same degree of palliation could be achieved with single-fraction radiosurgery, instead of six weeks of daily radiotherapy requiring daily anaesthesia. Much work needs to be done toward that goal.

We are pleased to present the first manuscript collection exclusively dedicated to synchrotron-based radiation therapy. The wide range of topics presented in this collection, based on presentations held at the 1st SYRA3 COST Conference *Radiation Therapy with Synchrotron Radiation: Achievements and Challenges,* with support of the Institute of Nuclear Physics at the Polish Academy of Sciences in the beautiful city of Krakow in March 2014, reflects the multidisciplinary international activities of SYRA3. The topics covered in this focus issue range from medical physics aspects [6] over pre-clinical studies [7–11] towards clinical applications [12,13] including an industrial perspective [14], and finally an outlook towards future prospects of compact sources [15] and proton microbeams [16].

Several publications have shown that the healthy vascular network is highly resistant to hectogray doses of radiation when delivered in arrays of micrometric-wide microbeams. The same resistance was instead not found in tumoral vasculature; this evidence has led to identify the anti-vascular effects to lead to tumor control by MRT. The paper by Bouchet et al. [7] reviews the most significant results of the effects of MRT on vasculature performed in different animal models.

Romanelli et al. [11] studied the short term effect of microbeam transections of the brain cortex. They irradiated the visual brain cortex regions in rodents to create microscopically narrow lesions (5 μm in thickness and spaced of 200 μm center-to-center). The procedure, well tolerated by rats, determined an incision-like path of neuronal loss while adjacent non irradiated columns remained intact. For the authors, these preliminary findings suggest that microbeam radiosurgery can affect the cortex at a cellular level providing a potential novel and attractive tool to study cortical function.

Grotzer et al. [12] discussed the candidate populations for the clinical application of MRT. They identified two targets in adults with glioblastoma multiforme and in pediatric patients with diffuse intrinsic pontine glioma. Both tumors are extremely difficult to manage with currently available therapy with overall little or no success, regardless of the therapeutic approach used [12].

In the current clinical practice of radiosurgery, treatment is usually defined by the total physical dose to an iso-surface which is conformed as close as possible to the gross tumor volume. In the paper by Millar et al. [13] the concept of biologically effective dose (BED) on treatment planning is discussed: BED allows a physical dose to be converted into a dose that describes the biological effect of the radiation on tumor or normal tissue and it takes into account also the repair of sublethal damage. This concept could be important to compare the effects of MRT versus other established techniques.

Bystander effects are thought to play an important role in MRT. Fernandez-Palomo et al. [8] investigated the bystander and abscopal effects in rats after MRT. Their findings strongly suggest that bystander effects (in partner animals) are not the same as abscopal effects (in the irradiated animal). Also, they have observed

that the presence of tumor tissue in the irradiated brain can modulate the abscopal effect in other organs of the directly irradiated animal and modify bystander response in unirradiated companion cage mates.

Bräuer-Krisch et al. [6] reviewed the medical physics aspects of radiotherapy with synchrotron radiation, giving particular emphasis to the dosimetry, microdosimetry and dose rate. A large team of international experts discussed the different methods for relative and absolute 2D and 3D dosimetry, including film, gels and solid state detectors for monochromatic and polychromatic energy deposition measurements.

Studer et al. [10] discussed the use of interlaced microbeams delivered to the somatosensory cortex to control the seizures in a genetic model of absence epilepsy. These antiepileptic effects were stable over 4 months and with low tissular and functional side-effects; the parcellization of the cortex prevented the pyramidal neurons, still physiological active, to synchronize. The method needs more tests on rodents and on non-human primates before potentially moving to treat pharmaco-resistant epilepsies in humans. The pathway and the potential targets are here presented.

Girst et al. [9] and Kłodowska et al. [16] extended the concept of microbeam to protons using an experimental [9] or a theoretical approach [16]. Girst et al. [9] used the ion microprobe SNAKE in Munich, able to produce focused proton microbeams ("proton microchannels") with the final aim of improving the normal tissue protection. This paper presents the first direct comparison between X-ray and proton microbeams, by irradiating skin tissues with a mean dose of 2 Gy either with parallel synchrotron-generated X-ray beams at the ESRF or with 20 MeV protons at SNAKE. Skin irradiation using either X-ray or proton microchannels maintain a higher cell viability and DNA integrity compared to a homogeneous irradiation, and thus might improve normal tissue protection after radiation therapy.

Kłodowska et al. [16] simulated proton microchannels of energy between 60 and 120 MeV and calculated the peak to valley dose ratios in a human head phantom at different depths considering different irradiation geometries. The obtained PVDR values are comparable with photon MRT data over depths of some 15–25 mm in tissue. Their findings suggest that by combining several ports it is possible to significantly boost the absorbed dose in the target volume, which needs to be confirmed by biology and radiobiology studies of normal and tumor tissues.

MRT is presently possible only at synchrotron radiation sources. The dissemination of the technique outside these large facilities will be possible only thanks to the presence of investments by the industry to produce easy-to-use and reliable radiotherapy units to be installed in the vicinity of large hospital centers. These subjects are discussed respectively in the paper by Wright [14] and Jacquet and Suortti [15].

Wright [14] examines the problems associated with the clinical implementation of MRT in hospitals, using dedicated machines able to deliver the MRT treatment. The paper discusses several irradiation parameters, including the beam size and energy and the irradiation geometry. It also identified lung cancer, one of the cancers with a very high incidence, as a target of primary interest from a population impact point of view. MRT might be of high interest in lung treatment if finally demonstrated that it can reduce radiation-induced fibrosis.

Jacquet and Suortti [15] present the characteristics of inverse Compton scattering X-ray sources, the compact X-ray machines presently under construction at different sites around the word. For ThomX, presently under construction in Orsay (France), the possibility of performing Stereotactic Synchrotron Radiation Therapy using quasi monochromatic X-rays is discussed from a beam flux point of view. Calculations show that ThomX has the potential of serving as the radiation source in future radiation therapy programs, and therefore it possess the characteristics to be integrated in hospital environment.

Should you have interest in the potential clinical applications of MRT we recommend the COST Action website http://www.syra3.eu for further information. We should be pleased to welcome you to our conferences or workshops and hope that you enjoy reading this issue of Physica Medica – European Journal of Medical Physics.

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