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Microbeam radiation therapy: Clinical perspectives

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ABSTRACT

Microbeam radiation therapy (MRT), a novel form of spatially fractionated radiotherapy (RT), uses arrays of synchrotron-generated X-ray microbeams (MB). MRT has been identified as a promising treatment concept that might be applied to patients with malignant central nervous system (CNS) tumours for whom, at the current stage of development, no satisfactory therapy is available yet. Preclinical experimental studies have shown that the CNS of healthy rodents and piglets can tolerate much higher radiation doses delivered by spatially separated MBs than those delivered by a single, uninterrupted, macroscopically wide beam. High-dose, high-precision radiotherapies such as MRT with reduced probabilities of normal tissue complications offer prospects of improved therapeutic ratios, as extensively demonstrated by results of experiments published by many international groups in the last two decades. The significance of developing MRT as a new RT approach cannot be understated. Up to 50% of cancer patients receive conventional RT, and any new treatment that provides better tumour control whilst preserving healthy tissue is likely to significantly improve patient outcomes.

Introduction

Despite the technical and scientific advances of radiotherapy (RT) over the past decades, only palliative therapy is available for children and adults with a number of high-grade tumours. This often only extends the survival of individual patients by a few months. As an example, diffuse intrinsic pontine gliomas, which constitute 15% of all childhood brain tumours (600 new cases/year in Europe), are inoperable. Their response to radiation and chemotherapy is only transient, with patients having a median overall survival of 10 months [1,2].

Microbeam radiation therapy (MRT), a novel radiotherapy method invented by Slatkin and coworkers in 1992 [3], is based on a spatial fractionation of synchrotron-generated X-ray beams. Spatial fractionation and the underlying laws of radiation physics were discovered by Alban Koehler at the beginning of the 20th century. It was used to reduce the extent of skin damage, a frequently occurring adverse effect of early radiotherapy. MRT was developed in a preclinical environment as a collaborative project involving physicists, engineers, biomedical scientists, and physicians, initially at the National Synchrotron Light Source at Brookhaven National Laboratory, Upton (USA), and later at the European Synchrotron Radiation Facility (ESRF), Grenoble (France).

MRT, based on the spatial fractionation of kilovoltage-energy X-ray beams, uses arrays of SRgenerated, collimated, planar, quasi-parallel microbeams (MBs; size, approximately 25–50 μm, spaced at 200–400 μm on centre). The synchrotron X-ray beam is segmented into a lattice of narrow, quasi-parallel, microplanar beams, typically 25- to 50-μm wide, separated by centre-to-centre distances (c-t-c) of 200–400 μm and delivered in a single treatment session, in a scanning mode. The very high in-beam MB 'peak' dose zones, in excess of 100 Gy, are separated by very low-dose 'valley' regions. These in-beam doses are orders of magnitude greater than those normally delivered in conventional RT. At a critical collimated beam width and separation in the order of tens and hundreds of microns, respectively, normal tissue can recover from hectogray exposure levels, which were previously considered to be lethal, whilst cancerous cells within the tumour are destroyed. Extremely high X-ray doses must be delivered at very high dose rates, within a very narrow time window, to prevent blurring of the MB tracks due to organ motion, so that the irradiation of an entire organ can be performed in a fraction of a second. The 6-GeV synchrotron ring at the ESRF is currently the only source of synchrotron radiation in Europe that is capable of generating intense X-ray microbeams,

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having a broad photon energy spectrum and fluence rates (i.e. X-ray beam intensities) high enough to deliver high absorbed physical radiation doses to deep targets in a scanning mode where a dedicated biomedical facility is available. Together with the adequate energy spectrum, the very low divergence of such X-ray beams is also conditional for preservation of the plane parallel beams and a sharp penumbra throughout the target, which is currently only feasible at such high energy synchrotron wiggler sources.

A Swiss-based research group for MRT has been intimately associated with the inventors of MRT for its development and validation over 20 years. The extensively equipped biomedical facility (ID17) at the ESRF, which is financed by 20 countries, acts as a central synchrotron RT research facility that plays a leading role in Europe and worldwide.

MRT in small animals

Preclinical long-term experiments that involved different species such as insects [4], birds [5], rodents [6–12], and pigs [13] have revealed an extraordinary tolerance of normal organs and blood vessels exposed to fractionated radiation doses in excess of 100 Gy delivered by arrays of MB. This tolerance was particularly evident in suckling rats and weaning piglets, whose irradiated brains are still developing [13–16].

MRT in small animal models has achieved therapeutic ratios that clearly exceed those obtained by conventional radiography with a homogeneous dose distribution, in a range of malignancies, including gliomas, gliosarcomas, human squamous cell carcinomas, and glioblastomas. These characteristics of MRT have been extensively demonstrated by results of preclinical experiments [12,17]. Furthermore, MRT-associated bystander effects have been identified [18–21]. The tumour control of MRT has been improved by combining MRT with various compounds [22–24], radiation-enhancing substances [25], gene-mediated immunoprophylaxis [26], and other adjuvant techniques. It can clearly be concluded that high-dose, high-precision radiotherapies with reduced probabilities of normal tissue complications offer prospects of improved survival outcome probability and decreased risk of therapy-related toxicity.

Several probable reasons why MRT provides a higher therapeutic index for tumours than broad beam irradiation have been elucidated, such as the following: (1) MBs produce steep dose gradients between tissue slices receiving the peak and valley doses; they have a 90%–10% dose fall-off, about 200 times steeper than that of a Gamma Knife [27]. The radiotoxic dose is therefore confined to a very narrow zone while the integrity and functionality of the adjacent normal tissue in the valleys between the peaks can be preserved. (2) Spatial fractionation results in a very large specific contact surface between peak and valley zones. This extended contact surface is instrumental for the repair of heavily irradiated tissues in peak regions. (3) In contrast to the high tolerance of the normal microvasculature [9] and arteries [7] to irradiation by MB, the tumour vasculature of 9L gliosarcomas in rats is selectively damaged by MRT [28] with ensuing tumour hypoxia and shrinkage. Conversely, normal brain tissues exposed to MB during MRT remain sufficiently perfused to maintain normoxia [17]. (5) MB irradiation of normal rat brains provokes proteomic responses that are indicative of oncogenesis and proteomic changes associated with bystander effects, indicative of apoptosis mediated by reactive oxygen species. Furthermore, potentially anti-oncogenic apoptotic proteomic changes indicate that the collective interaction of such MB irradiation-induced bystander effect proteins might confer a protective effect on normal tissues [20]. (6) Transcriptional gene expression analysis of intracerebral gliosarcomas in rats [12,29] and EM6.5 breast tumours in mice [30] have identified MRT induced immunity-related modulations, clearly different from transcriptional changes induced by unsegmented broad beams.

MRT for large animals

Although encouraging, previous preclinical results in small animals are not sufficient to justify MRT studies to advance directly to phase I human clinical trials. Before moving to human applications, MRT must be applied in therapeutic veterinary trials of larger animals such as pigs bearing intracerebral glial tumours [31], as well as companion dog and cat patients bearing spontaneous tumours. The use of larger animals in MRT studies is supported by the dimensional and physiological similarities of spontaneous tumours in dogs and cats compared to those in human malignancies, in contrast to implanted tumours of mice and rats [32–35]. The physical disadvantage of using rather low-energy photons to treat larger, deep-seated targets can be overcome by the use of conformal image-guided MRT that uses several ports.

These studies will further augment our understanding of how deeper-seated and larger tumour tissues respond to MRT and serve as an early warning system for unexpected late adverse effects. Considering that the time course of biological events is compressed in domestic and companion animals compared to humans and that the large animal phase I/II trial precedes human clinical trials by several years, one can re-assess and, if necessary, refine the treatment plan for human patients based on the results obtained in these larger animal studies.

MRT for human patients

MRT for human patients requires a careful, multi-disciplinary evaluation of epidemiological, medical, logistical, and ethical considerations, including quality of life in comparison to life span, and endpoint definitions. Candidate populations could be adult patients with glioblastoma multiforme (approximately 20,000 new cases/year in Europe). Current standard treatment consists of surgery followed by chemoradiation and adjuvant temozolomide [36], but no standard of care exists for patients with recurrent tumours.

Paediatric patients with diffuse intrinsic pontine glioma (DIPG; approximately 600 new cases/year in Europe) would be an excellent candidate population. DIPG remains a most frustrating tumour in paediatric oncology. Because of the location of tumours and the difficulty in distinguishing tumour tissue from normal structures, surgical debulking is restricted by the substantial risk of morbidity and mortality. The mainstay of therapy for intrinsic pontine glioma has been RT. While there is evidence that conventional RT provides short-term benefits (i.e. a temporary improvement in neurological function and thus an increase in the quality of life), long-term results have been dismal and the overall survival time has not changed [1,2].

To safely conduct human clinical trials with MRT, new hardware and software need to be developed and tested. A patient-positioning system for MRT is currently available for small animals and larger animals such as pigs, dogs, and cats, up to a weight of 40 kg. Designing and building a patient-positioning system that will move a heavier human patient with the required exactness/spatial precision are therefore necessary. The therapy accuracy system used in the large animal trials was based on computed tomographic images. For clinical trials in humans, therapy planning which incorporates magnetic resonance imaging findings is desirable, as it provides higher spatial resolution [37]. A marker system for reliable repositioning between image acquisitions and positioning for treatment could be either of the fiducial type or ensured by a stereotactic frame system. The preclinical veterinary trial in