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The preclinical set-up at the ID17 biomedical beamline to achieve high local dose deposition using interlaced microbeams

E. Bräuer-Krisch^a, C. Nemoz^a, Th. Brochard^a, G. Berruyer^a, M. Renier^a, B. Pouyatos^b, R. Serduc^b,

^aEuropean Synchrotron Radiation Facility, B.P.220, F-38043 Grenoble Cedex, France

^bINSERM unit 836, CHU Grenoble, Grenoble, France

corresponding author: *brauer@esrf.fr*

Abstract. Microbeam Radiation Therapy (MRT) uses spatially a fractionated "white beam" (energies 50-350 keV) irradiation from a Synchrotron Source. The typical microbeams used at ID17 are 25-100 μ m-thick, spaced by 200-400 μ m, and carry extremely high dose rates (up to about 16 kGy/s). These microbeams are well tolerated by biological tissue, i.e. up to several hundred of Gy in the peaks. When valley doses, caused by Compton scattering in between two microbeams, remain within a dose regime similar to conventional RT, a superior tumour control can be achieved with MRT than with conventional RT. The normal tissue tolerance of these microscopically small beams is outstanding and well documented in the literature. The hypothesis of a differential effect in particular on the vasculature of normal versus tumoral tissue might best be proven by using large animal models with spontaneous tumors instead of small laboratory animals with transplantable tumors, an ongoing project on ID17. An alternative approach to deposit a high dose, while preserving the feature of the spatial separation of these microbeams outside the target has opened up new applications in preclinical research. The instrumentation of this method to produce such interlaced beams is presented with an outlook on the challenges to build a treatment platform for human patients. Dose measurements using Gafchromic films exposed in interlaced geometries with their steep profiles highlight the potential to deposit radiotoxic doses in the vicinity of radiosensitive tissues.

1. Introduction

MRT is currently the only preclinical approach in radiation therapy using spatial fractionation with microscopically small beams[1]. Conventional radiation therapy (RT) with high energy sources or MeV accelerators allows only a very limited exploitation of the dose volume effect [2], which is most pronounced for beam sizes below 100 μ m full width half maximum (FWHM)[3,4]. The vast amount of data obtained with microscopically small beams produced by high-energy wigglers at third-generation Synchrotrons pave the ground for clinical trials. Indeed the possibility to deposit hundreds of Gray locally with minimal side-effects [5-7], while maintaining computed valley dose values below those prescribed in conventional RT, is of great clinical interest. The pet trials foreseen in 2013 represent an important milestone, where the hypothesis of a differential vascular effect between normal and tumoral tissue might best be proven [8]. This paper presents the technical solution used at

ID17 to interlace arrays of parallel microbeams in a given target by rotating the brain/animal around the geometrical center of the target, thus leading to a high homogenous dose distribution in depth, while sparing the surrounding tissue simply irradiated with the spatially fractionated beams (Fig. 1a). Different medical applications could benefit from this technique, even more so since the development of image guided conformal MRT, now possible at ID17. At the present state, the technique of interlaced microbeams is therefore ready for preclinical investigations on brain tumor treatments.

2. Instrumentation

The ID17 biomedical beamline uses the filtered white beam of a 21-pole wiggler source, resulting in a very high flux with dose rates at $16\,000\text{ Gy}\cdot\text{sec}^{-1}$ and a spectrum around 100 keV from approximately 50 keV to above 350 keV [9]. A Kappa goniometer with an additional high precision vertical translation allows the extended irradiation from various angles of a target positioned around a given center of rotation.

2.1. Interlaced Microbeams

The concept of interlaced and/or interspersed microbeams was introduced by Bräuer-Krisch *et al.* [10] and Dilmanian *et al.* [11]. Serduc *et al.* [12] has shown that interlaced beams can be juxtaposed within the living target in order to induce focal brain necrosis. At the ESRF, this technique has been exploited to treat epilepsy and other brain dysfunctions, which necessitate focal destruction of a brain region. Excellent precision could be achieved with the use of projection images of anatomical landmarks (i.e. cranial sutures) obtained for each subject directly on the MRT goniometer stage (see figure 1 and section 2.1.1).

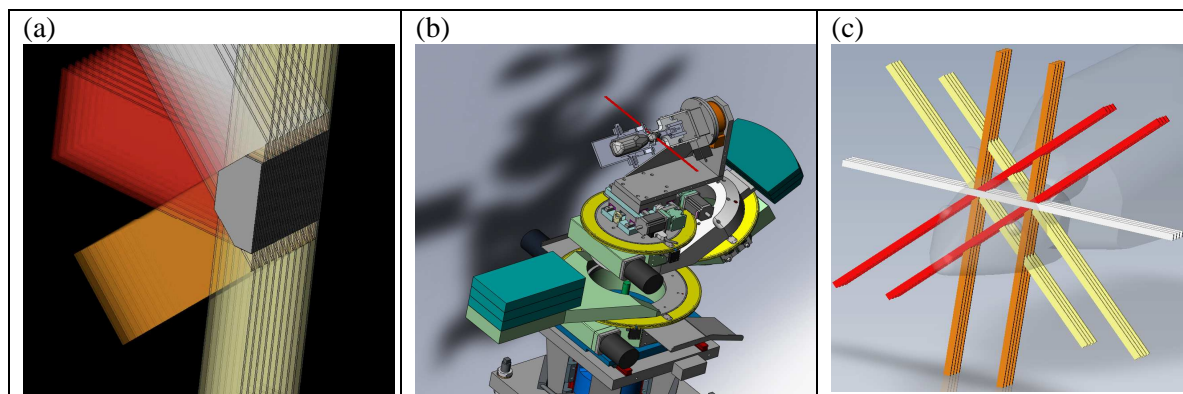


Figure 1: (a) Diagram of the 4-port microbeam interlacement. The region receiving a homogenous dose is displayed in gray (b) MRT Kappa goniometer with additional rotational stage on the top base plate. The red line indicates the approximate path of the beam when the stage is rotated by 45° . (c) Example of microbeam interlacement for irradiation of the focal regions in the two hemispheres of a rat brain.

2.1.1. The technical set-up to interlace microbeams for preclinical studies in rodents

The MRT goniometer allows targeting a brain region whose geometrical center is positioned in the center of rotation of the goniometer at different inclinations. However, we added a new rotation, exactly in the same plane as the MBs positioned on top of the goniometer, in order to juxtapose one microplanar beam exactly adjacent to another while a different port with a rotation of 45 degrees and a y-step of the microbeam width are selected between the 4 irradiations. Positioning of the target in the centre of rotation is performed by additional motors in z and y planes within the upper rotation, since the synchrotron beam is in a fixed position.

3. Results of interlaced microbeams in a human head phantom

This method was applied to a human head phantom to demonstrate that, with the combination of 50 μm -wide beams with a 200 μm ctc (center-to-center) spacing delivered through 4 equidistant and coplanar ports, a homogenous dose of 80 Gy could be deposited in depth. This approach induces radiotoxic effects in depth where MBs interlace, and assures good tissue sparing effect for the normal tissue only exposed to a single MB array. The measurements require an analysis with very good spatial resolution, feasible by the use of GafChromic® HD-810 films read out with a microdensitometer (3CS Microdensitometer, J. L. Automation). Results of measurements for clinically relevant field sizes of 3x3 cm^2 in a tissue equivalent phantom are presented hereafter.

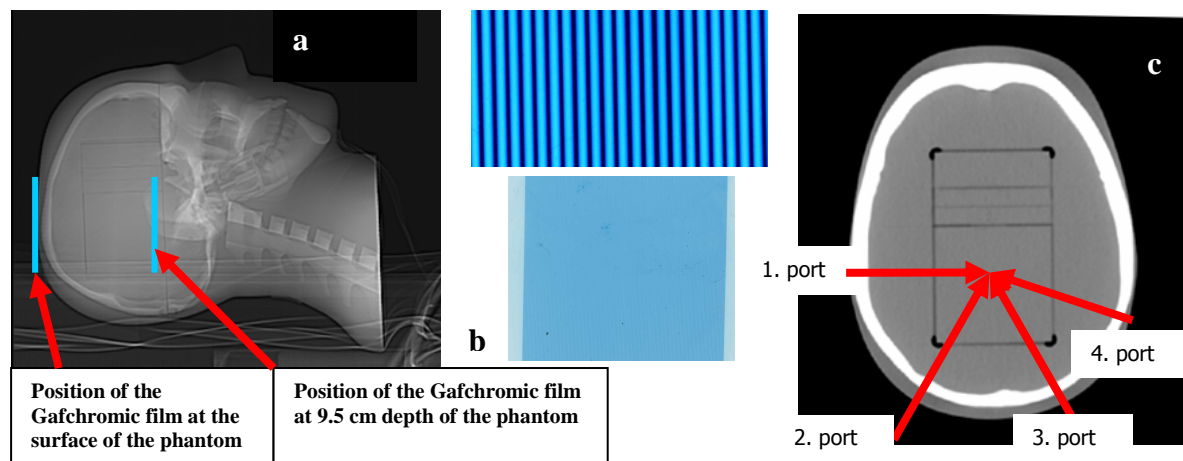


Figure 2: (a) Radiographic image of the human head phantom (Computerized Imaging Reference Systems, Norfolk, VA, USA); (b) MB exposed film at 3 mm depth on top and again homogeneously exposed film in 9.5 cm depth (80 Gy) ; (c) shows a cut through the horizontal plane of the head in the same direction traversed by the microbeams from 4 approximately equidistant ports.

The deposited dose in depth using the interlacing technique leads to a homogeneously exposed film which was as well read out using an Epson Scanner (type VPro 750) based on a set of calibrated films with a known dose. The MB exposed films were quantitatively evaluated using the microdensitometer. We show that an interlaced MB exposure with a 300 Gy peak entrance dose in each port using 50 μm -wide and 200 ctc spacing interlaced from 4 equidistant ports at a depth of 9.5 cm results in a homogenous dose in depth of ~ 80 Gy.

4. Conclusions

To bundle arrays of MBs and to deliver them from different ports in order to create a radiotoxic field in depth is an extremely demanding task from a technical point of view. However, this idea can be pursued if such radiation delivery can be combined with image guided and possibly cardio-synchronized conformal MRT.

Other preclinical research opportunities for MRT than treating epilepsy [13] may arise when using interlaced arrays of microplanar beams (IAMB) to create small lesions in the millimeter range in depth, *e.g.* to mitigate Parkinson disease [11,14,15]. As a safety measure, the non-optimal joining of microbeams leading to a PVDR as small as 5 was computed. , thus assuring a sufficiently high contribution of the valley dose. For a MB field as big as 3 cm x 3 cm, a 50 μm 400 ctc combination assures sufficient normal tissue sparing and allows for a 50 μm /100 ctc in depth if 4 equidistant ports are used. Similar ideas were presented using thicker beams [16], but the normal tissue tolerance of beam-sizes in the range of several hundreds of μm is not demonstrated yet..

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