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Spatial fractionation of the dose in proton therapy: proton minibeam radiation therapy

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Purpose: In radiation therapy, a renewed interest is emerging for the study of spatially fractionated irradiation. In this review, a few applications using spatial fractionation of the dose will be discussed with a focus on proton minibeam radiation therapy (pMBRT). Examples of calculated dose (1D profiles and 2D dose distributions) and biological evidence obtained so far will be presented for various spatially fractionated techniques GRID, MRT and MBRT. Recent results demonstrating that pMBRT leads to an increase in normal tissues sparing will be discussed, which opens the door to a dose escalation in the tumour and a possibly efficient treatment of very radioresistant tumours.

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Keywords: Proton, Minibeam radiation therapy, Pre-clinical research

1 Introduction

Radiation-induced toxicity continues being a major concern in radiotherapy. There are ever increasing
30 pieces of evidence of the influence of not only the dose, but the dose rate and the spatial fractionation of
the dose in RT. Along this line, we are witnessing a renewed interest in spatially fractionated radiation
therapy (SFRT), a strategy which has shown a remarkable capacity for tissue sparing. However, some
elements indicate that the radiobiological response of tissues to very heterogeneous dose distributions
might be poorly known. In this short review, a few applications using spatial fractionation of the dose will
35 be discussed with a focus on proton minibeam radiation therapy (pMBRT).

The concept of spatially fractionated radiation therapy was firstly introduced at the beginning of the 20th
century with the aim of achieving a better skin sparing. Indeed the risk of skin necrosis was frequently
reported when using poorly penetrating medium energy X-rays ($\approx 60\text{-}70\text{kV}$) to treat deep seated tumours.
40 The use of multi-perforated iron screens, proposed by A. Köhler (a German radiologist) in 1909 ([1]) and
widely employed until the 1950s, helped reducing these adverse effects. The implementation was based
on the collimation of an initial broad beam into a pattern of centimetre scale pencil beams to produce a
nonuniform dose distribution. The healing of normal tissues was thus improved thanks to the presence of
low dose irradiated tissues close to high dose areas in the pencil beam paths. The interest for SFRT
45 declined with the advent of deeply penetrating megavoltage linear accelerators and their associated
improved skin sparing due to dose build up effects. The use of SFRT was re-introduced in the early 1970s
using ^{60}Co units ([2, 3]), and then in the 1990s under the name of GRID therapy ([4]). GRID therapy has
been employed successfully in the palliative treatments of large and bulky tumours with early phase
clinical trials having shown remarkable success. Recent reviews present clinical data and discuss new
50 technological advances in GRID therapy ([5, 6]). One of the latest examples to date has been carried out
with proton beams ([7]).

In the early 1960s, studies on biological effects of cosmic radiation on mouse brains using deuterium
beams of various sizes ([8]) were conducted by the National Aeronautics and Space Administration
55 (NASA) and provided first insights on the impact of small beams and dose-volume effects (the maximum
tolerable doses increases as the irradiated tissue volumes is made smaller): a much higher tolerance to
incredibly high radiation doses was observed when micrometer scale beams were used. For example, an
incident dose of 4000 Gy to the mouse brain with a 25 μm beam showed no evidence of late tissue effect,

60 whereas an incident dose of 140 Gy delivered by a 1 mm beam was sufficient to induce radionecrosis or damage to vessels.

Then, in the 1990s, Slatkin and colleagues ([9]) profited from the advent of third generation synchrotron sources providing X-ray beams (X-rays are emitted tangentially from relativistic electron bunches circulating in a storage ring) with negligible beam divergence (<0.2 mrad) and high brilliance to propose
65 Microbeam Radiation Therapy (MRT) ([10]). Synchrotron beams allow to obtain a pattern of peaks and valleys that remain fairly constant with tissue depth ([11]). MRT combines the spatial fractionation of the dose with extremely narrow beams (25-100 μm). Indeed, the use of very narrow beams permits to maximally exploit the dose-volume effects [6]. Numerous experiments have then shown a spectacular
70 increase in dose of tolerances of normal (skin, brain) tissues ([12, 13]). Because of the need of extremely high dose rates to maintain the patterns of peaks and valleys, this technique is mainly confined to large synchrotron light facilities. MRT is therefore today an experimental concept at the pre-clinical stage, and the translation into clinical phases is still under development.

A good compromise can be achieved with minibeam radiation therapy (MBRT) which uses slightly wider
75 sub-millimetric field sizes (400-700 μm) than MRT, kilovoltage x-rays beams and spatial fractionation of the dose but offers technically easier realisation of dosimetry and positioning requirements ([14, 15]). Synchrotron-generated minibeam have first been shown to exhibit normal tissue sparing effects analogous to those obtained with MRT, and efforts were made to develop the use of non-synchrotron conventional small animal irradiators ([16, 17, 18]). Further improvements include the combination of
80 charged particles, in particular with proton minibeam radiation therapy ([19]). Indeed, proton beams offer several advantages over X-rays MBRT, such as the precise ballistics of protons in the Bragg-peak region and a reduction of the integral dose. The multiple Coulomb scattering of charged particles also enables treatment of the tumour with a homogeneous dose distribution, while the normal tissues at shallow depth still benefit from spatial fractionation of the dose.

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2 Proton minibeam radiation therapy

Proton therapy is a highly conformal technique that can maximize the dose gradient between tumour and surrounding structures. In contrast with photons, protons have the advantage of stopping at a given depth
90 and reduced range straggling, resulting in a significant reduction of the integral dose to surrounding tissues. This technique has then been widely used for radioresistant tumours close to a sensitive structure

or paediatric cancers, in which dose escalation in the target volume without increasing the dose to adjacent normal tissues is recommended ([20]). The combination of the advantages of protons with MBRT is called proton minibeam radiation therapy (pMBRT). pMBRT has been recently implemented at a clinical facility (Orsay proton therapy center), in a clinically relevant environment using high energy beams (100 MeV). The biological experiments reported so far showed a remarkable increase in normal tissue sparing, both for the skin ([21, 22]) and brain ([22]), along with an even higher control tumour effectiveness than standard therapy ([23]). pMBRT is still at the preclinical stage, but transition to the clinic is underway.

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In pMBRT, two delivery techniques have been implemented for preclinical research ([24, 25]). One is based on passive scattering (PS) and the other delivery technique is based on Pencil Beam Scanning (PBS), combined with the use of multislit collimators. The latter consists of magnetically scanning several pencil beams over the target volume with the possibility of modulating the path, energy and intensity of the beams, and provides high dose-rates (up to several Gy/s), a potential reduction in neutron production compared to the passive scattering technique and significant improvements in the conformity of the dose distribution thanks to intensity modulation (IMPT). An example of a spread-out Bragg peak and a dose distribution that can be obtained with pMBRT and scanned pencil beams is shown Figure 1: by means of intensity modulation of Bragg peaks, spatial fractionation is maintained at shallow depths while homogeneous dose distribution is obtained around the target.

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2.1 Dosimetric properties

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Contrary to conventional RT which provides homogeneous dose profiles, the lateral dose profiles in MBRT consist of peaks and valleys (see Figure 2). The peak-to-valley-dose ratio (PVDR) is a dosimetric parameter defined as the ratio of the peak dose over the valley dose which is frequently used to evaluate the potential sparing of normal tissues. High PVDR values and low valley doses are required to ensure tumour control and healthy tissue sparing respectively ([26]). The distance separating two minibeam centers is known as the centre-to-centre distance (c-t-c). GRID therapy typically uses large pencil beams (1 cm diameter), whereas MRT and MBRT use sub-millimetric beams of 25-100 μm and 400-700 μm respectively. GRID therapy uses arrays of beams separated by centre-to-centre (c-t-c) distances of a few cm, whereas MRT and MBRT typically use c-t-c distances from 200 to 400 μm and 2 to 6 mm

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125 respectively. Most spatially fractionated set-ups use 1D planar beams arrangements, but 2D lattice
structures have also been proposed. Examples of calculated lateral dose profile for various spatially
fractionated techniques (GRID, MRT and MBRT) are shown in Figure 2. Two clinical examples of dose
distributions that can be obtained with GRID and pMBRT plans using a proton PBS technique are also
shown in Figure 3 for a treatment of a glioma patient.

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2.2. Preclinical evidence

Normal tissue dose tolerances and tumour growth delay have been observed in several recent biological
experiments. The first long term evaluation of the effects of pMBRT on normal brain was performed by
135 Prezado et al ([27]). In this work, the whole brain of Fischer rats was irradiated at a dose close to the
maximum brain tolerance dose (25 Gy) within a single broad beam conventional irradiation, or received
pMBRT irradiation with peak doses of 58 Gy (corresponding to a mean dose of 25 Gy). The animals
were followed up for 6 months. A magnetic resonance imaging (MRI) study using a 7-T small-animal
MRI scanner was performed along with a histological analysis. Rats treated with conventional proton
140 irradiation exhibited severe moist desquamation, permanent epilation and substantial brain damage. In
contrast, rats in the pMBRT group exhibited no skin damage, reversible epilation and no brain damage. A
good sparing of the skin was also observed in an independent experiment by a German team ([21]), who
reported on reduced side effects in the mouse ear after pMBRT with 20 MeV protons.

145 In a second research study, the evaluation of the tumour effectiveness of pMBRT for the treatment of
RG2 glioma-bearing was performed ([23, 28]) showing superior or equivalent tumour control
effectiveness compared to standard proton therapy. RG2 glioma bearing rats were irradiated, receiving
conventional proton therapy or pMBRT with either a homogeneous or a heterogeneous dose distribution in
the tumour (25 Gy in one fraction were delivered). The whole brain (excluding the olfactory bulb) was
150 irradiated with peak doses of 70 Gy and a mean dose of 30 Gy. A significant proportion of long-term
survivals (> 6 months) free of tumour was obtained, reaching in some cases 67 %. No significant lesions
were observed.

The results of the experiments performed so far with very heterogeneous spatial distributions, such as
155 with GRID/MRT/MBRT, indicate the activation of different biological mechanisms (which might not be
specific to proton beams) from those involved when direct damage to DNA as a primary target by
ionizing radiation takes place. However, the biological basis of tissue response to spatial fractionation is

not yet completely understood, and some of the biological results obtained so far clearly suggest the participation of distinct biological mechanisms: in particular, dose-volume effects (migration of undamaged cells to repair the radiation damage [29]), cell signalling effects such as cohort effects (signalling between irradiated cells within an irradiated volume [30]) or bystander cellular responses (signalling between irradiated cells and nearby undamaged/unirradiated cells [31, 32]), the activation of the immune system ([33]), or the role of the vasculature (prompt vascular repair effect, [34]) among others were all identified as being involved in the healing process of radiation damage.

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3 Discussion and conclusion

170 Some recent results demonstrate that GRID/MRT/pMBRT leads to an increase in normal tissues sparing, which opens the door to a dose escalation in the tumour, and possibly an efficient treatment of very radioresistant tumours. In particular, the use of protons instead of photons for pMBRT seems to be advantageous because of a more localised release of the dose. The normal tissue dose tolerances and delay of tumour growth observed in recent biological experiments also showed a remarkable gain and
175 good rates of control. In addition, spatial fractionation may allow hypofractionated treatment of tumours as it spares healthy tissues at shallow depths ([35]). On the other hand, very short irradiation times and hypofractionated schemes are prerequisite to MBRT since any movement or misalignment of the healthy tissue would result in smearing and deterioration of the required dose distribution. In these conditions, the linear-quadratic model may not be sufficiently accurate to compare SFRT and conventional radiotherapy
180 for large doses per fraction, and the definition of tolerance doses as well as an optimisation of dose-time treatment protocols remain an important topic that needs to be fostered to advance pre-clinical work towards clinical trials.

Conflicts of interest

185 The authors have no relevant conflicts of interest to disclose.

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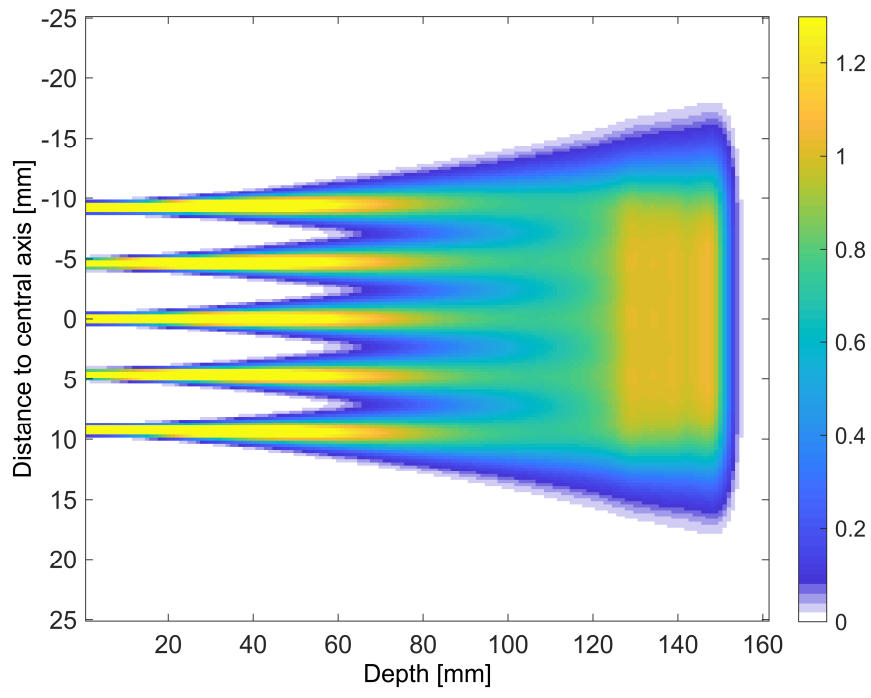
190 Figure 1. Example of a calculated spread-out Bragg peak and a dose distribution that can be obtained with pMBRT and pencil beam scanning.

Figure 2. Example of a calculated lateral dose profile in spatially fractionated techniques for classical GRID, MRT and MBRT techniques.

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Figure 3: Example of planned dose distribution of GRID and pMBRT using a proton PBS technique for the treatment of a glioma patient.

Figure 1



200 **Figure 2**

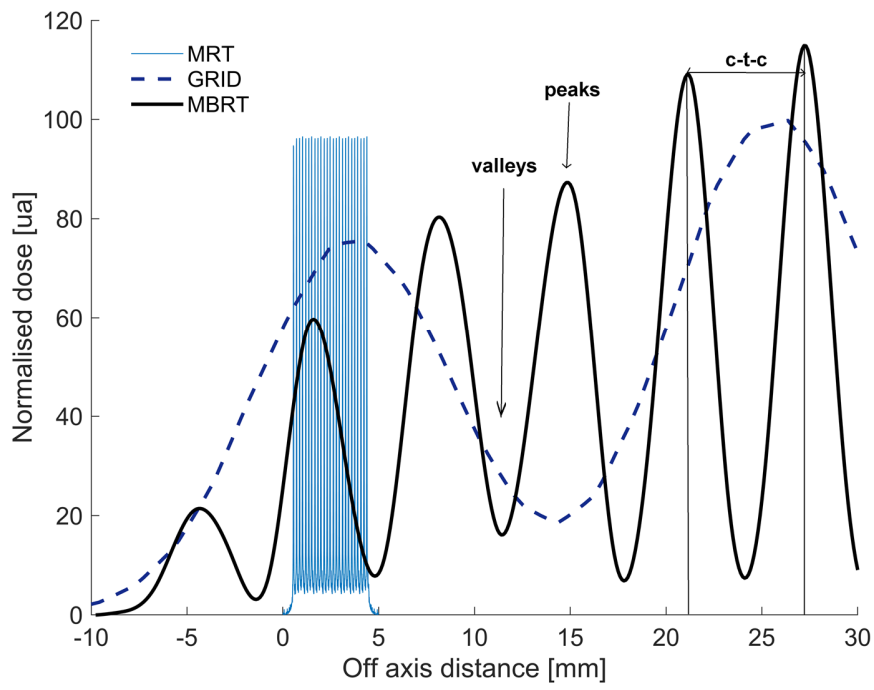
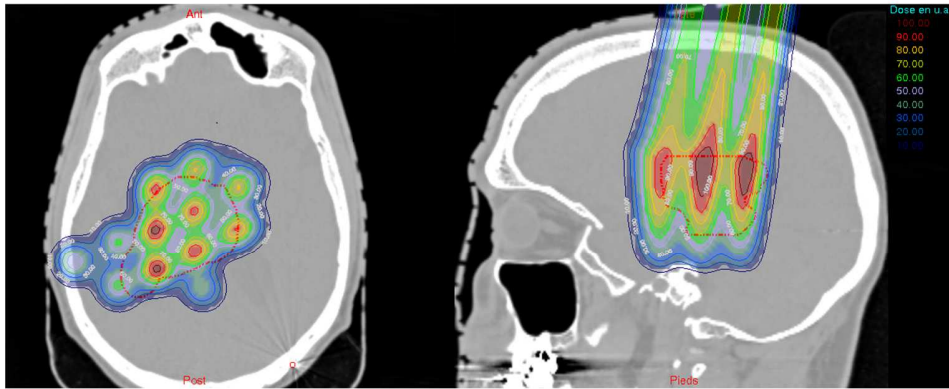
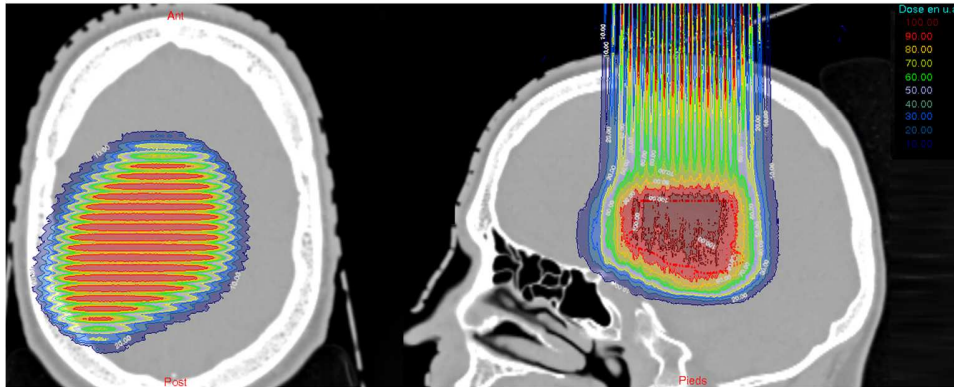


Figure 3

(a) Dose distribution of GRID therapy



(b) Dose distribution of PMBRT



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