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Proton minibeam radiation therapy widens the therapeutic window for radioresistant tumors

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Radiotherapy (RT) has a key role in cancer treatment. In fact, about half of the patients will receive RT at some point during their illness. Despite remarkable advancements in RT over the last two decades, significant limitations remain: the tolerance of surrounding normal tissues constitutes a ceiling on tumour doses. In consequence, the treatment of some radioresistant tumours (e.g. gliomas), tumours close to a sensitive structure (e.g. central nervous system) and paediatric cancers is limited. The main challenge in RT is, therefore, to find novel approaches allowing increasing the normal tissue resistance. Along this line we proposed in 2013 a novel concept: proton minibeam radiation therapy (pMBRT) [1]. It allies the physical advantages of protons with the normal tissue preservation observed when irradiated with submillimetric spatially fractionated beams (minibeam radiation therapy) [2]. We have recently implemented the technique [3] at a clinical center (Proton therapy center in Orsay). The technical developments for minibeam generation at a clinical center will be described. The first complete set of dosimetric data in such small proton field sizes was obtained. Due to proton lateral scattering, each proton minibeam of the array ("tooth of the comb") gets wider as a function of the depth, overlapping at the tumour position. As a consequence, a homogeneous dose distribution is generated inside the tumour (like in conventional RT), while the concept of spatial fractionation (peaks and valleys) and its advantages are maintained in the irradiated regions of normal tissue [1]. See Figure 1. In addition, a negligible dose is deposited in normal tissues after the Bragg peak.
We have recently performed a series of in vivo experiments. In the first one the whole brain of 7 weeks old male Fischer 344 rats (n=16) was irradiated with 100 MeV protons. Half of the animals received conventional seamless proton irradiation (25 Gy in one fraction). The other rats were irradiated with pMBRT (58 Gy peak dose in one fraction). The average dose was deposited in both cases. The animals were followed up for 7 months. A magnetic resonance imaging (MRI) follow up at a 7T small animal MRI scanner as well as histological analysis were performed. Rats treated with conventional proton irradiation exhibited severe skin and brain damage. In contrast, the pMBRT group presented neither skin nor significant brain damage.

These results indicate that pMBRT leads to an increase in normal tissue resistance. This net gain in normal tissue sparing can open the door to an efficient treatment of very radioresistant tumors, which are currently mostly treated palliatively. In a second experiment we have irradiated glioma (RG2) bearing rats with the same average doses. Long-term survivals have been obtained in the pMBRT group indicating tumor ablation without deleterious side effects. In conclusion, pMBRT widens the therapeutic window for brain tumors, potentially offering a curative option for gliomas, a very aggressive tumor, for which none efficient treatment exists nowadays. Additional experiments are planned in order to corroborate this result. If confirmed, it will pave the way to proceed towards clinical trials at Orsay Proton Therapy Center. This novel technique may specially benefit paediatric oncology (central nervous system whose treatments are very limited due to the risk of complications in the development of the infants). Furthermore, pMBRT is predicted to make proton therapy in general more amenable to administration in either a single dose fraction or in a very small number of fractions, which would significantly reduce the costs.

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