Proton minibeam radiation therapy widens the therapeutic window for gliomas.

Y. Prezado[1], W. Gonzalez[1], A. Patriarca[3], G. Jouvion[2], C. Nauraye[3], C. Guardiola[1], D. Labiod[4], M. Juchaux[1], L. Jourdain[5], C. Sebrie[5], F. Pouzoulet[4]

1. Laboratoire d'Imagerie et Modélisation en Neurobiologie et Cancérologie (IMNC), Centre National de la Recherche Scientifique (CNRS); Universités Paris 11 and Paris 7, Campus d'Orsay, 91405 Orsay (France).
2. Institut Pasteur, Histopathologie Humaine et Modèles Animaux, Institut Pasteur, 28 Rue du Docteur Roux, 75015 Paris (France)
3.Institut Curie - Centre de Protonthérapie d'Orsay, Campus Universitaire, Bât. 101, Orsay 91898, France
4. Institut Curie, PSL Research University, Translational Research Department, Experimental Radiotherapy Platform, Orsay, France
5. University Paris Sud, IR4M, Orsay, France

* Corresponding author: prezado@imnc.in2p3.fr

Purpose or Objective

The morbidity of normal tissues continues being the main limitation in radiotherapy. To overcome it, we proposed 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 this technique [3] at a clinical center (Proton therapy center in Orsay) and demonstrated that pMBRT leads to a significant increase of normal tissue tolerances [4] with respect to standard proton therapy. This work aimed at showing that this gain allows using potentially curative doses in the cases of radioresistant tumors, like gliomas.

Material and Methods

Two groups (n=10) of 7 weeks old male Fischer 344 rats were implanted 5000 RG2 rat glioma cells Intracranially. Half of the animals received a whole brain irradiation (pMBRT), 9 days after tumor inoculation. A clinically relevant proton beam energy (100 MeV) was used. The animals were irradiated in the plateau region. Figure 1 shows a schema of the irradiation settings. The dose distributions were completely inhomogeneous, with areas of very high doses in the minibeam paths (70 Gy in one fraction) and areas of low doses in the spaces between minibeams (around 10 Gy). The clinical status of the animals was evaluated daily. Any rat showing adverse neurological signs related to the tumour growth (loss of appetite, seizures, substantial weight loss among others) in the brain was be humanly killed. A third group (n=8) of normal rats were irradiated (whole brain) in the same configuration and followed for 6 months. A magnetic resonance imaging (MRI) study a 7T small animal MRI was performed 6 months after irradiation.

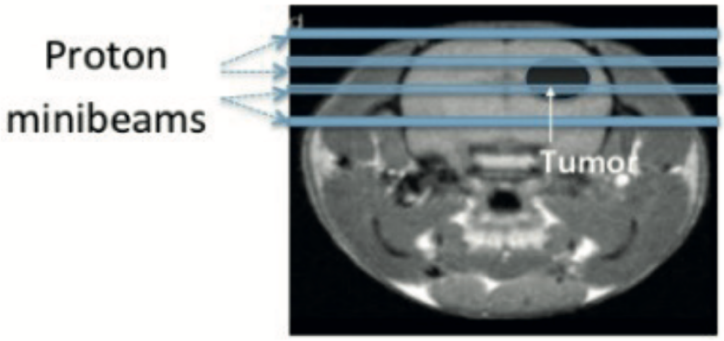

Figure 1. Scheme of the irradiation

Results

Figure 2 shows the survival probability curves (Kaplan-Meyer) for the two tumor bearing animals groups. The controls presented a mean survival time of 20.8 ±0.4. The group receiving pMBRT showed a substantial increase of mean survival time (as today, a factor 5 gain with respect to the controls). The existence of several long term survivals indicates tumor sterilization. The irradiated normal rats exhibited no clinical symptoms for 6 months after irradiation in contrast to rats irradiated in previous studies with lower doses [4]. No substantial damage was observed in the MRI evaluation.

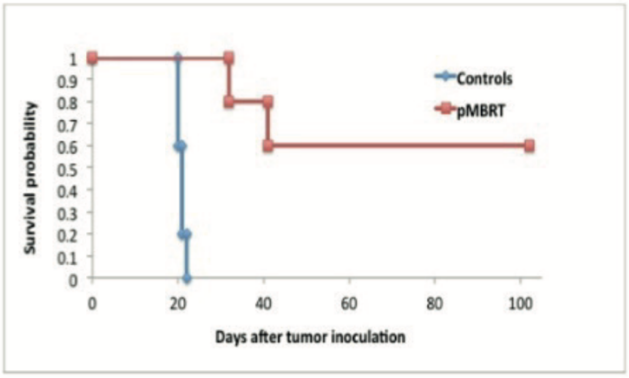

Figure 2: Cumulated survival probability curves for the two glioma bearing rats groups. A significant increase in mean survival time is observed in the pMBRT group.

Conclusion

The results of this pilot study suggest that pMBRT widens the therapeutic window for gliomas and might offer a curative option. The fact that a significant tumor control is even with inhomogeneous dose distributions contradicts the classical paradigm of standard radiotherapy and points at the participation of distinct radiobiological mechanisms.

[1] Prezado et al. Med. Phys. 40, 031712, 1–8 (2013).

[2] Prezado et al., Rad. Research. 184, 314-21 (2015).

[3] Peucelle et al., Med. Phys. 42 7108-13 (2015).

[4] Prezado et al., Nat. Scie. Reports, in press