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Mastering Synchrotron Microbeams for Radiotherapy: effective cancer treatment with remarkable healthy tissue tolerance

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Introduction
Radiotherapy of highly radiation-resistant brain cancers and non-small cell carcinomas in the head, neck and thoracic cavity is limited by the radiation tolerance of the brain and spinal cord. Synchrotron Microbeam Radiation Therapy (MRT) has a remarkably high normal tissue tolerance and allows delivery of extremely high irradiation doses. MRT uses collimated synchrotron radiation to produce quasi-parallel microbeams 25-50 μm wide and separated 100-400 μm apart. This creates high in-beam (peak) doses and low (valley) dose regions between microbeams. Our research at the Australian Synchrotron investigates the efficacy of MRT in treating cancer and its impact on the brain and spinal cord. Furthermore, our study showcases recent advancements in synchrotron cancer treatment technologies including state-of the art dosimetry, *in silico* Monte Carlo dose modelling, image-guided tumour targeting, individualized MRT irradiation planning, and includes long term preclinical brain cancer survival following MRT.

Methods
Our preclinical studies were performed in Hutch 2B of the Imaging and Medical Beam Line at the Australian Synchrotron. Juvenile Fischer and Wistar rats were used to investigate MRT of the brain and spinal cord, respectively, in two independent studies. The first study treated 9L glioblastoma cancers of the brain 12 days after implantation and investigated long term survival, brain chemistry and clinical signs following irradiation with 400 –900 Gy microbeams. The second study of the spinal cord determined the acute (up to 3 days post irradiation) and subacute (6 days post irradiation) response of the spinal cord to MRT for microbeam doses up to 800 Gy. Electrophysiology measurements, MR imaging, and motor and sensory function tests were used to determine spinal cord function before and after MRT.

Results
Preclinical irradiation of 9L tumours showed a 570% increase in the mean survival compared to control rats. Long-term survival was linked to adequate dose coverage of the tumour and tumour volume. Histological results showed early tumour response to microbeams 24 hours after MRT, and the reestablishment of functional neurological tissue in long-term survivors (up to 528 days post tumour implantation).
In the spinal cord, no neurologic deficits or loss in motoric abilities was observed up to peak doses of 400 Gy. Reversible neurologic deficits occurred at 450 Gy, and non-reversible neurologic deficits developed with peak doses above 450 Gy.
These results demonstrate a remarkable brain and spinal tissue tolerance towards synchrotron microbeam radiation doses. Our work will assist the design of future MRT studies, showcase MRT as a treatment modality for radiation-resistant brain cancer, and benchmark the tolerance of CNS tissues to MRT.

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