Memory and survival after bidirectional MRT: a study in two animal models of malignant brain tumour

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Rationale and objectives

Despite the many technical innovations we have seen in hospital equipment used for diagnosis and therapy over the last two decades, little has changed in the prognosis for patients with malignant brain tumours. Although radiotherapy has been identified in several studies as the single most important independent factor predicting outcome, radiotherapy with hospital-based equipment adds on average only 3 months to the live of a patient with glioblastoma multiforme, the most malignant type of human brain tumours (Mineo et al., 2007). Synchrotron microbeam radiation therapy (MRT) can be described as a special form of radiotherapy. X-ray doses up to two orders of magnitudes higher than that ordinarily used in the hospital can be deposited in the tumour location in one single fraction. The aim of our studies is to develop a suitable MRT protocol in which a radiosensitizer is used as adjuvant therapy. Since memory defects are frequently seen with conventional radiotherapy to the brain, we have been investigating the effects of our therapeutic approach on new memory formation. For this purpose, we have used the object recognition test as described by Ennaceur and Delacour (1998).

Methods

Our experiments were conducted in two animal models of malignant brain tumour, C6 and F98 glioma. To generate the tumours, 100,000 glioma cells were stereotactically implanted in the brains of adult rats, through a burr hole set 3 mm to the right of the midline and 3 mm behind the coronal suture. The animals underwent MRT in bidirectional mode with a skin entry dose of 350 Gy on day 13 after tumour implantation. We used 1 cm wide arrays consisting of 50 microplanar quasiparallel microbeams with a beam width of 25 μm and a centre-to-centre distance of about 200 μm. With the aim to increase the radiosensitivity of the tumour, we introduced experimental groups in which animals received Buthione–SR-Sulfoxamine (BSO) 2 hrs prior to MRT. BSO decreases glutathione levels in the tumour tissue and thus renders tumour cells more susceptive to damage by free radicals generated in the irradiation process. Glutamine (GLN) was studied for its cytoprotective capacities in the setting of MRT. Object recognition tests to assess the ability for new memory formation were conducted in tumour-bearing and tumour-free animals, in irradiated animals and non-irradiated controls on day 13 after tumour implantation, 2 weeks and 1 month after MRT. For long-term survivors, memory was retested in intervals up to 1 year after MRT.

Results

A significant increase in survival time was seen with our MRT protocol, in both C6 glioma and in the more aggressive F98 glioma. A further increase in survival time was seen after injection of BSO in both models (being statistically significant in F98 but not C6 glioma). In C6 glioma, the 1-year survival rate increased from 50% with MRT alone to 66.7% with administration of BSO prior to MRT. Overall survival times in the much more aggressive

F98 glioma are much shorter than in C6 glioma. The 1-month survival rate increased to 66.7% with MRT and BSO, from 25% with MRT alone.
Surprisingly, the survival increase seen with BSO administration prior to MRT was accompanied by a significant performance decrease in the memory test within the first two months after MRT. Glutamine, on the other hand, appeared to act protective for memory function.

Conclusion

Since administration of BSO has the desirable effect of prolonging the recurrence-free interval, we see two possibilities for our further studies: 1) combining the administration of BSO with a cytoprotective agent for the healthy brain tissue, or 2) testing another agent that will decrease glutathione levels in the tumour but have less adverse effects on memory function.

References

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