

## Microbeam radiation therapy (MRT): Milestones - Clinical prospects

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### Rationale and objectives

Collateral damage to vital normal tissues during radiotherapy can be reduced by using three-dimensional treatment planning and external sources of ionizing radiation. Nevertheless, pediatric oncologists try to postpone or forgo any radiosurgery or radiotherapy, especially for children under three years old because irradiating a child's CNS entails a substantial risk of dysfunctional central nervous system (CNS) development<sup>1, 2, 3</sup>. In radiosurgery, spatially accurate and highly conformal beams of radiation are targeted toward a well-delineated tumor in a single session<sup>5</sup>. High-dose radiosurgery using multiple millimeters-wide beams of X rays was first described in 1909<sup>6</sup>. In modern radiosurgery<sup>7</sup>, multiple millimetres-wide beams of linac-generated X rays, or of gamma rays, converge in the target. Might MRT, a radiosurgery mediated by multiple microscopically thin planar beams of synchrotron-generated X rays, yield larger therapeutic indices for CNS tumors than other forms of radiosurgery or radiotherapy?

### Methods

MRT, a spatially fractionated radiotherapy, uses an array of microscopically thin, nearly parallel synchrotron-generated X-ray beams<sup>8, 9</sup>. Peak radiation doses are up to fifty times higher than in other radiosurgeries. Unlike conventional radiotherapy, for which the effect of changing an irradiation parameter, e.g., the dose fractionation schedule, is predictable, methods to predict the effect of varying an MRT parameter are only beginning to be developed. Among MRT parameters are array width and height, slit width, spacing of microbeams, energy spectrum, changes in tissue dose microdistribution with tissue depth and, possibly in the future, the schedule selected for temporal fractionation of multidirectional MRT.

### Results

In animal experiments, MRT has shown unprecedented sparing of normal radiosensitive tissues as well as preferential damage to malignant tumor tissues growing into and around such normal tissues in laboratory animals<sup>10, 11, 12-15, 16-18, 19, 21, 22, 23-25, 26-28</sup>. MRT research at the National Synchrotron Light Source (NSLS), Upton, New York, and at the European Synchrotron Radiation Facility (ESRF), Grenoble, France, has shown that single-fraction, unidirectional MRT yields a larger therapeutic index than does single-fraction unidirectional broad beam irradiation for the intracerebral rat 9L gliosarcoma (9L GS)<sup>13, 15-17, 23-26</sup> and for the transplanted subcutaneous murine mammary carcinoma

EMT-613-15, as does bidirectional (orthogonally cross-fired) MRT for the subcutaneously transplanted, aggressively invasive, extraordinarily radioresistant murine squamous cell carcinoma VII20.

Since postponing radiotherapy may jeopardize survival of some children with brain tumors<sup>29</sup>, MRT has been undergoing and undergoes experimental assessment in living animals because it is believed to be potentially useful for inhibiting children's brain tumors while sparing nearby normal CNS tissues, which should reduce the burden of malignant cells and, therefore, enhance the effectiveness of ancillary therapies<sup>30</sup>. The relative sparing by X-ray microbeams of normal tissues of vertebrates - particularly of their normal central nervous system tissues - has been documented in suckling and adult rats<sup>18, 24, 26, 28</sup>, duck embryos<sup>12</sup>, and weanling piglets<sup>19</sup>. These preclinical results, although encouraging, are not yet sufficient to justify a Phase I (safety) trial of MRT for human patients because they are all based on small animal models, except for a set of studies at the ESRF that used the normal piglet cerebellum<sup>16</sup>. All other normal-tissue microbeam-tolerance studies at the NSLS and ESRF have used fruit-fly pupae<sup>21</sup>, rabbits, rats<sup>17, 18, 24-26</sup>, gerbils, mice<sup>14, 20, 22, 27</sup>, duck embryos<sup>12</sup>, and chick embryos<sup>10, 11</sup>.

### Conclusions

The 6 GeV ESRF ring is the only source of synchrotron radiation in Europe generating intense X ray microbeams for experimental MRT, having a broad energy spectrum of photons peaking in the 80 – 120 keV range and beam intensities high enough, potentially, to deliver an absorbed physical radiation dose to deep targets in large animals, small children, and adult humans; MRT requires the delivery of several hectogray doses within a fraction of a second, deep to the skin. Regulatory and logistic requirements for implementation of clinical MRT will be stringent. The impetus for investigating the potentially unique advantages of MRT for certain human diseases has been recognized and is sustained by the recent consensus of an ESRF scientific advisory panel of sufficient diversity and broad expertise in its membership to merit serious consideration by the ESRF directorate. Accordingly, we propose that ID17 be used to implement a large-animal veterinary MRT study for veterinary radio-oncology. In that way, a wider community of clinical veterinarians and physicians will be able to assess outcomes from MRT in relation to those from existing radiotherapies for similar lesions in large animals.

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