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Review

Effects of pulsed, spatially fractionated, microscopic synchrotron X-ray beams on normal and tumoral brain tissue

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ABSTRACT

Microbeam radiation therapy (MRT) uses highly collimated, quasi-parallel arrays of X-ray microbeams of 50–600 keV, produced by third generation synchrotron sources, such as the European Synchrotron Radiation Facility (ESRF), in France. The main advantages of highly brilliant synchrotron sources are an extremely high dose rate and very small beam divergence. High dose rates are necessary to deliver therapeutic doses in microscopic volumes, to avoid spreading of the microbeams by cardiosynchronous movement of the tissues. The minimal beam divergence results in the advantage of steeper dose gradients delivered to a tumor target, thus achieving a higher dose deposition in the target volume in fractions of seconds, with a sharper penumbra than that produced in conventional radiotherapy.

MRT research over the past 20 years has yielded many results from preclinical trials based on different animal models, including mice, rats, piglets and rabbits. Typically, MRT uses arrays of narrow (∼25–100 μm wide) microplanar beams separated by wider (100–400 μm centre-to-centre) microplanar spaces. The height of these microbeams typically varies from 1 to 100 mm, depending on the target and the desired preselected field size to be irradiated. Peak entrance doses of several hundreds of Gy are surprisingly well tolerated by normal tissues, up to ∼2 yr after irradiation, and at the same time show a preferential damage of malignant tumor tissues; these effects of MRT have now been extensively studied over nearly two decades. More recently, some biological *in vivo* effects of synchrotron X-ray beams in the millimeter range (0.68–0.95 mm, centre-to-centre distances 1.2–4 mm), which may differ to some extent from those of microscopic beams, have been followed up to ∼7 months after irradiation. Comparisons between broad-beam irradiation and MRT indicate a higher tumor control for the same sparing of normal tissue in the latter, even if a substantial fraction of tumor cells are not receiving a radiotoxic level of radiation. The hypothesis of a selective radiovulnerability of the tumor vasculature versus normal blood vessels by MRT, and of the cellular and molecular mechanisms involved remains under investigation. The paper highlights the history of MRT including salient biological findings after microbeam irradiation with emphasis on the vascular components and the tolerance of the central nervous system. Details on experimental and theoretical dosimetry of microbeams, core issues and possible therapeutic applications of MRT are presented.

Contents

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1. Introduction and historical overview on microbeam radiation therapy

High doses of kilovoltage X-rays, spatially fractionated by a stiff metal grid (1 mm-thick strands of iron wire delimiting 2.5 mm × 2.5 mm spaces), pressed hard on the skin, have palliated deep underlying cancers [1]; skin cells shielded by the iron grid quickly healed the resultant skin burns, thus preventing the feared skin radiation necrosis. A half-century later, skin-sparing megavoltage radiotherapy supplanted such millimeter-scale grid irradiations. To date, few radiooncologists still use modified versions of grid therapy [2–4].

Spatial fractionation of ionizing radiation in the microscopic range was first reported in the sixties. A 25 μm-wide 22 MeV deuteron microbeam, used to simulate the effects of cosmic radiation [5], failed to elicit cerebral damage in mice unless absorbed doses were over ∼3000 Gy [6]; the deuterons, however, reached only ∼1.5 mm tissue depth.

In the late 1980s, at the National Synchrotron Light Source (NSLS) of Brookhaven National Laboratory (BNL), U.S.A., Per Spanne, a Swedish radiation physicist, Daniel N. Slatkin and their colleagues attempted microtomography of the head of an anesthetized mouse using a ∼30 μm-diameter pencil beam of synchrotron X-rays with absorbed doses under 10 Gy being delivered to the brain. As the contrast was poor, they remembered the high tolerance of normal tissues for microbeams reported by Curtis [6] and thus increased the microbeam doses up to ∼200 Gy. The mouse recovered normally. One month later, a careful search of the brain revealed no histopathological evidence of damage along the beam's path. Therefore, it was decided to investigate the effects of histologically better traceable microplanar 50–150 keV synchrotron-generated X-ray beams on murine brains, using arrays of quasiparallel 25 μm-wide beam slices spaced 50–200 μm on centre [7]. The tissue lesions resembled those induced by deuteron microbeams [5,6]. Surprisingly, animals withstood absorbed doses of hundreds, even thousands of gray from X-rays delivered to microscopic slices of their central nervous system (CNS) tissues, in the absence of tissue necrosis [8,9]. Remembering that the use of synchrotron X-rays for radiosurgical applications had been proposed by Börje Larsson in 1983 [10], the radiotherapeutic potential of microbeam arrays was explored by irradiating transplantable intracerebral 9L gliosarcomas (9LGS) in rats, a tumor model that had been in use at BNL for over a decade [11]. It appeared that this "microbeam radiation therapy" (MRT), using arrays of microplanar, synchrotron-generated X-ray beams, safely delivered radiation doses to contiguous normal animal brain that were much higher than maximum doses tolerated by the same normal tissues of animals or patients from any standard millimeters-wide radiosurgical beam [12]. In 1994 Spanne, together with a Swiss-sponsored MRT research group, started developing MRT research using a dimensionally adjustable multislit microcollimator made by Archer [13]. Spanne's unfortunate death on September 1998 was a sad loss for his collaborators and colleagues, and delayed MRT research. However, preclinical experiments begun in 1995 at the ESRF have been pursued [14–18] as well as similar experiments at Brookhaven National Laboratory and later at several other centres worldwide.

Microplanar irradiation delivers peak radiation doses more than one order of magnitude higher than other radiosurgery techniques [19–22]. It spares fast-growing, immature tissues such as the duck brain in ovo [23] and the chick chorio-allantoic membrane *in vitro* [24]. *In vivo*, the cerebella of normal suckling Sprague–Dawley rat pups and of normal weanling piglets were irradiated by arrays of parallel, synchrotron-wiggler-generated X-ray microbeams in energies covering the MRT-relevant range (≈50–600 keV) at the ID17 beamline facility of the ESRF. Most animals developed normally over a span of at least one year after irradiation [15,16]. An example of a histological section of the hindbrain of the weaned piglets is shown in Fig. 1. Microbeams can selectively ablate slices of neurons, oligodendrocytes, and astrocytes in the CNS, without causing tissue necrosis. It has been reported that microbeams can induce temporary demyelination in two weeks without axonal or vascular damage, with remyelination following in 3 months post-irradiation [25]. Similarly, in the rat spinal cord exposed to a 270 μm-thick planar beam (entrance dose 740 Gy), proliferation, migration and differentiation of progenitor glial cells could have promoted production of new, mature and functional glial cells and consecutive remyelination [26]. Thus, MRT was assessed for its potential therapeutic effects in inhibiting growth of tumors while sparing nearby normal CNS tissues. A favorable therapeutic ratio may be particularly important for the

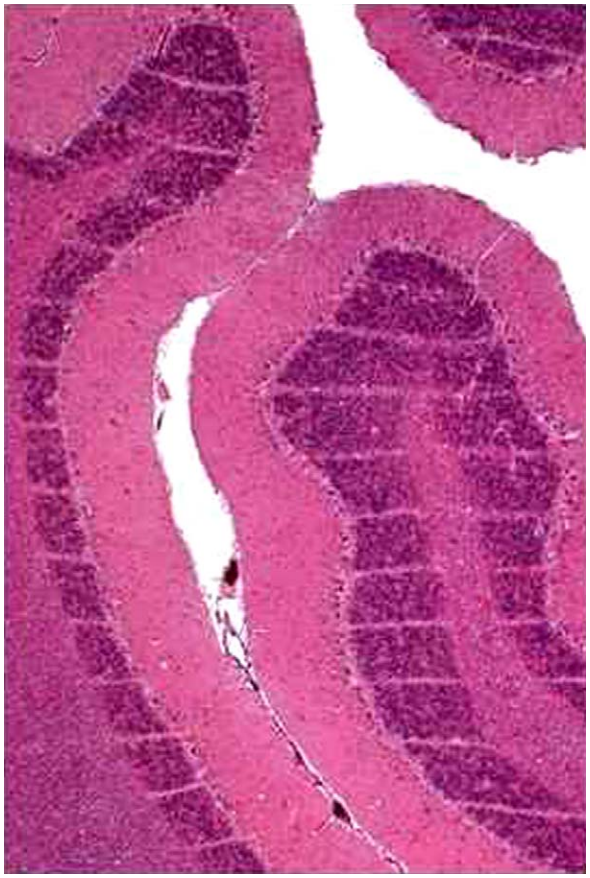

Fig. 1. Microbeam irradiated normal CNS tissue of weaned piglets (1.5 cm × 1.5 cm ∼28 μm-wide beams ∼210 μm on centre, 625 Gy). The histological sections look normal, except for "stripes" due to the dropout of neuronal/astroglial nuclei. This sharp spatial fractionation is preserved throughout the cerebellum. No tissue necrosis, hemorrhage or demyelination was observed.