Microbeam Radiation Therapy (MRT): achievements and future perspectives

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THE DOSE VOLUME EFFECT

22 MeV Deuteron beam; cerebral cortex of mice

Zeman et al, Radiat Res 15, 496, 1961
CONDITIONS TO EXPLOIT DOSE VOLUME EFFECT

1. the right spectrum

ESRF spectrum

1 MeV

2. Quasi planar parallel beams
Spatial fractionation of the Synchrotron beam -> array of collimated microbeams

Tecomet MSC, single stack

TMSC = Multislit collimator

Bräuer-Krisch et al, 2005, Rev Sci Instrum
INTRODUCTION TO MICROBEAM RADIATION THERAPY

ID17

ID17 biomedical beamline at the ESRF.

800 µm max

Goniometer stage

50 µm FWHM microbeams separated by 400 µm

MRT Multi-Slit Collimator (MSC)
MRT: HIGHER THERAPEUTIC RATIOS

Preclinical long-term experiments involving different species such as insects, (Schweizer, Spanne et al. 2000), birds, (Dilmanian, Morris et al. 2001) rodents, (Slatkin, Spanne et al. 1995; Zhong, Morris et al. 2003; Serduc, Verant et al. 2006; Serduc, Christen et al. 2008; van der Sanden, Bräuer-Krisch et al. 2010; Laiissue, Bartsch et al. 2013) and pigs (Laissue et al. 2001) have revealed an extraordinary tolerance of normal organs and blood vessels exposed to fractionated radiation doses in excess of 100 Gy delivered by arrays of MB. This tolerance was particularly evident in suckling rats and weaning piglets, in whom the irradiated brain is still developing. (Laissue, Blattmann et al. 2007). (Hanson et al. 2013; Laissue et al., 2001, 1999).

MRT in small animal models has achieved therapeutic ratios that clearly exceed those obtained by conventional X-rays: Bouchet, Lemasson et al. 2013; Bouchet, Bidart et al. 2014) Further, MRT-associated bystander effects have been identified. (Dilmanian, Qu et al. 2007; Fernandez-Palomo, Schultke et al. 2013; Smith, Wang et al. 2013; Mothersill, Fernandez-Palomo et al. 2014) The tumor control of MRT has been improved by combining MRT with various compounds,(Schultke, Juurlink et al. 2008; Bouchet, Boumendjel et al. 2012; Griffin, Koonce et al. 2012) radiation-enhancing substances,(Le Duc, Miladi et al. 2011) gene-mediated immunoprophylaxis,(Smilowitz, Blattmann et al. 2006) and other adjuvant techniques.

Animal models: insects, birds, mice, rats, piglets etc.
Different tumor models: 9L gliosarcome, F98, C6 etc.

Protocol:
Injection of 10 000 cells @ 3.5 mm from bregma, 6 mm deep Controls survive 19 days MRI for tumor presence
THE MRT PROJECT

Extraordinary normal tissue sparing
Cellular damage confined to microbeams
No macroscopic lesions
No changes in vascular permeability

Laissue et al., 2010]

MRT reduces tumor blood supply ➔ tumor hypoxia

[Bouchet et al., 2010]
Hyp: Preferential effects of MRT on tumor vessels / normal vessels

Mature vs Immature vessels

Differential effect on vasculature between tumor and normal tissue vasculature

Sensitivity to MBs depends on the developing state of the vasculature

chorioallantoic membrane (CAM)

- Significant increase in tumor vessel permeability at short term after MRT (D2-5)

- No change in normal brain tissue within the same period

Specific delivery of drugs - chemical compounds to tumoral tissue

Serduc et al 2010
Only 100 Gy peak entrance dose in the rat equivalent to what is realistically feasible in humans.

Best ever increase in lifespan obtained: 1220% !!!

Survival proportions

Rotation axes – seated patient

Such strategies highlight the potential of MRT, but remain in the far future technical feasibility must include studies on brain motion.

CURRENT STATUS OF MRT AT ESRF

Dosimetry protocol for broad beam dosimetry established

High resolution dosimetry (<20 micron) is feasible (10% error)

A TPS developed for MRT

A Patient safety system exists and is compatible for human trials

Irradiation of a first cat patient with spontaneous tumor

No adequate human patient positioning exists yet
SPIRAL MRT: A NEW CONCEPT / WORK BY MATTIA DONZELLI (POSTER # 27)

vertical scanning
phantom rotation
incoming X-ray beam
SPIRAL MRT: A NEW CONCEPT / WORK BY MATTIA DONZELLI

Theoretical dose delivery of 50 Gy in one single session while preserving spatially fractionated beams at the normal tissue.
SPIRAL MRT: A NEW CONCEPT / WORK BY MATTIA DONZELLI
CONCLUSIONS

Spiral MRT combines certain advantages from the spatially fractionated feature:

- The higher normal tissue tolerance due to the dose volume effect
- Homogenous Broad beam irradiation in the target volume (inferior repair)
- Feasible at slightly lower dose rates than those applied for MRT:
  
  100 Gy/sec instead of > 10 000 Gy/sec (ESRF)
  Compact sources, Carbon nanotube technology, smaller Synchrotrons?

However:
Probably loss of differential effects (tumor vasculature, bystander, gene expression etc.)
COLLABORATIVE RESEARCH FOR MRT

Thank you for your kind attention!