Microbeam Radiation Therapy: Definition

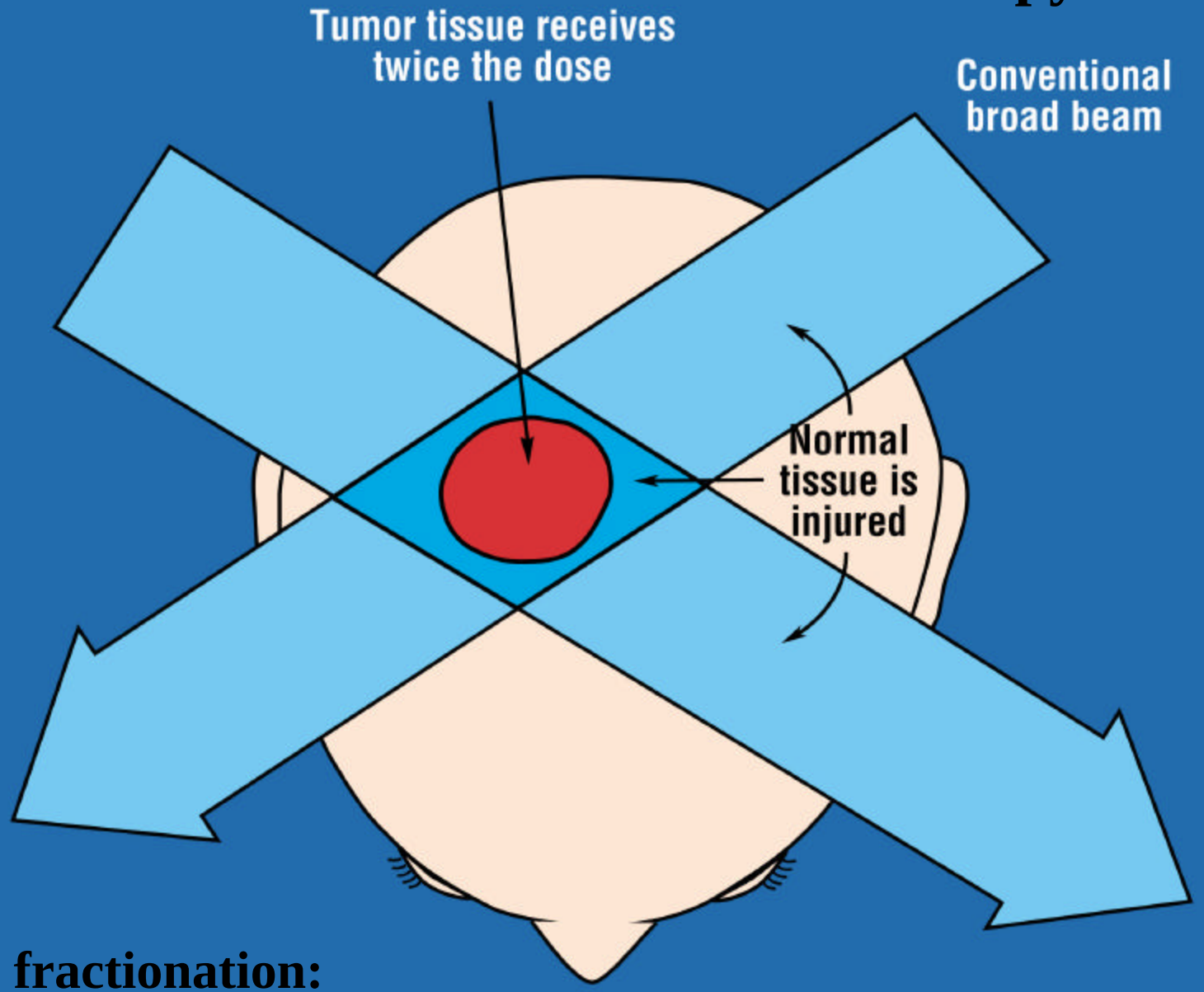
Microbeam radiation therapy uses synchrotron-generated arrays of parallel microplanar beams of x rays (microplanar beams, microbeams) commonly <100 μm wide.

Conventional Radiation Therapy and Radiosurgery of the Central Nervous System (CNS) Tumors

Although XRT is currently the primary treatment for tumors of the CNS, it has several shortcomings:

- It is palliative rather than curative in treating high-grade gliomas.
- Its use in pediatric neuro-oncology is limited to children above 3 years, and even there it is used judiciously.
- Re-treatment is possible only within a certain accumulative dose limit.
- It is administered in 30 or more fractions (except for radiosurgery which is not fractionated).

Conventional Radiation Therapy



Dose fractionation:
commonly 30 daily fractions of 2 Gy each

t cerebellum
adiated with microbeam triplets
000 Gy (visible)
l 250 Gy (not visible),
erved 30 day after irradiation

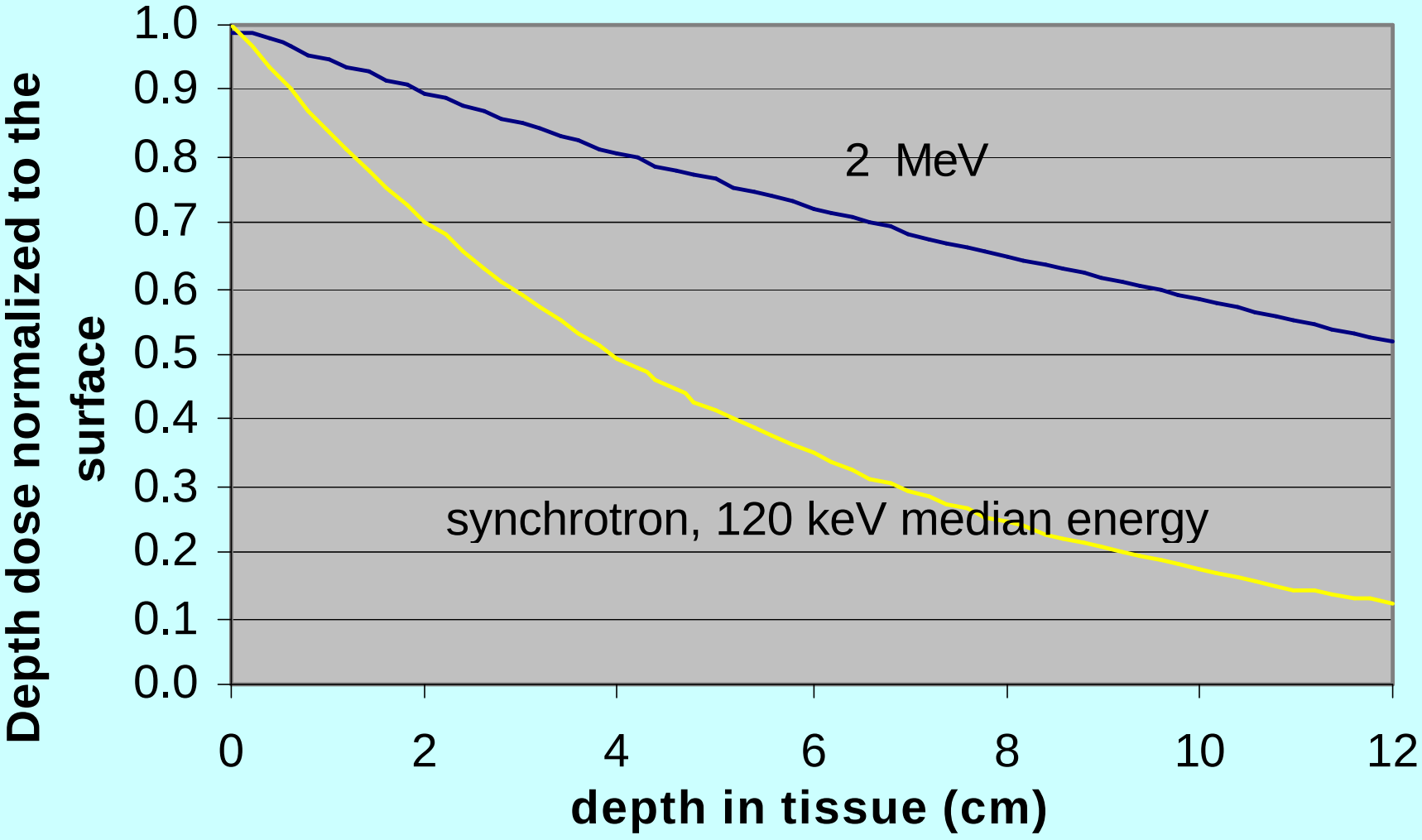
Tolerance of the CNS to Conventional Beams

Typical tolerance dose:

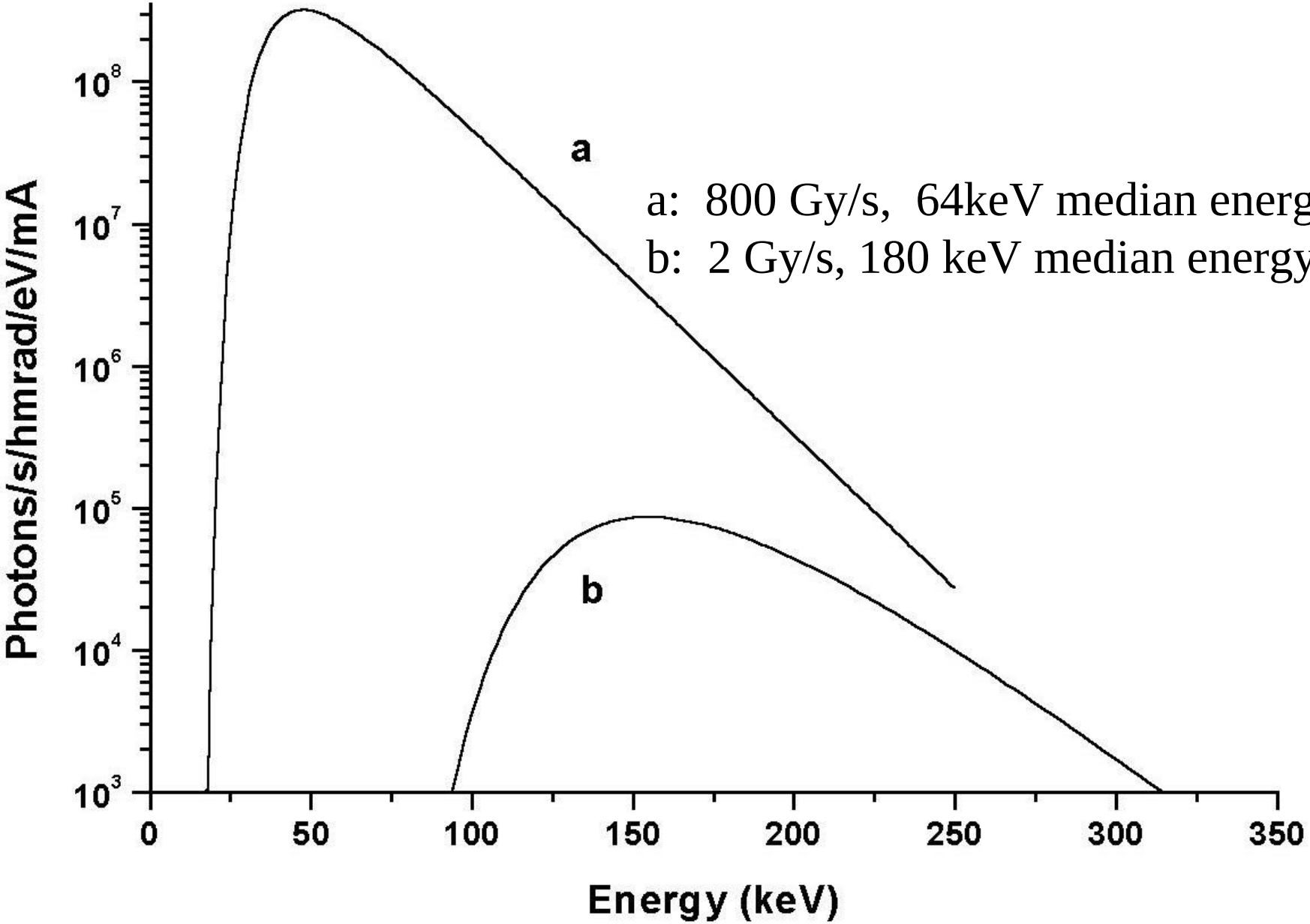
- 10 Gy to single-fraction dose
- 50 Gy to fractionated dose

MRT: Historical Notes

- 1950s and 1960s: Curtis, Zeman, et al. 25-µm deuteron beam.
- Late 1980s: Slatkin and Spanne, high dose Micro-CT; histological study with Laissue.
- Late 1980s: Dilmanian's Monte Carlo simulations; sharp edge of an x-ray beam at depth in tissue.
- 1992: Slatkin, Spanne, and Dilmanian received LDRD-type for work at the NSLS's X17B1 beamline. Laissue and Gebbers joined them. A PNAS paper was published (Slatkin et al., 1995).
- 1995 Spanne moved to ESRF. A European MRT program was initiated (Spanne passed away in the Swissair air crash in 1998).
- Presently: Work continues at BNL and ESRF. Applications in stem cell research and chemotherapy are also considered.

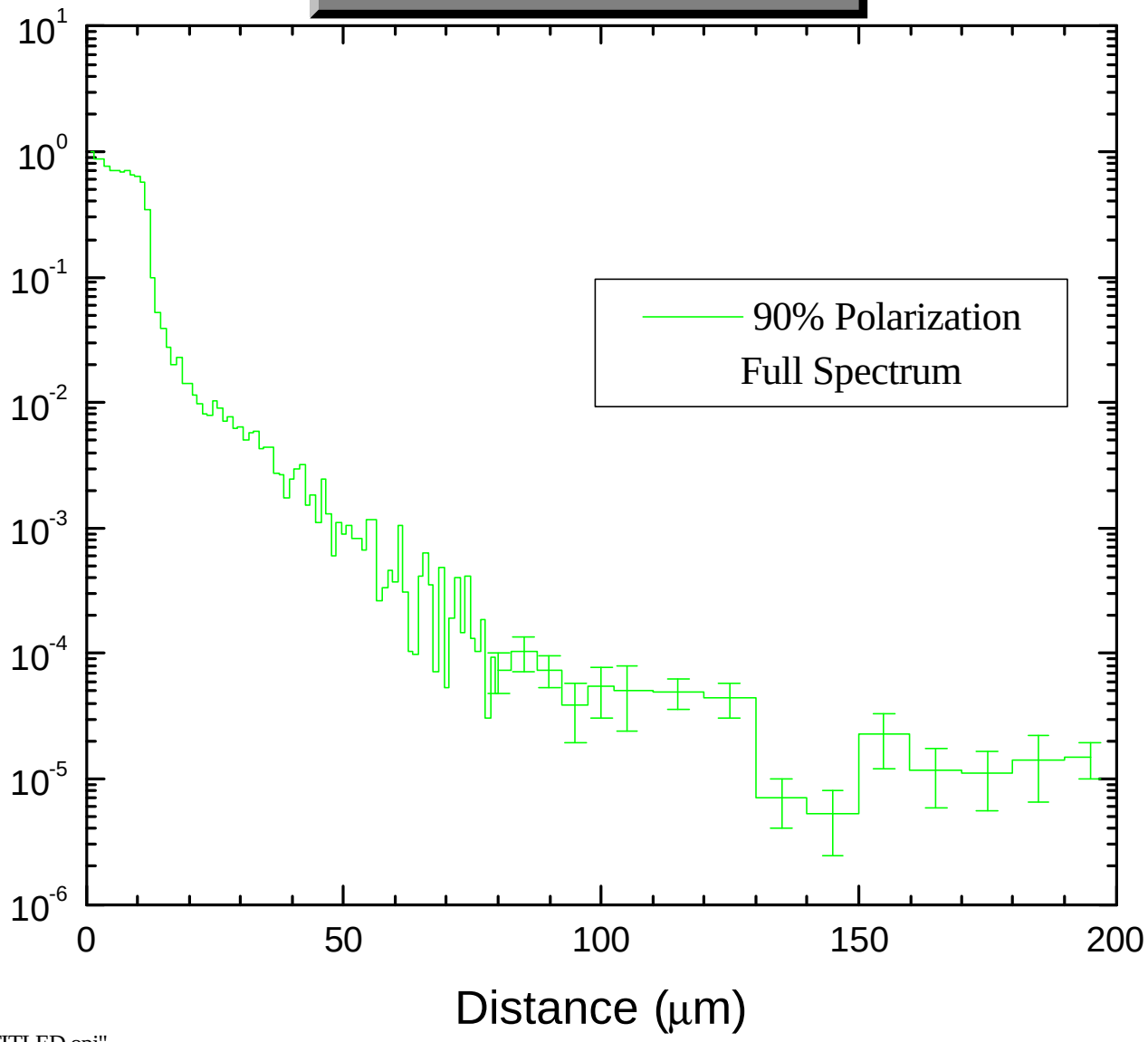

Depth dose normalized to the surface
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
2 MeV
synchrotron, 120 keV median energy
0
2
4
6
8
10
12
depth in tissue (cm)

Effects of Beam Filtration on Dose Rate and Beam Energy

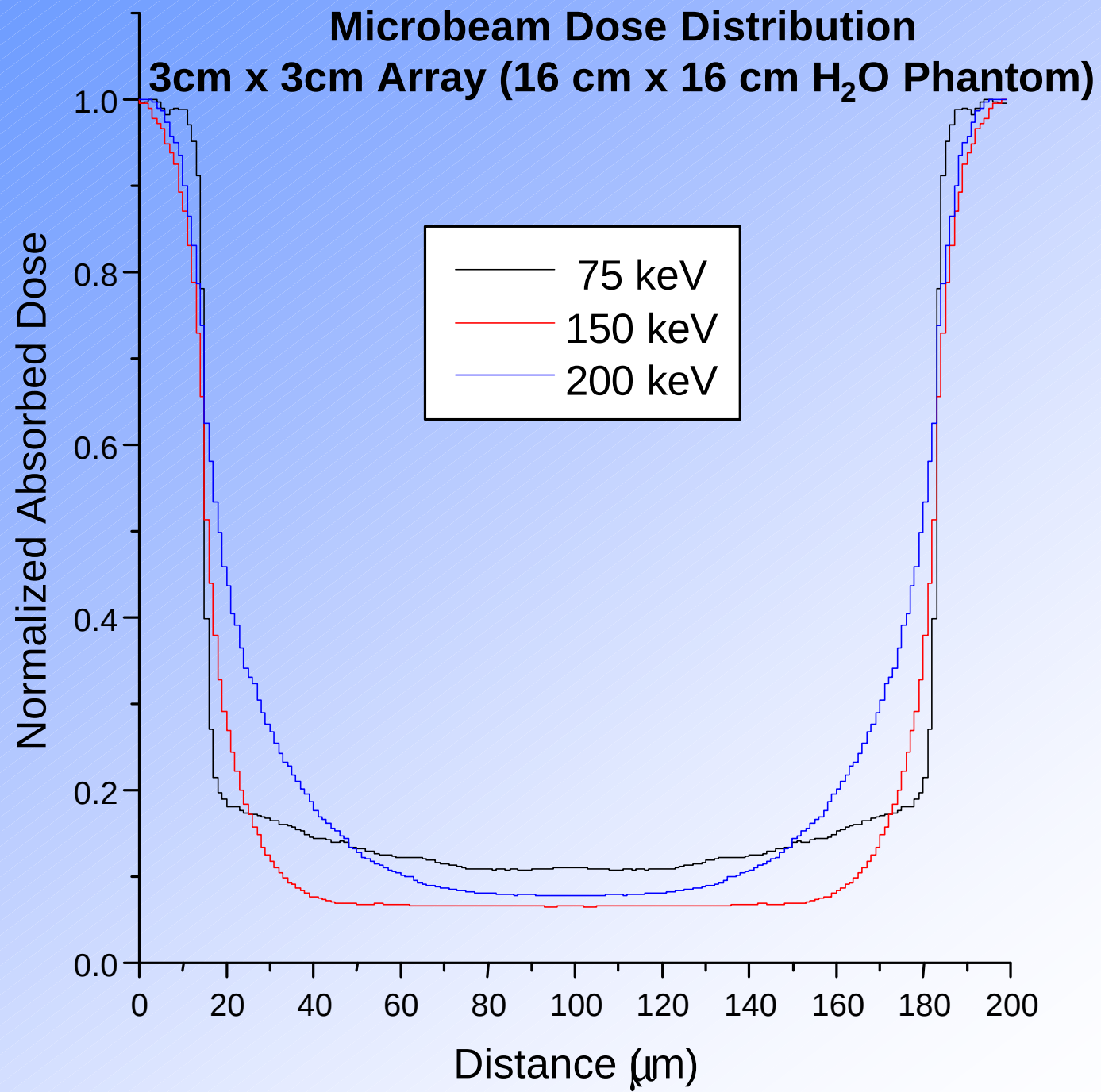


a: 800 Gy/s, 64keV median energy
b: 2 Gy/s, 180 keV median energy

The New EGS4 Simulation



"UNTITLED.opj"


Microbeam Dose Distribution
3cm x 3cm Array (16 cm x 16 cm H_2O Phantom)
Normalized Absorbed Dose
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
160
180
200
Distance (μm)
75 keV
150 keV
200 keV

Application of Microbeams in Radiation Therapy

Therapeutic index:

Qualitative Definition:

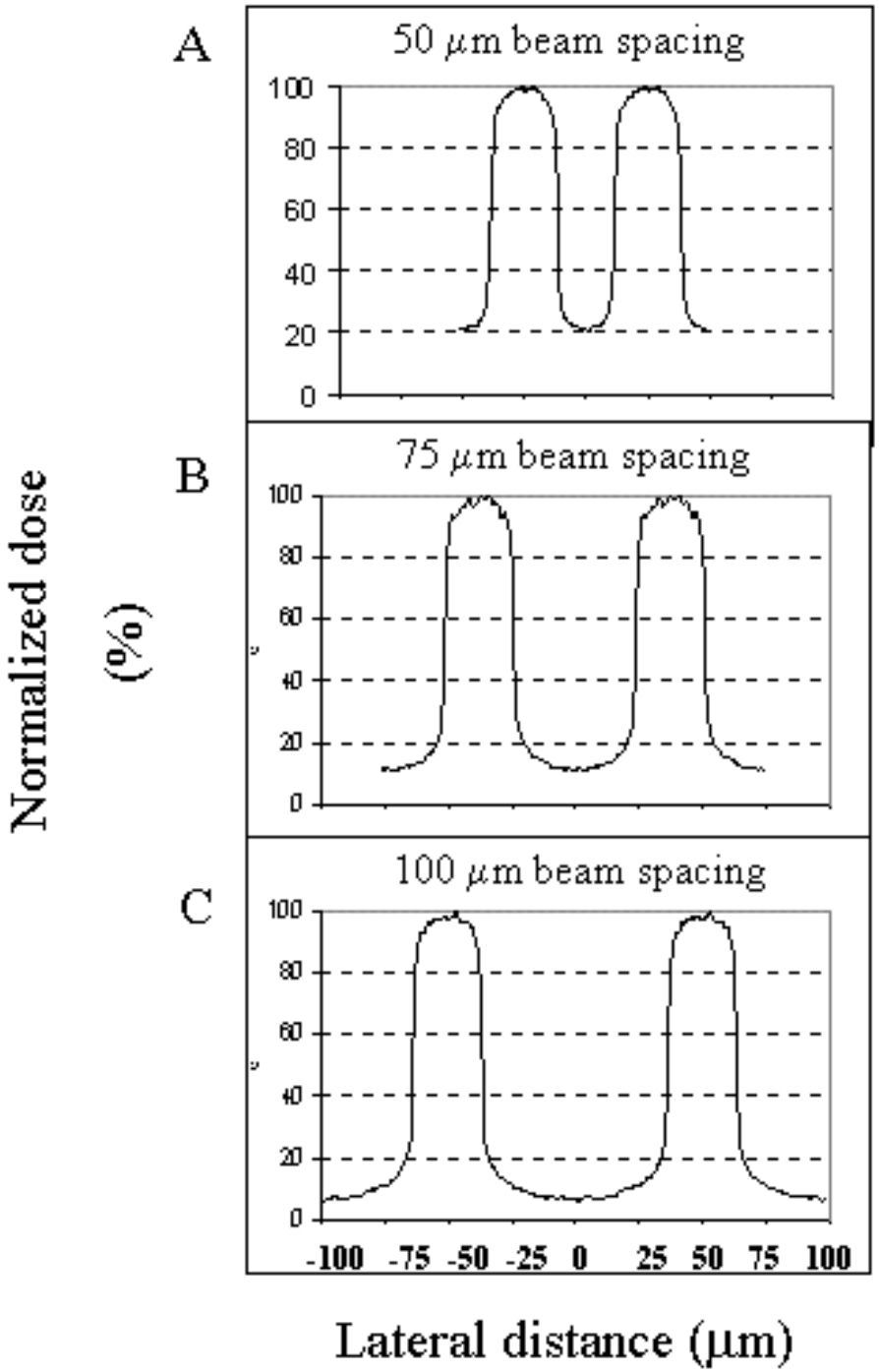
The Maximum dose that produces acceptable normal-tissue damage, divided by the minimum dose that controls the tumor

Quantitative Definition:

"ED_{50} (50% end-point-effect dose), divided by TCP_{50} (50% Tumor control probability)".

Therapeutic Index of the Rat 9L gliosarcoma (9LGS) Brain Tumor

Single-fraction, unidirectional MRT was compared with other investigators' findings with single-fraction unidirectional broad beams.



150, 250, and 300 Gy in-beam incident doses

250, 300, and 500 Gy doses

500 Gy dose

Monte Carlo Simulations for Calculating Microbeams' Dose Distributions in the Rat Brain

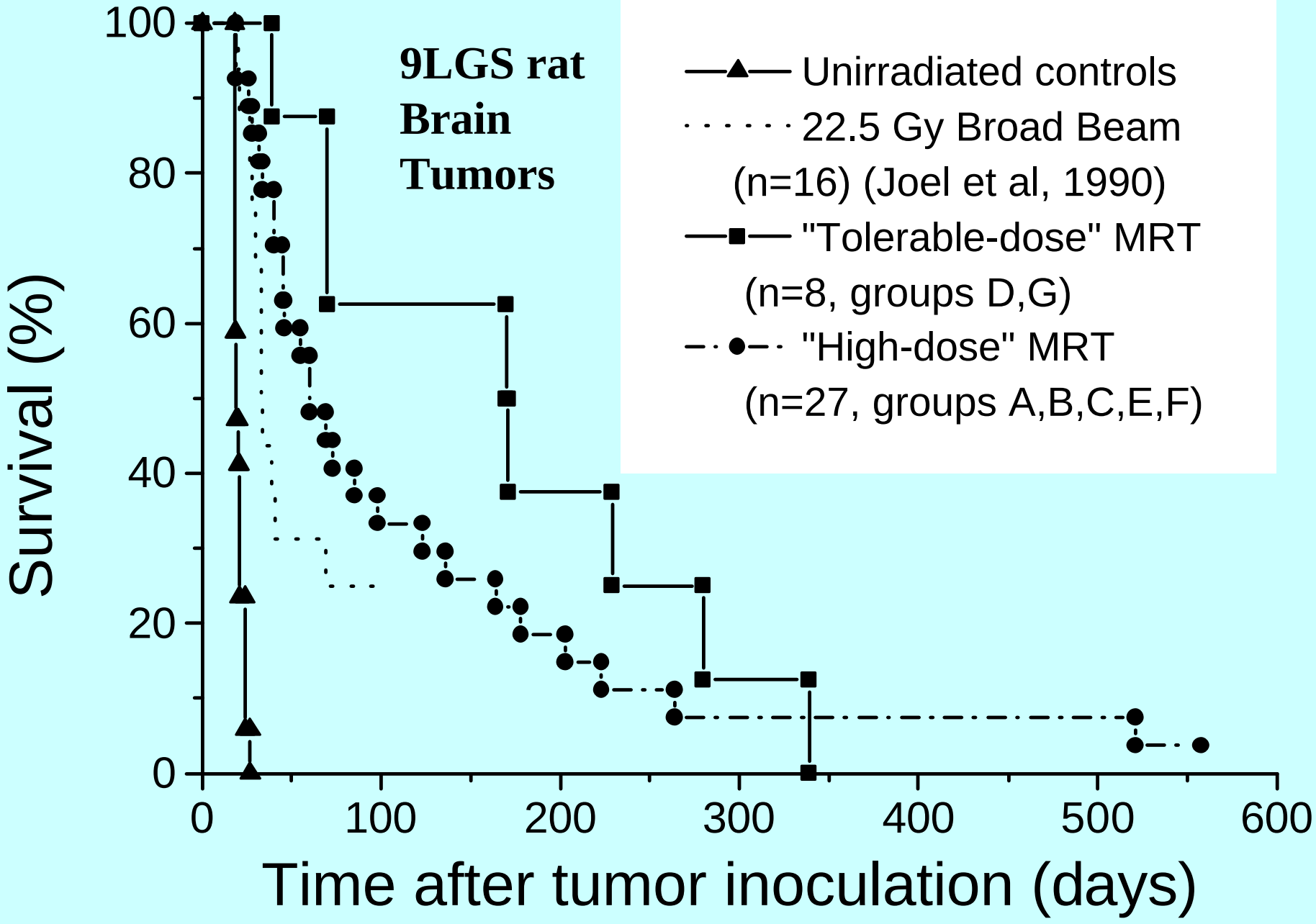
Irradiation parameters:

Lateral irradiation; 27 μm beam width; 9 mm x 9 mm array size; 75 keV median beam energy.

Beam spacing (μm)	Valley dose (% peak dose)	Integrated Dose (% peak dose)
50	19	63
75	9.2	44
100	5.3	33

Absolute Valley / Integrated Doses (Gy) at the Center of the Brain (27 μm beam width) for Different In-beam Doses

Beam spacing	150 Gy	250 Gy	300 Gy	500 Gy
50 μm	20 / 68	34 / 113	40 / 135	--------
75 μm	--------	17 / 79	20 / 95	33 / 158
100 μm	--------	--------	--------	19 / 118


9LGS rat
Brain
Tumors
Unirradiated controls
22.5 Gy Broad Beam
(n=16) (Joel et al, 1990)
"Tolerable-dose" MRT
(n=8, groups D,G)
"High-dose" MRT
(n=27, groups A,B,C,E,F)
Survival (%)
Time after tumor inoculation (days)
0
20
40
60
80
100
0
100
200
300
400
500
600

Intracerebral 9LGS: Comparing the Therapeutic Efficacy of MRT (Tolerable-dose) with Broad Beams

Quantity Compared and Statistical Test	MRT (Tolerable-dose)	Broad Beam
Median survival (95% confidence interval)	170 days (70, NA)	34 days (30, NA)
100-day survival ($p<0.03$)	63%	25%
Brain-tissue damage	Minor microcalcifications and local edema	Tumor scar, neuronal depletion, white-matter necrosis

MRT is better Tolerated than Broad Beams by the Rat Brain
Endpoint: White Matter Necrosis

MRT's Advantage (using in-beam MRT doses):

At least 10-fold advantage; white matter necrosis was detected only in some rats after High-dose MRT.

MRT's Advantage (using integrated MRT doses):

At least 3-fold advantage

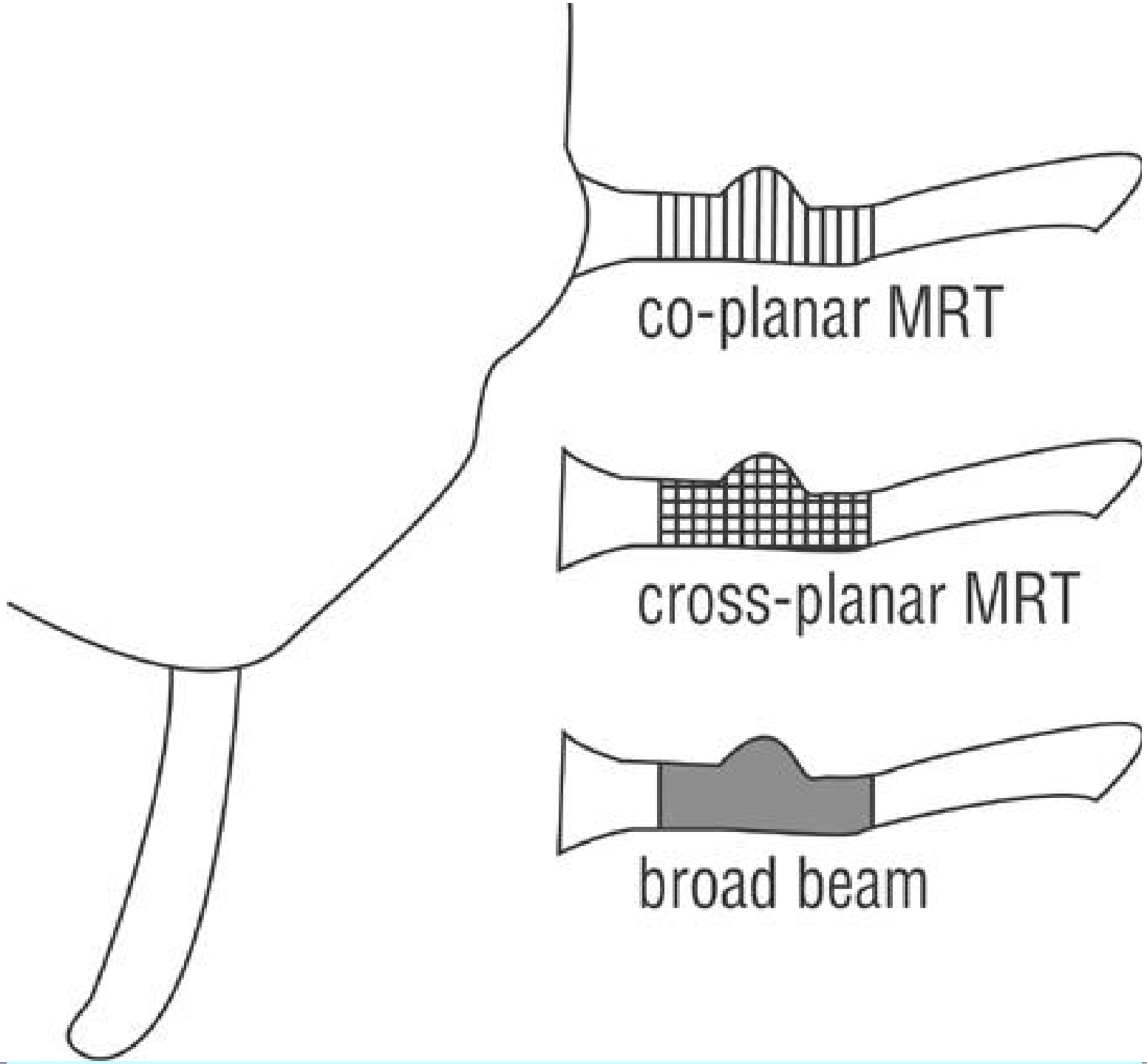
Conclusions about the Higher Tolerance of Normal Tissue to MRT

a. The MRT's effect of sparing normal tissues cannot be merely a result of the "volume effect", and biological effects must be involved.

b. Damage to the normal tissue elicited by MRT can be repaired except when the "valley" dose reaches the tolerance level for broad-beam irradiation.

Therapeutic Index of Subcutaneous Murine Mammary Carcinoma EMT-6

Single-fraction, unidirectional (co-planar and cross-planar) MRT was compared with with single-fraction unidirectional broad beams from the same synchrotron source.


co-planar MRT
cross-planar MRT
broad beam

EMT-6: Comparing the Therapeutic Efficacy of MRT (Cross-planar) with Broad Beams

Beam	Dose (Gy)	Tumor ablation	Moist desqua-mation	Complete epilation	Severe leg damage	Failure of nearly full hair regrowth
MBs (Cross-planar)	410	4/8	0/8	1/8	1/4	1/3
	520	4/8	0/8	2/8	0/4	1/4
	650	6/7	0/7	2/7	0/6	3/6
Broad beam	30	3/8	0/8	2/8	0/3	2/3
	38	3/7*	0/8	5/8	0/3	3/3
	45	6/8	7/8	6/8	2/6	4/4

EMT-6: Therapeutic Index Comparison

Data were pooled from the three dose groups in each method, assuming that the tumor ablation rates were the same (61% for MRT and 52% for broad beams). We then compared the proportions of animals with toxicity symptoms for each of the categories, using the chi squared method. The advantage of the cross-planar MRT over broad beam x rays was statistically significant:

- Moist desquamation ($P < 0.006$),
- Complete epilation ($P < 0.025$), and
- Failure of hair regrowth ($P < 0.013$).

Late Effects from MRT and Broad Beams in the EMT-6 Study

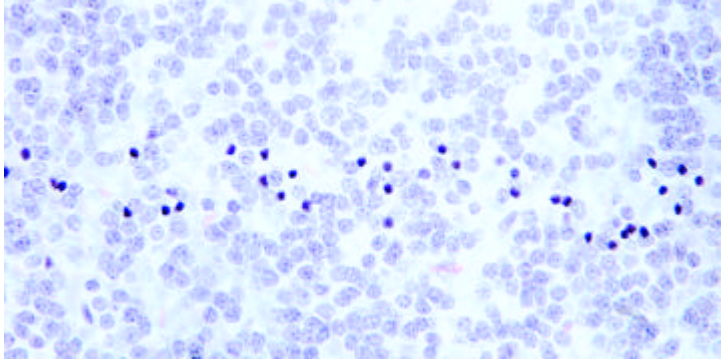
MRT cross-planar at 520 Gy, representing 50% tumor ablation and 75% nearly fully hair regrowth.

Broad beam at 38 Gy, representing 43% tumor ablation and 0% nearly fully hair regrowth.

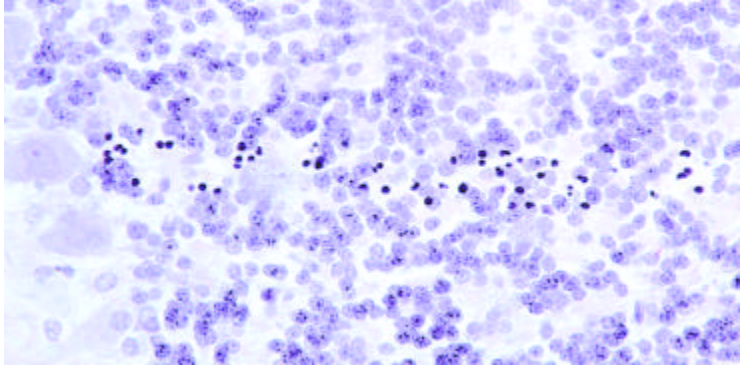
Normal, unirradiated control.

Published MRT Research at BNL and ESRF

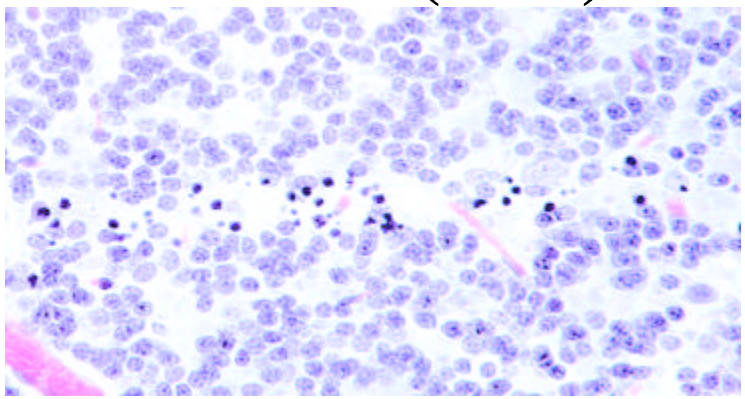
- **BNL:**
- **Tolerance by the rat brain (Slatkin et al. PNAS 1995).**
- **Efficacy in treating the 9LGS rat brain tumor (Slatkin et al., Rev. Sci. Instrum.1995; Laissue et al., Int. J. Cancer 1998).**
- **Tolerance by the duck embryo's CNS (Dilmanian et al., Cell. and Molec. Biol. 2001).**
- **Therapeutic index of 9LGS (Dilmanian et al., Neuro-Oncology 2002).**
- **Therapeutic index of EMT-6 murine mammary carcinoma (Dilmanian et al., Radiat. Res., 2003).**
- **Effect on the rat skin (Zhong et al., Radiat. Res., in press)**
- **ESRF:**
- **Tolerance by the weanling rat's cerebellum (Laissue et al., SPIE 1999).**
- **Tolerance by piglets' cerebellum (Laissue et al., SPIE 2001).**



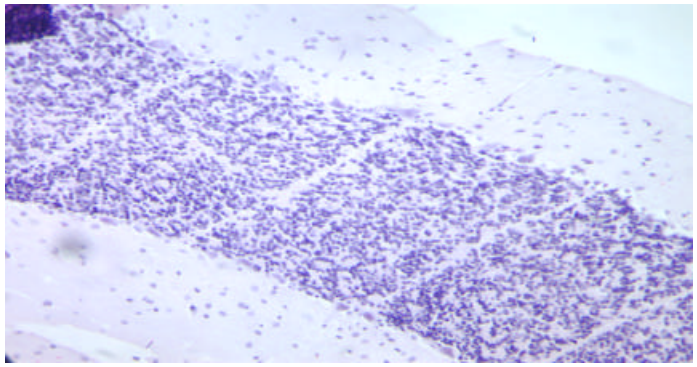
A MB path in the cerebellum 3 hr post-irradiation as darkened nuclei of neurons (400X).



An MB path seen in the cerebellum 2 d post-irradiation (400X).



The MB path in the cerebellum 4 d post-irradiation. Some of the neurons have disappeared.



The evenly-spaced MB paths at 16 d post-irradiation (200X) are demonstrated by fairly complete disappearance of neurons in the cerebellum.

Design of a Dedicated Synchrotron Source for Clinical MRT

Dilmanian, Krinsky, Bacarian, Slatkin, and Torikoshi suggested in the 2001 NSLS Annual Activity Report a design for a dedicated clinical MRT synchrotron with:

a) 2.8 GeV ring energy and 300 mA maximum ring current;

b) Six especially designed superconducting wigglers operating at 7 tesla, each providing beam to a single treatment room.

c) 10,000 Gy/s dose rate at about 130 keV median energy.

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