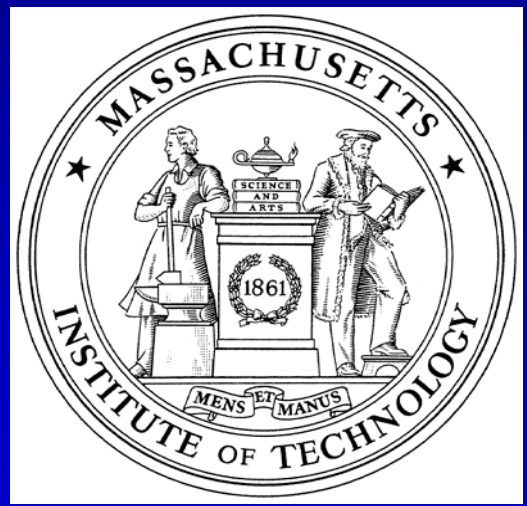
Boron Neutron Capture Therapy (BNCT)

- History
- Pre-clinical Research
- Clinical Trials



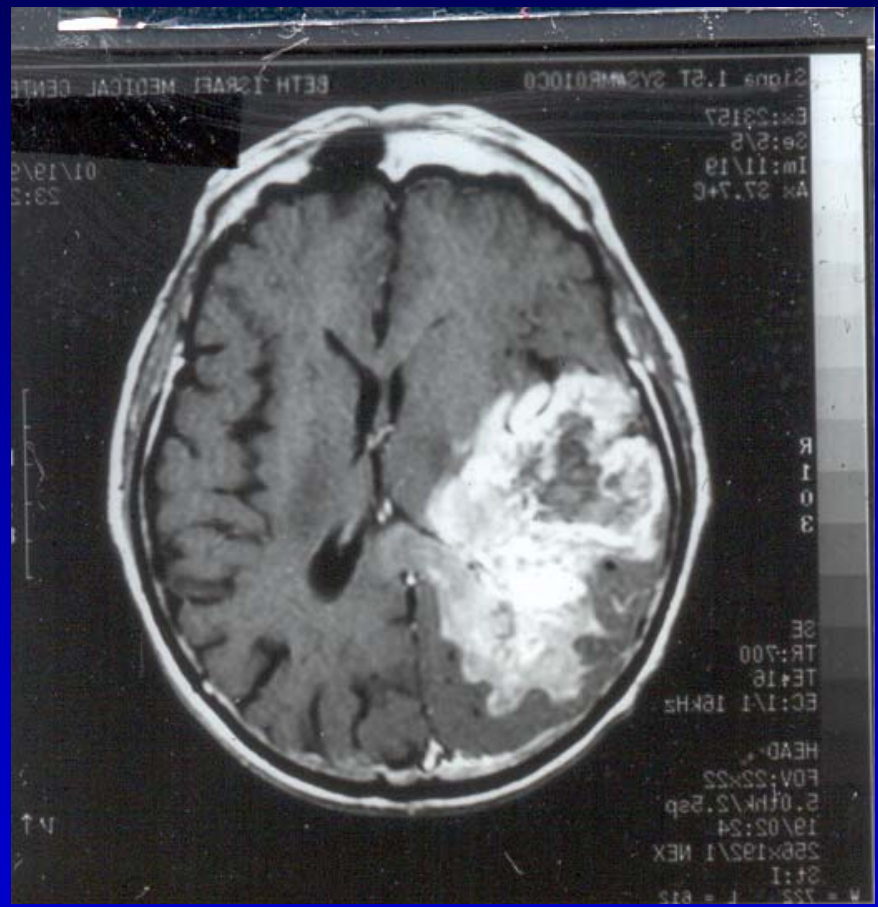
Glioblastoma multiforme

~ 7000 new cases/yr in the US.

Standard treatment: Surgery followed by radiation therapy.

Median survival is 10 to 12 months.

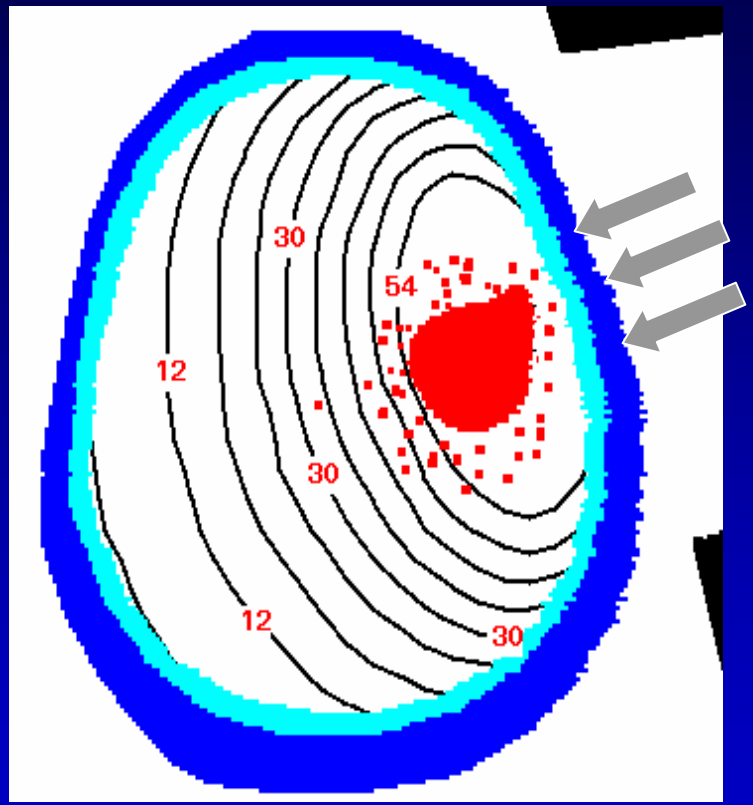
Glioblastoma multiforme



Boron Neutron Capture Therapy

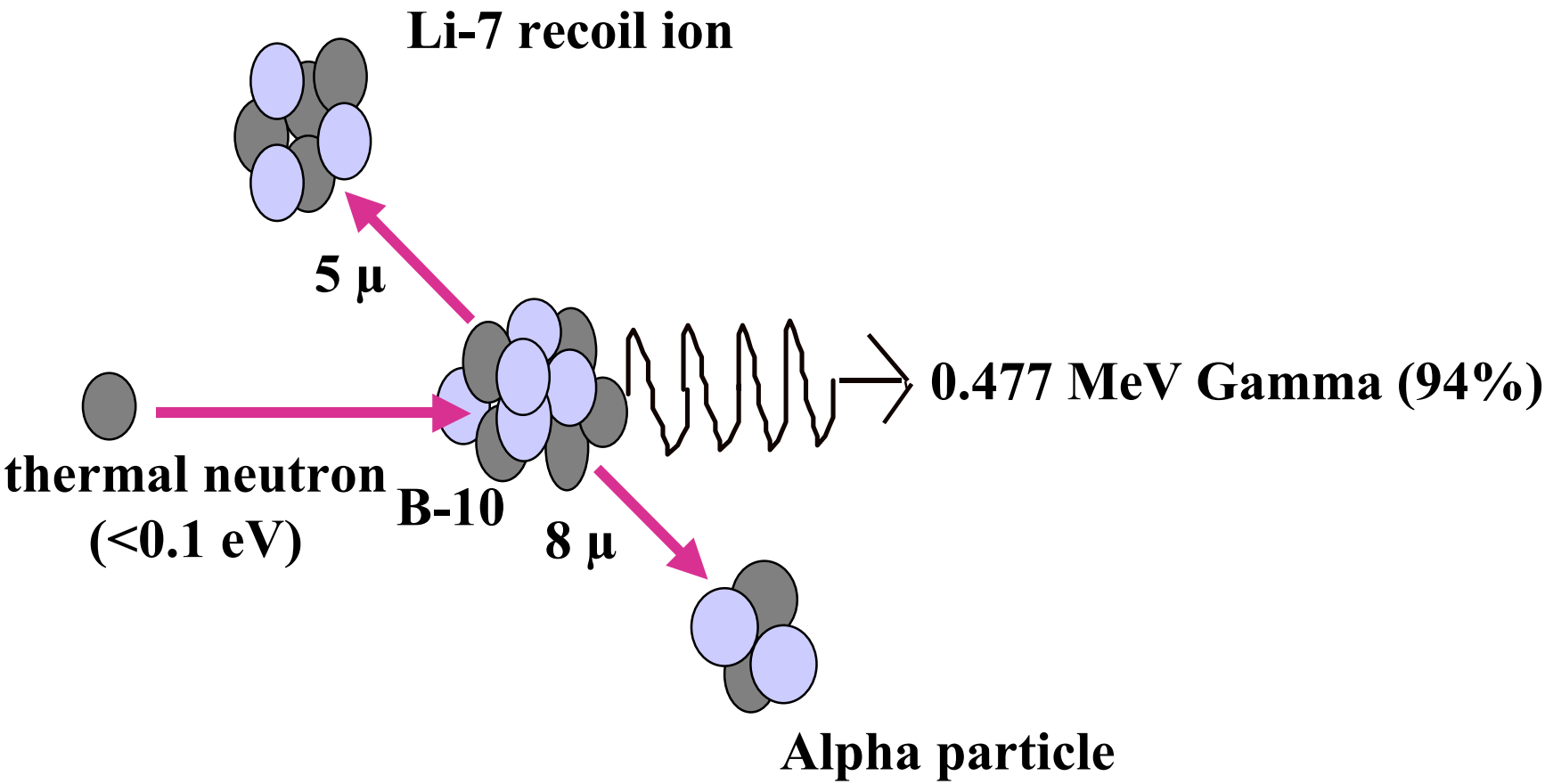
- Glioblastoma: the invasive nature makes treatment difficult.

- BNCT has the potential to selectively target these infiltrating tumor cells.



The BNCT Reaction

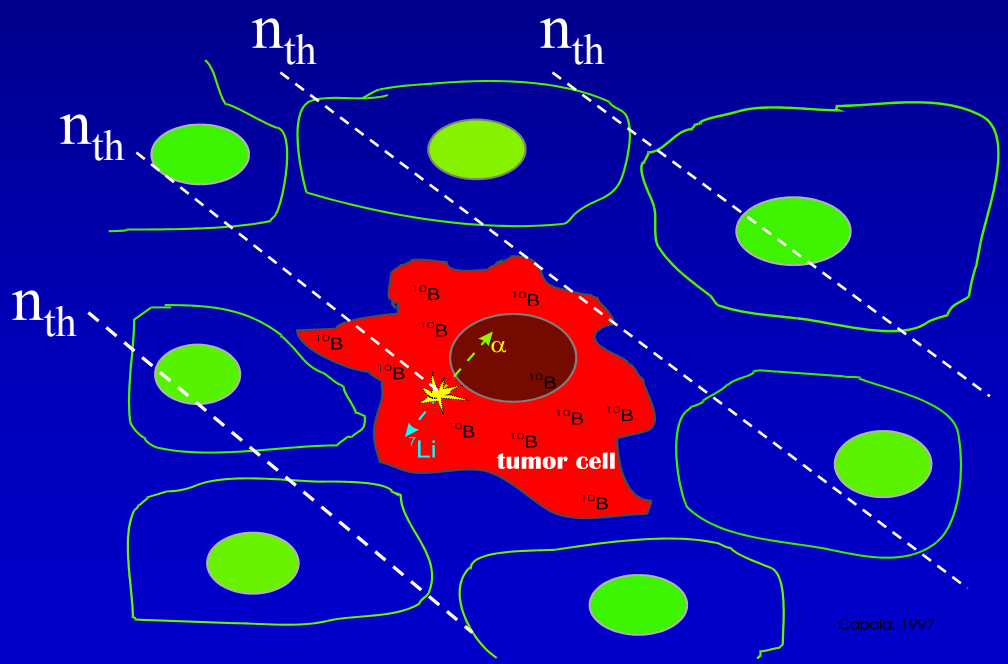
2.33 MeV of kinetic energy is released per neutron capture: initial LET 200-300 keV/µm

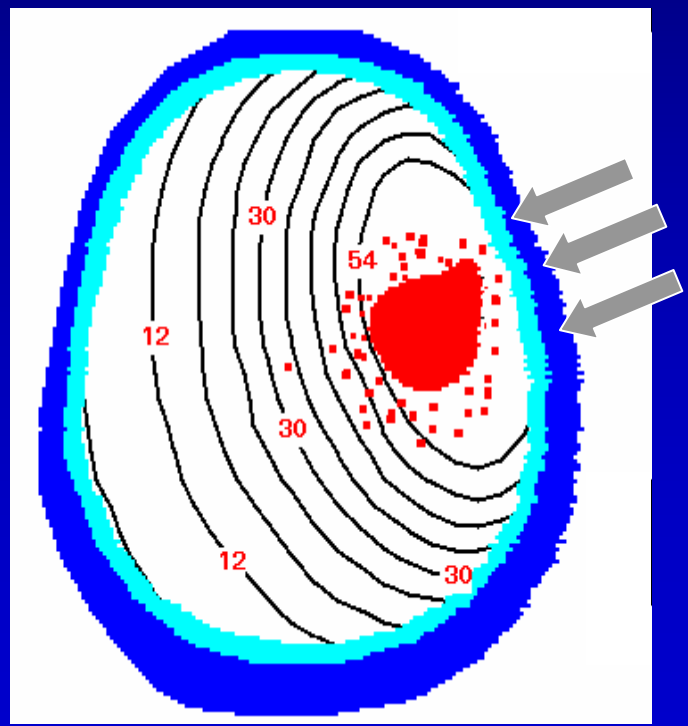


Thermal cross-section = 3837 barns (that's *very* big…)

Boron Neutron Capture Therapy

1. Selectively deliver ^{10}B to the tumor.
2. Irradiate the tumor region with low energy neutrons (n_{th}).
3. The short range of the $^{10}B(n,\alpha)^{7}Li$ reaction products restricts most of the dose to the boron-loaded cells.





BNCT Pre-History

1932: Chadwick discovers the neutron

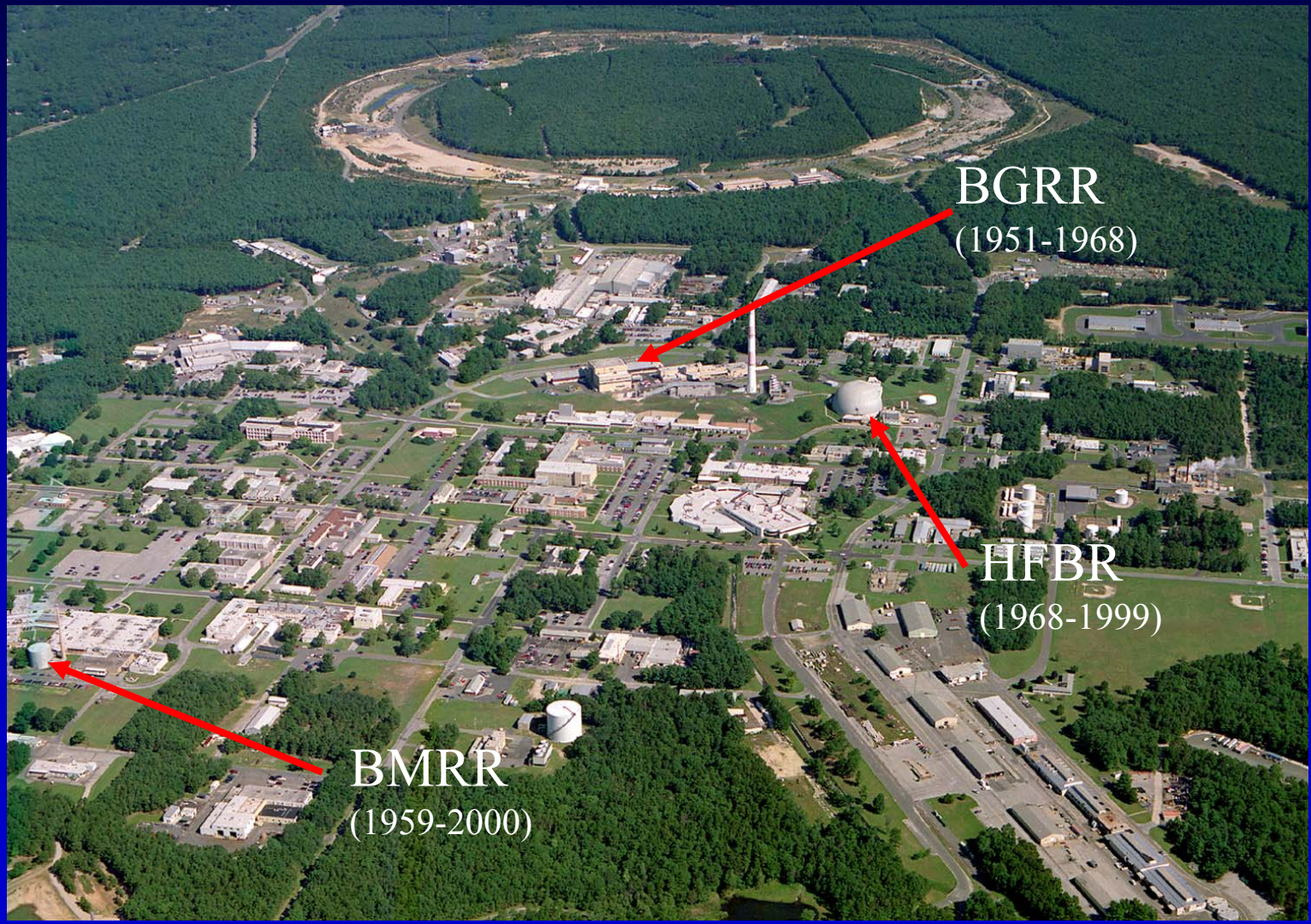
1935: Taylor and Goldhaber describe the $^{10}B(n,\alpha)^{7}Li$ reaction

1936: Locher proposes BNCT as a cancer therapy

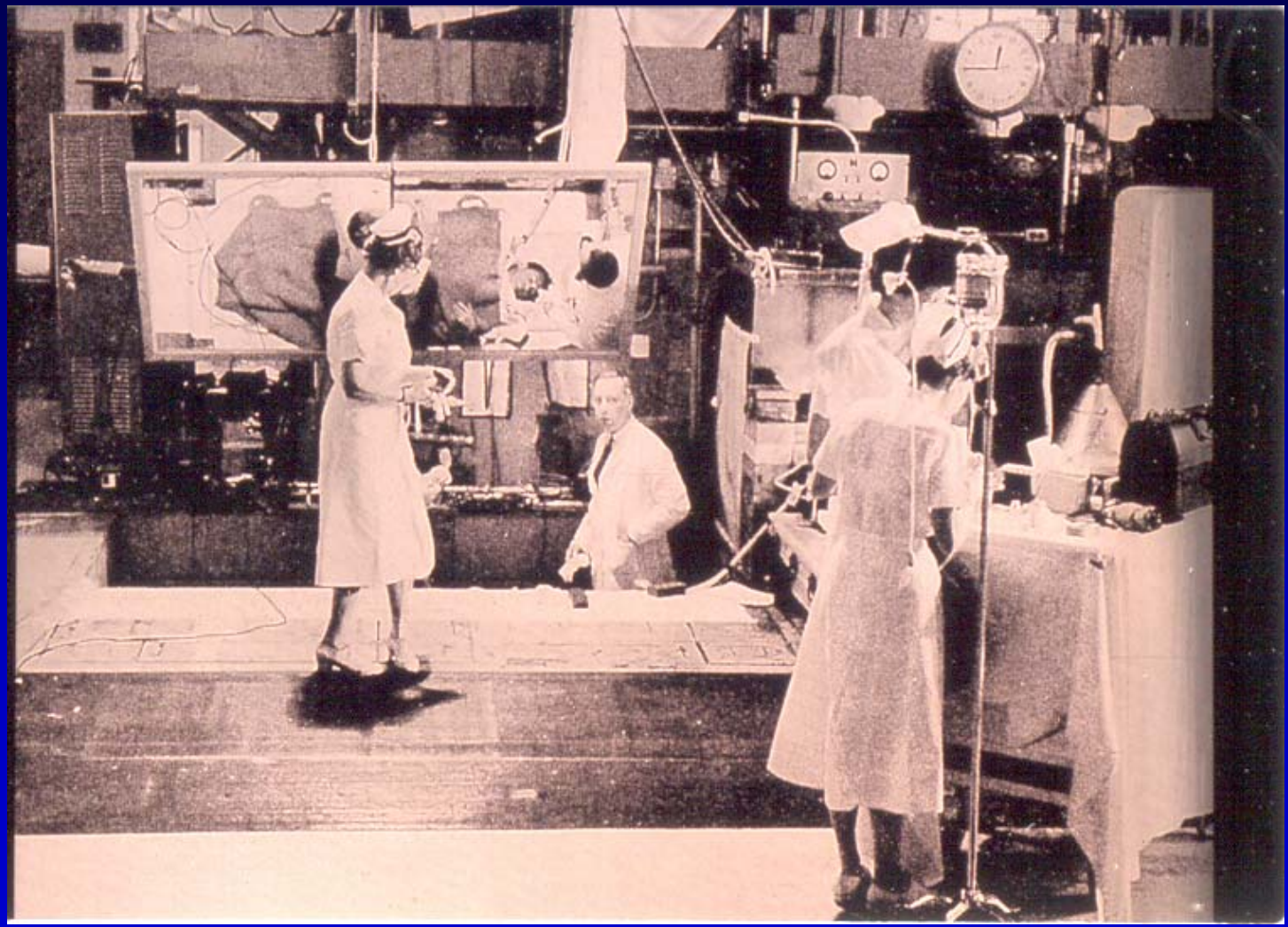
1951: Brookhaven Graphite Research Reactor

1951: W. Sweet, Chief of Neurosurgery at the MGH initiates BNCT clinical trial

Brookhaven National Laboratory



BNCT Clinical Trial: ~1953



BGRR Clinical Trial: 1951-1959

BNCT Clinical Trial: 1959-1961

Brookhaven Medical Research Reactor

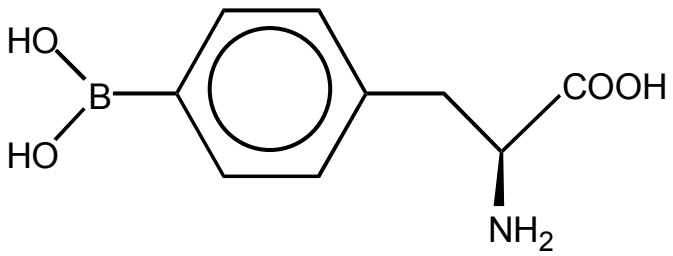
Beam shutter

BMRR schematic

Failure of the First BNCT Trials

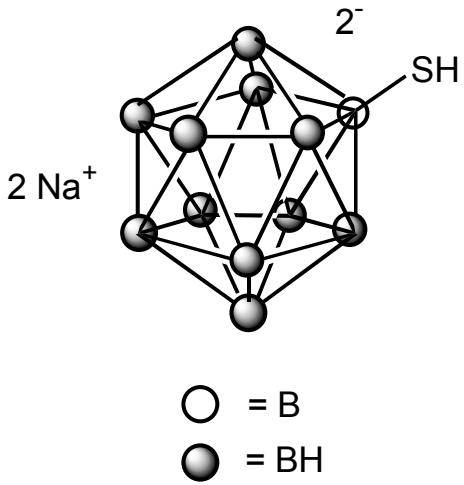
- Poor penetration of thermal neutrons in tissue.
- Boron levels in blood higher than those in tumor.
- Viable tumor was found at depth following doses that exceeded the tolerance of normal surface tissues.
- BNL and MIT clinical trials were stopped in 1961.

Improved boron delivery agents



L-BPA

(*p*-borono-L-phenylalanine)



BSH

($Na_2B_{12}H_{11}SH$)

Improvements in neutron beams

Thermal
< 0.4 eV

Epithermal
0.4 eV-10 keV

Improved
penetration

Surface sparing

BNCT dose components

- Boron dose - from products of $^{10}B(n,\alpha)^{7}Li$ reaction

- γ dose - from beam contamination and neutron capture reaction in hydrogen: $^{1}H(n,\gamma)^{2}H$
- Nitrogen dose - from products of $^{14}N(n,p)^{14}C$ reaction
- Fast neutron dose – from recoil nuclei (mostly protons)

Thermal Neutron Cross Sections

Nuclide	*Cross section (barns)*
^{10}B	3837
^{11}B	0.005
^{12}C	0.0035
^{1}H	0.33
^{14}N	1.70
^{35}Cl	43.6
^{23}Na	0.534
^{157}Gd	254,000
^{153}Gd	0.02

Photon-Equivalent Doses

IAEA Workshop (6/99) recommends that BNCT doses be expressed as a weighted dose D_w , with the unit Gy, using the following convention:

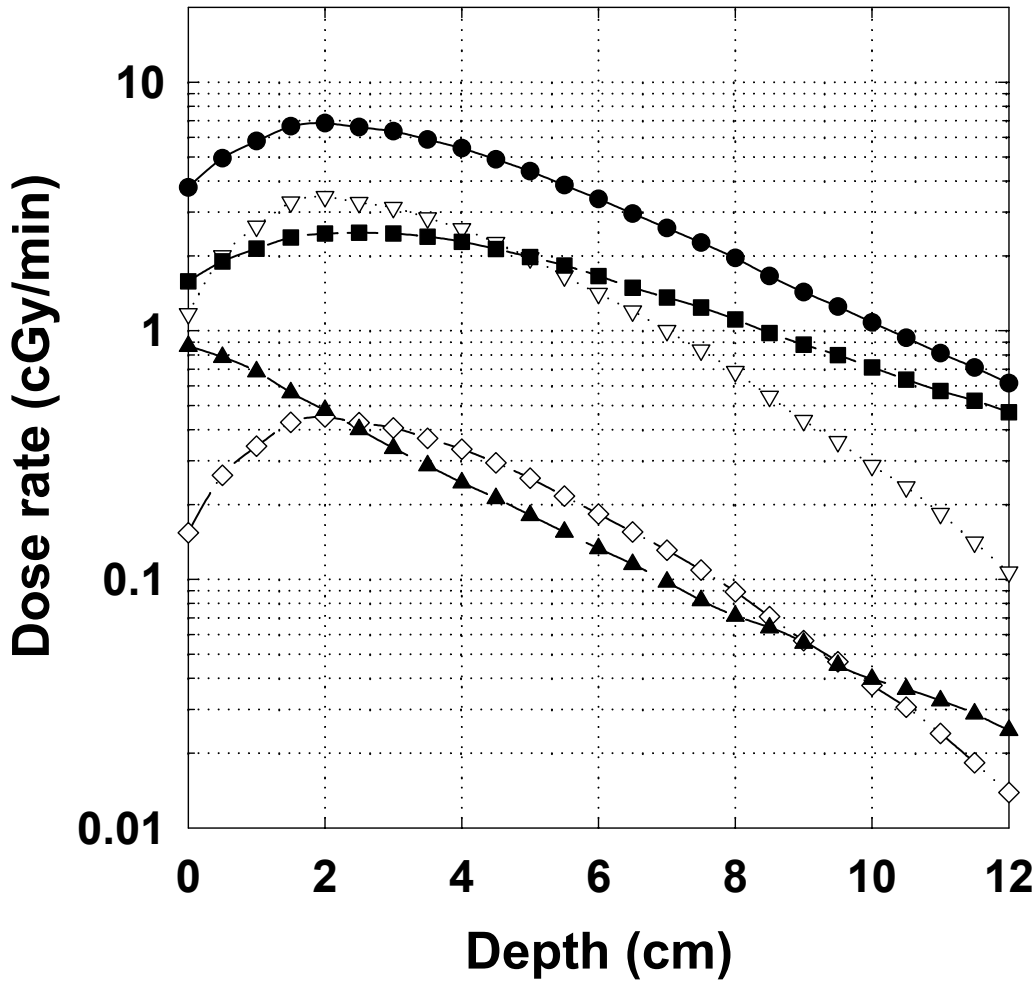
$$\mathbf{D_w = w_b.D_b + w_g.D_g + w_n.D_n + w_p.D_p}$$

Currently:
weighting factors termed **RBE** or **CBE** factors;
BNCT doses expressed in **Gy-Eq** units.

Beam components: depth-dose profile

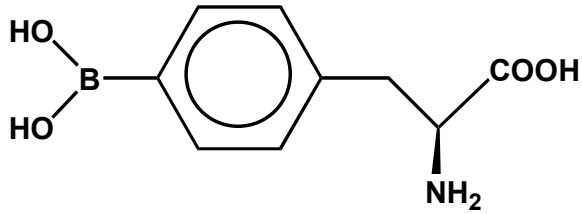
- ● total dose
- ▽ boron capture (13 µg ^{10}B/g)
- ■ gamma
- ♦ fast neutrons
- ◊ nitrogen capture

BMRR epithermal beam,
3 MW reactor power



The boron delivery agent

BPA concentrates in tumor to levels 3.5 - 4 times higher than blood or brain.



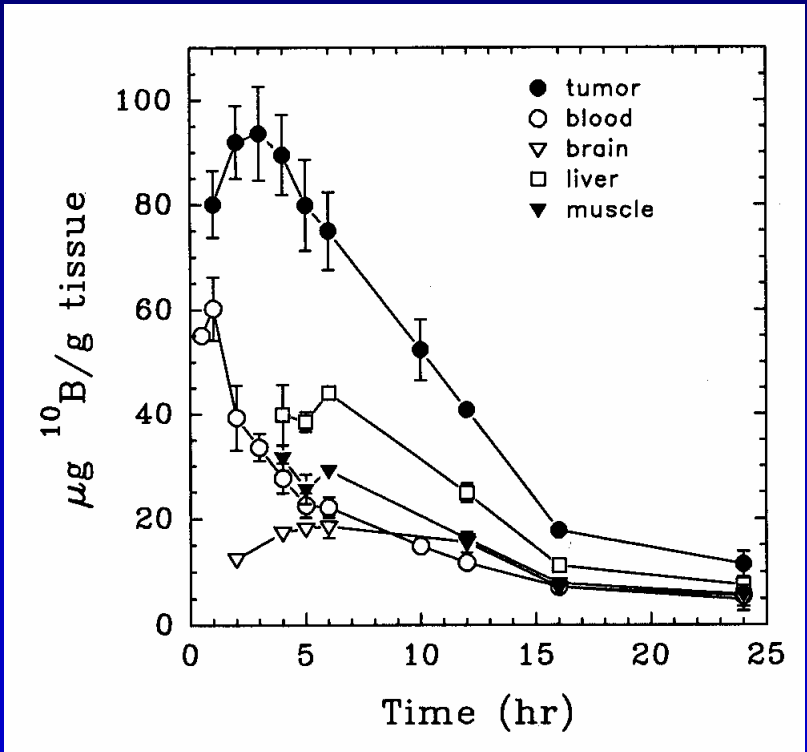
L-BPA

(*p*-borono-L-phenylalanine)

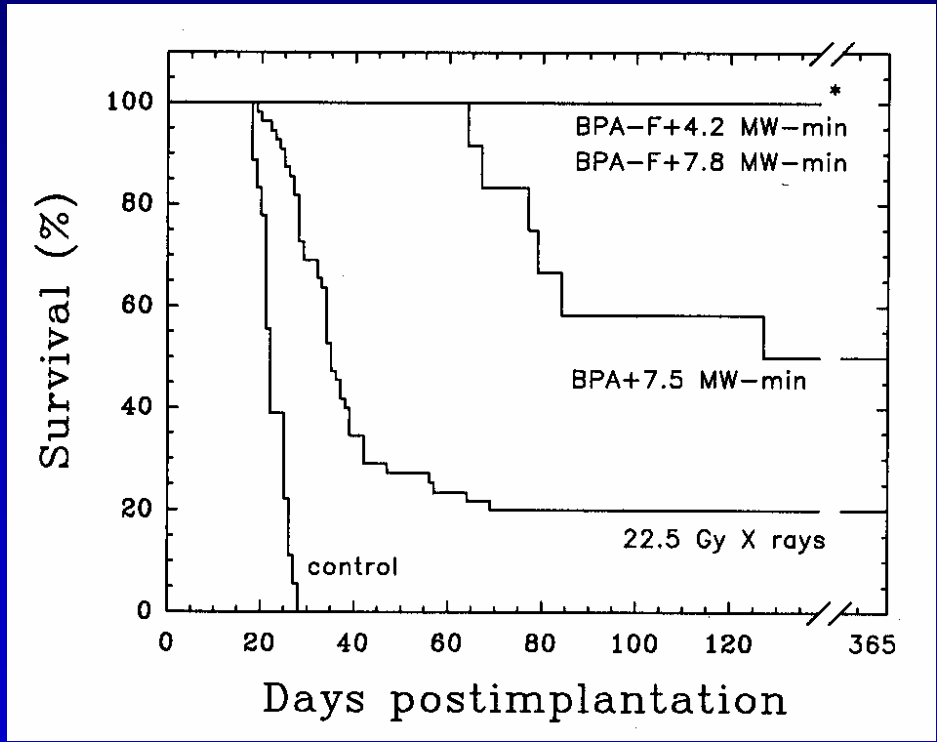
^{18}F PET study:
adapted from
Imahori *et al*.
JNM, 39, 325, 1998.

Rat 9L gliosarcoma

BPA biodistribution



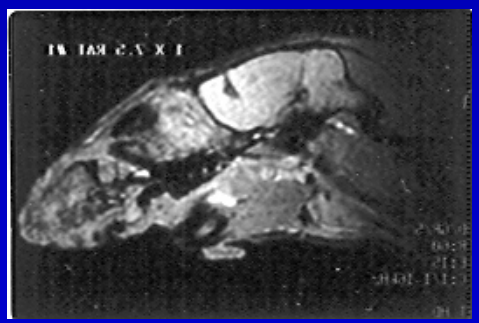
BNCT



Coderre et al., Radiat. Res., 129, 290, 1992

Selective tumor ablation

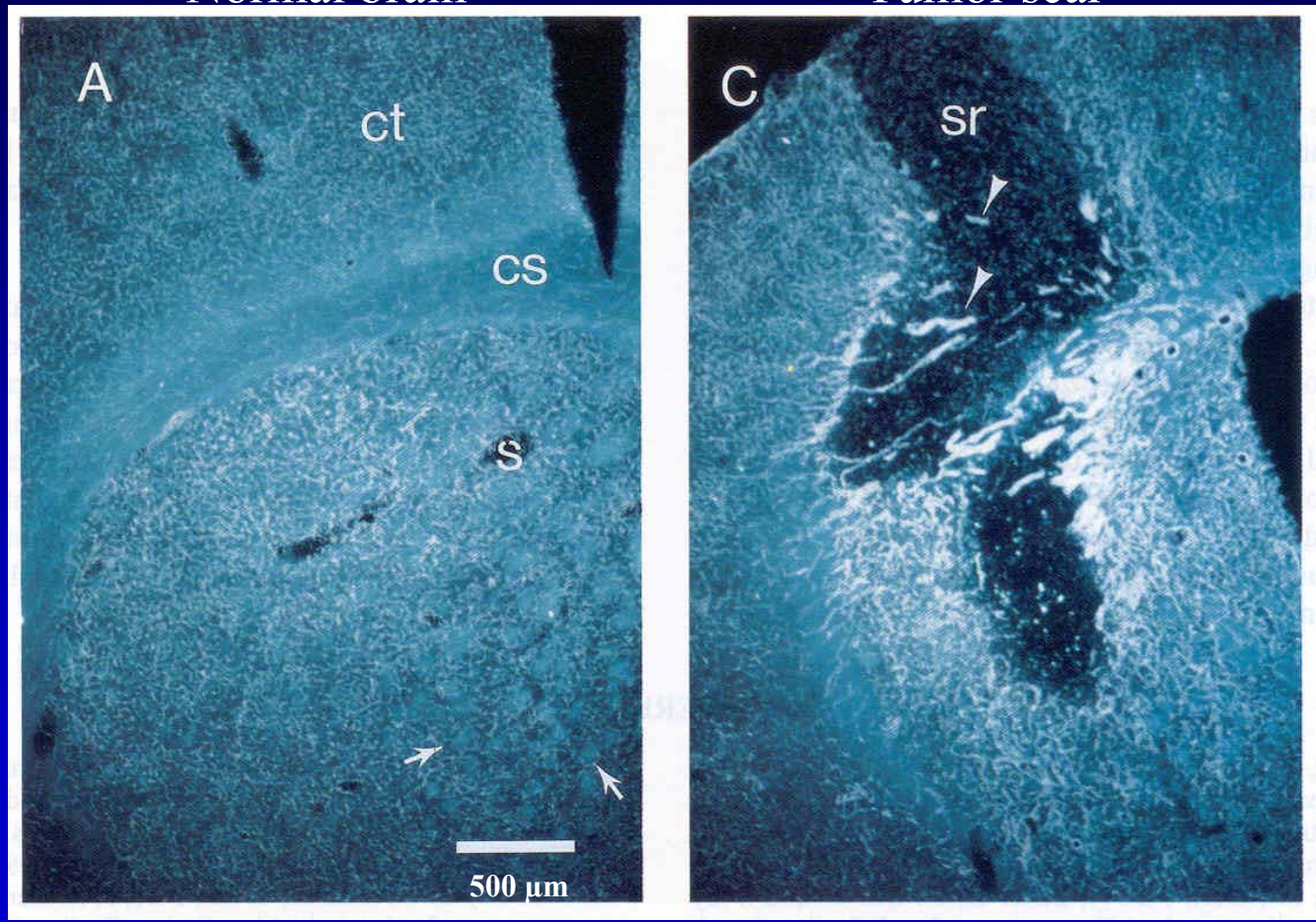
Rat 9L gliosarcoma:
1 year post-BNCT
MR images



Horseradish peroxidase perfusion

Normal brain

Tumor scar

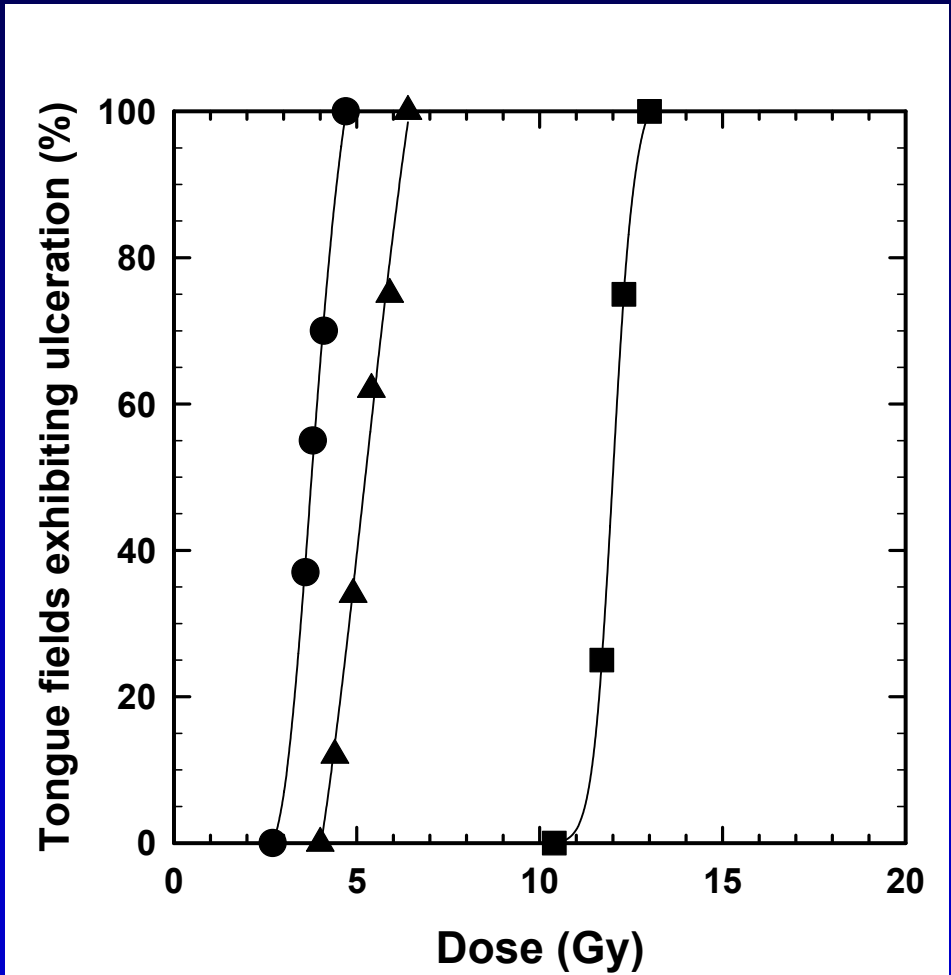


Coderre et al., Int. J. Radiat. Oncol. Biol. Phys., 28, 1067, 1994.

Dose response: ED_{50} endpoint

- ■ x rays
- ▲ thermal neutrons
- ● thermal neutrons + BPA

- **Compare isoeffective doses (ED_{50})**



Coderre et al., Radiat.Res., 152, 113, 1999

BNCT radiobiology

Tissues studied:	Weighting Factors Used in Clinical Trial
• tumor	3.8
• brain	1.3
• spinal cord	1.3
• skin	2.5
• oral mucosa	2.5

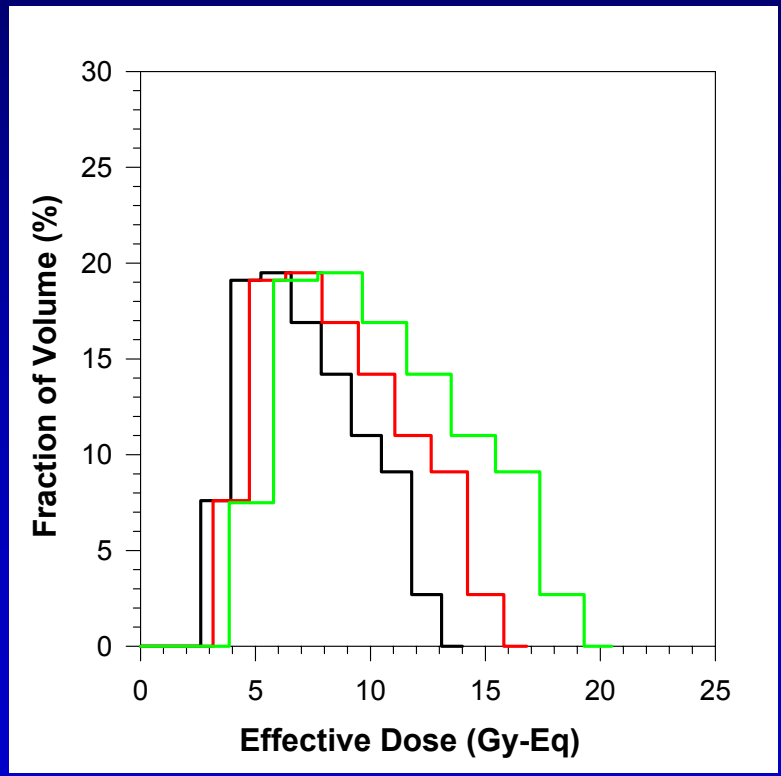
^{10}B biological effectiveness factors range from 1.3 to over 5.

An RBE of 3.2 is used for the high-LET beam components in all tissues.

Dog brain irradiations

Isodose contours

Dose volume histograms



Coderre et al., J. Neuro-Oncol., 48, 27, 2000.

Dog brain irradiations

Asymptomatic MRI changes

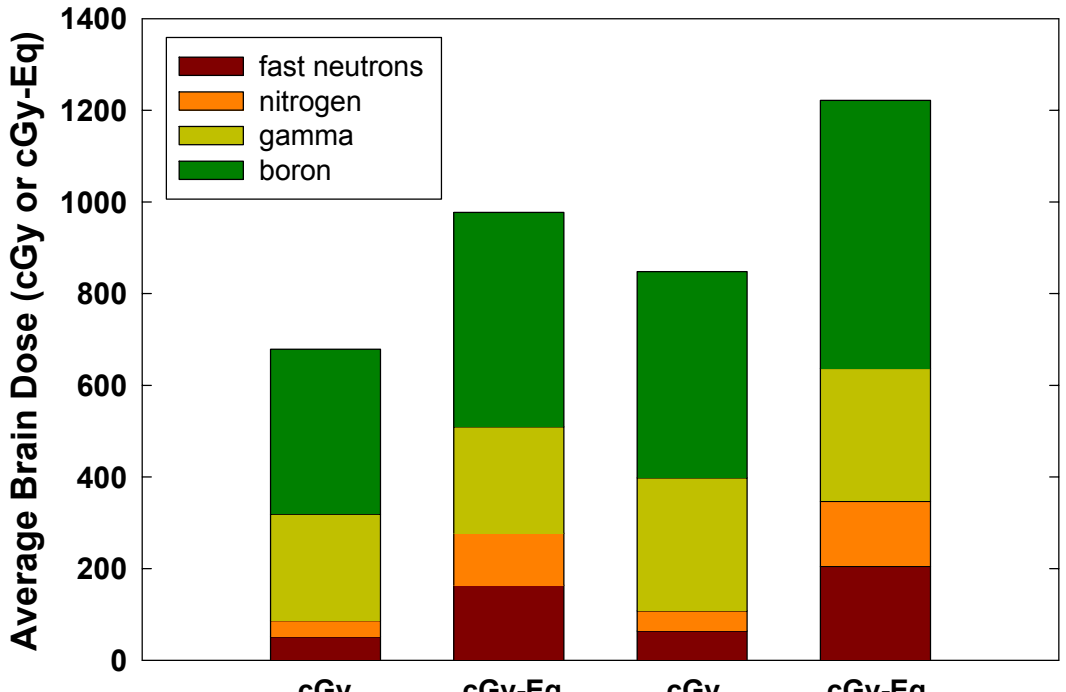
6 mos. post-BNCT

Massive edema at 5 mos.

Coderre et al., J. Neuro-Oncol., 48, 27, 2000.

Dog brain irradiations

- Average whole brain dose, single-field irradiation.
- 1 Gy = 1 joule/kg
- 2 Gy = conventional daily fraction for tumors (x 30d).
- 10 Gy whole body (brain) used in bone marrow transplant.

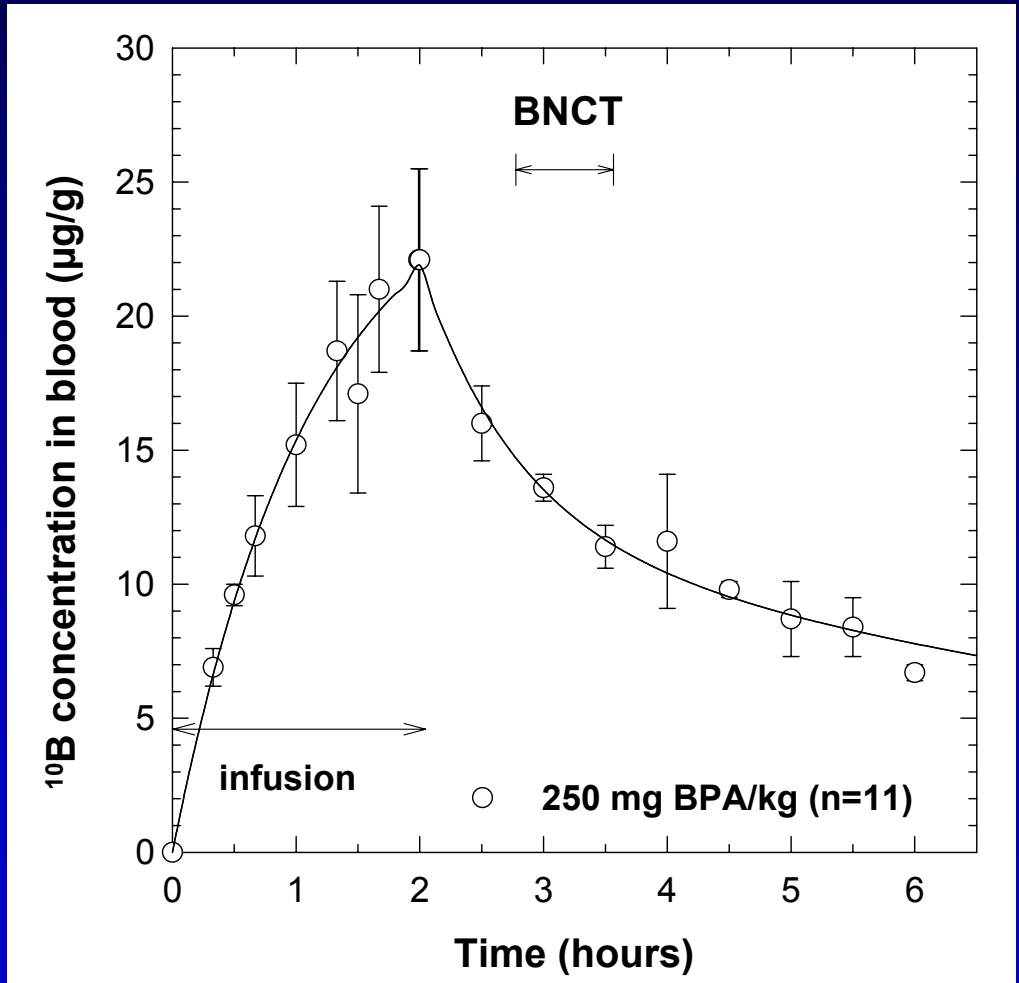


The BNCT procedure

Surgery 3-4 weeks prior to BNCT.

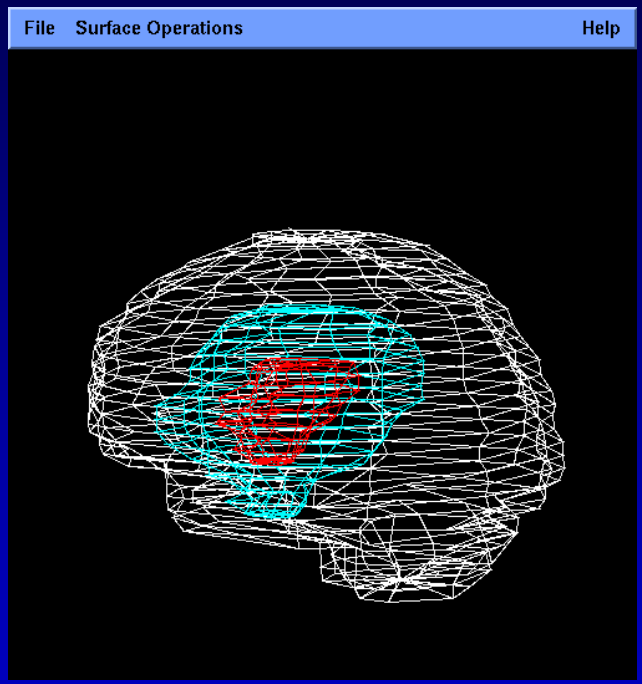
BNCT is given in a single session lasting less than 1 hr.

- 2-hr BPA infusion
- BNCT starts ~ 45 min after end of infusion

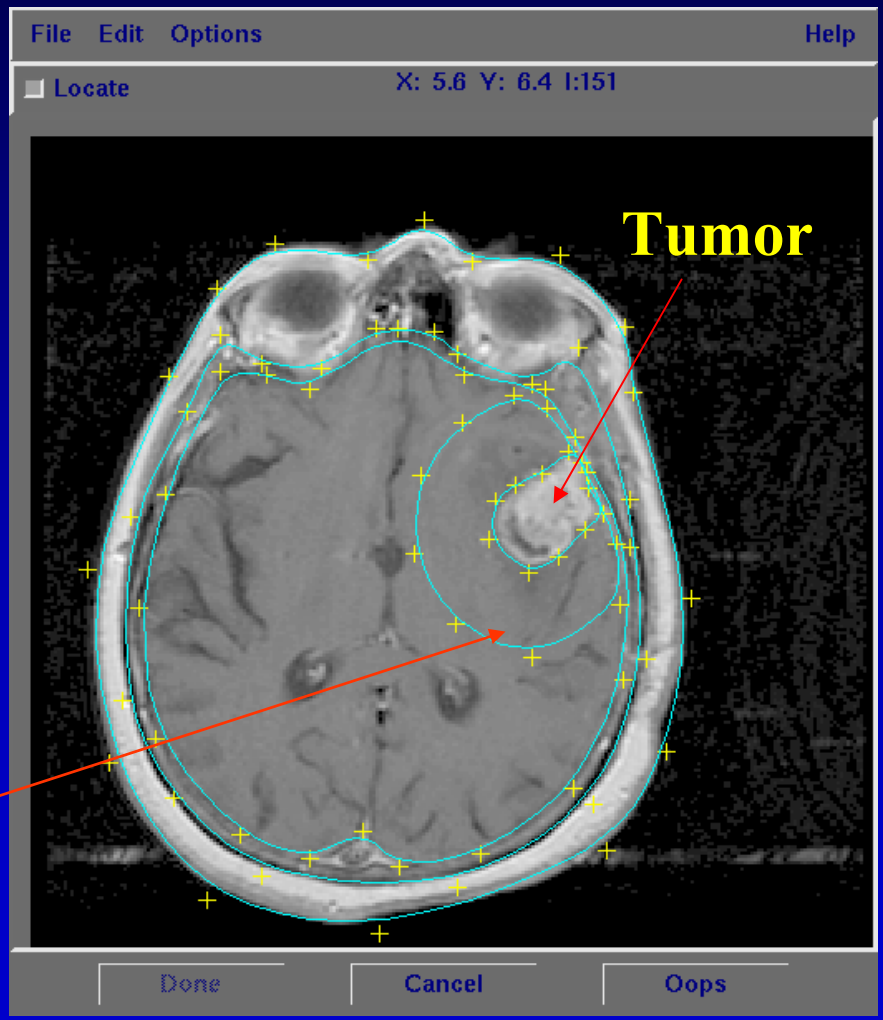


Coderre, et al., J. Neuro-Oncol., 33, 141, 1997.

Monte Carlo-based treatment planning

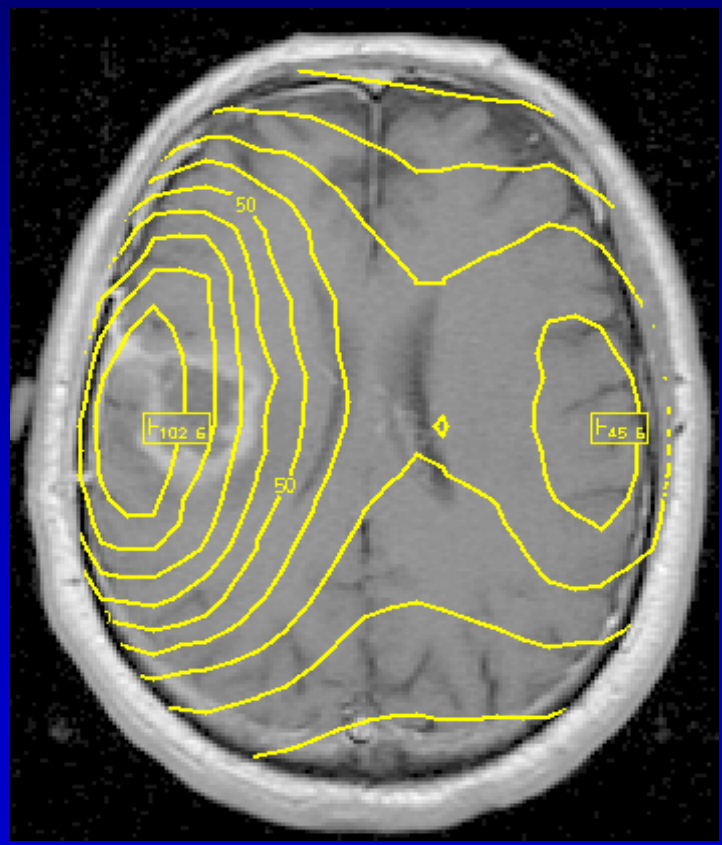


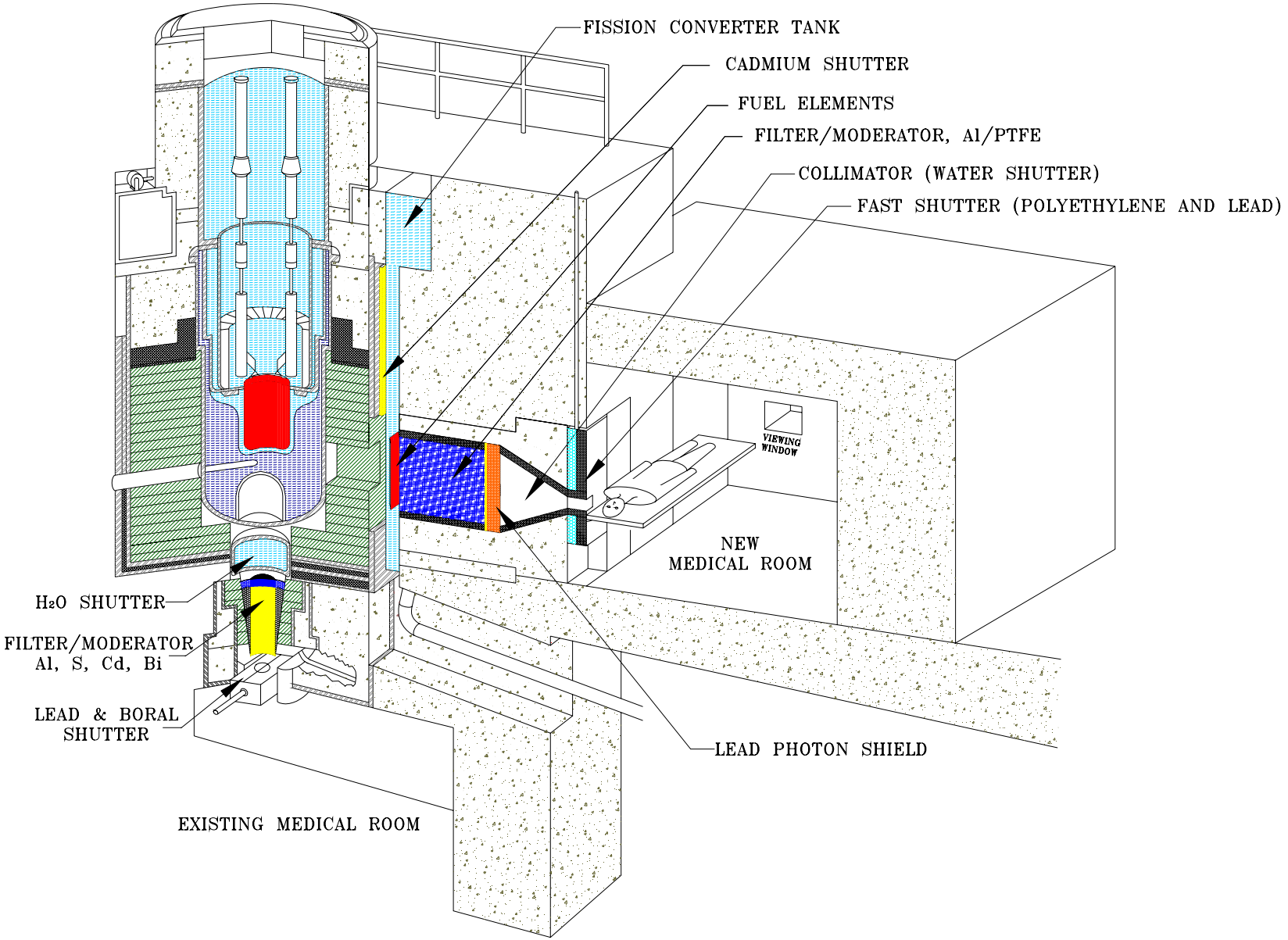
Target volume (tumor + 2 cm)



Brain

- One field versus two fields
- Peak dose, hemisphere dose, whole brain average dose





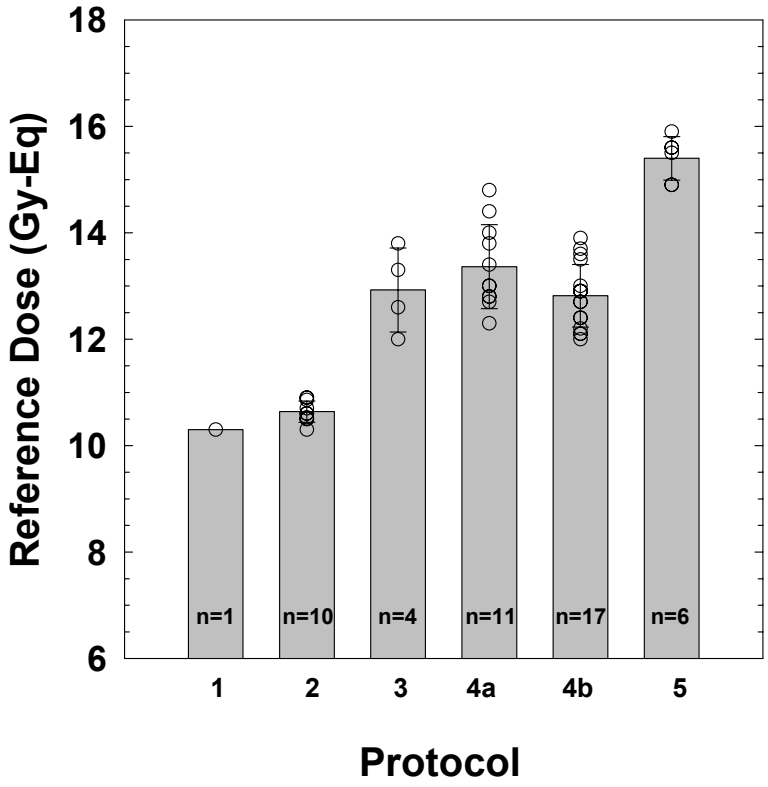
MITR-II showing current and new epithermal beam locations

Brain Doses

BNL BNCT clinical trial.

Reference (peak) doses in brain (maximum dose to a 1 cm^3 volume).

Doses escalated in 20% increments.



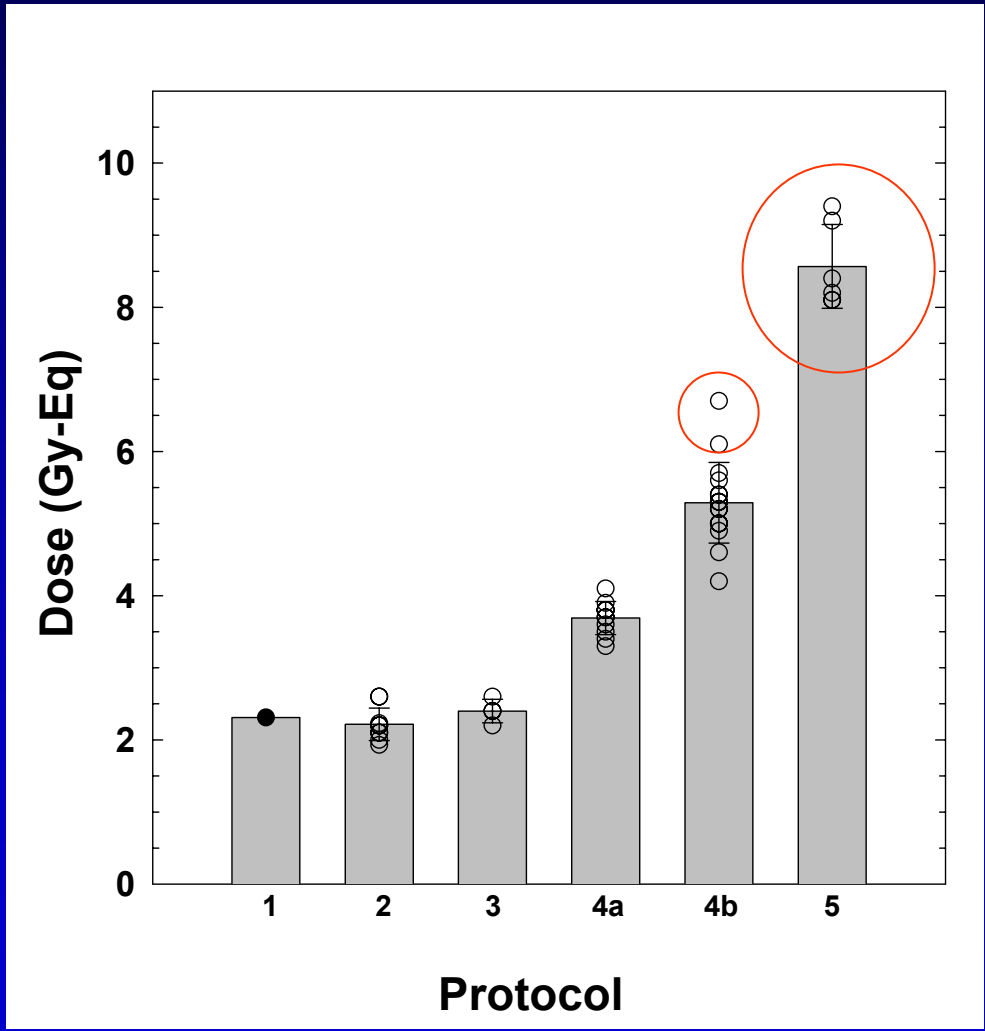
Chanana, et al., Neurosurg., 44, 1182, 1999.

Brain dose

BNL BNCT clinical trial:

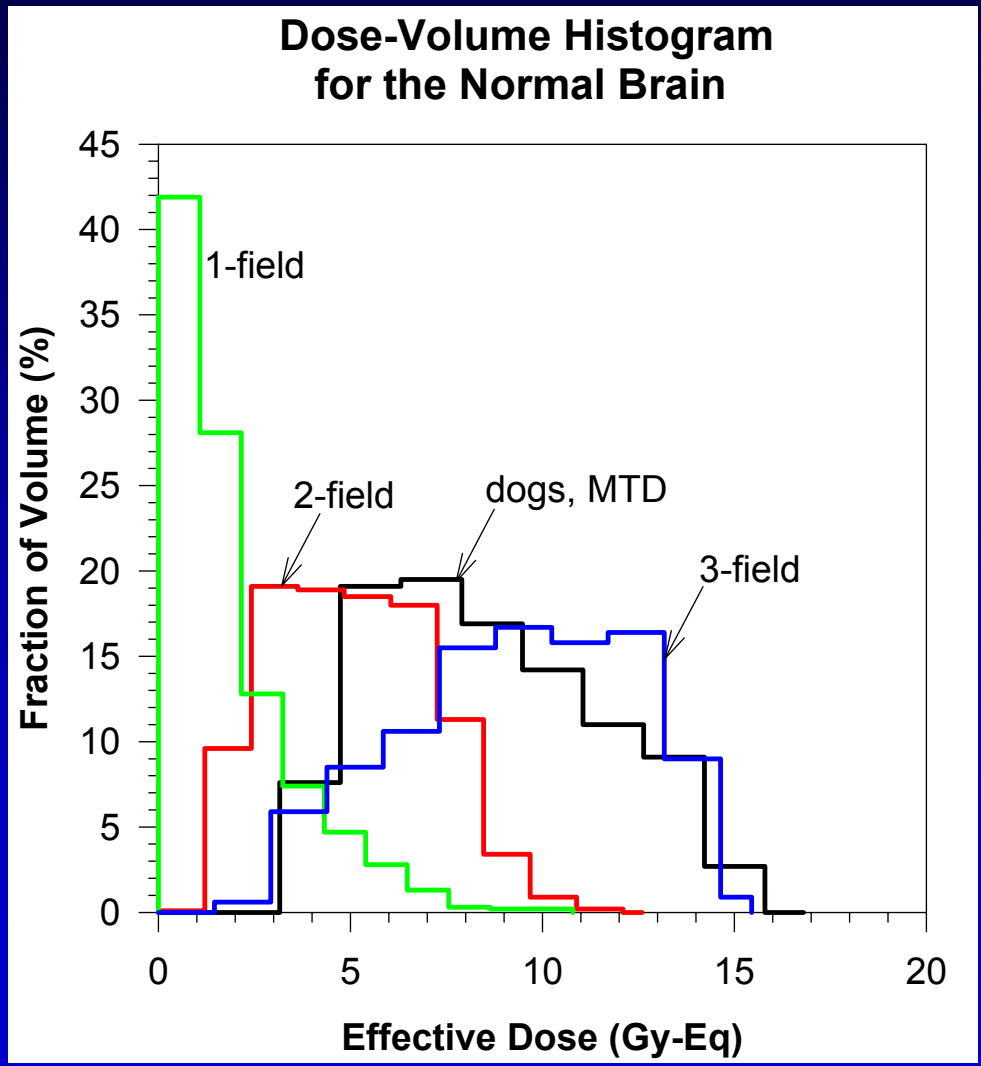
Whole-brain average doses.

CNS side effects observed in 2 pts in Protocol 4b and all pts in Protocol 5.

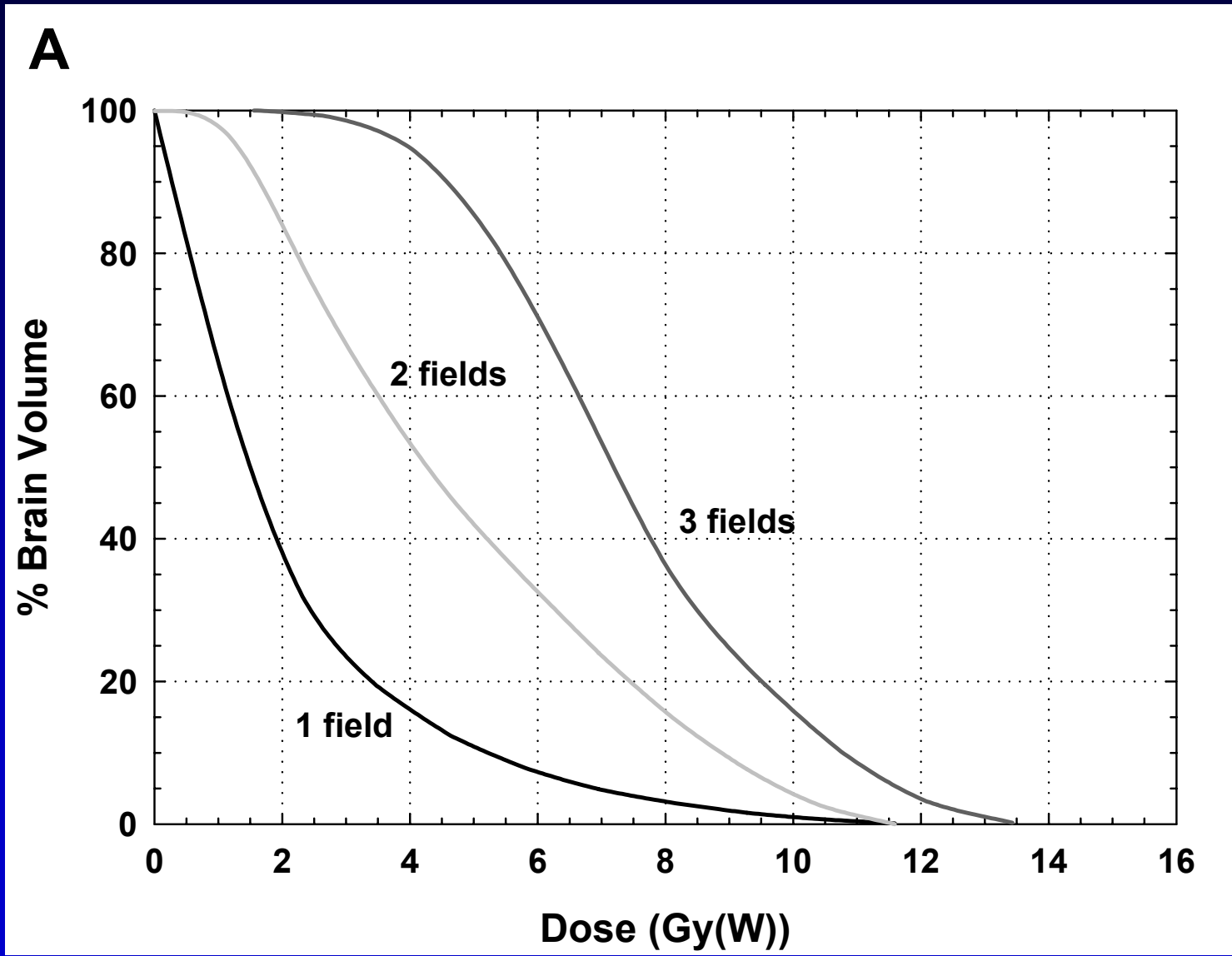


Brain: Dose Volume Histograms

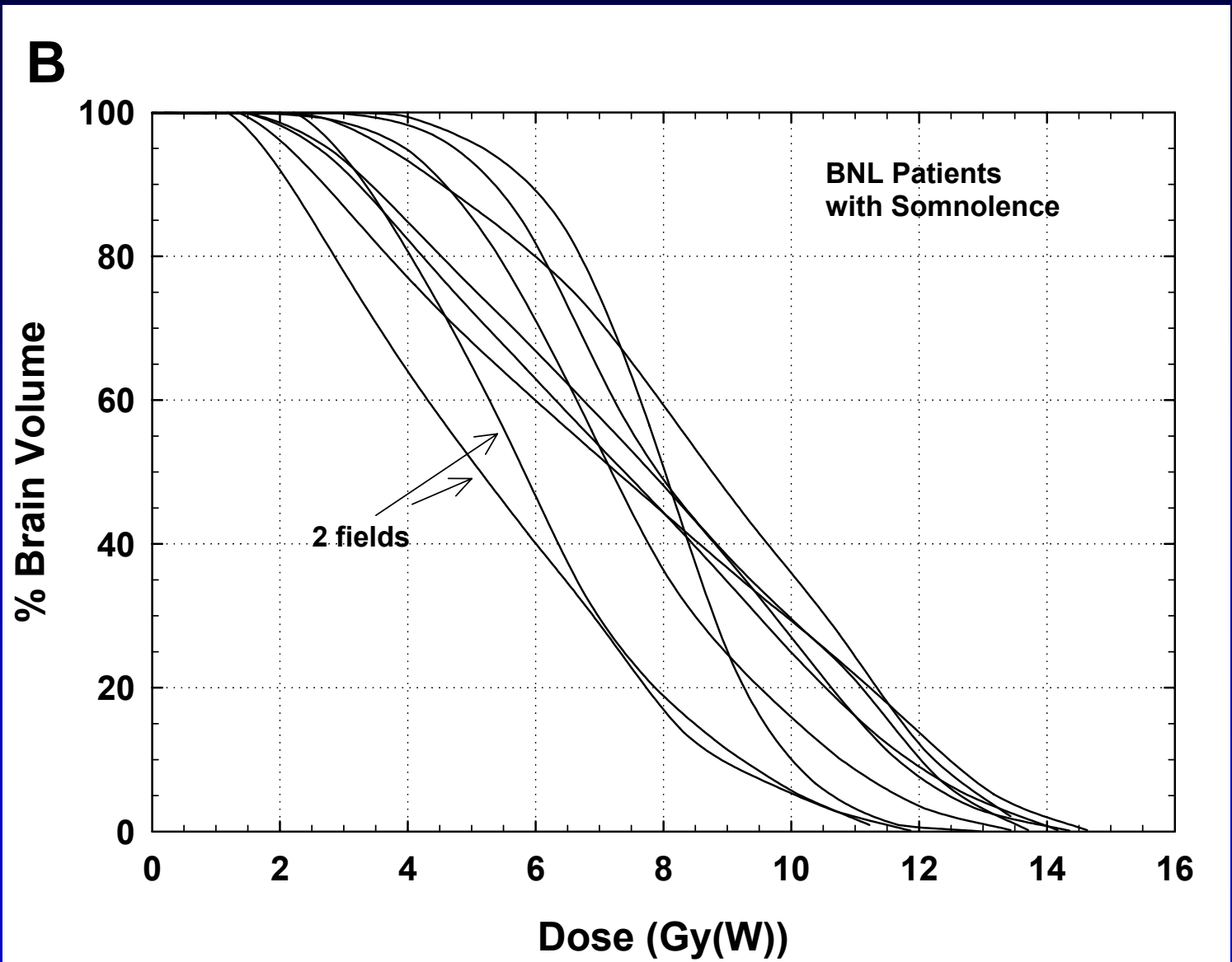
- Escalation of the dose in humans.
- Comparison to the maximum tolerated dose in dogs.



Normal Brain Tolerance



Normal Brain Tolerance



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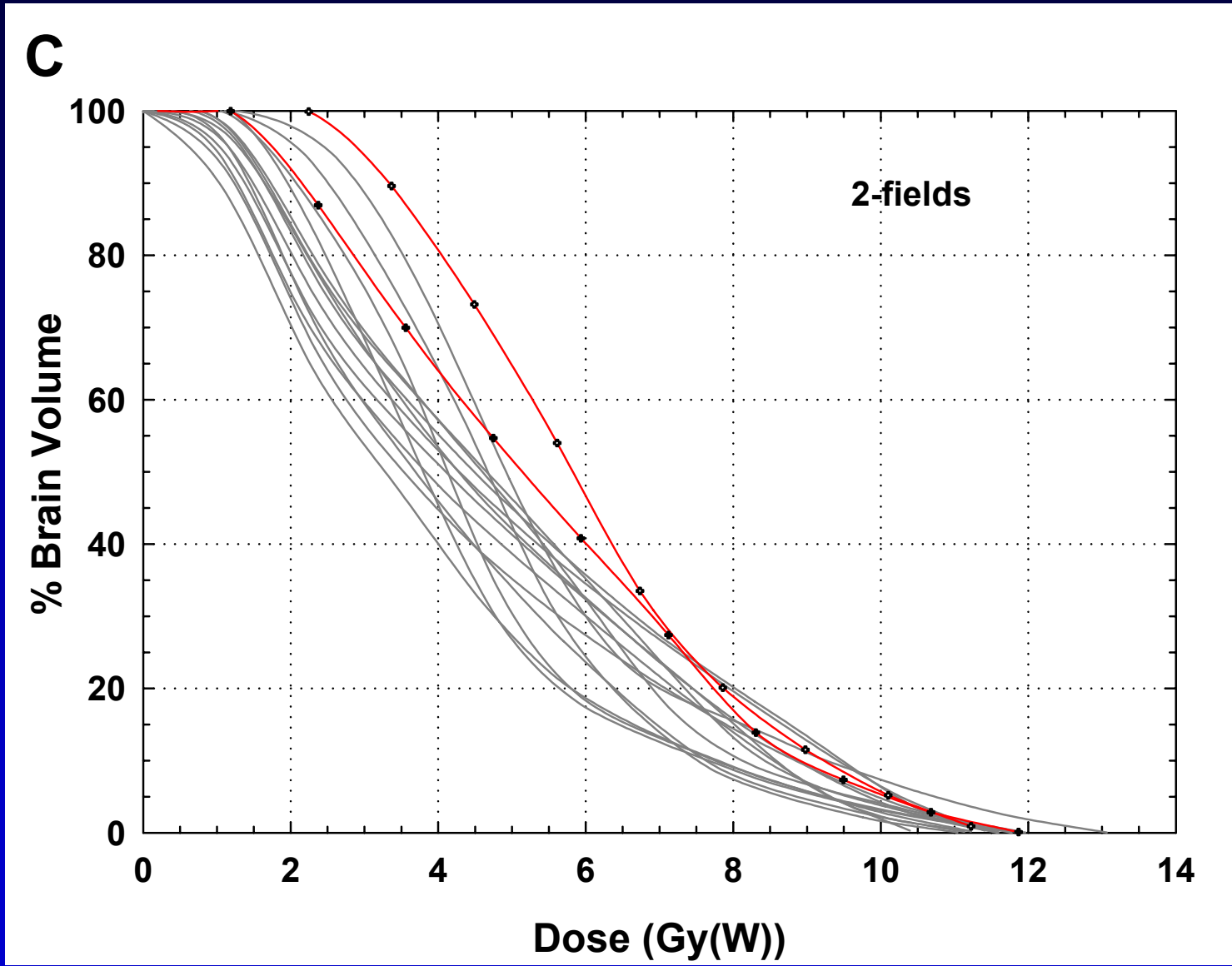
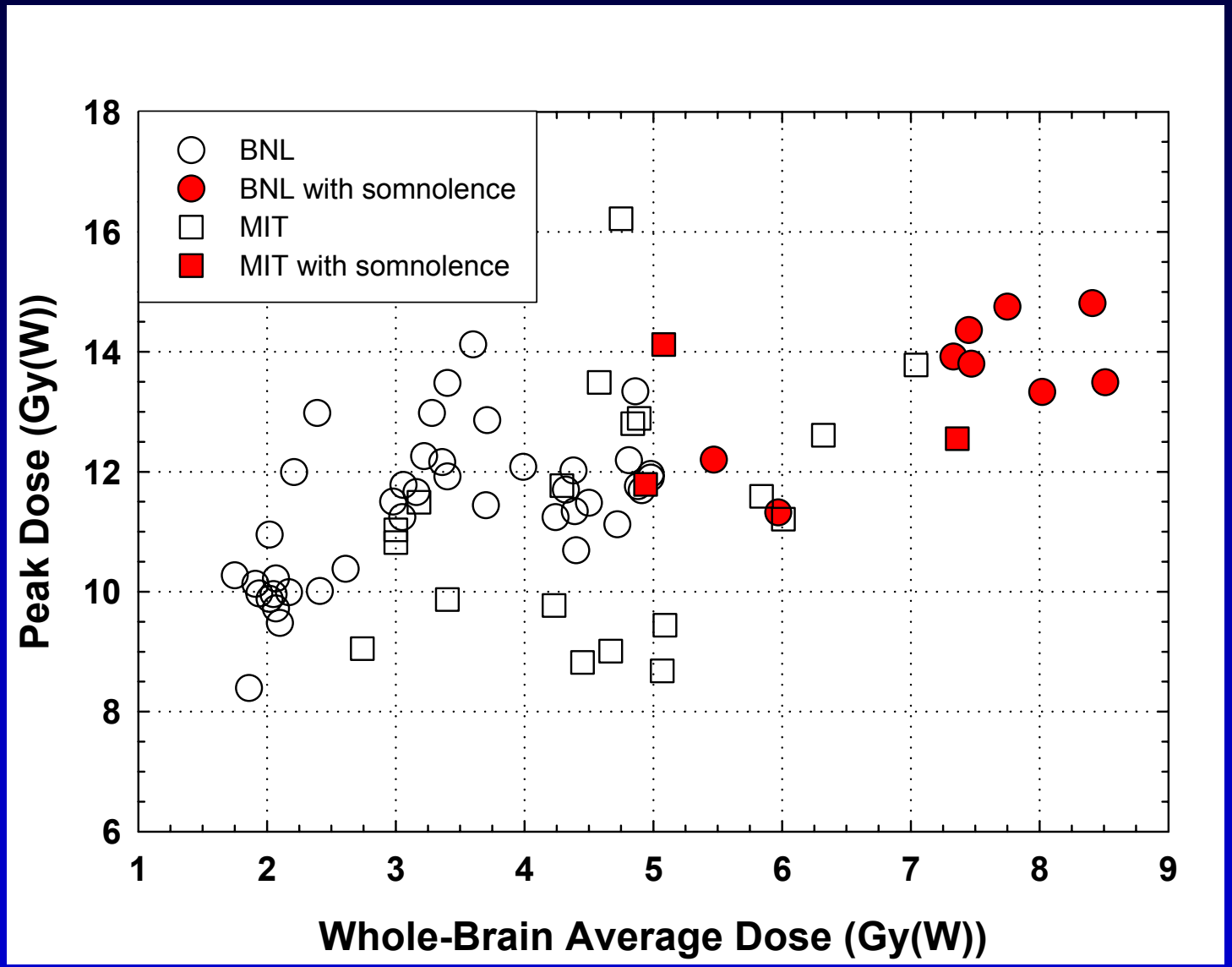
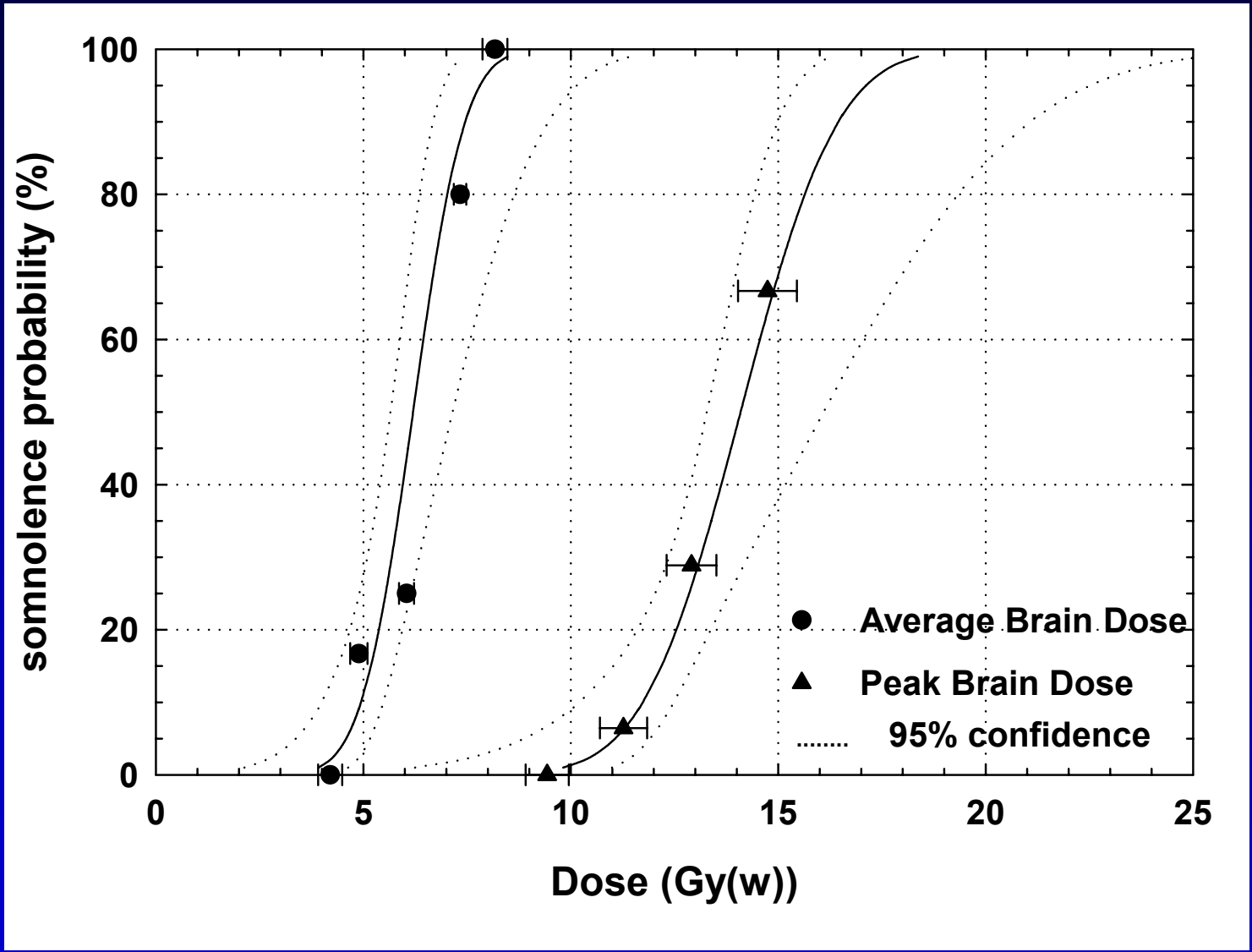


Normal Brain Tolerance



Normal Brain Tolerance



Patient survival data

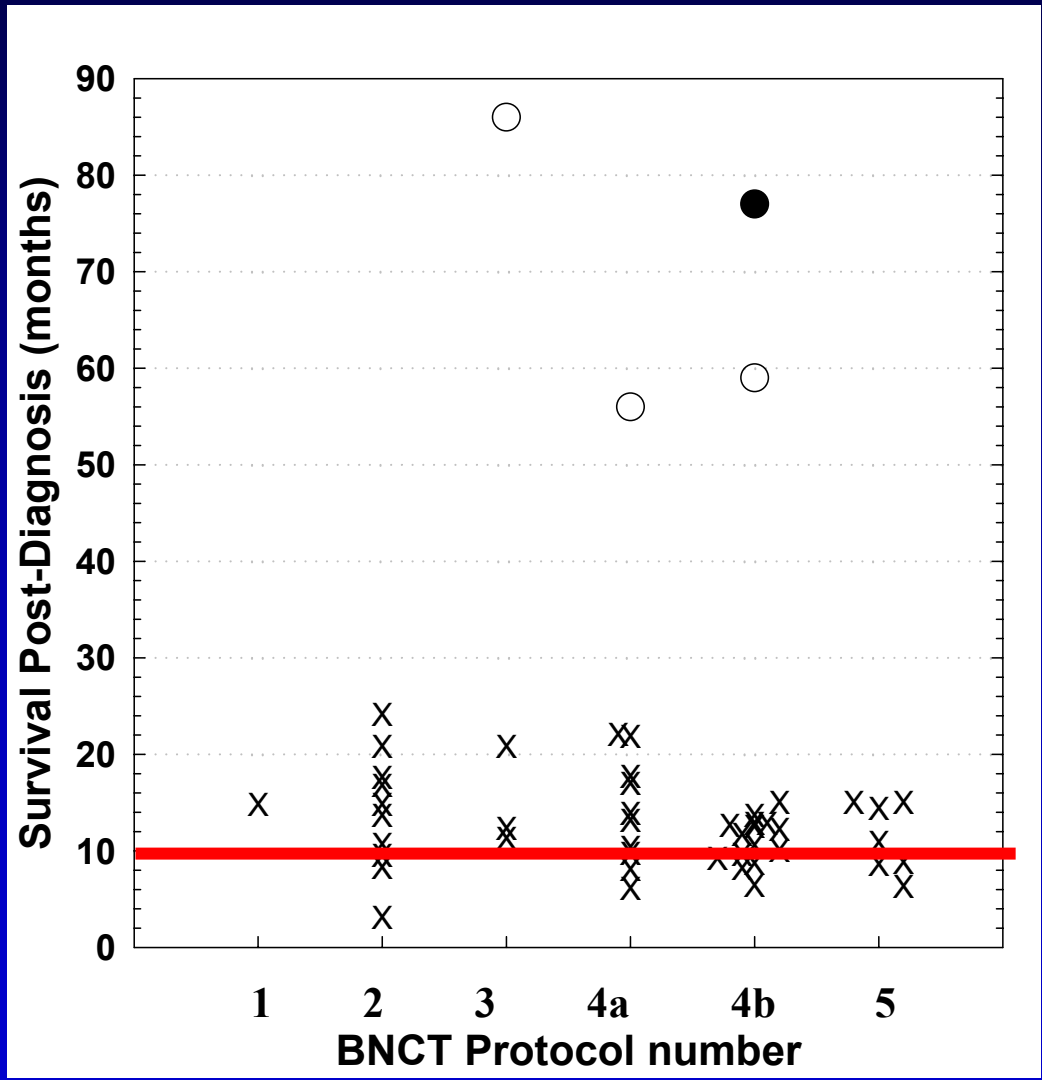
○ = alive
● = alive with recurrence
X = deceased

1 - 4a = single field
4b = two fields
5 = three fields

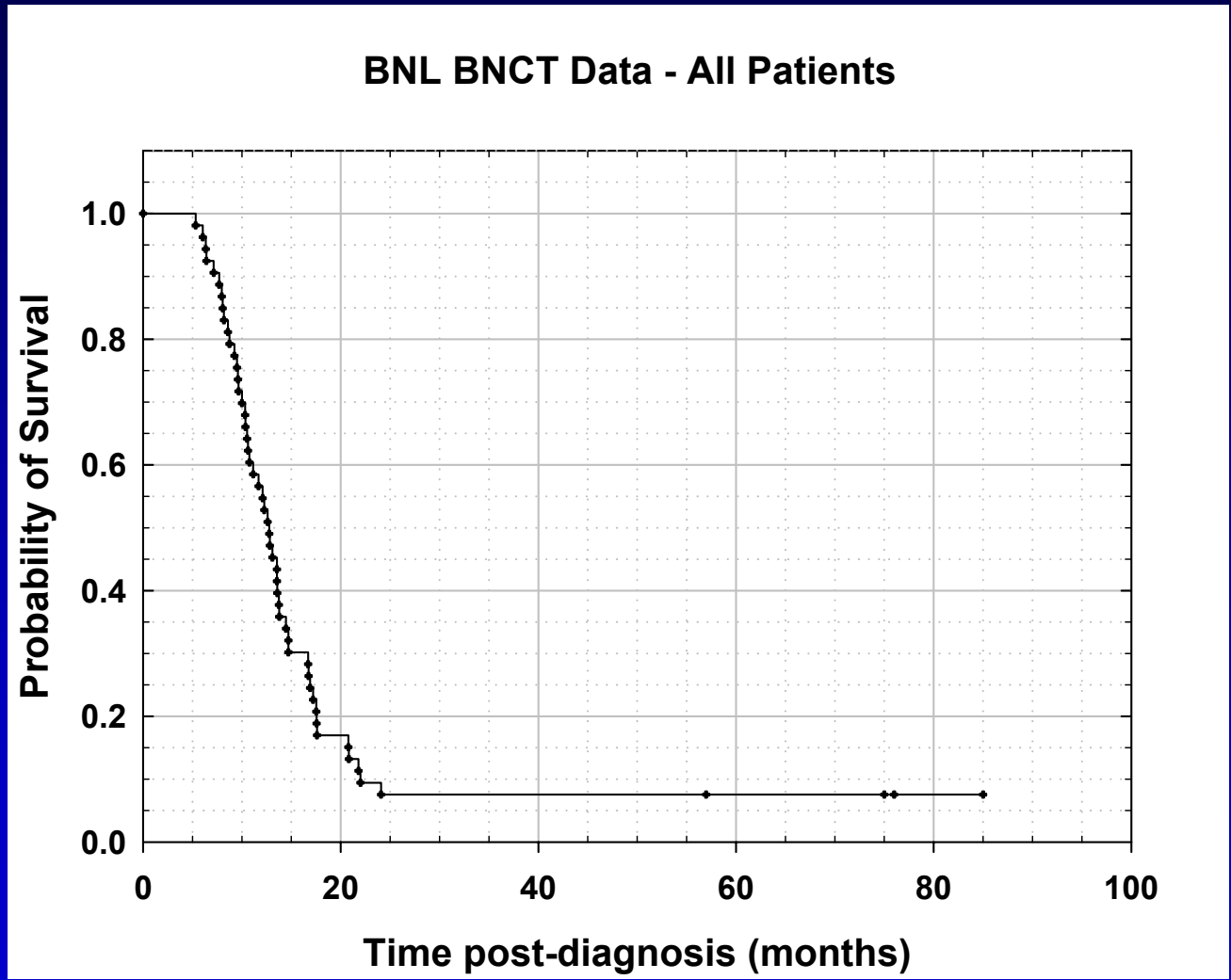
Approximate median survival with standard therapy

(Curran, JNCI, 85, 704, 1993)

Status as of 5/03



Patient survival data



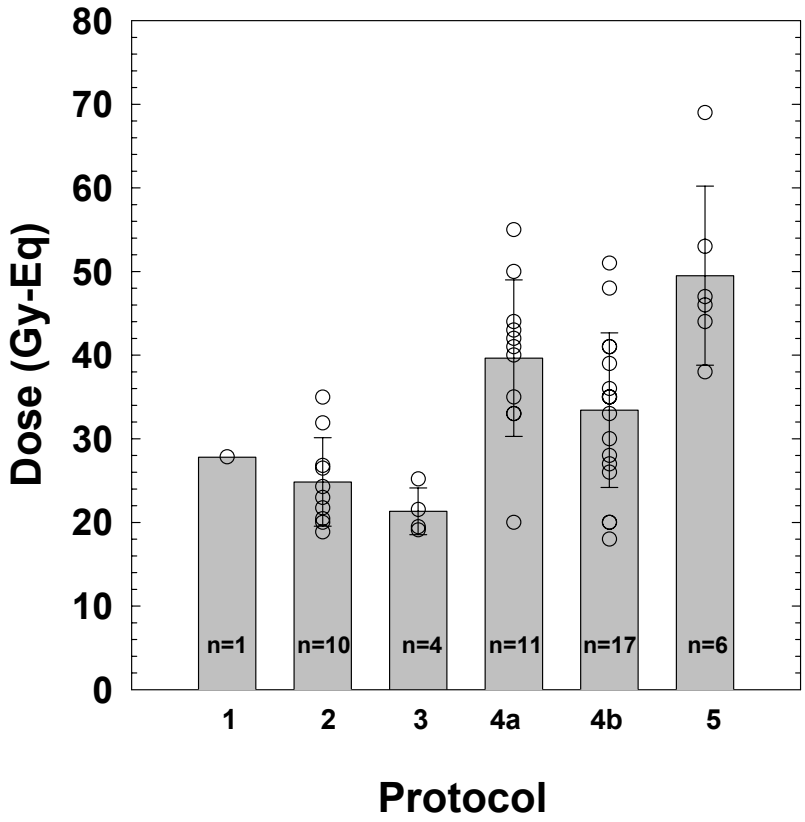
Clinical Trial Summary

- Escalation of neutron exposure may have reached CNS tolerance limits
- The BPA-F dose has only been marginally escalated so far.
- No tumor dose-response has been observed.

Tumor Doses

Minimum dose to the contrast-enhancing tumor volume.

- Calculated Gy-Eq doses are very high: 40, 50, 60 Gy-Eq in a single-fraction.
- Tumor recurrence has been local in the majority of cases.
- Tumor necrosis has been documented histologically.



Tumor: Questions

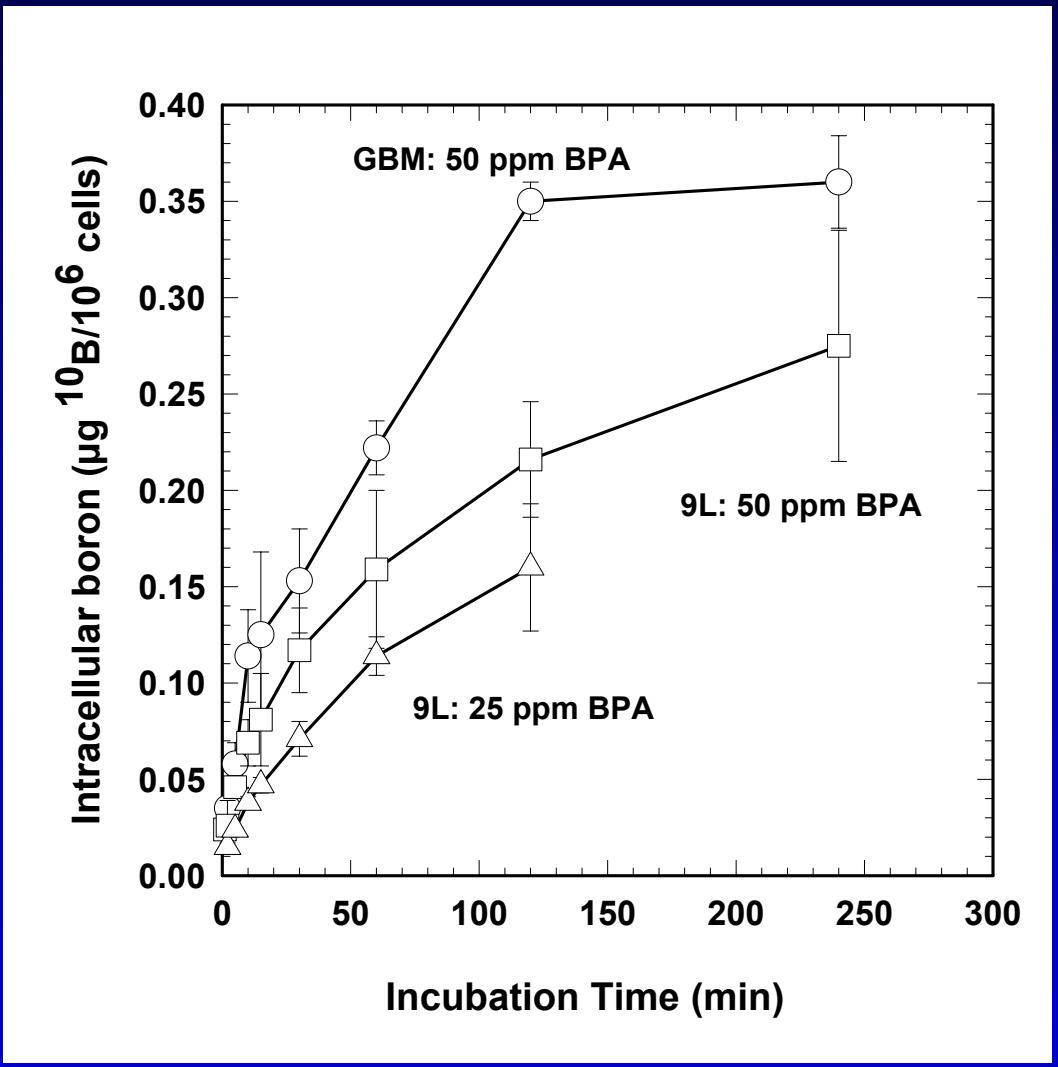
- Does surgery affect BPA uptake in tumor?
- Do all tumor cells take up boron?
- Do infiltrating tumor cells accumulate boron as well as the main tumor mass?

Dose Escalation in BNCT

- Increase boron concentration
- Increase neutron exposure

BPA pharmacokinetics

- Cells in culture take hours to fully load with BPA



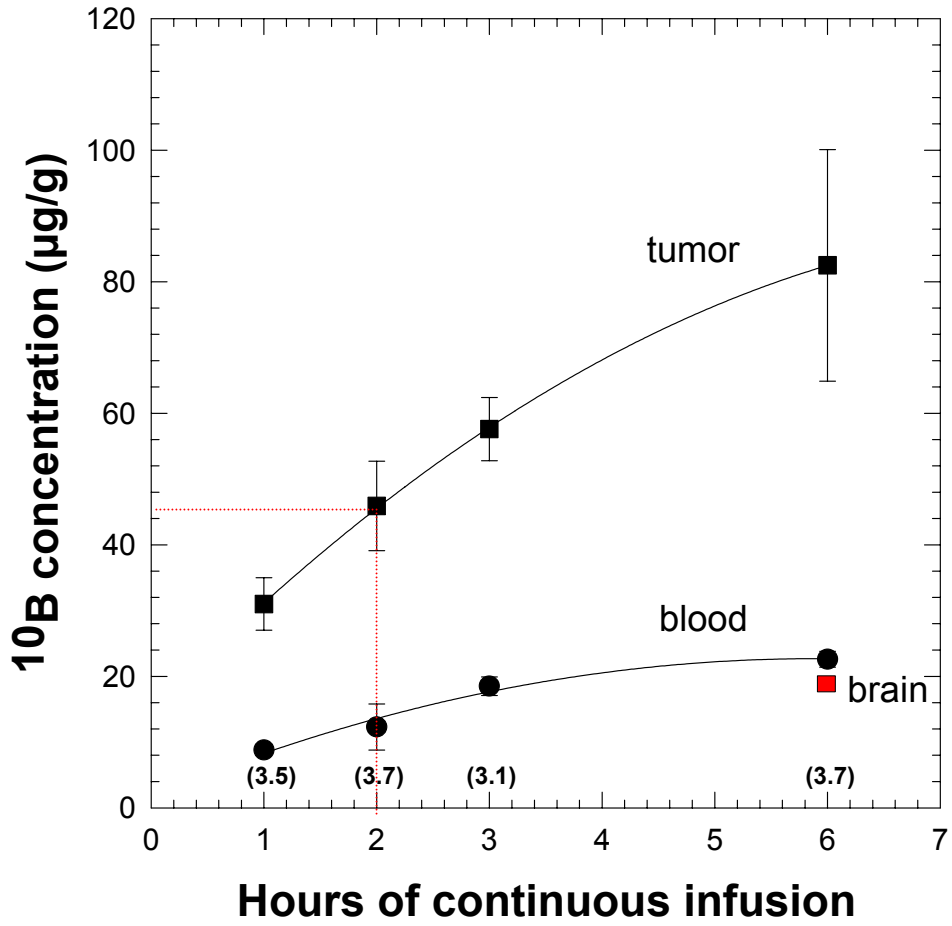
Wittig et al., Radiat. Res. 153, 173, 2000

BPA Dose Escalation

- Rat 9L gliosarcoma
- Infusion rate constant:

250 mg BPA/kg/hr

- Vary infusion time
- Sample tumor, blood 1 hr post-infusion

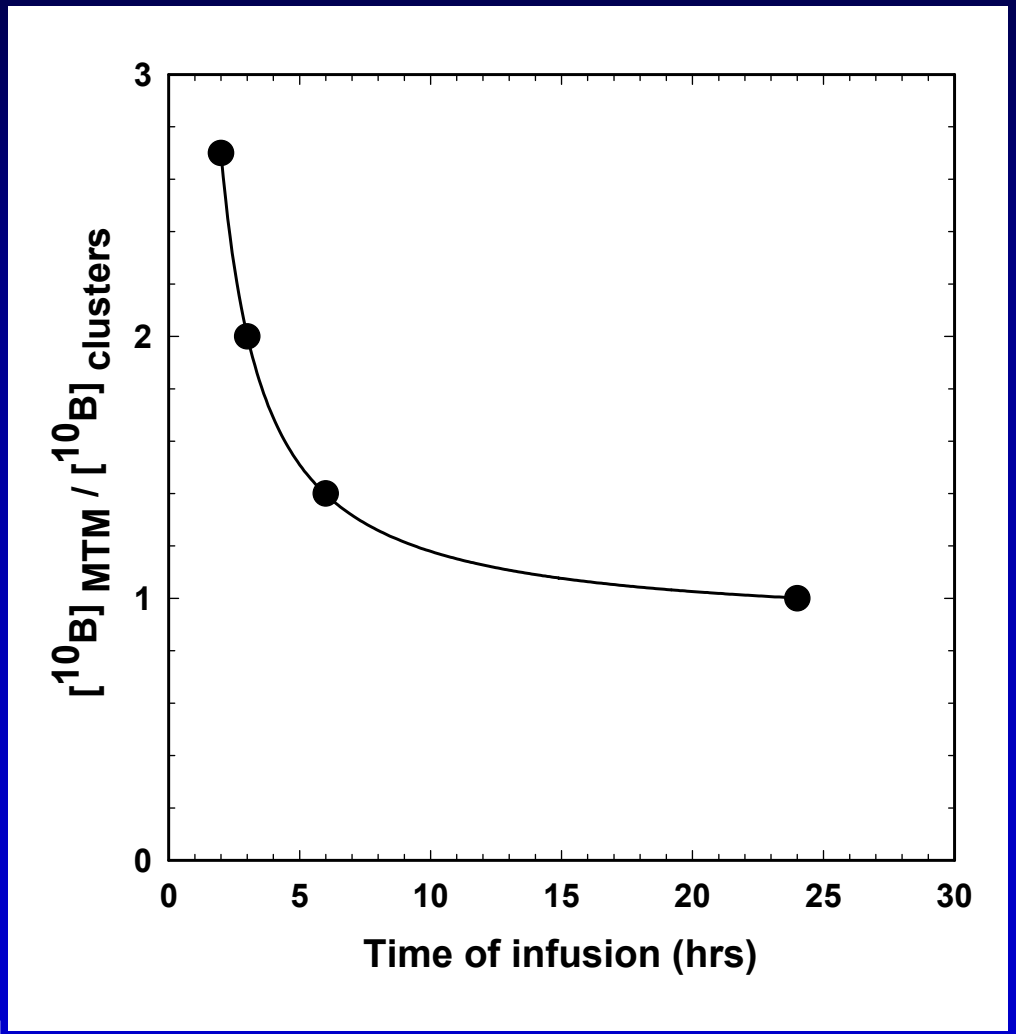


Joel et al., J. Neuro-Oncol., 41, 213, 1999.

Improve BPA delivery to tumor

- Rat 9L gliosarcoma
- Infiltrating tumor cells take hours to reach the same BPA level as the main tumor mass.

Ion microscopy at Cornell Univ.; D. Smith G. Morrison.



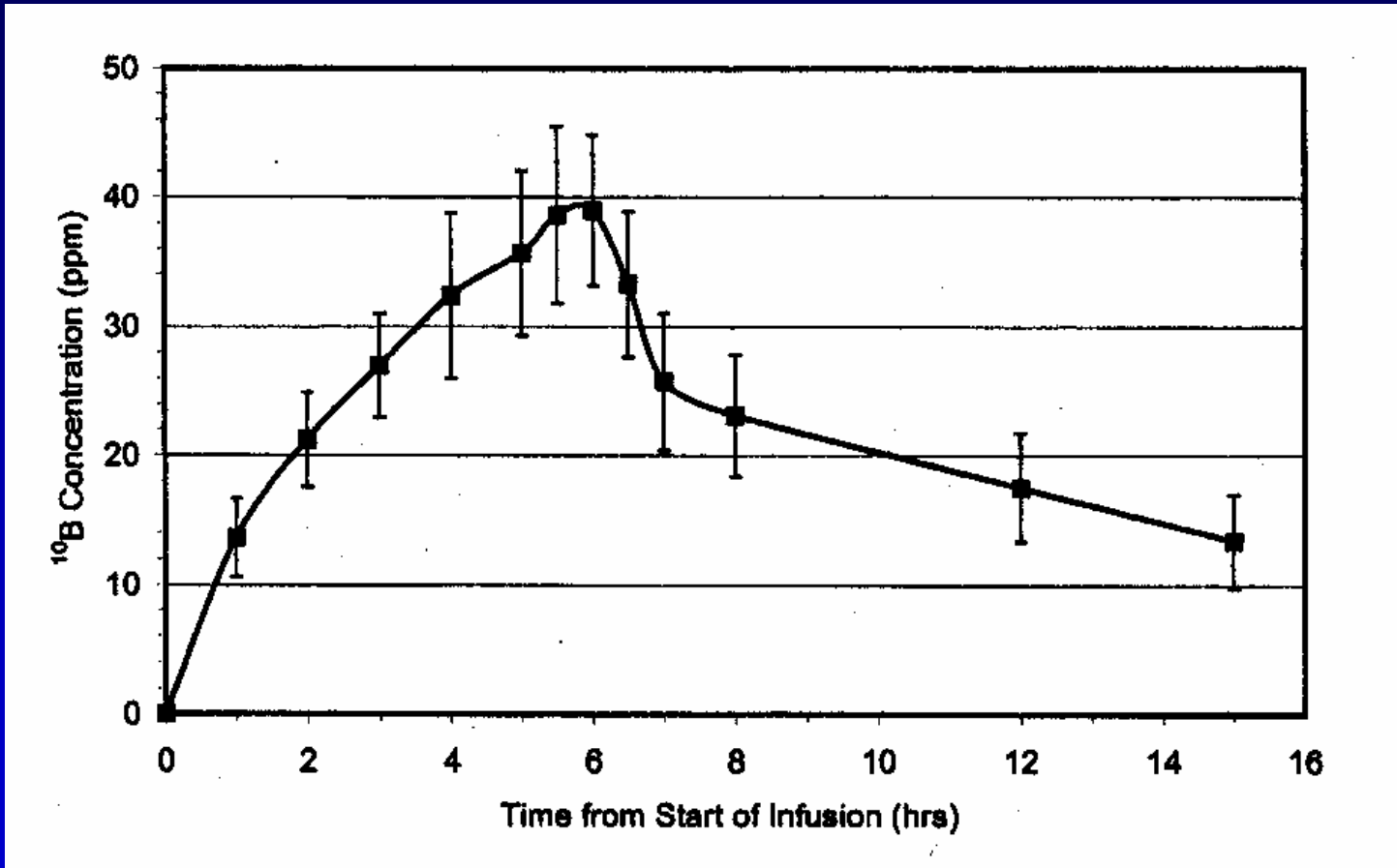
Smith et al., Cancer Res., 22, 8179, 2001

Clinical trial in Studsvik

6-hr
BPA
Infusion:
900 mg/kg

WB ave
dose
3-6 Gy-Eq

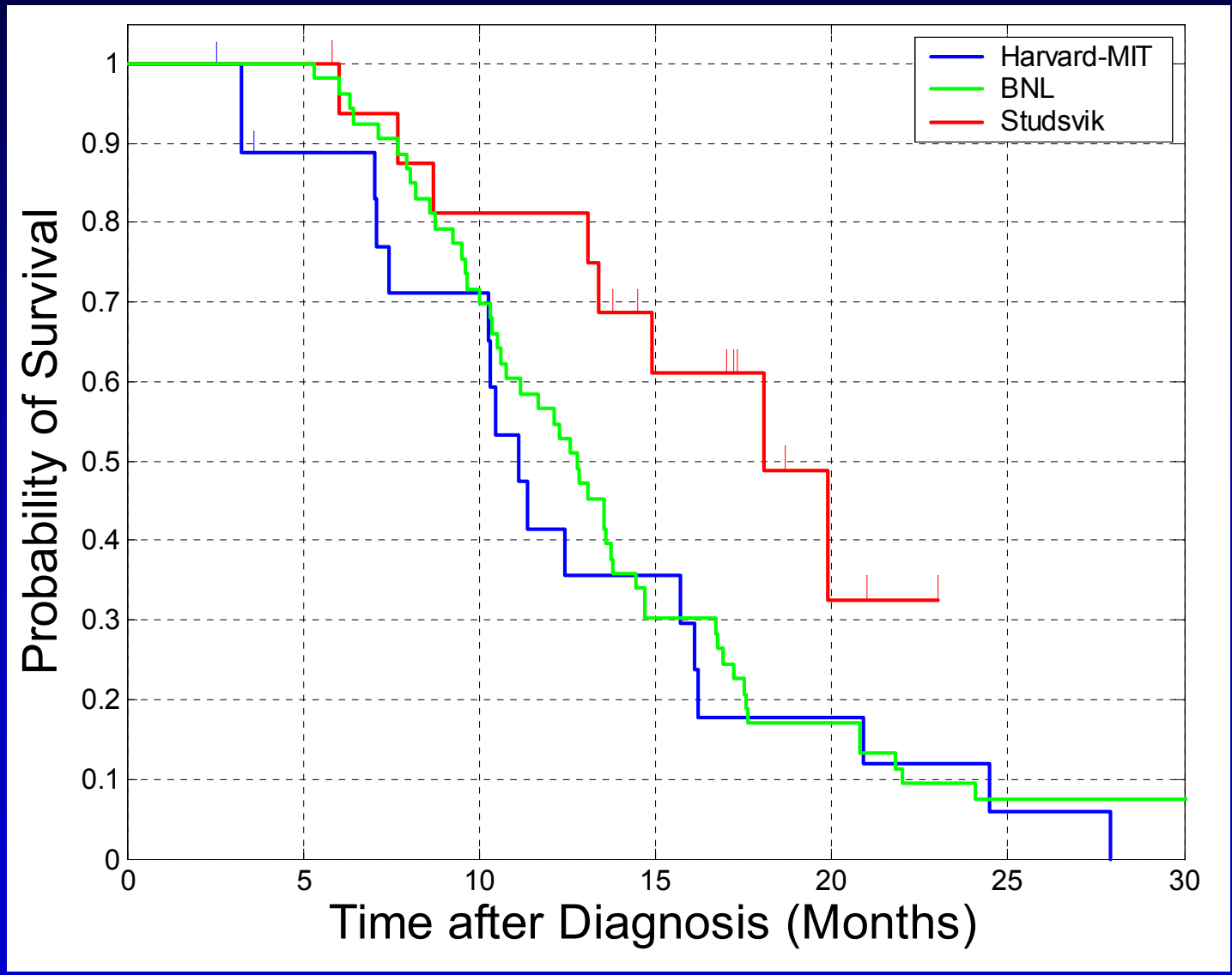
JNO, 62, 135, 2003



BNCT Patient Survival

Studsvik:
6-hour
BPA infusion

JNO, 62, 135, 2003



Currently…

- **BNCT clinical trial for GBM in Sweden evaluating 6-hour BPA infusions.**

- **MIT clinical trials now open:**
  - **Two BNCT fractions on consecutive days**
  - **GBM or melanoma metastatic to the brain**
  - **Cutaneous melanoma.**

- Other BNCT clinical trials underway in Finland, Japan, The Netherlands, Czech Republic.

Clinical Trials: New Directions

Other Sites

- Head and Neck
- Brain Metastases (multiple)
- Lung?

Criteria

- poor local control
- sensitive normal tissues limit dose
- current therapies not effective

Clinical Trials: New Directions

Retreatment: BNCT for recurrent GBM

Combinations

- BPA + another boron compound
  - (GB-10, BSH, CuTCPH, BOPP)
- BPA + radiosensitizer
  - Gd-texaphyrin
- BPA + photons
  - whole brain photons
  - radiosurgery