BNCT Politics

CANCER PATIENT VS. LAB

Woman Seeks Radiation Therapy / Page A7

Joann Magnus

'The bottom line is that I have to be alive in six months from here.'

A Treatment Before Its Time

LIer fights lab for experimental therapy

By Earl Lane
WASHINGTON BUREAU

Washington — There is no easy way to put it, no clinical euphemism that can soften it. Joann Magnus is facing death from an almost invariably fatal form of brain cancer.

Newsday, September 4, 1994

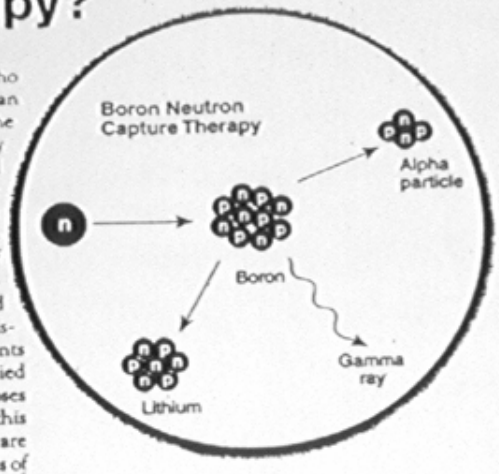
BNCT Politics

CANCER TREATMENT

Will History Repeat for Boron Capture Therapy?

Between 1951 and 1960, 70 people who were dying of brain cancer submitted to an experimental radiation treatment at the Massachusetts Institute of Technology (MIT) and the Brookhaven National Laboratory. Neurosurgeons injected the patients with boron compounds, cut openings in their skulls, placed them up against nuclear reactors, and sent beams of neutrons into their exposed brains. Publicity before the treatment had raised hopes, but the results were considered disappointing or even disastrous: The patients irradiated with low doses of neutrons died from their tumors; those who got high doses died from the radiation. But in spite of this unpromising history, U.S. researchers are about to try again. And both the advocates of boron neutron capture therapy (BNCT) and its critics fear that history may repeat itself.

Skepcics like Princeton University physicist William Happer, who directed Department of Energy (DOE) research during the 1980s, say the procedure remains dangerous. In the original trials, the nuclear reactions triggered by the neutron bombardment harmed patients, Happer points out, "and now they are going to do it again." Neurosur-



Science, Vol. 265,

July 22, 1994

Radiation OKd for LI Patient

By Earl Lane
WASHINGTON BUREAU

Washington — Review boards at Brookhaven National Laboratory and Beth Israel Medical Center in Manhattan gave approval yesterday for a Westbury woman with brain cancer to undergo an experimental radiation therapy at least a year before Brookhaven researchers had planned to start accepting patients.

Newsday, September 10, 1994

BNCT Politics

LIer Undergoes Novel Therapy

Brain treatment at lab's reactor

By Earl Lane
WASHINGTON BUREAU

After more than two months of waiting and pleading, Joann Magnus got her wish yesterday to be the first U.S. patient in more than 30 years to receive a novel form of radiation therapy for brain cancer.

The 50-year-old Westbury woman underwent the procedure, called boron neutron capture therapy, or BNCT, last night at Brookhaven National Laboratory's medical research center in Upton. The lab's team was assisted by doctors from Beth Israel Medical Center in Manhattan, where she has been treated for an aggressive and almost invariably fatal form of cancer called glioblastoma multiforme.

Magnus was described as "fully alert, conversational, jocular, very high-spirited and very thankful" by Beth Israel neurosurgeon Richard Bergland after the procedure was completed shortly after 8 last

Newsday, September 14, 1994

Washington Post, 12/94

Atomic Medicine's Second Chance

Brain Cancer Case Revives Boron Radiation Therapy Method Using Nuclear Reactor

By Faye Flam
Special to The Washington Post

When brain cancer struck Joann Magnus last May, physicians could offer the 50-year-old Long Island resident little hope. The mptoms hit suddenly—she noticed some sion problems, and within two weeks she uldn't speak or move her right arm or leg. octors ordered brain scans, which showed at a clump of malignant cells deep in the brain d grown out of control, shoving aside healthy sue and spreading beyond the reach of the rgeon's knife or effective drug treatments. Scared and frustrated, Magnus banked all r hopes on a long shot: a combination chemi- l and radiation therapy that had been devel- ed and then quickly abandoned by research- s in the late 1950s and early 1960s. In that a's zeal to experiment with the newly har- ssed power of the atom, a team of physicians d government scientists wheeled brain can- r patients up to nuclear reactors and adminis- red a regimen designed to set off tiny nuclear ictions within the brain. But this treatment— led boron neutron capture therapy—ended curing none of the patients and killed four. Still, some researchers remained convinced y could overcome the problems and eventu- y use this treatment to cure several deadly ncers, including the one that threatened Mag- s's life—glioblastoma. This relentless brain cer kills about 7,000 people each year. The

For Magnus, Bergland decided this was the best hope for survival.

Magnus and her family quickly became convinced he was right. At first, Brookhaven's Joel refused to disrupt his plan to complete the distribution studies, crucial for determining the best doses of boron and radiation. If he made an exception for Magnus, he would have to do more guesswork than he felt comfortable with. And if he got it wrong, Magnus might die—and the negative publicity would also kill years of work on a potentially lifesaving treatment.

But Magnus said she became determined to do everything in her power to get the treatment early. She and members of her family pleaded with Joel and his colleagues nearly every day. At the same time, she applied the persuasive skills she had honed in her career as a fund-raiser. She contacted the U.S. Department of Energy, the agency that runs the lab, eventually enlisting the help of high-level officials.

"I had nothing to lose," said Magnus. "And I don't believe in 'no.'"

With pressure coming from all quarters, Joel relented. On Sept. 13, Magnus received a single treatment. Doctors injected a boron-containing drug and put her head near the lab's nuclear reactor, giving her a 45-minute exposure to a stream of neutrons. The results have been dramatic: Magnus, who had lost her speech as the disease progressed, has regained her ability to talk. In early October, she returned to her job as a fund-raiser at the United Jewish Appeal.

BNCT Politics

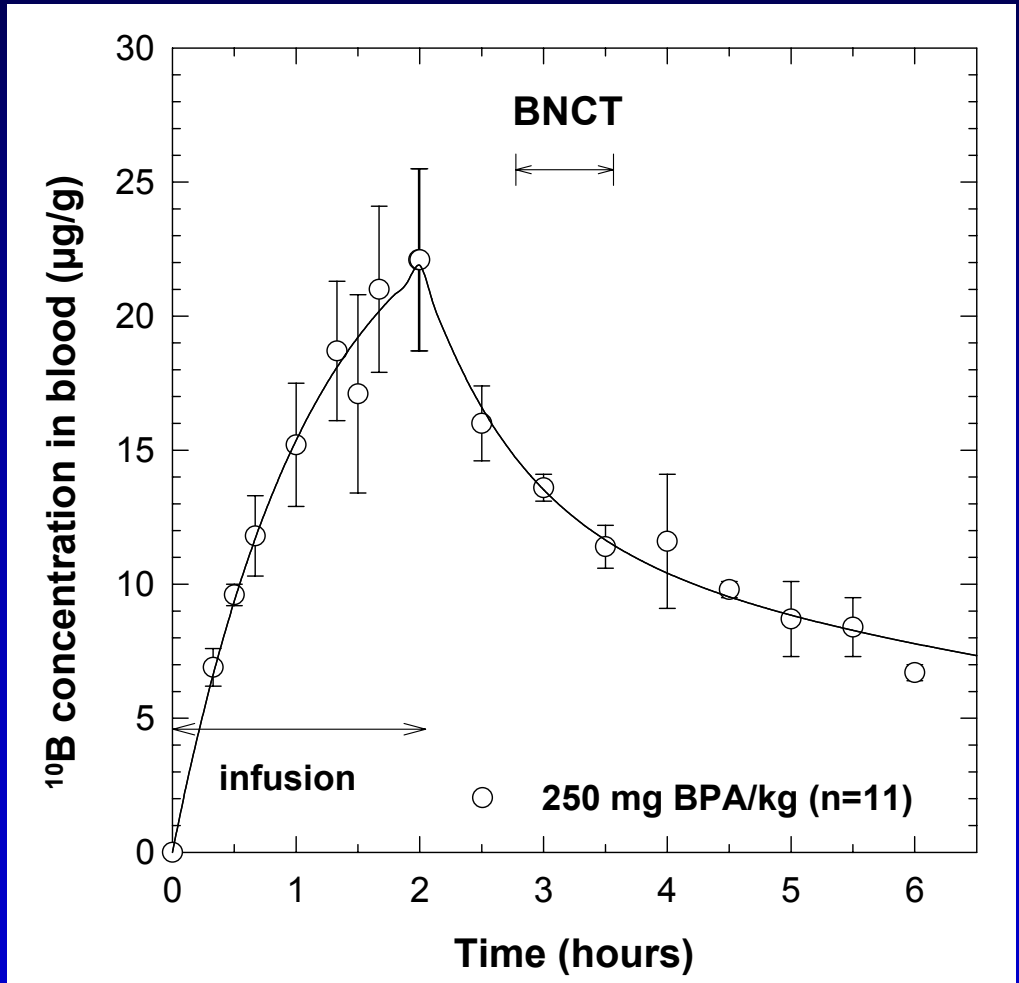
BNCT Politics

The BNCT procedure

Surgery 3-4 weeks prior to BNCT.

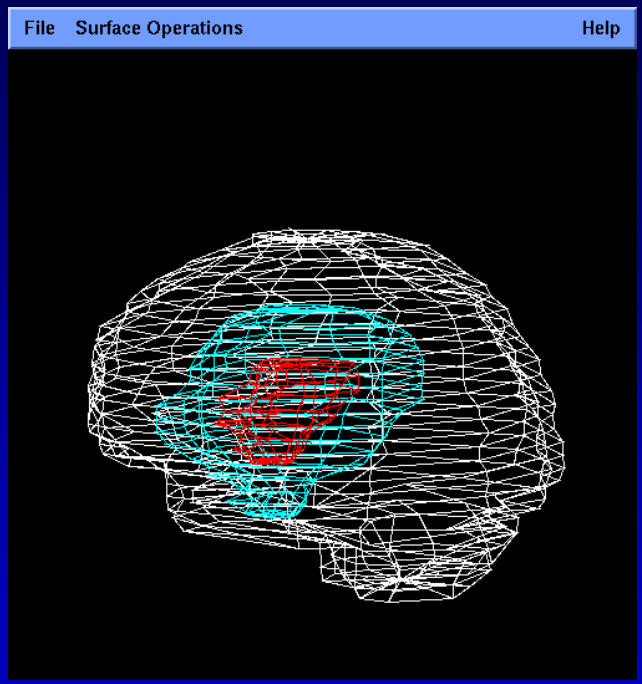
BNCT is given in a single session lasting less than 1 hr.

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

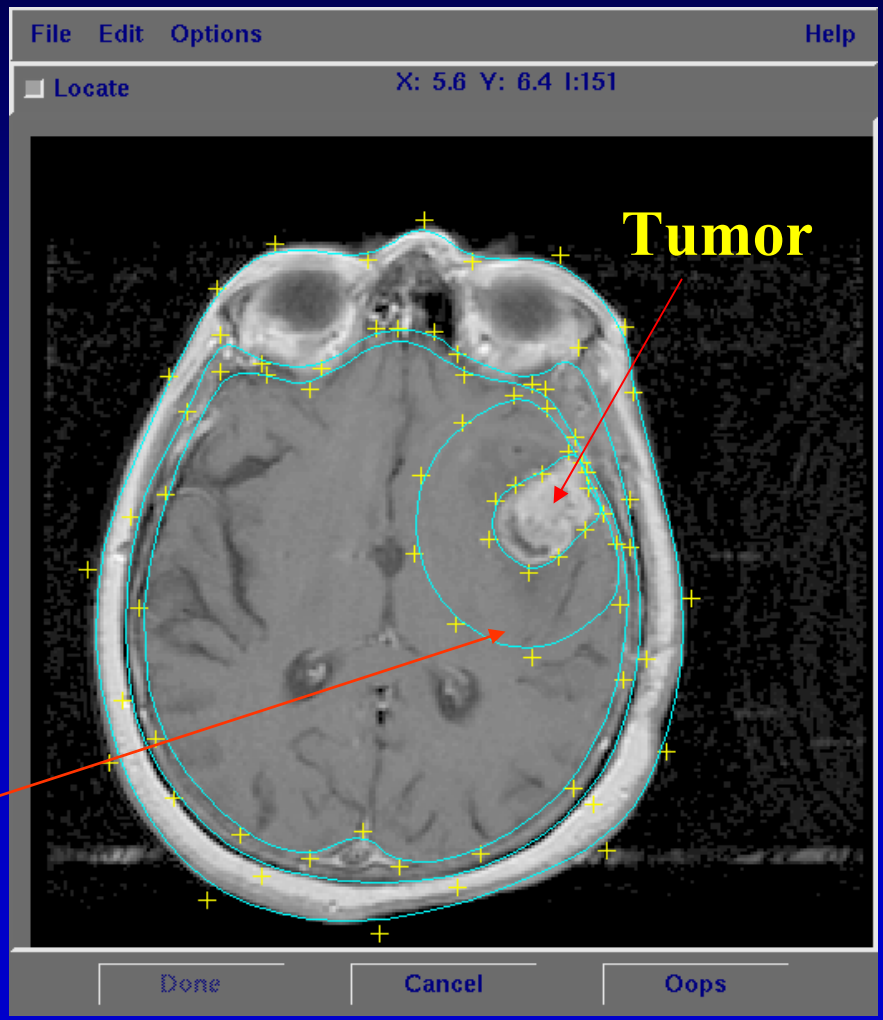


Coderre, et al., J. Neuro-Oncol., 33, 141, 1997.

Monte Carlo-based treatment planning

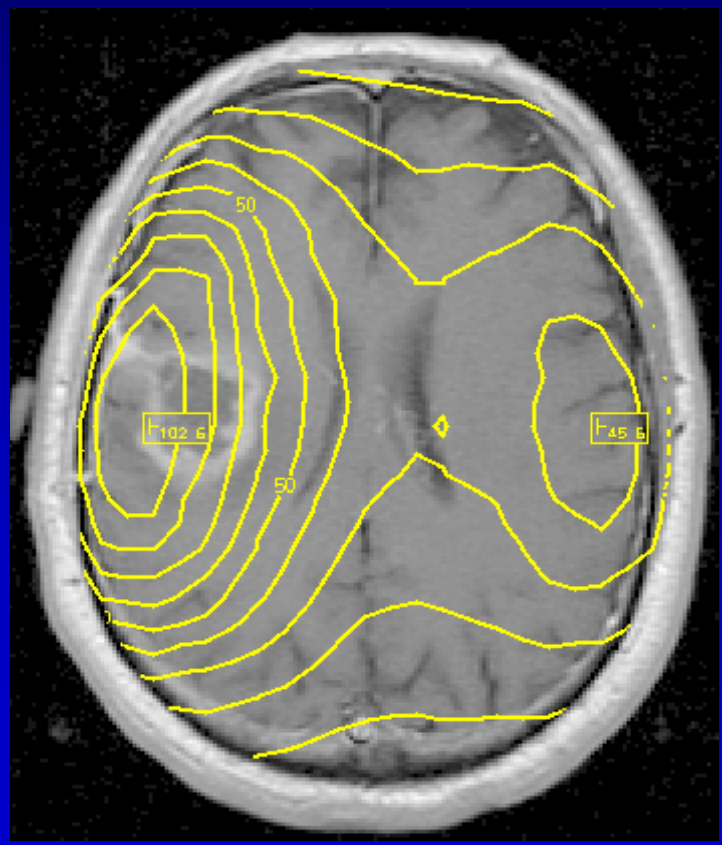


Target volume (tumor + 2 cm)

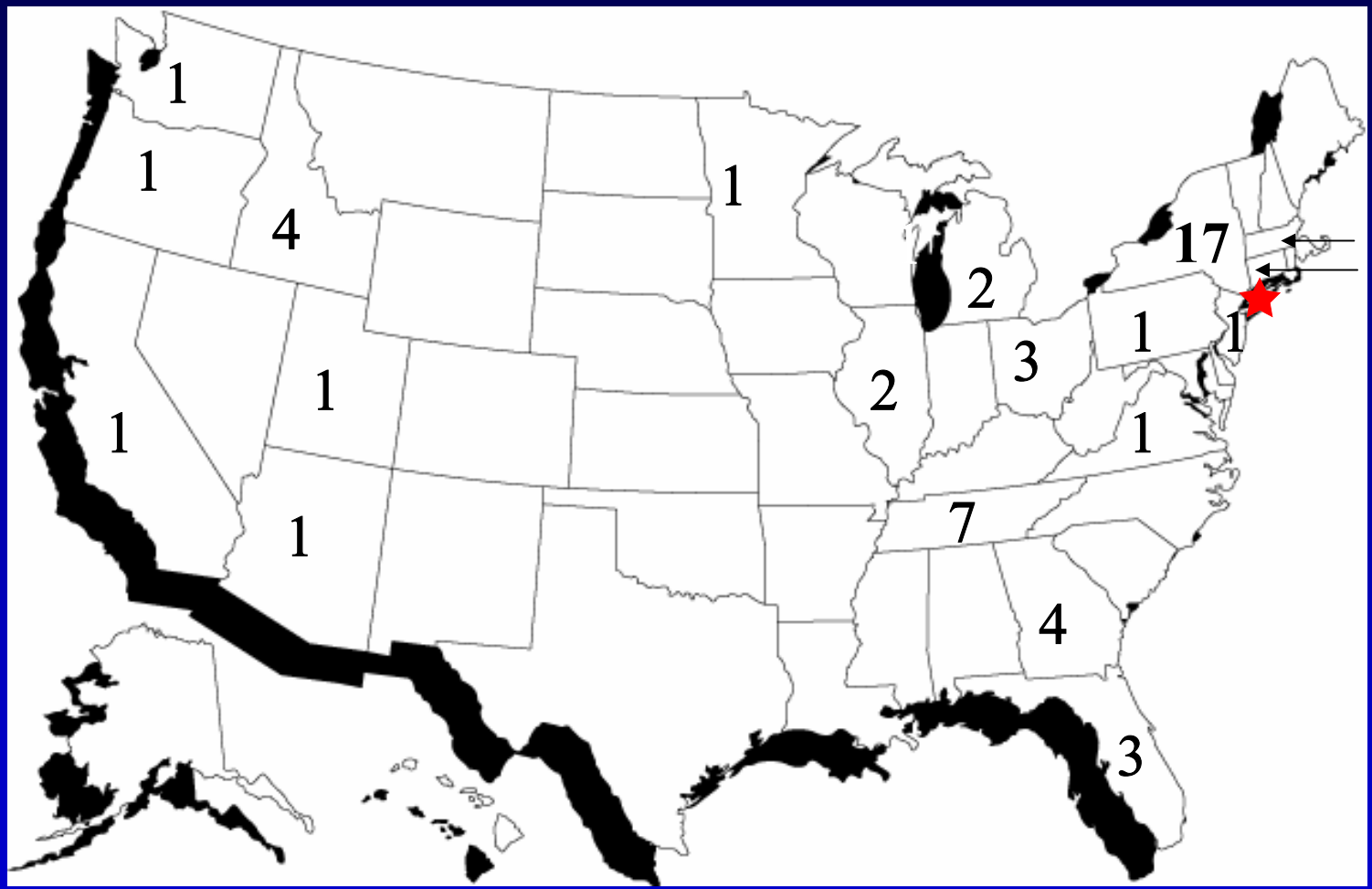


Brain

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

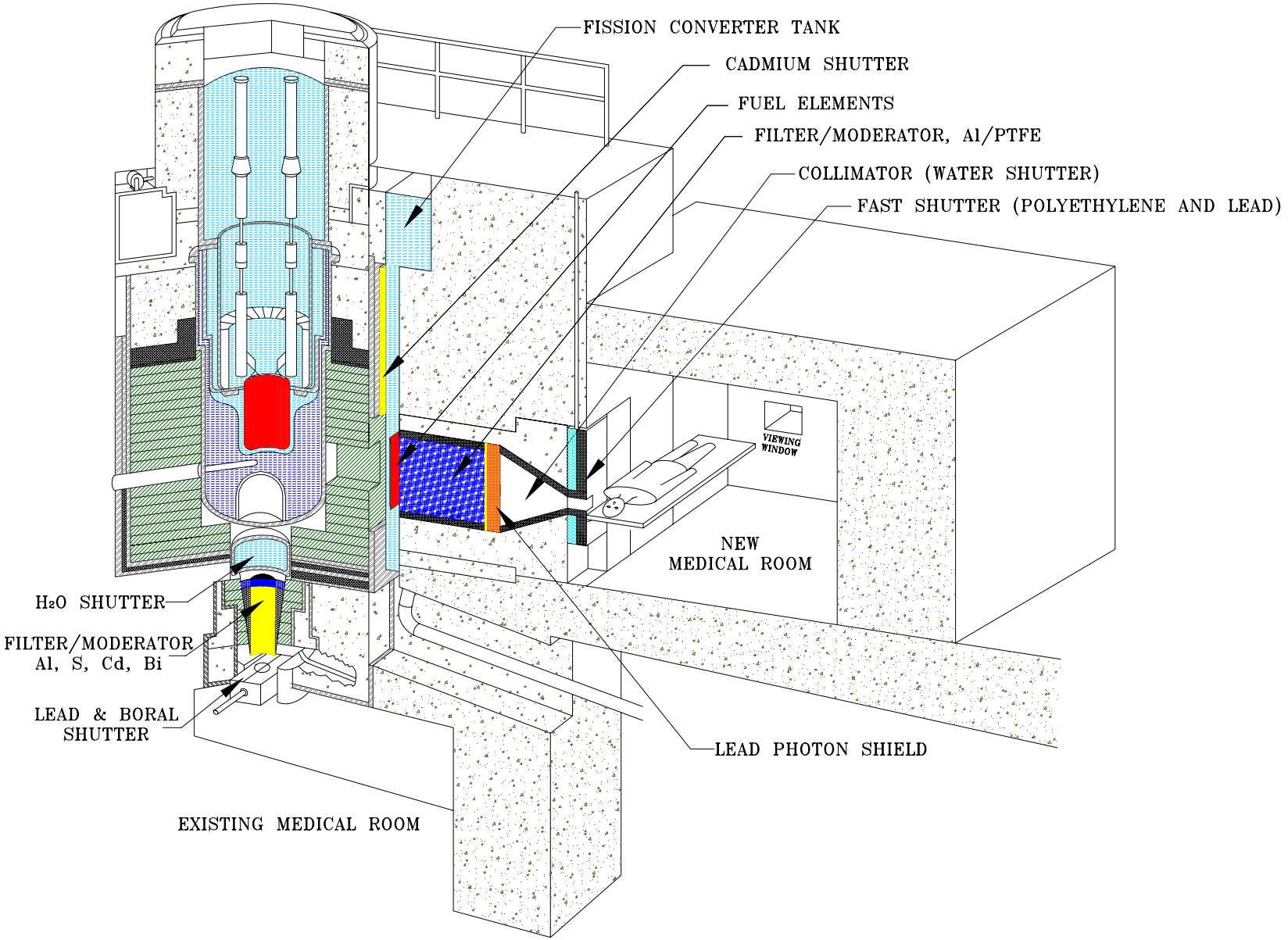


BNCT Patients



BNCT at the BMRR, 1997

The MIT Research Reactor



MITR-II showing current and new epithermal beam locations

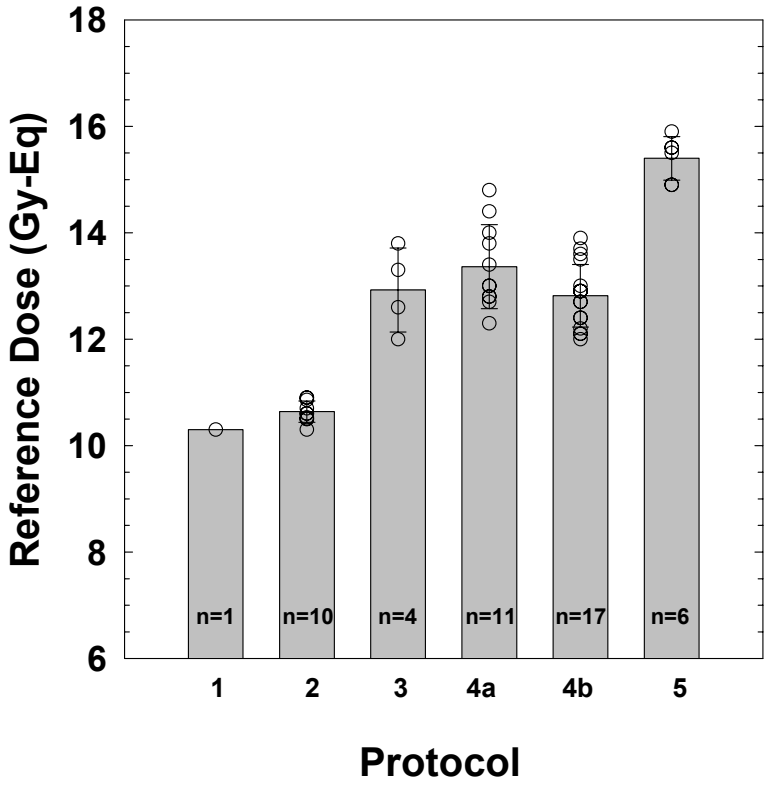
MIT BNCT Clinical Trial

Brain Doses

BNL BNCT clinical trial.

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

Doses escalated in 20% increments.



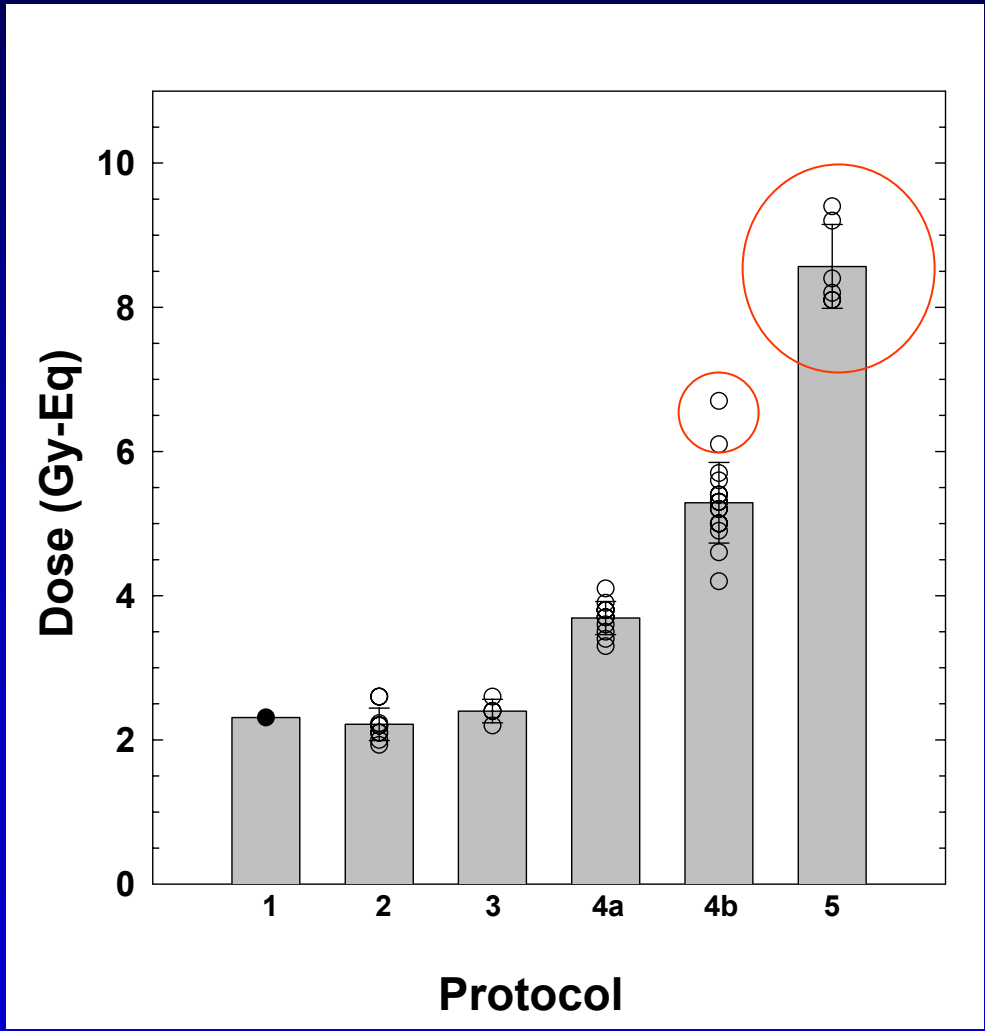
Chanana, et al., Neurosurg., 44, 1182, 1999.

Brain dose

BNL BNCT clinical trial:

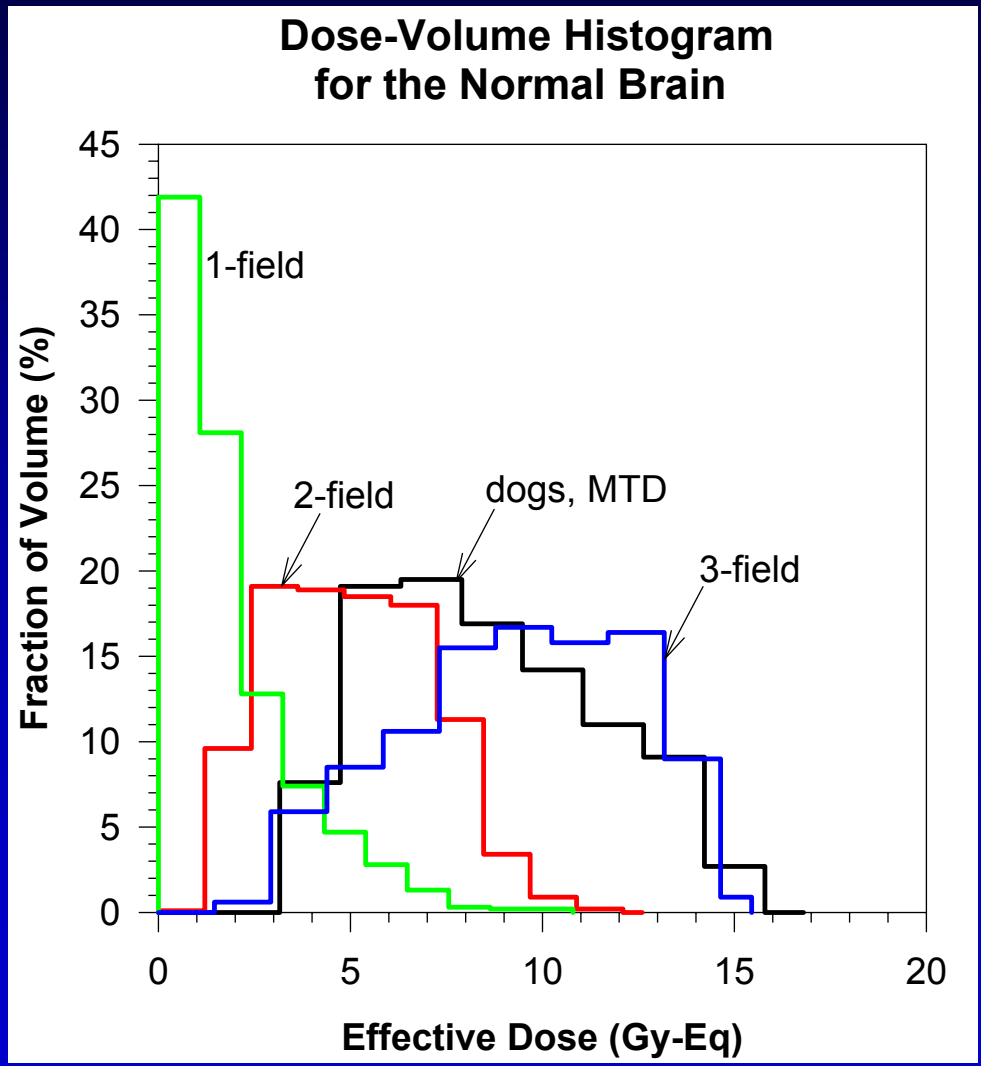
Whole-brain average doses.

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

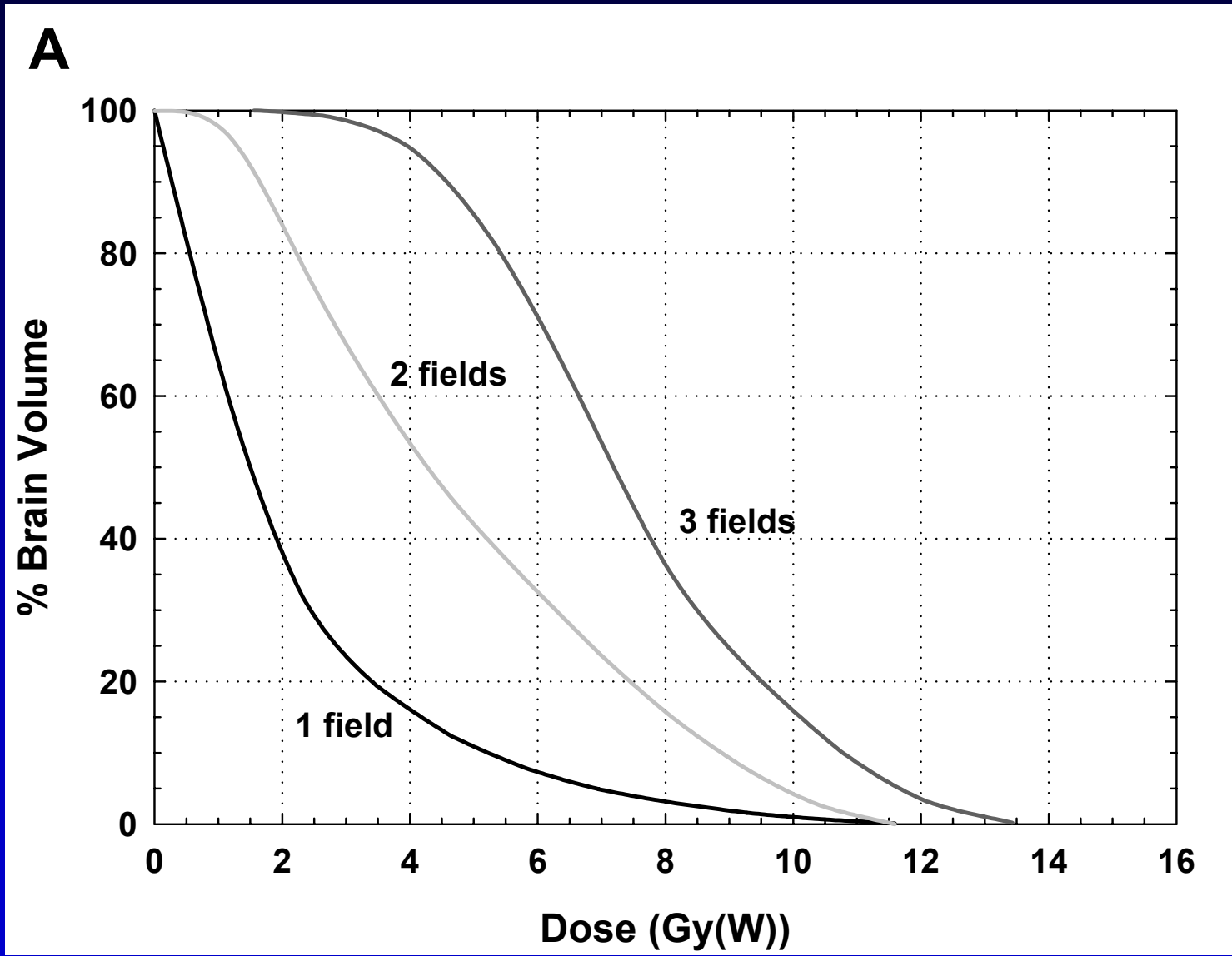


Brain: Dose Volume Histograms

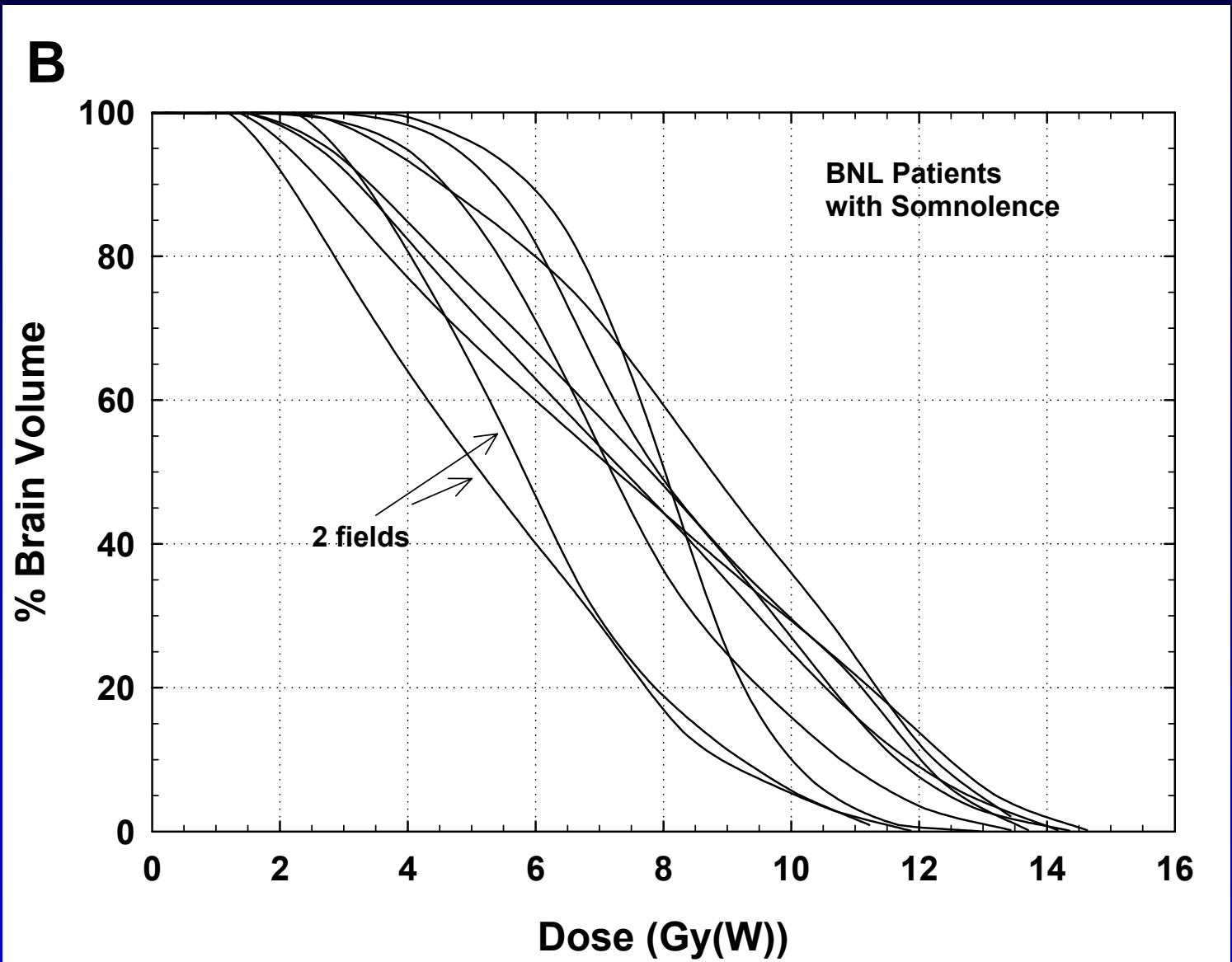
- Escalation of the dose in humans.
- Comparison to the maximum tolerated dose in dogs.



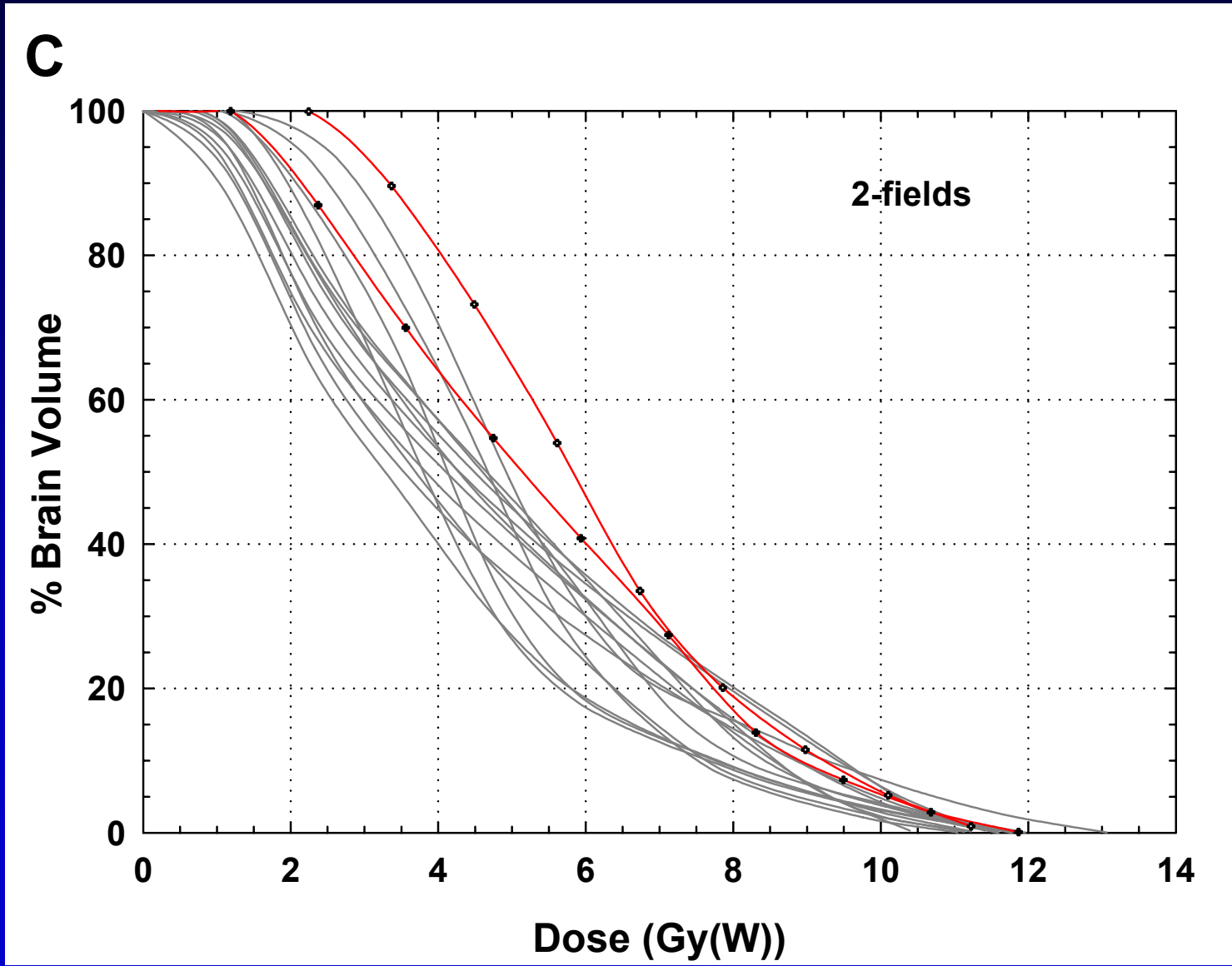
Normal Brain Tolerance



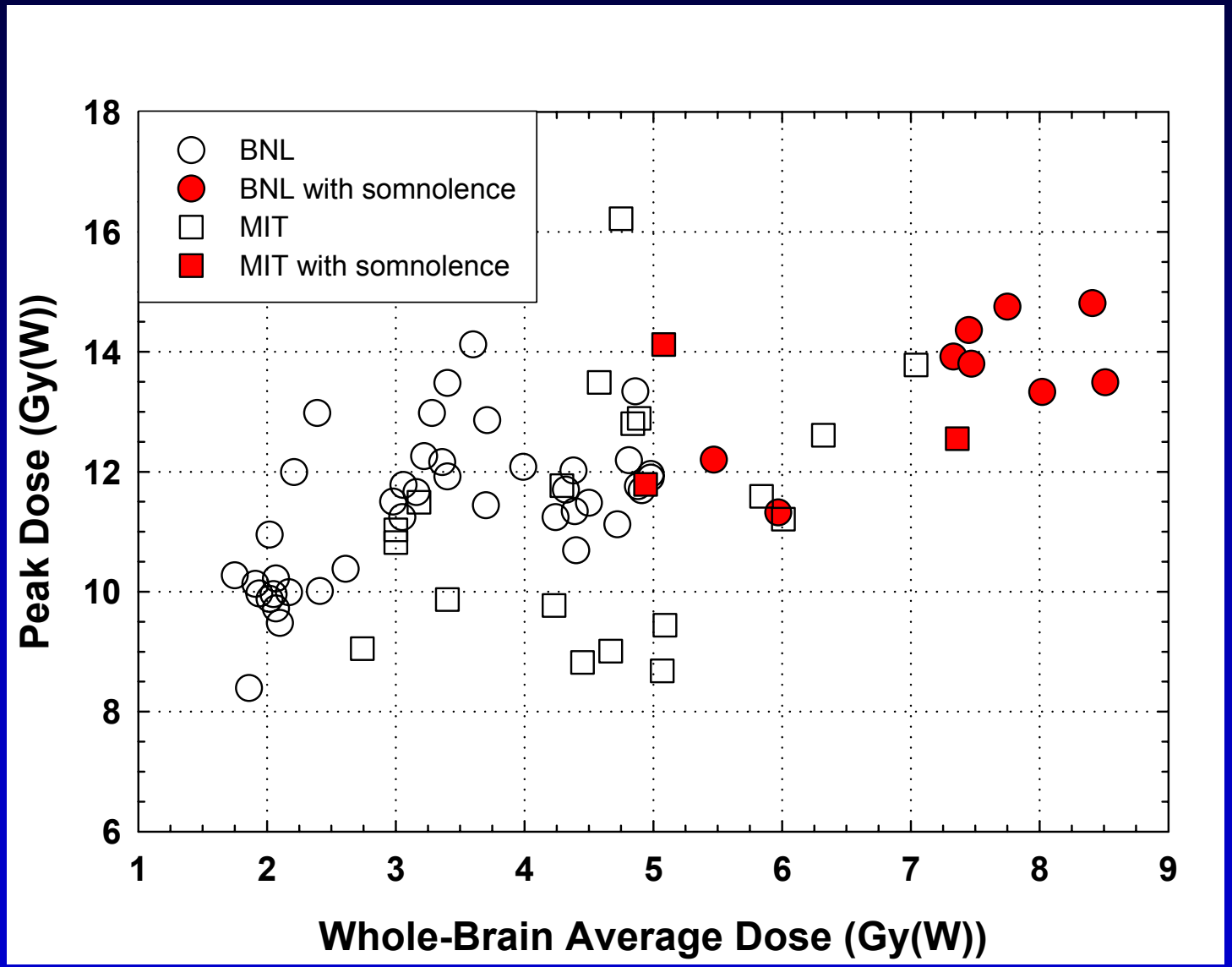
Normal Brain Tolerance



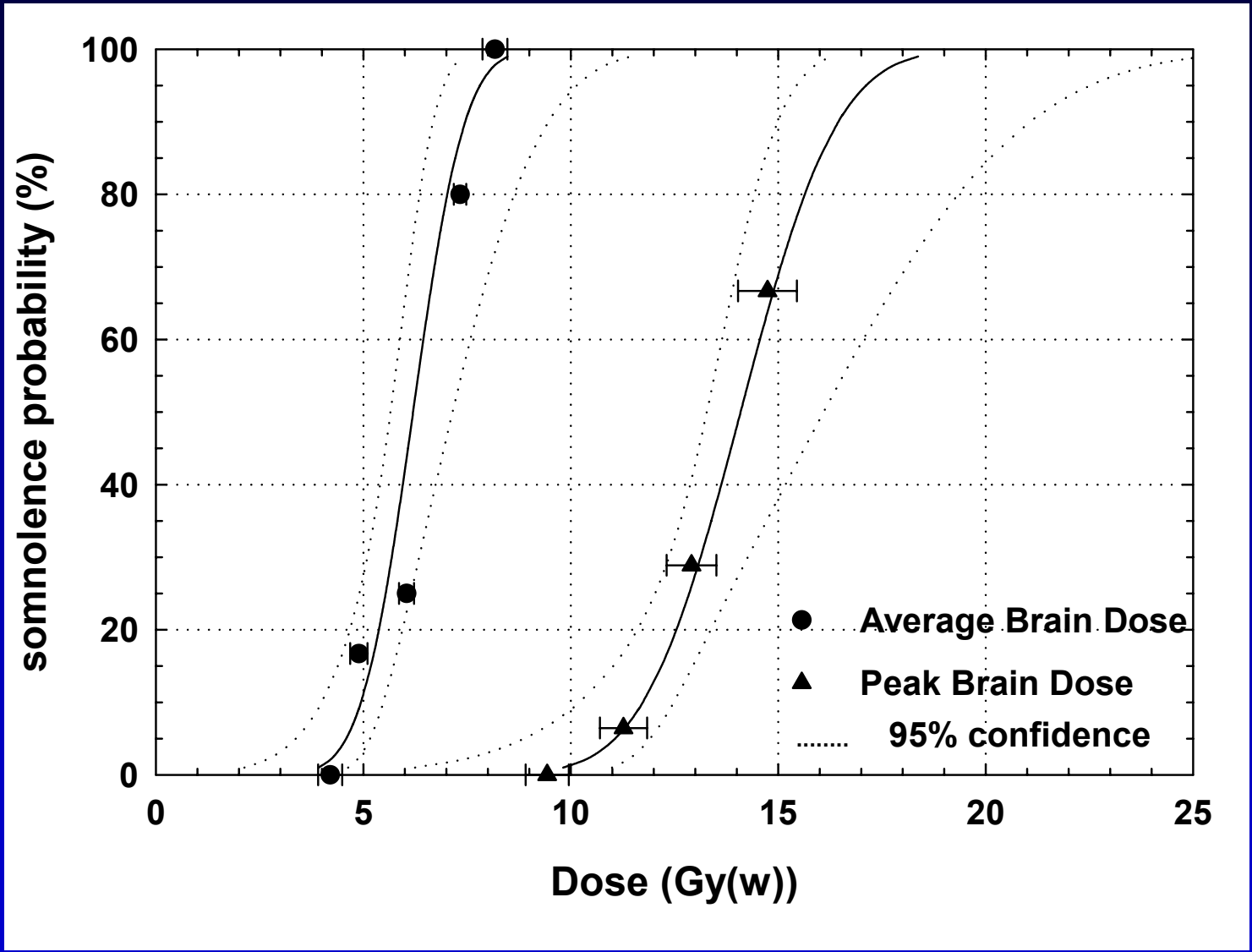
Normal Brain Tolerance



Normal Brain Tolerance



Normal Brain Tolerance



Patient survival data

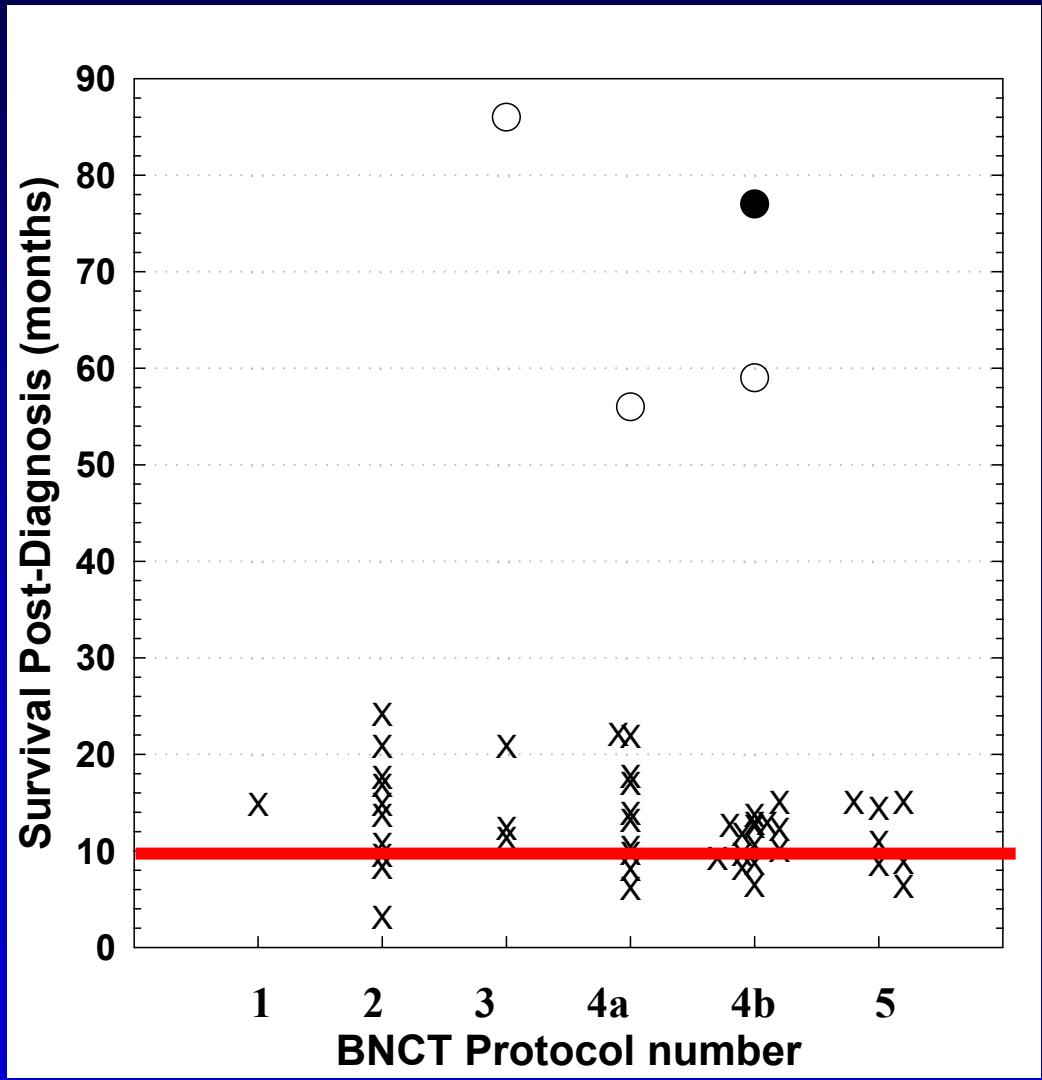
○ = alive
● = alive with recurrence
X = deceased

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

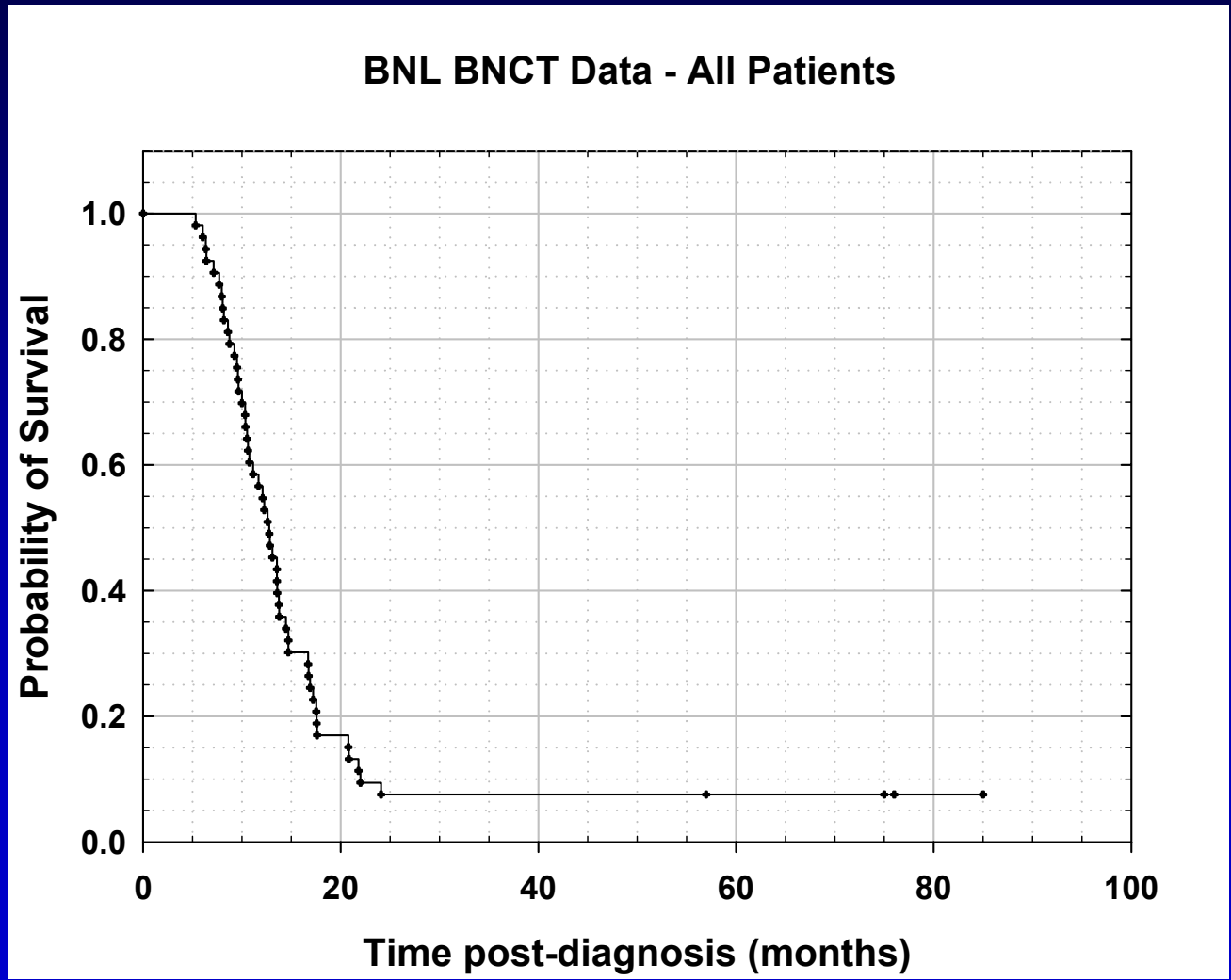
Approximate median survival with standard therapy

(Curran, JNCI, 85, 704, 1993)

Status as of 5/03



Patient survival data



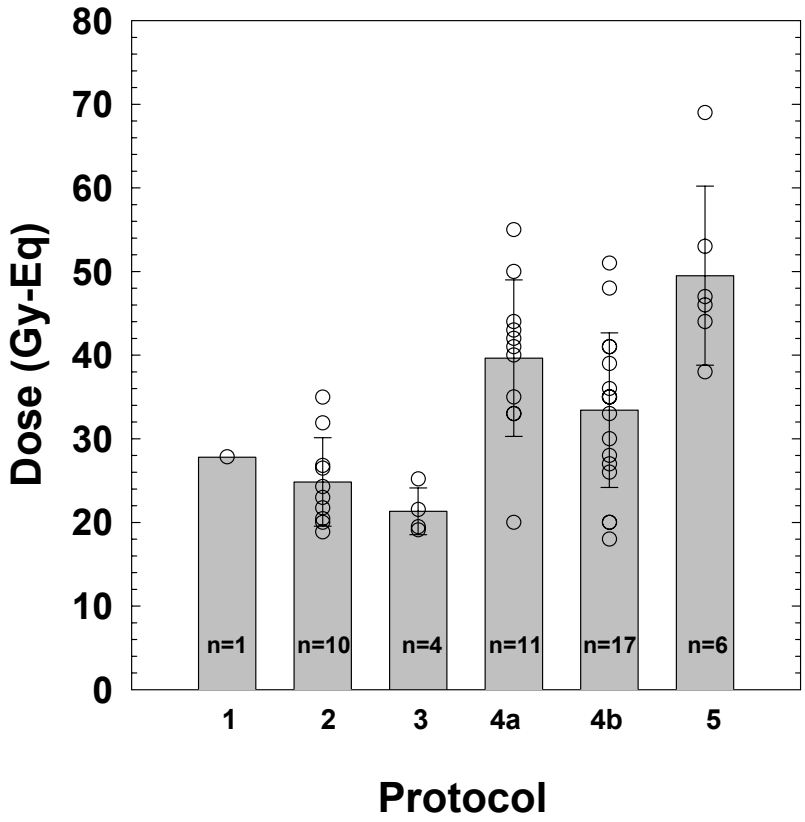
Clinical Trial Summary

- 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

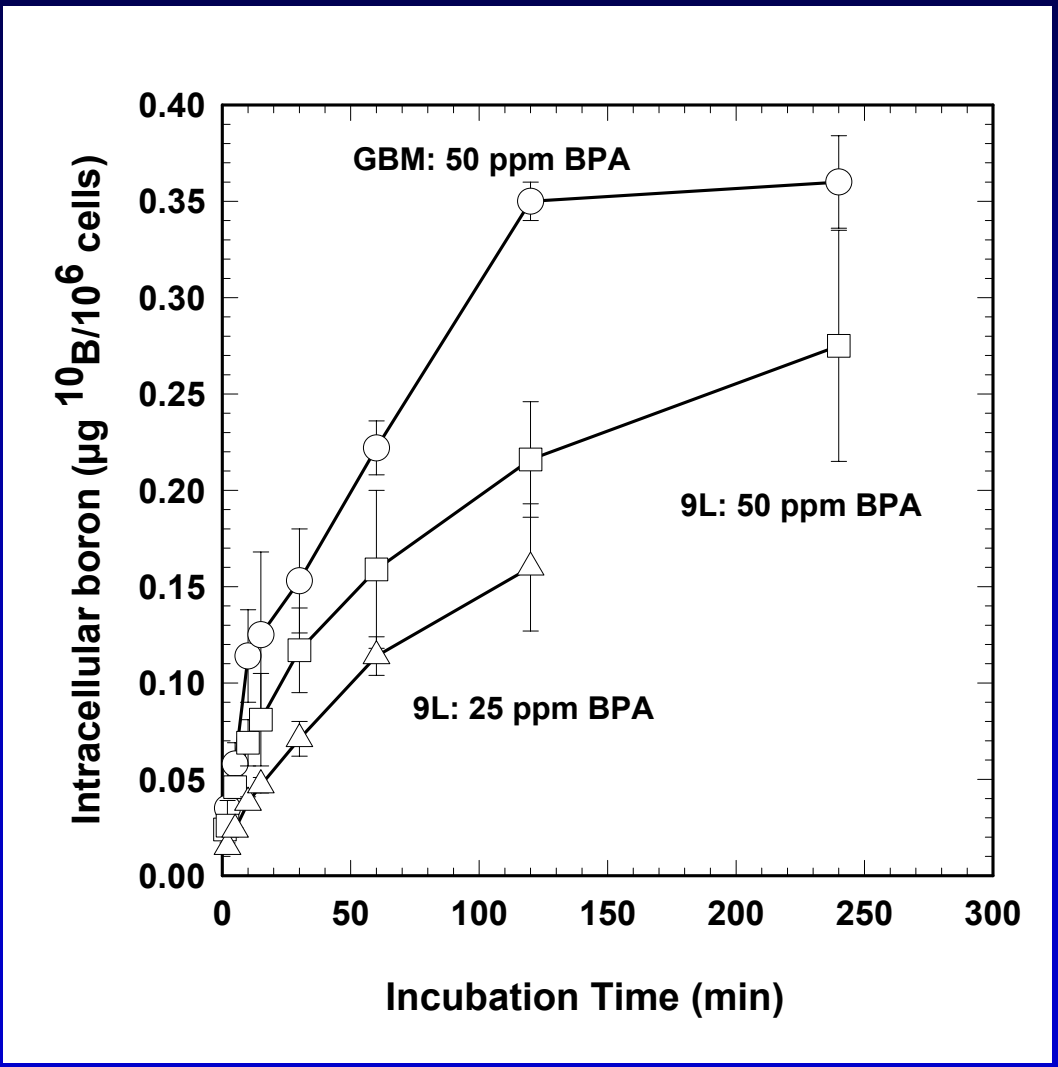
- Does surgery affect BPA uptake in tumor?
- Do all tumor cells take up boron?
- Do infiltrating tumor cells accumulate boron as well as the main tumor mass?

Dose Escalation in BNCT

- Increase boron concentration
- Increase neutron exposure

BPA pharmacokinetics

- Cells in culture take hours to fully load with BPA



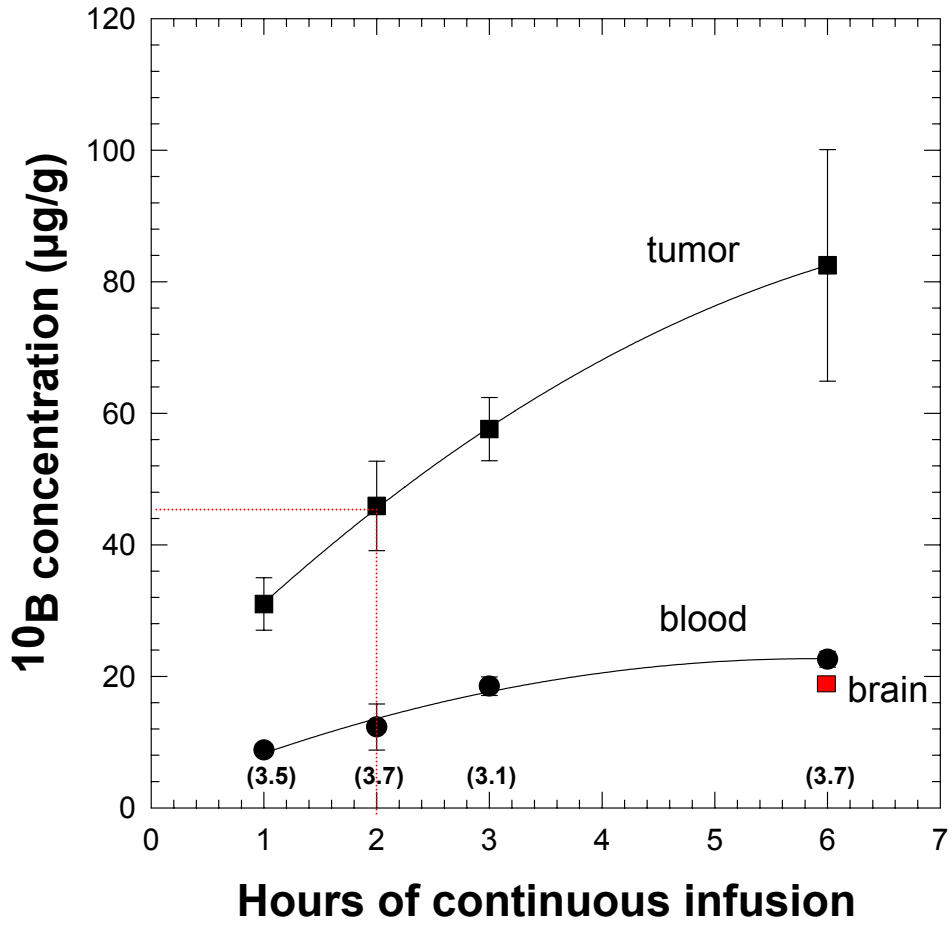
Wittig et al., Radiat. Res. 153, 173, 2000

BPA Dose Escalation

- Rat 9L gliosarcoma
- Infusion rate constant:

250 mg BPA/kg/hr

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

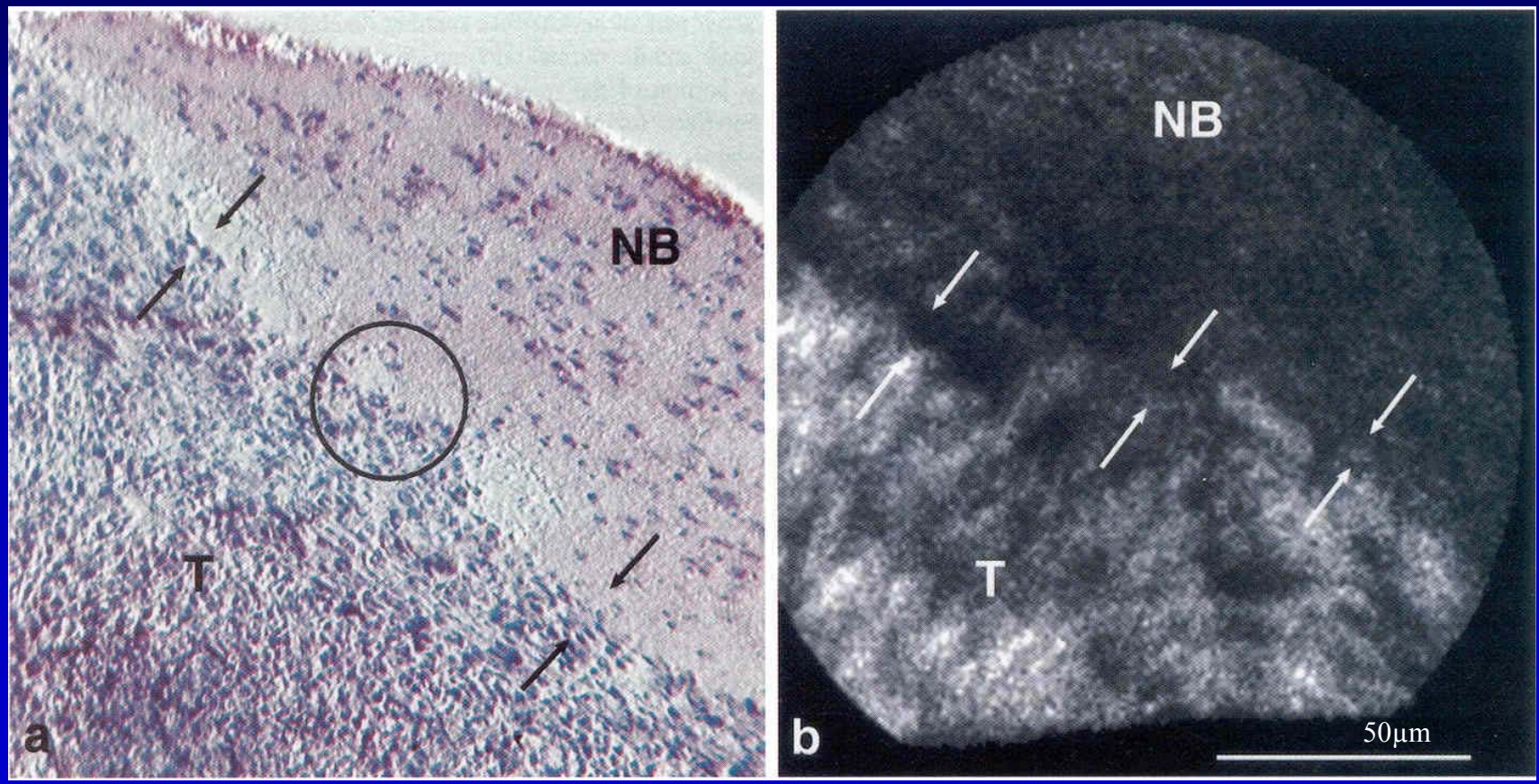


Joel et al., J. Neuro-Oncol., 41, 213, 1999.

Boron microlocalization by SIMS

Tumor/normal brain boundary

Boron concentration



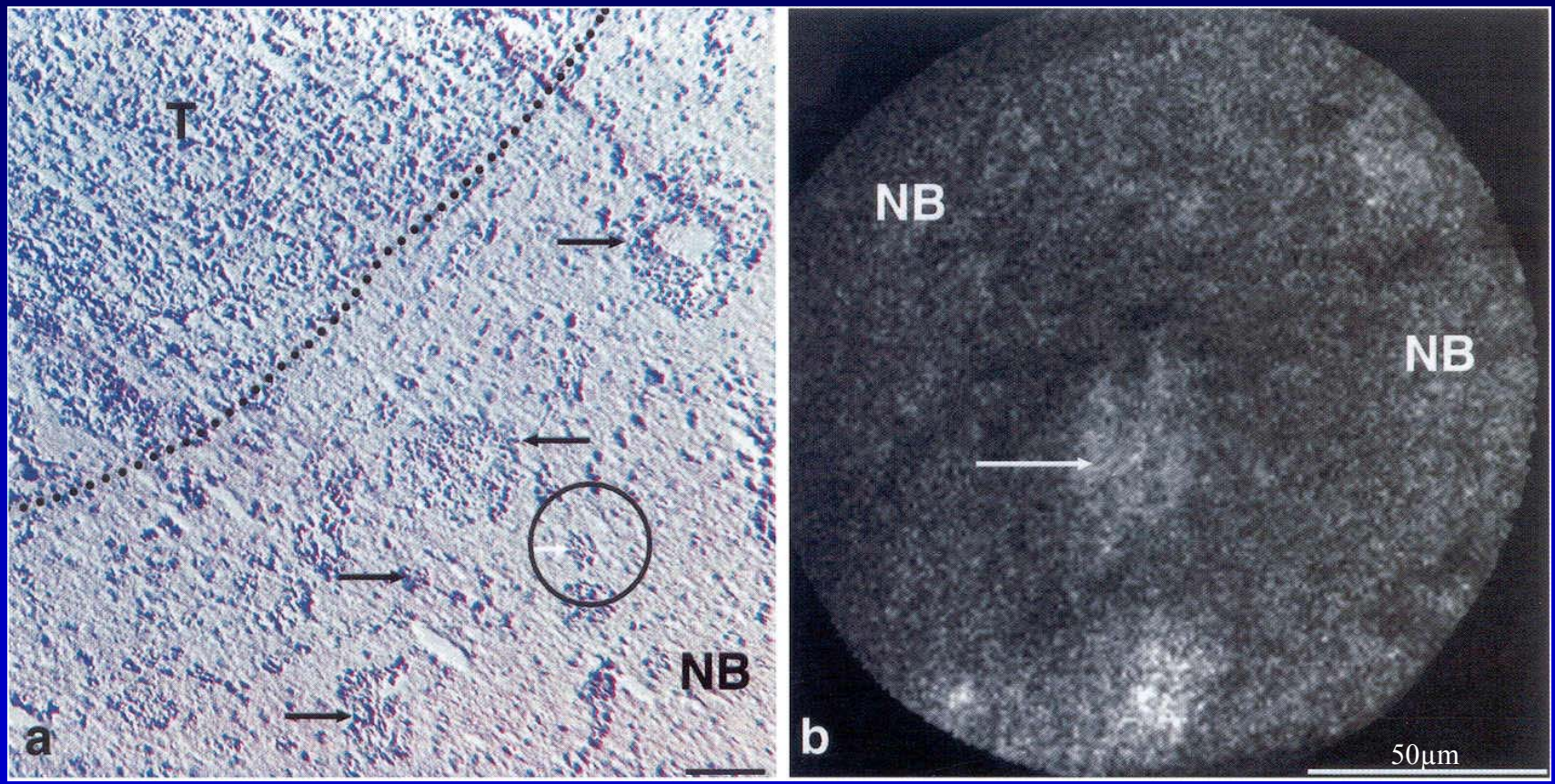
D. Smith, Cornell University

Cancer Res., 56, 4302, 1996.

Boron microlocalization by SIMS

Tumor boundary

Infiltrating tumor cells

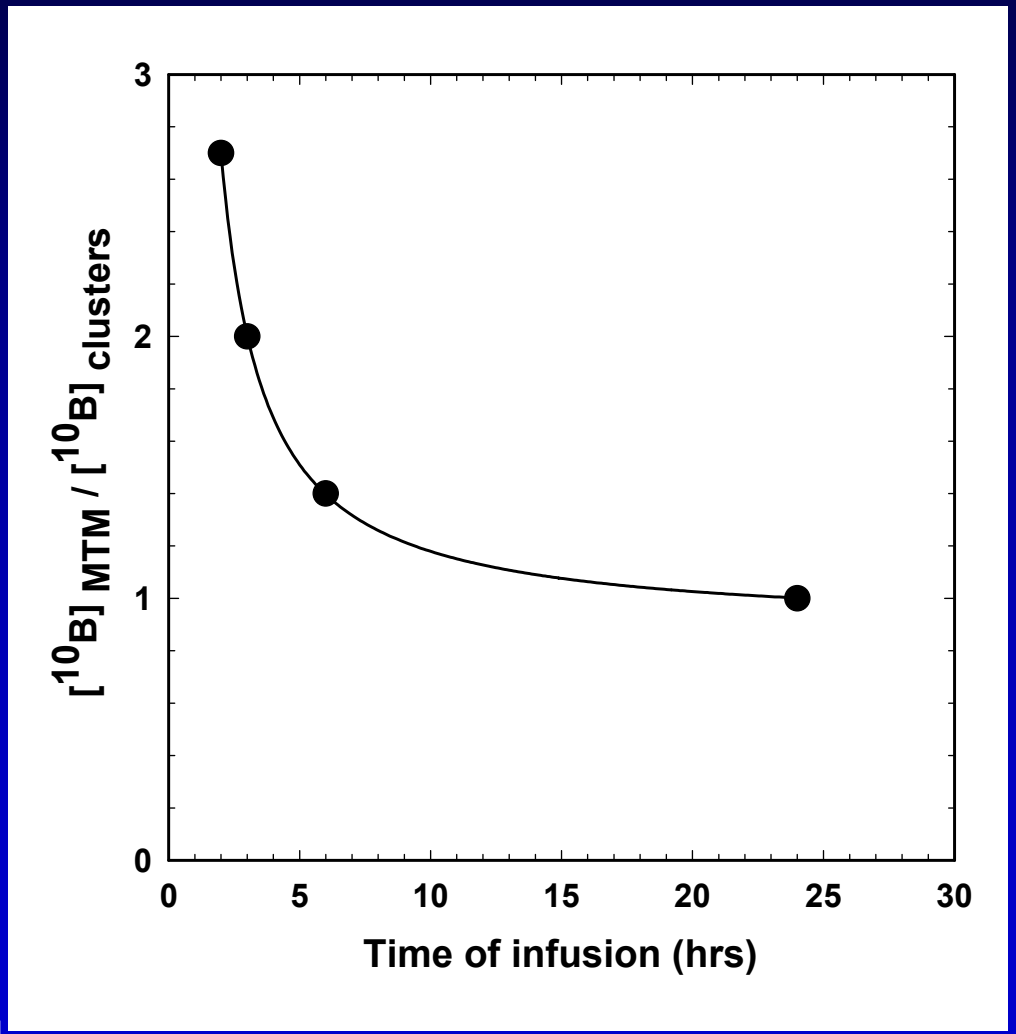


D. Smith, Cornell University

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.



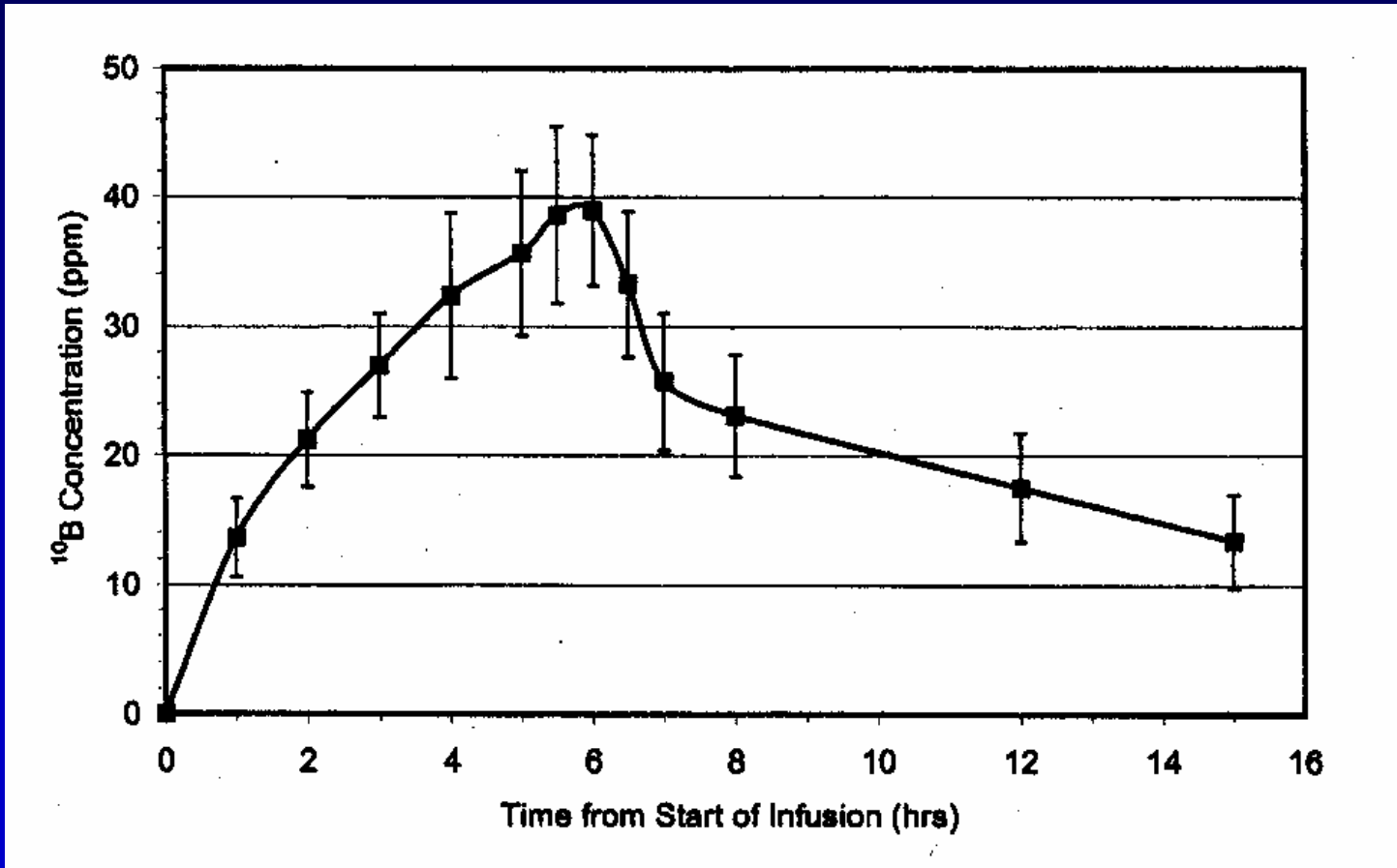
Smith et al., Cancer Res., 22, 8179, 2001

Clinical trial in Studsvik

6-hr
BPA
Infusion:
900 mg/kg

WB ave
dose
3-6 Gy-Eq

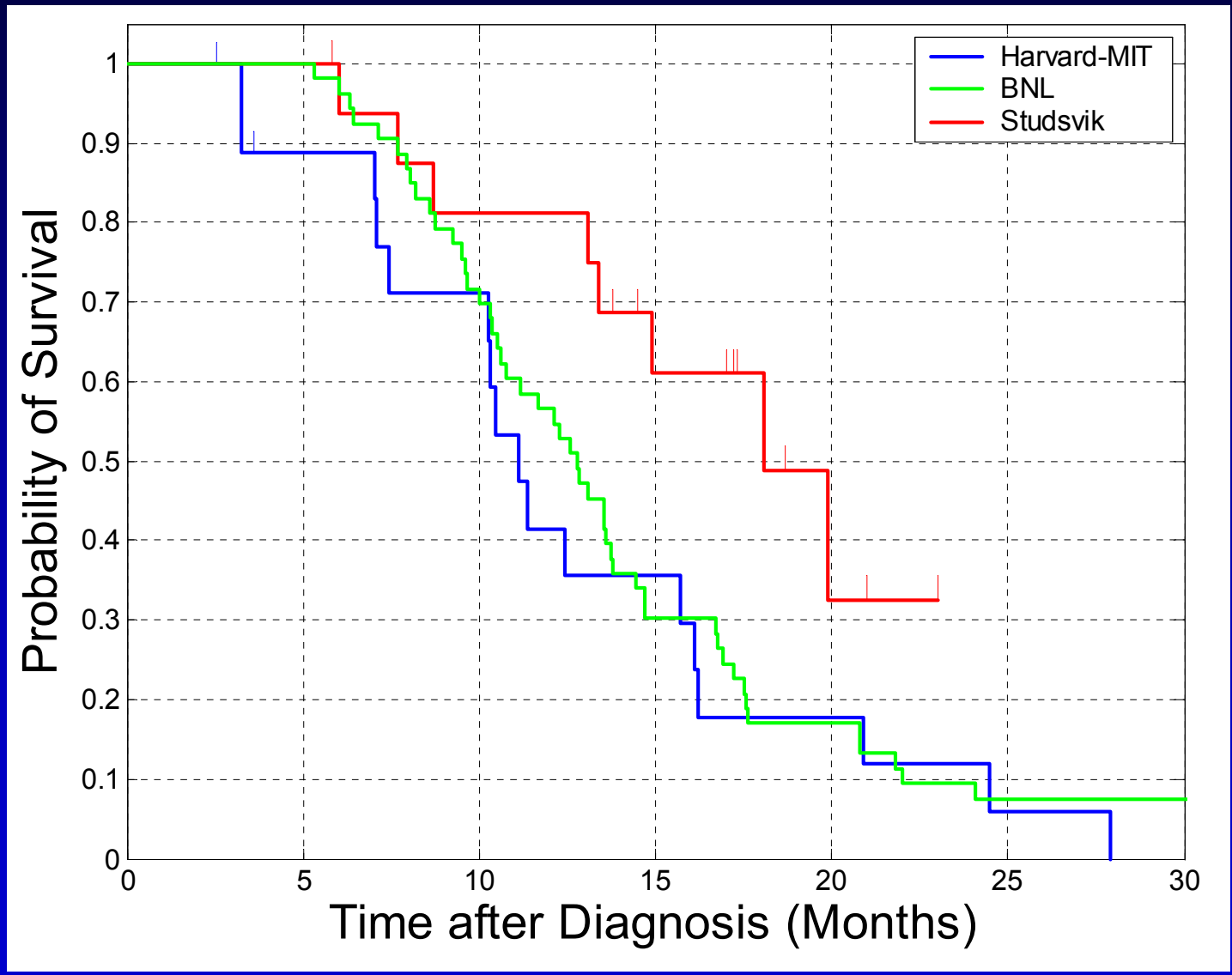
JNO, 62, 135, 2003



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.

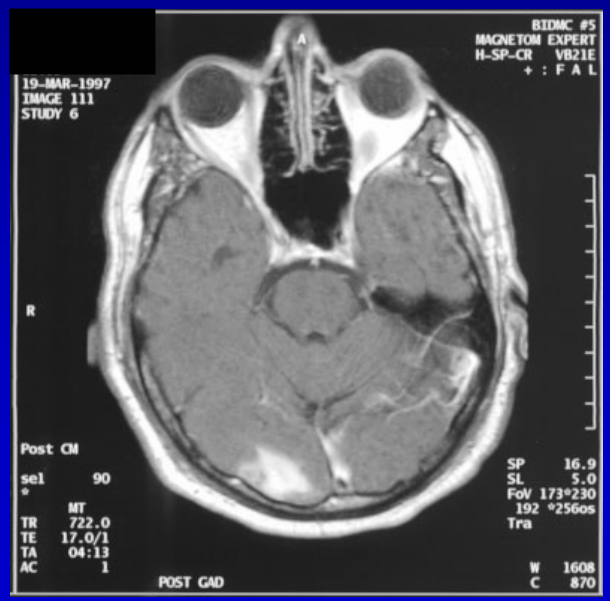
Complete radiographic response following BNCT for a metastatic melanoma in the occipital lobe

MIT/Harvard clinical trial

Left: Pre-BNCT MRI

Middle: Increased enhancement at the site of original tumor one month following BNCT.

Right: Loss of enhanced signal and mass effect seven months following BNCT.



Busse, et al., JNO, 62, 111, 2003

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