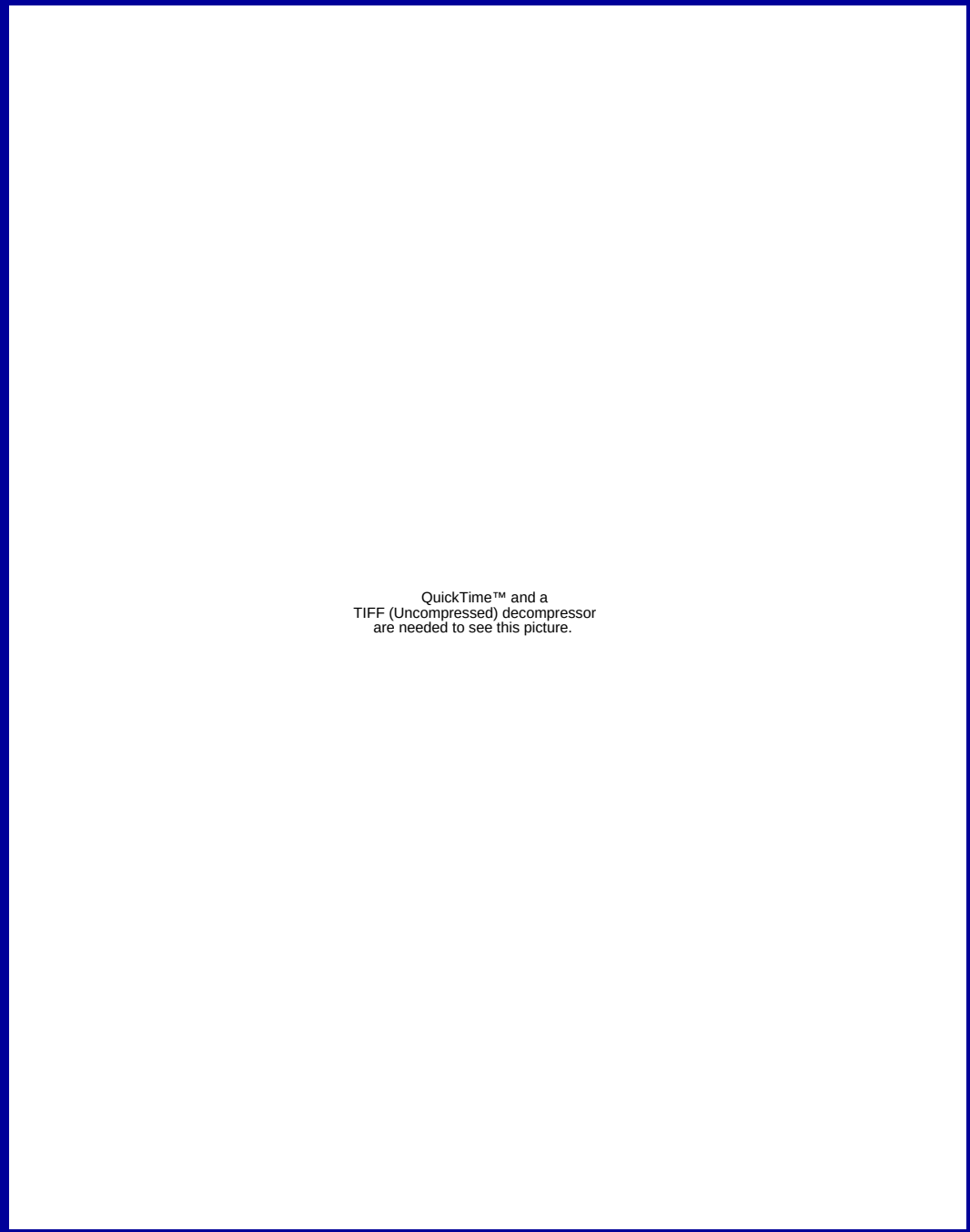
The RBE Trap

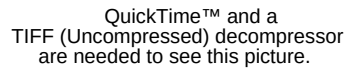
Lessons from the Neutron Radiotherapy Experience

Discussion Points

- RBE factors depend upon the particular tissue involved and the dose fractionation schema
- Attempting to use a single factor and extrapolate from low LET radiation data can lead to serious dosing errors
- Neutron tolerance doses based upon the treatment of over 10,000 patients should provide a good starting point for setting C-ion doses
- Partial tolerance estimates are a way of calculating doses in high & low LET radiation treatment schemas

RBE Definition

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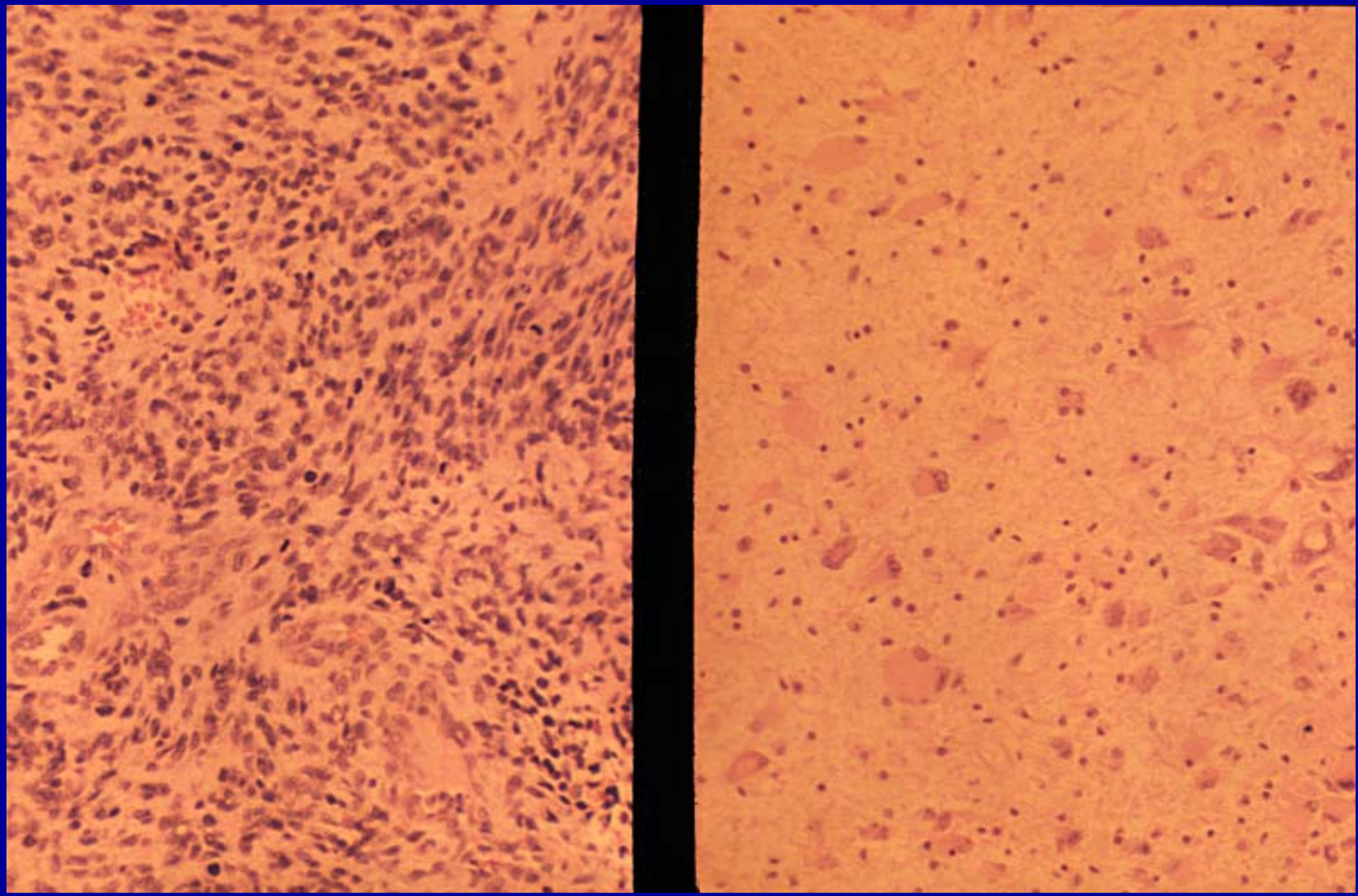
Early Neutron Studies

- Doses were set using photon tolerance doses and a constant RBE -- generally taken as 3
- High rate of complications -- particularly in CNS
  - High grade glioma studies -- clinical dose set to be 18 Gy-neutron

GBM Post-Treatment Gross Specimen

GBM Post-Treatment
Myelin Stain

GBM Histology



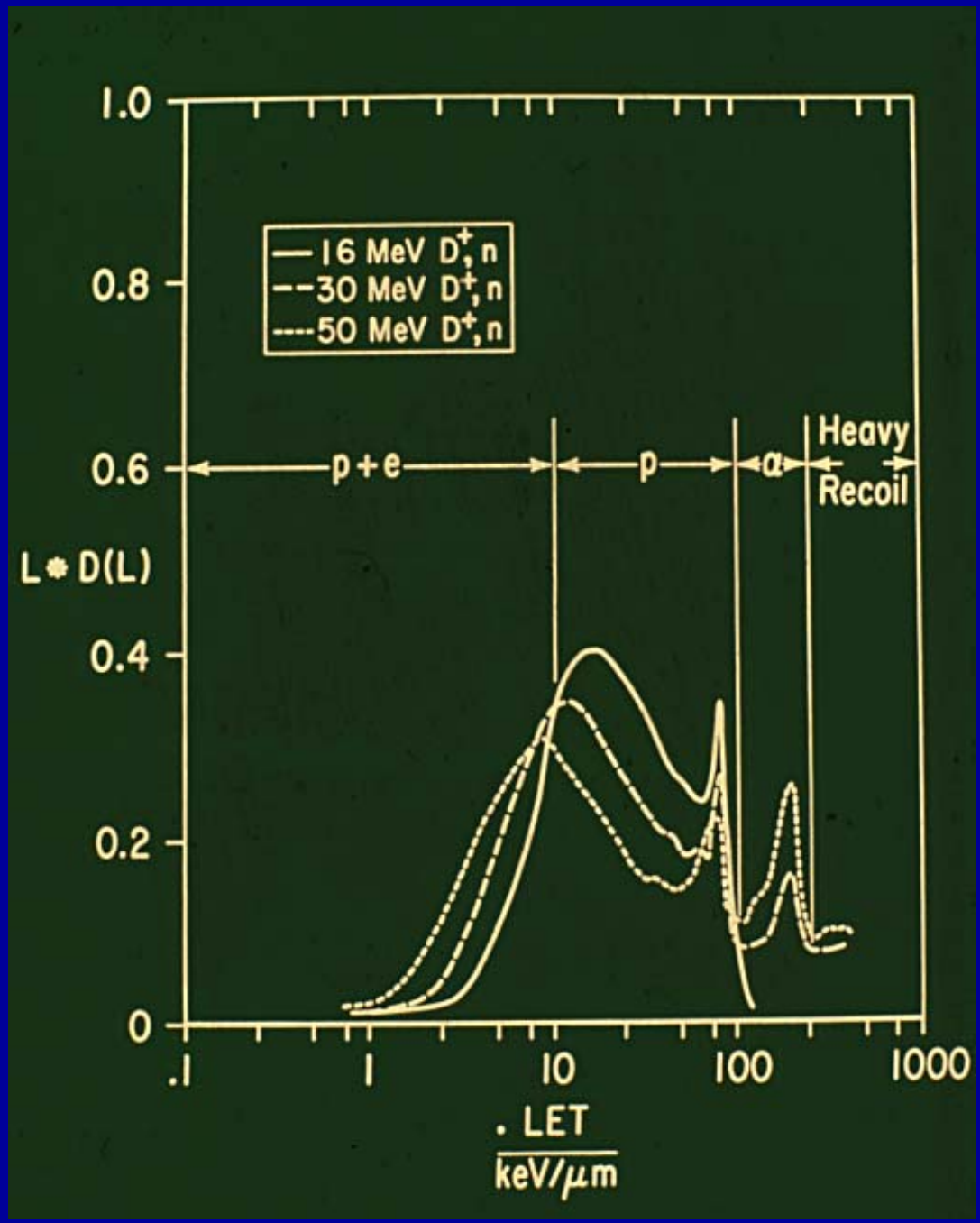
Pre-Treatment

Post-Treatment

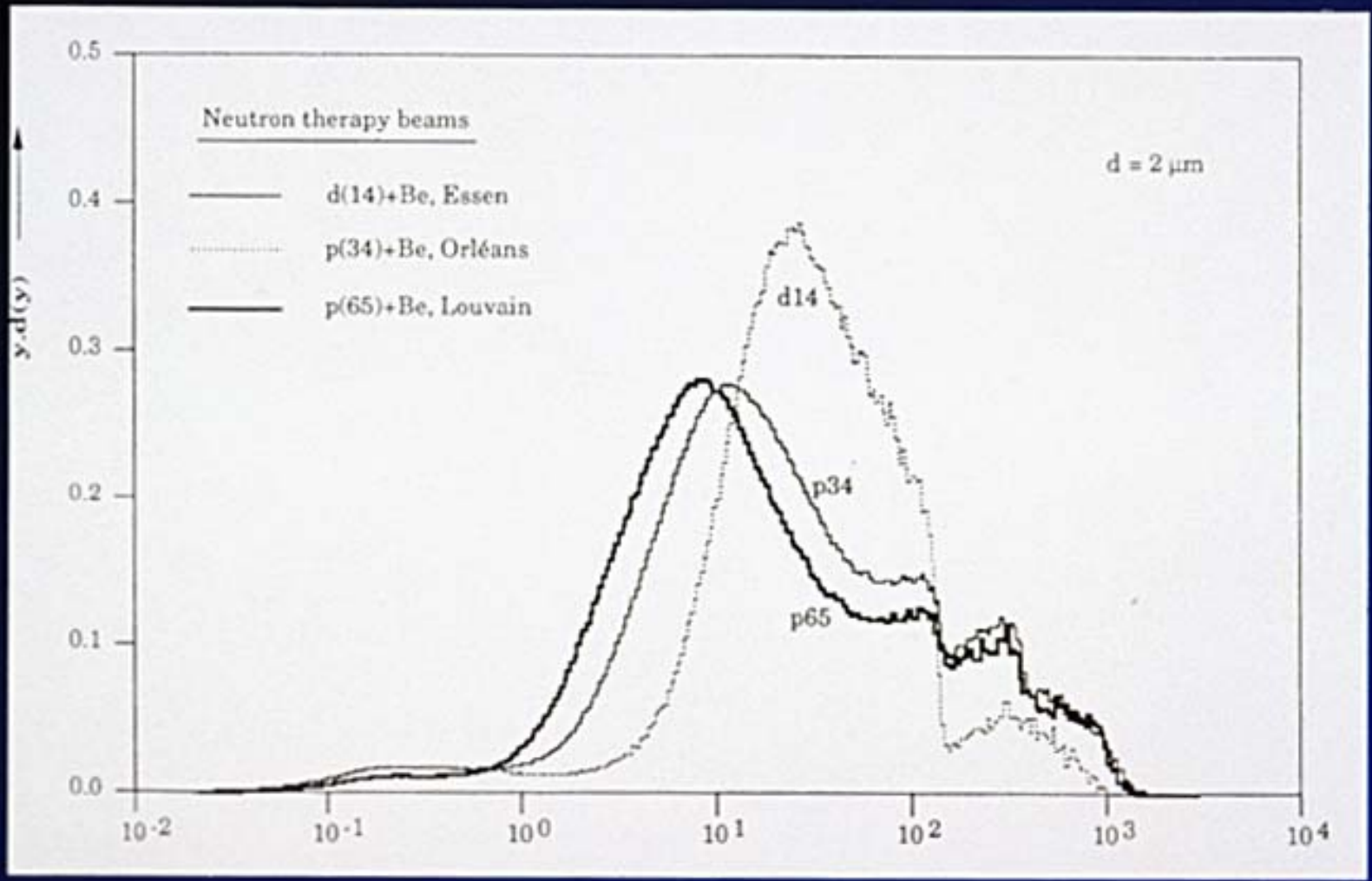
Anaplastic Astrocytoma Survival Data

Neutron Myelitis Cases from Literature

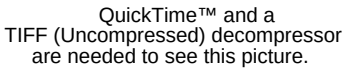
LET Spectrum is Beam Dependent



MICRODOSIMETRIC MEASUREMENTS OF NEUTRON THERAPY BEAMS



Lineal Energy (keV/micron)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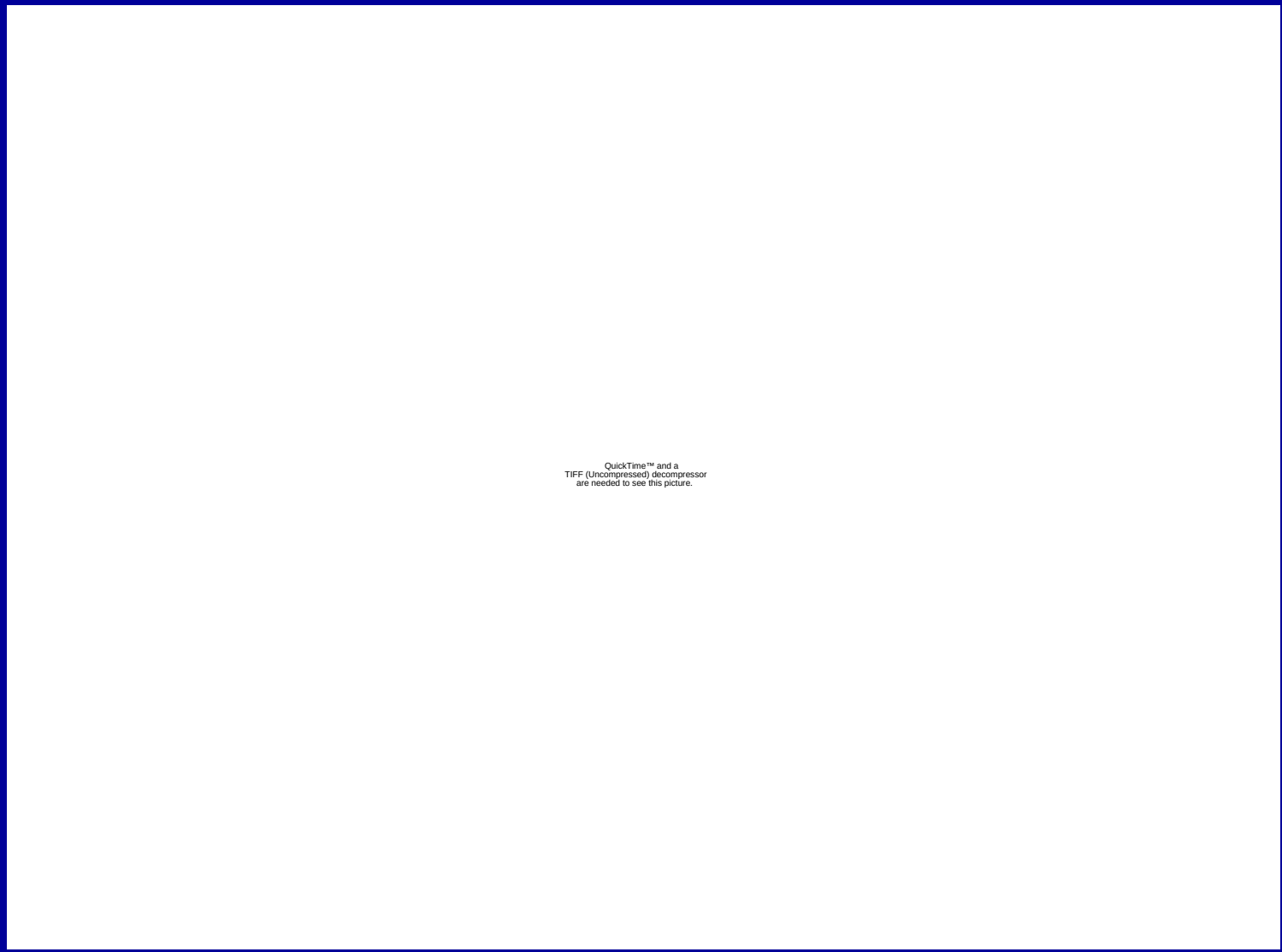
RBE vs. LET

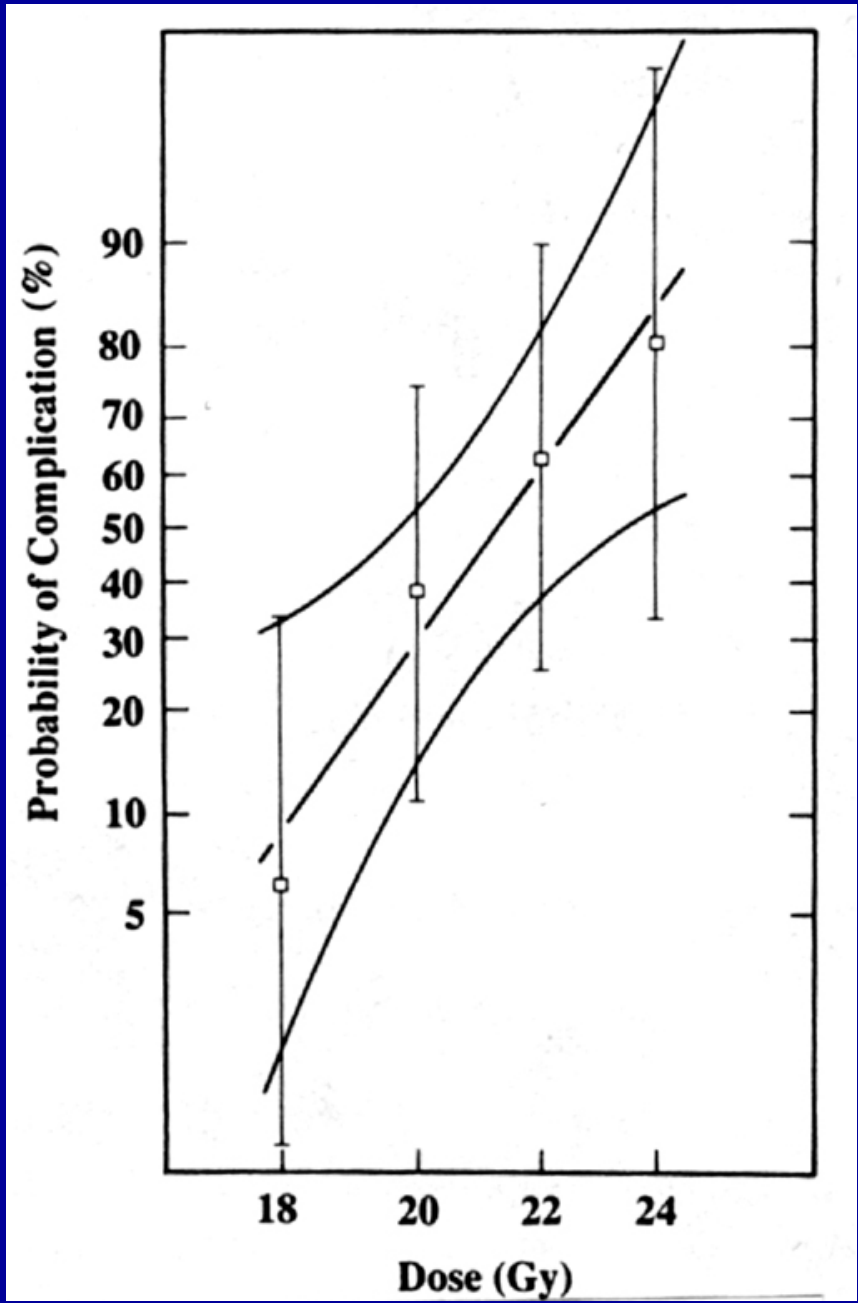


E. Zeman

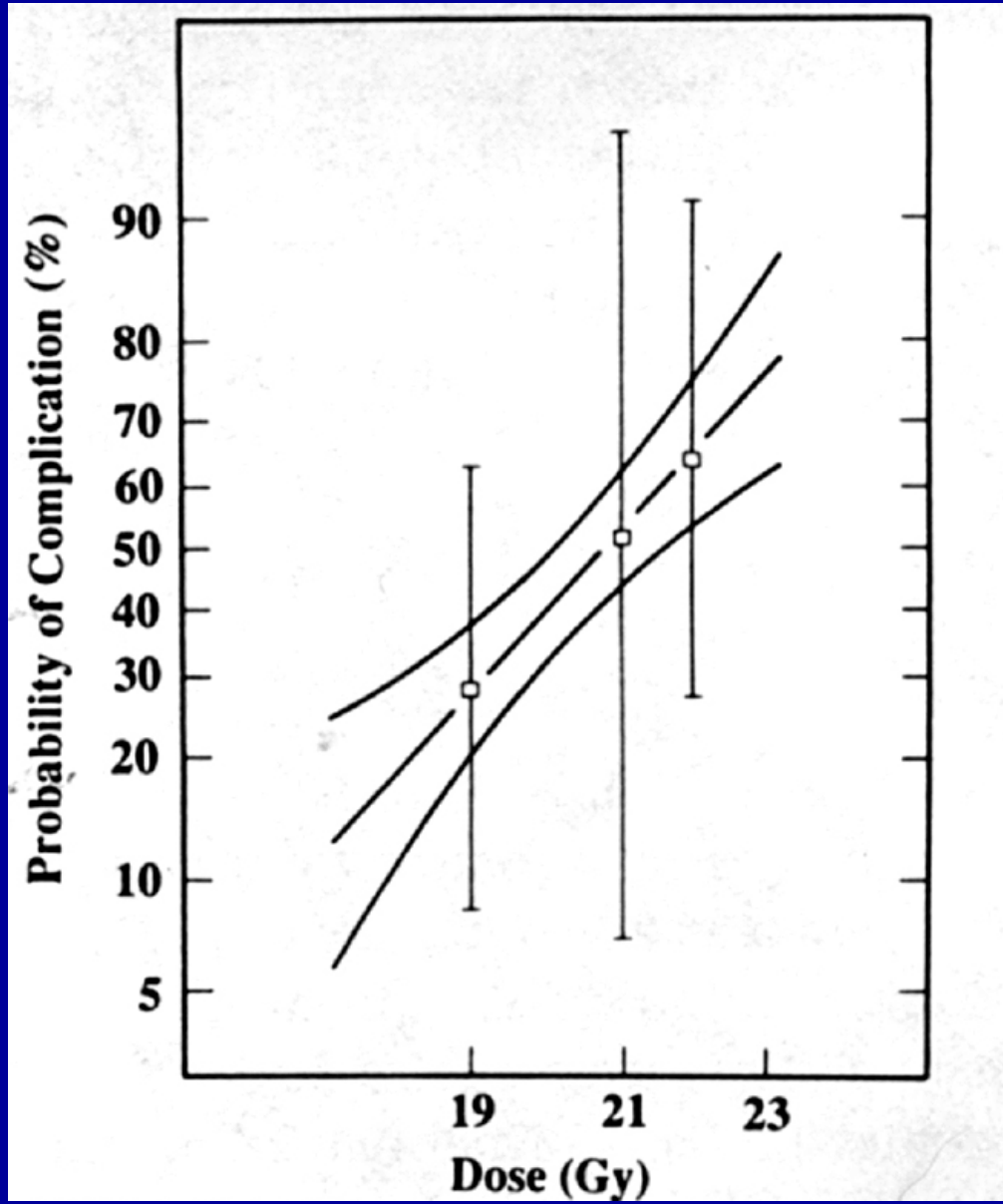
Dose Searching Studies Conducted when New NCI-Funded Facilities Became Operational

- Separate studies conducted for various regions of body
  - H&N
  - Thorax
  - Abdomen
  - Pelvis
  - Extremities
- Three randomized dose levels
  - Best estimate $\pm$ 10%
- Acute and late toxicities as end points

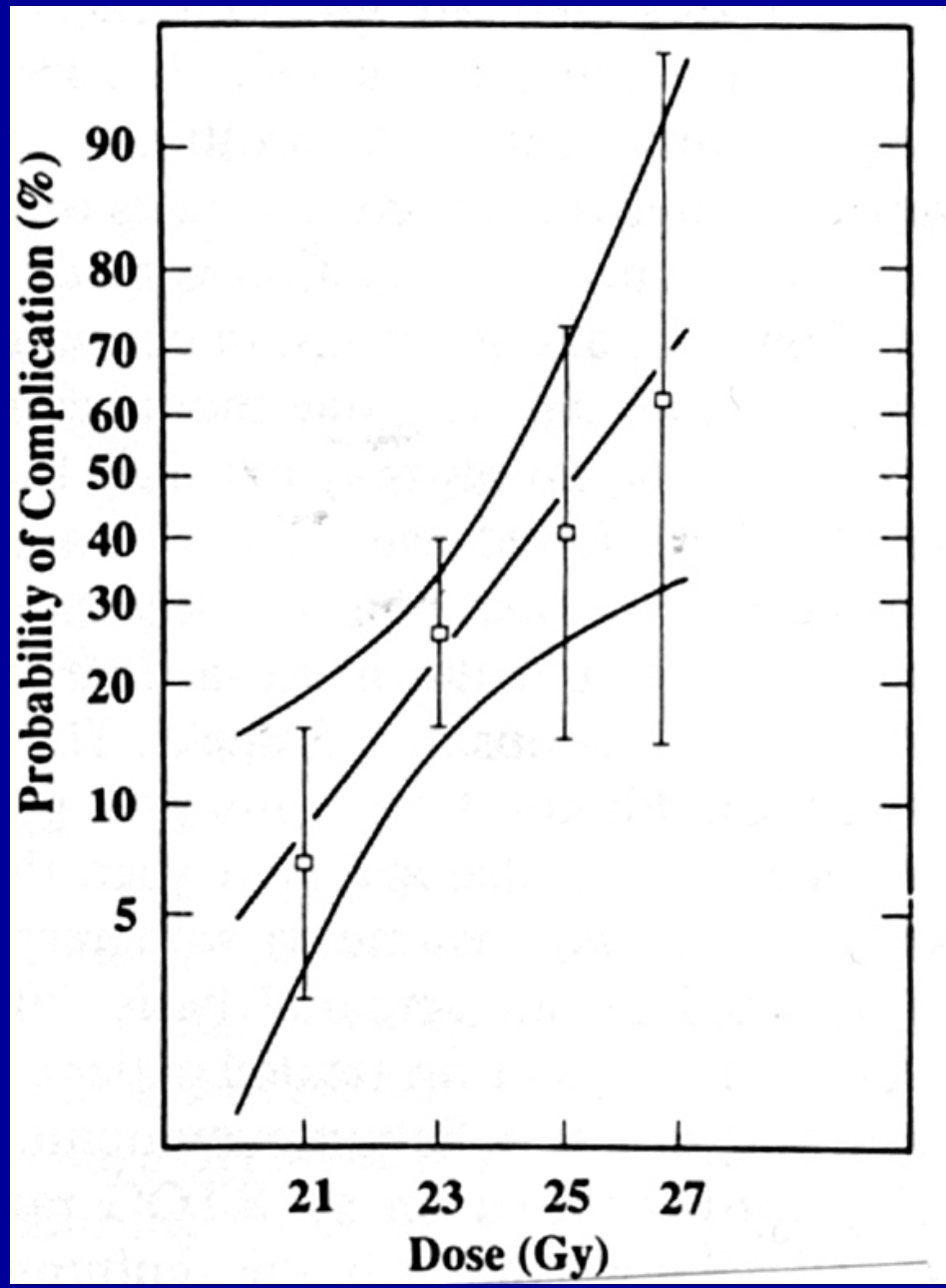
Logistic Dose Response Curves for Complications in the Pelvis (Schultheiss et al, 1990)



Logistic Dose Response Curves for Complications in the Thorax (Schultheiss et al, 1990)



Logistic Dose Response Curves for Osteoradionecrosis of Mandible (Schultheiss et al, 1990)

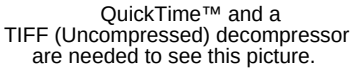


Organ Systems and Complication Endpoints Utilized in Survey of Neutron Treatment Facilities

Organ system	Survey endpoint
Brain	Necrosis
Spinal cord	Myelitis, myelopathy
Pharyngeal mucosa	Ulceration, necrosis
Esophagus	Stricture, ulceration, fistula
Heart	Fibrosis, loss of compliance
Lungs	Pneumonitis, fibrosis
Liver	Functional loss
Stomach	Ulceration, fistula
Kidneys	Functional loss
Small bowel	Obstruction
Large bowel	Obstruction
Bladder	Ulceration, contracture
Rectum	Bleeding, stricture
Bone	Fracture, osteoradionecrosis
Cartilage	Necrosis
Joint	Contracture, functional loss
Skin/subcutaneous tissue	Ulceration, necrosis

NEUTRON TREATMENT FACILITIES RESPONDING TO DOSE TOLERANCE SURVEY

Neutron facility[a]	Reaction	Relative scale factor	Total patients treated
Fermi Laboratories	66 MeV p→Be	0.95	1732
Louvain-la-Neuve	65 MeV p→Be	0.95	1050
University of Washington	50 MeV p→Be	1.0	752
	22 MeV d→Be	1.10	602
KAERI	50 MeV p→Be	1.0	150
UCLA	46 MeV p→Be	1.0	241
M. D. Anderson	42 MeV p→Be	1.0	383
TAMVEC	50 MeV d→Be	1.05	900
MANTA	35 MeV d→Be	1.10	177
NIRS	30 MeV d→Be	1.10	1723
Antoni van Leeuwenhoek	dT	1.10	435
Heidelberg	dT	1.10	250
King Faisal	26 MeV p→Be	1.10	50
Düsseldorf	14 MeV d→Be	1.15	503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Partial Tolerance Dose: Concept

- For “Radiation A”, the tolerance dose is $D_T(A)$
- For “Radiation B”, the tolerance dose is $D_T(B)$
- For a combination of radiation doses to this structure set
  - $D(A) / D_T(A) + D(B) / D_T(B) = 1$

Partial Tolerance Dose: Example

- Assume a situation where the optic chiasm has received 40 Gy-photon in a conventional fractionation schema. The accepted tolerance dose is 54 Gy.
- With fast neutron RT, the optic chiasm dose is 12 Gy-neutron.
- Hence, the remaining tolerance with additional neutron RT is 3.1 Gy-neutron.

Concluding Remarks

- RBE when used to set clinical radiation doses is dependent upon many factors
  - Dose fractionation schema
  - Tissue type
  - LET spectrum of beam in region of interest
- RBE range of C-ion beams is not too dissimilar to that of some of the neutron beams used clinically
- Use of tissue tolerance doses obtained from neutron radiotherapy work may be helpful to the C-ion investigators in setting initial doses
- Dose searching studies should be performed prior to randomized clinical trials