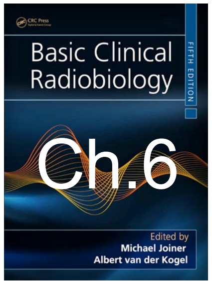
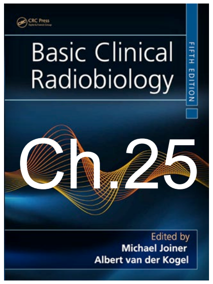
Basic Clinical Radiobiology

Particles in radiotherapy: protons, heavy ions, (neutrons)

Michael Joiner

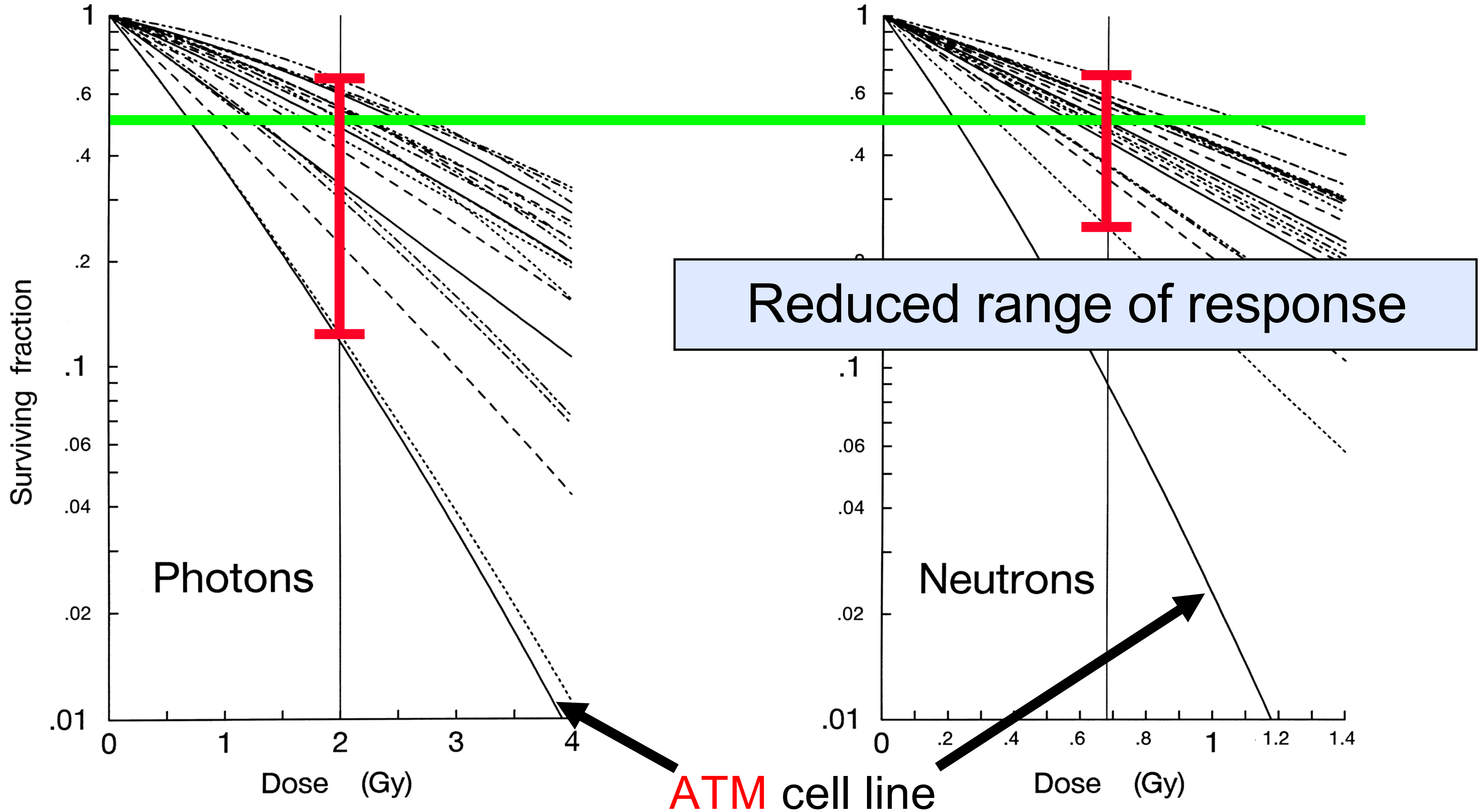
Toronto 2022



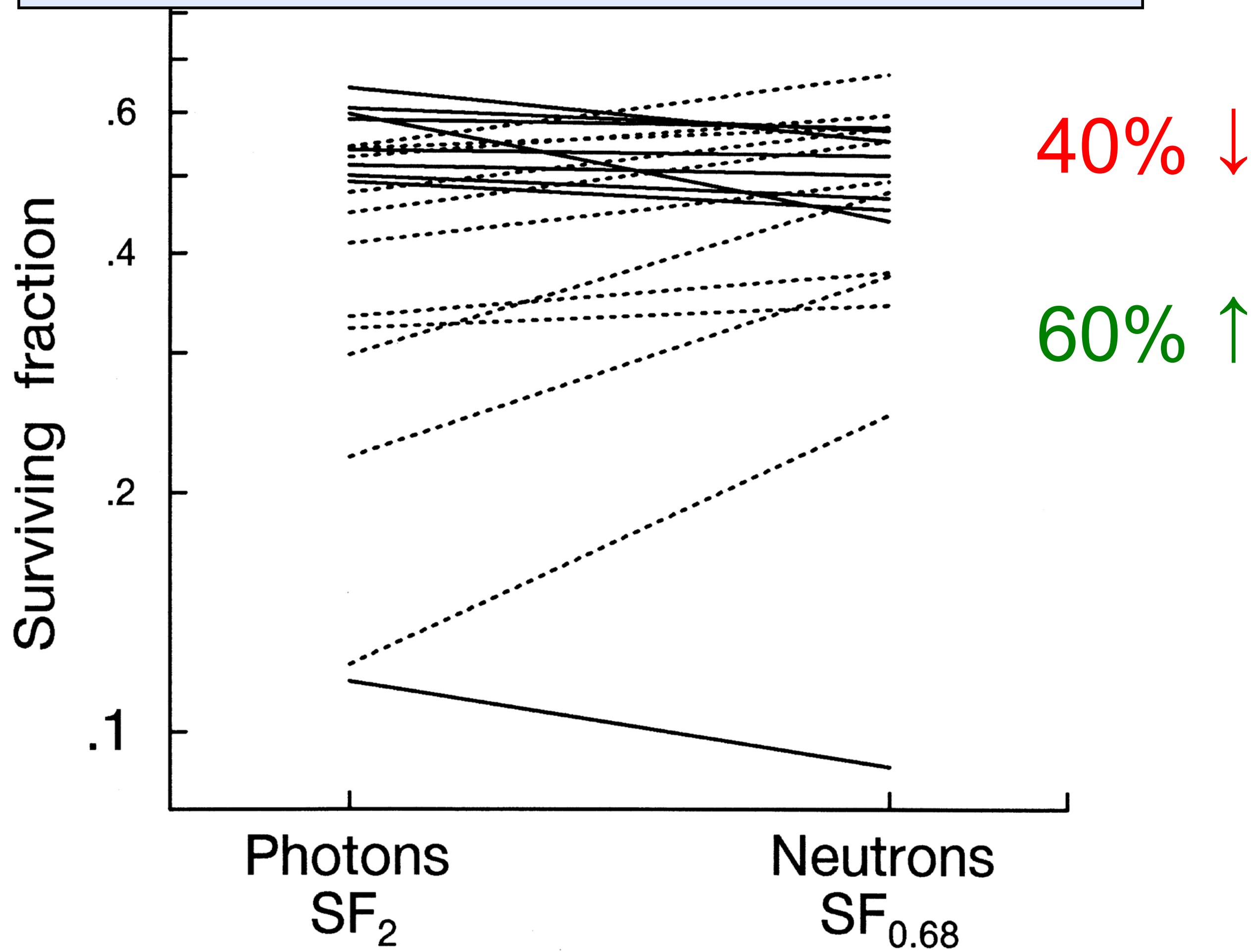


	Uncharged	Charged
Low LET	X rays γ rays	e^- p^+ He^{2+}
High LET	Neutrons	C^{6+} Ne^{10+} Si^{14+} Ar^{18+}

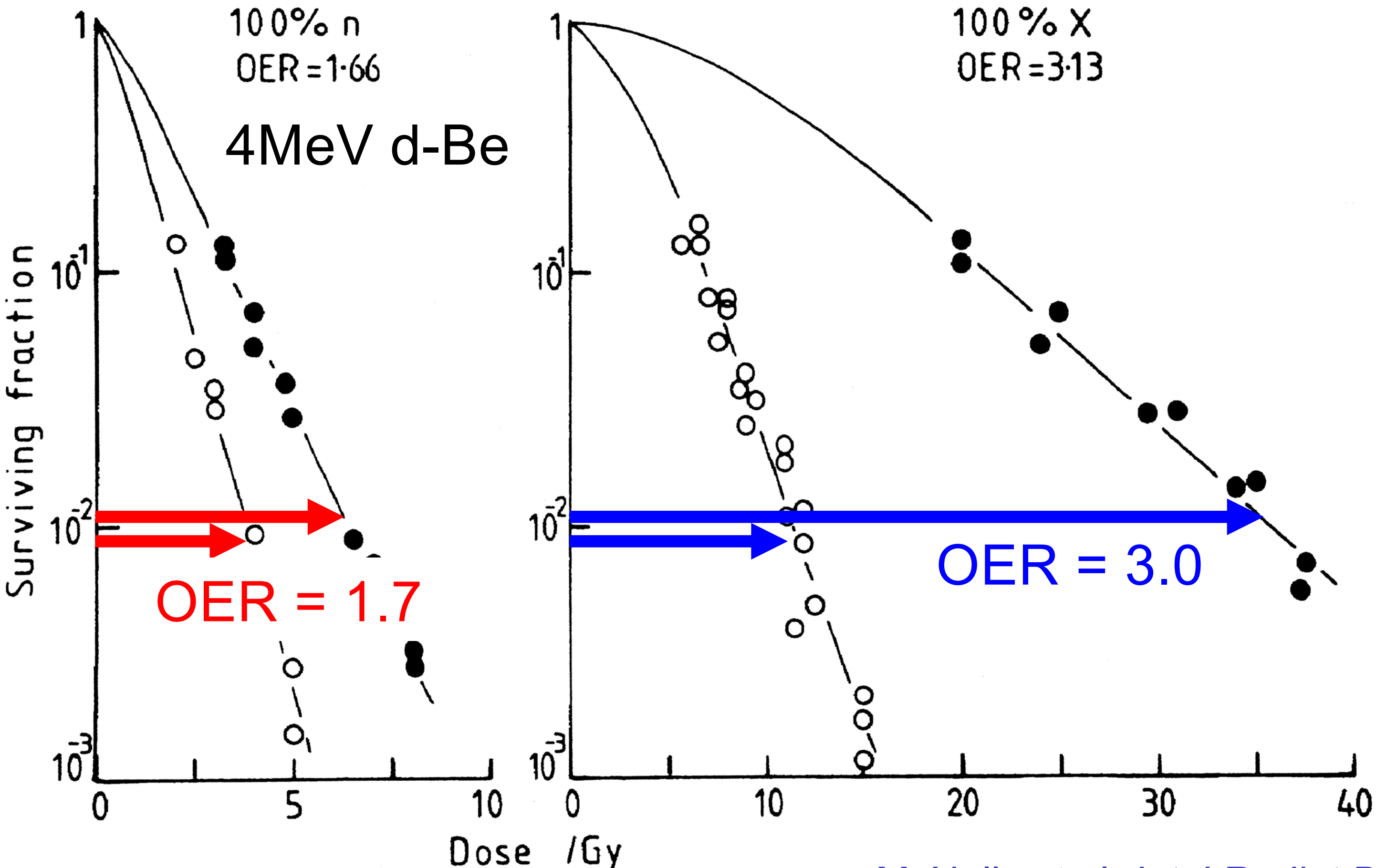
Biological
basis for *high-LET* therapy
(*e.g.* carbon ions, neutrons)


1
.6
.4
.2
.1
.06
.04
.02
.01
Surviving fraction
Photons
0
1
2
3
4
Dose (Gy)
Neutrons
0
.2
.4
.6
.8
1
1.2
1.4
Dose (Gy)
Reduced range of response
ATM cell line

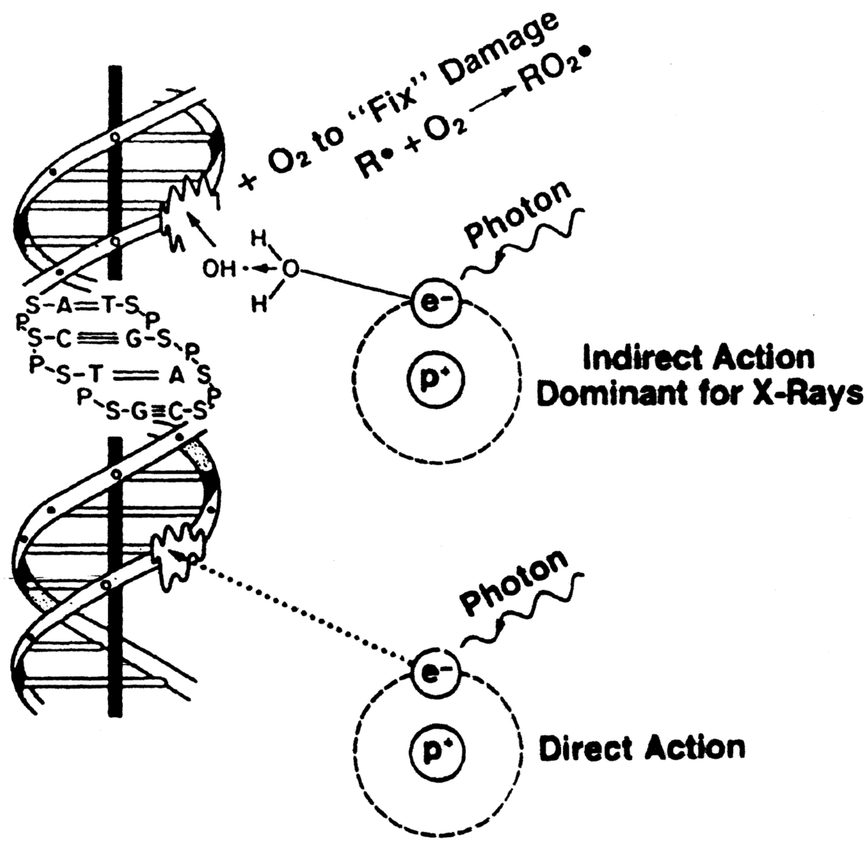
Change in relative radiosensitivity

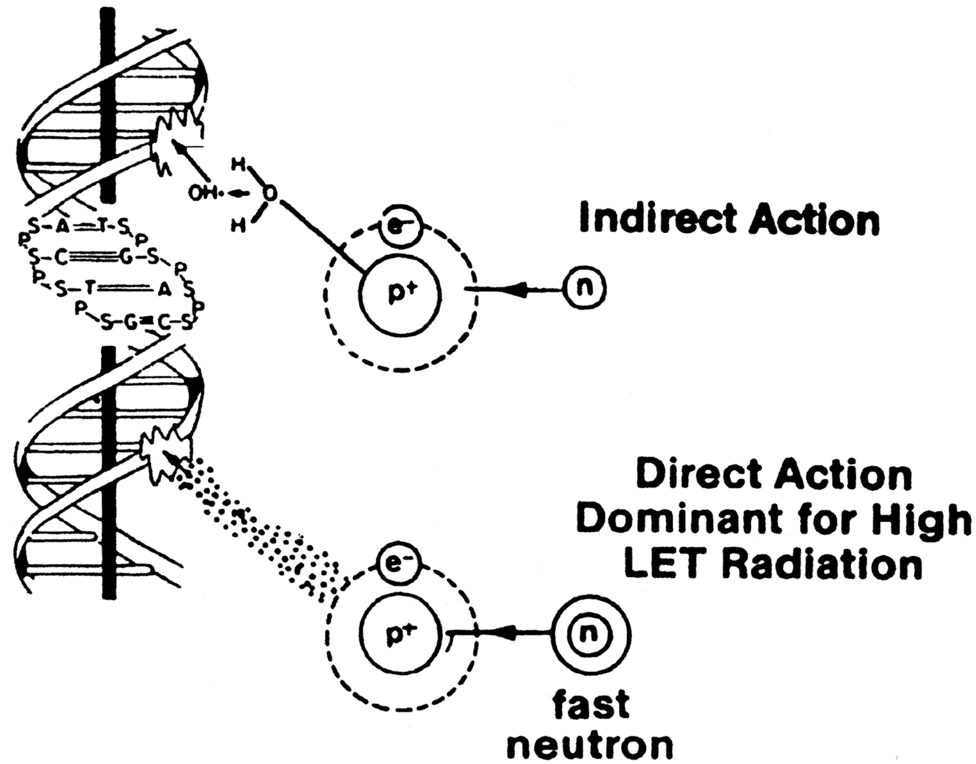


Reduced effect of oxygen

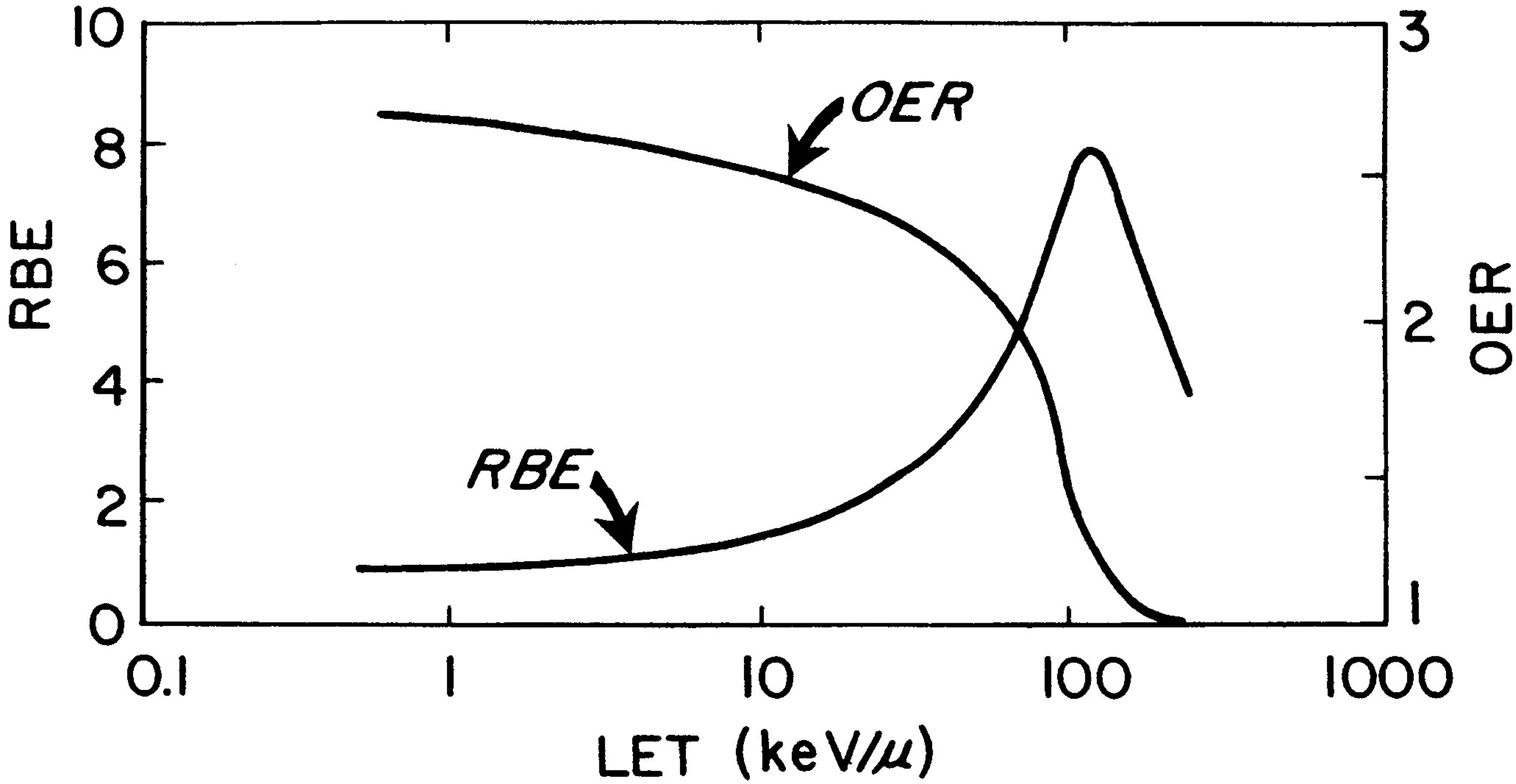


McNally et al. *Int J Radiat Biol* 1985;48:847

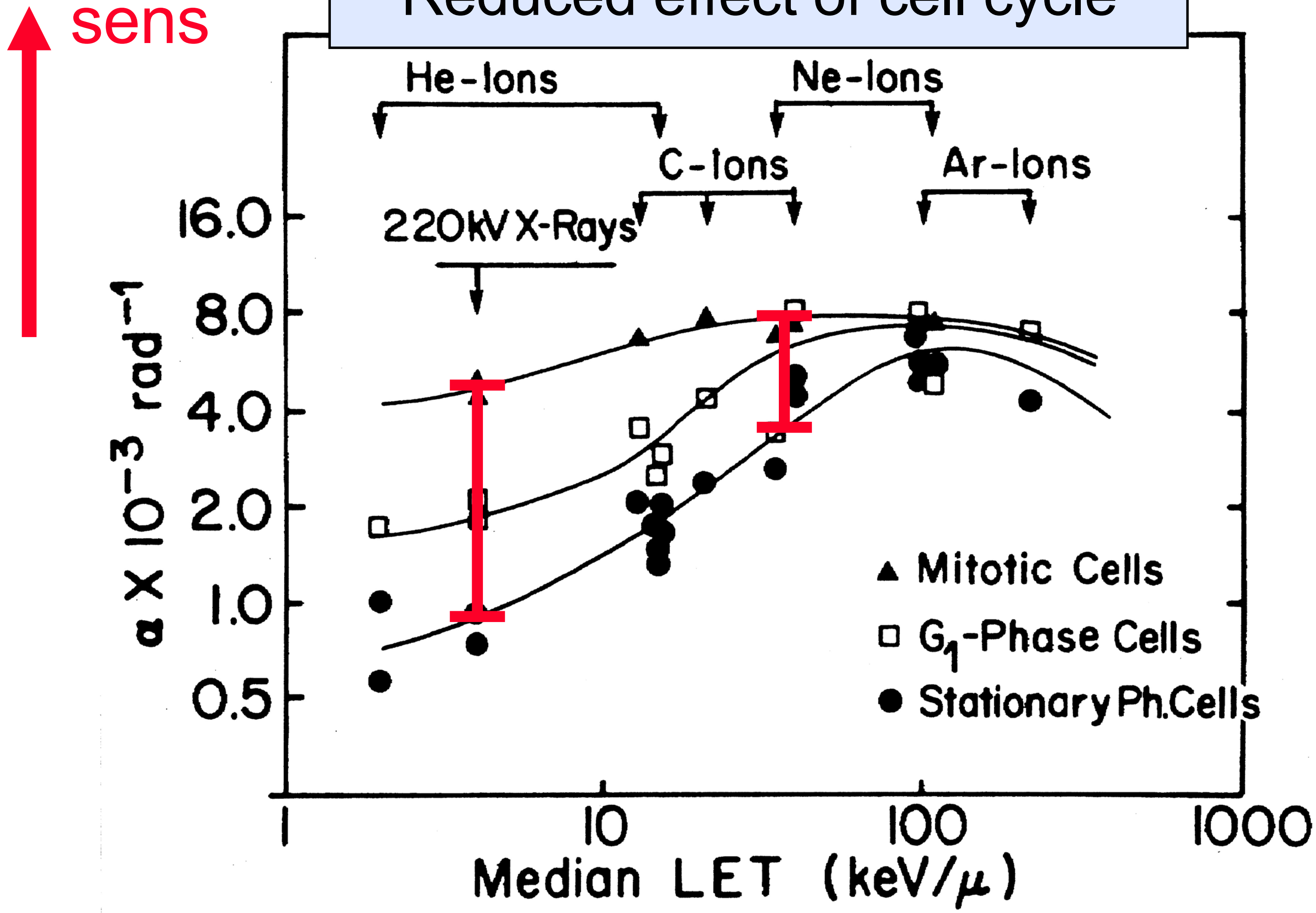

+ O₂ to "Fix" Damage
R• + O₂ → RO₂•
Photon
OH
H
O
e-
p+
Indirect Action
Dominant for X-Rays
Photon
e-
p+
Direct Action


OH
H
O
e-
p+
n
Indirect Action
e-
p+
n
Direct Action
Dominant for High
LET Radiation
fast
neutron

Variation of RBE and OER with LET



Reduced effect of cell cycle



Biological bases for high-LET therapy (*e.g.* carbon ions, neutrons)

- Reduced range of response
- Change in relative radiosensitivity
- Reduced influence of oxygen
- Reduced influence of cell cycle

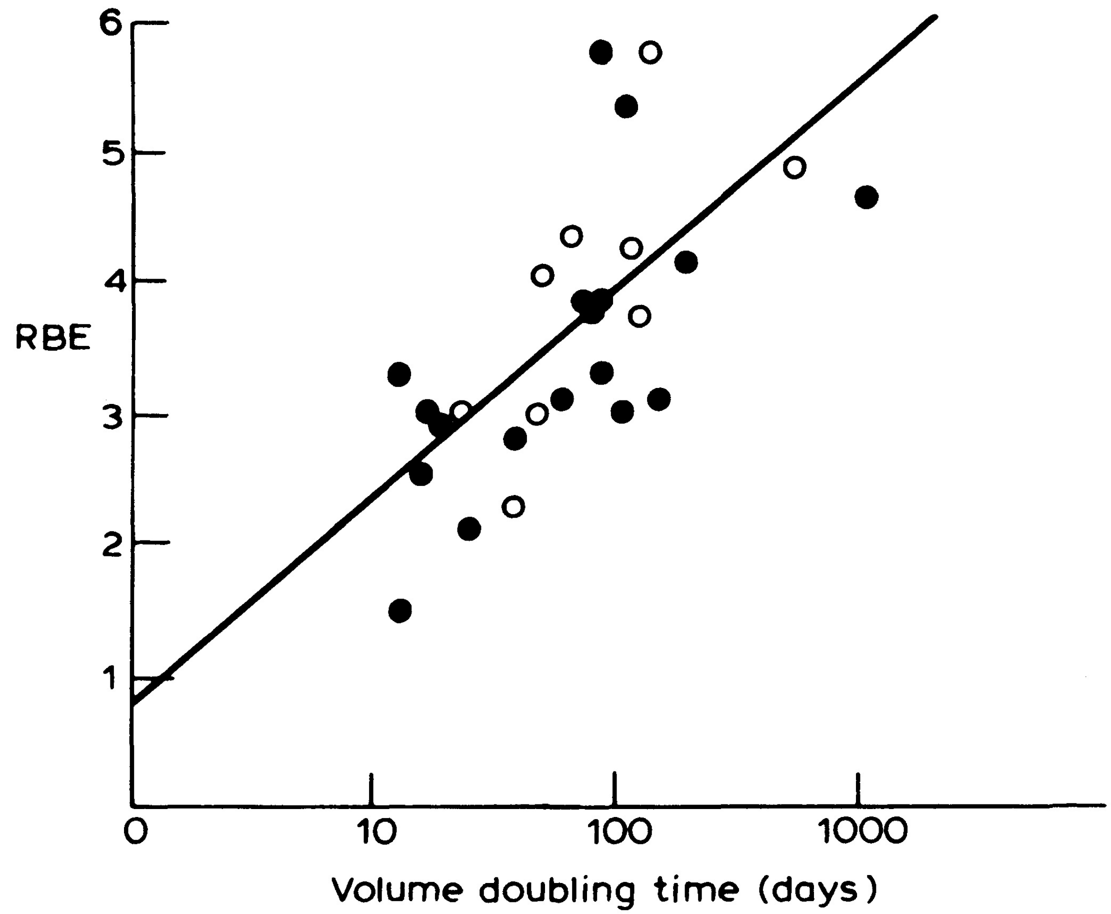
Clinical indications for high-LET therapy

1. Salivary gland tumours (locally extended)
2. Prostatic adenocarcinoma (locally extended)
3. Soft-tissue sarcoma (slowly growing, inoperable)
4. Paranasal sinuses (adenocarcinoma, adenoid cystic ca.)
5. Melanoma and rectal carcinoma (palliative treatment)

From Wambersie *et al*. (1994).

Neutron RBEs for pulmonary metastases as a function of tumor doubling time

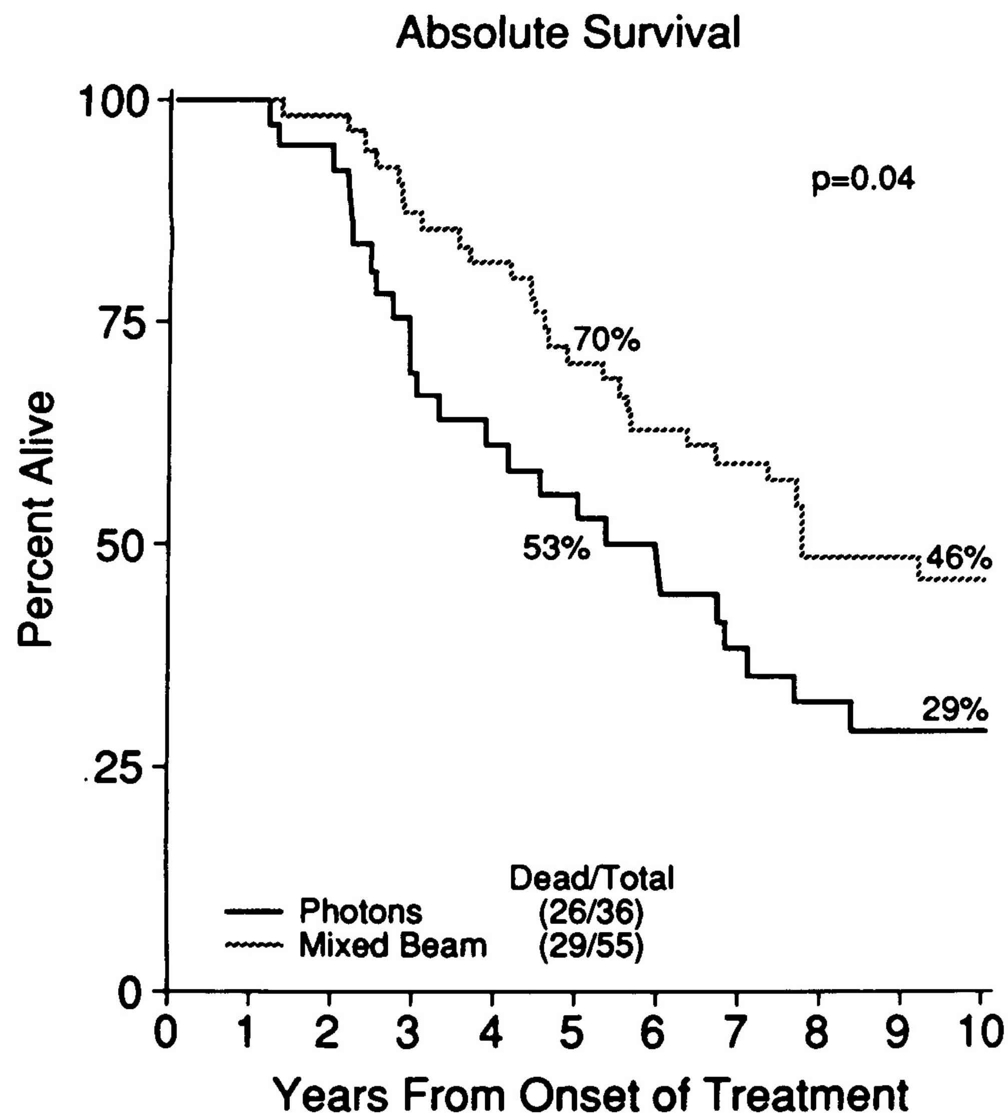
Slowly proliferating cells are less sensitive with photon therapy but not with neutrons, due to reduced cell-cycle effect. Hence, RBE tends to increase as doubling time increases



Randomized trial: photons vs mixed neutrons plus photons for prostate Ca

Prostate carcinomas are slow growing and so well suited for neutron therapy. Neutrons were used for a small “boost” volume in order to minimize late normal tissue damage.

Laramore et al. RTOG 77-04 1993



Physical

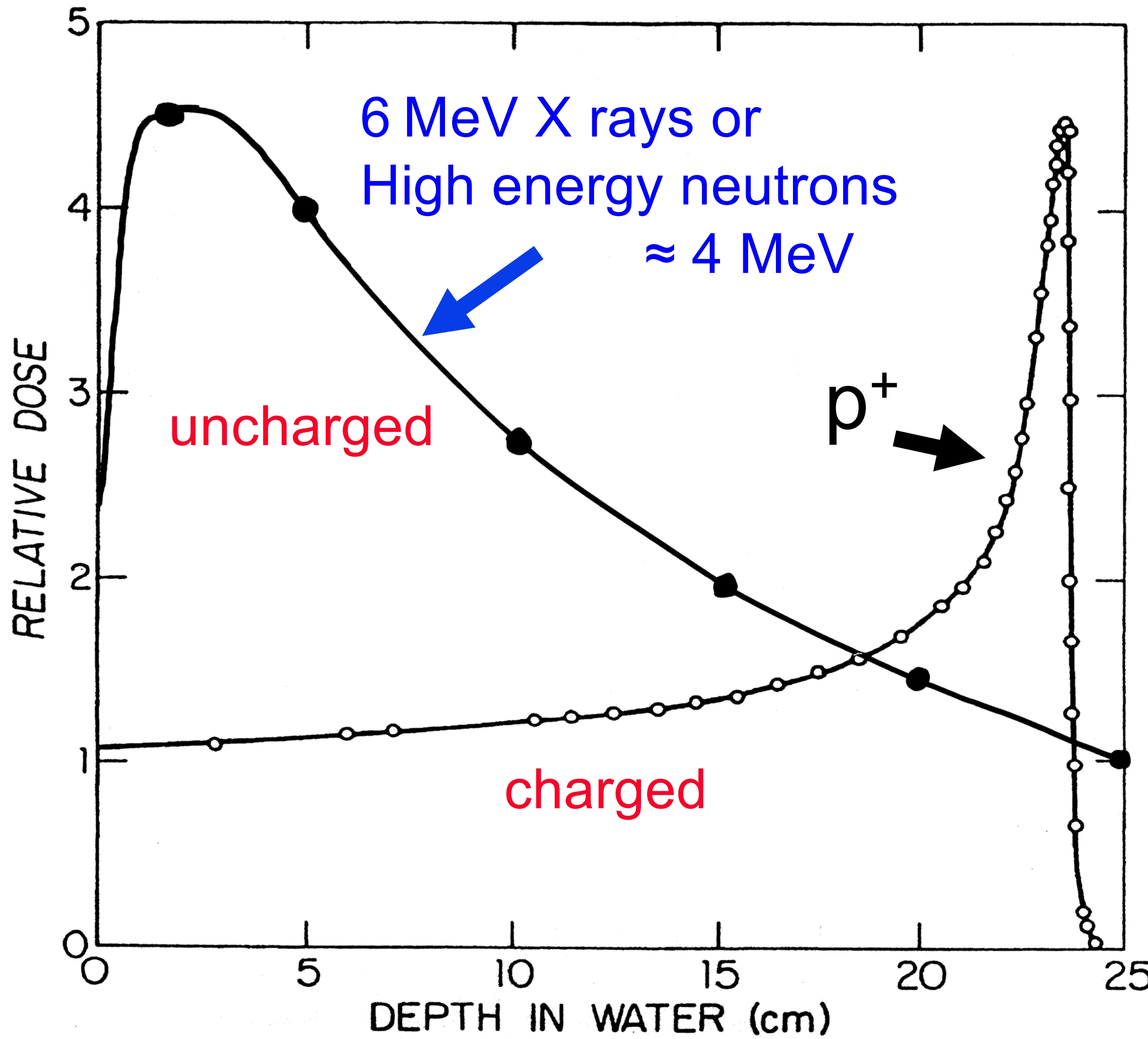
basis for *particle* therapy

(neutrons?, protons, carbon ions)

Fast neutron teletherapy

- **Physical characteristics were not bad**
  - skin sparing with high-energy beams
  - isocentric gantries not too expensive
  - multileaf collimators are possible
- **Biological advantages were key**
  - low OER
  - reduced cell-cycle effect
  - less repair of tumor cells esp low α/β

Bragg Peak

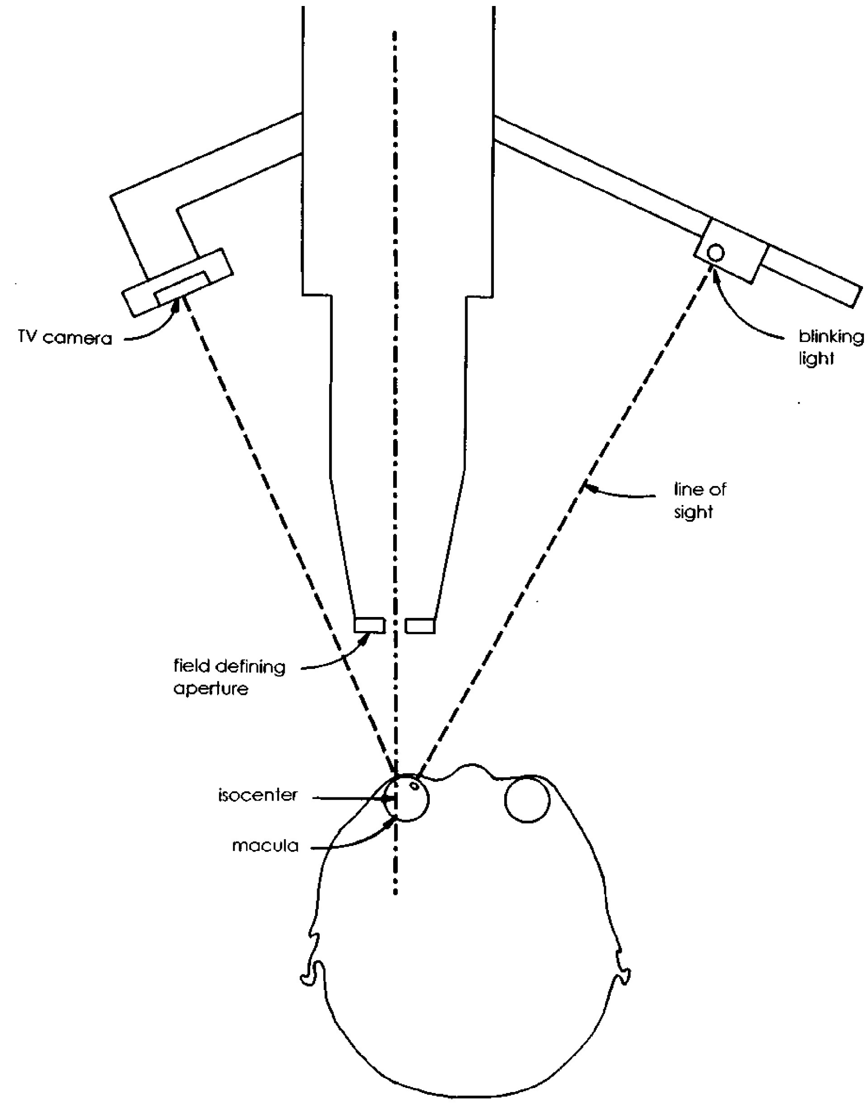

6 MeV X rays or
High energy neutrons
≈ 4 MeV
uncharged
charged
p+
RELATIVE DOSE
DEPTH IN WATER (cm)
0
1
2
3
4
5
0
5
10
15
20
25

Protons

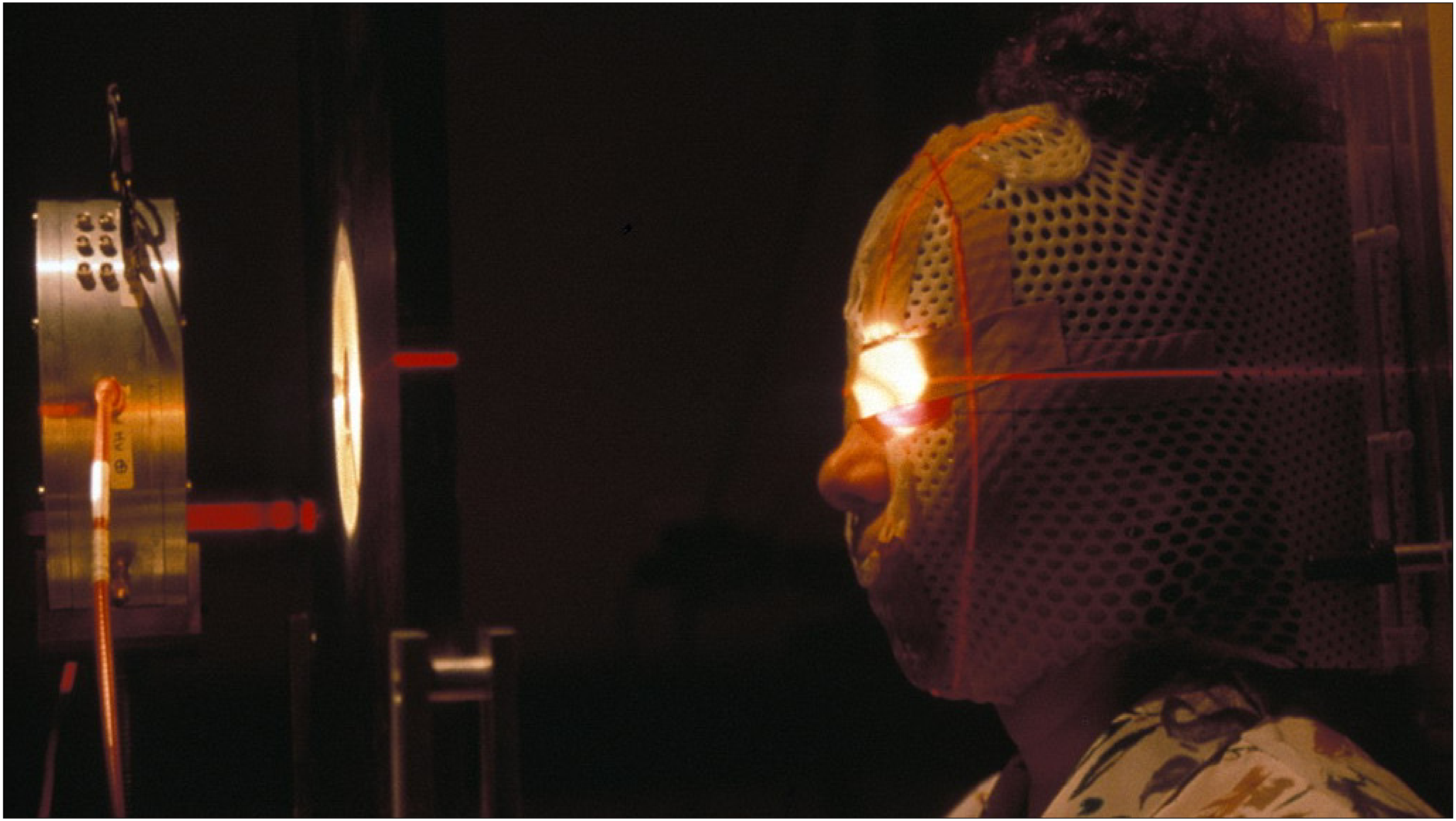
- **Small fields, low energies (~60 MeV)**
  - ocular lesions
- **Large fields, high energies (>150 MeV, now >300 MeV)**
  - treat any site
  - good for difficult plans, pediatrics?
  - expensive, but cost coming down…? or is it?
  - An evidence based review of proton beam therapy: The report of ASTRO's emerging technology committee *Radiother Oncol* 2012;103:8–11

Proton treatment for macular degeneration

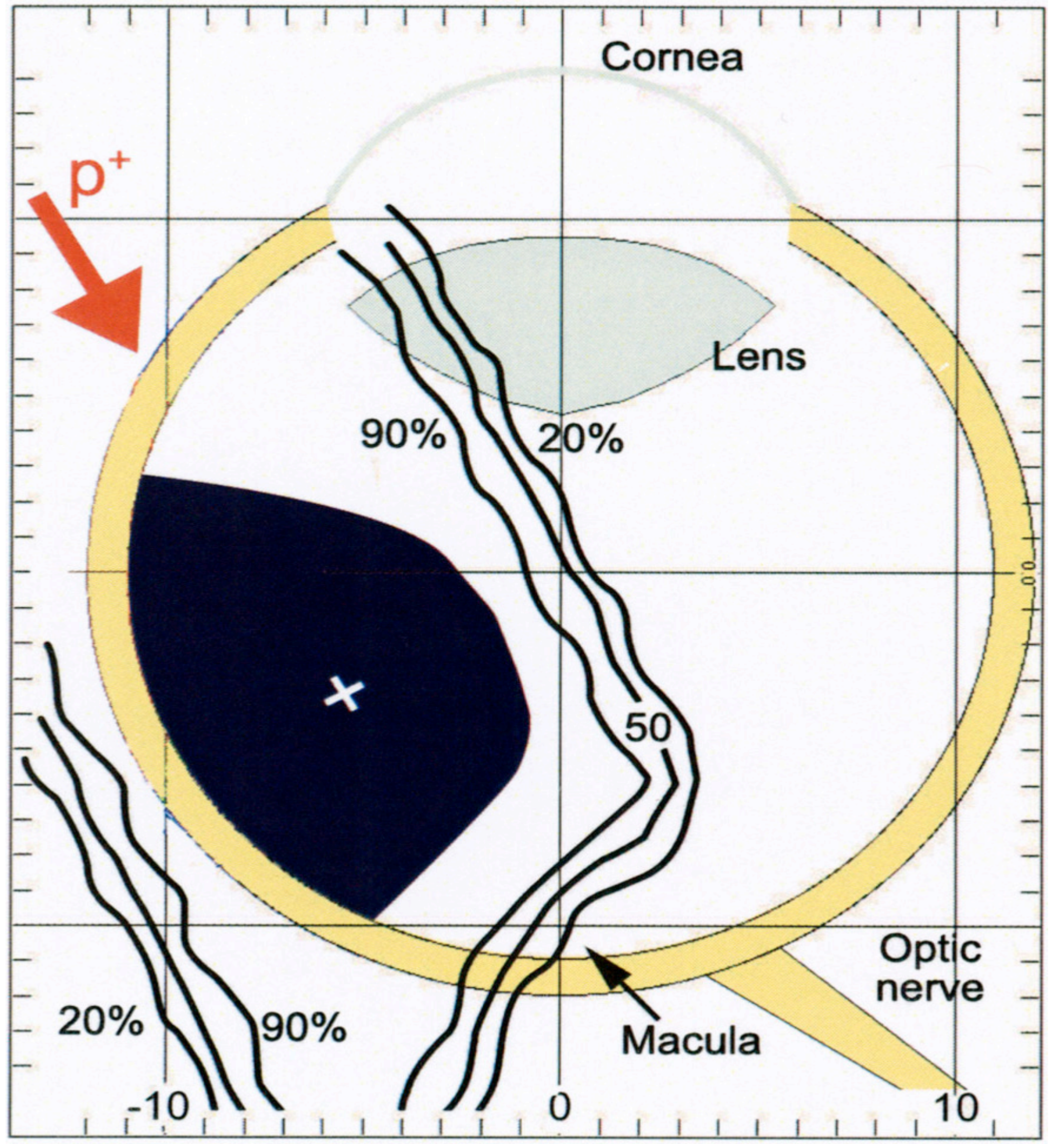
Also, occular melanoma



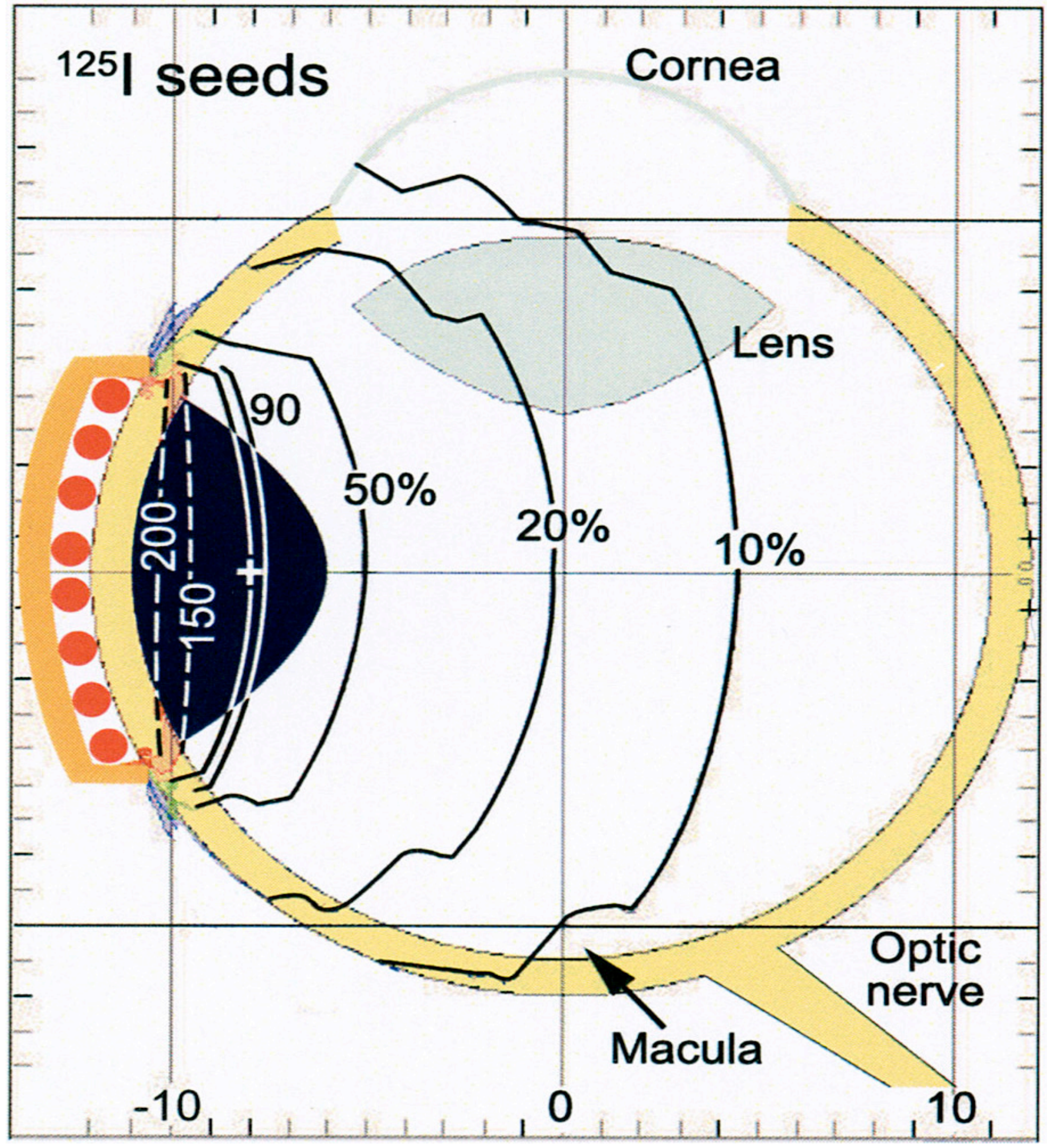
Moyers et al. *Med Phys* 1999;26:777



Protons



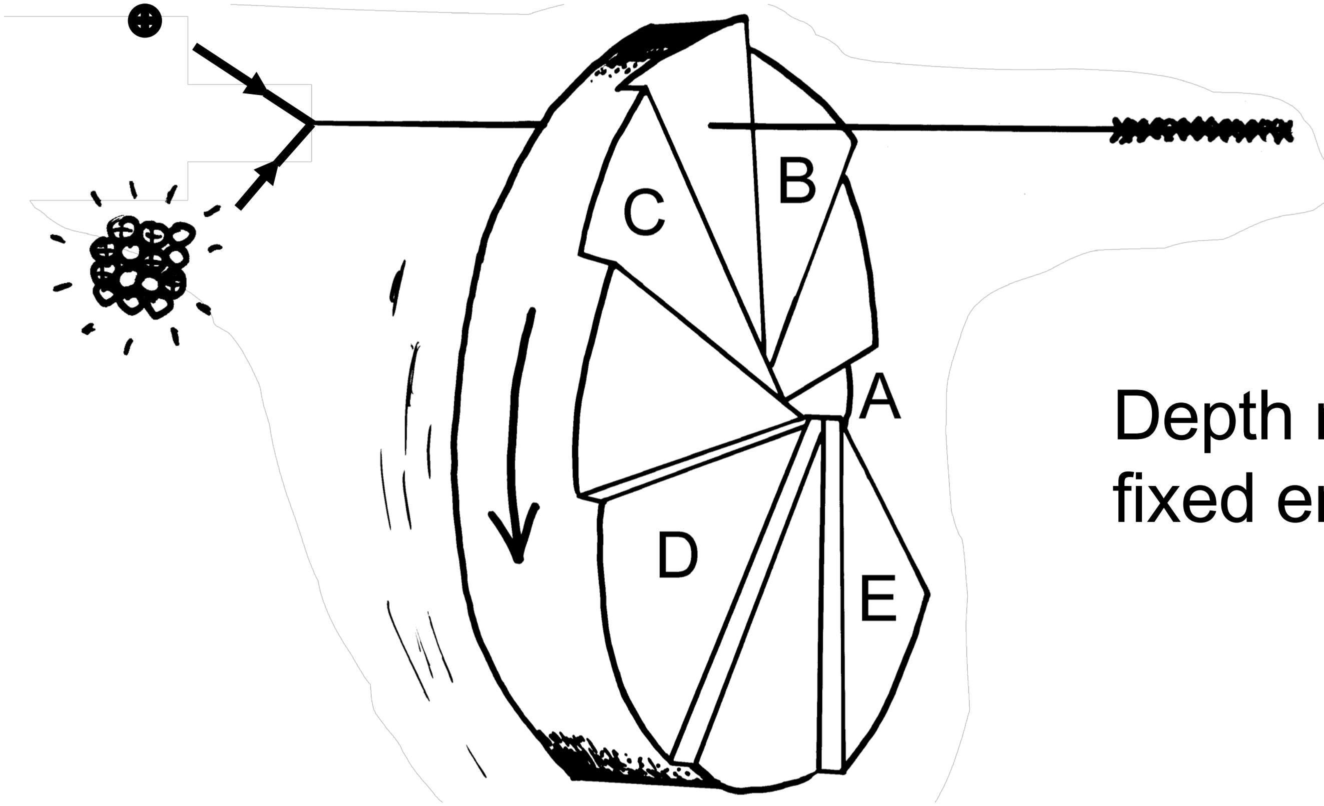
^{125}Iodine



125I seeds
Cornea
Lens
90
50%
20%
10%
200
150
Optic
nerve
Macula
-10
0
10

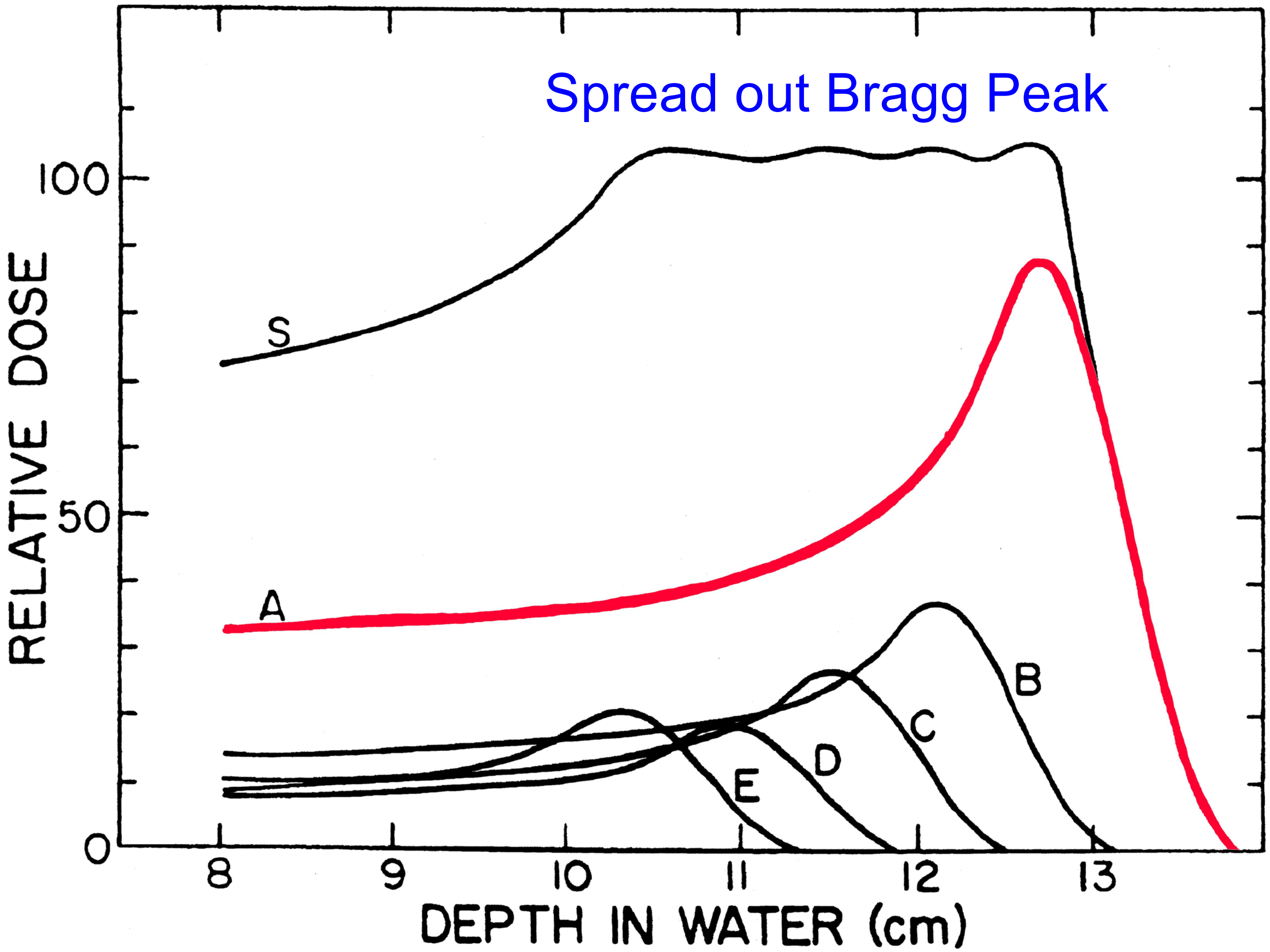
Bragg peak

- Depth can be changed by varying the energy
- Too narrow by itself for all but very small lesions
- Can be widened by mixing beams of several energies
  (diluted Bragg peak)
- But, any biological advantages (RBE?) of high-LET are reduced by diluting the Bragg peak
- Note also higher energies will reduce any RBE

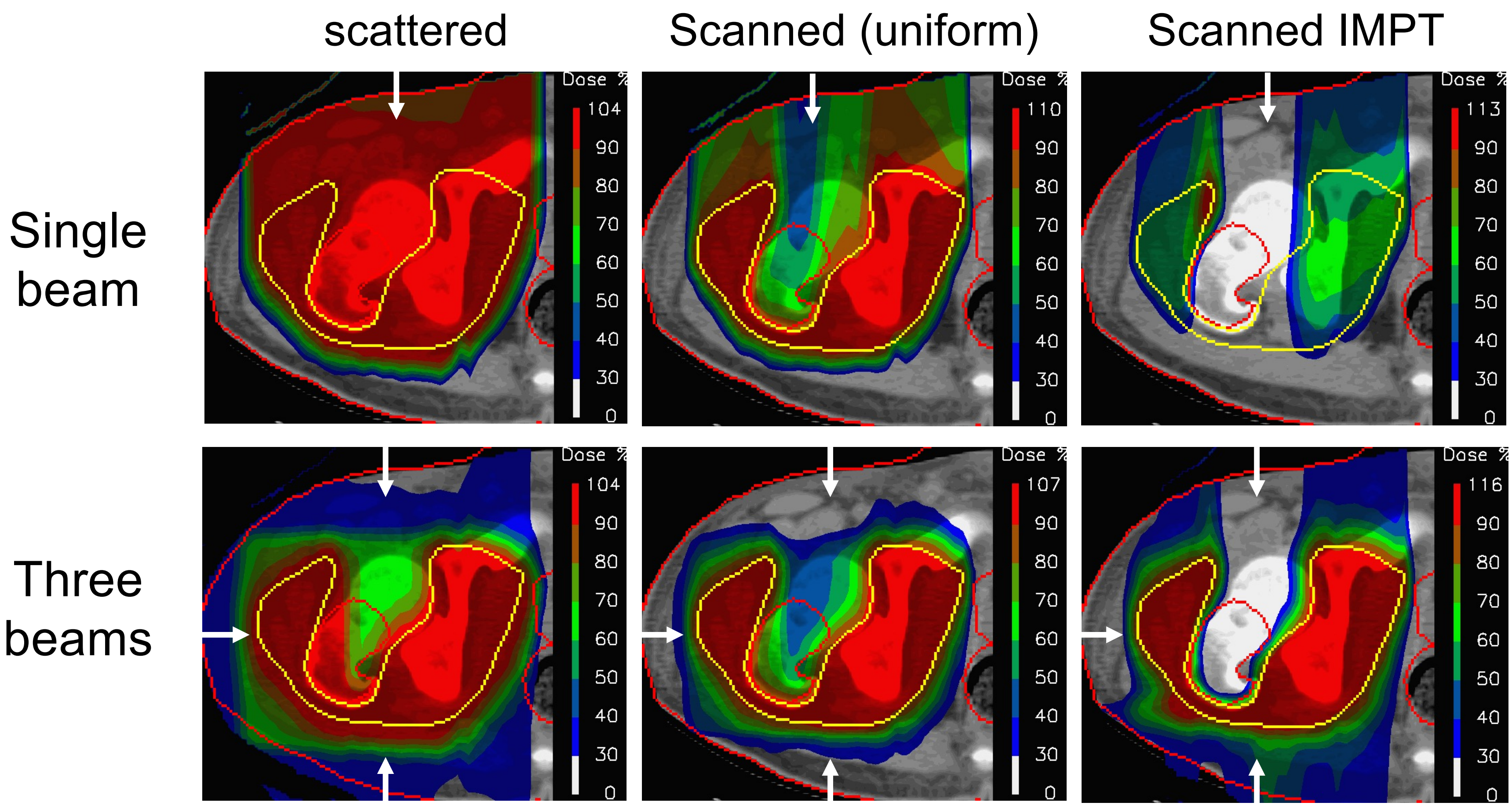


Depth modulating a fixed energy beam

Now use: variable energy cyclotrons or accelerators, spot-scanning beams

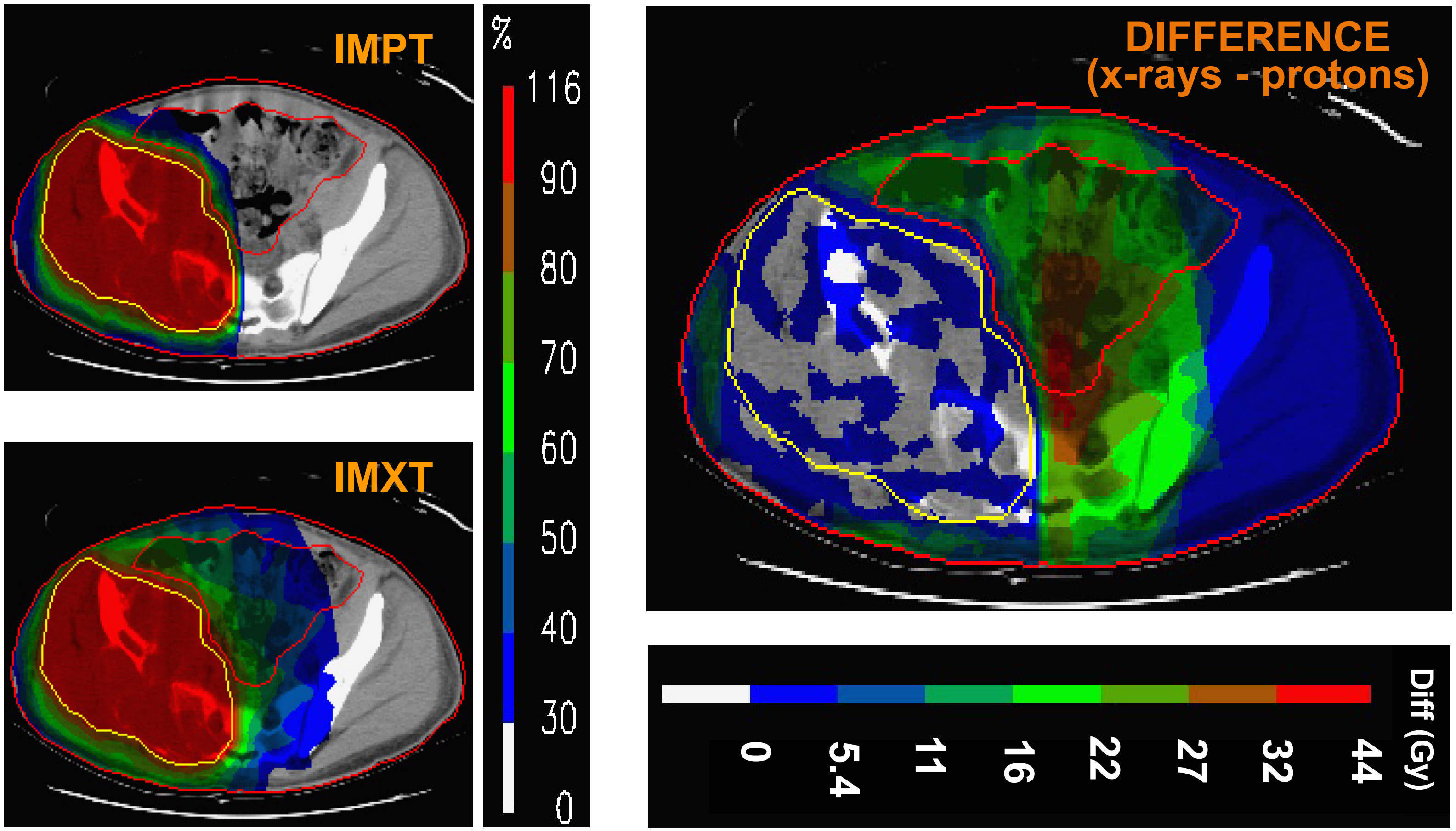

Spread out Bragg Peak
RELATIVE DOSE
DEPTH IN WATER (cm)
100
50
0
8
9
10
11
12
13
S
A
B
C
D
E

Intensity Modulated Protons for Bone Sarcoma



From M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007

IMPT vs IMXT for Ewing sarcoma



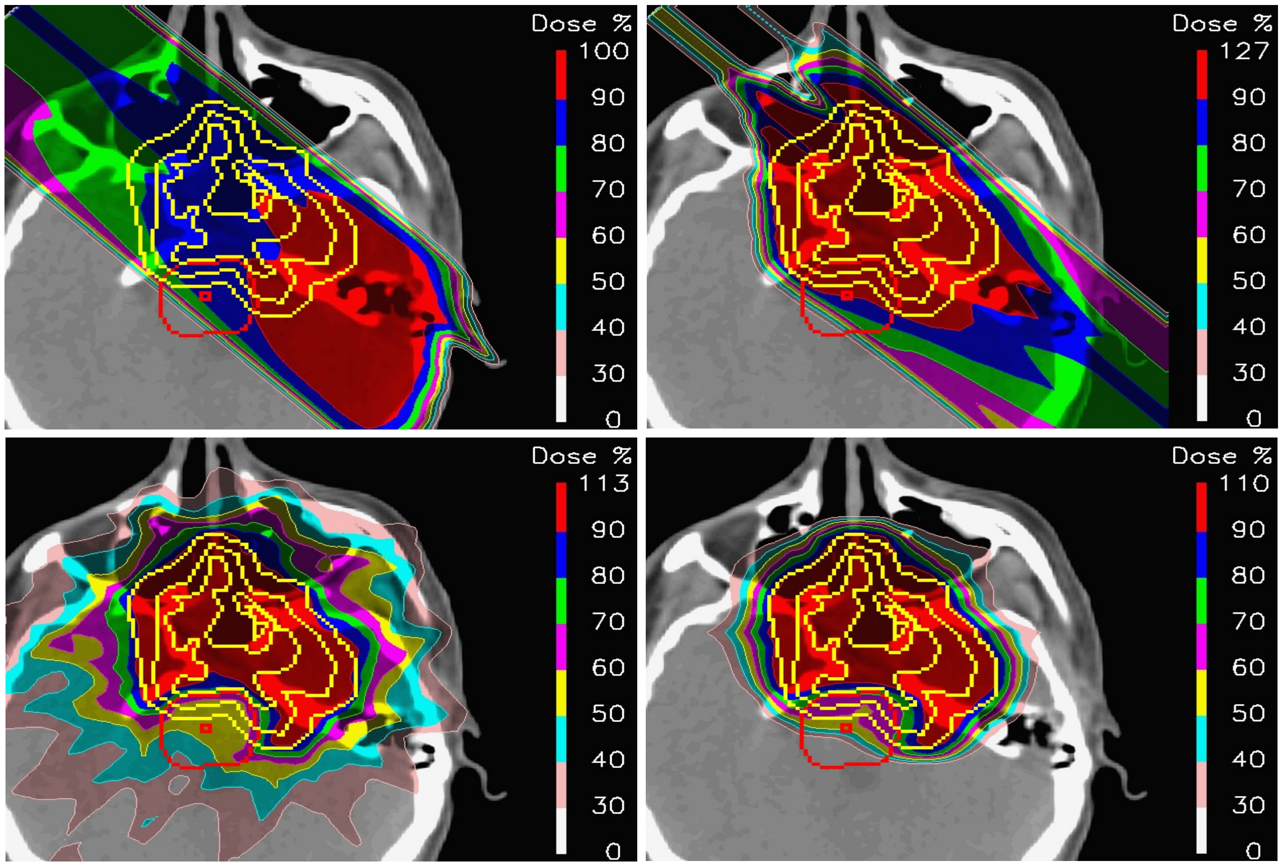
From M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007

Photons vs Protons for meningioma

photons protons

Single beam

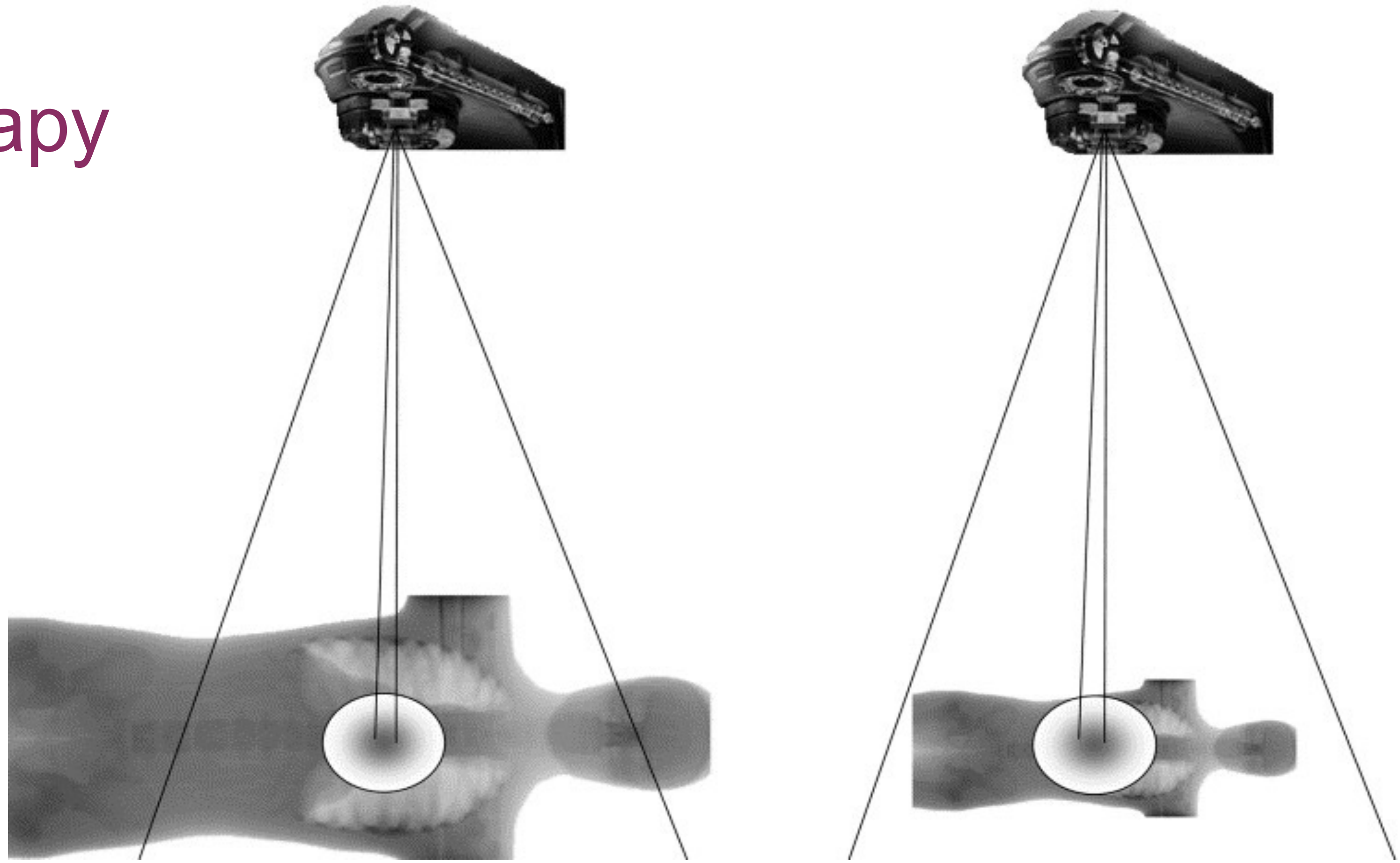
IMRT



From M. Goitein, Radiation Oncology: A physicist's-eye-view Springer, 2007

Radiotherapy in children

Same Leakage for Adult RT vs. Pediatric RT — But in Pediatric RT Scatter from the Treatment Volume Is More Significant



Hall, 2006

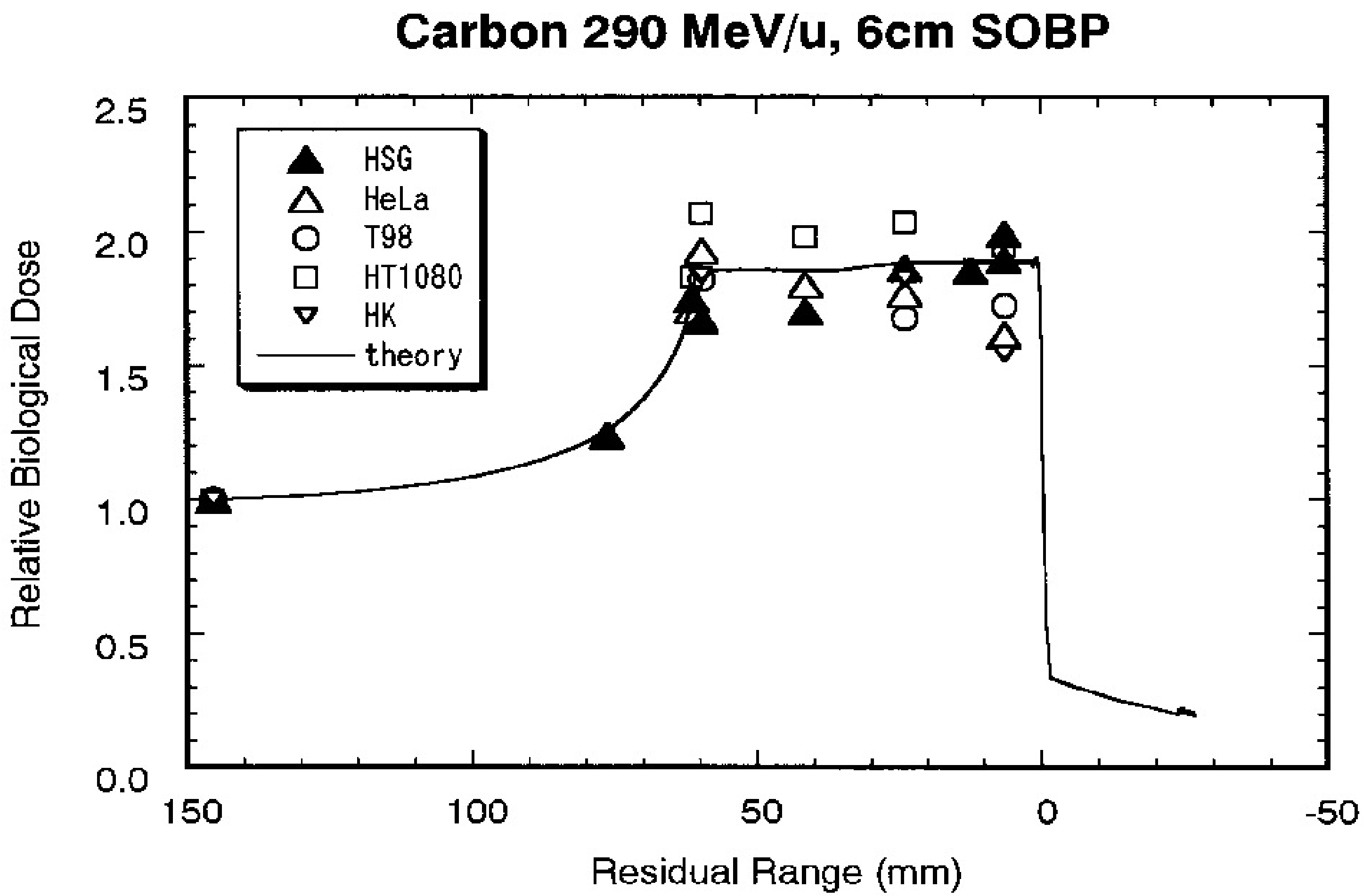
Proton therapy indications

REGION	LESION
Brain and spinal cord	Isolated brain metastases Selected brain tumor recurrences Pituitary adenomas Arteriovenous malformations (AVMs)
Base of skull	Meningiomas Acoustic neuromas Chordomas and chondrosarcomas
Eye	Uveal melanomas Macular degeneration
Head and neck	Nasopharynx (primary and recurrent) tumors Oropharynx (locally advanced) tumors Paranasal sinus tumors
Chest and abdomen	Medically inoperable non-small-cell lung cancer Chordomas and chondrosarcomas Hepatic tumors Retroperitoneal tumors Paraspinal tumors
Pelvis	Prostate tumors Chordomas and chondrosarcomas
Pediatric lesions	Brain and spinal cord tumors Orbital and ocular tumors Sarcomas of the base of skull and spine Abdominal and pelvic tumors

Heavy ions

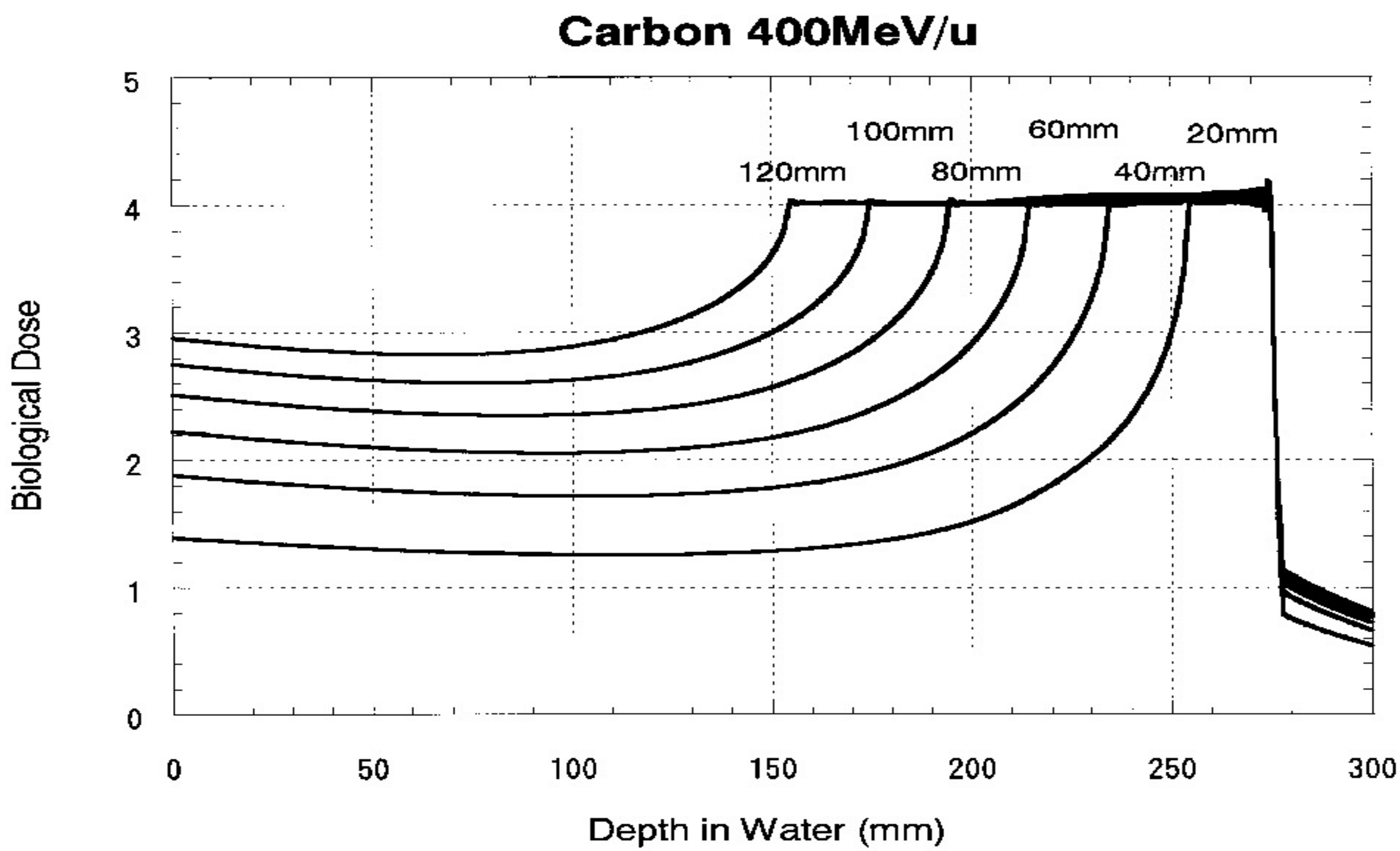
- **Physical advantages**
  - Bragg peak
  - adjustable Bragg peak depth
  - sharp beam edges (small penumbra)
- **Biological "advantages"**
  - low OER, reduced cell-cycle effect, less repair of tumor cells; high-LET benefits partially maintained even after spreading out the Bragg peak

Diluted Bragg peak: Chiba, Japan



400 MeV carbon diluted Bragg peak

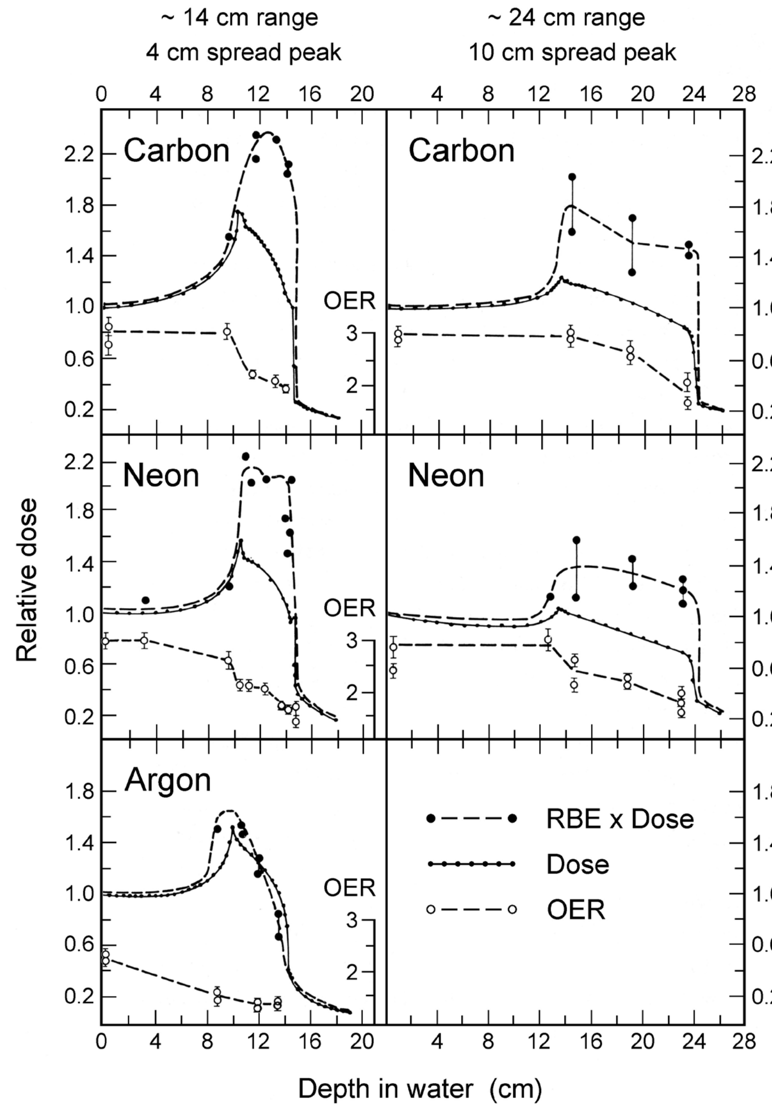
20–120 mm Lucite filtration

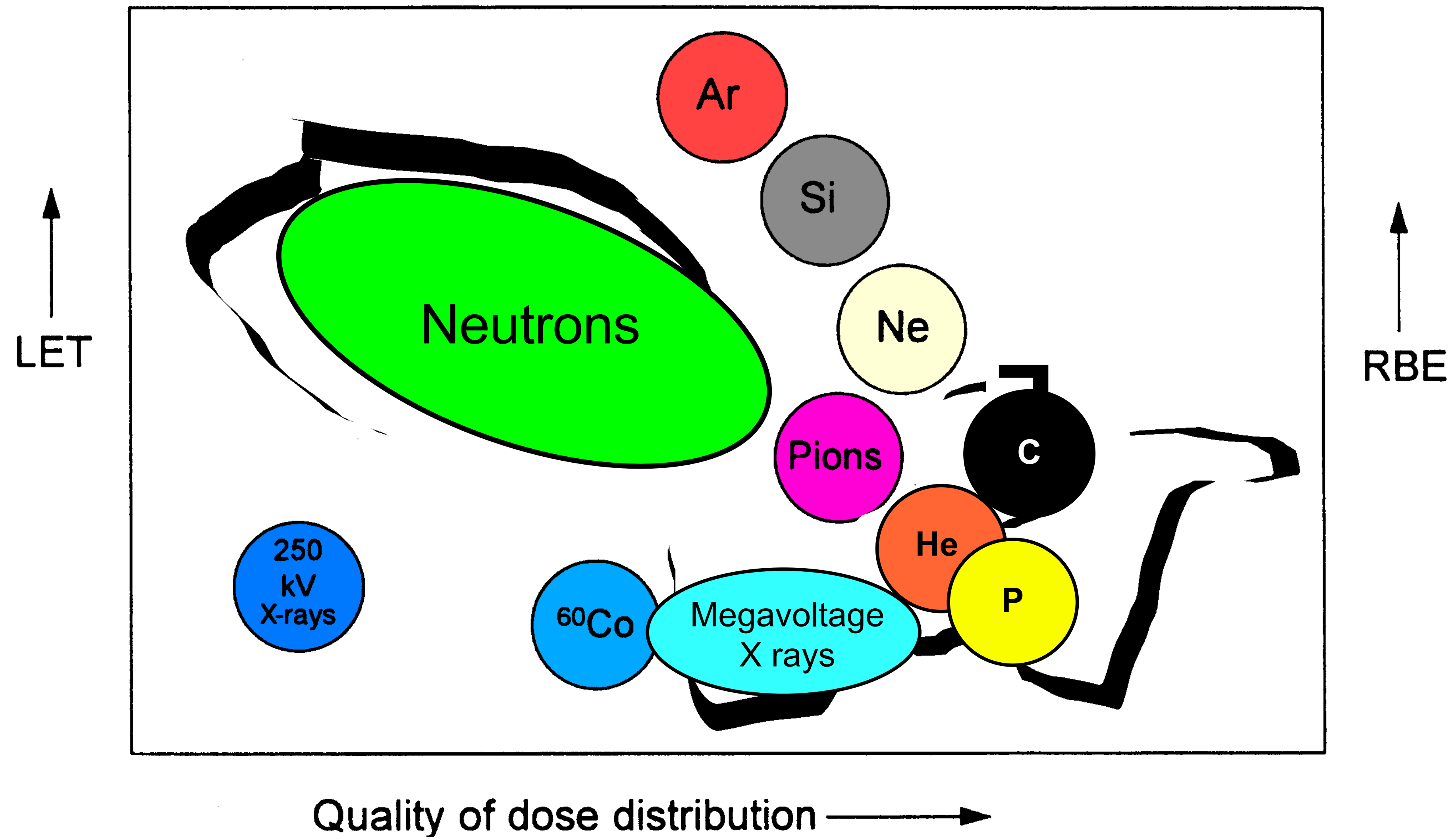


Blakely EA (1982).

Biology of bevalac beams: cellular studies.

In: *Pion and heavy ion radiotherapy: pre-clinical and clinical studies*
Ed. Skarsgard LD, pp. 229-250.
Elsevier, Amsterdam.




Ar
Si
Ne
Neutrons
Pions
C
He
P
250
kV
X-rays
60Co
Megavoltage
X rays
LET
RBE
Quality of dose distribution

Summary of biological and physics advantages

250 kVp	Skin cancers, historical
^{60}Co γ - 22 MeV X	"Conventional" radiotherapy – VMAT state-of-the-art
Protons	For difficult sites. Compare IMRT, Physics advantage?
Neutrons	High-LET therapy, Biggest biological advantage (RBE)
C, Ne, Si	Operating in Chiba, Japan and GSI Darmstadt-Heidelberg. Physics *and* Biological advantage?

Caution - again !

Commentary:
Glimelius et al. *Radiother Oncol* 2007;83:105−9

Protons:
Olsen et al. *Radiother Oncol* 2007;83:123−32

Hadrons:
Lodge et al. *Radiother Oncol* 2007;83:110−22

…compelling rationale, both physics and biology,
yet as of 2022 still no completed randomized trials…
And… cost effective ??