The Abdus Salam
International Centre for Theoretical Physics

United Nations
Educational, Scientific and
Cultural Organization

IAEA
International Atomic Energy Agency

310/1828 310/2

Workshop on Biomedical Applications of High Energy Ion Beams

Co-sponsored by: ICGEB and University of Surrey

12-16 February 2007

Venue:
Adriatico Guest House Giambiagi Lecture Hall
ICTP, Trieste, Italy

Radiobiology

Jolyon HENDRY
IAEA, Austria

Strada Costiera 11, 34014 Trieste, Italy - Tel. +39 040 2240 111; Fax +39 040 224 163 - sci_info@ictp.it, www.ictp.it

RADIOBIOLOGY OF ION BEAM RADIOTHERAPY

International Atomic Energy Agency

Jolyon H. Hendry

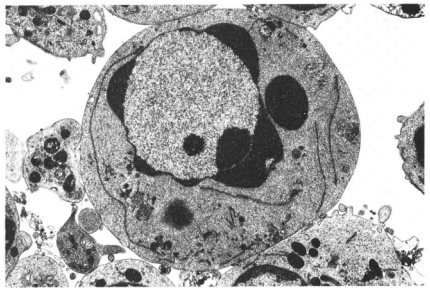
ARBR, DIVISION OF HUMAN HEALTH, NUCLEAR APPLICATIONS, IAEA, Vienna, Austria.

LECTURE FORMAT

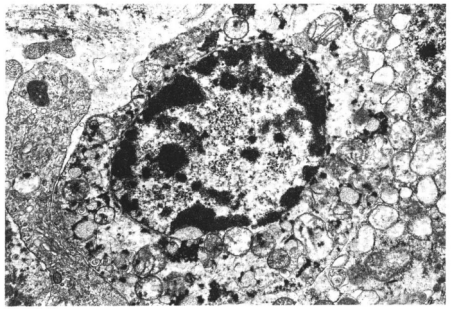
- Cell survival versus dose relationships
- Tumour and Normal tissue responses
- Rationale for ion beam therapy
- RBE: laboratory measurements and clinical values

Cell death definitions

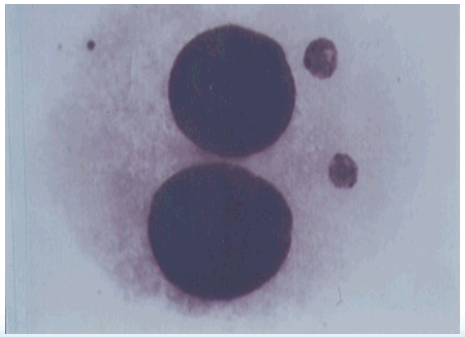
- **Apoptosis - nuclear margination and fragmentation, cell lysis, dense chromatin bodies phagocytosed by neighbouring cells.**



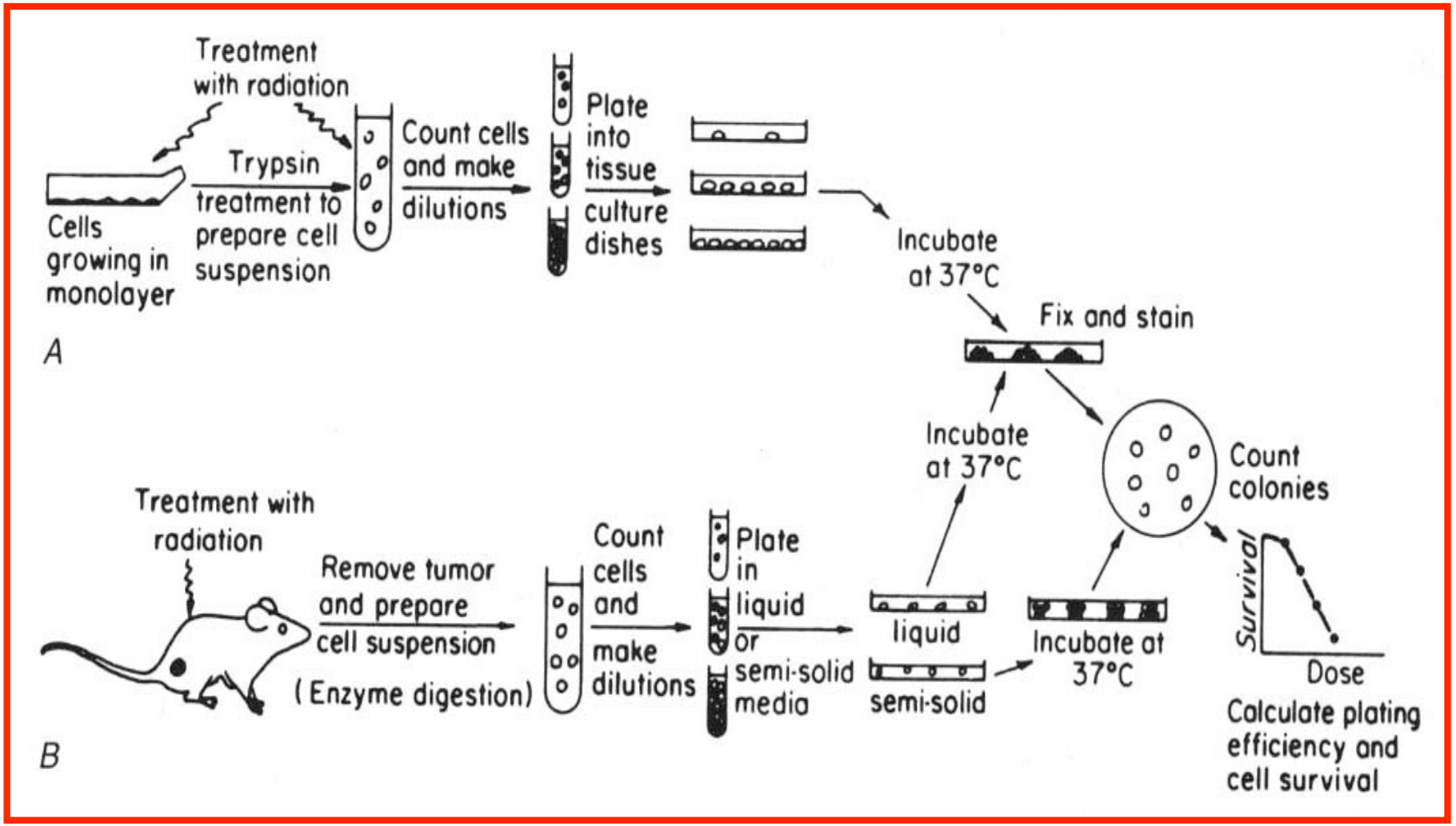
- **Necrosis - Membrane disruption, ion flux changes, organelle blebbing, cell disintegration.**



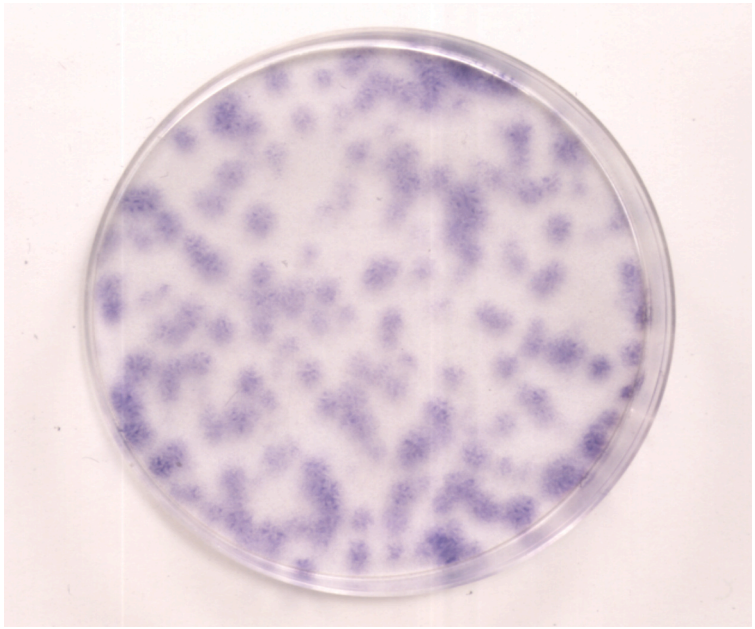
- **Reproductive/mitotic death - failure to complete mitosis successfully, loss of essential genetic information (micronuclei).**

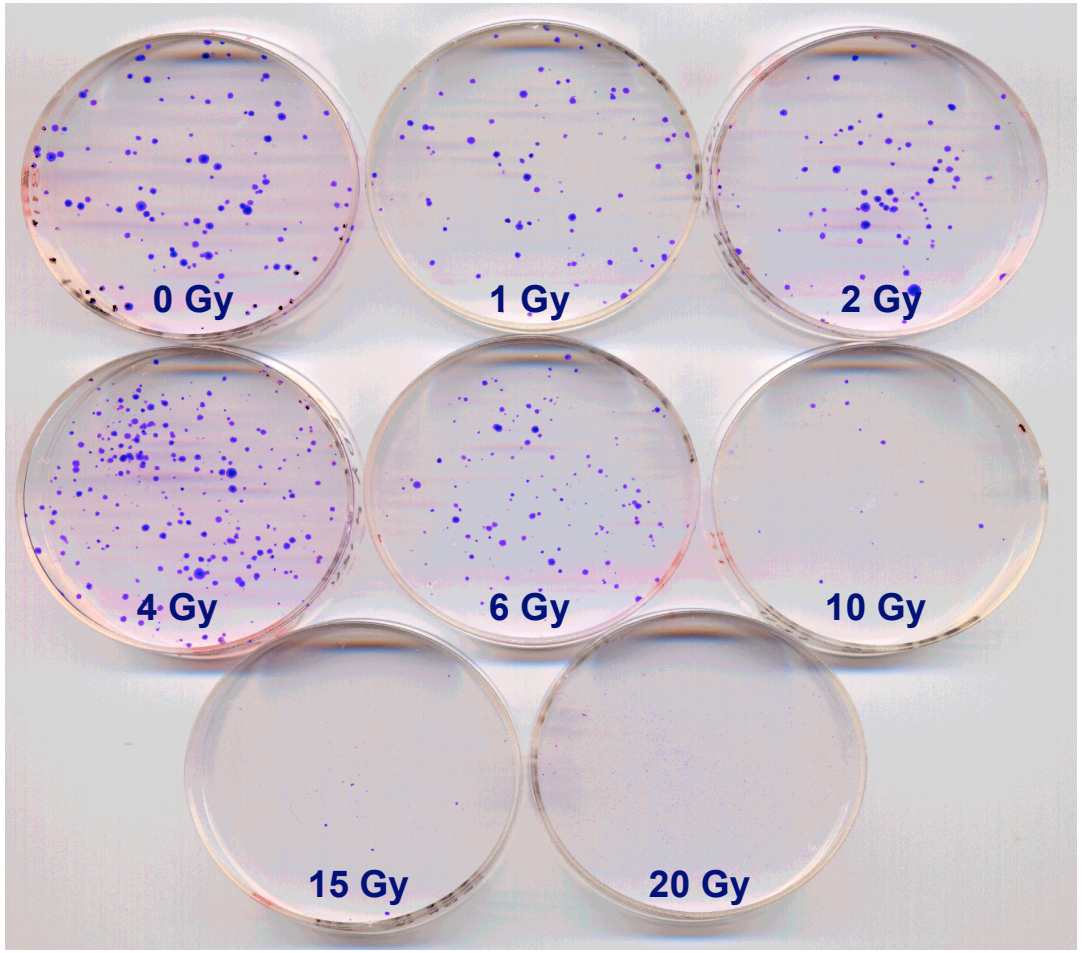


Survival curve determination



Colony assay: in vitro survival



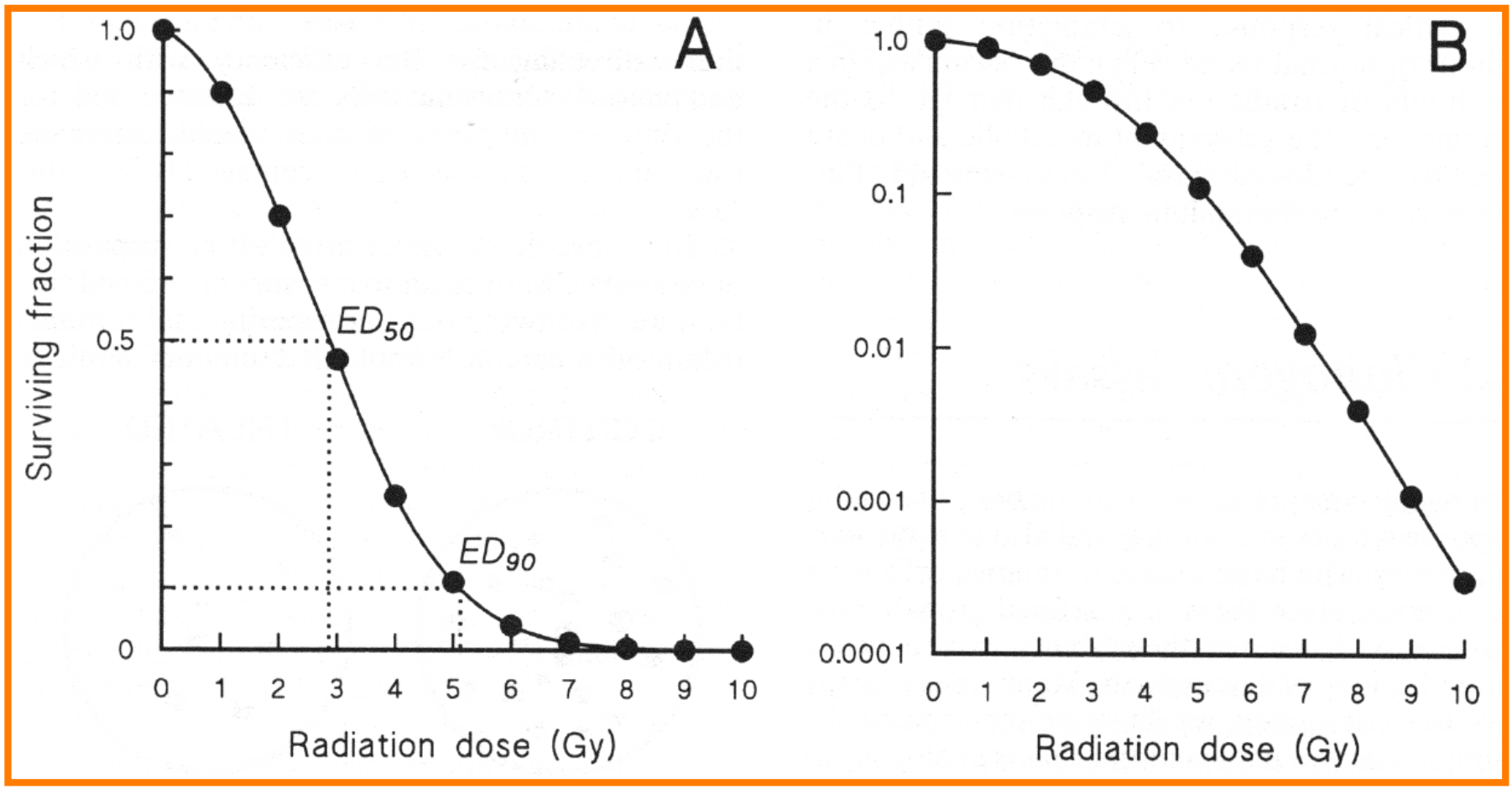


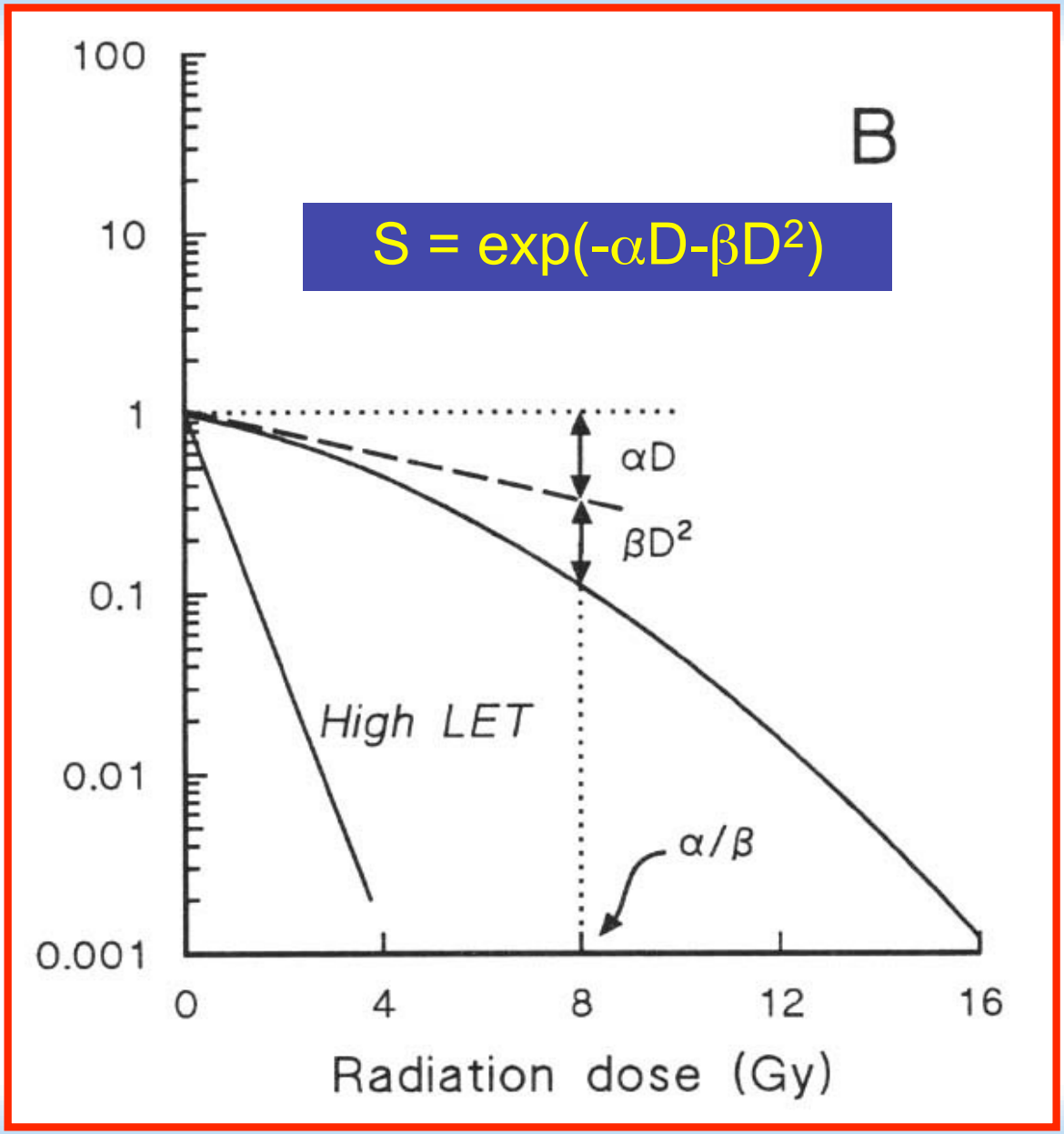
Courtesy of Brian Marples

Cell survival calculation

Dose (Gy)	Cells plated	Colonies counted	Plating Efficiency	Surviving Fraction
0	100	95	0.95	1.00
0.5	110	90	0.82	0.78
1	150	100	0.67	0.63
2	200	100	0.50	0.48
3	300	80	0.27	0.25
4	400	70	0.18	0.17
5	500	50	0.10	0.095
6	600	40	0.067	0.063

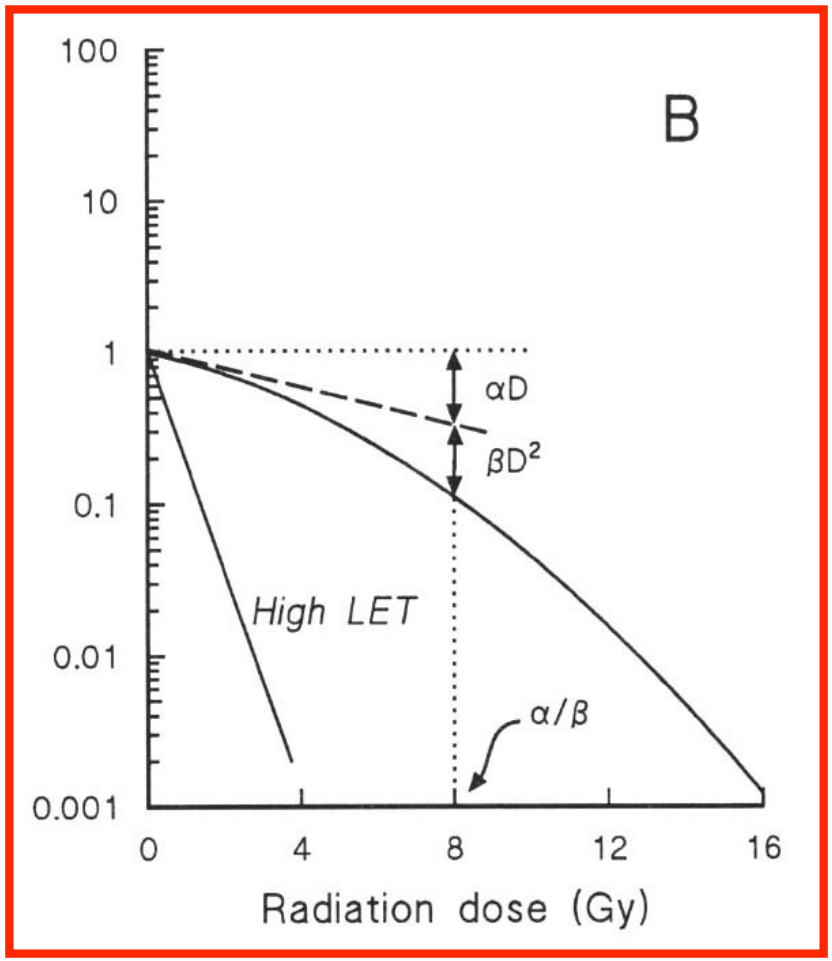
Cell survival curves

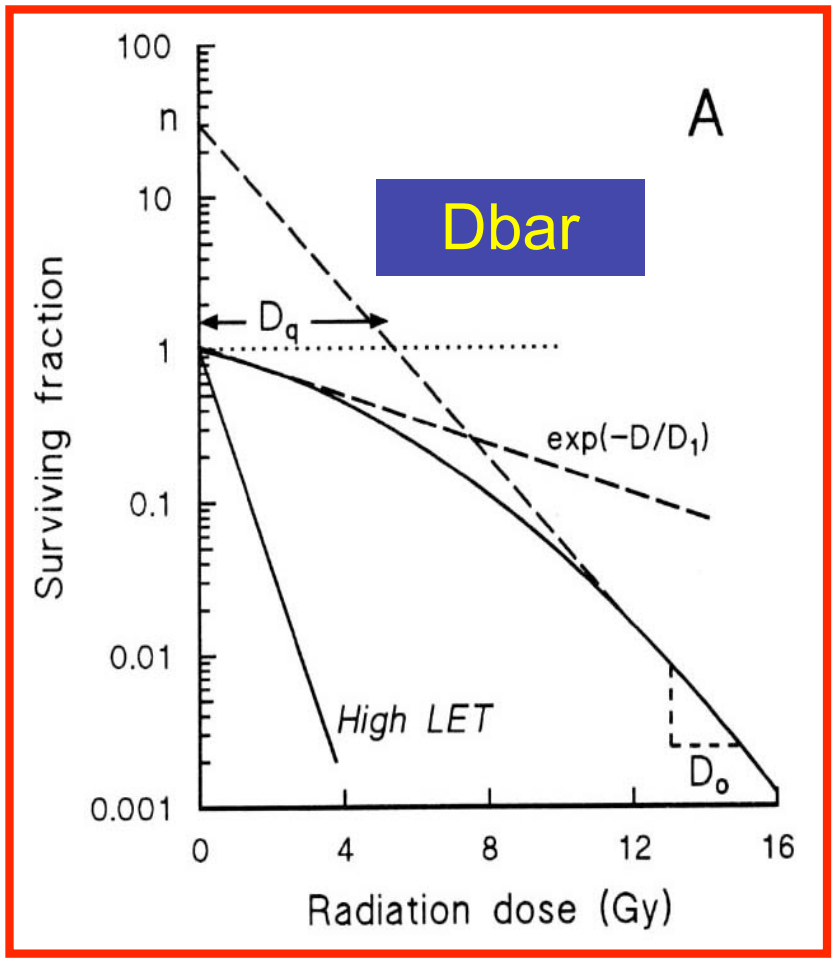




Linear quadratic survival curves

Linear Quadratic versus Multitarget



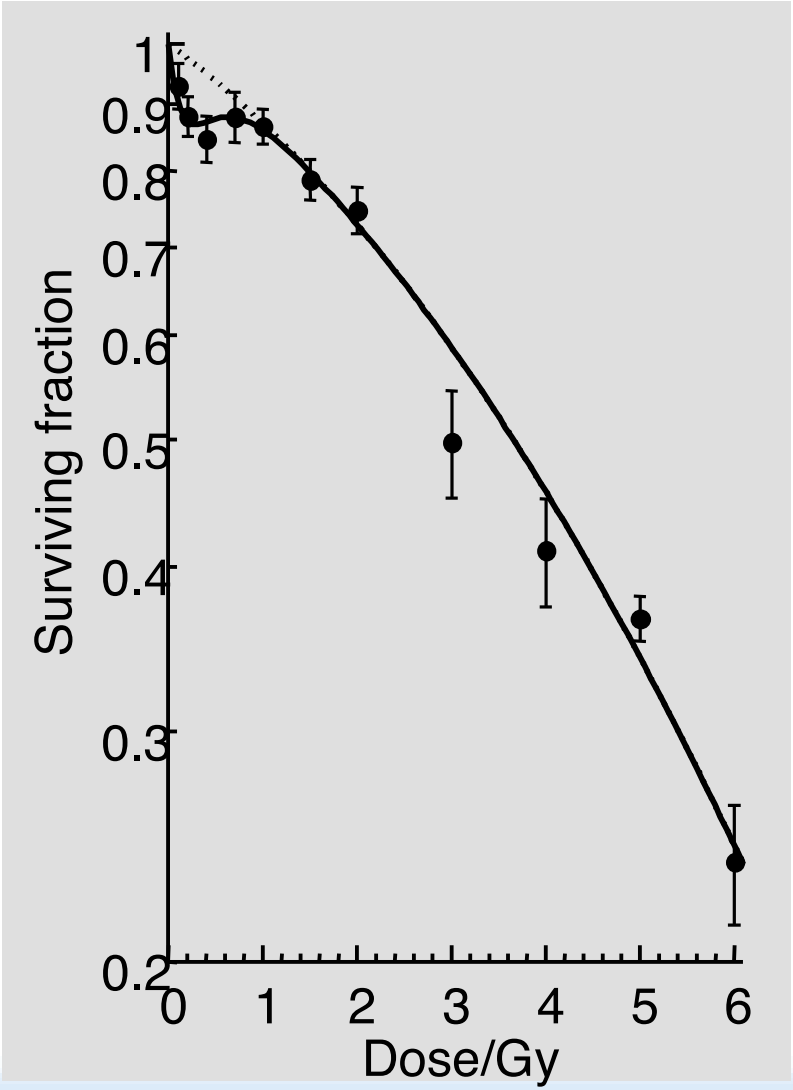


Definitions

- Alpha : the initial slope of the cell survival curve (Gy^{-1}).
- Beta : the dose-squared constant (Gy^{-2}), accounting for the continuous bending nature of the curve (=0 when full repair).
- Alpha/beta : dose at which same amount of kill is produced by each component.

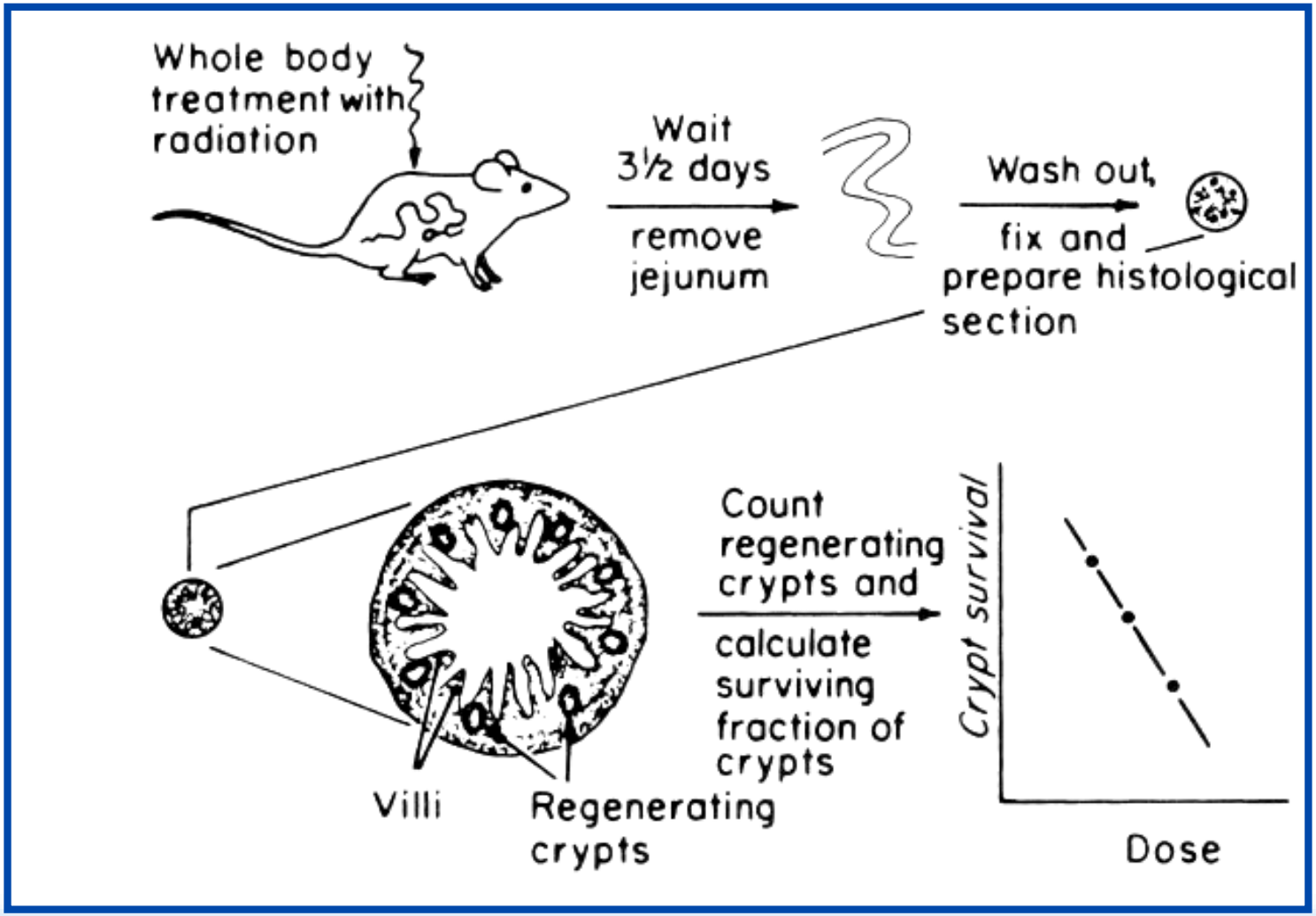
- N : extrapolation number on the y-axis of (log) survival.
- Do : mean lethal dose, *dose to kill the average cell* (Gy).
- Dbar : integral of the survival curve in linear coordinates, *the average dose to kill a cell.* Do=Dbar if survival curve is exponential.

Hyper-radiosensitivity (HRS) at low doses

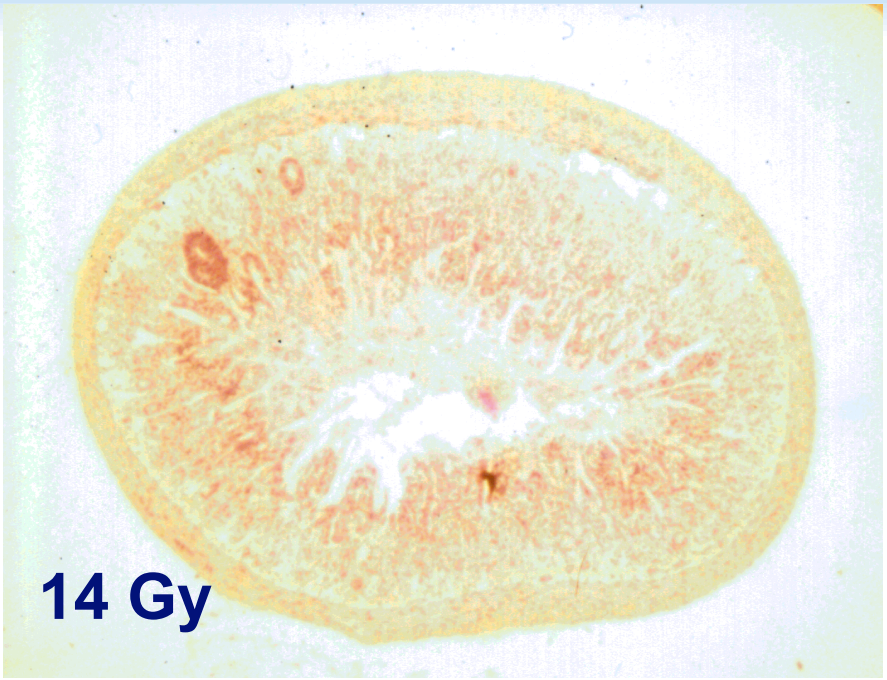


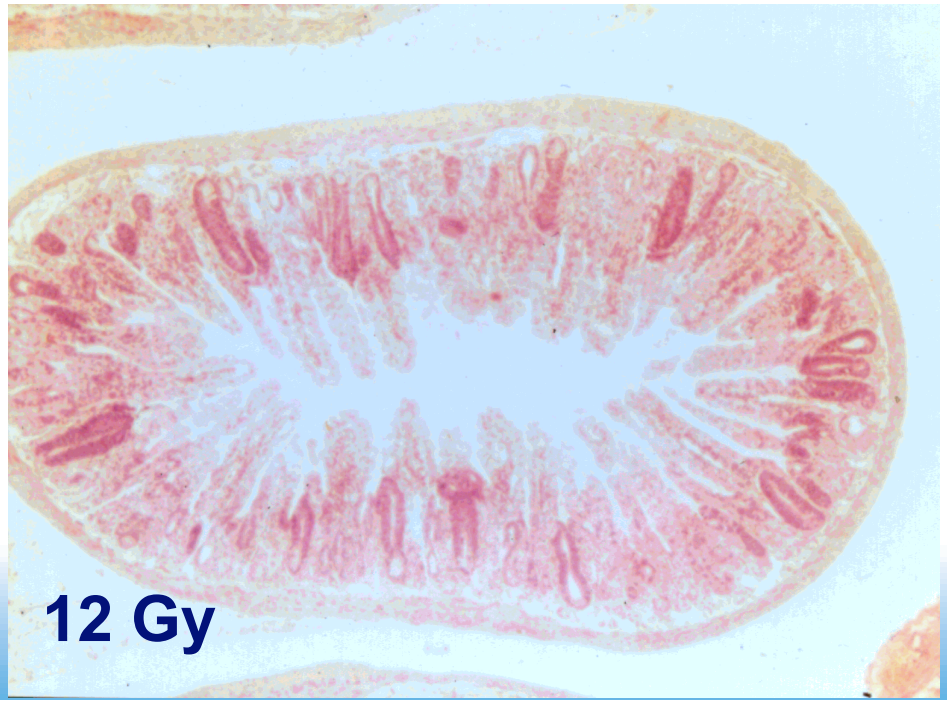
- Observed in many cell types, more in resistant tumour cells
- HRS at doses < 0.5 Gy, not found at high LET
- Proposed induced repair at higher doses, perhaps linked to G2 sensitivity
- Found in rodent kidney and skin, also some evidence in human skin
- Not yet exploited in clinical practice

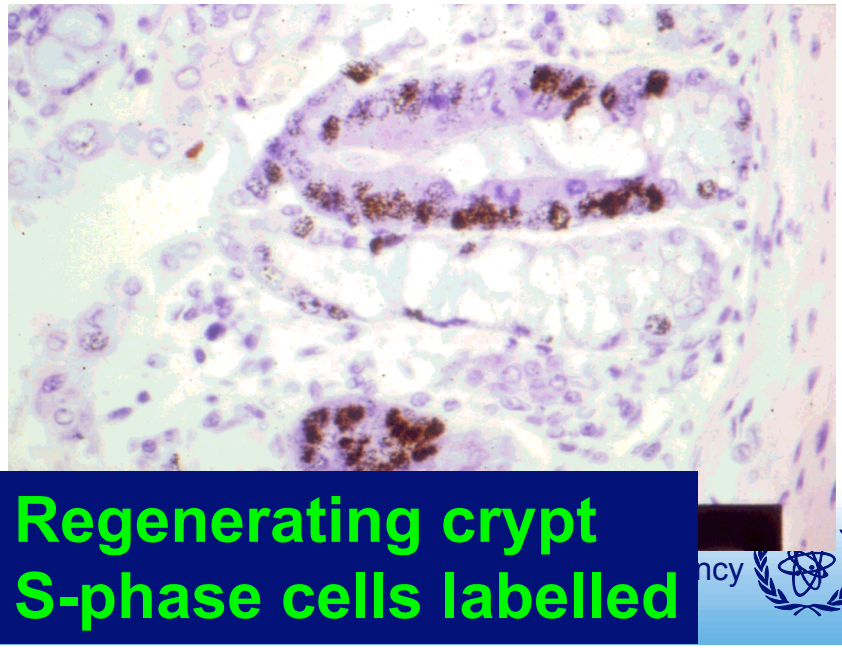
Intestinal crypt survival assay



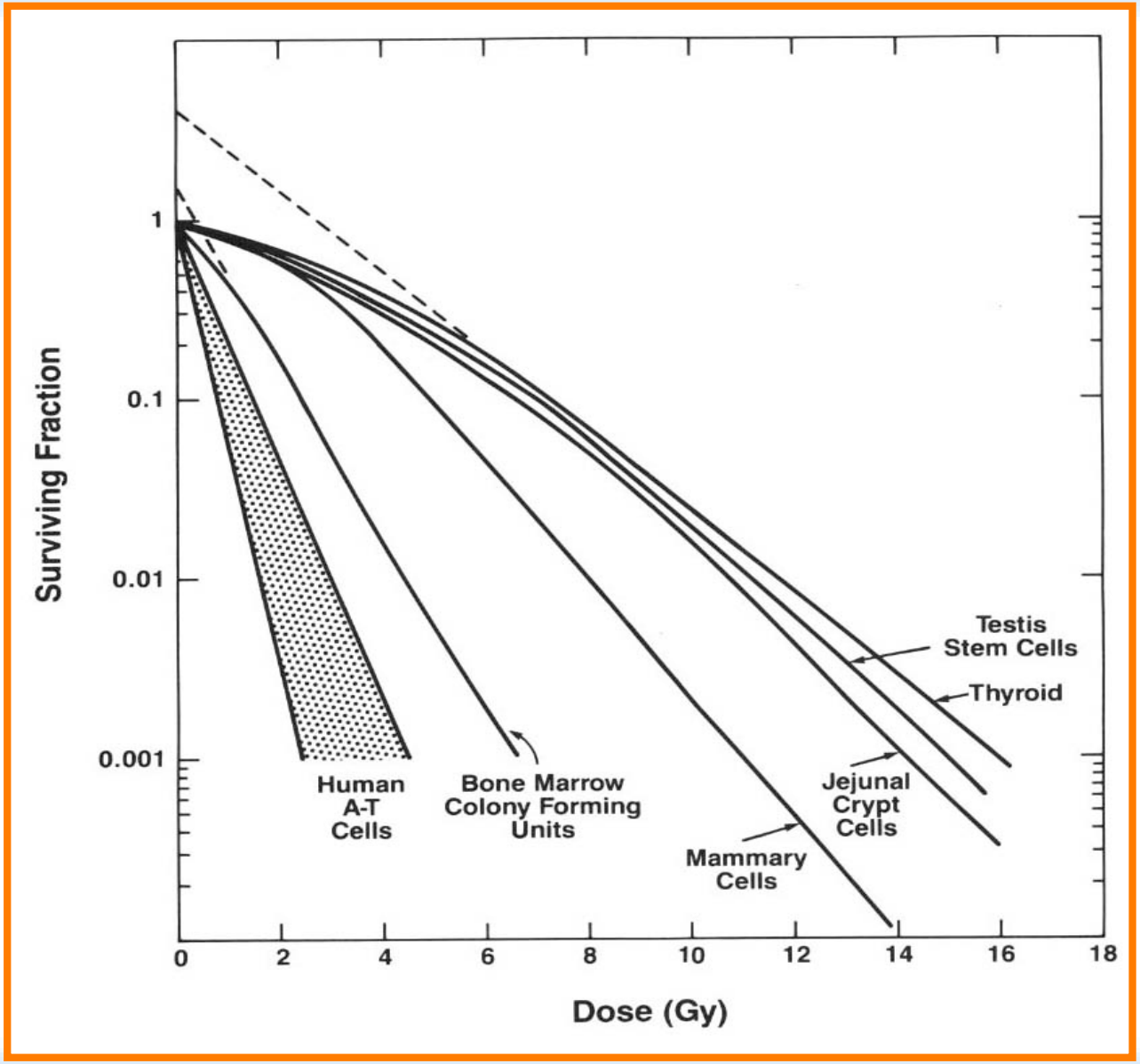
Intestinal crypt assay





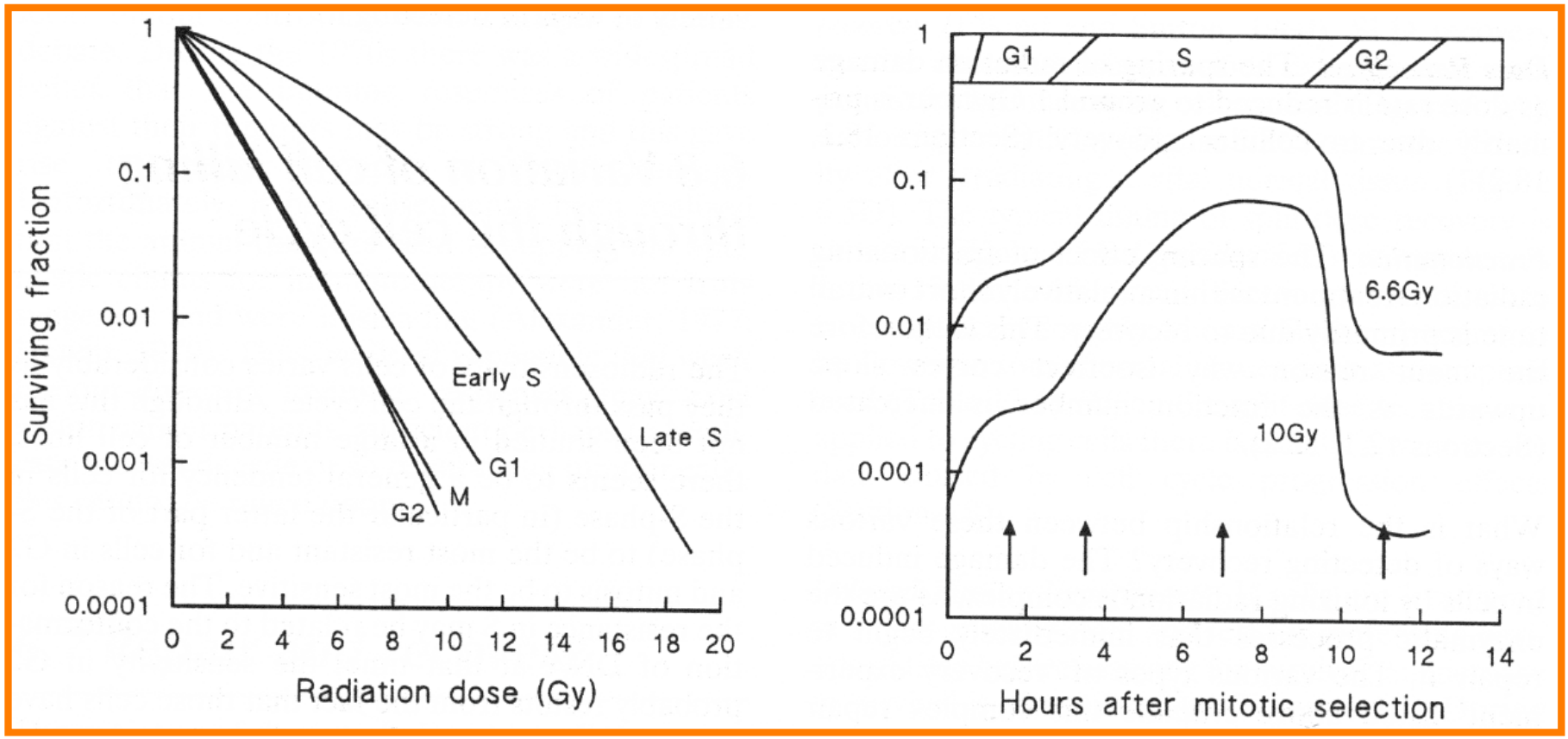


Regenerating crypt
S-phase cells labelled



Radio-sensitivity of normal cell types

Variation in radiosensitivity through the cell cycle

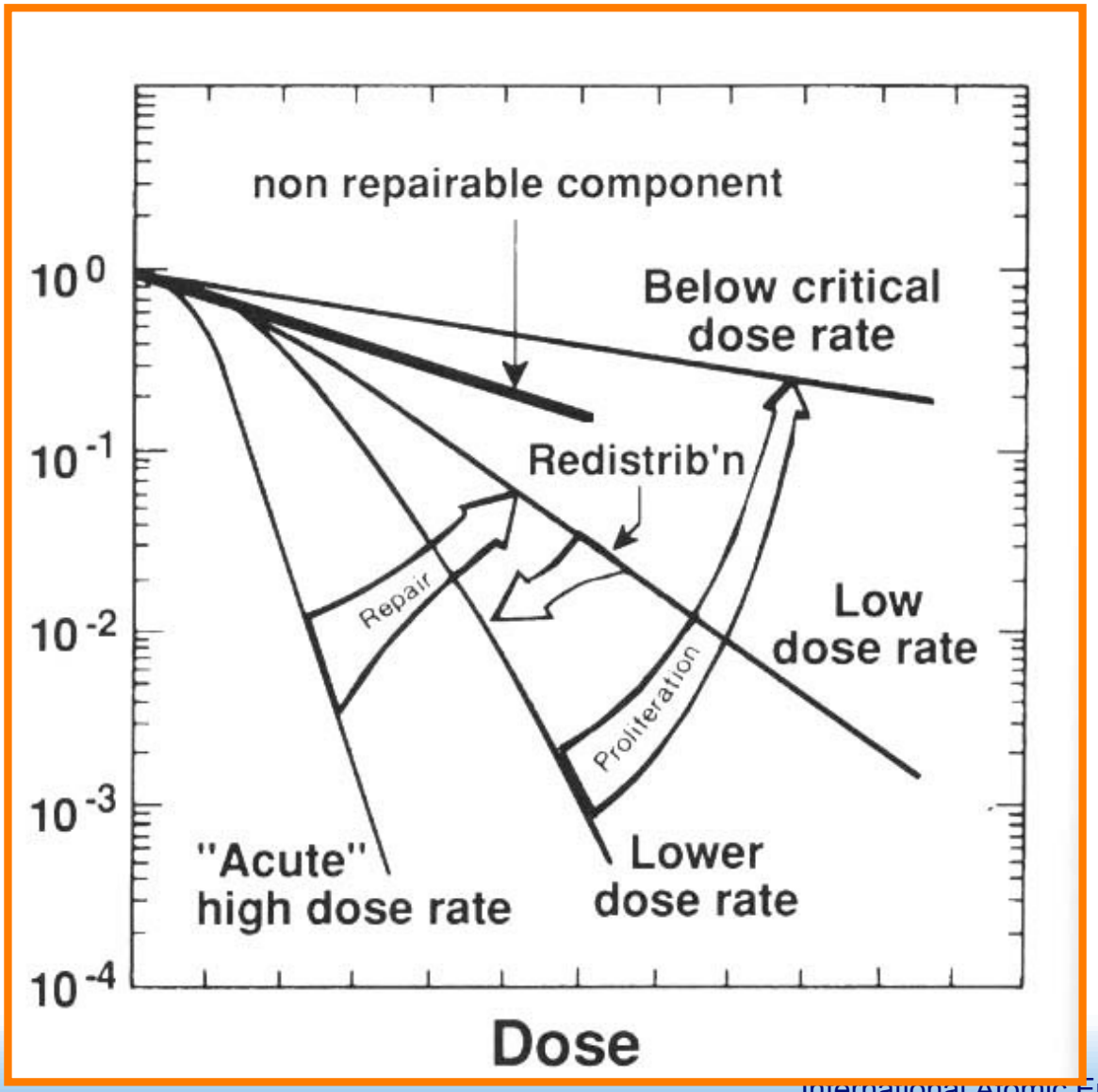


Cell cycle phase sensitivity

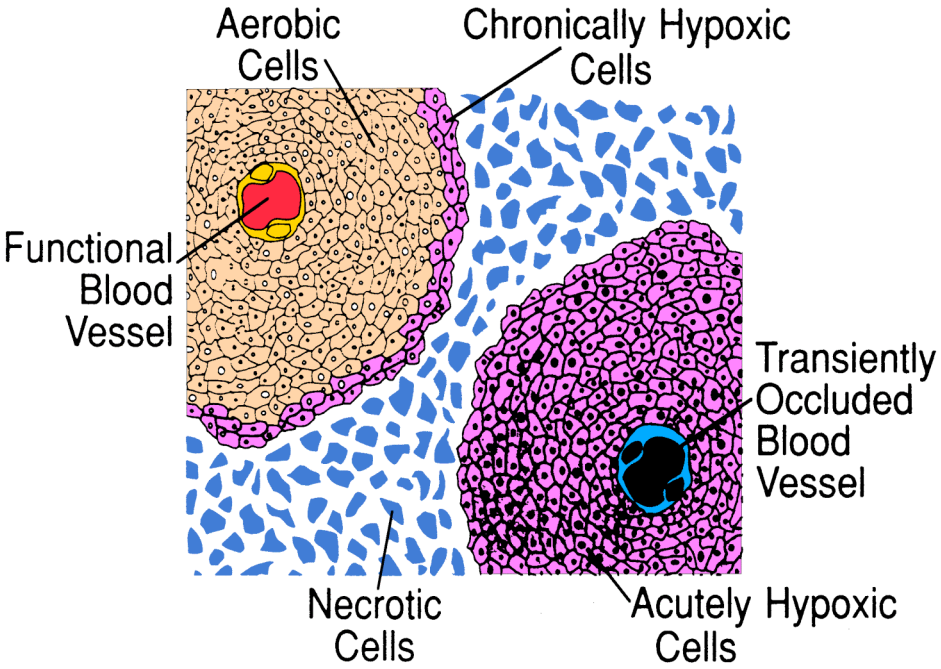
- radiosensitivity changes through the cell cycle
- order of resistance

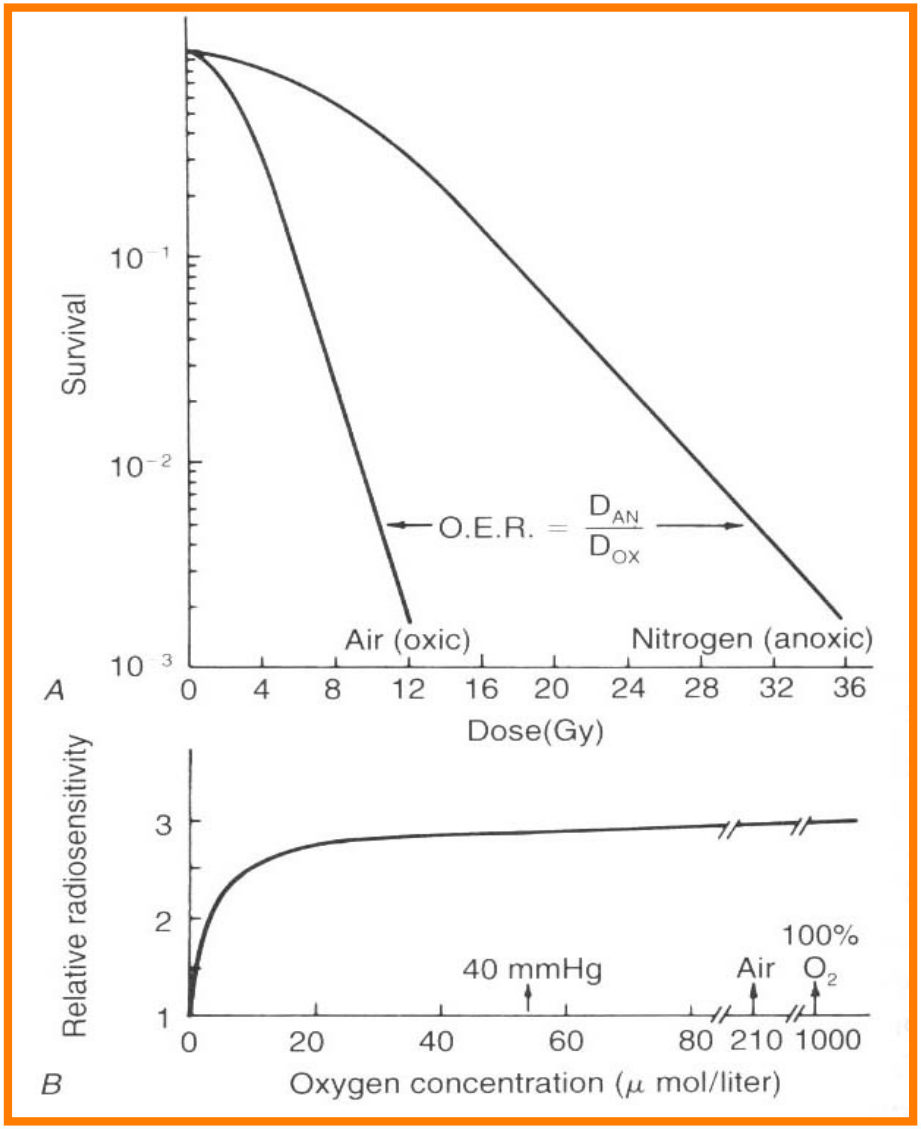
  late S > early S > G_1 > G_2 > M
- checkpoints arrest cell cycle at phase boundaries
- correlates to some extent with 'sulphydryl' levels
- accurate repair *(homologous recombination)* more in S, inaccurate repair *(non-homologous end-joining)* more in G2
- sensitivity variations smaller with high LET
- re-assortment: implications for dose fractionation

Dose rate effect



Oxygen effect



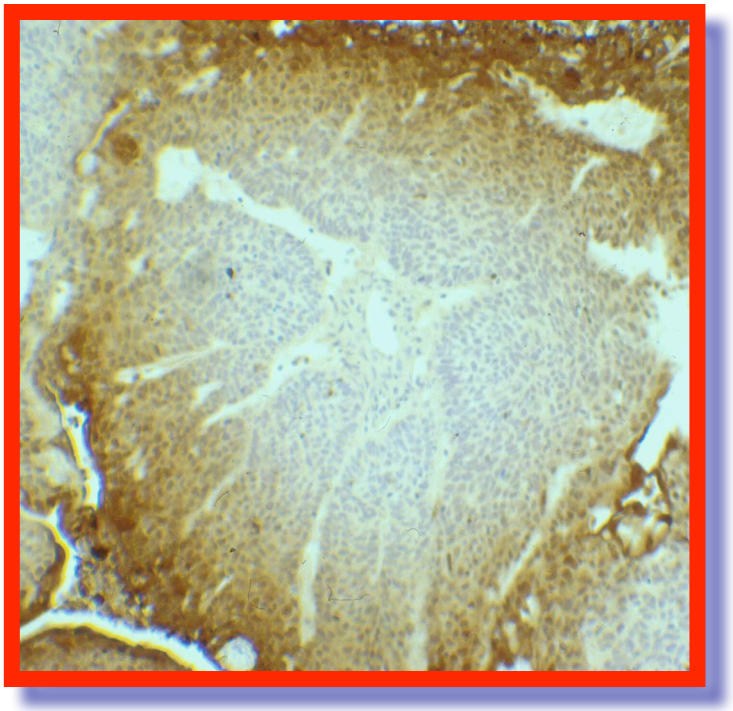


Oxygen enhancement ratio (OER)

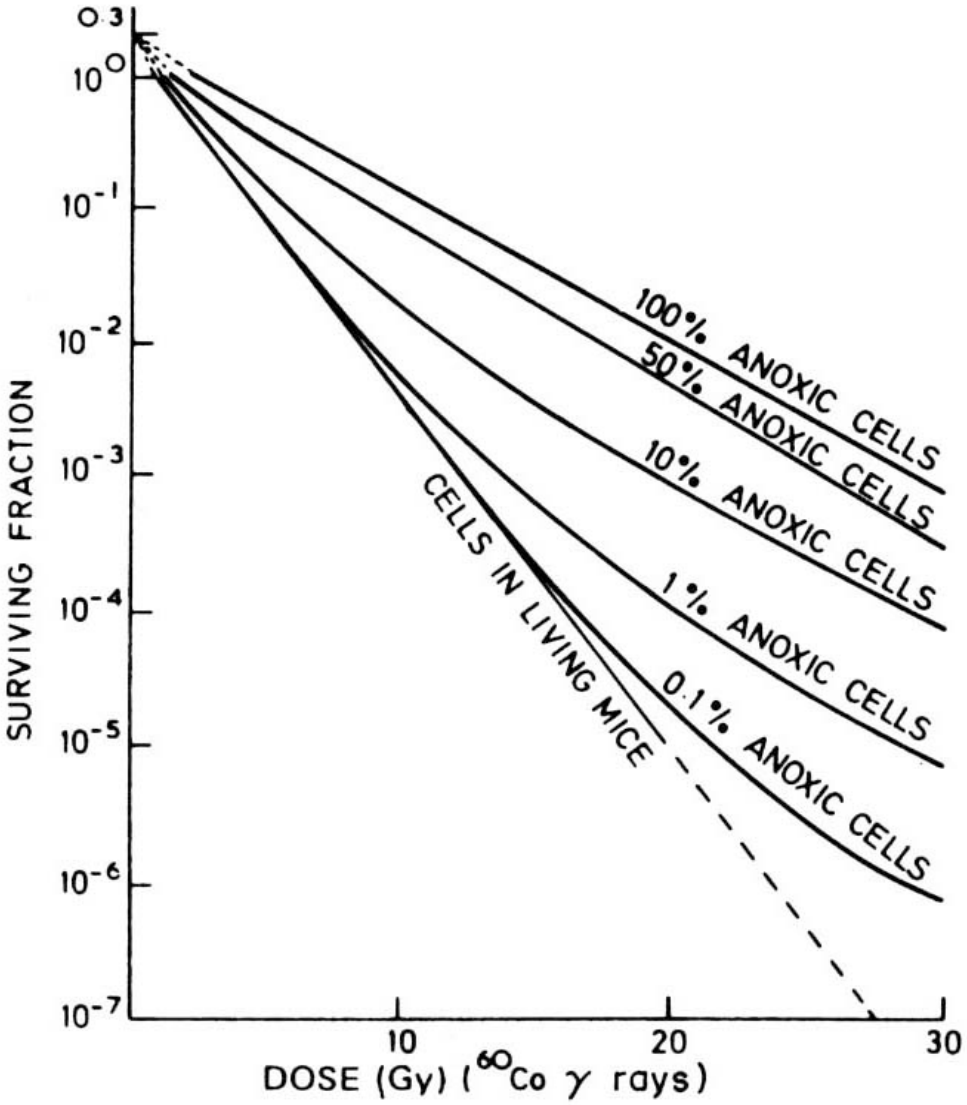
OER: Ratio of doses in hypoxic or oxic conditions required to achieve the same biological effect

- oxygen needs to be present at the time of the irradiation
- more damage in the presence of oxygen
  - free radicals and oxygen fixation process
- typical OER value for mammalian cells ~ 2 - 3 after low LET radiation
- OER reduced with high LET since less 'indirect' action
- concentration of oxygen important
  - rapid change between 0–0.5%, > 2% indistinguishable from 20%
  - important in tumours. Increasing oxygen concentration (hyperbaric) reduces hypoxia
  - radiosensitisers and cytotoxic bioreductive drugs reduce the effect of hypoxia

Hypoxic cells in tumours



Courtesy of Catharine West



Evidence for hypoxic cells in tumours

- Improvements in control with hyperbaric oxygen for cervix (Watson 1978, Br J Radiol 5:879) and bronchus (Dische 1978, Br J Radiol 51:888) tumours.
- Improvements in control with hypoxic cell radiosensitizers.
- Direct measurements of lower oxygen tensions in tumours and correlations with outcome.

Locoregional control and modification

	No. of trials	No.of patients	XRT + modifier (%)	XRT alone (%)	p
HBO / Oxygen	19	2488	62	53	<0.0001
Sensitiser	38	5422	46	42	0.004
Transfusion	1	135	84	69	0.05

Overgaard 1994

Nimorazole in head and neck cancer

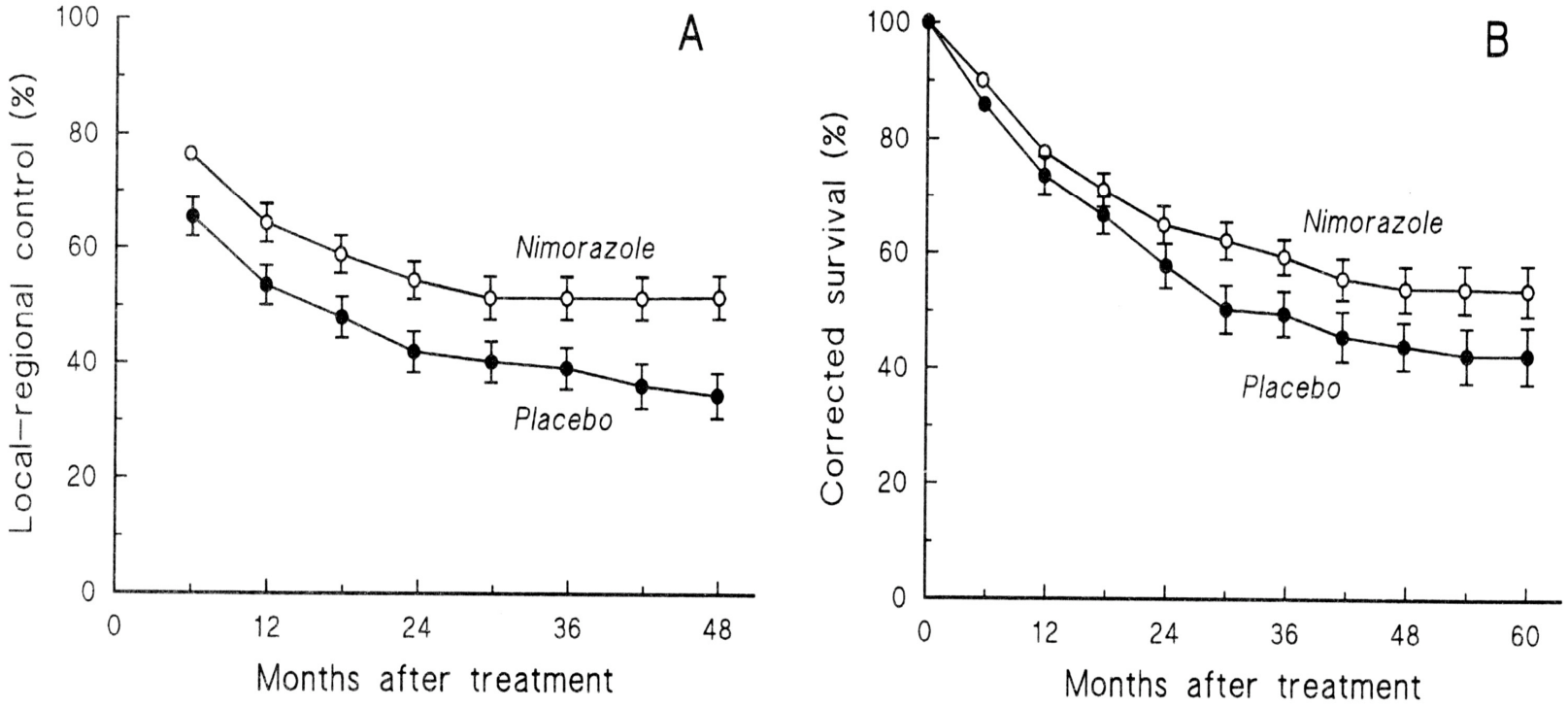


Figure 16.5 Results from the DAHANCA 5 study. Actuarial loco-regional tumour control (**A**) and corrected survival (**B**) in patients randomized to receive nimorazole (219 patients) or placebo (195 patients) in conjunction with radiotherapy for carcinoma of the pharynx and supraglottic larynx. From Overgaard *et al* (1991, 1992), with permission.

Sublethal damage repair (SLD)

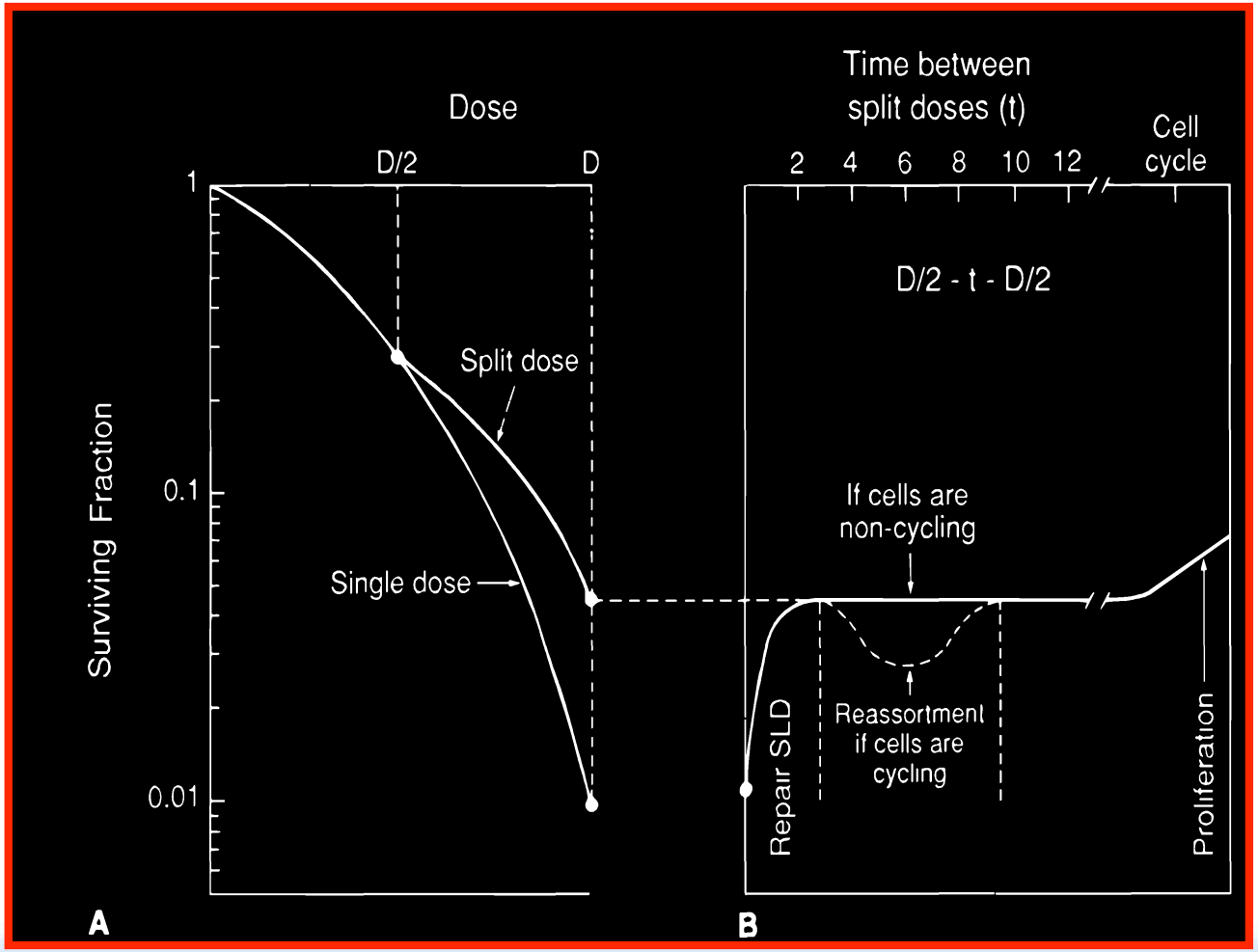
First described by Elkind and colleagues:

- operational term for the increase in survival when radiation dose is divided into fractions
- gives increase in radioresistance owing to increased time for repair
- the recovery of sublethal damage reflects the "repair" of DNA damage before sublethal lesions can interact to form lethal lesions
- significant for low LET (x-rays) but insignificant for high LET

Half-time of repair is about 1 hour *in vitro*, can be longer (biphasic) *in vivo*

Sublethal damage (SLD) repair

repair of sublethal damage as demonstrated by split-dose experiments



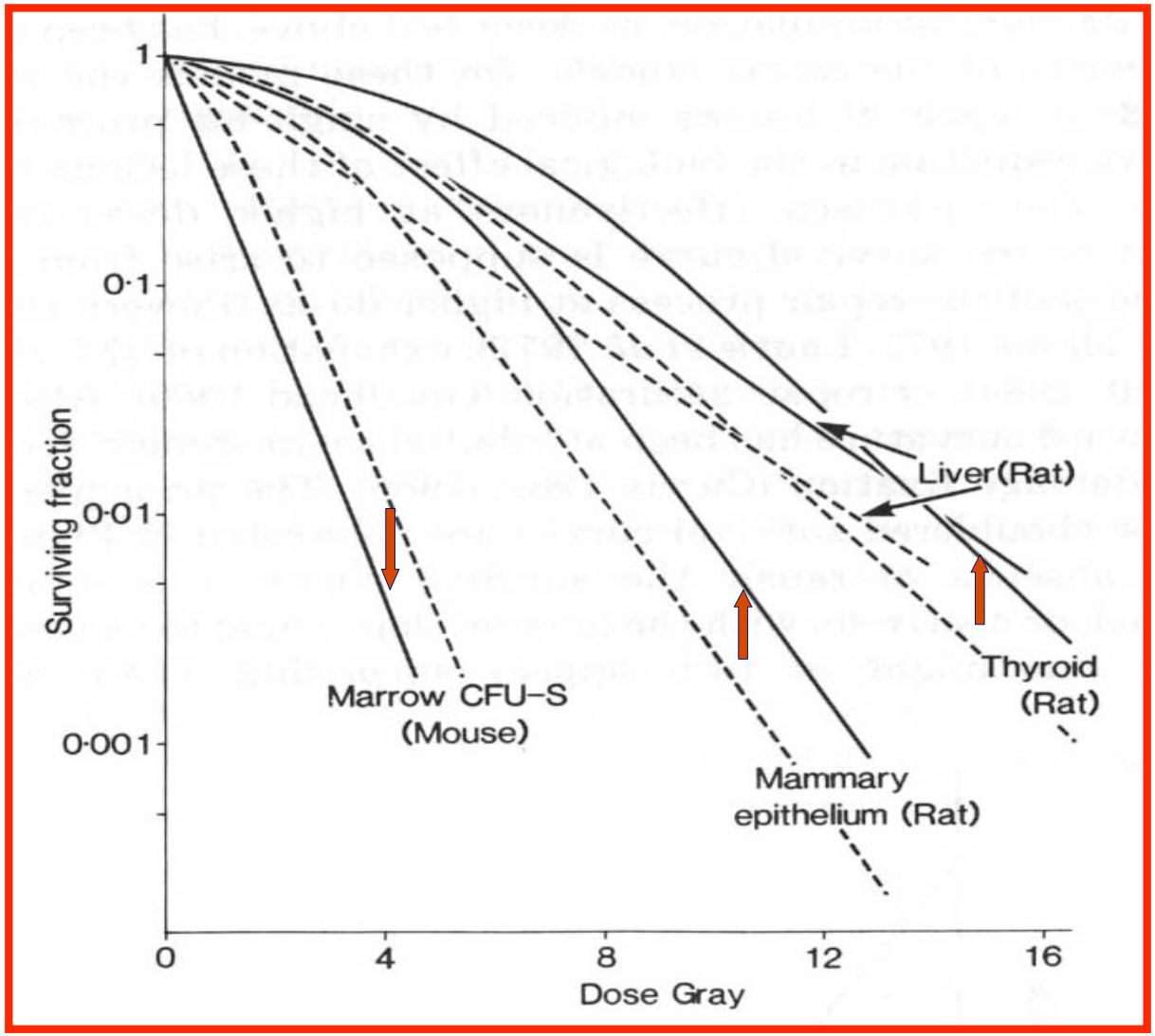
Potentially Lethal Damage (PLD)

the component of radiation damage modified by post-irradiation conditions

First demonstrated by Little and colleagues:

- **measured by an increase in survival**
- **varying the post-irradiation conditions influences survival**
- **if division (mitosis) is delayed, damage can be repaired and not fixed**
- **significant for low LET (x-rays) but insignificant for high LET**
- **suggestion that resistant tumours have large capacity for PLD repair**

Repair of PLD



Definitions

Sublethal damage - nonlethal injury that can be repaired or accumulate with further dose to become lethal.

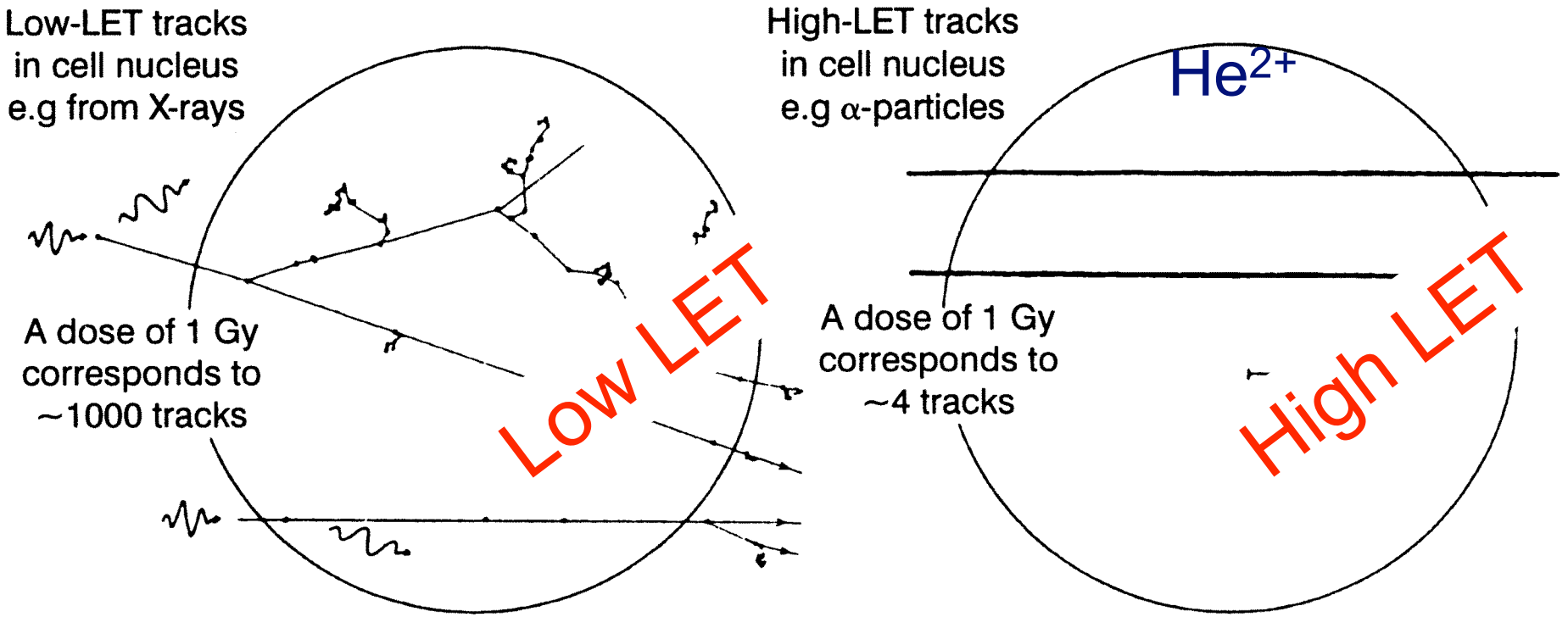
Potentially lethal damage - injury which can be repaired in the radiation-free interval between irradiation and mitosis, and is lethal if not repaired.

Slow repair - long-term recovery which takes place on a time scale of weeks to months, often associated with long-term intracellular repair.

Linear Energy Transfer LET: Principles

- Linear Energy Transfer (LET, unit is keV/µm) is the average rate at which charged particles deposit energy in matter along their path.
- For radiation producing secondary charged particles of variable energy, average LET values are used.
- LET is not constant along the path of a charged particle. Near the end of its path, energy deposition is much more concentrated (Bragg peak).
- LET influences the seriousness and repairability of biological damage.

Track structure and Microdosimetry



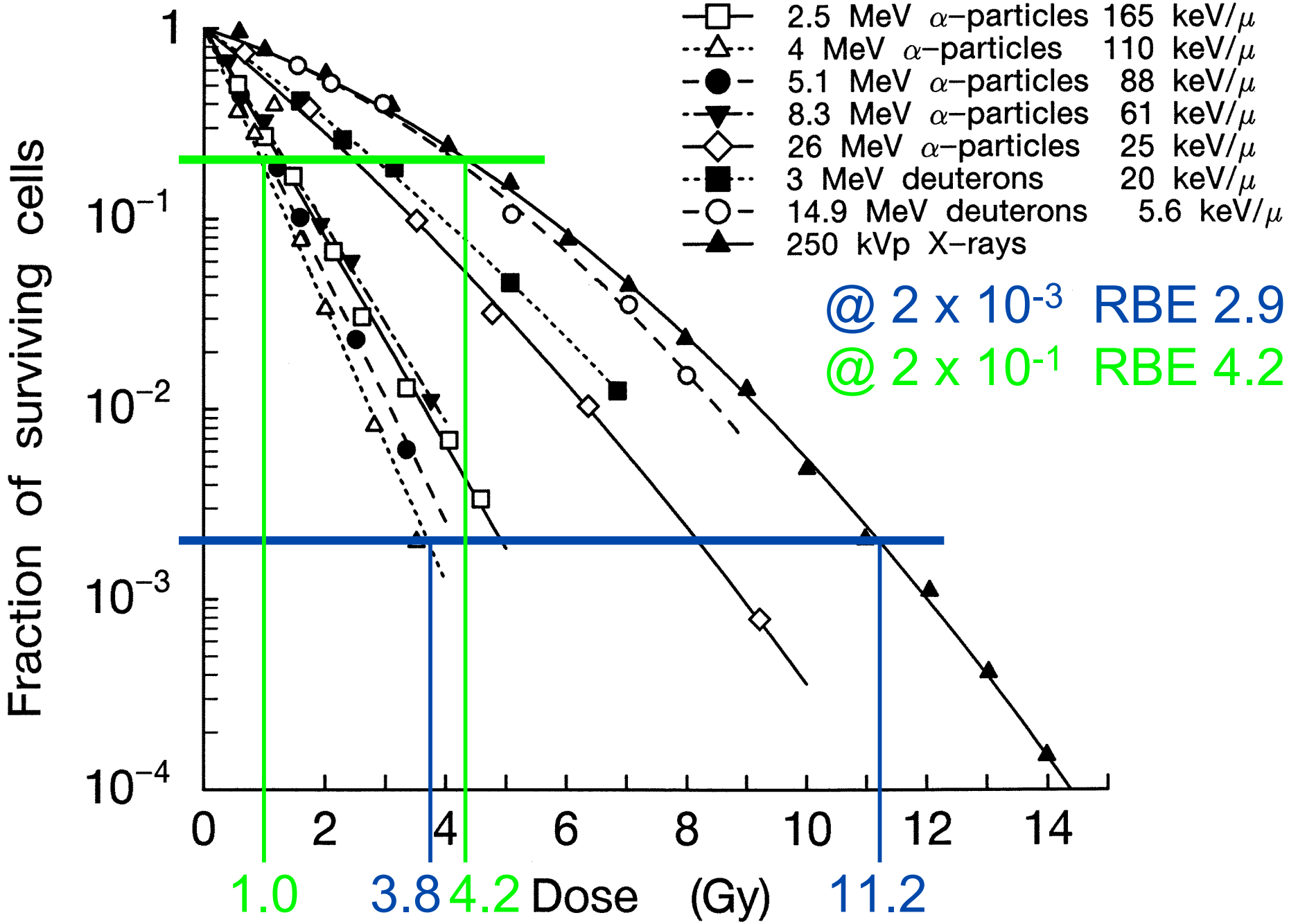
LET: Linear Energy Transfer.

A measure of track average ionization density.

This section adapted from Joiner in ESTRO Steel book.

Direct action of radiation

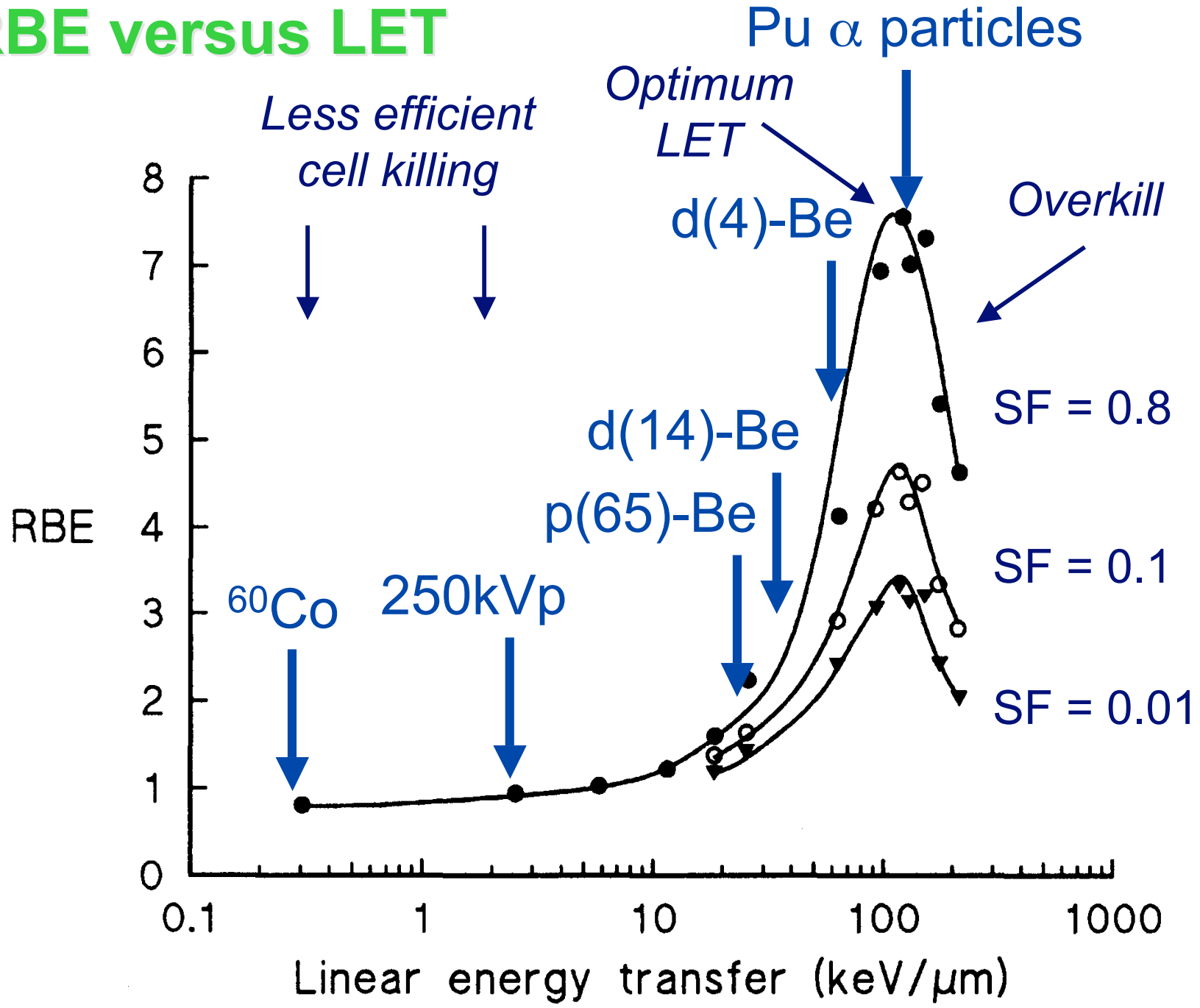
- 40% of the total damage is from direct action with low LET radiations
- Direct is main mode of action for high LET radiation
- High LET radiations interact predominately with nuclei
  - setting in motion more protons and other heavier nuclear particles
  - smaller particles (electrons) are produced which cause indirect damage but this is less significant c.f. direct action
- Direct action not modified by sensitizers or protectors


2.5 MeV α–particles 165 keV/μ
4 MeV α–particles 110 keV/μ
5.1 MeV α–particles 88 keV/μ
8.3 MeV α–particles 61 keV/μ
26 MeV α–particles 25 keV/μ
3 MeV deuterons 20 keV/μ
14.9 MeV deuterons 5.6 keV/μ
250 kVp X–rays
@ 2 x 10-3 RBE 2.9
@ 2 x 10-1 RBE 4.2
Fraction of surviving cells
1
10−1
10−2
10−3
10−4
0
2
4
6
8
10
12
14
1.0
3.8
4.2
Dose (Gy)
11.2

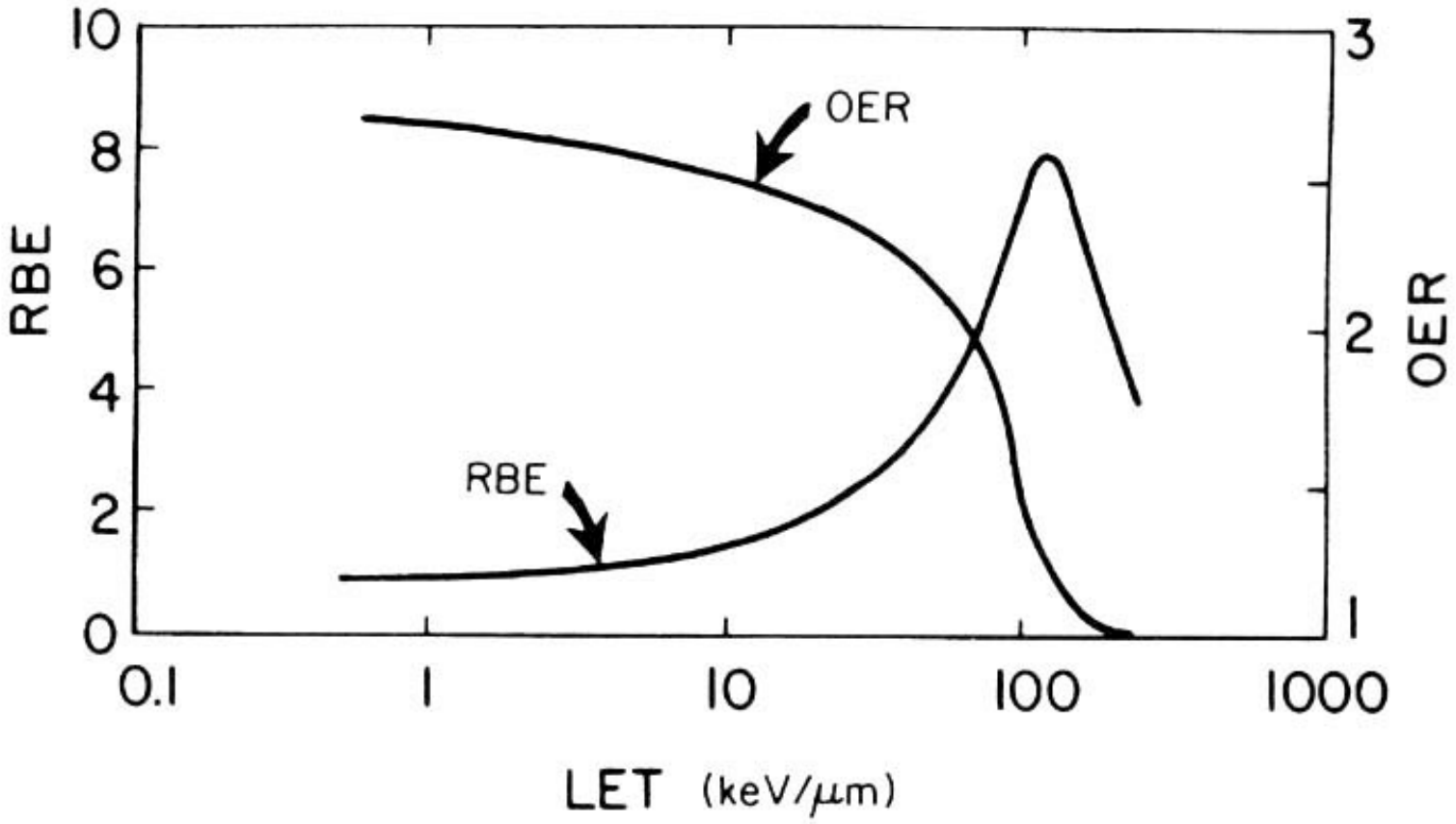
Relative Biological Effectiveness (RBE)

- **Defined against γ-rays:**
  The RBE of some test radiation (r) compared with γ-rays is defined as the ratio $D\gamma/D_r$, where Dγ and D_r, are, respectively, the doses of γ-rays and test radiation required for equal biological effect
- **RBE dependent on LET:**
  Overkill effect at very high LET
- **RBE larger at smaller doses:**
  Reflects the different shapes of low and high LET radiation survival curves
- **RBE varies with dose per fraction for high LET:**
  Reflects the lack of 'shoulder' on the survival curve (less beta)
- **High-LET RBE larger at low dose rate:**
  Effectiveness of high LET not reduced (little beta), compared to low LET radiation at lower dose rate
- **RBE dependent on cell and tissue type:**
  Higher for cells and tissues with high repair capacity

RBE versus LET

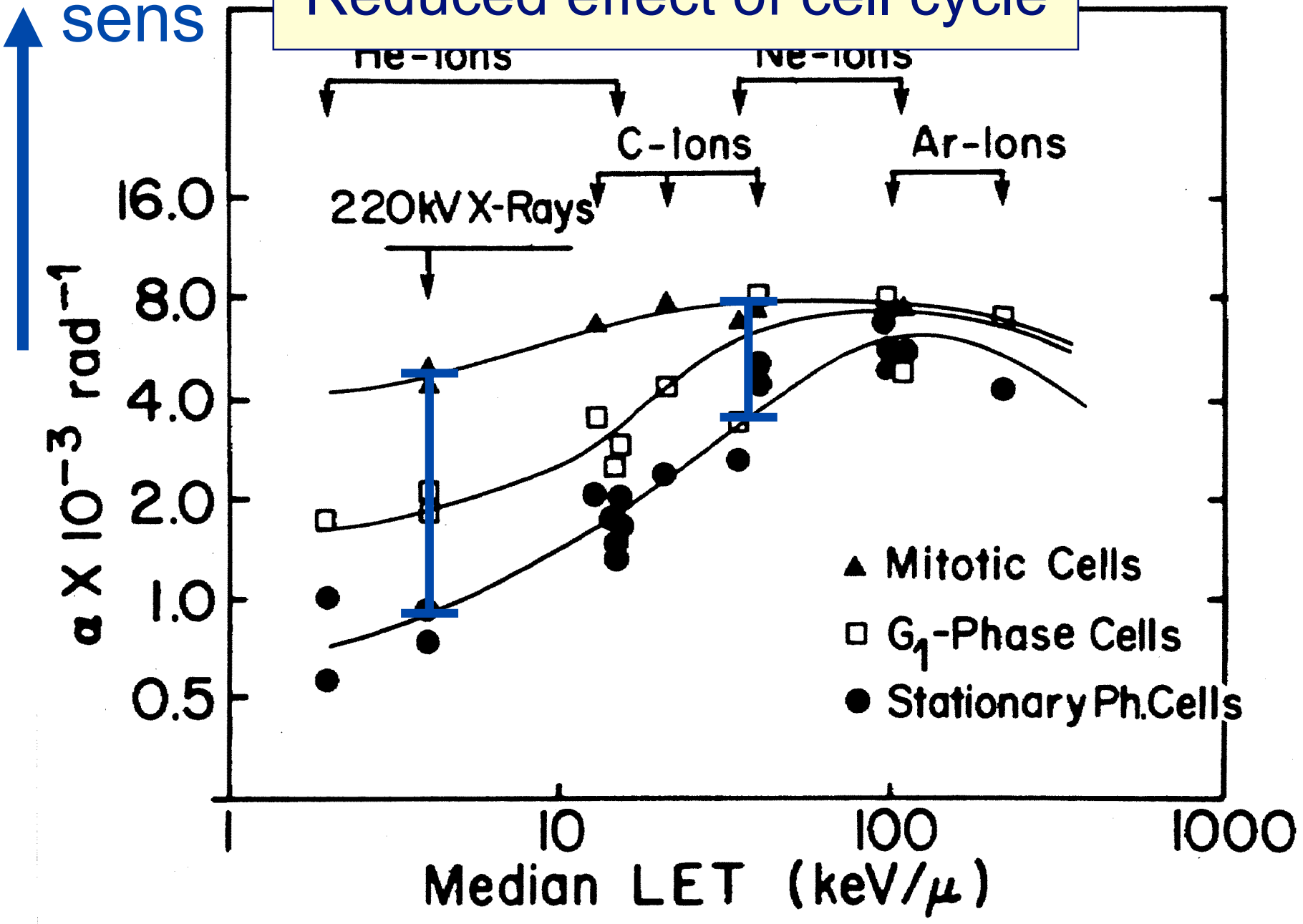


RBE and OER



The oxygen enhancement ratio is 2.5 - 3 for X-rays but decreases with LET to about 1.5 for neutrons and 1.0 for alpha particles.

Reduced effect of cell cycle



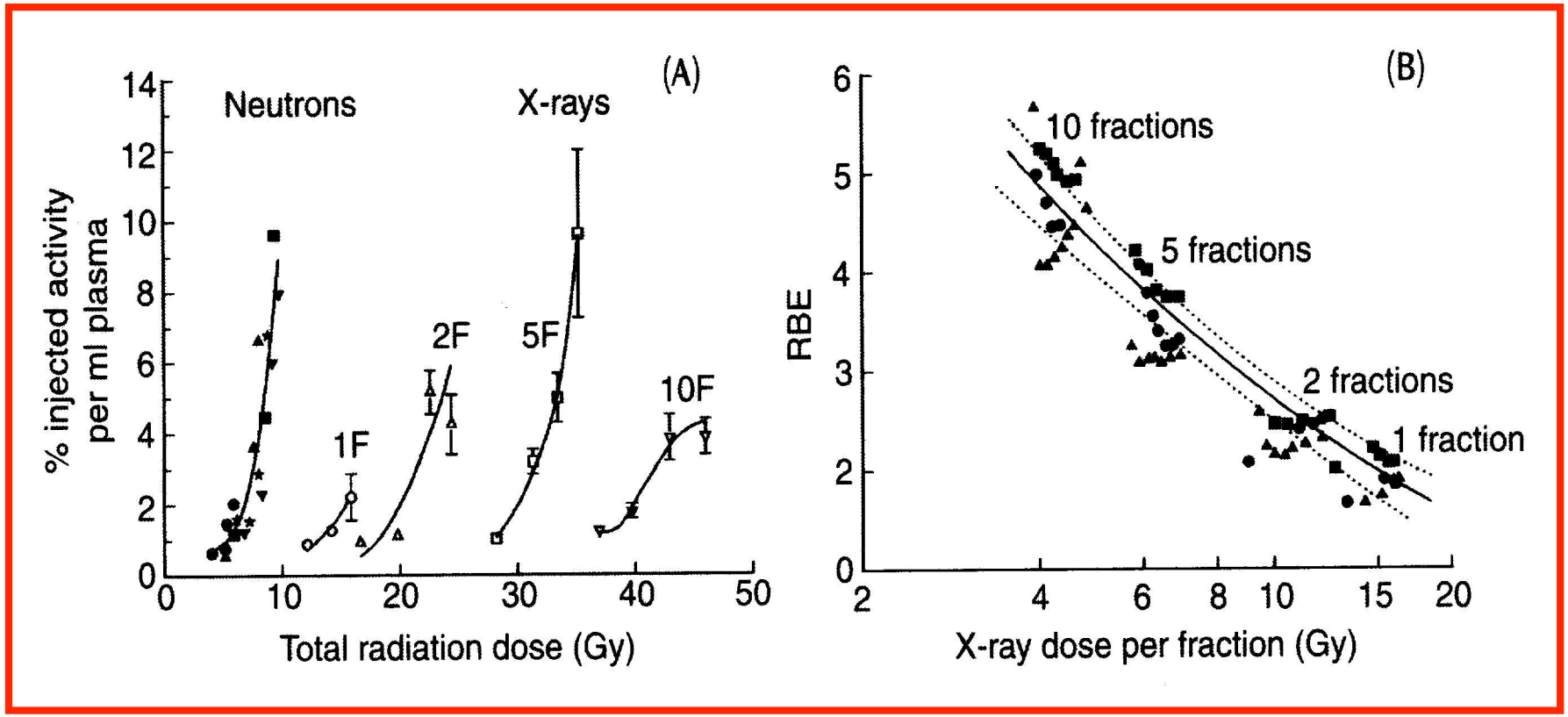
Definitions

- LET (Linear energy Transfer) - the rate of energy loss along the track of an ionising particle of specified energy (keV/micron).

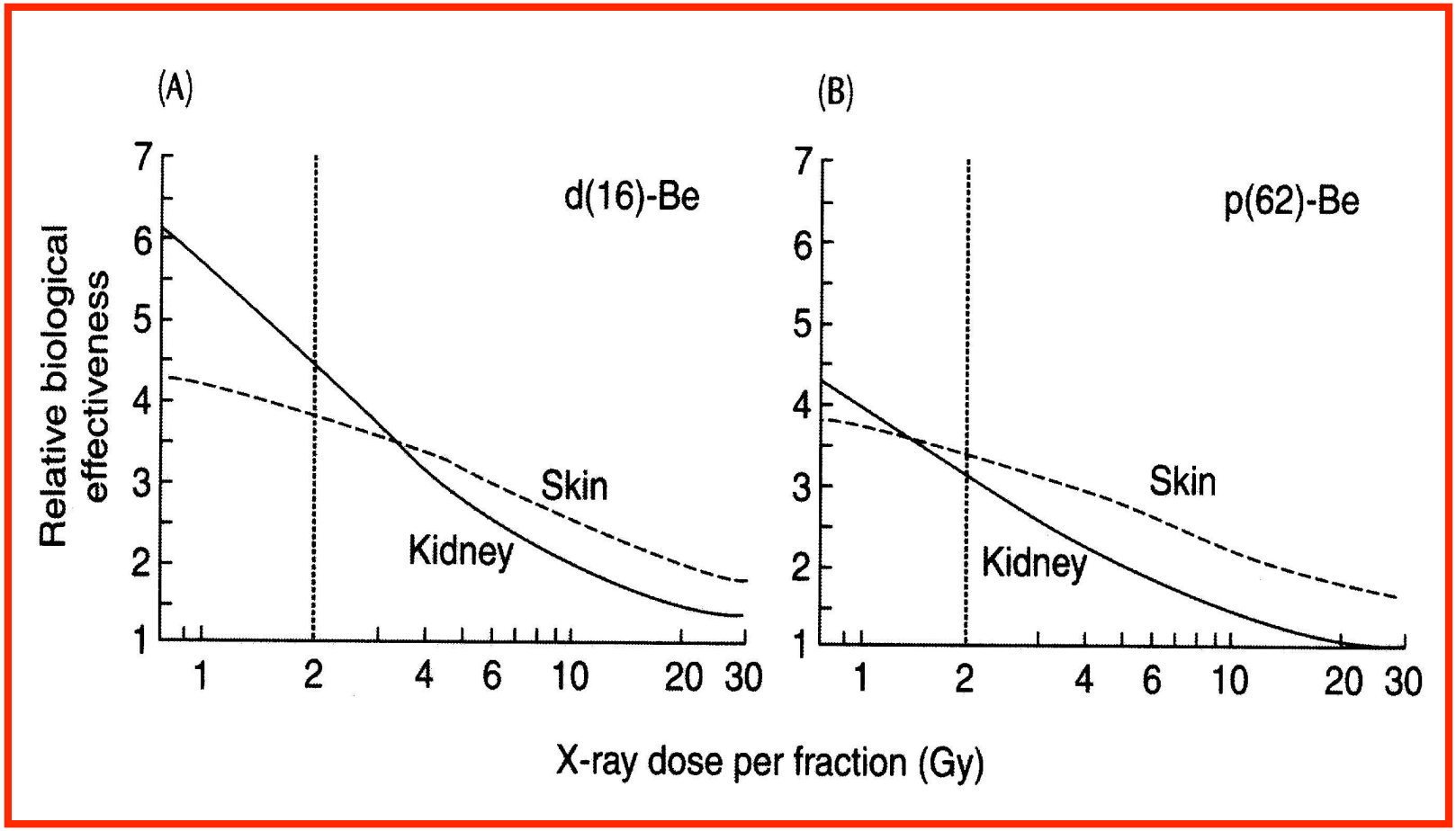
- RBE (Relative Biological Effectiveness) - the ratio of doses of a reference radiation quality and a test radiation type that produce equal effect.

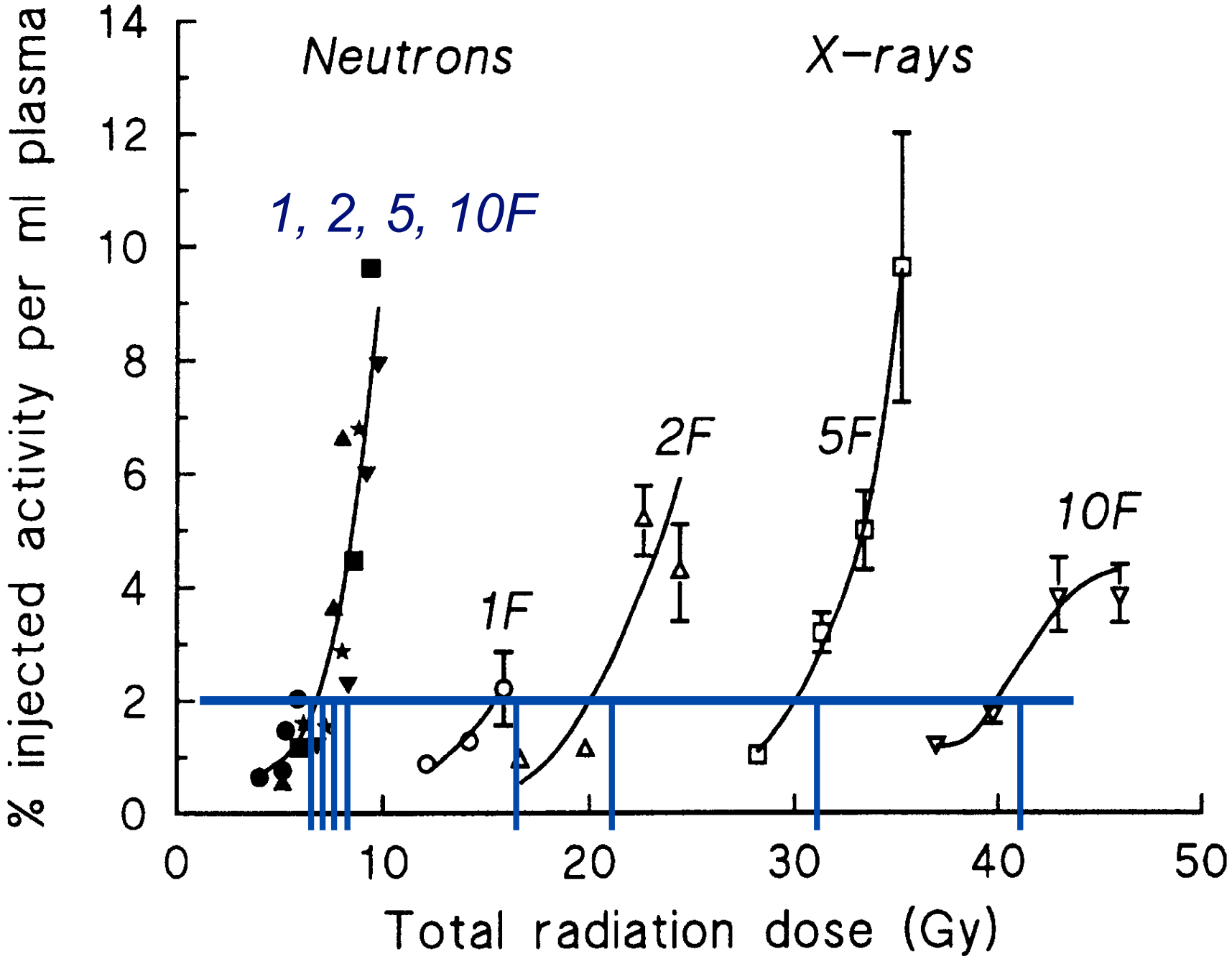
- OER (Oxygen Enhancement Ratio) - the ratio of dose given under anoxic conditions and the dose resulting in the same effect when given under oxic conditions.

RBE for kidney damage versus dose per fraction

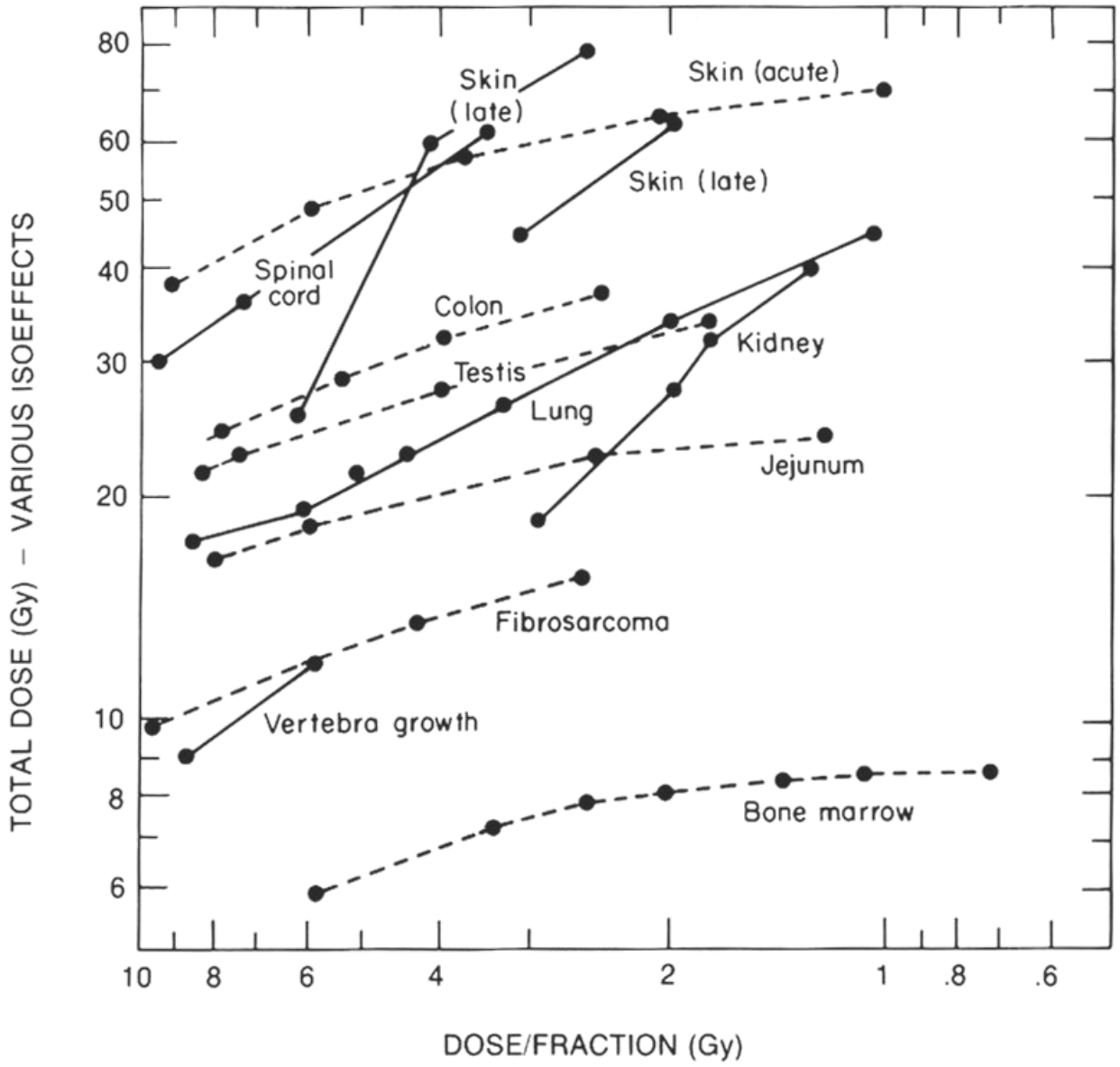


Neutron RBE and dose per fraction



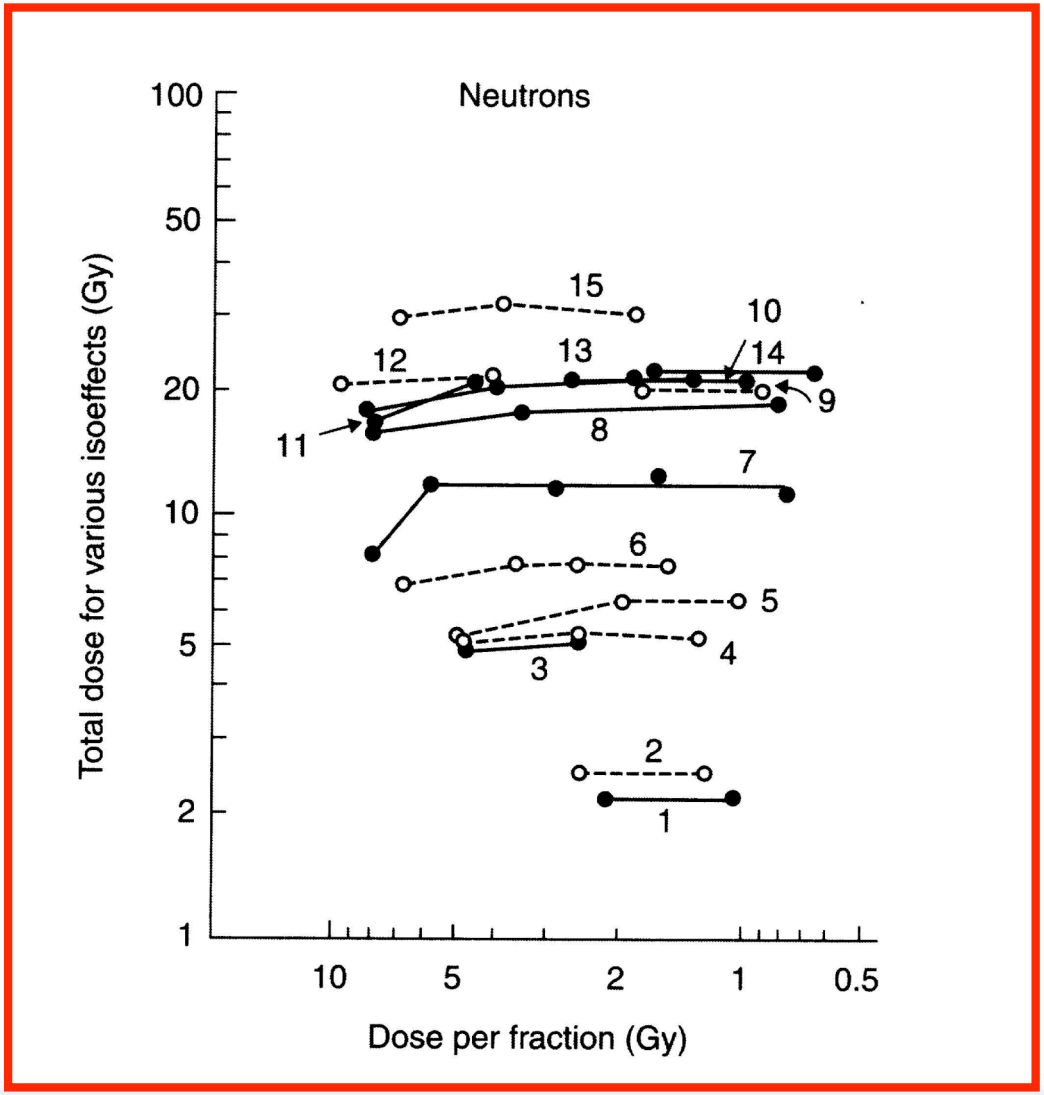

Neutrons
X-rays
1, 2, 5, 10F
1F
2F
5F
10F
% injected activity per ml plasma
Total radiation dose (Gy)
0
2
4
6
8
10
12
14
0
10
20
30
40
50

Iso-effective doses - Photons

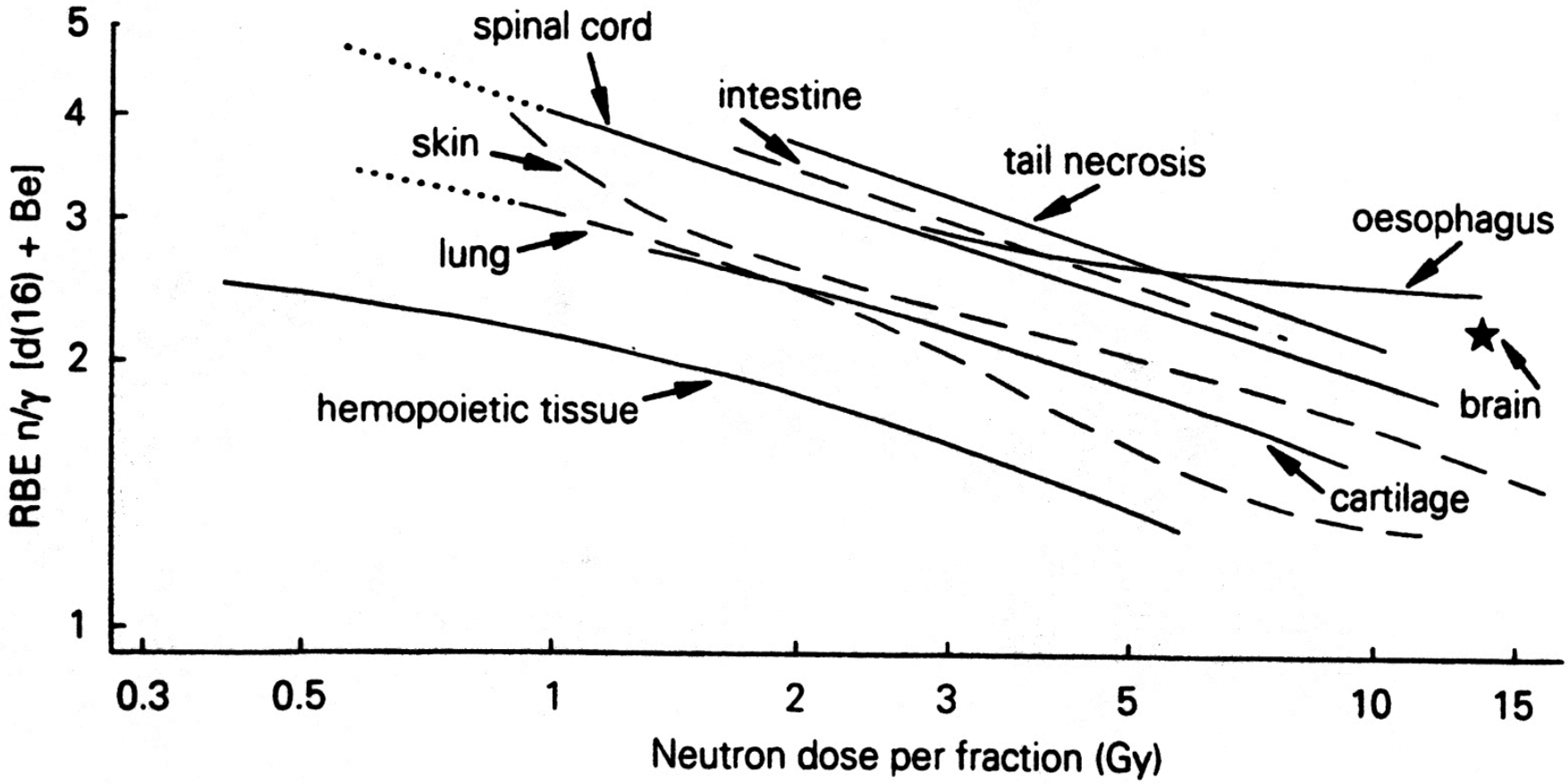


Agency

Iso-effective doses - Neutrons



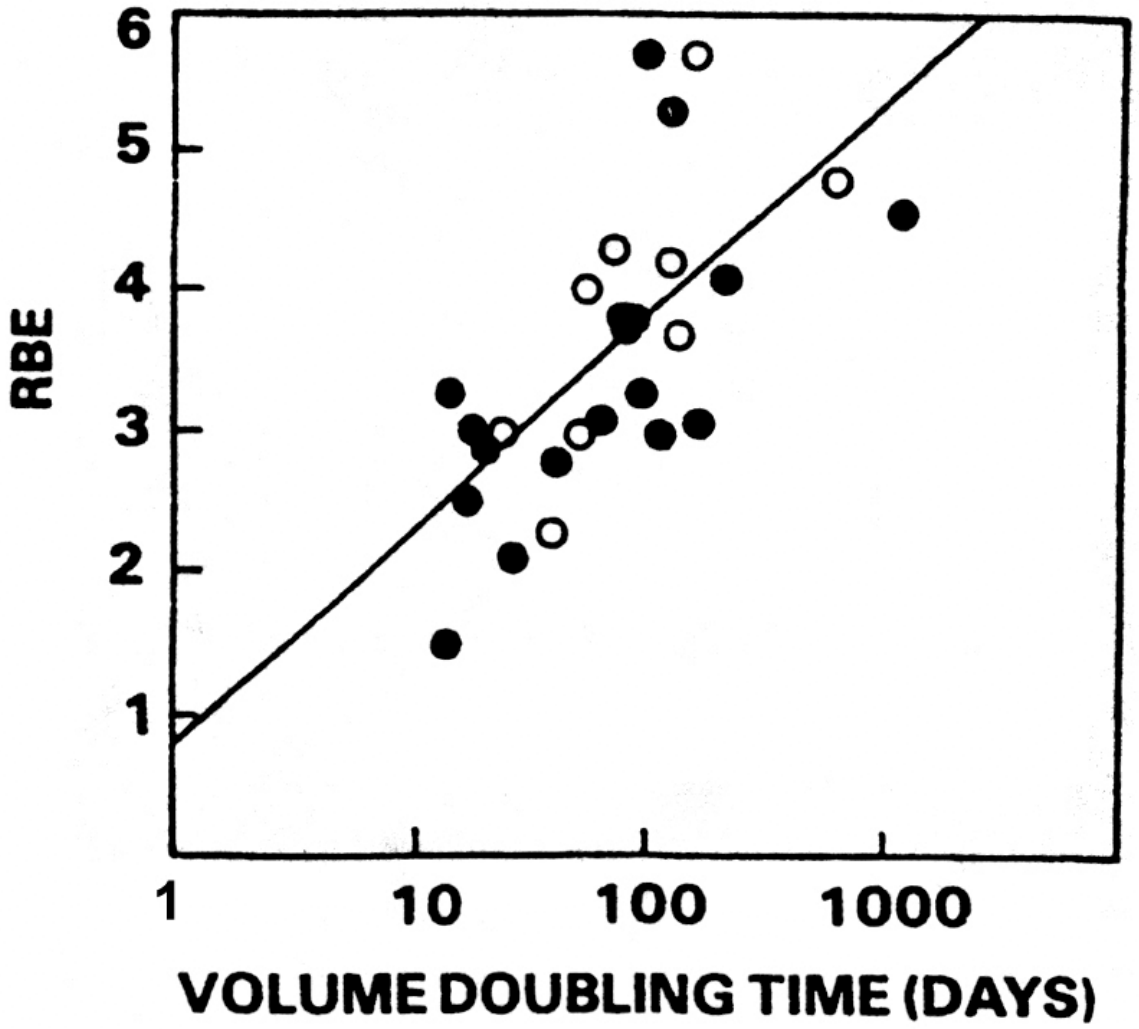
RBE vs neutron dose per fraction



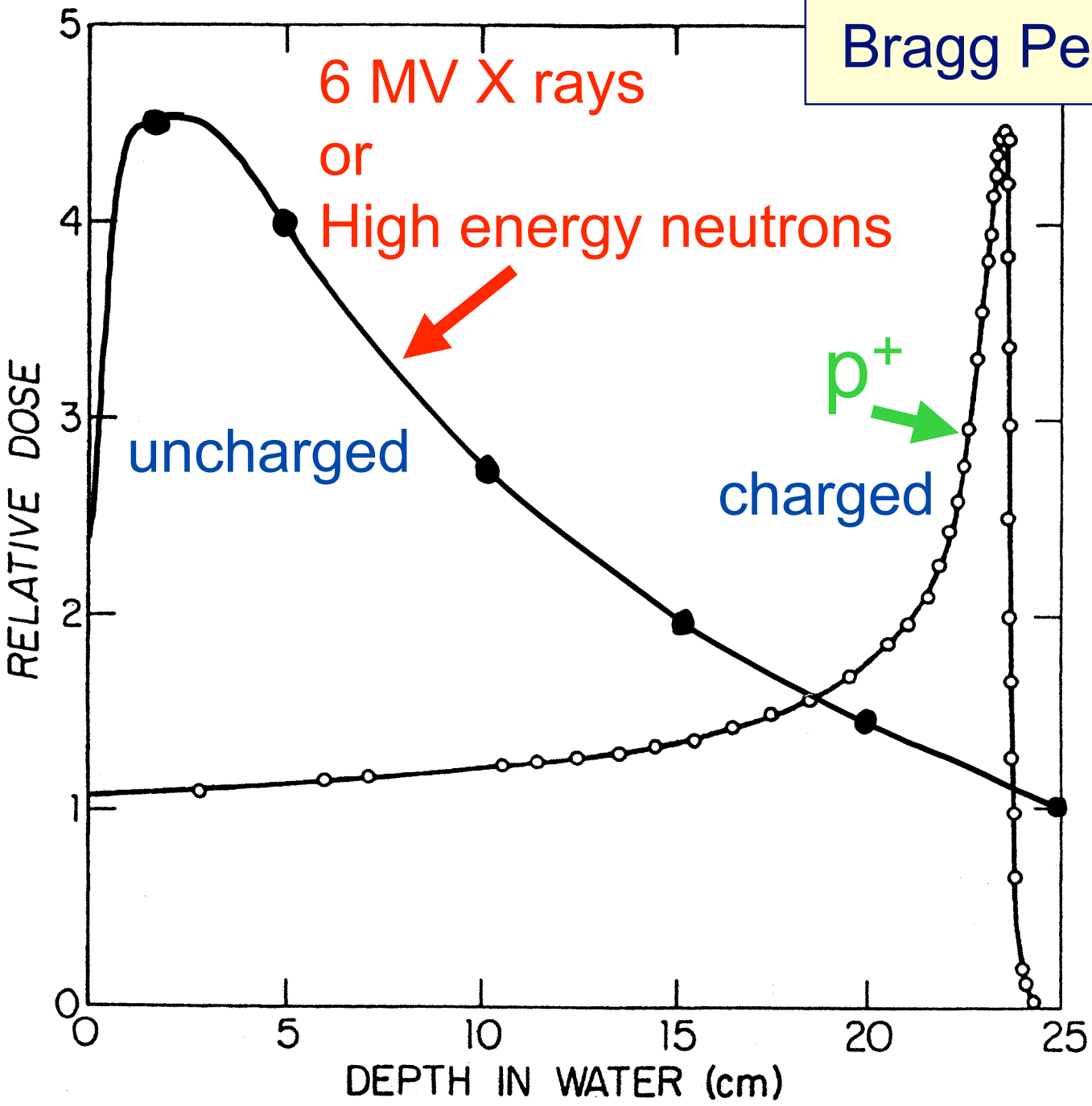
Biological basis for high-LET therapy

- Reduced range of radiosensitivity
- Reduced influence of oxygen
- Reduced influence of cell cycle
- But! – unfortunately, differential in early and late reactions also reduced

RBE of neutrons for regression of lung metastases (Batterman et al 1981)



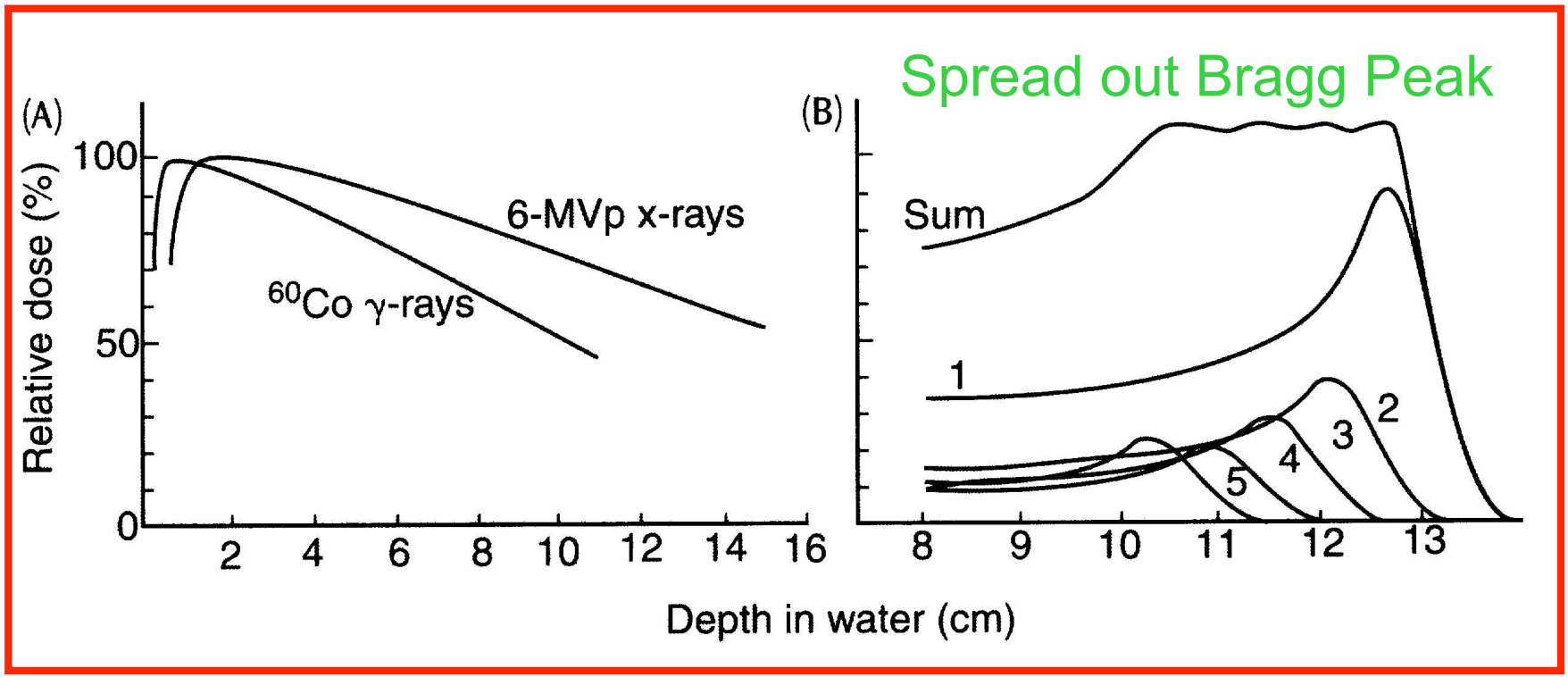
Bragg Peak


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

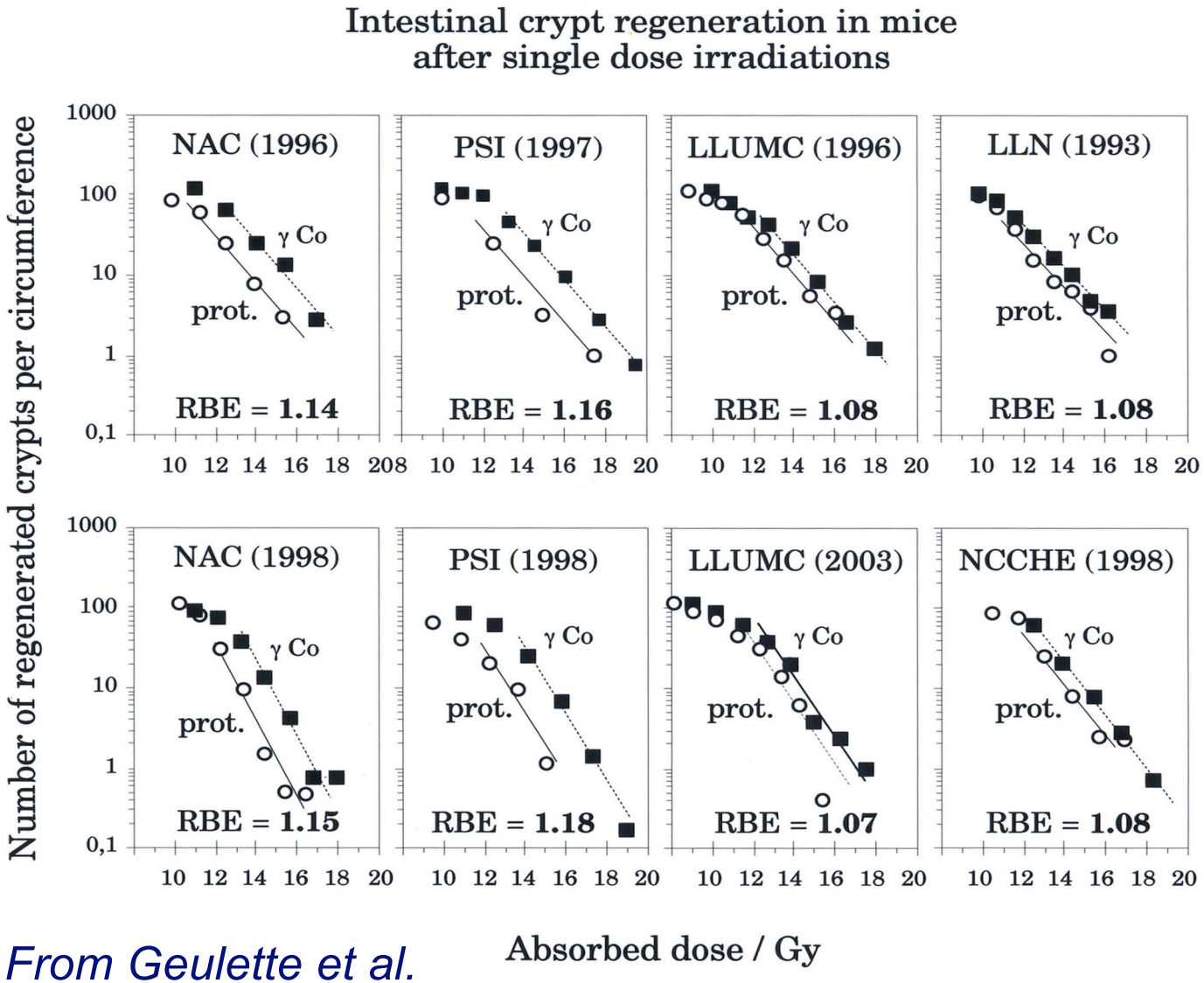
Depth-dose curves

Photons

Protons



Intestinal crypt survival after single doses

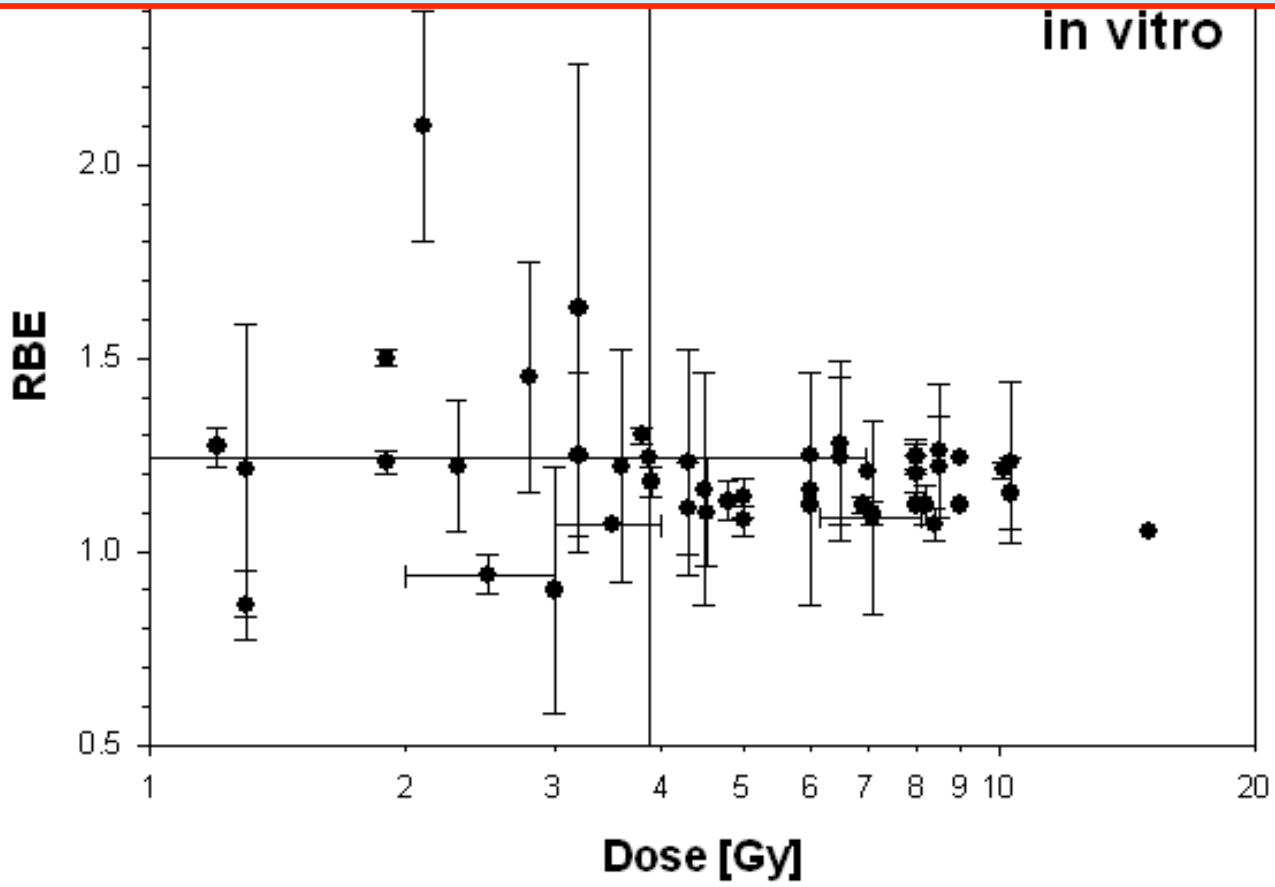


From Geulette et al.

Relative biological effectiveness (RBE) values for proton beam therapy.

Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD.

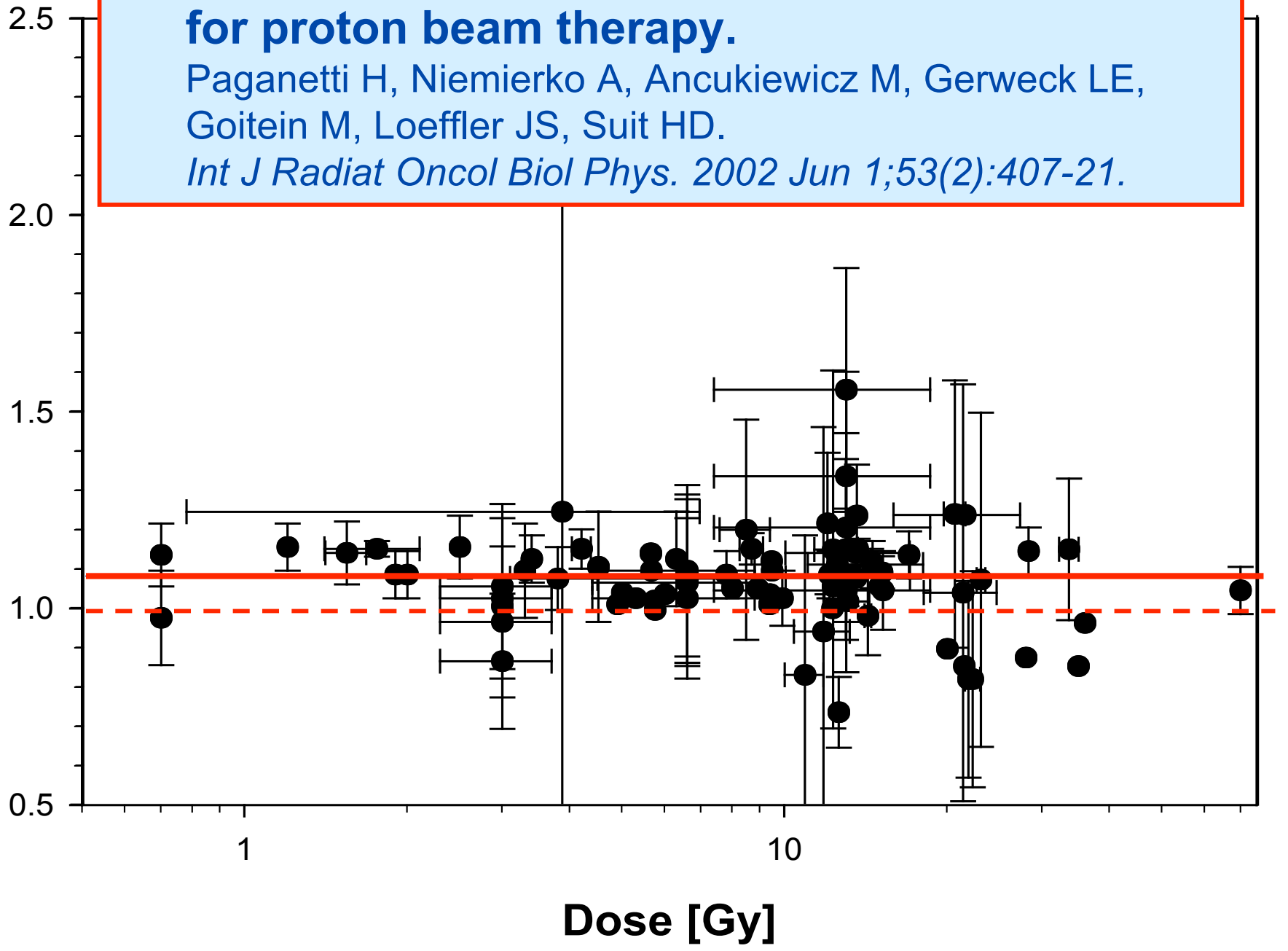
Int J Radiat Oncol Biol Phys. 2002 Jun 1;53(2):407-21.



Relative biological effectiveness (RBE) values for proton beam therapy.

Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD.

Int J Radiat Oncol Biol Phys. 2002 Jun 1;53(2):407-21.



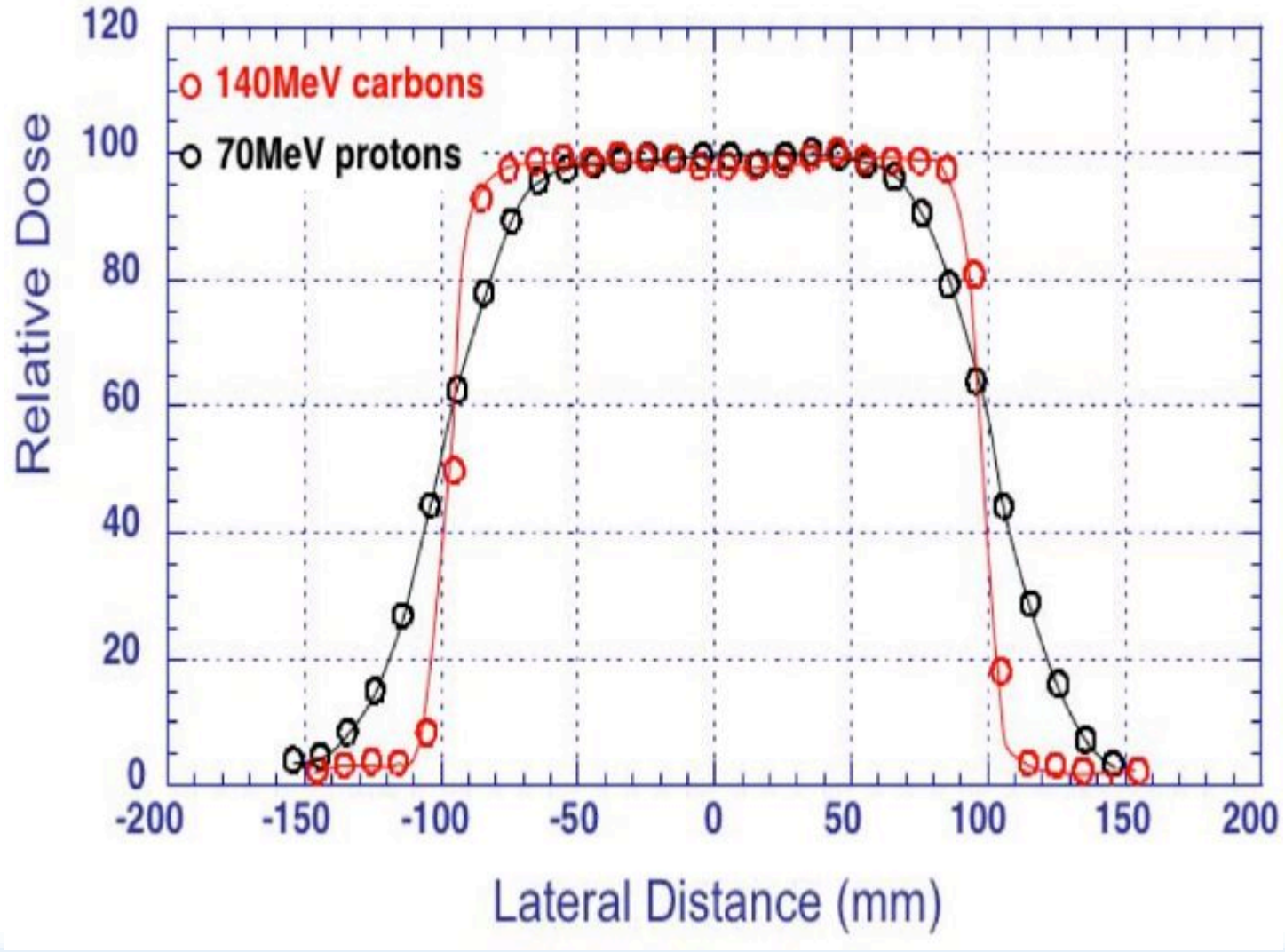
Patient Selection for Protons

- Well delineated tumours
- Tumours near critical structures/organs

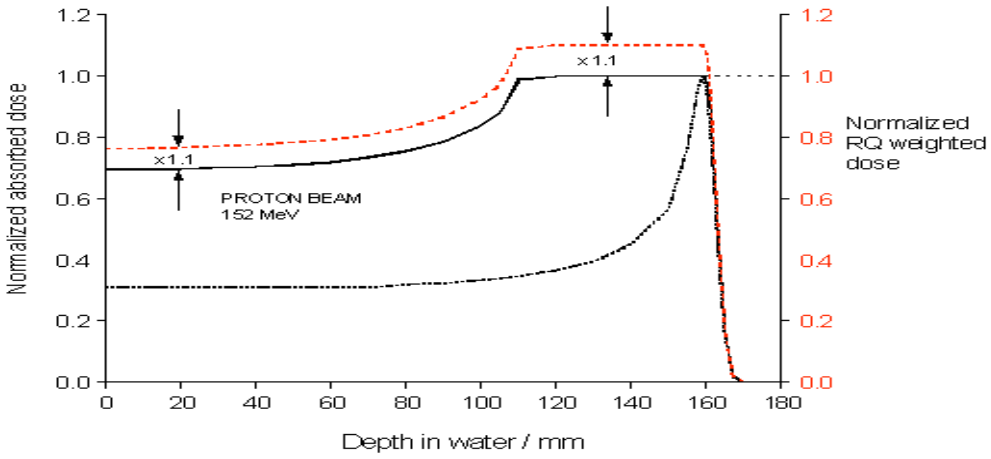
Patient Selection for Ions

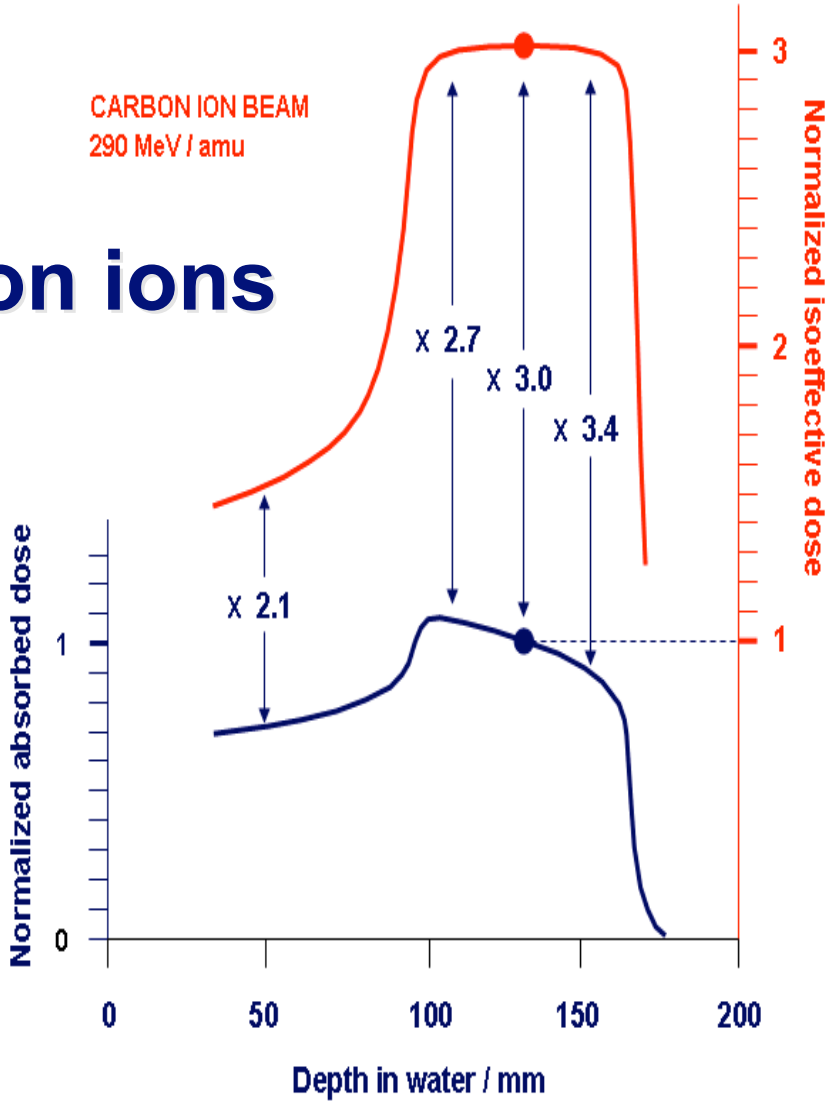
- Well delineated tumours
- Tumours near critical structures/organs
- Hypoxic tumours
- Very slow growing, high-repairing tumours

Carbon *vs* proton dose distributions

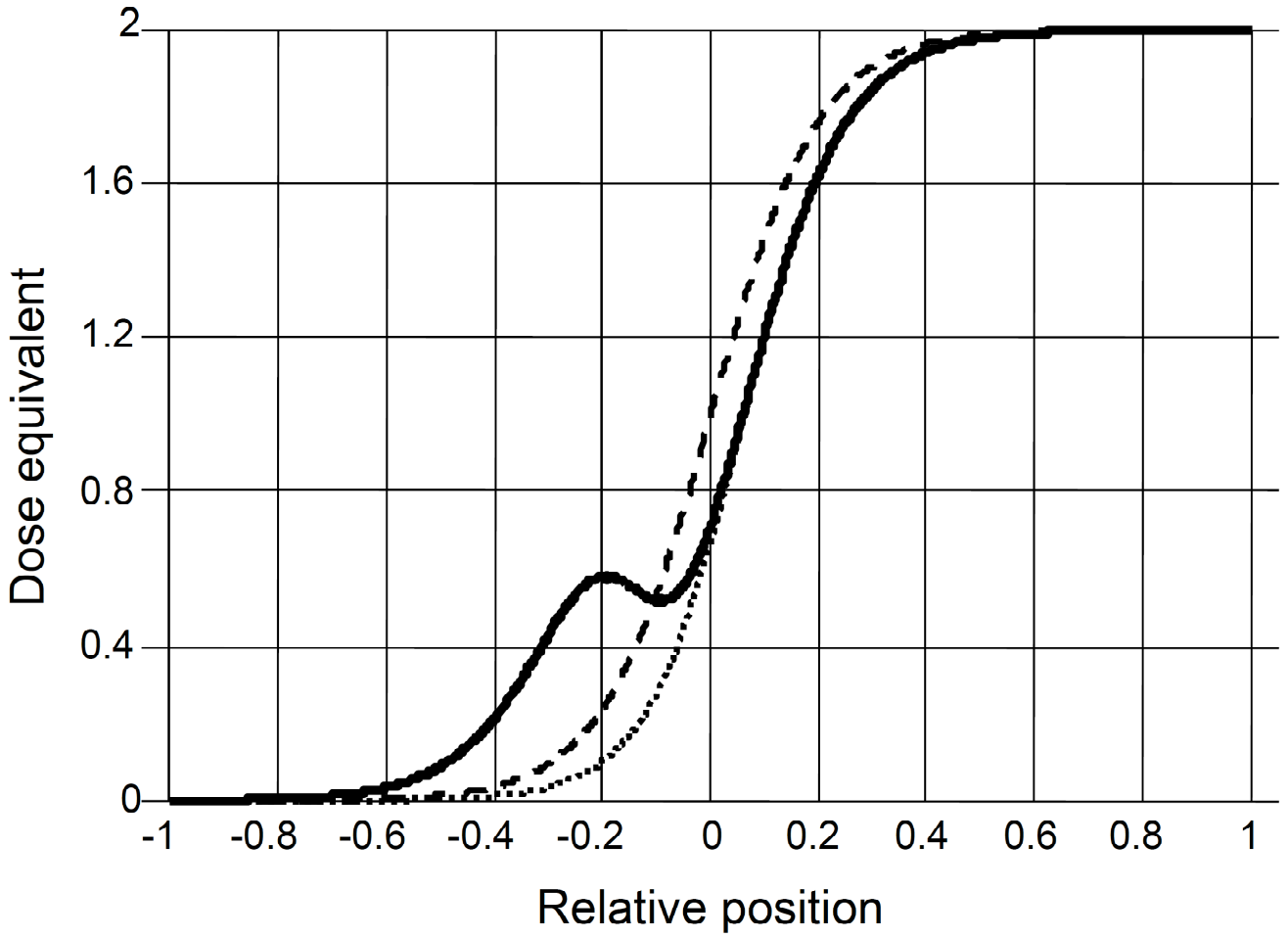


Protons *versus* Carbon ions





Dashed line = hypothetical physical dose transition from zero up to 2 Gy. Dotted line = “biological effective dose” (in equivalent 2-Gy fractions), based on LQ extrap. from high doses. Solid line = true “biological effective dose”, based on low-dose hyper-radiosensitivity (Joiner & Marples 2005)



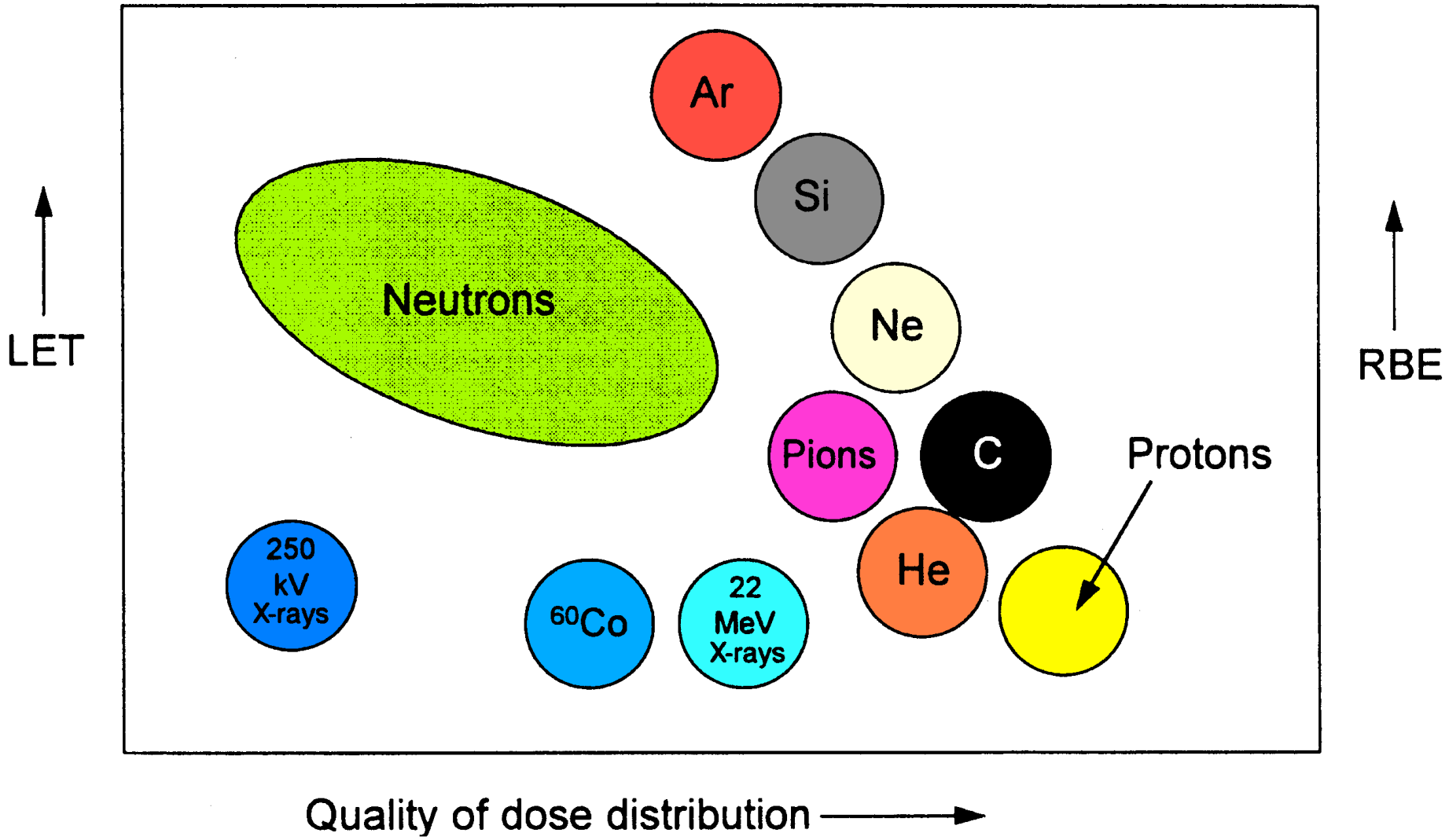
Edge effects

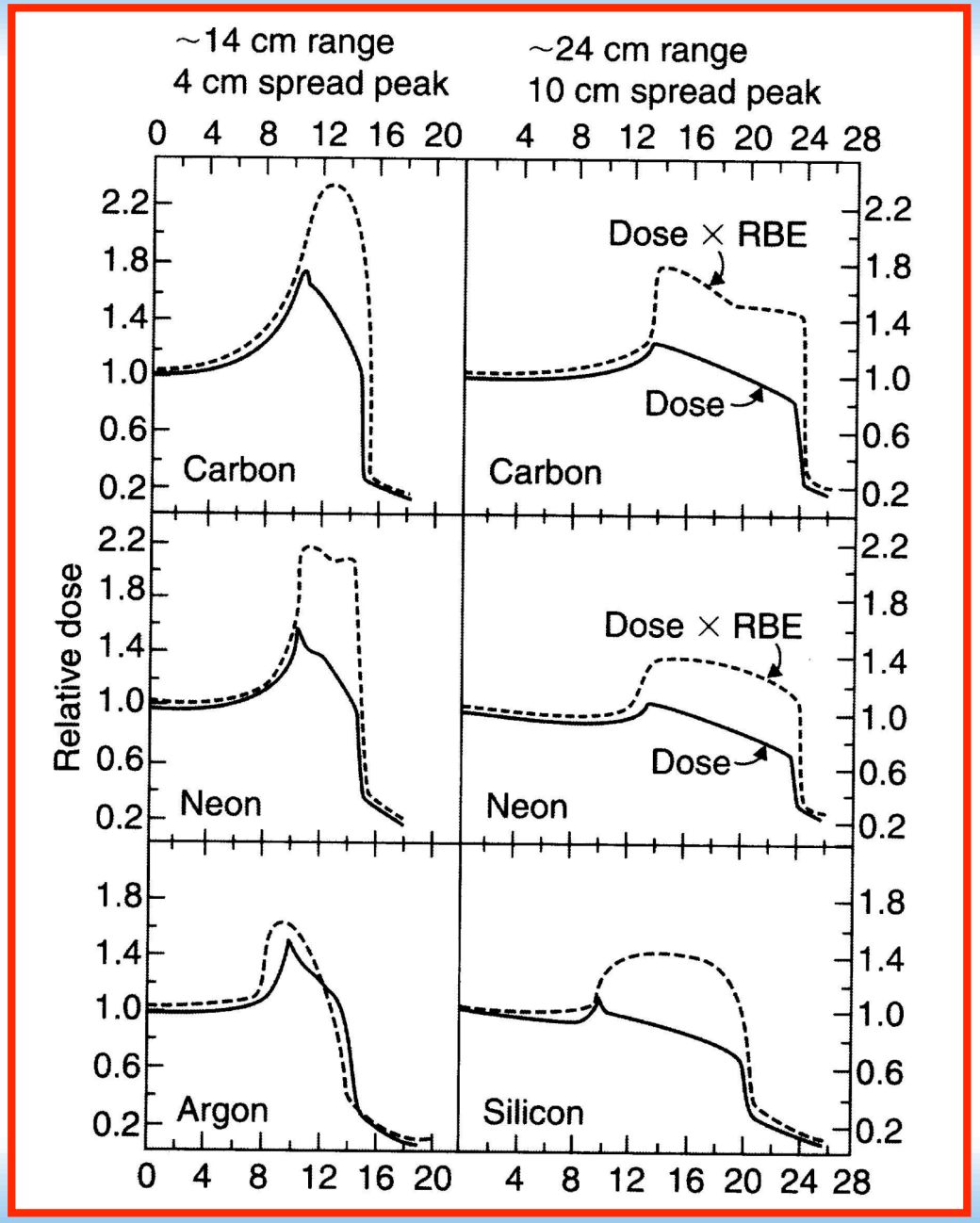
- **HRS:** If the high-LET dose to the target is chosen to be similarly effective to a low-LET treatment, then the edge of the field could be under-dosed.

- **Protons:** Most of the radiobiological data show an increase in RBE of 5-10 % (above the value 1.1) in the distal part of the spread-out Bragg peak (SOBP). Secondly, because of the significant increase in LET at the end of the proton tracks, the “biologically effective range” of the proton beam is increased in depth compared to the physical range. This increase reaches ~1-2 mm for ~100-200 MeV beams, respectively.

- **Ions:** There is a “fragmentation tail” at the end of the SOBP, as with protons. Hence the “biologically effective range” of the ion or proton beam is increased in depth compared to the physical range. This may compensate for the HRS effect with photons, absent for protons/ions.

LET and RBE for different radiation types



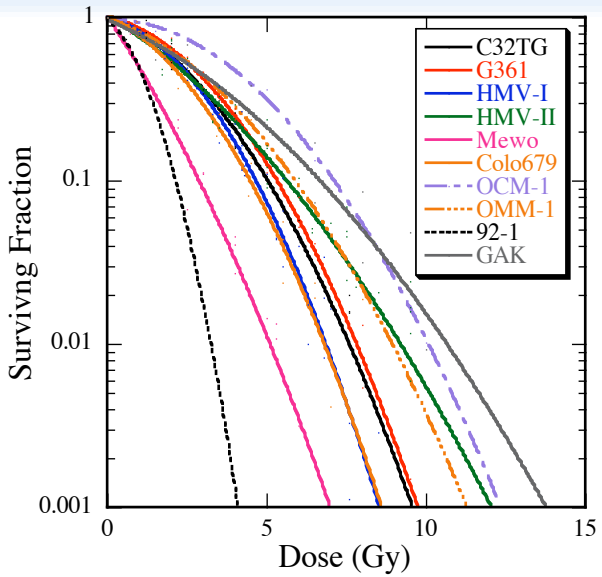


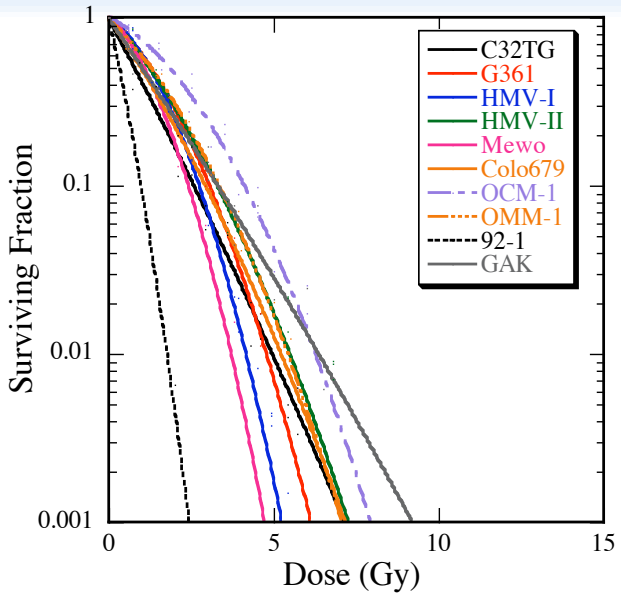
Biological effect versus depth

X rays

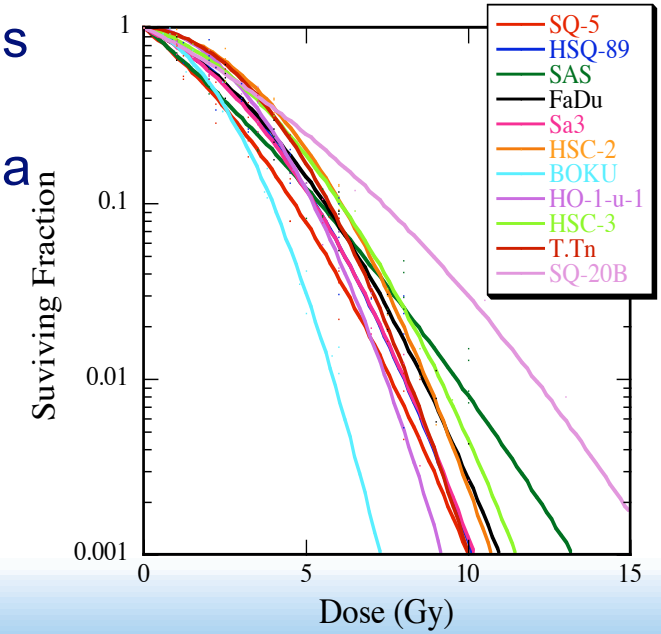
Carbon ions

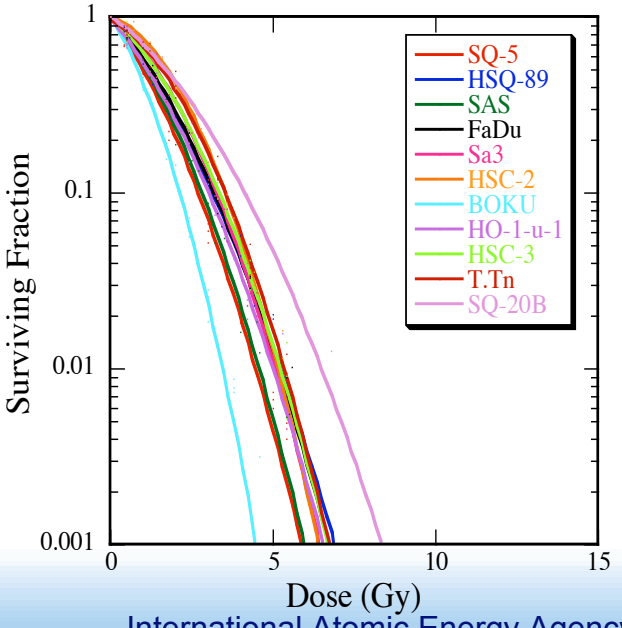
Malignant Melanoma





Squamous Cell Carcinoma

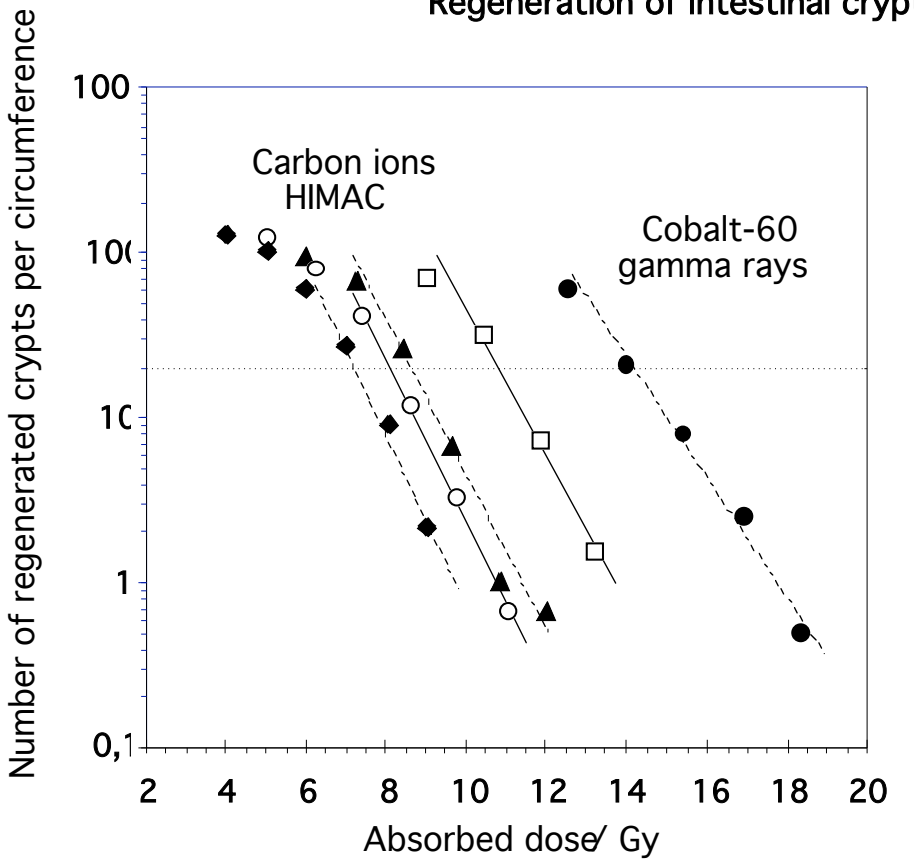


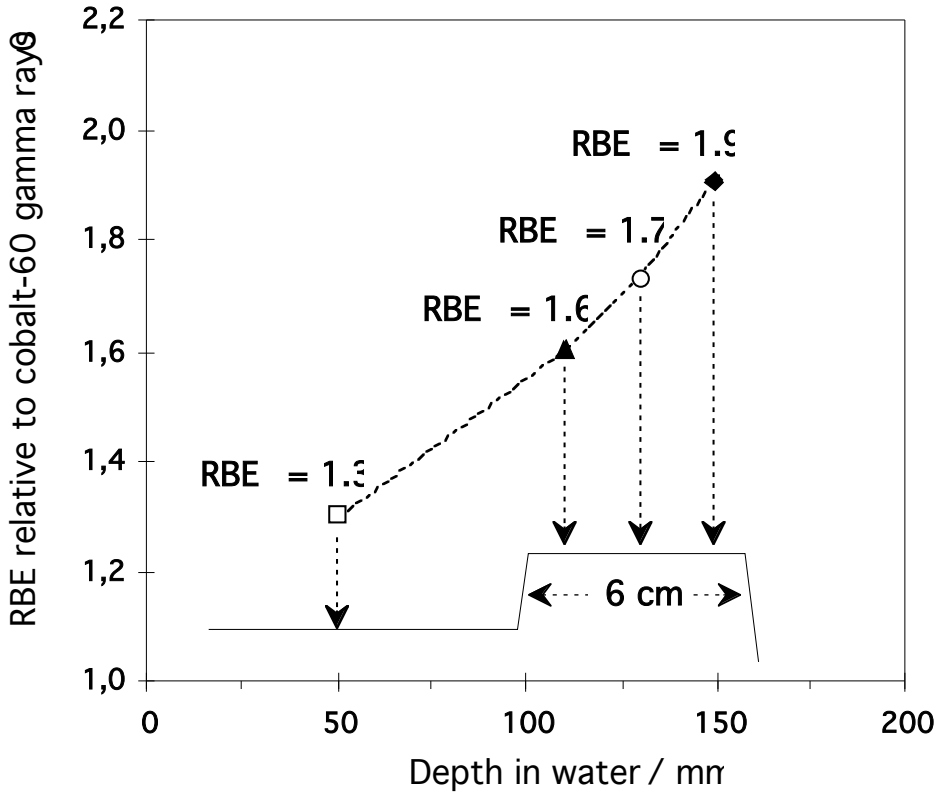


Courtesy of Koichi Ando

Carbon ions RBE versus depth

Carbon-12, 290 MeV/u (HIMAC, Japan) , 6-cm SOBP
Regeneration of intestinal crypts in mice after irradiation in a single fraction



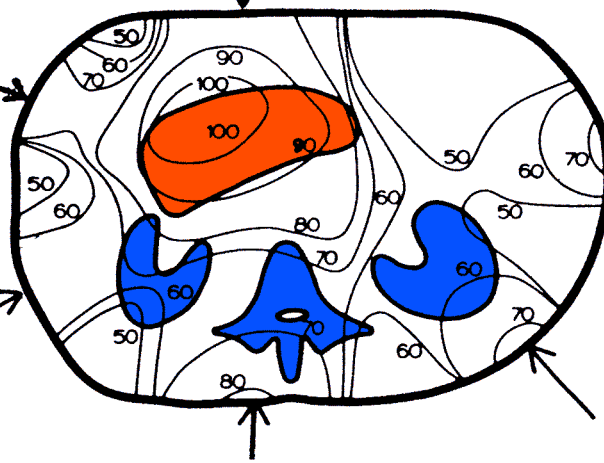


Gueulette et al.

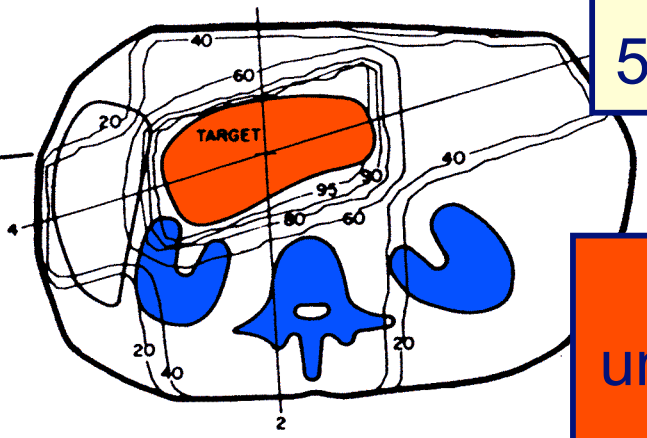
Charged particle treatment plans

normal tissue 70% dose

tumor uniformity 15%



250 kV X rays
6 fields



18 MV X rays
4 fields

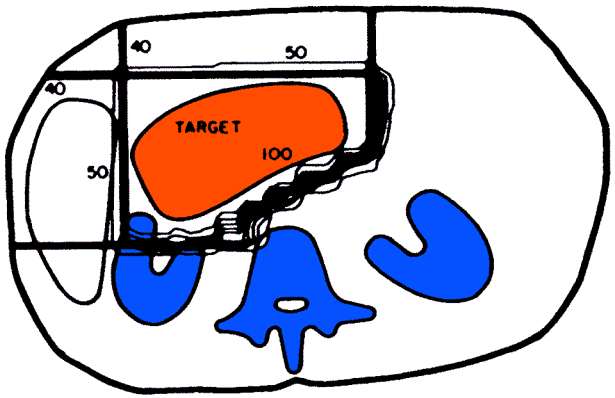
normal tissue 50% dose

tumor uniformity 5%

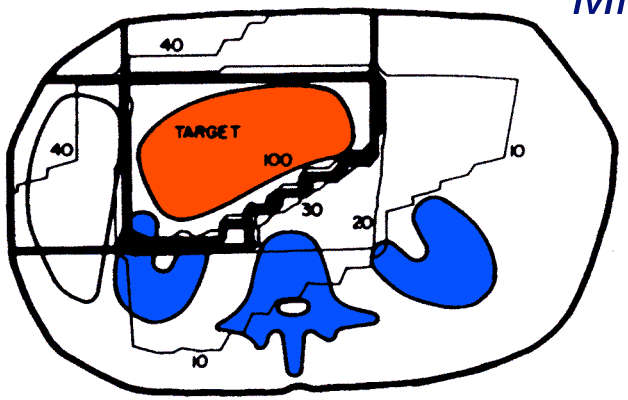
Courtesy of Mike Joiner

normal tissue 0% dose

tumor uniformity 2–3%



He ions



C ions

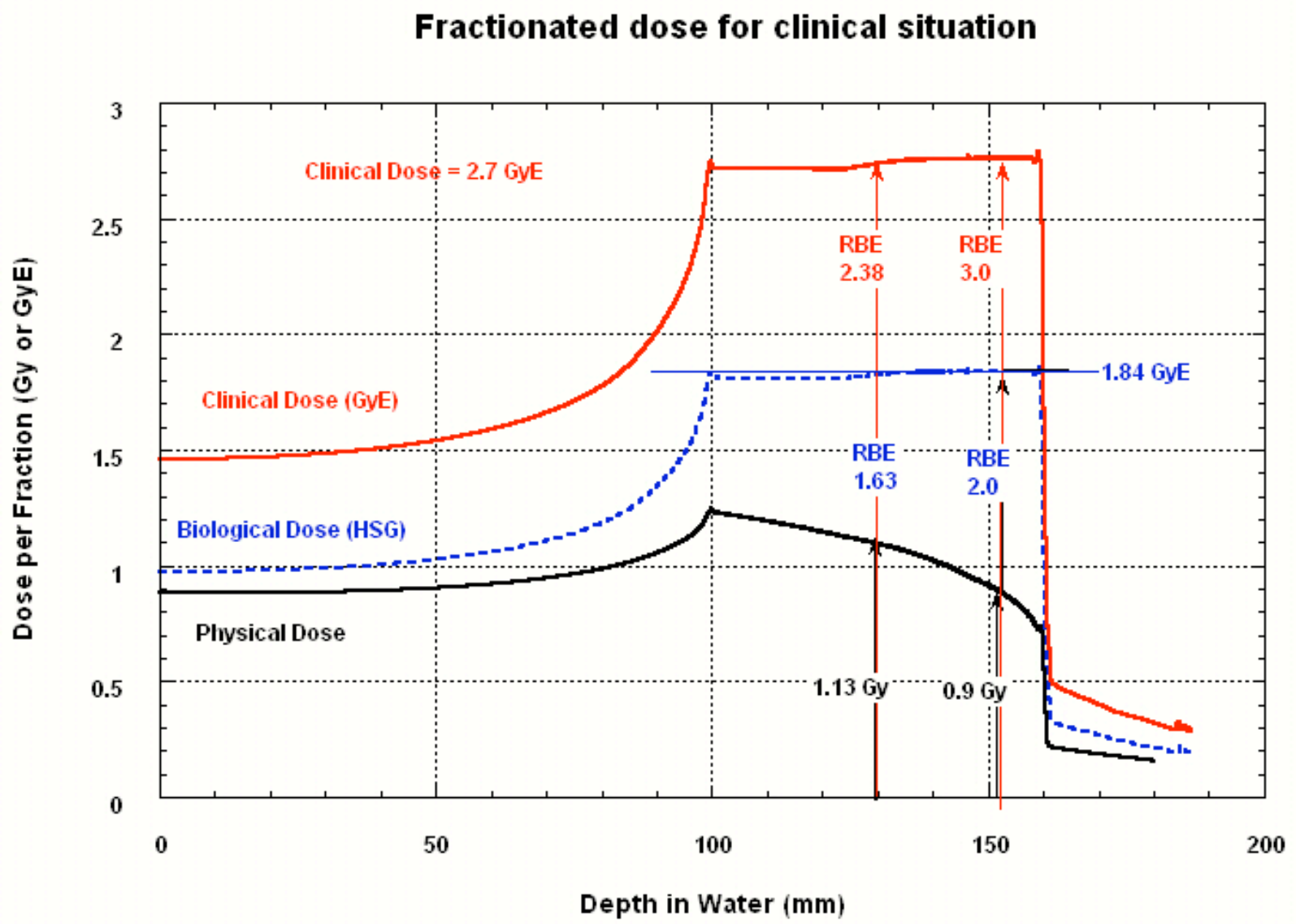
Determination of clinical RBE – NIRS, Chiba

- Assumed that carbon beam is clinically equivalent to fast neutrons at the point where dose-averaged LET value is 80 keV/μm, the neutron equivalent point.
- Therapy experience indicates that NIRS neutron beam has a clinical RBE of 3.0.
- Carbon ion RBE is normalized to 3.0 at the point in the SOBP where the LET is 80 keV/μm.
- Clinical SOBP shape is deduced by multiplying the biological SOBP shape by a constant factor equal to the ratio of the *clinical RBE* to the *biological RBE* determined at the neutron equivalent point.

J. Mizoe, K. Ando, T. Kanai, N. Matsufuji and H. Tsujii

Clinical RBE at the centre of the SOBP

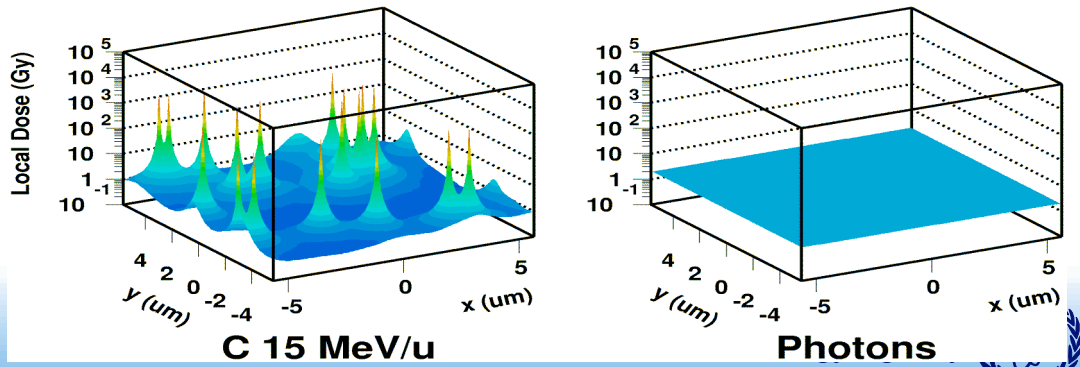
J. Mizoe, K. Ando, T. Kanai, N. Matsufuji and H. Tsujii



Darmstadt - "Local Effect Model"

- Based on radial track structure of particles, and photon response characteristics to fractionated doses.
- Predicts proton RBE 1.2-1.3
- Predicts fairly well observed lung Tumor Control Probability curves (Batterman neutrons, and NIRS ions)
- Skull base tumors in Darmstadt - photon α/β value for late reactions in brain, calculated local RBE at each point based on LEM, integrated over the tumour volume, optimize dose for minimum late reactions.

M. Scholtz et al



Principle differences

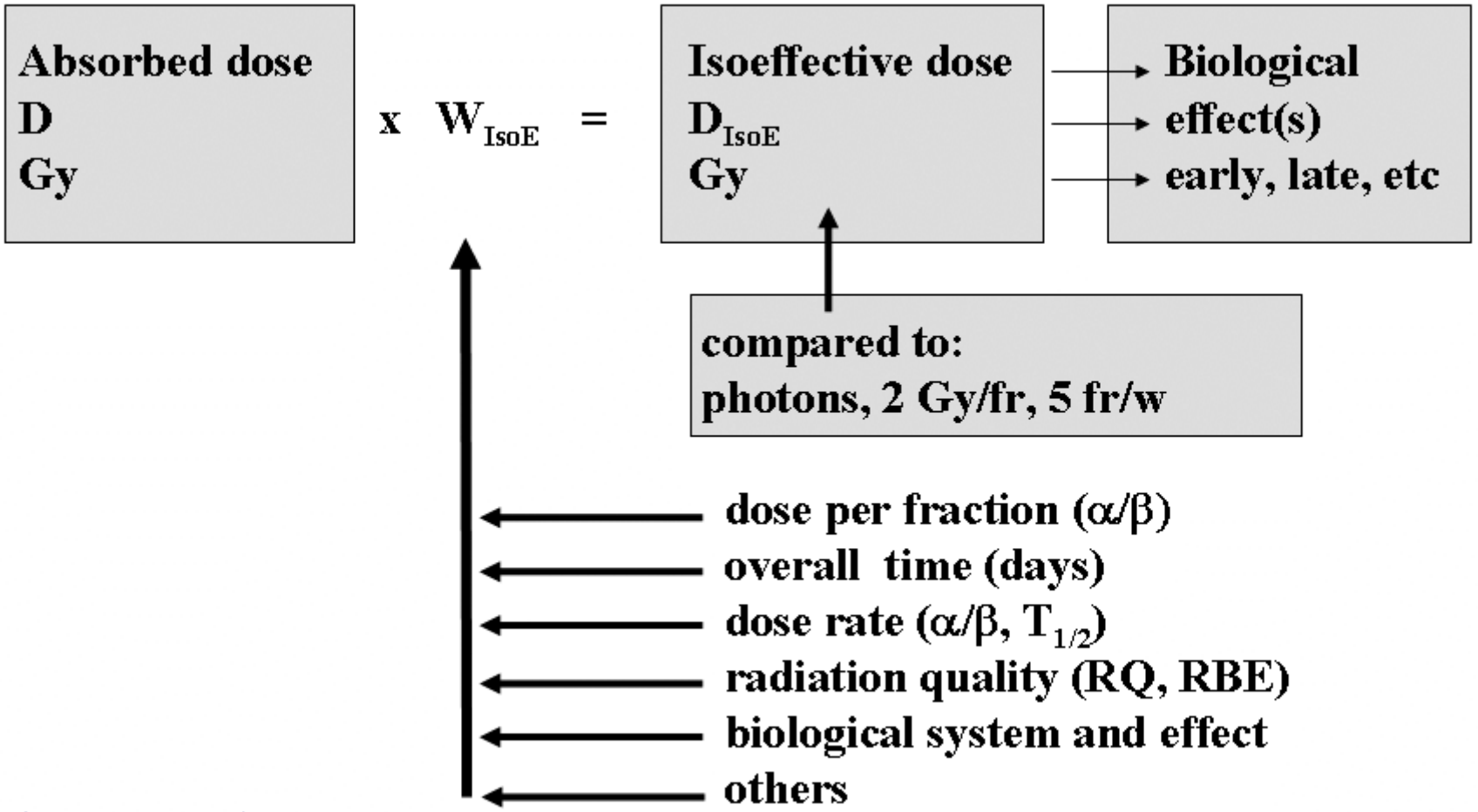
- principle differences between two methods:
  - alpha and beta values used in Tissue Effect Probabilities
    - Human Salivary Gland cells (NIRS)
    - photon biology and therapy experience (GSI)
  - physical model
    - dose-averaged LET and dose (NIRS)
    - radial track structure of each ion and fluence (GSI)
  - biological model
    - LQ model (NIRS)
    - LEM with modified LQ model (GSI)
- principle difference in results:
  - Dosimetry and biological RBE very similar, but GSI uses 15% higher clinical RBE than at NIRS

Recommendations for reporting ion beam therapy

- Reporting: an essential tool for exchanging information
- Irradiation conditions: Particle type; Energy spectrum; Beam delivery system (scattering or scanning); Beam number, size and orientation; Position and depth of any SOBP; Fractionation schedule.
- **Absorbed dose in Gy**
- **Isoeffective dose D_{IsoE} Gy**
- Reference point(s) or volume(s) for reporting

ICRU/IAEA

Isoeffective dose D_{IsoE} Gy

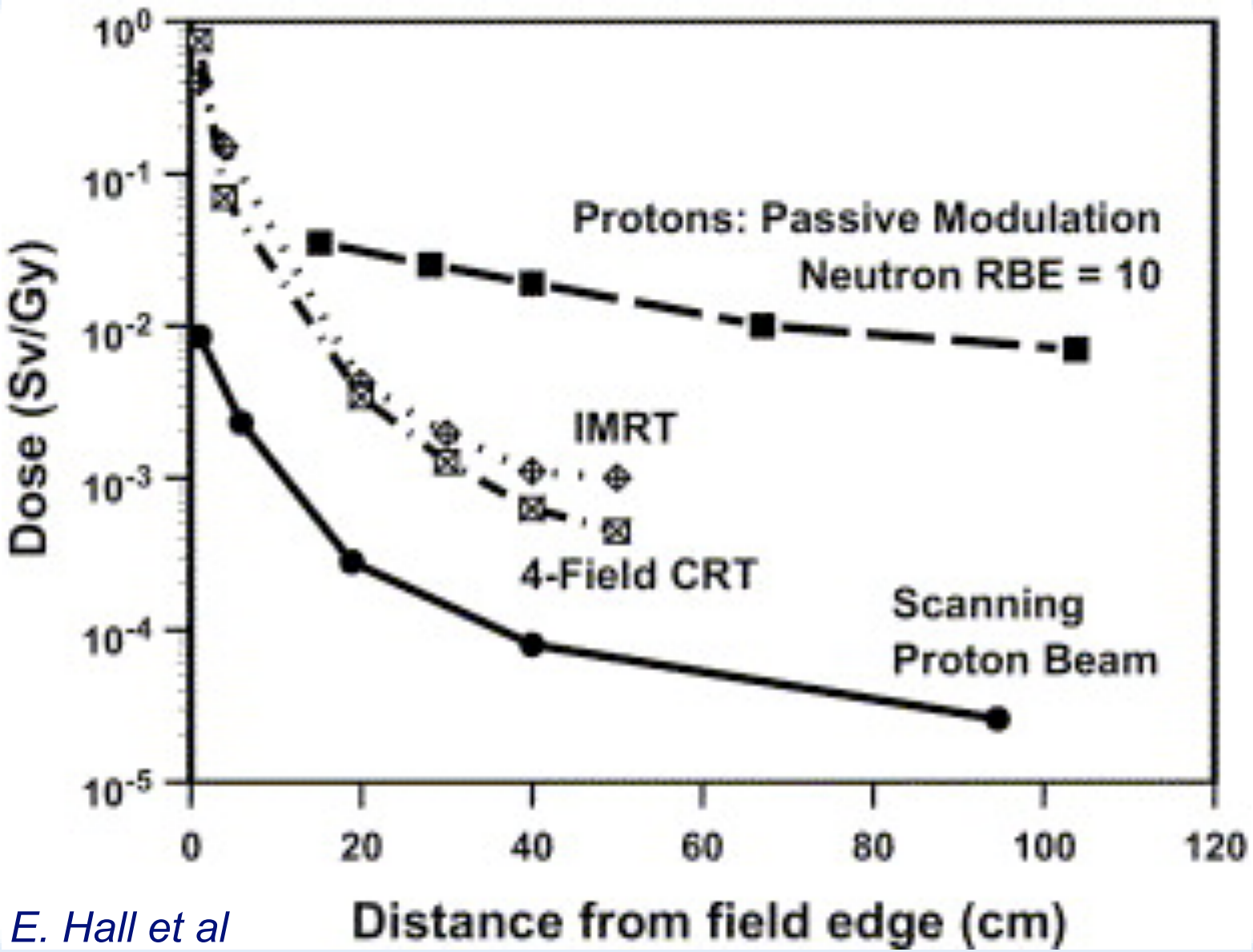


Courtesy of A. Wambersie

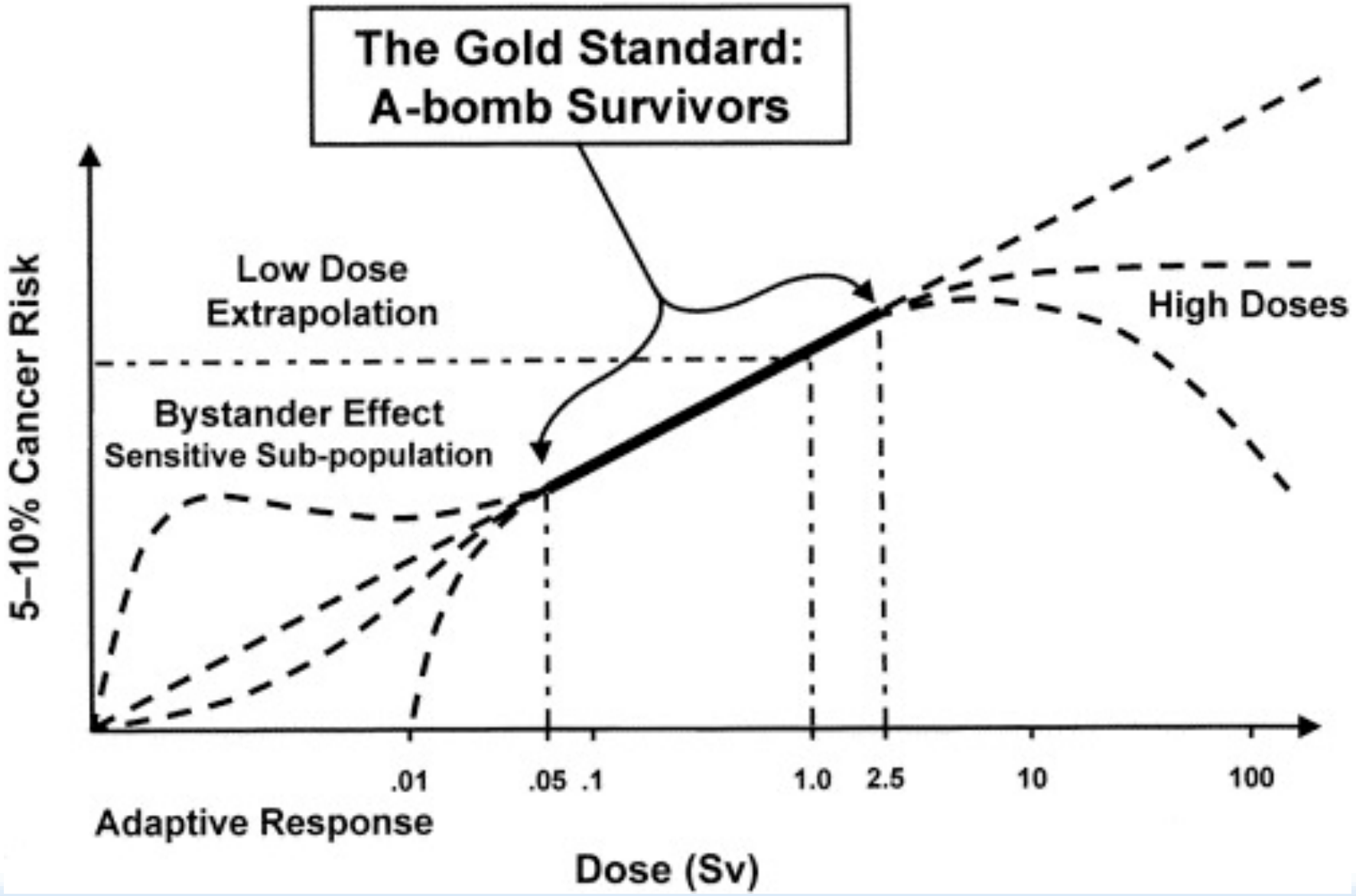
Proton therapy dose reporting

- D represents the proton absorbed dose, expressed in gray (Gy).
- D_{RBE} is the RBE-weighted proton dose and is the dose of photons which would produce the same therapeutic effect as a proton dose, D, given under identical circumstances; it is also expressed in gray (Gy).
- In the case of protons, where use of a generic RBE of 1.1 is recommended: $D_{RBE} = 1.1 \times D$

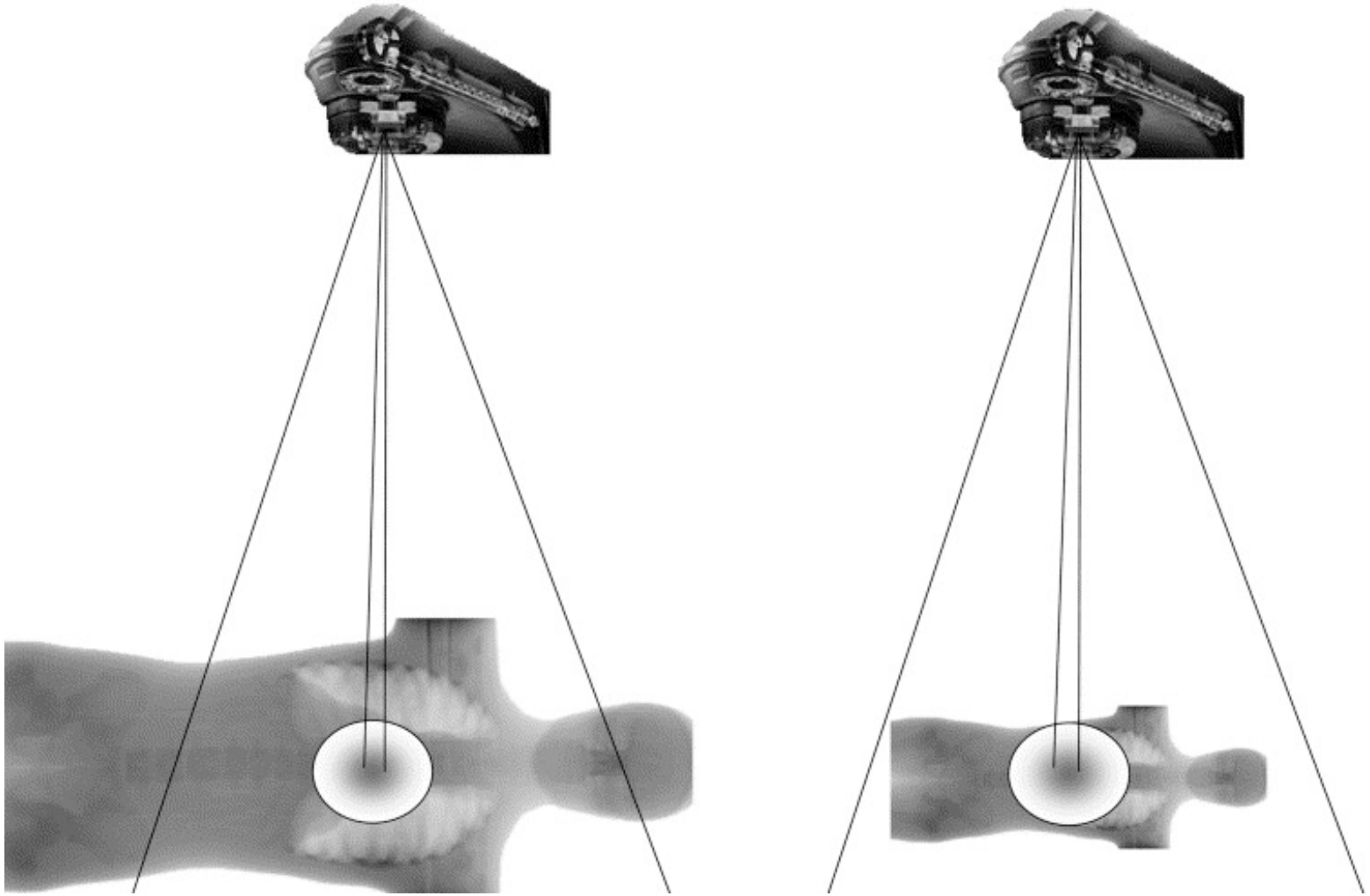
ICRU/IAEA


Dose (Sv/Gy)
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
Protons: Passive Modulation
Neutron RBE = 10
IMRT
4-Field CRT
Scanning
Proton Beam
0
20
40
60
80
100
120
Distance from field edge (cm)

E. Hall et al


The Gold Standard:
A-bomb Survivors
Low Dose
Extrapolation
High Doses
Bystander Effect
Sensitive Sub-population
5–10% Cancer Risk
.01
.05
.1
1.0
2.5
10
100
Adaptive Response
Dose (Sv)

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



Conclusions

- **Risk of second cancers about 1.5%/Sv for conventional RT**
- **Risk about doubled using IMRT vs conventional or 3D-CRT**
- **Risk 4-5x in children versus adults**
- **Risk even higher using protons with passive beam modulation, because of induced neutrons**
- **Protons and pencil beam scanning better than IMRT**

Hall, IJROBP, 65, 1, 2006

Knowledge bases

- **Radiobiology for the Radiologist**
  (Hall and Giaccia- 6th Edition)
- **Basic Clinical Radiobiology: ESTRO course book (Edited by Steel - 3rd Edition)**
- **The Basic Science of Oncology**
  (Tannock and Hill – 4th edition)

- **The IAEA Applied Sciences of Oncology modules on CD 2007**
- **IAEA/ICRU publication on RBE of ions 2007**
- **IAEA/ICRU publication on Dose reporting points for ion-beam therapy 2007**

Vienna International Centre