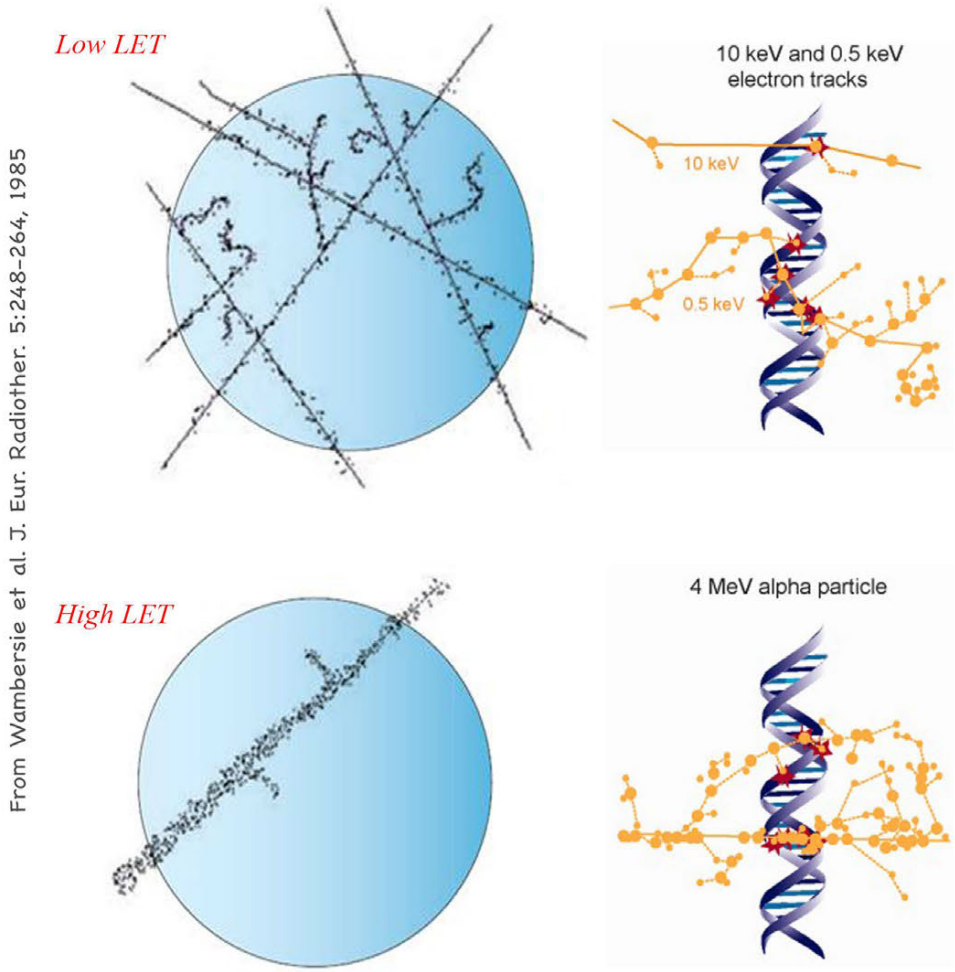
LET, RBE and High LET Radiotherapy

A. Linear Energy Transfer (LET): A Brief Physics Review

1) *once set in motion, charged particles dissipate their energy in discrete "events" along the incident particle's track; the density of these events per unit track length is determined by the particle's mass and charge* (greater charge and/or mass = denser distribution of events), *and is referred to as the radiation's LET or linear energy transfer*

by definition, the LET is *the average energy locally imparted to the medium by a charged particle of a specified energy divided by the distance traversed by the particle*

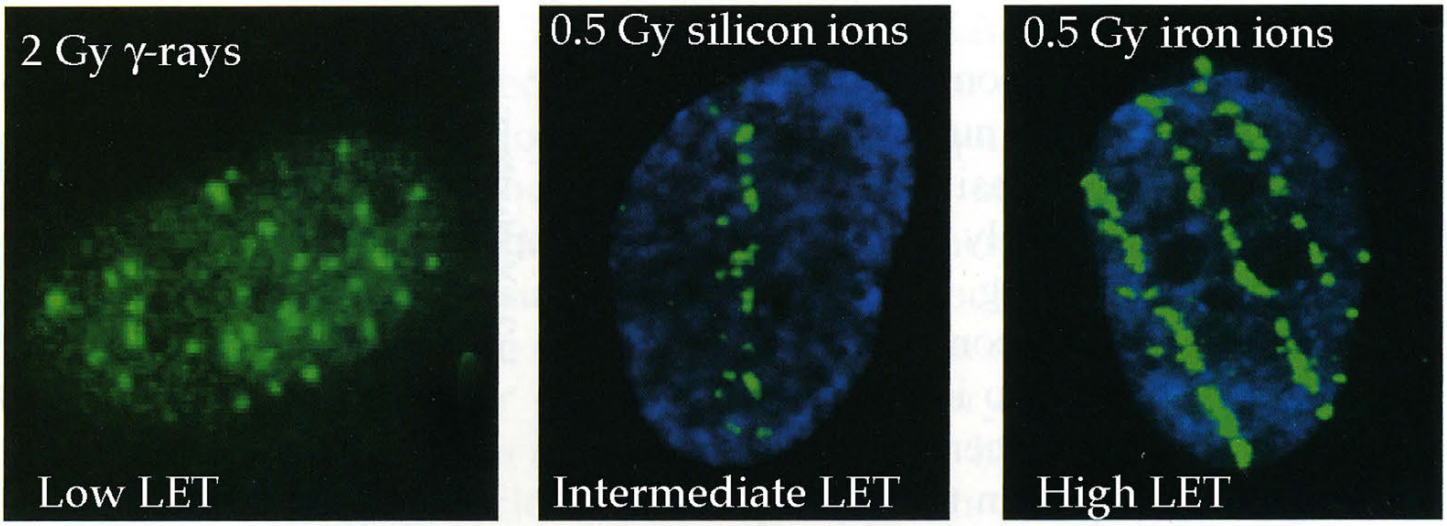
a. the units traditionally used to express LET are keV/μm



In the examples shown for γ-rays (top) *and neutrons* (bottom), *the macroscopic dose to the sensitive volume was the same, although microdosimetrically, the pattern of energy deposition was quite different.*

This explains why the high LET neutrons are more biologically-damaging per unit dose than the low LET γ-rays.

Modified from: Desai *et al*, Radiat Res *164*: 518-522, 2005

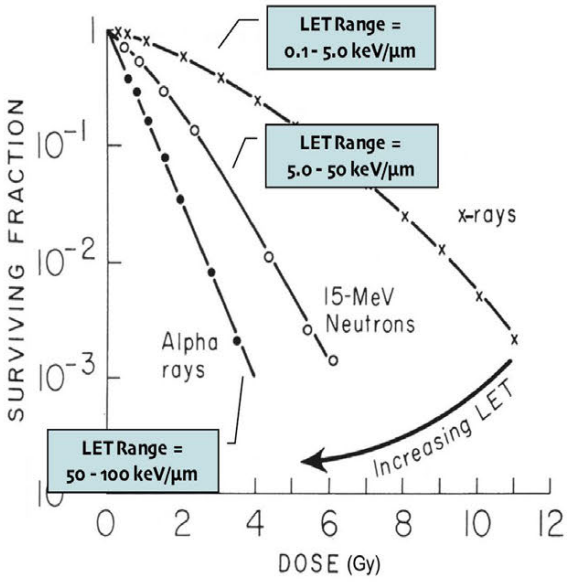


Appearance of low, intermediate and high LET tracks through cell nuclei, made visible by fluorescent staining for the presence of DNA repair-related enzyme complexes (γ-H2AX foci show up green, and the rest of the nucleus appears blue-ish). Human fibroblasts stained 10 minutes post-irradiation.

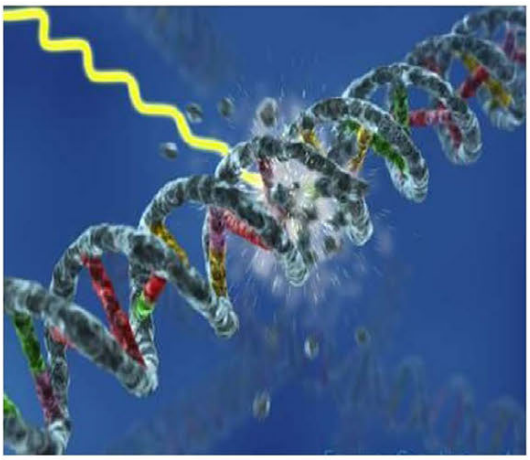
Linear Energy Transfer (LET) of Various Radiations

Radiation		LET (keV/μm)
Photons		
^{60}Co (~1.2 MeV)	Low LET	0.3
200-keV x-ray	Low LET	2.5
Electrons		
1 MeV	Low LET	0.2
100 keV	Low LET	0.5
10 keV	Low LET	2
1 keV	Low LET	10
Charged particles		
Proton 2 MeV	Low LET	17
Proton 10 MeV	Low LET	4.5
Proton 150 MeV	Low LET	0.5
Alpha particle 2.5 MeV	High LET	166
Alpha particle 5 MeV	High LET	90
Carbon ion 100 MeV	"Heavy Ions"	160
Iron ion 2 GeV	"Heavy Ions"	1000
Neutrons		
2.5 MeV	Intermediate LET	15–80
14.1 MeV	Intermediate LET	3–30

Tannock *et al. The Basic Science of Oncology, 4th Edition*, 2005



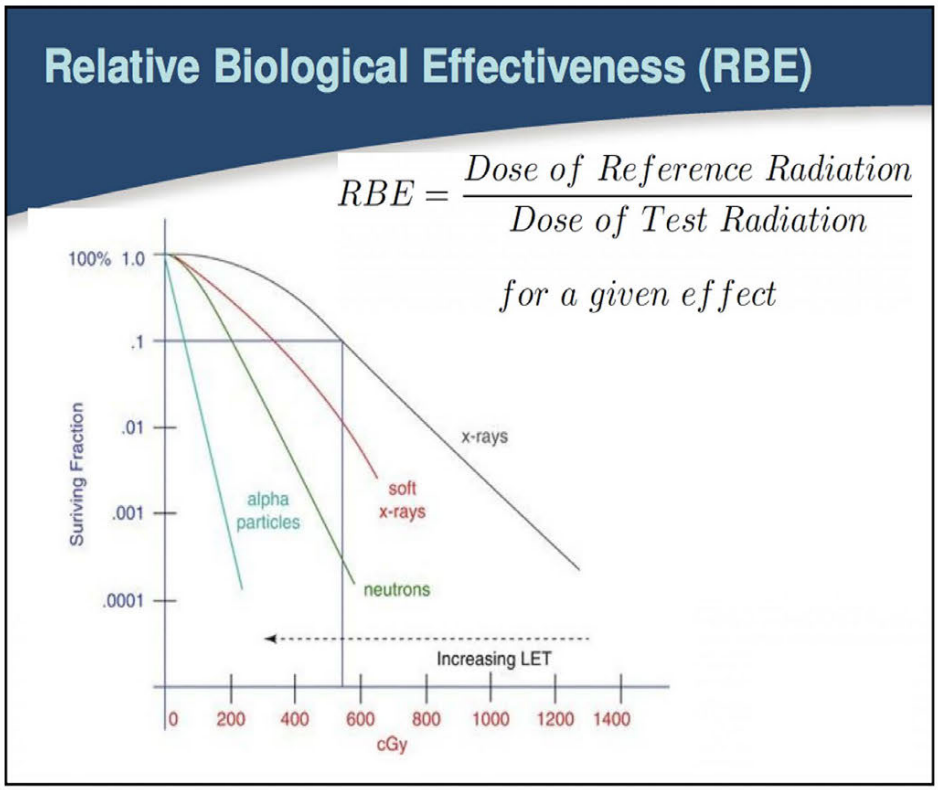
high LET radiations, to a point, are more effective at producing biological damage than low LET radiations, and this is true for many different biological endpoints from tissue damage to cell survival to chromosome aberrations to DNA damage, etc.



...yet how can you express this differing biological effectiveness for different types of radiation on a common scale?

B. **Relative Biological Effectiveness or RBE**: a unit-less quantity used as a correction factor for the purposes of expressing the relative biological potency of radiations of different LET

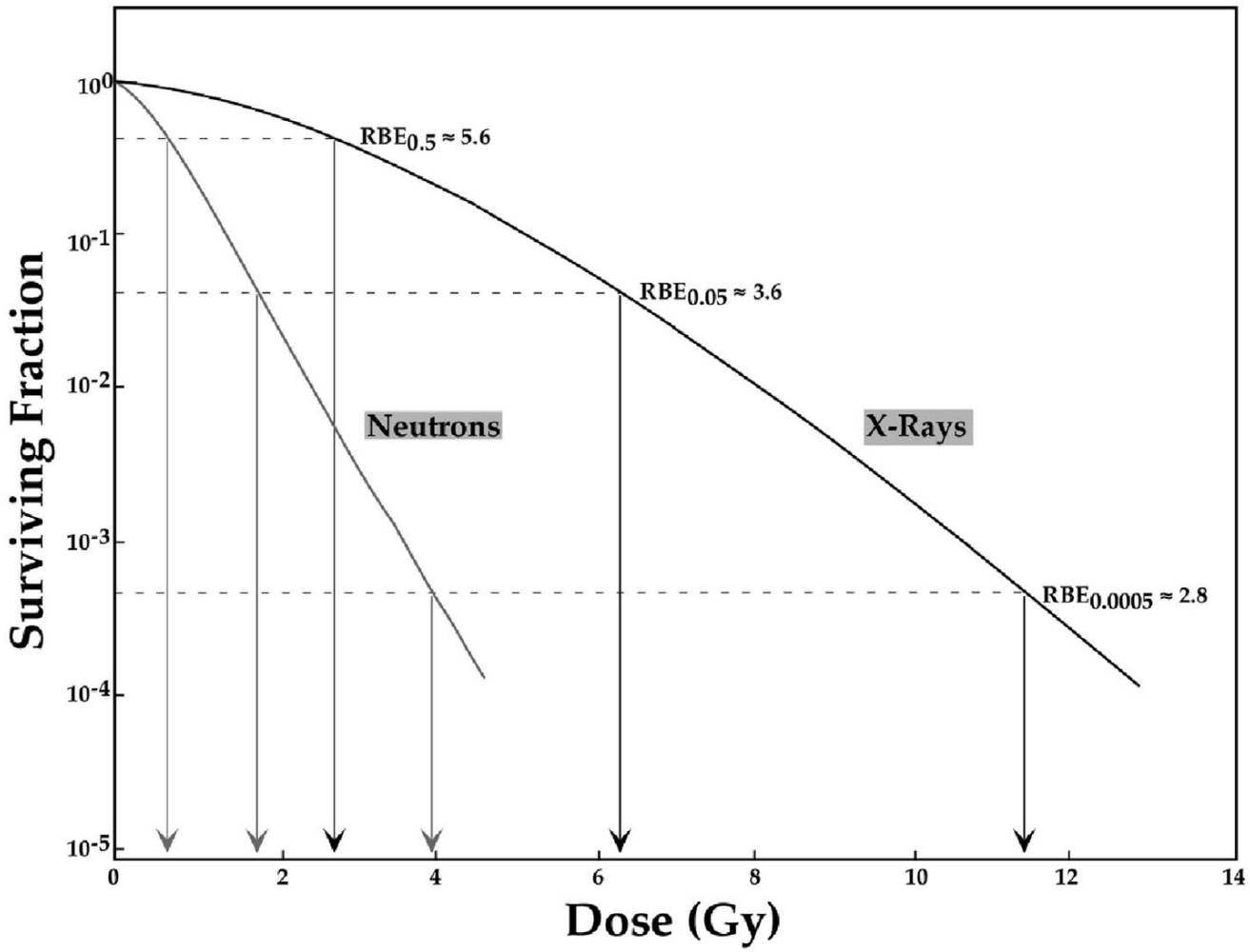
1] the formal definition of **relative biological effectiveness or RBE** is *the ratio of the dose of a standard type of radiation (usually, 250 kVp X-rays) to that of a test radiation which gives the same biological effect*



a. **in terms of radiosensitivity of cells and tissues, survival curves for high(er) LET radiation are both steeper in final slope *and* have a reduced or absent survival curve shoulder**

2] the concept of RBE can be a tricky business, since it depends critically on the nature of the endpoint being evaluated

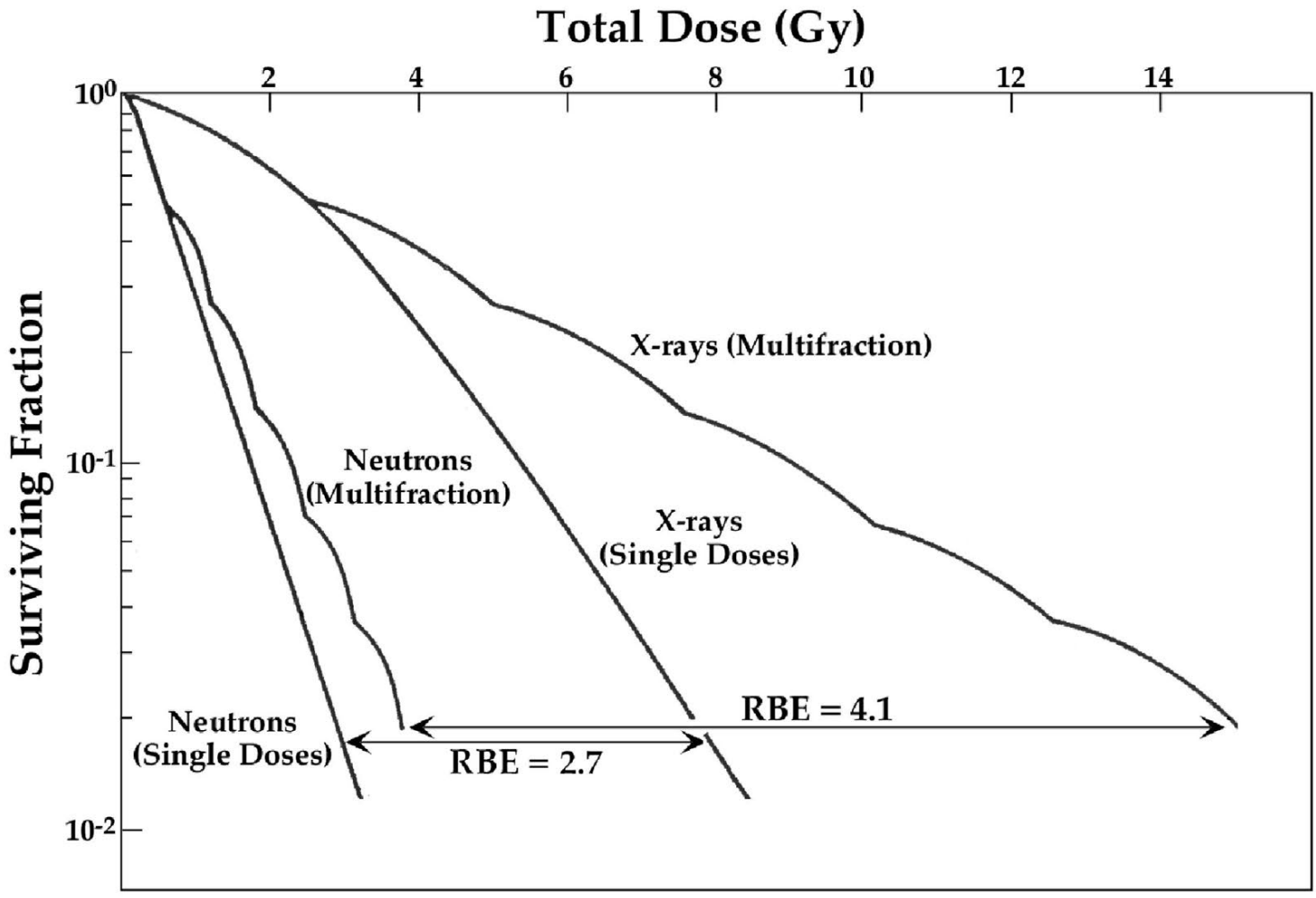
3] by way of example: use the survival of cells in culture as a function of X-ray or fast neutron dose as the endpoint for an RBE determination



a) because the survival curve for neutrons is both steeper *and* has a smaller shoulder compared to the curve for X-rays, it follows that the RBE will vary with the survival level chosen to construct the dose ratio

(1) accordingly, **the RBE evaluated at low doses (where survival would be higher and the endpoint "milder") is greater than at high doses (where survival is lower and the endpoint more severe)**

4] the situation becomes even more complicated when determining the RBE for a multifraction treatment; the RBE actually gets even higher than for single doses because the shoulder-removing feature of higher LET radiations is magnified with each successive dose fraction



Typical survival curves for mammalian cells exposed to x-rays and fast neutrons.

Single doses.

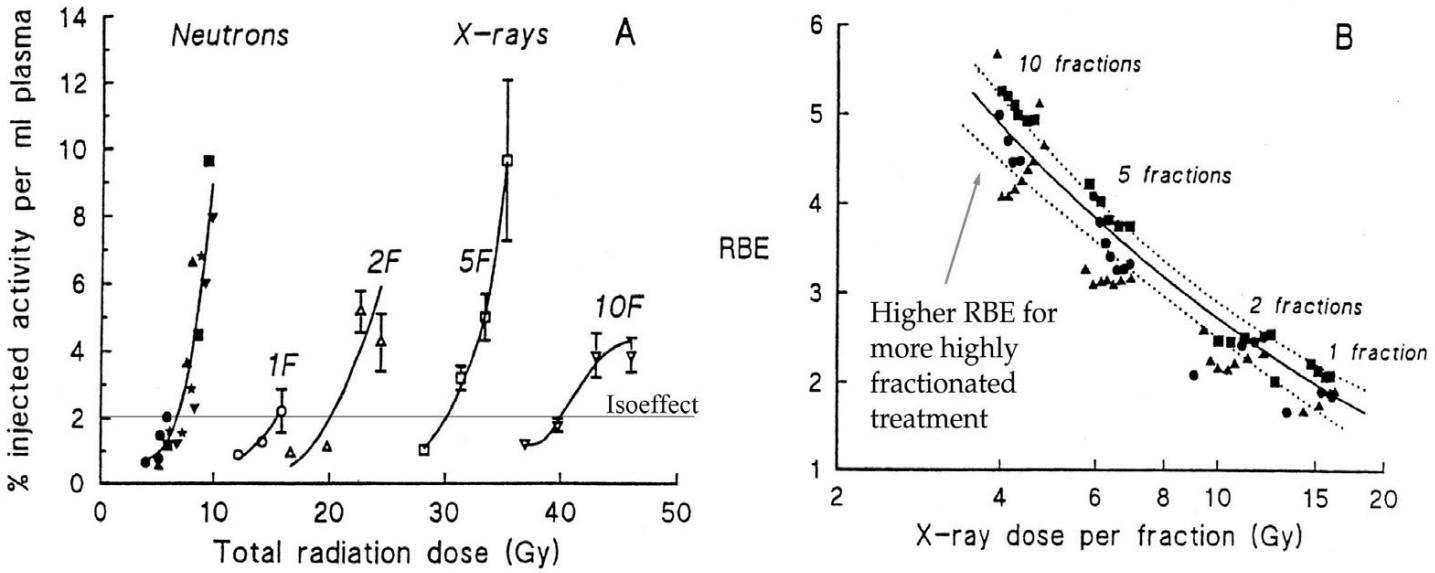
The survival curve for x-rays has a large initial shoulder; for fast neutrons the initial shoulder is smaller and the final slope steeper. Because the survival curves have different shapes, the RBE does not have a unique value but varies with dose, getting larger as the size of the dose is reduced.

Fractionated doses.

The effect of giving doses of x-rays or fast neutrons in four equal fractions to produce the same level of survival. The shoulder of the survival curves is re-expressed after each dose fraction: since the shoulder is larger for x-rays than for neutrons, this results in an enlarged RBE for fractionated treatments.

a) because of this, it follows that **the RBE evaluated for a multifraction treatment will always be greater than for a single-dose treatment**

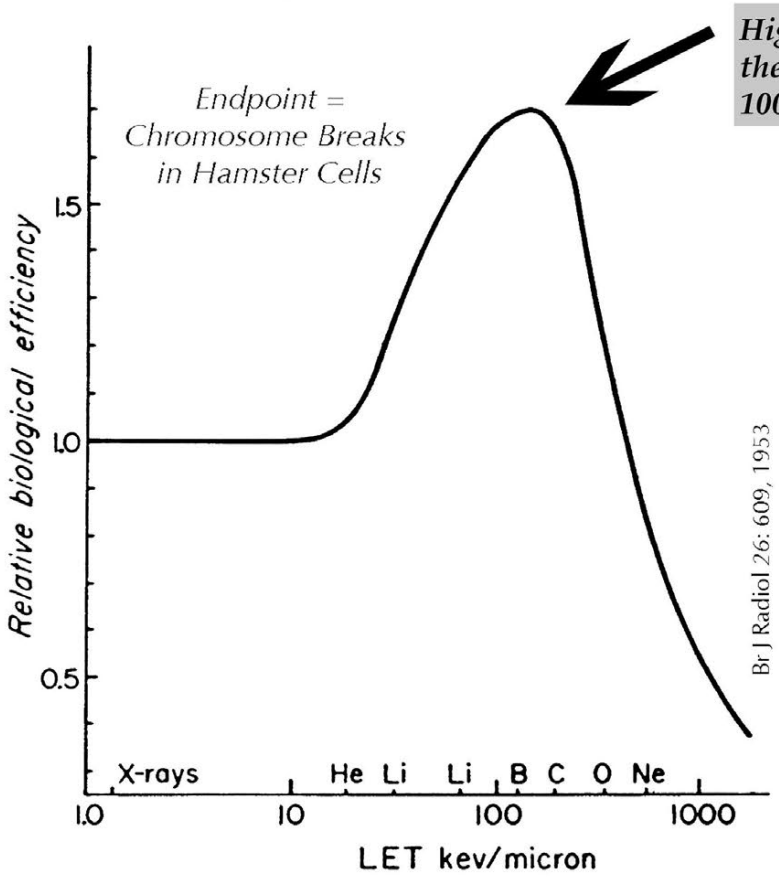
b) in addition, **when comparing the RBE's for two different fractionation schedules (or continuous dose rates), the RBE will be higher for the more highly fractionated (or lower dose rate) treatment**



RBE for kidney damage increases with decreasing dose per fraction. RBE values are derived from graphs similar to panel **A**, which shows dose–effect curves for ^{51}Cr-EDTA clearance following irradiation with 1, 2, 3, 5 and 10 fractions of neutrons or 1, 2, 5 and 10 fractions of X-rays. The RBE values in panel **B** were obtained with various renal damage end-points: isotope clearance (circles), reduction in haematocrit (squares) increase in urine output (triangles). From: Joiner and Johns, Radiat Res *109*: 456-468, 1987.

5] the dependence of RBE on LET:

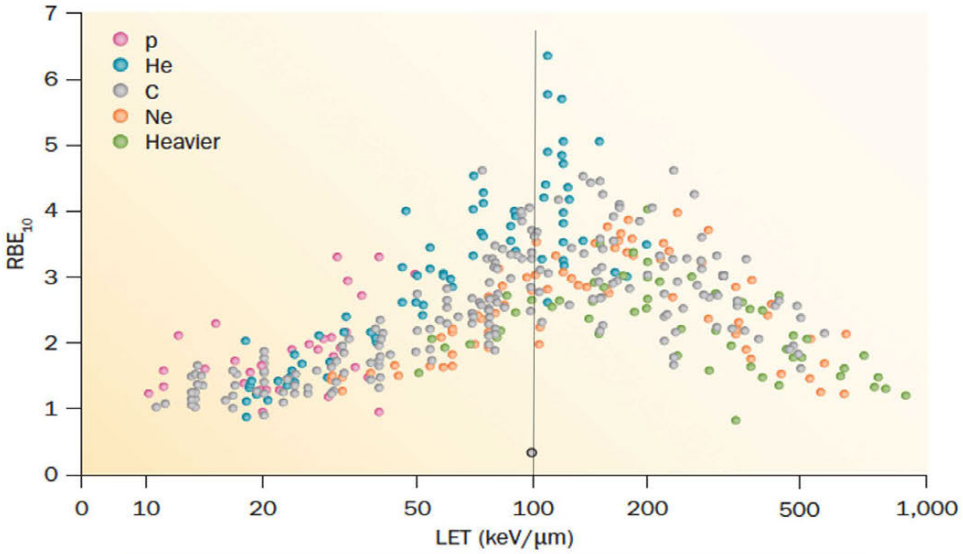
a. the relationship between RBE and LET is a complicated one--the RBE first rises to a maximum at an LET of about 100 keV/μm, and then declines again



Highest RBE occurs when the LET is approximately 100 kev/micron

Boards!

b. this "bell-shaped" relationship between LET and RBE seems to hold for many different radiobiological endpoints, including chromosome aberrations (previous page), cell survival as well as transformation and carcinogenesis



| RBE versus LET from published experiments on *in vitro* cell lines. RBE is calculated at 10% survival, LET values are given is keV/µm in water. Different colours indicate different ions, from protons to heavy ions. Data points are extracted from the Particle Radiation Data Ensemble (PIDE) database, which currently includes 855 survival curves for cells exposed to photons (α/β ratio ranging 1–30) and ions.

c. **the initial rise in RBE with increasing LET suggests that an increase in the density of energy deposition events leads to increased biological damage, but what about the drop at even higher LET's?**

(1) **this is called the "overkill effect", and probably relates to the fact that the extra energy deposited is being wasted on cells that have already been killed**; as such the kiling efficiency per unit dose goes down

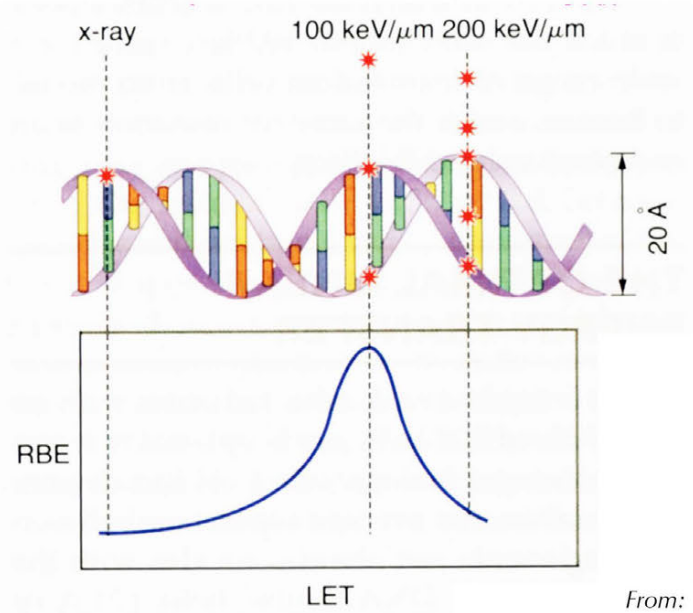


Diagram illustrating why radiation with a linear energy transfer (LET) of 100 keV/µm has the greatest relative biologic effectiveness (RBE) for cell killing, mutagenesis, or oncogenic transformation. For this LET, the average separation between ionizing events coincides with the diameter of the DNA double helix (i.e., about 20 Å or 2 nm). Radiation of this quality is most likely to produce a DSB from one track for a given absorbed dose.

From: Hall and Giaccia, Radiobiology for the Radiologist, 8th Edition, 2019

6] so, to summarize, RBE depends on:

LET (radiation quality)
Radiation Dose
Fraction Number
Fraction Size or Dose Rate
Endpoint Evaluated

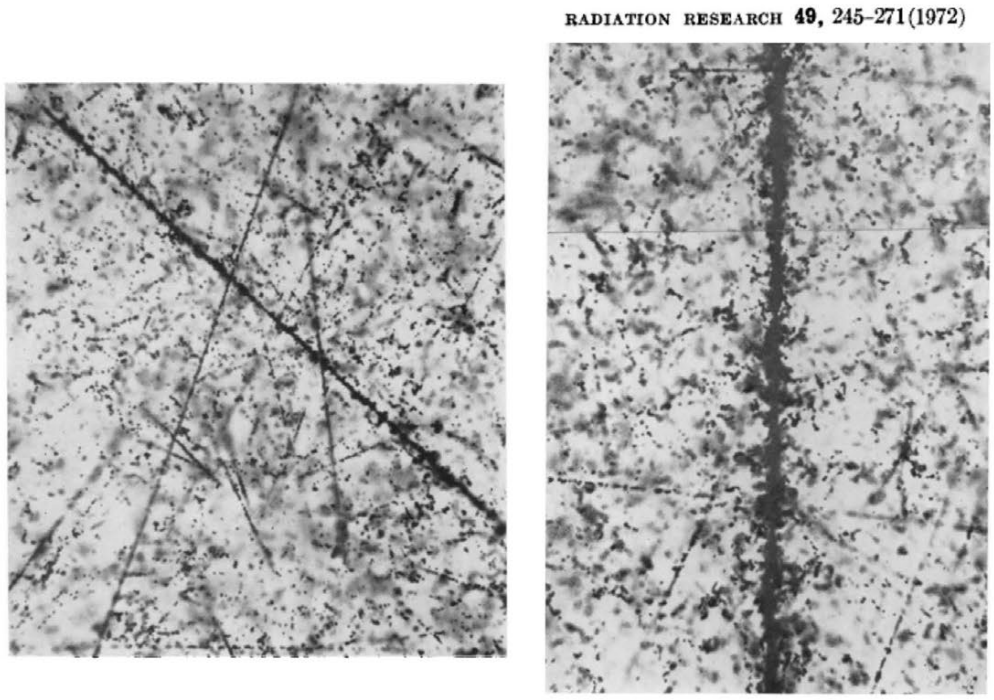
Radiation Weighting Factors in Radiation Protection: The Same Thing as RBE (more or less)

	Type and Energy Range	Radiation Weighting Factor, W_R
Low LET	Photons	1
	Electrons	1
	Protons	2
High LET	α-Particles, fission fragments, heavy nuclei	20
	Neutrons	≈ 5 - 20 (depending on neutron energy)

Based on International Commission on Radiological Protection: Relative biological effectiveness (RBE), quality factor (Q), and radiation weighting factor (W_R). ICRP Publication 92, Oxford, UK, Elsevier Science Ltd, 2004.

Boards!

High LET radiation is no small part of the reason why space travel is dangerous!

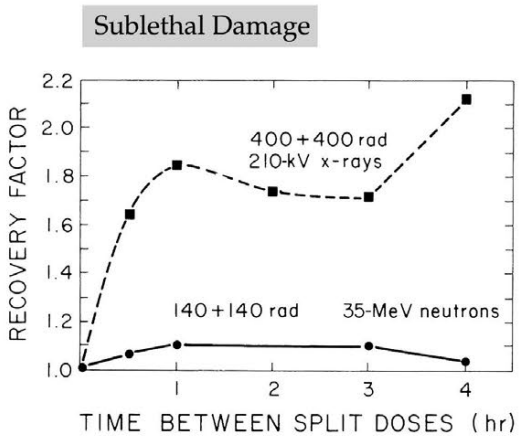


Micrographs from the exposed film badges of the Apollo 11 astronauts during their time on the lunar surface, showing the passage of low and intermediate LET particles, along with a few (really) heavy ions. There's a much higher flux of these things in deep space than in Earth orbit.

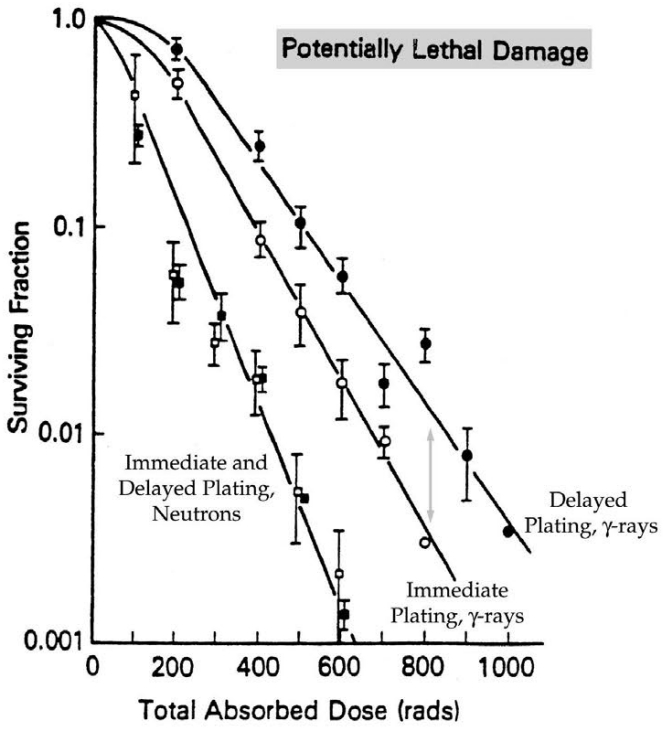
C. Effects of LET on Cellular Radiobiology

1) Cellular Recovery and Dose Rate Effects:

a] ***there is little or no sublethal or potentially lethal damage recovery following exposure to high LET radiation...this goes along with the idea that the DNA damage produced by high LET is more frequent, more "complex" and less repairable than for low LET***



Split-dose experiments with Chinese hamster cells. For 210-kV x-rays, two 4-Gy (400-rad) doses, separated by a variable interval, were compared with a single dose of 8 Gy (800 rad). For neutrons (35-MeV $d^+ \rightarrow$ Be), two 1.4-Gy (140-rad) doses were compared with a single exposure of 2.8 Gy (280 rad). The data are plotted in terms of the recovery factor, defined as the ratio of surviving fractions for a given dose delivered as two fractions compared with a single exposure. It is evident that repair of sublethal damage during the interval between split doses is virtually nonexistent for neutrons but is a significant factor for x-rays. (From Hall EJ, Roizin-Towle L, Theus RB, August RS: Radiology 117:173–178, 1975.)



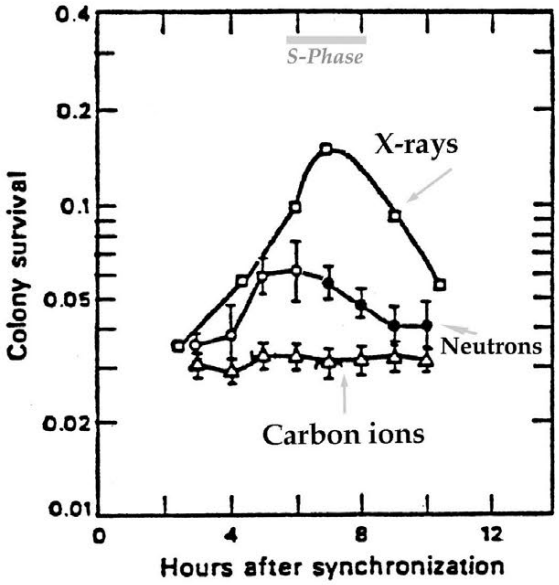
Potentially lethal damage: survival curves for plateau-phase CHO cells irradiated with ^{60}Co gamma rays (*circles*) or 50 MeV d⇒Be fast neutrons (*squares*) and plated either immediately (*open symbols*) or 8 hours after irradiation (*solid symbols*). Repair of potentially lethal damage occurs after irradiation with gamma rays but is not observed after neutron irradiation.

b] because the dose rate effect depends for the most part on cellular repair phenomena, it follows that ***there would be little or no dose rate effect for high LET radiation when compared to low LET***

2) Cell Cycle Effects:

a] ***for low LET radiation, cells in different phases of the cell cycle have very different inherent radiosensitivites (S phase cells being the most resistant and M phase cells being the most sensitive); for high LET radiation, this effect is either significantly "dampened" (neutrons), or else eliminated altogether***

From: Bird and Burki, Int J Radiat Biol 27: 105-120, 1975

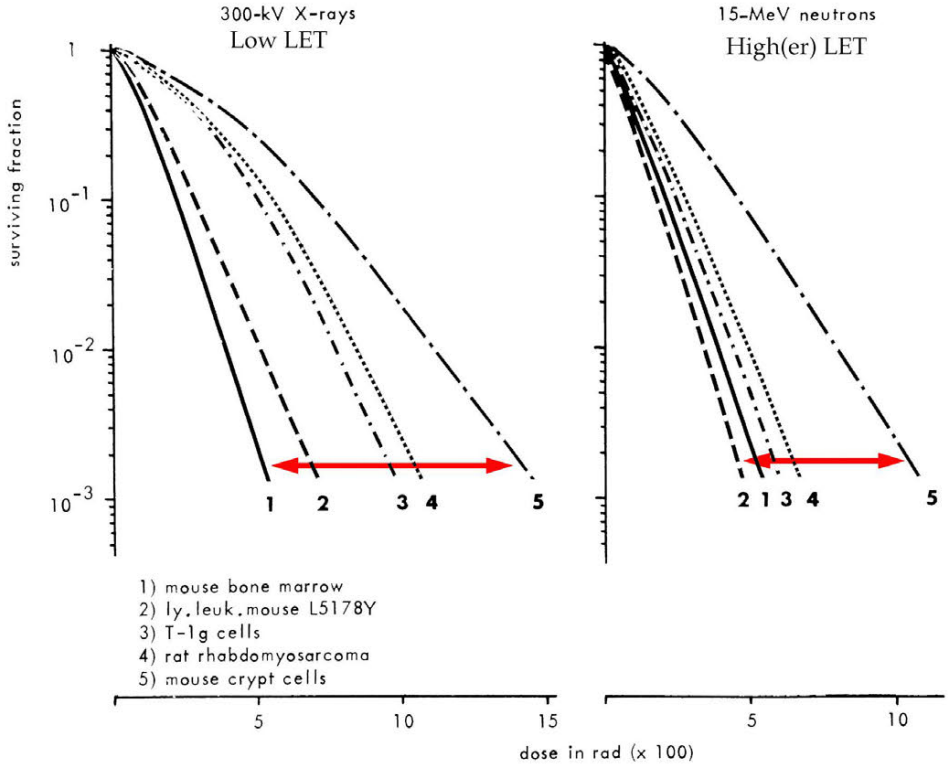


Response of synchronized V79 hamster cells irradiated with X-rays, neutrons or heavy ions (carbon nuclei).

The higher the LET of the type of radiation, the "flatter" the age response function.

3) Inherent Radiation Sensitivity:

a] as is the case for the age response function (above), **the natural variability in radiation sensitivity (i.e., cell survival curve shape) for different cell types is reduced, *although not eliminated completely*, for high versus low LET radiation**



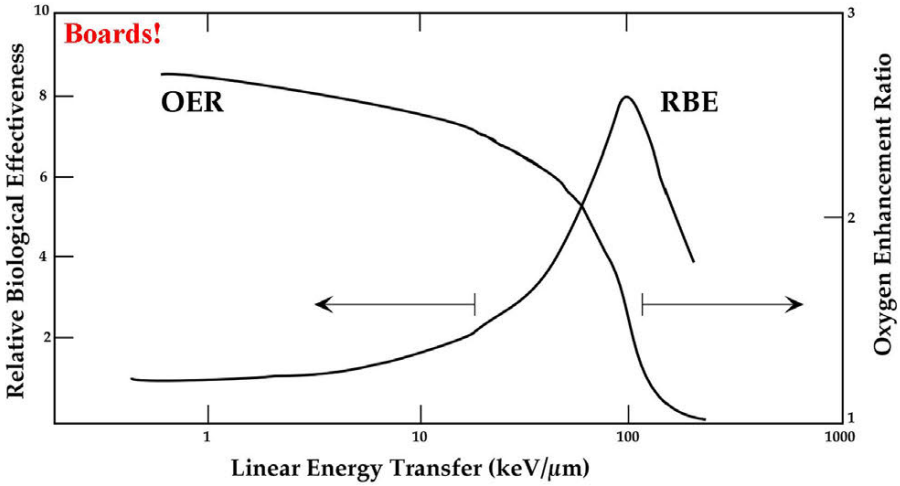
Survival curves for various types of clonogenic mammalian cells irradiated with 300-kV x-rays or 15-MeV $d^+ \rightarrow T$ neutrons: curve 1, mouse hematopoietic stem cells; curve 2, mouse lymphocytic leukemia cells L5178Y; curve 3, T1 cultured cells of human kidney origin; curve 4, rat rhabdomyosarcoma cells; curve 5, mouse intestinal crypt stem cells.

The variation in radiosensitivity among different cell lines is markedly less for neutrons than for x-rays (From Broerse JJ,Barendsen GW: Relative biological effectiveness of fast neutrons for effects on normal tissues. Curr Top Radiat Res Q 8:305–350, 1973.)

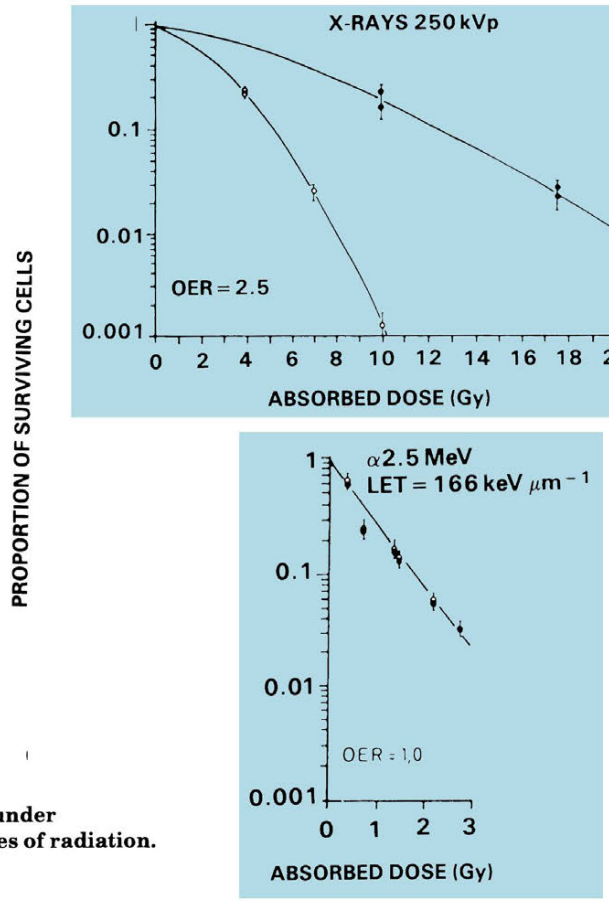
4) The Oxygen Effect:

a] ***in the relative absence of oxygen at the time of irradiation, it can take up to 3 times the dose of low LET radiation to produce a comparable biological effect (such as cell killing) to irradiation under well-aerated conditions...this is known as the oxygen effect, and the factor difference in radiosensitivity is called the oxygen enhancement ratio, or OER***

b] **however, as the radiation's LET increases, this difference in sensitivity between aerated and hypoxic cells decreases until, at an LET of about 100 keV/μm (which corresponds to the maximum RBE), the OER reaches 1.0, that is, NO oxygen effect**



Variation of the oxygen enhancement ratio (OER) and the relative biological effectiveness (RBE) as a function of the LET of the radiation involved. The data were obtained by using T1 kidney cells of human origin, irradiated with various naturally occurring α-particles or with deuterons accelerated in the Hammersmith cyclotron. Note that the rapid increase of RBE and the rapid fall of OER occur at about the same LET, 100 keV/μm.



Survival curves of human kidney cells T1 irradiated under hypoxic and aerobic conditions with different qualities of radiation.

From: Barendsen, GW. Curr Top Radiat Res Q 4: 293-356, 1968

D. A Place and a Need for High LET Radiotherapy???

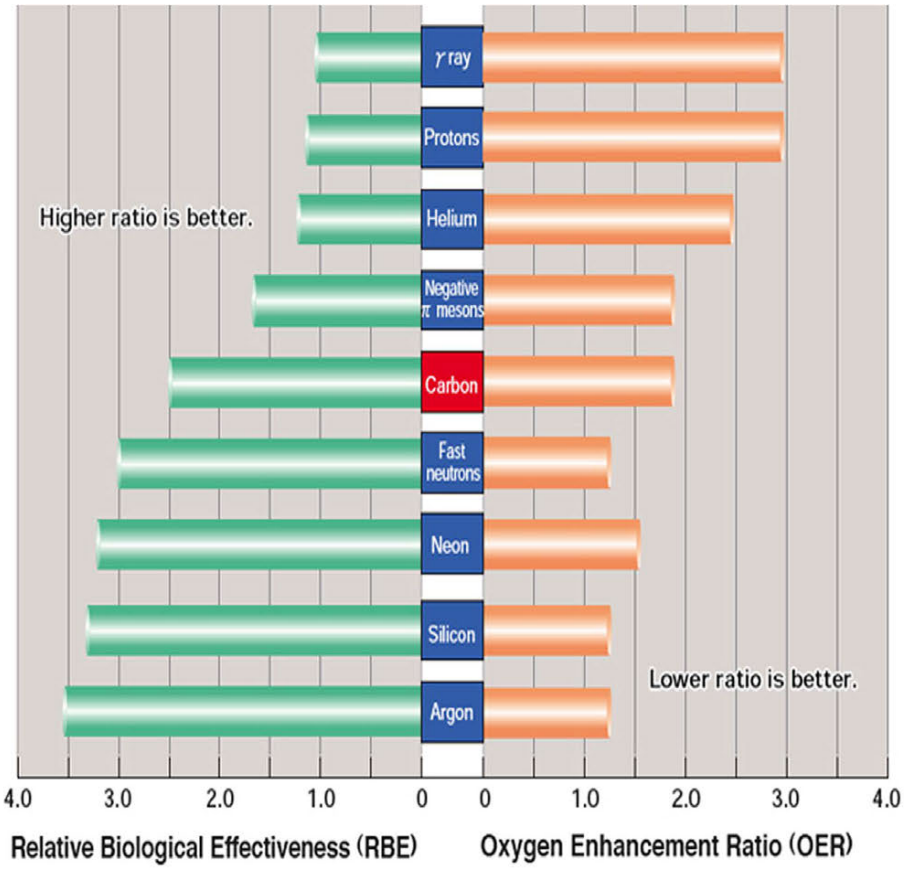
1) historical background - during the 1960's and 70's, a sizeable effort was made to develop high LET particle therapy facilities (at: Stanford, Berkeley, Harvard, Los Alamos, Chicago, etc.)

a] this renewed interest came after about 3 decades of relative disinterest, mainly because of some very serious late complications produced in earlier neutron therapy trials during the 1930's and 40's

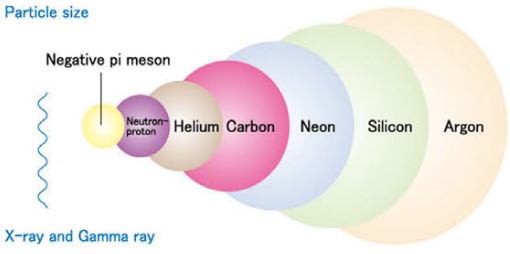
b] even though high LET radiotherapy is back in a big way – proton and heavy ion radiotherapy – concerns about expense, late effects and limited suitable patient populations remain...

2) why the interest in high LET radiotherapy in the first place?

a] historically, the original rationale for using high LET radiation was to maximize the RBE and minimize the OER (i.e., that the radiobiology was perceived to be advantageous)



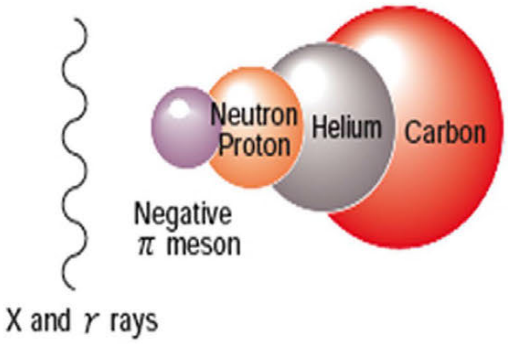
From: National Institute of Radiological Sciences, Japan 2003

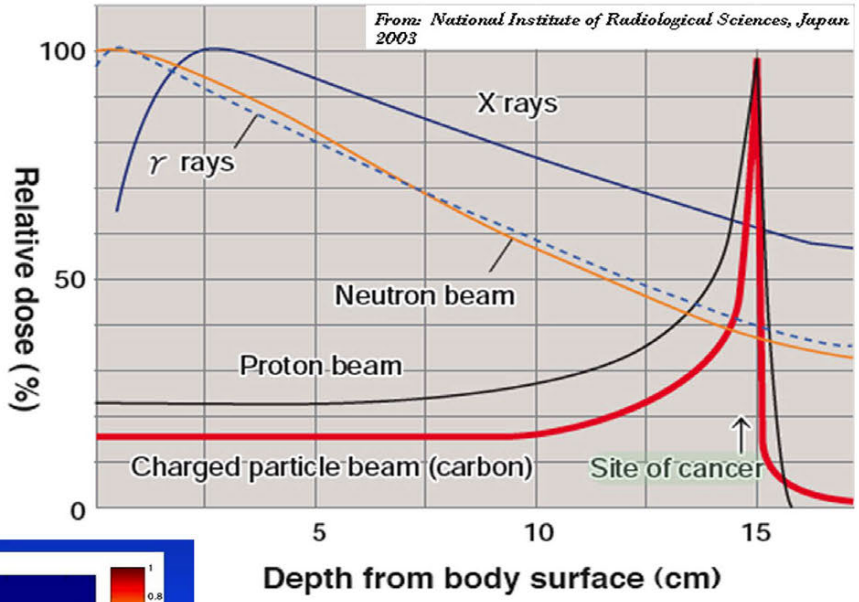


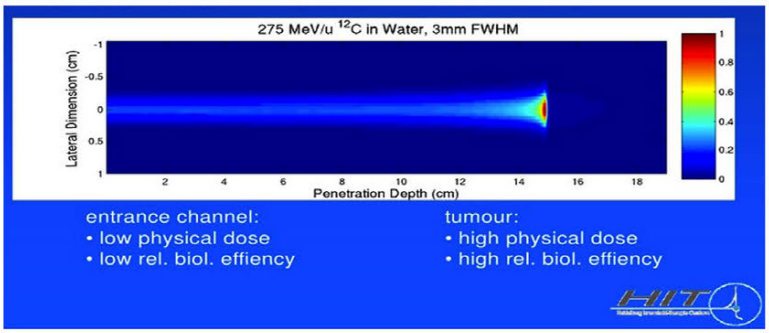
X and γ rays are forms of electromagnetic waves. Proton, fast neutron,and charged particle beams (carbon, neon, argon, etc.) are referred to as particle beams.

b] however, others argued that it was the superior depth-dose characteristics of charged particles (but not neutrons) that made them attractive for radiotherapy, especially in cases where tumors encroached closely on critical normal structures that couldn't tolerate high doses and/or for children where a reduced (or absent) exit dose was highly desirable

Depth Dose Distribution for High and Low LET Radiations





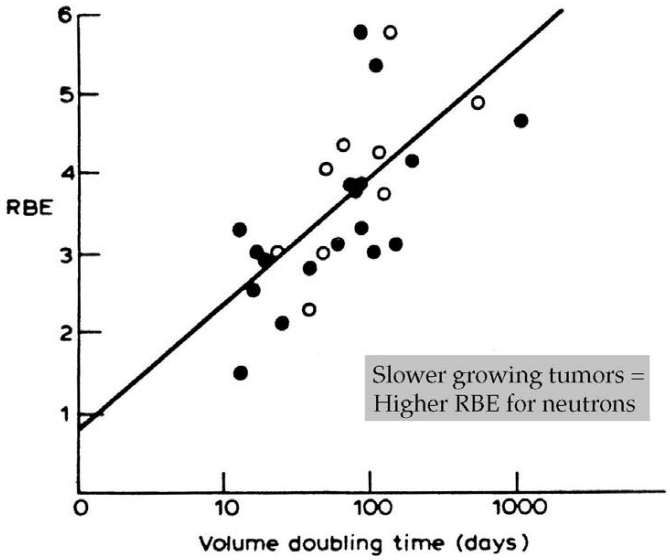


c] even more recently, a third rationale has emerged, that **RBE's have been shown in clinical trials to be larger for slowly growing tumors, such as sarcomas and salivary gland tumors (and, as many hope, prostate cancers too)**

Assuming there really is greater effectiveness of high LET for slower-growing tumors, the following types would be considered good candidates for this kind of treatment:

From: Wambersie *et al.* Acta Oncol 34: 261-274, 1994

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)



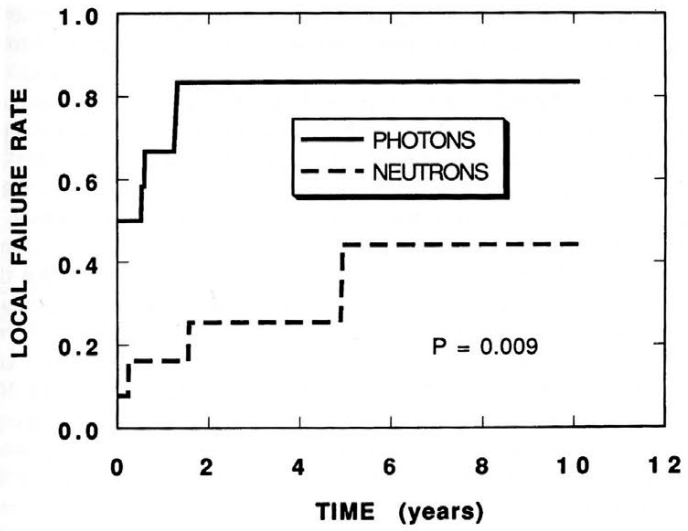
Values of relative biological effectiveness (RBE) relative to cobalt-60 γ-rays for volume changes of pulmonary metastases in patients as a function of the volume doubling time. The dots indicate the measured RBE values; the open circles are estimated values when only neutron irradiation was given. (From Batterman JJ: Clinical Application of Fast Neutrons: The Amsterdam Experience, p 43, Amsterdam, Rodipi, 1981)

3) Types of High LET Radiation for Radiotherapy Compared

a] **Fast Neutrons (energies ≥ 1 MeV)**: have depth-dose characteristics similar to megavoltage X- or γ-rays, but with the biological advantages of a higher RBE and a lower OER

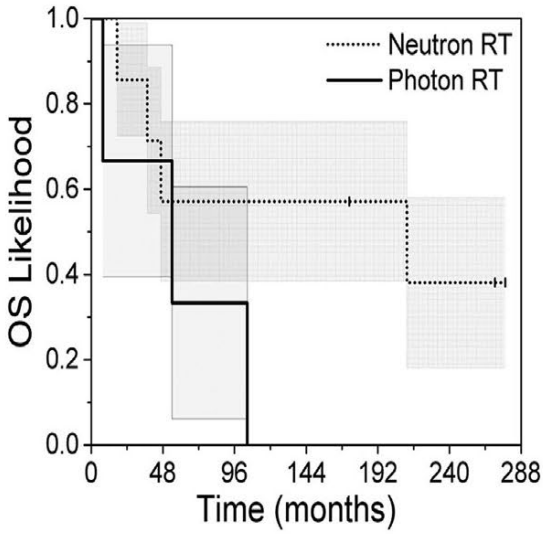
1. ***the first neutron radiotherapy trials were conducted at the Lawrence Berkeley Laboratory in California in the 1930's***; these trials were unsuccessful because of serious late complications in treated patients (Stone and Larkin, 1942), secondary to a lack of understanding of how the RBE changes with dose fractionation

2. ***later, in the 1960's and 70's, more clinical trials of fast neutrons were conducted at the Hammersmith Hospital in London and by the RTOG in the US*** in patients with advanced head and neck tumors of the oral cavity, hypopharynx, larynx and salivary glands; although tumor control was significantly improved in most cases, again, late complications reduced or eliminated most of the therapeutic gain



Actuarial locoregional control of unresectable salivary gland tumors in patients receiving neutron versus photon radiotherapy (RTOG trial 80-01).

From: Laramore et al. IJROBP *14*: 1093, 1988.



Survival outcomes for medullary thyroid cancer based on treatment modality. Kaplan-Meier curves demonstrating OS with 95% confidence interval. Vertical lines designate censored events. OS, overall survival; RT, radiation therapy.

T.R. Chapman et al Advances in Radiation Oncology: July–September 2016

3. today, although a few centers still do neutron radiotherapy using hospital-based cyclotrons, fast neutrons have never become a "mainstream" treatment

4) why have most of the neutron clinical trials been unsuccessful?

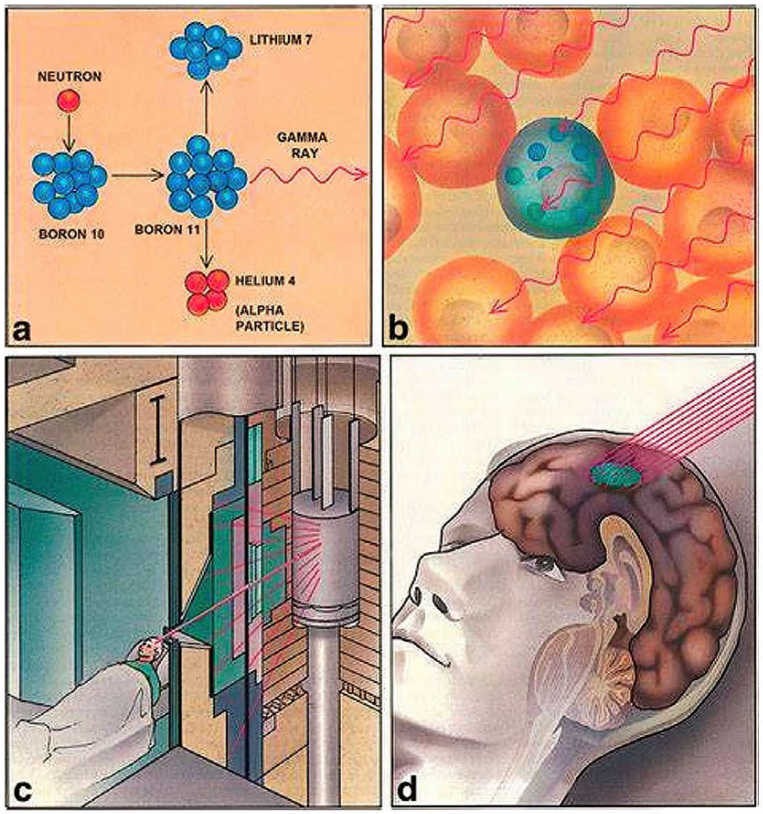
a. surely, one issue has been patient selection (or lack thereof); the most suitable candidates for neutron radiotherapy:

1. tumors known to be hypoxic
2. tumors known to be slow-growing
3. tumors that are otherwise unresectable
4. tumor cells known to be much more resistant than those in the dose-limiting normal tissue(s)

b. ...and in practice, #1 and #4 are seldom assayed today, let alone in decades past!

b] a newer take on neutron radiotherapy - **Boron Neutron Capture Therapy (BNCT)**

1) conceptually, *the idea of BNCT is to deliver a boron-containing drug to the patient's tumor, and then irradiate it with low energy thermal or epithermal neutrons (energy ranges from 10^{-2} to 10^{4} eV) that by themselves don't do much biological damage, but when interacting with the boron compound, produce short range, high LET α-particles*



Cancer Communications volume 38, Article number: 36 (2018)

2) some small clinical trials of BCNT have been conducted around the world, typically in cases of large, recurrent tumors such as glioblastoma, meningioma, head and neck cancers, cutaneous melanoma and a few others

a. no more than marginally improved tumor control rates have been noted, although reasonable palliation was seen in a few cases

3) **begging the question, what are the fundamental problems with BNCT?**

a. to date, existing boron compounds (e.g., sodium borocaptate and boronophenylalanine) are NOT fully selective for tumor cells, which would obviously be a prerequisite for BNCT to work well

b. thermal (especially) and epithermal neutrons do not have sufficient tissue penetrability to be useful for most types of deep-seated tumors

c. toxicity (symptomatic brain necrosis, edema, Grade 3+ skin reactions, etc.) and pseudo-progression have been reported in up to 25% of the few patients who have received BNCT

d. generating a variety of new boronated compounds for the purposes of improving tumor specificity, and creating dedicated technology and treatment facilities for BNCT would cost a small fortune, and wouldn't be at all feasible unless clinical efficacy was *way* improved

c] **Protons**: very attractive for radiotherapy due to their excellent physical dose distributions (e.g., very tight Bragg peak and *no* exit dose to speak of), but radiobiologically-speaking show little or advantage over X-rays, because the measured RBE is low (1.1-1.2 at most)...or is it?

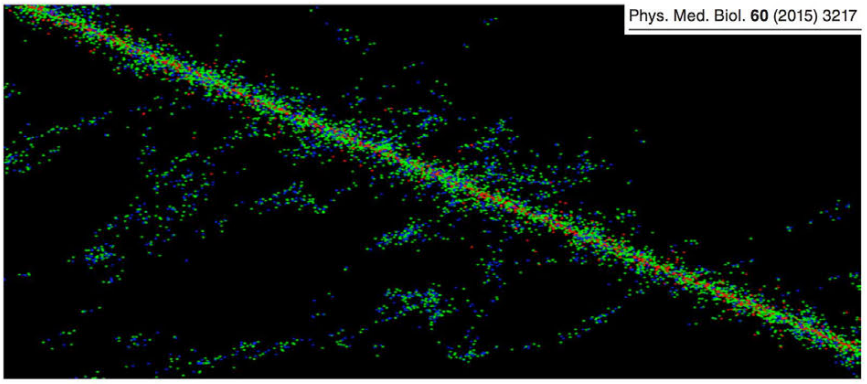
1) **as of 2022, there were 41 proton therapy facilities in the US** (with 5 more under construction); there are also 34 centers in Europe and 30 in Asia (19 in Japan alone!)

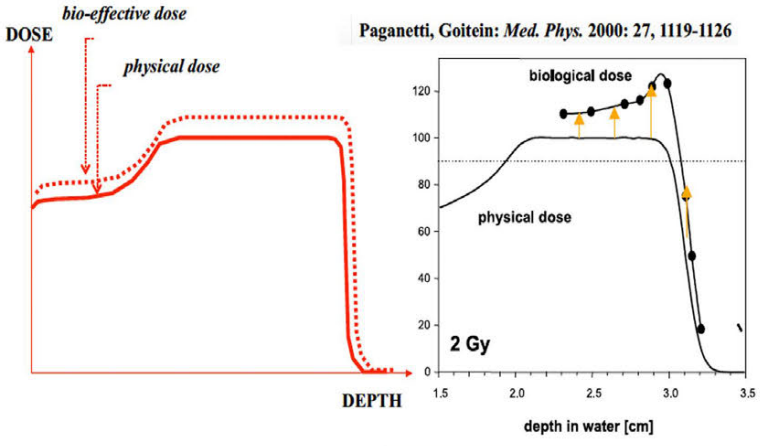
a] since the mid-1990s, about 300,000 patients have been treated with proton radiotherapy worldwide

2) the physics of protons makes them especially suited for treating tumors perilously close to critical structures, such as might be the case for **ocular melanomas, base-of-skull tumors, and some tumors of the paranasal sinues and/or that juxtapose the spinal cord, and for children, who could certainly do without a significant exit dose to still-growing normal tissues**

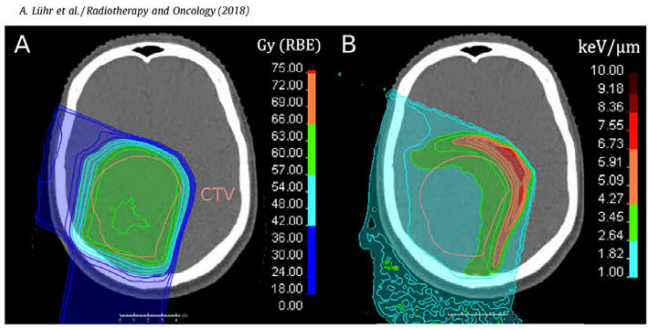
The ionization track structure of a low energy proton.

Red = primary proton ionizations
Green = secondary electron ionizations



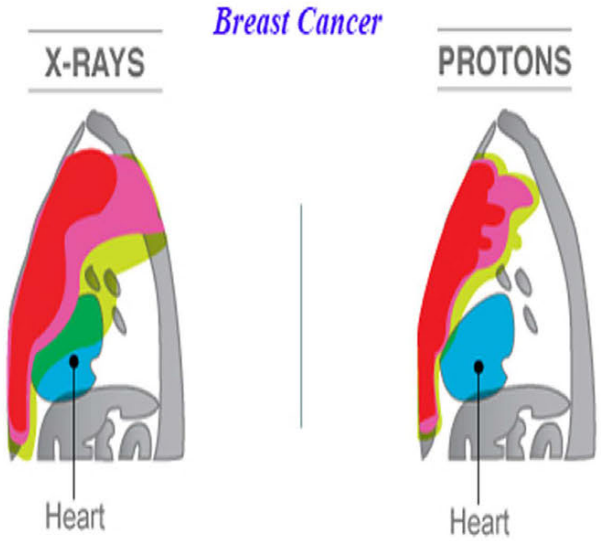


The fact that protons are a high LET type of radiation, yet show a low RBE has always been perplexing. However, maybe the issue is that the RBE is low *on average*, but could be significantly higher at the very end of the track where most of the energy is deposited. If so, **relying on the physical dose distribution could underestimate the "biological dose" by as much as 20-25%.**

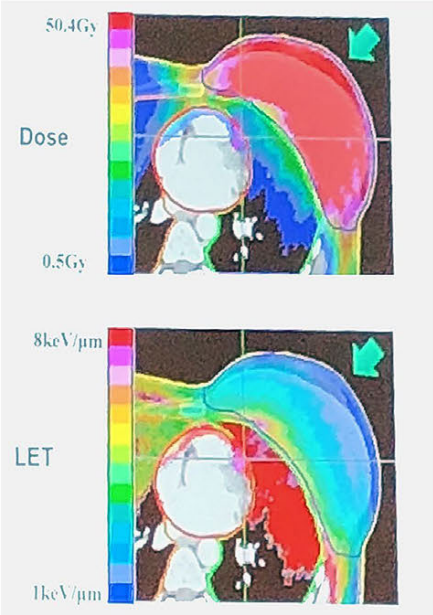


CT scans of a brain tumor patient treated with proton radiotherapy, with the physical dose distribution shown in Panel A (assumes a uniform proton RBE of 1.1), and an LET overlay, shown in Panel B.

Note that the highest LETs – and therefore RBEs – are at the very distal end of the beam path, and potentially extend beyond the tumor into the nornmal tissue by 1-2 mm.



Protons for breast or chest wall radiotherapy help keep dose out of the lung and off the heart (not to mention major coronary arteries and veins, plus some spinal cord)



Or do they?! When the dose distribution for breast irradiation with protons is corrected for LET, the "hottest" region is in the the ipsilateral normal lung and on the edge of the heart

So...if the proton RBE ***isn't*** a constant 1.1 (because the LET changes along the particle's path), how can this best be modeled, and what other factors come into play?

1) **at minimum, we'd need to consider the (macro) dose and dose fractionation pattern, the beam's energy, its LET and how it changes over the path length, and the organs-at-risk's "radiosensitivity", i.e., their α/β ratios, and whether the organ is serial or parallel in its functional organization**

a. we already know that the RBE increases with increasing LET, decreases with increasing total dose, and decreases with increasing α/β ratio, so that's a start

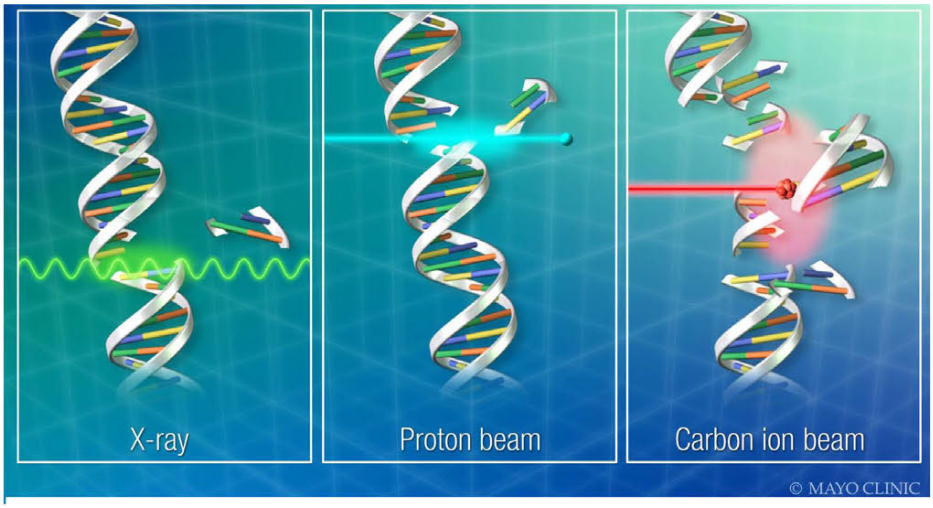
b. various mathematical models are currently under development to come up with an "RBE overlay" for treatment planning purposes, in order to avoid hot zones at the beam's distal end (particularly if they end up in normal tissue instead of the tumor)

2) unfortunately, ***what we don't yet know, and what is critically important, is whether making such an RBE correction during treatment planning actually changes patient outcomes***

d] Radiotherapy with even heavier charged particles (technically called "hadrontherapy")

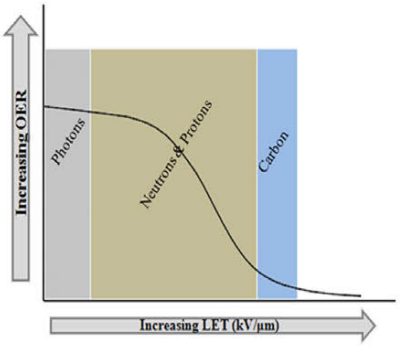
1. **Carbon ions are the next big thing in charged particle therapy because they should have both the depth dose advantage (even a little better than protons) and the radiobiological advantage (more like neutrons)**

a) as of mid-2019, there were 13 carbon ion radiotherapy facilities worldwide – several in Japan alone – but none in the US...until the recent announcement that the Mayo Clinic is planning to build one at its Jacksonville, FL facility (it will likely take 4-5 years before it's operational though)

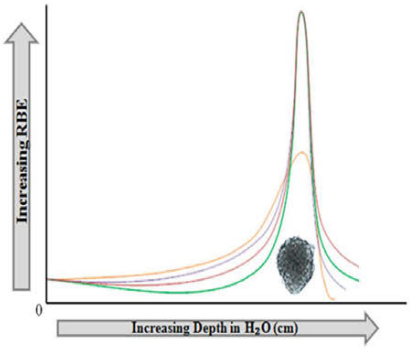


Radiation damage from carbon ions should be all "direct effect"

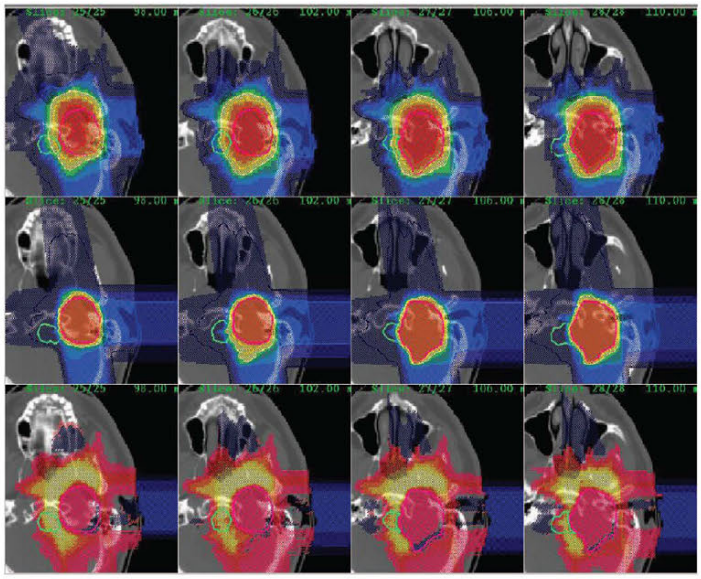
Carbon ions should have reduced OER



Carbon ions also have the depth dose and RBE advantages



Schlaff *et al. Radiation Oncology* 2014, **9**:88
http://www.ro-journal.com/content/9/1/88



Protons

Carbon Ions

Another advantage of carbon ions is that they should be even better than protons in terms of avoiding critical normal tissue structures

Dose Differential

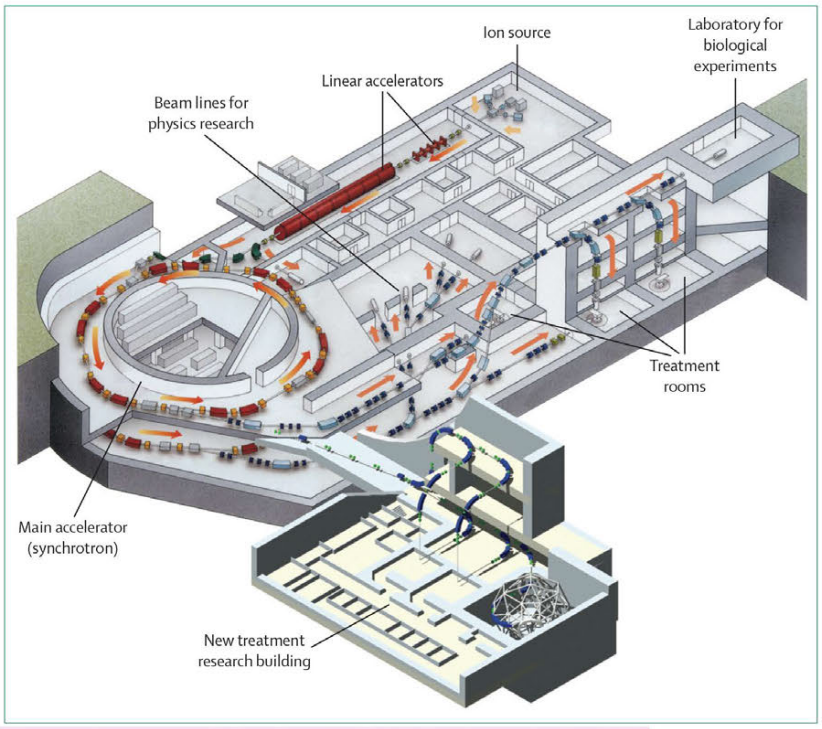
Red/Pink = areas where proton and carbon dose distributions differ by no more than 5%

Yellow/Orange = areas where protons deliver 10-20% higher dose than carbon ions

Ulli Weber, Gerhard Kraft
The Cancer Journal • Volume 15, Number 4, July/August 2009

Who does carbon ion radiotherapy?

1. two major centers have been operating the longest: ***the NIRS/HIMAC facility in Chiba, Japan, and the Heidelberg Ion Therapy Center (HIT) in Heidelberg, Germany***



www.thelancet.com/oncology Vol 16 February 2015

The HIMAC (Heavy-Ion Medical Accelerator in Chiba) facility (in operation since 1994)

Int J Radiat Oncol Biol Phys. 2021 Nov 1;111(3):597-609.

Rather impressive rotatable gantry at the Heidelberg Ion Facility

	Total number of patients (%)	Clinical practice
Prostate	1731 (22%)	1399
Bone and soft tissue	1033 (13%)	780
Head and neck	854 (11%)	529
Lung	795 (10%)	207
Liver	485 (6%)	250
Post-operative rectum	408 (5%)	338
Pancreas	353 (4%)	113
Gynaecological	207 (3%)	10
Eye	128 (2%)	86
CNS	106 (1%)	0
Para aortic lymph node	94 (1%)	87
Skull base	85 (1%)	56
Oesophagus	71 (1%)	0
Lacrimal gland	24 (<1%)	1
Scanning	11 (<1%)	0
Miscellaneous	1547 (20%)	715

Table 3: **Distribution of patients treated with carbon ion radiotherapy at the National Institute of Radiological Sciences by tumour type**

The Japanese have the most experience with carbon ion therapy, having treated thousands of patients over a 30 year period. Most patients either had inoperable cancers, cancers that were especially difficult to treat conventionally with X-rays and/or locally-advanced recurrent tumors.

Some studies report good-to-excellent 5 year overall survivals of 40-80% for the kinds of cancers that typically only have 0-30% 5 year survivals after radiotherapy with X-rays (e.g., sacral chordomas, pelvic osteo- and chondrosarcomas, retroperitoneal soft tissue sarcomas, etc.).

Unfortunately, it is virtually impossible for the Japanese to do large, randomized clinical trials in an academic setting because patients want carbon ions and none are willing to be assigned to the control group. Thus, most results come from smaller studies conducted as part of routine "clinical practice".

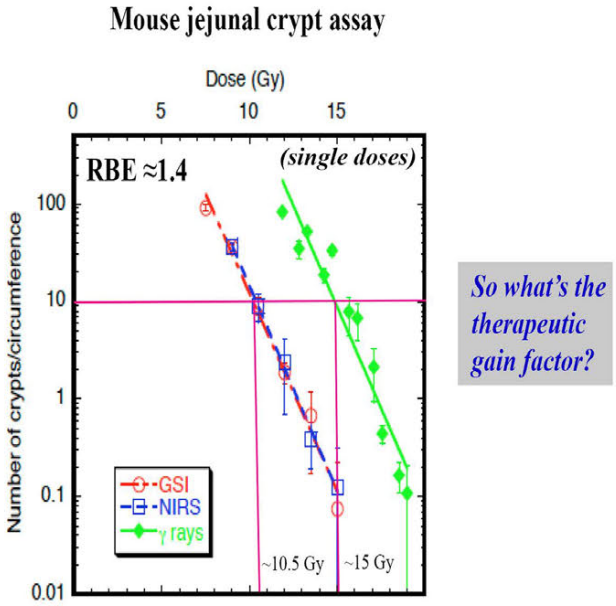
Carefully-controlled studies in laboratory rodents out of both Japan and Germany do seem to show significantly higher RBEs for carbon ions than for protons (when compared to photons):

TCD_{50} and RBE values measured in this study (6 fractions) and previous study (1 and 2 fractions) (9), including single standard errors and 90% confidence intervals (Rats bearing AT1 Dunning prostate adenocarcinoma flank tumors.)

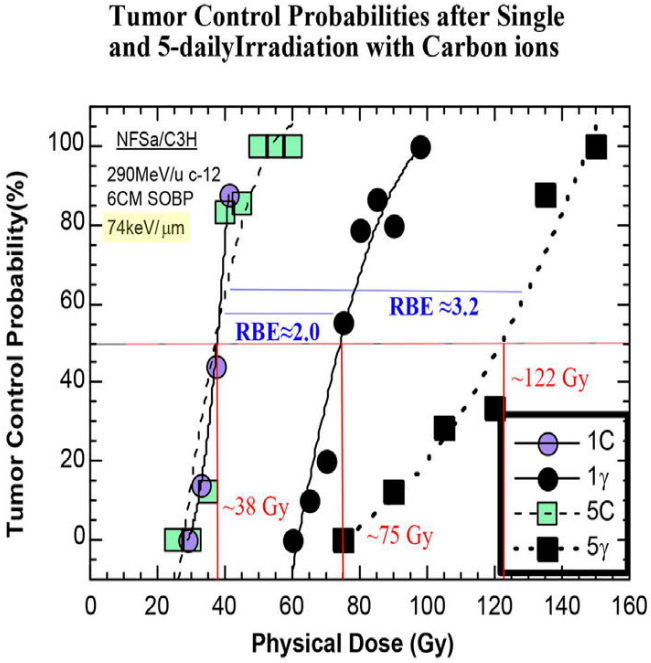
Study	TCD_{50} ± SE (90% CI) (Gy)		RBE ± SE (90% CI)
	Photons	Carbon ions	
1 Fraction*	75.7 ± 1.6 (69.9-78.6)	32.9 ± 0.9 (30.8-34.9)	2.30 ± 0.08 (2.17-2.44)
2 Fractions*	90.6 ± 2.3 (85.6-95.4)	37.9 ± 2.3 (33.6-42.6)	2.39 ± 0.16 (2.15-2.68)
6 Fractions	116.6 ± 3.0 (109.9-122.8)	43.7 ± 2.3 (39.1-47.5)	2.67 ± 0.15 (2.43-2.94)

Abbreviations: CI = confidence interval; RBE = relative biological effectiveness; TCD_{50} = dose at 50% tumor control probability.
The endpoint was local tumor control at 300 d; linear energy transfer equals 75 keV/µm (range, 64 to 96 keV/µm).
* Data from the previous study were re-evaluated by use of the actuarial approach for censored animals (as discussed in the text) instead of excluding these animals completely from the analysis. This slightly affected only TCD_{50} for 2 fractions of carbon ions (37.9 Gy instead of 38.0 Gy).

Int J Radiation Oncol Biol Phys, Vol. 86, No. 3, pp. 450–455, 2013



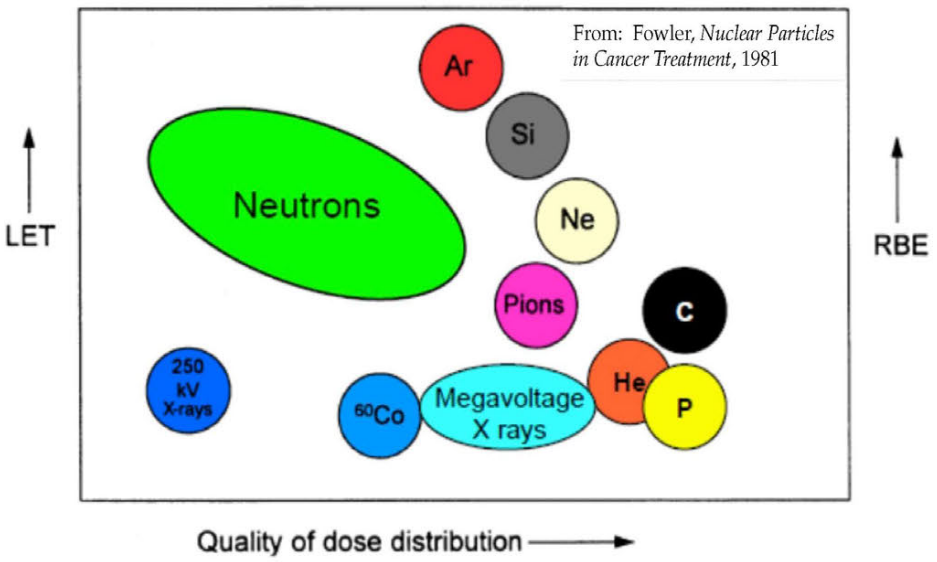
So what's the therapeutic gain factor?



In Summary...Charged Particle Radiotherapy

1) while the interest in high LET radiation therapy has waxed and waned over the years, **at present, most of the interest is focused on protons and carbon ions**

2) the heavier charged particles (like neon and argon ions) would, in theory, have the best mix of physics advantage and radiobiological advantage, however the prodigious costs, safety issues and awkwardness of patient throughput (i.e., most accelerators are associated with non-medical, high energy physics and weapons research facilities) make them unfeasible



radiations available for radiation therapy differ in the quality of beam that they produce, also in RBE.

Important Questions to Consider:

- ***Is a great dose distribution worth the expense, all else being equal?***

Comparison of IMRT, SBRT, protons, and carbon ions for prospective clinical trials*			
Radiation type	**Physical dose distribution**	**Fractionation**	**RBE**
IMRT	Excellent target conformality, high integral dose to normal tissue	Conventional to hyperfractionation	1 (low LET)
SBRT	Excellent target conformality, very high integral dose to normal tissue	Hypofractionation to oligofractionation	1 (low LET)
Protons	Excellent target conformality, ~60% lower integral dose to normal tissue compared with X-rays	Conventional to hypofractionation	1.1 (possibly higher in the distal part of the SOBP)
Heavy ions	As for protons, but with smaller lateral penumbra (reduced lateral scattering) and fragmentation tail beyond the Bragg peak	Conventional to oligofractionation	1 to 4 (depending on depth in the tissue, energy, tissue radiosensitivity, fractionation and so on)

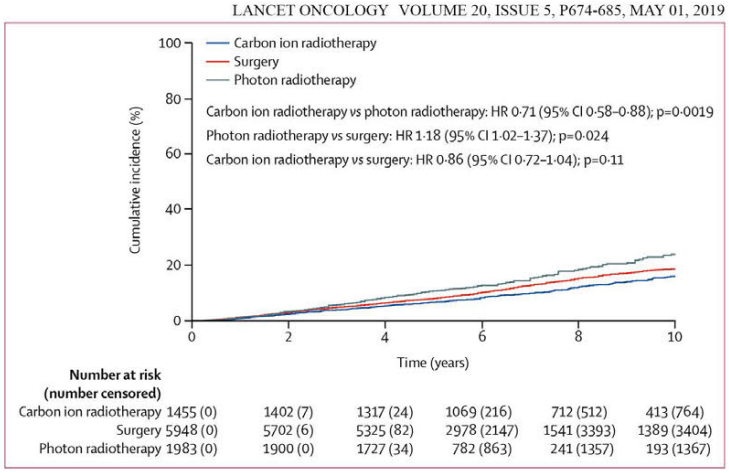
*These modalities differ in physical dose distribution, fractionation regimens, and radiation quality or LET. Abbreviations: IMRT, intensity-modulated radiotherapy; LET, linear energy transfer; RBE, relative biological effectiveness; SBRT, stereotactic body radiotherapy; SOBP, spread-out Bragg-peak.

- ***Will a big enough subset of patients benefit from high LET therapy to justify the cost of, for example, dedicated, self-contained treatment facilities?***

- ***Late effects from high LET treatment? (Carcinogenesis in particular.)***

In animal studies, high LET radiation (neutrons) *are* more carcinogenic per unit dose, however these experiments were done using big fields at minimum, if not whole body irradiation.

In clinical studies with human cancer patients however, the story could be dfferent because of highly conformal treatments and lack of exit doses characteristic of high LET beams. In this large retrospective series from NIRS in patients who received carbon ion radiotherapy for prostate cancer, the second cancer risk was significantly *lower* than for photons.



Cumulative incidence of subsequent primary cancers by treatment group

Pairwise hazard ratios (HRs) were calculated from cumulative incidence function models before propensity score weighting, which also included age, calendar year, and hormone therapy as covariates.

Appendix Materials
High LET Cheat Sheet!

Effect	High LET	Low LET
DNA damage	Mostly direct	70% is indirect
Ionizations	Dense	Sparse
Survival curve	Steeper slope; little or no shoulder	Shallower slope; larger shoulder
Alpha/beta ratio	Alpha is high, beta approaches zero	Alpha and beta components (typically)
Cell cycle effects	Little or none	Yes
SLDR	Little or none	Yes (but varies with cell type)
PLDR	Little or none	Yes (but varies with cell type)
OER	O_2 has little or no effect on radiosensitivity	O_2 enhances radiation damage
Radioprotectors	Little or no effect	Reduces radiosensitivity