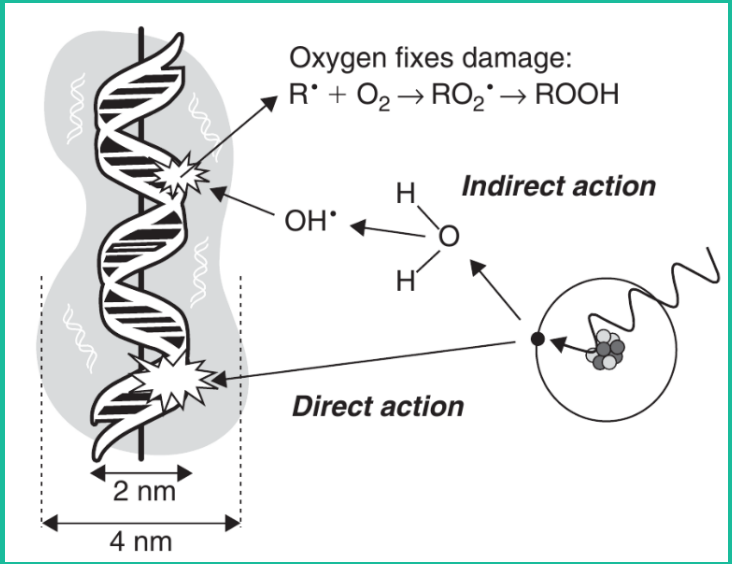

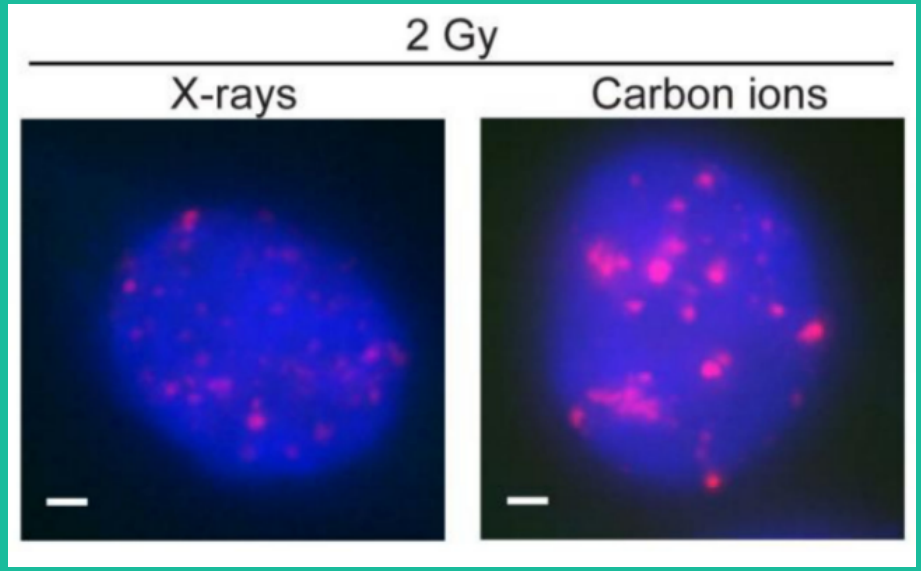

4: Biological effects of ionizing radiation

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14/05/2024

Question:
What are possible radiation effects on DNA? How much is the background radiation we receive daily (on average in “standard” conditions)?

Classification of DNA damage

- Natural DNA damages are common events since each human cell is subject to about 70000 lesions per day, classified as:
- **Base damages**: this is a very common type of genomic damage consisting of a chemical modification to a base of a nucleotide. It includes different effects. About 25% of the spontaneous lesions are base damages.

- **Single Strand Breaks (SSB)**: it occurs when one of the two DNA helix structure is damaged. Spontaneous SSBs are very frequent, estimated to be about 55000 per cell per day (~ 75% of the total lesions).

- **Double Strand Breaks (DSB)**: if two SSB affect the same DNA molecule on both the helix, the damage is more severe with respect to SSB and it is defined as DSB. The estimated frequency of DSB per cell per day is about 25/70000.

Classification of DNA damage

- **Clustered lesions**: referred to complex lesions or locally multiplied damaged sites. It is defined as the case in which two or more lesions are located within 10 or 20 base pairs (~1-2 helical turns of the DNA). This category has great variability due to the multiplicity of the type of lesions and the number of lesions per cluster. Due to its complexity, clustered lesions are the most difficult to be repaired, showing a great level of damage and mutability due to inaccurate repair. It is very rare in nature if not induced by ionizing radiations or chemicals

- The effectiveness of ionizing radiations are various depending on the different DNA repair systems that contrast the diverse forms of damages caused by different agents

- The main goal of PT is to produce permanent damages in the tumorous tissues by means of clustered DSB lesions

DNA damage and reparability

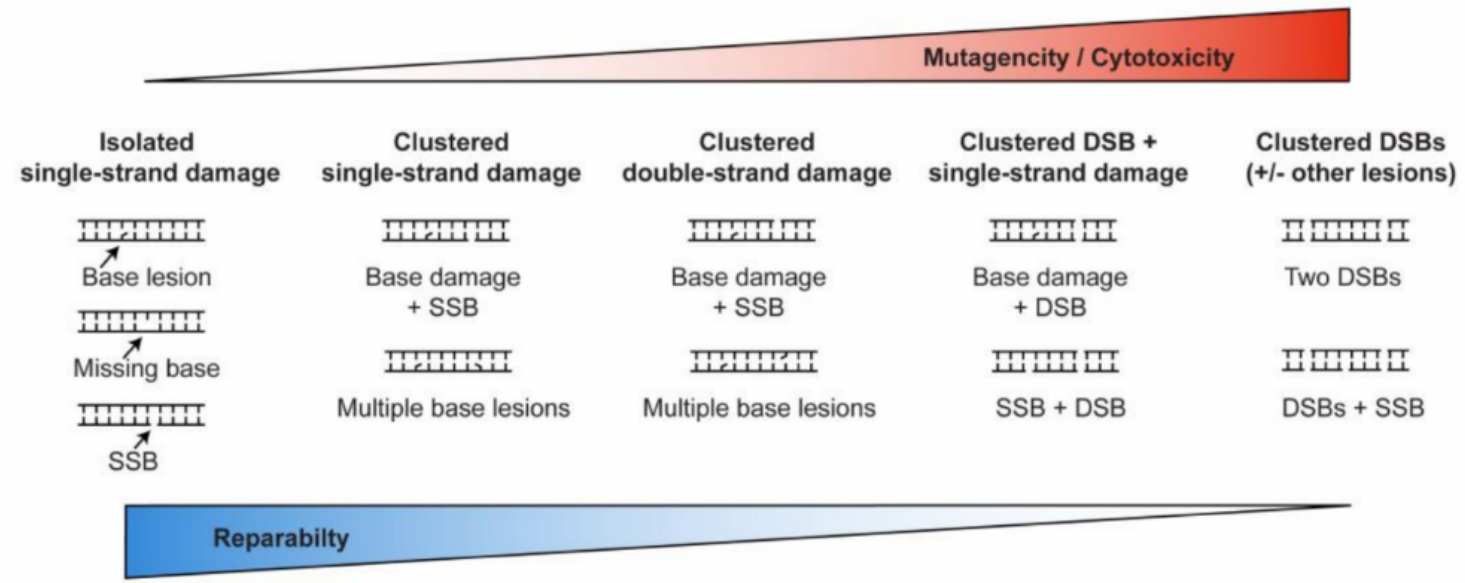


Figure 1.9: Classification of DNA damages. The damage complexity increase from left to right, corresponding to an increase of mutagencity and cytotoxicity and a decrease of the reparability [49].

Jac Nickoloff, Neelam Sharma, and Taylor. Clustered dna double-strand breaks: Biological effects and relevance to cancer radiotherapy. Genes, 11:99, 01 2020.

Question:
Is there a way to evaluate if a DNA damage is due to an external radiation effect or due to “natural“ DNA mutation?

Physic quantity: LET

- **Linear energy transfer** (LET) can be defined as the amount of energy (dE) locally transferred from an ionizing particle to the material traversed per unit distance (dl):

$$\mathrm{LET}_{\Delta} = \left(\frac{dE}{dl}\right)_{\Delta}$$

- The Δ is an upper threshold for the energy of secondary electrons, adopted to consider only the amount of energy deposited close to the primary particle track
- linear energy transfer is defined by where refers to the energy loss due to electronic collisions *minus* the kinetic energies of all secondary electrons with energy larger than Δ.

Question:
Hey, the definition of LET seems familiar, isn't that the definition of…?

Physic quantity: LET

- LET is also called "restricted linear electronic stopping power"
- If no upper limit is considered, the unrestricted LET (LET∞) is equal to the electronic stopping power
- Units of measurement:
  LET is expressed in terms of keV/mm or MeV/cm
- Whereas stopping power, the energy loss per unit distance, focusses upon the energy loss of the particle, linear energy transfer focuses upon the energy transferred to the material surrounding the particle track, by means of secondary electrons
- Since one is usually interested in energy transferred to the material in the vicinity of the particle track, one excludes secondary electrons with energies larger than a certain value Δ

LET values

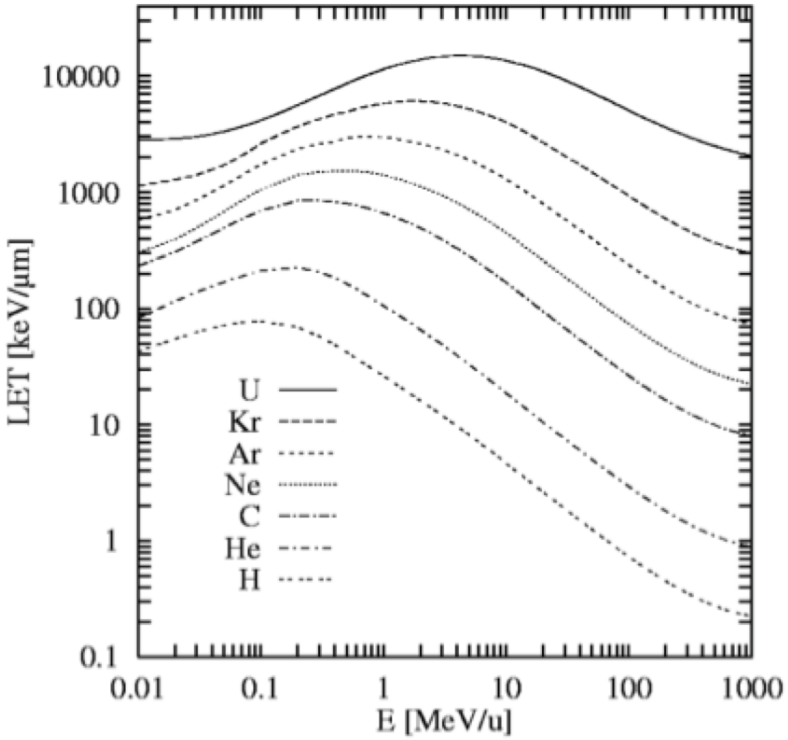
Table 1.1: Average LET values of different radiations in water [50].

Radiation	Cut off energy Δ (eV)	LET_Δ (keV/µm)
^{60}C gamma rays	Unrestricted	0.239
	100	0.229
22 MeV X-rays	100	0.19
2 MeV electrons (whole track)	100	0.20
^{3}H β particles	100	4.7
50 kV X-rays	100	6.3
5.3 MeV α particles (whole track)	100	43

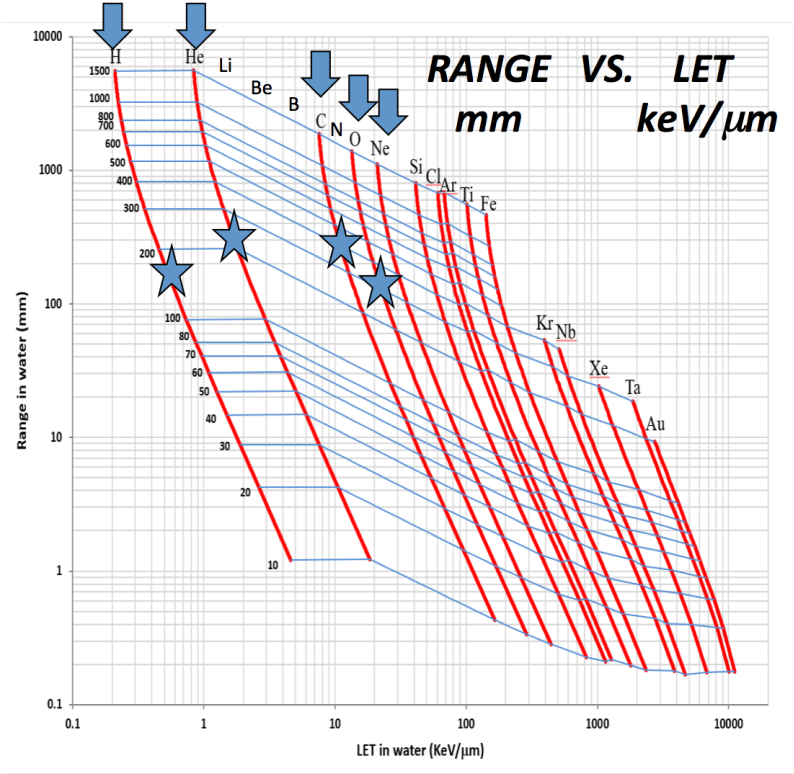
Michael F. L'Annunziata Handbook of Radioactivity Analysis 2012.

- **The relevance of the DNA damages that a ionizing particle can produce in a cell is directly related to the LET**
- **X-rays and γ-rays** adopted in conventional radiotherapy are considered as **low LET** radiation
- At the energy of interest for the medical treatments, their interactions with matter is based on the Compton scattering and the photoelectric effect
- **heavy charged particles** adopted in PT are considered as **high LET** particles
- due to their enhanced energy deposition density along the track path, they tend to create more DSB and clustered lesions

LET values



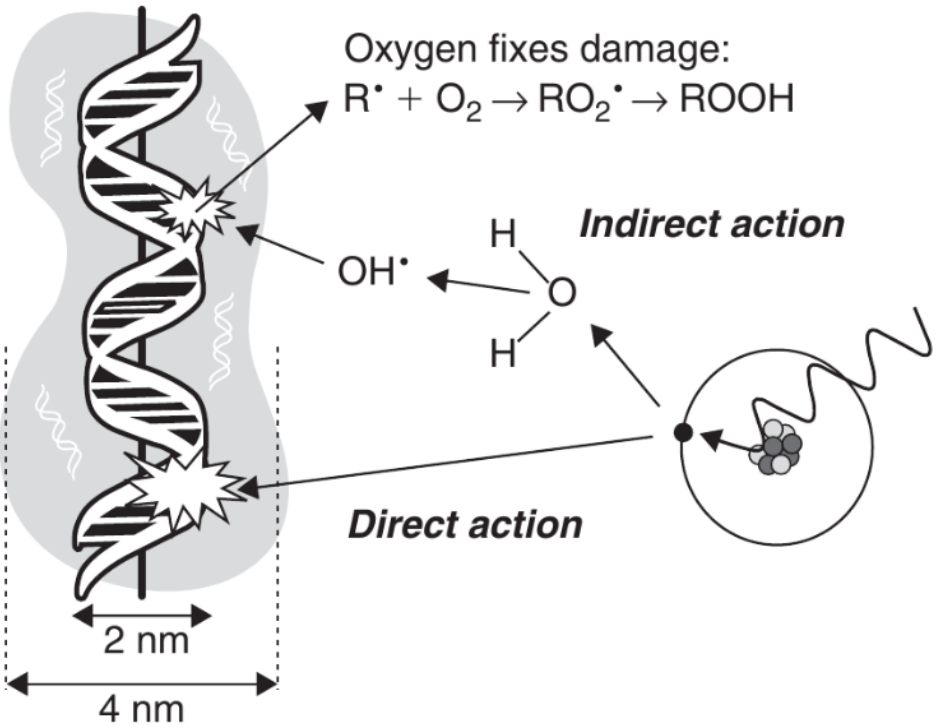
LET of particles nearby the Bragg peak in water related to dose imparted in PT



NSRL BEAMS Brookhaven National Laboratory

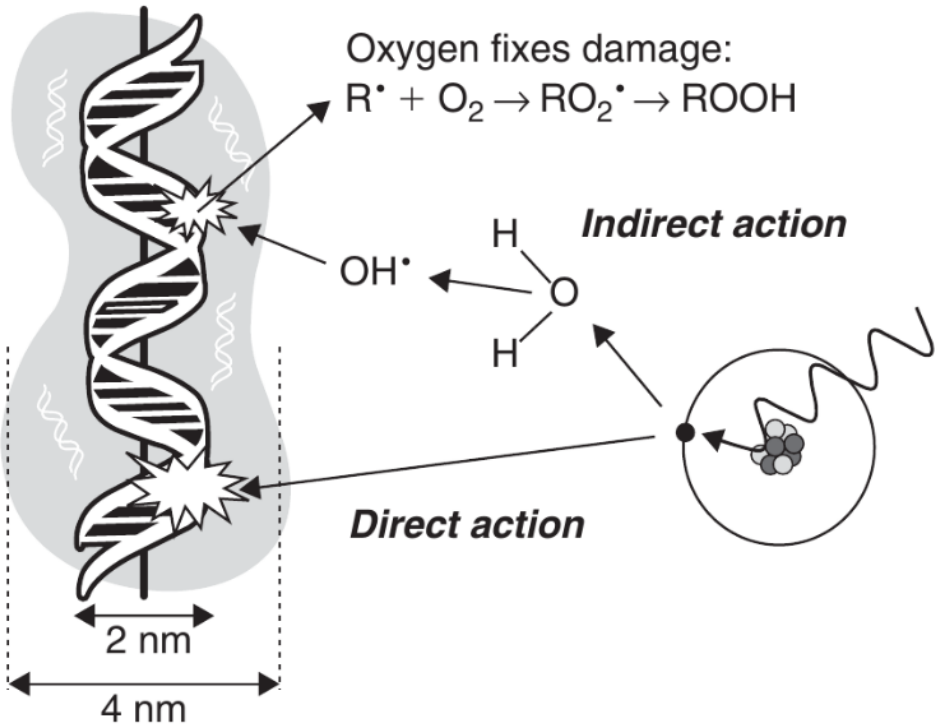
Adam Rusek 2015

DNA damage



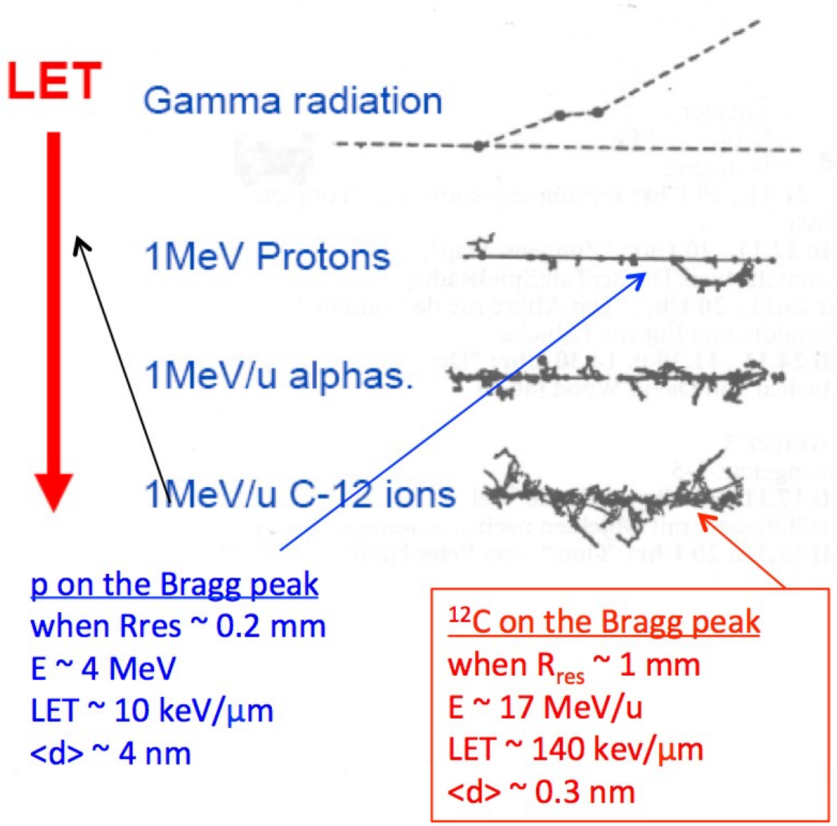
- The main goal of PT treatments is to damage the DNA
- It is the largest molecule in the cell, it is present only in two copies with a very limited turnover and it is central to all the cellular functions
- **The DNA can be damaged both directly and indirectly by by the incident radiation**
- **Direct damage:**
  Radiation directly ionises the DNA

DNA indirect damages



- **Indirect damage:**
  Ionizing radiation interact with water molecules inside the tissue, producing free radicals (OH) that damage the DNA
- **oxygen-fixation hypothesis:**
  When radiation is absorbed in a biological material, free radicals are produced. These radicals are highly reactive molecules and it is these radicals that break chemical bonds, produce chemical changes and initiate the chain of events that result in biological damage

Ionization density



The ionisation density is related to LET and related to the DNA damage

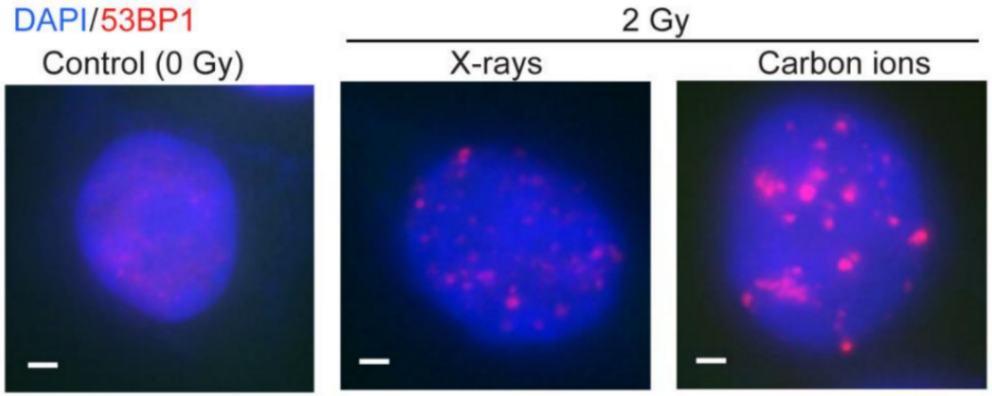
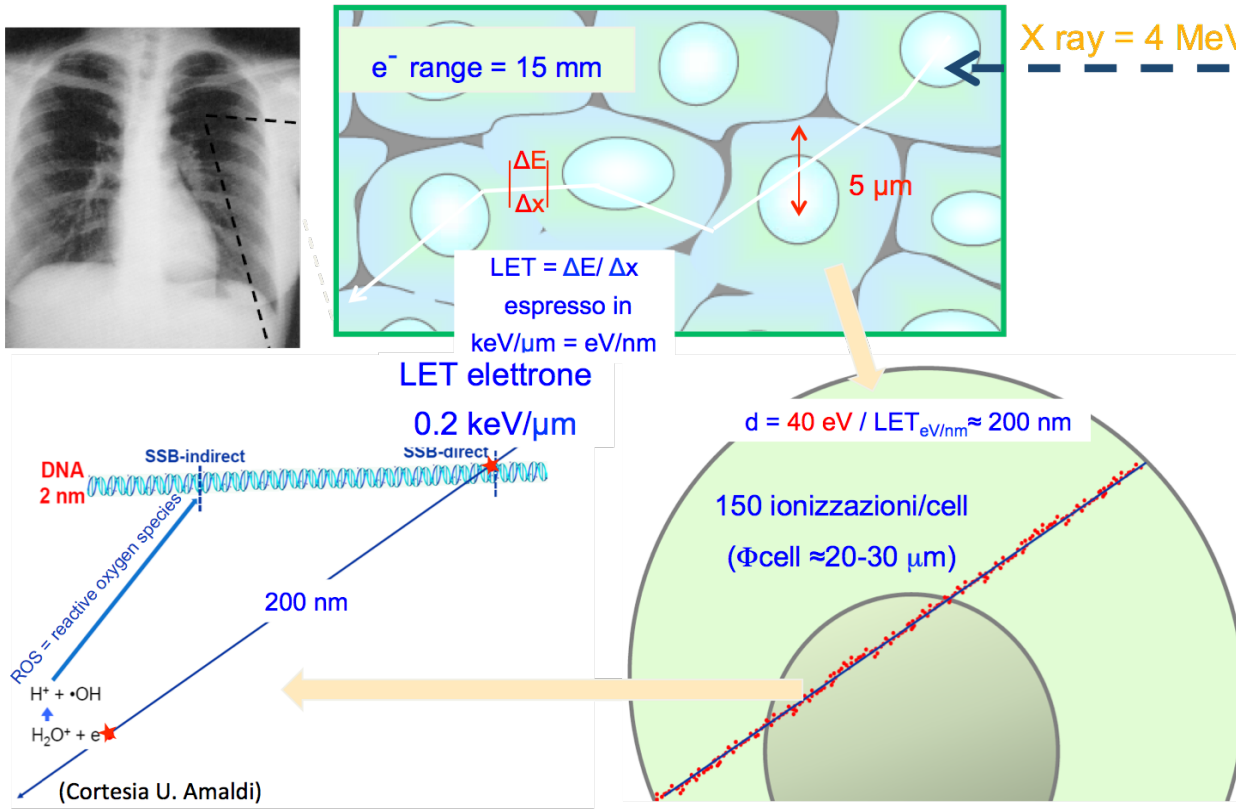


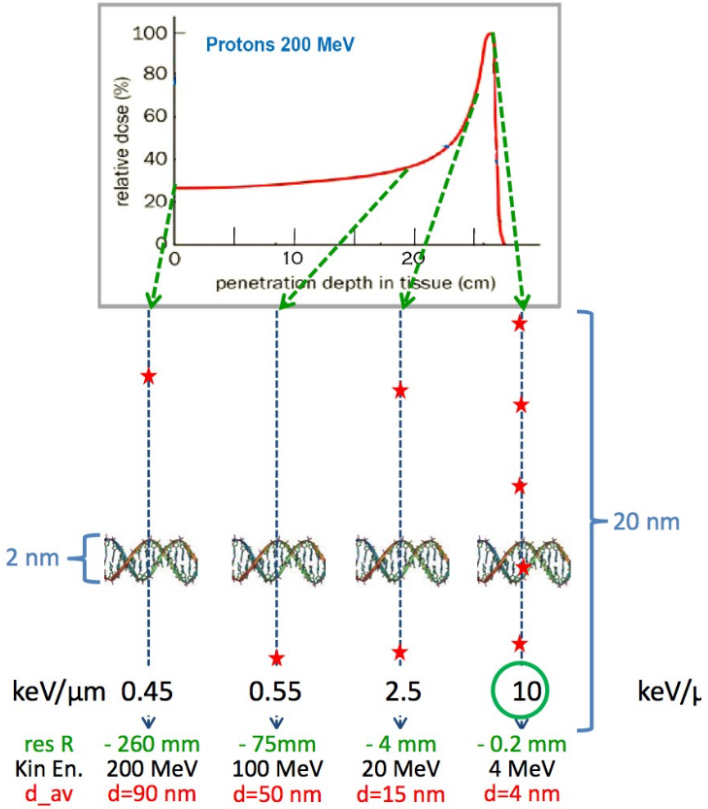
Figure 1.10: Pictures of a RKO colon carcinoma cell under normal conditions (left) and irradiated with 2 Gy of X-rays (center) and carbon ions (right). Cell nuclei are stained in blue with DAPI and DSB damages are stained in red with 53BP1. White scale bars are 1 nm [49].

Ionization density: photons



- Typical cell size: 20-30μm
- dE~40eV ; LET~0.2 ev/nm
- Ionization density~1/(200 nm)
- Ionization density~150/cell
- At the scale of the cell nucleus, **γ-rays deposit much of their energy as single isolated ionizations or excitations** and much of the resulting DNA damage is efficiently repaired by enzymes within the nucleus

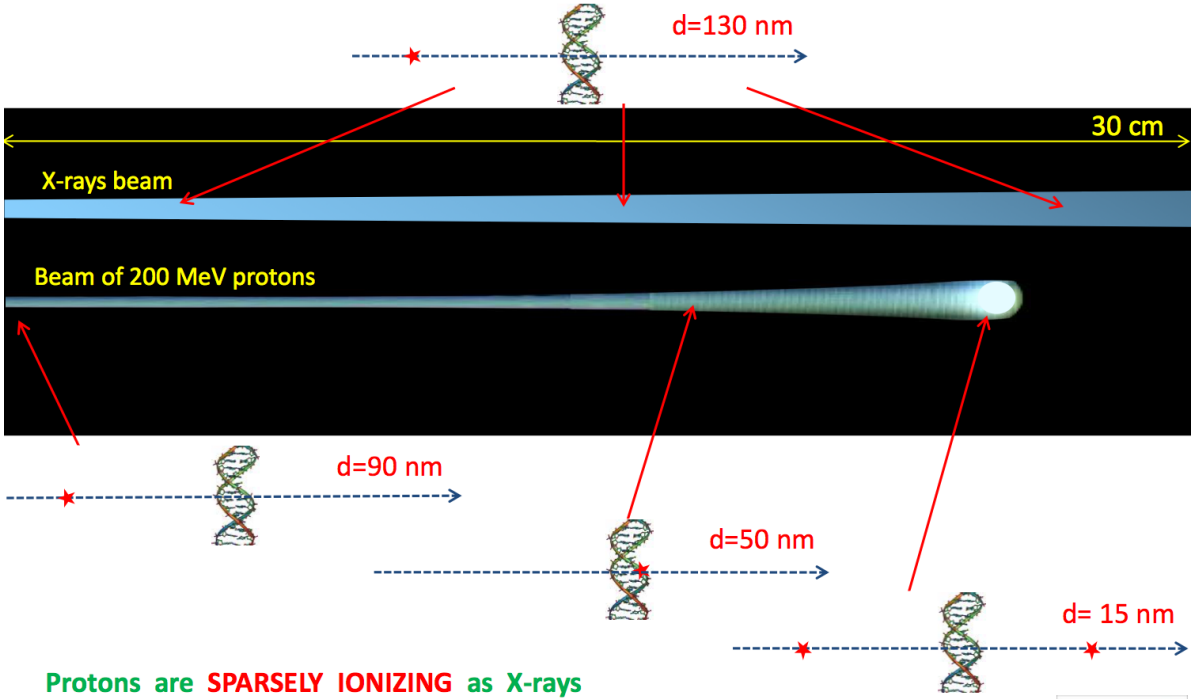
Ionization density: protons



- Protons are sparsely ionizing radiation
- The LET, the particle energy and the ionization density varies along the penetration depth
- **In the Bragg peak the LET and the ionization density are higher**
- The probability to cause more severe damage to the DNA is higher in the Bragg peak
- The biological effectiveness in the BP is enhanced

Ionization density: protons

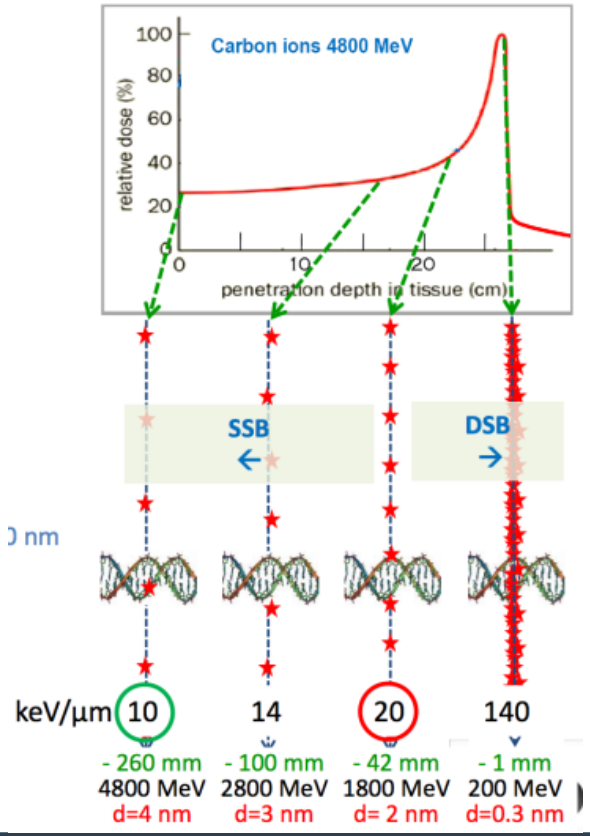
Protons: 1. more favorable dose 2. same '**indirect effects**'



Protons are SPARSELY IONIZING as X-rays

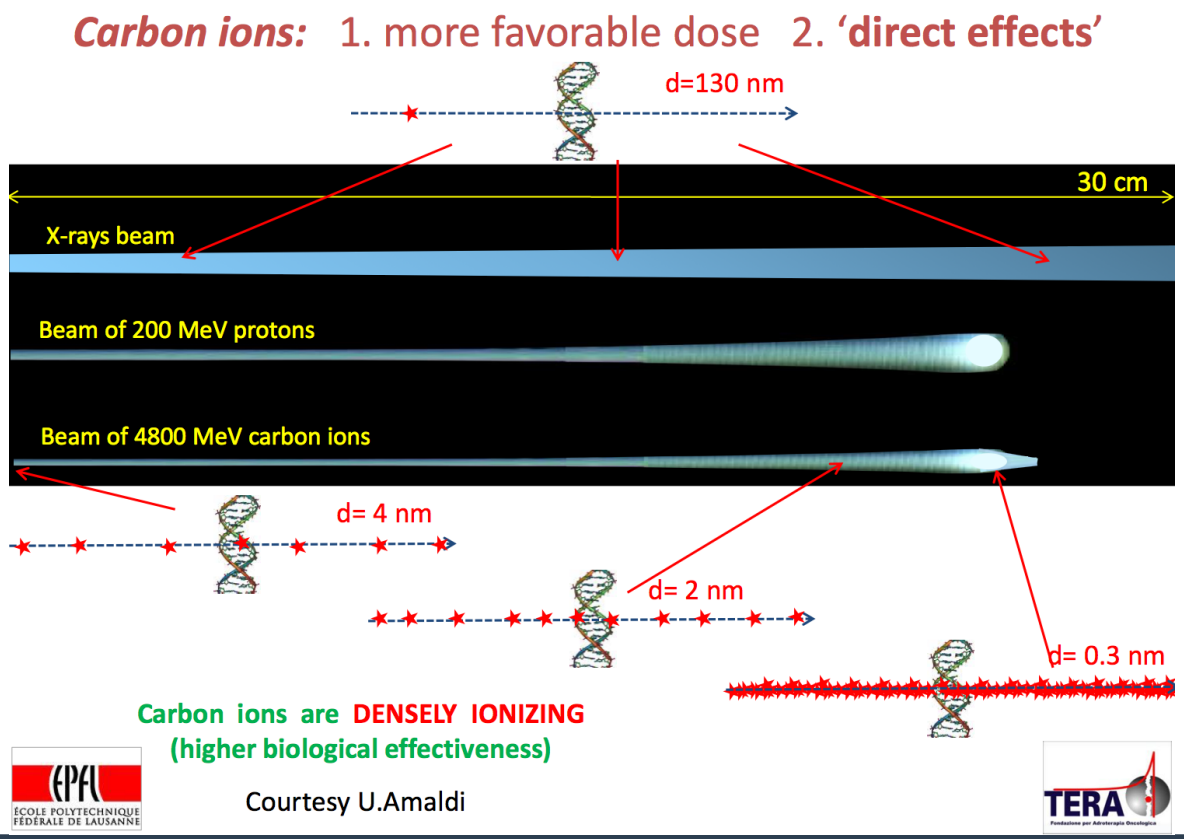
Courtesy U.Amaldi

Ionization density: ^{12}C ions



- **^{12}C ions are highly ionizing radiation**
- The LET, the particle energy and the ionization density varies along the penetration depth
- In the Bragg peak the LET and the ionization density are higher
- The probability to cause more severe damage to the DNA is higher in the Bragg peak
- The biological effectiveness in the BP is enhanced
- **Check the numbers**: the ionization of the heavy charged ions at the entrance channel is similar to the ionization of protons at the BP

Ionization density: ^{12}C ions



Ionization density: ^{12}C ions

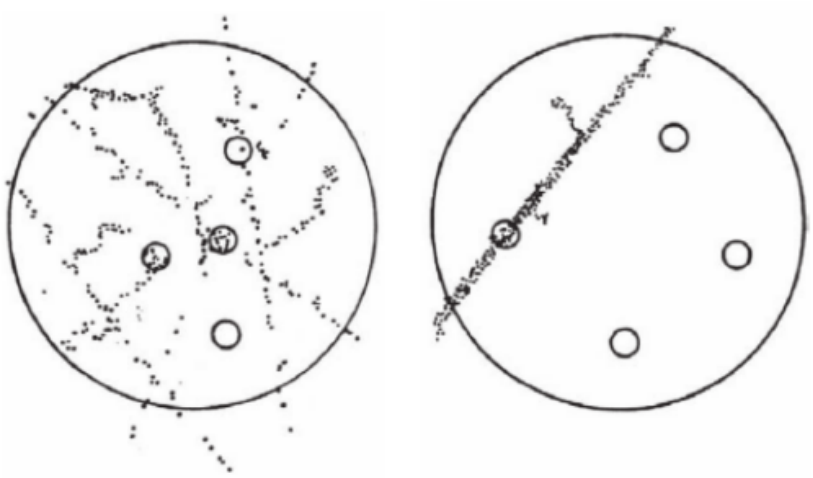
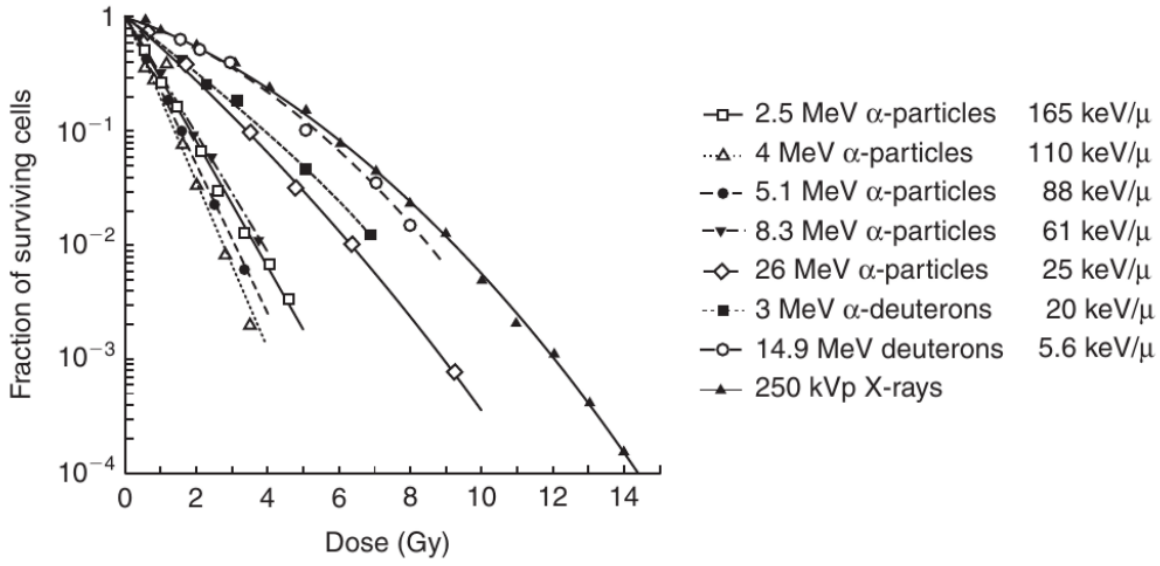


Figure 1.7: Ionization density in a medium irradiated by X-rays (a) and high LET particles (b). The small circles represent biological targets and the dots represent ionization produced along the tracks [1].

Survival curves

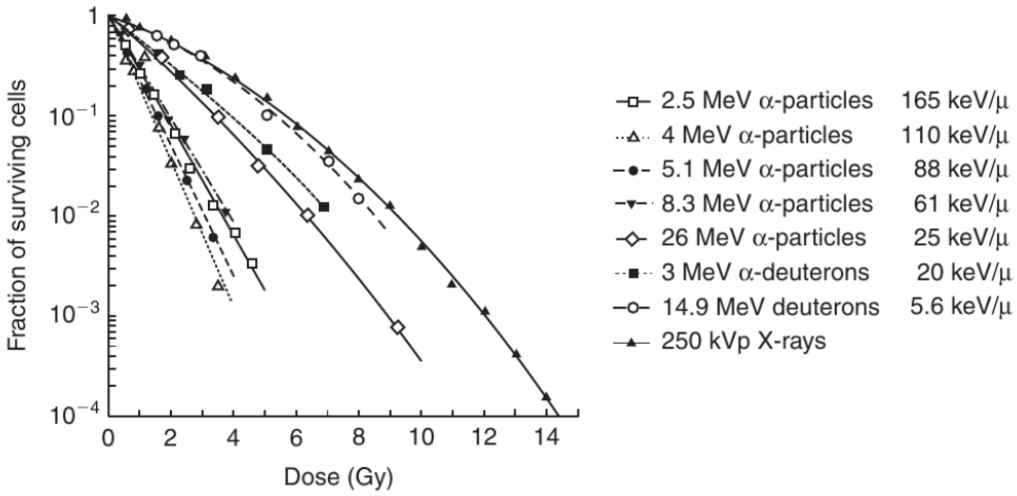
In order to quantify the biological enhanced effectiveness of charged hadrons over the photons adopted in classical radiotherapy, different parameters have to be introduced

Cell survival curve represents the fraction of surviving cells with reproduction capability as a function of the absorbed dose



- At high doses, all the survival curves tend to have a linear evolution,
- In the low dose region, only the particles associated with a low LET values have a shoulder with a non linear tendency

Survival curves



- The conventional parametrization of the survival curves is the Linear Quadratic model:

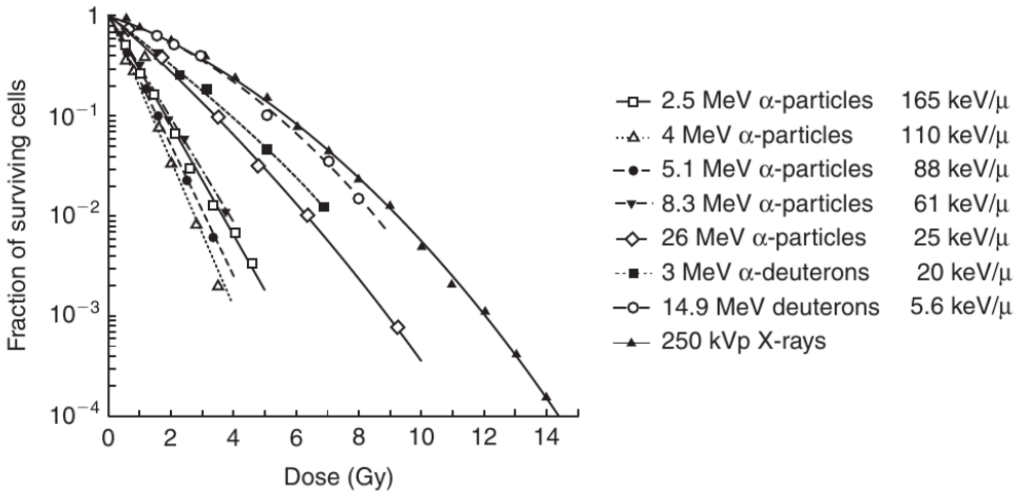
$$S(D) = e^{-\alpha D - \beta D^2}$$

S is the survival fraction, D is the absorbed dose, α and β are experimental parameters

- α is related to the slope of the linear component of the curves and it is usually considered when single ionisation events causing lethal damages occur

- The quadratic term β is related to two distinct ionisation events, each one not causing lethal damage, while their interaction as a double does

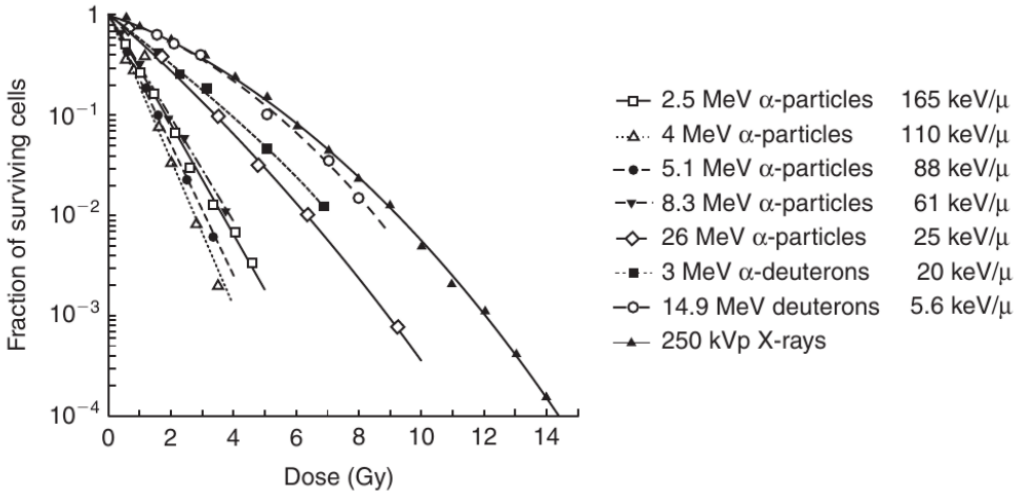
Survival curves



- The ratio **α/β describes the shoulder of the survival curves** at low doses and it gives indications related to the reparability of the damages.
  It depends both on the target tissue and on the incident particle properties.
  High α/β ratio is associated to particles with high LET and it corresponds to radiations that can provide more severe and irreparable damages to the target cells

- Given the same type of radiation, particles with lower energies are associated with higher values of LET and higher values of α/β ratio due to the LET dependency on the particle velocity (LET~ β^{-2})

α/β



Large α/β ratios

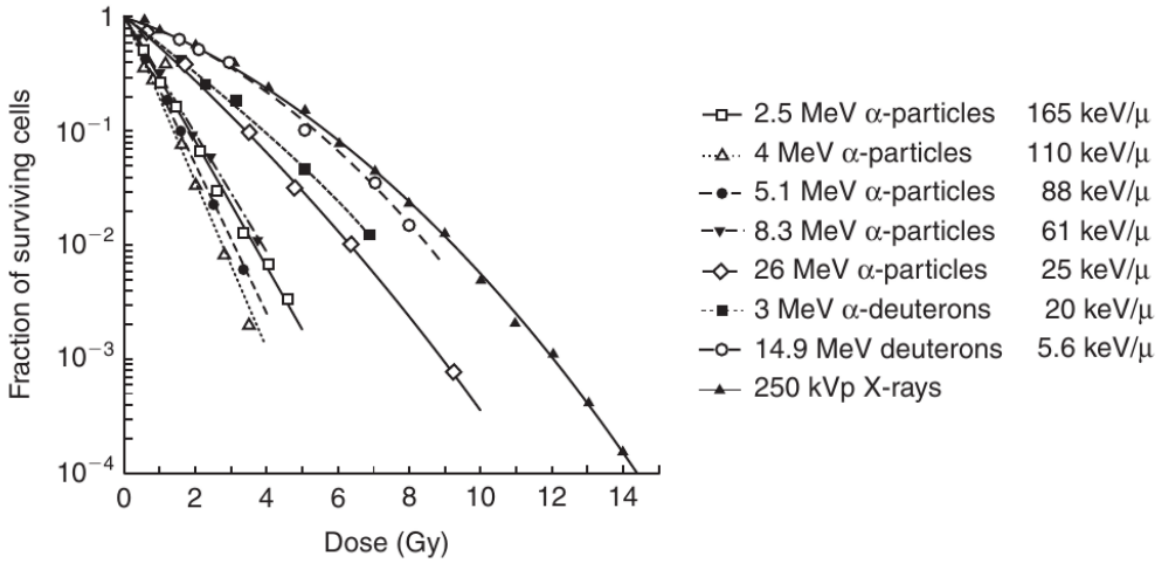
- α/β = 10 to 20
- Early or acute reacting tissues
- Most tumours

Small α/β ratio

- α/β = 2
- Late reacting tissues, *e.g.* spinal cord
- potentially prostate cancer

Question:
the curve associated with the 2.5 MeV α particles has the highest LET values, but not the highest α/β ratio, guess why

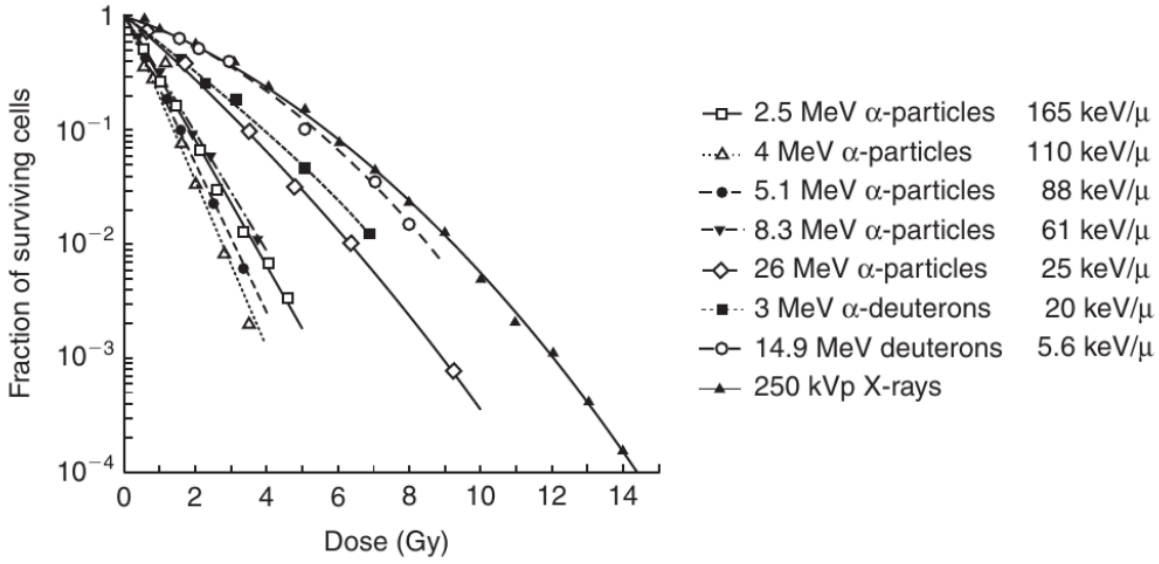
Overkill effect



- **the curve associated with the 2.5 MeV α particles has the highest LET values, but not the highest α/β ratio**
- **This is given by the combination of the overkill effect and the stopping power behaviour at low energies**
- the projectile delivers more energy than the necessary to kill a cell, wasting the dose release

Question:
How the stopping power behaviour at low energies can have an effect on the LET and the α/β ratio?

Fluence effect



- Given an absorbed dose value, the enhancement of the energy loss at low energy range leads to the reduction of the incident particle fluence with the consequent reduction of the number of damaged target cells

Relative Biological Effectiveness (RBE)

- The α/β ratio is a parameter strictly related to the linear quadratic model and it is not sufficient to fully take into account the different biological aspects
- A more comprehensive parameter is the Relative Biological Effectiveness (RBE) defined as the ratio of a reference radiation dose (Dref) and the dose of the interested radiation (Dtest) that produces the same effect (isoeffect):

$$\mathrm{RBE} = \left.\frac{\mathrm{D_{ref}}}{\mathrm{D_{test}}}\right|_{\mathrm{iso}}$$

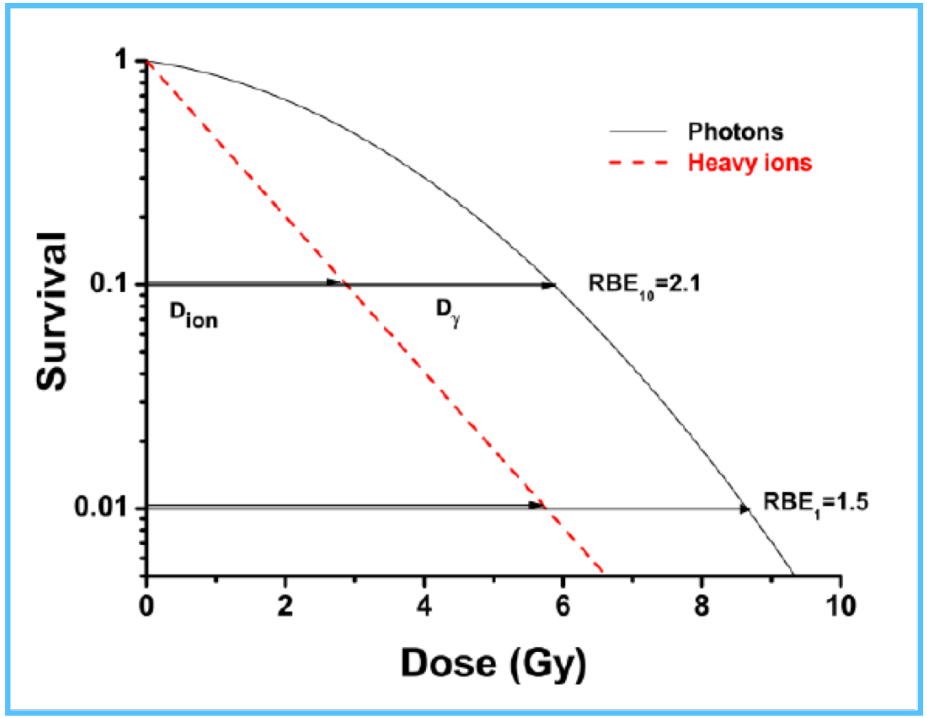
  The reference radiation commonly adopted is the 250 kVp X-rays or the 60Co γ rays, since they are low LET radiation sources regularly available in clinical or experimental facilities

- **The RBE is one of the most important parameter for the treatment planning**

Easy question:
what is the unit for the RBE?

Question:
How to measure the RBE experimentally?

RBE dependances

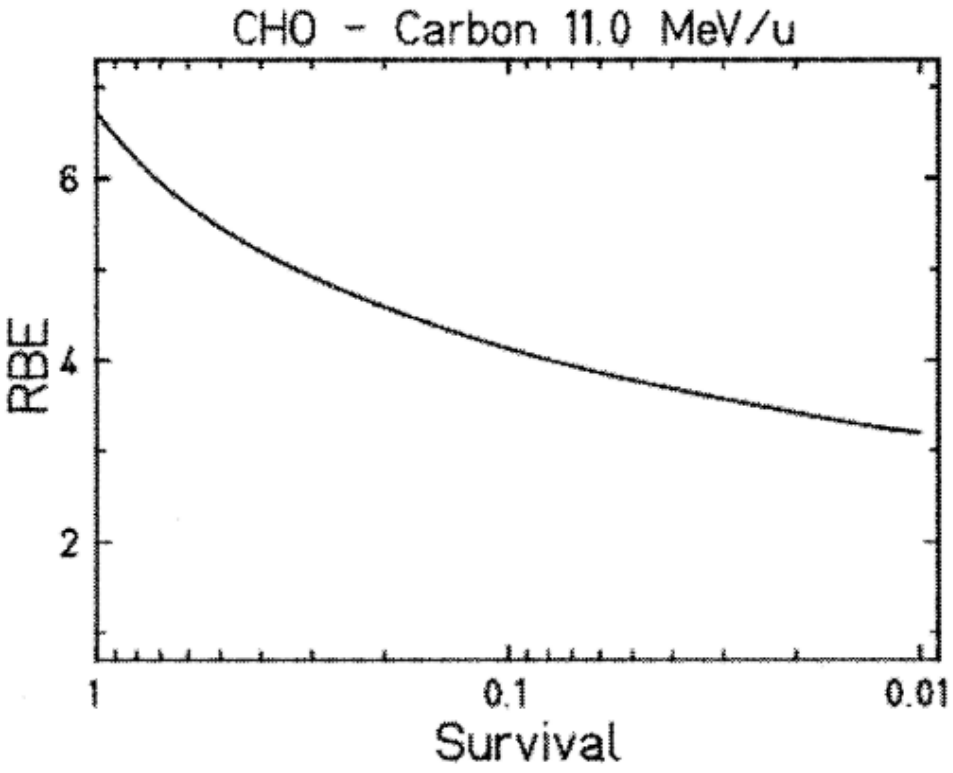


- Typically, the RBE is determined from cell survival curves and the isoeffect is set to be at some percentage of the survival fraction
  In the example: RBE_{10} =2.1; RBE_1 =1.5
  But other criteria can be considered

The RBE depends on different parameters:

- The definition of RBE itself
- Biological effect considered for “isoeffect” (e.g.: survival rate, number of damaged cells etc.)
- Specific type and conditions of target cells
- Incident radiation, dose etc.

RBE vs survival fraction

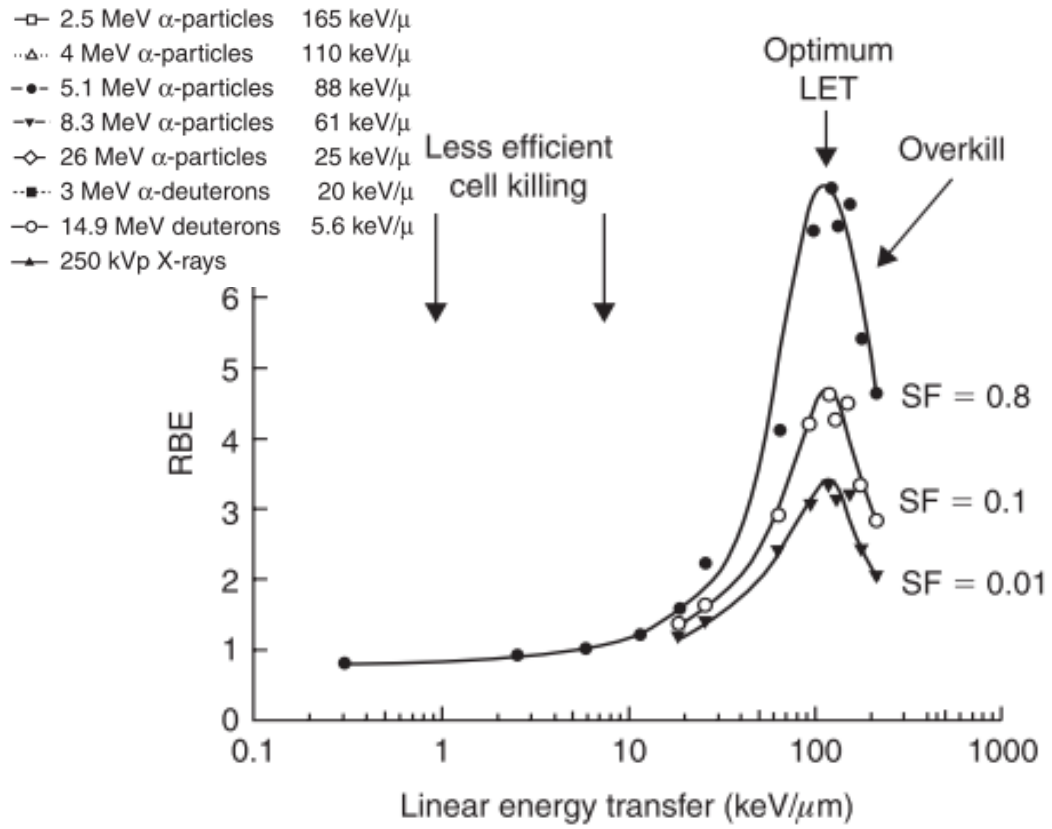


- The RBE is greatest for high survival and decreases towards lower survival
- reaching an asymptotic value at a survival close to 100% that is given by the ratio of the α values of the two dose response curves for x-rays and particles, respectively
  E.g.:

$$\mathrm{RBE}_{\alpha} = \frac{\alpha_C}{\alpha_X}$$

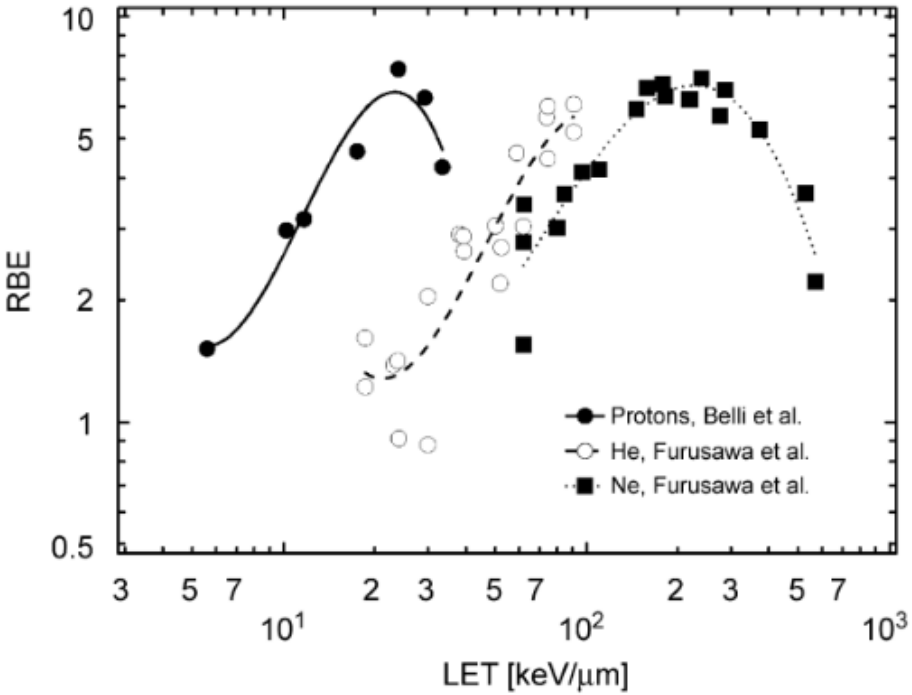
α_C and α_V are the α values of the carbon and x-ray curves,

RBE vs LET



- The RBE depends on the LET: it increases with LET up to an ion-dependent maximum value
- At high LET value, the RBE decreases due to the overkill effect
- Radiation of optimal LET deposits the right amount of energy per cell, which produces just enough DNA double-strand breaks to kill the cell
- This optimum LET is usually around 100keV/μm but does vary between different cell types and depends on the spectrum of LET values in the radiation beam as well as the mean LET

RBE vs LET



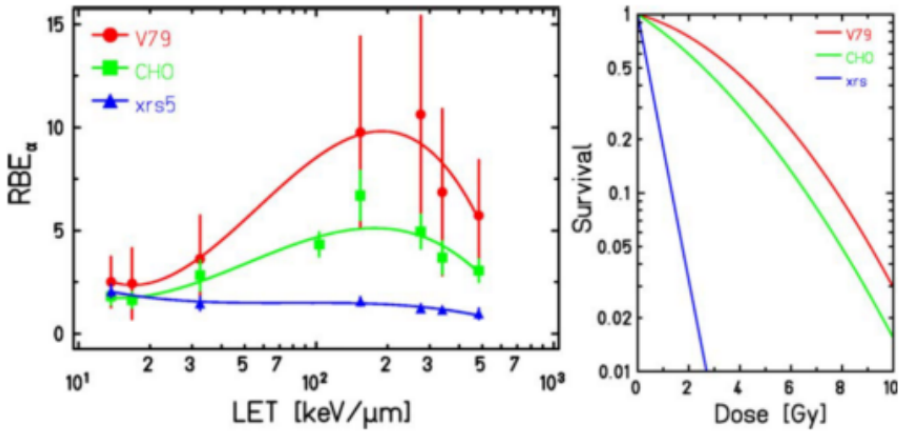


Figure 1.15: Left: Dependence of RBE$_\alpha$ on three hamster cell lines CHO, V79, and XRS after carbon irradiation. Right: Survival curves of the same cell lines. Figure from

RBE vs LET

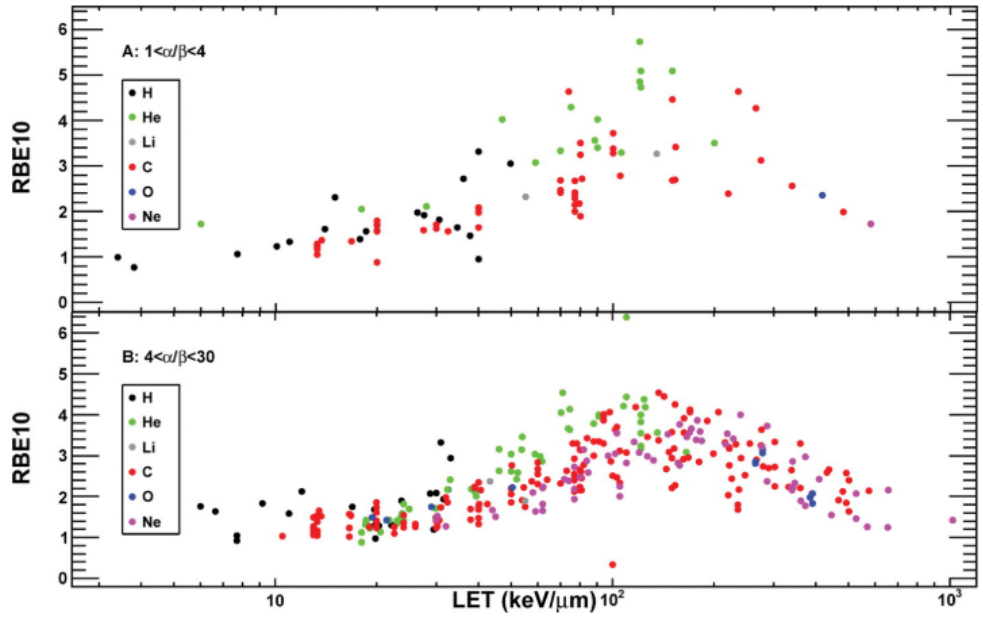
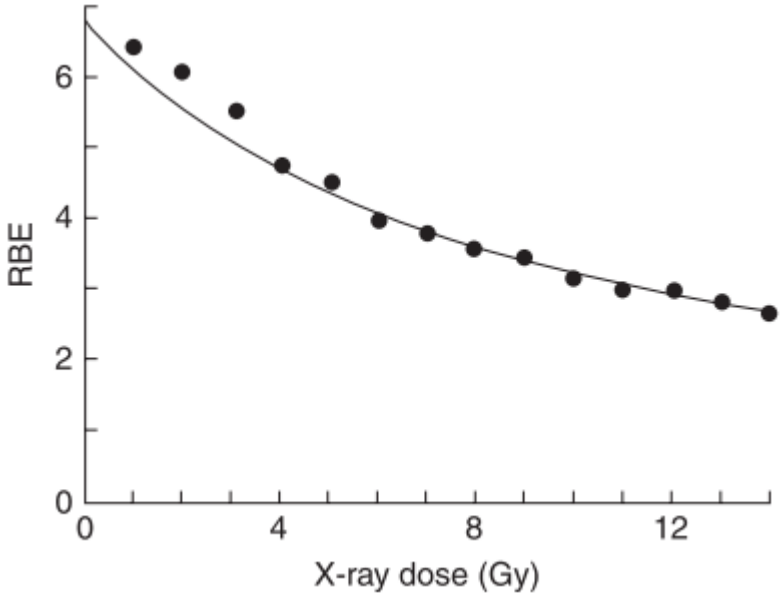


Figure 1.10: RBE at 10% survival level of different monoenergetic particle beams as function of LET, grouped in different sensitivity ranges (α/β) [55].

RBE vs Dose



RBE for test doses of 4MeV α-particles plotted against a reference dose of 250kVp X-rays, for the T1g human cells irradiated in vitro.

- The RBE for the 4.0MeV α increases with decreasing dose because the low-LET X-ray survival response is more curved and has a bigger shoulder than the high-LET survival response
- Using the LQ model for the survival fraction curves, the RBE can be predicted mathematically as a function of the reference dose (d_R) or the test dose (d_T):

$$\mathrm{RBE} = \frac{K + \sqrt{K^2 + 4Kd_R(1 + d_R/V)/C}}{2(1 + d_R/V)}$$

$$\mathrm{RBE} = \frac{-V + \sqrt{V^2 + 4VKd_T(1 + d_T/C)}}{2d_T}$$

where $K=\alpha_T/\alpha_R$; $V=\alpha_R/\beta_R$; $C=\alpha_T/\beta_T$

Values of RBE in protontherapy

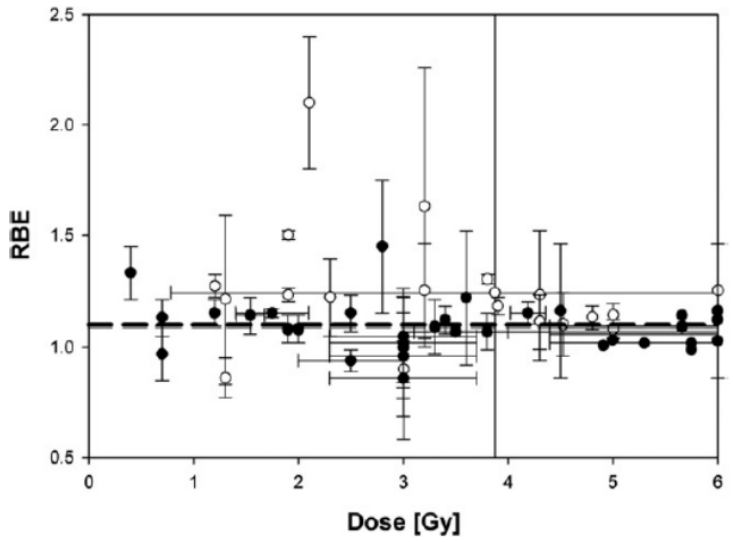


Figure 2.1: Experimental RBE values (relative to ^{60} Co) as a function of dose/fraction for cell inactivation measured *in vitro* (open circles) and *in vivo* (closed circles). The thick dashed line illustrates an RBE of 1.1 [43].

- **In protontherapy the RBE is assumed to be a fixed value of 1.1**
- This value was deduced as an average value of in vivo measured RBE value,mostly done in the early days of proton therapy, for the center of the target volume, at 2 Gy, averaged over various endpoints
- Data show different values of RBE both for in vitro systems and for in vivo systems, respectively 1.22±0.02 and 1.10±0.01 for an average RBE in the center of a spread-out Bragg peak (SOBP) relative to ^{60}Co photon radiation for 65-250 MeV proton irradiation

Values of RBE in protontherapy

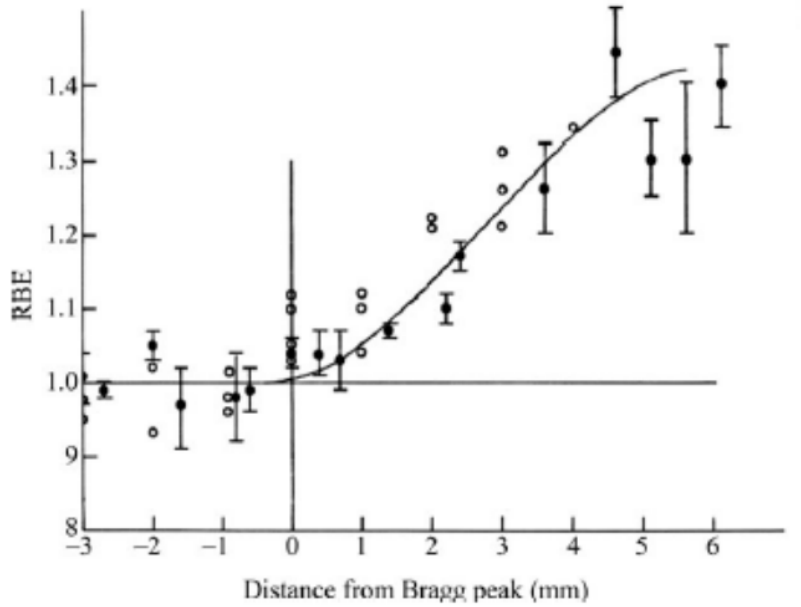


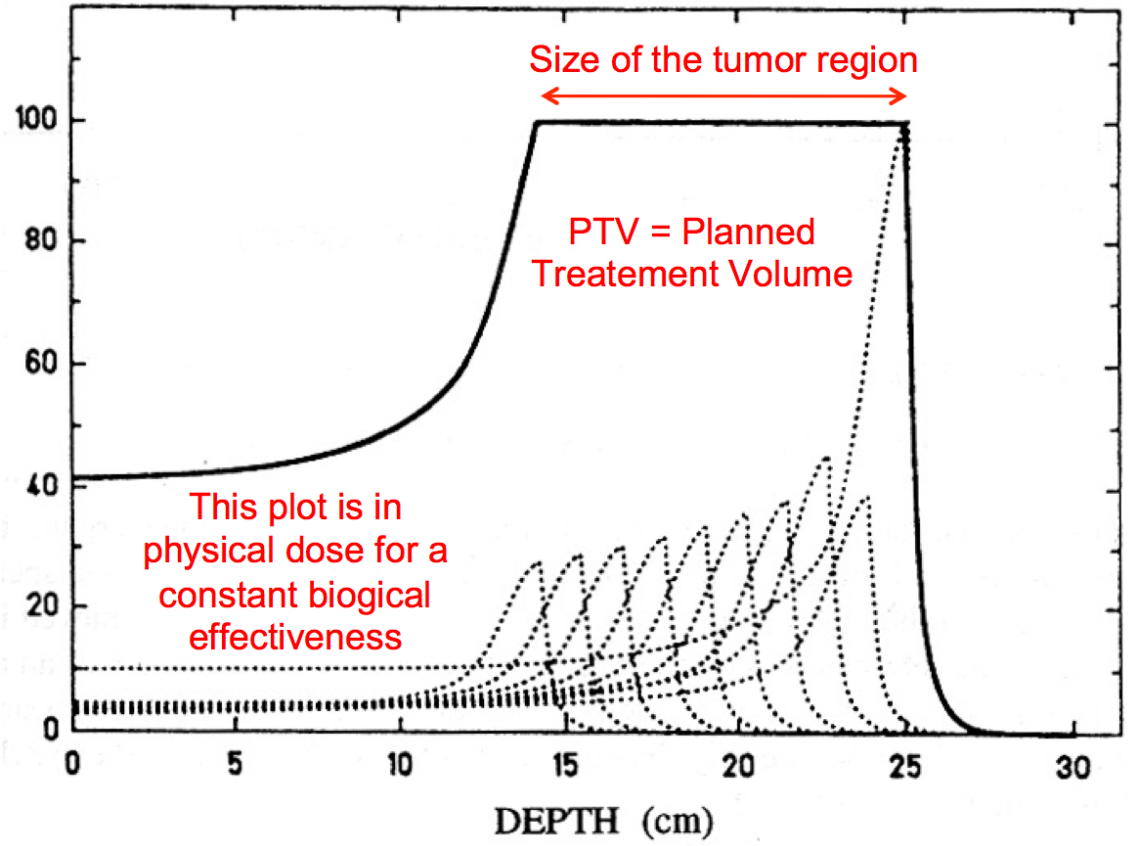
Figure 2.3: RBE determination for H4 cells at surviving fraction of 0.1 in an unmodulated 160 MeV proton beam and in the distal region of a 5 cm SOBP produced by the same beam. The measurements cover a range from

- RBE increases significantly over the initial few mm of the declining edge of the SOBP
- This trend has to be taken into account when there are organs at risk behind the tumor.

Question:
"In treatment planning, how can I effectively account for the RBE and its impact on biological response? Considering that I have limited control over beam parameters (e.g.: # particles, direction etc. How can I ensure optimal treatment outcomes while accounting for RBE variability?

Question:
Hey, wait a moment, there is a more trivial question: the Bragg peak is narrow, how can I treat a 3d tumour volume?

Spread Out Bragg Peak (SOBP)



- In order to cover the tumour volume along the beam longitudinal coordinate, a single beam with a given energy is not sufficient since the Bragg peak is too narrow
- Different beams with slightly different energies are superimposed to obtaining a broad irradiation profile called Spread Out Bragg Peak (SOBP)

RBE in PT

- The RBE is one of the main parameter for the treatment planning.
- The biological dose D_{bio} is calculated by means of the RBE and the physical absorbed dose D_{phys}

$$D_{bio} = RBE\, D_{phys}$$

- The distribution of physical absorbed dose has to be properly adjusted according to different values of RBE in order to fulfil the medical prescriptions
- The RBE depends on different parameters:
  -radiation type, energy, target cell phase, oxygenation etc.
- There are different models for the RBE to take into account the variability

Spread Out Bragg Peak (SOBP)

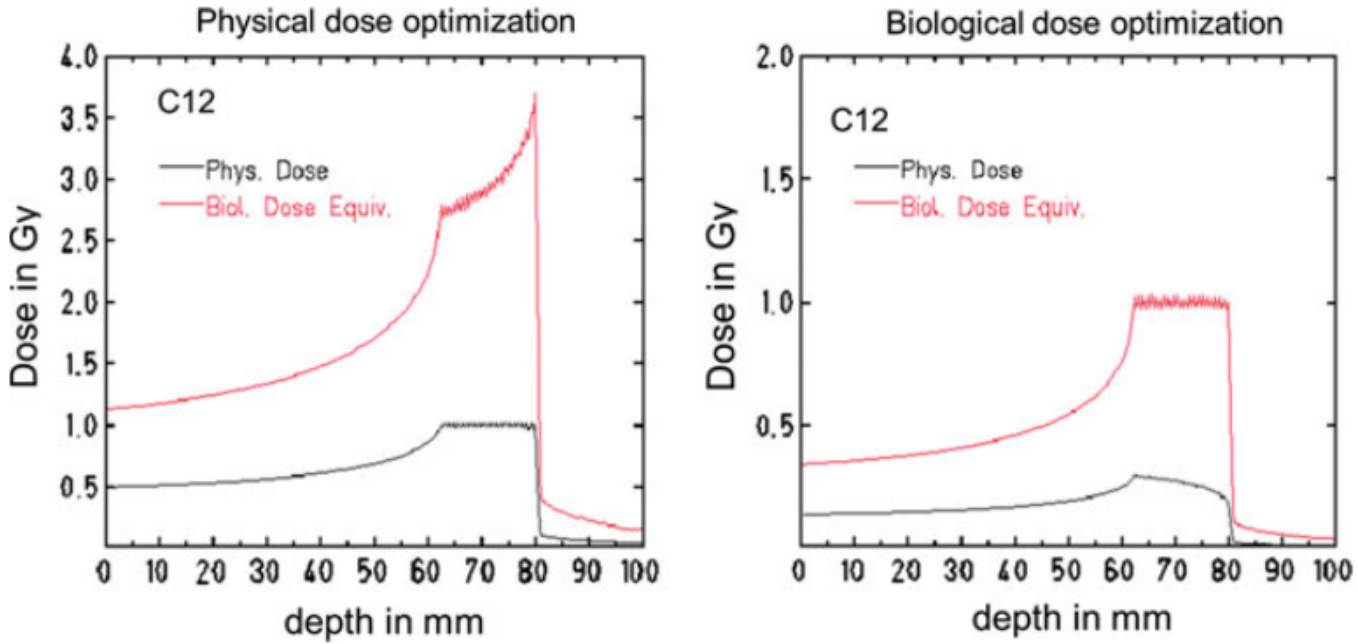


Fig. 19 Correspondent of absorbed dose for 1 Gy physical dose (*left*) and 1 Gy (RBE) biological effective dose in a planned target volume at 60–80 mm in depth (M. Krämer GSI)

Spread Out Bragg Peak (SOBP)

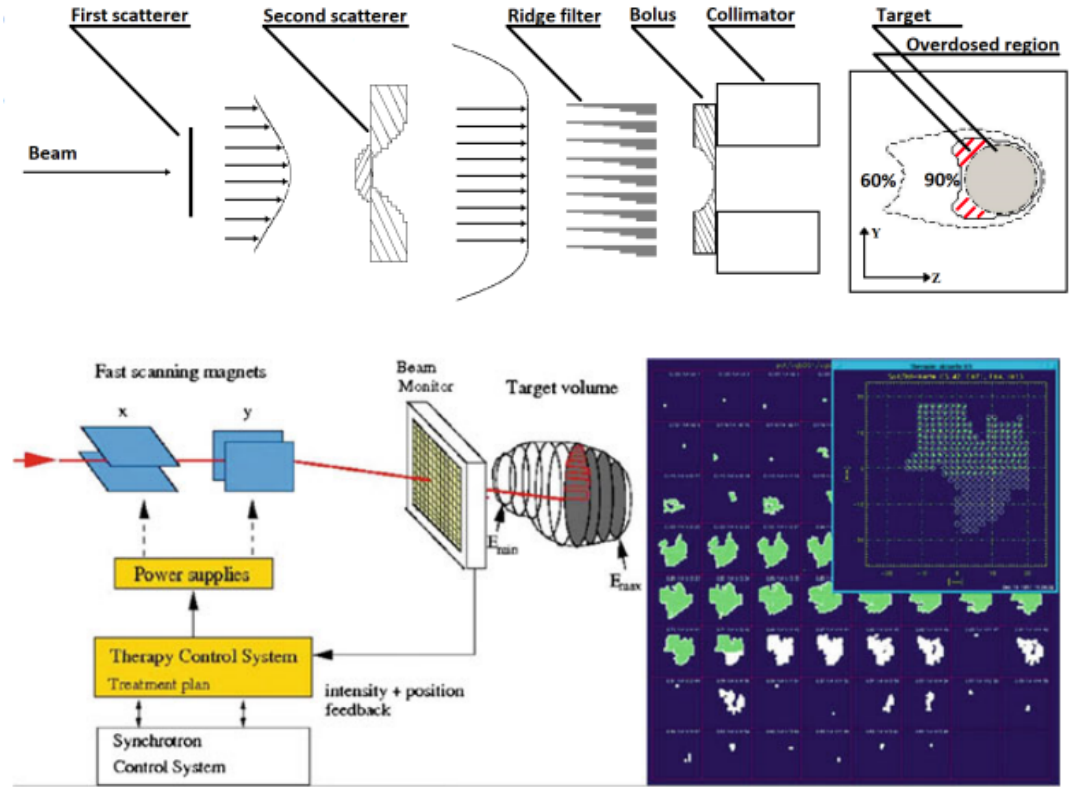


Fig. 17 Principle of the intensity-controlled raster scanning system at GSI [8]. The position of the

There are two methods to create a SOBP:

- **Passive modulators**: place passive material layers with grooves called ridge filters. The filters are developed to produce a constant biological effect
- **Active modulation**: the target volume is divided into layers with an equal beam energy and each layer is composed of a grid of points called voxels. Then, a pencil beam is delivered by means of a magnetic scanning system to each voxel, modifying the beam energy between the layers.

Question:
Is a passive system suitable for ^{12}C?

Question:
Well of course no, but why?

Passive system for ^{12}C

Completely passive system not advisable:

-Smaller scattering implies larger thicknesses and distances and thus larger energy loss and beam loss which implies larger energy and current from the accelerator

-Fragmentation of impinging ions causes a higher dose delivered after the tumor and larger production of neutrons.

-The amount of material in the beam line is considerable, leading to an increase in nuclear fragments produced by nuclear interactions with the material of the beam modifiers. These nuclear fragments have lower energies and lead to a higher LET and thus an increased biological effective dose of the beam already in the entrance region.

RBE models

(Probably) the two main RBE models adopted in clinics are:

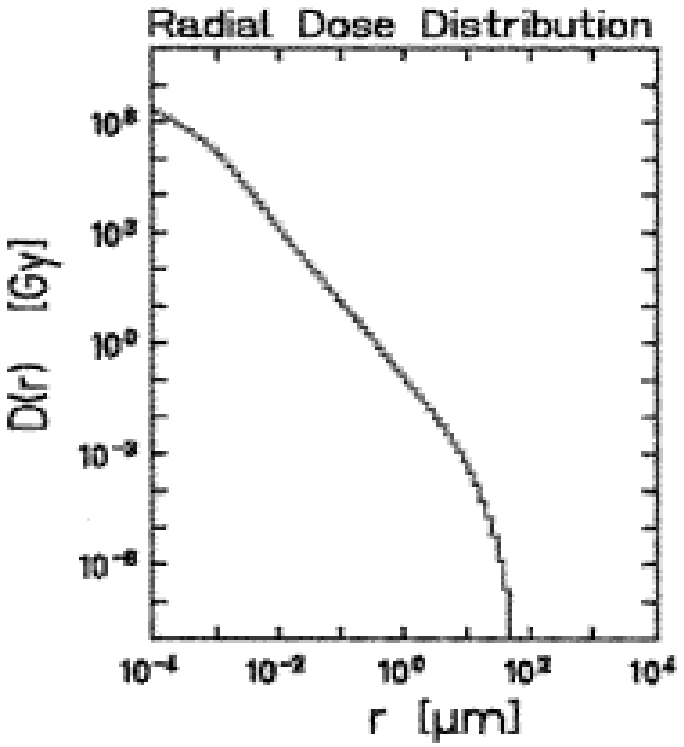
- **Microdosimetric Kinetic Model (MKM)**:
  -Adopted mostly in Japan.
  -Firstly proposed by Hawkins (1994)
  -Improved and extended by different studies, above all from Japanese researchers
  -In this model the RBE trend is described as due to the variation of the energy deposited in microscopic sub-cellular volume

- **the Local Effect Model (LEM):**
  -Adopted mostly in Europe(HIT, GSI in Germany and CNAO in Italy)
  -developed at GSI by Scholz & Kraft (1996).
  -It relates the response of biological tissues after ion irradiation to the corresponding response after X-ray irradiation, assuming that the radiation biological effect is entirely determined by the spatial local dose distribution within the cell nucleus. For a given cell, the differences in the biological action of charged particles are attributed to the different spatial energy deposition pattern, i.e. track structure.

LEM model

- The LEM is based on the use of the concept of the “local dose”, which is defined as the expectation value of the energy deposition at any position in the radiation field for a given pattern of particle trajectories
- The main assumption of the LEM is that equal local doses should lead to equal local effects, independent on the radiation quality
- The biological damage depends only on the quantity of energy deposited by the particles. All the energy is released by the secondary electrons
- The radiation target is only the cell nucleus that is considered homogeneous, with constant density and radiosensibility
- The effectiveness of particles is thus calculated based on the microscopic local dose distribution pattern of ion traversals within the cell nucleus

LEM model

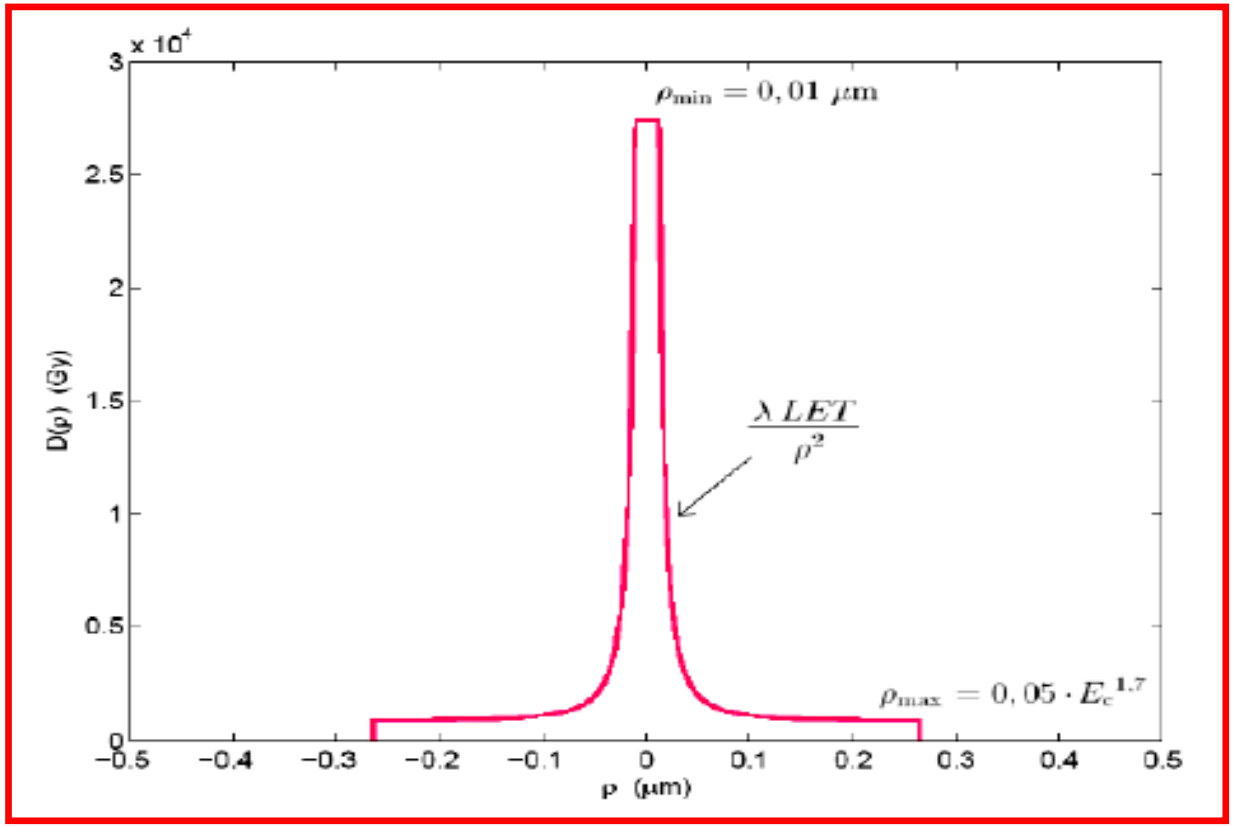


- Difference between 12C ion and photon are given by the different spatial distribution of the energy release
- The dose distribution as function of the particle trajectory distance r is given by:

$$D(r) = \begin{cases} \lambda\ LET/r_{min}^2 & : \quad r < r_{min} \\ \lambda\ LET/r^2 & : \quad r_{min} \leq r \leq r_{max} \\ 0 & : \quad r > r_{max} \end{cases}$$

where:
λ is a normalization constant for the LET
r_{min}~10nm
$r_{max}=gE^d$ (g= 0.05, d=1.7) is determined by the range of the highest energetic electrons produced by the primary track

LEM model


x 10^-4
3
2.5
2
1.5
1
0.5
0
D(ρ) (Gy)
$\rho_{min} = 0,01\ \mu m$
$\frac{\lambda\, LET}{\rho^2}$
$\rho_{max} = 0,05 \cdot E_c^{1.7}$
−0.5
−0.4
−0.3
−0.2
−0.1
0
0.1
0.2
0.3
0.4
0.5
ρ (μm)

LEM model

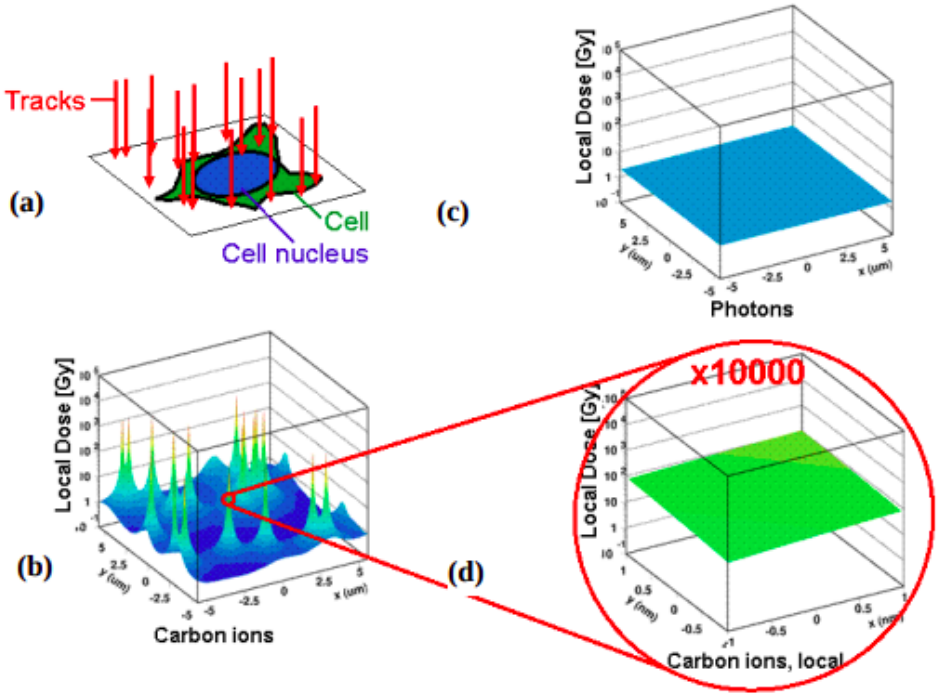
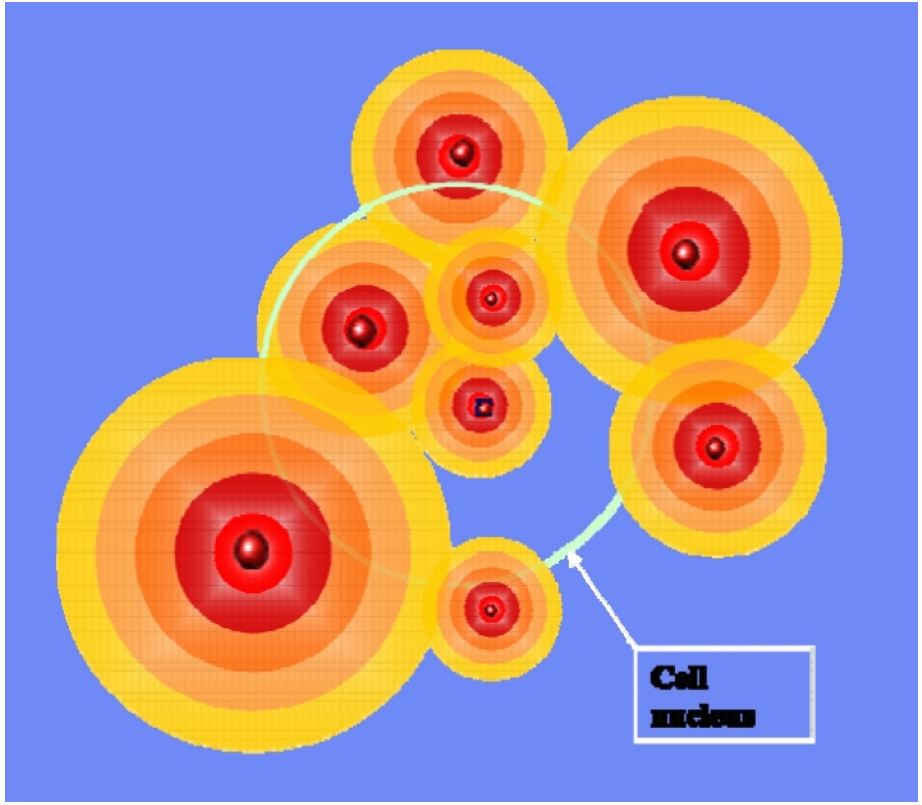


Figure 1:
Comparison of the microscopic local dose distributions of carbon ions and photons for the same macroscopic dose of 2 Gy. For a random distribution of particle traversals through a cell as depicted in (a) the corresponding local dose distribution is characterized by extremely high spikes close to the particle trajectory (b). In contrast, for photons the distributions is expected to be flat (c). Locally, i.e. in nm dimensions, the distributions of particles can also be approximated by a flat distribution (d), thus allowing the link to the photon distribution.

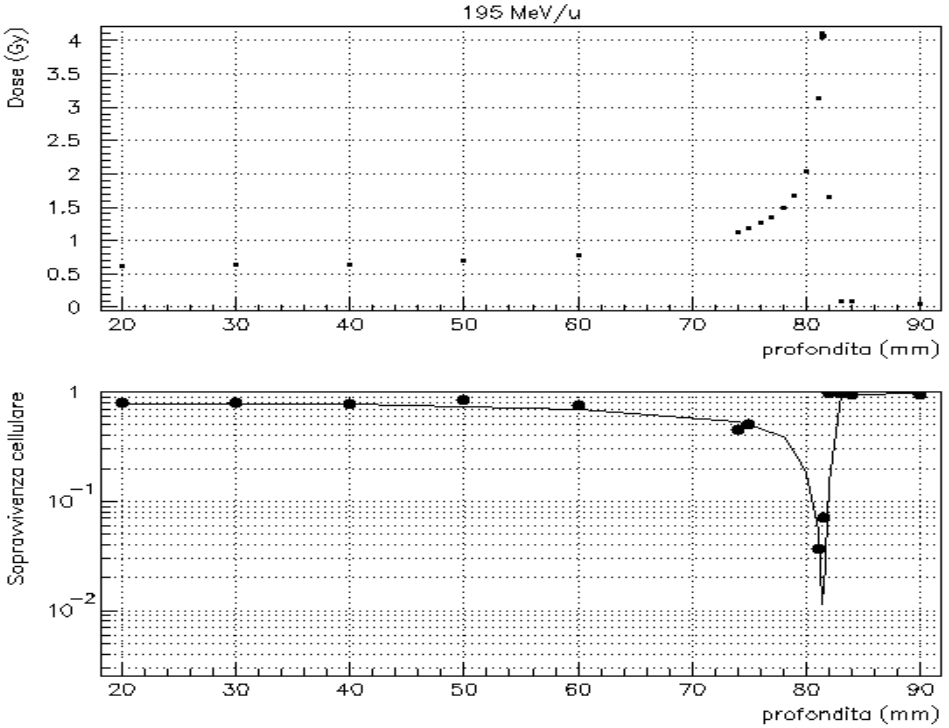
LEM model



$$d\left(\vec{r}\right) = \sum_{j=1}^{n_t} d_j\left(\vec{r}\right)$$

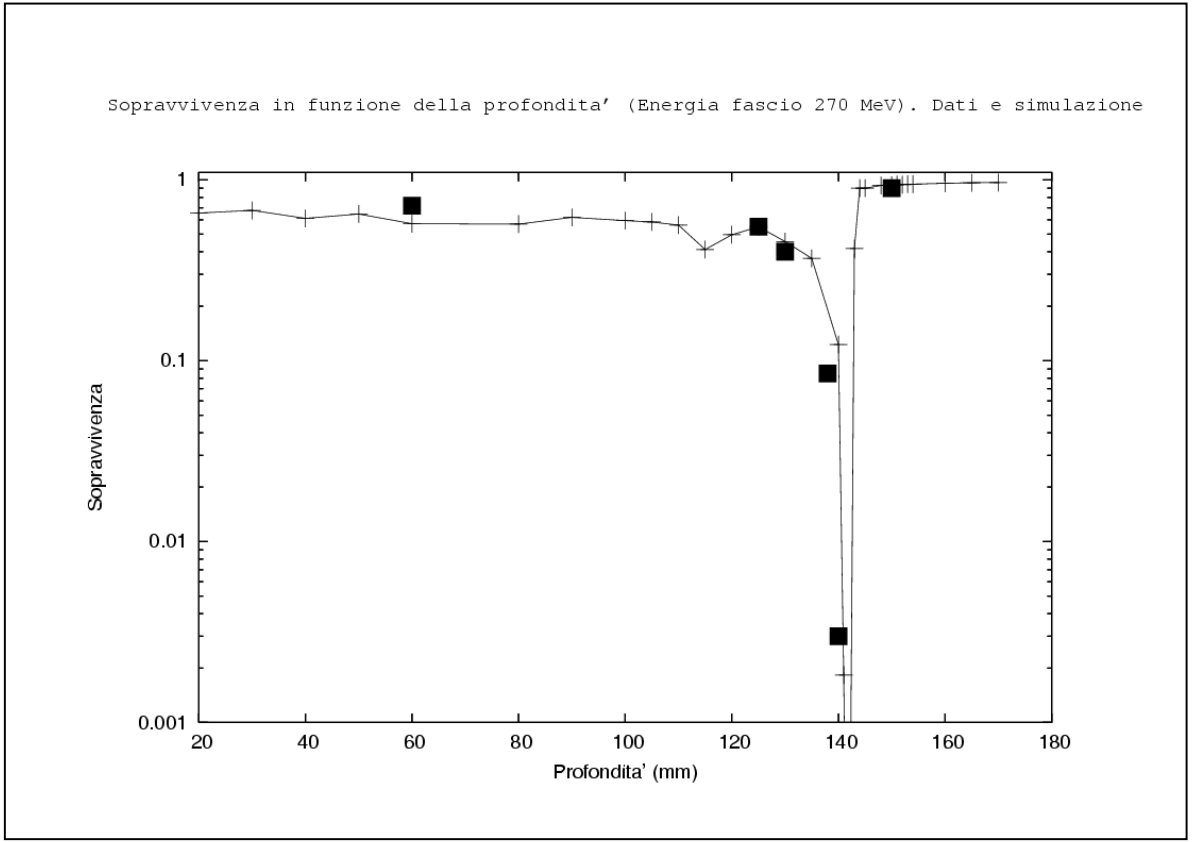
- The local dose for a given number of incident particles at a given position is calculated by the sum of all the dose released by the all the tracks in that position
- The local biological effect is calculated from the local dose and a dose-effect parametrization derived from the X-ray survival curves

LEM model

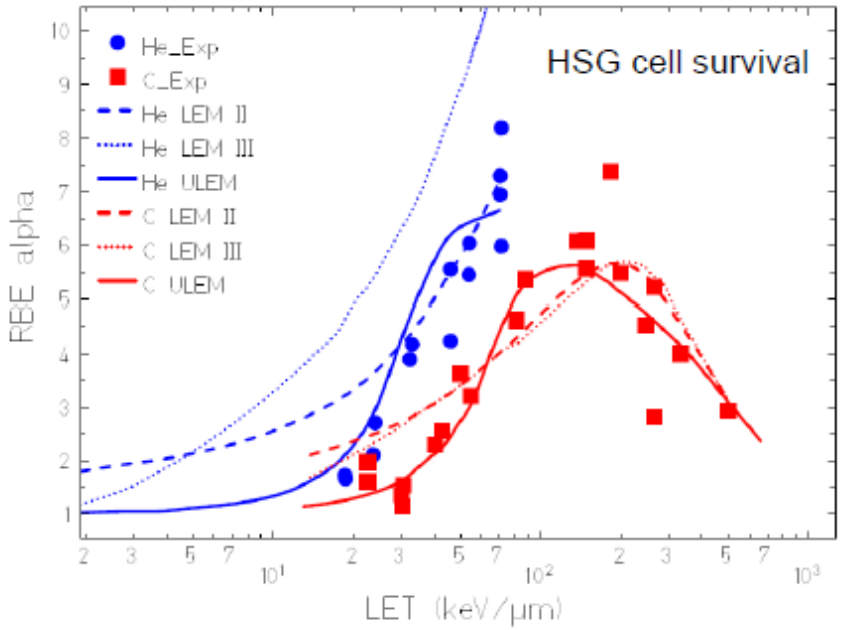


Experimental (dots) and theoretical calculation (solid line) from the LEM model on the survival curves of CHO cells with ^{12}C @ 195MeV/u

LEM model


Sopravvivenza in funzione della profondita' (Energia fascio 270 MeV). Dati e simulazione
Sopravvivenza
1
0.1
0.01
0.001
20
40
60
80
100
120
140
160
180
Profondita' (mm)

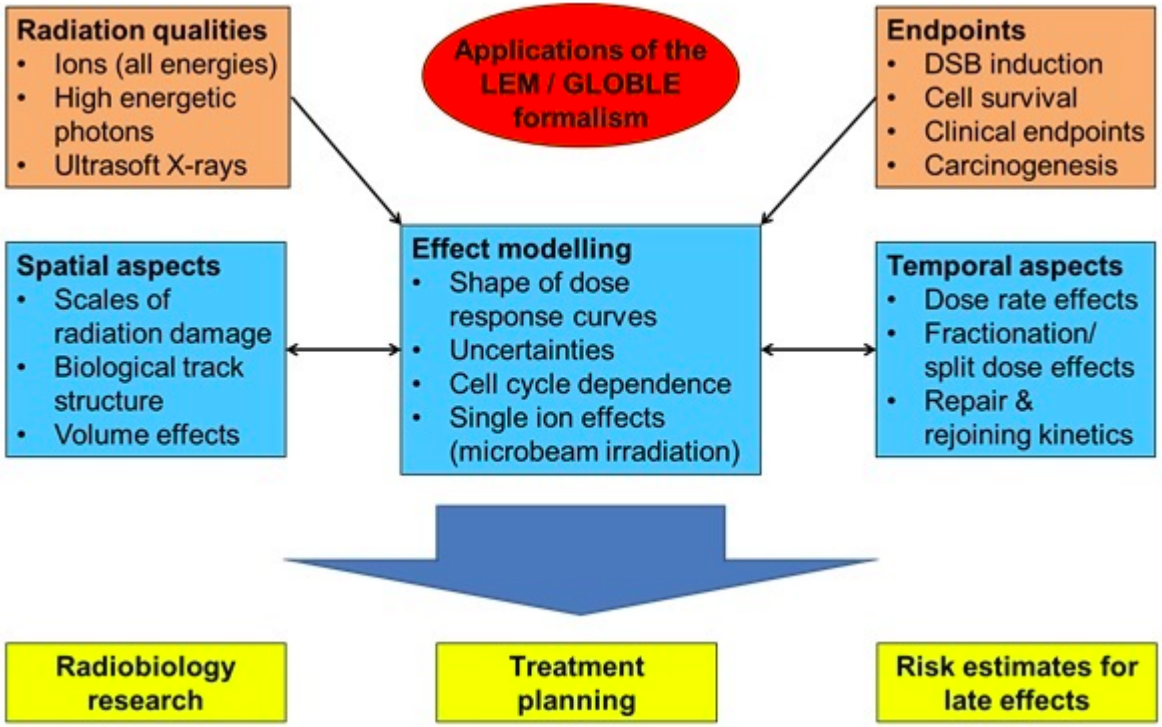
LEM model



Exp. Data: Furusawa et al., Rad. Res. 2000
LEM II: Elsässer et al., Rad. Res. 2007
LEM III: Elsässer et al., IJROBP 2008
LEM IV: Elsässer et al., IJROBP 2010

The Local Effect Model (LEMIV) is based on the distribution of DSBs that are determined by considering the local dose

LEM model


Radiation qualities
• Ions (all energies)
• High energetic photons
• Ultrasoft X-rays
Applications of the LEM / GLOBLE formalism
Endpoints
• DSB induction
• Cell survival
• Clinical endpoints
• Carcinogenesis
Spatial aspects
• Scales of radiation damage
• Biological track structure
• Volume effects
Effect modelling
• Shape of dose response curves
• Uncertainties
• Cell cycle dependence
• Single ion effects (microbeam irradiation)
Temporal aspects
• Dose rate effects
• Fractionation/ split dose effects
• Repair & rejoining kinetics
Radiobiology research
Treatment planning
Risk estimates for late effects

OER

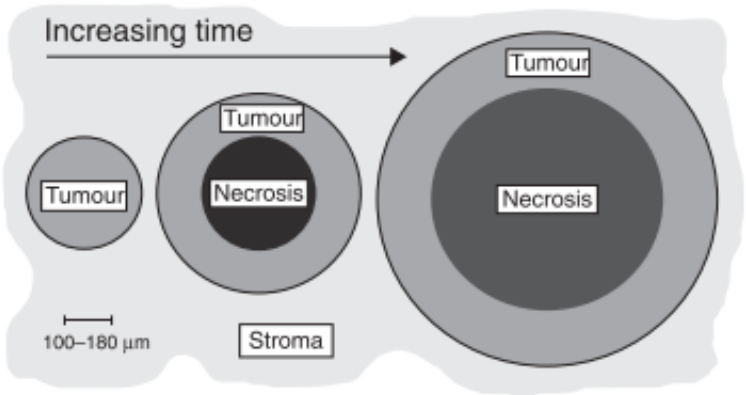


Figure 15.4 Simplified description of the development of microscopic regions of necrosis in tumours. Conclusions by Thomlinson and Gray from studies on histological sections of human bronchial carcinoma showing the development of necrosis beyond a limiting distance from the vascular stroma. Adapted from Hall (1988), with permission.

- Most solid tumours to grow they need to develop their own blood supply
- This new vasculature is formed from the already established normal tissue vessels by a process referred as angiogenesis
- **The formation of the neo vasculature usually lags behind the more rapidly increasing number of neoplastic cells**
- The neo vasculature is unable to meet the increasing nutrient demands of the expanding tumour mass
- All these factors combine to result in the development of microregional areas within tumours that are nutrient deprived acidic and oxygen deficient

OER

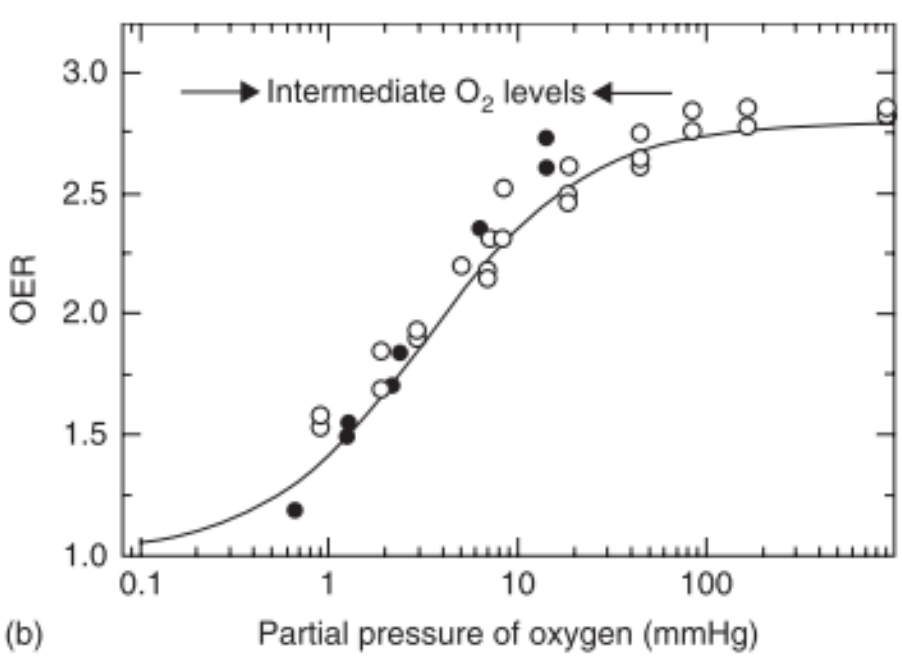
- The LET indirect damage mechanism depends on the oxygenation level of the target tissue
- The presence of oxygen atoms in a target material can remarkably modify the biological effectiveness of a radiation (check slide 12: oxygen-fixation hypothesis)
- This effect is quantified by the Oxygen Enhancement Ratio (OER): defined as the ratio between the radiation dose in hypoxia condition (Dhyp) over the radiation dose in aerobic condition (Dair), for the same biological effect (isoeffect):

$$\mathrm{OER} = \left.\frac{\mathrm{D_{hyp}}}{\mathrm{D_{air}}}\right|_{\mathrm{iso}}$$

- Most solid tumours need to develop their own blood supply system, but this angiogenesis process usually lags behind the faster increase of the number of neoplastic cells
- This leads to the development of hypoxic microregional tumorous areas that are nutrient deprived and with a lack of oxygen

Question:
How is the OER dependence on the tissue oxygenation level?

OER

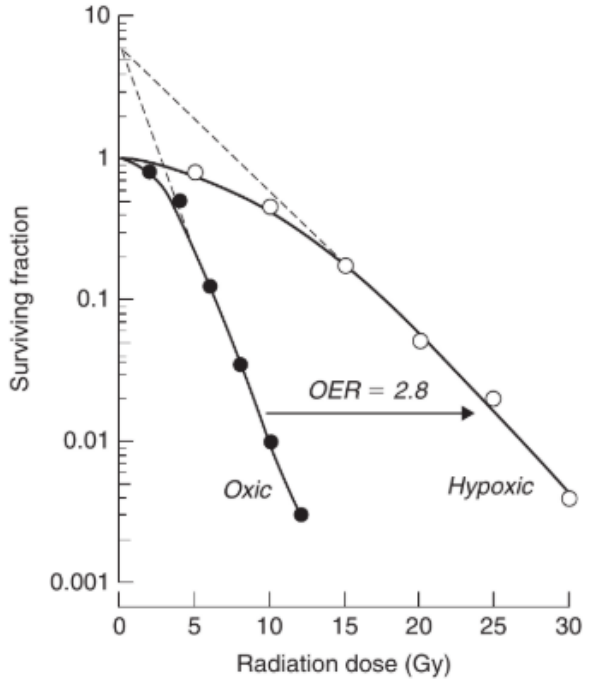


Published OER values at different oxygen partial pressures adapted from Koch et al. (1984) (closed circles) and Whillans and Hunt (1982) (open circles)

- The oxygen effect occurs only if oxygen is present either during irradiation or within a few milliseconds thereafter
- By definition, the OER under anoxic conditions is 1.0
- As the oxygen tension increases there is a steep increase in radiosensitivity (and thus in the OER)
- A further increase in oxygen concentration after the steep rise at 0.5-20mmHg produces a much smaller though definite increase in radiosensitivity

Question:
What is the effect of the oxygen concentration on the survival curves?

OER

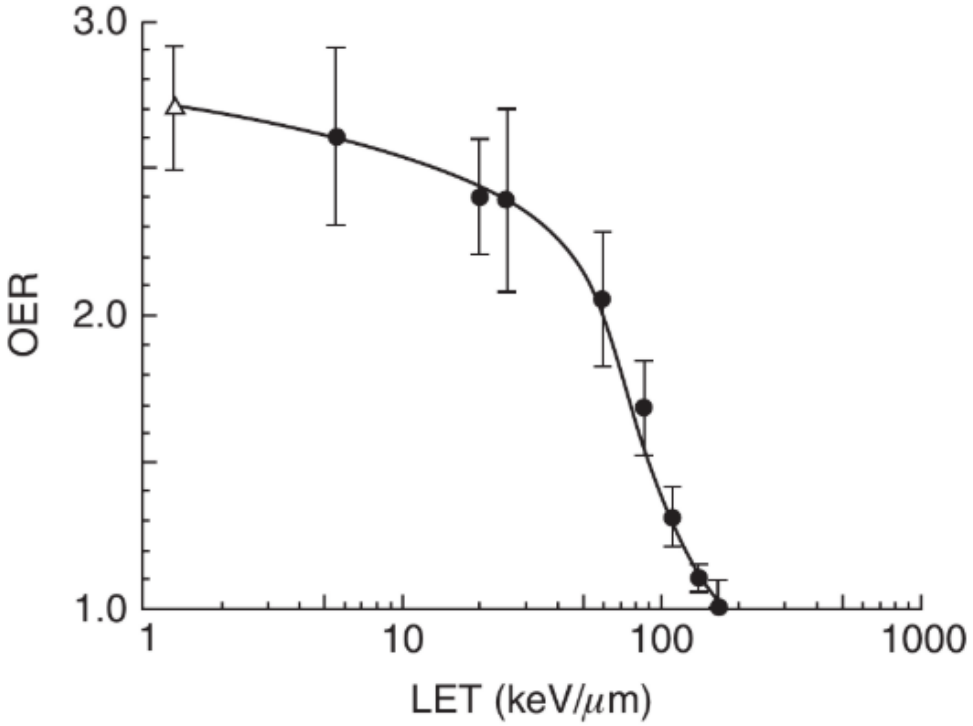


Survival curves for cultured mammalian cells exposed to X-rays under oxic or hypoxic conditions

- Contrary to tumorous tissues, normal tissues are considered to be well oxygenated, thus more sensitive to the radiation effects.
- Hypoxic cells are much less sensitive to radiation than well-oxygenated cells
- Hypoxic cells are believed to be an important cause of treatment failure after radiotherapy
- Hypoxic cells in tumours are also known to be resistant to certain chemotherapeutic agent
- For most cell types, the OER for X-rays is around 3.0.

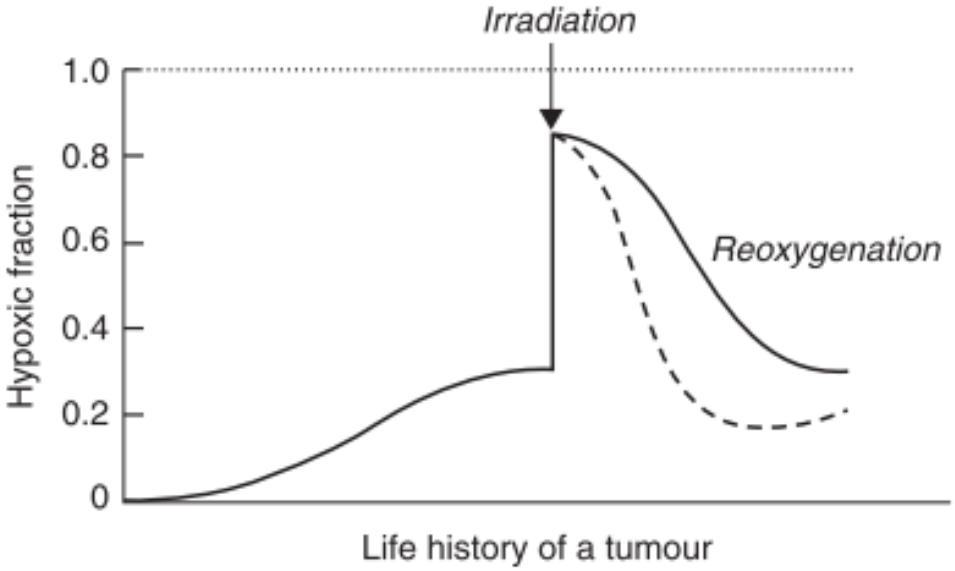
Question:
What is the expected relation between LET and OER?

OER vs LET



For the high ionizing particles adopted in PT, the OER is close to 1 due to their different cell killing mechanism, mainly based on clustered direct damages and without the need of mediators like free radicals

OER and reoxygenation



- The mechanisms underlying reoxygenation in tumours are not fully understood
- Some tumours reoxygenate rapidly, others more slowly
- Small lesions are well oxygenated but as the tumour grows the hypoxic fraction rises.
- A large, single dose of radiation kills oxic cells and raises the hypoxic fraction.
- The subsequent fall is termed reoxygenation

OER and reoxygenation

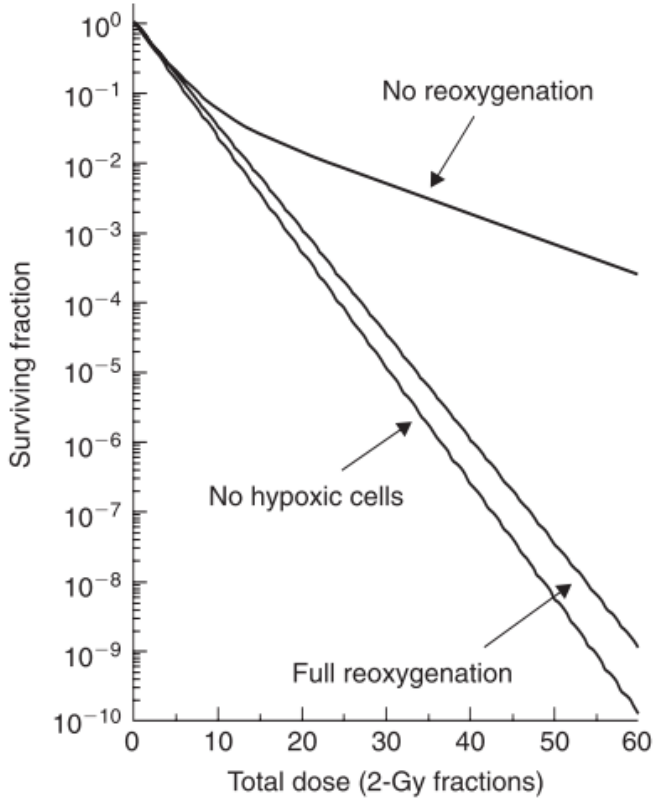
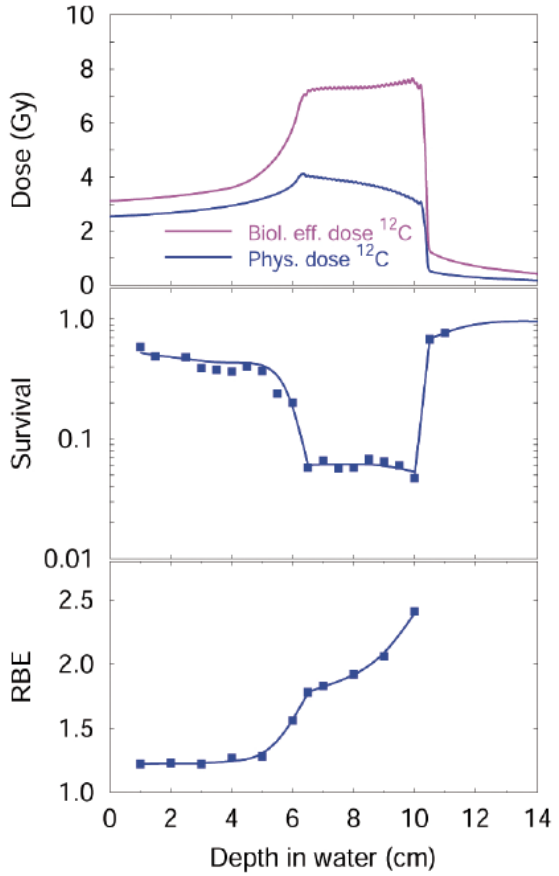
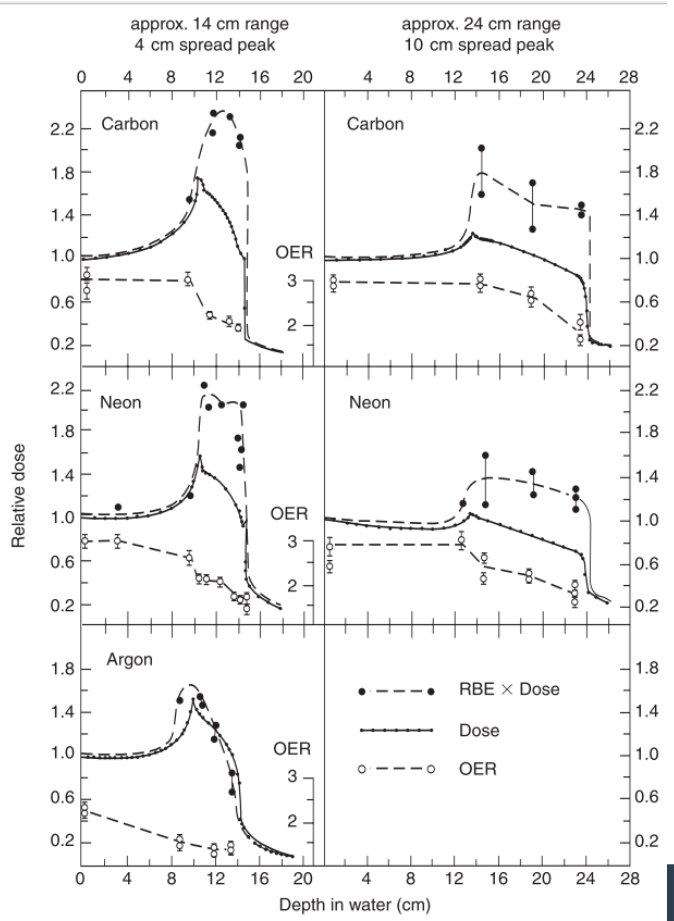


Figure 15.10 Calculated cell survival curves following repeated 2-Gy fractions of radiotherapy for tumours initially containing 90 per cent well-oxygenated cells and 10 per cent hypoxic cells (upper and middle lines) compared with no hypoxic cells (lower line). The upper line shows the progressive depletion of oxic and hypoxic cells in the absence of reoxygenation. The middle line assumes that, after each dose fraction, full reoxygenation restores the hypoxic fraction to its pre-treatment level. A surviving fraction at 2 Gy (SF_2) of 0.47 for oxic cells has been assumed with an OER of 2.8 relative to fully hypoxic cells.

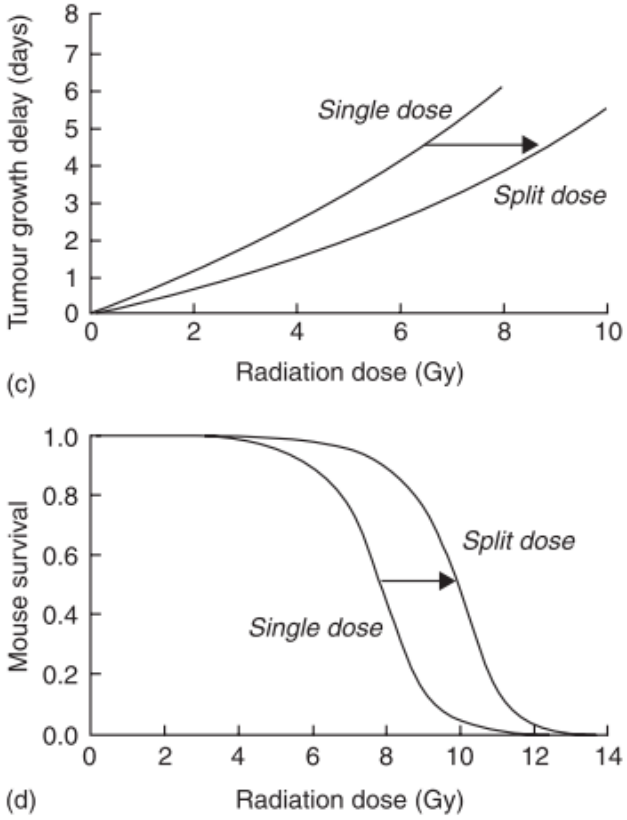
Biological effective dose





In order to have a uniform dose over the tumour volume, a calculation of the LET and RBE along the beam path inside the patient is needed

Recovery from sublethal damage

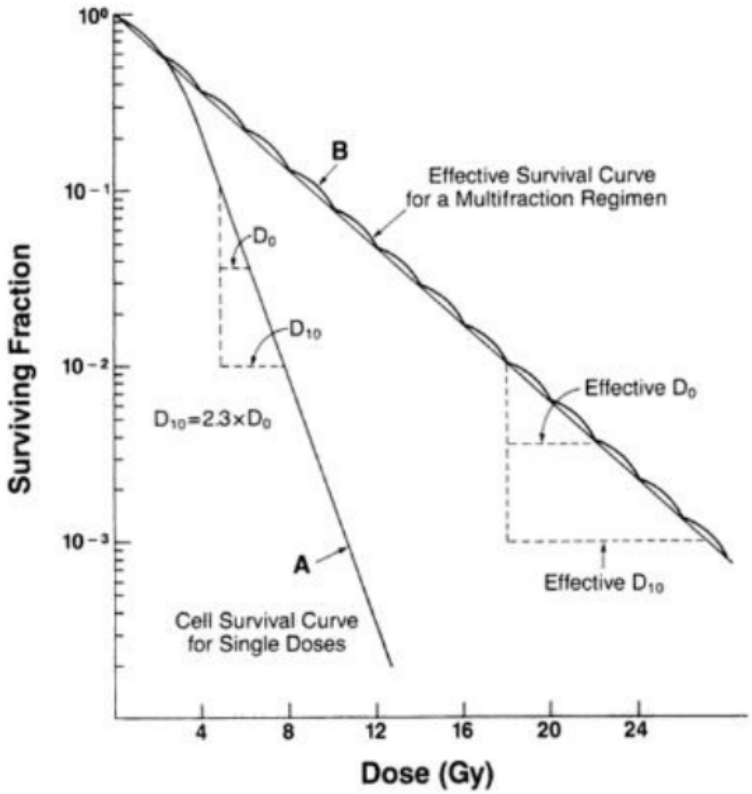


Most of the damage induced in cells by radiation is satisfactorily repaired

- Evidence from studies of strand breaks in DNA, the vast majority of which disappear during the first few hours after irradiation
- Evidence from studies both on *in vitro* cell lines and *in vivo* on tumour and normal tissue

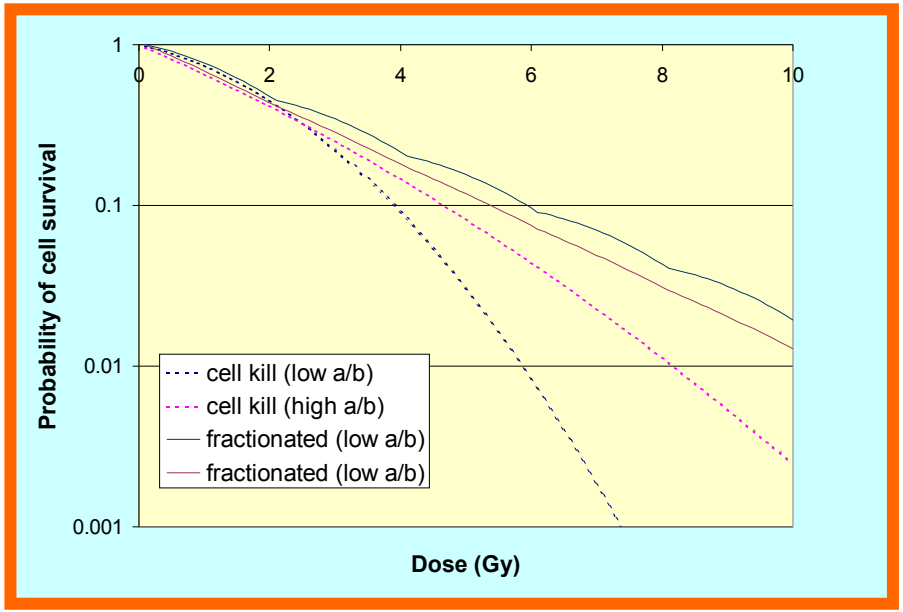
Questions:
Can I somehow exploit this effect?

Fractionation



Questions:
Fractionation will be more effective on tissues with low or high α/β?

Fractionation



- The survival curve function depends also on the target tissue (slide 23)
- The fractionation tends to spare late reacting normal tissues (low α/β)
- the smaller the size of the fraction the more sparing for tissues with (low α/β)
- Early reacting tissues with high α/β ratio are less sensitive to fractionation
- The fractionation prolongs treatment

Fractionation

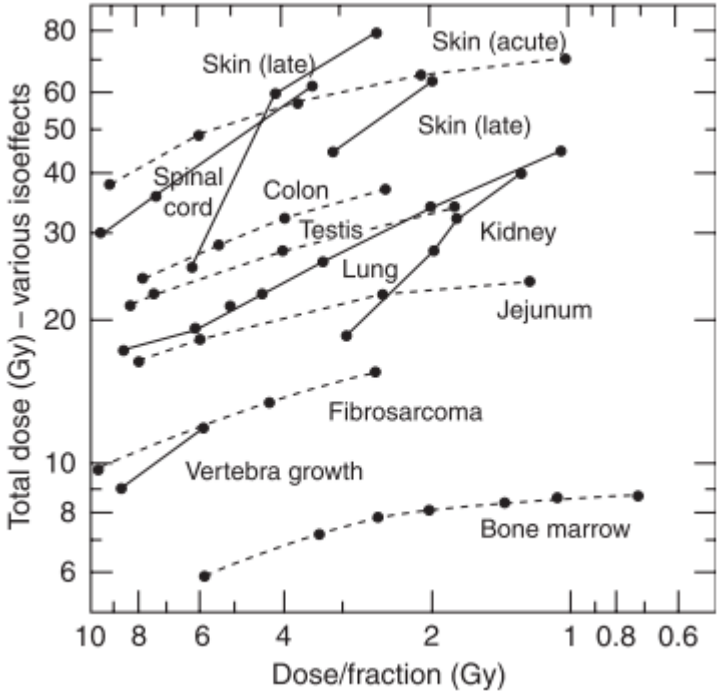


Figure 8.1 Relationship between total dose and dose per fraction for a variety of normal tissues in experimental animals. The results for late-responding tissues (unbroken lines) are systematically steeper than those for early-responding tissues (broken lines). From Thames *et al.* (1982), with permission.

The dashed lines show isoeffect curves for acutely responding tissues and the full lines are for late- responding tissues.

Fractionation

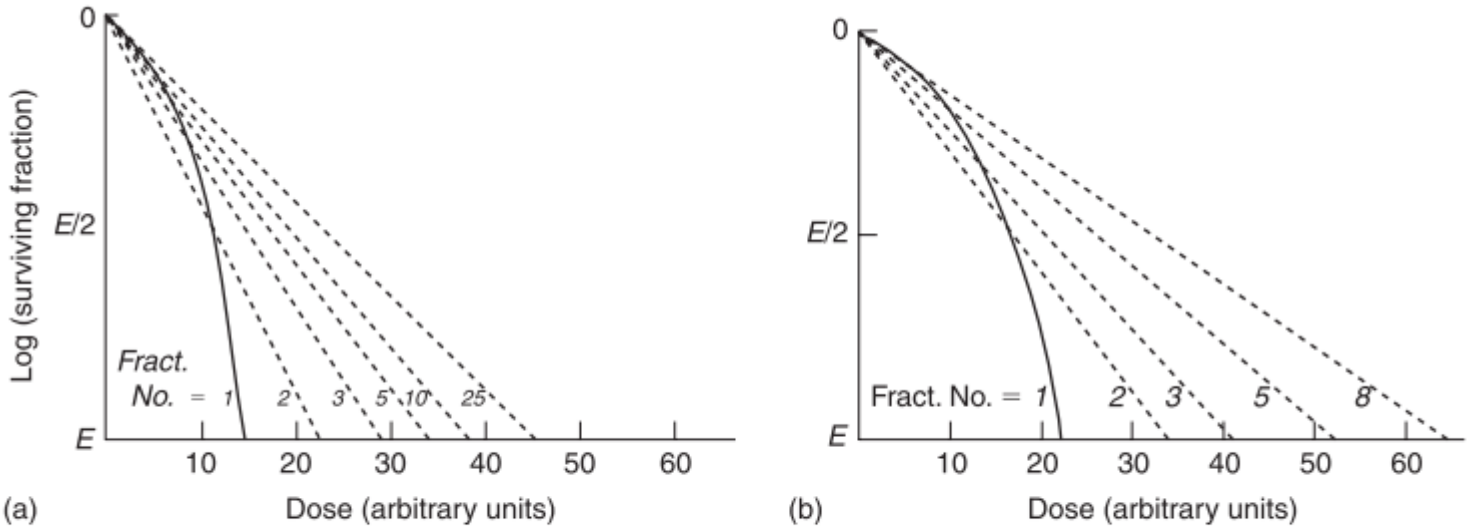


Figure 8.3 Schematic survival curves for target cells in (a) acutely responding and (b) late-responding normal tissues. The abscissa is radiation dose on an arbitrary scale. From Thames and Hendry (1987), with permission.

the late-responding survival curve (b) is more ‘bendy’ (lower α/β), the isoeffective total dose increases more rapidly with increasing number of fractions than the early-responding tissue in which the survival curve bends less sharply (a)

Question:
How is the dependence of RBE with the fractionation?

RBE and fractions

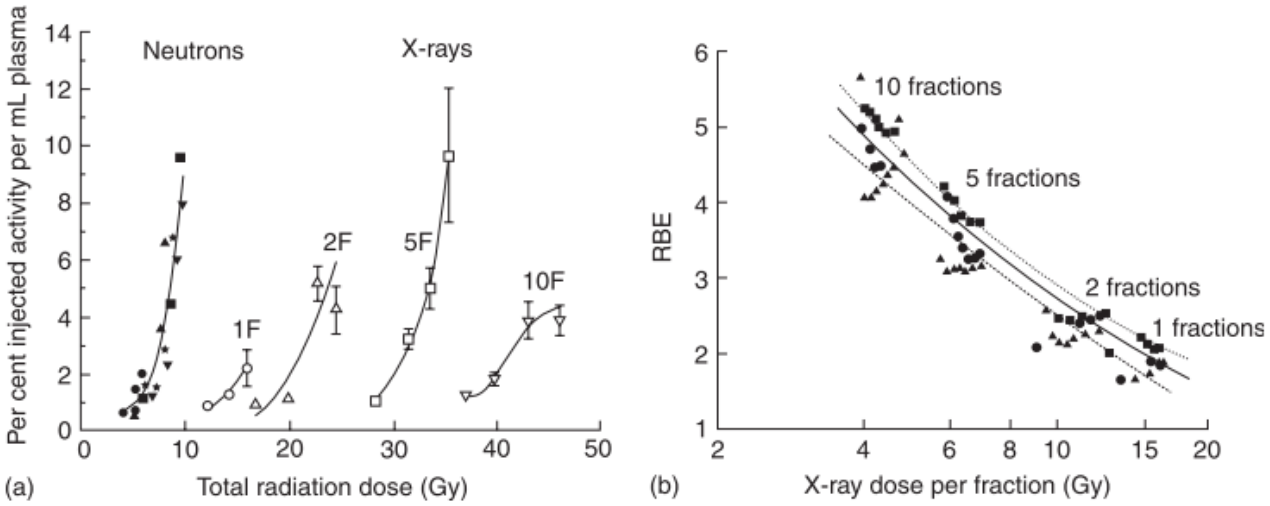
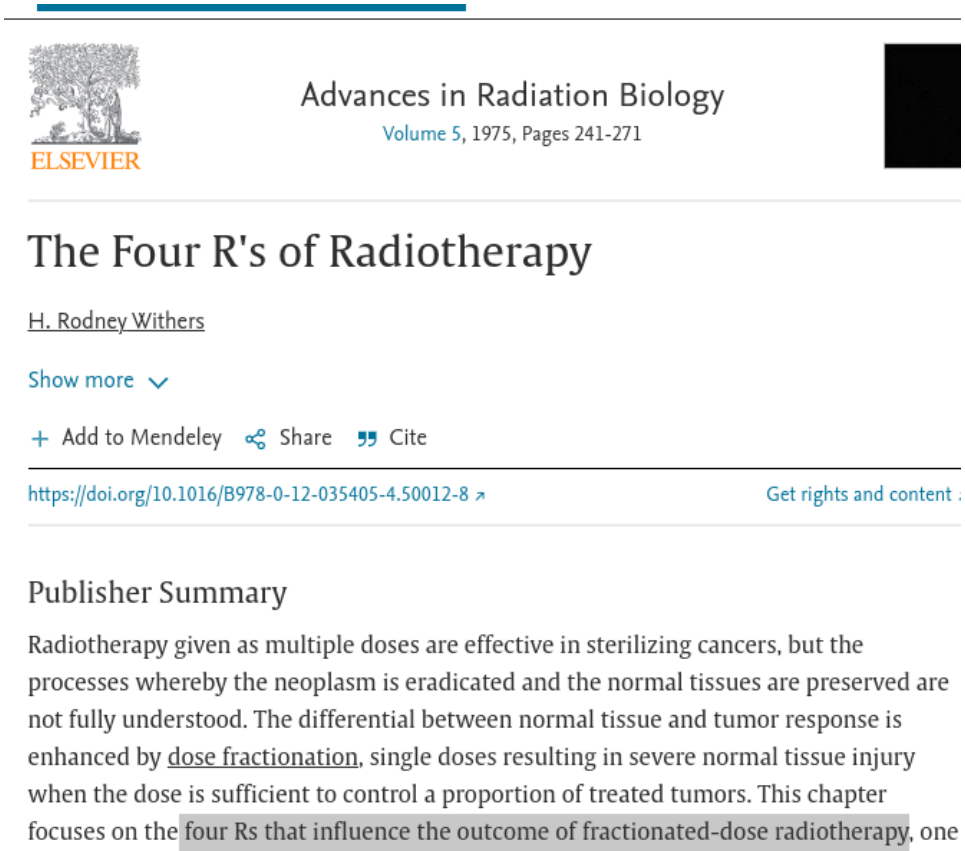


Figure 6.6 The relative biological effectiveness (RBE) for kidney damage increases with decreasing dose per fraction. The RBE values are derived from graphs similar to (a), which shows dose–effect curves for ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) clearance following irradiation with 1, 2, 3, 5 and 10 fractions of neutrons or 1, 2, 5 and 10 fractions of X-rays. The RBE values in (b) were obtained with various renal-damage endpoints: isotope clearance (circles); reduction in haematocrit (squares); and increase in urine output (triangles). From Joiner and Johns (1987), with permission.

- study the loss of renal function in mice after external-beam radiotherapy. This was done by measuring the increased retention of EDTA in the plasma 1 hour after injection; normally functioning kidneys completely clear this substance from the body within this time
- fractionation makes almost no difference to the tolerance dose but for X-rays a much higher total dose is required to produce renal damage when the treatment is split into two, five or ten fractions

The four R’s of Radiotherapy



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Advances in Radiation Biology

Volume 5, 1975, Pages 241-271

The Four R's of Radiotherapy

H. Rodney Withers

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Publisher Summary

Radiotherapy given as multiple doses are effective in sterilizing cancers, but the processes whereby the neoplasm is eradicated and the normal tissues are preserved are not fully understood. The differential between normal tissue and tumor response is enhanced by dose fractionation, single doses resulting in severe normal tissue injury when the dose is sufficient to control a proportion of treated tumors. This chapter focuses on the four Rs that influence the outcome of fractionated-dose radiotherapy, one

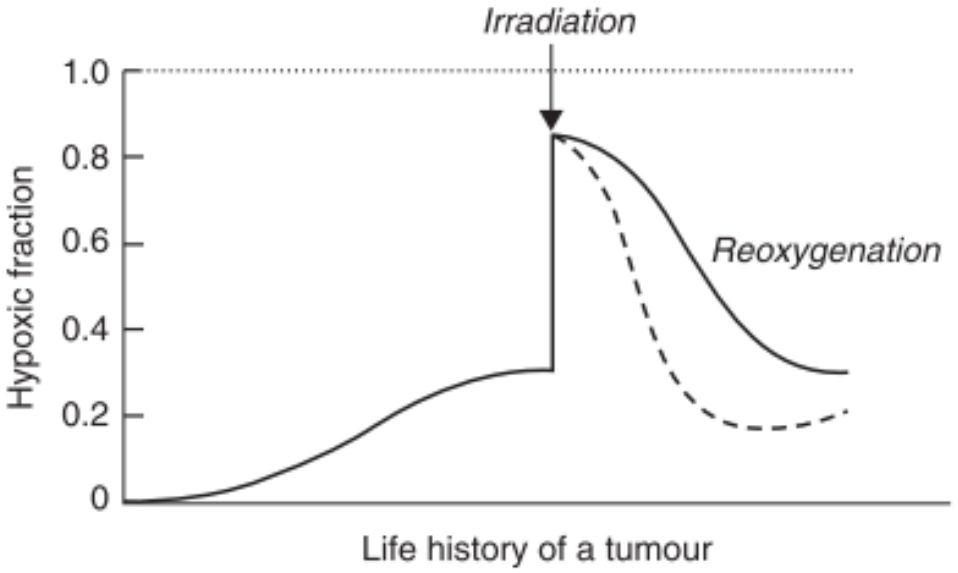
Reoxygenation

Redistribution

Repair

Repopulation (or Regeneration)

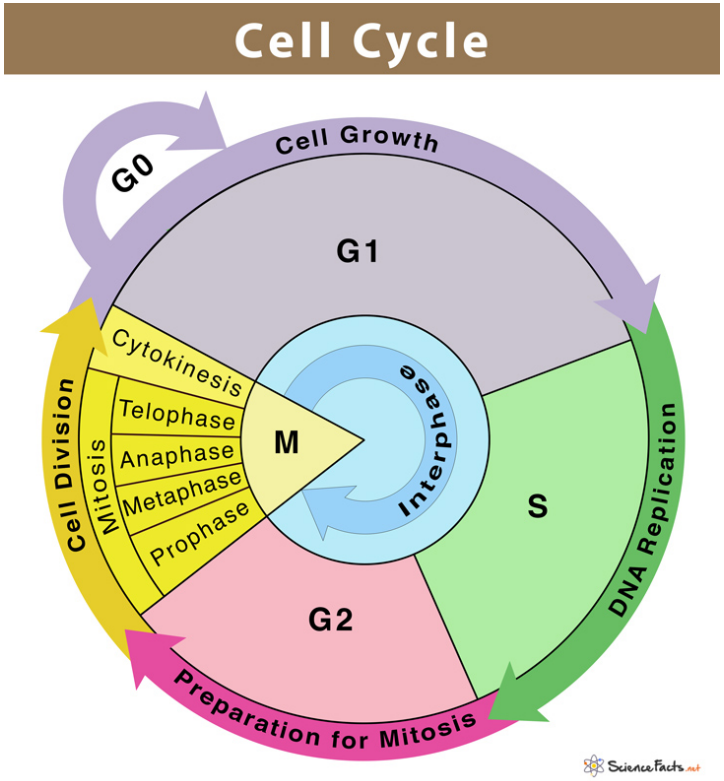
Reoxigenation



Reoxygenation

- Oxygen is an important enhancement for radiation effects (“Oxygen Enhancement Ratio”)
- Hypoxic tumour cells are less sensitive to radiation.
  Fractionating radiotherapy allows to kill oxygenated tumour cells first, and the time between fractions allows the relatively hypoxic cells to improve their oxygen supply
- See slide 55

Cell phases



- The effect of low-LET radiation on cells is strongly influenced by their position in the cell cycle
- The cell cycle is characterized by four periods:
  -Mitosis (M), where division takes place
  -gap G1 when DNA has not been synthesized
  -DNA synthesis (S)
  -gap G2 where DNA has been synthesized
- cells in S phase are more radioresistant than cells in G2 or mitosis
- as LET increases, the variation in radiosensitivity through the cell cycle decrease, so at very high LET radiosensitivity varies little with the phase of the cell cycle

Redistribution

Redistribution

- The radiosensitivity of cells depends on their stage in the cell cycle.
- The distribution of cells in different phases of the cycle is normally not something which can be influenced
- Dividing the total dose of radiation into multiple fractions maximizes the probability of irradiating cells when they are in the most radiosensitive period of their cell cycle
- Radiation itself introduces a block of cells in G2 phase which leads to a synchronization. One must consider this when irradiating cells with breaks of few hours.

Repair

Repair

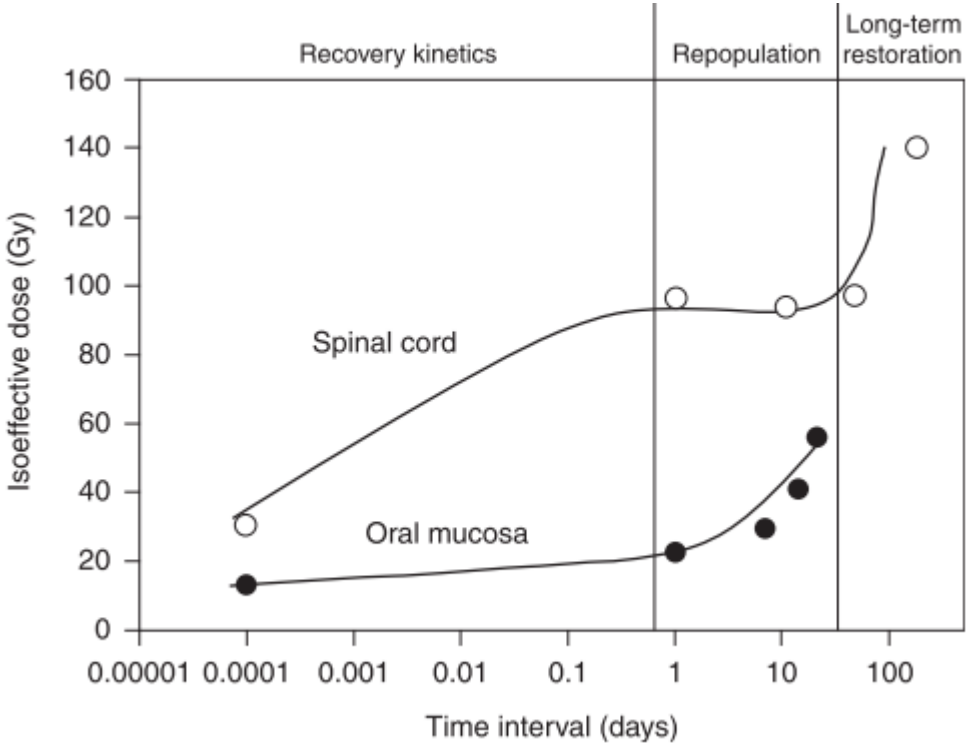
- Healthy cells have a greater ability to repair DNA damage than malignant cells.
- Fractionating the total radiation dose allows healthy cells to repair the sublethal damage between fractions, while, malignant cells are less able to recover from radiation damage to their DNA
- The half time for repair, t_r, is of the order of minutes to hours.
- It is essential to allow normal tissues to repair all repairable radiation damage prior to giving another fraction of radiation.
- This leads to a minimum interval between fractions of 6 hours
- Spinal cord seems to have a particularly slow repair - therefore, breaks between fractions should be at least 8 hours if spinal cord is irradiated

Repopulation

Repopulation

- Cell population also grows during radiotherapy and this repopulation partially counteracts the cell killing effect of radiotherapy
- The potential doubling time of tumours, T_p (*e.g.* in head and neck tumours or cervix cancer) can be as short as 2 days - therefore one loses up to 1 Gy worth of cell killing when prolonging the course of radiotherapy
- The repopulation time of tumour cells appears to vary during radiotherapy - at the begining it may be slow (*e.g.* due to hypoxia), however a certain time after the first fraction of radiotherapy (often termed the “kick-off time”, T_k) repopulation accelerates.
- Repopulation must be taken into account when protracting radiation *e.g.* due to scheduled (or unscheduled) breaks such as holidays.
- Also normal tissue repopulate - this is an important mechanism to reduce acute side effects from *e.g.* the irradiation of skin or mucosa
- Radiation schedules must allow sufficient regeneration time for acutely reacting tissues.

Repopulation



Changes in normal tissue tolerance with time

- At short durations of radiation exposure (<1 day), increasing completeness of recovery from sublethal damage increases tissue tolerance.
- At intermediate intervals from 1 day to several weeks (i.e. the duration of radiotherapy) tolerance increases by repopulation in early-responding tissues such as oral mucosa but not in late-responding tissues such as spinal cord.
- For long intervals clearly beyond the overall treatment time in radiotherapy, an increase in radiation tolerance by long term restoration is seen in some (e.g. spinal cord), but not all, late-responding tissues.

Time dependence

Considering t the time between fractions, and T the overall treatment duration:

Reoxygenation need minimum T

Redistribution need minimum t

Repair need minimum t for normal tissues

Repopulation (or Regeneration) need to reduce T for tumours

- It is not possible to achieve all at once optimum t and T parameters to obtain the better response for all the “R” effects
- **Need to optimize fractionation schedule for individual circumstances**
- **Parameters: Total dose, Dose per fraction, Time between fractions, Total treatment time**

LQ model

The surviving fraction (SFd) of target cells after a dose per fraction d is:

$$SF_d = \exp(-\alpha d - \beta d^2)$$

Radiobiological studies have shown that each successive fraction in a multidose schedule is equally effective, so the effect (E) of n fractions can be expressed as:

$$\begin{aligned} E &= -\log_e(SF_d)^n = -n\log_e(SF_d) \\ &= n(\alpha d + \beta d^2) \\ &= \alpha D + \beta d D \end{aligned}$$

where the total radiation dose D=nd.
This equation may be rearranged into the following forms:

$$1/D = (\alpha/E) + (\beta/E)d$$

$$1/n = (\alpha/E)d + (\beta/E)d^2$$

$$D = (E/\alpha)/[1 + d/(\alpha/\beta)]$$

LQ model

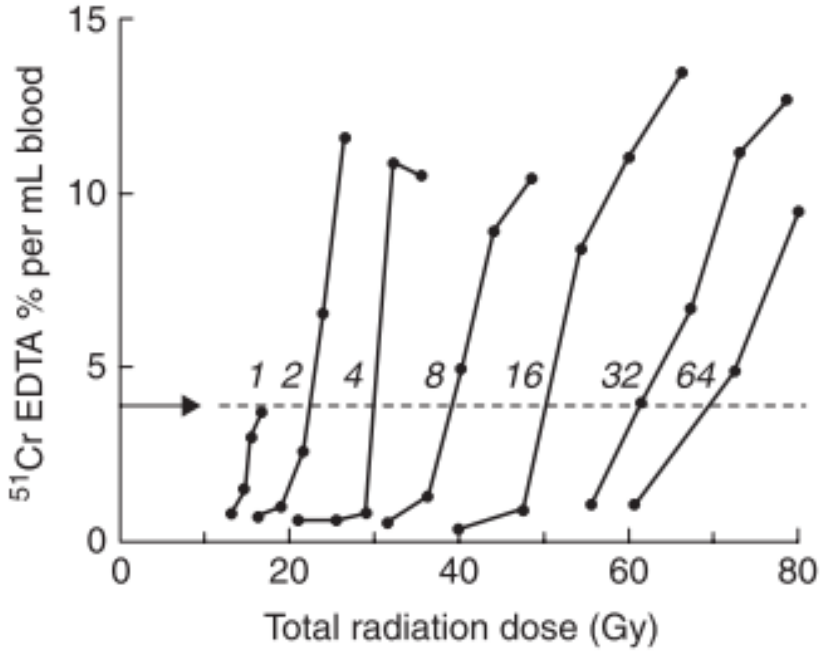


Figure 8.4 Dose–response curves for late damage to the mouse kidney with fractionated radiation exposure. Damage is indicated by a reduction in ethylenediaminetetraacetic acid (EDTA) clearance, curves determined for 1–64 dose fractions, illustrating the sparing effect of increased fractionation. From Stewart *et al.* (1984), with permission.

LQ model

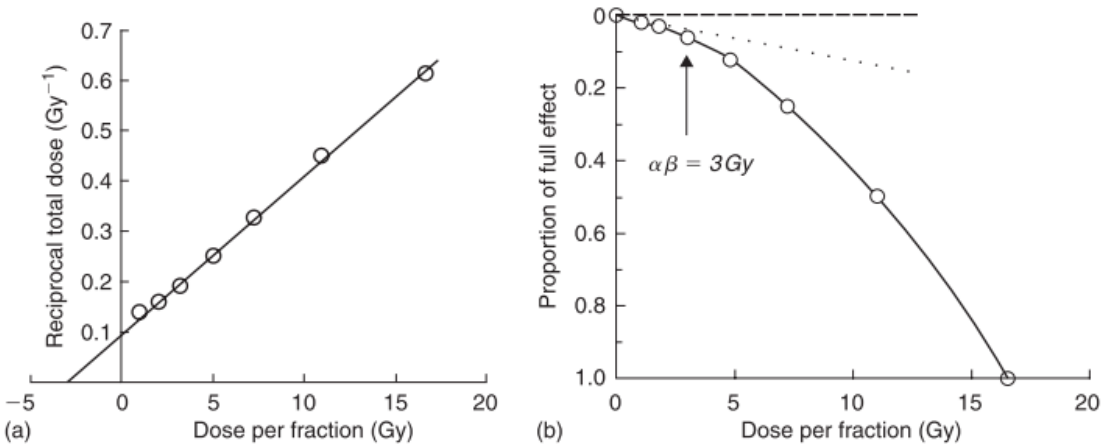


Figure 8.5 The data of Fig. 8.4 after two different transformations. (a) A reciprocal-dose plot according to equation 8.2. (b) Transformation according to equation 8.3 with the same data plotted as a proportion of full effect.

radiation dose for each fraction number. To apply the LQ model to this example, we first measure off from the graph the total doses at a fixed level of effect (shown by the arrow) and then plot the reciprocal of these total doses against the corresponding dose per fraction. Equation 8.2 shows that this should give a straight line whose slope is β/E and whose intercept on the vertical axis is α/E. That this is true is shown in Fig. 8.5a: the points fit a straight line well. This line cuts the x-axis

An alternative way of deriving parameter values from these data is to plot the reciprocal of the number of fractions against the dose per fraction, as suggested by equation 8.3. Figure 8.5b shows that this gives the shape of the putative target-cell survival curve with the y-axis proportional to $-\log_e(SF_d)$. (Statistical note: this method com-

LQ model

What change in total radiation dose is required when we change the dose per fraction?

$$E/\alpha = D[1 + d/(\alpha/\beta)] = \text{BED}$$

For isoeffect in a selected tissue, E and α are constant
BED:biologically effective dose
BED is the theoretical total dose that would be required to produce the isoeffect E using an infinitely large number of infinitesimally small dose fractions
(if d→0, BED=D=nd)

The first schedule employs a dose per fraction d1 and the isoeffective total dose is D1
Considering a dose per fraction d2 and the new (unknown) total dose D2, D2 is related to D1 by the equation

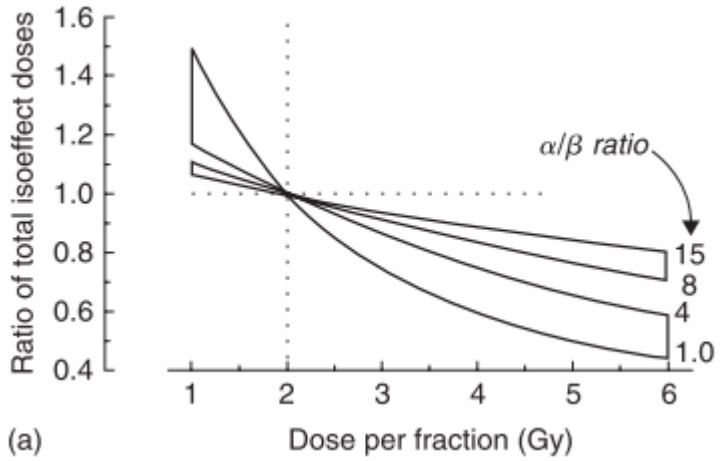
$$\frac{D_2}{D_1} = \frac{d_1 + (\alpha/\beta)}{d_2 + (\alpha/\beta)}$$

LQ model

- One should calculate the “equivalent” fractionation schemes
- Determine the radiobiological parameters
- Determine the effect of treatment breaks
  (e.g.: do we need to give an extra dose for the long weekend break?)

- For short interfraction intervals, a correction may be necessary for incomplete repair
- The basic LQ model is appropriate for calculating the change in total dose for an altered dose per fraction, assuming the new and old treatments are given in the same overall time.
- For late reactions it is usually unnecessary to modify total dose in response to a change in overall time, but for early reactions (and for tumour response) a correction for overall treatment time should be included to take into account the repopulation effect

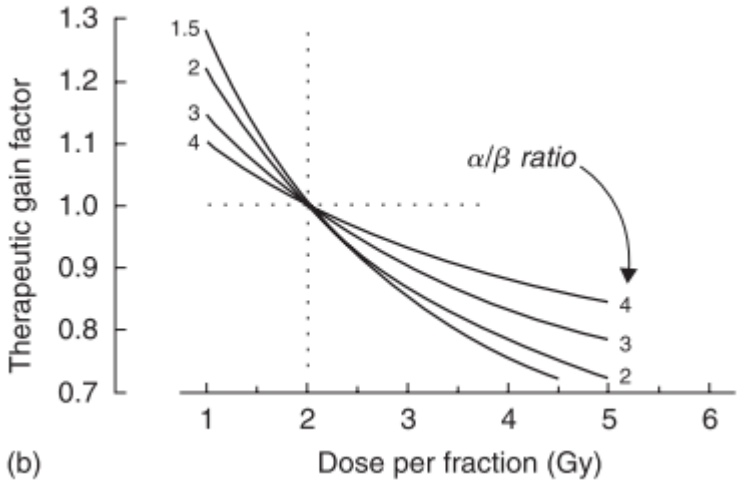
Hypo-hyper fractionation



Theoretical isoeffect curves based on the linear-quadratic (LQ) model for various α/β ratios. The outlined areas enclose curves corresponding to early-responding and late-responding normal tissues.

- when dose per fraction is increased above a reference level of 2Gy (hypofractionation), the isoeffective dose falls more rapidly for the late-responding tissues than for the early responses
- when dose per fraction is reduced below 2Gy (hyperfractionation), the isoeffective dose increases more rapidly in the late-responding tissues
- **Late-responding tissues are more sensitive to a change in dose per fraction**
- the change in total dose and the potential error is greater for the lower α/β values

Hypo-hyper fractionation



Therapeutic gain factors for various α/β ratios of normal tissue, assuming an α/β ratio of 10 Gy for tumours

- It is possible to calculate a therapeutic gain factor (TGF) for a new dose per fraction from the ratio of the relative isoeffect doses for tumour and normal tissue
- hyper- fractionation is predicted to give a therapeutic gain, and hypofractionation a therapeutic loss
- However, hypofractionation may be used as a convenient way of accelerating treatment, being more favourable in terms of both tumour control and late normal-tissue effects
- Advantage of low dose per fraction would be nullified, or reversed, for tumours with low α/β. If an increase in acute normal-tissue reactions prevented the total dose from being increased

Hypo-hyper fractionation

- Accelerated radiotherapy is the use of a reduced overall treatment time with a conventional dose per fraction, achieved using multiple fractions per day. The aim is to reduce the protective effect of tumour-cell repopulation during radiotherapy
- Multiple fractions per day should be given as far apart as possible and certainly not closer than 6 hours, in order to avoid incomplete repair
- Hypofractionation is the use of doses per fraction higher than 2.0Gy, which will increase late-responding normal tissue damage compared with conventional fractionation. Hypofractionation is routinely applied for palliation, but for certain curative situations hypofractionation may also be an option
- In clinical practice, typical number of fractions for conventional and protontherapy is of the order of 35, while for ^{12}C therapy is of the order of 15


Questions?

Thesis

Tematiche di tesi di laurea

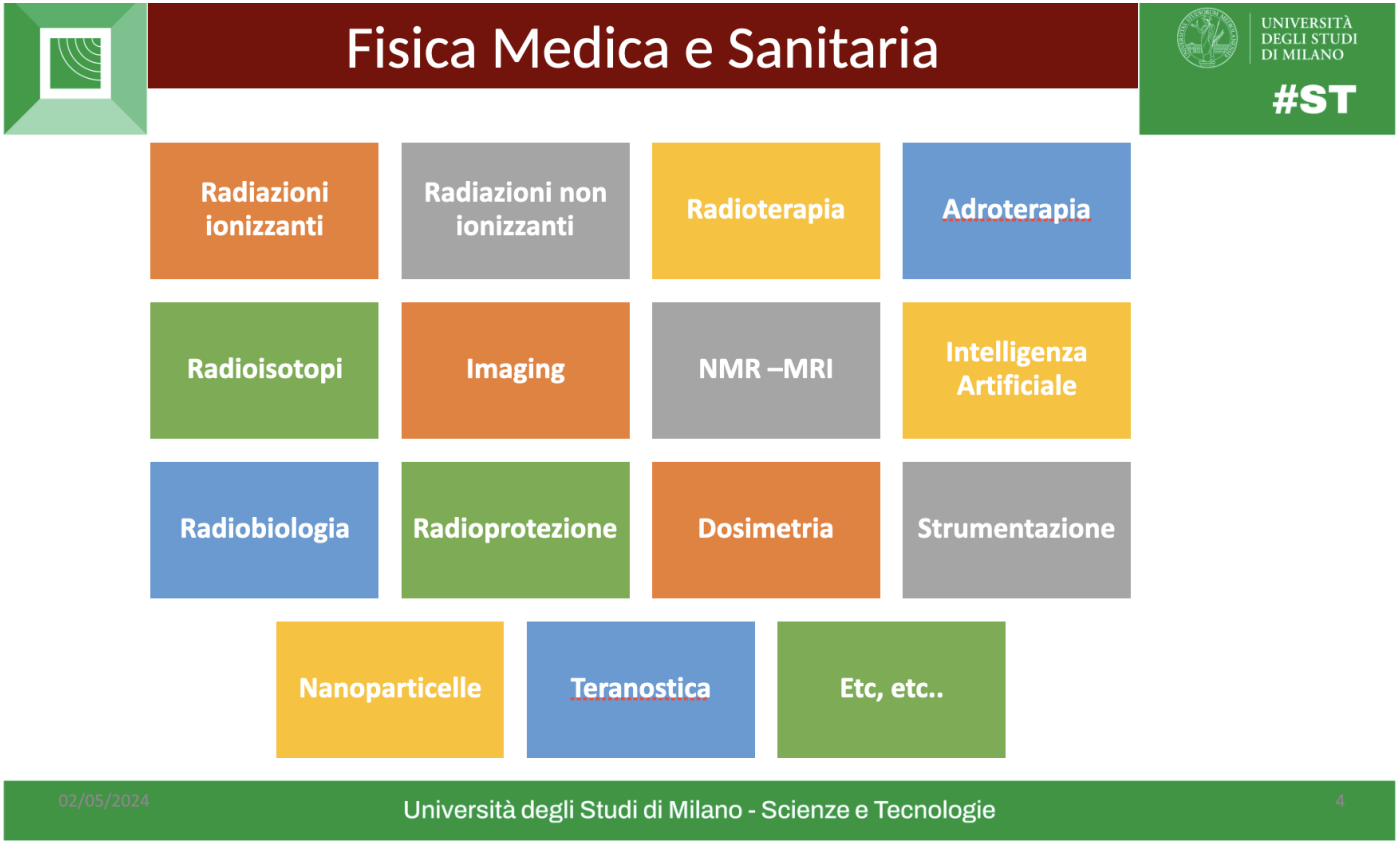
Le tesi si svolgono presso il Dipartimento di Fisica – via Celoria

- Sviluppo di biomateriali avanzati per applicazioni biomediche come drug delivery, cell delivery e dosimetria 3D.
- Utilizzo di nanoparticelle inorganiche come radiosensibilizzanti di cellule tumorali in applicazioni radioterapiche.
- Applicazione di tecniche di micro-fabbricazione per lo sviluppo di attuatori bio-ibridi.
- Sviluppo e caratterizzazione di nuovi materiali e metodologie per la rivelazione e dosimetria delle radiazioni ionizzanti.
- Studio con simulazione Monte Carlo di trattamenti di radioterapia con fasci esterni in modalità FLASH
- Sviluppo e validazione di tecniche innovative di range monitoring in adroterapia
- Applicazioni nell'ambito dell'imaging biomedico con la "facility" BriXSinO

Le tesi che si svolgono al Dipartimento di Fisica – Laboratorio Acceleratori Superconduttività Applicata – LASA sono di tipo sperimentale:

- Studio della produzione di radionuclidi per teranostica
- Determinazione della concentrazione di radon indoor
- Studio concentrazione di inquinanti nel particolato atmosferico
- Studio dell'uptake di NPs per studi di nanotossicologia

Thesis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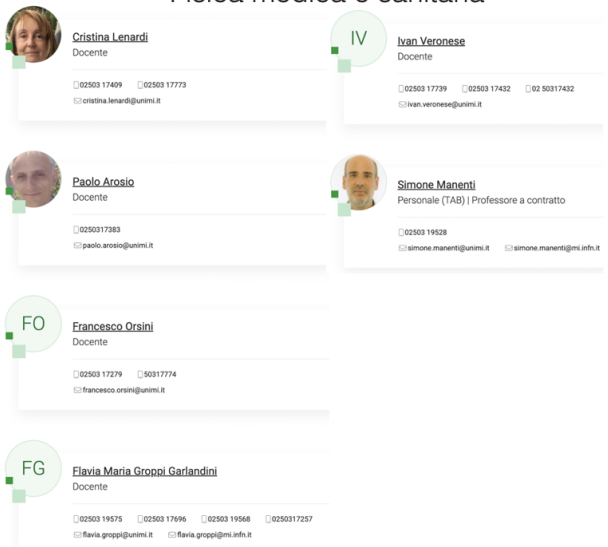
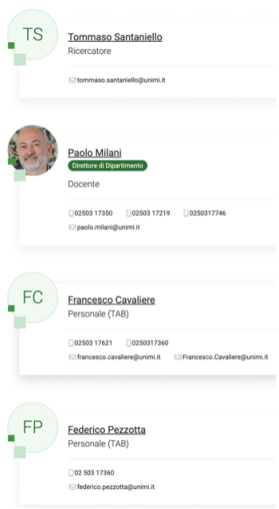
Fisica Medica e Sanitaria

https://fisica.unimi.it/it/ricerca/attivita-e-risultati-di-ricerca/aree-e-linee-di-ricerca/fisica-applicata-alla-medicina

Fisica medica e sanitaria



Stampa 3D e realtà virtuale



Fisica nucleare applicata