RADIATION ONCOLOGY

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TYPES OF RADIATION

Photons

- Electromagnetic rays (mutually perpendicular electric and magnetic waves)
- X-rays originate outside of nucleus, typically as excess energy shed by an incoming electron when bending around a nucleus
- Gamma-rays originate within the nucleus during radioactive decay or fluorescence
- Ionizing radiation is that with photon energies > 1 keV

Protons

- Generated by cyclotron beams.
- Travel mainly in a straight line through atomic electron clouds.
- Lose energy through interaction with orbital electrons.
- As protons have greater mass, they only lose a very small fraction of their kinetic energy with each interaction, and thus scatter only minimally.

Protons

- The interactions (and energy loss) become more frequent at slower energies.
- The slower the proton moves, the more energy it loses to the tissue electrons, in a feed-forward loop, until it abruptly loses all energy.
- This region of rapid energy loss (and its deposition into the tissue) is called the Bragg peak.
- There is virtually no exit dose.
- The distance at which Bragg peak occurs, and the energy is deposited, can be calculated very precisely (unlike with electrons).

Protons

- Able to sculpt dose volume about tumors and deliver lower doses of radiation to surrounding normal tissues.
- Incoming protons also interact with the nucleus, and may enhance cell kill by 10%.
- <u>No obvious clinical advantage over electron beam</u>.

Electrons

- Electrons (β-, β+)
- Do not travel in straight lines in tissue, but are deflected by coulombic repulsions from atomic orbital electrons.
- Lose on average 50% of their energy on interaction.
- Well-defined penetration "range" in tissue (continuous slowing down approximation range) for 12MeV electrons is 2 cm.
- Electrons for therapy are produced in a linear accelerator.
- ^{131}I is a β-emitter administered orally in therapy of thyroid cancer.

^{60}Cobalt

- Half life 5.263 yrs.
- Z (Atomic number) of 27
- γ-rays produced: 1.17 MeV, 1.33 MeV.
- β-decay (neutron conversion to proton) to ^{60}Ni. .
- β-rays produced: 0.32 MeV (99%) and 1.48 MeV (1%)
- Principal use of ^{60}Co is in teletherapy, brachytherapy (remote afterloading), and gamma knife radiosurgery.

Neutrons

- Reactor generated.
- Neutrons interact by colliding with protons.
- ^{10}B has high-cross sectional area, favoring interaction with neutrons.
- This leads to a sudden large loss (deposition) of energy in a single event.
- The fall-off in dose is exponential (as the interactions are random).
- In tissues, 50% of dose is at 10 cm

Neutrons

- Neutrons have high LET (kilovolt/volt energy deposition in tissue) as well as high biological effect.
- kV (Kilovolt) =12.4/ λ (wavelength in Angstroms)
- <u>High LET radiation is effective in hypoxic tissues.</u>
- Shielding by combination of hydrogen rich (concrete) and highly absorbing (^{10}B) materials.

Pions

- Mesons are unstable and decay
- Negative π-mesons have enhanced biological effect and Bragg peak effect.
- 15% of mass of proton
- Cyclotron produced
- No clinical advantage to use

Alpha particles

- Produced by radioactive decay of heavy radionuclides (proton rich isotopes).
- At the same energy, they travel much more slowly than protons due to their much higher mass as are Helium nuclei.
- Have higher Bragg peak.
- They also interact with nuclei more often, and may lose a large amount of their large kinetic energy in a single interaction.
- <u>This accounts for biological effectiveness.</u>
- Their effective range is 1-2 mm.
- Shielding by low-Z materials.

INTERACTION WITH TISSUES

Interaction of X-rays and γ-rays with tissue

- Excitation
- An inner shell electron is imparted with sufficient energy to move to a higher energy shell, but not enough energy to separate from the nucleus.
- It then immediately returns to its original shell to fill the vacancy, and in the process sheds the excess energy as electromagnetic radiation (photon) .
- This radiation is characteristic for a given element as it is a function of the difference in shell energy levels, and is called characteristic radiation .
- The chemistry of the atom is ultimately unchanged.

Interaction of X-rays and γ-rays with tissue

- Ionization
- An inner shell electron is imparted with sufficient energy to separate from the nucleus (> binding energy).
- A higher shell electron descends to fill the vacancy, and in the process sheds its excess energy as electromagnetic radiation.
- The electromagnetic energy is the same as the energy difference between the shells.
- In large atoms, yet higher shell electrons may then descend in a cascade, resulting in multiple emissions.

Interaction of X-rays and γ-rays with tissue

- Once a valence shell electron is lost, the atom is ionized.
- The emitted x-ray(s) are called characteristic x-rays, and are unique to each element.
- On average it takes 33 KeV to eject an electron from an atom, and thus ionize the atom.

Coherent Scattering

- Incoming photon is deflected (absorbed and immediately re-emitted), with minimal direction and energy change.
- Not relevant at energies used for therapy.
- Dependent upon Z.

Photoelectric Absorption

- Strongly enhanced in high-Z tissues such as bone.
- Incoming photon interacts with innermost shell electrons (85% K-shell, 14% L-shell, 1% rest) and is absorbed by them .
- This may cause the electron to be excited to a higher shell or ejected from the atom.
- If ejected, a photo-electron, it causes projectile damage in tissue.
- The vacancy is filled from higher shells, leading to characteristic x-rays.
- These characteristic x-rays may be immediately re-absorbed by the same atom's electrons (common).

Photoelectric Absorption

- If the x-rays have sufficient energy, they may excite or eject another electron in a second ionization event.
- If ejected, an Auger electron, it too causes projectile damage in tissues .
- The remaining atom may become a free radical, if valence electrons are affected.
- Absorption common at low energies (80-100 keV).
- <u>Not relevant at energies used for therapy.</u>
- Related to $(Z/e^{-})^{3}$.

Compton Scattering

- Most dominant interaction in soft tissues at energies used in therapy.
- Incoming photon interacts with outermost electrons, and is reflected.
- This Compton photon can undergo additional interactions.
- In the process, the incoming photon ejects a valence electron.
- This causes projectile damage in the tissue and accounts for ~75% of radiation damage.

Compton Scattering

- The atom becomes a free radical, causing biological damage in the tissue.
- Accounts for ~25% of radiation damage.
- The probability of a Compton interaction is inversely proportional to the energy of the incoming photon.
- It is independent of atomic number.
- Thus, at energies used for therapy, bone and soft-tissue interfaces are barely distinguishable.

Compton Scattering

- At treatment energies, the Compton scattering direction is forward-peaked.
- Less than 20% of energy is lost at interaction.
- The ejected electron can interact numerous times before losing sufficient energy to be absorbed via photoelectric absorption.
- <u>This is the main tissue effect at energies 30 keV - 30 MeV.</u>

Pair production

- Occurs only at high photon energies (>1.02 MeV) and in high-Z tissues.
- Incoming photon (energy) is converted to mass (electron and positron) in the vicinity of atomic nucleus.
- Additional energy over 1.02 MeV is converted to kinetic energy, and divided between the two particles.
- Positron then interacts with an electron (not necessarily from same atom), is annihilated, and is converted back into two photons, each of 0.51 MeV.

Pair production

- The electron causes projectile damage in the tissue.
- Linear energy transfer is related to ion pair formation per unit path length and is the reciprocal of velocity (squared) and Z.

Photodisintegration

- Occurs only at very high photon energies (>7 MeV).
- Incoming photon deposits so much energy, the nucleus disintegrates.
- Source of low-level neutron production.
- <u>Not relevant at energies used in therapy.</u>

Interaction of electrons with tissue

- Two fundamental interactions:
- <u>Bremsstrahlung</u>
- Results from the bending of electrons around nucleus.
- Energy lost as x-rays.
- Related to Z^2.

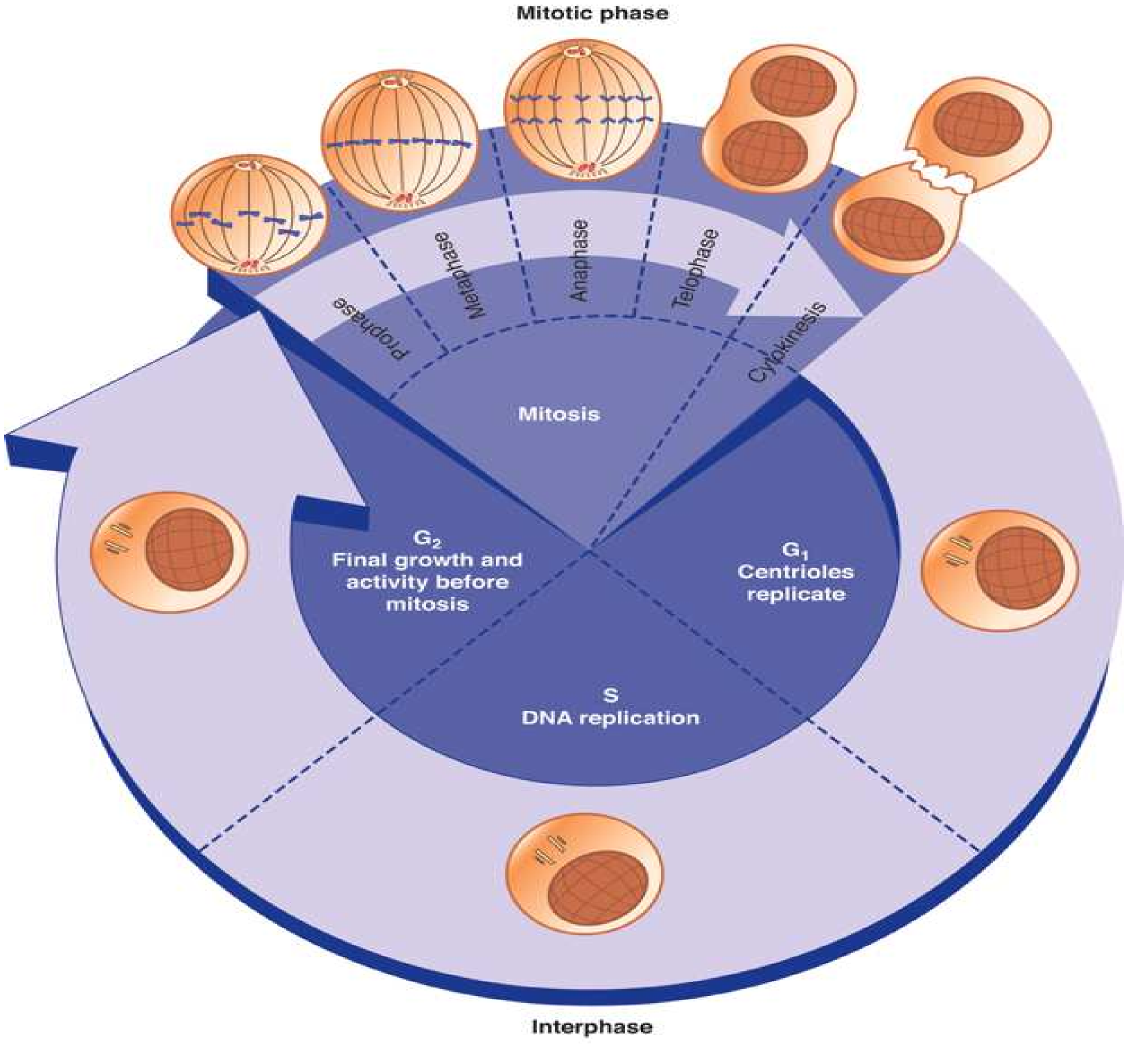
Interaction of electrons with tissue

- Ionization
- Results from impact with orbital electron and ejection of electron with filling of the vacancy and shedding of energy as characteristic x-rays
- Any given electron can in a single interaction lose a very small or very large fraction of its energy, and be deflected by a very small or very large amount.
- This leads to large variation among incoming electrons in their path (and distance) into the tissue.
- This is caused range-straggling.

Tissue damage

- Radiation produces a double stranded DNA break using a single radiation track.
- Individual breaks can be repaired (first order kinetics)
- A single radiation track may give rise to a lethal lesion by point mutation in vital gene, by a deletion eliminating a vital gene, by induced apoptosis, as examples.
- If more than one unrepaired break is present in the cell at the same time (arising from two separate radiation tracks), a lethal lesion may result (from repair errors).

Cell cycle



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Cell cycle

- If cells have short G1, then are most sensitive to radiation in G2 and M.
- If cells have long G1, are radiosensitive only at the end of G1.
- S phase is generally radioresistant.
- p53wt required for radiation induced apoptosis.
- Hypoxic resistance in p53 deficient cells
- FAS mediated (CD95) apoptosis with a cytochrome-c mechanism as well

Linear quadratic model

- The yield (Y) of lethal lesions is the sum of lethal lesions produced from :
- A single radiation track (which are linearly related to dose, αD)
- Lethal lesions produced from two radiation tracks (which are quadratically related to dose, βD^2)
- Because it is possible that two separate breaks can be repaired prior to resulting in a lethal event, time factor (G) to show dependence on dose protraction. For single fractions, $G=1$, and:
- $Y = \alpha D + G\beta D^2$, the standard linear-quadratic model equation.

Linear quadratic model

- Lethal lesions are thought to follow Poisson distribution from cell to cell. Therefore, the surviving fraction (SF) is:
- $SF = e^{-(Y)} = e^{-(\alpha D + G\beta D^2)}$
- For fractionated treatments (total daily dose is divided into fractions administered over the course of a day), the relative effectiveness of the unit dose is $1 + dn(\beta / \alpha)$ where dn is the dose fraction.
- Homogenous tissue distribution is assumed (no “hot” or “cold” spots).

Linear quadratic model

- For cells with high repair potential, whose α/β ratio is small, doubling the radiation dose leads to more than doubling the effect on survival fraction (SF).
- Such cells are sensitive to changes in fraction size when radiation is given in fractions
- For cells with low repair potential, whose α/β ratio is large, increasing radiation dose has lesser effect than when given in fractions.

Linear quadratic model

- The linear quadratic model is well validated for doses up to 10 Gy/fraction, and could be reasonably used to about 18 Gy/fraction.
- The linear quadratic model does not reflect vascular and stromal damage produced at high doses per fraction.
- The linear quadratic model also ignores the impact of radioresistant subpopulations of cells.

Linear energy transfer

- LET is a physical quantity that is used to define the quality of an ionizing radiation beam.
- Best defined for protons, α-particles, and heavy nuclei (HZE ions found in cosmic rays)
- dE/dl (keV/μM)
- Energy (E) locally imparted to the medium by a charged particle traveling a distance l.
- Varies over the particle track
- The demarcation between low and high LET is 10 keV/ μM.

Linear energy transfer

- Low LET
- Sparsely ionizing radiations
- Relative biological effect (RBE) generally independent of LET
- RBE compares dose of test radiation to standard dose to produce similar effect
- ^{60}Co γ-rays as standard_

Linear energy transfer

- β-particles strongly scattered by nuclei (Rutherford scattering)
  - Produce secondary electrons while ionizing atoms
  - Produce bremsstrahlung (deceleration)photons
  - Short maximum range
- Muons decay into electrons
  - Produce fewer bremsstrahlung photons

Linear energy transfer

- γ-rays are photons that may be absorbed in a single process
- LET refers to ionization of secondary electrons (Compton electrons)
- Absorption obeys an exponential law
- Absorption defined by half-value thickness

Linear energy transfer

250 kVp X-rays	2 keV/μM (normal x-ray dose)
1 MeV electrons	0.25 keV/μM
3 MeV X-rays	0.3 keV/μM
^{60}Co γ-rays	0.3 keV/μM
10 keV electrons	2.3 keV/μM

Linear energy transfer

- <u>High LET</u>
- Densely ionizing radiations within a narrow diameter around a track
- Continuous deceleration
- Changing particle cross section generally increases LET to a Bragg peak where it achieves thermal equilibrium with the absorber and comes to rest (or is stopped)

Linear energy transfer

- RBE rises increases with LET increases to a maximum, and then declines
- Mammalian cells generally experience a peak RBE at 100 keV/µM
- 14 MeV neutrons 12 keV/µM
- Heavy, charged particles 100-200 keV/µM

Equivalent dose

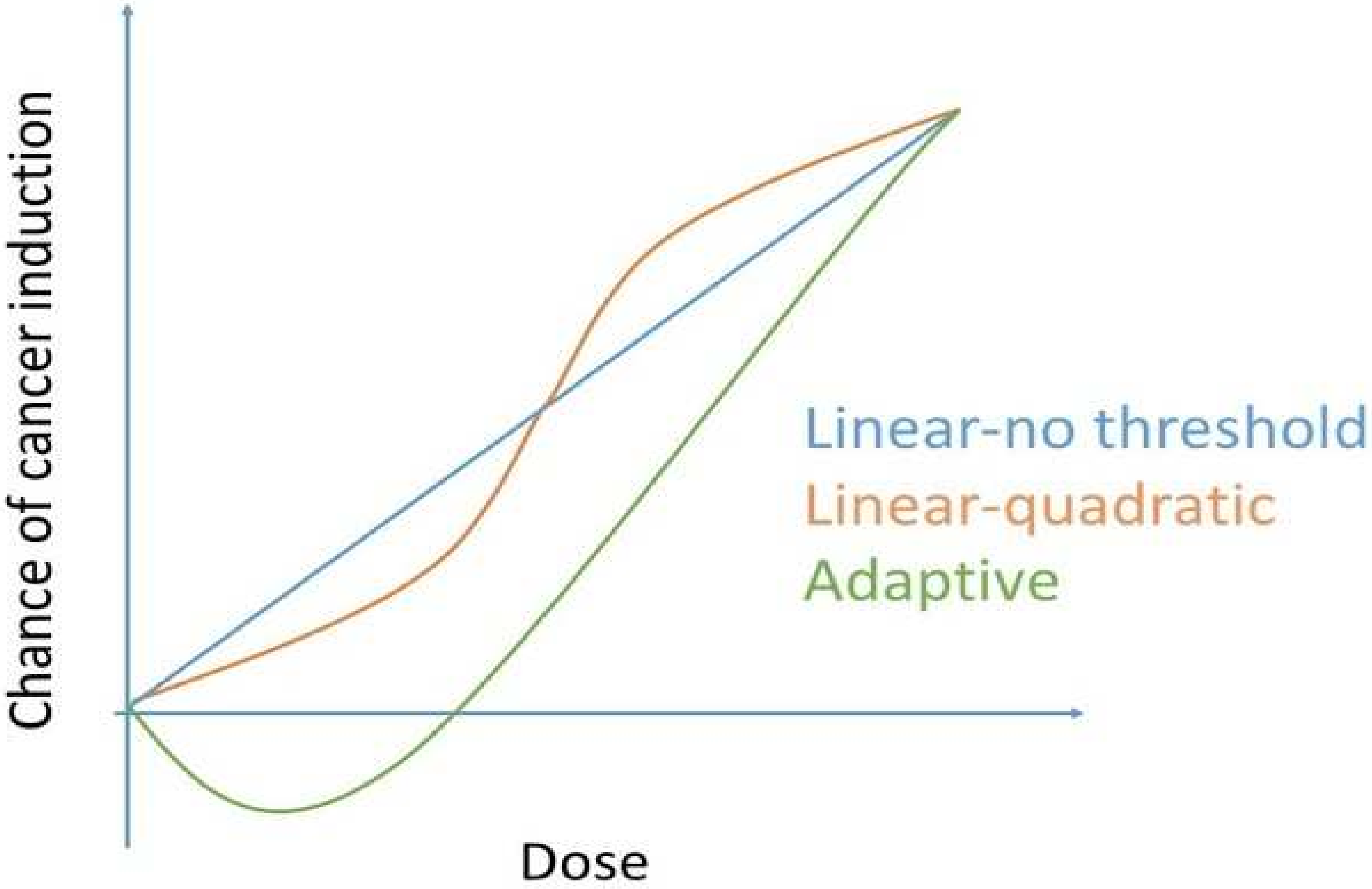
- Equivalent dose (H_T) is the total absorbed dose of a single administration
- The standard administration is 1.8-2.0 Gy/d
- $H_T = DW_R$
- D is dose
- W_R is the radiation weighting fraction
- Photon, all energies = 1
- Electron, muons, all energies = 1
- Protons, charged pions = 2
- α-particles, fission fragments, heavy ions = 20
- Neutrons range from 5-20 dependent upon energy

Effective dose

- The effective dose is used to compare the stochastic risk of non-uniform exposure to radiation.
- The effective dose is calculated by multiplying the equivalent dose (H_T) by a tissue weighting factor (W_T).
- Tissue weighting factor (W_T) is the measure of risk of stochastic effects of the radiated tissue (risk of cancer induction).
- It accounts for the variable radiosensitivities of various organs and tissues to ionizing radiation

Effective dose

- The sum of weighting factors equals 1.0
- W_T = 0.12: stomach, colon, lung, red bone marrow, breast, remainder tissues
- W_T = 0.08: gonads
- W_T = 0.04: urinary bladder, esophagus, liver, thyroid
- W_T = 0.01: bone surface, skin, brain, salivary glands



https://radiopaedia.org/articles/stochastic-effects?lang=us

Fractionation

- If a dose is split into two fractions, with a time interval of several hours, then a portion of the sublethal events that resulted from the first dose have been repaired prior to the second dose
- Normal tissues are relatively spared through repair of sublethal damage and repopulation of cells
- Repair is more important for slowly proliferating tissues as they do not suffer much early cell death with radiation (e.g., kidney)
- Cell repopulation important for cells capable of rapid proliferation (e.g., marrow, mucosa, skin
- Accelerated repopulation begins within 2-4 weeks of initiation of radiation therapy

Fractionation

- Re-oxygenation and redistribution of tumor cells during the interval period leads to greater killing with the second dose
- Radiation induces permanent damage to oxygenated tissues as it generates reactive oxygen species
- Tumors >1mm in size are partially hypoxic
- The effect of radiation on tissues is to lead to more synchronous cell behavior
- Cells move from one phase to another between doses
- Some cells will be blocked in G_2 (mitotic delay) while others will redistribute to more sensitive phases of the cell cycle

Dosing

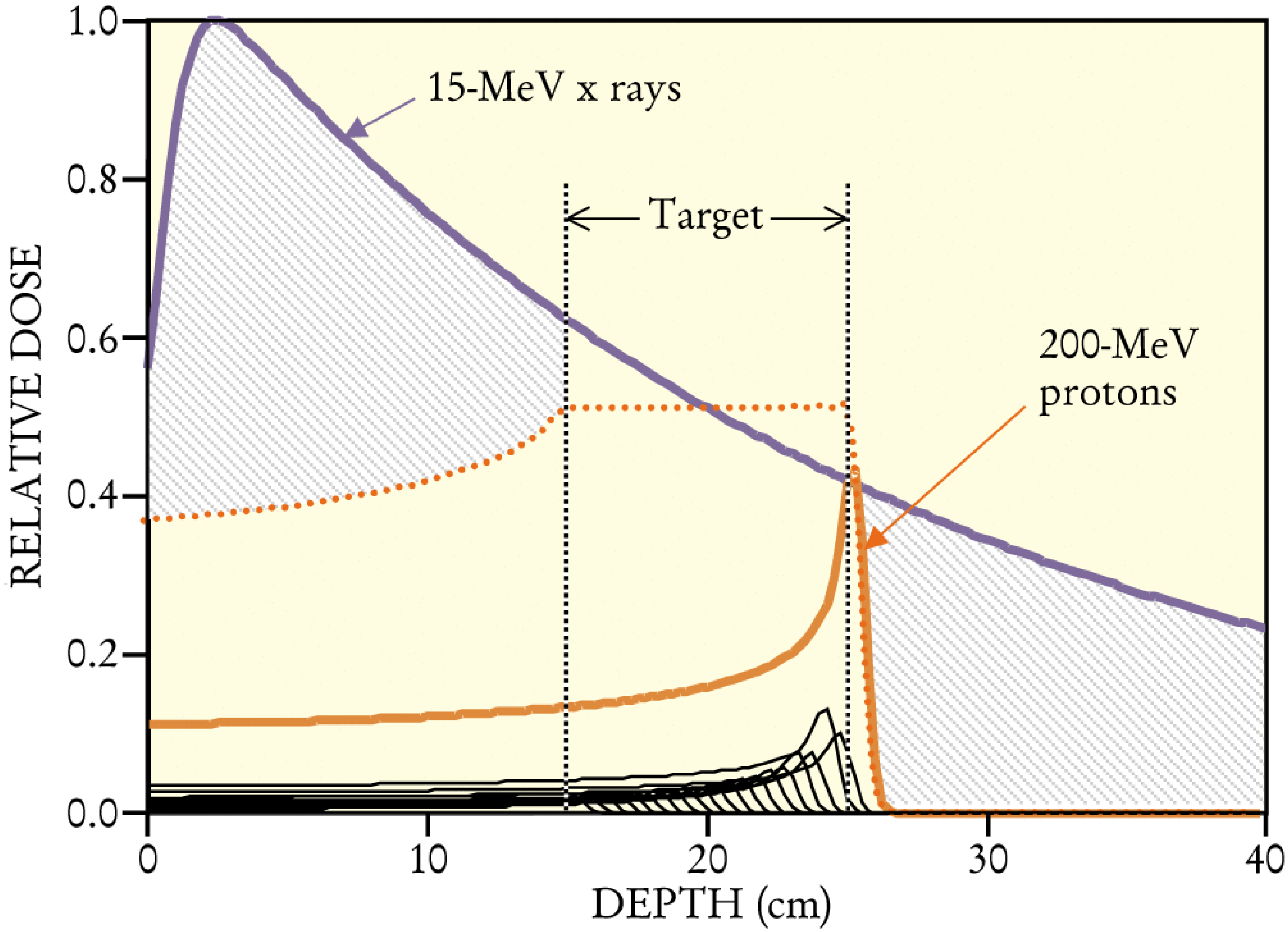
- Hyperfractionation
- Increased total dose with dose per fraction reduced and number of fractions increased
- Thought to increase the ratio of irreparable to reparable cell injury (α/β).
- There are more acute reactions associated with its use.
- Fewer long-term complications.
- Accelerated fractionation
- Overall time of dosing reduced without changing dose, dose per fraction, or number of fractions
- Accelerated hyperfractionation
- Hypofractionation
- Increase fraction dose while diminishing number of fractions

Dosing

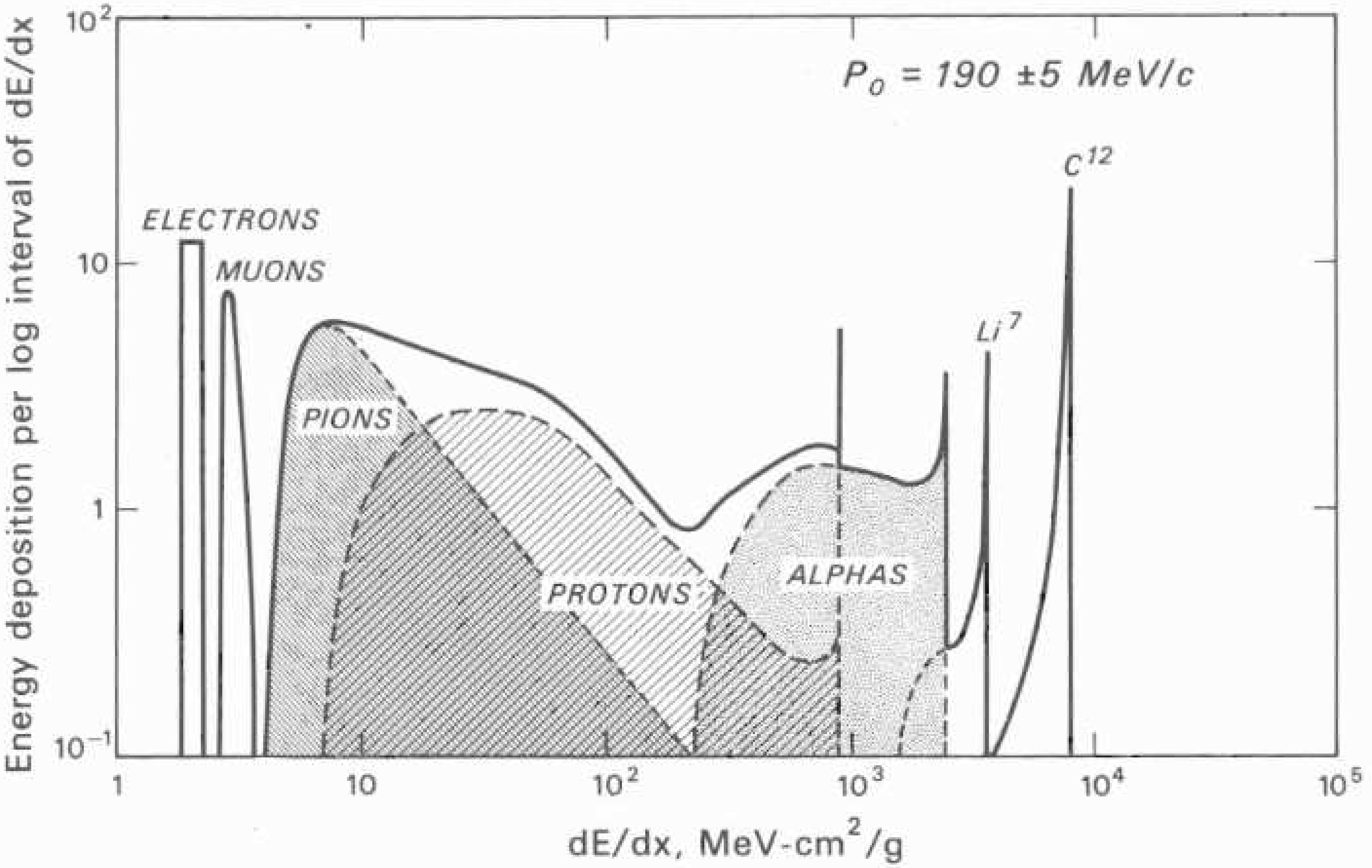
- Moderate hypofractionation not inferior to standard fractionation
- Standard fraction: 1.8-2.0 Gy
- Hypofraction: 3.0-3.4 Gy
- Consistent with an α/β ratio of 1.3-1.8 Gy

Distibution

- Depth of deposition decreases exponentially with higher energies.
- Depth increases as distance from radiation source.
- Depth increases with field size due to scattered radiation at depth.
- Isocentric fields have 6% variation across the field.



https://physicstoday.scitation.org/doi/10.1063/1.1522213



DBL 673-1581

https://lss.fnal.gov/conf/C711204/p.33.pdf

Shielding

- Shielding by medium-Z metals to provide electrons to slow the protons down.
- High-Z materials should be avoided, as they produce secondary x-rays and neutrons.
- High-Z materials are preferred for absorption of γ-rays.

Permissible radiation dose

- Occupational exposure: 20 mSv/year (effective dose)
- Lens of eye: 20 mSv/year
- Skin (average dose over 1 cm^2 of the most highly irradiated area of skin): 500 mSv/year
- Hands and feet: 500 mSv/year

Permissible radiation dose

- Females of reproductive capacity: 13 mSv/any three month period
- This restriction is to protect a recently conceived fetus within a woman who may be unaware of her pregnancy
- Fetus (during declared term of pregnancy): 1 mSv/over declared term of pregnancy
- Sv unit is the sievert; old terminology, rem

RADIATION THERAPY

Radiation therapy

- There are two main types of radiation therapy:
- 1. External beam therapy is local
- Applied to a specific site.
- Three types of particles are employed:
- Photons
- Photon beams can reach tumors deep in the body. As they travel through the body, photon beams scatter little bits of radiation along their path. These beams do not stop once they reach the tumor but go into normal tissue and past it.

Radiation therapy

- Protons
- Proton beams can also reach tumors deep in the body. However, proton beams do not scatter radiation on their path through the body and they stop once they reach the tumor.
- Electrons
- Electron beams cannot travel very far through body tissues. Therefore, their use is limited to tumors on the skin or near the surface of the body.
- 2. Internal therapy is systemic

Types of external beam therapy

- <u>3-D conformal radiation</u>
- Conforms to the shape of the tumor by delivering beams from many directions.
- The precise shaping makes it possible to use higher doses of radiation to the tumor while sparing normal tissue.

Mechanisms

- <u>Intensity-modulated radiation therapy (IMRT)</u>
- IMRT uses many more smaller beams than 3-D conformal and the strength of the beams in some areas can be changed to give higher doses to certain parts of the tumor.
- Permits sculpting of dose volume about tumor.
- Less xerostomia, ototoxicity, and neurocognitive deficit with use in head and neck tumors.

Types of external beam therapy

- Image-guided radiation therapy (IGRT)
- IGRT is a type of IMRT where fields are altered during the treatment course based upon repeated scanning of the tumor.
- Tomotherapy
- CT scanning prior to delivery of each dose to permit precise tumor targeting and sparing of normal tissue.
- A type of IMRT.

Types of external beam therapy

- Stereotactic radiosurgery
- Use of focused, high-energy beams to treat small tumors with well-defined edges in the brain and central nervous system.
- Gamma knife is a type of stereotactic radiosurgery.
- Stereotactic body radiation therapy
- Used for small, isolated tumors outside the brain and spinal cord, often in the liver or lung.
- It delivers a highly precise beam to a limited area.

Types of internal radiation therapy

- <u>Brachytherapy</u>
- Seeds, ribbons, or capsules that contain a radiation source are placed in the body, in or near the tumor.
- A local treatment and treats only a specific part of the body.
- It is often used to treat cancers of the head and neck, breast, cervix, prostate, and eye.

Types of brachytherapy

- Interstitial brachytherapy
- The radiation source is placed within the tumor.
- This technique is used for prostate cancer, for instance.
- Intracavity brachytherapy
- The radiation source is placed within a body cavity or a cavity created by surgery.
- For example, radiation can be placed in the vagina to treat cervical or endometrial cancer.
- Episcleral brachytherapy
- The radiation source is attached to the eye.
- This technique is used to treat melanoma of the eye.

Types of brachytherapy

- The patient is radioactive during therapy.
- Low-dose rate implants
- Short term placement of radiation source.
- High-dose rate implants
- Daily placement of radiation source for short time periods.
- Permanent implants
- Decay leads to 99% loss of radiation within 5 half-lives.

Internal radiation therapy

- Systemic therapy
- A liquid source is administered and distributed systemically.
- Usually ^{131}I for treatment of thyroid cancer.
- Advanced prostate cancer and gastrointestinal-neuroendocrine tumors may be treated as well with radionuclide targeting.
- The patient is radioactive during therapy.

Modifiers

- Caffeine is a radio-sensitizer as is hydroxyurea.
- Alcohol potentiates the effect of heat.
- Hyperthermia (43C) potentiates radiation effect.
- For each degree Celsius above 43C, half the time of exposure at 43C is required to generate the same effect
- For each degree below 43C, four times the time of exposure at 43C is required to generate the same effect.
- Fluropyrimidines, Cis-platinum enhance cell killing.
- Ethoyl (amifostine) is radio-protective.

Definitions

- $kv=12.4/\lambda$ (in Ångstroms)
- R(oentgen)=.000258c/kg air
- A rad is equal to 100 ergs/g tissue
- A Gray is equal to 100 rad
- rem reflects biological response
- replaced by Sievert
- 100 rads is 1 sievert