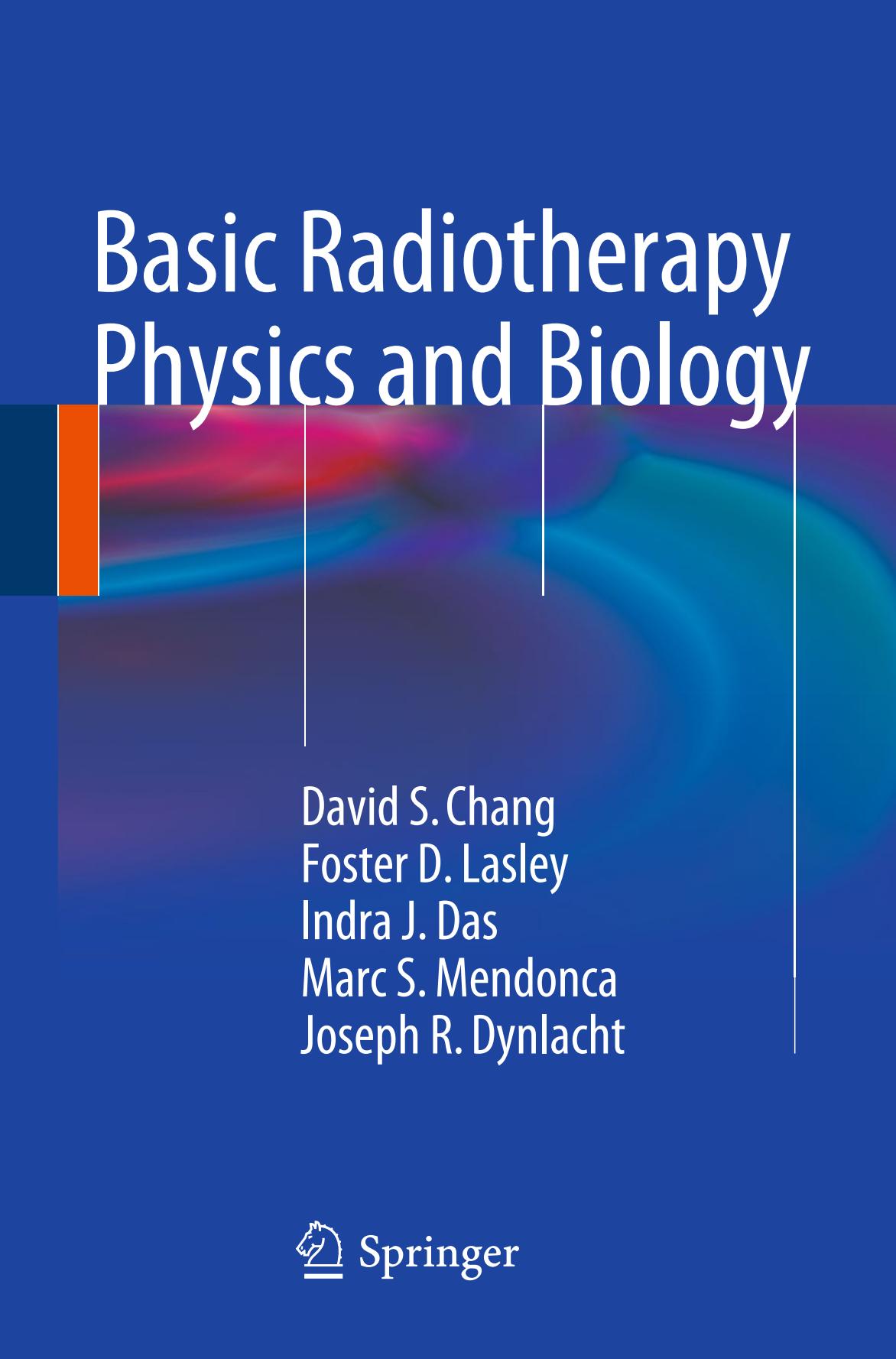


Basic Radiotherapy Physics and Biology



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Springer

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Preface

Many radiation oncology textbooks are written in a formal academic style. When studying these highly detailed books, many residents struggle to find a good balance between time and comprehension. *Basic Radiotherapy Physics and Biology* is a by-product of long hours spent in preparation for the American Board of Radiology (ABR) Radiation Therapy Physics and Biology examinations. It is written in a concise and humorous style so that information may be rapidly reviewed, whether for daily use or for exam preparation. Using mnemonics, rules of thumb, and simple figures, we have attempted to make our text as “digestible” as possible. The intended audience for this book includes radiation oncology residents, radiation therapists, dosimetrists, physicists, medical students and other readers motivated to learn about the physics and biology of radiation therapy.

The topics contained in this book are directly based on the *ABR Radiation Oncology Study Guide* that is available on the ABR website. Whereas the *ABR Study Guides* are formatted as a long list of topics, *this book* is organized into two equal parts. The physics topics are covered in Chapters 1 through 16 and the biology topics are covered in Chapters 17 through 32. Each chapter consists of a series of concepts explained with bullet points of text, together with figures, equations, and mnemonics where appropriate and concise. A few math-heavy chapters also include a section entitled “Rules of Thumb.” These rules intend to summarize mathematical concepts in plain language, favoring ease-of-use over detail. The book also includes two appendices of reference information: a glossary of terms and physical constants and a list of radionuclides used in imaging and radiotherapy.

This book does not cite specific references, as it is a collection of basic rules and principles and not a rigorous scholastic work. Those who wish to delve into the primary literature should refer to one of the many comprehensive textbooks and research papers that already exist. Instead, our book is designed as a quick reference, helpful for exam preparation and daily clinical practice in the real world.

It is our hope that this book will be of great value to all students and would-be students in every discipline of radiation oncology.

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Part I
Radiation Therapy Physics

1

Atomic and Nuclear Structure

Atomic and Nuclear Nomenclature

- The **atom** includes a **nucleus** and **electrons**.
 - Electrons determine the chemical properties of an atom.
 - “**Nuclide**” refers to the composition of the nucleus (number of protons and neutrons).
 - “**Nucleons**” include **protons** and **neutrons**.
- **The Numbers:**
 - **A = Atomic Mass Number** (Total protons + neutrons)
 - **Z = Atomic Number** (Total protons)
 - **Z** determines the number of electrons, and therefore the chemical properties of the atom.
 - **N = Neutrons = A – Z**

- **The four “isos”:**
 - **Isotope:** same number of **protons**, different neutrons.
 - Same chemical behavior, different mass and different nuclear decay properties.
 - Ex: ^{125}I and ^{131}I both behave like iodine, but have different half-lives.
 - **Isotone:** same number of **neutrons**, different protons.
 - Rarely used.
 - **Isobar:** same number of **nucleons**, different nuclide. (more protons and less neutrons, or vice versa)
 - “bar” = same mass - think barbell.
 - **Beta decay** (See Chapt. 2) and **electron capture** always result in an **isobar**.
 - Ex: ^{131}I decays to ^{131}Xe , which has the same mass number but is a different nuclide.
 - **Isomer:** same **nuclide**, different energy state. (excited vs. non-excited)
 - **Isomers** release their energy through **gamma decay** (See Chapt. 2).
 - Ex: $^{99\text{m}}\text{Tc}$ decays to ^{99}Tc , releasing its excess energy without changing the number of protons or neutrons.

The Four Fundamental Forces

- In order of descending strength these are:
- **Strong Nuclear Force:**
 - The strongest force in nature; “glues” the nucleus together.
 - Holds the nucleus together, counters the repulsive effect of protons’ positive charge.
- **Electromagnetic (Coulombic) Force:**
 - ~1/100 as strong as the strong force.
 - Opposites attract. Electrons are attracted by the positively charged nucleus and are more attracted as they get closer; Valence electrons are not strongly attracted and their movements are responsible for all chemical reactions.
 - Protons repel each other within the nucleus but are held in place by the strong force.
- **Weak Nuclear Force:**
 - ~1/1,000,000 as strong as the strong force.
 - Works inside particles (between quarks) and is responsible for radioactive decay.
- **Gravity:**
 - $\sim 1 \times 10^{-39}$ as strong as the strong force.
 - Not important on the atomic scale.

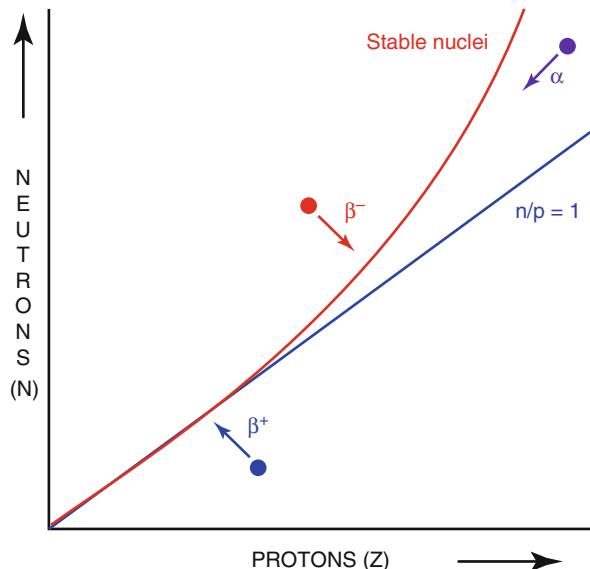
On Mass

- **Mass** and **energy** are always interchangeable based on Einstein's $E = mc^2$.
 - Energy can be converted to mass and mass can be converted to energy by multiplying by c^2 (speed of light squared).
 - As particles approach the speed of light, the velocity must remain constant so as the particle gains energy, it actually gains mass.
- There are two common ways to measure **mass**.
- **Atomic mass units (AMU)**:
 - Defined as 1/12 the mass of a Carbon-12 atom.
 - This is slightly less than the mass of the component particles, due to the **binding energy** of the carbon atom. (see below)
 - **Proton mass = 1.0073 AMU**
 - **Neutron mass = 1.0087 AMU** (slightly larger than a proton)
 - **Electron mass = .0005 AMU** (approx. 1/2,000)
- **Energy equivalent (MeV/c²**, may be shortened to just “**MeV**”):
 - Defined as the equivalent amount of energy (mc^2), measured in mega electron volts.
 - **Proton mass = 938.3 MeV**
 - **Neutron mass = 939.6 MeV**
 - **Electron mass = 0.511 MeV (or 511 keV)**
 - **1 AMU = 931.5 MeV**

Nuclear Binding Energy

- When particles are bound to each other they give off energy.
 - Stars shine as they perform fusion and synthesize nuclei!
 - **Nuclear binding energy** is the energy from binding neutrons and protons into a nucleus.
- This energy is “paid for” in mass, according to $E = mc^2$.
 - This “**mass deficit**” is equal to the **binding energy**.
 - **Ex: Carbon-12** (¹²C) contains 6 protons and 6 neutrons.
 - The sum of masses should be **12.09565 AMU**, but ¹²C has a mass of **12.00000 AMU**.
 - The mass deficit is **.09565 AMU**, or **89.1 MeV** and this is the binding energy that holds the nucleus together.
- In order to un-bind something, you need to spend at least as much energy as the binding energy.
 - You cannot split a carbon nucleus with 18 MeV photons from an average linac, but you could with a cyclotron throwing 200+ MeV protons.

Fig. 1.1 Stable nuclei (red line) initially follows a 1:1 ratio of neutrons to protons but gradually requires more neutrons to keep the nucleus stable.



On Nuclear Stability

- **Neutron-to-proton (n/p) ratio:**
 - Protons generally hate each other due to their charge; they need neutrons to keep the peace.
 - Too many neutrons and the nucleus just becomes uncomfortable.
 - Unstable nuclei will decay toward more stable products. The mode of decay depends on the n/p ratio.
 - See Chapt. 2 for more detail on nuclear decay.
- For elements up to **Z = 20 (Calcium)**, the magic n/p ratio is **1:1**.
 - Ex: Stable carbon (^{12}C) has $n = 6$, $p = 6$.
- For elements heavier than **Z = 20**, the magic n/p ratio is **>1:1**.
 - Ex: Stable gold (**Au-197**) has $n = 118$, $p = 79$ (Fig. 1.1).

Binding Energy Per Nucleon

- As atomic number increases, strong force increases and therefore total binding energy increases.
- At the same time, after a certain threshold (**iron, Z = 26**) the repulsive electrostatic force of protons begins to take over (since they hate each other).
 - Even though the total binding energy continues to increase, the binding energy per nucleon starts to decrease.
 - Binding energy must be at least 8.6 MeV per Nucleon to remain stable.
 - When atoms are unstable, weak forces allow nucleon transformations (example: a proton may turn into a neutron).

- Unstable atoms larger than Tellurium ($Z=52$) may break off in large chunks (usually in even numbers like alpha particles).
- Bismuth ($Z=83$)** is the heaviest stable nucleus, after which total binding energy decreases and all nuclei become unstable.

Pairing of Nucleons

- Paired nucleons are generally more stable than odd-numbered ones.
 - Most stable nuclei are “even-even”, with an even number of protons and an even number of neutrons.
 - A few stable nuclei are “odd-even” or “even-odd”.
 - Only four stable “odd-odd” nuclei exist: **H-2** (1n, 1p), **Li-6** (3n, 3p), **B-10** (5n, 5p), and **N-14** (7n, 7p).
- For this reason, it is much easier to emit an alpha particle (2n, 2p) than a lone neutron or proton in heavier nuclei.

Bohr Model of The Atom

- This is the “classical” description of electrons orbiting the nucleus like planets around the sun: (Fig. 1.2)
 - Within an atom, electrons may only travel in discrete orbits (energy shells) with discrete energies.

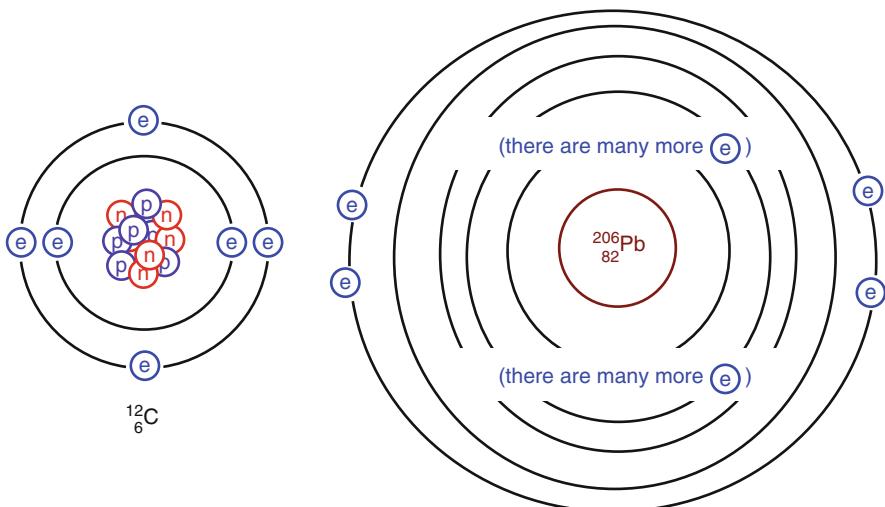


Fig. 1.2 Bohr model of the atom has a nucleus (like the sun) with electrons revolving around it (like planets). As electrons are added, they fill higher energy orbitals (further away from the nucleus) in fixed paths.

- Electrons may only gain or lose energy by changing orbits or by exiting the atom.
- This model works great for a hydrogen atom (and for the ABR exam) but it is a gross oversimplification of the more accurate quantum mechanical model.
- **Electron binding energy:**
 - Electrons are bound to the nucleus by the attraction between negative and positive charge.
 - This attraction means that it takes energy from outside to separate the nucleus from the electron.
 - Electron binding energy (the energy required to knock an electron loose) increases with proximity to the nucleus by radius squared (r^2).
 - Electron binding energy increases with increasing charge of the nucleus (Z).
 - Inner shell electrons have a large binding energy because they are very close to the nucleus.
 - Even though they have a higher “binding energy” these electrons are said to be at a “lower energy level”.
 - Valence (outer) electrons have little binding energy because they are further away and are easily removed.
- Any change in orbit is associated with a change in energy. (see section “[Electron Transitions](#)” below).
 - Pushing energy into an atom can knock an electron loose from its valence shell (or raise the shell to a higher shell).
 - When an electron moves from a higher shell to a lower shell, it actually gives off energy, either in the form of a photon or by kinetic energy and knocking another electron to a higher shell.

Electron Orbit (Energy Levels)

- Each electron fits into energy levels in an orderly fashion with a particular address.
- **Principle quantum number (n)** = 1, 2, 3, etc. or K, L, M, N, etc.
- **Orbital quantum number (l)** – can have $(n - 1)$ values.
 - Named s, p, d, f for sphere, peanut, dumbbell, fan
 - Ex: if $n = 3$, then there are 1 orbitals 0,1,2
- **Magnetic quantum number (ml)** – can have $2l + 1$ values.
 - Numbered negative $(n - 1)$ through positive $(n - 1)$.
 - Ex: $n = 3, l = 2$, therefore ml can be $-2, -1, 0, +1, +2$
- **Spin quantum number** – for our purposes, either $+1/2$ or $-1/2$.
- **Outer (valence) shell** can have up to eight electrons.
 - These are generally s^2 and p^6 .

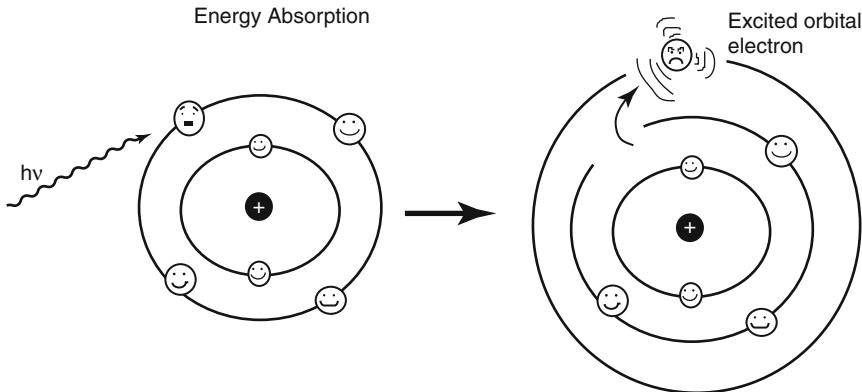


Fig. 1.3 Energy absorption: There is a relatively content orbital electron (it is not as happy as the inner circle electrons). There is an unpleasant orbital above his head that is empty and has a lower binding energy. The orbital electron is hit square in the jaw with a photon an intermediate amount of energy and it absorbs the entire amount and therefore is knocked into a higher orbital. Had he absorbed energy higher than his binding energy, it might have been knocked completely out of the atom (ionization).

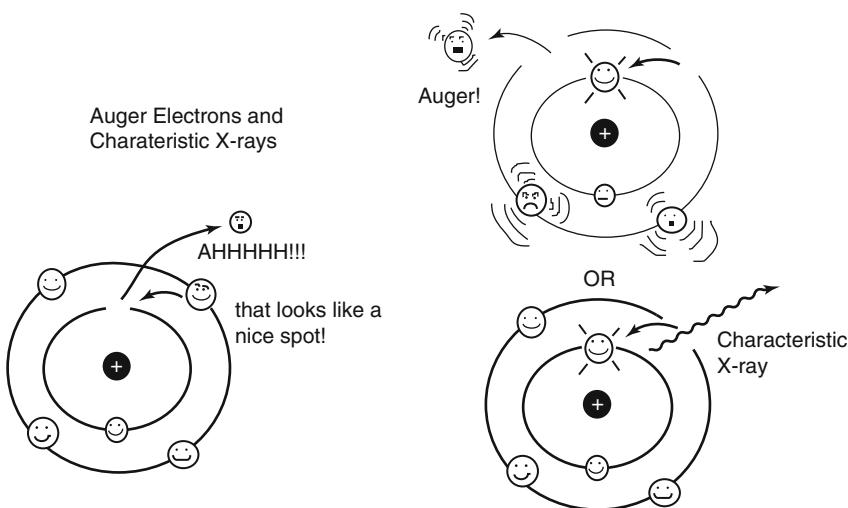


Fig. 1.4 Energy emission consequences: Somehow, a very happy electron was kicked out of the inner orbital and completely disappeared (many things can cause this). An ambitious electron in a higher energy orbital decided to move closer to the nucleus which had a lower energy level (higher binding energy). Since it moved to a lower energy level, it had to give up some of that energy. There are two ways that an electron can give off energy when it drops to a lower energy level. It can emit a **characteristic x-ray** (basically the opposite of Fig. 1.3), or it can transfer that energy to the entire orbital which makes everyone in the orbital angry until they actually kick out another electron (called an **Auger electron**).

Electron Transitions (Absorption and Emission of Energy)

- Whenever an electron absorbs energy, it becomes uncomfortable.
 - The electron may move to a higher shell, or it may be ejected from the atom.
 - If an electron moves to a lower energy shell, excess energy may be carried away as the electron's kinetic energy, or it may be emitted as a photon (Fig. 1.3).
- When a vacancy exists in a lower shell, an electron will “fall” into a more comfortable position.
 - The electron loses energy, so this energy must be transferred to some other particle.
 - When energy is transferred to a photon it is known as a **characteristic X-ray**.
 - This is known as “characteristic” because the energy levels are unique to a given nuclide and orbital.
 - When energy is transferred to another electron it becomes an **Auger electron**.
 - The energy of the **Auger electron** is equal to the energy transferred, minus the binding energy that had to be overcome in order to eject an electron (Fig. 1.4).

2

Radioactive Decay

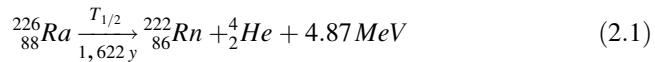
Definitions

- **Alpha (α) particle:** A particle emitted by the nucleus through α decay, containing 2 protons and 2 neutrons.
 - Identical to a helium nucleus.
- **Beta (β) particle:** A particle emitted by the nucleus through β decay, either negatively or positively charged.
 - β^- particle: basically an electron but from the nucleus. (“negatron”, normal matter).
 - β^+ particle: A positron. (antimatter, positively charged version of electron)
- **Gamma (γ) ray:** A photon emitted by the nucleus. (different from an x-ray which is from an electron interaction but may have the same energy range).

- **Internal conversion electron:** Emitted when a nucleus transfers energy to an orbital electron instead of emitting a gamma ray.
- **Characteristic X-ray:** A photon emitted by an electron transitioning from one shell to another.
 - Other than the source of production, a 30-keV X-ray is identical to a 30-keV γ – ray.

Formalism: Decay Schemes

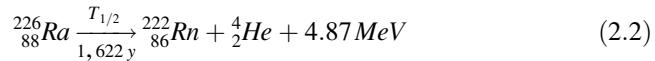
- Radioactive decay may be described by a reaction scheme, such as:



- These schemes allow us to track mass, charge, and energy.
 - Mass, charge and energy are always conserved. In order to gain charge a nucleus must emit a negative charge, etc.
- Decay energy is shared between the decay products, depending on the mode of decay.
 - In **α – decay**, almost all of the energy goes into the α – particle.
 - In **γ – decay**, all of the energy goes into the photon (or an internal conversion electron, in internal conversion).
 - In **β – decay**, energy is shared between a beta particle and a neutrino or an antineutrino.

Alpha (α) Decay

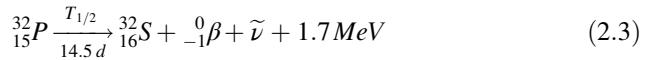
- **The nucleus is bloated, proton heavy and wants to lose weight!**
 - The “pairing rule” states that particles are more stable in pairs.
 - Therefore, nuclei emit alpha particles (2 neutrons and 2 protons) instead of single protons or neutrons.
- Occurs in very heavy ($Z > 52$) nuclei, such as:



- Decay energy is split between the daughter nucleus and the alpha particle, but almost all of it goes to the alpha particle.
 - Typical alpha energies range from **2 to 8 MeV**.
 - Alpha particles are **monoenergetic**.

Beta (β) Decay

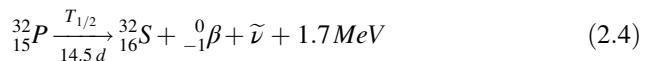
- Occurs in nuclei that need to gain or lose protons, such as:



- Beta decay is always **isobaric** (see Chapt. 1), meaning there is no change in atomic mass number.
 - Unlike alpha decay there is only minimal mass change.
- There are three different beta decay modes:
 - Beta-minus and beta-plus actually produce beta radiation.
 - Electron capture is a “beta” process but produces gamma radiation.
- Beta particles are **Polyenergetic** because the energy is shared between the beta particle and the neutrino/antineutrino.
 - Neutrinos and antineutrinos do not really interact with regular matter, so they do not contribute to radiation dose.
 - The average energy of a beta particle is approximately 1/3 of the maximum energy.

Beta-Minus (β^-) or Negatron Emission

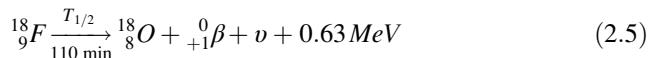
- The nucleus is proton-poor and wants more protons!



- Thanks to weak nuclear force interactions, one of the neutrons is able to turn into a proton.
 - Atomic number goes up by 1; mass stays the same.
- In doing so, the nucleus spits out an **electron** and an antineutrino.
 - The electron is also known as the **β^- particle or negatron**.
 - When you create matter (β^-) you also create antimatter (antineutrino).

Beta-Plus (β^+) or Positron Emission

- The nucleus is proton-rich and wants more neutrons!

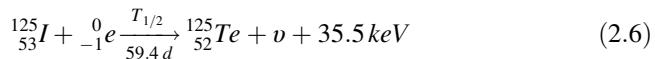


- One of the protons turns into a neutron, basically the exact opposite of beta-minus decay.
 - Atomic number goes down by 1; mass stays the same.

- It spits out an anti-electron (**positron**) and a neutrino.
- **Positrons** are antimatter with mass! When the positron meets a regular electron, it annihilates!
 - This releases the electron and positron's mass as energy.
 - The rest mass of an electron is **0.511 MeV**; so two identical **0.511 MeV** photons are emitted in opposite directions. This is useful for imaging (PET scans).
- Since the positron carries **1.02 MeV** of annihilation energy, it costs **1.02 MeV** to make the positron.
 - Therefore, the kinetic energy is 1.02 MeV less than if the particle had decayed by electron capture.

Electron Capture (EC)

- The nucleus is proton-rich and wants more neutrons!



- When nucleus is proton rich but does not have an excess of 1.02 MeV, the nucleus eats one of its electrons.
 - During electron capture it emits a neutrino, but most of the decay energy remains in the daughter nucleus.
 - This energy is immediately emitted as a **gamma ray** or as **internal conversion electrons**.
 - (see section “[Gamma Emission](#)”)
- Proton-rich nuclei with insufficient energy to produce a positron can only decay by electron capture.
 - More energetic nuclei can decay by either **beta-plus** or **EC**.
- Because there is a vacancy in one of the inner electron shells, one of the outer shell electrons will fall into this vacancy and produce **characteristic X-rays** or **Auger electrons**.
 - Electron capture with internal conversion results in two electron vacancies! (Fig. [2.1](#))

Gamma Emission

- The nucleus is excited and wants to settle down!
 - Excess energy is released as a **photon**.
- Gamma emission is always **isomeric** (no change in atomic mass or atomic number).

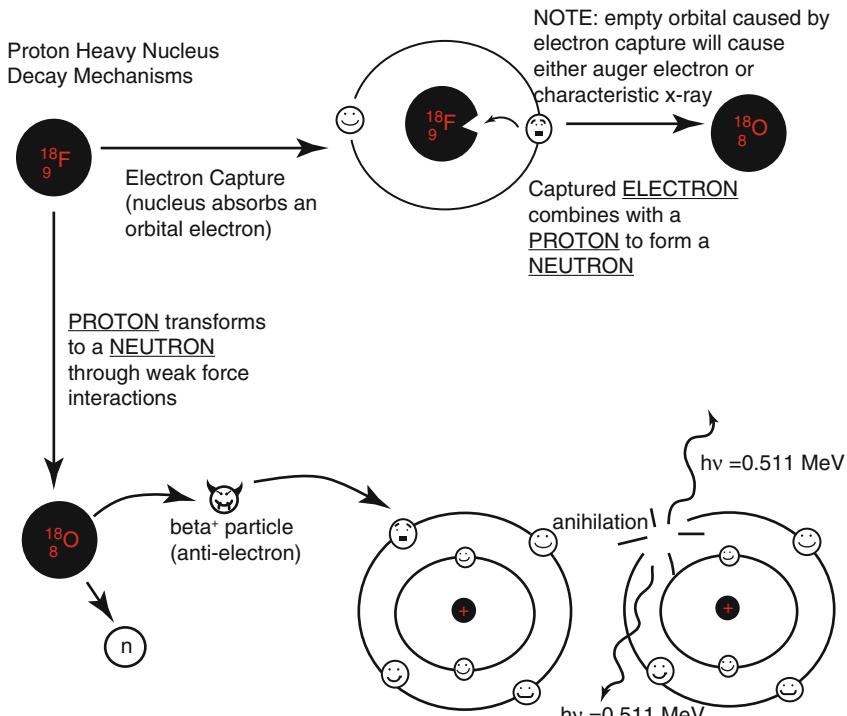
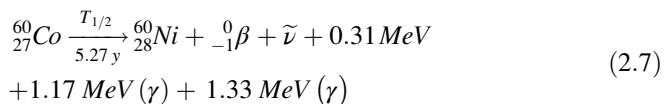


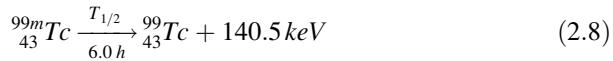
Fig. 2.1 Decay mechanisms of a proton-heavy nucleus: If a nucleus has too many protons or not enough neutrons, the weak forces will allow a proton to actually change into a neutron. The total charge must remain neutral so this can be accomplished either by eating an electron or releasing a positron (the evil anti-electron). If electron capture occurs, the nucleus takes a proton and an electron combined to make a neutron. This leaves a hole in a lower energy electron shell and will lead to either characteristic x-rays or an auger electron being emitted (See Fig. 1.4). If positron emission occurs, there will also be an annihilation reaction when the positron meets an electron producing 2 gamma rays of 0.511 MeV.

- Most gamma emission occurs during or after alpha or beta decay:
 - When the nucleus is excited it gets rid of energy through gamma emission or internal conversion.
- For example, ^{60}Co decays to an excited ^{60}Ni which immediately releases the excess energy as $\gamma -$ rays.



- The $\beta -$ rays are negligible (they do not escape the machine head) so we call ^{60}Co a gamma emitter with 2 photon energies of 1.17 and 1.33 MeV (average 1.25 MeV).

- **Metastable** nuclear isomers such as ^{99m}Tc can exist in an excited state and emit gammas more gradually:



Internal Conversion

- **The nucleus is excited and it kicks out an electron!**
 - Instead of releasing excess energy as a photon, the nucleus transfers that energy to an inner shell electron.
 - This electron is **not** a beta particle. It does not emerge from the nucleus, it is a pre-existing electron.
- For example, ^{125}I decays by electron capture with energy of **35.5 keV**. (see above)
 - Most of the time, it releases internal conversion electrons instead of gamma rays.
 - If **35.5 keV** is used to eject an electron with a binding energy of **8.5 keV**, the electron is emitted at **27 keV**.
 - Since different electrons have different binding energies, IC results in a spectrum of energies.
- This produces a vacancy in an inner electron shell. Outer shell electrons will fill the vacancy, producing **characteristic X-rays** or **Auger electrons**. (see Chapt. 1)
 - The useful radiation from an ^{125}I brachytherapy seed is actually **characteristic X-rays** (Fig. 2.2).

Mathematics of Radioactive Decay

- **Units of Activity:**
 - **1 Curie (Ci)** = 3.7×10^{10} disintegrations per second
 - **1 Becquerel (Bq)** = 1 disintegration per second
 - The **Bq** is the SI unit, but the **Ci** is commonly used in the clinic.
- **Exponential Decay:**
 - Activity (A) is proportional to number of atoms present (N), multiplied by the decay constant λ . The decay constant is unique to each radionuclide.

$$A = -\lambda N \quad (2.9)$$

- Atoms decay over time as a mathematical function of the natural log (e) raised to the power of its unique decay constant multiplied by time, therefore, atomic decay over time is expressed as follows:

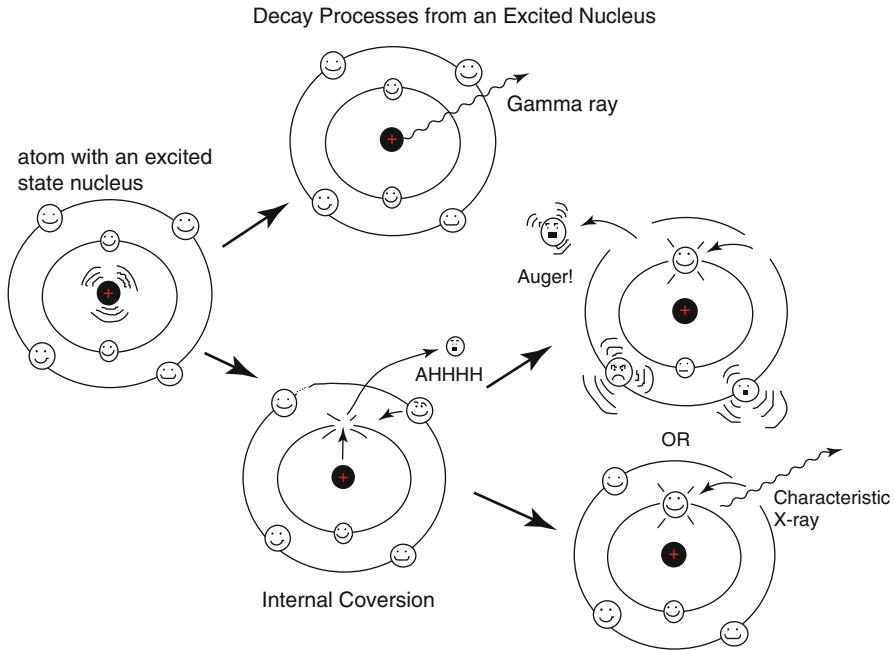


Fig. 2.2 Decay processes from an excited nucleus: when a nucleus is in an excited or metastable state (usually from a previous nuclear reaction like beta emission), it can get rid of that extra energy by two main mechanisms: **Gamma emission** and **Internal conversion**. In gamma emission, the excess energy is simply released as a photon (gamma ray) with the exact amount of energy needed to become stable. In internal conversion, all that energy is transferred to a low energy orbital electron and it is ejected from the atom. (this is very similar to the photo-electric effect in Chapt. 4) Once a nice new slot has opened up, a higher energy electron is free to take the nice new comfortable spot and will cause either a characteristic x-ray or transfer the left over energy to an auger electron (see Fig. 1.4)

$$A(t) = A_0 e^{-\lambda t} \quad (2.10)$$

- **Half-Life:** How long it takes to decay to half the original activity:

$$t_{1/2} = \frac{\ln 2}{\lambda} = \frac{0.693}{\lambda} \quad (2.11)$$

- Nuclides with a long half-life have a low activity, and vice versa. Think of hot fast-burning nuclei versus slow smoldering nuclei.
- **Mean Life:** Defined quite simply as $1/\lambda$:

$$\tau = t_{avg} = \frac{1}{\lambda} = 1.44 \times t_{1/2} \quad (2.12)$$

- This is equal to the hypothetical amount of time it would take a source to completely decay, if it decayed at a constant rate equal to its initial activity (which never happens).
- Mean life is useful for calculating dose and dose rate of permanent brachytherapy implants (see Chapt. 11).
- **Effective half-life:** When an isotope is being excreted from the body, its half-life is shorter than its physical half-life.
- If t_p is the physical half-life, and t_b is the biological (excretion) half-time, then t_{eff} is the effective half-life:

$$\frac{1}{t_{eff}} = \frac{1}{t_b} + \frac{1}{t_p}; t_{eff} = \frac{(t_b \times t_p)}{(t_b + t_p)} \quad (2.13)$$

Radioactive Equilibrium

- Sometimes there are multiple radioactive species in sequence, each with its own half-life. If placed in a sealed container, these may reach “equilibrium” over time.
 - For example, a radium source contains ^{226}Ra which decays to ^{222}Rn which decays to further radionuclides.
 - The first nuclide in the decay chain is called the **parent** while the second nuclide is the **daughter**.
- **Secular Equilibrium:** When daughter half-life is **much** shorter than the parent half-life.
 - The daughter activity builds up over time, until it is roughly equal to the parent activity.
 - You can only produce the daughter nuclide as fast as the parent will decay, so the activity (disintegrations per second) is bottlenecked at the first step.
 - After the buildup period, the apparent activity and half-life of the daughter are basically the same as the parent.
 - **EXAMPLES:**
 - ^{226}Ra (half-life 1,620 years) → Rn-222 (4.8 days)
 - ^{222}Rn is much more active than ^{226}Ra .
 - Radium needles are composed of a platinum tube full of radium salts that decay into radon gas that is trapped in the tube. The radon delivers the actual gamma radiation.
 - ^{90}Sr (half-life 29.12 years) → ^{90}Y (64 h).
 - ^{90}Sr applicators may be used by themselves (such as in eye plaques), or the ^{90}Y may be extracted for further use. (Such as in radioactive microspheres)
 - **Transient equilibrium:** When daughter half-life is only a little shorter than the parent half-life.

- The daughter activity builds up as the parent activity decays.
- Eventually the daughter activity slightly exceeds the parent activity, and both curves decay together.
- During transient equilibrium, the daughter nuclide appears to have slightly more activity and the same half-life as the parent.
- **EXAMPLE:** Heart scans use ^{99m}Tc (metastable technetium) which comes with love from the Moly the cow, born and raised at your friendly nuclear reactor.
- ^{99}Mo (half-life 66 h) \rightarrow ^{99m}Tc (6 h).
- Note: ^{99}Mo sources really are called cows.
- A radionuclide generator regularly “milks” the Tc-99m from the “cow” ^{99}Mo .
- Each time this occurs, there is another gradual buildup of Tc-99 m and the new transient equilibrium is reached where it is theoretically slightly higher than that of ^{99}Mo .
- Actually it never quite surpasses ^{99}Mo because the production efficiency is about 88 %.
- **No equilibrium:** When daughter half-life is longer than parent half-life.
 - All of the parent nuclide decays into daughter, and there is no equilibrium.
 - **Ex:** ^{131}Te (30 h) \rightarrow ^{131}I (192 h)

Daughter Elution

- When the daughter nuclide is extracted from a parent for use (ie, ^{99m}Tc , ^{90}Y) it is called “daughter elution” or “milking the cow.”
 - This is useful for tabletop production of a short half-life nuclide.
- Every time the daughter is removed from the parent there is another buildup period: Parent nuclide produces daughter nuclide until they reach either secular or transient equilibrium.

Naturally Occurring Radioisotopes

- These are mostly atomic numbers 81–92 in 4 series plus some weird ones.
- **Thorium series** ($4n$)
- **Neptunium series** ($4n + 1$)
- **Uranium Series** ($4n + 2$), (most important) – starts with ^{238}U and includes ^{226}Ra and ^{222}Rn
- Actinium series ($4n + 3$)
- **Oddballs** (not part of a well defined decay series)
 - ^3H , ^{14}C (carbon dating), ^{40}K (bananas), ^{50}V , ^{87}Rb , ^{115}In , ^{130}Te , ^{138}La , ^{142}Ce , ^{144}Nd , ^{147}Sm , ^{176}Lu , ^{187}Re , ^{192}Pt

Man-Made Radioisotopes

- **Nuclear bombardment** – stable nuclei may be bombarded with protons, neutrons or other particles to get new radioactive species.
 - **Neutron bombardment** – the longer a neutron hangs around a nucleus, the higher the probability of causing a nuclear reaction, therefore neutrons need to be slow or “thermal” with energy around 0.025 eV. There are four main neutron reactions.
 - **(n,γ)** – most common – nucleus absorbs a neutron, gets excited, and releases a gamma ray.
 - Example: $^1\text{H} + \text{n} \rightarrow ^2\text{H}$ (hydrogen bombarded with a neutron becomes deuterium).
 - **(n,α)** – neutron goes in, alpha particle (helium nucleus) breaks off from nucleus.
 - Example: $^{10}\text{B} + \text{n} \rightarrow ^7\text{Li} \pm ^4\text{He}$ (this reaction is the basis for neutron detection).
 - **(n,p)** – neutron goes in, proton is kicked out (No neutron to proton transformations).
 - Example: $^{32}\text{S} + \text{n} \rightarrow ^{32}\text{P} + ^1\text{H}$ (this is how you make ^{32}P for craniopharyngioma treatments).
 - **Fission!!!** – see below.
 - **Charged Particle Bombardment**
 - Protons – throwing protons at something will often create positron emitters (like ^{18}F used in PET scans) but can also cause other reactions noted below.
 - **(p,γ)** – proton goes in, excite nucleus and gamma rays come out.
 - **(p,n)** – proton goes in, neutron gets kicked out.
 - **(p,d)** – proton goes in, deuteron (^2H) gets kicked out.
 - Heavier particles – alpha particles (^4He nuclei) and deuterons (^2H nuclei) can also be used – both are capable of being incorporated into the nucleus with the end result being the expulsion of a proton or a neutron.
- **Fission – NUKE!**
 - ^{235}U or ^{239}Pu absorbs a thermal (slow moving) neutron and splits, usually into two major products of unequal masses around 90–100 and 130–140, plus additional neutrons or smaller nuclei, and a lot of energy.
 - Most sources show ^{235}U splitting into ^{92}Kr and ^{141}Ba with 3 neutrons and 200 MeV.
 - ^{238}U makes up 99.2 % of natural uranium, is less likely to undergo fission and will not sustain a chain reaction even if it does.
 - Uranium enrichment increases the percentage of ^{235}U to increase the ability to sustain fission.
 - Low enriched (3–4 % ^{235}U) is used for power plants, and some can even use un-enriched uranium.

- Nuclear weapons require at least 20 % ^{235}U with special engineering; most developed countries use around 80–90 % ^{235}U , or plutonium.
- When a fission reaction takes place, it releases neutrons that can cause another fission reaction. The chain reaction can sustain itself if it reaches “critical mass”.
- For nuclear power plants, you try to control this by absorbing some of the neutrons with boron, cadmium or water but in a weapon, you just let the reaction go nuts.
- Nuclear reactors are used to make MANY of our sources: ^{90}Sr , ^{90}Y , ^{131}I (NOT ^{125}I or ^{123}I), ^{89}Sr , ^{192}Ir , ^{60}Co , ^{137}Cs .

See Appendix [B](#) for complete list of nuclides.

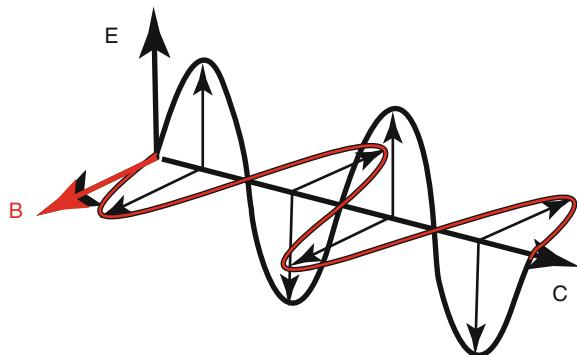
3

Production and Properties of Radiation

Definitions

- A = Amplitude of a wave
- ν = Frequency of a wave
- λ = Wavelength of a wave
- p = Momentum of a particle
- h = Planck's constant = 6.62×10^{-34} J s
- c = Speed of light = 3×10^8 m/s
- **Bremsstrahlung:** "braking radiation"; photons that are produced whenever a fast moving electron slows down near nucleus.
- **kilovolts peak (kVp):** Maximum accelerating voltage of an X-ray tube.

Fig. 3.1 Electromagnetic radiation wave form: there is an electrical sine wave (Black “E”) and a magnetic sine wave (Red “B”) that are perpendicular to each other.



Particulate Radiation

- Particles include electrons, protons, carbon ions (and other ions), pions and whatever else comes out of big accelerators like CERN.
 - Photons and other bosons are NOT considered particles for the purpose of radiation therapy as they are considered carriers for forces – in the case of photons, electromagnetic force.
- Relativistic energy equation – all particles must obey the law $E = mc^2$, therefore as you increase the energy for particles already at 99.9 % of the speed of light, the mass increases (note that the particles get heavier but not larger in size).
- The resting mass of a particle can be converted to pure energy if you destroy it.

Electromagnetic (EM) Radiation

- Carried by photons (a type of boson).
- Wave-particle duality – EM radiation can be either a wave or a particle (photons) depending on how you look at it. Actually, everything can be described as both, but photons are extra special because they carry electromagnetic force in the form of two sine waves (electric field and magnetic field) that are perpendicular to each other (Fig. 3.1).

Wave Equations

$$A = A_0 \sin(2\pi\nu t) \quad (3.1)$$

$$\nu = c/\lambda \quad (3.2)$$

- This means that you can always interchange ν and λ by dividing the speed of light (c) by the other term.
- Photons possess momentum by $p = h\nu/c$ where c is the speed of light, h is planck's constant and ν is frequency (we never use this).

- Photons possess energy by $E = h\nu$ (we use this a little more often).
- Since h and c are constants, we can rearrange and simplify everything to say electromagnetic wave length and energy are connected as:

$$E \text{ (keV)} = \frac{1.24}{\lambda \text{ (nm)}} \quad (3.3)$$

Electromagnetic Spectrum (Remember This from Fourth Grade?)

- In order of increasing energy: Radio waves → microwaves → infrared → rainbow colors, light → UV rays → x-rays, gamma rays and Cosmic rays.
- **Here are a couple valuable points:**
 - EM radiation actually becomes **ionizing** in the **extreme UV spectrum** since the ionization threshold for a hydrogen atom is 13.6 eV and higher (91.2 nm wavelength and smaller).
 - X-rays are **>124 eV** (around 10 nm) and therefore well above the energy threshold to cause ionizations.
 - By definition, **X-rays** come from electron interactions, **γ-rays** come from the nucleus (like the difference between electrons and beta particles).
 - They can have the same energies but are named based on their origin.
- As a side-note, UV radiation can still cause chemical reactions by exciting valence electrons, altering chemical bonds without actually ionizing. This is why sun-tanning is bad and still cancer-causing even though there is no “ionizing” radiation involved.

Production of Radiation

- **Radioactive decay** – for full details, see Chapt. 2.
- Photons can be produced by the nucleus (**γ-rays**, ex: ^{60}Co) or by interactions of electron orbitals (**X-rays**, Ex: ^{125}I).
- Electrons may be ejected as **Auger electrons** or as **Beta Particles**.
- Alpha particles are produced by radioactive decay of heavy nuclei.

X-ray Tube

Diagnostic Energies

- Used for plain X-ray imaging, mammography, CT scans, etc.
- **Brehmsstrahlung x-rays** are produced whenever fast-moving electrons interact with matter.

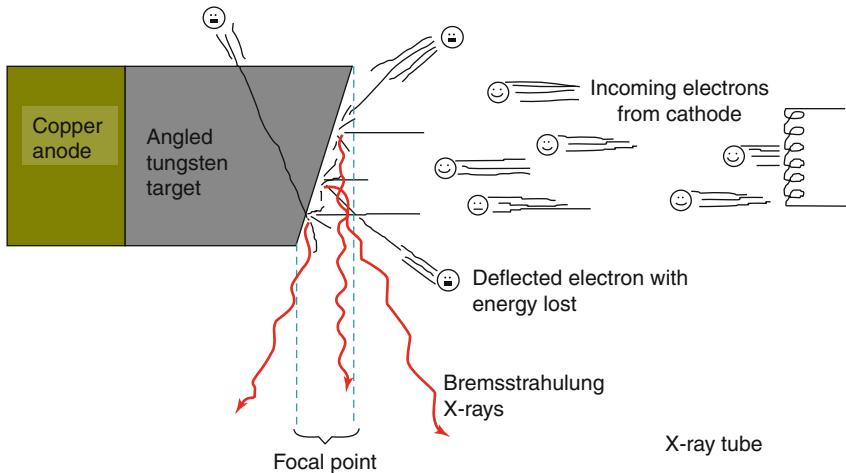


Fig. 3.2 X-ray tube: electrons are created at a hot filament that acts as a cathode. The electrons then are attracted towards the positively charged copper anode and strike the tungsten target that is placed in front of it. Whenever electrons slow down, crash or change their course, they emit bremsstrahlung x-rays. The tungsten target is angled in such a way that the majority of the bremsstrahlung x-rays are directed in a specific direction. The angle of the target affects the width of the focal point from which the x-rays generally originate. For imaging purposes, you want as small of a focal point as possible while still being able to deflect x-rays in the proper direction.

- An **X-ray tube** must first accelerate the electrons, in order to make X-rays through Bremsstrahlung.
- **Electrons are produced:**
 - A **Cathode** (usually a tungsten wire) is heated, liberating electrons via **thermionic emissions**. These electrons float around the filament in a sort of cloud.
- **Electrons are Accelerated:**
 - The slow moving cloud of electrons must be accelerated by a **very high voltage electric field in a vacuum** (must be a vacuum or else the electrons will collide with molecules).
 - Acceleration potential is measured in kilovolts (kV).
 - Electrons travel from the **cathode** to the **anode**, accelerating to between 50 and 99 % of the speed of light!
- **Electrons are Decelerated:**
 - The fast moving electrons run into a **TARGET** that is in front of the anode. The **electrons have their paths bent and slowed down by high-Z material (tungsten or molybdenum)** which produces Bremsstrahlung radiation (Fig. 3.2).

Table 3.1 Nomenclature of photon energy ranges: Diagnostic x-rays typically in the energy range of 20–150 kV in order to maximize photoelectric effect (see Chapt. 4)

X-ray name	Energy	Treatment depth	Uses	Modern utilization
Diagnostic	20–150 kV	—	Imaging	Imaging
Superficial	50–200 kV	0–5 mm	Skin	Rarely
Orthovoltage	200–500 kV	4–6 cm	Skin, ribs	Rarely
Megavoltage	1–25 MV	1–30 cm	Deep tissues	Common

Superficial x-rays closely overlap the diagnostic range and historically were used for superficial skin conditions. Orthovoltage x-rays typically range from 200 to 500 kV and are still used today for skin conditions due to their shallow penetration and narrow penumbra compared to similarly targeted electrons. Megavoltage photons are typically what is used for modern radiotherapy. It is now possible to create extremely high photon energies, however 18 MV is usually the upper limit of what is used practically due to neutron contamination and an enlarging penumbra with increasing energy.

Side Notes

- This process is extremely inefficient since around **99 % of the energy is converted to heat**. X-rays may go in any direction, including into the tungsten target where they get absorbed and do nothing.
- By setting the target at a slight angle ($7\text{--}18^\circ$) you can create a **small focal spot** where x-rays preferentially come out at a right angle to the incident electron beam. You want as small a focal spot as possible (0.3–3 mm) for good image quality.
- **kVp:** Peak kilovoltage potential in an X-ray tube. Because X-ray tubes are powered by alternating current (AC), the voltage is not constant, therefore **kVp** is the highest “peak” voltage.

X-ray Tube Evolution

- X-rays were first produced in the late 1800’s and were quickly utilized to treat cancer.
- Gradually, these devices improved by better target systems and cooling the anode with either oil or water, often using a rotating anode.
- In the 1930’s–1940s there were **orthovoltage** units that could deliver energies between 200 and 500 kV, which can treat to a useful depth of around 4–6 cm (Table 3.1).

Cobalt-60 Radiotherapy

- Teletherapy
 - Historically, external beam radiotherapy was delivered by x-ray tubes, which deposited most of the dose to the skin.
 - Dose measured in “skin erythema dose units” – the amount of radiation to make the skin very red or necrose.
 - Not able to reach deep tissues.
 - Cobalt-60 (^{60}Co) discovered with the development of nuclear reactors.
 - Not found naturally on earth but present in supernovas.
 - ^{60}Co undergoes beta decay to become activated ^{60}Ni which becomes stable after giving off two gamma rays with energies of 1.17 and 1.33 MeV.
 - With an average energy of 1.25 MeV, deep tissues are able to be treated with sparing of the skin.
 - 1951 – first cobalt teletherapy unit began to be used for external beam cancer treatment.
 - Largely replaced by linear accelerators (see below) in first-world countries.
 - Still used today in third world countries where electrical power is expensive or unreliable.
- Gamma Knife
 - Invented shortly after cobalt teletherapy developed.
 - Multiple cobalt sources (usually 201 sources) with holes (apertures) that direct focused radiation to a spherical isocenter.
 - The size of the isocenter sphere can be changed by changing the size of the apertures but the position of the isocenter can only be changed by moving the head to different positions within the helmet.
 - Still used today to treat intracranial lesions.

Linear Accelerators (Linacs)

- Cobalt machines had demonstrated the treatment benefits of megavoltage photons which allowed better penetration into the body with sparing of the skin.
- The concept of wave guides and the linear accelerator was first thought of in the 1920's (by either a Swedish guy or a Hungarian American depending on who's side you are on).
- These were not used for medical purposes until after World War II when Varian brothers developed the microwave technology for radio-frequency based particle acceleration.

Operational Theory of Wave Guides

- Electrons are created using an electron gun.
 - This is a cathode-anode system using electrons created by thermionic emissions from a hot tungsten filament, similar to an x-ray tube, except

Klystron and wave guide

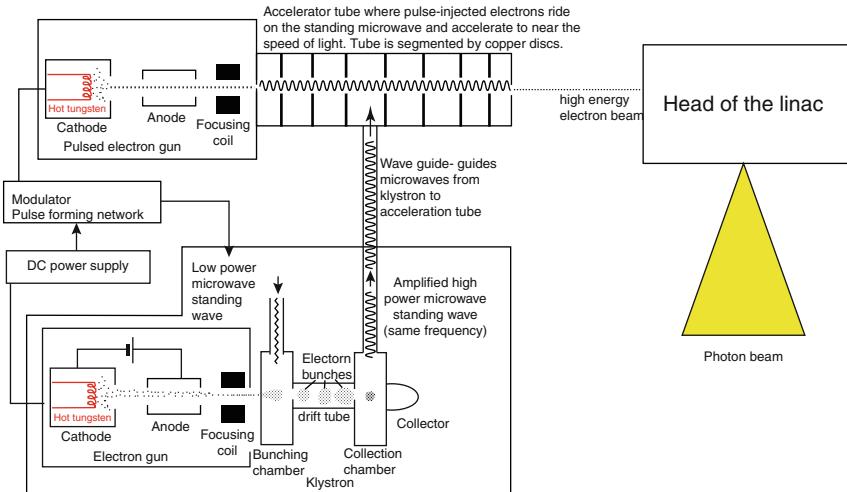


Fig. 3.3 Klystron, wave guide, and accelerator tube: Two different electron guns are working at the same time. The Klystron uses electrons and a property called bunching to magnify low intensity microwaves into very high intensity microwaves (acts as an amplifier). These microwaves are then transported to the accelerator tube where pulsed electrons from a second electron gun ride on microwaves to be accelerated close to the speed of light. The end result is a narrow electron beam which can then be manipulated into treatment electron beams or photon beams through the head of the linear accelerator.

the anode guides the electrons into an accelerator tube (or the Klystron for producing microwaves).

- A Wave guide then uses microwaves to accelerate the electrons to just under the speed of light.
 - It is the accelerator tube that allows the production of very high energy photons and electrons.
 - Traveling wave guides – the beginning and end of the wave are not fixed and so the electrons are **surfing on microwaves**.
 - Standing wave guides – there is a wave and a reflected wave that produce a standing wave (imagine oscillating a slinky or a phone cord connected to the wall). These are expensive to produce but allow a more physically compact system and are what is used most of the time these days.
- It is worth noting that there is a strong magnetic field guiding the wave-guide structure to ensure the electrons move in a straight line with a diameter of about 2 mm (Fig. 3.3).

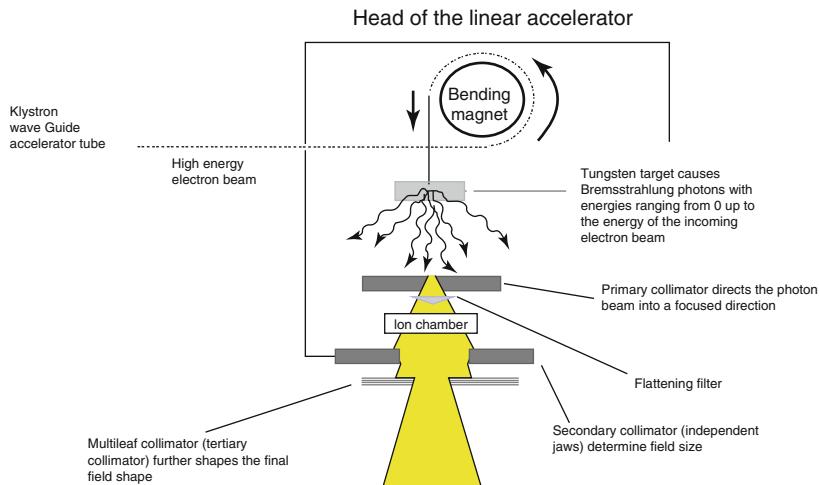


Fig. 3.4 Head of a linear accelerator in photon mode: Incoming electron beam from the linear accelerator body is bent 270° around a bending magnet (not all machines use 270° bending magnet) and strikes a tungsten target. The primary collimator directs the beam into the flattening filter. The ion chamber is then able to provide a feedback to reveal the amount of radiation that is actually being emitted for the given amount of power provided. The beam is then shaped by secondary and tertiary collimators into the final size and shape for treatment.

Bending Magnet Systems

- The waveguide structure pretty much moves in a straight line but that makes positioning logically difficult. Fortunately electrons can have their path bent by magnets to whatever direction is desired since they are charged particles. These magnets are usually located in the head of the Linac and bend the electrons 270° so that there is a divergence and then a convergence of an electron pencil beam. This also allows electrons that are not the desired energy to crash into the walls in the process of bending around the magnet (see Fig. 3.4).

Flattening Filters (Photon Mode)

- When a photon beam passes out of the primary collimator, it tends to be very intense at the center and fades out around the periphery (sort of like a flashlight beam). The flattening filter makes the beam have a relatively constant intensity throughout.
 - Please note that this is calibrated to the isocenter (100 cm) and therefore the beam may still be uneven at different depths.
 - Some applications such as stereotactic body radiation therapy (SBRT) prefer treatment without a flattening filter so that the beam is purposely more intense in the center.

Scattering Foils (Electron Mode)

- The scattering foil works similar to the flattening filter by taking the pencil beam of electrons and scattering them over a wide area. Think of what happens when you spray a water hose through a screen door.

Electron Cones (Applicators)

- When functioning in electron mode, there tends to be a significant amount of lateral scatter and divergence due to electromagnetic forces (negative electrons repel each other), even after exiting the secondary collimators. The electron cones shape the beam into the final size and are usually positioned only a few centimeters from the target.

Targets

- Most targets in linear accelerators are made of tungsten due to its **high atomic number ($Z = 74$)** and its **high melting point ($3,422^{\circ}\text{C}$)**. High atomic numbers are more likely to produce bremsstrahlung photons but a lead target would likely melt in an electron pencil beam so Tungsten is a good compromise.
- The process of bremsstrahlung radiation is more efficient than in x-ray tubes due to the higher energy, but still about 90 % of the energy is lost to heat.

Monitor Chamber

- Immediately after the primary collimator and flattening filter is the monitor chamber. This allows you to know about how much radiation you are delivering.
- The relationship between **Monitor Units (MU)** and Dose is complicated, and is explored in Chaps. 8, 9 and 10.

Collimation Systems

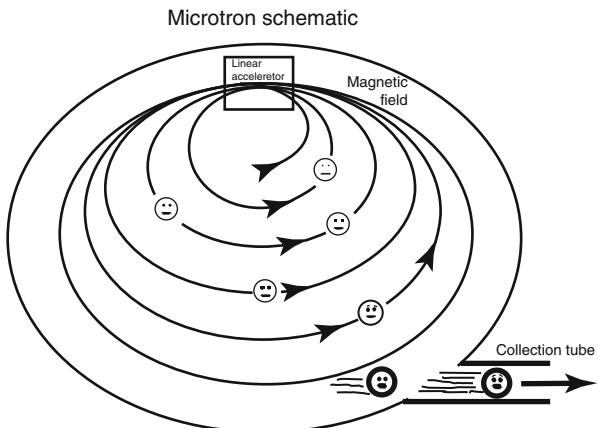
- Primary and secondary collimators: The primary collimator basically works to point the beam in the forward direction, while the secondary collimator works to define the field size.
- Collimator Jaws:
 - Part of **secondary collimator**. A solid block that may be moved in a symmetric or asymmetric fashion.
 - If one jaw is closed to midline and the other is wide open, this is called a half-beam block.
 - Moving the collimator jaw with the beam on can create a dose gradient called a “non-physical” or “soft” wedge. For details on wedging, see Chapt. 9.
- Multileaf Collimators (MLC):
 - May be part of **secondary collimator**, or may be a tertiary add-on.

- An array of tiny leaves that can be moved in and out of the beam path to create a variety of shapes.
- There is more leakage through MLCs than through a collimator jaw, so you want the jaws to come as close as possible to the boundaries of your MLC.
- For more details on MLCs, see Chapt. 8.
- Other Collimation Systems
 - **Cerrobend**
 - Prior to the development of MLCs, radiation beams were shaped by pouring physical blocks in the shape of your target out of liquid metal (cerrobend – a mix of bismuth, cadmium and lead an alloy with a melting point of 70°C).
 - Intensity of a beam may be shaped by making some parts thicker and some parts thinner (called a compensator).
 - **Apertures**
 - Small holes that allow radiation through with a specific shape (usually a circle) and size.
 - Some apertures change size using an iris mechanism.
 - Often used in stereotactic systems.
 - **Wedges**
 - Made of metal (often steel).
 - There are multiple gradients of wedges that can be inserted into the head which can give a wedged profile to the beam.
 - These have been largely replaced by soft-wedges [see Chapt. 9]
- Light Fields (Including Field Size Definition) –
 - A light is present within the head of the linear accelerator that will shine through the collimators to give shape of the field.
 - This may be used as a general guideline for treatment setup but remember that field size is defined at isocenter, so unless the patient's skin is at the isocenter, the actual size of the field will be different.

Microtron (Fig. 3.5)

- Basically a linear accelerator where the accelerated electrons travel in a circle and re-enter the accelerator to go even faster (or gain mass as they approach the speed of light).
- The loop is controlled by a magnetic field and with each pass of the electron as it gains energy, the loop becomes larger.
- The electrons are eventually captured by a collector tube at the desired energy with the associated radius of the loop.
- This concept can produce electrons of very high energy (up to 1,500 MeV).
- Another form of microtron is called a racetrack microtron that uses straight courses with bending magnets on the ends to swing the beam in a “racetrack shape” (See Fig. 3.5).

Fig. 3.5 Microtron: The electrons are injected into the linear accelerator and are bent around in a loop by a magnetic field. Each time the electrons enter the accelerator, they gain speed until they approach the speed of light, at which point they begin to gain mass relativistically. They are eventually ejected through a collection tube.



- This is similar to the synchrotron or cyclotron discussed below except that the circles are generated through an accelerator structure and not generated by electromagnets.
- The microtron was invented around the same time as the linear accelerator and used clinically in the 1970's, but for all practical purposes, a regular linear accelerator is much simpler that is widely used.

Cyclotron (Fig. 3.6)

- A cyclotron uses D-shaped electrodes ("dees") that accept alternating voltage in the setting of a static perpendicular magnetic field.
- The frequency of the alternating polarity must match the target particle's "cyclotron resonance frequency" and thus you get a particle that develops a spiral shaped path, gaining speed and relativistic mass with each revolution until it either crashes into the wall, or is collected in the beam tube.
- This allows acceleration of any charged particle for radiation therapy, they are primarily used to accelerate protons.

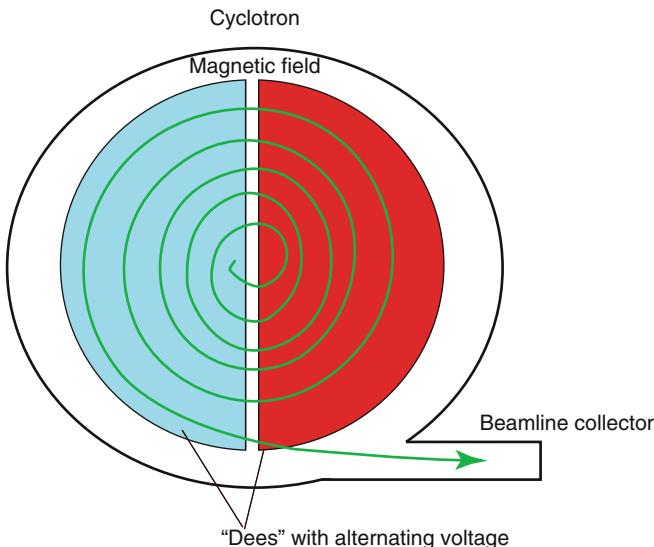


Fig. 3.6 Cyclotron: alternating “dees” or D shaped electrodes alternate voltage at a specific frequency within a magnetic field to accelerate particles in a circle. With each pass, the circle grows wider as the particle gains energy until it is eventually collected.

Synchrotron (Fig. 3.6)

- While the cyclotron uses a constant guiding magnetic field that alternates at a constant frequency, a synchrotron has a variable frequency guiding magnetic field that adapts to the changing mass of particles at every segment as they approach the speed of light.
- Instead of 2 D’s in a disc, a synchrotron actually looks more like a long thin toroid with magnetic segments that eventually feeds into a storage ring with the useful beam line coming out at a tangent from an outer storage ring.
- One could almost think of it like multiple linear accelerators arranged in a spiral, getting faster and faster as you moved outward. The difference is that instead of linear accelerators, they are electromagnets pulsing on and off at frequencies that are slightly different as the particles move through.
- As the spiral moves wider and the magnets become more powerful, the particles can attain extremely high energies (giga-electron volt range).
- This is how large particle colliders like the Large Hadron Collider at CERN operate and that is why they are often several miles wide and utilize superconducting magnets.
- In radiation oncology this is another available method for accelerating protons and heavy ions.

4

Interactions of Electromagnetic Radiation with Matter

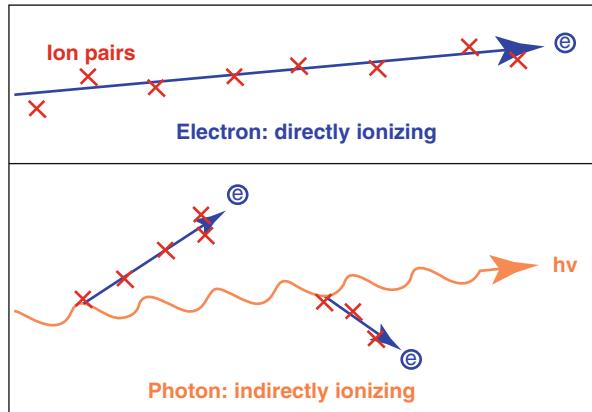
How Do Photons Interact?

- This section is all about interactions of photons with matter.
 - While “matter” is generic, in biological tissue it is usually water.
- Since photons have no charge, they are **indirectly ionizing**.
 - This is in contrast to charged particles such as electrons and protons, which are **directly ionizing** (Fig. 4.1).

Definitions

- **Electromagnetic Radiation:** Photons. They have both electrical and magnetic properties and are not deflected by either electrical or magnetic fields.

Fig. 4.1 Directly vs indirectly ionizing radiation. Charged particles directly ionize other atoms in the medium by exerting coulombic forces to budge electrons directly off of atoms (see Chapt. 5). Indirectly ionizing radiation is not charged and largely relies on secondary electrons to cause the actual ionizations.



- **Absorption:** Loss of photons from a beam due to photon energy being absorbed by matter.
- **Scatter:** Loss of photons from a beam due to photons changing direction.
- **Attenuation:** Loss of photons from **Absorption AND Scatter**.
 - Please refer to Chapt. 7 for more detail.
- **E:** Photon Energy
- **Z:** Atomic Number

Coherent Scatter (aka Rayleigh Scatter)

- Occurs at energies of: 1 keV–1 MeV.
- Dominant Interaction at: <10 KeV (Fig. 4.2).

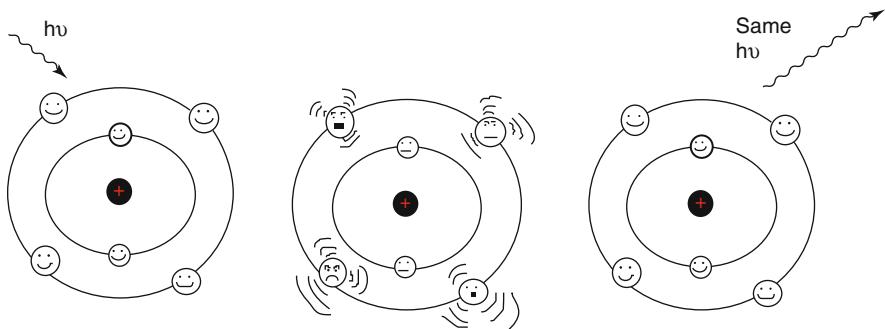


Fig. 4.2 Coherent scatter: the incoming photon is very low energy and is absorbed by the electron orbitals (not enough energy to kick an electron out of the atom) and it causes an excited state (the electrons become very angry). Finally, the electrons settle down and release all that negative energy in the form of another photon with the same energy as the one that caused all the excitement in the first place. The net effect is that a photon bounces off of the atom.

- **PHOTONS BOUNCE OFF OF ELECTRONS** – it is actually more complicated but think of it that way.
 - Actually, a photon is absorbed by the electrons of an atom and they begin oscillating at a high frequency.
 - When they settle down, the energy is released as another photon with the same energy as the old one.
 - No net energy is absorbed.
 - The only effect is that a photon changes direction.
 - This does NOT cause ionization, no dose is deposited.
- **Probability of interaction is directly proportional to Z.**
 - Happens more in **lead** ($Z=82$) than **water** ($Z=1$ and 8), but not overwhelmingly so.

Photoelectric Effect

- Occurs at energies of: **1–150 keV**.
- Dominant Interaction at: **10–26 keV** (Fig. 4.3).
- Photon interacts with an atom and causes it to eject an electron or an x-ray.
 - A photon with energy similar to (but no lower than) the binding energy of an electron will kick out that electron.
 - With a nice new comfortable position available, a less comfortable electron will take its place.

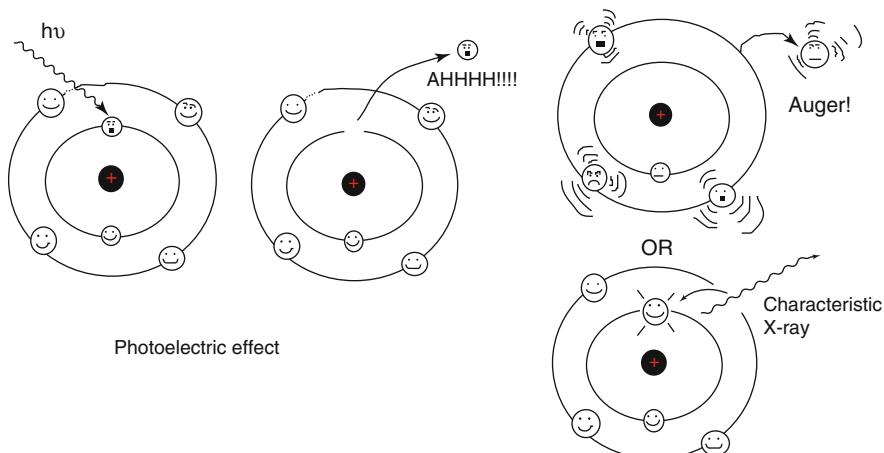


Fig. 4.3 Photoelectric effect: an incoming photon with energy greater than the binding energy of an inner electron knocks it completely out of the atom. The nice comfortable open spot means that a higher energy electrons want to fill it and will therefore shed the extra energy in the form of an Auger electron or a characteristic x-ray (see Chapt. 1).

- This process is similar to internal conversion decay (Chapt. 2) except with the energy coming from a photon instead of the nucleus.
- It either causes **characteristic x-rays** or **Auger electron** emission (see Chapt. 1).
- **Probability of interaction** is proportional to Z^3/E^3 :
 - Z^3 (Atomic number cubed): Happens WAAAY more in **lead ($Z = 82$)** than **water ($Z = 1$ and 8 for H and O respectively)**.
 - $1/E^3$ (inverse Energy cubed): happens A LOT at low energy and not at all with higher energies.
- **Photoelectric effect** causes ionization! And effectively breaks molecular bonds causing all kinds of damage!
- **Photoelectric effect** is the most important interaction for diagnostic imaging because of the Z^3 dependence:
 - Bone absorbs a LOT MORE x-rays than soft tissue, showing up clearly on film.

Compton Scatter

- Occurs at energies of: Any.
- Dominant Interaction at: 26 keV–24 MeV (Fig. 4.4).
- PHOTON IS A CUE BALL IN A GAME OF POOL (electrons are the other balls).
 - The photon literally hits an electron and it flies out of orbit with the photon being deflected as well.

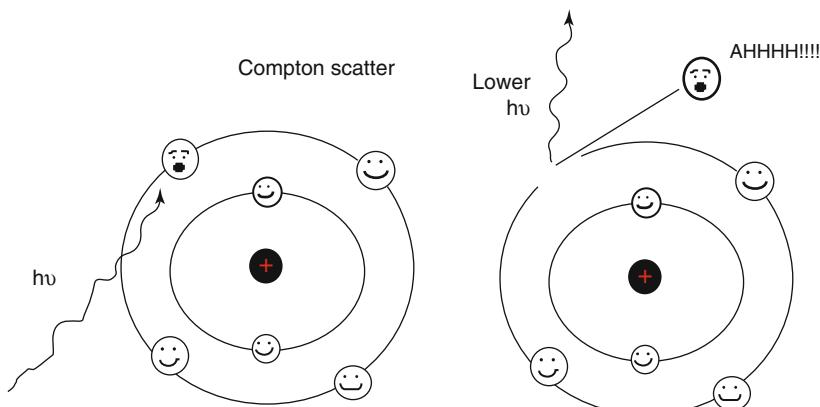


Fig. 4.4 Compton scatter: an incoming photon hits an electron and knocks it out of the atom like a cue ball hitting another pool ball. Part of the energy is transferred to the electron (which is then free to do damage by exerting coulombic forces) and the electron's new energy (plus the binding energy of the electron) is lost by the photon.

- The electron can go straight forward or any angle up to 90° , like an angle shot.
- The wider the deflection angle, the slower it will go (same as in pool).
- The photon (cue ball) gets bounced too:
 - At 90° deflection, energy is **0.511 MeV** (resting energy of electron).
 - If it is a direct hit on the electron, the photon bounces back 180° , energy is **0.255 MeV** (half of 0.511).
 - At glancing angles, the photon barely changes direction or energy.
- **Probability of interaction** is proportional to **electron density**:
 - This is roughly proportional to **mass density** for most materials. Therefore, one gram of water is similar to one gram of fat or bone.
 - This is **independent of Z** and therefore less sensitive to bone, lead, and other higher-Z materials.
 - This makes Compton effect **most useful** for delivering a uniform dose in radiotherapy.
 - It is bad at producing a sharp image of bone and tissue.

Pair Production

- Occurs at energies of: **1.02 MeV and above**.
- Dominant Interaction at: **10 MeV and above** (Fig. 4.5).
- **PHOTON IS A FIREWORK** – a photon with at least 1.02 MeV (usually much more) interacts with the electric field of an atomic nucleus, and explodes into an electron and a positron (evil anti-electron in figure).
 - The pair moves generally forward and splits the energy in excess of the 1.02 MeV needed to create them (this is the resting energy of the positron and electron by $E = MC^2$).

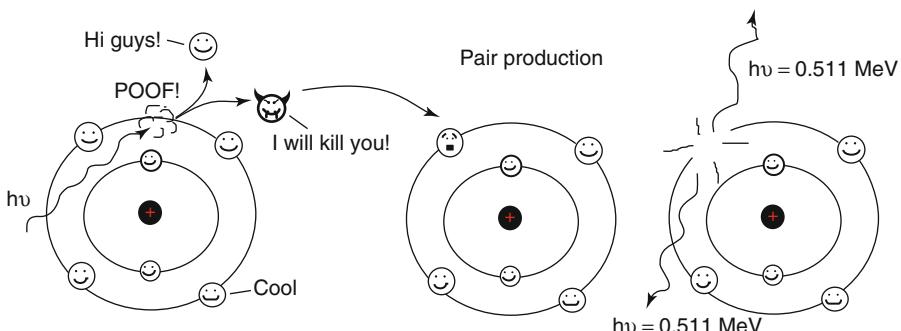


Fig. 4.5 Pair production: A photon is traveling with so much energy that when it hits the electric field of the electron orbitals, it explodes into an electron and an evil positron out of thin air. The electron wonders off and exerts coulombic forces but the evil positron not only causes ionizations by coulombic forces, but it eventually slows down and finds an electron somewhere else and annihilates it! The resulting mutual annihilation sends two photons in opposite directions with an exact energy of 0.511 MeV.

- The electron goes off to do whatever it wants but the positron bounces around until it slows down enough to meet another electron and then annihilates the electron (and itself in the process), sending off two photons in opposite directions, each with 0.511 MeV (these can go wreak their own havoc).
- **Probability of interaction** is proportional to Z^2 , and **dramatically increases with E**.
 - While small amounts of pair production occur at lower energies, it is really only significant above 6–10 MeV.
 - Pair production adds scatter radiation outside the field, thanks to the positron and annihilation photons.
 - This is generally undesirable in radiotherapy if you want tight margins between tumor and protected tissue.
 - This is irrelevant for imaging due to the very high energies required.

Triplet Production

- Similar to pair production but the photon interacts with the electric field of an orbital electron (in an atom).
- The orbital electron is ejected, as well as the electron and positron created out of thin air! (vacuum, really).
- Probability is **proportional to Z** and the threshold energy is **2.044 MeV** (twice as much as pair production).
- Not a large contributor to radiotherapy dose.

Photonuclear Disintegration

- **PHOTON IS A JACK-HAMMER** – at energies above about 8–16 MeV, a photon can actually smash into the nucleus of high-Z atoms and chip off neutrons or even larger chunks (Fig. 4.6).

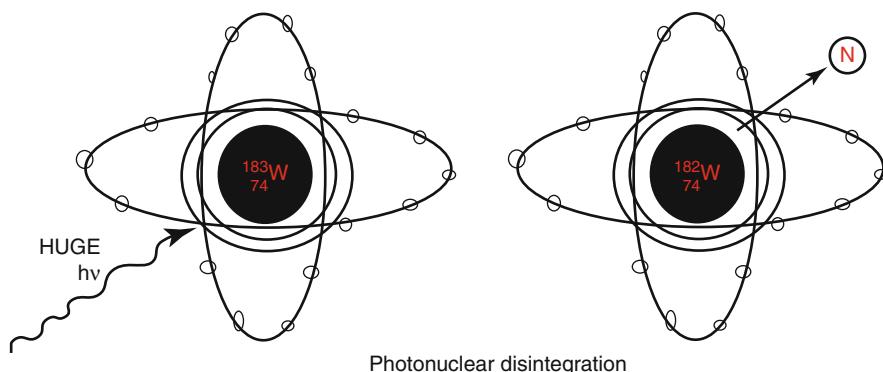


Fig. 4.6 Photonuclear disintegration: A photon hits a nucleus with so much force that it actually knocks a chunk of the nucleus out of the atom (usually neutrons).

- When operating a Linac **above 10 MV**, the higher energy photons can interact with the metal components of the head of the machine and send neutrons flying into the patient.
 - This is generally a BAD thing as neutrons have much greater late toxicity than photons.
- Not a large contributor to total dose, but is the main source of neutron contamination.

5

Interactions of Particulate Radiation with Matter

Definition of Range

- Particulate radiation has a finite **range** which is approximately how far they can travel in a medium before stopping.
- For our purposes, whenever we say range we mean R_{CSDA} , range defined by the continuous slowing down approximation (CSDA).

Types of Particulate Radiation

- **Charged and Uncharged Particles**
 - Charged particles can directly interact with electrons and nuclei, through coulombic interactions. Therefore they are “**directly ionizing**” and are generally less penetrating than uncharged particles.

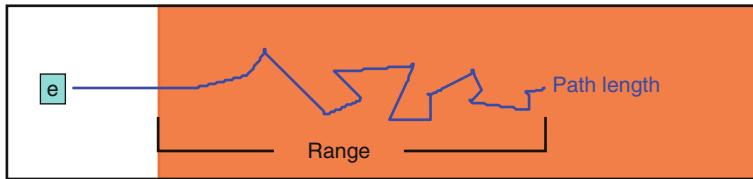


Fig. 5.1 Path length vs range: electrons usually have a tortuous path, thus path length is always greater than range.

- Uncharged particles cannot interact through coulombic forces so they are **indirectly ionizing**. Heavy uncharged particles are more likely to interact with nuclei than with electrons, and they are relatively more penetrating.
- **Light and Heavy Particles**
 - “**Light**” particles are particles with a mass similar to electrons (basically just electrons and positrons).
 - Due to their mass, they change directions (scatter) very easily.
 - Path length is much longer than range! (Fig. 5.1).
 - “**Heavy**” particles are significantly heavier than electrons, basically everything else. For example, a proton has $\sim 1,800\times$ the mass of an electron.
 - Due to their mass, they travel in a nearly-straight line.
 - Path length is roughly equal to range.

How Do Charged Particles Interact?

- Unlike photons, charged particles are **directly ionizing**.
- Charged particles have a **variable velocity**, unlike photons which always move at the speed of light.
 - **Velocity** and **energy** are directly related to each other; when a particle gains energy it moves faster.
- Particles gradually lose energy as they interact with the medium.
 - This is in contrast to photons which undergo **attenuation**: decreasing the number of photons in the beam, without changing the energy of the individual photons (Fig. 5.2).
- **Two basic types of collisions:**
 - **Elastic Collisions**: think of a game of pool.
 - Kinetic energy and momentum are both conserved; energy is transferred between the particle and the medium.
 - All of the energy is kept in the form of motion.
 - **Inelastic Collisions**: think of a bullet going through a wall.
 - Kinetic energy and momentum are not conserved; the particle transfers energy to the medium and slows down.
 - This energy may be released as a photon, or it may be transferred to an electron (causing ionization).

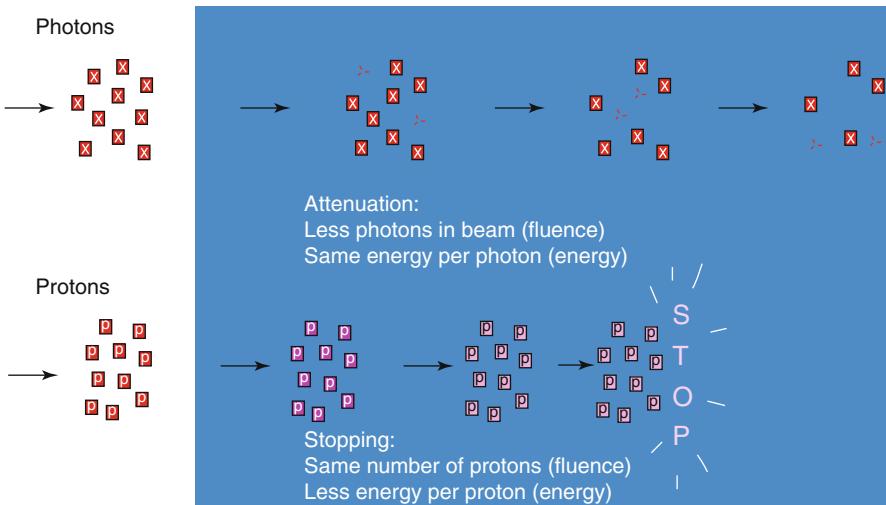


Fig. 5.2 Attenuation vs stopping power: Indirectly ionizing particles (photons) will undergo multiple scatterings and collisions in a random fashion that will decrease the number of photons (fluence – see Chapt. 6). Protons and other particles will have paths that decrease in energy as they interact with more atoms through coulombic force but gradually they will slow down and eventually come to a stop with some degree of certainty for a given starting energy. Think of stopping power as the amount of power it takes to stop Mr. Particle (see Fig. 5.3).

Charged Particle Specifications

- The **W value** is the average energy needed to produce an ion pair in a gas.
 - For example, in dry air at standard temperature and pressure, **W** is approximately **33.97 eV**.
 - **W** is very small compared to the typical energy of charged particles (a few MeV for electrons, hundreds of MeV for heavier particles). Each particle makes a lot of ions!
- **Specific ionization** is the number of ion pairs produced per unit path length.
 - **Specific ionization** is higher at low energies, and lower at high energies.
 - This is because a high energy particle moves too fast to have time to interact with surrounding materials.
- **Linear energy transfer (LET)** and **Stopping Power** are closely related concepts that measure the energy transfer between a charged particle and the medium.
 - **Stopping Power** is the amount of energy the particle loses per unit path length; think of it as the amount of “drag” on the particle.
 - **LET** is the amount of energy that the particle deposits in local ionizations per unit path length. Think of it as the amount of damage a particle leaves in its track.
- **Specific ionization, Stopping Power and LET** all increase as a particle slows down. This is because it has more time to interact with the medium (Fig. 5.3).

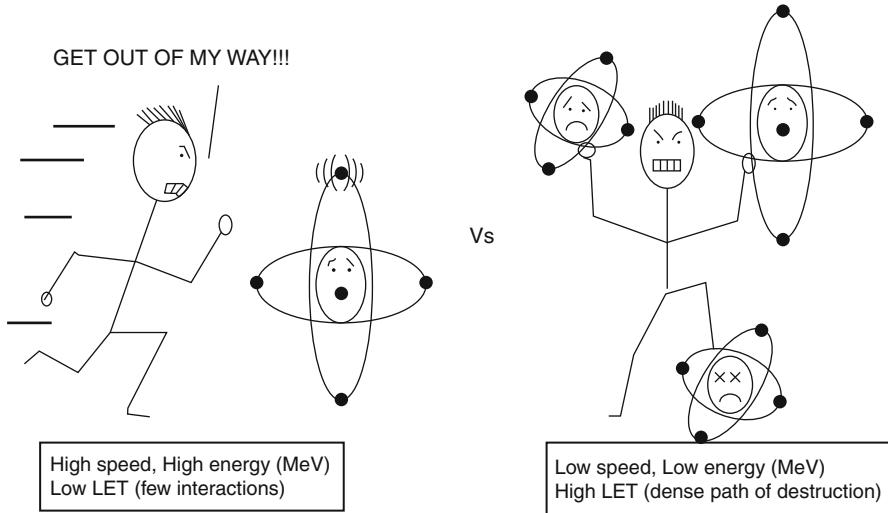


Fig. 5.3 Particle energy and LET: Mr. Particle is a mean dude but if he is traveling too fast, he can really only throw passing insults at electrons. If he slows down or even stops, all hell breaks loose!

Linear Energy Transfer Relationships

- LET is a measure of the interaction between a particle and a medium.
- LET increases with the particle's charge (Q):
 - Approximately proportional to Q^2 .
 - Ex: A 10 MeV carbon ion ($Q = +6$) has a LET of 200 keV/ μm , while a 10 MeV proton ($Q = +1$) has a LET of 4 keV/ μm .
- LET decreases with the particle's velocity (V):
 - Approximately inversely proportional to V^2 .
 - At energies much lower than the particle's rest mass (mc^2), V^2 is proportional to Energy (E).
 - At higher energies V approaches the speed of light (c) and cannot increase any further.
 - Ex: A 2 MeV proton has a LET of 16 keV/ μm , a 10 MeV proton has a LET of 4 keV/ μm , and a 200 MeV proton has a LET of 0.4 keV/ μm .
- LET increases with the medium's density (ρ):
 - Approximately proportional to ρ .
 - A particle encounters much more atoms when passing through lead as opposed to air.
- LET decreases with the medium's atomic number (Z):
 - Even though there are more atoms to beat up in a block of lead, those atoms are a lot tougher to beat up.

- This can be seen as a screening effect. In a high-Z medium, the large number of electrons around each nucleus cancels out or “screens” some of the nuclear charge.
- Hence **Pb** has lower **LET per unit mass** than water.

Stopping Power and Dose

- Stopping power includes two components:
 - **Collisional stopping power (S_c)** – Energy lost due to collisions with the medium. This directly contributes to **dose**, as the energy is deposited locally.
 - **Radiative stopping power (S_r)** – Energy lost to radiative processes such as Bremsstrahlung (see Chapt. 3). Does not usually contribute to **dose**, as this energy is radiated away.

Electron Interactions

- **Inelastic collision with atomic electron:**
 - The incident electron transfers some of its energy to an atomic electron, which remains bound (excitation, not ionization).
 - The atomic electron will eventually release this energy as a characteristic X-ray.
 - The target electron remains bound: there is a loss of kinetic energy.
- **Elastic collision with atomic electron:**
 - The incident electron transfers some of its energy to an atomic electron, ejecting it from the atom (**direct ionization**).
 - Kinetic energy is conserved; it is now split between two electrons.
 - The secondary electron may produce additional ionizations (Fig. 5.4).
- **Inelastic collision with nucleus (Bremsstrahlung):**
 - When an electron interacts with the nucleus, it slows down and changes direction.
 - This loss of energy causes a photon to be emitted. The photon is called a **bremsstrahlung x-ray** and is responsible for the production of X-rays in X-ray tubes and linacs.
- **Elastic collision with nucleus:**
 - Since the electron is so much lighter than the nucleus it does not really transfer energy to the nucleus.
 - Therefore it merely bounces off (scatters), changing direction without transferring energy (Fig. 5.5).
- **Electron scatter and dose shape**
 - Because electrons scatter so easily, if you look at billions of electrons in an electron beam, each one will follow a unique path through the medium.
 - This is responsible for many of the characteristics of electron beam shapes in the clinic.
 - See Chapt. 10 for more details on electron beam dosimetry.

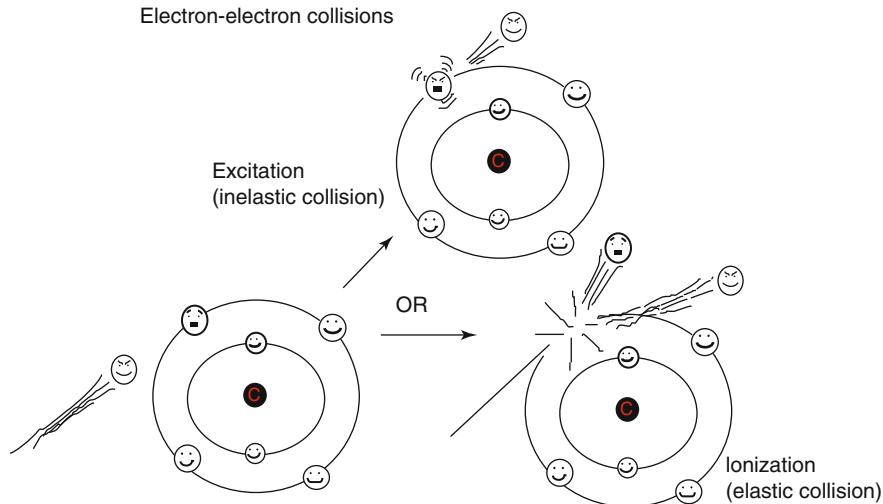


Fig. 5.4 Electron-electron collisions: Mr. Electron mostly interacts with other electrons. He can pass by and raise the energy of an electron orbital which makes the orbital electron very angry and more inclined to break chemical bonds. When he does this, he slows down a little and loses some of his kinetic energy in the process of making the orbital electron angry; therefore this is considered an inelastic collision. Alternatively, he can actually hit an orbital electron with enough force to knock him completely out of the atom with an elastic collision where almost no kinetic energy is lost.

Heavy Charged Particle Interactions

- These principles are the same for protons and “heavy ions” (alphas, carbon ions, neon ions, and other heavy things).
- **Inelastic Collision with Electrons:**
 - As a heavy charged particle speeds through a medium, its positive charge attracts **thousands of orbiting electrons**.
 - Some electrons are merely excited, others are **ionized**.
 - Each interaction slows the charged particle a little. As it slows, it is more likely to interact with both electrons and the nucleus.
 - The charged particle is very heavy, so it does not change direction appreciably (Fig. 5.6).
- **Nuclear Interactions:**
 - Once the charged particle slows to around **0.01 MeV** or so, it is able to interact with the nucleus.
 - Heavy charged particles can experience **Bremsstrahlung** but they have so much mass that this effect is minimal.
 - Interactions between a charged particle and the nucleus can result in various nuclear reactions (see Chapt. 2), causing some secondary particles and residual radioactivity.

Electron collisions with nucleus

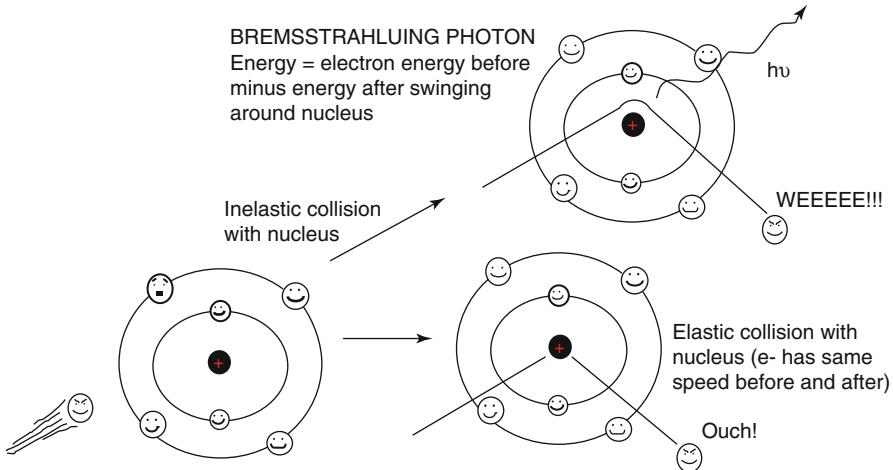


Fig. 5.5 Electron collisions with the nucleus: Electrons cannot do a lot of damage to the nucleus but running close to the nucleus can change the path of the electron. If the electron swings around the nucleus without actually hitting it, the electron will slow down and lose some of the energy as a bremsstrahlung x-ray. This is considered an inelastic collision because some of the kinetic energy is lost to the photon. Alternatively, the electron can bounce directly off of an atom with an elastic collision and no kinetic energy is lost, the electron is simply moving in a different direction.

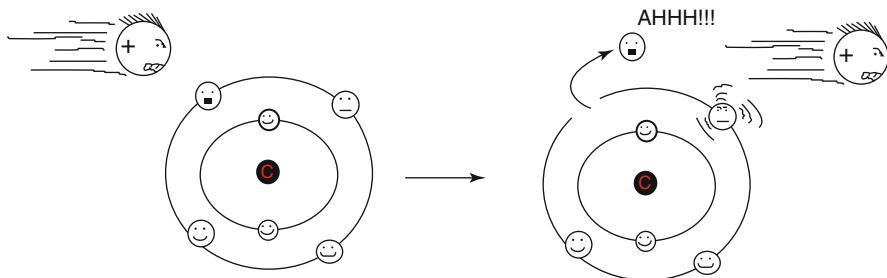


Fig. 5.6 Heavy charged particle inelastic collisions: Mr. Proton is speeding by an electron orbital and sucks an electron right off of its orbital causing ionization. Every time he does this, he slows down a little and ultimately creates havoc.

- **Depth dose characteristics (Bragg peak):**
 - As a charged particle is slowed by interactions with the medium, it interacts more and more (**higher LET**) until it finally stops.
 - The burst of energy released around the stop point is known as the **Bragg Peak** (Fig. 5.7).

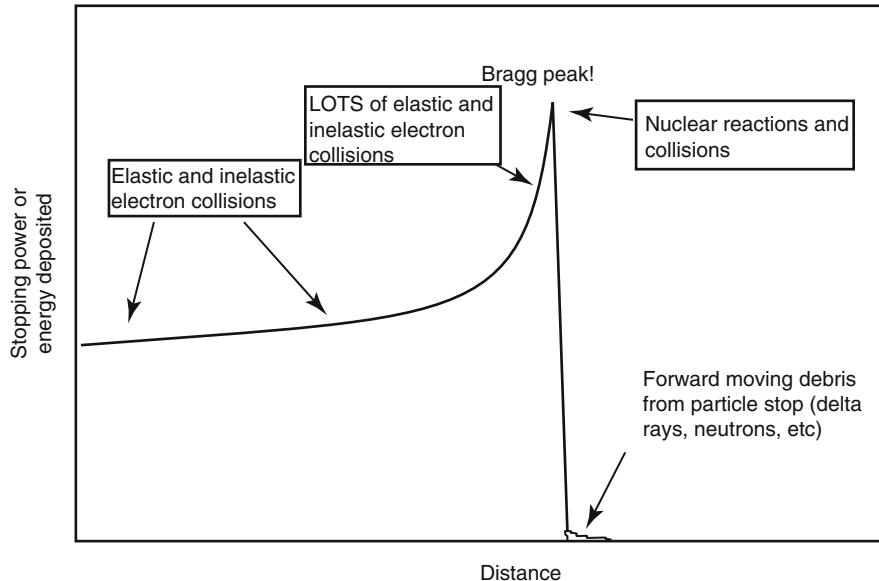


Fig. 5.7 Energy deposition of a charged particle: As a charged particle moves through the medium, it slows down more and has time to do more damage until it comes to a stop and does mega-damage. Even after the final peak of rage, there is a small amount of secondary damage from the debris that was caused at the bragg peak.

Neutron Interactions

- Since neutrons have no charge, they are not slowed down by electrons. Therefore, they predominantly interact with atomic nuclei.
- Speed (energy) is a major factor for how they interact:
 - **Thermal (slow) neutrons** have an energy of around 0.025 eV, the approximate thermal energy of room temperature.
 - **Fast neutrons** have a much higher energy in the keV-MeV range.

Fast Neutron Interactions

- **Elastic collisions with hydrogen nuclei (protons)**
 - Since the neutron has roughly the same mass as a proton, this is the most efficient way for it to transfer kinetic energy.
 - The neutron effectively acts like a cue ball with hydrogen atoms.
 - Neutrons are much less likely to interact with heavier nuclei. Therefore, lead is very poor at blocking neutrons, while water and plastics work well because they contain lots of hydrogen.
 - **This is the predominant interaction for fast neutrons.**
 - This results in a **recoil proton** which can deposit additional radiation dose (see **charged particles** section shown in Fig. 5.8).

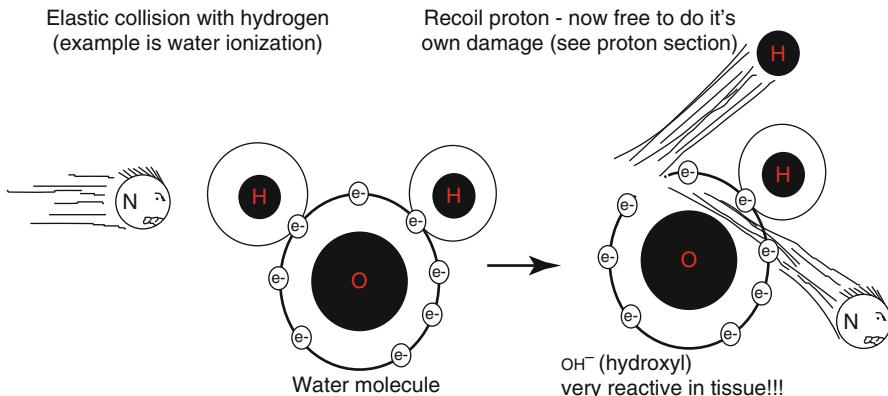


Fig. 5.8 Neutron elastic collisions: Neutrons can knock hydrogens right out of their chemical bonds similar to the way electrons knock other electrons out of orbit.

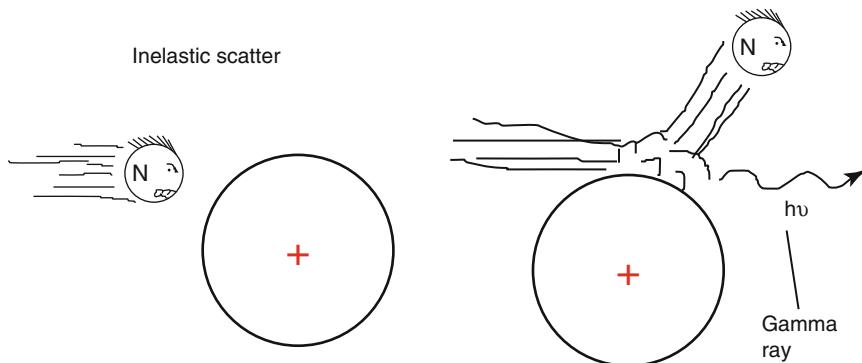


Fig. 5.9 Neutron inelastic collisions: Neutrons can bounce off of heavier nuclei and will emit a gamma ray as they slow down and lose energy. This is similar in concept to bremsstrahlung x-rays.

- **Inelastic Scatter**

- Sometimes a neutron will bounce off of a nucleus and lose energy by emitting a gamma ray (Fig. 5.9).

- **Nuclear Spallation**

- At energies above **7 MeV**, the neutron can undergo an inelastic with so much energy that it breaks up the target nucleus.
 - This is called **spallation** and the resulting nuclear fragments are called **spallation products**.
- The spallation products are heavy charged particles, usually alpha particles, and they cause dense ionization nearby (Fig. 5.10).

Neutron inelastic collision with carbon producing three alpha particles



Alpha particles are densely ionizing charged particles (high LET)

Fig. 5.10 Neutron inelastic collision with spallation: Fast neutrons that directly hit a larger nucleus can actually split the atom. This is called spallation and the spallation products (other heavy charged particles) can produce heavy secondary damage to the surrounding atoms.

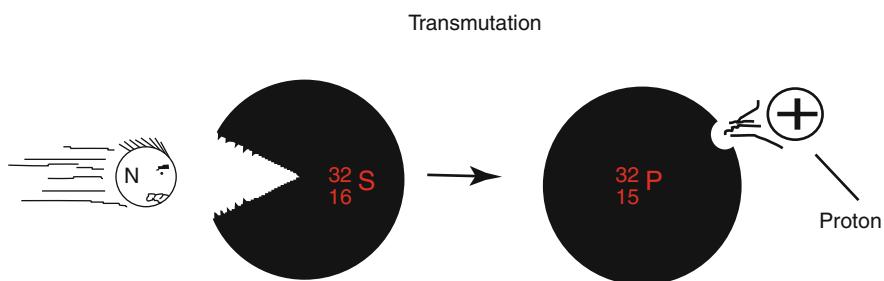


Fig. 5.11 Transmutation: Slow neutrons can actually be absorbed into a nucleus and interact with the internal nuclear forces such that the atom ejects a proton or larger particle and becomes a completely different atom (with different chemical properties).

Slow Neutron Interactions

- Once a neutron is sufficiently slow, it can participate in nuclear reactions!
- **Radiative Capture**
 - The nucleus absorbs the neutron, gaining 1 AMU but not undergoing any further transformations.
- **Transmutation**
 - The nucleus absorbs the neutron and ejects a proton or alpha particle.
 - This changes the atomic number and therefore completely changes the chemical properties of the atom!
 - When this happens to an atom that is part of a molecule, it will break chemical bonds and disrupt the molecule (Fig. 5.11).

- **Fission**

- This occurs when slow neutrons encounter a fissile substance such as uranium or plutonium (see Chapt. 2).
- Not relevant to the medical field, except for nuclear accidents and/or terrorism.

Pions

- **Bonus particle!** As of 2014, nobody uses these for therapy anymore, but who knows, they may come back eventually.
- A Pi-meson or **pion** is a subatomic particle made up of a quark-antiquark pair, as opposed to protons and neutrons which contain three quarks.
 - Roughly $273 \times$ electron mass: still considered a “heavy particle” although much lighter than a proton.
 - Can be negative, neutral, or positively charged.
 - Negative pions can be “fairly easily” produced by smashing a beryllium target with 400–800 MeV protons (the average cyclotron used for proton radiotherapy goes no higher than 250 MeV).
- **Initially**, the negative pion interacts **much like a proton**:
 - It gradually slows down, depositing more and more dose as it slows, with a dose distribution similar to a proton.
- When the Pion comes to a stop (at the **Bragg peak**), it is attracted into a nucleus. Once inside, the nucleus becomes very unstable and explodes into a “**Star Formation**” composed of protons, neutrons, alpha particles and other nuclear fragments.
 - These fragments deposit a very large amount of energy near the Bragg Peak (Fig. 5.12).

Ionization and Biological Action

- Charged particles (electrons, protons, heavy ions and pions) are considered “**directly ionizing**” because they can directly interact with the electrons around an atom.
- This is in contrast to uncharged particles (neutrons and photons) which cannot directly interact with electrons, and create ionization through secondary particles. This is “**indirectly ionizing**”.
- The biological mechanism of radiation damage in living cells is **DNA damage**.
- Ionizations may damage DNA in one of two ways:
 - **Direct Action** is direct ionization of the DNA itself, and is not oxygen-dependent.
 - **Indirect Action** is ionization of water, creating hydroxyl radicals that can react with and damage DNA. This damage is greatly amplified by oxygen.

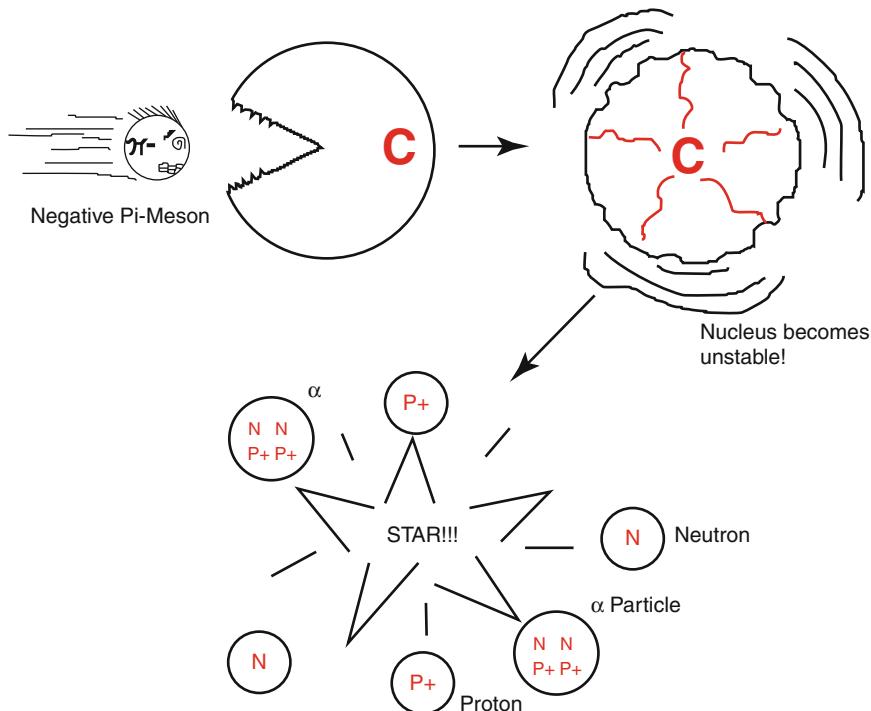


Fig. 5.12 Star formation: a slow moving negative pi-meson can be absorbed by a nucleus and cause it to become unstable and explode with many charged particles (all of which may damage nearby atoms).

- **Indirect Action dominates at low LET:**
 - Photons, electrons and fast protons are considered low-LET radiation. Their biological effect is highly oxygen-dependent.
- **Direct Action dominates at high LET:**
 - Alpha particles and carbon ions are considered high-LET radiation. Their biological effect is oxygen-independent.
- Do not confuse **directly ionizing** with **direct action**!
 - A 6 MeV electron beam is **directly ionizing** but its biological effect is mainly **indirect**.
- See Chapt. 22 for more details on LET and oxygen effect.

6

Quantification and Measurement of Dose

Definitions

- Gy: Gray: SI derived unit of **absorbed dose** in Joules per kilogram.
 - $1 \text{ Gy} = 100 \text{ rads}$
 - $10^{-6} \text{ Gy} = \text{micro- } (\mu\text{Gy})$
 - $10^{-3} \text{ Gy} = \text{milli- } (\text{mGy})$
 - $10^{-2} \text{ Gy} = \text{centi- } (\text{cGy}) = 1 \text{ rad}$
- Sv: Sievert: SI derived unit of **equivalent radiation dose** and **effective radiation dose** (also in Joules per kilogram)
 - Different from Gy and used for safety and regulations. Involves weighting factors for absorbed dose.
 - $1 \text{ Sv} = 100 \text{ rem}$ (older unit of equivalent/effective dose).

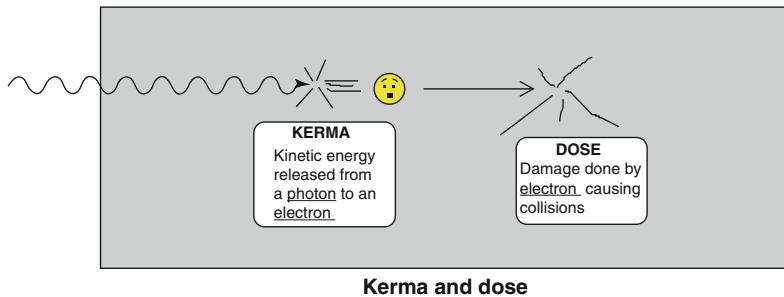


Fig. 6.1 KERMA vs Dose: KERMA is the kinetic energy transferred from the photon to the electron. Dose is the energy deposited to the medium in the form of ionizations and excitations.

- 10^{-6} = micro- (μSv)
- 10^{-3} = milli- (mSv)
- **R:** Roentgen: older unit of measurement for air KERMA or exposure
 - 10^{-3} = milli- (mR)
 - $1 \text{ R} = 2.58 \times 10^{-4}$ Coulombs per Kilogram
 - C/kg is the SI unit for air KERMA or exposure – there is no eponym presently.
- d_{\max} : the depth where the maximum dose is deposited (usually given in centimeters).
- D_{\max} : the maximum dose as a percentage of the prescription dose (describes the magnitude of a hot spot).

KERMA and Dose

- **KERMA** – Kinetic Energy Released in Media (the A was added to prevent it from being a dirty word in German apparently). Technically, it is defined as:

$$K = \frac{dE_{tr}}{dm} \quad (6.1)$$

- E_{tr} is the sum of the initial transferred kinetic energies of all charged particles set in motion by photons in mass (m).
- In other words, **KERMA** is the energy **transferred to the secondary electrons from the primary photons**. It is NOT the same as absorbed dose but it has the same basic units of measurement (J/kg) (Fig. 6.1).

Equation Terms

- **Linear attenuation coefficient (μ):**
 - The fraction of how many photons are removed per path-length either from scattering out or from transferring their energy to electrons.
 - Measured in cm^{-1} .
 - Dependence:
 - Electron density: heavier atoms like calcium in bone get more photoelectric effect and pair production.
 - Physical density (ρ): Muscle attenuates more than lung even though both tissues are mostly water by mass.
 - By dividing μ over ρ , you get the “average **mass energy transfer coefficient**” with units of Kg^{-1} denoted below:

$$\left(\frac{\bar{\mu}_{tr}}{\rho} \right)$$

- **Energy fluence (E ϕ) or flux (Ψ)** is the total energy per unit area (**a**) of a beam, as follows:

$$\Psi = E \times \phi = E \frac{n(\text{number of particles})}{a(\text{area in cm}^2)} \quad (6.2)$$

Kerma Equations

- Since we now have energy fluence over a beam cross section (Ψ) and energy lost per unity mass in a linear fashion, we can combine the mass energy transfer coefficient, Eqs. 6.1 and 6.2 into the following equation:

$$K = \Psi \times \left(\frac{\bar{\mu}_{tr}}{\rho} \right) \quad (6.3)$$

- Even though the energy initially comes from photons, it is the electrons set in motion by the photons that do the final damage (or dose). Most of the energy from the electrons (at least for our purposes) can be considered **collisional Kerma (K_c)**.
- Some of the electrons will bend their path, especially if there is metal or other high Z material nearby and create bremsstrahlung photons which then escape the medium and contribute nothing to the absorbed dose. This is called **radiative Kerma (K_r)**.

$$K = K_c + K_r \quad (6.4)$$

- Only K_c contributes to absorbed dose and we do not really care about K_r because it is a small number translates to a correctional factor.

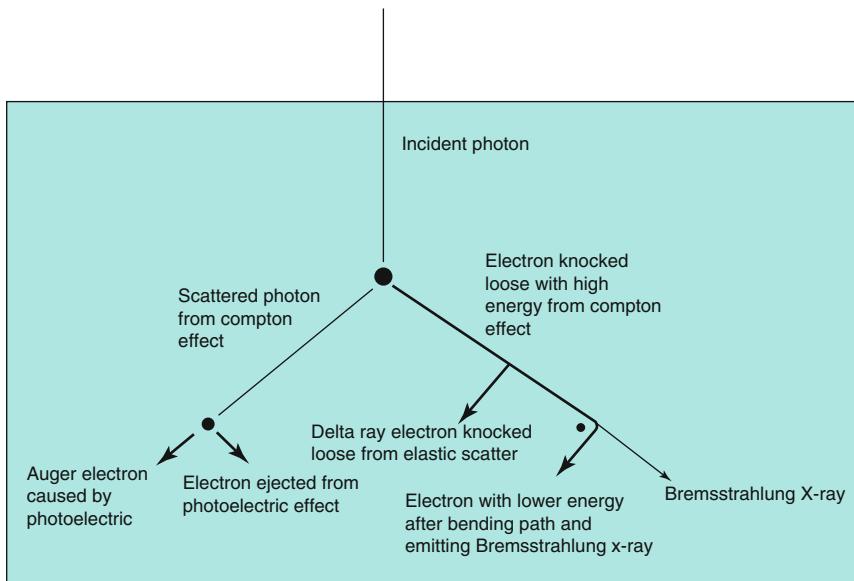


Fig. 6.2 History of an incident photon: In this figure, the path length of photons are thin lines while the path of electrons are heavy lines. In this example, four different electrons and a Bremsstrahlung x-ray are set into motion by a single initial photon. KERMA is the sum of the kinetic energies of these electrons set into motion by the initial photon. All of these secondary electrons will go on to produce ionizations and excitations. The energy deposited by these secondary electrons is dose and the energy deposition will tend to occur deeper than the KERMA transfer.

Since we are only interested in K_c , we can rearrange Eq. 6.3 to describe what we are looking at when we turn a beam on:

$$K_c = \Psi \left(\frac{\mu_{tr}}{\rho} \right) \times (1 - \bar{g}) \quad (6.5)$$

- Where g is the fraction of energy lost to electrons causing bremmstrahlung photons (it is a substitution for what would have been the K_r term) (Fig. 6.2).

Kerma → Dose

- Photons cause a cascade of electrons (through KERMA) but the electrons do the real ionizing damage (deliver the “dose”).
- Since the most important interaction is Compton scatter which generally propel electrons forward, it makes sense that the most damage done by electrons will not be directly at the surface but will actually be slightly deeper.
- The depth of greatest damage or “maximal absorbed dose” is d_{\max} . The energy transfer from photons and the dose of energy absorbed are related.

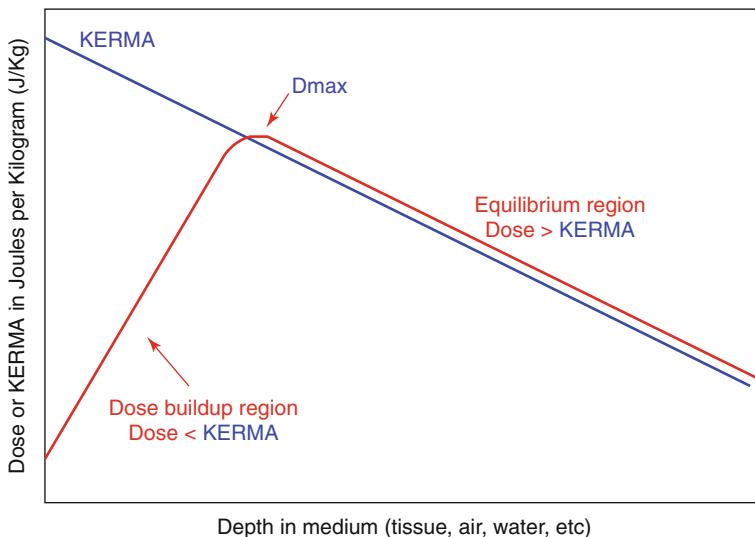


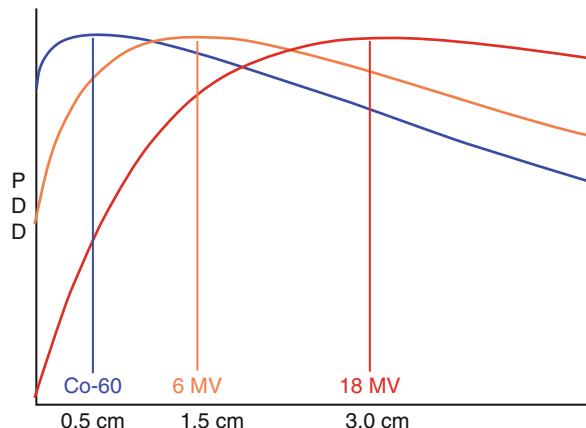
Fig. 6.3 Dose vs. KERMA at depth. After equilibrium dose is always higher than KERMA.

- In the buildup region, KERMA is greater than dose. The dose and KERMA curves eventually cross and then descend on a relatively straight linear slope where the curves are parallel but dose is slightly greater than KERMA (Fig. 6.3).
- The amount of dose buildup from KERMA is based on the photon energy.
 - As photon energy increases, the buildup region also increases and the d_{\max} becomes deeper.
 - There is also less dose fall-off with depth (high energies penetrate deeper).
 - In general, we describe doses in percentages, in order to make curves that show the percent of dose at depth (PDD). We will discuss this in much greater detail in the chapter on photon dosimetry (Chapt. 9) (Fig. 6.4).

Relative Biologic Effectiveness (RBE) (see Chaps. 19 and 22)

- Not every joule energy of radiation performs the same amount of damage in a complex cell.
- Often measured in Gy equivalent or cGy (cobalt Gy equivalent).
- The main damage that kills a cell is a double stranded DNA break.
 - Radiation that is more likely to break both strands of DNA at the same time is more efficient at killing with the same amount of absorbed dose.
 - If you pack all that energy transfer into one small but powerful explosion and that explosion happens to be very near the DNA double strand, then you are sure to destroy that DNA (Alpha particles, carbon ions, etc.).

Fig. 6.4 Percent Depth dose of various photon energy spectrums with extended view of x axis.



- If you stretch that energy into a long strand of energy loss (high energy photons), then you will produce lots of little single strand breaks and hopefully, two of them will be close enough that the whole DNA scaffold will fall apart in an un-repairable fashion.
 - Higher dose per fraction means higher probability of DS breaks.
- **Factors that affect RBE**
 - **Linear Energy Transfer (LET)** which describes the amount of radiation deposited per unit length.
 - Heavy particles and slow neutrons typically have High LET.
 - High energy photons typically have low LET.
 - Even though all photons have the same relative weighting ratio of 1, lower energy photons actually have a higher LET than high energy photons because they deposit more energy in a small space than the high energy photons.
 - Magnitude of dose per fraction and fractionation schedule (think of the power of stereotactic body radiotherapy when compared to standard fractionation).
 - Dose rate (sometimes cells can repair sublethal damage).
 - Most important when considering brachytherapy.
 - This has also been brought up for external beam cases where there is a very long setup time between different beams to the same target.
 - Very little effect on high LET radiation.
 - Biologic system
 - Inherent repair mechanisms.
 - Dividing time of target cells.
 - Endpoint desired (or trying to avoid) due to damage.
- Protons have an RBE of about 1.1, although it may be higher at the tip of the Bragg peak. Neutrons and heavy particles are much more complex but can

have an RBE as high as 40 depending on the energy and the target tissue. This concept will be discussed in much greater detail in the radiation biology sections.

Dose Equivalent (see Chapt. 22)

- The **International Commission on Radiation Protection (ICRP)** has created weighting factors (W_R) to account for the differences in dose quality for the different types of radiation.
- Used for radiation protection calculations.
- Expressed in Sieverts (Sv) instead of Gray.
- Not precise for biologic damage but is a conservative estimate for radiation protection and is relatively close to the biologic dose (RBE) discussed previously.
- Weighting factors according to ICRP report 103.
 - Photons and electrons get a weighting of 1 ($W_R = 1$).
 - Protons and charged pions get a weighting factor of 2.
 - Alpha particles and other heavy nuclei get a weighting factor of 20 (in other words the energy deposited from 1 Gy of alpha particles is expected to do 20 Gy worth of damage in the tissues, except it is expressed as 20 Sv).
 - Neutrons vary by velocity (energy).
 - 1 MeV neutrons get a weighting factor of about 20.
 - 10–100 MeV or between 0.1 and 0.01 have weighting factors of between 5 and 10.
 - >100 or <0.01 MeV weighting factor is around 2.5.

Exposure

- Exposure (air KERMA) is charge released into air.
- Used for radiation measuring devices.
- When photons interact with air, an ion pair is produced, with one positive and one negative charge. If we measure the difference in charge (dQ), divided by mass (dm) then we can measure “exposure” (X) by the following equation:

$$X = \frac{dQ}{dm} \quad (6.6)$$

- The classical unit is the Roentgen, which is often pronounced “renkin” and denoted by R .
- The SI unit is the Coulomb per kilogram (C/kg) and does not have an eponym.

$$1R = 2.58 \times 10^{-4} C/kg \text{ air} \quad (6.7)$$

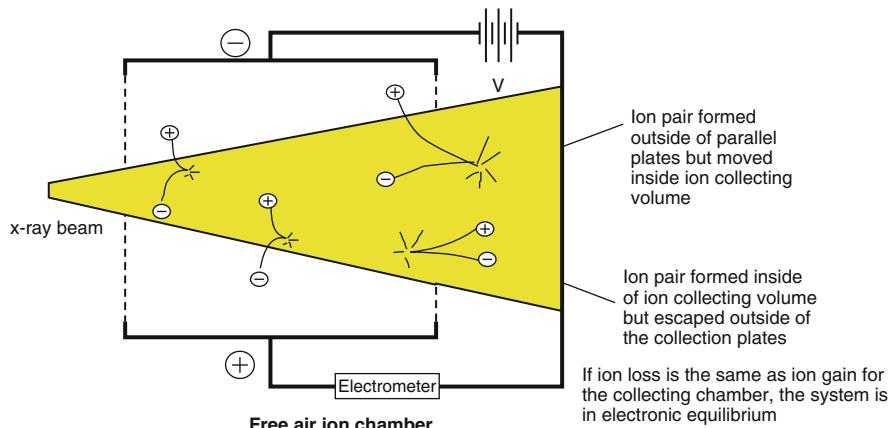


Fig. 6.5 Free air ion chamber and electronic equilibrium: ionizing radiation causes ionizations in air. If a voltage potential is applied between a volume of air, the ions will move towards their respective electrode and the charge can be measured in C/kg. In order to be accurate, ions entering the volume from the outside must be equivalent to ions escaping the volume of measurement, known as electronic equilibrium.

Methods of Measuring Dose

An Explanation of Gas-Filled Detectors

Imagine if you had two large plates with a potential difference (positive and negatively charged such that if you connected the plates, you would get an electrical current, similar to a capacitor). Now imagine that a photon comes between those plates and splits a nitrogen molecule in the air into an electron and a nitrogen ion. The electron would move to the positive end and the nitrogen ion would move to the negative plate. You now have a net charge difference (dQ = differential of charge) that can be measured with an electrometer. Now multiply this concept by about a billion. When you have billions of these reactions, you can measure the amount of photons coming through by looking at the difference in charge (dQ) divided by the mass of the air between the plates (dm). This satisfies Eq. 6.6. Some of the ionizations that happen will send electrons outside of the plates, but some of the ionizations will also occur in a region outside of the plates and send ions into the path of the plates. As long as the rate of ions moving in is the same as those moving out, you have electronic equilibrium. You must attain electronic equilibrium or else you will not be truly measuring air KERMA accurately (Fig. 6.5).

- **Calculation of absorbed dose from exposure (e.g., f factor)**
 - Under certain circumstances, you can actually determine dose directly from radiation exposure in air (ion chamber). The formula is relatively simple even though it looks complicated:

$$Dose = Exposure \times (\text{Various conversion factors}) \quad (6.8)$$

$$D_{med} = X \times f_{med} \times A \quad (6.9)$$

- D_{med} = dose in the medium
- X = exposure – what your instruments will tell you
- A = conversion factor ($\frac{\Psi_{med}}{\Psi_{air}}$) or the ratio of energy fluence in the medium to fluence in air
- f_{med} = **roentgen-to-rad factor** – for most things in the body, this is **slightly less than 1** (except for bone at photon energies below about 200 keV where it can be as high as 4.25 due to photo-electric effect).
- **Bragg-Gray cavity theory:** For photons above 3 MeV (Most therapeutic photons in the modern era), exposure cannot be directly measured due to the long range of secondary electrons in air.
 - The Bragg-Gray cavity theory states that if you have a gas-filled chamber (cavity) embedded in a medium, and the cavity is small enough that its existence would not change the number or distribution of electrons that would have been there anyway, then you CAN measure dose based on exposure with the following relationship:

$$D_{med} = J_g \times \left(\frac{\bar{W}}{e}\right) \times \left(\frac{\bar{S}}{\rho}\right)_g^{med} \quad (6.10)$$

- D_{med} is absorbed **dose** in the medium.
- $J_g \times \left(\frac{\bar{W}}{e}\right)$ = energy absorbed per unit mass of the cavity of gas (what you can detect from the small ion chamber embedded in the medium).
- $\left(\frac{\bar{S}}{\rho}\right)_g^{med}$ is a conversion factor (the ratio of the mass stopping power of the medium to that of the gas for electrons).
- **Ion chambers**
 - The gold standard for radiation measurement is the free air ionization chamber. Unfortunately, this setup requires size requirements that are proportional to the electron range in air (which can get very large for megavoltage photon beams). Additionally, since the medium is free air, the setup is very sensitive to changes in temperature, pressure, humidity and the electrical field. For these reasons, true free air ion chambers usually only exist at national standards laboratories (where you send in your testing gear to be calibrated).
- **Thimble chambers**
 - To make the ion chamber more compact, you can have a central electrode and an outer shell. The number of electrons entering must be the same as those exiting in order to achieve electronic equilibrium, and this would normally require a very large air cavity.
 - This can be overcome however if you make walls around the air cavity that were much more dense than air but had the same atomic numbers as

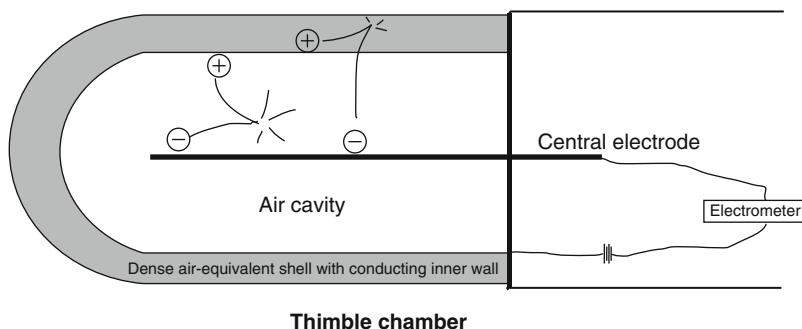


Fig. 6.6 Thimble chamber: instead of parallel plates, a central electrode and a conducting shell can be used to measure charge. The dense air equivalent shell allows the chamber to be significantly reduced in size while still maintaining electronic equilibrium and therefore accurate measurements.

air molecules. With the “dense air equivalent” shell around the air cavity, the chamber can be made small enough to be clinically useful.

- If it is small enough to be inserted into a material such that the distribution of electrons would not be much different if it were not present, then it meets the Bragg-Gray cavity criteria and can be used to calculate dose in that region. Exposure for a thimble chamber can be calculated as follows:

$$X = \frac{Q}{\rho \times v} \times \frac{1}{A} \quad (6.11)$$

- X = exposure
- Q = charge measured by the electrometer
- $\rho \cdot v$ = mass of air (density of air times volume of air)
- A = conversion factor accounting for the fluence difference if the chamber were not present (slightly less than 1.00).
- Because the thimble chamber still uses air, the density of air is still sensitive to ambient pressure and temperature and these must be taken into account and corrected for during measurements (Fig. 6.6).
- **Condenser chamber**
 - Works as a capacitor and measures voltage drop in the presence of radiation with a known conversion factor for voltage drop per roentgen of exposure.
 - Each chamber has a maximum sensitivity but in general, the maximum is 2 MeV photons due to electrons jumping from the metal stem or the insulator material (called stem effect or stem leakage). These detectors are no longer used in radiation therapy.
- **Farmer chamber**
 - Generally the work horse of the radiation oncology department and is relatively stable and reliable chamber for photons of all energies in the therapeutic range.

- The thimble wall is made of pure graphite and the central electrode is made of aluminum or graphite.
- Has a guard electrode to prevent leakage current from the collector electrode and to define the collecting volume more consistently.
- AAPM TG-21** – Calibration of a chamber and measuring dose.
 - First protocol – very complicated with many correction factors.
 - TG-21** has fallen out of use in the modern era as **TG-51** is both simpler and more accurate.

$$D_{med} = M \times N_{gas} \times P_{ion} \times P_{repl} \times P_{wall} \times \left(\frac{L}{\rho} \right)_{air}^{med} \quad (6.12)$$

- D_{med} = dose to the medium (what you want to find out).
- M = charge measured on the electrometer.
- N_{gas} = calibration of gas cavity in terms of absorbed dose to the gas per unit charge or electrometer reading – unique for each ionization chamber.
- P_{ion} = correction factor for ion recombination.
- P_{repl} = correction factor for perturbation of fluence due to the chamber being present.
- P_{wall} = correction factor for the wall of the chamber.
- $\left(\frac{L}{\rho} \right)_{air}^{med}$ = average restricted mass collisional stopping power of electrons – dependent on energies.
- The important thing to remember about TG-21 is that it is **dose to a medium based on air KERMA (exposure) measurement calibration** and has many variables that require reference to tables of stopping power ratios and mass energy absorption coefficients.
- AAPM TG-51** which is slightly more accurate but immensely more simple and based on an **absorbed dose-to-water calibration factor**.
 - The equation is as follows:

$$D_w^Q = M \times k_Q \times N_{D,w}^{60co} \quad (6.13)$$

- D_w^Q = dose to water at the reference point in beam quality Q.
- M = charge measured with the electrometer.
- k_Q = Quality conversion factor that is specific to each thimble chamber and energy – should be listed on the packaging of your thimble chamber or on a table in the TG-51 protocol. By definition, $k_Q = 1.000$ for a ^{60}Co beam with any chamber.
- $N_{D,w}^{60co}$ = Absorbed dose-to-water calibration factor for ^{60}Co .
- Thermoluminescent dosimetry (TLD)**
 - Basic idea: **Cumulative radiation dose is stored in a crystal** that can be read later by heating it.
 - Have been largely replaced by **OSLDs** in the modern era.

- What actually happens is that ionizing radiation causes electrons in crystal's electron orbitals to jump to a higher state and instead of relaxing to the ground state, they are trapped due to impurities (usually magnesium) in the crystal lattice. Later, they can be heated and cooled which allows the electrons to fall back to the ground state. When this happens, photons are released that can be measured. A few downsides include the fact that these crystals can be saturated, and also over a long time, the electrons will escape the traps on their own and therefore give an inaccurate reading. Common crystals include LiF, CaF₂, and Li₂B₄O₇. These are typically used in American personal dosimeter badges and rings (most of the rest of the world uses film badges). They can also be used in small spaces.
- **Optically Stimulated Luminescence Dosimeter (OSLD):**
 - It rides on the same concept as TLD but instead of heating the material, it can be stimulated with laser to release the trapped electrons. One example material is Aluminum oxide doped with carbon and it releases luminescence of 420 nm when illuminated with a stimulation light of 540 nm.
- **Calorimetry**
 - Basic idea: **Ionizing radiation heats up water.** You can measure the temperature change in a body of water or graphite and get the dose that was delivered.
 - $1 \text{ Gy} = 2.4 \times 10^{-4} \text{ }^{\circ}\text{C}$ in water
 - Note that this is a really small temperature change!
 - Ionizing radiation can cause excitations or ionizations that eventually lead to electrons moving to higher shells which leads to molecules vibrating faster which is basically the concept behind heat. In fact, all (or a large known fraction) of the absorbed radiation eventually appears as heat and therefore, this can be measured with very high accuracy in theory. This requires special equipment with high precision and is not considered very practical.
- **Film**
 - Basic idea: **Radiation exposes film similar to a camera**
 - **Radiographic Film:**
 - A plastic film is covered with silver bromide and when the film is hit by photons (light or ionizing radiation) a chemical reaction takes place such that when the film is developed, metallic silver is left on the film and the rest is washed off to leave an image. The amount of radiation corresponds with the amount of silver left over and therefore the darkness. Electron beams and megavoltage photon beams can have their isodoses measured relatively accurately but more importantly, the shape of a beam can be determined. Downsides of film are light contamination, confounding effects of kilovoltage x-rays (photoelectric effect on silver), and film processing inaccuracies.

- **Radiochromic Film:**
 - Uses a different material that is closer to tissue equivalence and produces a colored picture instead of a silver one. Advantages for this type of film include more beam energy independence and insensitivity to visible light (though it is still sensitive to UV light).
- **Chemical dosimetry**
 - Basic Idea: Radiation causes a chemical reaction. If you can measure the chemicals that reacted, you can measure the radiation that hit the chemistry set.
 - Many systems exist but the only one worth mentioning is “Fricke” dosimetry where irradiated ferrous ions (Fe^{2+}) are oxidized by radiation into ferric ions (Fe^{3+}). The recipe for such a dosimeter is 1 mmol/L ferrous sulfate, 1 mmol/L NaCl, and 0.4 mol/L sulfuric acid.
 - The concentration of ferric ions can then be easily measured by spectrophotometry (UV absorption peaks at 224 and 304 nm). Unfortunately, not all photon energies create the same number of reactions, so there are tables of “G values” which are the number of molecules produced per 100 eV of energy absorbed. The number is about 15.5 molecules per 100 eV absorbed and this G value does not change much for energies used in radiation oncology.
- **Solid state diodes**
 - Basic idea: Silicon chip acting as an ion chamber.
 - A silicon crystal is mixed with different impurities on two sides. One side is the N-type region that is electron rich. The other side is the P-type region that is full of electron holes (positive region). These almost act as the parallel plate electrodes in the ion chamber.
 - The area between these two regions is the “depletion zone” and this acts like the air cavity in an ion chamber. When ionizations occur from photons, the depletion zone ionizes into electrons and holes.
 - The electrons move to the p-type region and the “holes” move to the n-type region. This creates an electric current that can be measured to extreme precision.
 - The geometry of practical diodes actually resembles a thimble chamber and it is mounted on a coaxial cable. Silicone is about 1,800 times more dense than air and the energy required to produce an electron-hole pair is about 1/10 of the energy required to make an ion pair in an ion chamber, so the current produced per unit volume is about 18,000 times that of an ion chamber and therefore they are extremely sensitive.
 - Unfortunately, they have detector positioning variability and energy dependence in photon beams (though not in electron beams), and mild temperature dependence. They also take on damage over time. Their main use is in patient dose monitoring.

- **Metal oxide semiconductor field effect transistors (MOSFETs):**
 - Solid state detector for radiation dosimetry (similar in principle to diodes)
 - Due to small size ($0.2 \times 0.2 \text{ mm}^2$ in area and $0.5\text{--}1.0 \mu\text{m}$ thickness of SiO_2) it offers high degree of spatial resolution and suitable in small field dosimetry.
 - MOSFET exhibits linear dose response with $\pm 2\%$ reproducibility.
 - The MOSFET response is independent of dose rate from 100 to 600 MU/min, and dose per pulse from 0.2 to 0.5 mGy/pulse for 6 MV photons.
 - Limited lifetime: some temperature dependence, and some energy and directional dependence due to the Si substrate behind the sensitive volume.
 - A major disadvantage of all MOSFET detectors is their short life that depends on the maximum accumulated dose before hole-traps become saturated.
 - The saturation value of the signal varies with the sensitivity of the MOSFET (expressed as mV/cGy).
- **Scintillation detectors**
 - Basic idea: small amounts of incident radiation generate visible light photons that can be measured precisely.
 - When charged particles strike a scintillator, atoms are excited such that they release photons that can be measured by a photomultiplier tube. This is a precise setup that can measure very tiny amounts of radiation along with information on the intensity and energy of incident radiation. This is sometimes used in radiation survey meters for radiation safety monitoring.

7

Characteristics of Photon Beams

Definitions

- **Energy (E)** measures the amount of energy in each photon.
- **Intensity (I)** and **Fluence (ϕ)** measure the total number of photons per unit area, $#/cm^2$.
- **Attenuation** measures the decrease in **intensity** (number of photons) as a beam passes through matter.
 - **Attenuation** is a concept specific to photons. Charged particles do not undergo **attenuation**, but rather undergo **slowing** and **stopping**.

Intensity Versus Penetration

- It is easy to get confused between these two concepts. They are very different!
 - **Intensity** (fluence, number of particles) tells you how much dose a beam can give, but not how deep that will go.
 - **Penetration** (energy, beam quality) tells you how deep the beam will go, but not how big that dose will be.
- When dealing with **filtration** and **beam hardening**, **intensity** and **penetration** are actually inversely related.
 - **Filtration** decreases **intensity** but increases **penetration** by selectively filtering out lower energy photons in a poly-energetic beam.

Attenuation Coefficients

- **Linear attenuation coefficient (μ)** measures the rate at which photons are attenuated per centimeter of material encountered (see Chapt. 6 for details).
- **Mass attenuation coefficient (μ/ρ)** is the linear attenuation coefficient divided by the density of the attenuating material. This is used for calculations such as “how much mass is needed for shielding?”
- **Partial attenuation coefficients ($\mu_1, \mu_2, \mu_3, \dots$)** are used to analyze different components of attenuation.
 - For example, “attenuation due to photoelectric effect”, “attenuation due to Compton scatter”, and “attenuation due to pair production”.
- The sum of all partial coefficients should equal the total (**linear**) **attenuation coefficient**.

Mathematics of Attenuation (Fig. 7.1)

- A narrow beam of mono-energetic photons attenuates in a simple exponential fashion:

$$I(x) = I_0 \times e^{-(\mu x)} \quad (7.1)$$

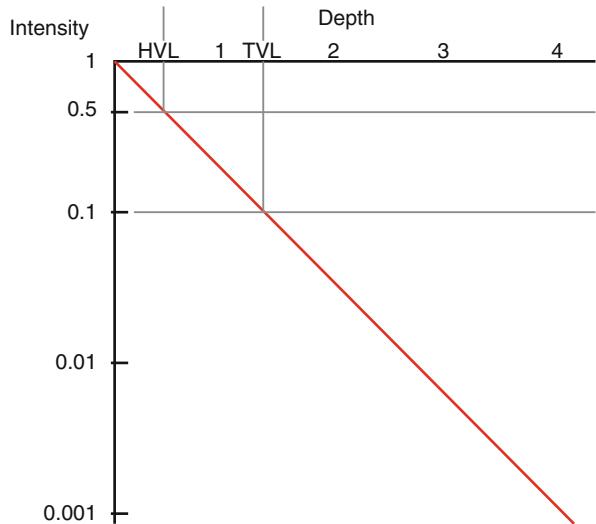
- Starting at an initial intensity of I_0 , I decreases exponentially with **Depth (x)**.
- This equation should look familiar; it is similar to **Activity (A)** versus **Decay Constant (λ)** and **Time (t)** (see Chapt. 2).

$$A(t) = A_0 \times e^{-(\lambda t)} \quad (7.2)$$

- **Attenuation coefficient** relates to **half-value layer (HVL)** like **decay constant** relates to **half-life**:

$$HVL = 0.693/\mu \quad (7.3)$$

Fig. 7.1 Simple attenuation. Intensity decreases by a factor of 2 with every half value layer, and by a factor of 10 with every tenth value layer.



$$I(x) = I_0 \times e^{-(0.693x/HVL)} \quad (7.4)$$

$$I(x) = I_0 \times 2^{-(x/HVL)} \quad (7.5)$$

- A **tenth-value layer** can be defined as 3.3 **half-value layers**, or $2.3/\mu$. This is the depth at which the primary beam has one-tenth its original intensity. This is often used for shielding calculations for a radiation facility.

$$TVL = 2.3/\mu = 3.3 \times HVL \quad (7.6)$$

Attenuation Geometry

- What is “good geometry” and “bad geometry” in the context of attenuation measurements?
- **Narrow beam geometry** is an ideal situation where only the primary beam is measured. This maximizes the accuracy of attenuation measurement and is called **good geometry** (Fig. 7.2).
- The contribution of scatter and secondary radiation can be minimized by:
 - Very small field size (narrow beam).
 - Very long source-to-target distance.
 - Very long target-to-detector distance.
- Narrow beam geometry produces the most reproducible **attenuation coefficient (μ)** because it does not include field size and scatter effects; both of them are effectively **zero**.

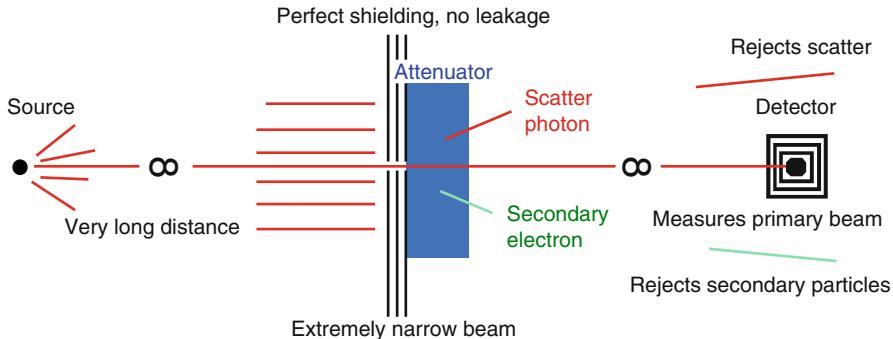


Fig. 7.2 Narrow beam geometry uses a combination of narrow beam and long distance to minimize the amount of scatter and secondary particles that reaches the detector.

- **Broad beam geometry** allows scatter and secondary radiation to reach a detector.
 - In the context of measuring primary beam attenuation, this is **bad geometry**.
 - Broad beam measurements are useful for calculating **shielding** requirements for a radiation facility (see Chapt. 14).

Narrow Beam Versus Broad Beam Attenuation

- A **broad beam** has a smaller attenuation coefficient than a **narrow beam**.
 - Some of the attenuation is “canceled out” by **scatter**, therefore the coefficient is smaller.
- A **broad beam** has a **thicker HVL** than a **narrow beam**.
 - You need a thicker barrier to shield against a broad beam.
 - This makes sense because you have to shield against both **primary beam** and **scatter**, (as opposed to just the primary beam).

Monoenergetic and Polyenergetic (Spectral) Beams

- A **monoenergetic** photon beam has a fixed energy, and does not change with attenuation at any depth.
- However, a **polyenergetic** (spectral) photon beam changes in energy as it is attenuated.
 - Low energy photons attenuate more rapidly than high energy photons.
 - Thus, the average photon energy will increase as the beam is attenuated (Fig. 7.3).
- This phenomenon is known as **beam hardening**, also known as **filtration**.

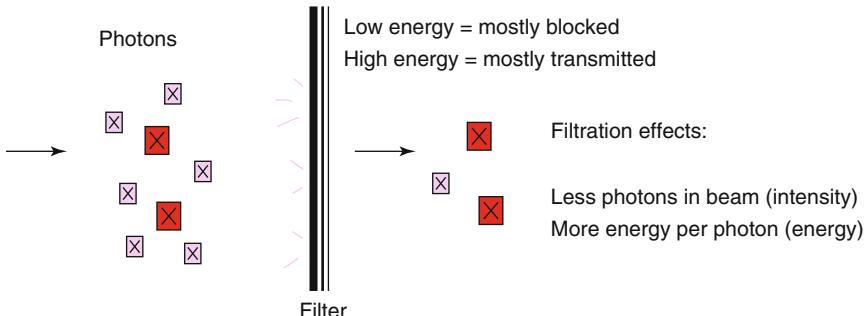


Fig. 7.3 Filtration. Placing a filter in a polyenergetic beam will selectively attenuate the lower energy photons. This increases the average energy of the beam, but decreases the intensity of the beam.

- Due to **beam hardening**, the second **HVL** is thicker than the first **HVL**, the third is even thicker, etc.

$$HVL_1 < HVL_2 < HVL_3 \quad (7.7)$$

- Most of **beam hardening** occurs over the first **tenth-value layer** (3.3 HVLs).
 - For shielding calculations it is assumed that after the first **TVL**, all subsequent **TVLs** remain the same.

Filtration in Clinical X-Ray Beams

- The **inherent filtration** of an x-ray beam depends the type of X-ray target:
 - **Reflection targets** have **minimal inherent filtration**, only the glass and oil in the X-ray tube.
 - Diagnostic and kilovoltage/orthovoltage X-rays.
 - **Transmission targets** have **high inherent filtration** as the beam passes through the entire target.
 - Megavoltage X-rays.
- **Added filtration** comes from any devices placed into the beam:
 - **Uniform filters** are placed in kilovoltage beams to increase the **beam quality (effective energy)**.
 - **Flattening filters** are placed in megavoltage beams to eliminate the “forward peak”. Therefore they provide more filtration at the center and less at the periphery.
 - Because the peripheral beam is less penetrating, it may cause superficial hot spots known as “**horns**” (Fig. 7.4).

Fig. 7.4 Photon beam horns. In a megavoltage beam, there is much less filtration on the beam edges than in the center. For this reason the beam edges are hot superficially, but cold at depth.

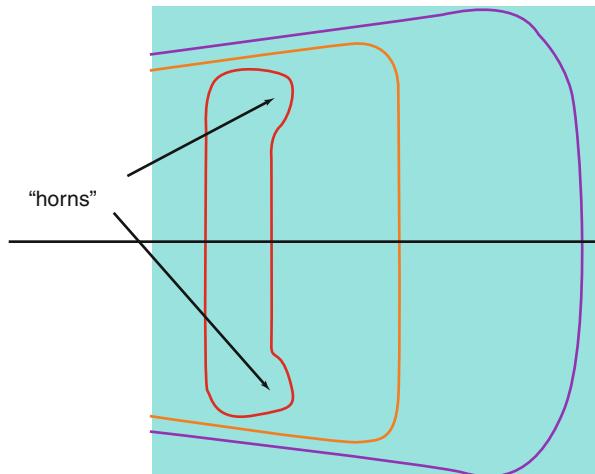
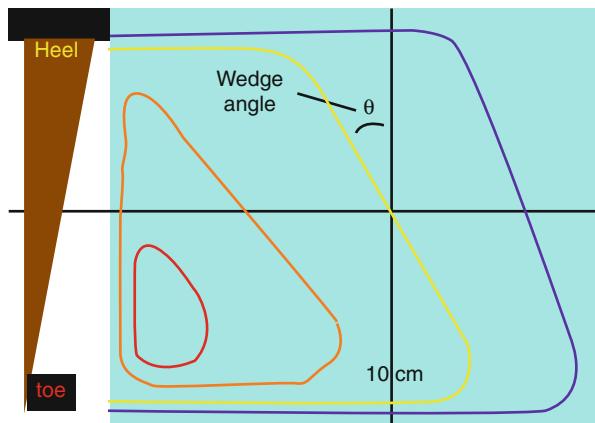


Fig. 7.5 Wedge Angle: Due to beam hardening, the “heel” of the wedge is more penetrating than the “toe”. This causes the isodose lines to become less sharply angled with depth.



- **Physical wedges** result in a less intense but more penetrating beam at the **heel**. This causes the angle of the isodose lines to decrease with depth (Fig. 7.5).
- For kilovoltage X-rays, **filters** are constructed of a series of metals arranged from **high atomic number (high-Z)** to **low-Z**. This is done to decrease the production of **characteristic X-rays**.
 - **Example:** A Thoraeus filter is made of **Tin ($Z = 50$)**, **Copper ($Z = 29$)**, and **Aluminum ($Z = 13$)**.
 - **Tin** absorbs part of the primary beam and produces mid-energy characteristic X-rays.
 - **Copper** absorbs the characteristic X-rays from **tin** and produces low-energy characteristic X-rays.

- **Aluminum** absorbs the characteristic X-rays from **copper** and produces minimal characteristic X-rays because it is very light.
- The order of these materials is very important. A Thoraeus filter will not function properly if inverted.

Beam Quality

- X-rays are produced when **monoenergetic electrons** strike a target, creating **Polyenergetic photons** via bremsstrahlung (see Chapt. 3).
 - Measuring the exact energy spectrum is difficult and not practical for the clinic.
- **Beam Quality** is a description of how penetrating the photon beam is.
 - “**High beam quality**” means highly penetrating and “**Low beam quality**” means less penetrating.
 - This does not guarantee a high quality image or treatment!
- There are many ways to specify **beam quality**.
- **Peak (Nominal) Energy** is the most simplistic measure:
 - **50 kVp, 250 kVp, 6MV, 18MV, etc.**
 - Two **50 kVp** beams may have very different penetration depending on how much filtration there is.
 - Therefore, peak energy is a very imprecise measure of **beam quality**.
- **Half-Value Layer (HVL)** is used to specify beam quality in the diagnostic (kilovoltage) and orthovoltage range:
 - Specifically, this is **HVL₁** measured under **narrow beam** geometry.
 - Peak Energy and **HVL** are often combined to specify orthovoltage beam quality.
 - For example, “**250 kVp, HVL = 2 mm Cu**” may specify a therapeutic orthovoltage beam.
- Commonly used metals for measuring **HVL**:
 - **Aluminum (Al), Z = 13:** for 100 kVp unit.
 - **Copper (Cu), Z = 29:** for 250 kVp unit.
 - **Tin (Sn), Z = 50:** for 500 kVp.
 - **Lead (Pb), Z = 82:** for Co-60 and higher.
- **Percentage Depth Dose (PDD)** is used to specify beam quality for megavoltage beams (**TG-51**).
 - This is measured in **water**, at **10 cm depth**, with a **10 × 10 cm²** field size and **100 cm SSD**.
 - This is called **%dd(10)_x** in **TG-51** nomenclature.
 - Other measures of megavoltage beam quality exist, but **%dd(10)_x** is the most up-to-date standard.
 - For example, “**%dd(10)_x = 67 %**” may specify a therapeutic megavoltage beam.

Effective Energy

- **Effective Energy** is the energy of a **Polyenergetic photon beam** with the same **beam quality** as the beam being measured.
 - The effective energy of **kV** beams is based on **HVL**.
 - The effective energy of **MV** beams is based on **PDD**.
- **Rule of thumb:** The **effective energy** of an **X-ray beam** is approximately **1/3 of the peak energy**.
 - For example, a **4MV x-ray beam** has an approximate **effective energy** of **1.33 MeV**.
 - This is rather similar to **Cobalt-60 (1.25 MeV)**.

8

Dosimetry of Photon Beams in Water

Definitions

- **D** = Dose
- **d** = Depth (sometimes called z)
- **D_{max}** = Maximum dose to a point, defined as = 100 %
- **d_{max}** = The depth of **D_{max}** (sometimes called **z_{max}**)
- **SSD** = Source-to-surface (skin) distance
- **SAD** = Source-to-axis distance
- **PDD** = Percent depth dose
- **TAR** = Tissue-air ratio
- **TPR** = Tissue-phantom ratio
- **TMR** = Tissue-maximum ratio
- **SAR** = Scatter-air ratio

- **MU** = Monitor Unit
- **K** = Calibration factor (cGy/MU)
- **OF, S_{cp}** = Output Factor
- **ISF** = Inverse Square Factor
- **S_c** = Collimator scatter
- **S_p** = Phantom scatter
- **WF** = Wedge factor
- **TF** = Tray factor

How Does a Dose Calculation Work?

- What is a **Monitor Unit (MU)**?
 - **MU** for linacs is analogous to “beam on time” for Co-60 and orthovoltage units.
 - **MU** is measured by an ion chamber inside a linear accelerator (linac) head.
- Linacs are calibrated so that **1 MU = 1 cGy** under specific **reference conditions**, variable among institutions.
 - Measured in water phantom.
 - **SSD setup** ($SSD = 100$) vs **SAD setup** ($SSD < 100$).
 - **$10 \times 10 \text{ cm}^2$ field size**, almost always.
 - **Reference Depth** varies ($d_{\max}, 5, 10 \text{ cm}$).
- As we change our prescription depth, field size, shape etc., we will need more or less beam to deliver the same dose.
 - The purpose of dose calculation is to figure out how much **MU**!

SSD and SAD Setups

- **SSD setup** uses a constant distance between the source and the surface/skin.
 - **SSD** can be changed as needed (100, 110 cm, etc.).
 - Increasing the depth of the prescription point will increase its distance from the source.
 - **PDD** is used for **SSD** dose calculations.
- **SAD setup** uses a constant distance between the source and isocenter.
 - This allows for rotation around a fixed isocenter, and is therefore much more common for modern-era radiation therapy.
 - **SAD** is a fixed value for any given machine (80 cm for Co-60, 100 cm for linac).
 - **TAR/TMR/TPR** (collectively known as **TXR**) are used for **SAD** dose calculations.

Hand Calcs (SSD Setup)

$$Dose = MU \times K \times ISF \times PDD \times S_c \times S_p \times WF \times TF \quad (8.1)$$

$$MU = \frac{Desired_Dose}{K \times ISF \times PDD \times S_c \times S_p \times WF \times TF} \quad (8.2)$$

- What are all of these factors?
 - **K = Output Factor** (cGy per MU):
 - **K** = 1.0 if linac was calibrated to d_{max} at 100 SSD.
 - Otherwise it may be different, and may also vary with field size.
 - **ISF** = Inverse square factor:

$$ISF = \left(\frac{SSD_{ref} + d_{max}}{SSD + d_{max}} \right)^2 \quad (8.3)$$

- **SSD_{ref}** = SSD under reference conditions.
- **PDD, S_c, S_p, WF and TF** are each discussed below.

Percent Depth Dose (PDD)

- **PDD** is defined as a percentage of D_{max} , measured at different depths within a water phantom at a fixed **SSD** (usually 100 cm).
- Due to the fixed **SSD**, the source-to-detector distance will increase with increasing depth.
 - **PDD** changes with depth due to buildup, attenuation and distance (inverse-square factor).
- The shape of the **PDD** curve depends on beam energy:
 - Higher energy beams have a larger buildup region and therefore have a lower **PDD** at low depth ($< d_{max}$).
 - Higher energy beams are more penetrating and therefore have a higher **PDD** at high depth ($> d_{max}$).
 - The surface dose, **PDD(d = 0)**, decreases significantly with beam energy. This is responsible for skin sparing and the build-up effect at superficial depths.
- **PDD (10 × 10 cm² field, d = 10)** increases with beam energy and is used to measure **beam quality** in **TG-51**.
 - For a detailed discussion of beam quality see Chapt. 7.

Extended SSD

- Does extending the SSD make you hot or cold?
 - **It depends!** What is the question being asked? (Fig. 8.1)

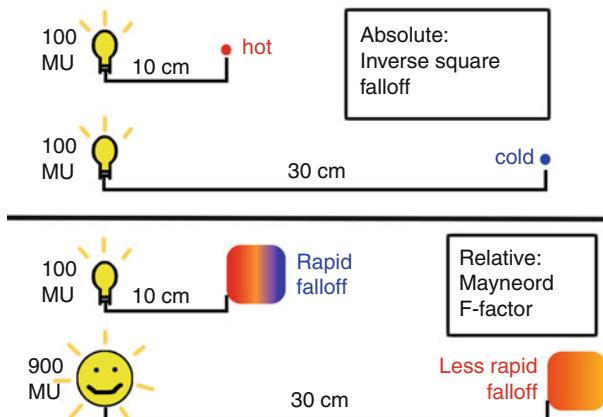


Fig. 8.1 Extended SSD effects. When SSD is extended, dose decreases according to the Inverse Square law (an absolute decrease). However, dose will no longer fall off as rapidly with depth (a relative increase).

- Radiation is like heat; if you put wings directly on the grill they will cook much faster than if you put them on the top rack.
 - **Extended SSD** decreases the **inverse square factor (ISF)**, so it takes more beam-on time (**MU**) to deliver the same dose.
- The wings on direct heat are more likely to burn the skin before cooking the center, while wings on the top rack will cook more evenly.
 - Dose homogeneity improves with **extended SSD**.
 - **10 cm depth** is very deep relative to **20 cm SSD**, but not so deep relative to **200 cm SSD**.
 - Therefore **PDD** increases with **SSD**.
 - The magnitude of this increase can be calculated by the **Mayneord F-Factor** (named after the British physicist who first described it).

Mayneord F-Factor

- **Mayneord F-factor Mnemonic:**

“**old and deep**” (old SSD + d) * “**new and shallow**” (new SSD + d_{max}), over the opposite, and then squared.

$$\frac{PDD_2}{PDD_1} = \left(\frac{(SSD_1 + d) \times (SSD_2 + d_{max})}{(SSD_2 + d) \times (SSD_1 + d_{max})} \right)^2 \quad (8.4)$$

- The F-factor (the bracket term in Eq. 8.4) is usually a small adjustment. Under normal circumstances it is just a few percent.
 - If you do a F-factor calculation and end up with 1.10 or 1.20, you probably made a mistake. Double-check your numbers.

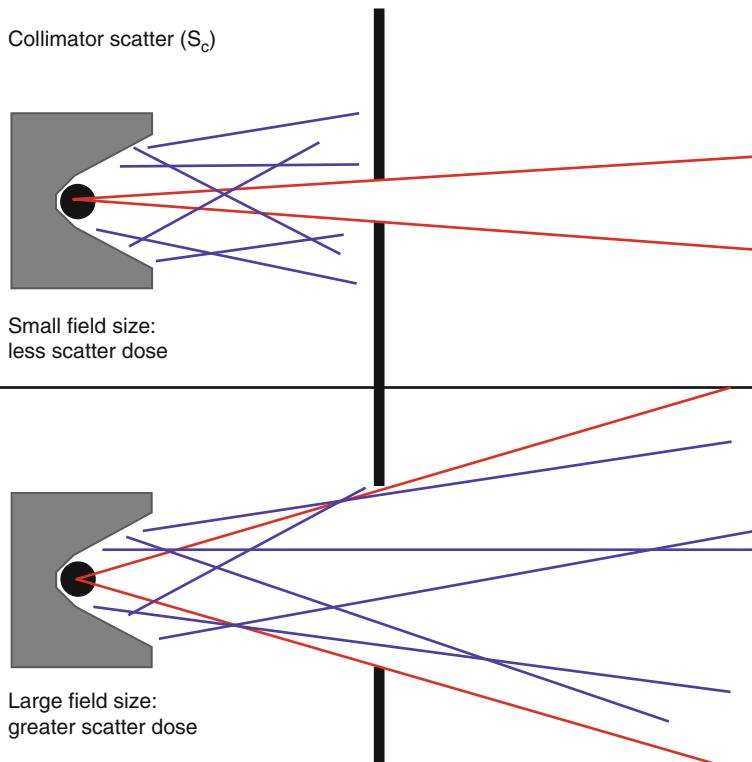


Fig. 8.2 Collimator scatter. Scatter increases with field size, as depicted above.

SC and SP: Scatter Factors and Field Size

- Increasing the field size increases output (cGy/MU) – why?
 - Primary dose** does not change.
 - Scatter dose** increases with field size.
 - Scatter dose is zero for an infinitely narrow beam, because anything that scatters exits the beam.
 - A broader beam allows more of the scatter to remain inside the field.
- Scatter factors** are divided into two components:
 - Collimator scatter (S_c)** comes from the linac head (mostly the primary collimator, not the collimator jaws) (Fig. 8.2).

$$S_c(r) = \frac{\text{Dose in air for field size } r}{\text{Dose in air for reference field } (10 \times 10 \text{ cm}^2)} \quad (8.5)$$

- Phantom scatter (S_p) comes from the phantom.

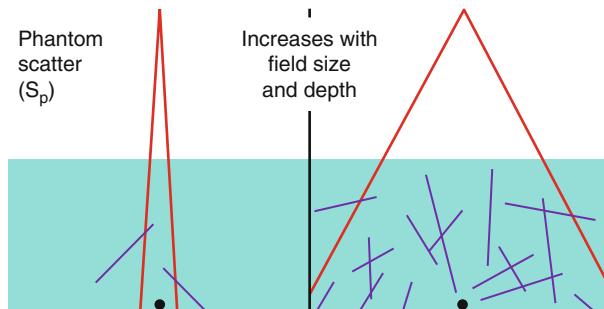


Fig. 8.3 Phantom scatter. Scatter increases with field size, as depicted above.

- Measuring dose in a phantom gives a combination of collimator and phantom scatter. Therefore the collimator scatter must be divided out:

$$S_{c,p}(r) = \frac{\text{Dose in phantom for field size } r}{\text{Dose in phantom for reference field size}} \quad (8.6)$$

$$S_p(r) = \frac{S_{c,p}(r)}{S_c(r)} \quad (8.7)$$

- When blocks (MLCs) are used, the field size for S_p will be smaller than the field size for S_c . This is because the blocked field is smaller than the collimator jaw settings.

- **Equivalent Squares (EqSq)**

- S_c and S_p are measured with square fields.
 - When treating with non-square fields, one must calculate the **equivalent square**.
 - What is the **equivalent square of a rectangle**?

$$EqSq = \frac{4A}{P} \quad (8.8)$$

Where A is area and P is perimeter of the field.

- What is the **equivalent square of a circle**?

$$EqSq = \sqrt{\pi r} \quad (8.9)$$

- What is the **equivalent square of a complex shaped field**?
 - This may be calculated by the **Clarkson method**, described later in this chapter.

Beam Modifier Factors: WF and TF

- **Wedge Factor (WF)** is a correction for having a wedge in the field. (For more details on wedges, see Chapt. 9).
 - **Physical wedges** attenuate the beam, so **WF > 1.0** for a physical wedge.
 - **Non-physical** (electronic or soft) **wedges** are software-defined, so they may or may not have a **WF** depending on how the machine is programmed.

$$WF = \frac{\text{Dose with wedge}}{\text{Dose without wedge}} \quad (8.10)$$

- **Tray Factor (TF)** is a correction for attenuation from the blocking tray (if physical blocks are used).
 - **TF > 1.0**.

$$TF = \frac{\text{Dose with tray}}{\text{Dose without tray}} \quad (8.11)$$

- **Other beam modifiers** (such as a beam spoiler) may have their own **attenuation factor**.

PDD Versus TMR (SSD VS SAD)

- What is the difference? (Fig. 8.4).

Hand Calcs (SAD Setup)

$$\text{Dose} = MU \times K \times ISF \times TMR \times S_c \times S_p \times WF \times TF \quad (8.12)$$

$$MU = \frac{\text{Desired_Dose}}{K \times ISF \times TMR \times S_c \times S_p \times WF \times TF} \quad (8.13)$$

- **K = Output Factor (cGy per MU):**
 - **K = 1.0** if linac was calibrated to **d_{max}** at 100 SAD.
 - Otherwise may be different.
- **ISF = Inverse square factor:**

$$ISF = \left(\frac{SAD_{ref}}{SAD} \right)^2 \quad (8.14)$$

- This is generally equal to 1.0 for **SAD** setup because **SAD** is a fixed number.
- **S_c, S_p, WF and TF** are the same as for **SSD** setup.

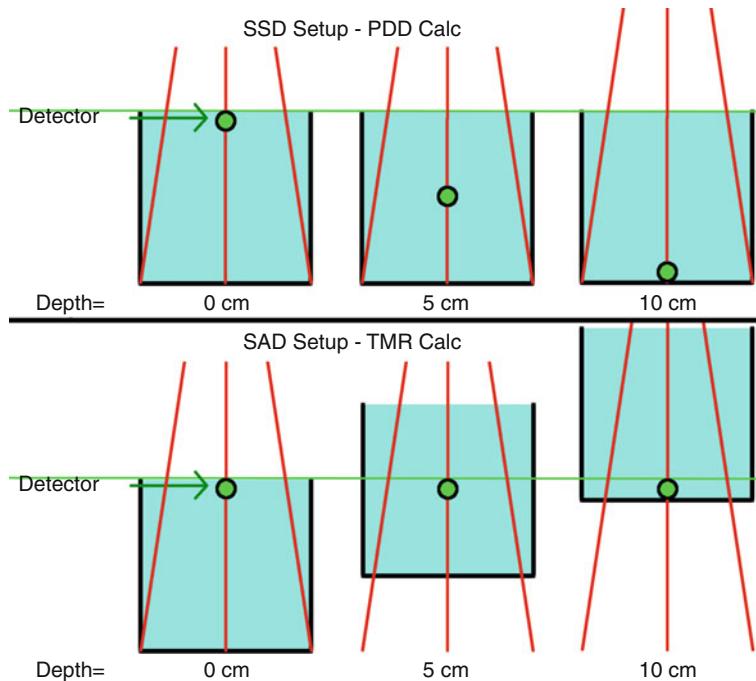


Fig. 8.4 PDD versus TMR. PDD is measured by moving the detector to different depths in a stationary phantom. Dose falls off due to both attenuation and distance (inverse square). TMR is measured by moving the phantom to different depths with a stationary detector. Dose falls off due to attenuation only.

Tissue-X-Ratios (TAR, TMR, TPR)

- These numbers are used for the calculation of SAD setups.
 - The generic term “TXR” is often used, because all three are very similar to each other.
- **TAR = Tissue-Air Ratio**

$$TAR(d) = \frac{\text{Dose at depth } d \text{ in phantom}}{\text{Dose at same point in free air}} \quad (8.15)$$

- **TAR** is mainly used for ^{60}Co because it is difficult to perform “free air” measurements at higher energies.
- **TAR** is different from **TPR/TMR** because it includes **phantom scatter (S_p)**.
- **TMR = Tissue-Maximum Ratio**

$$TMR(d) = \frac{\text{Dose at depth } d \text{ in phantom}}{\text{Dose at depth } d_{\max} \text{ in phantom}} \quad (8.16)$$

- **TMR** is always ≤ 1 , since dose can never exceed D_{\max} .

- **TPR = Tissue-Phantom Ratio**

$$TPR(d) = \frac{\text{Dose at depth } d \text{ in phantom}}{\text{Dose at depth } d_{ref} \text{ in phantom}} \quad (8.17)$$

- If $d_{ref} = d_{max}$, then **TPR = TMR**.
- **BSF = Back-Scatter Factor = TAR(d_{max})**
 - The D_{max} is a few percent higher in tissue than in air because back-scatter adds to maximum dose.
- **TXRs** can be easily interconverted:

$$\frac{\text{TAR}(d)}{\text{BSF}} = TMR(d) = TPR(d) \times TMR(d_{ref}) \quad (8.18)$$

Scatter-Air Ratio (SAR)

- This is a method to divide **TAR** into primary and scatter components. **SAR** is used for **Clarkson** calculations, described later.
- First measure **TAR(d, r)** at varying field size r .
- Extrapolate the **TAR** curve back to zero field size, **TAR₀(d)**.
 - Since an infinitely narrow field should exclude scatter dose (see **narrow-beam attenuation**), **TAR₀** is assumed to equal the primary beam dose.
- **Calculating scatter contribution (SAR):**
 - Subtract the primary beam dose from the total dose to obtain scatter dose:

$$SAR(d, r) = TAR(d, r) - TAR_0(d) \quad (8.19)$$

Rotational (Arc) Therapy (Fig. 8.5)

- Divide the arc into many equally spaced beam angles.
- Calculate a **TMR** for each beam angle.
- The average of all **TMRs** = total **TMR** for the arc.
- Photon arcs place the maximum dose at the isocenter, with dose falloff in all directions.
- Areas not covered by the arc will not have any entrance dose but may still receive exit dose. Amount of low-dose wash increases with size of field.

Isodose Curves

- Isodose lines represent radiation dose in a 2D fashion, as shown in Fig. 8.6.

Fig. 8.5 Rotational arc therapy. Arc therapy may be approximated as the sum of many different beam angles.

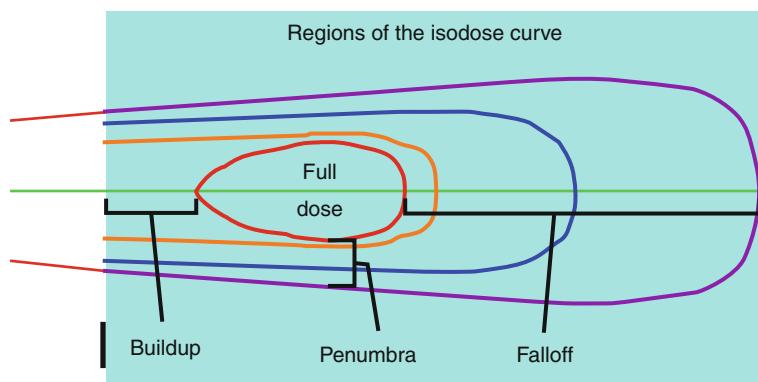
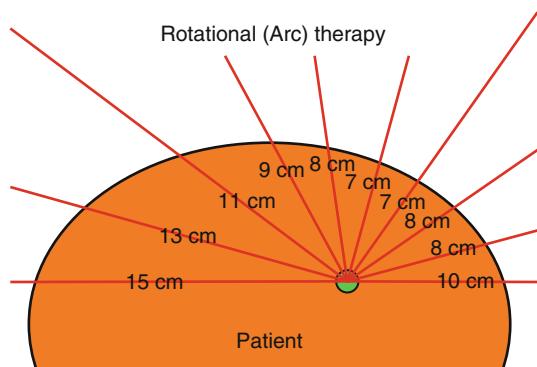


Fig. 8.6 Regions of the isodose curve. Isodose lines are a visual representation of calculated radiation dose. The areas of less than full dose can be divided into buildup, penumbra, and falloff regions.

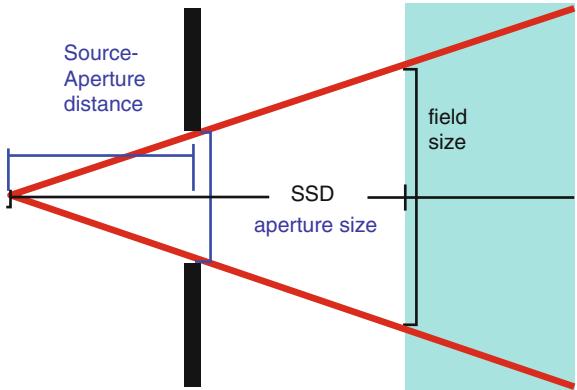
High Dose: The In-Field Region

- The field edges are defined by the **50 % isodose lines**.
 - That way if two abutting fields are matched to each other, $50\% + 50\% = 100\%$.
- The central field is defined by **80 % of the field width**.
 - In a $10\text{ cm} \times 10\text{ cm}$ field, the central $8\text{ cm} \times 8\text{ cm}$ is flat and symmetrical, but the far-left and far-right 1 cm may get less than full dose.

Field Shaping

- Refer to Chapt. 9 for a detailed discussion of field weighting and wedges.
- **Field Shaping Apertures (Blocks, MLCs)**

Fig. 8.7 De-magnification. When using a field shaping device, the aperture is always smaller than the field size. This ratio may be calculated by similar triangles.



- Note that the opening (aperture) in a block is significantly smaller than the actual field size, due to de-magnification: (Fig. 8.7).
- De-magnification can be calculated with **similar triangles**.

$$\frac{x_1}{d_1} = \frac{x_2}{d_2} \quad (8.20)$$

- Note that when using **MLCs**, the light field is slightly smaller than the actual radiation field.
 - The **MLCs** completely block visible light, but radiation can leak through the leaf tips.

Clarkson Method

- A method of dose calculation for complex shaped fields:
 - Divide field into many **rays**, and calculate a **SAR** based on the length of each ray.
 - Add **SAR** for each in-field ray section.
 - Subtract **SAR** for each blocked ray section.
 - **SAR** for the field = average of all **SARs**.
 - Note that this method is really calculating **phantom scatter (S_p)**. **TAR** includes S_p but not S_e (Fig. 8.8).

$$TAR(d, r) = TAR_0(d) + SAR(d, r) \quad (8.21)$$

- The dose under a block (or MLC) can also be calculated by Clarkson method:
 - **Transmission (“Leakage”): Jaws ~0.1 %, Blocks or MLCs ~1–3 %.**
 - Multiply **TAR₀** by the transmission factor to obtain the **primary beam dose**.

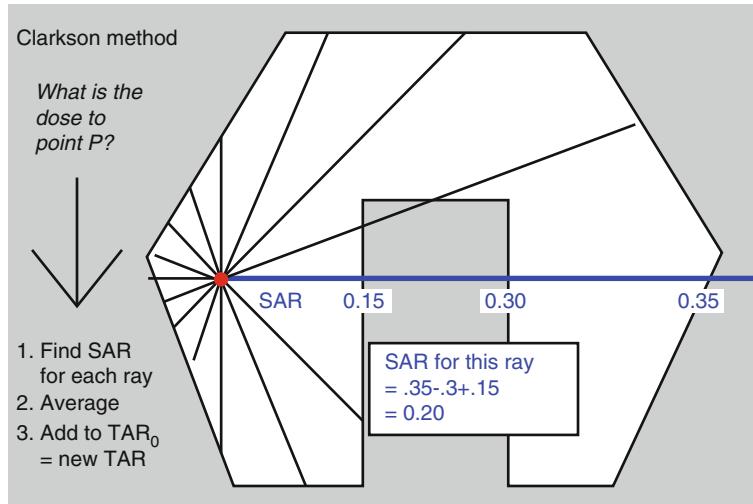


Fig. 8.8 Clarkson method of scatter calculation. A complex shaped field is divided into many small rays. Scatter (SAR) is calculated for each ray and then averaged.

- **Scatter:** Usually the predominant factor.
- SAR is calculated just like above to obtain the **scatter dose**.
- **How to Measure Scatter from an Area to a Point:** (Fig. 8.9).

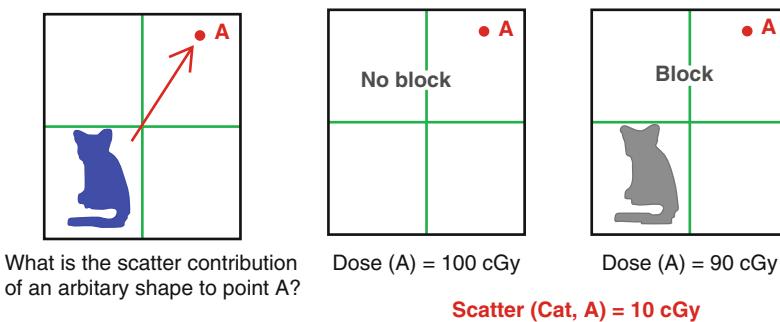


Fig. 8.9 Measuring out-of-field scatter dose. If you place a block in a large field and the measured dose changes by X cGy, that means the blocked area must have contributed X cGy of scatter.

Off-Axis Ratio (OAR)

- If dose is prescribed to a point outside of the central axis, an OAR must be included:

Fig. 8.10 Photon beam horns. This figure is repeated from Chapt. 7.

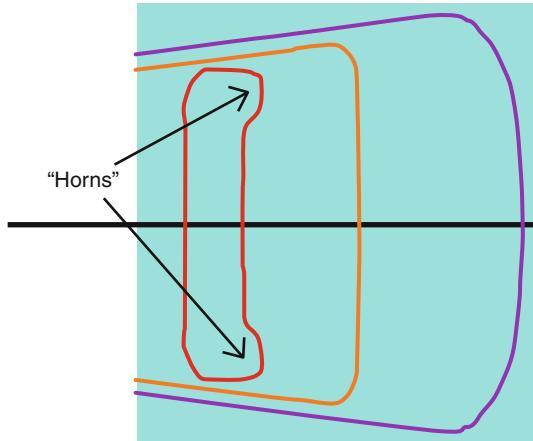
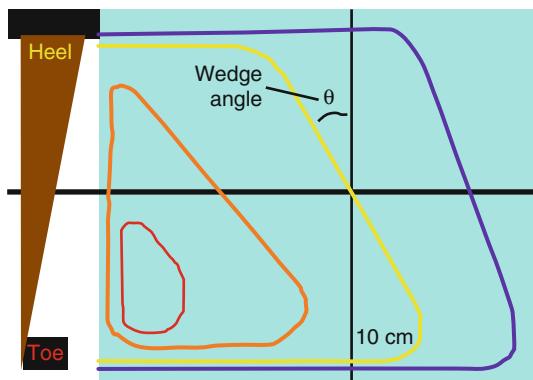


Fig. 8.11 A wedged field. This figure is repeated from Chapt. 7.



$$OAR(x, d) = \frac{\text{Dose at offaxis point} \times \text{at depth } d}{\text{Dose at central axis at depth } d} \quad (8.22)$$

- OAR is defined as 1.0 at the central axis.
- OAR changes with depth due to **flattening filter** effects:
 - The beam is **flat** ($OAR = 1.0$) at **10 cm** depth.
 - **Shallow:** Edges hotter than center ($OAR > 1.0$).
 - These hot spots are called the beam “horns”.
 - **Deep:** Center hotter than edges ($OAR < 1.0$) (Fig. 8.10).
- In a **wedged field**:
 - $OAR << 1.0$ at the heel.
 - $OAR >> 1.0$ at the toes (Fig. 8.11).

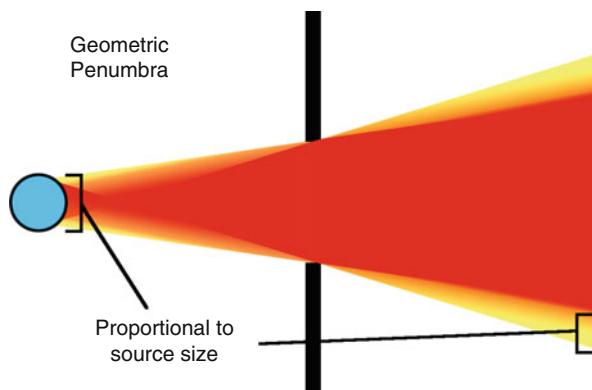
Superficial Dose: The Buildup Region

- Photons are indirectly ionizing and the dose is deposited by secondary electrons.
 - Most of the electrons generated at the surface deposit their dose at a depth corresponding to electron energy.
 - The higher the photon energy, the greater the range of secondary electrons.
 - Therefore **surface dose** decreases with energy and is relatively low (~15–40 %) for **6 MV** or higher.
- The region between the surface ($d = 0$) and d_{\max} is called the **buildup** region, because dose is still building up.
 - **~0.5 cm** for **Co-60**
 - **~1.0 cm** for **4 MV**
 - **~1.5 cm** for **6 MV**
 - **~2.0–2.5 cm** for **10 MV**
 - **~3.0–3.5 cm** for **18 MV**
 - **~4.0–5.0 cm** for **25 MV**
- Ways to increase superficial dose:
 - **Decreased beam energy.**
 - **Increased field size** increases electron contamination of the field.
 - **Beam spoilers** (any material placed in the beam) to intentionally generate secondary electrons.
 - **Obliquity** (aka **Tangentiality**) decreases d_{\max} and increases surface dose.
 - **Bolus** moves the patient's skin to a non-zero depth.
- **Photons vs. Electrons**
 - Several aspects of superficial dose are **opposite** for photons and electrons.
 - **High Energy:** less superficial dose for photons, more superficial dose for electrons.
 - **Small Field Size:** less superficial dose for photons, more superficial dose for electrons.
 - See Chapt. 10 for details.

Lateral Dose: The Penumbra Region

- **Penumbra** is the area at the beam edge where there is rapid lateral dose fall-off.
- There are various measures of **penumbra**, such as distance from 90 to 50 % isodose line, or 80–20 % isodose line.
- There are two main contributions to **penumbra**:
- **Geometric Penumbra** is due to finite source size.
 - This is important for Cobalt-60 (large source size).
 - It is much less of a factor for megavoltage linacs (Fig. 8.12).

Fig. 8.12 Geometric penumbra. This blurring of the field edge is directly proportional to the physical size of the source. Linac targets are much smaller than Co-60 sources, so this is a minor effect for linacs.



- **Transmission Penumbra** is due to transmission through the block or MLC edge.
 - This is most significant with **MLCs**.
 - Some **MLCs** are designed to intentionally broaden the penumbra to decrease the “stair step” phenomenon (Fig. 8.13a, b).
- **Physical Penumbra** is due to physical processes depositing dose outside of the field edge.
 - **Charged particle disequilibrium:** Secondary electrons deposit dose laterally.
 - This is the most important cause of penumbra for megavoltage photons.
 - Penumbra is broader with **increased beam energy** and **decreased target density**.
 - Therefore ≥ 10 MV is discouraged in the lung.
 - **Photon scatter** is the second most important factor.
 - **Photon leakage, electron contamination** and **neutron contamination** are minor factors.

Rules of Thumb

- The goal of dose calculations is to determine how many **MUs** are required to deliver a given dose (**cGy**).
- **PDD** is used for **SSD** setup, **TXR** for **SAD** setup.
- **1 MU = 1 cGy** under reference conditions, by definition.
 - If your **MU** is much lower or higher than **cGy**, you need to figure out why.
- **“My MU are a lot higher than my dose. Why?”**
 - Prescription SSD > reference SSD
 - Prescription depth > reference depth
 - Field size < 10 cm
 - Wedges, IMRT, or other beam modifiers
 - Calculation error

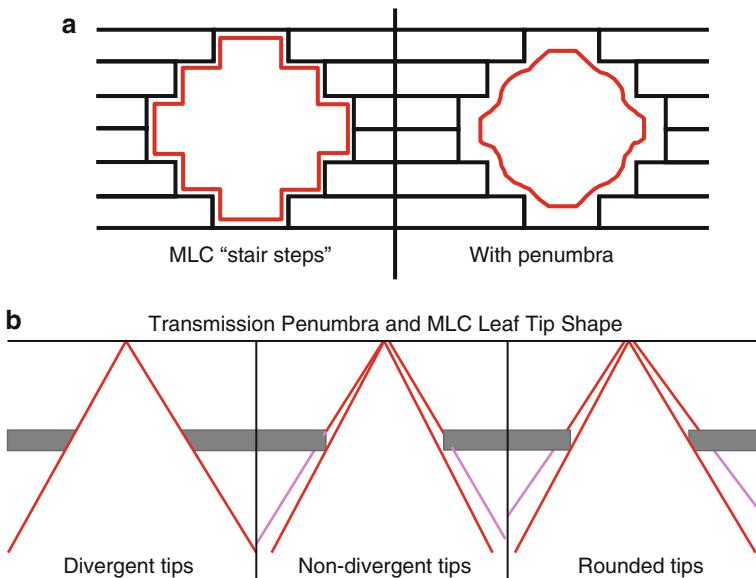


Fig. 8.13 (a, b) Transmission penumbra. If collimator tips do not diverge with the beam, differential transmission will slightly blur the field edge. In case of MLCs this effect may be desirable, as it mitigates the “stair step” phenomenon.

- **“My MU are a lot lower than my dose. Why?”**
 - Prescription SSD < reference SSD
 - Prescription depth < reference depth
 - Field size > 10 cm
 - Calculation error
- **Extended SSD Effects**
 - ISF is much lower - \rightarrow you need much more MU.
 - PDD is slightly higher - \rightarrow your dose fall off with depth is slightly less.
 - **Mayneord F-factor** calculates how large the PDD increase is. This should be no more than a few percent.
- **Dose Under a Block**
 - **Leakage Dose**
 - Jaws ~0.1 %
 - Blocks, MLCs ~1–3 %
 - **Scatter Dose** may be much higher than that!
 - This can be calculated by Clarkson method, or empirically measured.

9

Dosimetry of Photon Beams in a Patient

Dose Calculation: Water Versus Patient

- Please refer to Chapt. 8 (**Photon Dosimetry in Water**) for the basic dose calculation equations.
 - This chapter assumes you already know how to calculate dose to water.
- Dose to patient is different from dose to water because:
 - Patient surface is not perfectly flat.
 - Patient tissue is not perfectly water-equivalent: it contains air, bone, metal etc.
 - Clinical treatments often contain more than one radiation field. When matching fields, beam geometry must be matched to minimize hot and cold spots.

Fig. 9.1 Tissue excess and deficit. These values are measured as centimeters of deviation from a perfectly flat surface.

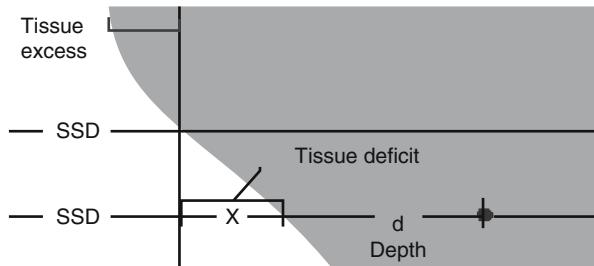
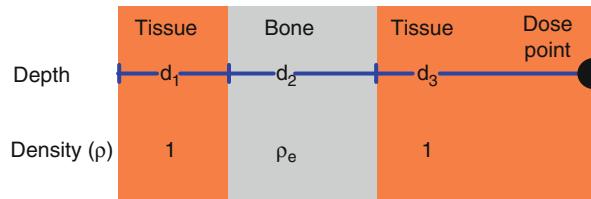


Fig. 9.2 Inhomogeneity correction. An inhomogeneity can be characterized by its location (depth), density and thickness as depicted above.



Corrections For Patient Contour

- Unlike a water phantom, patients have a non-flat surface. Therefore, corrections must be made for their contour.
- The difference between a flat surface and the patient surface is known as “tissue deficit” or “tissue excess”.
 - x = **tissue excess** (negative number for tissue deficit)
 - d = **depth in tissue**
 - r = **field size** (Fig. 9.1)
- Several different methods exist to calculate the dose with an irregular surface.

Inhomogeneity Corrections

- High-density tissue (bone) increases attenuation, while low-density tissue (lung) decreases attenuation.
- Therefore the dose distal to an inhomogeneity will be different than the dose in a homogeneous phantom (Fig. 9.2).

Classical Methods

- Uses beam data measured in water, and applies simple correction factors for irregularities in surface contour and inhomogeneities in tissue.
- These methods are rarely used in modern era radiotherapy.

- **Irregular Contour Corrections:**
 - **Effective SSD Method:** Uses a SSD/PDD calculation and corrects for depth in tissue.
 - **TAR Ratio Method:** Uses a TAR correction factor based on the thickness of tissue excess or tissue deficit.
 - **Isodose Shift Method:** Uses a “shift factor” to move the isodose lines based on tissue excess or deficit.
- **Inhomogeneity Corrections:**
 - **TAR ratio method:** Uses the “radiographic depth” to calculate a new TAR.
 - **Batho power law method:** Calculates TAR based on an exponential function of depth.
 - **Isodose Shift Method:** Uses a “shift factor” based on the thickness and nature of the inhomogeneity.

Model Based Calculations

- Modern treatment planning systems use computer models to calculate dose.
 - These are all based on **Monte Carlo (MC)** simulated pencil beam kernels.
- In order from least sophisticated to most sophisticated, the common computer models are:
 - **Pencil beam (PB) kernel:** Only accounts for central axis of the beam.
 - **Superposition/Convolution** method: Also accounts for lateral inhomogeneities.
 - **Collapsed Cone** method: Also accounts for lateral inhomogeneities.
 - **Analytical anisotropic algorithm (AAA)**
 - **Accuros**
 - **Monte Carlo:** The most accurate and computationally intensive algorithm.
- The details of computer based models are beyond the scope of this review book.

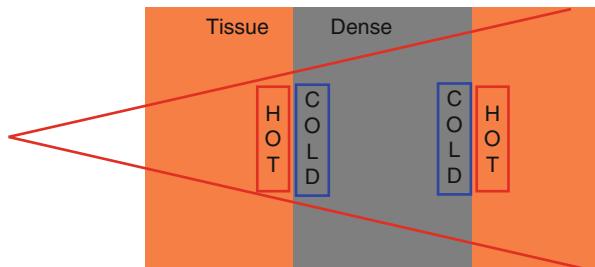
Inhomogeneity Perturbations

- At an interface between “less dense” and “more dense”, there is a loss of **electronic equilibrium** needed to calculate dose in medium.
 - High density tissue generates more secondary electrons and low density tissue generates less secondary electrons (Fig. 9.3).
- The high-density side is relatively **underdosed** because there are not enough electrons coming from the low-density side.
 - **Tissue next to lung/air may be underdosed.**
- The low-density side is relatively **overdosed** because there are too many electrons coming from the high-density side.
 - **Tissue next to bone/metal may be overdosed.**
 - Photon scatter may also contribute to this hot spot, especially with a metal/tissue interface.

- Doses at an inhomogeneity interface are difficult to calculate or measure accurately, but several of the algorithms described above can handle inhomogeneities.

Fig. 9.3 Interface effects.

When a photon beam encounters an inhomogeneity, hot and cold spots occur due to differences in secondary electron production.



Parallel Opposed Fields

- Evenly weighted parallel opposed fields are the simplest method to create a “uniform” dose.
- Tissue Lateral Effect** (aka hourglass effect): Dose is always higher superficially than at depth.
 - Larger **separation** increases the max dose, as D_{\max} increases faster than D_{exit} decreases.
- Depth = Separation/2**
 - This is a common test-taking mistake.
 - Always know whether you are using **depth** or **separation**, or you will be off by a factor of 2 (Fig. 9.4).
- How to calculate the lateral dose?**

$$\begin{aligned} D_{\max}(\text{beam}_1) &= \frac{100\%}{PDD(d_{\text{midplane}})} \\ D_{\text{exit}}(\text{beam}_2) &= \frac{PDD(d_{\text{exit}})}{PDD(d_{\text{midplane}})} \\ D_{\text{total}} &= \frac{D_{\max}(\text{beam}_1) + D_{\text{exit}}(\text{beam}_2)}{2} \end{aligned} \quad (9.1)$$

- How to keep D_{\max} low:** (and what are the tradeoffs?)
 - Increased beam energy:**
 - You lose superficial dose.
 - Extend SSD:**
 - Mayneord F-factor works in your favor.
 - More time consuming setup.
 - Add more fields:**
 - A 3- or 4-field combination will reduce the superficial dose compared to AP/PA, at the cost of increasing complexity of treatment.

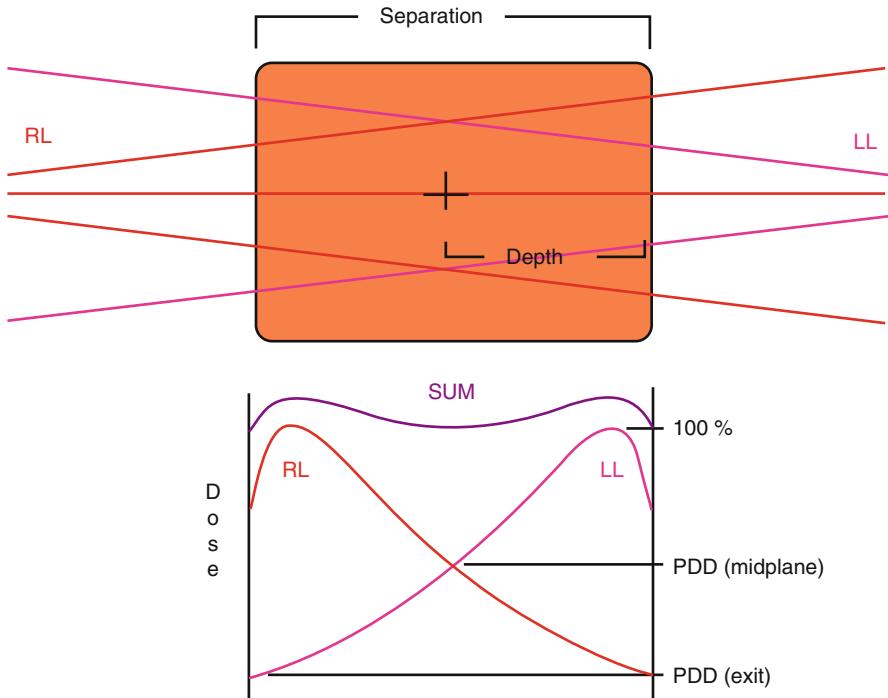


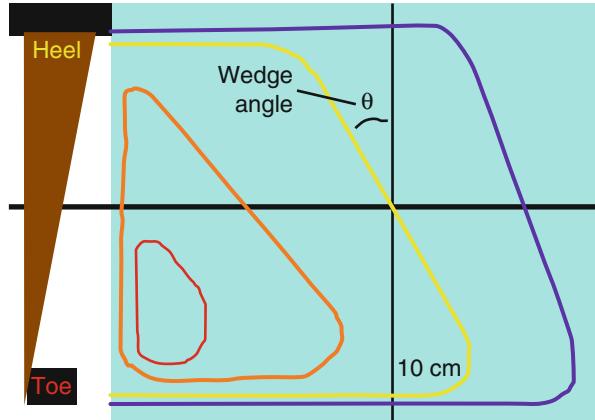
Fig. 9.4 Tissue lateral effect. In a radiation treatment with parallel opposed beams, the peripheral dose is always higher than the central dose. This effect increases with separation and decreases with beam energy.

Wedges

- A **wedge** produces a sloped isodose distribution with less dose on one side (the heel) and more dose on the other (the toe).
 - A **physical wedge** is a wedge-shaped piece of metal.
 - A **non-physical wedge** or **soft-wedge** is a software program that moves the collimator jaw in a calibrated fashion to produce a wedge-shaped dose distribution.
 - Each linac manufacturer has a unique soft wedge with a different proprietary name.
- **Physical wedges** generate **scatter**. **Non-physical wedges** do not.
 - Scatter increases dose outside the field, so any organs sensitive to very low dose are at increased risk. (such as the contralateral breast during whole breast RT).
 - This may also slightly increase surface dose.
- **Physical wedges** also cause **beam hardening**, so the angle of the isodose lines decreases at very deep depths (Fig. 9.5).

Fig. 9.5 Wedge angle.

Wedge angle is defined by the angle between the wedged isodose line and a straight line at 10 cm depth. This figure is repeated from Chapt. 7.



- **Wedge Angle** is defined as depicted above.
- **Wedge Factor (WF)** is defined as the ratio of dose with wedge to dose without wedge for the same field.
 - WF depends on beam energy, wedge angle, field size and depth.
 - **BE VERY CAREFUL WITH WF!** Any error can cause a serious dosimetric error and mistreatment.
- **Wedges** may be used with parallel opposed fields to compensate for a sloping patient contour:
 - Breast Tangents
 - Neck Lateral
 - Thorax AP/PA
- **How to judge the wedge angle?**
 - **Under-wedged** = 1 large hot spot at the heel.
 - **Over-wedged** = 2 large hot spots at the toes.
 - **Optimal wedge** = 3 small hot spots, at toes and heel (Fig. 9.6).
 - **Intentional under-wedging** can increase the superficial dose.
 - This is commonly done in larynx fields to avoid under-dosing the anterior commissure.
 - **Wedges** can improve dose homogeneity in parallel opposed fields (such as whole breast) but they are strictly inferior to compensators or field-in-field technique.
- **Wedge pairs** area very common radiotherapy beam arrangement.
 - Remember the direction of the wedges: **Heels together**. (there is no place like home) (Fig. 9.7).
 - Simple equation for **optimal wedge angle**:

$$\text{Wedge Angle} = \frac{(180 - \text{Hinge Angle})}{2} \quad (9.2)$$

Fig. 9.6 Hot spots and wedging. The “optimal” wedge angle produces three very small hot spots, while “underwedging” or “overwedging” results in much larger hot spots.

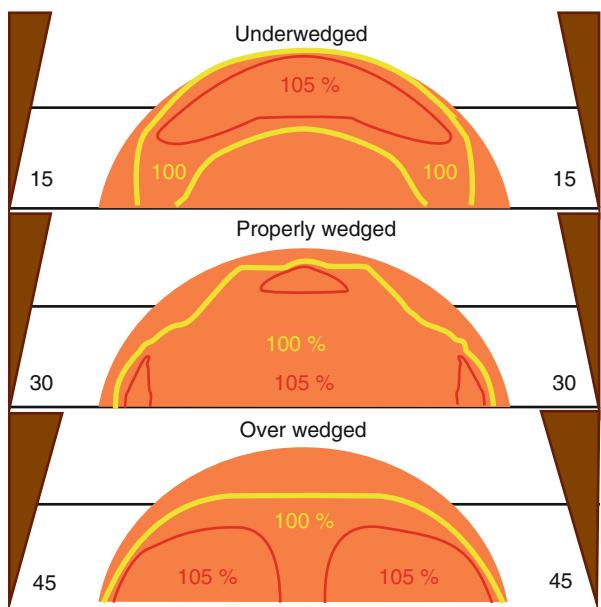
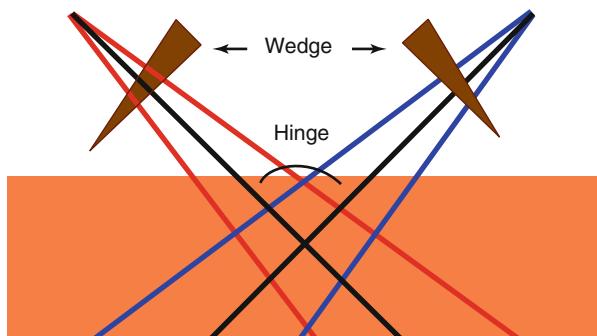


Fig. 9.7 Wedge pair. This technique is used to create a homogeneous field with non-opposed beams.



- **A Three-Field Box** (Wedged laterals and PA) uses wedges to compensate for an “unbalanced” beam (Fig. 9.8).
 - Heels toward the “unbalanced” beam.
 - Optimal wedge angle depends on many factors including beam weights. No easy equation, use computer planning to determine the angle.

Mixed Modality Therapy (Photon/Electron Mix)

- Refer to Chapt. 10 (Electron Dosimetry) for details.

Fig. 9.8 Three field box.
This technique is used to treat a box-shaped field while avoiding the use of an anterior beam. This may decrease bowel dose when treating the pelvic tumors.

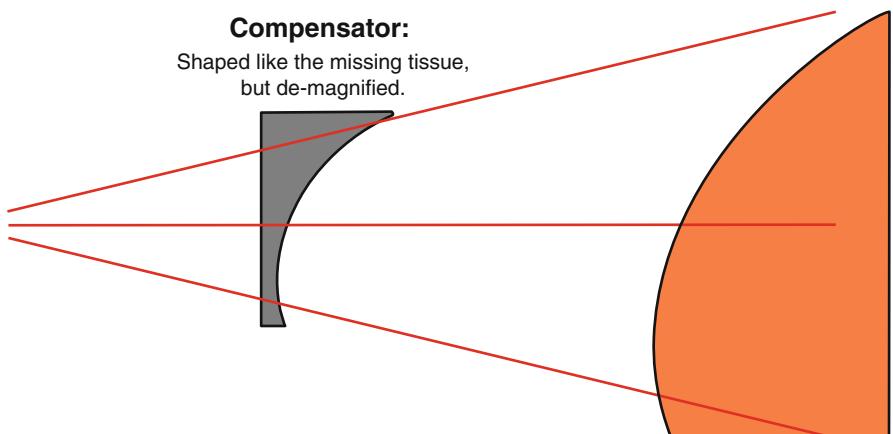
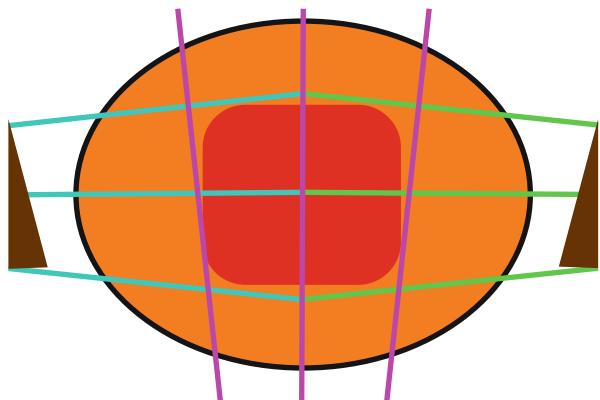


Fig. 9.9 Compensators. The purpose of a compensator is to make up for tissue deficit.

Compensators

- Compensators are used to improve dose homogeneity by compensating for tissue deficit.
 - May be made of tissue-equivalent material (ie **Lucite**) or high-density material (ie **brass, cerrobend or lead**) (Fig. 9.9).
- Compensator thickness is equal to the **tissue deficit** multiplied by the **ratio of attenuation factors**.
 - For a tissue equivalent compensator: 1 cm tissue deficit = 1 cm compensator thickness.
 - For a high density compensator: 1 cm tissue deficit = significantly less compensator thickness.

- Like blocks, compensators must be **de-magnified** by the ratio of source-to-compensator distance to SSD.
- “**Electronic compensators**” use MLCs and multiple segments to create a fluence map, approximating the dose distribution from a physical compensator.

Field Matching

- The dose at a field edge is 50 %, by definition. Therefore if two field edges were perfectly aligned there should be a uniform 100 % dose at the junction.
 - However, divergent field edges will result in cold spots and hot spots.
- The simplest way to match two fields is to use **half-beam blocks**.
 - This is known as **mono-isocentric technique** because the isocenter is placed at the field junction.
 - Limitation: You can only use half of your maximum field size (Fig. 9.10).
- Matching two parallel PA fields requires a **Skin Gap** due to divergence. Calculate using similar triangles as shown in Fig. 9.11.

$$g = d \times \frac{y_1}{SSD_1} + d \times \frac{y_2}{SSD_2} \quad (9.3)$$

- Note that if **SAD** technique is used, **SAD** may be substituted for **SSD** and the above equation is still valid.
- Beams may also be rotated to match divergence: (Fig. 9.12).

$$\theta = \left(\arctan \left(\frac{y}{SAD} \right) \right) \quad (9.4)$$

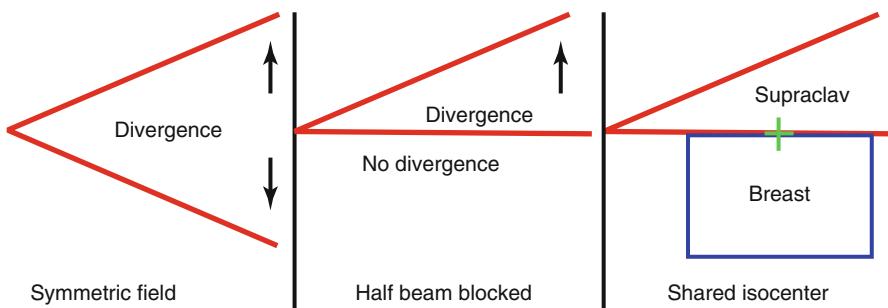


Fig. 9.10 Half-beam block. Since there is no divergence at the isocenter, the simplest way to eliminate divergence is to block half of the beam.

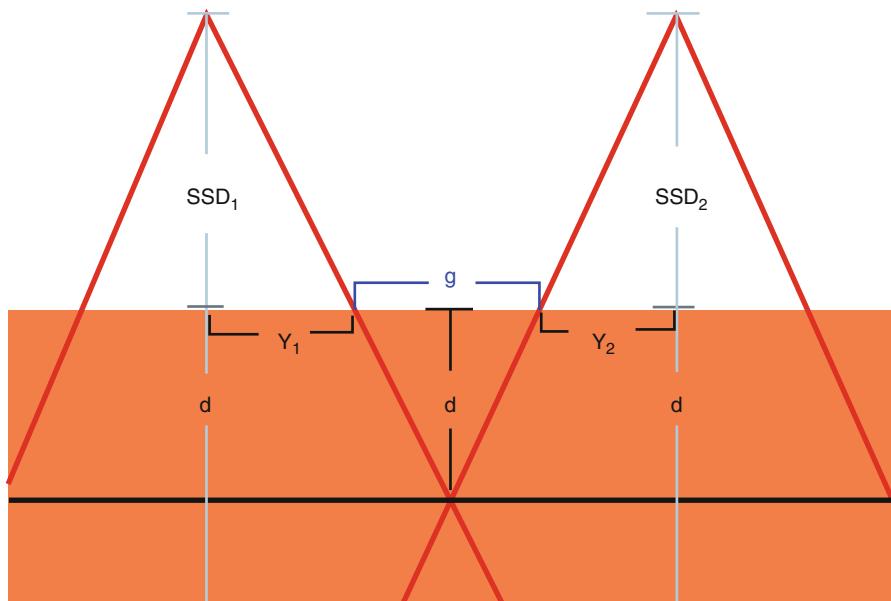
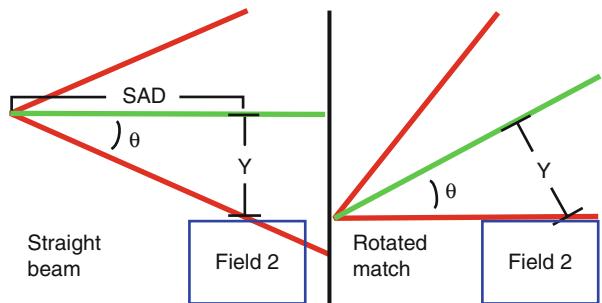


Fig. 9.11 Parallel field matching. When treating a field length much larger than your maximum field size, you will need to match two parallel fields. This will require a skin gap (g). The size of this gap may be calculated by the equation 9.8.

Fig. 9.12 Rotational match. In order to eliminate beam divergence of angle θ , the beam angle may be rotated by angle θ .



Craniospinal Field Matching (Fig. 9.13)

- Because the cranial fields are non-coplanar with the spine field, both a **collimator rotation** and **couch kick** are required.
 - Both of these rotations are performed on the brain field. The spine field remains a straight PA.
 - Collimator rotation** matches the anterior upward divergence of the spine field.

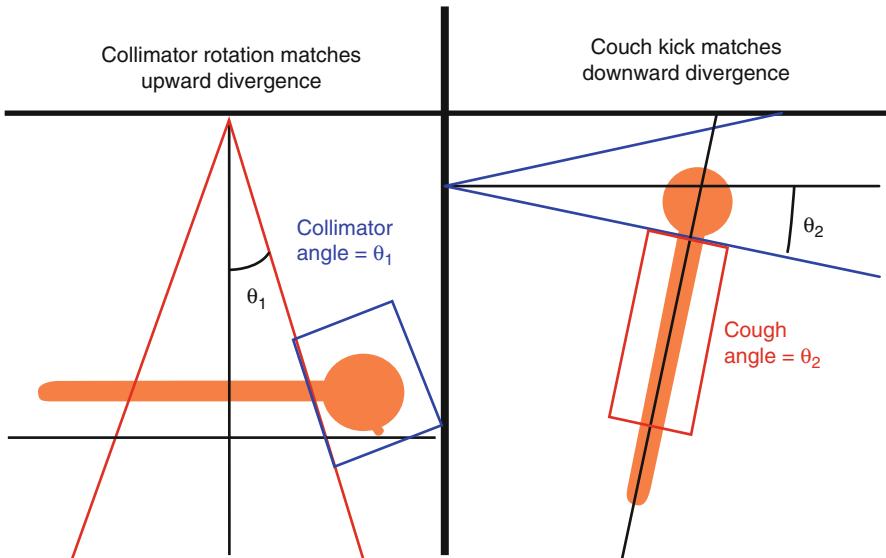


Fig. 9.13 Craniospinal field matching. A collimator rotation on the brain field is used to match the upward divergence of the spine field. A couch kick on the brain field is used to eliminate its downward divergence.

$$\theta_1 = \arctan\left(\frac{\text{spine } y_1}{SAD}\right) \quad (9.5)$$

- **Couch kick** matches the lateral downward divergence of the brain fields.

$$\theta_2 = \arctan\left(\frac{\text{brain } y_2}{SAD}\right) \quad (9.6)$$

- An **additional gap** may be used to ensure that there is no overlap. (the exact number of millimeters is institution dependent, based on personal experience and machine factors).
- **Feathering** is a dose smearing process in which the field junction is moved in between fractions so that any hot or cold spots are “smeared out” (Fig. 9.14).

Maximizing Superficial Dose

- The **skin sparing** effect of megavoltage photons is useful unless you are trying to treat the skin.
- Skin dose is a function of head design, SSD, energy, field size, medium in the beam and angle of the beam.

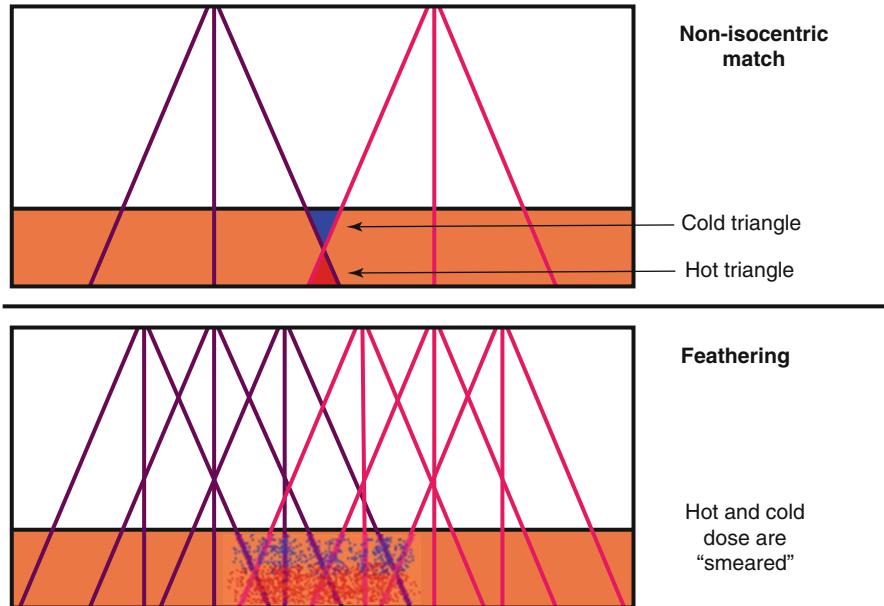


Fig. 9.14 Feathering. A non-isocentric match results in a “cold triangle” and a “hot triangle”. The field junction is moved in between fractions, causing the mismatch to smear out over a larger area. This decreases the magnitude of underdose or overdose.

- **How do you increase the superficial dose?**
 - **Low energy (Co-60, 4MV)** can increase superficial dose but many clinics do not have such low energy beams.
 - **Isocentric (SAD)** treatments usually give higher surface dose compared to **SSD** techniques.
 - Intentional **electron contamination** of a photon beam:
 - **Very large field size:** Electron scatter from collimator jaws.
 - **Beam spoiler:** A plate of material (Lexan etc.) is placed into the field to generate secondary electrons.
 - **Bolus** moves the buildup region outside the patient (Fig. 9.15).
- **Bolus materials** in order of increasing tissue-equivalence:
 - Rice bags
 - Wet gauze
 - Wet towels
 - Superflab
 - Custom wax bolus
 - Immersion in water
- **Oblivity (also known as Tangentiality):**
 - Oblique beam incidence will increase the surface dose:
 - Secondary electrons take the path of least resistance and go toward air.

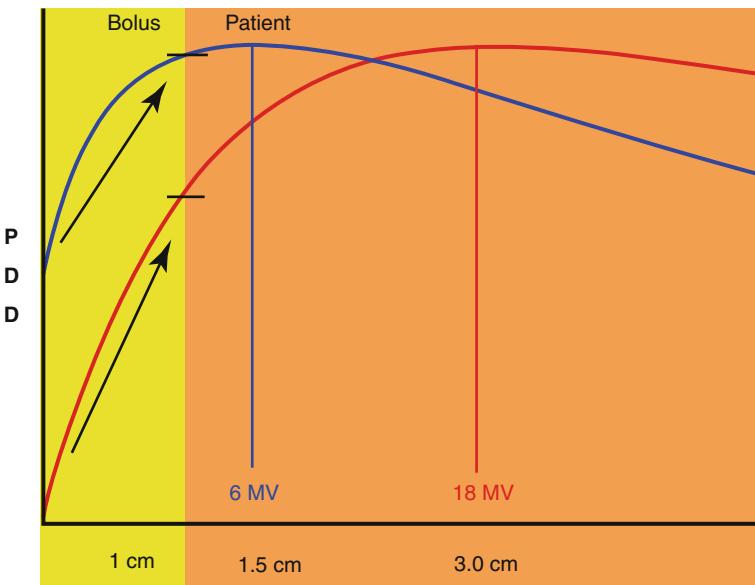


Fig. 9.15 Bolus effect. Placing bolus material on top of the skin allows the dose buildup to occur inside the bolus, increasing skin dose.

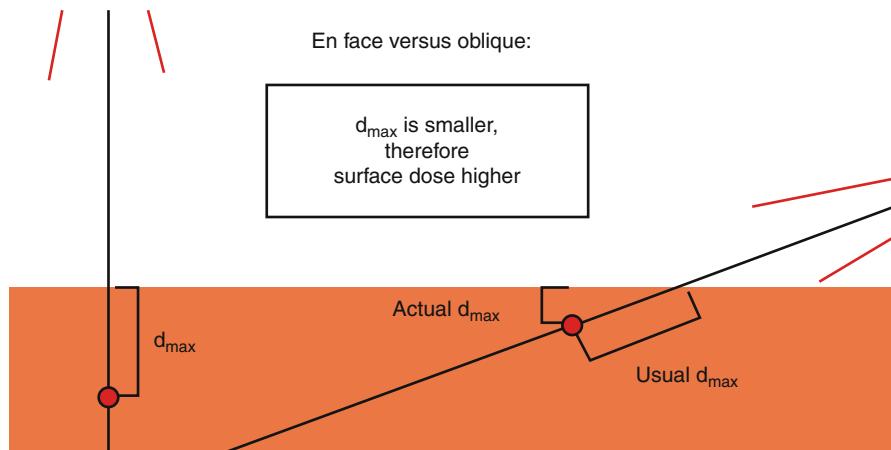


Fig. 9.16 Obliquity effect. D_{max} occurs at a shallower depth than usual, as depicted above.

- This is most relevant to breast and chestwall tangents (Fig. 9.16).

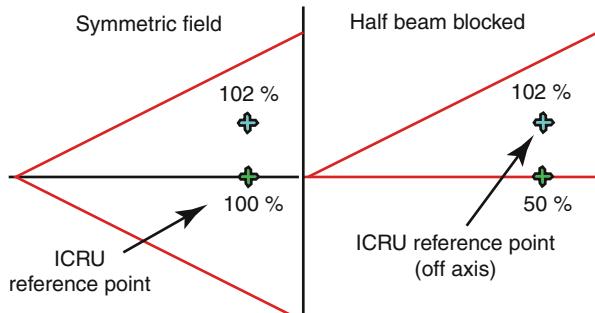
$$\text{Obliquity Factor (OF)} = \frac{\text{Surface Dose (oblique)}}{\text{Surface Dose (en face)}} \quad (9.7)$$

- Obliquity factor is one reason why the top of the head gets the worst alopecia after whole brain RT. (“reverse mohawk effect”).

Dose Specification (ICRU 50 and 62)

- ICRU 50 defined GTV, CTV, PTV, TV and IV:
 - Gross target volume (GTV): Visually, palpably or radiographically apparent disease that is intended to be treated.
 - Clinical target volume (CTV): Volume suspected to harbor microscopic (subclinical) disease. Includes “margin around GTV” and “elective CTVs”.
 - Planning target volume (PTV): CTV plus margin for setup error.
 - Treated volume (TV): Volume encompassed by an isodose line appropriate for treatment of disease. (ideally a high isodose line).
 - Irradiated volume (IV): Volume encompassed by an isodose line appropriate for normal tissue toxicity. (ideally a low isodose line).
 - Dose should be reported to an **ICRU Reference Point**, as well as minimum and maximum PTV dose.
 - **ICRU Reference Point** requirements:
 - Clinically relevant and representative of dose throughout the PTV.
 - Easy to define in an unambiguous way.
 - Located in an area where dose can be accurately calculated.
 - Located away from penumbra or steep dose gradients.
 - The **prescription dose** may be expressed as a percentage of the **reference point dose**.
 - “Prescribed to the 95 % isodose line.”
 - The **PTV volume dose** should be within 95–107 % of prescription dose. (when possible).
- ICRU 62 introduced several new concepts:
 - Internal margin (**IM**): Physiologic variations in shape and position.
 - Internal target volume (**ITV**) = **CTV + IM**.
 - Setup margin (**SM**): Uncertainty of dose calculation, therapy machine alignment and patient setup.
 - Planning risk volume (**PRV**): Organs at risk (OARs) plus **IM** and **SM**.
 - Combination of margins should be based on clinical appropriateness, do not use the same margins for every patient.
 - **CI** = Conformity index = $\text{Volume}(\text{TV})/\text{Volume}(\text{PTV})$.
 - **CI** is a simple ratio and does not guarantee that the **TV** encompasses the **PTV**.
 - The concept of **ICRU Reference Point** is not valid for **IMRT** because **IMRT** fluence and volume dose are non-homogeneous.
 - Instead of reporting an ICRU reference dose, report volume doses (DVHs for target volumes and organs at risk) instead.

Fig. 9.17 Off axis reference point. When treating with a half beam block, the isocenter can no longer be used as a dose reference point as it is on the block edge. Instead, an off axis point must be chosen as a reference point.



Dose Specification for Half Beam Blocks

- Half-beam blocks are commonly used to eliminate divergence and simplify field matching (Fig. 9.17).
- The prescription point (**ICRU Reference Point**) cannot be at the isocenter because the field edge is at isocenter.
 - The dose would be 50 % with a steep gradient.
- Therefore, the dose must be prescribed to an off-axis point.
 - Use off-axis ratio to calculate off-axis dose.
 - See Chapt. 8 for details.

Prescribing and Delivering Dose (ICRU 50/62)

- This is the standard way to prescribe and report dose to a non-IMRT plan.
- **Prescription dose** should be defined as cGy/fraction (fxn) and number of fractions. (ie, 200 cGy * 30 fxns = 6,000 cGy).
- The **prescription dose** should be expressed as a percentage of the **dose to ICRU reference point (D_{ref})**.
 - For example, “We prescribed 200 cGy/fxn to the 90 % isodose line.”
 - The dose to D_{ref} can be calculated as follows:

$$D_{ref} = \frac{\text{Prescription Dose}}{\text{Prescription IDL}} \quad (9.8)$$

- Ex: 200 cGy/fxn prescribed to the 90 % IDL means that $D_{ref} = 222$ cGy/fxn.
- Each beam should contribute a portion of the **reference dose**, and this defines the **beam weight**.

$$D_{ref} = D_1 + D_2 + \dots + D_i$$

$$D_i = D_{ref} \times \frac{\text{Beam Weight (i)}}{\text{Total Beam Weight}} \quad (9.9)$$

- **Ex:** $D_{ref} = 222 \text{ cGy}$, therefore:
 - To treat with equally weighted AP/PA:
 - $D_{AP} = 111 \text{ cGy}$, $D_{PA} = 111 \text{ cGy}$.
 - To treat with equally weighted four-field box:
 - $D_{AP} = 55.5 \text{ cGy}$, $D_{PA} = 55.5 \text{ cGy}$.
 - $D_{Rt\ Lat} = 55.5 \text{ cGy}$, $D_{Lt\ Lat} = 55.5 \text{ cGy}$.
- Finally, calculate **MU** for each beam to deliver the desired dose:
 - **Ex:** $D_{AP} = 111 \text{ cGy}$, $D_{PA} = 111 \text{ cGy}$:
 - If the AP beam delivers 1.0 cGy/MU , it needs 111 MU .
 - If the PA beam delivers 1.11 cGy/MU , it needs 100 MU .

Dose Delivery Accuracy and Precision

- Linacs are generally calibrated to $\sim 2 \text{ mm}$ and 2% precision, except for stereotactic setups which are **1 mm**.
- Please refer to Chapt. 13 for details on linac precision.

Rules of Thumb

- **Irregular patient contour:**
 - **Tissue deficit** moves IDLs **away from surface**.
 - **Tissue surplus** moves IDLs **toward surface**.
- **High density structures** (bone, metal):
 - **Adjacent hot spot** due to secondary electrons and scatter.
 - **Distal cold dose** due to attenuation.
- **Low density structures** (lung, air):
 - **Adjacent cold spot** due to loss of secondary electrons and scatter. (buildup effect).
 - **Distal hot beam** due to decreased attenuation.
- **Tissue Lateral Effect:**
 - Lateral hot spots with any parallel opposed plan.
 - Increases with separation, decreases with beam energy.
 - If it is too hot, add more beams.
- **Wedges:**
 - **Toes hot = over-wedged**.
 - **Heel hot = under-wedged**.
 - **Wedge Pair:**

$$Wedge = \frac{(180 - Hinge)}{2}$$

- **Matching:**
 - **Skin gap = similar triangles**, use SSD if SSD setup and SAD if SAD setup.
 - **Angled match:**
- **Craniospinal:**
 - **Collimator rotation** matches upward divergence of spine fields.
 - **Couch kick** matches downward divergence of brain fields.
- **Oblique fields:** Decreased d_{\max} , increased surface dose.

10

Dosimetry of Electron Beams

Definitions

- **D** = Dose
- **d** = Depth (sometimes called z)
- **D_{max}** = Maximum dose to a point, defined as = 100 %
- **d_{max}** = The depth of **D_{max}** (sometimes called **z_{max}**)
- **SSD** = Source-to-surface distance
- **PDD** = Percent depth dose
- **MU** = Monitor Units
- **K** = Output Factor
- **ISF** = Inverse Square Factor
- **OF** = Obliquity Factor
- **R₉₀** = Distance of 90 % dose from surface



Fig. 10.1 Range and Path Length: Because range is measured in a straight line, it is always much smaller than path length.

- R_{50} = Distance of 50 % dose from surface
- R_p = Practical range
- R_{\max} = Maximum range

Dose: Hand Calcs

$$\text{Dose} = MU \times K \times ISF \times PDD \times OF$$

$$MU = \frac{\text{Desired-Dose}}{K \times ISF \times PDD \times OF} \quad (10.1)$$

- **K = Output Factor = 1.0 cGy/MU** for standard electron cone and large field size.
 - This makes electrons very easy to calculate.
 - **K** may change with electron cone (applicator factor) and with small cutouts (field size).
 - When in doubt, **K** should be measured for a given applicator-cutout combination. (empiric **K**).
 - **ISF** is different from photons due to **effective SSD** – this is discussed later in the chapter.
 - **PDD** is a prescription isodose line, for example “we prescribed **200 cGy** to the **90 %** isodose line.”
 - **OF = Obliquity Factor**, an increase in dose that occurs with oblique beam entry.

Electrons: Range

- Electrons are **charged particles**. Therefore, as they interact with medium (tissue, water, etc.) they slow down and lose energy, eventually coming to a stop.
 - Refer to Chapt. 5 for more details on charged particle interactions.
- The path of an electron can be measured two different ways: (Fig. 10.1).
 - **Range (CSDA)**: The straight-line distance traveled by the electron, equal to **clinical depth**.
 - **Path length**: actual length of the path, always much longer than Range.
 - Imagine pulling at a spring until it stretches out straight. Its length would increase a lot.

- Each electron in a beam takes a unique path, so range varies from electron to electron.
 - Therefore, an electron beam gives rise to multiple different **Range** values as shown in Fig. 10.2.

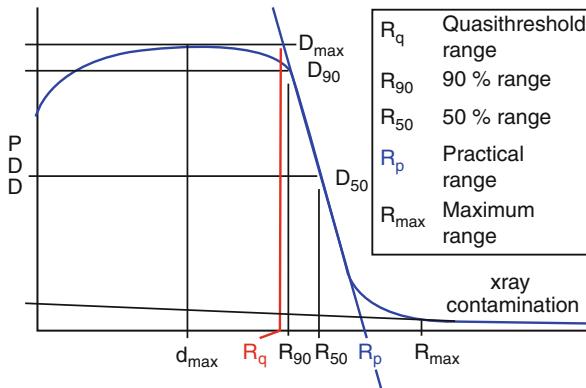


Fig. 10.2 Electron range metrics. R_{90} and R_{50} are defined by the depth of the 90 and 50 % isodose lines. A straight line is drawn between R_{90} and R_{50} and used to calculate extrapolation values. Extrapolating back to 100 % gives the R_q , while extrapolating forward to 0 % gives the R_p . R_{\max} is the maximum range of electrons, after which dose is entirely due to Bremsstrahlung x-rays.

Electrons: Shape of Pdd Curve

- Electrons are directly ionizing so there is no charged-particle buildup like with photons.
- So, why is not surface dose 100 %? (it is more like 75–95 %).
 - **Multiple scattering** causes an increase in dose at depth, so the max dose is higher than the surface dose (Fig. 10.3).
- After d_{\max} , dose decreases as electrons reach the end of their range (R_{50} , R_p , R_{\max}).
 - Low energy electrons have a very sharp distal dose fall-off, while higher energy electrons have a more gradual distal fall-off (Fig. 10.4).
- Beyond R_{\max} , dose decreases to a low but non-zero number.
 - **Bremsstrahlung X-rays** (<5 % of electron dose).
 - This dose increases with electron energy and with materials in the electron beam. The **scattering foil** is a major contributor to bremsstrahlung.
 - Bremsstrahlung dose is greatest at central axis and less at field edges.

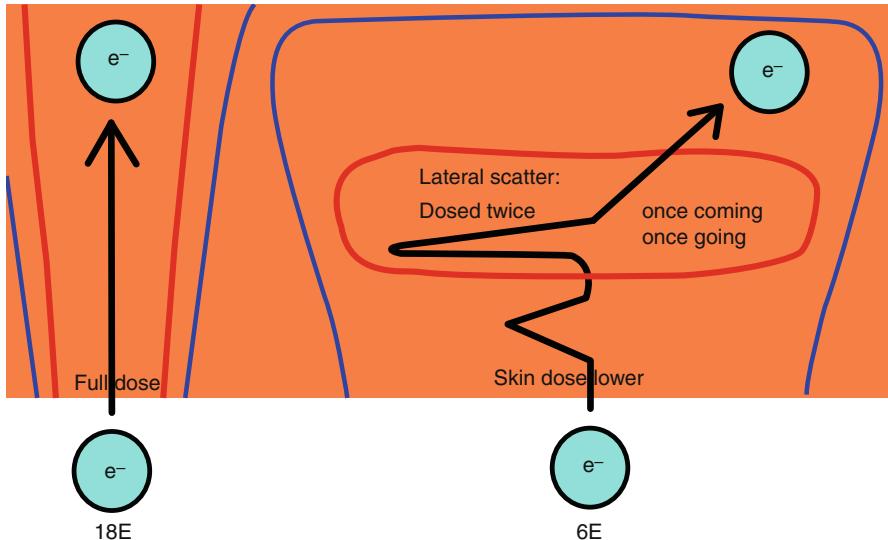
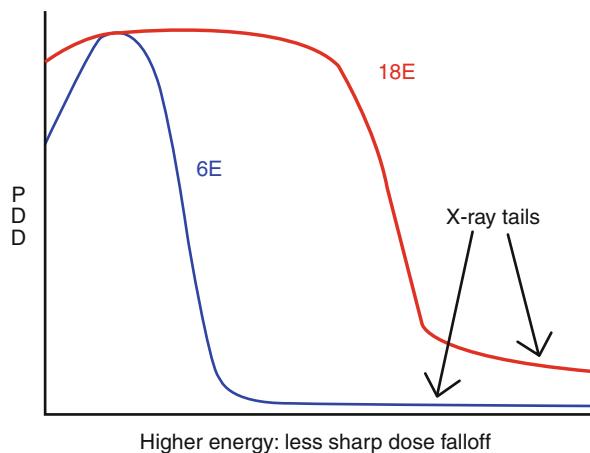


Fig. 10.3 Multiple scatter and depth dose. Scatter causes a dose buildup effect at a small depth ($\sim 1\text{--}2$ cm) from the surface. Higher energy electrons scatter less, so surface dose increases with energy, unlike with photons.

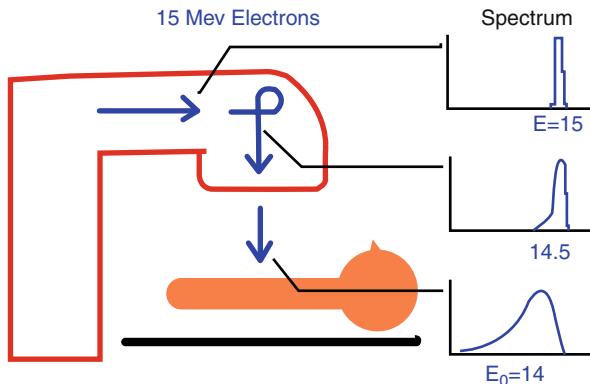
Fig. 10.4 Dose Falloff from Electrons. Higher electron energies have a longer range, but they suffer from a less sharp distal dose falloff and a larger Bremsstrahlung X-ray “tail”.



Electrons: Energy Spectrum and Range

- The nominal energy of an electron beam is equal to the electron energy **in the accelerator**. This is a mono-energetic value.
 - So “**15 MeV electrons**” have exactly **15 MeV** just before passing through the window of the waveguide.

Fig. 10.5 Electron beam spectrum. Electrons exit the waveguide with a single well-defined energy, but their energy begins to “straggle” even inside the linac head. Electron energy at the patient’s surface, E_0 , is slightly lower than the nominal energy. Energy spectrum is shown at various locations.



- Electrons lose energy in the scattering foil, monitor chamber, and while traveling through air.
 - This causes “energy straggling”, resulting in a poly-energetic spectrum (Fig. 10.5).
- **E = Nominal Energy** (i.e., 15 MeV).
- **E_0 = Mean energy at patient surface = $2.33 \text{ MeV} * R_{50}$** (by definition).
 - E_0 is the primary measure of **beam quality** for electrons.
 - This number is always slightly less than the accelerator energy. **15 MeV** electrons may have an $E_0 = 14 \text{ MeV}$.
- Within the patient (or phantom), mean electron energy decreases linearly with depth z, as described by **Harder's equation**:

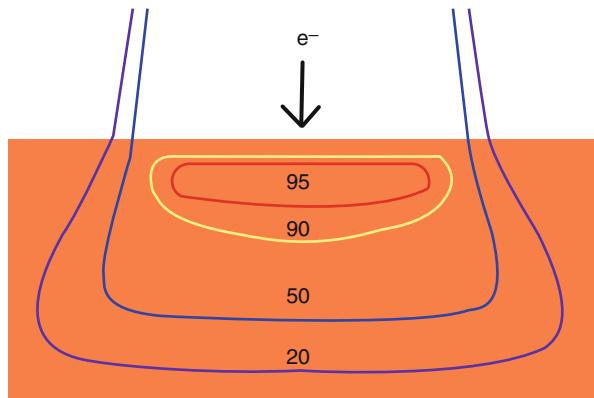
$$E_Z = E_0 \times \left(1 - \frac{z}{R_p}\right) \quad (10.2)$$

- **Approximate Electron Range vs. Nominal Energy (E):**
 - R_p (practical range) $\sim = E/2 \text{ cm}$
 - This is a very reliable number.
 - R_{80} (range of 80 % IDL) $\sim = E/2.8 \text{ cm}$
 - Different sources quote different numbers.
 - R_{90} (range of 90 % IDL) $\sim = E/3.2 \text{ cm}$
 - Different sources quote different numbers.

Electrons: Isodose Shape and Energy Selection

- Electron IDLs have a characteristic shape due to scatter (Fig. 10.6).
- Clinical energy selection should be based on target volume coverage by the X % isodose line.
 - **Ex:** “9 MeV electrons prescribed to the 90 % IDL”.

Fig. 10.6 Electron isodose lines. High isodose lines (95, 90 %) “pull in” at depth, while low isodose lines (50, 20 %) “bow out” at depth.



- If CTV coverage is not adequate, there are two main ways to improve it:
 - Prescribe to a lower IDL:
 - Drawback = hotter hot spot (D_{max}).
 - Select a higher electron energy:
 - Drawback = longer range, more dose to deep normal tissues.

Electron Field Shaping: Cones and Cutouts

- Electrons spread out as they pass through air. Therefore, **collimator jaws** are **useless** for setting electron field size.
- Electron applicators (“**cones**”) extend from the linac head to very near the patient, decreasing the air gap.
 - Air gaps between **cone** and patient result in a poorly defined field edge. (wide penumbra).
- The **electron output factor (K)** depends on the electron cone but should be very close to 1.0.
 - Typically, field size is determined by **electron cone** size, not collimator jaw settings. (the jaws are held in the same position).
 - If the collimator jaws change position, **K** will change dramatically due to **collimator scatter**.
- Custom blocks (“**cutouts**”) should be thick enough to completely stop the electrons.
 - The closer the block is to the skin (less air gap), the sharper the field edge.
 - Although there is no forward scatter (the electrons are completely stopped), there is very high side-scatter and back-scatter.
 - If a block is touching the patient, it should be coated with wax to avoid over-dosing the patient with backscatter electrons.

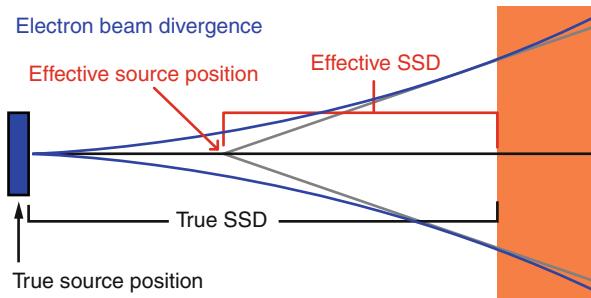


Fig. 10.7 Electron Effective SSD. Because electrons are negatively charged, they repel each other as they travel through air. As a result, electron beams diverge more than they would based on geometry alone. They diverge as if they had a shorter SSD, which is known as the “effective SSD”.

Electron Field Size Effects

- **Field Size effects on Output and PDD:**
 - If the field radius exceeds the practical electron range ($r > R_p$), it does not matter how big it is.
 - The electrons from the edge of the field cannot reach the field center, so they do not affect it.
- **This makes electrons very easy to calculate:**
 - **1MU = 1 cGy at d_{max} , 100 SSD.**
- **As the field size shrinks to $< R_p$:**
 - Some of your electrons escape out of the field, especially at depth.
 - K decreases: You need more beam to give the same dose.
 - d_{max} decreases: The dose becomes more superficial.
 - PDDs decrease with depth.
 - **Surface dose** increases.
 - R_p is unchanged because electron energy is unchanged.
- In a complex shaped field, **any parts of the field narrower than R_p may be underdosed.**
 - Therefore, electron fields require more margin from CTV to block edge compared to photon fields.
 - Approximately **2 cm** for electrons compared to **8 mm** for photons.
- SSD and Effective SSD (aka virtual SSD) (Fig. 10.7).
 - Electron divergence can be extrapolated to a position known as the **effective (“virtual”)** source.
- For **extended SSD**, the inverse-square factor must be calculated with **effective SSD** rather than true SSD.

$$ISF = \left(\frac{SSD_{eff}}{SSD_{eff} + \Delta SSD} \right)^2 \quad (10.3)$$

- **Example:** A 6MV electron beam with a **true SSD** of **100 cm** has an **effective SSD** of **80 cm**.
 - What is the **ISF** at **SSD = 110 cm**?
 - $ISF = (80/90)^2 = 0.790$
 - What is the **ISF** at **SSD = 125 cm**?
 - $ISF = (80/105)^2 = 0.580$

Obliquity Effects

- Obliquity greatly alters electron dose distribution:
- **Decreased d_{max}** and **increased surface dose**.
 - This is the same effect as in photons but much stronger.
- **Increased dose at D_{max} :**
 - This is different from photons.
 - The **obliquity factor (OF)** is a measure of how much the dose increases with oblique angles.

$$OF(\theta) = \frac{\text{Dose at oblique angle } \theta}{\text{Dose en face}} \quad (10.4)$$

Loss of normal PDD curve:

- Oblique angles decrease the depth dose, but do not change the electron range (Fig. 10.9).
- This is usually undesirable, and tangential electron fields are avoided in most standard treatments. However, they are desirable for total skin electron therapy.

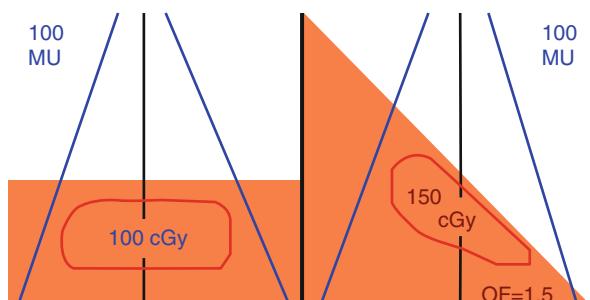


Fig. 10.8 Electron obliquity effects. Unlike photons, electrons deliver much higher dose to oblique surfaces than to flat ones.

Fig. 10.9 Electron tangent PDD curve. High obliquity results in a loss of the steep distal fall-off. Instead, dose fall-off starts at a shallow depth and continues all the way to R_p .

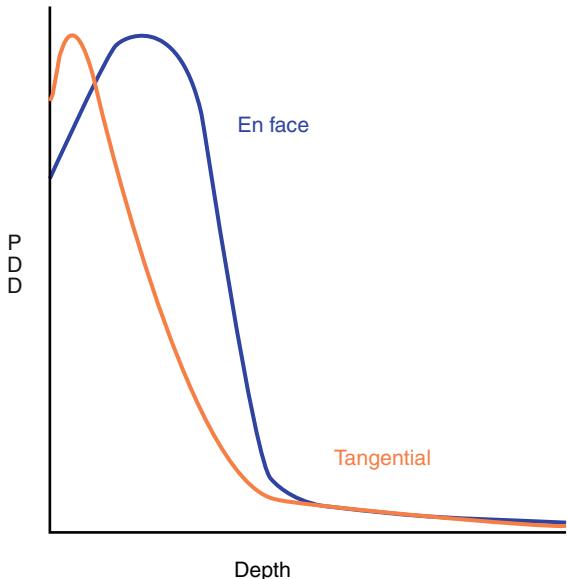
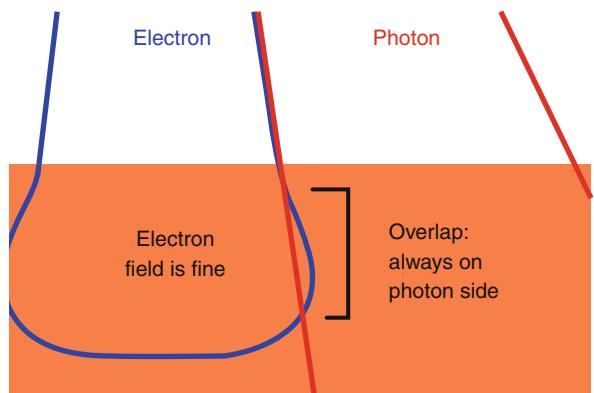


Fig. 10.10 Electron-Photon Match. When two fields are directly juxtaposed, electrons will “bow in” to the photons and cause a hot spot on the photon side.



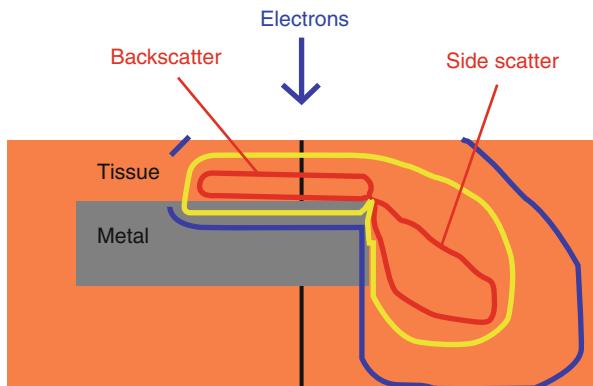
Electron Field Matching

- **Electron-electron Match:**
 - Both electron fields will bow into each other and cause severe hot spots.
Avoid if possible.
- **Electron-Photon Match:** (Fig. 10.10)
 - A skin gap may be used to limit this hot spot.
 - No easy equation - > use treatment planning system.
 - Like all skin gaps, this results in a superficial cold spot.
 - Gantry rotation may also be used to limit this hot spot.
 - Can rotate the electron field away from the photon field, or vice versa.
 - This also results in a superficial cold spot.

Electrons and Inhomogeneities

- Range of electrons is determined by **electron density**. (roughly proportional to mass density, Hounsfield Units).
 - Electrons have a shorter range in high-density tissue, and a longer range in low-density tissue.
- Equivalent thickness = thickness * CET**
- Coefficient of equivalent thickness (CET)** = roughly equal to electron density.
 - $CET(\text{lung}) = 0.25$
 - 1 cm of lung will have the same effect on an electron beam as 0.25 cm of water.
 - $CET(\text{bone}) = 1.6$
 - 1 cm of bone will have the same effect on an electron beam as 1.6 cm of water.
- Edge effects:** due to differential scatter (Fig. 10.11).
 - “Electrons take the path of least resistance”:** This rule of thumb states that the hot spot always occurs in the lower density medium.
 - When tissue abuts metal, tissue is overdosed.
 - When tissue abuts air, the air is overdosed and tissue may be underdosed.
 - Beware of electron inhomogeneity effects around air cavities. This may be pronounced in head and neck plans.

Fig. 10.11 Electron Edge Effects. A high-density structure such as metal will cause severe scatter in an electron field. Backscatter results in a proximal hot spot, and side scatter results in a “rabbit ear” shaped hot spot.

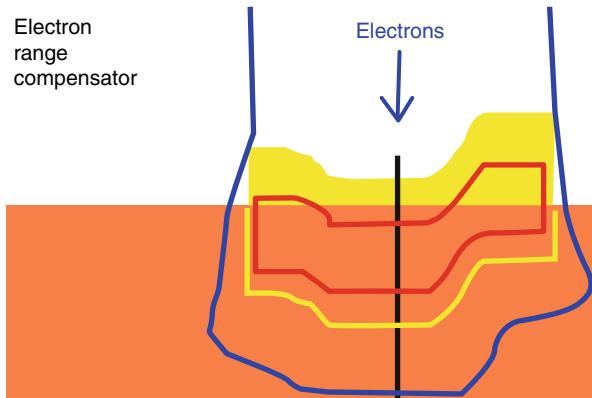


Bolus

- Just like with photons, bolus increases surface dose.
- However, bolus **also** decreases the range of electrons.
 - Ex:** 12 MeV electrons have an 80 % IDL at 4 cm. With 0.5 cm bolus the 80 % IDL is at 3.5 cm.

- Irregular shaped bolus may be used to smooth out obliquities and irregular patient contours.
- Irregular shaped bolus may also be used as a “range compensator” as shown in Fig. 10.12.

Fig. 10.12 Electron Range Compensator. Placing bolus material in an electron field not only changes the depth dose, it changes the range in tissue. This may be used to shape the distal edge of the radiation field.



Beam Spoilers

- A beam spoiler degrades the energy (range) of electrons.
 - This pulls in the isodose lines just like adding bolus.
- It also adds some surface dose, but less than bolus (because it is not actually touching the patient).

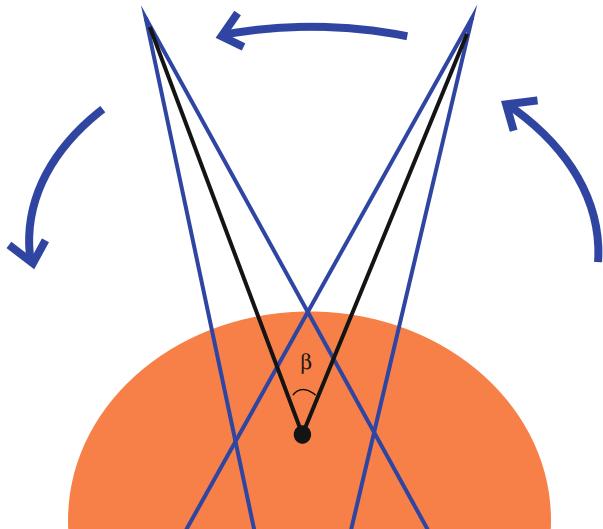
Electron Arcs

- Sometimes used for chestwall irradiation.
- Very complicated to calculate.
- Most important feature is the **characteristic angle (β)**. This determines the PDD and amount of photon contamination (Fig. 10.13).
- **Larger β** = less photon contamination = **better**.
- **Smaller β** = more photon contamination = **worse**.
- Blocking (cutouts) may be placed on skin.
 - Arc is started and stopped **past** the blocks to ensure a uniform dose.

Total Skin Electron Irradiation (TSEI)

- Many different techniques exist for TSEI.
- Extended SSD with matched upper and lower fields.
 - Pointing beam up or down minimizes photon dose, as central axis is away from midline.

Fig. 10.13 Electron arc irradiation. The characteristic angle β is defined by the amount of arc rotation required to make two directly abutting but non-overlapping fields. Larger values of β are desirable.



- **Multiple body positions** (at least 6) to ensure uniform skin coverage.
 - **1 cycle = 6–12 fields = ~300 cGy.**
 - **2–3 fractions/cycle.**
 - **1–2 cycles/week.**
- **Beam spoiler:** degrades energy, so less penetration into deep tissues. Also generates scatter to increase skin dose.
- Use patient dosimetry (**diodes** etc.) for skin folds (groins, buttocks, etc.) and scalp.
 - May need to boost any areas that are under-dosed.
- May use lead shielding as needed (eyes, fingernails, etc.).

Rules of Thumb

- **Electron fields are easy to calculate:**
 - **1 MU = 1 cGy at the 100 % isodose line (D_{max}) for standard jaw settings, large field size and no obliquity.**
 - For small field size, **output factor (K)** should be measured.
- **For electrons of nominal energy = E MeV:**
 - R_p (practical range) $\sim = E/2 \text{ cm}$
 - R_{80} (range of 80 % IDL) $\sim = E/2.8 \text{ cm}$
 - R_{90} (range of 90 % IDL) $\sim = E/3.2 \text{ cm}$
- **Surface Dose increases with energy:**
 - **~70–80 % at 6 MeV**
 - **> = 95 % at 18+ MeV**

- **Effective (virtual) SSD is shorter than true SSD.**
 - Inverse-square factor should use effective SSD.
- **“Electrons bow into photons.”**
 - The hot spot is always on the photon side of match.
- **“Electrons take the path of least resistance.”**
 - At a density interface (such as metal next to tissue), a hot spot will appear in the lower density structure.
- **Obliquity** = hot spot near surface (**obliquity factor**), higher surface dose, less sharp distal falloff.
 - Avoid tangential electron fields.

11

Physics and Dosimetry of Brachytherapy

Definitions

- AAPM TG-43: Task Group Report 00 of the American Association for Physics in Medicine.
- **Activity (A)**: Amount of radioactive material.
 - Units: 1 Curie (Ci) = 3.7×10^{10} Becquerel (Bq)
- **Radius (r)**: aka distance, depth.
- **Dose Rate (\dot{D})**: not to be confused with total dose (**D**)
- **Initial Dose Rate (\dot{D}^0)**
- **Exposure Rate Constant (Γ)**, aka **Gamma Constant**: Exposure rate per millicurie of isotope at 1 cm distance.
- **Exposure Rate (\dot{X}) = ΓA**

- **Milligrams Radium Equivalent (mgRaEq):**
 - $1 \text{ mgRaEq} = 8.25 \text{ R} \cdot \text{cm}^2 \cdot \text{h}^{-1} \cdot \text{mg}^{-1}$ exposure rate
- **Air kerma strength (S_K):** Kerma (kinetic energy released in matter) measured in air @ 1 m.
 - $1 \text{ U} = 1 \text{ cGy} \cdot \text{cm}^{-2} \cdot \text{h}^{-1} = 1 \mu\text{Gy} \cdot \text{m}^{-2} \cdot \text{h}^{-1}$
 - Proportional to **Activity**.
- **Dose rate constant (Λ):** Dose rate to water for 1U air kerma strength at 1 cm ($\text{cGy} \cdot \text{cm}^{-2} \cdot \text{h}^{-1}/\text{U}$).
- **Low Dose Rate (LDR): 0.4–2 Gy/h**
- **Medium Dose Rate (MDR): 2–12 Gy/h**
- **High Dose Rate (HDR): >12 Gy/h**
- **Pulse Dose Rate (PDR):** HDR fractionated over time to approximate LDR dose rates.
- Details of the units and activities along with dosimetry can be found in **AAPM TG-43**.

The Historical Role of Radium

- ^{226}Ra brachytherapy was used for many decades prior to ^{60}Co , ^{137}Cs , ^{192}Ir , or megavoltage X-rays.
- **Radium sources** consist of radium chloride powder placed within a double-sealed platinum tube.
- ^{226}Ra comes to a **secular equilibrium** with ^{222}Rn and its decay products by emitting alpha rays.
 - This results in accumulation of multiple radioactive daughter nuclides emitting alphas, betas and gammas.
 - The encapsulation is designed to absorb everything except for the gammas.
 - Average photon energy **0.83 MeV** (range 0.18–2.29 MeV).
- ^{226}Ra is no longer used because of the risk of radon gas leakage and other safety concerns.
- Many LDR brachytherapy systems are based on “milligrams radium equivalent” (**mgRaEq**).
 - For a source of activity A and gamma constant Γ :

$$\text{Radium Equivalent (mCi)} = \frac{\Gamma A \times mg \times Ra \times Eq}{8.25 R/cm^2/hr} \quad (11.1)$$

Commonly Used Therapeutic Radionuclides

- Common sealed source nuclides include ^{226}Ra , ^{192}Ir , ^{137}Cs , ^{125}I , ^{103}Pd , and ^{60}Co .
- Common unsealed source include ^{131}I , ^{90}Y , and ^{32}P .

- Nuclides are chosen for their desired characteristics such as type of radiation, half-life, energy, etc.
 - ^{125}I and ^{103}Pd emit very low energy characteristic X-rays (22–28 keV); this gives them a very steep dose fall-off.
 - The other sealed source nuclides are high energy gamma emitters.
 - Most unsealed source nuclides emit short range beta radiation with a short half-life, thus limiting the risk of systemic and environmental contamination.
- Refer to **Appendix B** for a list of nuclides used in imaging and therapy.

Production of Radionuclides

- **Naturally Occurring:** Byproducts of uranium decay, these nuclides can be mined from the Earth.
 - ^{226}Ra , ^{223}Ra , ^{222}Rn among others.
- **Fission Byproduct:** Obtained from nuclear reactors.
 - ^{137}Cs , ^{131}I , ^{90}Sr among others.
- **Neutron Bombardment:** Creates beta-minus emitters. Cyclotrons can produce high intensity proton and neutron flux. Nuclear reactors can produce very high intensity neutron flux.
 - ^{198}Au , ^{192}Ir , ^{153}Sm , ^{125}I , ^{103}Pd , ^{89}Sr , ^{60}Co , ^{32}P among others.
- **Proton Bombardment:** Creates beta-plus emitters, often used for PET imaging. Protons are accelerated by a cyclotron.
 - ^{123}I , ^{18}F , ^{15}O , ^{11}C , ^3H among others.
- **Daughter Elution:** A longer-lived mother nuclide (“cow”) decays into a shorter-lived daughter nuclide (“milk”) that can be repeatedly eluted for clinical use. This is an example of transient equilibrium.
 - ^{90}Y , $^{99\text{m}}\text{Tc}$ among others.

Sealed Source Properties

- Classically, source strength is measured as activity (Ci or Bq) or milligrams radium equivalent (mgRaEq).
 - Two sources with the same **Activity (Ci)** may emit very different amounts, energies and types of radiation due to **encapsulation** and **filtration**. Hence, their dose rate may be different.
- Source strength is specified as air kerma rate at a distance of 1 m as mentioned above. ($1 \text{ U} = 1 \mu\text{Gy/h/m}^2$).

Unsealed Source Properties

- Unsealed sources do not have to worry about encapsulation so they simply are specified as **nuclide**, **activity**, and **chemical formulation**. (ie elemental vs. colloidal vs. antibody-bound).

- An unsealed source will have separate **physical** and **biological** half-lives.
 - **Effective half-life equation:**

$$t_{\text{eff}} = \frac{(t_{\text{biol}} \times t_{\text{phys}})}{(t_{\text{biol}} + t_{\text{phys}})} \quad (11.2)$$

- See Chapt. 2 for more half-life equations.

Implant Instrumentation and Technique (Ircu-38 and 58)

- An **intracavitary implant** is placed within an **applicator** such that the sources do not directly contact tissue.
 - Tandem and ovoids (ie, Fletcher-Suit)
 - Ring and tandem
 - Vaginal cylinder
 - Partial breast balloon brachytherapy
 - Endobronchial
- An **interstitial implant** is inserted into tissue.
 - Template-based catheters
 - Free-hand catheters
 - Permanent seeds
- **Other types**
 - Surface applicator (eye plaque, intraoral, skin)
 - Intravascular
 - Intraoperative
- **Unsealed sources** may be given systemically (oral, intravenous) or injected in a specific location (intracystic, intra-articular).

Brachytherapy Dose Rate

- **LDR** implants deliver dose over days (temporary) to months (permanent).
 - Temporary LDR implants: Typical dose rates are approx. ~60 cGy/h or 1 cGy/min.
 - Permanent implant dose rates are much lower, but total dose is very high such as in prostate seed implants (120–145 Gy).
 - Normal tissue sparing effect due to sublethal damage repair (SLDR), see Chapt. 29 for radiobiology details.
- **HDR** implants typically deliver dose over a few minutes, with typical dose rates >50 cGy/min (>3,000 cGy/h).
 - Like external beam RT, fractions are given over a time scale shorter than that of DNA repair.
 - Computer-controlled **HDR** afterloaders allow for detailed optimization of dwell positions and times.

- Geometric normal tissue sparing is used to make up for loss of biological normal tissue sparing.
- **PDR** is a method that uses an **HDR** afterloader to deliver fractions every hour or so, to approximate **LDR** dose rates.

Permanent Implants: Decay Equations

- Dose is delivered over the entire life of the isotope, so activity will decay with time:

$$\text{Activity: } A(t) = A_0 e^{-\lambda t} \quad (11.3)$$

$$\text{Half-Life: } t_{1/2} = \frac{0.693}{\lambda} \quad (11.4)$$

$$\text{Mean Life: } \tau = \frac{1}{\lambda} = 1.44 \times t_{1/2} \quad (11.5)$$

- Since dose rate is proportional to activity:

$$\text{Dose Rate: } \dot{D}(t) = \dot{D}_0 e^{-\lambda t} \quad (11.6)$$

- Total dose is equal to dose rate * mean life:

$$\text{Total Dose: } D = \dot{D}_0 \tau = 1.44 \times \dot{D}_0 \times t_{1/2} \quad (11.7)$$

Beta Emitter: Simple Dose Calc

- If a beta emitter is evenly distributed in a mass of tissue and never leaves the tissue, dose can be calculated very easily:
 - Average beta energy $\bar{E} = \text{max beta energy}/3$
 - **1 eV = 1.6×10^{-19} J**
 - **M** = mass of tissue
 - **1 Gy = 1 J/kg**

$$\text{Dose Rate: } \dot{D} (\text{Gy/s}) = \frac{A(Bq) \times \bar{E}(J)}{M(\text{kg})} \quad (11.8)$$

$$\text{Total Dose: } D = \dot{D}_0 \tau = 1.44 \times \dot{D}_0 \times t_{1/2}(s)$$

Photon Emitters in Air: Exposure and Dose Rate

$$\text{Exposure Rate (air): } \dot{X} = \frac{\Gamma \times A}{r^2} \quad (11.9)$$

- Gamma (Γ) is called the **exposure rate constant** for a good reason, it can directly calculate exposure rate in air.

$$\text{Dose Rate (air): } \dot{D} = f \times \dot{X} \quad (11.10)$$

- f = f-factor (cGy per R conversion factor)

Photon Emitters in Water: Γ Based Dose Calc

- Assumes an isotropic (equal in all directions) dose distribution.

$$\dot{D}(r) = \frac{f \times \Gamma \times Aa \times (r)}{r^2} \quad (11.11)$$

- Gamma (Γ) measures exposure rate in air
- f = f-factor (R-to-rad conversion factor)
- A = Activity (Ci)
- $a(r)$ = attenuation function
 - This accounts for photon attenuation by the medium.
 - This is very similar to the radial dose function, $g(r)$. See section below.

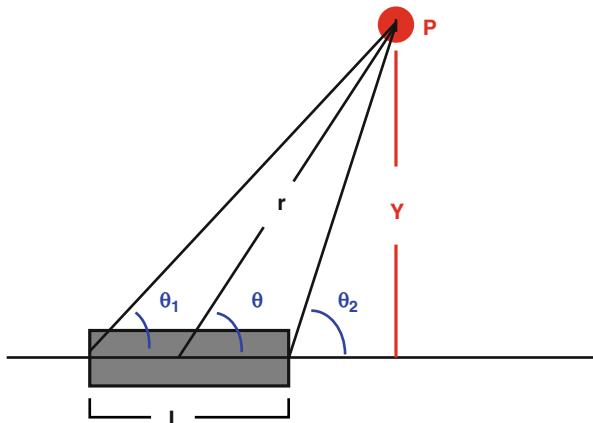
Photon Emitters in Water: TG-43 Dose Calc: Radial Dose Function (g)

- Accounts for the shape and attenuation of the source.

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \frac{G(r, \theta)}{G(1, \pi/2)} \times F(r, \theta) \times g(r) \quad (11.12)$$

- S_k = Air Kerma Rate
- Λ = Lambda (Dose Rate) Constant
 - Converts kerma in air to dose in water.
- $G(r, \theta)$ = Geometry Factor
 - Modified inverse-square equation that accounts for the linear shape of the source.
- $F(r, \theta)$ = Anisotropy Factor
 - Accounts for attenuation within the source.
- $g(r, \theta)$ = Radial Dose Function
 - Accounts for attenuation and scatter within the medium (water).

Fig. 11.1 Geometry factor (G). G is a function that calculates the inverse-square falloff of a line source. For a point source, G is equal to the inverse square factor.



TG-43 Dose Calc: Geometry Factor (G)

- $G(r,\theta)$ is known as the **geometry factor** and defines the inverse-square dose falloff with distance (Fig. 11.1).
- For a point source, $G(r) = 1/r^2$ (inverse square).
- For a line source, $G(r,\theta) = (\theta_2 - \theta_1)/Ly$.
 - This is an integral of the inverse-square distance to every point on a line.
 - For distances much larger than the source length, $G(r,\theta)$ will approximately equal $1/r^2$.

TG-43 Dose Calc: Anisotropy Factor (F)

- All sources have some degree of **anisotropy**. This means that the dose varies with angle to the source (Fig. 11.2).
- This is because of differential **attenuation** from the source encapsulation (Fig. 11.3).
 - $F(r,\theta)$ is defined as 1.0 at perpendicular angles ($\theta = \pi/2$), and its value changes as you move off-axis.
 - This is analogous to an **OAR** for external beam. [see Chapt. 8].

TG-43 Dose Calc: Radial Dose Function (g)

- $g(r)$ is the **radial dose function** and describes the change in radial dose falloff when measured in water instead of air.
 - This is analogous to a **TAR** for external beam [see Chapt. 8].
 - **Scatter** increases depth dose.
 - **Attenuation** decreases depth dose (Fig. 11.4).

Fig. 11.2 Anisotropy factor (F). This correction factor compensates for variation in attenuation with the angle to the source.

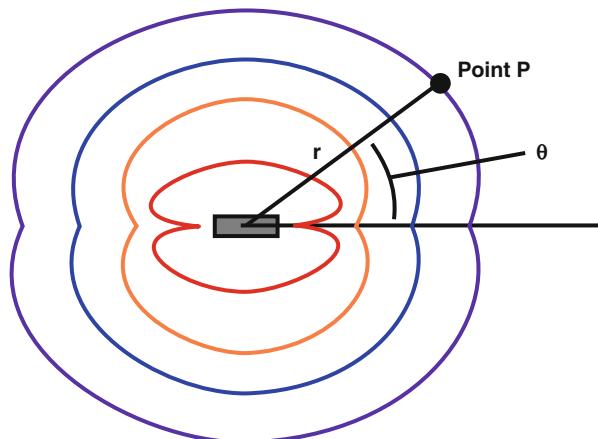


Fig. 11.3 Differential attenuation. Due to the cylindrical shape of a sealed source, radiation exiting the source at an oblique angle must pass through more encapsulation, thus self attenuation and lower dose.

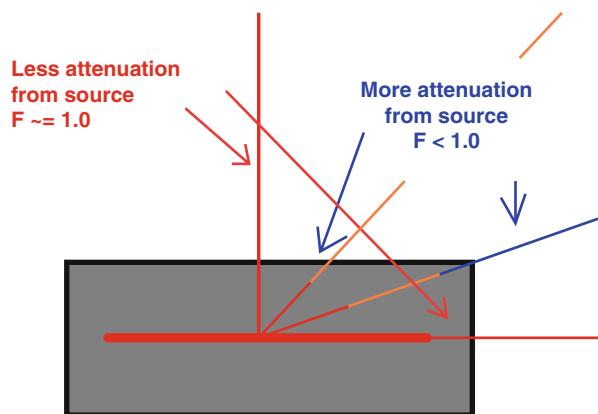


Fig. 11.4 Radial dose function (g) and type of sealed source. This function compensates for the difference between dose to air and dose to water. Low energy sources fall off very rapidly with distance, while high energy sources do not.

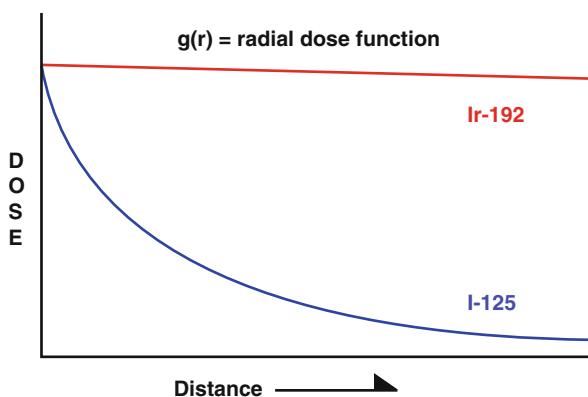
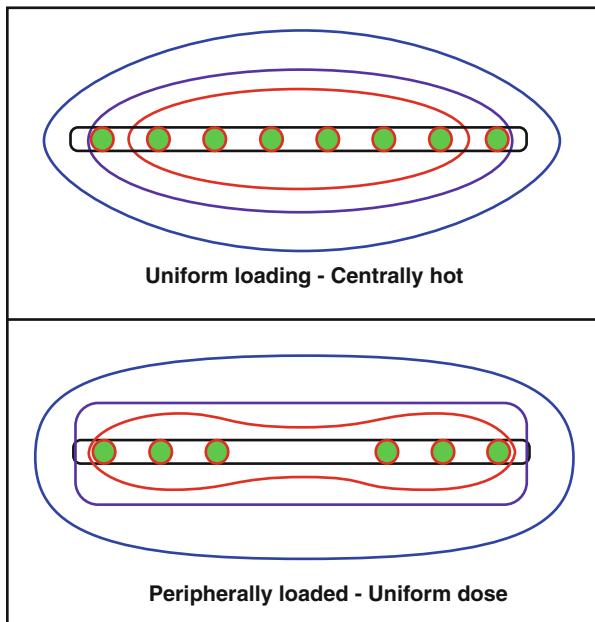


Fig. 11.5 Brachytherapy loading principles. A uniformly loaded catheter will always give a higher dose to the center. This effect may be countered with peripheral loading.



- For high-energy gamma sources: Scatter and attenuation roughly cancel out over short distances ($r < 5$ cm):
 - $g(r) \approx 1$. Dose falloff in water is very similar to dose falloff in air.
- For low-energy x-ray sources (^{125}I , ^{103}Pd) attenuation dominates over scatter.
 - $g(r) \ll 1$. Dose falls off much more rapidly in water than in air.

Loading Patterns: Basic Principles (Fig. 11.5)

- In a uniformly loaded catheter, the center will receive more dose than the ends.
- Therefore if you want a homogenous dose, you need **peripheral loading** – more source strength at the ends.
- This is true for both **LDR** and **HDR**.

Classical Dose Systems (Interstitial)

- Prior to computer planning era, pre-calculated tables were used to calculate how much radium was needed to load an implant. These are of mainly historical interest (Fig. 11.6).
- **Paterson-Parker (Manchester):**
 - Different dose-loading tables for single plane, two-plane, and volume implants.
 - **Peripherally loaded** – non-uniform loading.

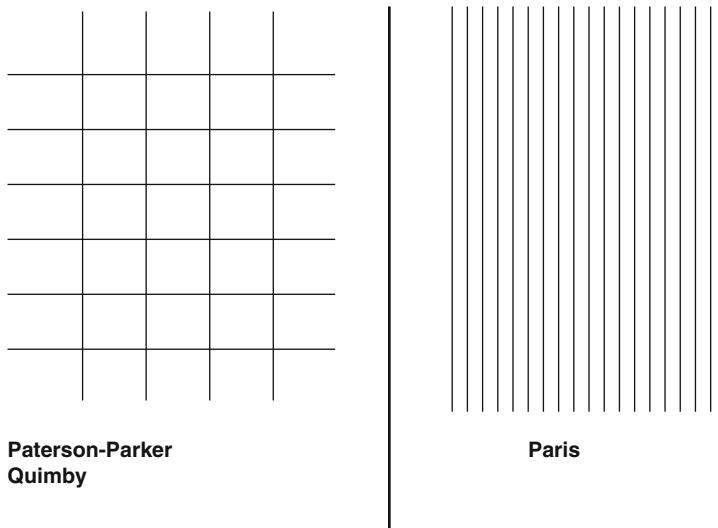


Fig. 11.6 Historical brachytherapy loading systems. The Paterson-Parker and Quimby systems utilize crossed ends, while the Paris system does not.

- **Uniform dose** within implanted volume.
- **Crossed ends** – needles/catheters run perpendicular to each other.
- **Quimby**
 - Different dose-loading tables for single plane, two-plane, and volume implants.
 - **Uniform loading**.
 - **Central hot spot** within implanted volume.
 - **Crossed ends** – needles/catheters run perpendicular to each other.
- **Paris**
 - Volume implants with multiple parallel needles or catheters.
 - **Uniform loading**, identical for all needles.
 - **Uniform spacing** of all needles.
 - **Central hot spot** within implanted volume.
 - **Parallel ends** – no crossing of needles.
- **Other**
 - **Prostate** – computer planning is preferred over fixed systems.

Classical Dose Systems (Intracavitary)

- **Fletcher-Suit (named after Gilbert Fletcher and Herman Suit)**
 - Dose is prescribed to **Point A**:
 - **2 cm** superior to the top of the ovoids as seen on a lateral film, and:
 - **2 cm** lateral to the tandem, in a direction perpendicular to the tandem as seen on an AP film.

- This is supposed to represent the **paracervical triangle** where the uterine vessels cross the ureter.
- Revised Point A** is 2 cm superior to the flange:
 - Unlike classical Point A, this point can be visualized on AP film alone (no need for laterals).
 - Point H** is the prescription point used by the American Brachytherapy Society.
 - Find the intersection between the tandem and a line drawn between the mid-dwell positions of both ovoids.
 - Move cephalad along the tandem by 2 cm plus the radius of the ovoids.
 - Then, move lateral by 2 cm.
 - This is intended to be the same point as **classical Point A**, but with more reproducible delineation.
 - However, it is a bit lower than **classical Point A**.
- Typical **LDR** dose rate is 50–60 cGy/h to **Point A** (Fig. 11.7).
- Additional dose measurements at:
 - Point B** is 3 cm lateral to **Point A** (5 cm from midline), represents the **obturator nodes**.
 - Point P** is the bony pelvic sidewall, either at the level of **Point A** or at the top of the acetabulum.

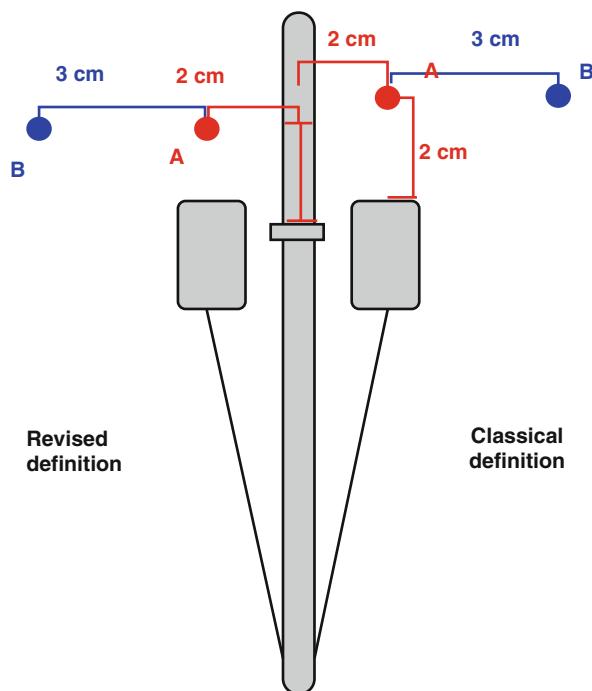


Fig. 11.7 Definitions of Point A. Point A is the typical prescription point for cervical brachytherapy. The original definition is 2 cm lateral to the tandem and 2 cm above the top of the ovoids. The revised definition is 2 cm lateral to the tandem and 2 cm above the top of the flange.

- **Bladder Point** is defined by the posterior extent of the bladder directly behind the Foley catheter.
- **Vaginal Point** is defined by the posterior extent of the vaginal packing, at the level of the midpoint of both ovoids.
- **Rectal Point** is defined as 5 mm posterior to the vaginal point.

Rules of Thumb

- **How do we specify source strength?**
 - **Activity (A)** [Ci, Bq]:
 - **Gamma constant (Γ)** [$R/cm^2/h$] measures exposure in air per mCi.
 - **Exposure rate in air = $A\Gamma$.**
 - **Air kerma strength, AKS (S_k)** [$cGy/cm^2/h, U$]:
 - **Lambda constant (Λ)** measures dose rate to water per unit of AKS.
 - **Dose rate in water = $S_k\Lambda$.**
- **Milligrams Radium Equivalent:**
 - A 1 mgRaEq source is a source with the same air exposure rate as 1 mg of Radium:

$$\text{mg RaEq} = \frac{\Gamma A}{8.25 R/cm^2/hr}$$

- **Effective Half-Life (Unsealed Source):**

$$t_{\text{eff}} = \frac{(t_{\text{biol}} \times t_{\text{phys}})}{(t_{\text{biol}} + t_{\text{phys}})}$$

- Always shorter than biological or physical half-life.
- **Permanent Implant Equations:**

$$\text{Mean Life: } \tau = \frac{1}{\lambda} = 1.44 \times t_{1/2}$$

$$\text{Dose Rate: } \dot{D}(t) = \dot{D}_0 e^{-\lambda t}$$

$$\text{Total Dose: } D = \dot{D}_0 \tau = 1.44 \times \dot{D}_0 \times t_{1/2}$$

- **TG-43 Calcs:**

$$\dot{D}(r, \theta) = S_k \times \Lambda \times \frac{G(r, \theta)}{G(1, \pi/2)} \times F(r, \theta) \times g(r)$$

- **S_k** = Air kerma strength
- **Λ** = Dose rate factor (Lambda Constant)
- **G** = Geometry factor (analogous to inverse square factor)

- **F** = Anisotropy factor (analogous to off-axis ratio)
- **g** = Radial dose function (analogous to TAR)
- **Dose Falloff:**
 - Inverse Square is almost always a larger factor than tissue attenuation. (**G** falls off faster than **g**).
 - High energy sources (Not ^{125}I or ^{103}Pd): Attenuation and scatter approximately cancel out ($\mathbf{g} \approx 1$).
- **Uniform loading = Central Hot Dose**
- **Peripheral loading = Uniform Dose**
- **Classical Brachytherapy Systems:**
 - **Paterson-Parker:** crossed needles, peripheral loaded, uniform dose.
 - **Quimby:** crossed needles, uniform loaded, quite hot in the center.
 - **Paris:** Parallel needles (not crossed), centrally hot.
 - **Fletcher-Suit:** Intracavitory implant, classical point A is higher than revised point A.
 - Classical definition requires heavier loading (more activity) for the same “Dose to Point A”.

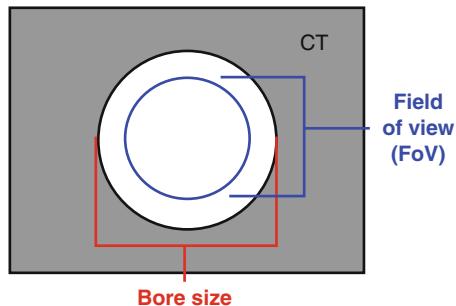
12

Advanced Treatment Planning for EBRT

What Is Advanced Treatment Planning?

- This chapter focuses on advanced treatment planning techniques:
 - Imaging techniques
 - Immobilization techniques
 - Treatment Planning and Evaluation techniques
- See Chapt. 9 for details on basic treatment planning:
 - Irregular surface compensation
 - Wedges
 - Bolus
 - Field matching (gap calculation)
 - ICRU reference dose definition

Fig. 12.1 CT bore size and FoV. The field of view is always significantly smaller than the bore size, so if a patient barely fits into a machine you will not obtain an accurate image of the patients.



2D Radiography

- Plain film must be selected based on:
 - Energy (kV film is very different from MV film)
 - Sensitivity (is it a 2 cGy port film, or a 200 cGy whole fraction verification?)
- Electronic imaging is performed by:
 - Fluoroscopy – Conversion of X-rays to visible light.
 - Ionization chamber array – Limited resolution.
 - Amorphous silicon panel – Most modern technology.
- Real time imaging may be performed with fluoroscopy or by setting a digital flat-panel to “fluoro” mode.
- Diagnostic-energy radiographs are characterized by:
 - Kilovolts peak (kVp): maximum X-ray energy. Increasing kVp increases exposure and penetration but decreases contrast.
 - Milliamp-seconds (mAs): product of tube current and time. Increasing mAs increases exposure only.
 - Magnification: image on film is always larger than true size, because of beam divergence.

$$\text{Magnification} = \frac{\text{FFD}}{\text{FAD}} \quad (12.1)$$

FFD = Focus-Film Distance

FAD = Focus-Axis Distance

Computed Tomography (CT)

- Measures Hounsfield units (HU), can be converted to electron density for treatment planning.
 - Air = -1,000 HU, Water = 0 HU, Bone \approx 1800 HU.
 - Electron density can be used for dose calculation.
- Limited bore size and field of view (FoV): (Fig. 12.1).
- Finite slice thickness (typically ranges from 1 to 5 mm).

- Only images the **axial** plane – sagittal and coronal planes are digitally reconstructed and less accurate.
 - High resolution in the axial plane.
 - Low resolution in the craniocaudal direction.
- Susceptible to **metal artifact**.
- Susceptible to **motion artifact**, unless **4DCT** is used.

Cone Beam CT (CBCT)

- Obtained using rotation of a 2D imager.
- Unlike regular CT, CBCT has equal resolution in all directions. Compared to regular CT:
 - **Lower** resolution in axial plane.
 - **Higher** resolution in craniocaudal plane.
- If the desired FoV is smaller than the imaging panel, it can operate in **whole fan** mode.
 - CBCT images the entire field at all times.
 - Requires a 180° rotation minimum.
- If desired FoV is larger than the imaging panel, can operate in **half fan** mode to double the FoV:
 - Half of the field is imaged at any given time.
 - Requires a 360° rotation minimum (Fig. 12.2).

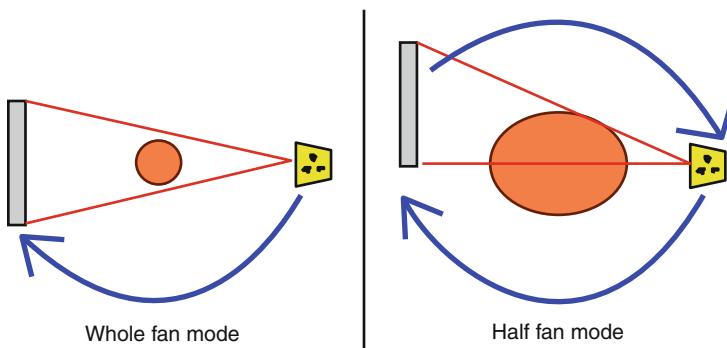


Fig. 12.2 CBCT fan modes. Whole fan mode is used to image small fields, while half fan mode is used to image large fields.

Digital Tomosynthesis

- Uses the same principle as **CBCT** but attempts to synthesize a 3D image with less than 180° of rotation.
 - The larger the angle of rotation, the more accurate the image. (at 180+ degrees it becomes a **CBCT**).
 - Smaller rotational angles cause more artifacts.

- **Tomosynthesis** is used to obtain CT-like images with shorter imaging time and less imaging dose.

Magnetic Resonance Imaging (MRI)

- Measures **proton spin** using magnetic and radiofrequency fields.
 - Does **not** give direct electron density information.
- Not limited to the axial plane; can take true sagittal and coronal images.
 - **True 3D** sequences have equal resolution in all planes. Ideal for image fusion.
- **T1**: water dark, fat bright. Brain is “right side up”. (white matter white, grey matter grey).
- **T2**: water bright, fat dark. Brain is “upside down”. (white matter grey, grey matter white).
- **T2FLAIR**: water dark, fat dark. Brain is “upside down”.
- **Other**: many, many different MR imaging sequence modalities.
- Very limited **FoV**, different MR coil for each part of the body.
- Much worse **metal artifact**. (even for MR-safe metals).
- Much worse **motion artifact**.
 - Due to long scan times, patient has more time to move.

Image Resolution

- Plain film and electronic film have sub-mm resolution, equal in all directions.
- Fluoroscopy generally has lower resolution than static film.
- **CT** has very high resolution in the axial plane, but much lower resolution craniocaudal.
 - Axial resolution = mm or sub-mm.
 - Craniocaudal resolution = slice thickness, which is usually several mm.
- **MRI** has good resolution and is capable of producing **3D** sequences with equal resolution in all planes.
 - However, **MR** images are limited by motion artifact.

Windowing and Leveling

- **CT** and **MR** data have a very broad range of intensities.
 - If the full range was displayed on screen it would look “washed out”.
- **Window** and **Level** allow one to select a range of intensities to display on screen.
- **Level** = the center of the intensity range.
 - **Ex**: a CT with **L = 50** will display **HU = 50** as the average “gray” color.
- **Window** = the width of the intensity range.

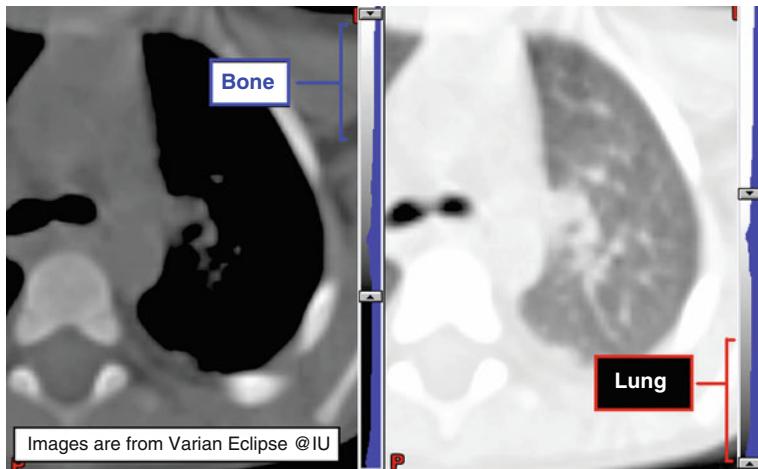


Fig. 12.3 CT windows. The same CT data set can be displayed in very different ways. This example shows bone windows versus lung windows. By scrolling panel on right one can change window and level.

- **Ex:** the same CT with **W = 100** will display **HU** values between **(0–100)** as a grayscale.
 - **HU < 0** will be completely black.
 - **HU > 100** will be completely white (Fig. 12.3).

Additional Imaging Modalities

- **Ultrasound (US):**
 - Measures **echo** of high frequency sound waves.
 - Generates 2D images, often in real time.
 - **Doppler** may be used to image blood flow.
 - Transducer must be placed within a few cm of the structure being imaged.
 - Sound transmission is blocked by **density interfaces** (tissue/air or tissue/bone), limiting the anatomic sites that can be imaged.
 - Often used for brachytherapy (intra-operative imaging).
- **Nuclear isotope imaging:**
 - In general, this allows the imaging of biological uptake but has lower resolution compared to CT or film.
 - **¹⁸FDG-PET** uses **¹⁸F**, a positron emitter.
 - Images sugar (glucose) uptake.
 - Positron annihilation results in pairs of 511 keV photons, detected by a specialized **coincidence detector**.
 - **Other PET** uses different isotopes and tracer molecules.
 - **Na¹⁸F PET** images blastic and lytic bone lesions.

- **^{11}C Acetate PET** images ketone body uptake.
- Other PET isotopes are currently experimental.
- **$^{99\text{m}}\text{Tc}$ MDP bone scan:** images blastic bone lesions.
- **$^{99\text{m}}\text{Tc}$ sestamibi:** images myocardial perfusion.
- **$^{99\text{m}}\text{Tc}$ MAG3:** images renal perfusion.
- **$^{99\text{m}}\text{Tc}$ sulfur colloid:** Radioactive blue dye used for sentinel node biopsy.
- **^{123}I iodine scan:** Used for imaging (not treatment) of thyroid carcinomas.
- **^{131}I iodine scan:** Used for treatment of thyroid carcinoma, can also be imaged.

Patient Setup Considerations

- Must be comfortable enough to hold position for simulation and treatment.
- Must be easily reproducible day to day. Highly mobile body parts such as head and extremities may require immobilization devices.
- Patient setup considerations:
 - Supine vs prone vs more exotic positions.
 - Dentures, obturators, other prosthetics: Leave them on or take them off?
 - What degree of immobilization is desired? What devices are desired?
 - What bolus is desired? Does a custom bolus need to be created?
 - Will skin folds create an undesirable “self bolus” effect?
 - Will the patient + devices fit into the CT field of view?
 - Will the shoulders or arms interfere with the beam?
 - Will the shoulders or arms interfere with the treatment machine? (such as electron cone – shoulder collisions).

Advanced Immobilization Devices

- Stereotactic radiation treatments (**SRS, SBRT, SABR**) require very high precision to provide accurate dose to target and avoid over-dosing normal tissue.
 - Immobilization devices are very important.
- **Cranial Immobilization:**
 - **Invasive Head Frames** pierce the skin and attach to the skull.
 - **Noninvasive Head Frames** do not pierce the skin. They use bite blocks +/- other features (ear buds, etc.).
 - **Frameless devices** use Aquaplast +/-bite block.
- **Extracranial Immobilization:**
 - **Stereotactic body frames** encompass the torso with some form of rigid registration.
 - **Internal fiducials** that can be imaged.
 - **Indexed frames** attach to the couch in a well-defined position.
 - **Other body molds** such as Alpha Cradle, HipFix etc.

- **Rectal balloons** for prostate.
- **Respiratory Management:**
 - Abdominal compression (solid plates vs. belts)
 - Voluntary breath hold
 - Assisted breath hold (Air valve device)
 - Respiratory gating

Conventional Simulation

- The purpose of **SIM** is to do the following:
 - To set up a reproducible patient position and create any devices needed.
 - To select isocenters and beam angles that can be easily and reliably set up.
 - To take simulation films that can be used as a reference for treatment setup.
 - To obtain treatment planning data such as external contour, target volumes, etc.
- The **SIM** should have the same isocentric setup as a treatment machine.
 - Light field, optical distance indicator (ODI).
- The isocenter filmed during **SIM** must be the same as the treatment isocenter.
- **Imaging**
 - Radiography (“plain film”): Images are taken at PA, lateral, and each additional desired beam angle.
 - Fluoroscopy: May be used for patient and isocenter positioning, and for measuring breathing motion.
- **Patient Data**
 - A conventional simulator is incapable of acquiring a detailed patient contour.
 - Wires, rods, calipers, etc. may be used to take measurements of the skin surface.
 - Target and avoidance volumes are defined on plain film.

CT Simulation

- Requires a **CT scan** encompassing all body parts that beams may enter or exit through.
- **CT** data can be directly used for computer-based dose calculations. (**3D planning**).
- Isocenter skin marks are made at the time of **CT** but may be changed at the time of treatment. (“iso shift”).
- **Digitally Reconstructed Radiograph (DRR)**
 - A computer rendering that approximates a radiograph taken at an arbitrary angle and isocenter.
 - Significantly worse resolution than a plain film.
 - Resolution may be improved by using very thin slice CT.
 - Allows for selection of isocenter and beam angle after the time of simulation.

- **Volume Rendering**
 - Contoured structures may be 3D rendered.
 - It is also possible to render density interfaces, such as blood vessels in lung or brain.
 - This is commonly used in diagnostic radiology, not so much in rad onc.
- **Image Registration**
 - Simulation CT may be registered (“fused”) with outside imaging, such as prior CTs and MRs.
 - Various algorithms exist for rigid and deformable registration, treatment planning system (TPS) dependent.
- **Limitations of CT**
 - Patient pose must fit within the CT bore.
 - Field-of-view (FOV) is always smaller than the bore.
 - Artifacts occur if patient is too close to the bore.
 - Finite **slice thickness**.
 - Craniocaudal resolution limited by slice thickness, unlike plain film which has sub-mm resolution in all directions.
 - **4D** technology is required to image breathing motion.

Verification Simulation

- Prior to start of treatment, the isocenter position and each beam angle may be filmed to verify accurate setup.
- This may be done with:
 - Conventional simulator (2D)
 - kV and/or portal imaging on the linac (2D)
 - Verification CT on CT sim (3D)
 - Cone beam CT on the linac (3D)
 - Other devices (manufacturer dependent)

Portal Imaging

- **Portal Imaging** visualizes the actual treatment field on the actual treatment machine.
 - **Single exposure:** Only images the field itself.
 - **Double exposure:** Exposed once with the treatment field and once with an open field, allowing a full field of view for normal anatomy.
- **Portal Films:** there are two types of plain film:
 - **Localization film:** requires a few cGy to expose, may be used to image patient prior to treatment.
 - **Verification film:** requires ~2 Gy to expose, used to film the full-duration treatment.

- **Electronic Portal Imaging Device (EPID):** Faster than film, but size of image is limited by size of the electronic imaging panel. (generally smaller than a plain film).

3D Treatment Planning

- **3D planning requires:**
 - Use of CT data for target volume delineation.
 - Use of CT data for normal tissue delineation.
 - Use of CT data for radiation field design.
 - Beam's eye views (BEVs) and DRRs.
- **3D Beam Angle Selection:**
 - **Coplanar beams** do not include a couch kick. They will always be in the axial plane.
 - **Noncoplanar beams** use couch kicks and will enter and exit above or below the axial plane.
 - Allows more freedom in selecting angles that avoid organs at risk.
 - Drawbacks include: increased setup time and difficulty, collision risk, requires extended CT scan length to encompass all beam entries.
- **3D Structure Sets and Dose Volume Histograms**
 - A **DVH** is a method of displaying dose-volume statistics.
 - There are two basic types of **DVH**: (Fig. 12.4).
 - DVHs allow you to visually judge how much dose a structure is receiving, and how homogeneous it is.
 - However, a DVH does not tell you **where** in a structure the high-dose and low-dose areas are located.
 - Must review dose on actual images!

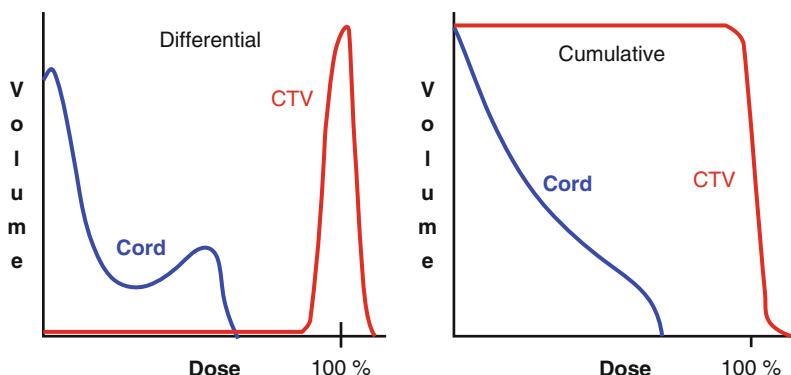


Fig. 12.4 Differential and cumulative DVHs. A differential DVH displays the volume of a structure receiving exactly X dose. A cumulative DVH displays the volume of a structure receiving X dose or greater.

- **Biological dose statistics**
 - **Tumor Control Probability (TCP)** is a synthetic number calculated by applying a chosen radiobiological formula to your DVH statistics.
 - **Normal Tissue Complication Probability (NTCP)** is a similar value calculated for normal tissue toxicity.
 - **TCP** and **NTCP** concepts may be used for dose-escalation or alternate fractionation calculations.
 - These numbers are theoretical and not clinical (yet).

Non-IMRT Dose Optimization Techniques

- **Methods to increase CTV dose:**
 - Larger margins between CTV and block edge.
 - At the cost of increased normal tissue dose.
 - Adding bolus.
- **Methods to improve normal tissue sparing:**
 - Smaller margins between CTV and block edge.
 - At the cost of decreased CTV dose.
 - Choosing different beam angles to avoid specific organs.
 - Increased # of beam angles will increase **conformality** (decreased volume of high dose) at the cost of **integral dose** (increased volume of low dose).
- **Simple methods to improve dose homogeneity:**
 - Decrease beam weighting on the hot side.
 - Increase beam weighting on the cold side.
 - Add or adjust wedges, heels toward hot areas.
- **Complex methods to improve dose homogeneity:**
 - **Dose Compensation**
 - Use a physical or electronic compensator to selectively attenuate dose in areas that would otherwise be overdosed.
 - **Field Within Field** (aka “forward-planned IMRT”)
 - Treat the large field to partial dose.
 - Block the hot spots and treat the smaller field.
 - If there are still hot spots ->block those hot spots and continue treating an even smaller field.

Intensity Modulated Radiotherapy (IMRT)

- **Inverse planned IMRT** uses inverse-planning software to calculate **non-homogenous fluence maps**.
 - This contrasts with the “flatness” of an open field (Fig. 12.5).

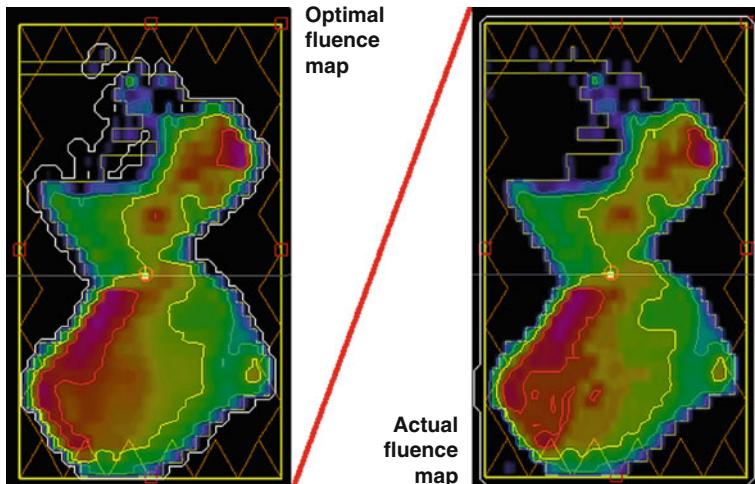


Fig. 12.5 IMRT fluence maps. Most treatment planning algorithms first compute “optimal fluence maps” (fluence desired by algorithm) and then convert these to “actual fluence maps” (fluence deliverable by linac). Some algorithms are capable of direct aperture optimization, optimizing linac and MLC movements without going through an intermediate step.

- **IMRT Optimization Software:**
 - Physician provides dose constraints. A computer algorithm calculates a set of optimal **fluence maps** that attempt to meet the constraints.
 - Various algorithms exist including “simulated annealing” and “Pareto front optimization”.
- **IMRT Delivery:**
 - **Fixed Gantry Techniques**
 - **Step-and-shoot:** Each aperture is broken down into a number of **segments**. In between segments, the beam is turned off.
 - **Sliding window:** Each aperture is treated with continuously moving MLC leaves while the beam is on.
 - **Arc-based Techniques (RapidArc, VMAT, etc.)**
 - Continuous gantry movement with continuous MLC movement with the beam on.
 - Requires specialized hardware and software.
 - **Helical Tomotherapy**
 - A specialized machine that delivers dose continuously while rotating rapidly around the patient in a **CT-like** fashion.
 - Very good at conformality, but unable to utilize noncoplanar angles. (close axial distance between CTV and OAR is difficult).

- **Robotic (CyberKnife)**
 - Beam delivery from many different beam angles (“nodes”) chosen from a map of possible robot arm positions.
- **Intensity modulated proton therapy (IMPT)**
 - Spot scanning with a proton pencil beam.
 - Remains exotic and experimental as of 2014.

13

Linac Quality Assurance

What Is Quality Assurance?

- **AAPM definition of QA:** “To assure that machine characteristics do not deviate significantly from their baseline values acquired at the time of testing and commissioning.”
 - Linac measurements are taken during acceptance and commissioning.
 - The **AAPM** requires daily, monthly, and annual QA tests to ensure that linacs are able to deliver treatment as planned.
 - **TG-40** set standards for basic linacs without MLCs, on-board imaging, or respiratory gating.
 - **TG-142** adds standards for MLCs, IMRT, SBRT, on-board imaging and respiratory gating.

- **QA intervals and instrumentation:**
 - **Daily QA** may be done using relatively imprecise “spot check” instruments such as a daily QA device.
 - **Monthly QA** should use more precise instrumentation than **daily QA**, as determined by the physicist.
 - **Annual QA** should use the most precise commissioned instruments, including **TG-51** calibration with National Institute for Standards and Technology (NIST)-traceable ion chambers.
- **Tolerance level and action level:**
 - The **tolerance levels** are considered “acceptable” for clinical treatment.
 - Tolerances are typically **3 %** for daily checks, **2 %** for monthly/annual checks, or **1 %** for stereotactic.
 - If the equipment consistently violates tolerance levels, treatment should be stopped until the equipment is brought into compliance.
 - However, **daily output checks** may be more variable due to their rapid and imprecise nature.
 - An **action level** of **5 %** is recommended for stopping treatment after a daily output check deviation.
 - If the deviation is between **3** and **5 %**, treatment may continue “for the short term” until the discrepancy can be addressed.

Who Is Responsible for QA?

- The **chief radiation oncologist** (aka **physician director**) is ultimately responsible for everything that relates to patient care, including the proper functioning of equipment.
- A **qualified medical physicist** (**QMP**) should lead the **quality assurance** (**QA**) team.
 - The **QMP** is responsible for knowing how to operate and interpret **QA** equipment, and for training other personnel to use the **QA** equipment.
 - A **quality assurance committee** (**QAC**) should include at least one physician, physicist, and therapist.

Linac Regulations and Recommendations (TG-142)

- **Daily QA**
 - $\pm 3\%$ X-ray and electron output constancy
 - ± 2 mm laser line accuracy (1 mm for SRS)
 - ± 2 mm collimator size indicator (1 mm for SRS)
 - ± 2 mm ODI accuracy
 - **Functional:** Door interlock, door closing safety, audiovisual monitors, radiation area monitor, beam on indicator, stereotactic lockouts (if applicable).

- **Monthly QA**

- ±2 % X-ray and electron output constancy
- ±2 % backup monitor chamber constancy
- ±2 % dose rate output constancy
- ±1 % X-ray and electron beam profile constancy (central axis PDD/TMR)
- ±2 % electron energy constancy
- ±2 mm/1 % light field – radiation coincidence (1 mm/1 % on each side)
- ±1 mm laser distance check device
- ±1° gantry/collimator angle indicators
- ±2 mm accessory trays (i.e., graticules)
- ±2 mm jaw position indicators (1 mm for asymmetric)
- ±1 mm cross-hair centering
- ±2 mm/1° couch position indicators (1 mm/0.5° for SRS)
- ±2 mm wedge placement accuracy
- ±1 mm compensator placement accuracy (for IMRT compensators)
- ±2 mm localizing laser accuracy (1 mm for IMRT/SRS)
- **Functional:** Wedge and block latching, laser guard interlock, respiratory gating (if applicable)

- **Annual QA**

- ±1 % X-ray and electron flatness and symmetry change from baseline
- ±1.0 MU/2 % SRS arc MU set vs delivered
- ±1.0/2 % SRS arc rotation set vs delivered
- ±1 % X-ray and electron output calibration in a water phantom (TG-51)
- ±1 % X-ray field size output factor ($\geq 4 \times 4$ cm)
- ±2 % X-ray small field size output factor ($< 4 \times 4$ cm)
- ±2 % electron applicator output factor
- ±1 % X-ray beam quality (PDD₁₀ or TMR₁₀)
- ±1 mm electron beam quality (R₅₀)
- ±2 % physical wedge transmission factor constancy
- ±2 % X-ray and electron output constancy (≥ 5 MU)
- ±5 % X-ray output constancy (2–4 MU)
- ±2 % X-ray output constancy vs dose rate
- ±1 % X-ray and electron output constancy vs gantry angle
- ±1 % X-ray and electron off-axis factor vs gantry angle
- ±1 mm collimator rotation isocenter
- ±1 mm gantry rotation isocenter
- ±1 mm couch rotation isocenter
- **Functional** electron applicator interlocks
- ±2 mm radiation-mechanical isocenter coincidence (1 mm for SRS)
- ±2 mm tabletop sag
- ±1° table angle
- ±2 mm table maximum range of movement
- **Functional** stereotactic accessories and interlocks

Additional Linac QA

- TG-142 has additional daily, weekly, monthly and annual QA guidelines for devices and treatment modes such as:
 - Multi-leaf collimators
 - Non-physical wedges
 - Static and dynamic IMRT
 - On-board imaging devices (MV, kV, and CBCT)
 - Total body irradiation (TBI)
 - Total skin electron treatment (TSET)
 - Respiratory gating
- These are too lengthy to list here.
- Note that all **weekly QA** applies to linac add-ons. (MLCs, on-board imaging, etc.)
 - There is no **weekly QA** for basic linac functions.

Measurement Techniques

- **Daily QA** tasks are performed by the therapists, with rapid dosimetry equipment that can check many things at once.
 - For example, a square- or cube- shaped dose monitor (flat-panel detector or ion chamber array) can check linac **output**, **flatness** and **symmetry**, **laser alignment**, **field size**, and **ODI** all at the same time.
 - The **qualified medical physicist (QMP)** must be notified of any out-of-tolerance results.
- **Monthly QA** should be performed or directly supervised by the **QMP**.
 - The equipment should either be **different from** the daily QA equipment, or **cross-calibration** of the daily QA equipment should be performed.
- **Annual QA** must be performed by the **QMP** and must use water phantoms and calibrated NIST-traceable ion chambers.

14

Radiation Protection and Safety

Regulatory Bodies

- Protection standards set by the **ICRP** (International Commission on Radiological Protection) and the **NCRP** (National Council on Radiation Protection and Measurements – the Americans).
- **NRC** (Nuclear Regulatory Commission) – these are the guys who license all **nuclear reactor produced** materials or byproduct material.
- **Individual State Agencies/Laws** – oversee naturally occurring radioactive material, cyclotron produced material (generally positron emitting stuff), and all types of X-ray generators.
- **DOT** (department of transportation) oversees **transport** of radioactive material.
- **FDA** oversees pharmaceutical aspects of radioactive material.

Types of Radiation Effects and Limits

- **Stochastic and Non-Stochastic effects:** (Please see Chapt. 31).
 - Non-stochastic are deterministic with an effect that occurs after a certain threshold dose.
 - Stochastic effects are probabilistic with no lower safe threshold.
- **Measurements:**
 - For radiation protection, we use **Sieverts (Sv) or millisieverts (mSv)** instead of Gray or any other measurements of dose or exposure (see Chapt. 6).
- Dose limits for Areas:
 - **Unrestricted areas: 0.02 mSv/h (or 2 mrem/h)** or 0.1 mSv/week (10 mrem/week) for shielding calculations.
- Dose limits for general public per year:
 - **Total – 5 mSv** (including embryo or fetus undeclared).
 - **Lens of eye – 15 mSv**
 - **Other Organs – 50 mSv**
- Dose limits for radiation workers:
 - **Multiply general public limits by 10**
 - Total – 50 mSv total body
 - Lense of eye – 150 mSv
 - 500 mSv organs.
 - (there are no fetus radiation workers – child labor laws).
- Children, or general public in continuous exposure situations **should not get >1 mSv**.
- Fetus declared is **0.5 mSv/month** (which is almost the same as five total for undeclared).
- Appropriate visitors to hospitalized brachytherapy patients may get up to **5 mSv** (Figs. 14.1 and 14.2).

Structural Shielding Design for External Beam Therapy: How to Build a Bunker

- **TERMS: know these terms!!!** (from NCRP reports 49, 51, 149 and 151).
 - **Primary barriers** – The walls behind the main target areas.
 - **W (workload)** – expressed in milliampere minutes per week (maximal mA × minutes of beam-on time) for equipment below 500 kvp (diagnostic)
 - For megavoltage machines, Expressed as weekly dose delivered at 1 m from the source (**cGy/week at 1 m**) – this can be estimated by multiplying number of patients per week by the dose per patient (since SAD calculations have dose to isocenter which is usually at 1 m). Assuming 250 per week (50 per day) with 200 cGy per fraction (standard fractionation), that comes to a workload of around 50,000 cGy/week.
 - **U (use factor)** – fraction of operating time during which the radiation is directed towards a particular barrier.

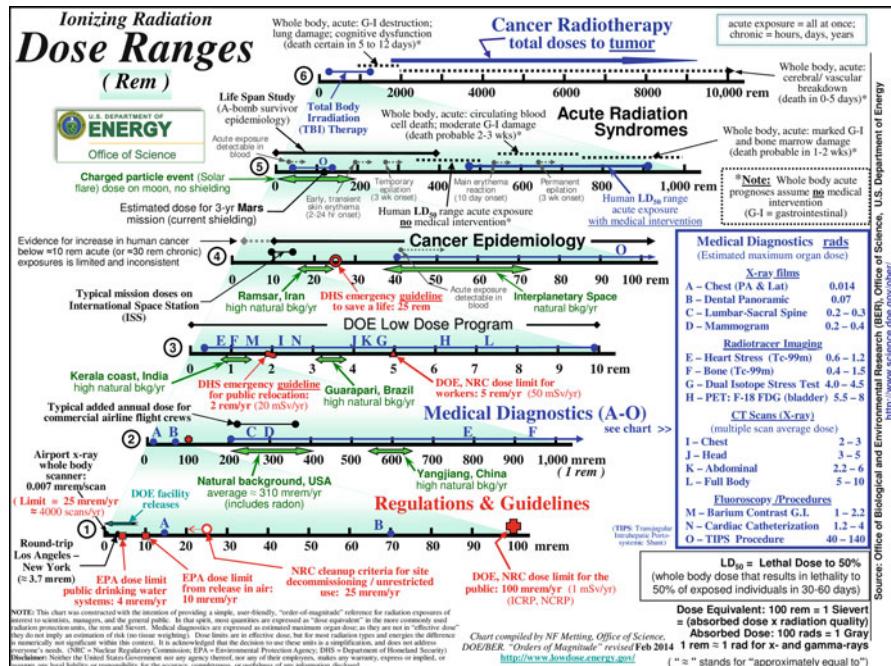


Fig. 14.1 Ionizing radiation dose ranges measured in Rem (older measurement of equivalent dose) (Source: Office of Biological and Environmental Research (BER), Office of Science, US Department of Energy, <http://www.science.doe.gov/ober/>).

- If you do a lot of ten field IMRT, it will be all over the place. If you do all opposed laterals, it will be split 50 % on the right and left walls.
- If you do all TBI or TSI, it will be 100 % on one wall.
- Use factor in **secondary barrier calculations is always 100 % or 1** for all barriers.
- Floor should usually be 1 (for all the single field things you do).
- Ceiling should be $\frac{1}{4}$ – $\frac{1}{2}$ depending on techniques.
- Walls are usually $\frac{1}{4}$.
- **T (occupancy factor)** – fraction of operating time during which the area is occupied. Someone actually tabulated the following relative occupancy times:
 - Full occupancy ($T = 1$) – work areas, offices, nurses' stations.
 - Partial occupancy ($T = 1/4$) – corridors, restrooms.
 - Occasional occupancy ($T = 1/8$ – $1/16$) – waiting rooms, stairways, elevators, outside areas, janitor closets.
 - Zero occupancy ($T = 0$) – underground.
- **d (distance)** – distance in meters from radiation source (remember inverse square law – it is pretty important).

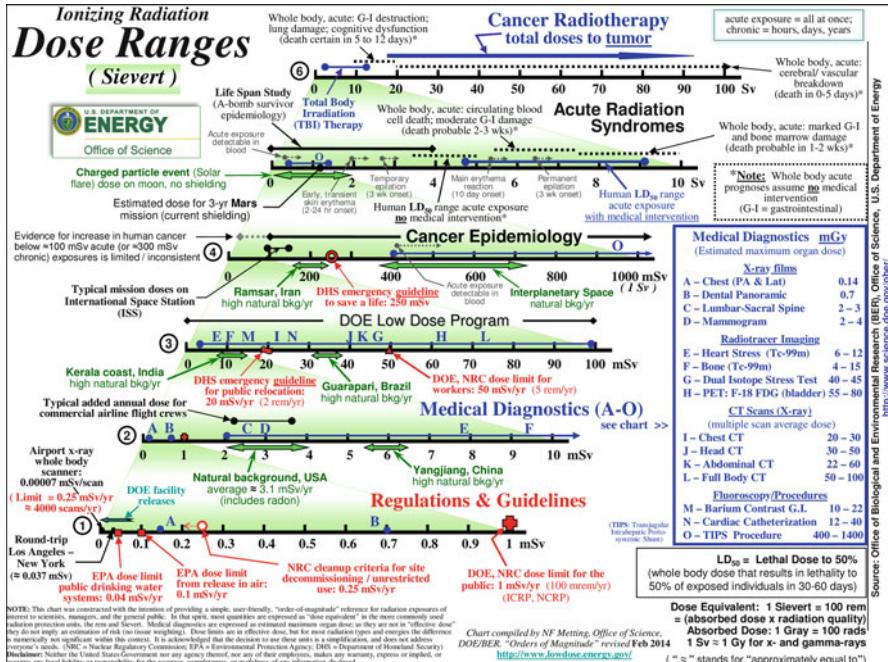


Fig. 14.2 Ionizing radiation dose ranges measured in Sieverts (SI units) (Source: Office of Biological and Environmental Research (BER), Office of Science, U.S. Department of Energy, <http://www.science.doe.gov/ober/>)

- **P** (permissible dose equivalent for area)
- **Controlled area** (overseen by radiation safety officer) – **0.1 cGy/week**.
- **Uncontrolled area** – **0.01 cGy/week**.

$$P = \frac{WUT}{d^2} \times B \quad (14.1)$$

- **B** – transmission factor of a barrier to reduce the expected radiation to P level.
 - This is dependent on energy.
 - Before you start pouring concrete for your brand new fancy machine, use this equation to figure out how thick it needs to be for each wall or door:

$$B = \frac{P \times d^2}{WUT} \quad (14.2)$$

- Concrete is what is typically used for Linac vaults.
- There are tables for the amount of various materials needed for various transmission factors (B) usually described in tenth-value layers or TVL's that

can be found in NCRP report 51 (which is impossible to find) or from one of the newer reports like NCRP report 144 (costs around \$100).

- If you do not want to calculate things, **8.6 ft or 260 cm of concrete** is usually sufficient as a primary barrier for a machine running up to 18 MV photons.

Secondary Barriers

- meant to protect against **Scatter** and **Leakage**.
- basically another layer of concrete around the whole room but mostly on the walls of those off-axis areas that will not have the beam pointed at it.
- Secondary shielding is usually half of the primary barrier (where there is no primary barrier).
 - So if you do not want to think, **just use 130 cm or 4.3 ft of concrete**.
- Use factor (**U**) is always **1** and hence is no longer in the equations.
- More terms for secondary barrier equations:
 - **α – ratio of scattered to incident exposure.**
 - Varies for different angles and for different beam energies.
 - There are tables in NCRP report 51 and 151 but just remember 0.1 % or **0.001** which is α at 90° from the primary beam.
 - **F** – area of the beam incident at the scatterer.
 - Usually this is multiplied by 1/400 because 400 cm^2 is the area of the beam for which α is given.
 - (If your area happens to be around 400 cm^2 , the term drops out).
 - **d'** – distance from scatterer to the area of interest (again used in inverse square fashion).
 - **B_s** – Barrier transmission for scatter factors.
 - **B_L** – Barrier transmission for leakage factors.
- **Scatter equations:**

$$B_s = \frac{P \times d^2}{WUT} \times \frac{400d'^2}{\alpha F} \quad (14.3)$$

Now assuming $U = 1$ and $\alpha = 0.001$, Eq. 14.3 can be rewritten as follows:

$$B_s = \frac{P \times d^2 d'^2}{0.001 \times WT} \times \frac{400}{F} \quad (14.4)$$

(where $400/F$ will be close to 1 or so).

- **Leakage**
 - NCRP report 102 states regulations for leakage limits, but regardless, you will always have some leakage and should **use 0.1 % (multiply workload by 0.001) for the leakage factor**.

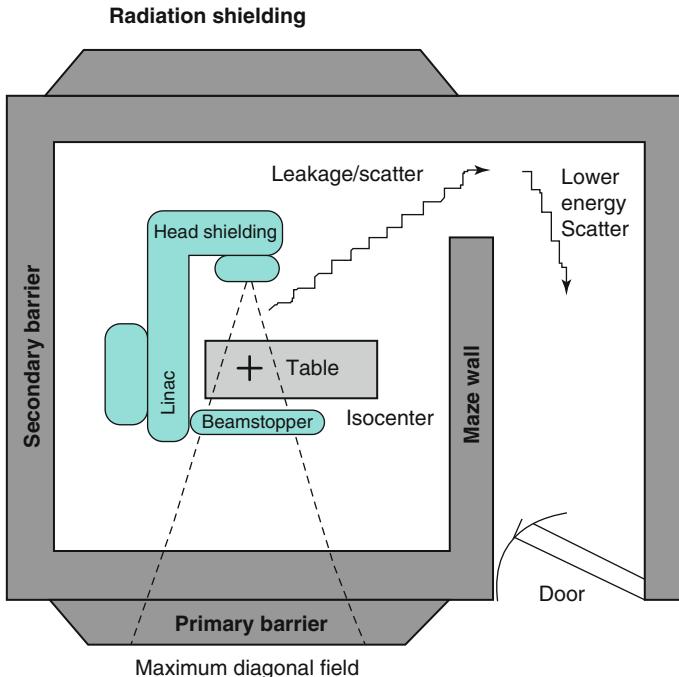


Fig. 14.3 Radiation shielding around a linear accelerator.

$$B_S = \frac{P \times d^2}{0.001 \times WT} \quad (14.5)$$

- **Machine shielding** (beam stoppers and head shielding) – Some linacs have beam stoppers built within the machine to come out behind the patient when using high energy modes (16 MV) to help people with shielding if their vaults were only made to 6 MV or Cobalt specifications. Head shielding is also present to prevent leakage and scatter. Head leakage is not allowed to be more than 0.1 % of the useful beam.
- **Doors** – doors to linac rooms need to have the same shielding factors as walls and typically are gigantic and made of lots of high Z metal (usually lead) with neutron shielding (borated polyethylene – see below). In order to help with this, use a Maze.
- **Maze** – if you want a smaller door that can open significantly faster, a good configuration is a maze. This allows for far less shielding in the door because most of the radiation at the door will be from radiation that has already scattered many times and can be estimated at 500 kVp, meaning you only need about 6 mm of lead (about a quarter of an inch) (Fig. 14.3).

Neutron Shielding

- Photonuclear Disintegration
 - When linacs operate at energies >10 MV, you can sometimes get photonuclear disintegrations in the walls or targets of the linac – this produces neutrons at a broad spectrum but maxing out at about 1 MeV. (See Chapt. 4).
 - Since neutrons are relatively large and uncharged, they interact far more with nuclei (especially hydrogen) than with electron orbitals, so electron density does not matter as much as having lots of nuclei around.
 - **Wax or borated polyethylene** (boron and carbon atoms connected to **LOTS of hydrogen atoms**) work great to slow down fast neutrons (thermalize them) so that they can be stopped. As neutron is captured, it produces capture gammas that are stopped with the lead or steel shielding on a door.
 - Concrete works great too, so the shielding you use for x-rays will usually work fine for walls – furthermore, maze configurations are also excellent for protecting the door, especially if they are >5 m.
 - When neutrons slow down or stop, they can release x-rays (inelastic scatter, see Chapt. 5) or gamma rays from neutron capture reactions in the shielding.
 - This means that if you do not expect the neutrons to slow down significantly from a good maze, you will need a lot of lead on the door to protect against those secondary photons.
 - These photons can be as high as 8 MeV but are usually around 1 MeV.

Radiation Protection for Brachytherapy Procedures

- Whenever dealing with safety for radioactive sources, it is important to always remember three factors: **Time** (as little time exposed as possible), **Distance** (radiation falls off from a point source by the inverse square law) and **Shielding** (keep big heavy barriers between yourself and the source).
- **Source storage and transport containers** – sources should be sealed in lead-lined safes with lead-lined drawers and the areas should be ventilated directly to the outside.
 - An L-Block should be available to load and unload the sources within the “hot-room”.
 - Lead-lined safe carts (“pigs”) should be used to cart around the radioactive material to its intended destination.
- **Patient room** – shielding for brachytherapy follows the same rules as external beam shielding with workload, used factor, occupancy and the same permissible requirements.
 - In General, an HDR room must be specifically licensed as such (not just any shielded room). With that said, old linac vaults will usually pass the tests.
 - The tenth value layer thickness (TVL – amount of material required to reduce an incident beam to 1/10 of its initial intensity) for Cobalt-60 and Cesium-137 are 39.8 mm and 21.6 mm for lead and 19.9 and 16.6 cm for

concrete respectively. This is much lower than what is required for even a 6 MV linear accelerator: 56.1 mm lead or 34.5 cm concrete.

- **Special considerations for high dose rate brachytherapy** – Make sure to perform the required source shielding tests for the after-loader after any maintenance (including source changes). Also make sure that personnel know how to respond in an emergency (how to make the source retract).
- **Release of patients treated with temporary implants**
 - Patients that have received either implantable brachytherapy or unsealed sources may be “released into the wild” if it is unlikely that any innocent bystanders would ever receive more than 5 mSv or 0.5 rem (remember the public limits from earlier?).
 - You must provide written instructions to the patient (or caretakers, parents, etc) regarding keeping dose as low as possible if the dose is expected to be greater than 1 mSv or 0.1 rem.
 - Additional requirements include the following measurements from NRC reg guide 8.39: (Table 14.1).
- **Leak testing of sealed sources** – Sealed sources must be tested for leaks about every 6 months and records must be kept for 3 years. If there exists 185 Bq (0.005 mCi) of removable contamination, you must take the source and either fix it, store it, or dispose of it and then file a report to the NRC in 5 days.
- **Routine radiation surveys** – surveys must be performed after a source is implanted and after it is removed. Surveys must also be performed routinely around source safes (storage safes and afterloader safes) to ensure that radiation levels do not exceed the Sealed Source and Device Registry. Surveys should be repeated after any repairs, installations or source replacements.
- **Personnel monitoring** – Basically, everyone working in a controlled area must use personal dosimeters (TLD badge, TLD ring, film badge, electronic dosimeter, OSL, etc). Official definitions for who should wear one are anyone expected to receive 25 % of maximum permissible dose (NCRP definition) or 10 % of maximum permissible dose (NRC definition).

Protection against nonionizing radiation – make sure to wear sunscreen outside and do not look directly at the treatment room lasers.

Table 14.1 Activities and dose rates at 1 m from the patient before they may be released into the general public.

Radionuclide	Activity (mCi)	Dose rate @ 1 m (mSv/h)
I-125	9	0.01
Pd-103	40	0.03
Ir-192	2	0.008
I-131	33	0.07

Administrative Requirements

- In order to be a licensee of radioactive material by the NRC, there are **three main requirements** to be submitted:
 - **Request for license application**, renewal or amendment before submitting to the NRC.
 - **Authorized users** (usually a radiation oncologist who logs lots of time in brachytherapy or GK or an interventional radiologist who uses a lot of unsealed source injections), or an authorized nuclear pharmacist, or an authorized medical physicist.
 - **Radiation protection program** changes that do not require a license amendment.
- In general, a licensee must also report Medical events to the NRC and the patient within 24 h, with a written report in 15 days.
 - The precise definition of a medical event changes frequently with NRC bureaucracy (and you should stay up to date as to what those are), but in general, medical events almost always include the following:
 - Delivered doses that are different from what was intended
 - Treating the wrong target
 - wrong patient
 - Any serious medical consequences or deaths that were an accident.
- There are a few positions that are mandated by the NRC as well:
 - **Radiation Safety Officer (RSO)** – responsible for implementing the radiation protection program – authority, duties and responsibilities must be submitted in writing.
 - **Radiation Safety Committee** – if a licensee uses more than one type of radioactive material, there must be a safety committee that oversees all of it. It must include the following:
 - **RSO** – by default
 - An **authorized user** (usually the prescribing physician)
 - A representative of the **nursing** service
 - A representative of **management** who is not the RSO or an authorized user
- **Radiopharmaceutical therapy** – the authorized user must possess a dose calibrator that can measure the activity administered to each patient. Otherwise, follow the safety precautions and regulations previously described for brachytherapy.

Final Notes

- This chapter has attempted to outline the broad concepts and important specifics for radiation safety, however it is not meant to be used as a reference. For official guidelines, one should consult the NRC and NCRP guidelines as well as any State laws that may apply.
 - <http://www.nrc.gov/>
 - <http://www.ncrponline.org/>

15

Quality Management Program

Radionuclide Regulations and the NRC

- The NRC has the power to regulate **nuclear material** in the USA.
- **Nuclear material** comes in three categories:
 - **Nuclear source material:** Naturally occurring Uranium and Thorium.
 - **Special nuclear material:** Enriched Uranium (^{235}U) and Plutonium (**Pu**). This material is “special” because it can be used in nuclear weapons.
 - **Nuclear byproduct material:** All artificially produced radioactive nuclides other than plutonium, plus naturally occurring ^{226}Ra , and tailings or waste from uranium and thorium mining and processing.
- For radiotherapy purposes we are only concerned with **nuclear byproduct material**.

- The **NRC** does not regulate:
 - X-ray, electron, proton, or ion therapy.
 - Naturally occurring radionuclides other than uranium, thorium, or radium.
- The **NRC** has delegated its authority to several **agreement states**, allowing those states to regulate **byproduct material** within their own borders.
 - In **non-agreement states** the **NRC** directly regulates byproduct material.
- The concept of **written directives** and **medical events (misadministration)** were originated by the **NRC**, but each state has its own regulations for X-ray and electron therapy.
- All use of byproduct material must be supervised by an **authorized user** or **authorized nuclear pharmacist** identified on a NRC license.
 - **Authorized users** are usually nuclear medicine or radiation oncology MDs.
- A **Radiation Safety Officer (RSO)** must be appointed with the responsibility to:
 - Identify radiation safety problems.
 - Initiate, recommend or provide corrective actions.
 - Stop unsafe operations.
 - Verify implementation of corrective actions.
- **Written directives** must be documented and followed for all “therapeutic dose” radionuclide use.
- Initial nuclide **activity** is measured by a NRC licensed manufacturer, preparer, or producer, and should be measured by the licensee prior to patient use.
 - **Activity** should be mathematically corrected for decay if it decays by $\geq 1\%$.
- A **source inventory** of all byproduct material, except for gamma knife sources, must be performed every **6 months**:
 - Source **type, number, physical location, and activity** must be recorded.
 - **Leak testing** of all **sealed sources** in use with a half-life exceeding 30 days, except for ^{192}Ir ribbons.
 - Records must be kept for at least 3 years.

Quality Management Program/Plan (QMP)

- A **QMP** is a set of written procedures that ensures that radiation is administered as ordered.
- The exact regulations for a **QMP** vary between the **NRC** and various states, but are generally similar.
- The basic idea behind a **QMP** is the following:
 - A licensed **practitioner** must sign a **written directive** that includes patient, site, radiation modality and dose.
 - There must be a **quality assurance mechanism** to ensure that dose calculations are done properly, that the **written directive** is followed, and that any deviations from the written directive are documented.
 - For linac radiotherapy this generally includes some form of **weekly chart check**.

- The identity of non-practitioner operators (radiation therapists) must be documented.
- There must be a mechanism for written **revisions** to **written directives**.
- There must be a mechanism to document and report accidental events (**misadministration** or **medical events**).
- Each radiotherapy institution must have its own **QMP** that is approved by the state (for linacs) and by the **NRC RSO** (for brachy).

Written Directive (NRC)

- A **written directive** is required for ^{131}I doses exceeding 30 μCi , and for any “therapeutic” dosage of radiation from a byproduct material.
- In the case of medical emergency, an oral directive is acceptable but a **written directive** must be signed within 48 h.
- The **written directive** must contain the patient’s name and:
 - **Unsealed Sources:** Radioactive drug, dose, and route of administration.
 - **Gamma knife:** Dose, treatment sites, and target coordinates for each treatment site.
 - **Teletherapy:** Total dose, dose per fraction, number of fractions, and treatment site.
 - **HDR brachytherapy:** Nuclide, treatment site, total dose, dose per fraction, and number of fractions.
 - **Non-HDR brachytherapy:**
 - Before implantation: Treatment site, nuclide and dose.
 - After implantation but before completion of the procedure: Nuclide, treatment site, number of sources, and total source strength and exposure time (or total dose).
- A written **revision** to a **written directive** must be dated and signed prior to the revised treatment.
- Copies of written directives must be kept for a minimum of **3 years**.

Medical Event, aka Misadministration

- The NRC changed the name from **misadministration** to **medical event**.
 - Many state regulations still use the word **misadministration**, so a linac accident may still be called a **misadministration**.
- **Medical events** include all of the following:
 - **Wrong dose** ($\pm 20\%$ of total dose or $\pm 50\%$ of a single fraction).
 - **Wrong drug** (different nuclide or chemical composition).
 - **Wrong patient**
 - **Wrong site**, excluding migration of correctly implanted permanent seeds.
 - **Wrong mode** of treatment (such as LDR instead of HDR).

- **A leaking sealed source**
- Any event that results in or will result in unintended permanent functional damage as determined by a physician.
- The incorrect dose exceeds 0.05 Sv to the total body or 0.5 Sv to skin, a single organ or tissue.
- All **medical events** must be reported within 24 h to:
 - The referring physician.
 - The subject of the medical event, or an appropriate responsible relative or guardian, unless telling the individual would be harmful or the individual cannot be reached.
 - The NRC Operations Center.
- State regulations for linac accidents are generally very similar to NRC regulations for radionuclide accidents.

16

Special Topics: Hyperthermia and Computers

Hyperthermia

If ionizing radiation is good at killing cells, and microwaves are good at cooking food, why not do both to the tumors? (see Chapt. 30 for more details).

- The use of temperatures between 39 °C (102 °F) and 47 °C (116 °F) to achieve selective cell killing but does NOT use ablative temperatures >50 °C (122 °F) that might cook a tumor and surrounding tissue.
- There are many benefits to providing hyperthermia concurrently with ionizing radiation, discussed in much greater detail in Chapt. 30.
- Heat (thermia) may be applied externally or using implantable device inside the tumor using the following techniques:
 - hot water
 - microwave

- radiofrequency
- ultrasound
- Primary limitation of heat therapy is the technical limitations:
 - Applying heat selectively to the tumor while sparing normal tissues.
 - Applying heat within the proper time frame of radiation therapy.
 - Reducing invasive techniques, especially if they would be required on a daily basis.
 - Expensive devices or power requirements.
- Another limitation is the inability to achieve uniformity (some areas will be heated more than others) due to thermal diffusion of tissue.
 - Heat can be carried away by the heat-sink effect of venous blood flow (think of water-cooled machinery).
 - Heat sink effect has a slight benefit to normal tissues so they will not receive as much heat as tumor cells, and tumors that do experience vasodilatation can become better oxygenated, but this makes heat dosing logistically difficult.
- Overall, hyperthermia has many benefits but is so technically difficult that it is usually reserved for academic studies or for superficial tumors (melanoma, neck nodes, or superficial breast cancers) or recurrent tumors. Even in these cases, it is not standard of care.

Computers: Miscellaneous Topics That Are Important!

- **DICOM** – Digital Imaging and Communications in Medicine – this is the standard format for medical imaging. Version 3.0 was developed in 1993 but for some reason, there are still departments that do not use this. If you ever request films from an outside facility, it would be wise to request that they are in either DICOM or DICOM-RT format.
 - DICOM files also batch important information about the file such as patient name, ID, date of birth, slice thickness, kVp, and pixel representation.
 - DICOM-RT files can include contouring structures, dose, and radiotherapy plans.
 - Pixel representation is how the data is sent – either big bytes first (big Endian) or little bytes first (little Endian).
 - There are many variations of the DICOM features. Many free-ware programs on the internet are available that can read non-standard imaging files. Usually imaging studies when loaded on a compact disk also carry the read in format data that may be slightly different than DICOM-RT format.
- **PACS** – Patient Archiving and Communication System – PACS provide massive data storage from any imaging device on a single platform. Every hospital usually has its own PACS system and just about all of them will accept DICOM files (though not all will generate them naturally unfortunately, but they can usually convert their own file format into DICOM). Huge amount of storage and further reading any study is made possible by a PACS.

Image Registration

- In the treatment of cancer with radiation, often we use historical CT scans, MRIs or PET scans that are taken on completely different days and are often reconstructed in three dimensions using different algorithms for many reasons:
 - Resolving and understanding the change in target due to growth or reduction or weight- gain or loss.
 - Defining structure sets from uniqueness of imaging modalities such as CT, MRI and PET.
- **Image registration** is a process to unify various images into a single coordinate system for visualizing multiple image sets taken at different points in time, different modalities and different conditions of the same patient.
 - Positron Emission Tomography
 - Image registration in PET imaging had been a difficult process due to loss of anatomical information. Thanks to innovation of CT-PET device, registration is seamless as data are taken in a single coordinate system where anatomy is displayed on the physiological image in same coordinate.
 - There continues to be a slight problem in CT-PET due to temporal variation as images are taken at different time phase (you still cannot run them both at the EXACT same time, however such problems have not been a major issue and active research is continuing to improve temporal changes in PET images by gated PET imaging.
 - CT-CT/CT-MRI
 - Many algorithms are available.
 - point to point mapping.
 - surface matching.
 - pixel by pixel matching.
 - interactive, and mutual information.
- Algorithms in general can be divided into linear (rigid) and elastic (non-rigid) transformation.
 - The **linear transformation** (rigid) uses rotation, scaling and translation to match images.
 - The **elastic matching** uses additional features of elastically distorting a pixel based on tissue characterization is an example of **deformable registration**
 - (example – the ability to fuse images of the neck in the flexed and extended positions or fusing images of a child in different phases of growth).
 - There are several types of software in market that provides satisfactory deformable registration such as Velocity and MIM.
- **Image fusion**
 - When images are set in a single coordinate system, any two images can be registered within that single coordinate system and hence called image fusion.
 - Fused images could be created from single or multi-modality images such as CT, MRI, and PET.

- The image fusion mechanism provides viewing of two images superimposed on each other. One can select the weight (transparency) of image to view one or other image set.
- This provides opportunity to draw contours of MRI to CT or from PET to CT data set for treatment planning.
 - Example: in radiosurgery application CT, MRI and angiographic images are also fused to view the details of abnormalities.
 - Example: In prostate cancer, ultra-sound images are fused to CT-data set for brachytherapy treatment.

Treatment Planning Software

- **Measurement based (based off of empirical historical data)**
 - May be used on 2D or 3D data sets.
 - Based on measured data in water phantoms.
 - Accounts for correction factors for surface irregularities, beam modifiers and tissue heterogeneity.
 - Relatively reliable for regular fields and fewer required corrections and less reliable for more complex treatments like IMRT.
 - Examples:
 - Hand-calculations (SAD/SSD based)
 - TAR/TMR
 - Batho
 - Power law
 - Clarkson Method
 - MRI based stereotactic brain treatments (based on measurements since there is no electron density dataset).
- **Model based (all modern CT-based treatment systems)**
 - Rely on 3D CT data sets – cannot be used on 2D data sets.
 - Usually based on simplified equations derived from Monte Carlo simulations (see below).
 - Generally accurate for homogenous and non-homogenous (bone, lung, metallic interfaces), and irregular fields with non-uniform fluence.
 - **Monte Carlo** – best of model based calculations for all radiation types.
 - Calculates potential “**histories**” or theoretical particle path lengths using the physical constants of both the particles and the medium along with probabilistic equations and other complex physics equations for **each particle that enters the body** (billions of calculations) (Fig. 16.1).
 - All events and by products of interactions are accounted for as they travel in media.
 - This is the standard by which all other model based calculations are measured.

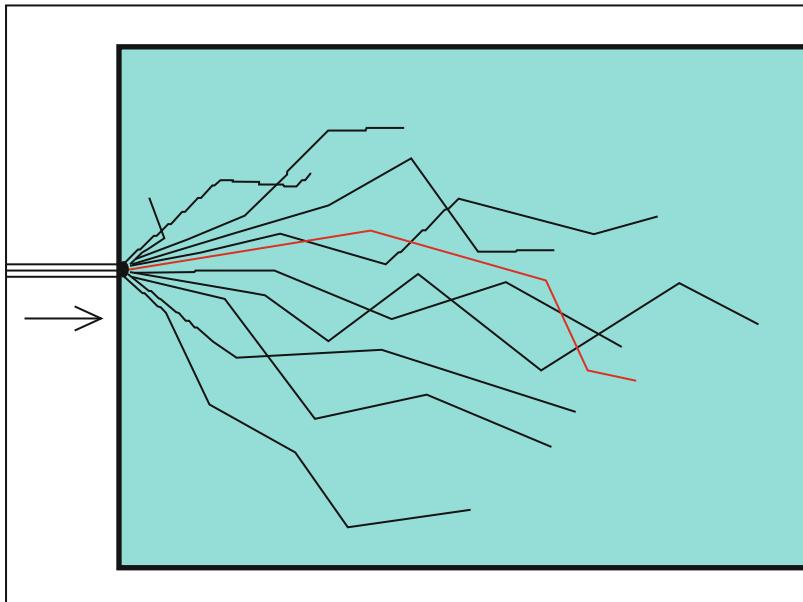


Fig. 16.1 Monte Carlo algorithm: Each potential particle history is mapped using physical constants and interaction probabilities. As the number of histories increases, the accuracy of the model increases. Mapping 2 Gy of radiation over a $3\text{ cm} \times 3\text{ cm}$ field would require close to 10^{11} histories, which is not reasonable for present day machines, however 10^7 histories comes extremely close to an exact distribution and is achievable.

- Requires very large computing capabilities and not practical for regular use with present-day technology as of this writing (perhaps in the future though).
- There are multiple different Monte Carlo programs compiled for different settings and different particles. Examples:
 - EGS (Electron Gamma Shower)
 - Penelope
 - FLUKA
 - GEANT
 - MCNP
- **Pencil beam**
 - Photon interacts with medium and produces electrons.
 - Electrons tend to have tortuous paths with multiple angle changes as they bounce around from coulombic forces. A pencil beam algorithm assumes that these scattering angles are small and therefore a beam about the size of a pencil should scatter out in a Gaussian distribution (bell curve) at all depths.

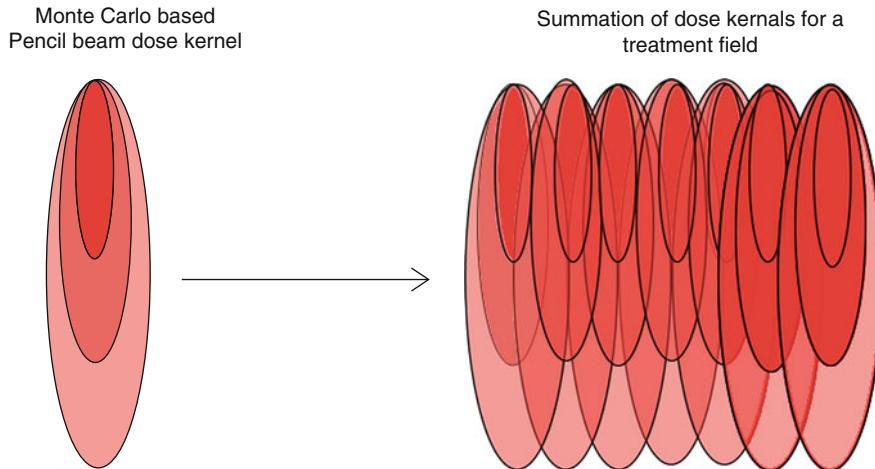


Fig. 16.2 Pencil Beam algorithm for calculating dose: A pencil beam distribution is approximated using Monte Carlo methods and then these pencil beams are stacked to approximate a treatment field. Colors represent isodose levels.

- Wide angle scattering actually happens in reality (and can be modeled through Monte Carlo simulations) but this is expected to be minimal in homogenous material and is therefore left out of the equations.
- The isodose plot of a pencil beam calculated from these equations looks like a tear-drop for electrons, and when spread over a large field, this closely resembles observations of actual homogenous dose distributions.
- This algorithm is most accurate in the central region of large regular fields but is still reasonably accurate at contour irregularities and in the penumbra region.
- The algorithm tends to fail with inhomogeneities (crossing from tissue into bone or air). This is especially true where the inhomogeneity is smaller than the pencil beam spread or instances of multiple inhomogeneities (Fig. 16.2).
- **Convolution/superposition**
 - Utilizes both Monte Carlo derived parameters and analytically derived calculations.
 - Convolution is a mathematical operation using two functions to produce a third function that is typically viewed as a modified version of one of the initial two.
 - Consists of two separate functions that are integrated:
 - **TERMA – Total Energy Released in Media by photons** (related to collision KERMA).

- **Kernel – primary dose** and **scatter** dose from photons, expressed separately either as a pencil beam (see above) or as a point (more accurate).
- Heavy weight is placed on the primary photons and less weight on scattered photons. Subsequently, a separate kernel accounts for electrons set in motion away from the primary photon – this is based on Monte Carlo simulations.
- Early convolution models (without superposition) used only Monte Carlo based pencil beam approximations of primary dose but excluded any scatter dose.
- Works well in flat homogenous fields.
- breaks down in heterogeneity (similar to pencil beam).
- Superposition adds the scatter factors – both photons and electrons.
- There are separate functions for the tungsten target, flattening filter, collimators, and other modifiers that operate on the dose kernel equation.
- Attenuation of the beam is accounted for by CT number of each voxel within the CT simulation scan.
- **Collapsed Cone Convolution Superposition**
 - Radiation dose is deposited by the secondary particles that carries the energy extracted (from the beam) away some distance away where they are created.
 - This process goes into all directions (360°) from all irradiated locations. A fast calculation method to estimate this is to divide the directions of energy spread into discrete cones that each are collapsed into a line, and arranging such lines all over the space where the dose is to be calculated.
 - The energy flow along such a line collects and redistributes the dose depositing spread in the directions of the cone the line stems from.
 - The shape is governed by beam energy and medium where interaction is taking place.
 - In short, collapsed cone is a fast and extremely accurate dose calculation method that estimates the energy transport and dose deposition caused by secondary particles in photon beams by dividing the full sphere of scatter directions into a set of discrete cones that are collapsed and represented by their central axis directions.
 - These collapsed cones then can be used with usually convolution/super-position concept as described above.
 - Most treatment planning software vendors utilize this method under proprietary names (example: Eclipse – AAA algorithm by Varian).
- Further advancements in treatment algorithms rely on solving the Boltzmann transport equation and can closely approximate Monte Carlo simulations (Example: Acuros by Varian).

Simulated Annealing (Inverse Planning in IMRT)

- For intensity modulated radiotherapy (IMRT), one strategy is to manually plan a treatment to give the most conformal dose with the greatest sparing – alternatively one could instead plug in a set of variables and have a computer come up with an answer.
- Simulated annealing is a mathematical system using cost functions and probabilistic search procedures to provide global minimizations for the function.
 - Factors that go into the program:
 - Target volumes and organ at risk (OAR) volumes.
 - Prescription dose.
 - Dose tolerances (max, min, dose-volume histogram parameters, etc.).
 - Level of importance (is it more important to spare normal tissues or cover the target with maximal dose).
 - Gradient “tightness” – how much of a dose gradient are you willing to accept between a target and an organ at risk.
 - Gradients that are too loose will result in bad plans.
 - Gradients that are too tight will usually fail IMRT QA (quality assurance) and will also raise the importance of treatment setup to avoid target underdose and OAR overdose.
 - OPTIONAL – beam angles and beam sizes.
 - How it works (in general):
 - The computer will come up with a rough plan based on the initial parameters (arbitrary initial state).
 - The computer will then make a tweak to the weight or fluence map of one or more beams and compare with the previous state to see if it is a better plan or if it is a worse plan.
 - This tweaking step is repeated thousands of times, each time moving to a lower minimum state.
 - Initially, large tweaks.
 - Gradually, smaller tweaks as it appears that the algorithm is reaching a local minimum state (achieving the best mix of cost functions by their hierarchical order).
 - Sometimes, optimizations can become stuck in a non-optimum state such that small tweaks in any direction do not appear to produce a better plan but it is not the absolute minimal state (not the optimal plan).
 - The local minimum is saved and then the algorithm either restarts or starts making large tweaks again to see if it could find a better local minimum (Fig. 16.3).

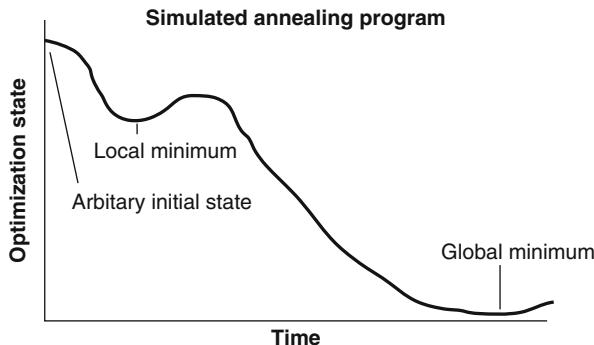


Fig. 16.3 Simulated annealing program: The program starts with an initial treatment plan (arbitrary initial state) – it then tweaks the plan many times, searching for a better plan iteratively. Eventually the program reaches a solution where small tweaks do not improve the plan (local minimum) so it makes a large jump and continues tweaking until it reaches the global minimum (the best overall plan).

- The total number of solutions to a treatment plan (good or bad) is nearly infinite. The longer you let the simulated annealing plan work, the better plan you will get.
- Theoretically, if you let the program run infinitely, you could find a perfect plan.

Part II

Radiation Therapy Biology

17

Molecular Biology and Signaling

A Note on Nucleic Acids (DNA)

- As a radiation biology text, this book focuses mostly on DNA and genes.
 - Information flows DNA → RNA → protein. This can also be described as gene → transcript → gene product.
- DNA is composed of sugars, phosphates, and bases. The bases carry the information (code).
 - Purines (A, G) pair with pyrimidines (T, C).
 - Purines are large while pyrimidines are small.
 - “Big man, small name.”
- DNA is wrapped around histones to form chromatin. Chromatin is the basic building block of chromosomes.

Fig. 17.1 A chromosome may contain one or two copies of each chromatid, but DNA is always double stranded.

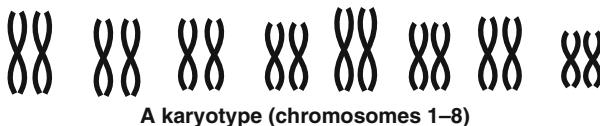
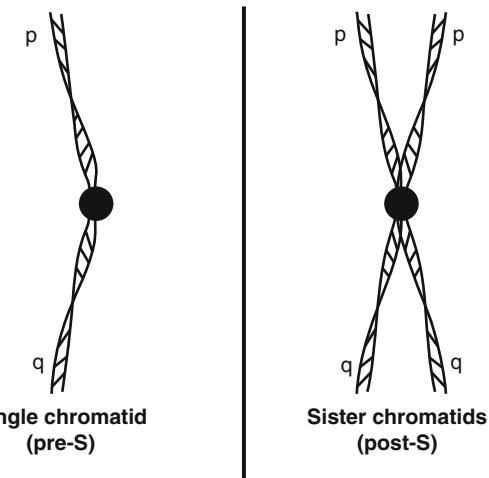
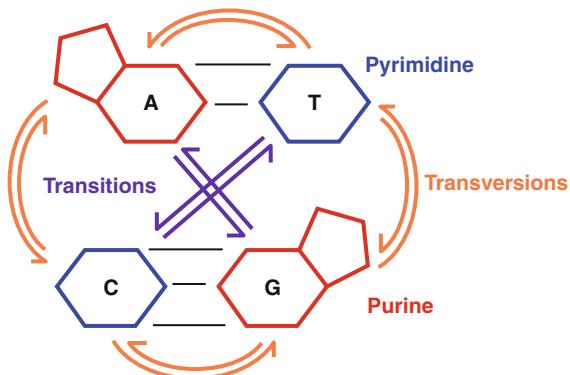


Fig. 17.2 DNA in a (partial) karyotype. Most of the cells in our body are not in M phase, and do not have condensed chromosomes visible.

- When talking about “single strand”, “double strand”, “chromatid”, and “chromosome” it is easy to become confused because so many structures come in pairs (Fig. 17.1):
- Unreplicated chromosomes (Pre-S) exist as a p- and q- chromatid, with no sister chromatids.
- Because humans are diploid, there are two of each chromosome.
 - However, unless you are a clone your two Chromosome 4's are different from each other: One comes from your mom, the other comes from your dad.
- Replicated chromosomes (Post-S) exist as identical sister chromatids, bound together by a centromere.
 - You still only have one maternal chromosome 4 and one paternal 4, but each one has 2 p-arms and 2 q-arms.
- We are used to seeing replicated chromosomes because only **M-phase chromosomes** are visible on traditional karyotype (light microscopy) (Fig. 17.2).

Fig. 17.3 Point mutations are classified as transitions (purine to purine or pyrimidine to pyrimidine) and transversions (purine to pyrimidine).



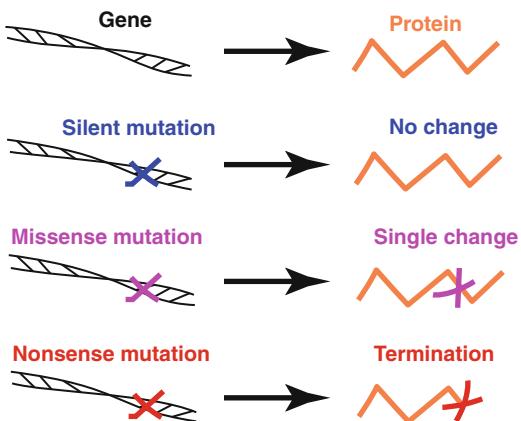
A Note on Gene Function

- There are several ways to change the function of a gene. You can change the gene itself (**mutation**), you can change gene function without altering the gene (**epigenetic change**), or you can change the function of the gene product (protein).
- **Mutation** is pretty straightforward: The DNA is different so it behaves differently.
- **Epigenetic changes** are changes in gene function that do not alter the gene itself.
 - **Gene Expression:** Changes in the amount of mRNA transcribed from the gene.
 - **Splice Variants:** Changes in which parts of the gene are included in the final mRNA.

Point Mutations and Chromosomal Mutations

- Mutations may be classified by size:
 - **Point mutations:** 1 to a few bp in size.
 - **Gross mutations** (thousands to millions of bp).
 - **Aneuploidy** (whole chromosomes, tens to hundreds of millions of bp)
- **Point mutations** affect one or a few base pairs.
 - Single nucleotide mutations are also called single nucleotide polymorphisms (**SNP**) (Fig. 17.3):
 - Mutations in coding regions are classified as **silent, missense or nonsense mutations** (Fig. 17.4):
 - Mutations in non-coding regions may affect the expression and splicing of coding regions, but they are not as easy to describe.
 - **Small Insertions and Deletions** (a few base pairs) also count as point mutations.
 - These occur when DNA replication “stutters” and either skips or repeats a sequence.

Fig. 17.4 Point mutations in a coding region of a gene may also be classified based on the change in the protein (gene product).



- **Chromosomal Mutations** (aka **gross mutations**) are large enough to affect the structure of an entire chromosome, generally millions of base pairs in length.
 - **Gross deletions** occur when pieces of DNA break off of the chromosome and are permanently lost.
 - **Translocations** occur when broken DNA sequences are re-attached to the wrong chromosome.
 - **Amplifications** occur when a DNA sequence is replicated multiple times in the same cell cycle.
- **Aneuploidy** is the loss or gain of entire chromosomes.
 - The normal human cell has two pairs of chromosomes 1–22 and two sex chromosomes (X, Y male or X, X female) i.e. **46XX** or **46XY**, anything different from this is aneuploidy. (except for germ cells).
 - Aneuploidy happens when chromosomes fail to divide properly during mitosis.
 - Most of these cells die (mitotic catastrophe) but surviving ones become aneuploid.
 - **Hypodiploidy** is having less than 46 chromosomes.
 - **Hyperdiploidy** is having more than 46 chromosomes.
 - **Tetraploidy** is having exactly twice the normal number of chromosomes (92). This happens after **cell fusion**.

Loss of Heterozygosity

- Humans have two copies of each chromosome and therefore each gene. This provides protection against recessive mutations. Even with one copy mutated of a gene, the healthy copy of a gene can take over its function.
 - A cell or individual carrying a recessive mutation is **heterozygous** at that locus (Fig. 17.5).

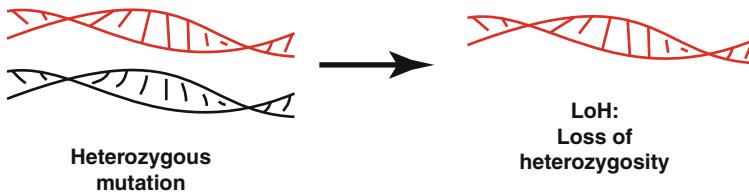
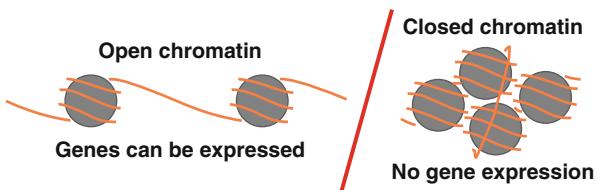


Fig. 17.5 Loss of heterozygosity (*LoH*) occurs when a gene is nonfunctional on both the maternal and paternal chromosome.

Fig. 17.6 Chromatin may exist in a “closed” (inactive) state or an “open” (active) state. This is regulated by acetylation and methylation.



- **Loss of Heterozygosity (*LoH*)** is used to describe any gene locus that is mutated and/or lost on both chromosomes.
 - This is a “two hit” mechanism of mutation. One chromosome is defective for a long time (possibly inherited), while the other chromosome is newly deleted.

Gene Expression

- Most of the cells in your body have the same genome, yet a skin cell acts very different from a brain cell.
- How does a cell regulate its gene function without changing its genome?
- **Increased Gene Expression:**
 - **Positive Transcription Factors:** Signaling proteins may directly bind DNA to induce or suppress transcription.
 - **Chromatin Acetylation:** Opens up chromatin and induces gene expression.
- **Decreased Gene Expression:**
 - **Negative Transcription Factors (Repressors)**
 - **Chromatin Methylation:** Closes down chromatin and prevents gene expression (Fig. 17.6).
- **Transcript (mRNA) modification:**
 - Many human genes have multiple splice variants, so that one gene can produce different gene products.
- **Overexpression and Silencing** describe an overall increase or decrease in gene expression. These terms include both mutation (gene amplification or deletion) and epigenetic changes.

Post-translational Modification

- Once a gene has produced a protein, that protein's function may be regulated by other processes within the cell.
- **Protein modification:**
 - Phosphorylation
 - Hydroxylation
 - Dimerization
 - Crosslinking
- **Changes in protein lifetime:**
 - Ubiquitination: The small protein ubiquitin “tags” a protein for degradation by the **proteasome** (the cell’s garbage collector).
- **Change in protein location:**
 - Cytoplasm
 - Nucleus
 - Plasma membrane
 - Mitochondrion
 - Endoplasmic Reticulum
 - Other organelles

Phosphorylation and Dephosphorylation Reactions

- Phosphate groups are the most common high-energy chemical group in the cell. Therefore, **phosphorylation** is a common mechanism for modification of protein function.
 - **Kinases** add phosphate.
 - **Phosphorylases** remove phosphate.
- Serine, Threonine, and Tyrosine amino acid residues can bind phosphate.
- Kinases and phosphorylases are classified by what amino acid they are capable of acting on.
 - Tyrosine Kinases (**TKs**) – includes all of the Growth Factor Receptors.
 - **EGFR, Her2/Neu, PDGFR, VEGFR, IGFR**
 - Serine/Threonine Kinases
 - **MAPK, ERK, TGF β R.**

Molecular Signaling: Receptors and Ligands

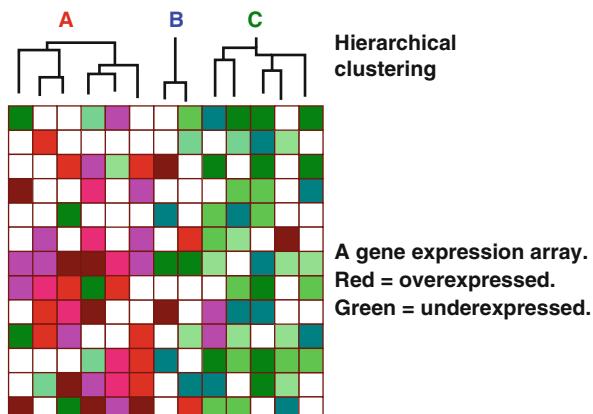
- **Receptors** are classified based on their location and function:
- **Membrane-bound receptors** bind **ligands** located outside the cell.
 - Ion channel type receptors can selectively allow ions or other small molecules to flow in or out of the cell.
 - Receptor Kinases work through phosphorylation, including all of the growth factor receptors.

- G-Protein Coupled Receptors (**GPCRs**) require GTP-binding proteins (G-proteins) to work. Most GPCRs are also receptor tyrosine kinases.
- **Cytoplasmic signaling molecules** transmit information from membrane-bound receptors to the nucleus.
- **Transcription factors** bind DNA, directly altering gene expression.
 - **Nuclear Receptors** are transcription factors that can directly respond to ligand.
 - Transcription factors may be held in the cytoplasm where they are inactive. In response to a signal, they translocate into the nucleus where they can bind DNA. NF – κB is an example of such a transcription factor.
- **Ligands** are classified into several types:
 - **Water soluble ligands** cannot pass through the cell membrane without a specific transport channel. These include neurotransmitters, growth factors, antibodies, and most nutrients and metabolites.
 - **Lipid soluble ligands** can freely travel through the cell membrane. This includes the steroid hormones and thyroid hormone, as well as lipid-soluble metabolites.
 - **Membrane bound ligands** are molecules expressed on the surface of other cells, such as the **MHC** groups responsible for T cell mediated immunity.

Gene Expression Profiling

- A **multi-gene array** (“gene chip”) can measure numerous genes at the same time:
 - **mRNA** is harvested from a tissue sample. (normal tissue, tumor, experimental animal, cell culture).
 - **mRNA** is converted into complementary DNA (**cDNA**) by reverse transcriptase.
 - RNA is too unstable to use directly.
 - **cDNA** is also known as the “transcriptome”.
 - **cDNA** is labeled with a fluorescent dye and placed on a library of known DNA sequences.
 - Fluorescence is measured by laser scanning.
- By using **cDNA** derived from two different tissue samples, one labeled green, one red, you can compare gene expression “at a glance”.
 - Control is green and experimental is red.
 - Therefore, red gene sequences are overexpressed and green gene sequences are underexpressed (Fig. 17.7).
- **Hierarchical clustering** is a statistical method that allows researchers to cluster gene expression patterns into groups.
 - For example, the four genetic subtypes of breast cancer are “Luminal A”, “Luminal B”, “Her2”, and “Basal-like”.

Fig. 17.7 Gene expression arrays can show the relative expression of up to thousands of target genes at once. Cluster analysis can then be used to group genes together to fit a specific pattern. A, B, and C are arbitrary labels for “clusters” of similar specimens.



Types of Cell Death

- There are several ways in which cell death may occur:
- **Necrosis** is typically unorganized and provokes an inflammatory response by loss of cell integrity.
- **Apoptosis** is organized, planned cell death that does not provoke an inflammatory response.
- Cells with lethal DNA damage may not die until they attempt to divide and fail mitosis. This is called **mitotic catastrophe**.
- For more details see Chapt. 20.

Radiation-Induced Molecular Signals

- Cells may respond to ionizing radiation in several ways. Often times, different responses compete against one another.
- **DNA Repair:** Activation of molecular systems to repair the DNA damage caused by radiation.
- **Cell Cycle Arrest:** Prevents the cell from cycling with damaged DNA. Can promote repair and survival, but slows down cell growth.
- **Apoptosis:** Programmed cell death, removes damaged cells from the body. Not all tissues undergo apoptosis, and many cancer cells are apoptosis-deficient.
- **Proliferation:** The opposite of cell cycle arrest and apoptosis. Produces new cells to compensate for cell killing.
- **Inflammation:** Increased blood flow and immune system activity as a result of cytokine induction, causes some cells to grow (proliferation) and other cells to die (apoptosis or necrosis).
- **Fibrosis:** Production of scar-like extracellular stroma, common late toxicity of irradiation.

Acute Effects: DNA Damage

- DNA damage is detected by the proteins **ATM/ATR**.
- When a cell recognizes that it is damaged, it will attempt to repair the damage. At the same time it must decide how it will react to this damage.
 - See Chapt. 19 for details on DNA repair.
- The cell may decide to stop growing, and even kill itself (apoptosis) if too badly damaged.
 - **p53 pathway**: A protein that is pro-repair, pro-arrest, and pro-apoptosis.
 - **Ceramide pathways**: A lipid that is pro-arrest and pro-apoptosis.
 - “Arrest and death” pathways tend to prevent malignancy as they prevent mutated cells from proliferating.
 - However, cell loss in normal tissues can lead to loss of function.
- Or the cell may decide to proliferate and survive, compensating for damage by growing faster.
 - **Fos/jun/myc pathway**: Pro-growth and anti-apoptosis.
 - “Survival and growth” pathways can predispose to malignancy as they allow mutated cells to grow.
 - However, they are also responsible for re-populating normal tissues after an injury.

Late Effects: Inflammation and Fibrosis

- Wounds leave scars... and so does radiation!
- Inflammation is a normal response to injury, and they can help to fight infection.
 - Increased blood flow.
 - Enhanced immune response.
 - Increased cell turnover: both cell death and proliferation are increased.
- Later on, fibrosis (hardening of the tissue) occurs.
 - Increased production of scar-like extracellular matrix.
- **TNF α , TGF β , PDGF, FGF, and IL-1** are inflammatory mediators that may also play a role in fibrosis.

18

Cancer Genetic and Molecular Characteristics

Genetic Changes in Cancer

- Analysis of cancer cells shows that most of them have highly abnormal DNA, with multiple changes compared to healthy cells.
- As discussed in Chapt. 17, many different types of mutation may occur.
- Mutations occur through several mechanisms:
 - **Heritable:** Present at birth.
 - BRCA1/2 mutations cause heritable breast/ovarian cancer.
 - FAP and MSH/MLH mutations cause heritable colon cancer.
 - Rb mutations cause heritable Retinoblastoma and soft tissue sarcomas.
 - p53 mutations cause Li-Fraumeni syndrome, with multiple malignancies.
 - **Spontaneous:** Random mutations due to aging, oxidation, and the process of DNA replication and mitosis.

- Genomic instability: Loss of DNA repair and apoptosis pathways leads to accumulation of spontaneous mutations over time.
- **Chemical induced:** Many chemicals (tobacco smoke, etc.) cause base damage or DNA crosslinks, and are more likely to cause point mutations.
- **Radiation induced:** Radiation causes double strand breaks and is more likely to cause gross mutations.
- **Cell fusion:** Two cells combine into one, doubling DNA content (tetraploidy) and increasing the rate of mutation.
- Abnormal genes may also be introduced by a virus:
 - **HPV** is the widely-publicized virus responsible for cervical cancers and some head and neck cancers.
 - **EBV** is responsible for nasopharyngeal cancers and Burkitt lymphoma.

Epigenetic Changes in Cancer

- As described in Chapt. 17, epigenetic changes are changes in gene function without any change in the gene itself.
- The most common epigenetic change is chromatin modification.
 - **Methylation** decreases gene expression.
 - **Acetylation** increases gene expression.
- Hyper-methylation is the most common form of **epigenetic silencing**.
 - Cancer cells use methylation to turn off tumor suppressor and DNA repair genes. This may leave them vulnerable to DNA damaging agents (chemo, radiation).
 - **MGMT methylation** in glioblastoma correlates with response to **temozolomide**.

Multi-Step Model of Carcinogenesis

- Cancer is a disease of uncontrolled proliferation, invasion, and metastasis. It usually takes many changes to turn a normal cell into a cancer cell.
 - A cell with uncontrolled proliferation but no invasion or metastasis may form a tumor, but it is likely to be benign or pre-malignant.
 - For example, genital warts are typically benign, but with high-risk HPV subtypes they may become malignant.
- **Initiation** is the first mutation(s) that promotes uncontrolled proliferation.
- **Promotion** is a second mutation(s) that has little effect in a normal cell, but after **initiation** can cause a further increase in proliferation.
- **Progression** can lead to additional mutations that confer malignant characteristics such as invasion and metastasis (Fig. 18.1).

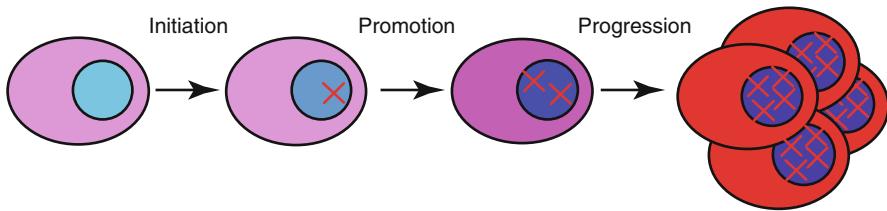


Fig. 18.1 Multiple mutations are required to turn a normal cell into a cancer cell. These are referred to as initiation, promotion, and progression.

- Genetic analysis of benign, premalignant and malignant tumors shows that mutations frequently happen in a specific order:
 - For example, **APC** and **K-Ras** are commonly mutated in benign colon adenomas. (initiation).
 - **CIN** and **DCC** are commonly mutated in dysplastic colon adenomas. (promotion).
 - **p53** is commonly mutated in invasive colon cancer. (progression).

Clinical Significance of Cancer Genomics

- Gene profiling technologies have allowed for measurement of gene expression in human tumors; this is increasingly used for prognostic and therapeutic decision making.
- **Cytotoxic therapy** (classical chemotherapy) damages DNA or inhibits metabolic pathways common to many human cells.
 - Genomics may be used to predict efficacy and toxicity of cytotoxic drugs.
- **Targeted therapy** is designed to specifically inhibit certain cell signaling pathways.
 - Genomics may be used to identify specific mutations or molecular pathways that can be targeted by drugs.
 - Not all targeted therapies target oncogenes.
- **Prognostic gene panels** attempt to predict tumor behavior and treatment response.
 - The **Oncotype DX** multi-gene panel is used to predict the utility of chemotherapy in early stage invasive breast cancer.
 - The **Oncotype DCIS** multi-gene panel may predict the utility of whole-breast irradiation in DCIS.

Oncogenes and Tumor Suppressors

- An **oncogene** (“tumor gene”) is a gene that encourages tumor formation.
 - Oncogenes may act through one of the following:
 - Encouraging proliferation.
 - Encouraging survival. (anti-apoptosis).
 - De-activating tumor suppressors.

- Oncogenes may become activated through mutation, amplification or overexpression.
- A **proto-oncogene** is the normally functioning version of an oncogene.
 - For example, normal b-Raf is a **proto-oncogene**, mutant b-Raf is an **oncogene**.
- A **tumor suppressor** is a gene that can prevent tumor formation.
 - Tumor suppressors may act through one of the following:
 - Promoting cell cycle arrest.
 - Promoting apoptosis.
 - Promoting DNA repair.
 - Inhibiting oncogenes.
 - **Rb** and **p53** can both cause **G₁ arrest**.
 - **p53** can also cause **G₂ arrest**.
 - Tumor suppressors may become deactivated through **mutation** or **epigenetic silencing**.
 - Tumor suppressors may also have a pro-apoptotic function.
 - **Rb** and **p53** are both pro-apoptotic and pro-arrest.
 - Tumor suppressors may act by inhibiting oncogenes.
 - **NF1** (neurofibromatosis type 1 gene) inhibits **Ras**.
 - Tumor suppressors may be DNA repair genes.
 - **BRCA1/2** and **MLH/MSH** are DNA repair genes that strongly predispose to cancer if damaged.

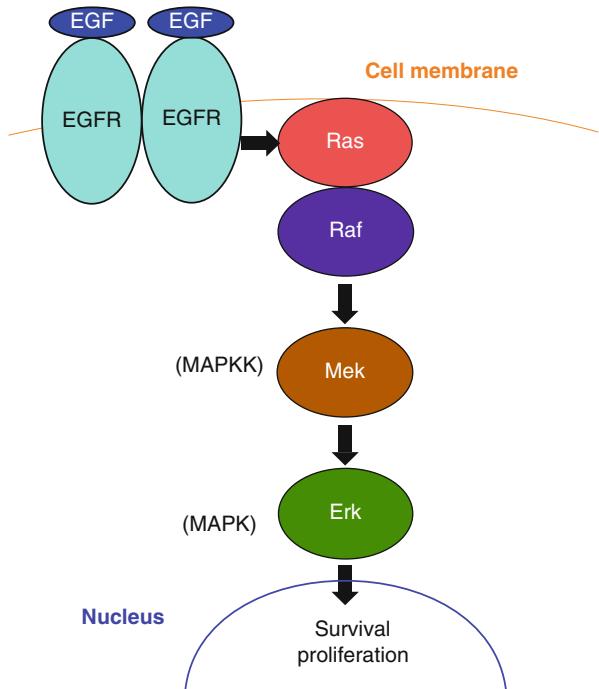
Principles of Targeted Therapy

- It is much easier to inhibit an overactive oncogene than to restore a silenced tumor suppressor.
- Monoclonal Antibody-based drugs (**-mabs**) are very large and cannot easily cross cell membranes. Therefore their targets are limited to cell-membrane receptors and ligands.
 - Antibodies are very specific for one target molecule, and have difficulty crossing the blood-brain barrier.
- Small molecule inhibitor drugs (**-ibs**) can cross cell membranes and target either extracellular or intracellular targets.
 - Tyrosine kinase inhibitors (**TKIs**) may or may not cross the blood-brain barrier.
 - Most **TKI** drugs inhibit multiple tyrosine kinases at the same time.

The EGFR-MAPK Signaling Pathway

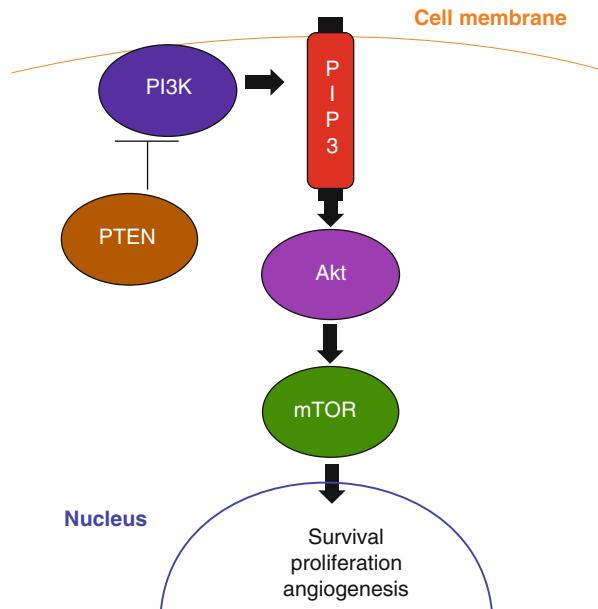
- This is a pro-growth and pro-survival signaling pathway that contains many clinically relevant drug targets (Fig. 18.2).
- **The EGFR family:** These tyrosine kinase receptors sit in the cell membrane and receive growth and stress related signals including **EGF** and are frequently mutated in cancer.

Fig. 18.2 An illustration of the EGFR-MAPK pathway.



- **EGFR (ErbB, Her1)**: Implicated in squamous cell cancers, targeted by drugs including cetuximab, panitumumab, erlotinib, gefitinib.
- **HER2/neu (EGFR2, ErbB2)**: Implicated in breast cancers, targeted by drugs including trastuzumab, pertuzumab, and lapatinib.
- **EGFR3** and **EGFR4** also exist.
- **Ras**: A membrane bound “G-protein” (GTP binding protein) that transmits signal from EGFRs.
 - **K-Ras**: Commonly mutated in colon and lung cancer, confers resistance to EGFR inhibitors.
 - Inhibiting EGFR does nothing if the mutation is downstream of EGFR.
 - **H-Ras** and **N-Ras** also exist.
- **Raf**: A cytoplasmic signaling protein that transmits signal from Ras.
 - **b-Raf**: Commonly mutated in melanoma, renal and liver cancers. Targeted by drugs including sorafenib and vemurafenib.
 - **a-Raf** and **c-Raf** also exist.
- **Mek (MAPKK, MAP2K)**: An intermediate signaling protein between Raf and Erk (MAPK).
 - Multiple subtypes exist.
- **Erk (MAPK)**: A signaling protein that activates pro-growth and pro-survival factors in the nucleus.
 - Multiple subtypes exist.

Fig. 18.3 An illustration of the PI3K-Akt-mTOR pathway.



Angiogenesis and VEGFR

- Angiogenesis is the growth of new blood vessels. This signaling pathway encourages angiogenesis and cell survival, both of which can help tumors grow.
- **VEGFR (Flt/Flk):** These tyrosine kinase receptors sit in the cell membrane and receive angiogenesis signals from **VEGF**.
 - Multiple subtypes exist.
 - Targeted by drugs including bevacizumab, pazopanib, sunitinib and sorafenib.

The PI3K-Akt-mTOR Pathway

- This series of signaling molecules is pro-angiogenesis, pro-growth and anti-apoptosis. It may be activated by VEGFR, IGFR HIF1 and other upstream signals (Fig. 18.3).
- **PI3K:** This membrane-bound protein manufactures PIP3, a signaling lipid implicated both in cancers and diabetes.
 - **PTEN** is a tumor suppressor that mainly inhibits PI3K.
- **Akt (PKB):** A signaling protein that is closely associated with mTOR, and leads to pro-survival, anti-apoptotic pathways.
- **mTOR:** A signaling protein that is implicated in immune function, obesity, cancer, and various other processes.

- Targeted by drugs including sirolimus (rapamycin), temsirolimus, and everolimus. These immunosuppressive drugs also have an anti-cancer effect in some kidney cancers and lymphomas.

Other Oncogene Drug Targets

- **BCR-ABL** and **c-kit** are pro-growth tyrosine kinases found in lymphomas and other cancers.
 - Targeted by the tyrosine kinase inhibitor imatinib.
- **ALK** is a kinase found in some lung cancers and lymphomas.
 - Targeted by the ALK inhibitor crizotinib.
- Oncogenes may act by deactivating tumor suppressors.
 - **HPV E6** and **E7** deactivate **p53** and **Rb** respectively, causing squamous cell cancers.
 - Oncogenes may act by preventing apoptosis.
 - **Bcl-2** and other anti-apoptotic genes are frequently overexpressed in tumors.

Oncogene Signaling and Radiation Therapy

- **p53** is mutated in roughly 50 % of all human cancers, and is greatly involved in the DNA damage response.
 - Cancer cells deficient in **p53** are deficient in RT-induced DNA repair, cell cycle arrest, and apoptosis.
 - This may increase radiosensitivity in some cells due to loss of repair and cell cycle arrest.
 - This may decrease radiosensitivity in some cells due to loss of apoptosis.
- **NF – κB** is a pro-survival and pro-inflammatory signaling molecule that is commonly overexpressed in cancer cells.
 - Tumors with normal levels of **NF – κB** are much more likely to undergo apoptosis in response to radiation therapy.
 - Tumors with **NF – κB overexpression** are highly resistant to radiation-induced apoptosis.

Invasion and Metastasis

- The genetic basis of invasion and metastasis is less well understood than proliferation.
- Invasion requires the loss of normal cell-cell adhesion and degradation of the normal extracellular matrix.
 - Deletion of **E-CAD** and **N-CAM** causes loss of adhesion.
 - Matrix metalloproteinases (**MMPs**) degrade cell matrix.

- Metastasis requires the ability to enter and exit blood or lymph vessels, and to thrive in a new environment.
 - Loss of apoptosis, increased survival and growth signals.
 - “Seed and soil”: certain cancers tend to metastasize to specific sites. For example, lung cancer makes brain mets, prostate cancer makes bone mets.

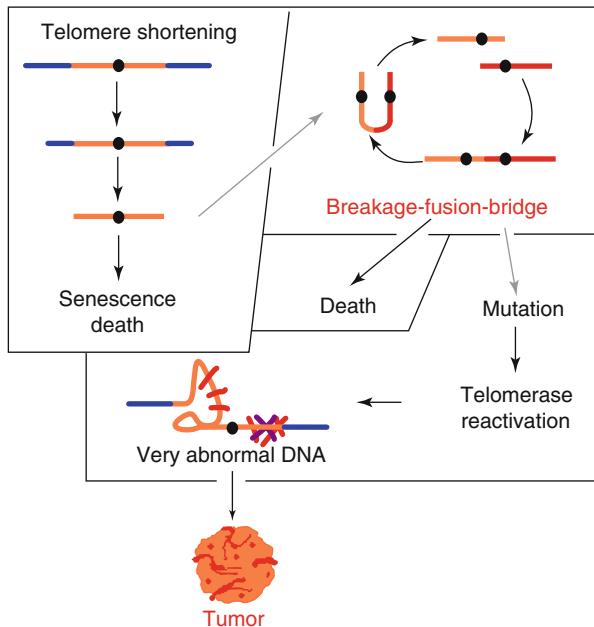
Quiescence and Senescence

- A cell that is normally capable of dividing may stop dividing for many reasons: extrinsic signaling, loss of nutrients, DNA damage, et al.
- **Quiescence** is a reversible growth arrest but cells may resume proliferation at a later time. It is frequently induced when cells are exposed to suboptimal growth conditions (low nutrients, growth factors, very low oxygen levels).
- **Senescence** is a permanent growth arrest induced by aging, DNA damage, or other noxious stimuli.
 - Permanent down-regulation of multiple growth factor pathways.
 - Expression of the cyclin dependent kinase inhibitor 2A p16 or p16ink4A which inhibits cdk4 activity.
 - Expression of Senescence-associated Beta-galactosidase.

Telomeres and Cancer

- DNA in eukaryotic cells is linear, unlike in bacteria.
- Problems with **linear DNA** include:
 - **Sticky ends** – unwanted end-to-end joining leads to mutations and anaphase bridges.
 - **Cannot be completely replicated** – a small amount of DNA on each end is lost with each replication cycle.
- **Telomeres** are repetitive DNA sequences that cap both ends of the chromosome and prevent sticking.
 - A small amount of telomere is lost with each replication cycle.
 - As cells age their telomeres shorten until the cell becomes senescent.
 - The number of divisions a normal cell can undergo before senescence is known as the **Hayflick limit**.
- **Telomerase** allows cells to regenerate telomeres:
 - Most normal cells do not express telomerase.
 - Immortal stem cells and germ cells do.
 - Cancer cells must express telomerase or telomerase-like activity to maintain their ability to proliferate (Fig. 18.4).
- **Breakage-fusion-bridge (BFB) hypothesis:** Cells that try to divide despite insufficient telomere length undergo cycles of DNA breakage, fusion, and anaphase bridges.

Fig. 18.4 Telomeres grow shorter with each cell cycle. When they are too short chromosomes become sticky, causing a “crisis” of breakage-fusion-bridge events. This usually causes cell death but may also lead to tumor formation.



- This is known as “**crisis**” and is almost always lethal. (mitotic catastrophe).
- Surviving cells have grossly mutated DNA with multiple deletions, translocations, and aneuploidy.
- A cell that survives crisis may reactivate telomerase and escape from crisis.
- It then resumes proliferation, propagating mutations to all of its daughter cells.

19

Molecular Mechanisms of DNA Damage and Repair

Types of DNA Damage

- Oxidation, chemotherapy and radiation therapy can all damage DNA. There are many ways in which this can occur.
- **Base Damage:** A DNA base is chemically altered. This may cause a point mutation, or it may predispose to additional DNA damage.
- **Base Mismatch:** A mistake during DNA replication leads to insertion of the wrong base. This will cause a point mutation if it is not repaired.
- **Pyrimidine Dimers:** Two adjacent pyrimidine bases are cross-linked by ultra-violet light. This will cause a point mutation if it is not repaired prior to replication.

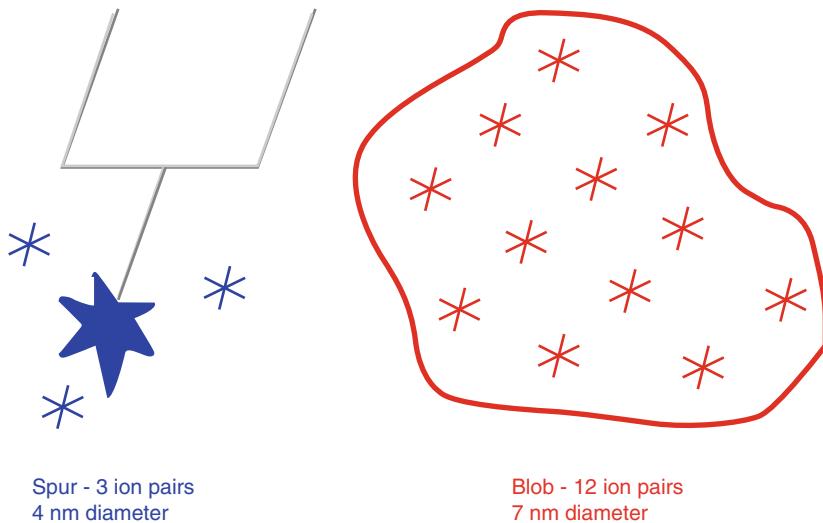


Fig. 19.1 Ionizing radiation can form clusters of ion pairs in water. “Spurs” contain 3 ion pairs across ~4 nm and predominate after exposure to low-LET irradiation. “Blobs” contain 12 ion pairs across ~7 nm and predominate after exposure to high-LET irradiation.

- **Intercalation:** This occurs when abnormal chemical groups (such as chemotherapy drugs) are interposed in the DNA helix. This may prevent gene function and replication.
- **Crosslinking:** This occurs when abnormal chemical bonds are formed within the DNA molecule. This may prevent gene function and replication, or cause DNA strand breaks.
- **Single strand breaks (SSBs):** The sugar backbone is broken on one strand but not the other. This is easily repaired as long as the other strand is still intact.
- **Double strand breaks (DSBs):** When the DNA is broken on both strands, it has “sticky ends” that can react with other DNA strands. This causes chromatid and chromosome aberrations that may be mutagenic or lethal.

Ionizing Radiation and DNA Damage

- Each Gy of ionizing radiation causes approximately:
 - $>5,000\times$ base damage
 - $1,000\times$ SSBs
 - $40\times$ DSBs
- The DSB is the primary “mechanism of action” of ionizing radiation. The number of DSBs correlates with cell killing, the other types of damage do not.
 - In contrast, chemotherapy-induced DNA damage depends on the drug and may include base damage, intercalation, crosslinking, and DSBs (Fig. 19.1).

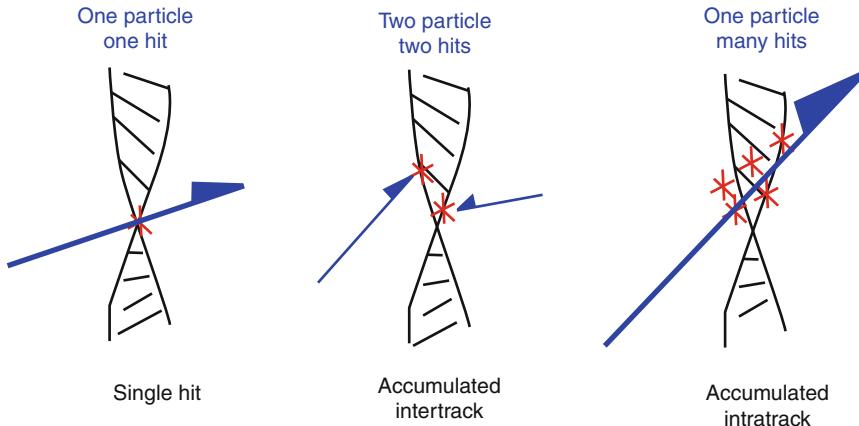


Fig. 19.2 Radiation induced DSBs may be induced several ways. The main difference is whether the damage is done by a single particle or by multiple particles.

- **Locally multiply damaged sites** are defined as multiple DNA lesions close to one another. These are caused by multiple ionization of water, as shown in Fig. 19.2.
 - Base damage and SSBs are easily repaired when alone, but may be very difficult to repair if clustered.
 - Two SSBs occurring close to one another are likely to become a DSB.

Single Hits and Accumulated Damage

- Conceptually, there are several ways for lethal damage (DSBs) to occur. For example (Fig. 19.2):
- **Single hit and Accumulated Intra-track:** Damage is done by a single particle.
 - The number of DSBs formed by this mechanism is determined by total dose, but not by dose rate.
 - These lesions are more likely with **high-LET** irradiation.
- **Accumulated Inter-track:** Damage is done by two separate particles, such as two SSBs combining into a DSB.
 - The number of DSBs formed by this mechanism is determined by total dose and dose rate.
 - With low dose rate irradiation, DNA repair can prevent non-DSB damage from accumulating into DSBs.

Assays for DNA Damage

- **Neutral and alkaline elution**
 - DNA fragments are bound to a filter or column and eluted over time. Fragmented DNA is smaller and therefore elutes faster.

- Under **neutral pH** DNA is double stranded so you can measure **DSBs**.
- Under **alkaline pH** DNA is single stranded so you can measure **SSBs**.
- **Pulsed field electrophoresis**
 - Samples of lysed cells are placed within a gel and electrophoresed to measure DNA fragmentation.
 - Strand breaks are reflected by the presence of smaller DNA fragments.
 - Neutral and alkaline pH may be used.
- **Comet assay (Single Cell Electrophoresis)**
 - A single cell or small numbers of cells are placed within a gel on a slide, and the slide is electrophoresed.
 - Intact DNA is too large and cannot move; fragmented DNA migrates through the gel and forms a “tail”.
 - Neutral and alkaline pH may be used.
- **Plasmid based assays**
 - Plasmids (circular DNA) can be made to fluoresce only if they are broken (i.e., linear instead of circular).

Chromatid and Chromosome Aberrations

- **Aberrations** are **gross mutations** created by double strand breaks.
 - Broken DNA is sticky. If not repaired or mis-repaired, DNA fragments will stick together in the wrong order.
- **Chromosome aberrations:** An aberration occurs in an unreplicated chromosome. When the chromosome is replicated, the aberration is identical in both chromatids.
- **Chromatid aberrations:** An aberration occurs in a replicated chromosome, affecting individual chromatids.
- Some types of aberrations may be either chromosome or chromatid, while others are limited to one type.
- Aberrations may be visible on microscopy, depending on the size of the aberration.

Stable and Unstable Aberrations

- An **unstable aberration** declines in number over time, because it is highly likely to cause cell death.
- A **stable aberration** can persist for years, because it is unlikely to cause cell death.
- **Unstable aberrations** prevent chromosomes from properly segregating during mitosis (Fig. 19.3).
- **Stable aberrations** do not affect chromosome segregation during mitosis (Fig. 19.4).

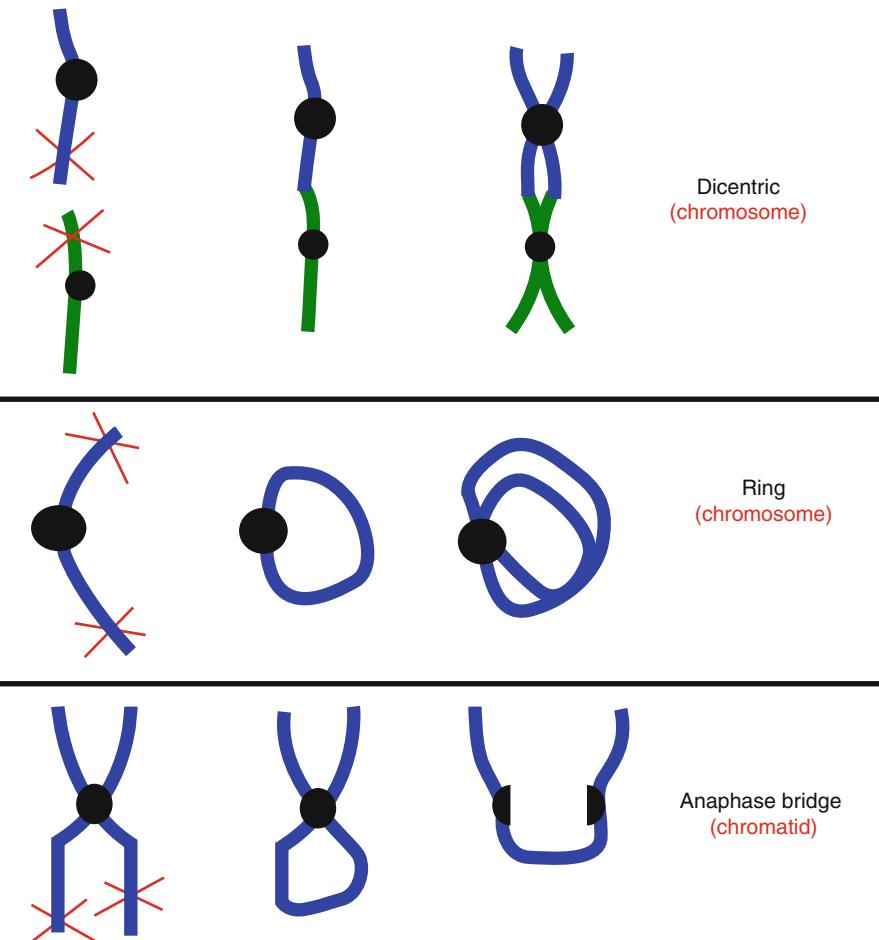


Fig. 19.3 Unstable aberrations include dicentrics, rings, and anaphase bridges.

Measuring DNA Damage

- **Peripheral Blood Lymphocyte Assay**
 - Peripheral blood lymphocytes are very sensitive to radiation, and you can count DNA aberrations in the blood:
 - **Conventional light microscopy** generally measures unstable aberrations that disappear over days-months.
 - **Fluorescence in situ hybridization (FISH)** can measure unstable and stable aberrations. Stable aberrations may persist for years.
- Total-body radiation doses ≥ 0.2 Gy will produce measurable chromosome aberrations in lymphocytes.
 - A linear-quadratic mathematical model can be used to estimate absorbed dose from the number of aberrations. (see below).

Fig. 19.4 Stable aberrations include deletions and symmetrical translocations.

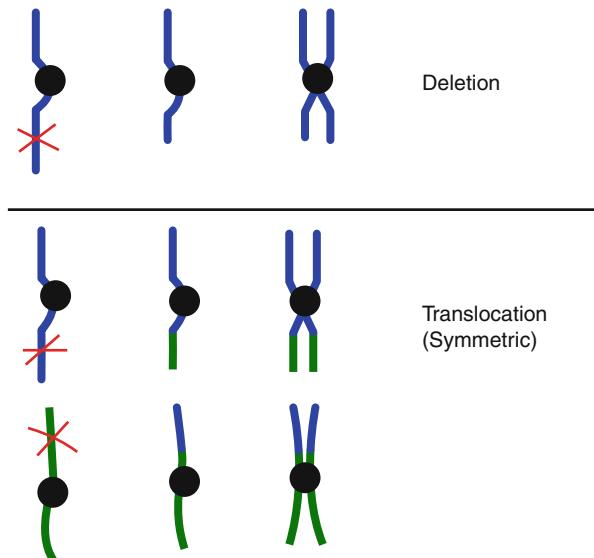
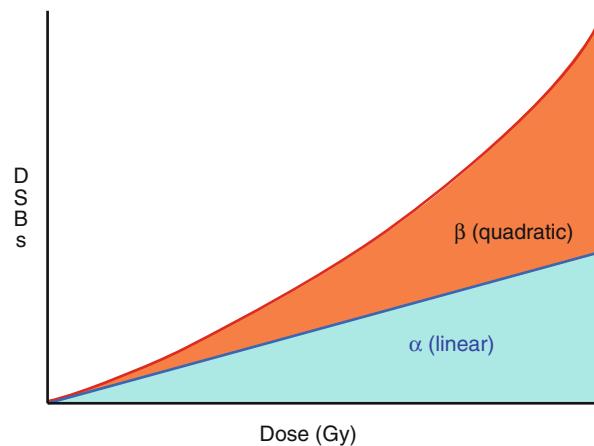


Fig. 19.5 DSB production in cells is a linear-quadratic function of dose. Total DSBs can be expressed as the sum of “linear” damage (not fraction-size dependent) and “quadratic” (fraction-size dependent) damage.



- Total-body radiation doses >4 Gy cannot be estimated by this technique, because the lymphocytes undergo rapid **apoptosis** and disappear.

Dose-Response: Linear-Quadratic Curve

- Plotting DNA damage versus Absorbed Dose results in an upward-sloping curve with a linear-quadratic shape (Fig. 19.5).
- Linear damage is directly proportional to dose, and is measured by the coefficient α .

- This represents single-hit damage and intra-track accumulated damage, which are completely independent of fraction size or dose rate.
- Quadratic damage is proportional to dose squared, and is measured by the coefficient β .
 - This represents inter-track accumulated damage, which is strongly dependent on fraction size and dose rate.
- This curve is the rationale behind the **linear-quadratic (α/β)** model of cell survival.
 - See Chapt. 21.

DNA Repair: Base Damage and Mismatch

- **Base excision repair (BER)** removes a single damaged base.
 - Can only repair very small lesions. Bulky damage must be repaired by other mechanisms.
 - **APE1**, **XRCC1**, and **PARP** recognize base damage and remove the damaged base.
 - **Pol β** and **Ligase 3** fill in the gap.
- **Nucleotide excision repair (NER)** removes the damaged base and several adjacent nucleotides.
 - This allows the repair of bulky lesions including UV, alkyl groups, and platinum.
 - **XP family** (XPC, XPB, XPD, XPG, XPA) plus **RPA**, **ERCC1** and **CSA** are responsible for repair.
 - Mutation of XP genes causes xeroderma pigmentosum (XP).
- **Mismatch Repair (MMR)**
 - Repairs base mismatches and strand crosslinks during DNA replication.
 - Defective MMR causes **Microsatellite Instability (MSI)**, a characteristic pattern of mutations.
 - The **MLH/MSH/PMS** gene family is responsible for mismatch repair. Mutation of these genes causes **Lynch Syndrome**.

DNA Repair: SSBs and DSBs

- **SSB repair:** SSBs are formed at a high rate during irradiation and chemotherapy.
 - SSBs are rapidly repaired by DNA ligases, and have little effect unless they combine into a DSB.
- **DSB recognition and signaling:** Before a DSB can be repaired; the cell has to recognize that it has occurred.
 - **ATM** and **ATR** are the initial signaling molecules that detect **DSBs**.
 - These recruit the “**MRN Complex**” of **MRE**, **rad50**, **NBS1**. These proteins go on to activate DSB repair pathways.
 - As part of DSB signaling, **p53** and **Chk1/Chk2** are activated to cause cell cycle arrest.

- Depending on the cell type and amount of damage, this activation may lead to apoptosis.
- **Homologous recombination repair (HRR)**
 - HRR is the predominant form of DNA repair during **late-S** and **G2**, when sister chromatids are available.
 - A homologous DNA sequence from a sister chromatid is used as a template to restore the broken DNA sequence.
 - This is relatively **error-free**.
 - Can repair **DSBs** and **crosslinks**.
 - Molecules involved in this pathway include **rad52**, **the rad51 complex**, **BLM/WRN/RECQL**, and **BRCA1/BRCA2**.
 - BRCA1/2 mutations are responsible for hereditary breast and ovarian cancer syndrome.
- **Non-Homologous End Joining (NHEJ)**
 - NHEJ is the predominant form of DNA repair during **G0/G1**, as no sister chromatids exist. Can also occur in S and G2 phases, although HRR is preferred.
 - **Error-prone**, may lead to mutation or cell death.
 - Two broken ends are joined together in a process that may delete some of the DNA near the junction.
 - Molecules involved in this pathway include **Ku70/80**, **Artemis**, **DNA-PK**, **XRCC 4**, and **Ligase 4**.
- DSBs are the main mechanism of radiation-induced cell killing, so any defect in DSB repair can increase radiation sensitivity (Fig. 19.6).

Human Genetic Diseases Due to Deficient DNA Repair

(many are also associated with a pre-disposition to cancer)

- **NER disorders (genes in parentheses)**
 - **Xeroderma pigmentosum (XP- gene family)**
 - Photosensitive and very high skin cancer risk.
 - UV hyper-sensitive, not radiosensitive.
 - **Cockayne Syndrome (CSA/CSB)**
 - Photosensitive but no cancer risk.
 - UV hyper-sensitive, not radiosensitive.
- **MMR disorders**
 - **Lynch Syndrome (MLH/MSH gene family)**
 - Extremely high risk of colorectal cancer.
 - Not radiosensitive, but may be hyper-sensitive to chemotherapy.
- **HRR disorders**
 - **Hereditary Breast and Ovarian Cancer Syndrome (BRCA1/BRCA2)**
 - Self-explanatory syndrome name.
 - Despite the DNA repair defect, BRCA1/2 patients are not extremely radiosensitive.

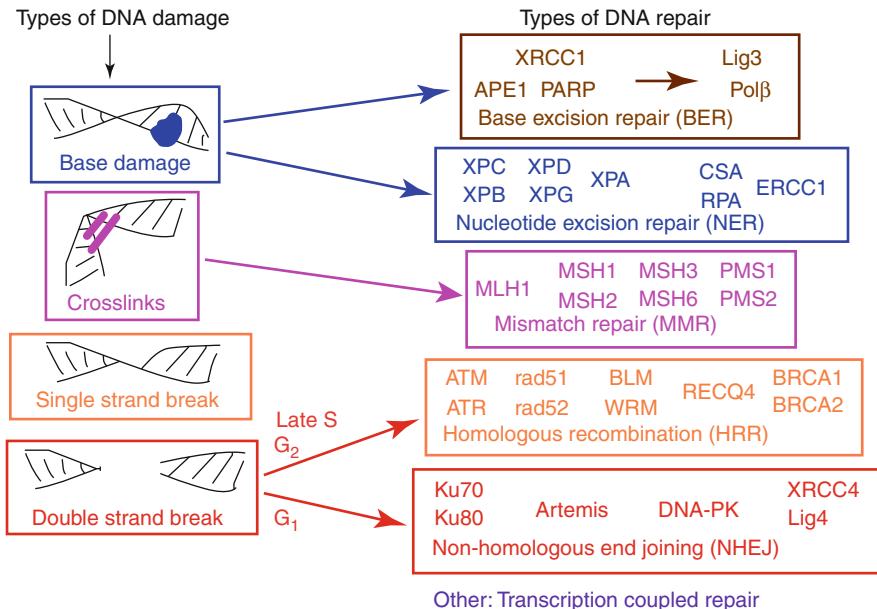


Fig. 19.6 DNA damage may be repaired by one of many different pathways, depending on the type of the damage and the phase of the cell cycle.

- **Disorders affecting multiple repair pathways**
 - **Ataxia Telangiectasia (ATM)**
 - Multiple neurologic and immunologic symptoms, plus high risk of multiple cancers.
 - Extremely radiosensitive.
 - **Ataxia Telangiectasia Like Disorder (Mre11)**
 - Clinically similar to ataxia-telangiectasia.
 - Extremely radiosensitive.
 - **Nijmegen Breakage Syndrome (Nbs1)**
 - Extremely radiosensitive.
 - **Li-Fraumeni Syndrome (p53)**
 - Numerous cancers at a young age.
 - Somewhat radiosensitive, and very high rate of radiation-induced malignancies.
- **Other disorders associated with radiosensitivity**
 - Basal cell nevoid syndrome, Cockayne syndrome, Fanconi anemia, Gardner syndrome, Usher syndrome, Warner syndrome, Bloom syndrome, Down syndrome.

20

Cell Death and Survival Assays

Definition of Cell Death

- In radiobiology we usually refer to **reproductive cell death**.
 - Death is defined as **loss of reproductive (“clonogenic”, “colony forming” capability)**.
- This definition is very relevant to a tumor. If tumor cells cannot reproduce, they are no longer clonogenically viable.
- This is also relevant to rapidly dividing normal tissues such as those in the gut or bone marrow.
- This is not so relevant to highly differentiated normal tissues that normally do not divide. For example, nerves and muscles are “dead” by this definition.

- A cell with severely damaged DNA may grow and divide for a short time before becoming unable to divide.
 - This cell is reproductively **dead**. It is incapable of producing a colony *in vitro* or reestablishing a clone *in vivo*.

Mechanisms of Cell Death

- **Necrosis**
 - Un-planned, un-organized cell death.
 - Random destruction of proteins and DNA.
 - DNA “smears” on a gel, no ladder.
 - Cell swells as it dies.
 - Cell membrane falls apart.
 - Highly pro-inflammatory.
 - May be caused by anything – trauma, heat, cold, hypoxia, oxidative stress, acid or alkaline pH, toxins, etc.
- **Apoptosis**
 - The most common form of **programmed cell death**.
 - Also known as **interphase death**, to differentiate it from mitotic death.
 - Cell dies in an orderly and controlled fashion.
 - Controlled digestion of proteins and DNA.
 - DNA “laddering” can be measured.
 - Cell shrinks as it dies.
 - Cell membrane stays intact.
 - Cell breaks into membrane-covered “blebs” also known as “apoptotic bodies”.
 - No inflammatory response.
 - An important part of embryonic development.
 - For example, you have fingers because the cells in between your fingers underwent apoptosis.
 - Apoptosis occurs in response to radiation in some but not all cells.
 - Very radiosensitive cells like normal lymphocytes, lymphoma and neuroblastoma cells have a lot of apoptosis.
 - Very radioresistant tumor cells like melanoma and glioblastoma have no meaningful apoptosis.
- **Alternative forms of programmed cell death**
 - **Autophagy**: Self-digestion with lysosomes, typically in response to nutrient deprivation.
 - **Anoikis**: Programmed cell death that occurs when cells are placed in an unfamiliar organ or tissue. Cancer cells must overcome anoikis to metastasize.

Cell Death After Irradiation

- **Mitotic Catastrophe** (aka mitotic death)
 - This occurs when cells are unable to properly segregate their chromosomes during mitosis. Cell death occurs from massive DNA damage.
 - Mitotic catastrophe is caused by lethal DNA aberrations, which are caused by DSBs from irradiation.
 - Refer to Chapt. 19 for more details.
 - The DNA aberration is not lethal until the cell attempts mitosis, so there is a time delay between irradiation and mitotic catastrophe.
 - This is why it takes days to weeks for a tumor to regress after irradiation.
- **Senescence** (cessation of cell cycle)
 - Cells remain intact but become unable to divide due to DNA damage. This makes them “reproductively dead” even though the cells are still there.
 - Senescence is a normal part of cellular aging but may also happen in response to injury, including radiation.
 - p16 and β – galactosidase are molecular markers of senescence.

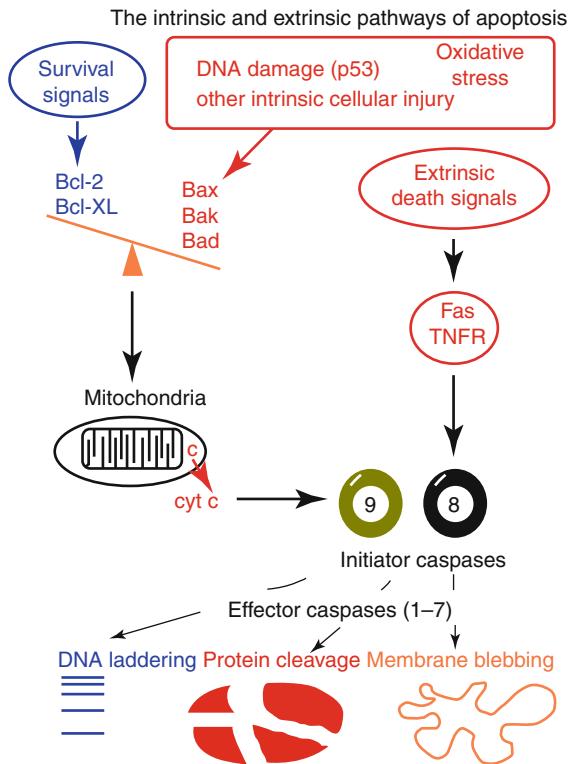
Tissue Effects After Irradiation: When?

- **Apoptosis** usually begins within **6–24 h** after irradiation, however delayed apoptosis (several days) has also been observed.
 - Apoptotic bodies are rapidly degraded by bystander cells, so they quickly disappear.
- **Mitotic catastrophe** usually happens within one to two cell cycles. (**15 h to 2 weeks** in actively cycling cells).
- Necrosis may be observed for days to a small number of weeks after irradiation. At very high doses it may occur within hours of irradiation.
- **Late responses:** Irradiated tissues may show changes **months to years** after radiation.
 - These changes may not be directly linked to cell killing.
 - Fibrosis, microvascular changes, chronic inflammation, decreased wound healing.

Molecular Pathways of Apoptosis

- Apoptosis requires an orderly sequence of events to destroy the cell without causing any inflammation.
- There are two major mechanisms to initiate apoptosis:
- **Intrinsic pathway of apoptosis** is initiated by cellular stress or DNA damage.
 - **ATM** senses **DNA damage and signals p53** which activates pro-apoptotic **Bax/Bak/Bad**. This leads to pore formation in the mitochondrial membranes.

Fig. 20.1 The intrinsic and extrinsic signaling pathways of apoptosis. Apoptosis is initiated by caspase 8 (extrinsic) and caspase 9 (intrinsic), which can be remembered as billiard balls! If the cell is behind the 8-ball, it is dead.



- Once the mitochondria become sufficiently porous, **cytochrome c** leaks out and activates **Caspase 9**, the intrinsic pathway **initiator caspase** that goes on to activate killer caspases such as 3 and 6.
- This can be part of the radiation response in some normal cells such as lymphocytes or in cancers such as lymphoma.
- Anti-apoptotic **Bcl-2** and **Bcl-XL** suppress mitochondrial pore formation and are therefore pro-survival.
- Extrinsic pathway of apoptosis** is initiated by the **Fas** or **TNFR** receptor.
 - These bind death-promoting ligands **FasL** and **TNF** respectively.
 - This leads to cleavage and activation of **caspase 8**, the extrinsic-pathway **initiator caspase**.
 - Tumors can express death ligands in order to cause apoptosis in T-cells, suppressing the immune response (Fig. 20.1).
- Once **caspase 8 or 9** (initiator caspases) are activated, they rapidly activate **caspases 1, 3, 4, 6, 7** (effector caspases).
 - The effector caspases form an irreversible protease cascade, each protease activating more proteases to cause cell death.

- The cell membrane remains intact, so cell contents do not leak out into the interstitial space. Instead, cell contents are neatly packaged into apoptotic bodies for digestion by neighboring cells.
- Cancer cells are often deficient in apoptosis. This may happen one of two ways:
 - **Increased anti-apoptotic signal:** For example, **EBV** makes a viral homolog of **Bcl-2**. This predisposes to lymphomas and nasopharyngeal cancers.
 - **Decreased pro-apoptotic signal:** For example, **HPV** makes **E6** and **E7** which suppress **p53** activity. This predisposes to squamous cell cancers.

Survival of Viruses, Bacteria, and Eukaryotic Cells After Irradiation

- Radiosensitivity depends on three things: DNA content, repair mechanisms, and apoptosis.
 - More DNA = easier target to hit = more sensitive
 - More repair = less sensitive
 - More apoptosis = more sensitive
- **Mammalian cells** are highly radiosensitive because they have lots of DNA and can undergo apoptosis.
 - **~2 Gy** can kill approximately half of mammalian cells, **~70 Gy** delivered in 2 Gy fractions can sterilize a tumor.
- Yeast and bacteria are far more resistant, due to much lower DNA content and lack of apoptosis.
 - **~10s-100s of Gy** will kill half of bacteria and yeast.
 - A food processing irradiator may deliver up to 20,000 Gy to sterilize bacteria.
- **Viruses** are extremely radioresistant because they have so very little DNA compared to a cell. Certain bacteria such as *Micrococcus* (*Deinococcus radiodurans*) are radioresistant due to DNA repair.
 - Lethal dose = Totally impractical # of Gy.

A Word on Assays

- **In vitro assays** measure the survival of cell lines under non-physiologic conditions.
 - This allows for very careful control of all variables:
 - Oxygen, temperature, nutrient levels.
 - Precise drug concentrations.
 - In vitro assays are non-physiological:
 - Single cell type with no vasculature.
 - No normal tissue or immune cells present.
 - Cannot measure late effects.

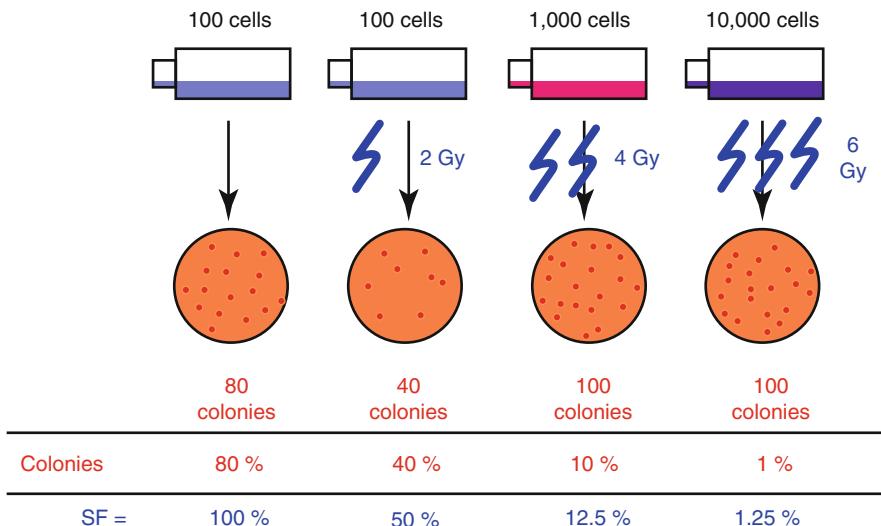


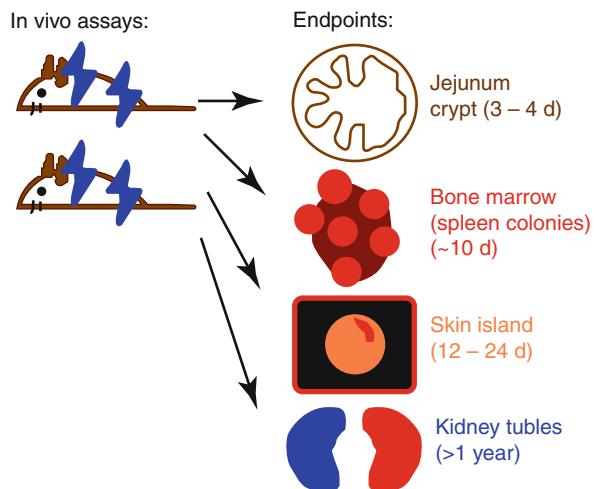
Fig. 20.2 The clonogenic survival assay. Surviving fraction may be calculated by dividing the percent colonies formed by the plating efficiency (percent colonies formed without irradiation).

- **In vivo assays** measure cell survival, normal tissue function, or tumor growth in an experimental animal.
 - Advantages of in vivo assays include:
 - Tissues and vasculature are intact.
 - Tumor can interact with surrounding normal tissues.
 - Can measure late effects if you wait long enough.
 - Oxygen, temperature, nutrient and drug concentrations may be controlled to some extent.
 - Animal experiments are still very different from human patients:
 - Animal cells have different tolerances for radiation and chemotherapy.
 - Many experimental animals are not immuno-competent so there are no immune effects.

In Vitro Clonogenic Survival Assays

- **Clonogenic survival** is defined by the ability to form colonies. Therefore survival is measured by plating out cells and seeing how many colonies they form (Fig. 20.2).
- Even in the absence of radiation, not every cell put on a plate will form a colony.
 - **Plating Efficiency (PE)** = % colony formation with no dose.

Fig. 20.3 Animal normal tissue assays. The time it takes to measure each endpoint depends on whether it is an early or late responding tissue.



- Therefore, the % colonies formed at any given dose level must be divided by the % colonies at zero dose to get the **surviving fraction (SF)**.

$$SF(Dose) = \frac{\% \text{ colonies (Dose)}}{\% \text{ colonies (No dose)}} \quad (20.1)$$

Effects of Fraction Size, Dose Rate and Cell Type

- Cell survival *usually* decreases as fraction size and dose rate increase. This is due to decreased repair.
 - For a detailed discussion see Chapt. 21.
- Non-dividing cells are the most radioresistant, while rapidly dividing cells with active apoptosis are highly radiosensitive.
 - For a detailed discussion see Chapt. 26.

In Vivo Normal Tissue Assays

- Jejunal crypt stem cell assay (Fig. 20.3)**
 - Early responding tissue.
 - Mouse intestines are irradiated with enough dose (≥ 11 Gy) to destroy the villi.
 - After **3.5 days** some of the jejunal crypts will start to regenerate.
 - 1 regenerating crypt = 1 surviving clonogenic cell.
 - Endpoint = crypts per circumference**
- Bone marrow stem cell assay (Till and McCulloch)**
 - Early responding tissue.
 - Donor mice** irradiated with a test dose.

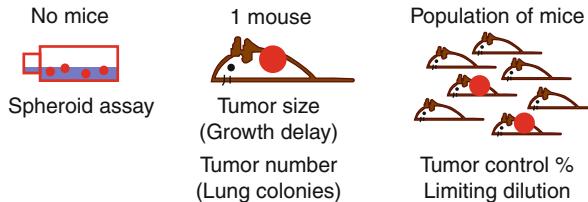


Fig. 20.4 Experimental tumor models. Tumors differ from single cells because they are macroscopic in size, so the center of a tumor has less access to oxygen and nutrients than the core

- **Recipient mice** irradiated with a supralethal dose ≥ 9 Gy. (All bone marrow cells are killed).
- **Donor bone marrow** injected into **recipient mice**.
- Donor stem cells form **colonies** in the spleen which can be easily counted. (this takes ~ 10 days).
 - 1 colony = 1 surviving clonogenic cell.
 - **Endpoint** = colonies per 10^n donor stem cells.
- **Skin clone assay**
 - Early responding tissue.
 - High dose radiation used to create a “moat” of dead skin, with an “island” of intact skin in the middle.
 - The skin “island” is then irradiated with a test dose.
 - This area of skin regrows after **12–24 days** as a series of nodules.
 - 1 nodule = 1 surviving clonogenic cell.
 - **Endpoint** = skin nodules per cm^2 .
- **Kidney tubule assay**
 - Late responding tissue.
 - For each mouse, one kidney is irradiated and one is spared.
 - **Wait 60 weeks.**
 - Compare number of intact kidney tubules on irradiated side vs. unirradiated side.
 - **Endpoint** = % of tubules intact.

Experimental Tumor Models

- **Spheroid systems** (Fig. 20.4).
 - Must use a tumor cell line that grows as **spheroids** in cell culture. (clumps of many cells, not single cells).
 - Spheroids are more “in vivo like” than a monolayer of cells, but less complex than an animal model.
 - Spheroids are irradiated while intact, and separated into single cells for plating out and counting colonies.

- **Tumor growth measurements**
 - Control animals have untreated tumors.
 - Experimental animals receive radiation to their tumors.
 - Primary endpoint = **growth delay**.
(Days for treated tumor to grow to X size) – (Days for untreated tumor to grow to X size).
- **Tumor lung colony assay.**
 - Must use a mouse tumor with very high tendency to form lung metastases. (i.e., mouse sarcoma).
 - Inject tumor cells into recipient mouse, wait for lung colonies to form, and count them.
 - Count **lung colonies** in mice injected with irradiated and unirradiated tumor cells:

$$SF(Dose) = \frac{\text{Colonies (Dose)}}{\text{Colonies (No dose)}} \quad (20.2)$$

- **TCD₅₀ tumor control assay**
 - Groups of animals with the same tumor are treated with different doses of radiation.
 - Primary endpoint = **Tumor Control Dose 50 (TCD₅₀)**.
 - Dose required to control 50 % of tumors.
 - Very reproducible number for established tumor cell lines in inbred animals.
 - Used to compare tumor control doses with single-fraction and fractionated radiation.
- **Tumor limiting dilution assay**
 - **Transplantable leukemia** in **mice** can be transmitted by intra-peritoneal injection.
 - Primary endpoint = **Tumor Dilution 50 (TD₅₀)**.
 - Number of leukemia cells required to induce a leukemia in 50 % of recipient mice.
 - Compare leukemia cells from irradiated and unirradiated leukemic mice:

$$SF(Dose) = \frac{\text{TD}_{50} (\text{No dose})}{\text{TD}_{50} (\text{Dose})} \quad (20.3)$$

- **In Vivo/In Vitro assay**
 - Must use a tumor cell line that is capable of growing both **in vivo** (in a mouse) and **in vitro** (on a plate).
 - Tumors are grown and treated in mice.
 - Tumors are then excised, plated out, and colonies are counted like in a cell culture assay.
 - This allows for an **in vitro** measurement of cell survival after irradiation under **in vivo**.

21

Fractionated Radiation Survival Models

Fractionation Definitions

- **Standard Fractionation:** Once daily, 5 days/week, no more than 2 Gy/fraction.
 - **Split Course:** RT with planned treatment breaks.
- **Altered Fractionation:** Anything other than standard fractionation.
- **Accelerated Fractionation:** Any fractionation schedule that gives >10 Gy/week. Subtypes include:
 - Pure accelerated fractionation (2 Gy/fx, 6–7 fx/week)
 - Accelerated hypofractionation (>3 Gy/fx)
 - Accelerated hyperfractionation (>1 fx/day)
- **Hypofractionation:** Increased fraction size, with or without decreased number of fractions/week.

- **Stereotactic Radiation (SRS/SBRT/SABR):** RT delivered with stereotactic localization techniques in five fractions or less.
- **Fractionated Stereotactic RT (FSRT):** RT delivered with stereotactic techniques and more than five fractions.
- **Hyperfractionation:** Decreased fraction size with more than one fraction per day (BID or TID).
- **Concomitant Boost (CB):** Two fractions per day with one fraction to a large field and the other to a boost volume.
- **Simultaneous Integrated Boost (SIB):** One fraction per day with a higher dose to a boost volume and a lower dose to the large field.

The “4 R’s” of Radiobiology

- Fractionated RT is biologically superior to single-fraction RT in most situations, and the “**Four R’s**” describe the biological effects of fractionation:
 - **Repair** (sublethal and potentially lethal damage repair)
 - **Reoxygenation** (acute and chronic hypoxia)
 - **Redistribution** (cell cycle and dose rate effects)
 - **Repopulation**
- **Repair** is discussed in this chapter.
 - Repair increases cell *survival* after fractionated radiation, both for tumors and normal tissues.
- **Oxygen Effect** and **Reoxygenation** are discussed in Chaps. 22 and 23.
 - Reoxygenation can increase tumor cell *killing* in previously hypoxic areas of tumors, but does not affect well oxygenated normal tissues.
- **Redistribution** and **Repopulation** are discussed in Chapt. 24.
 - Redistribution can increase tumor cell *killing* as they enter more radiosensitive parts of the cell cycle.
 - Repopulation increases tumor and normal cell *survival* over the course of a prolonged treatment time.
- The so-called “**fifth R**” is **Radiosensitivity**, which varies between different tissues and tumors.

Sublethal and Potentially Lethal Damage Repair

- There are two different types of repairable damage that are measured by different assays.
 - **SLDR** and **PLDR** both contribute to the survival of cells, tissues, or tumors after irradiation.

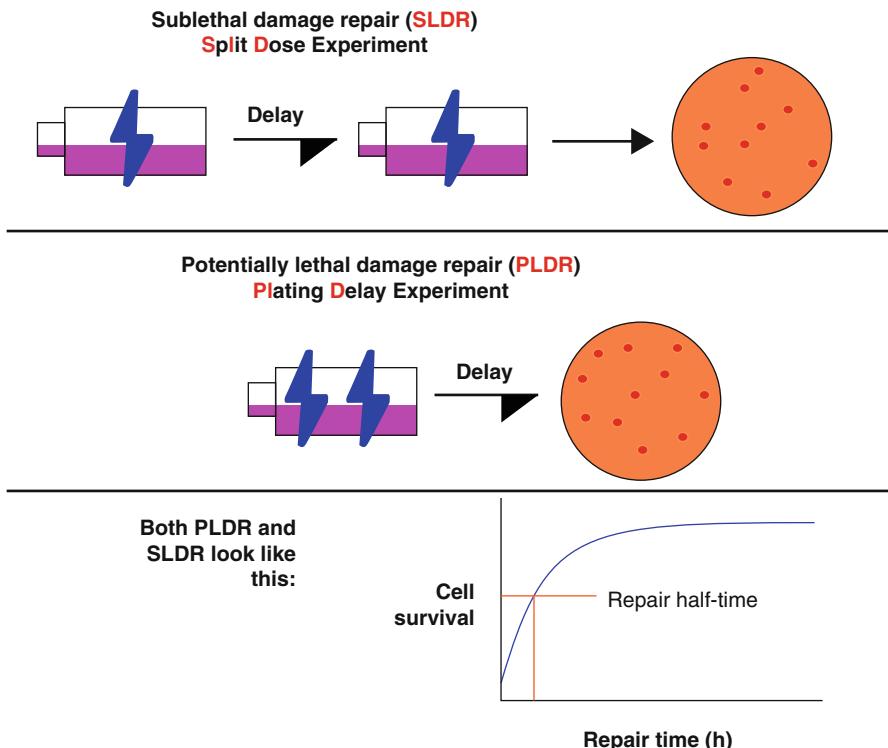


Fig. 21.1 Sub-lethal and potentially lethal damage are two different types of repairable damage. These are measured by a “Split Dose” and a “Plating Delay” experiment, respectively.

Sublethal Damage Repair (SLDR)

- **Definition of SLD:** DNA damage that is never lethal by itself but can become lethal if combined with additional damage.
 - See “Accumulated Intertrack Damage” (Chapt. 19).
- Two radiation doses must be given. Cells are given time to repair between the two doses.
- After the second dose, cells are immediately plated out to measure survival.
- **Mnemonic:** **SLD = Split Dose** experiment.

Potentially Lethal Damage Repair (PLDR)

- **Definition of PLD:** DNA damage that is **lethal during cell division** but can be repaired prior to cell division.
- A single radiation dose is given.
- After irradiation, cells are given time to repair under non-growth conditions, prior to plating out and measuring survival.
- **Mnemonic:** **PLD = Plating Delay** experiment (Fig. 21.1).

Half-Time of Repair

- Repair occurs fairly rapidly, with a repair half-time of **~1 h** in cell culture.
- Repair times may be longer for late-responding normal tissue.
- Repair is essentially complete by **6 h** post-radiation.
 - Most twice-daily radiotherapy regimens use a minimum of **6 h** between fractions.
 - Three times daily regimens may “cheat” with a 4 h minimum, mostly for scheduling reasons.

A Note on Mathematical Modeling

- This chapter focuses on survival models for irradiation: single hit multitarget, two component, linear-quadratic, and models of biologically effective or equivalent dose.
- All of these mathematical models are different ways to interpret the available data (cell survival, tumor control).
 - The **linear-quadratic (α/β) model** is most commonly used in the clinic due to its simplicity.
 - Far more sophisticated models exist in the literature.

Poisson Statistics: What Are They?

- **Poisson statistics** describe a *large number* of random events happening to a *large number* of subjects, averaging out to a *small number* of events per subject (Fig. 21.2).
 - This is a pretty good approximation of radiation hitting cells.
 - At an average of **X events per subject**:
 - (e^{-X}) subjects have no events.
 - $(1 - e^{-X})$ subjects have at least one event.

Poisson Statistics and Cell Survival

- The Poisson model is used for *surviving fraction (SF)* of cells:
 - At an average of **X lethal hits per cell**:
 - (e^{-X}) cells survive. (No hits)
 - $(1 - e^{-X})$ cells die. (at least 1 hit)
 - Based on this equation,
 - **@ 1 hit per cell: SF = 0.37 (i.e. D_{37} or D_0)**
 - **@ 2 hits per cell: SF = 0.14**
 - **@ 2.3 hits per cell: SF = 0.10**
 - **@ 3 hits per cell: SF = 0.05**
 - D_0 is defined as *the radiation dose resulting in 37 % survival*. This is assumed to be equal to the radiation dose necessary to cause one lethal hit per cell.

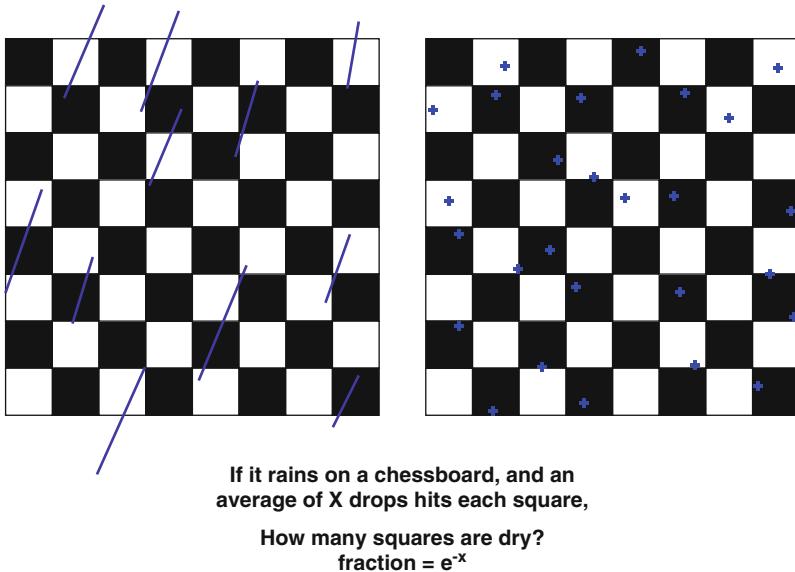


Fig. 21.2 Poisson statistics. This class of statistics may be described by the “raindrop analogy” as shown above. This is relevant to radiotherapy as radiation hitting cells is rather similar to raindrops hitting a board.

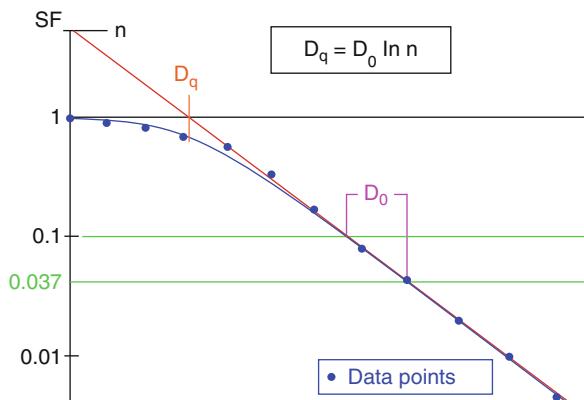
- Poisson is also used for *tumor control probability (TCP)*:
 - At an average of **X surviving tumor cells per patient**:
 - (e^{-X}) patients are cured (no tumor cells).
 - $(1 - e^{-X})$ patients recur. (at least 1 tumor cell).
 - Based on this equation,
 - @ 1 tumor cell per pt: **TCP = 0.37**
 - @ 0.5 tumor cells per pt: **TCP = 0.61**
 - @ 0.1 tumor cells per pt: **TCP = 0.90**
 - @ 0.05 tumor cells per pt: **TCP = 0.95**
 - @ 0.01 tumor cells per pt: **TCP = 0.99**
 - **Rule of Thumb:** To achieve a certain **TCP**, you should aim for a tumor cell survival of **(1 – TCP)**.

Single-Hit, Multi-Target Model

- This model assumes that each cell has multiple independent targets, all of which must be hit to produce cell killing.
- For a single dose D , surviving fraction equals:

$$SF(D) = 1 - \left(1 - e^{-\frac{D}{D_0}}\right)^n \quad (21.1)$$

Fig. 21.3 The single-hit survival curve. Notice that it is curved at low doses and straight at high doses. This allows you to calculate D_0 by taking measurements in the high-dose region.



- D_0 (“D-not”) = Dose required to cause 1 hit per cell
- n = Extrapolation Number
- $D_q = D_0 * \ln n$ = Quasi-threshold Dose
- This looks complicated but it is much easier to understand if you draw a picture, as shown in Fig. 21.3.

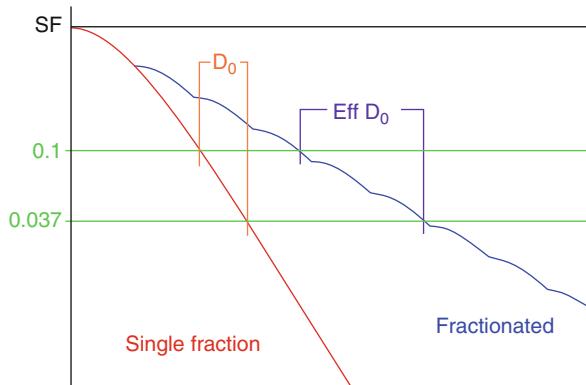
Single-Hit Model: Drawing a Survival Curve

- Plot your SF datapoints on a semi-log chart.
 - **In SF** = logarithmic y axis
 - **Dose** = x axis
- Draw a straight line that connects all of the high dose points (Fig. 21.3).
 - **Y axis intercept** = $\ln n$
 - **X axis intercept** = D_q
 - **Slope** = $D_0 = D_q / \ln n$

Single Hit Model: D_0 and D_q

- The high dose portion of the curve is actually a straight line:
 - D_0 is defined as the additional dose required to reduce surviving fraction to 37% of what it was before.
 - Do not measure D_0 at $SF = 0.37$. Remember that D_0 applies to the high-dose portion of the curve!
 - Instead, measure the difference in dose between $SF = 0.1$ and $SF = 0.037$.
 - D_0 is a measure of the cell’s inherent radiation sensitivity.
 - Most D_0 values are somewhere around 1 Gy.
 - $D_{10} = 2.3 \times D_0$ = A dose that will reduce surviving fraction by tenfold (i.e., from $SF = 0.1$ to $SF = 0.01$).

Fig. 21.4 D_0 versus effective D_0 . When radiation is fractionated, you need much more dose to achieve the same amount of cell kill. Therefore, effective D_0 is always larger than D_0 .



- The low dose portion of the curve is known as the “shoulder”:
 - D_q tells you how wide the shoulder is.
 - D_q is a measure of the cell’s repair capacity. More repair means a larger D_q and larger shoulder.

Single-Hit Model: Advantages and Disadvantages

- **Advantages:**
 - The high-dose portion of the curve is a straight line.
 - You can draw a single-hit curve with a pencil and ruler.
 - This makes it the simplest of the cell survival models and useful for “paper napkin” calculations.
 - This straight-line component correlates well with cell-culture experiments.
 - The single hit model is more accurate at high doses than at low doses.
- **Disadvantages:**
 - The low-dose portion of the curve greatly underestimates cell kill.
 - Unlike the linear-quadratic model, the single-hit model is not based on a molecular mechanism.
 - Unlike the linear-quadratic model, there is not a simple equation for “equivalent dose” given a daily fractionation schedule.

Fractionated Radiation and Effective D_0

- A fractionated radiation survival curve has a shallower slope compared to a single-fraction survival curve.
 - Assuming complete repair in between fractions, the shoulder is repeated with each fraction (Fig. 21.4).
- The slope of a fractionated survival curve is called the **effective D_0** .

- For a single fraction of \mathbf{D} Gy with a surviving fraction of SF_D :

$$Effective D_0 = -\ln(SF_D)/D \quad (21.2)$$

$$Effective D_{10} = -\log(SF_D)/D = 2.3 \times Effective D_0 \quad (21.3)$$

- After X fractions to total dose XD Gy:

$$SF_{XD} = SF_D^X = e^{-\frac{XD}{Effective D_0}} \quad (21.4)$$

- Effective D_0** is always larger than true \mathbf{D}_0 .
 - At $SF_2 \text{ Gy} = 0.5$, **Effective $D_0 = 2.89$ Gy.**
 - Compare this to a typical \mathbf{D}_0 of ~ 1.1 Gy.

Fractionated Radiation: Solving Survival Questions

- First figure out if the question is asking for a **surviving fraction (SF)** or a **tumor control probability (TCP)**.
 - (1) “What is the dose needed to kill 99% of tumor cells?”
 - This is asking for a **SF = 0.01**.
 - (2) “What is the dose needed to give 99% tumor control of a tumor with 10^9 cells?”
 - This is asking for a **TCP = 0.99**, which equals **0.01** tumor cells.
 - SF = 0.01/10⁹ = 10⁻¹¹**
- Then figure out an **effective D_0** ($=\ln(SF)/D$)
- Effective $D_{10} = 2.3 * Effective D_0$**
- Each Effective D_{10} will reduce SF by tenfold:
 - To achieve a SF = 0.01, Total Dose = $2 * eff D_{10}$.
 - To achieve a SF = 10^{-11} , Total Dose = $11 * eff D_{10}$.

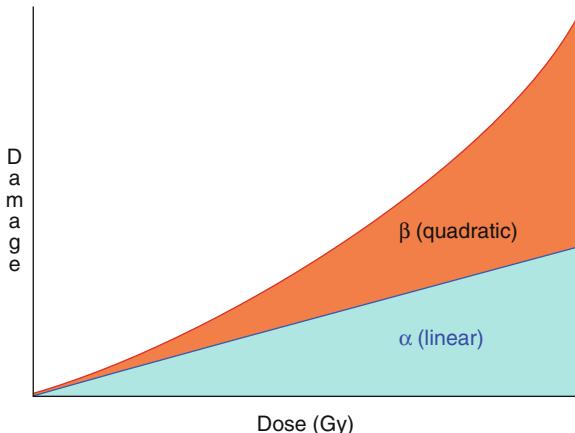
Linear-Quadratic (LQ, Alpha-Beta) Model

- The **Linear-Quadratic Model** was developed after the in vitro observation that DNA damage follows a linear-quadratic relationship with dose \mathbf{D} (Fig. 21.5).
- Lethal DNA aberrations = $\alpha D + \beta D^2 = Cell Kill$**

$$SF_D = e^{-(\alpha D + \beta D^2)} \quad (21.5)$$

- Unlike the single-hit model, the **LQ Model** accounts for two different types of lethal hits which are based on known molecular mechanisms of DNA damage:
 - Single hit kill (α)** is unrepairable damage and is independent of fractionation or dose rate.
 - This corresponds to single hit and intra-track accumulated damage (see Chapt. 19).

Fig. 21.5 The linear-quadratic DNA damage curve. Total DNA damage can be expressed as the sum of “linear” damage (not fraction size dependent) and “quadratic” (fraction size dependent) damage. Figure repeated from Chapt. 19.



- **Two hit kill (β)** is repairable damage and depends on fractionation and dose rate.
 - This corresponds to inter-track accumulated damage (see Chapt. 19).
- The α/β ratio is the dose at which α kill and β kill are equal.
 - **Low α/β ratio** (“high repair”) tissues are relatively resistant at small fraction size and relatively sensitive at large fraction size.
 - **High α/β ratio** (“low repair”) tissues are relatively sensitive at small fraction size and relatively resistant at large fraction size.

Alpha-Beta Ratios of Tissues and Tumor

- Most acute-reacting tissues are believed to have α/β ratio ≈ 10 .
- Most late-reacting tissues are believed to have α/β ratio ≈ 3 .
- CNS tissue (brain, cord) is believed to have α/β ratio $\approx 1-2$.
- Most tumors are believed to have an α/β ratio ≥ 10 .
- Some low α/β tumors may have an α/β ratio $\approx 1.5-4$.
 - Breast and Prostate are the “classic” low α/β tumors.

Alpha-Beta Model and Dose Fractionation

- Based on the LQ model, the rationale for dose fractionation is that tumors have a higher α/β ratio than normal tissues (Fig. 21.6).
- By using smaller fraction sizes the normal tissues (low α/β) are relatively spared.
- Late reacting tissues, such as CNS, are especially sensitive to fraction size due to their low α/β ratio.
- Tumors with low α/β ratio may not benefit as much from fractionation.

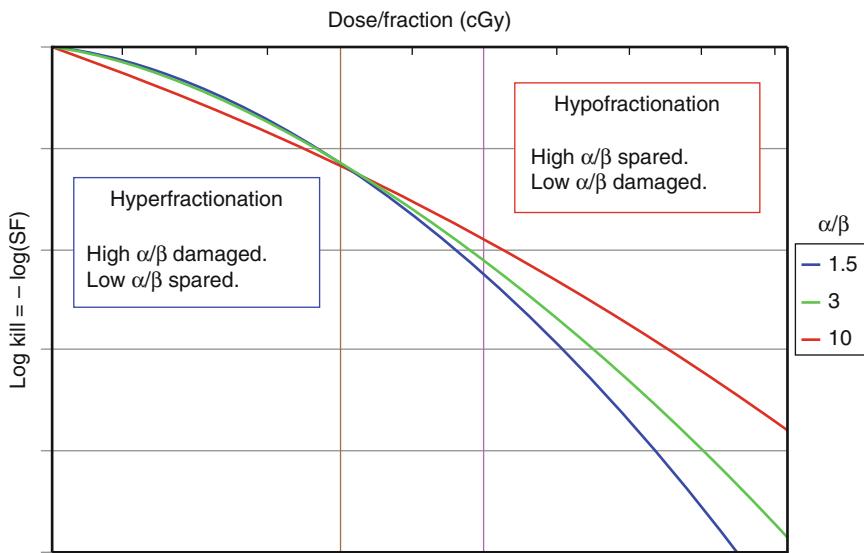


Fig. 21.6 Fraction size and relative kill. Small fraction sizes are relatively more effective at killing high α/β tissues. Large fraction sizes are relatively more effective at killing low α/β tissues.

Alpha-Beta Model: Biologically Effective Dose

- One advantage of the linear-quadratic model is that it is easy to calculate effective doses for different fraction sizes.
 - This makes it very useful in clinical practice.
- Biologically effective dose (BED)** is an extrapolated dose given over infinitely many fractions.
 - This is the opposite of Nominal Standard Dose (NSD), shown later in this chapter, which is an equivalent single fraction dose.
- For **n** fractions of **d** dose per fraction:

$$BED_{\alpha/\beta} = n \times d \times \left(1 + \frac{d}{\alpha/\beta}\right) \quad (21.6)$$

- Note that **BED** is *always* greater than physical dose (**nd**).
- Example Question (1):**
 - You want to limit the spinal cord ($\alpha/\beta = 2$) to no more than 98 Gy BED_2 . What constraint should you use for treating the spine with 3 Gy daily fractions?
 - Each 3 Gy fxn: $BED_2(3 \text{ Gy}) = 3 * 2.5 = 7.5 \text{ Gy}_2$.
 - $98 \text{ Gy}_2 / 7.5 = 13.07$ fractions.
 - $13 \times 3 \text{ Gy} = 39 \text{ Gy}$ maximum dose.

- A closely related number is the **Equivalent Dose in 2 Gy Fractions (EQD _{$\alpha/\beta,2$})**.

$$EQD_{\alpha/\beta,2} = n \times d \times \left(\frac{\alpha/\beta + d}{\alpha/\beta + 2} \right) \quad (21.7)$$

- This number can be used to sum up partial treatment courses given at different fraction size.
- **Example Question (2):**
 - You want to treat a lung cancer to 60 Gy in 2 Gy fractions, but the first five fractions are given at 3 Gy/fx due to SVC syndrome.
 - Assuming $\alpha/\beta = 3$, how much additional dose should you deliver at 2 Gy per fraction?
 - $3 \text{ Gy} \times 5: EQD_{3,2} = 15 * 6/5 = 18 \text{ Gy equivalent}$
 - $60 - 18 \text{ Gy} = 42 \text{ Gy remaining}$
 - So you would give an additional 42 Gy @ 2 Gy/fxn.

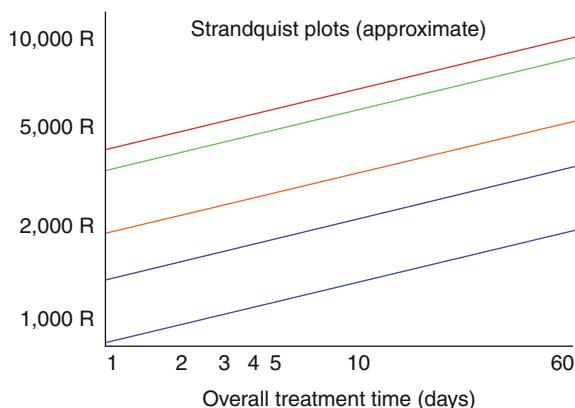
Alpha-Beta Model: Correction Factors

- The **Thames H-factor** is an incomplete repair correction factor that is applied to regimens delivered twice or three times daily. It varies roughly from 0 to 1.
 - For alpha-beta calculations, dose per fraction is multiplied by $(1 + H_m)$, where m is the number of fractions per day.
 - **Example:** You are treating a lung with 45 Gy @ 1.5 Gy BID, spaced 6 h apart. Assuming that $H_2 = 0.2$, what is the equivalent dose @ 1.8 Gy/day?
 - Effective fraction size = $1.5 \text{ Gy} \times 1.2 = 1.8 \text{ Gy}$.
 - So this is equivalent to 45 Gy @ 1.8 Gy daily.
- The **g-factor** is a number used to convert continuous irradiation (such as LDR brachytherapy) into an equivalent daily fraction size.
- The **accelerated repopulation correction factor (D_{prolif})** corrects for proliferation during a prolonged treatment time (see Chapt. 24 for details on accelerated repopulation).
 - After a “kickoff time” T_k , tumor cells begin proliferating much faster than normal.
 - For an overall treatment time $T > T_k$:
 - **Corrected EQD₂** = $EQD_2 - ((T - Tk) * D_{prolif})$
 - So if $D_{prolif} = 0.7 \text{ Gy/day}$, you lose 0.7 Gy of effective dose for each day of accelerated repopulation.

Ellis Nominal Standard Dose (NSD)

- An empiric equation based on the **Strandquist Plots**:
 - Back in the 1930–1940s, Strandquist treated a bunch of skin cancers and plotted radium exposure versus skin erythema, desquamation, necrosis, and tumor cure.

Fig. 21.7 The Strandquist plots (approximate). These parallel lines represent various skin-related endpoints such as erythema, desquamation and necrosis.



- He found that the relationship between total dose and overall treatment time formed a series of parallel lines on a logarithmic chart.
- This predates the linear quadratic model by many decades (Fig. 21.7).
- Unlike newer models, the Ellis NSD has no theoretical basis whatsoever, it is an empiric “curve fitting” model.
- The NSD can accurately predict acute skin toxicity and skin cancer response, because that is where the data came from.
 - The NSD makes no attempt to predict late toxicity.
- There are two versions of the equation: one with time and fractionation, another with just fractionation.
- For N fractions delivered over T days:

$$NSD = N^{0.24} \times T^{0.11} \quad (21.8)$$

or

$$NSD = N^{0.33} \text{ (ignoring time)} \quad (21.9)$$

$$NSD (\text{rets}) = \frac{\text{Dose (Gy)}}{\text{NSD Factor}} \quad (21.10)$$

Very Large Fractions: SBRT/SRS

- The LQ model of cell killing does not appear to be accurate for very large fractions.
 - LQ predicts extremely high quadratic killing, but this does not correlate with experimental observations.
 - At very large fraction size, there may be additional mechanisms for cell killing and cell survival.

- At very large fraction size, cell survival may be dominated by a small population of radioresistant cells.
- Many different models exist for predicting cell kill at very large fraction size.

Other Radiation Survival Models

- The **Single-Hit, LQ, and NSD** models are popular because they are simple enough to calculate by hand.
- More complicated mathematical models exist and are briefly mentioned below.
- **Two-Component Model:**
 - Combines a single-hit single-target (D_1) and a single-hit multi-target model (D_0, D_q).
 - Behaves fairly similar to **LQ** model, except it stops curving at very high doses.
- **Universal Survival Curve (USC) / Single Fraction Equivalent Dose (SFED):**
 - Combines a **LQ** and **single-hit** (D_0) curve so that it stops curving at very high doses.
 - Used for calculating **SRS/SBRT** doses.
- **Lethal-Potentially Lethal (LPL) Model**
 - Damage is classified as lethal or potentially lethal.
 - Potentially lethal damage is either repaired over time or mis-repaired into lethal damage.
 - Multiple potentially lethal hits can become lethal.
 - Shape of curve is extremely similar to **LQ** model, but **LPL** can more accurately model dose-rate and fractionation factors.
- **Repair Saturation Model**
 - Initial damage follows a straight-line exponential function, but is repaired into a survival curve with a shoulder.
 - At high doses repair becomes saturated and is unable to keep up with damage, which is assumed to be linear.
 - Shape of curve is very similar to **single-hit** curve.
- **Induced Repair Model**
 - Used to explain hyper-radiosensitivity at very low dose per fraction.
 - Follows a radiosensitive **L-Q** curve at low dose and a radioresistant **L-Q** curve at high dose.

22

Oxygen Effect, Relative Biological Effectiveness and Linear Energy Transfer

Oxygen Effect

Why?

- **Oxygen Fixation Hypothesis:**
- Ionizing Radiation creates ion pairs in water.
 - Note that this is a form of **indirect action**.
 - Direct action creates ion pairs in DNA, and is unaffected by oxygen.
- Within nanoseconds: Ion pairs in water react with molecules to form free radicals. ($\text{R}\cdot$).
- Within microseconds: Free radicals are eliminated by sulphhydryl-containing free radical scavengers, such as glutathione (GSH).
- Oxygen reacts with free radicals in DNA to form peroxides ($\text{ROO}\cdot$) which **cannot be easily repaired**.
 - This is known as “oxygen fixation” (Fig. 22.1).
- Oxygen increases indirect effects of ionizing radiation if it is present during or within microseconds after irradiation.
- It does not matter what the oxygen concentration is seconds pre- or post- irradiation.
- Therefore, transient hypoxia is a big deal! See Chapt. 23 for details.

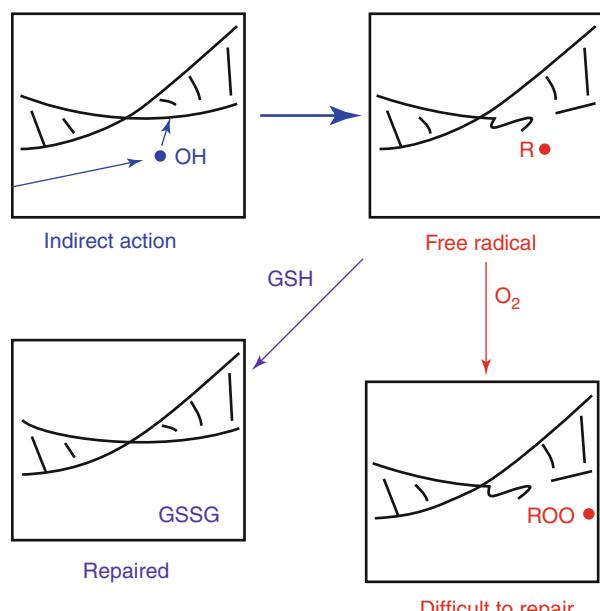


Fig. 22.1 The oxygen fixation hypothesis. Free radicals are easily repaired by antioxidants, but molecular oxygen can convert them into peroxides that are more difficult to repair.

How Much Oxygen Is Needed for the Oxygen Effect?

- The Oxygen Effect operates at very low concentrations of O₂:
 - 0.001 % O₂** (0.008 mmHg): Fully anoxic, no oxygen effect.
 - 0.5 % O₂** (4 mmHg): Half oxygen effect.
 - 2 % O₂** (16 mmHg): Full oxygen effect, no significant difference with further increase of O₂.
- Oxygen levels for comparison:
 - 0.13 % O₂** (1 mmHg): Fully hypoxic tissue.
 - 2–5 % O₂** (20–40 mmHg): Venous blood.
 - 8–13 % O₂** (60–100 mmHg): Arterial blood.
 - 20 % O₂** (150 mmHg): Room air.
 - 100 % O₂** (760 mmHg): Pure oxygen.
- Note that normal tissue should not be hypoxic!
- Even the lowest oxygen tensions in a living human are well above what is needed for full oxygen effect.
- Therefore, hypoxia protects tumors, it does not protect normal tissues.
- See Chapt. 23 for a detailed discussion of hypoxia in tumors.

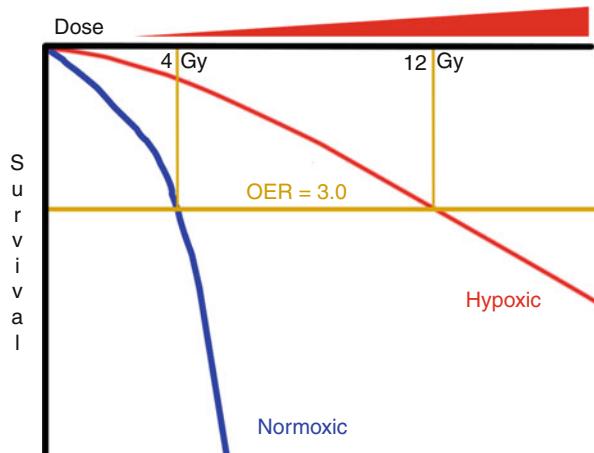
Oxygen Enhancement Ratio (OER)

- OER is defined as a **ratio of doses** that achieve the same biological endpoint (such as cell survival):

$$OER = \frac{\text{Dose (Hypoxic) to cause an effect}}{\text{Dose (Normoxic) for same effect}} \quad (22.1)$$

- Keep in mind it is a ratio of doses, not a ratio of survival or log kill or tumor control or anything else.
- A clinically relevant **OER** (for megavoltage photons) is somewhere around 3.0 (2.5–3.5):
 - In order to kill as many cells as 2 Gy of Co-60 under normoxic conditions, you would need 6 Gy of Co-60 under fully hypoxic conditions.
 - It is easy to see why hypoxia can be such a big deal for clinically relevant tumors!
- OER** is somewhat greater at high fraction size (~3.5) compared to low fraction size (~2.5).
 - Small fractions:** Survival curve is dominated by the most sensitive cells (G₂/M) which have the lowest OER.
 - Large fractions:** Survival curve is dominated by the most resistant cells (S) which have the highest OER.
 - This behavior is the opposite of RBE.

Fig. 22.2 Oxygen enhancement ratio: OER is defined as a ratio of doses that achieve the same effect, as shown by the horizontal orange line.



- **OER** varies depending on the type of radiation:
 - Damage from **low LET** radiation is mostly mediated by indirect action and has a very large oxygen enhancement ratio. (OER ~3).
 - **High LET** radiation causes more damage through direct action, which is not oxygen dependent. (OER ~1) (Fig. 22.2).

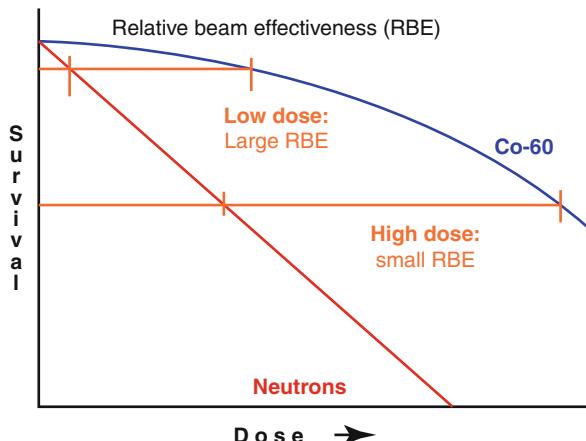
Relative Biological Effectiveness (RBE)

- Not all radiation is created equal! 1 Gy of 1 GeV carbon ions is very different from 1 Gy of Co-60 gamma rays.
- **RBE** is defined as a **ratio of doses** that achieve the same biological endpoint:

$$RBE = \frac{\text{Dose of standard radiation to cause an effect}}{\text{Dose of test radiation for same effect}} \quad (22.2)$$

- Keep in mind it is a ratio of doses, not a ratio of survival or log kill or tumor control or anything else.
- Standard radiation may be defined as **250 kVp x-rays** (as in Hall and Giaccia) or **Co-60** (as in “Cobalt Gray Equivalent”) (Fig. 22.3).
 - At an **RBE** of 3, you need 3 Gy of standard radiation to achieve the same cell kill as 1 Gy of test radiation.
- **RBE** is usually measured by acute effects, so it does not predict late effects (this is a big problem for neutron irradiation).
- **RBE** varies by cell type:
 - Radioresistant cells are resistant to standard radiation, so the **RBE** of high-LET radiation increases.

Fig. 22.3 RBE and Dose:
RBE is defined as a ratio of doses that achieve the same effect, as shown by the horizontal line. RBE is greater at small fraction size than at large fraction size.



- **RBE** is greatest at a small fraction size:
 - **Small fractions:** Repair predominates for standard radiation, but is ineffective for high-LET radiation.
 - **Large fractions:** Repair is overwhelmed even with standard radiation.
 - This behavior is the opposite of **OER** (OER is greatest with large fraction sizes).
- Compare this to **Quality Factor (QF)** aka **Weighting Factor (W_R)**, which is the number used for radiation protection purposes (see Chapt. 14).
 - **QF** is a conservative number and over-estimates the effect of particulate radiation.
 - **QF** does not predict tumor response or normal tissue acute effects.
 - **QF** is intended as a “ballpark estimate” of normal tissue late effects, carcinogenesis and heritable risk.

Linear Energy Transfer (LET), RBE and OER

- **LET** is a measure of how densely ionizing a radiation beam is (Fig. 22.4).
 - See Chapt. 5 for a detailed discussion of **LET**.
- As **LET** increases, **RBE** increases until it reaches a peak at 100 keV/ μm .
 - Decreased repair due to high density of ionizations.
 - Increased direct action, less oxygen dependent.
 - 100 keV/ μm corresponds to one ionization per 2 nm, which is the diameter of a DNA strand, and is considered the optimal LET for cell killing.
- After 100 keV/ μm , **RBE** decreases with **LET** (Fig. 22.5).
 - Overkill effect: A single particle deposits much more energy than is required to kill a cell. Therefore, it kills less cells per absorbed dose.
- **OER** strictly decreases as **LET** increases.
 - $\text{LET} < 1 \text{ keV}/\mu\text{m}$: $\text{OER} = 2.5\text{--}3.5$
 - $\text{LET} > 100 \text{ keV}/\mu\text{m}$: $\text{OER} = 1.0$

Fig. 22.4 A diagram of low LET radiation versus high LET radiation. Both deposit the same radiation dose (ionizations, red stars). However, the low LET ionization events are widely scattered while the high LET ionization events occur in a dense track.

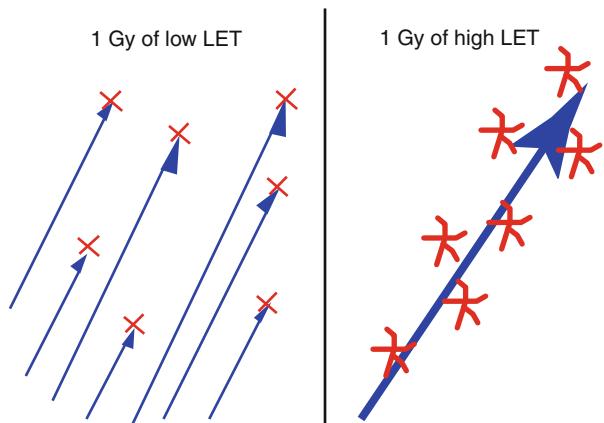
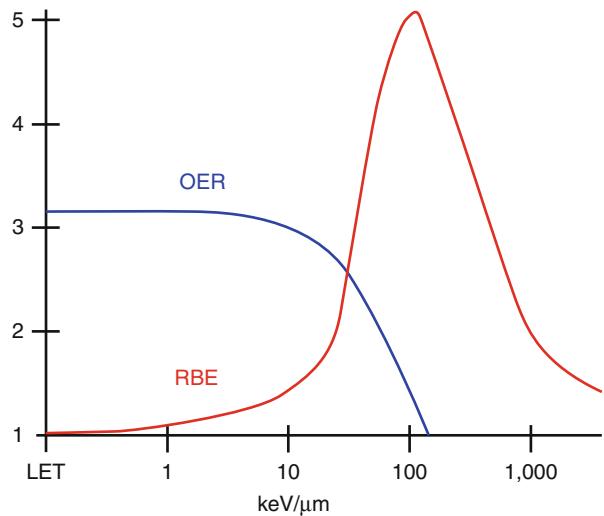


Fig. 22.5 OER and RBE versus LET: As LET increases, RBE peaks around $\sim 100 \text{ keV}/\mu\text{m}$ before it trends back down. OER strictly decreases with LET until it reaches 1 at $\sim 100 \text{ keV}/\mu\text{m}$.



- Typical LET for different forms of radiation:
 - Megavoltage X, γ , e^- : **LET 0.2–0.5 keV/ μm**
 - Fast protons: **LET 0.5 keV/ μm**
 - Kilovoltage X, γ : **LET 2–4 keV/ μm**
 - Slow protons: **LET ~5 keV/ μm**
 - Fast neutrons and alphas: **LET ~100 keV/ μm**
 - Heavy ions (carbon etc): **LET 200–1,000 keV/ μm** .

23

Tumor Micro-environment

Tumor Vasculature

- One of the most important limiting factors in a tumor's growth is its blood supply.
 - Many tumors grow in cords surrounded by normal stroma. This allows them to take advantage of normal blood vessels.
 - Many tumors secrete growth factors that promote the in-growth of new blood vessels.
 - This process is known as **angiogenesis**.
 - **VEGF** is the most famous angiogenic growth factor and is the target of bevacizumab (Avastin).
- Tumor vasculature is “leaky”, poorly organized and less effective than normal blood vessels.

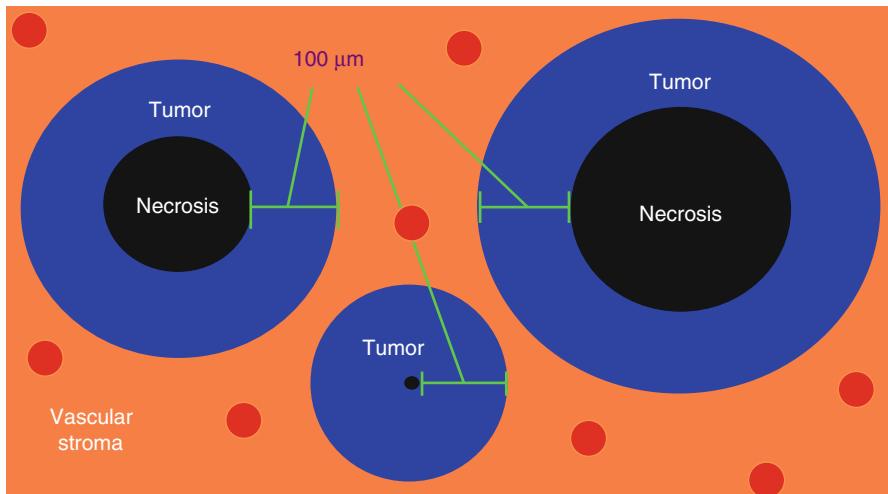


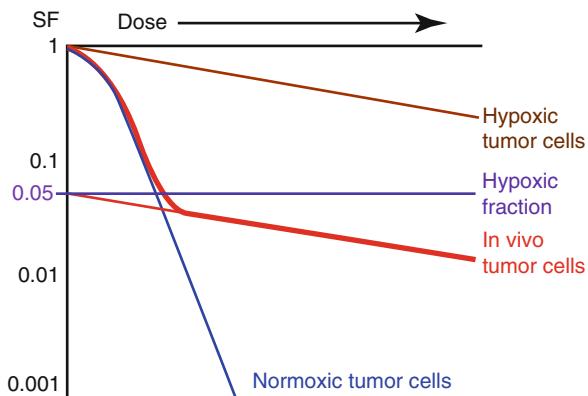
Fig. 23.1 The Thomlinson-Gray hypothesis. Tumors grow in cords surrounded by normal stroma. Regardless of the size of the cord, only the outermost ~100 μm contain viable cells. This is due to the diffusion distance of oxygen.

- The **normalization hypothesis** states that anti-angiogenic therapy can actually improve tumor perfusion by removing abnormal, leaky vessels.
- Therefore anti-angiogenic therapy may actually increase oxygenation and drug delivery to tumors.
- Many tumors have necrotic regions where oxygen pressures are so low that tumor cells die of anoxia.
- Hypoxia greatly decreases the efficacy of low-LET radiation, as discussed in Chapt. 22.

The Thomlinson-Gray Hypothesis

- In 1955, Thomlinson and Gray found that human lung cancers grew in **tumor cords** surrounded by vascularized normal stroma.
 - All tumors larger than ~200 μm had a necrotic core.
 - Only the outermost 100 μm of any cord contained viable cells, the inner portion was necrotic (Fig. 23.1).
- The **Thomlinson-Gray hypothesis** states that the thickness of viable tumor is limited by the diffusion of oxygen.
 - The diffusion distance of oxygen is ~70 μm , after which oxygen tension drops off dramatically.
 - Between 70 and 100 μm , cells are chronically hypoxic.
 - After 100 μm cells begin to die from anoxia. This causes a necrotic core.
- Between the 1950s and now, various oxygen-measuring experiments have confirmed the Thomlinson-Gray hypothesis.

Fig. 23.2 In vivo survival curve: Tumors in an experimental animal were irradiated and then plated out to count cell survival (red). The resulting survival curve can be thought of as the sum of two curves, one for normoxic tumor cells (blue) and one for hypoxic tumor cells (brown).



Mixed Normoxic/Hypoxic Survival Curves

- Like a human tumor, a tumor in an experimental animal will contain both normoxic and hypoxic tumor cells.
- Irradiating the animal tumor and then plating out cells to measure survival will result in a curve that looks like this (Fig. 23.2).
- This “two phase” survival curve can be broken down into two different curves:
 - In the low dose region, normoxic cells outnumber hypoxic cells and so it looks like a normoxic survival curve.
 - In the high dose region, normoxic cells are all killed so it looks like a hypoxic survival curve.
- The **hypoxic fraction** can be estimated by extrapolating the hypoxic portion of the curve back to zero dose.
 - If the curve crosses the Y-axis at $SF = 0.05$, then approximately 5 % of the tumor cells are hypoxic.
- The **OER** can be estimated by the ratio between the D_0 in the high-dose region and in the low-dose region (Powers-Tomlach method).
 - For example:
 - Low Dose $D_0 = 1.1$ Gy
 - High Dose $D_0 = 2.6$ Gy
 - $OER = 2.6/1.1 = 2.4$

Direct Measurement of Hypoxia

- **Oxygen Probes** are microscopic electrodes placed into tumors to directly measure oxygen pressure.
 - The Eppendorf probe is the “gold standard” of oxygen measurement. They are very accurate and can be moved to measure oxygen at different points.

- However, this is inherently invasive – sticking needles into multiple points of your specimen.
 - Difficult and painful for actual patients.
- **Hypoxia Markers** include exogenous and endogenous chemicals that exist under hypoxic conditions.
 - **2-nitroimidazole drugs (pimonidazole, EF5)** form macromolecular adducts only under hypoxic conditions. These adducts can be stained by **IHC**.
 - **CA9** and **HIF1** are endogenous biomolecules that are part of the hypoxia response. These can also be stained by **IHC**.
 - However, these molecules can also be upregulated or mutated in non-hypoxic conditions.
- **DNA damage assays** can be performed immediately after irradiation. Hypoxic cells suffer less damage.
- **Radiotracer imaging** can be performed using radiolabeled compounds that localize to hypoxic or oxic areas:
 - **Oxygen-15 PET** is the gold standard of oxygen imaging, but **O-15** has a half-life of 2 min so it is very expensive and difficult to use.
 - “Hypoxic PET markers” such as **F-MISO**, **F-EF5**, **Cu-ASTM**, and **I-IAZA** localize to hypoxic regions, but may not correlate as precisely with oxygen levels.

Transient and Chronic Hypoxia

- Tumor vasculature is unstable. Blood vessels can occlude, congest, or otherwise stop working.
- Cells supplied by temporarily blocked blood vessels experience **transient (acute) hypoxia**.
 - These cells are radioresistant due to hypoxia (remember that it only needs to be hypoxic for a few microseconds to be resistant).
 - However, once the transient hypoxia goes away the cells are fully oxygenated and healthy.
- Cells too far away from any blood vessels experience **chronic hypoxia**.
 - These cells are radioresistant, but may be weakened or killed by hypoxia.
 - Alternatively, hypoxia may make them more prone to mutation and metastasis.
 - Chronically hypoxic cells can oxygenate one of two ways:
 - **Angiogenesis**: growth of new vessels.
 - **Tumor shrinkage** bringing existing vessels closer.

Reoxygenation After Irradiation

- **Reoxygenation** is one of the “Four R’s” of fractionation (Fig. 23.3).
- Reoxygenation has been extensively studied in animal tumors.

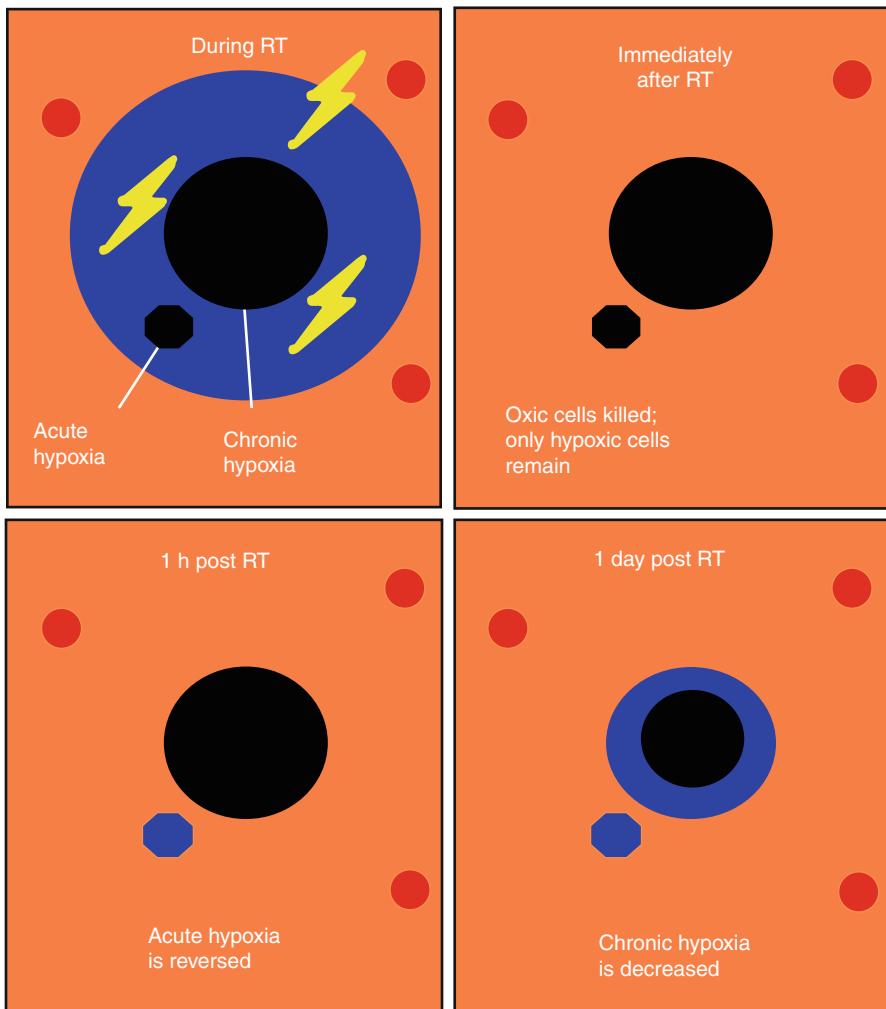


Fig. 23.3 Time scale of reoxygenation. After a radiation dose sufficient to kill normoxic cells but not hypoxic cells, only the hypoxic cells will remain. Re-oxygenation occurs within hours for acute hypoxia, but takes days to reverse chronic hypoxia.

- Reoxygenation happens in **two phases**:
 - Fast component: Occurs within 1 h to a few hours.
 - Slow component: Takes several days.
 - This is believed to be due to **acute** and **chronic** hypoxia.
- Some tumors reoxygenate quickly and completely, while other tumors reoxygenate slowly and incompletely.

- **During a course of fractionated RT:**
 - A tumor that completely reoxygenates between fractions will display similar radiosensitivity during the entire course of radiation.
 - A tumor with incomplete reoxygenation will become more and more hypoxic as additional fractions of radiation are given. This greatly decreases radiosensitivity.
- The doses of fractionated RT required to cure a completely hypoxic tumor are clinically impractical, so reoxygenation is vital to the success of radiotherapy.

Hypoxia and Tumor Progression

- Multiple clinical studies have shown that tumor hypoxia correlates strongly with local failure, distant metastasis and cancer related death.
 - This occurs even in cancers treated with surgery alone! Therefore, it is not purely a function of radioresistance.
- There are at least three mechanisms by which hypoxia drives tumor aggression.
 - **Genomic Instability:**
 - The combination of hypoxia and reoxygenation induces mutation and suppresses DNA repair, causing genomic instability.
 - Cells deficient in apoptosis are better at surviving hypoxia. They are also more likely to mutate because they do not die when DNA is damaged.
 - **Hypoxia Induced Genes:**
 - **HIF-1, NF-κB, CREB** and other oncogenes are strongly induced by hypoxia.
 - These genes activate pathways for surviving and adapting to hypoxia, including angiogenesis and tissue remodeling (invasion).
 - **Metastasis:**
 - Hypoxia dramatically increases the metastatic potential of tumor cells.

Hypoxia Inducible Factor 1 (HIF-1)

- **HIF-1** is the signaling molecule responsible for the classic hypoxia signaling pathway.
- **HIF-1** consists of two subunits, **HIF-1α** and **HIF-1β**. Out of these two, **HIF-1α** is actively regulated.
- Under normoxic conditions **HIF-1α** is constantly degraded:
 - **HPH** hydroxylates (requires O₂)
 - **VHL** ubiquinates, targeting **HIF-1α** for degradation.
- Under hypoxic conditions **HIF-1α** accumulates and dimerizes with **HIF-1β**. This activates downstream pro-angiogenesis and pro-growth genes (Fig. 23.4).
- Loss of **VHL** can also activate **HIF-1**:
 - This causes **von Hippel Lindau (VHL)** syndrome, which includes multiple malignant and benign tumors such as retinal angiomas and renal cell carcinoma.

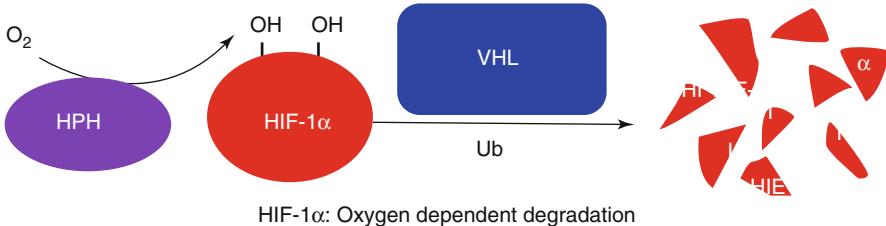


Fig. 23.4 HIF-1 regulation. Under normal circumstances HIF-1 α is continuously degraded in an oxygen-dependent manner. When oxygen is depleted HIF-1 α is no longer degraded and it accumulates.

Tumor Composition in Patients

- Most radiobiological and animal models assume that a tumor is composed of a clone of identical tumor cells.
- However, all human tumors have heterogeneous populations of tumor cells with different mutations.
 - When a tumor relapses after a complete response, it may be due to a very small number of very resistant cells.
- The **tumor stem cell hypothesis** was proposed to explain this phenomenon. According to this hypothesis:
 - Most of the clonogenic activity of a tumor comes from a small number of cells, the tumor stem cells.
 - Tumor stem cells are relatively resistant to therapy.
 - A course of treatment can kill off all of the non-stem cells in a tumor, causing a “complete response”.
 - However, if some tumor stem cells survive, they will eventually repopulate the tumor.
- Human tumors also contain many host cells, including vascular and stromal elements, plus immune cells.
 - Immunotherapy and anti-angiogenic therapy work on host cells rather than tumor cells.
 - Even cytotoxic chemotherapy and radiation therapy may have some part of their effectiveness mediated by immune and vascular/stromal effects.
 - Tumor cells may express molecules that evade or suppress the immune system.
 - The “in situ vaccine” hypothesis suggests that when a tumor is treated by radiation or chemotherapy, the dying tumor cells provoke an immune response. This may be responsible for some of the effectiveness of treatment.

24

Cell and Tissue Kinetics

Cell and Tissue Kinetics: Why Do We Care?

- Redistribution and Repopulation are two of the four “R’s” of radiobiology (below).
- Redistribution between different parts of the cell cycle can cause different effects depending on dose-rate and fractionation.
- Repopulation simply increases cell survival during a protracted course of treatment. Some tumors and normal tissues repopulate faster than others.

The “4 R’S” of Radiobiology

- Repair
- Reoxygenation

- Redistribution
- Repopulation
- The “fifth R” of Radiosensitivity

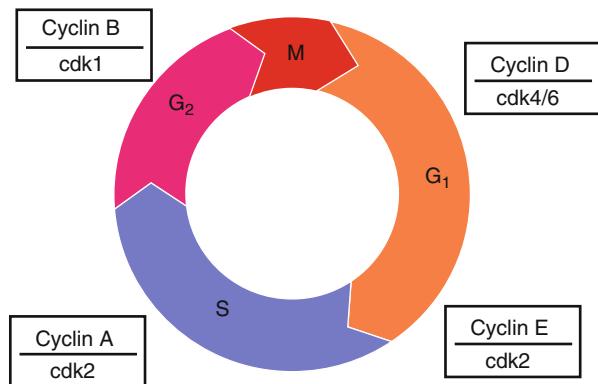
Definitions

- **G₁**: Gap phase 1, DNA is un-duplicated.
- **S**: Synthesis phase, DNA is being duplicated.
- **G₂**: Gap phase 2, DNA is fully duplicated.
- **M**: Mitosis phase, chromosomes condense, the nucleus and cell divides.
- **T_C**: Cell cycle time (total duration of all phases)
- **T_{G1}**: G₁ phase duration
- **T_S**: S phase duration
- **T_{G2}**: G₂ phase duration
- **T_M**: M phase duration
- **MI**: Mitotic index
- **LI**: Labeling index
- λ : Cell distribution correction factor
- **T_{vol}**: Tumor volume doubling time
- **T_d**: Tumor diameter doubling time
- **T_{pot}**: Potential doubling time of tumor
- **GF**: Growth fraction
- **CLF (ϕ)**: Cell loss factor

Molecular Biology of the Cell Cycle

- The cell must pass through **checkpoints** to continue through the cell cycle.
- Each checkpoint is governed by **Cdk-Cyclin** complexes and their inhibitors.
- These regulatory molecules change the amount and activity of other proteins, leading to cell cycle progression.
 - **G₁/S: Cyclin D, Cdk4/6**
 - **G₁/S: Cyclin E, Cdk2**
 - **S: Cyclin A, Cdk2**
 - **G₂/M: Cyclin B, Cdk1** (Fig. 24.1).
- The **G₁/S** checkpoint is frequently inactivated in human tumors:
 - The **Cyclin D/cdk4/6** complex is inhibited by **p21** and **p15/p16 (INK4A)**.
 - Mitogenic signals cause Cyclin D activation.
 - The activated **Cyclin D/cdk4/6 complex** partially phosphorylates and activates the retinoblastoma tumor suppressor **Rb** which leads to release of the **E2F** transcription factor family.
 - Release of **E2F**, leads to transcription of **Cyclins E and A**, and genes involved in DNA synthesis.

Fig. 24.1 The cell cycle. The cell has checkpoints regulated by the Cdk-Cyclin complexes that respond to other signals in the cell.



- Cyclin E/Cdk2 and Cyclin A/Cdk2 complexes further phosphorylates Rb, leading to transition into and through S phase.
- p53 blocks the G₁/S transition by induction of p21 in response to DNA damage or other cellular stress.
- Rb or p53 are frequently defective in tumors. They may be directly mutated, or may be inhibited by other pathways.
 - This allows for uncontrolled entry into S phase.
- The G₂/M cell cycle transition is regulated by the CyclinB/Cdk1 complex which phosphorylates histone H1 and nuclear lamins leading to chromosome condensation and dissolving of the nuclear membrane in preparation for mitosis.
 - The G₂/M checkpoint can also be induced by p21 binding.
 - It is important to remember that the G₂/M checkpoint remains intact in most cancers.

Imaging the Cell Cycle

- Light microscopy:
 - Can detect M-phase cells by morphology and chromosome condensation.
 - Cannot tell the difference between G₁, S and G₂.
 - Mitotic Index (MI) = % of cells in M phase.
- ³H-Thymidine:
 - Tritium (³H) is a low energy (19 keV) beta emitter commonly used in the laboratory. It is detected by autoradiography.
 - Culturing cells in ³H-Thymidine will label cells in S-phase as it is readily incorporated in replicating DNA.
 - Labeling Index (LI) = % of cells in S phase.
- Microscopy and autoradiography of ³H-Thymidine labeled cells can be used to measure MI and LI simultaneously.

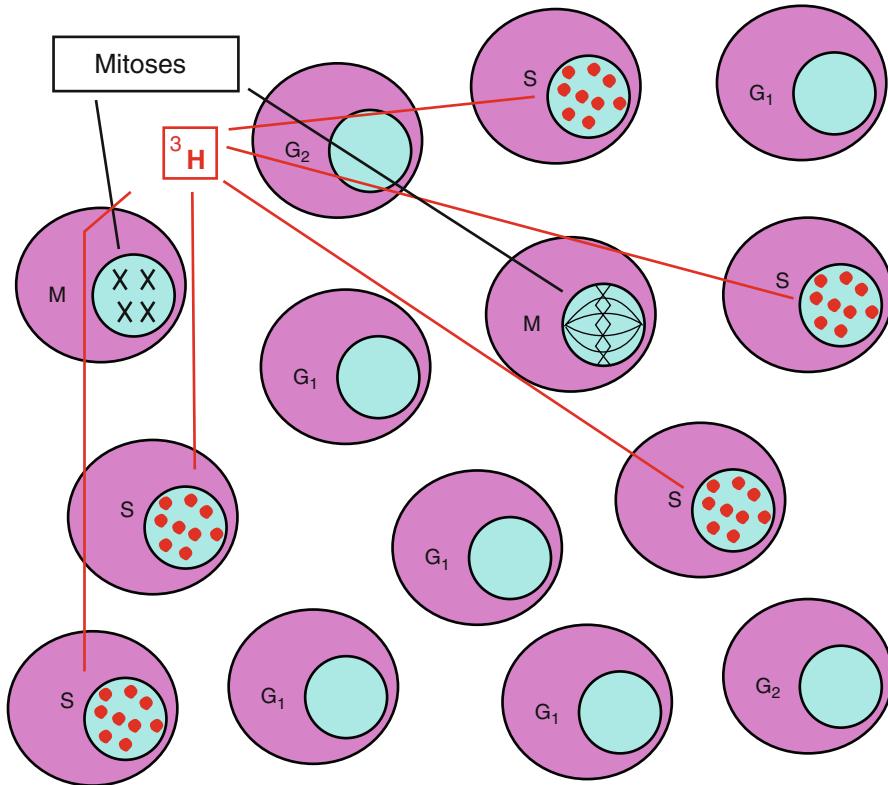


Fig. 24.2 Light microscopy can be used to view cells in mitosis and therefore measure the mitotic index. The addition of tritiated thymidine allows cells in S-phase to be imaged by autoradiography, permitting measurement of the labeling index.

Cell Cycle Kinetics: Measuring T_M and T_S (Fig. 24.2)

- Cells are unevenly distributed throughout the cell cycle because cells double during mitosis.
 - Therefore we introduce a correction factor λ :

$$MI = \frac{\lambda \times T_M}{T_C} ; T_M = \frac{\lambda \times MI}{T_C} \quad (24.1)$$

- Typically, $\lambda \approx 0.693$ for M phase.
- The same applies to LI and T_S :

$$LI = \frac{\lambda \times T_S}{T_C} ; T_S = \frac{\lambda \times LI}{T_C} \quad (24.2)$$

- The value of λ for S phase can vary, but is < 1 .

- Using the above two equations you can measure T_M and T_S quite easily.
- On average, T_S is around 1/3 of the cell cycle.

Cell Cycle Kinetics: Measuring T_C , T_{G1} , T_{G2}

- **Percent labeled mitosis over time:**
 - All of the labeled cells are initially in **S phase**, so no mitoses are labeled.
 - Over time, the labeled cells will move into **M phase** and all of the mitoses are labeled.
 - After a while the labeled cells progress through **G1**, **S**, and **G2**. No mitoses are labeled.
 - If you wait long enough they will go through a second **M** phase.
- Much more laborious and cumbersome than flow cytometry, therefore rarely used any more.

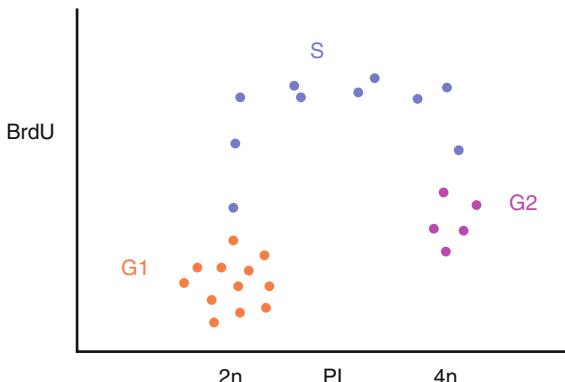
Cell Cycle Measurement: Flow Cytometry

- **Flow Cytometry** uses fluorescent colors and lasers to rapidly count and sort cells.
 - Cells may be fixed and labeled with a fluorescent dye or antibody conjugated to a fluorescent probe.
- It can measure cell cycle kinetics much faster than light microscopy and autoradiography.
- **DNA Content (measurement of cell cycle distribution):**
 - Cells are stained with propidium iodide (**PI**), a dye which binds DNA stoichiometrically.
 - The flow cytometer measures the amount of dye bound to DNA in individual cells. A distribution may be obtained.
 - Peaks in the cell cycle distribution appear at **G1** (DNA not yet replicated) and **G2/M** (fully replicated DNA), with **S** phase having an intermediate DNA content.
- **S Phase Labeling:**
 - Cells are stained with bromodeoxyuridine (**BrdU**), which is incorporated into newly synthesized DNA of S-phase cells only.
 - S-phase cells labeled with BrdU are detected based on the fluorescence of anti-BrdU antibodies (Fig. 24.3).

Cell Cycle Parameters

- T_S , T_{G2} , and T_M vary relatively little among mammalian cells.
 - $T_S = 6\text{--}8 \text{ h}$
 - $T_{G2} = 3\text{--}4 \text{ h}$
 - $T_M = 1 \text{ h}$

Fig. 24.3 Example of bivariate flow cytometric analysis of propidium iodide and bromodeoxyuridine staining to measure cells in G1, G2/M and S phase.



- The time T_{G1} is much more variable, as noted below:
 - CHO** hamster cells have a $T_{G1} = 1$ h.
 - HeLa** human tumor cells have a $T_{G1} = 11$ h.
 - Slow growing human cells can have a T_{G1} of several days.

Tissue (Tumor) Kinetics

- In a tissue (or tumor), not every cell is actively cycling. Some cells are quiescent, senescent, or dying.
- Growth Fraction (GF)** = % of cells that are cycling.
 - Example numbers are 90 % for lymphoma, 40 % in squamous, and 6 % in adenocarcinoma.
- Cell loss factor (CLF, ϕ)** is the percent of newly produced cells that die or fail to continue dividing.
 - Most human tumors have a ϕ of around 77 %.
 - Tumors with a low ϕ may be more resistant to cell death, suggesting possible resistance to therapy.
- Potential doubling time (T_{pot})** is defined as the time for tumor volume doubling in the absence of cell loss.
- Volume doubling time (T_{vol})** is the observed time for tumor volume doubling:

$$T_{pot} = \frac{T_C}{GF} ; T_{vol} = \frac{T_{pot}}{1 - \phi} \quad (24.3)$$

- Diameter doubling time (T_d)** is equal to $3 \times T_{vol}$ (Fig. 24.4).
 - One diameter doubling = three volume doublings.
 - Two tumors with the same volume doubling time may have very different kinetics:
 - A tumor with fast T_{pot} and large Φ grows quickly and responds quickly.
 - Classic example: Squamous cell CA.

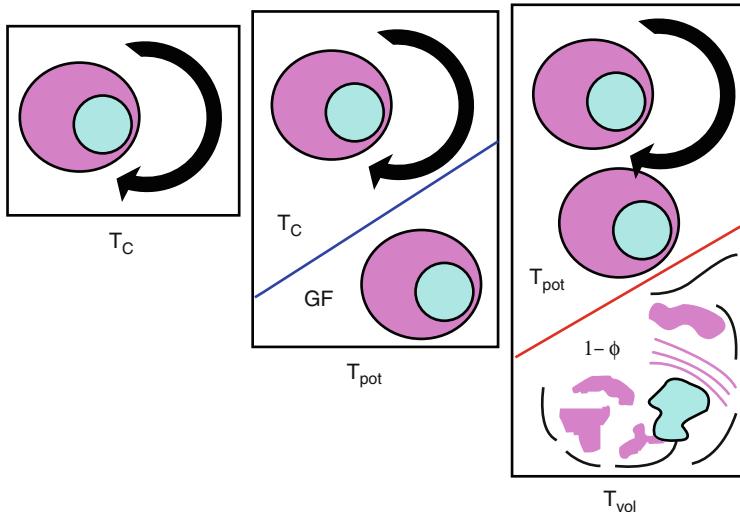


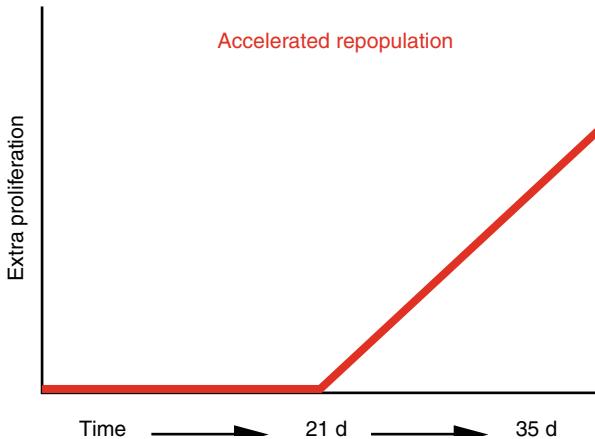
Fig. 24.4 The time it takes for a cell to move from G1 through mitosis is the cell cycle time (T_C). Cell cycle time (T_C) divided by the growth fraction (GF) is the potential doubling time (T_{pot}). The potential doubling time (T_{pot}) divided by the cell loss time is the volumetric doubling time (T_{vol}). See Eq. 24.3.

- A tumor with slow T_{pot} and small Φ grows slowly and responds slowly (if at all).
- Classic example: Sarcoma.

Growth Kinetics of Clinical Tumors

- An “average” human tumor has a cell cycle time (T_C) of 2d and a potential doubling time (T_{pot}) of 5d.
- With a cell loss factor (Φ) of 75 % this gives:
 - Volume doubling time (T_{vol}) = **20d**.
 - Diameter doubling time (T_d) = **60d**.
- Of course, these numbers vary a lot from patient to patient, or even for two metastases in the same patient.
 - As tumors grow, they may become more necrotic. This increases Φ and slows down T_{vol} and T_d .
- **Accelerated repopulation** is a phenomenon in which prolonged cytotoxic treatment stimulates tumor cells to rapidly divide.
 - This is a well known phenomenon in squamous cell cancers of the head and neck, and uterine cervix (Fig. 24.5).
- **Accelerated repopulation** is characterized by these parameters:
 - “**Kickoff time**” (T_k): ~21–28 days delay from the start of treatment to the start of accelerated repopulation.

Fig. 24.5 Once treatment has started, some tumors may undergo accelerated repopulation that begins at a “kickoff time”.



- T_{pot} : Once accelerated repopulation starts, T_d approximates T_{pot} . This is much faster than the usual T_{vol} .

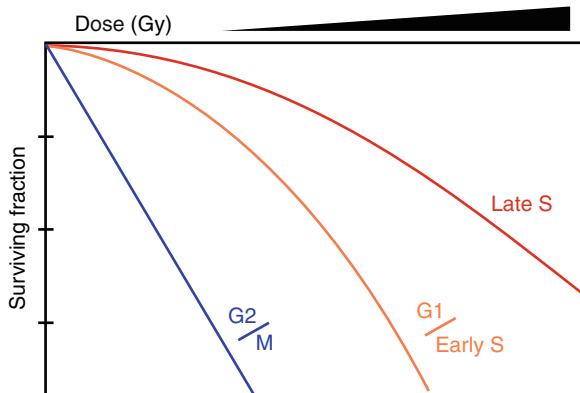
Accelerated Repopulation and Effective Dose

- For overall treatment times that exceed T_k , extra dose must be given to counteract accelerated repopulation.
- The daily dose required to counteract accelerated repopulation is known as D_{prolif} .
 - For H&N, lung and CNS tumor cells, this number varies from **0.4** to **0.8 Gy/day**.
 - See Chapt. 21 for details.
- During a prolonged treatment time, accelerated repopulation increases the survival of both tumor cells and proliferating normal tissues such as skin and mucosa.
 - However, non-proliferating normal tissues cannot repopulate.
 - Giving extra dose for prolonged treatment time comes at a risk of increased late toxicity.
 - This is one reason why split course therapy (intentional treatment breaks) has fallen out of favor.

Cell Cycle Synchronization

- Why use synchronized cells?
 - In order to measure cell cycle dependent effects.
- Mitotic Harvest (“Shakeoff”)
 - Cells are grown as an adherent monolayer on the surface of a container.

Fig. 24.6 Dose response curves for cells from the various phases of the cell cycle typically demonstrate that G₂/M phase cells are more radiosensitive while late S phase cells are more radioresistant.



- Mitotic cells temporarily lose their adherence and can be physically dislodged and used in experiments.
- **Hydroxyurea (HU)**
 - HU selectively kills S-phase cells.
 - If cells are incubated in HU, they accumulate at the G₁-S checkpoint.
- **Other drugs**
 - Any drug with selective killing or blocking of a specific phase of the cell cycle may be used to synchronize cells.

Cell Cycle and Radiosensitivity

- **Overall Sensitivity (D₀)**
 - Cells are **most sensitive** to RT in G₂/M.
 - A cell in G₂/M does not have enough time to repair DNA damage before dividing.
 - DNA damage leads directly to mitotic catastrophe.
 - Cells become gradually **less sensitive** in G₁ to early S, and are **least sensitive** to RT in late S.
 - Homologous recombination repair is most active during late-S phase, after most of the DNA has been replicated.
- **Shoulder Size (D_q)**
 - There is practically **no shoulder** to the survival curve in G₂/M, suggesting that very little repair takes place.
 - There is a moderate shoulder in G₁ to early S.
 - There is a very large shoulder in late S (Fig. 24.6).
- **Oxygen Dependence (OER)**
 - OER is highest in S phase due to **increased DNA repair** under hypoxic conditions.
 - Remember, oxygen makes DNA damage more difficult to repair.

- This causes the **OER** fraction size effect:
 - **Small fractions:** Killing is dominated by the most sensitive cells (**G₂/M**) with the **lowest OER**.
 - **Large fractions:** Survival is dominated by the least sensitive cells (**late S**) with the **highest OER**.
- **High LET Radiation**
 - Cell cycle dependence still exists for high-LET radiation but it is greatly decreased.

Fractionated RT and Reassortment

- S phase cells are radioresistant. It takes very high doses to kill them in a single fraction.
- With fractionated radiation, tumor cells can **re-assort** in between fractions.
 - Radioresistant S-phase cells move into more sensitive parts of the cell cycle, **improving** the therapeutic ratio of fractionated radiotherapy.
- In certain low dose rate (**LDR**) scenarios, cells can progress through the cell cycle and accumulate at the radiosensitive **G₂** phase.
 - This greatly increases radiosensitivity and is known as the **inverse dose-rate effect** (Cell survival decreases with lower dose rates instead of increasing).
 - See Chapt. 29 for details on low-dose-rate therapy.

25

Acute Effects of Total Body Irradiation (TBI)

Where Does the Data Come from?

- Human data
 - Atomic bombings in Japan:
 - Hundreds of thousands of exposures, but any inaccuracies or missing data from 1945 are likely to remain inaccurate or missing.
 - According to Hall and Giaccia, there were 403 accidents and 120 deaths from 1944 to 1999.
 - Radiation dose estimates are likely to be more accurate, especially in more recent disasters.
 - Patients were more likely to have received prompt medical care.

- **Animal data**

- Dogs and rhesus monkeys have similar radiosensitivity to humans.
- Smaller animals are generally more radioresistant.

What About Intentional TBI?

- The **acute radiation syndrome** described in the literature is based on very high dose rate exposures such as from nuclear bombs and criticality accidents.
- **Intentional TBI** is administered at very low dose rates (5–10 cGy/min) and thus may have a different toxicity profile.
 - The clinical data shows significant dose-rate dependence for pulmonary toxicity (radiation pneumonitis).

Prodromal Radiation Syndrome

- Characterized by **neuromuscular** and **gastrointestinal** symptoms.
- Occurs after a dose of ≥ 1 Gy, but severity is dose-related.
- Occurs within 5–15 min of acute exposure and can last for several days. Duration is also dose-related.
- At a dose expected to be lethal in 50 % of subjects (**LD₅₀**):
 - **~3–4 Gy** without medical intervention.
 - Fatigability, anorexia, nausea/vomiting.
- At **supralethal dose** (>8 Gy):
 - Immediate diarrhea, fever, hypotension.
 - If doses are known to be un-survivable, these patients should be provided with palliative care only.

Cerebrovascular Syndrome

- Occurs after a dose of **~100 Gy**.
- Death within **24–48 h**.
- Characterized by disorientation, incoordination, shortness of breath, hypotension, loss of consciousness, seizures and death.
- Believed to be caused by increased intracranial pressure due to permeability of cerebral blood vessels.
- Un-survivable.

Gastrointestinal Syndrome

- Occurs after a dose of ≥ 10 Gy.
- Death within **3–10 days**.
 - This timeframe is equal to the lifespan of intestinal epithelial cells.

- Characterized by nausea, vomiting, and prolonged diarrhea, followed by sepsis and death due to GI infection.
- Secondary to **loss of villi** throughout the GI tract, with resultant permeability and gut bacteria translocation.
- Currently believed to be un-survivable.

Hematopoietic Syndrome

- Occurs after a dose of ≥ 2.5 Gy.
- Likely to be lethal at doses ≥ 4 Gy **without intervention**.
- Death occurs within **30–60 days**.
 - This timeframe is similar to the lifespan of neutrophils and platelets.
- Lethal dose is expressed as **LD_{50/60}**, the 50 % lethal dose at 60 days.
- Characterized by a **latent period** in between the prodromal syndrome (few days) and symptomatic cytopenias (few weeks).
 - There may not always be a clearly defined latent period; symptoms can merge gradually from prodromal to hematopoietic.
- **Symptomatic period:** fatigue, anemia, hemorrhage, fever/chills, mouth ulcers, epilation.
 - Symptoms are due to pancytopenia.
 - Death occurs mostly due to infection (neutropenia, leukopenia).
- May be treated with supportive care (antibiotics, growth factors) or stem cell transplant.

Mean Lethal Dose and Dose-Time Response

- The **LD₅₀** for humans is approximately **3–4 Gy** without medical intervention, and **4–8 Gy** with standard medical care.
 - The **LD₅₀** may or may not be increased by stem cell transplantation.
 - The **LD₅₀** is likely to be lower in nuclear terrorism or warfare, as timely treatment of mass casualties will be difficult and individuals will have combined radiation injury and trauma or burns.
- **Cytopenia timecourse:**
 - Radiation kills off hematopoietic stem cells; most mature functional cells are relatively resistant.
 - Except lymphocytes which undergo apoptosis.
 - Cytopenias occur as functional cells die and cannot be replaced due to loss of stem cells.
 - Therefore the time-course of cytopenia is dependent on the lifespan of the mature cell.
 - **Lymphocytes** begin to drop immediately.
 - **Granulocytes** begin to drop within days.
 - **Platelets** drop after a few weeks.

- Erythrocyte (RBC) lineage is relatively radioresistant, and anemia usually does not occur from erythrocyte lineage suppression.
- WBC and platelet nadir typically occurs around 3–4 weeks, although this may be dose dependent.
- If complete neutropenia occurs within <3 days it indicates a supralethal dose.

Dose Estimation in Radiation Disasters

- **Symptoms:**
 - Immediate diarrhea, fever, or hypotension indicates a massive, unsurvivable dose.
 - Lack of nausea after a few hours indicates a sub-lethal dose.
 - Victims with nausea as their initial symptom are most likely to have received a potentially lethal but potentially survivable dose.
- **Timecourse:**
 - Very rapid drop in blood cell counts (nadir <3 days) indicates supralethal dose.
 - Gradual drop in counts (nadir ~3 weeks) indicates potentially survivable dose.
- **Peripheral blood lymphocytes:**
 - Peripheral blood lymphocytes are extracted and cultured in vitro.
 - During mitosis, these cells may display chromosomal aberrations such as rings and dicentrics.
 - Counting the aberrations per cell can provide an accurate estimate of total-body radiation doses over **~0.25 Gy**.
 - **Stable aberrations**, such as translocations, persist for the remainder of that individual's lifetime.
 - **Unstable aberrations**, such as rings and dicentrics, decline over time as the affected cells die.

Supportive Care

- Isolation and antibiotics are the most important component of supportive care.
 - Patients receiving near-lethal doses will be profoundly immunosuppressed for several weeks.
 - Contact (barrier) isolation is vital.
 - Neutropenic precautions, avoid soil organisms.
- Give platelets when platelets drop.
- Give PRBCs if bleeding occurs.

Radioprotectors and TBI Lethality

- Amifostine has been shown to increase the **LD₅₀** in animals.
- For obvious reasons this has never been tested in humans.

- **Amifostine** must be administered 30 min prior to irradiation to have an effect.
- Causes severe nausea and vomiting at the doses required for radioprotection.
- Therefore it is not a practical “antidote” for mass-casualty events such as nuclear accidents or terrorism.

Stem Cell Rescue

- **Allogeneic stem cell transplants** are used to treat various malignancies and hematologic conditions.
 - Myeloablative (full-intensity) protocols often include **TBI** as part of the conditioning regimen.
 - Fractionated TBI may be given at a dose of 11–13 Gy delivered BID or TID for 4 days.
 - Partial transmission lung blocks may be used to decrease pulmonary toxicity.
 - Stem cell transplantation is performed within days after TBI. Patients then require intensive medical care for many weeks.
- Bone marrow (stem cell) rescue has been attempted for nuclear accident survivors, but it is uncertain how much benefit it gives in the accidental setting.
 - Highly unlikely to have a good HLA match in a nuclear disaster setting.
 - Narrow dose window of utility.
 - **<8 Gy**: patients may be able to survive with standard medical care, such as antibiotics, transfusions and growth factor support.
 - **>10 Gy**: patients are likely to die even if transplanted.
 - GI syndrome is likely to occur, and donor cells may fail to engraft due to damage to bone marrow stroma.

26

Normal Tissue Radiation Responses

Types of Normal Tissue Effects

- **Early effects** occur within 60 days of irradiation and are due to acute cell killing.
 - These generally involve tissues with rapid cell turnover.
 - As long as enough stem cells survive to repopulate the tissue, early effects can be completely repaired over time.
- **Late effects** occur >60 days later and are due to effects other than acute cell killing.
 - Mechanisms include vascular damage, fibrosis, and damage to parenchymal cells in organs.
 - These generally involve tissues without rapid cell turnover, and cannot be completely repaired.

- **Consequential Late effects** are permanent tissue damage secondary to early effects.
 - These are caused by a very severe early effect that never completely heals.
 - For example, skin necrosis requiring a skin graft.

Fraction Size and Treatment Time Effects

- Acute effects are less sensitive to fraction size (high α/β) but more sensitive to overall treatment time.
 - Toxicity based on **Total Gy** and **Gy per week**.
 - Prolonging the course of radiation allows for repopulation.
- Late effects are more sensitive to fraction size (low α/β) but less sensitive to overall treatment time.
 - Toxicity based on **Total Gy** and **Gy per fraction**.
 - Fractionation allows for increased repair, but little or no repopulation occurs within a clinically relevant time span.
- When re-treating a previously irradiated area keep in mind:
 - Late effects are never completely repaired. This is the concept of **remembered dose**, which decreases the tissue's tolerance to re-irradiation.
 - Acute reacting tissues do not “remember” much dose. They can be considered “completely” repaired after 2 months or so, unless severe enough to become consequential late effects.

Stem Cells: Latency and Functional Subunits

- In a tissue with dividing stem cells and non-dividing functional cells, the functional cells are largely unharmed by radiation while the stem cells are killed.
 - There is a **latency period** before any tissue dysfunction becomes apparent.
 - The **latency** time is equal to the lifespan of the functional cell.
- Following this, any surviving stem cells will attempt to regenerate the tissue.
- Each stem cell can only regenerate a finite volume of organ. This volume is called the **functional subunit** (FSU).
 - Kidneys, lungs, livers, and exocrine glands are organized into structurally defined FSUs (nephrons, bronchial trees, portal triads, etc).
- A **structurally defined FSU** is an anatomic structure that defines a group of cells.
 - Kidneys, lungs, livers, and exocrine glands are organized into structurally defined FSUs (nephrons, bronchial trees, portal triads, etc).
- A **structurally undefined FSU** is not an anatomic structure at all.
 - For example, stem cells in the skin can only migrate a finite distance, but this is not limited by any specific anatomic boundary.
- A **tissue rescue unit** is the minimum number of FSUs required for organ function.

Serial and Parallel Organs and Volume Effect

- In a **serial organ** (CNS, GI tract) loss of function in one part of the organ will cause the entire organ to stop functioning.
 - Therefore there is no **threshold volume** – high dose to even a small volume can cause critical injury.
 - The probability of damage is proportional to the volume irradiated:
 - If 50 Gy to spinal cord has a 1 %/cm chance of myelopathy, irradiating 1 cm of cord may be reasonable but irradiating 30cm of cord would not be reasonable.
 - The risk of injury is dominated by the **highest dose**.
 - The spinal cord can tolerate 36 Gy to the whole organ, but cannot tolerate 74 Gy to one spot.
- In a **parallel organ** (kidney, lung, liver) loss of function in one part of the organ only affects that part of the organ.
 - There is a **threshold volume** effect: you can take out an entire kidney without causing renal failure if the other kidney is healthy.
 - Partial organ effect does not always correlate with whole organ function.
 - For example, chest CTs after chest wall irradiation will show changes in a small slice of lung within the radiation field.
 - However, the rate of symptomatic pneumonitis is very low.
 - The risk of injury is dominated by the **average dose** over the whole organ volume.
 - The lung cannot tolerate 36 Gy to the whole organ, but can easily tolerate 74 Gy to one spot.
- Skin and mucosa are neither serial nor parallel but they behave clinically like **parallel organs**.
 - This is because desquamating a small area of skin is much more tolerable than desquamating a large area.

Casarett's Classification of Radiation Sensitivity

- Arranged from most sensitive (Group I) to least sensitive (Group IV).
- **Group I: Vegetative Intermittent**
 - Divides constantly with no differentiation.
 - Includes basal epithelial cells (skin, intestinal crypts, etc), undifferentiated hematopoietic stem cells and germ cells.
- **Group II: Differentiating Intermittent**
 - Divides for a finite amount of cycles before differentiating into a non-dividing cell.
 - Includes all of the cells that are intermediate between stem cells and differentiated cells. For example, myelocytes, spermatogonia, etc.
- **Group III: Reverting Postmitotic**
 - A normally non-dividing cell that retains the potential to divide (“revert”).

- Includes liver, kidneys and glandular tissues such as pancreas, adrenal, thyroid and pituitary.
- **Group IV: Fixed Postmitotic**
 - A permanently non-dividing cell.
 - Includes permanent cells such as nerves and muscles, as well as short-lived differentiated cells such as neutrophils, red blood cells, and superficial epithelial cells.
- **Exceptions:**
 - **Connective tissue stroma** (fibroblasts and endothelium) are intermediate between II and III.
 - **Peripheral blood lymphocytes** are incredibly sensitive to apoptosis and are very radiosensitive despite being **Group IV**.
 - Other peripheral blood cells (granulocytes, RBCs and platelets) are very radioresistant.
 - Therefore the latency time of cytopenias after RT is based on the lifespan of the differentiated cell (Fig. 26.1).

Michalowski Classifications

- Tissues are either **hierarchical** or **flexible**.
- This model predicts the time-course of radiation toxicity.
- **Hierarchical (H-type)** tissues regenerate in a fixed pathway of **stem cell** → **maturing cell** → **functional cell**.
 - Radiation kills stem cells, which leads to depopulation of functional cells after a **predictable latency** time.
 - Bone marrow, intestinal epithelium, and epidermis are hierarchical tissues.
- **Flexible (F-type)** tissues have no hierarchy. Non-dividing cells can be triggered to divide if needed.
 - Radiation causes cells to become unable to divide, but this does not become apparent until the cell is actually triggered to divide (may be many years later).
 - The time-course and degree of organ dysfunction are **unpredictable**.
 - Liver, thyroid, and dermis are flexible tissues.

Cytokines and Growth Factors

- Radiation induces the cytokines **IL-1**, **IL-6**, and the growth factor **bFGF**. These molecules act as short-term radioprotectors.
- **bFGF** is produced by medium sized blood vessels but not by the smallest capillaries. This is believed to be one reason why larger blood vessels are more radioresistant than the microvasculature.

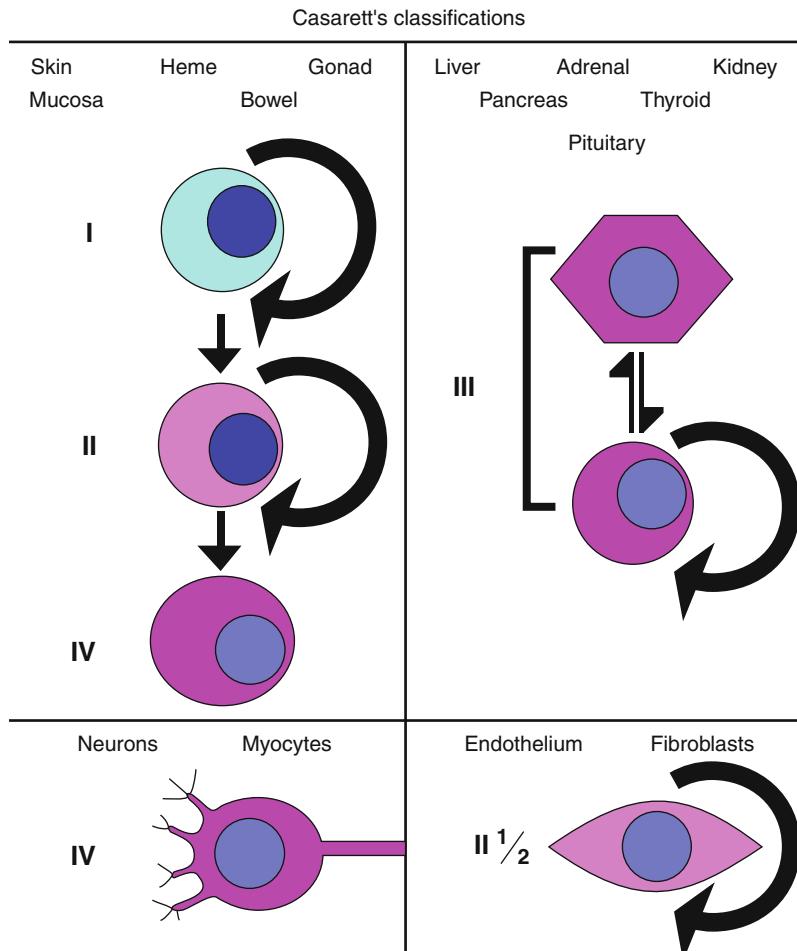


Fig. 26.1 Casarett's classifications. For skin, mucosa, gonads, bowel and hematologic cells, the progression is from vegetative intermitotic to differentiating intermitotic to fixed postmitotic. For cells of the liver, adrenal gland, kidney, pancreas, thyroid and pituitary, the cells are often reverting intermitotic. Nerve and muscle cells are typically fixed postmitotic by the time of birth (with few exceptions), and endothelium and fibroblasts contain elements that would be described as both reverting intermitotic and differentiating intermitotic.

- Radiation also induces the growth factors **TGF β** and **TNF α** , which are pro-inflammatory and pro-fibrotic molecules.
 - These are involved in late fibrosis and late vasculopathy.
 - Increased serum concentrations of **TNF α** correlate with late toxicities of radiation.

Normal Tissue Response: Skin

- Epidermis is an acute responding tissue while dermis is a late responding tissue.
- Acute response: Happens in **epidermis**.
 - Erythema: due to vascular dilation and edema, can happen quickly after large single doses.
 - Desquamation: Keratinizing skin cells last for 14 days, so desquamation is generally delayed by around 14 days.
 - Epilation: due to hair follicle germinal cells, delayed by 2–3 weeks, takes 3 months to regrow.
- Late response: Happens in **dermis**.
 - Telangiectasias and fibrosis are due to chronic vascular damage and inflammation.
- Human epidermis is a fraction of a millimeter in thickness. It reacts to **surface dose** and not depth dose.
- Skin tolerance is around **60 Gy** in standard fractionation, although this depends on the surface area of skin irradiated.
 - Small skin cancers can be treated with higher doses.
 - Large areas like a chest wall may experience severe acute toxicity at **50 Gy** or less.

Normal Tissue Response: Hematopoietic

- Hematopoietic stem cells (**HSCs**) are among the most radiosensitive cells in the body.
- Total Body Irradiation:
 - Hematopoietic tolerance is a **LD₅₀** of **3–4 Gy** in a single fraction, without stem cell transplant.
 - The purpose of myeloablative conditioning for stem cell transplant is to ablate the host's **HSCs**. Therefore TBI doses exceed **HSC** tolerance.
- Partial Body Irradiation:
 - Death of **HSCs** in one part of the body induces accelerated growth and differentiation of hematopoietic cells elsewhere in the body.
 - Heavily irradiated bone marrow (>30 Gy) may never fully recover. This may be seen as abnormal marrow signal on MRI persisting for many years.
 - Extramedullary hematopoiesis (spleen, liver, soft tissue) may occur.
- Differential Effects by Cell Lineage:
 - **Lymphocytes** (including plasma cells) are the most sensitive and nadir within **hours to a few days**. Unlike the other lineages, even mature lymphocytes are radiosensitive due to apoptosis.
 - **Granulocyte** lineage is intermediate in sensitivity. Only the stem cells are killed, the differentiated cells continue their normal lifespan, with a nadir at **2–4 weeks**.

- **Platelet** lineage is somewhat less sensitive, and platelets also nadir at **2–4 weeks**.
- **Red blood cell** lineage is relatively radioresistant. Hemoglobin is largely unaffected by TBI unless bleeding occurs.

Normal Tissue Response: Oral Mucosa

- Mucositis occurs within ~2 weeks of RT and is a dose limiting factor in head and neck.
- Mucositis involves sloughing of mucosal epithelium with formation of fibrinous exudate.
- Healing occurs within 1 month unless mucositis was severe enough to cause permanent alteration in function.
 - Some patients with very severe mucositis end up with permanent dysphagia/odynophagia.
- Tolerance dose is somewhere around **70 Gy** (with chemo) to **75 Gy** (without chemo) with standard fractionation.
 - This value depends on site of RT, irradiated volume, and definition of tolerance (with or without feeding tube).

Normal Tissue Response: Salivary Glands

- Salivary glands include the parotids, submandibulars, and countless minor salivary glands.
- Salivary glands are considered both an acute and late responding tissue. Xerostomia begins within 2–3 weeks but recovers very little over time.
- Decreased xerostomia risk if bilateral parotid mean dose <**25 Gy**, or if single parotid mean dose <**20 Gy** while other parotid is treated to high dose.
- There is some evidence that RT dose to submandibular and minor salivary glands is also very important to xerostomia risk.

Normal Tissue Response: Esophagus

- Acute esophagitis occurs within 1–2 weeks of RT, is characterized by pain and dysphagia, and heals within 1–2 weeks post RT.
- Late esophageal toxicity includes fibrosis (strictures causing dysphagia) and necrosis (ulceration).
- Esophagus tolerance depends on the intent and endpoint.
 - When treating the esophagus with concurrent ChemoRT, treatment related mortality is higher at **64 Gy** than at **50.4 Gy** (Minsky).
 - When treating H&N or lung, risk of symptomatic esophagitis appears to depend on multiple dose-volume characteristics.
 - Circumferential irradiation is associated with higher late stricture risk.

Normal Tissue Response: Stomach

- Acute gastritis is characterized by nausea and vomiting immediately after RT.
- Chronic gastritis, pain, delayed gastric emptying may occur months after RT.
- Ulceration and bleeding may occur months after RT.
- **Whole stomach: 45 Gy** tolerance dose.

Normal Tissue Response: Lung

- The lung is a subacute to late responding tissue, with classic radiation pneumonitis occurring at 6 weeks to 6 months post RT.
- Late pulmonary fibrosis may occur years post RT.
- The lung is a parallel organ and therefore irradiated volume is extremely important. Very small lung volumes may be treated to very high doses without toxicity, as in SBRT.
- Pneumonitis risk increases gradually with increasing lung dose.
 - There may be a small risk even at low doses (i.e. whole breast irradiation) and a much larger risk at higher doses.
- Therefore there is no single set of lung constraints. Depending on the treatment site and intent, different lung tolerances may be used.
 - **V5 (bilateral) < 70 %**
 - **V20 (bilateral) < 40 %**
 - **V20 (bilateral) < 30 %**
 - **V20 (ipsilateral) < 30 %**
 - **Mean lung dose < 20 Gy**
- **Whole lung** irradiation of **12 Gy in 8 fractions** is tolerable in children with metastatic tumors. However, the same dose of **total body irradiation** is associated with pneumonitis and pulmonary fibrosis, so lung blocks may be used during TBI.
- Patients with other comorbid lung injury (COPD, bleomycin exposure, pneumectomy) have a higher risk of radiation pneumonitis.

Normal Tissue Response: Kidney

- The kidney is a late-responding tissue, with gradual decline in renal function for many years post-irradiation.
- Kidneys are parallel organs and irradiated volume is very important.
- Kidney tolerance is very dependent on comorbid kidney injury, such as chemotherapy, hypertension, diabetes, age.
 - Plenty of cancer patients have kidney failure even without any radiation to kidneys!
- Whole kidney **TD₅ = 15–18 Gy** (QUANTEC)
- Whole kidney **TD₅₀ = 28 Gy** (QUANTEC)

Normal Tissue Response: Liver

- The liver has an extremely high regenerative capacity. 2/3 of the liver can be surgically removed and the remaining liver will regenerate to full size.
 - Therefore there is a very strong dose-volume effect.
 - Liver failure is much less likely if some part of the liver is spared (completely outside field).
- Liver is a late responding tissue, taking years to manifest any symptoms of injury.
 - Except for patients with preexisting cirrhosis.
 - Most primary liver tumors occur in cirrhotic patients.
- Whole liver $\text{TD}_5 = 30\text{--}32 \text{ Gy}$ in a healthy liver, 28 Gy with Child-Pugh A cirrhosis (QUANTEC).
- Whole liver $\text{TD}_{50} = 42 \text{ Gy}$ in a healthy liver, 36 Gy with Child-Pugh A cirrhosis (QUANTEC).

Normal Tissue Response: Bladder

- Bladder is a late responding tissue with a latency of several months.
- Loss of bladder surface cells causes irritation and proliferation of deeper stromal cells such as fibroblasts.
- This leads to irritability, fibrosis, and progressive reduction in bladder capacity.
- **Whole bladder RT:** Tolerance dose 65 Gy.
- **Prostate:** $V_{65} < 50\%$, $V_{70} < 35\%$, $V_{75} < 25\%$, $V_{80} < 15\%$.

Normal Tissue Response: Heart

- Late responding tissue, toxicity can be delayed by years to decades.
 - Very sensitive to fraction size.
- Pericarditis and cardiomyopathy depend on total heart volume irradiated, whole heart RT can result in a subacute pericarditis.
 - Whole heart dose of **26 Gy**: 15 % risk of pericarditis.
 - When designing mediastinal fields or mantle fields for lymphoma, try to block heart to some extent.
- Cardiotoxic chemotherapy (Adriamycin) can further increase the risk of cardiac morbidity.
- Accelerated atherosclerosis is due to the combination of RT to coronary vessels, and comorbid risk factors like HTN, HLD, tobacco.
 - Advise patients in risk factor reduction.
 - Coronary vessels may be contoured as an additional structure for 3D planning.

Normal Tissue Response: Bone and Cartilage

- Late toxicity, different for children and adults.
- Irreversible growth suppression occurs after doses of **10–20 Gy** in children.
 - Irradiating a partial vertebral body is discouraged due to risk of scoliosis from imbalanced growth.
- Osteoradionecrosis or fracture may occur in any bone receiving **>65–70 Gy**. This toxicity may be delayed by months to years.

Normal Tissue Response: CNS

- Spinal cord is more sensitive than brain.
- Very sensitive to fraction size – CNS α/β is **1–2**.
- Acute: Transient demyelination (Somnolence syndrome, Lhermitte sign).
- Late: Vascular changes (micro-infarcts, micro-hemorrhage, moyamoya), cognitive dysfunction, myelopathy (cord) or necrosis (brain).
- Spinal cord tolerance is around **50 Gy** (without chemo), **45 Gy** (with chemo), in standard fractions.
- Brain can tolerate **72 Gy** to small volumes.
- Brainstem can tolerate **54–60 Gy** (the exact number is controversial).

Normal Tissue Response: Peripheral Nerves

- Brachial plexus tolerance is around **60 Gy**.
- Injury to the brachial plexus leads to irreversible pain and weakness of the upper extremity, with a several month to few year latency period.
- Other peripheral nerves may be injured by irradiation but are less well studied.

Normal Tissue Response: Gonads

- The testes are one of the few organs in the body that are more sensitive to fractionated RT than to single fractions.
- Sperm production is extremely radiosensitive; **0.1 Gy** can decrease sperm count and **6 Gy** can cause permanent sterility.
 - Sperm count takes **~74 days** to nadir.
 - Radiation is not a reliable form of sterilization, there are case reports of men fathering children after **8 Gy TBI and stem cell transplant**.
- Larger doses (≥ 20 Gy) are required to decrease testosterone production.
- The ovaries are also very radiosensitive but the dose required to cause clinical symptoms depends on age.
 - Older women have fewer oocytes remaining so even tiny doses (**2 Gy**) can cause immediate ovarian failure.

- Younger women (teenage girls) may require over **12 Gy** to cause ovarian failure.
- Radiation induced ovarian failure behaves clinically like any other source of ovarian failure (surgical, chemo-induced, or natural menopause).

Normal Tissue Response: Genitalia

- The skin on vulva and penis are similar to skin elsewhere but due to location and moisture, any skin reaction is very unpleasant.
- The vagina is remarkably radioresistant, and can generally exceed **100 Gy** with LDR brachytherapy before developing ulcerations or fistulas.

Scoring Systems for Tissue Injury

- Late Effects of Normal Tissue, Subjective Objective Management Analytic (LENT-SOMA)** (1992):
 - Toxicities are graded 1–5, where 1 is asymptomatic or minimally symptomatic and 5 is complete loss of organ function.
 - Rarely used in modern protocols.
- RTOG Common Toxicity Criteria (CTC)** (1995):
 - Graded all toxicities 1–5, where 1 is asymptomatic or minimally symptomatic and 5 is **death**.
 - RTOG CTC only applies to radiation toxicities.
 - Toxicities classified into “Early” and “Late”.
- Common Toxicity Criteria (CTC) v2.0** (1999):
 - Added chemotherapy toxicities.
- Common Toxicity Criteria for Adverse Events (CTC-AE) v3.0** (2003):
 - Much longer and more detailed than **CTC v2.0**.
 - Includes “adverse events” other than treatment toxicities, such as comorbid medical and psychiatric events, motor vehicle accidents, etc.
- Common Toxicity Criteria for Adverse Events (CTC-AE) v4.0** (2009):
 - The latest version (**v4.0**) is up to 764 categories and 195 pages long.
- One drawback of all of the above scoring systems is that management decisions can affect toxicity grading.
 - Two patients are wheezing, one gets an inhaler and one does not. The first patient is scored as “Grade 2” pulmonary toxicity while the second is “Grade 1”.
 - CTC-AE v4.0** eliminates some but not all of these “management decision” grades.

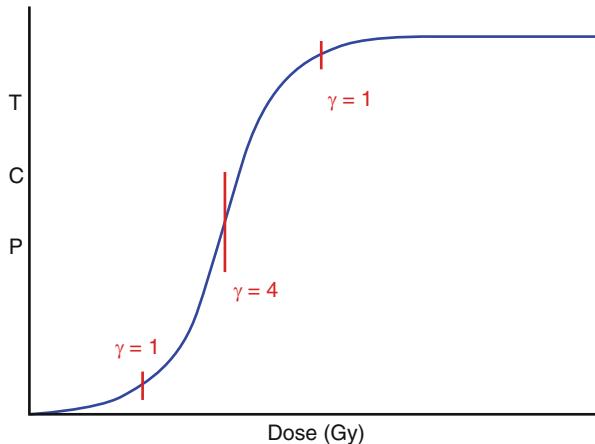
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Therapeutic Ratio

Tumor Control Probability (TCP) Curves

- A **TCP curve** is created by plotting some measure of tumor control probability against the total dose.
- This may be done with clinical or experimental data, or with theoretical models.
- Even when plotting clinical data, a theoretical model must be used to model the response of tumor cells to radiation therapy.
 - See Chapt. 21 for details of single-target and linear-quadratic models.
- A **TCP curve** is characterized by a sigmoid shape, in which there is little dose-response at very low or very high doses, and a steep dose-response at intermediate doses.

Fig. 27.1 TCP curve showing various γ values.



Calculation of TCP

- Assuming that a single clonogenic cell is capable of reproducing an entire tumor, the probability of tumor control is equal to the probability that no clonogenic tumor cells are present.
- Using simple Poisson statistics (see Chapt. 21), if there are an average of X clonogenic tumor cells present, tumor control probability is equal to e^{-X} .
- Rule of Thumb:** To achieve a certain TCP, you should aim for a tumor cell survival of $(1 - \text{TCP})$.
 - So to achieve 90 % TCP, you need a tumor cell survival of **0.1 tumor cells per patient**.
 - This means that if you start out with **10^9 tumor cells**, you need to achieve a surviving fraction of **10^{-10}** .

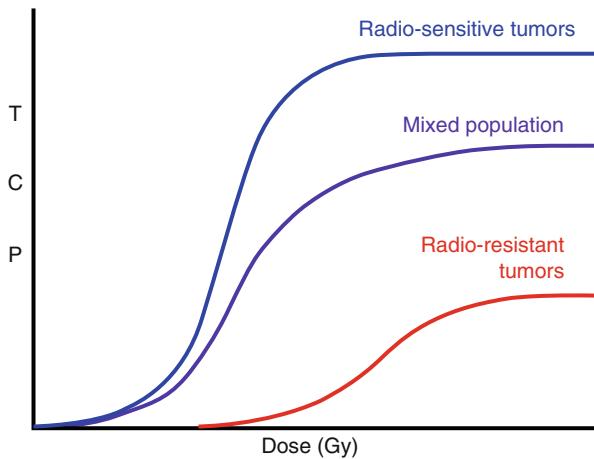
Factors Affecting Shape and Slope of TCP Curves

- The slope of a tumor control probability curve is known as γ .
 - γ is a ratio of **absolute** change in response probability to **relative** change in dose.

$$\gamma = \frac{\Delta \text{Response (absolute\%)}}{\Delta \text{Dose (relative\%)}} \quad (27.1)$$

- At $\gamma = 2$, a 1 % increase in dose will increase TCP by 2 %.
- As demonstrated in this graph, γ is highest near the middle of the TCP curve (Fig. 27.1):
- There is a shallow dose-response (low γ) at very low and very high doses, and a much steeper dose-response at intermediate doses.

Fig. 27.2 TCP curve showing a mixture of sensitive and resistant tumors.

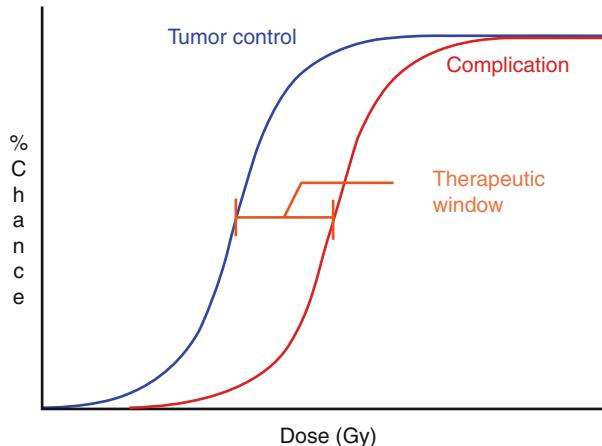


- The slope of a **TCP** curve depends on how the dose is given:
 - If dose escalation is performed by adding more fractions at a fixed fraction size, the measured γ will be lower than if dose escalation is done by increasing fraction size (Fig. 27.2).
- A mixed population of tumors will always show a weaker dose-response than a homogeneous population.
 - Very sensitive tumors are controlled even at the lowest dose levels, and very resistant tumors are uncontrolled even at the highest dose levels.
- Geographic miss becomes even more important at very high levels of **TCP**.
 - Patients with viable tumor outside of the radiation field will fail no matter how high the dose is escalated.

Normal Tissue Complication Probability (NTCP)

- A NTCP curve is constructed the same way as a TCP curve, by plotting the probability of normal tissue injury against the dose.
- Normal tissue tends to have a steeper dose response than tumors.
- Different normal organs have different volume-dependence as seen in Chapt. 26.
 - The **LKB** model takes this into account with a volume exponent, n .
 - Tissues with a large volume effect (parallel tissues) have a larger n , while tissues with a small volume effect (serial tissues) have a smaller n .
- Normal organs are rarely homogeneously irradiated. Therefore there must be a mechanism to account for different volumes of irradiation:
 - The **Lyman-Kutcher-Burman (LKB) model** takes a **dose volume histogram (DVH)** and calculates an equivalent dose and volume assuming uniform irradiation to a partial organ.
 - Take this type of analysis with a grain of salt, it is a mathematical approximation and does not have a strong biological basis.

Fig. 27.3 The therapeutic window is the difference between the TCP curve and the NTCP curve.



Therapeutic Window and Therapeutic Ratio

- The “therapeutic window” is a figurative space in between treatment failure and toxicity.
 - This is a conceptual window and not a quantitative number.
 - The larger the window, the more likely the treatment is to be safe and effective (Fig. 27.3).
- Therapeutic ratio** is the difference between tumor control and normal tissue toxicity.
 - One popular measure of **therapeutic ratio** is the **probability of uncomplicated cure**; as defined by $(\text{probability of cure}) \times (1 - \text{probability of complication})$.
 - In other words:

$$TR = TCP! \times (1 - NTCP) \quad (27.2)$$

- Keep in mind that this is just one way to define **TR**.
- Therapeutic ratio** depends greatly on the definition of “complication”.
 - Most patients have some level of toxicity, especially for sites like H&N.
 - What level of toxicity is acceptable versus unacceptable?

Tumor and Normal Tissue Repopulation

- When treatment is prolonged (as in split course radiation), both tumors and normal tissues can repopulate (Fig. 27.4).
- This increases the dose required to achieve the same **TCP** or **NTCP**, and is visualized as a right-shift of **TCP** and **NTCP** curves (Fig. 27.5).
 - In general, tumors repopulate more effectively than normal tissues.
 - Late-responding tissues do not repopulate effectively over clinically relevant time-scales.

Fig. 27.4 Some tumors will undergo accelerated repopulation after a certain amount of time under treatment. This is called the kickoff time. This effect can often decrease the therapeutic window.

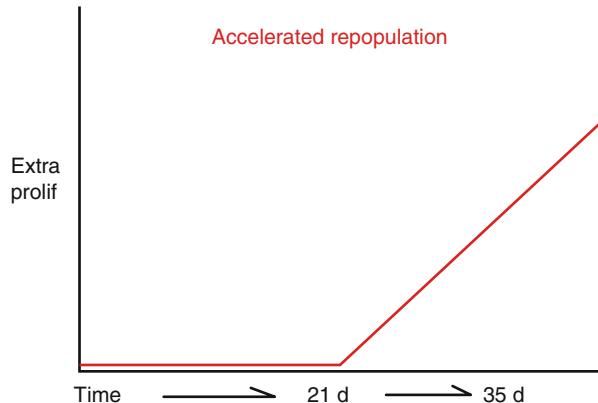
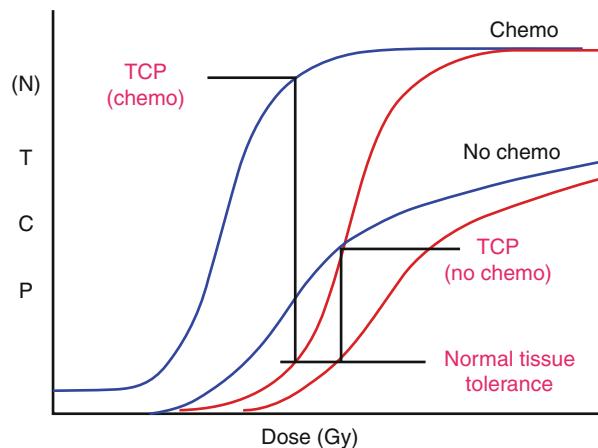


Fig. 27.5 TCP curves (blue) and NTCP curves (red) showing the affect of radiosensitizing chemotherapy (left-shifted) compared to no chemotherapy (right-shifted).



- In general, treatment prolongation narrows the therapeutic window and is a bad thing.
 - There is plenty of human data suggesting decreased survival with prolonged overall treatment time, especially in squamous cell cancers.

Sensitizers, Protectors and Combined Modality

- The purpose of any combined modality therapy is to improve the therapeutic ratio.
- Mechanisms to improve therapeutic ratio include:
 - Selective sensitization of tumor.
 - Selective protection of normal tissue.

- Independent (additive or synergistic) killing of tumor.
- Selective killing of radioresistant (i.e., hypoxic) tumor.
- Combined modality therapy may or may not increase therapeutic ratio.
 - For example, concurrent cisplatin for head and neck irradiation increases both toxicity and cure rates. If your definition of therapeutic ratio places equal weight on toxicity and cure, it may not “improve” at all.
- See Chapt. 28 for more details.

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Combined Modality Therapy

Radiosensitizers

- Unlike chemotherapy, these drugs have little to no tumoricidal effect unless given in combination with radiation.
- **Halogenated Pyrimidines**
 - **Bromodeoxyuridine (BUdR) and Iododeoxyuridine (IUDR)**
 - Nucleotide analogues that are taken up and incorporated into newly synthesized DNA.
 - Only cells with active DNA synthesis will incorporate these analogues.
 - DNA containing nucleotide analogues is more susceptible to strand breakage from ionizing radiation, therefore tumor is selectively radiosensitized.

Radioprotectors

- These drugs are designed to selectively protect normal tissues from radiation damage.
- **Sulfhydryls (WR-series compounds)**
 - Powerful free radical scavengers, developed during Cold War in anticipation of nuclear war.
 - **Amifostine** is the only FDA-approved radioprotector.
 - Administered 30 min prior to RT, greatly decreases mucositis and xerostomia.
 - Normal tissue selectivity is based on:
 - Slower penetration of tumors compared to well-vascularized normal tissues.
 - **Alkaline phosphatase** required to activate amifostine. Many tumors are deficient in this enzyme.
 - Can cause nausea and hypotension, and therefore is rarely used in modern clinical practice.

Oxygen Modifying Therapy

- Hypoxia is a well known determinant of radioresistance. Many strategies have been developed to cope with hypoxia.
- **Direct Oxygen Modification:**
 - **Transfusions:** RBCs, the oldest oxygen modifying therapy. The clinical evidence for radiosensitization by transfusion is mixed.
 - **Hyperbaric Oxygen (HBO₂):** Administered in a pressurized dive tank. Equipment and potential hazards make this option impractical for most medical centers.
 - **Carbogen:** A gas mixture of 95 % O₂ and 5 % CO₂, hyper-oxygenates tissues like **HBO₂** but is easier to administer.
 - **Nicotinamide:** a vasodilator that decreases acute hypoxia.
 - **Accelerated radiation with carbogen and nicotinamide (ARCON):** A clinically relevant treatment regimen developed in the Netherlands.
- **Hypoxic Radiosensitizers:**
 - These compounds increase the yield of DNA damage from irradiation under hypoxic conditions, much like oxygen itself.
 - **Nitroimidazoles** have a longer diffusion distance than oxygen and can therefore penetrate into a poorly vascularized tumor.
 - These include **misonidazole**, **etanidazole**, **nimorazole** and **pimonidazole**.
 - Radiolabeled nitroimidazoles can be used to image hypoxic tumor cells.
 - Effective use as radiosensitizers is limited by cumulative neurotoxicity that develops at concentrations required during fractionated RT.
 - **Nimorazole** is clinically used as a radiosensitizer in Danish head-and-neck trials.

- **Hypoxic Cytotoxins:**
 - These compounds have inherent tumoricidal activity even in the absence of radiation.
 - **Mitomycin C** – chemotherapy drug, slightly more toxic to hypoxic cells. Very myelosuppressive, used routinely in anal cancer.
 - **Tirapazamine** – Hypoxia-specific toxin that works very well in mice but is more toxic in humans. Used in ongoing clinical trials for hypoxic H&N tumors.

Hypoxia Imaging

- The “Gold Standard” used for invasive hypoxia detection is **the oxygen probe**. Use of these probes is painful for patients.
- The non-invasive “gold standard” is hypoxia imaging with **O-15 PET** (radioactive oxygen).
 - **O-15** has a half-life of 2 min so it has to be manufactured at or near the imaging site.
- **18F-MISO** and **62Cu-ATSM** are longer-lived positron emitters that accumulate in hypoxic cells and can be used for PET imaging.
- It is theorized that hypoxia-specific sensitizers and cytotoxins will be more effective when coupled with hypoxia imaging.
 - Select out a group of highly hypoxic tumors that will respond better to hypoxia-specific agents.
 - This is not yet proven by clinical data (as of 2013), but there are ongoing trials.

Dose Reduction Factor and Enhancement Factor

- Protectors are characterized by a **dose reduction factor (DRF)**, calculated as a **ratio of radiation doses** that achieve the same biological endpoint.

$$DRF = \frac{\text{Dose (with protector) to achieve an effect}}{\text{Dose (no protector) for the same effect}} \quad (28.1)$$

- Amifostine has a **DRF** of 1.8–2.7 for an endpoint of total-body irradiation lethality in mice.
- Sensitizers are characterized by an **enhancement ratio (ER)**, calculated as a ratio of doses that achieve the same biological endpoint:

$$ER = \frac{\text{Dose (no sensitizer) to achieve an effect}}{\text{Dose (with sensitizer) for the same effect}} \quad (28.2)$$

- **Misonidazole** has an **ER** as high as 1.8 for an endpoint of cell survival after single fraction irradiation under hypoxic conditions.

- **Hypoxia-specific sensitizers** are never as effective in patients as one would expect from their **ER**. Why?
 - During a course of fractionated radiation, some portion of the tumor will undergo **reoxygenation**.
 - In the cells that successfully reoxygenate, real **O₂** is more effective than any drug.

Systemic Therapy Agents: Mechanism of Action

- **Classic Alkylators:** Kill cells by attaching alkyl groups to DNA.
 - Not usually cell cycle specific.
 - May or may not be radiosensitizing.
 - Penetrates blood-brain barrier.
 - Includes **cyclophosphamide, ifosfamide, temozolomide, busulfan, melphalan, dacarbazine, BCNU, CCNU**, et al.
- **Platinum:** Has both alkylating and cross-linking properties. Both can damage DNA.
 - Not cell cycle specific.
 - Very radiosensitizing (careful – sometimes FX are additive).
 - Includes **cisplatin, carboplatin, oxaliplatin**, etc.
- **Antibiotics:** Kill cells by inhibiting DNA and RNA synthesis.
 - Not cell cycle specific.
 - Very radiosensitizing – especially **adriamycin**.
 - Includes **doxorubicin, daunorubicin, actinomycin D, bleomycin, mitomycin C** etc.
- **Antimetabolites:** Analogues of normal metabolites in cells. Kill cells by replacing normal metabolites with drug, inhibiting a variety of pathways.
 - S-phase specific (e.g., 5FU = DNA synthesis toxin).
 - Very radiosensitizing – especially **gemcitabine**.
 - Includes **methotrexate, 5-FU, capecitabine, gemcitabine, cytarabine, hydroxyurea** etc.
- **Vinca alkaloids:** Derived from the *Vinca* periwinkle. Kill cells by blocking microtubule assembly.
 - M-phase specific (“spindle toxin”).
 - Does not cross blood-brain barrier, and is lethal if it gets into the CSF.
 - Includes **vincristine, vinblastine, vindesine, vinorelbine** etc.
- **Taxanes:** Originally derived from the *Taxus* pacific yew (now mostly synthetic). Kill cells by blocking microtubule disassembly.
 - M-phase specific (“spindle toxin”).
 - Radiosensitizing.
 - Includes **paclitaxel, docetaxel, cabazitaxel** etc.

- **Topoisomerase poisons:** Topoisomerases normally cut, twist, and re-ligate DNA. Topoisomerase poisons prevent re-ligation, leading to double strand breaks.
 - Partially S-phase specific (can also kill cells during RNA synthesis).
 - Not so radiosensitizing.
 - Includes **etoposide, topotecan, irinotecan** etc.
- **Hormonal Therapies:** Direct or indirect inhibition of hormones or hormone receptors.
 - Can only kill hormone-dependent cells (e.g., prostate and breast).
 - Includes **tamoxifen, raloxifene, anastrozole, letrozole, exemestane, finasteride, dutasteride, bicalutamide, flutamide, leuprolide, goserelin, ketoconazole, abiraterone** etc.

Targeted Therapies

- Each of these drugs is designed to inhibit a specific molecular pathway or family of pathways.
- **Monoclonal Antibodies (-mabs):** These bind a specific protein. They are very bulky and cannot cross the blood-brain barrier or the cell membrane.
 - Includes cetuximab, trastuzumab, pertuzumab, bevacizumab, rituximab, tositumomab, ibritumomab, brentuximab, alemtuzumab, etc.
- **Tyrosine Kinase Inhibitors (TKIs, -ibs):** Small molecules that inhibit multiple tyrosine kinases involved in cell survival and growth signaling.
 - Includes lapatinib, erlotinib, gefitinib, sunitinib, sorafenib, imatinib, dasatinib, ruxolitinib, crizotinib, vemurafenib, etc.
- **Other Inhibitors (-ibs):** Inhibition of enzymes that are not tyrosine kinases.
 - Includes sirolimus, everolimus, bortezomib, olaparib, vorinostat, thalidomide, lenalidomide, etc.
- **Receptor Agonists:** Activates rather than inhibits receptors.
 - Includes bexarotene.
- **Immunotherapies:** Activates immune system to fight cancer cells.
 - **Cytokines** include interferons and interleukins and are small molecules that activate the immune system.
 - **Ipilimumab** and **anti-PD-L1** are monoclonal antibodies that activate the immune system.
 - **Cancer vaccines** include **sipuleucel-T** and **algenpantucel-T**.

The Oxygen Effect for Chemotherapy

- Some drugs act through free radicals, and therefore require oxygen to work, just like radiation.
 - Includes **bleomycin, procarbazine, dactinomycin**.

- Other drugs are more active under hypoxic conditions.
 - Includes **mitomycin-C, doxorubicin, and tirapazamine.**
- Many chemotherapy drugs do not have any oxygen interaction.
- However, just like oxygen, many drugs are limited by diffusion distance and cannot penetrate a poorly vascularized tumor.

Multiple Drug Resistance

- The theory of multi-agent chemotherapy states that combining drugs with different modes of action makes it less likely for cancer cells to develop resistance.
- However, cancer cells often develop resistance to many drugs at the same time.
- Known mechanisms include:
 - **Membrane channel pumps:** The multiple drug resistance (MDR) gene encodes a protein that ejects toxins from the cell, capable of binding multiple classes of drugs.
 - **Free radical scavengers:** Overexpression of glutathione-producing or -restoring genes can increase the cell's capability to repair free radical damage.
 - **DNA repair:** Overexpression of DNA repair pathway proteins can overcome DNA-damaging agents such as alkylators and platinum.

Concurrent Chemotherapy and Radiotherapy

- Agents with **additive** cell kill: Killing is roughly equal to simple logarithmic addition.
 - **Ex:** Radiation alone gives one log kill ($SF = 10\%$), 5-FU alone gives one log kill ($SF = 10\%$), concurrent 5FU-RT gives two log kill ($SF = 1\%$).
- Agents with **synergistic** cell kill: Killing is significantly greater than simple logarithmic addition.
 - **Ex:** Radiation alone gives one log kill ($SF = 10\%$), gemcitabine alone gives one log kill ($SF = 10\%$), concurrent gem-RT gives four log kill ($SF = 0.01\%$).
- No **cross-resistance:**
 - Chemotherapy resistant cells may not be resistant to radiation.
 - Radiation resistant cells (hypoxic, S-phase, mutant p53) may be more sensitive to chemotherapy.
- **Reoxygenation:**
 - Chemotherapy may indirectly (through tumor shrinkage) or directly (bevacizumab) promote oxygenation of tumor.
- **Selectivity:**
 - In order to be clinically useful, a systemic agent must have greater cytotoxicity for tumor than for normal tissue.
 - Similarly, a useful radiosensitizer should have greater sensitization of tumor than normal tissue.

Photodynamic Therapy

- **Psoralens, porphyrins** and **aminolevulinic acid (ALA)** are activated by specific wavelengths of visible or UV light, generating toxic free radicals.
 - Visible and UV light can only reach very superficial lesions.
 - Commonly used for cutaneous malignancies (basal, squamous, and lymphoma) and endoscopic ablation of esophageal lesions.

Gene Therapy

- Types of anti-cancer gene therapy:
 - Introduce genes into healthy T-cells or dendritic cells to boost anti-tumor immunity.
 - Introduce tumor suppressor genes into cancer cells to discourage growth.
 - Introduce “suicide” genes that selectively kill cancer cells.
 - Introduce “suicide” genes that are selectively activated by irradiation.
 - Introduce immunogenic genes into cancer cells to provoke anti-tumor immunity.
- Methods to introduce genes into human cells:
 - **Physical:** Electroporation and ballistic (can only be done ex vivo, such as in apheresis WBCs).
 - **Plasmid:** DNA sequences coated with lipid or polymer envelope that promotes uptake by cells.
 - **Viral:** Modified retrovirus, adenovirus, lentivirus, or herpes virus. Virus has to be resilient enough to evade immune system but not so resilient that it reactivates and kills the patient.
- As of 2014, gene therapy is not yet standard of care for any human tumors.

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Biology of Brachytherapy, Particle Therapy, and Alternative Radiation Modalities

Brachytherapy Definitions

- **Brachytherapy:** Radiotherapy delivered using nuclides placed within or in contact with the target volume.
- **Sealed Source:** Fully encapsulated.
 - **Low Dose Rate (LDR):** $\leq 2 \text{ Gy/h}$.
 - **Temporary**
 - **Permanent**
 - **Medium Dose Rate (MDR):** $2\text{--}12 \text{ Gy/h}$.
 - Almost never used for clinical treatment.
 - **High Dose Rate (HDR):** $>12 \text{ Gy/h}$.
 - **Pulse Dose Rate (PDR):** HDR treatment for a few minutes every hour, such that the dose rate averaged over days is in the **LDR** range.
- **Unsealed Source:** Brachytherapy using freely floating radionuclides (injected into a specific location, or administered systemically).

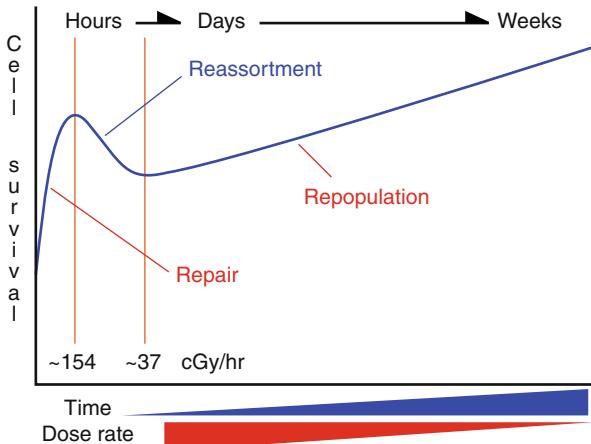
A Note on Brachytherapy

- Biologically speaking, there are several major differences between brachytherapy and EBRT:
 - **Dose Rate:** EBRT (excluding TBI) is usually performed at high dose rate. **Brachy** may be **HDR, LDR** or **PDR**.
 - **Dose Gradient:** Most EBRT plans attempt to achieve a uniform dose within the target volume. **Brachy** always produces steep dose gradients.
 - **Fractionation:** **Brachy** is performed in far fewer fractions compared to **EBRT**.
 - **LDR** implants may be performed in a single procedure (especially permanent implants).

Brachytherapy: Dose Rate Effects

- To a first approximation, the **LDR** survival curve is equal to the survival curve of **many small fractions** of EBRT/HDR.
 - This is the biological rationale for the use of **PDR** therapy.
- **Classic Dose-Rate Effect:** **LDR** treatment results in decreased cell killing and no shoulder on the survival curve, compared to **HDR/EBRT**.
 - The magnitude of this effect directly correlates with the amount of **sublethal damage repair (SLDR)** in that cell type.
 - This is responsible for differential sparing of normal tissue with **LDR**, and is the biological rationale for the superiority of **LDR**.
 - Intrafraction repair goes from 0 to 100 % between dose rates of **1 Gy/min** and **0.01 Gy/min (60 cGy/h)** (Fig. 29.1).

Fig. 29.1 Dose-rate to cell survival curve that illustrates the general improvement in cell kill with increasing dose rate with the exception of the region containing the inverse dose-rate effect.



- **Inverse Dose-Rate Effect:** In some rapidly cycling cells, cell killing actually increases between ~ 154 and ~ 37 cGy/h. This is a cell cycle effect.
 - At 154 cGy/h the cell cycle is completely arrested, so radioresistant S-phase cells are radioresistant.
 - At 37 cGy/h the cell cycle is allowed to progress into the radiosensitive G₂/M, causing cell killing.
 - This is another rationale for the superiority of **LDR**, proliferating cancer cells sensitize themselves but non-proliferating cells do not.
- **Very Low Dose Rate:** Below the “critical dose rate”, fast-growing cells are able to repopulate faster than they are killed.
 - For example, mouse jejunum treated at <0.54 cGy/min (**32 cGy/h**) shows very little killing.
 - **Permanent implants** have an extremely low dose rate. Therefore they are ineffective on rapidly proliferating tumors.
 - A typical **I-125** prostate seed implant has a dose rate of ~ 7 cGy/h.
 - Fortunately, prostate CA is a very slowly proliferating tumor.

Dose Rate and Clinical Endpoints

- **Mazeron** did two studies on interstitial **LDR** implants: one on the oral cavity and one on the breast.
 - **Oral Cavity:** Dose rates <50 cGy/h were associated with less necrosis, with similar local control as long as total dose was adequate.
 - **Breast:** Between 30 and 90 cGy/h, higher dose rates were associated with improved local control.

- Typical temporary implant **LDR** dose rates are 50–60 cGy/h to the prescription point. However, higher or lower dose rates may be used depending on clinical judgment and implant geometry.
 - Higher dose rate = more efficacy, more toxicity.
- Permanent implant **LDR** dose rates are variable, and mostly depend upon which isotope is being used.
 - Shorter half-life = higher dose rate.
- Dose rate effects are **largely irrelevant** for **HDR**, as the dose rate is too high to allow intrafraction repair or reassortment.

Brachytherapy: Choice of Nuclide and Implant

- **Ra-226** was used for many decades but is almost never used anymore due to risk of radon leakage.
- **Permanent LDR** implants generally use **I-125**, **Pd-103**, or less commonly **Au-198**.
- **Temporary LDR** implants may use **Au-198**, **Ir-192**, **Cs-137**, **Co-60** or others.
- **HDR** implants almost always use **Ir-192**.
- Implants are classified as **interstitial** (such as prostate or breast brachy) or **intracavitory** (such as GYN brachy).
- See Chap. 11 for a more detailed discussion of brachytherapy techniques.
- See Appendix B for information on nuclide origins, energies and half-lives.

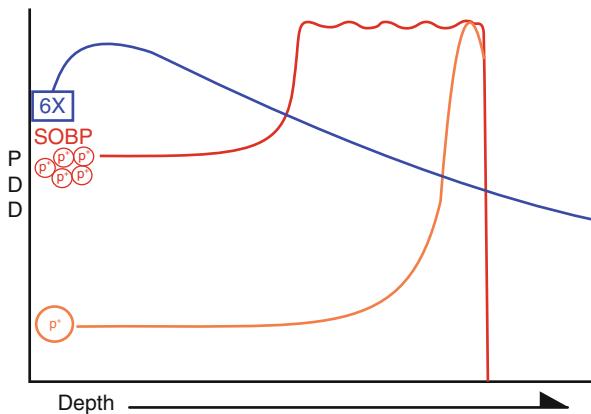
Unsealed Sources

- **I-131** is a beta-emitter that is taken up by thyroid tissue as well as differentiated thyroid cancers.
- Bone-seeking nuclides include **Sr-89**, **Sm-153** and **Ra-223** and are used to treat widespread bony metastases.
- **P-32** is a beta-emitter that can be used to treat the lining of a cyst, joint space, or body cavity.

Radioimmunotherapy (RIT)

- Radionuclide-antibody conjugates are used to target high doses of radiation specifically to tumor.
 - **I-131** is a mixed beta/gamma emitter.
 - **Y-90** is a pure beta emitter.
- **I-131 antiferritin** and **Y-90 antiferritin**: Targets ferritin-rich tumors such as Hodgkin lymphoma and hepatocellular carcinoma.
- **Y-90 ibritumomab tiuxetan (Zevalin)**: Targets CD20 (like rituximab), used to treat rituximab-refractory non-Hodgkin lymphoma.
- **I-131 tositumomab (Bexxar)**: Also targets CD20 and has been used for recurrent and refractory non-Hodgkin lymphoma.

Fig. 29.2 Comparison of dose profiles between 6 MV photons (blue), a pristine Bragg peak from a mono-energetic proton beam (tan), and a poly-energetic proton beam illustrating a spread out Bragg peak (red).



Proton Beam Therapy

- Protons are used for their **Bragg peak** -> no exit dose and greatly decreased integral dose.
 - Advantages are mostly physical not biological, however new data suggest different genes may be induced after proton versus X-rays treatment (Fig. 29.2).
- Biological effectiveness is very close to photons, with a standard **RBE = 1.1** (in Co-60 Gy equivalents).
 - **OER** = same as Co-60 photons.
- The biological effectiveness of the back edge of the Bragg peak is not well defined (RBE could be > 1.1).
 - Therefore, the distal edge of a proton beam should not be placed inside a critical normal structure.
- A single (“pristine”) Bragg peak is too narrow to treat anything, so therapeutic proton beams use a **Spread Out Bragg Peak (SOBP)** with multiple Bragg peaks at different ranges.
 - The entry dose of a **SOBP** is much higher than that of a pristine Bragg peak.
- Proton beams are produced by cyclotrons, which are much larger and more expensive than linacs.

Fast Neutron Therapy

- A **fast neutron** is approximately ≥ 6 MeV.
- **Neutrons** were used for their low OER (ability to kill hypoxic cells) and high RBE in specific tumor types (such as salivary gland tumors).
 - Neutrons can achieve higher local control of salivary gland tumors when compared to photons.
 - Unfortunately they also have dramatically worse late toxicities, limiting their clinical use.
- Neutrons are an uncharged particle, so they do not have a Bragg peak.

Boron Neutron Capture Therapy (BNCT)

- **Boron** absorbs **slow neutrons** (0.025–10 keV) and fragments into alpha particles, delivering very high dose locally.
- Must pre-treat with a boron containing drug that selectively localizes to tumor.
- Slow neutrons have very poor penetration of tissue, can only treat superficial tumors (approx. 2–3 cm).

Heavy Ion Therapy

- **Heavy ions** are defined as charged particles heavier than a proton. **Carbon-12** is the most popular heavy ion.
- **Carbon-12** and other **heavy ions** have **high-LET** biological effect, as well as a **Bragg peak**.
 - Both physical and biological advantages.
 - **High RBE** and **low OER** → can overcome hypoxia.
- Effective dose in **Bragg peak** is not well defined. Both physical dose and RBE are greatly increased.
 - There is great uncertainty about the efficacy and long-term toxicity of heavy ion therapy.
- Heavy Ions are accelerated by synchrotrons, which are even larger and more expensive than proton beam cyclotrons.
 - As of 2014, heavy ion therapy is not available in the USA.
 - Germany and Japan have carbon ion facilities.

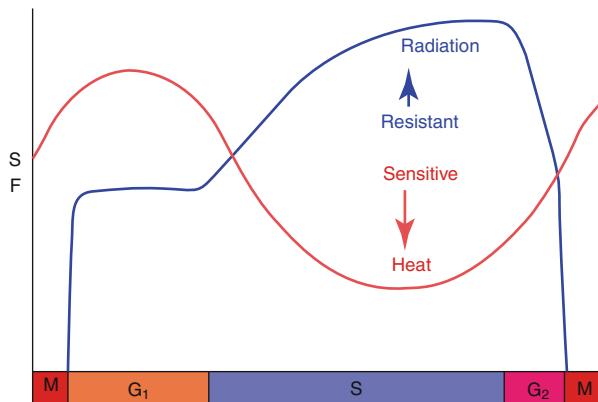
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Hyperthermia

Definition of Hyperthermia

- **Hyperthermia** is the use of temperatures between 39 °C (102 °F) and 47 °C (116 °F) to achieve selective cell killing. It may be used alone or in combination with radiotherapy, chemotherapy, or both.
- In the context of radiation biology, **hyperthermia** is not meant to “cook” the tumor and therefore describes non-ablative temperatures (<50 °C or 122 °F) as opposed to the higher temperatures used in surgery.

Fig. 30.1 Sensitivity (as indicated by relative surviving fraction) of cells throughout the cell cycle to radiation (blue) or hyperthermia (red).



Rationale for Hyperthermia

- Use of hyperthermia has mostly been explored as a potential adjunct to radiation therapy, because hyperthermia and RT may produce additive or synergistic effects depending upon the sequencing of the two treatments:
 - There are no intrinsic differences between tumor and normal cells with respect to hyperthermic sensitivity. However, extrinsic differences are exploitable:
 - Poorly vascularized tumors may be easier to heat than well vascularized normal tissue.
 - Hypoxia, low pH, and S-phase may increase sensitivity to hyperthermic killing (Fig. 30.1).

Cytotoxicity of Heat

- Heat damages cells by denaturing and inducing aggregation of proteins. Denaturation and aggregation of nuclear proteins may inhibit repair of radiation-induced DNA damage.
 - This is unlike radiation-induced DNA damage, which does not involve proteins at all.
- **S-phase cells are most sensitive to hyperthermia** (S-phase is also the most radio-resistant phase).
- Heat damages cells easier when there is less blood vasculature act as a heat-sink to cool the tumor (hypoxic or poorly vascularized cells are more radio-resistant).
- Hyperthermia kills non-dividing cells as well as dividing cells (unlike radiation which generally only kills dividing cells).
- Cell kill is **much** higher with concurrent heating and irradiation, compared to sequential heat and RT. However, this is often impractical clinically.

- Two mechanisms of heat radiosensitization:
 - Vasodilation (decreased hypoxia).
 - Inhibition of repair of radiation-induced DNA damage.

Heating and Temperature Monitoring

- Heating may be performed with:
 - Hot water bath
 - Microwave energy
 - Radiofrequency energy
 - Ultrasound energy
- The heat source may be:
 - Systemic: Total body hyperthermia.
 - External: Heat source directed toward the tumor.
 - Internal: Heat source implanted within the tumor.
- Temperature should be monitored at multiple points, as heating is often non-uniform.
- The main barrier to uniform heating is the **heat sink** effect; venous blood effectively carries away heat.

Heat in Tumors Versus Normal Tissues

- Tumors may receive a higher dose of heat because they are poorly vascularized and do not enjoy the **heat sink** effect of normal blood flow.
- Normal tissues are able to vasodilate and increase blood flow to get rid of heat; many tumors cannot, or may even suffer decreased blood flow.
- Tumors have a high prevalence of hypoxia and acid pH, both of which increase heat-related cytotoxicity.

Thermal Dose

- Thermal Dose is expressed as **cumulative equivalent minutes at 43 °C to 90 % of monitored points (CEM 43 °C T₉₀)**.
- Above 43 °C, treatment time needs to decrease by a factor of 2 for each 1 °C temperature increase to achieve a similar biological effect.
- Below 43 °C, treatment time needs to increase by a factor of 4–6 for each 1 °C temperature increase.

Thermal Enhancement Ratio (TER)

- TER is a **ratio of radiation doses** that achieve the same endpoint in the absence and presence of heat:

$$TER = \frac{\text{Dose (No heat) to cause an effect}}{\text{Dose (With heat) for same effect}} \quad (30.1)$$

- For a **1 h CEM 43 °C T₉₀** hyperthermia treatment:
 - **TER ≈ 2.0** (normal tissue)
 - **TER ≈ 4.3** (tumor)
- Theoretically, this means that a **2 Gy fraction** with heat (**1 h CEM**) is equivalent to **4 Gy** to normal tissue, and **8.6 Gy** to tumor.

Heat Shock Proteins and Thermotolerance

- Exposure of cells to heat induces the expression of **heat-shock proteins (HSPs)**, an adaptive (protective) response to heat.
- Onset and decay of **thermotolerance** (transient resistance to heat killing) correlates with appearance and disappearance of HSPs.
 - For exposure to low-temperature hyperthermia (**39–42.5 °C**) cells can become thermotolerant during a prolonged heating period, thus resulting in a plateau of the survival curve.
 - For high-temperature hyperthermia (**43–47 °C**) cells exposed to brief heat treatments may become thermotolerant to a second exposure during post-heat incubation at **37 °C**.
- **Thermotolerance** may last for up to 1–2 weeks *in vivo*, and is believed to greatly decrease the effectiveness of fractionated thermal killing in the clinic.
 - For this reason, hyperthermia protocols usually only include one to two heat treatments per week.

Hyperthermia and Radiotherapy

- Heat alone is rarely capable of producing consistent responses in most human tumors, for several reasons:
 - Difficulty of uniformly heating a macroscopic tumor volume.
 - Difficulty of accurately measuring the temperature within the tumor.
 - Thermotolerance after the first heat fraction.
- Therefore, since it has been demonstrated *in vitro* and *in vivo* that heat sensitizes mammalian cells to ionizing radiation, hyperthermia is sometimes combined with radiotherapy to increase the therapeutic ratio.
- Clinical hyperthermia protocols have used temperatures of **41–43 °C**, with a goal of **1 h CEM 43 °C T₉₀** delivered once or twice a week.
- Theoretically, hyperthermia should work best if given simultaneously with RT. For practical reasons (interference of RT machines with hyperthermia machines) it is usually given immediately before or after.
- Low temperature (**41 °C**) hyperthermia has been shown to improve the oxygenation of hypoxic tumors.

Hyperthermia: Difficulties

- **Uniform heating:**
 - Very easy to get cold spots where blood flow carries away heat. May also get hot spots in poorly vascularized areas.
 - A small difference in temperature (1°C) causes a two- to sixfold change in equivalent thermal dose (CEM).
 - Most heating devices must be in contact or close proximity to the tissue being heated.
 - Difficult to heat deep-seated tumors.
 - Temperature monitoring is often difficult, and requires multiple invasive probes.
- **Timing:** For best results, tumor must be heated during, or immediately before or after RT.
- **Interference** between heating and radiotherapy equipment:
 - Microwave and radiofrequency heating devices give off electromagnetic interference that can harm other equipment, such as radiotherapy linacs.
 - Therefore they cannot be used in the same room.
 - Moving the patient from the hyperthermia suite to the radiotherapy vault presents a logistical challenge.
- Heat works best if given in 1–2 fractions per week, while radiation works best when given in many small daily fractions.

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Carcinogenesis and Heritable Effects

Deterministic and Stochastic Effects

- A **deterministic** (non-random) **effect** occurs after exceeding a threshold dose, and the severity of the effect correlates with the dose.
 - For example, radiation induced skin erythema.
- A **stochastic** (random) **effect** occurs randomly with a probability that is proportional to dose, and the severity of the effect is random.
 - Both secondary malignancies and heritable mutations are stochastic effects.

Equivalent Dose and Effective Dose

- Absorbed dose is measured in Gy, but this does not take into account the type of radiation, or the type or volume of tissue irradiated.

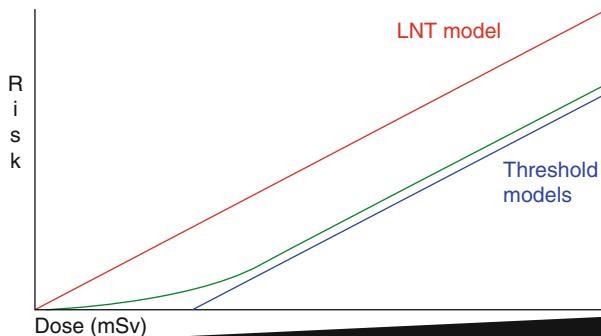


Fig. 31.1 Cancer risk to dose models including linear no threshold model (red) and linear threshold models (blue). The true cancer risk from low doses of radiation may more closely resemble the shape of the green curve.

- For radiation safety purposes, dose is multiplied by a **weighting factor (WF)** that corrects for the type of radiation.
 - This number is known as **equivalent dose** and is measured in **Sieverts (Sv)**.
 - **WF** varies with type of radiation:
 - Photons and electrons, **WF = 1**.
 - Protons, **WF = 2**.
 - Neutrons, **WF varies, up to 20**.
 - Heavy ions, **WF = 20**.
- In addition, partial-body exposures can be multiplied by a **tissue weighting factor (W_T)** to obtain an **effective dose**.
 - **Effective dose** is also measured in **Sv** but depends upon the volume of tissue irradiated.
- So let us say a chest X-ray gives **0.5 mGy** to the chest:
 - The **equivalent dose** is **0.5 mSv** to the chest.
 - The **effective dose** is closer to **0.1 mSv** (approximately - the real number actually depends on male vs. female, due to breasts).

Dose Response for Radiation-Induced Cancers

- The **linear no threshold (LNT)** model assumes a direct linear relationship between dose and carcinogenesis.
- This is in contrast to dose-response models that have a threshold beneath which radiation carcinogenesis does not occur.
- Radiation hormesis models hypothesize that extremely low doses of radiation may actually be beneficial (Fig. 31.1).
- The current human evidence is insufficient to either prove or disprove the existence of a threshold.
 - The **LNT** model is the most conservative approach, so it is used for radiation protection purposes.

Mechanism for Carcinogenesis

- Ionizing radiation causes double strand breaks, leading to chromosomal aberrations, mutations, and genomic instability.
 - Aberrations may be lethal, or may be permanently passed on to cellular progeny.
 - Cells that survive radiation with aberrations and genomic instability are believed to be involved in radiation –induced carcinogenesis.
- Radiation-induced mutations are typically **large-scale** deletions, duplications, translocations, chromosomal aberrations or aneuploidy.
- Radiation can also cause point mutations (single nucleotide polymorphisms, transitions, transversions, frameshifts, micro-deletions or insertions).
 - These are more characteristic of random (sporadic) and chemical induced mutations.

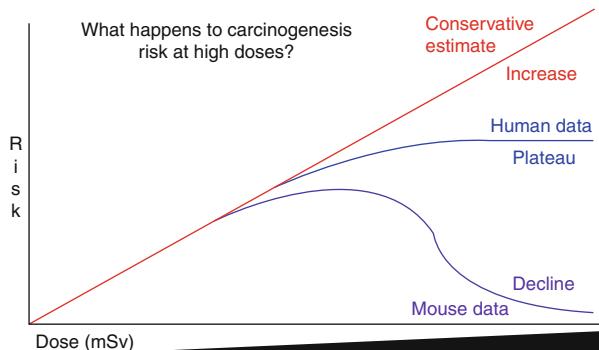
Radiation Protection Organizations

- The **Biological Effects of Ionizing Radiation (BEIR)** is an academic committee devoted to the basic science behind radiation protection.
- The **United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)** is a reporting and regulatory agency.
- The **International Commission on Radiation Protection (ICRP)** is an advisory agency.
- The **National Council on Radiation Protection and Measurements (NCRP)** is a US council that publishes reports and recommendations.
- The only consistent **human data** for long-term effects of radiation exposure are the **Japanese atomic bomb survivors**.

Absolute and Relative Risk of Carcinogenesis

- Approximately **40 %** of all humans will suffer a malignancy at some point in their lifetime.
- For the vast majority of people exposed to radiation, the absolute risk of a **radiation-induced malignancy** is much smaller than the absolute risk of **sporadic malignancies**.
- The **BEIR** and **ICRP** models of radiation carcinogenesis assume that radiation is a **relative modifier** of malignancy.
 - That is, radiation multiplies the frequency of malignancy by a dose- and age- dependent factor.
 - This model implies that radiation-induced malignancies are likely to have an age- and site- distribution similar to sporadic malignancies, whether or not that is true.

Fig. 31.2 At high doses, the LNT model predicts increasing incidence of cancer with increasing dose, but data suggests this may not be the case.



Radiation and Chemotherapy Carcinogenesis

- Chemotherapy drugs are known to cause second malignancies, most prominently leukemia risk with alkylating agents.
- The **latency** of secondary leukemias is significantly **shorter** (few years) than solid tumors (decades).
- Combined chemotherapy and radiotherapy is likely to increase secondary malignancy risk.

Dose–Response Curves for Carcinogenesis

- Gray (1950s) studied leukemia induction after total-body irradiation in mice, and found a **bell-shaped curve** of carcinogenesis.
 - Increasing the radiation dose increases carcinogenesis risk only at low doses.
 - After 2 Gy or so, radiation is more likely to cause cell killing than mutation. Carcinogenesis risk plateaus and then declines (Fig. 31.2).
- Human data has suggested a plateau in dose–response after ~10 Gy, but there is no evidence of a decline at any dose.
 - Radiation protection estimates assume a **linear** relationship between dose and carcinogenesis, without any high-dose plateau or decline.
 - Again, this is because a linear relationship is the most conservative estimate, not because it is the most biologically plausible.

ICRP Carcinogenesis Risk Estimates

- Carcinogenesis risk estimates were derived from Japanese nuclear bomb survivors who were irradiated with high-LET radiation at an extremely high dose-rate.

- The dose and dose-rate effectiveness factor (**DDREF**) corrects for the decreased biological effectiveness of low-LET, low-dose and low-dose-rate irradiation.
 - **Low DDREF exposures** are defined as **low-LET** radiation with a dose rate less than **0.1 Gy/h**, or total dose less than **0.2 Gy** at any dose rate.
 - **High DDREF exposures** are **high-LET** radiation, or dose greater than **0.2 Gy** and dose-rate over **0.1 Gy/h**.
- For the purposes of carcinogenesis, we should use **effective dose (Sv)**. This is an equivalent dose weighted for volume of tissue irradiated.
- According to **ICRP 60**, the total risk of radiation induced malignancies is:
 - **10 %/Sv** for entire population and **high DDREF**.
 - **8 %/Sv** for working population and **high DDREF**.
 - **5 %/Sv** for entire population and **low DDREF**.
 - **4 %/Sv** for working population and **low DDREF**.
- The numbers are slightly lower for “working population” because children are excluded.
- The **ICRP** numbers are widely used to estimate the risk of secondary malignancies from diagnostic studies, airline screening X-rays, nuclear accidents, etc.
- **Example:** 80 million people are screened by airport X-rays, receiving **0.25 µSv** each. How many second malignancies do you expect?
 - $0.25 \times 10^{-6} \times 5 \% = 1.25 \times 10^{-8}/\text{person}$.
 - $1.25 \times 10^{-8} \times 8 \times 10^7 = 1 \text{ secondary malignancy}$.

Carcinogenesis Risk Estimates in Radiation Therapy

- The definition of a **Sv** uses linear weighting of dose by the volume and type of tissue irradiated:
 - **60 Gy** * tissue weighting factor **0.04 = 2.4 Sv**.
 - **20 Gy** * tissue weighting factor **0.12 = 2.4 Sv**.
- Whether this can be used to directly calculate second malignancy risk in radiotherapy patients is debatable:
 - **2.4 Sv** * **8 %/Sv = 19.2 %** ICRP risk estimate (both cases).
 - However, you could argue that the true number is lower due to the “plateau effect” of high doses.
 - If so, 60 Gy to a small volume should be much less carcinogenic than 20 Gy to a large volume.

Carcinogenesis Risk and Age, Gender, Time

- Compared to the whole population, an individual patient may have more or less carcinogenesis risk based on several factors:
- **Age:** Children are much more susceptible to radiation-induced malignancy.

- Children <5yo are ~3× more susceptible than the population average, or ~10× more susceptible than older adults.
- **Gender:** Women are more susceptible to radiation-induced malignancy because of breast cancer.
- **Time:** Radiation-induced malignancies occur years to decades after irradiation. A patient with a short life expectancy is very unlikely to develop a radiation-induced malignancy.

Known Radiotherapy Induced Malignancies

- **Prostate Cancer:** Compared to patients treated with surgery, patients treated with radiation had a 34 % increased relative risk of second malignancy at 10 years.
 - The most common 2nd malignancies were bladder and rectum.
 - The largest relative increase was in-field sarcoma.
- **Cervical Cancer:** Compared to patients treated with surgery, patients treated with radiation had increased risk of cancers of the bladder, rectum, vagina, uterus, cecum, bone, and non-Hodgkin lymphoma.
 - Younger age at time of irradiation correlates with 2nd malignancy.
- **Hodgkin Disease:** Female HD survivors have a 3–17× increased risk of breast cancer compared to the general population.
 - Depending on age of irradiation, may have up to 50 % lifetime risk of developing breast cancer.
 - **Second primary malignancies** are the most likely cause of death in long-term HD survivors.

Genetic Risks of Radiation: Animal Models

- Animal studies indicate a significant risk of inherited mutations in the progeny of irradiated animals:
 - **Fruit flies (*Drosophila*)** have a very high rate of inherited mutations.
 - **Mice** have a somewhat lower rate of inherited mutations.
- The **doubling dose** is defined as the dose of radiation required to double the spontaneous rate of heritable disease.
 - **0.05–1.5 Gy** in *Drosophila*.
 - **Approx. 1 Gy** in mice.
- The **megamouse study** irradiated millions of mice and observed their progeny for mutations at seven genetic loci. This led to the following conclusions:
 - Different genes showed greatly variable radiosensitivity for heritable damage, with up to 35-fold variability.
 - **Low dose rate** (0.8 cGy/min, 48 cGy/h) irradiation produced much less heritable damage than high dose rate irradiation.

- Mouse oocytes are much more radiosensitive than human oocytes, so data on females is difficult to extrapolate to humans.
- Heritable damage is greatly decreased by allowing a time interval of several months between irradiation and conception (extrapolated to **6 months** for human males; unknown for females).

Genetic Risks of Radiation: Human Data

- According to **UNSCEAR** estimates, ~73 % of humans have at least one harmful mutation. (This includes “multifactorial disease” such as a family history of diabetes or hypertension).
 - It is difficult to observe radiation-induced heritable disease in humans because the baseline prevalence is so high.
 - No statistically significant increase in heritable effects has **ever** been observed in humans. Therefore, heritable disease risk estimates are extrapolated from animal data.
- **UNSCEAR Report 2001:**
 - Heritable disease risk of **0.41–0.64 %/Gy** per child of an individual irradiated at low dose rate and low LET.
 - Risk increases to **0.53–0.91 %/Gy** per child if 2nd-generation (grandchildren) are included.
 - Heritable disease risk is probably higher for high dose rate and high LET, but not high enough to be directly observed in atomic bomb survivors.
 - The population risk is lower than the per-child risk because some people have already finished having children, or will never have children.
- The **UNSCEAR** estimate for heritable damage after large-population radiation exposure is:
 - **0.2 %/Gy** for the entire population.
 - **0.1 %/Gy** for the working population.
- Note that **heritable damage risk** is a function of **gonad dose** only. It does not matter how much dose is absorbed by the brain, breasts, lung, rectum, etc.

Genetic Risks and Radiation Therapy

- Sperm production is lost after **6–8 Gy**, while ovarian function is lost after **2–12 Gy** depending on age.
 - Older women = closer to menopause = less dose required to induce menopause.
- **Sperm** take 2–3 months to mature, so there is a delay between testicular irradiation and loss of fertility.
 - Infertility occurs at much lower doses than hormonal changes (hypogonadism).
- **Ovarian failure** occurs immediately after radiation, and includes all of the hormonal symptoms of menopause.

- Doses of radiation insufficient to prevent fertility may increase the risk for heritable disease by approximately **0.53–0.91 %/Gy**.
- Based on mouse data, waiting at least 6 months between irradiation and conception may decrease this risk, although some genetic risk may persist indefinitely.

Radiation Protection Guidelines

- These rules and regulations are designed to limit radiation risk to the public, to radiation workers, and to children/fetuses.
- The permissible dose limits vary between nations.
- The **US NCRP** regulations give dose limits for individuals and for areas:
- **Individual Dose Limits**
 - **Radiation worker, infrequent exposure:**
 - **50 mSv total body, 150 mSv lens, 500 mSv other single organ.**
 - **General public, infrequent exposure:**
 - **5 mSv total body, 15 mSv lens, 50 mSv other single organ.**
 - **General public, continuous exposure:**
 - **1 mSv total body**
 - **Declared fetus:**
 - **0.5 mSv/month**
- **Area Dose Limits**
 - **Uncontrolled Area: $\leq 0.02 \text{ mSv/h}$ AND $\leq 0.1 \text{ mSv/week}$.**
 - At the maximum dose rate of 0.02 mSv/h, the area can only be occupied for 5 h a week without exceeding the weekly limit.
 - **Controlled Area: $\leq 1 \text{ mSv/week}$.**

Take Home Points

- Carcinogenesis risk and heritable damage risk are both considered **stochastic effects**; as far as anyone knows there is no “safe” threshold dose.
- **Equivalent dose (Sv)** is weighted for radiation type.
- **Effective dose (Sv)** is weighted for both radiation type and volume of tissue irradiated.
- **Dose and dose rate effectiveness factor (DDREF)** is defined as either “low” or “high”:
 - **Low DDREF** = Low LET radiation with either Dose $< 0.2 \text{ Gy}$, or Dose Rate $< 0.1 \text{ Gy/h}$.
 - **High DDREF** = Dose $> 0.2 \text{ Gy}$ and Dose Rate $> 0.1 \text{ Gy/h}$, or High LET radiation at any dose and dose rate.
- The **radiation induced malignancy risk** is calculated using **effective dose (Sv)**:
 - **10 %/Sv** for entire population and **high DDREF**.
 - **8 %/Sv** for working population and **high DDREF**.

- **5 %/Sv** for entire population and **low DDREF**.
- **4 %/Sv** for working population and **low DDREF**.
- The **heritable damage risk** is calculated using **gonad dose (Gy)**:
 - **0.41–0.64 %/Gy/child** of an irradiated individual.
 - **0.2 %/Gy/individual** for the entire population.
 - **0.1 %/Gy/individual** for the working population.
 - Waiting a number of months between irradiation and conception may decrease the risk of heritable damage.

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Radiation Effects in the Embryo and Fetus

Stages of in Utero Development

- **Preimplantation (conceptus):** Limited number of cells, no differentiation.
 - Days 0–5 in mice, Weeks 0–2 (Days 0–9) in humans.
- **Organogenesis (embryo):** Cells begin to differentiate into organs and tissues.
 - Days 5–13 in mice, Weeks 2–6 (Days 10–42) in humans.
- **Fetal Growth (fetus):** Structures are formed, and only need to grow and mature.
 - Days 13–20 in mice, Weeks 6–40 in humans (Fig. 32.1).

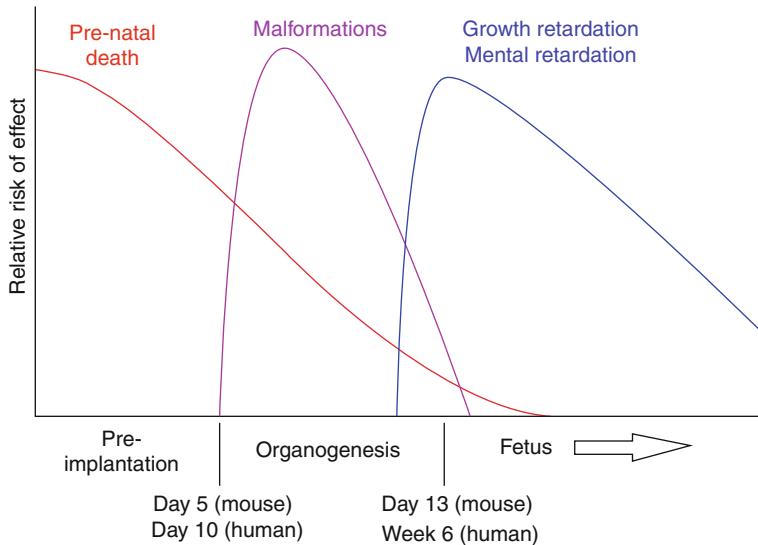


Fig. 32.1 Relative risk of various effects of ionizing radiation administered during specific phases of intrauterine development.

Of Mice and Men

- The mouse is the most common experimental animal for gestational defects.
- In mice, the **conceptus**, **embryo**, and **fetal** stages are roughly equal in length, with full-term gestational period of **20 days**.
- In man, the **fetal** stage is overwhelmingly longer, comprising the majority of the **9 months**.
- Mice appear to be more susceptible to organ malformations while humans appear to be more susceptible to growth retardation and mental retardation.

Preimplantation Damage: All or Nothing

- The pre-implantation **conceptus** has the highest radiosensitivity, **0.05–0.15 Gy** can cause significant killing.
- Damage shows an **all-or-nothing** effect:
 - Mild damage is completely repaired, no abnormalities are seen.
 - Significant damage results in failure to implant. At this early stage the pregnancy is likely to go undetected.
- Atomic bomb survivor data shows a deficit in children born after radiation exposure @ **0–4 weeks** gestational age, implying a high rate of pre-natal death.
 - However, children irradiated between **0 and 2 weeks** gestational age did not have an elevated rate of abnormalities.

Embryonic Damage: Malformations

- The embryo is extremely sensitive to radiation, with a dose of **1 Gy** resulting in a **100 % rate of severe malformations** in rats.
 - In contrast, human A-bomb data did not show any excess malformations. However, therapeutic doses of pelvic irradiation did cause gross malformations.
- Damage is related to organ formation:
 - Neural tube defects – Anencephaly, craniocoele, meningocele, etc.
 - Coelomic defects – Evisceration, intestinal malformations.
 - Cardiac, pulmonary, renal, genitourinary, ophthalmic, bone/joint, etc.
- **Temporary growth retardation** occurs in animals, with growth catching up after birth.
 - This phenomenon does not appear to happen in humans. Low birth weight correlates with small adult height and weight.
- Very likely to cause intrauterine or neonatal death.

Fetal Damage: Organ Growth Defects

- The fetus is much less sensitive to radiation compared to the conceptus and embryo. Damage primarily decreases organ size.
 - Doses of **0.1 Gy** and above are required to produce a measurable effect.
- Radiation kills a fraction of cells in the growing fetus, leading to permanent decrease in size.
 - **Permanent growth retardation:** Low birth weight and small adult height/weight.
 - **Mental retardation:** Due to decreased number and migration of neurons and glia.
 - **Microcephaly** (humans): Combination of overall growth retardation and low brain size. May occur even in the absence of mental retardation.
- Radiation effects depend on time of irradiation.
- In **A-bomb survivors** exposed in utero:
 - **0–7 weeks:** Growth retardation and microcephaly, with or without mental retardation.
 - **8–15 weeks:** Severe mental retardation, approx. **30 IQ/Gy**. Severe growth retardation and microcephaly.
 - **16–25 weeks:** Mild-moderate mental retardation, minimal-mild growth retardation.
 - **26+ weeks:** Much less likely to cause severe defects.
 - No excess of organ malformations were observed.

Prenatal Radiation and Carcinogenesis

- Data comes from **obstetric X-rays** in 1950s.
 - Very low dose (**2.0–4.6 mGy**) compared to A-bomb or therapeutic irradiation experience.
 - Majority of radiation exposures occurred in the 3rd trimester of pregnancy. (**26+ week gestational age**).
- Approximately **40 %** increased **relative risk** in childhood cancers with an obstetric X-ray.
- **Absolute risk** estimate (Doll and Wakeford) is **6 %/Gy** for low-dose fetal irradiation, which is only slightly higher than the **ICRP 4 %/Sv** for adults and **5 %/Sv** for the general public.

Therapeutic Radiation in Pregnancy

- Goldstein and Murphy (1929) studied the children of 38 women who were treated with therapeutic radiation (such as for cervical cancer) while pregnant.
 - The fetal doses were poorly defined as they did not have accurate dosimetry in 1929.
 - However, the radiation doses were certainly much higher than the doses from A-bomb or diagnostic X-ray series.
 - Presumably closer to 45 Gy than 1 Gy.
- Multiple malformations were reported including spina bifida, clubfeet, skull defects, hydrocephaly, alopecia, limb defects, and blindness.
- Irradiation prior to **3 weeks** was unlikely to produce malformations, more likely to cause abortion.
- Irradiation between **4 and 11 weeks** gestational age was most likely to produce severe **malformations**.
- Irradiation between **11 and 16 weeks** produced **severe mental retardation** and growth retardation, and mild malformations.
- Irradiation after **16 weeks** produced **mild mental retardation** and growth retardation.
- Irradiation after **30 weeks** produced no gross abnormalities.
- This all matches up quite well with the theoretical and animal models.

Appendix A: Glossary of Terms and Physical Constants

Basic Physics and Radioactive Decay (Chaps. 1, 2, 3, 4 and 5)

°	Degrees
A	Activity (of a nuclide), or Amplitude (of a wave), or Atomic Mass Number (number of nucleons), or Amperes (current) A_0 Initial activity
α (alpha)	Alpha particle, 2 neutrons and 2 protons
β (beta)	Beta particle, an electron or positron β^- Electron β^+ Positron
Bq	Becquerel, one disintegration per second 10^6 = mega- (MBq) 10^9 = giga- (GBq)
c	Speed of light in a vacuum, 3×10^8 m/s
C	Coulombs, or Carbon atom
°C	degrees Celsius
Ci	Curie, 3.7×10^{10} disintegrations per second 10^{-6} = micro- (μ Ci) 10^{-3} = milli- (mCi)
d	distance, or deuteron
D	Dose D_0 Initial dose
Da	Dalton (atomic mass units) $1 \text{ Da} = 931.5 \text{ MeV}/c^2$
e	Electron or positron, also the elementary charge, 1.602×10^{-19} C e^- Electron e^+ Positron
e^x	Natural exponent

E	Energy
	$E = mc^2$ equivalent energy of a mass m
	$E = h\nu$ energy of a photon with wavelength ν
eV	Electron-volt, 1.602×10^{-19} J
	10^3 = kilo- (keV)
	10^6 = mega- (MeV)
	10^9 = giga- (GeV)
f	Roentgens-to-rads conversion factor
γ (gamma)	Gamma ray, a photon
Gy	Gray
	10^{-6} = micro- (μ Gy)
	10^{-3} = milli- (mGy)
	10^{-2} = centi- (cGy) = 1 rad
h	Planck's constant, 6.62×10^{-34} J-s or 4.132×10^{-15} eV-s
H	Hydrogen
	H^+ Proton
$h\nu$ (h-nu)	Photon, or the energy of a photon
hr	hour
IR	Ionizing radiation
J	Joules
$^{\circ}$ K	degrees Kelvin
KERMA, or K	Kinetic energy released in media
LET	Linear energy transfer
λ (lambda, lowercase)	Decay constant
m	Mass, or meters
	10^{-9} = nano- (nm)
	10^{-6} = micro- (μ m)
	10^{-3} = milli- (mm)
	10^{-2} = centi- (cm)
	10^3 = kilo- (km)
mc^2	Energy equivalent of a mass
	Rest mass of electron = 0.511 MeV
	Rest mass of neutron = 939.55; 939.55 MeV
	Rest mass of proton = 938.26 MeV
mgRaEq	Milligrams radium equivalent
min	minutes
μ (mu)	Attenuation coefficient
n	neutron
N	Number of neutrons, or any generic "number"
N_A	Avogadro's Number = 6.022×10^{23}
ν (nu)	Frequency, or Neutrino
p	Momentum, or proton
P	Pressure, or Phosphorous
	Standard Pressure = 101.33 kPa = 1 atm

ϕ (phi)	Fluence
ψ (psi)	Flux (= Energy * Fluence)
Q	Charge
r	Radius
rad	cGy 10^{-3} = milli- (mrad) 10^3 = kilo- (krad)
R	Roentgen, 2.58×10^{-4} C/kg 10^{-3} = milli- (mR)
R, R _{CSDA}	Range, continuous slowing down approximation
RBE	Relative biological effectiveness
ρ (rho)	Mass density
s	Seconds 10^{-9} = nano- (ns) 10^{-6} = micro- (μ s) 10^{-3} = milli- (ms)
Sv	Sievert 10^{-6} = micro- (μ Sv) 10^{-3} = milli- (mSv)
t	Time $t_{1/2}$ Half-life τ (tau) or t_{avg} Mean life
T	Temperature Standard Temperature = 295.15K = 22 °C
v or V	Velocity
V	Volt, or Volume
W	Energy per ion pair (in eV)
X	Exposure
yr	year
Z	Atomic number, number of protons

Dose Specification and Calculation (Chaps. 6, 7, 8, 9, 10 and 11)

A	Activity
BSF	Backscatter factor (a component of TAR)
CT	Computed tomography
d	depth, or distance d_{max} = depth of maximum dose
D	Dose D_{max} = maximum dose \dot{D} Dose rate D_0 Initial dose
f	Roentgens-to-rads conversion factor

F	Mayneord F-factor
$F(r,\theta)$	Anisotropy factor (for brachytherapy line sources)
$g(r)$	Radial dose function (for brachytherapy sources)
$G(r,\theta)$	Geometry factor (for brachytherapy line sources)
Γ (Gamma)	Exposure Rate Constant (for brachytherapy sources)
HDR	High dose rate brachytherapy
HVL	Half-value layer
I	Intensity I_0 = Initial intensity
ISF	Inverse Square Factor = $1/r^2$
K	Calibration Factor (cGy/MU)
KERMA, or K	Kinetic energy released in media
kVp	Kilovolts peak
LDR	Low dose rate brachytherapy
λ (lambda, lowercase)	Decay constant
Λ (lambda, uppercase)	Dose rate constant
mAs	Milliamp-seconds
MDR	Medium dose rate brachytherapy
mgRaEq	Milligrams radium equivalent $1 \text{ mgRaEq} = 8.25 \text{ R/cm}^2/\text{h}$ (exposure rate at 1 cm)
MLC	Multi-leaf collimator
MU	Monitor units
ODI	Optical distance indicator
OF	Obliquity Factor
PDD	Percent depth dose
PDR	Pulse dose rate brachytherapy
RT	Radiotherapy
S_c	Collimator scatter factor
S_K	Air kerma strength
S_p	Phantom scatter factor
SABR	Stereotactic ablative radiotherapy
SAD	Source-axis distance SAD Setup A treatment setup that uses constant SAD
SAR	Scatter-air ratio (a component of phantom scatter and TAR)
SOBP	Spread out Bragg peak
SSD	Source-skin (surface) distance SSD Setup A treatment setup that uses constant SSD
TAR	Tissue-air ratio
TBI	Total body irradiation
TF	Tray factor (for photon dose calculations)
TMR	Tissue-maximum ratio (for photon dose calculations)
TPR	Tissue-phantom ratio (for photon dose calculations)

TV	Treated volume (Volume receiving high dose)
TVL	Tenth-value layer
U	Unit (of air kerma strength)
WF	Wedge factor (for photon dose calculations)
X	Exposure \dot{X} Exposure rate

Radiation Treatment Planning (Chaps. 9 and 12)

AP	Anteroposterior beam
BEV	Beam's eye view
CBCT	Cone beam computed tomography
CT	Computed tomography
CTV	Clinical target volume = GTV + margin for microscopic spread
d	single fraction dose (compared to D as total dose)
D	Total Dose (may include multiple fractions)
DRR	Digitally reconstructed radiograph = 2D image generated from 3D data
DVH	Dose-volume histogram
EBRT	External beam radiotherapy
EPID	Electronic portal imaging device
FoV	Field of view (for CT or MR imaging)
GTV	Gross tumor volume
HU	Hounsfield units
IDL	Isodose line
IM	Internal margin = margin for internal motion and deformation
IMRT	Intensity modulated radiotherapy
ITV	Internal target volume = CTV + IM
IV	Irradiated volume = Volume receiving low dose
mAs	Milliampere-seconds
MC	Monte Carlo (treatment planning algorithm)
MR,	Magnetic resonance, imaging
MRI	
OAR	Organ at risk
ODI	Optical distance indicator
PA	Posteroanterior beam
PACS	Picture Archiving and Communication System
PET	Positron emission tomography
PRV	Planning risk volume = OAR + margin
PTV	Planning target volume = (CTV or ITV) + SM
RT	Radiotherapy
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiotherapy

SM	Setup margin = uncertainty in patient positioning and machine precision
SRS	Stereotactic radiosurgery
TBI	Total body irradiation
TPS	Treatment Planning System
TV	Treated volume = Volume receiving high dose
US	Ultrasound (imaging)
VMAT	Volumetric modulated arc therapy (a subtype of IMRT)

Radiation Protection and Quality Assurance (Chaps. 14, 15, 16, 31 and 32)

α	Scatter fraction (for secondary scatter)
B	Barrier factor
F	Beam area factor (for secondary scatter)
HVL	Half-value layer
MOSFET	Metal oxide semiconductor field effect transistor
OSLD	Optically stimulated luminescent dosimeter
P	Permissible dose
QA	Quality assurance
QAC	Quality assurance committee
QMP	Qualified medical physicist
RSO	Radiation safety officer
T	Occupancy factor
TLD	Thermoluminescent dosimeter
TVL	Tenth-value layer
U	Use factor
W	Workload
W_R	Weighting factor (for different types of radiation)

Molecular Biology (Chaps. 17, 18 and 19, 22, 23 and 24)

46XX	A normal female karyotype with 46 total chromosomes, 44 autosomes and XX sex chromosomes
46XY	A normal male karyotype with 46 total chromosomes, 44 autosomes and XY sex chromosomes
A	Adenine, a purine base in DNA and RNA
BER	Base excision repair, repairs non-bulky base damage
bp or BP	Base pair (DNA)
C	Cytidine, a pyrimidine base in DNA and RNA.

cDNA	Complementary DNA, DNA reverse-transcribed from RNA for analysis.
DNA	Deoxyribonucleic acid
DSB	Double strand break (in DNA)
FISH	Fluorescence in situ hybridization, a technique for visualizing DNA and/or proteins
G	Guanine, a purine base in DNA and RNA.
G_0	Gap phase 0, occurs in non-dividing cells
G_1	Gap phase 1, occurs prior to S phase
G_2	Gap phase 2, occurs after S phase
GF	Growth fraction, the percentage of observed cells that are actively cycling.
GSH	Glutathione, reduced form (an active anti-oxidant)
GSSG	Glutathione, oxidized form (a used anti-oxidant)
HRR	Homologous recombination repair, repairs DSBs
HSP	Heat shock protein
λ (lambda)	Cell distribution correction factor, always between 0.5 and 1
LI	Labeling index, the % of observed cells in S phase
LoH	Loss of heterozygosity, deletion of part of a chromosome.
M	Mitosis phase, nuclear and cell division occurs
MI	Mitotic index, the % of observed cells in M phase
MMR	Mismatch repair, repairs DNA mismatches and cross-links.
MSI	Microsatellite instability
NER	Nucleotide excision repair, repairs bulky base damage
NHEJ	Non-homologous end joining, repairs DSBs
O	Oxygen
-OH	Hydroxyl group, part of a larger molecule
-OOH	Peroxide group, highly reactive and damaging to larger molecules
ϕ (phi)	Cell loss fraction, the percentage of newly produced cells that die or senesce
-P	Phosphate group (PO_4), part of a larger molecule
PI	Propidium iodide, a dye used to stain DNA
RNA	Ribonucleic acid
RTK	Receptor tyrosine kinase
S	Synthesis phase, DNA is replicated
SSB	Single strand break (in DNA)
T	Thymine, a pyrimidine base in DNA
T_C	Total cell cycle time
T_{G1}	G_1 phase time
T_S	S phase time
T_{G2}	G_2 phase time
T_M	M phase time
TK	Tyrosine kinase, may be a receptor or non-receptor
TKI	Tyrosine kinase inhibitor

U	Uracil, a pyrimidine base in RNA
X	X-chromosome
Y	Y-chromosome

Cell Survival Assays and Models (Chaps. 20 and 21)

α (alpha)	The linear component of linear-quadratic cell kill
β (beta)	The quadratic component of linear-quadratic cell kill
γ (gamma)	The slope of the tumor control dose-response curve
BED	Biologically effective dose, or biologically equivalent dose (EQD is preferred for equivalent dose)
CHO	Chinese hamster ovary cell line
d	Dose per fraction
D	Total dose
D_0 (D-zero or D-not)	Additional radiation dose that reduces cell survival to 0.37x its previous value
D_{10} (D-ten)	Additional radiation dose that reduces cell survival to 0.1x its previous value
D_{prolif}	Daily dose required to counteract proliferation
D_q	Quasithreshold dose, the “shoulder width” of a survival curve
DRF	Dose Reduction Factor (of a radioprotector)
EQD	(biologically) Equivalent Dose
ER	Enhancement Ratio (of a radiosensitizer)
$Gy_{3,2}$	Gy of biologically equivalent dose with α/β ratio of 3 Gy and a fraction size of 2 Gy
Gy_2	Gy of biologically effective dose with α/β ratio of 2 Gy
H_2	Thames H-factor for 2 fractions per day
HeLa	Human cell line (Henrietta Lacks)
LQ, or L-Q	Linear quadratic survival model
n, or N	Number of fractions
NSD	Ellis Normalized Standard Dose
NTCP	Normal tissue complication probability
OER	Oxygen Enhancement Ratio
PE	Plating efficiency
PLDR	Potentially lethal damage repair
RBE	Relative biological effectiveness
SF	Surviving fraction
SLDR	Sublethal damage repair
T	Time
	Tk Kickoff time, delay between start of treatment and start of accelerated repopulation
TCD_{50}	Tumor control dose 50, radiation dose causing a 50 % probability of tumor control

TCP	Tumor control probability
TD ₅₀	Tolerance dose 50, radiation dose causing a 50 % probability of toxicity
TD ₅₀	Tumor dilution 50, number of tumor cells required to cause a tumor in 50 % of experimental animals
TR	Therapeutic ratio

Macroscopic Biology (Chaps. 25, 26, 27, 30, 31 and 32)

BID	Twice daily
BNCT	Boron neutron capture therapy
CEM 43°	Cumulative equivalent minutes at 43 °C, a measure of thermal dose
CNS	Central nervous system
CTC-AE	Common Toxicity Criteria for Adverse Events, a toxicity grading schema
DDREF	Dose and dose-rate effectiveness factor
FSU	Functional subunit
GI	Gastrointestinal
HD	Hodgkin disease (lymphoma)
HLA	Human leukocyte antigen (used to match transplant donor and recipient)
HSC	Hematopoietic stem cell(s)
HSCT	Hematopoietic stem cell transplant
LD ₅₀	Lethal dose 50, radiation dose causing a 50 % probability of lethality LD _{50/60} Lethal dose 50 at 60 day follow-up
LENT-	Late Effects of Normal Tissue, Subjective and Objective
SOMA	Management Analytic, a toxicity grading schema
LNT	Linear no-threshold model of carcinogenesis
RBC	Red blood cell(s)
TBI	Total body irradiation
TER	Thermal enhancement ratio
TID	Three times daily
WBC	White blood cell(s)
WF	Weighting factor, equivalent to W _R for radiation protection

List of Biomolecules

AR	Androgen receptor, a nuclear receptor
ATM/ATR	Part of the DSB detection pathway
Bcl-2, Bcl-XL	Pro-survival, anti-apoptosis genes

bFGF	Basic fibroblast growth factor
BRCA1/2	Homologous Recombination Repair genes, implicated in hereditary breast and ovarian cancer
cdk	Cyclin dependent kinase cdk4/6, cdk2, cdk1
cdki	Cyclin dependent kinase inhibitors
Chk1/2	Cell cycle checkpoint molecules, promote cell cycle arrest
Cyclins	Cell cycle regulatory molecules, associated with cdks Cyclin D, E, A, B
Cyt c	Cytochrome c, an energy producing mitochondrial molecule that causes apoptosis if it enters the cytoplasm
E6/E7	Viral genes carried by HPV, they inhibit p53 and cause squamous cell cancers
EBV	Epstein-Barr virus, responsible for infectious mono and nasopharyngeal cancer
EGF	Epidermal growth factor
EGFR family	EGF Receptors, membrane bound receptor tyrosine kinases targeted by multiple drugs EGFR/Her1/ErbB1 EGFR2/Her2/ErbB2 Her3/ErbB3 Her4/ErbB4
ER	Estrogen receptor, a nuclear receptor
HIF1	A hypoxia signaling molecule, includes HIF1 α and HIF1 β
HPV	Human papillomavirus. High risk subtypes are responsible for all cervical cancers and many head and neck cancers
HSP	Heat shock protein
IFN α and other IFNs	Interferons, a family of pro-inflammatory cytokines
IL-1 and other IL-s	Interleukins, a family of pro-inflammatory cytokines
MLH/MSH/PMS family	Mismatch repair genes, defects cause Lynch Syndrome
MRE/rad50/NBS1 (MRN Complex)	Part of the DSB signaling pathway
NFk β	A pro-inflammatory, pro-survival molecule found in hypoxia, angiogenesis and invasion
p15/p16(INK4A)	Cell cycle inhibitors, inhibit Cyclin
p53	A DNA damage response gene, inhibits the cell cycle and encourages apoptosis
PR	Progesterone receptor, a nuclear receptor
RAR/RXR	Retinoid receptors, nuclear receptors
TGF β	Transforming growth factor beta, a pro-inflammatory molecule

TNF α	Tumor necrosis factor alpha, a pro-inflammatory molecule.
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptors, membrane bound receptor tyrosine kinases, targeted by multiple drugs
VHL	The von Hippel Lindau gene, degrades HIF1 α . Defects cause von Hippel Lindau syndrome, multiple tumors including renal cell CA
XP family	Nucleotide excision repair genes, defects cause Xeroderma Pigmentosum

List of Drugs

^{18}FDG	Radiolabeled glucose for PET imaging
^3H -Thymidine	Radiolabeled thymidine for S phase imaging
5-FU	A nucleoside analogue chemotherapy drug
ALA	Aminolevulinic acid, a drug used in photodynamic therapy
Amifostine	A sulfhydryl radioprotector
Anastrozole	An aromatase inhibitor anti-estrogen
BrdU or BUdR	Bromodeoxyuridine, a nucleoside analogue radiosensitizer, also used for S-phase staining
Busulfan	An alkylating chemotherapy drug
Capecitabine	A chemotherapy prodrug that produces 5-FU
Carbogen	A gas mixture of 95% O ₂ and 5% CO ₂ used as oxygen modifying therapy
Cetuximab	An anti-EGFR1 monoclonal antibody
Cisplatin, Carboplatin,	Platinum chemotherapy drugs, cross-links
Oxaliplatin	DNA
Cyclophosphamide (Cytoxin)	A nitrogen mustard chemotherapy drug, alkylating agents
Docetaxel	See paclitaxel
Doxorubicin (Adriamycin),	Anthracycline-class chemotherapy drugs, intercalates in DNA
Daunorubicin, other “rubicins”	An anti-EGFR tyrosine kinase inhibitor
Erlotinib	A nitroimidazole hypoxic radiosensitizer
Etanidazole	A topoisomerase poison chemotherapy drug
Etoposide	A nucleoside analogue chemotherapy drug
Gemcitabine	A LHRH-analogue anti-hormonal therapy
Goserelin	Hyperbaric oxygen, used as oxygen modifying therapy and for wound healing
HBO ₂	Hydroxyurea, a S-phase specific toxin
HU	An alkylating chemotherapy drug
Ifosfamide	

Irinotecan	A topoisomerase poison chemotherapy drug
IUDR	Iododeoxyuridine, a nucleoside analogue radiosensitizer
Leuproreotide	A LHRH-analogue anti-hormonal therapy
Melphalan	An alkylating chemotherapy drug
Methotrexate	An anti-folate chemotherapy drug
Misonidazole	A nitroimidazole hypoxic radiosensitizer
MMC	Mitomycin C, a chemotherapy drug and hypoxic cytotoxin
Nicotinamide	A vasodilator used as oxygen modifying therapy
Nimorazole	A nitroimidazole hypoxic radiosensitizer
Paclitaxel, Docetaxel and other “taxel”s	Taxane-class chemotherapy drugs, microtubule toxins
Pimonidazole	A nitroimidazole hypoxic radiosensitizer
Rituximab	An anti-CD20 monoclonal antibody
Sorafenib, Sunitinib	Multi-specific tyrosine kinase inhibitors
Tamoxifen	A selective estrogen receptor modulator
Temozolomide	An alkylating chemotherapy drug
Tirapazamine	A hypoxic cytotoxin
Trastuzumab	An anti-Her2 (EGFR2) monoclonal antibody
Vincristine, vinblastine and other “vin-”s	Vinca alkaloids, microtubule toxin chemotherapy drugs

Organizations and Standards

AAMD	American Association of Medical Dosimetrists
AAPM	AAPM Task Group Report #000
TG-000	
AAPM	American Association of Physicists in Medicine
ABR	American Board of Radiology
ACR	American College of Radiology
ADCL	Accredited Dosimetry Calibration Laboratory
ASTRO	American Society for Radiation Oncology
BEIR	Biological Effects of Ionizing Radiations (reports)
CERN	European Organization for Nuclear Research (Conseil Européen pour la Recherche Nucléaire)
DICOM	Digital Imaging and Communications in Medicine
DOT	Department of Transportation
FDA	Food and Drug Administration
ICRP	International Commission on Radiation Protection
ICRU	International Commission on Radiation Units
NCCN	National Comprehensive Cancer Network

NCI	National Cancer Institute
NCRP	National Council on Radiation Protection and Measurements
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NRC	Nuclear Regulatory Commission
RTOG	Radiation Therapy and Oncology Group
SI	International System of Units (Système International d'unités)
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation

Appendix B: List of Radionuclides for Radiotherapy and Imaging

Listed in order from heaviest to lightest.

Sealed sources		Origin	Energy	Half-life
²²⁶ Ra	Radium	Uranium decay (²³⁸ U)	0.83 MeV gamma	1,601 years
²²² Rn	Radon	Uranium decay (²²⁶ Ra)	0.83 MeV gamma	2.7 days
¹⁹⁸ Au	Gold	Neutron bombardment	0.411 MeV gamma	2.7 days
¹⁹² Ir	Iridium	Neutron bombardment	0.38 MeV gamma	74 days
¹³⁷ Cs	Cesium	Fission byproduct	0.662 MeV gamma	30 years
¹³¹ Cs	Cesium	Fission byproduct	30 keV Xray	9.7 days
¹²⁵ I	Iodine	Neutron bombardment	28 keV Xray	60 days
¹⁰³ Pd	Palladium	Neutron bombardment	21 keV Xray	17 days
⁶⁰ Co	Cobalt	Neutron bombardment	1.25 MeV gamma	5.26 yrs

Unsealed sources		Origin	Energy	Half-life
²²³ Ra	Radium	Uranium decay (²³⁵ U)	6 MeV alpha	11.4 days
¹⁵³ Sm	Samarium	Neutron bombardment	810 keV beta-	47 hr
¹⁷⁷ Lu	Lutetium	Neutron or proton bombardment	490 keV beta-, 210 keV gamma	6.7 days
¹³¹ I	Iodine	Fission byproduct	606 keV beta-, 364 keV gamma	8 days
⁹⁰ Sr	Strontium	Fission byproduct	546 keV beta-	29 yrs
⁹⁰ Y	Yttrium	Daughter elution (⁹⁰ Sr)	940 keV beta	50 days

(continued)

Unsealed sources	Origin	Energy	Half-life
⁸⁹ Sr	Strontium	Neutron bombardment	583 keV beta–
³² P	Phosphorous	Neutron bombardment	695 keV beta–

Imaging nuclides	Origin	Energy	Half-life
¹²³ I	Iodine	Proton bombardment	159 keV gamma
¹¹¹ In	Indium	Proton bombardment	208 keV gamma
^{99m} Tc	Technetium	Daughter elution (⁹⁹ Mo)	140 keV gamma
⁶⁴ Cu	Copper	Daughter elution (⁶⁴ Zn)	653 keV beta+
¹⁸ F	Fluorine	Proton bombardment	630 keV beta+
¹⁵ O	Oxygen	Proton bombardment	1.73 MeV beta+
¹¹ C	Carbon	Proton bombardment	960 keV beta+
³ H	Tritium	Neutron bombardment	19 keV beta–

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