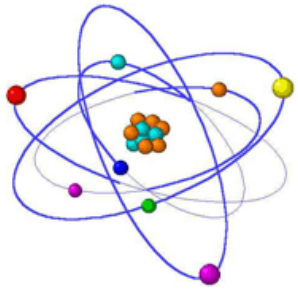
Radioisotope and Radiation Applications (FS2013)



Radiotherapy: Basics and Classical Methods (Week 3b)

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01.10. 2013

Radiotherapy (Basics & Classical Methods): Outline

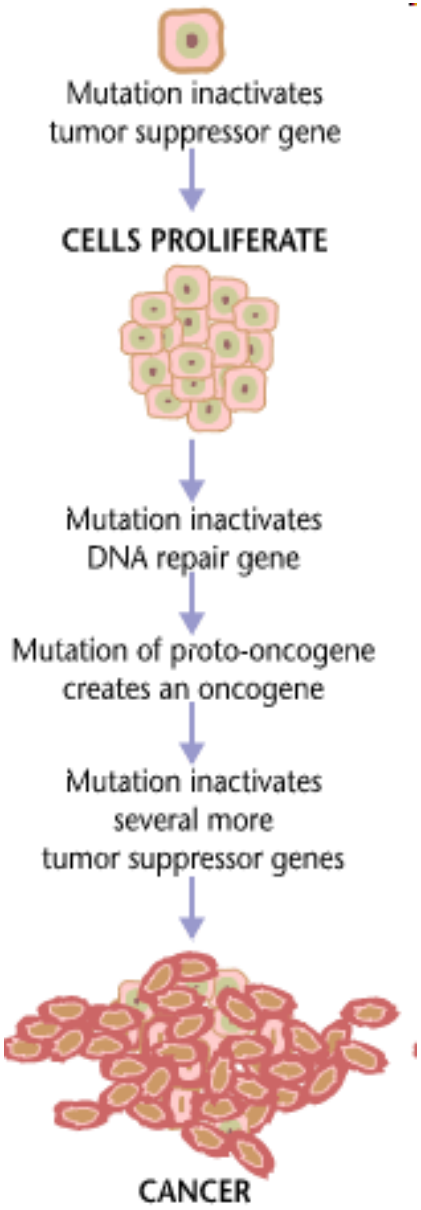
- Therapy and Radiotherapy
- Basics of Carcinogenesis
- Biological Principles
- Radiotherapy: Types and Techniques
- External Beam Radiotherapy
  - Clinical Radiation Generators
  - Photon Beam Therapy
  - Dose Distribution and Scatter Analysis
  - Electron Beam Radiotherapy
- Classical Brachytherapy
- Radioisotope Therapy

Therapy and Radiotherapy

- **Therapy or treatment is the attempted remediation of a health problem, usually following a diagnosis.**
- **Radiation therapy or radiotherapy or radiation oncology is the attempt to remedy a health problem by making use of ionizing radiation.**
- **Usually radiotherapy is applied to fight cancer, because radiation is an efficient cell killer:**
  - It is often used as a primary therapy, but can also be combined with surgery, chemotherapy, hormone therapy or some mixture of the three.
  - The precise treatment intent (curative, adjuvant, neoadjuvant, therapeutic, or palliative) will depend on the tumor type, location, and stage, as well as the general health of the patient.
  - The primary objective of radiotherapy is to cause **reproductive cell death**, not functional cell death!
- **The application of radiotherapy to non-malignant diseases is limited by worries about the risk of radiation induced cancers.**
- **The use of ionizing radiation in diagnosis and medical imaging was discussed in the previous lecture.**

Basics of Carcinogenesis

- Carcinogenesis is the process by which normal cells are transformed into cancer cells.
- In ordinary cell division the **balance between proliferation and apoptosis** is maintained by tightly regulating both processes to ensure the integrity of organs and tissues.
- Carcinogenesis is caused my mutations in the DNA of normal cells that upsets this balance and results in uncontrolled and often rapid proliferation of cells. The mutations can lead to benign tumors that may finally turn into malignant tumors (cancer).
- **Neoplasia** denotes the abnormal proliferation of cells, resulting in a structure known as a **neoplasm**, which usually causes a lump or tumor.



Carcinogenesis: Mechanisms

- **Knudson hypothesis**: cancer is the result of accumulated mutations to a cell's DNA, **5 hits or more** have to occur.
  - Each hit produces a change in the genome which is transmitted to its progeny.
  - There is a lag period between exposure (first hit) and development of clinically apparent cancer. Altered cells show no abnormality during lag period.
  - Empirical evidence: frequency of cancer in industrialized nations seems to increase according to the 6^{th} power of age, which could be explained by assuming that the outbreak of cancer requires the accumulations of 6 consecutive mutations.
- **Mutations to certain types of genes are necessary for carcinogenesis**, i.e., several genes that regulate cell growth must have been damaged:
  - **Activation of proto-oncogenes** which promote cell growth and mitosis.
  - **Deactivation of tumor suppressor genes** that discourage cell growth, or temporarily halt cell division to perform DNA repair.
- Cancer is a genetic disease:
  - Mutation of tumor suppressor genes can be passed not only to the next generation of cells, but also to the offspring and can lead to increased likelihoods for cancers to be inherited.
  - Thus members within families can have increased incidence and decreased latency of multiple tumors.
- Many mutagens are also carcinogens, but some carcinogens are not mutagens. Alcohol, estrogen, e.g., are thought to promote cancers through their stimulating effect on the rate of cell mitosis.
- Many type of cancers originate from viral infections.
- The **cancer stem cell paradigm** proposes that some or all cancers arise from transformation of adult stem cells (=somatic stem cells).
- The process of carcinogenesis is formally a process of Darwinian evolution, known as **somatic or clonal evolution**:
  - Cells in neoplasms compete for resources (e.g., oxygen, glucose, space).
  - A cell that acquires a mutation that increases its fitness will generate more daughter cells than competitor cells.
  - Thus a population of mutant cells (a clone) can expand in the neoplasm.

Characteristics of Cancerous Cells

- Generally cancer cells are undifferentiated and stem cell like, therefore they reproduce rapidly, and:
  - The probability that many cells are in vulnerable cell cycle stages is high.
  - Cancer cells have a diminished ability (less time) to repair sub-lethal damage compared to most healthy differentiated cells.
- The DNA damage is inherited through cell division, accumulating damage to the cancer cells, causing them to die or reproduce more slowly.
- The periphery of a tumor is usually highly oxygenated, inside the tumor the oxygen content is lower.

However: Radiation interacts stochastically, and complete removal may not be possible.

Biological Principles: Cell Response

- Traditional radiation therapy uses mostly low to moderate dose irradiation (no acute radiation syndrome), therefore **most** of the **damage** is done **through the indirect mechanism**:
  - Radical formation with chemical damage to DNA.
  - DNA cell repair mechanisms are important for both healthy tissue and tumor cells.
- Cell damage and repair:
  - Potentially lethal damage (PLD):
    - It can be repaired, if cells are prevented from reproducing, 6 h after irradiation.
    - Significant for X-rays, but not for irradiations with neutrons.
    - Resistant human tumors could have large amounts of PLD repair.
  - Sub-lethal damage (SLD):
    - Increased survival if dose is split into fractions.
    - SLD repair occurs in tumor and normal tissues.
    - SLD repair is significant for X-rays, almost non-existent for neutrons.

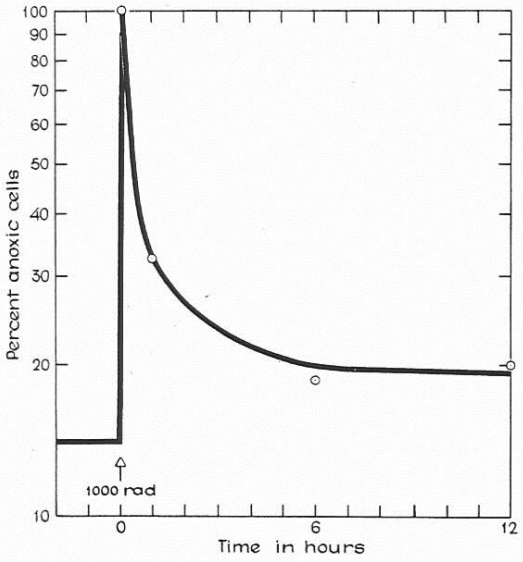
Biological Principles: Radiosensitizers

Radiosensitizers and radioprotectors:

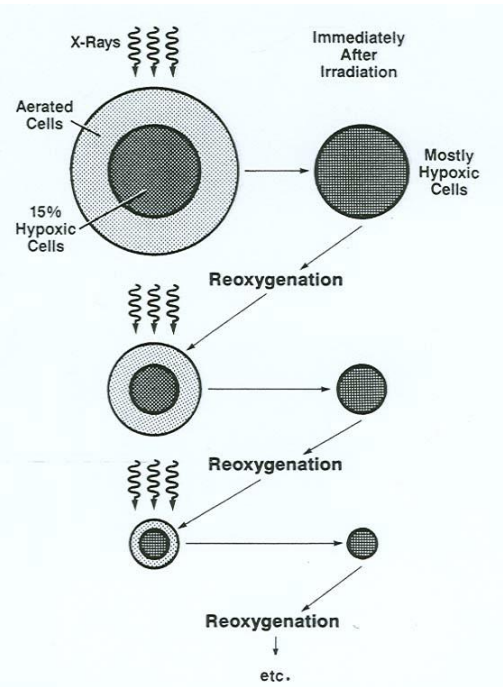
- Radiosensitizers increase radiosensitivity of hypoxic tumor cells:
  - **Reduce local failure of radiotherapy**.
  - Various chemical agents, e.g.: Misodinazole (neurotoxic), pimonidazole, RSU1069.
- Radioprotectors reduce radiosensitivity:
  - **Free-radical scavengers**.
  - Donors of H facilitate chemical repair of DNA
  - Sulfhydril (SH-): cysteine, Phosphorthioate (SPO_3-) WR-638, WR-2721 (amifostine).

Re-oxygenation

- Oxygen is a very powerful radiosensitizer (indirect damage).
- **Hypoxia confers resistance to radiation damage**.
- In humans, it is not proved that tumor reoxygenation takes place, but:
  - Clinical evidence: with 60Gy spread in 30 treatments many tumors are eradicated.
  - Some tumors don't respond to radiotherapy: poor re-oxygenation?



Percentage of hypoxic cells in a transplantable mouse sarcoma as a function of time after a dose of 10 Gy (1,000 rad) of x-rays. Immediately after irradiation, essentially 100% of the viable cells are hypoxic, because such a dose kills a large proportion of the aerated cells. In this tumor the process of reoxygenation is very rapid. By 6 hours, the percentage of hypoxic cells has fallen to a value close to the preirradiation level. (From Kallman RF, Bleehen NM: Post-irradiation cyclic radiosensitivity changes in tumors and normal tissues. In Brown DG, Cragle RG, Noonan JR (eds): Proceedings of the Symposium on Dose Rate in Mammalian Radiobiology, Oak Ridge, TN, 1968, pp 20.1–20.23. CONF-680410. Springfield, VA, 1968, with permission.)

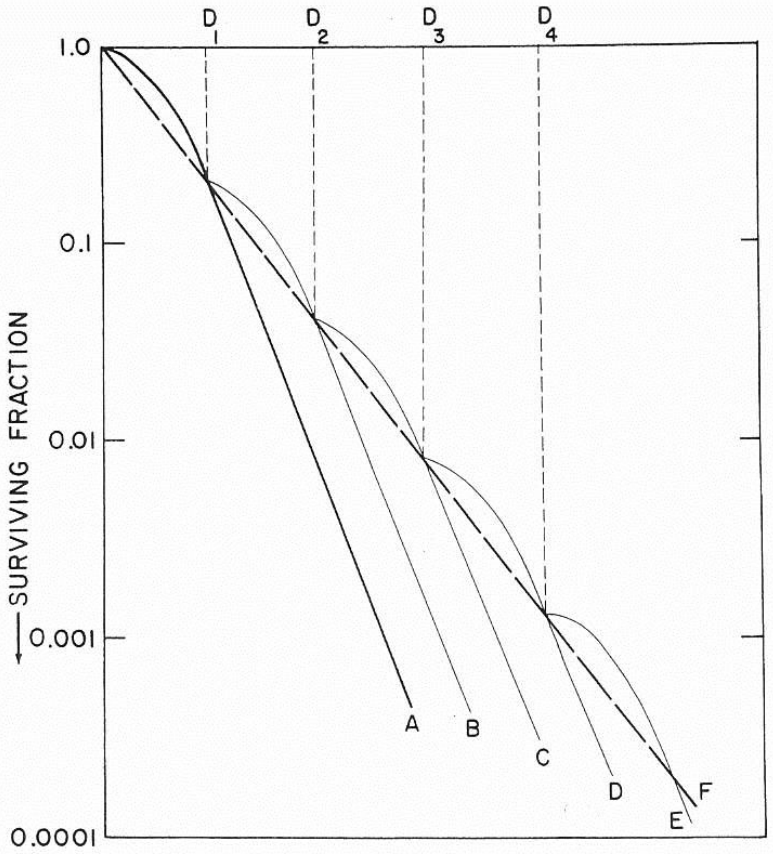


The process of reoxygenation. Tumors contain a mixture of aerated and hypoxic cells. A dose of x-rays kills a greater proportion of aerated than hypoxic cells, because they are more radiosensitive. Immediately after irradiation, most cells in the tumor are hypoxic. But the preirradiation pattern tends to return because of reoxygenation. If the radiation is given in a series of fractions separated in time sufficiently for reoxygenation to occur, the presence of hypoxic cells does not greatly influence the response of the tumor.

Biological Principles: Radiotherapy Strategies

❑ Fractionation:

- The total dose delivered is given in fractions:
  - More effective.
  - Prevent damage to healthy tissue.
- Based on the **4-Rs of radiotherapy**:
  - **R**epair of sub-lethal damage.
  - **R**e-assortment of cells within their cycle into radiosensitive phases.
  - **R**epopulation, counteracted by another dose.
  - **R**e-oxygenation.
- Dividing a dose into **well-timed** fractions:
  - Spares normal tissue because of repair of sub-lethal damage and cellular repopulation.
  - Increases tumor damage because of re-oxygenation and re-assortment.



Idealized fractionation experiment. Curve A is the survival curve for single acute exposures of x-rays. Curve F is obtained if each dose is given as a series of small fractions of size D_1 with an interval between fractions sufficient for repair of sublethal damage to take place. Multiple small fractions approximate to a continuous exposure to a low dose rate. (From Elkind MM, Whitmore GF: Radiobiology of Cultured Mammalian Cells. New York, Gordon and Breach, 1967, with permission.)

Radiation Therapy: Types

- Radiation therapy may be divided into two main types:
  - External beam radiotherapy (or teletherapy) and
  - Internal radiation therapy (brachytherapy, targeted radiotherapy).

- In **external beam radiotherapy** the radiation is delivered from a distant source, from outside the body, and directed at the patient's cancer site.
- **Internal radiotherapy** involves placing radiation sources as close as possible to the tumor site, and one may distinguish:
  - Sealed or closed source therapy: **brachytherapy**, the source is placed to a macroscopic location (as close as possible to the tumor).
  - Unsealed or open source therapy: **radioisotope therapy** (RIT) is a targeted radiotherapy, molecular location (by chemical properties or radiopharmaceuticals).

Radiotherapy: Techniques

- **Classical Techniques (topic of this lecture):**
  - Classical X-Ray Therapy
  - Electron Beam Therapy
  - Classical Brachytherapy
  - Radioisotope Therapy

- **Modern Techniques (topic of next lecture):**
  - 3-D Conformal radiotherapy
  - Intensity Modulated Radiation Therapy
  - Stereotactic Radiosurgery
  - High Dose Rate Brachytherapy
  - Radioimmunotherapy
  - Proton Therapy (heavy particles)

External Beam Therapy (1)

- **External beam radiotherapy (teletherapy):**
  - An external beam of particles (X-rays, γ-rays, charged particles, …) is pointed to a particular part of the body.
  - It is the most frequently used form of radiotherapy.
- Energy of the radiation beam:
  - For X-rays is expressed in kV or MV.
  - For therapeutic electrons and γ-photons it is expressed in terms of MeV.
  - The beam is made up of a spectrum of energies:
    - The **maximum energy** is approximately equal to the beam's maximum **electric potential times the electron charge**.
    - The ***mean* X-ray energy** is only about **1/3 of the maximum energy**. Useful X-rays are produced when electrons are accelerated to a high energy.
- Some examples of X-ray energies used in medicine are:
  - superficial X-rays - 50 to 150 kV
  - orthovoltage X-rays - 150 to 500 kV
  - supervoltage X-rays - 500 to 1000 kV
  - megavoltage X-rays - 1 to 25 MV

External Beam Therapy (2)

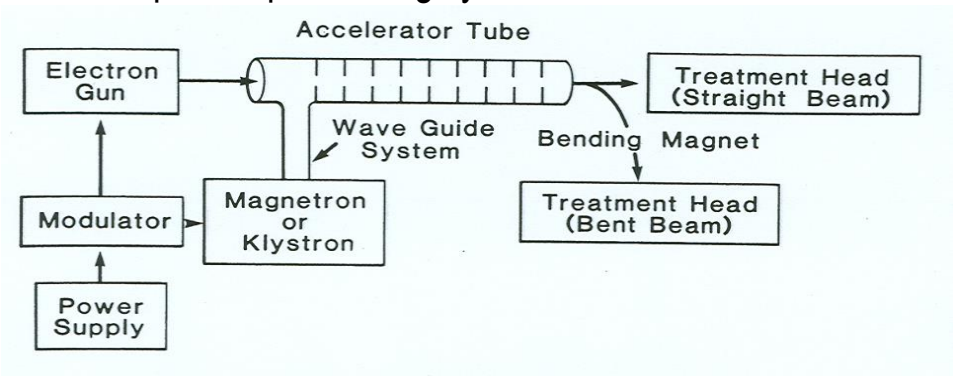
- Medically useful γ-rays can also be derived from a radioactive source.
  - ^{60}Co, ^{192}Ir, ^{137}Cs, or ^{226}Ra (no longer used clinically).
  - Monochromatic beams; usually their energy lies in the range from 300 keV to 1.5 MeV.
- Therapeutic radiation is mainly generated by using the following equipment:
  - **Orthovoltage units**:
    - Applied for "deep" and "supervoltage" therapy depending on their energy range.
    - Have essentially the same design as diagnostic X-ray machines. Limited to voltages less than 600 kV.
  - **Linear accelerators ("LINACs")**:
    - Produce megavoltage X-rays and MeV electron beams.
    - Medical LINACs produce X-rays and electrons with energies in the range from 4 MeV up to around 25 MeV.
  - **Cobalt units**:
    - Produce stable, dichromatic beams of 1.17 and 1.33 MeV (average energy 1.25 MeV).
    - Cobalt units have partly been replaced by linear accelerators, with higher energy radiation.
    - Cobalt treatment is still in widespread use worldwide: machinery relatively reliable and simple to maintain compared to the modern LINAC.

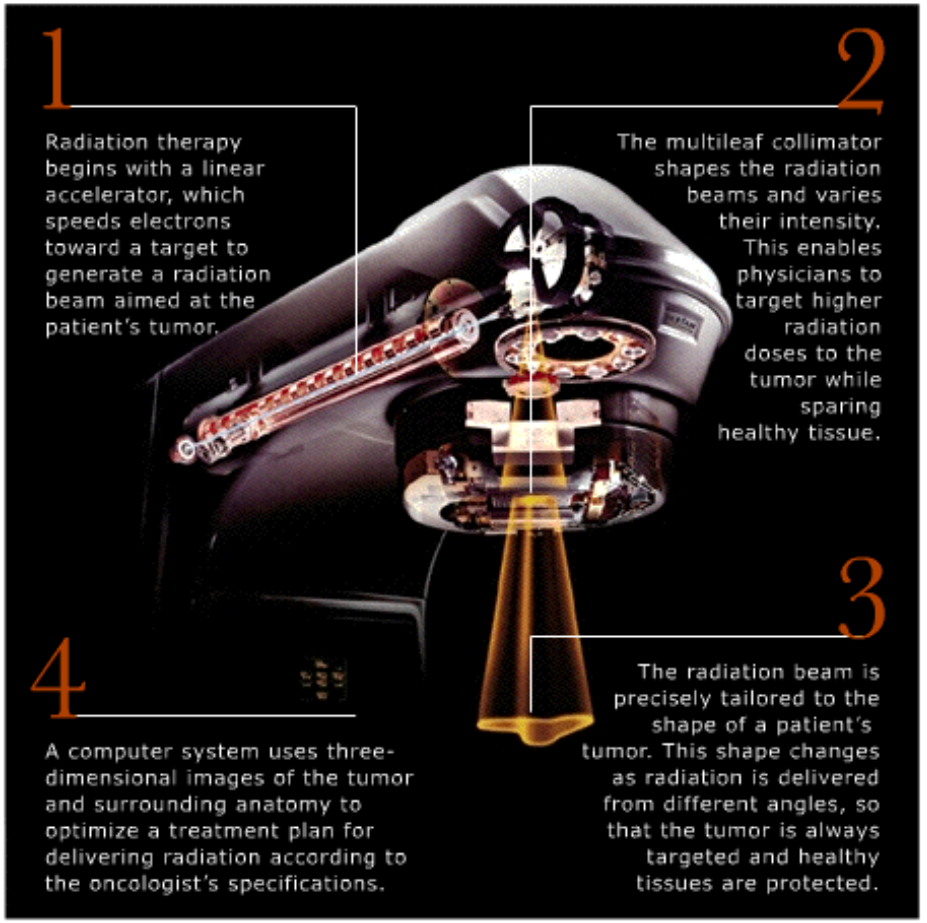
Clinical Radiation Generators: Overview

- Sub-megavoltage therapy:
  - X-ray photons are produced with energies below 1MeV.
    - They have low penetrating power: up to ~2 cm (superficial tumors).
    - High dose to tumor results in high dose to skin.
    - Still used, but replaced by megavoltage therapy.
    - Produced in direct-voltage accelerators.
- Megavoltage therapy:
  - Particles with energies above 1MeV.
  - High penetrating power.
  - Low dose to skin.
  - Produced in:
    - Direct-voltage accelerators: Van De Graff X-ray generators (up to 10MV).
    - Alternate gradient (magnetic-induced) accelerators: Betatron.
    - Synchronous accelerators: electron, proton synchrotron.
    - Resonance (microwave) accelerators: LINACs
    - Radionuclide machines.

LINACs: Resonance (Microwave) Accelerators

- Linear Accelerator (LINAC):
  - Uses high frequency (3 GHz) electromagnetic waves to accelerate charged particles.
  - Electrons can be used as high-energy beam to treat superficial tumors.
  - It can produce high energy X-ray photons to treat deep tumors.
- A medical LINAC consists of:
  - A magnetron to produce microwaves.
  - A klystron to amplify the microwaves.
  - X-ray beams are produced via Bremsstrahlung when the electron beam is dumped on a high-Z target (tungsten).
  - A treatment head to choose between electron beam and X-rays.
  - Beam collimators and monitoring system.
  - A gantry to rotate the radiation source.
  - A patient positioning system.



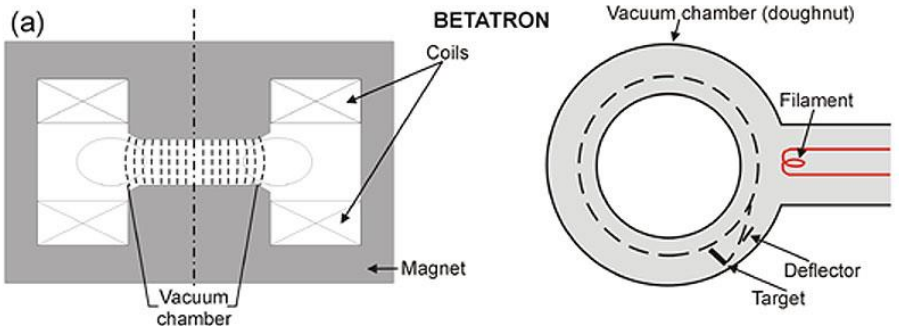


Source: http://www.varian.com

Alternate Gradient Accelerators

Betatron:

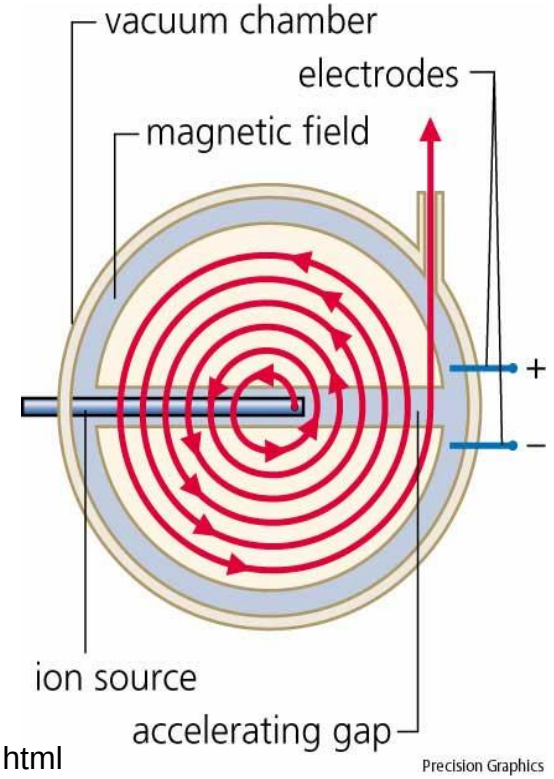
- Acceleration of e^- in a changing magnetic field.
- Can provide X-ray and electron therapy beams from ~6 to 40 MeV, but are inherently low-electron-beam current devices.



http://www.prometheus.uni-tuebingen.de/sec/vl/documents/11/mediabe/

Cyclotron:

- Charged particle accelerator.
- Source of high-energy p+ and n (spallation).
- Acceleration in constant magnetic field with alternating potential.
- Energies as high as 30 MeV.

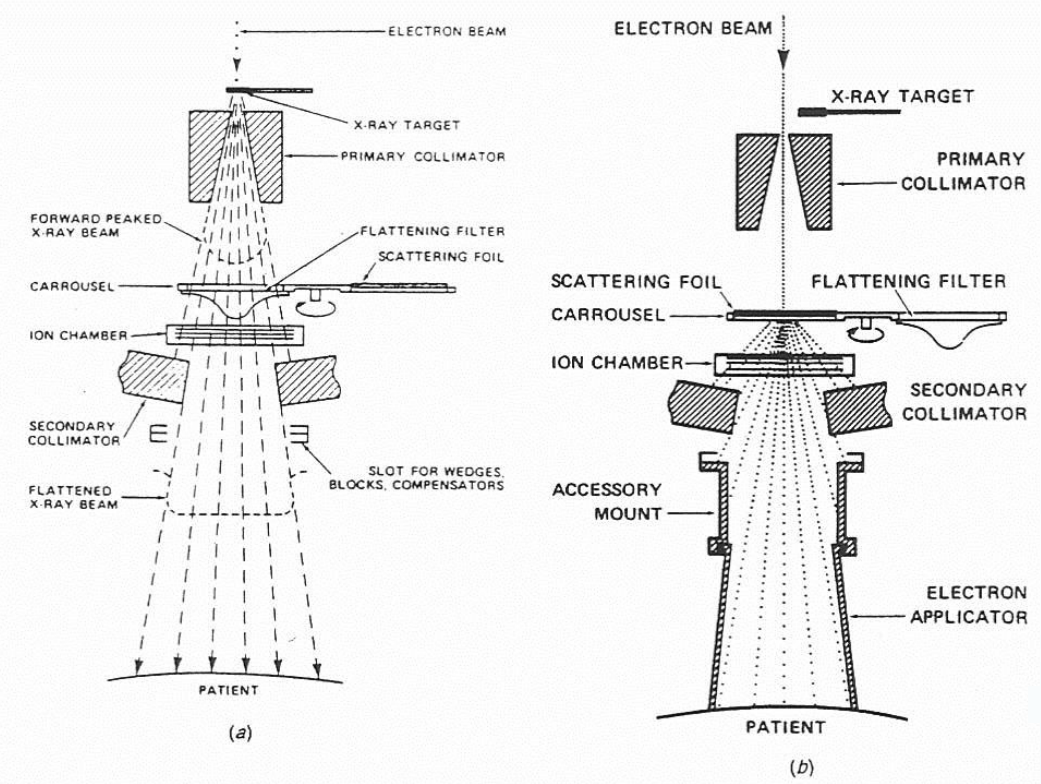


Microtron:

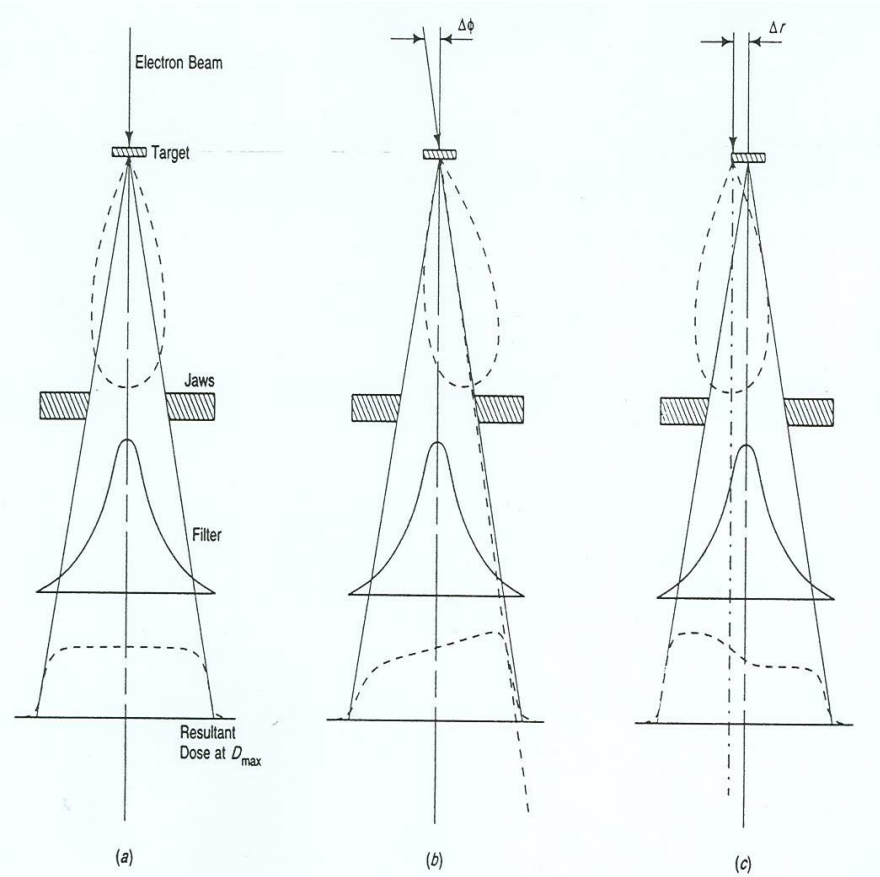
- Combines LINAC and cyclotron.
- More flexible for treatment than LINAC (smaller size, small beam energy spread, easy energy selection, simple beam transport system).

http://www.yourdictionary.com/ahd/c/c0837600.html

Treatment Head and Flattening Filter



(a) Beam subsystem for X-ray beam treatment. (b) Beam subsystem for electron beam therapy. (Courtesy of Ref. 25)



Flattened X-ray field distributions. (a) Symmetrical, electron beam axial at X-ray Target; (b) asymmetrical, electron beam tilted at X-ray target; and (c) asymmetrical, electron beam displaced at X-ray target. (Courtesy of Ref. 6)

Radionuclide Machines

- Of all radionuclides used as γray sources, ^{60}Co has proved to be the most suitable for therapy.
- The ^{60}Co production machine:
  - By irradiation of stable ^{59}Co with neutrons in reactors: $^{59}Co(n,\gamma)^{60}Co$.
  - Source in form of solid cylinders or disks encased in two stainless-steel capsules each sealed by welding.
  - Beta-decay of ^{60}Co gives electron (E_{max}=0.32MeV) and two γ-photons of 1.17 and 1.33 MeV.
  - Beam heterogeneity due to secondary interactions: bremsstrahlung, γ-scattering, e^- production.
  - Typical ^{60}Co sources are cylinders: not-point source creates a "**penumbra**" region.

TELETHERAPY SOURCE CHARACTERISTICS

Radionuclide	Half-Life (yr)	γ-Ray Energy MeV	Γ Value[a] $\left(\frac{Rm^2}{Ci-h}\right)$	Specific Activity Achieved in Practice (Ci/g)
Radium-226 (filtered by 0.5 mm Pt)	1,622	0.83 (avg.)	0.825	~0.98
Cesium-137	30.0	0.66	0.326	~50
Cobalt-60	5.26	1.17, 1.33	1.30	~200

[a]Exposure rate constant (Γ) is discussed in Chapter 8. The higher the Γ value, the greater will be the exposure rate or output per curie of the teletherapy source.

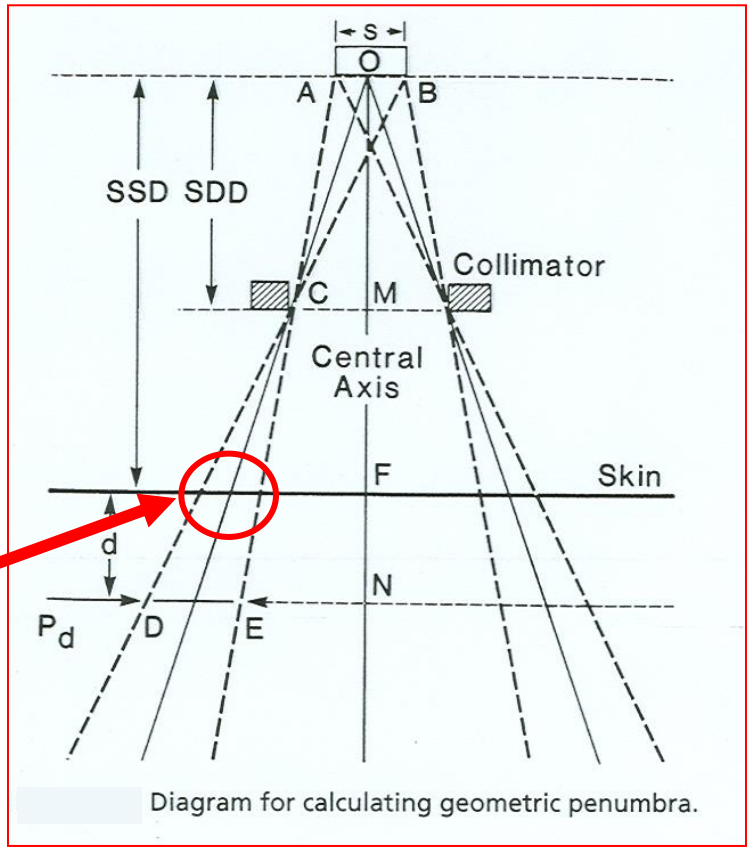
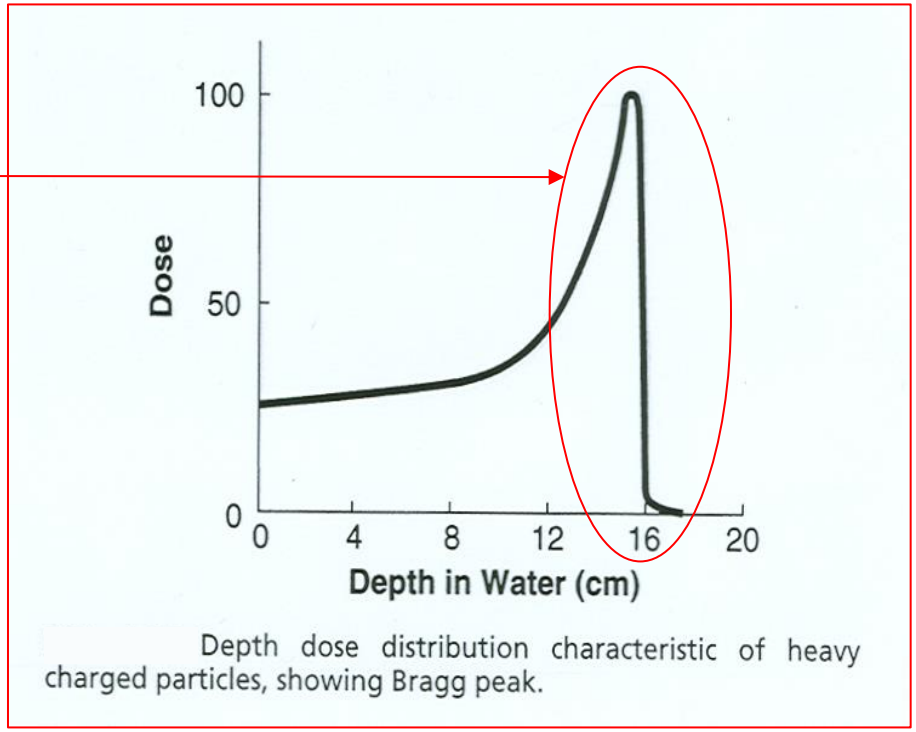


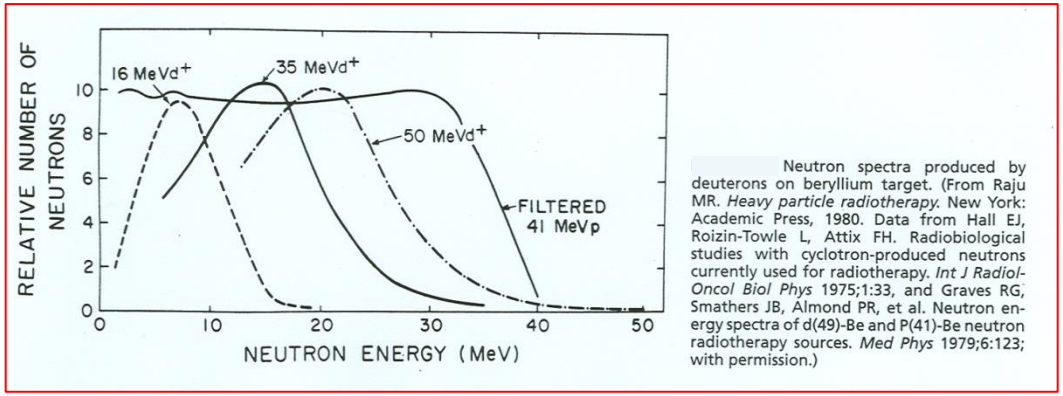
Diagram for calculating geometric penumbra.

Light and Heavy Particle Machines

- Heavy particle beams:
  - Good dose localization.
  - Better therapeutic gain (**Bragg Peak**).
- Particles used:
  - n, p^+, $^2H^+$, $^4He^{2+}$, π^-, high-E heavy ions.
  - Still experimental. Role not yet established.
  - Very costly.
- Generators:
  - neutrons:
    - D-T fusion generator (14MeV),
    - Cyclotron with D-Be reaction (~25 MeV)
  - p^+ and heavy ions:
    - Cyclotron or LINAC (150-600 MeV)
  - **pions π^-**:
    - p^+ cyclotron with Be target (100MeV).
    - Larger Bragg peak from nuclear disintegration.



Depth dose distribution characteristic of heavy charged particles, showing Bragg peak.



Neutron spectra produced by deuterons on beryllium target. (From Raju MR. *Heavy particle radiotherapy.* New York: Academic Press, 1980. Data from Hall EJ, Roizin-Towle L, Attix FH. Radiobiological studies with cyclotron-produced neutrons currently used for radiotherapy. *Int J Radiol-Oncol Biol Phys* 1975;1:33, and Graves RG, Smathers JB, Almond PR, et al. Neutron energy spectra of d(49)-Be and P(41)-Be neutron radiotherapy sources. *Med Phys* 1979;6:123; with permission.)

Photon Beam Radiotherapy

- Principal means of external beam radiotherapy in most of the world.
- It requires the following main steps after diagnosis:
  - Accurate localization of the tumor and its volume.
  - Determination of the most appropriate beam characteristics.
  - Simulation of the treatment on a specially calibrated conventional diagnostic X-ray machine, and portal imaging.
  - Development of a treatment plan based on dosimetric measurements and calculations.
  - Carry-out the actual irradiation according to the plan.
  - Follow-up with medical tests and other therapeutic measures.

Dose Distribution and Scatter Analysis (1)

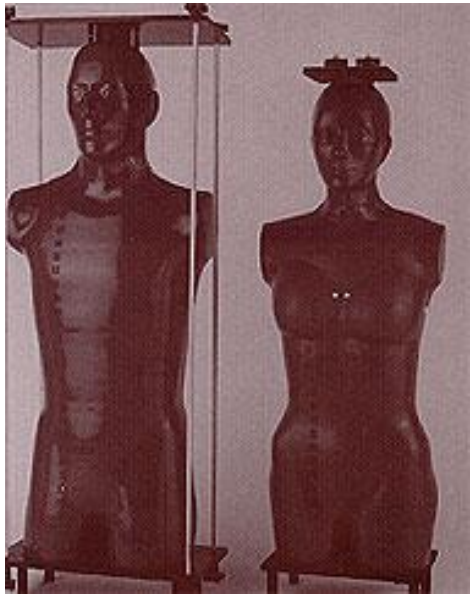
- Measuring **dose distribution** in patients is difficult.
- They are **obtained from measurements in phantoms**.
- The data are used by dose calculation systems to predict the dose in actual patients.
- Phantoms are usually made of water:
  - Absorption and scattering properties of water are similar to those in muscle and soft tissue.
  - Other materials in phantoms should be tissue equivalent: same effective atomic number, electron density (Compton interaction), and mass density.

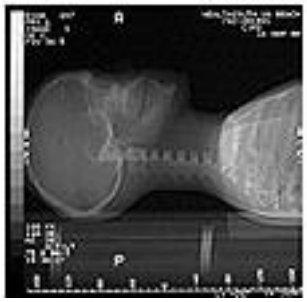
Electronic density:

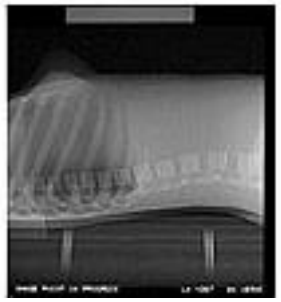
$$\rho_e = \rho_m N_A \left(\frac{Z}{A}\right) \quad \text{with} \quad \frac{Z}{A} = \sum_i a_i \left(\frac{Z_i}{A_i}\right)$$

a_i is the weight fraction of the i[th] element of atomic number Z_i and atomic weight A_i.

Phantoms







PHYSICAL PROPERTIES OF VARIOUS PHANTOM MATERIALS

Material	Chemical Composition	Mass Density (g/cm^3)	Number of Electrons/g ($\times 10^{23}$)	Z_{eff}[a] (Photoelectric)
Water	H_2O	1	3.34	7.42
Polystyrene	$(C_8H_8)_n$	103–1.05	3.24	5.69
Plexiglas (Perspex, Lucite)	$(C_5O_2H_8)_n$	1.16–1.20	3.24	6.48
Polyethylene	$(CH_2)_n$	0.92	3.44	6.16
Paraffin	C_nH_{2n+2}	0.87–0.91	3.44	5.42
Mix D	Paraffin: 60.8 Polyethylene: 30.4 MgO: 6.4 TiO_2: 2.4	0.99	3.41	7.05
M 3	Paraffin: 100 MgO: 29.06 $CaCO_3$: 0.94	1.06	3.34	7.35
Solid water[b]	Expoxy resin-based mixture	1.00	3.34	

[a] Z_{eff} for photoelectric effect is given by Eq. 6.4.
[b] Available from Radiation Measurements, Inc. (Middleton, Wisconsin).
Data are from Tubiana M, Dutreix J, Duterix A, Jocky P. Bases physiques de la radiotherapie et de la radiobiologie. Paris: Masson ET Cie, Éditeurs, 1963:458; and Schulz RJ, Nath R. On the constancy in composition in polystyrene and polymethylmethacrylate plastics. Med Phys 1979;6:153.

There exist recipes for tissue substitutes based on epoxi resins with particulate fillers.
The compositions are adjusted to achieve the following properties:

- Mass attenuation coefficient.
- Mass energy absorption coefficient.
- Electron mass stopping power.
- Angular scattering power ration.

Tabulation available in an ICRUM Report.

Dose Distribution and Scatter Analysis (2)

Depth Dose Distribution:

- The absorbed dose in the patient varies with depth. Variation depends on:
  - Beam energy (or beam quality).
  - Depth.
  - Field size.
  - **Distance from source (source to skin surface distance SSD).**
  - Beam collimation system.
- An essential step in dose calculations is to establish dose depth variation along the central axis of the beam.
- The following quantities have been defined for this purpose:
  - Percentage depth dose.
  - Tissue-air ratios.
  - Tissue-phantom ratios.
  - Tissue-maximum ratios.

Dose Distribution and Scatter Analysis (3)

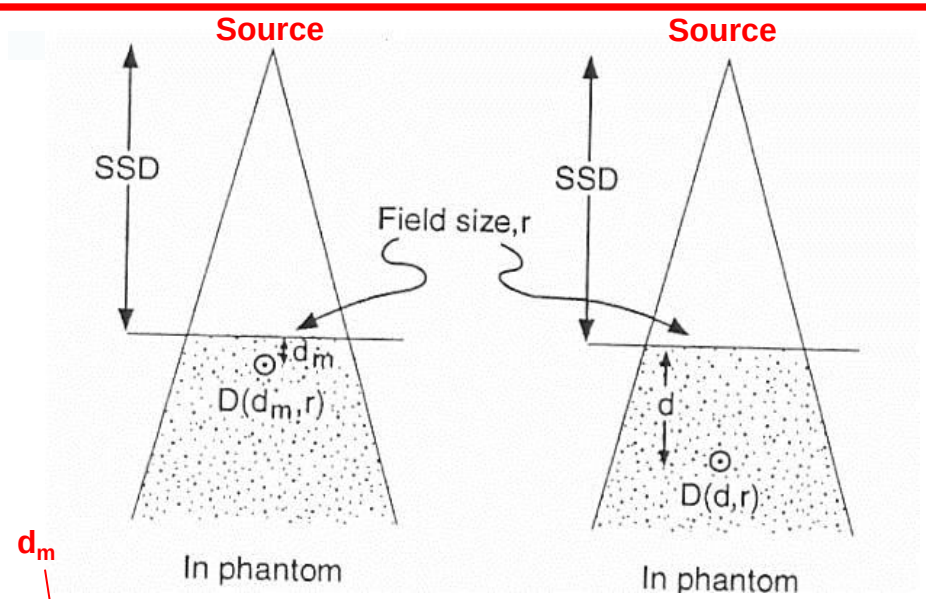
Percentage Depth Dose (P,%DD)

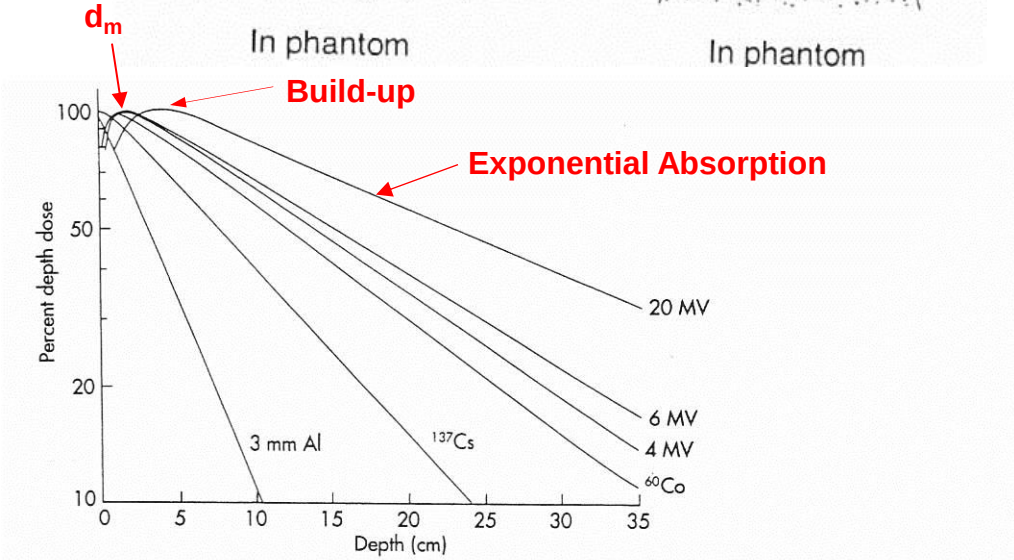
- Dose at depth normalized to dose at reference depth, percent depth dose P:

$$P = \frac{D_d}{D_{d_0}} 100$$

  - Low-E X-rays: ref. depth @surface $d_0=0$
  - High-E photons: ref. depth @position of peak absorbed dose $d_0 = d_{max} = d_m$

- High-E beams have higher penetrating power: exponential absorption.
- For high-E beams there is a dose build-up region between the surface and d_m.
- *P* increases with increasing field size (scattering).
- *P* increases with SSD (inverse square fall-off).





Percent depth dose for 100 cm^2 area X-ray and gamma-ray beams of different energies as a function of depth in water. The *SSD* is 100 cm for all beams except the 3.0 mm Al (*SSD* = 15 cm) X-ray beam and the 137 Cs beam (*SSD* = 35 cm). (From: Hendee WR, Medical Radiation Physics, ed 1, Chicago, 1970, Mosby-Year Book, used with permission.)

Percentage Depth Dose

The percentage depth doses are measured and tabulated for square fields.

Percent Depth Doses for 6 MV X Rays (Varian 6-100, 100 cm SSD)

Depth (cm)	Field Size (cm × cm)												
	4 × 4	6 × 6	8 × 8	10 × 10	12 × 12	14 × 14	16 × 16	18 × 18	20 × 20	25 × 25	30 × 30	35 × 35	40 × 40
1.0	97.8	98.0	98.1	98.2	98.3	98.4	98.5	98.6	98.7	99.0	99.2	99.5	99.8
d_{max}	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
2.0	98.1	98.5	98.5	98.5	98.5	98.5	98.5	98.5	98.5	98.5	98.5	98.5	98.5
3.0	93.5	94.0	94.4	94.7	94.8	94.9	94.9	94.9	95.0	95.0	95.0	95.1	95.2
4.0	88.5	89.4	90.0	90.4	90.8	91.0	91.3	91.4	91.5	91.6	91.6	91.7	91.8
5.0	83.5	85.0	86.1	86.8	87.2	87.4	87.5	87.6	87.7	87.9	88.2	88.4	88.7
6.0	79.3	80.8	81.9	82.6	83.2	83.5	83.7	83.8	84.0	84.2	84.6	84.8	85.2
7.0	74.4	76.4	77.8	78.6	79.2	79.6	79.8	80.1	80.2	80.6	81.1	81.5	82.0
8.0	70.1	72.0	73.6	74.6	75.4	75.8	76.2	76.5	76.8	77.3	77.7	78.0	78.5
9.0	65.3	67.6	69.4	70.6	71.4	72.0	72.6	73.0	73.3	73.8	74.3	74.7	75.2
10.0	61.9	64.1	65.6	66.8	67.8	68.5	69.0	69.6	70.0	70.6	71.0	71.6	72.0
11.0	57.6	60.2	62.0	63.4	64.4	65.2	65.8	66.2	66.7	67.2	67.7	68.2	68.8
12.0	53.9	56.2	58.2	59.6	60.6	61.4	62.0	62.6	63.0	64.0	64.5	65.1	65.6
13.0	50.6	52.8	55.0	56.6	57.8	58.6	59.2	59.7	60.1	60.9	61.6	62.3	63.0
14.0	47.5	49,.8	51.8	53.4	54.6	55.5	56.2	56.8	57.2	58.0	58.8	59.4	60.1
15.0	44.7	46.7	48.6	50.2	51.6	52.6	53.4	54.0	54.4	55.4	56.1	56.7	57.3
16.0	41.7	43.7	45.6	47.4	48.8	49.8	50.6	51.4	51.9	53.1	53.8	54.2	54.5
17.0	39.2	41.2	43.0	44.5	45.8	47.0	47.8	48.6	49.2	50.4	51.2	51.8	52.2
18.0	36.8	38.6	40.4	41.9	43.2	44.4	45.3	46.0	46.8	48.0	49.0	49.5	50.0
19.0	34.6	36.4	38.4	39.9	41.2	42.2	43.1	43.8	44.4	45.6	46.5	47.1	47.6
20.0	32.6	34.5	36.2	37.7	38.9	39.8	40.7	41,4	42,9	43.3	44.1	44.8	45.4
22.0	28.8	30.6	32.2	33.7	35.0	36.0	36.8	37.6	38.1	39.2	40.1	40.8	41.6
24.0	25.3	27.0	28.6	30.0	31.2	32.2	33.0	33.6	34.2	35.5	36.4	37.0	37.7
26.0	22.4	23.9	25.2	26.4	27.6	28.6	29.4	30.2	30.8	32.1	33.0	33.5	34.1
28.0	19.9	21.3	22.6	23.7	24.8	25.6	26.5	27.2	27.9	29.1	29.8	30.4	31.0
30.0	17.5	18.8	20.0	21.1	22.2	23.0	23.8	24.4	25.0	26.2	27.0	27.6	28.2

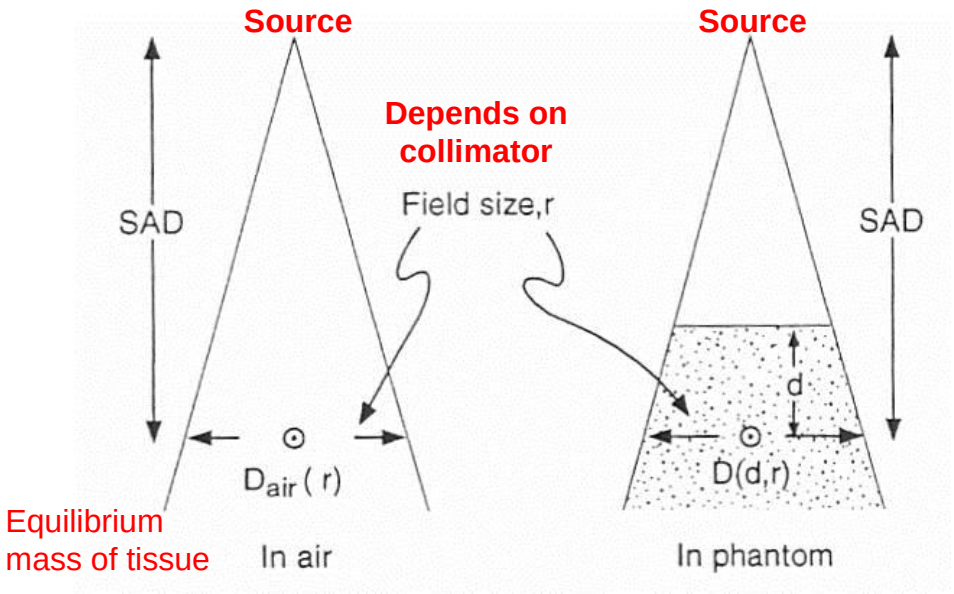
Used with permission from Coffey II CW, et al: X-ray beam characteristics of the Varian Clinac 6-100 linear accelerator, Med. Phys. 7:716, 1980.

Dose Distribution and Scatter Analysis (4)

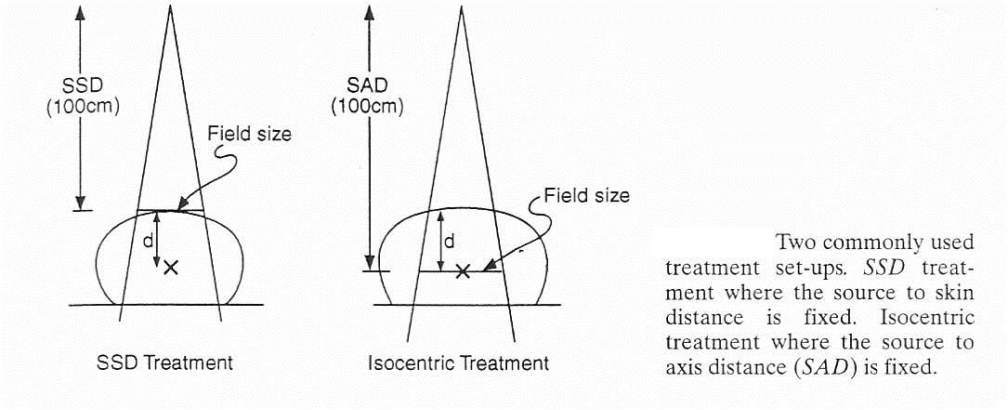
- Tissue-Air Ratio (TAR):
  - Tries to remove the SSD dependence of the percent depth dose.
  - Ratio of the dose at a given point in the phantom (D_d) to the dose in free air (D_{air}) at the same point:

$$TAR(d,r) = \frac{D(d,r)}{D_{air}(r)}$$

  - TAR is nearly independent of the distance from the source (better than 2%).
  - Similar variation as percent depth dose with energy, depth, and field size.
  - *TAR* is used for:
    - Isocentric treatment planning.
    - Irregular fields (i.e., not rectangular, square or circular).
  - *TAR(d,0)* is related to primary dose at *d*.



Standard SSD = 100 cm



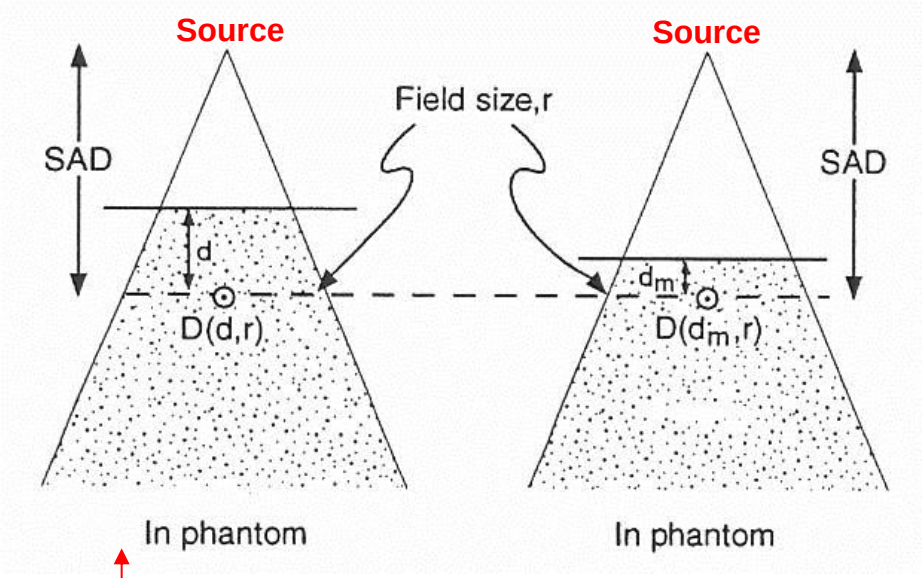
Dose Distribution and Scatter Analysis (5)

Backscatter Factor (BSF):

- Ratio of dose in phantom at depth of maximum dose to the dose in air at the same location.

$$BSF(r) = \frac{D(d_m, r)}{D_{air}(r)}$$

- BSF is large for low-E, and much smaller for MV photon beams.



Scatter-Air Ratio (SAR):

$$SAR(d,r) = TAR(d,r) - TAR(d,0)$$

- Useful to calculate the scattered dose and for irregular fields.

Tissue-Maximum Ratio (TMR):

$$TMR(d,r) = \frac{D(d,r)}{D(d_m,r)}$$

$$TMR(d,r) = \frac{TAR(d,r)}{BSF(r)}$$

Electron Beam Therapy (EBT) (1)

- Electrons are produced in LINACs.
- Advantage with respect to photons: sharp drop-off in dose beyond the tumor.
- Suitable for treating superficial lesions (less than 5 cm deep).
- The clinically useful energy range for electrons is 6 to 20 MeV.
- **Physics**: e^- interact with matter via Coulomb interactions.
  - They continuously lose energy via:
    - Inelastic collisions with atomic electrons (**ionization and excitation**).
    - Bremsstrahlung.
    - Elastic scattering with atomic electrons.
    - Elastic collisions with nuclei.
  - With decreasing energy the probability of large angle scattering increases.
  - The effects of tissue heterogeneities are very important:
    - Scattering and dose distribution are very sensitive to Z and electronic density.

Electron Beam Therapy (EBT) (2)

- Is the most important parameter in EBT treatment planning:

$$\bar{E}_o = (2.33\,\text{MeV/cm})\ R_{50}$$

  - R_{50} is the depth at which the dose is 50% of the maximum dose.

- The mean energy at depth z is:

$$\bar{E}_Z = \bar{E}_0 \left(1 - \frac{z}{R_p}\right)$$

  - R_p is the practical range of electrons.
  - As a rule of thumb: the energy loss in water for electrons is about **2 MeV/cm**.

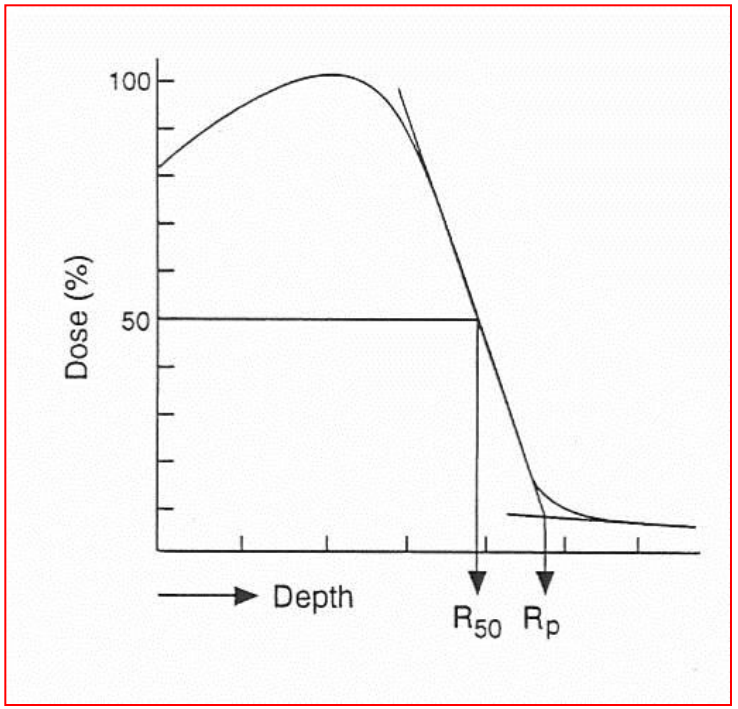
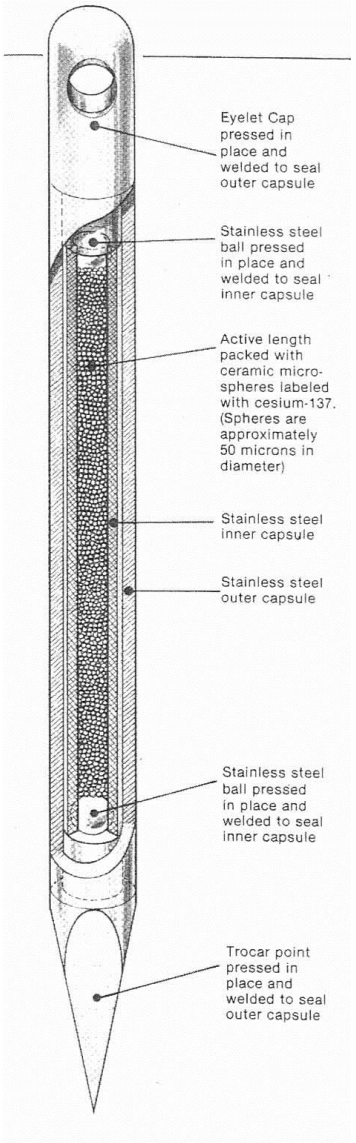


Diagram showing the depth of 50% dose, R_{50}. Also depicted is the depth of practical range, R_p.

Classical Brachytherapy (1)

- Brachytherapy, also known as sealed source radiotherapy, is a form of radiotherapy where a radioactive source is placed inside or next to the area requiring treatment.
- Brachytherapy is commonly used to treat localized prostate, cervical cancer and cancers of the head and the neck.
- Brachytherapy can be split into four main types:
  - **Mold brachytherapy:**
    - Treatment of superficial tumors using sealed sources placed close to the skin.
    - Dosimetry is often performed with reference to the Manchester system: a rule based approach to ensure that the dose to all parts of the target volume is within 10% of the prescription dose.

Radioactive Seeds for Prostate Cancer



^{137}Cs Radioactive Seed

Classical Brachytherapy (2)

Interstitial brachytherapy:

- Sources are inserted into tissue according to the Manchester or Paris systems.
- Modern methods tend to use ^{192}Ir wire (60Gy).
- Temporary or permanent (short half-lives).
- ^{125}I or ^{103}Pa used for prostate.

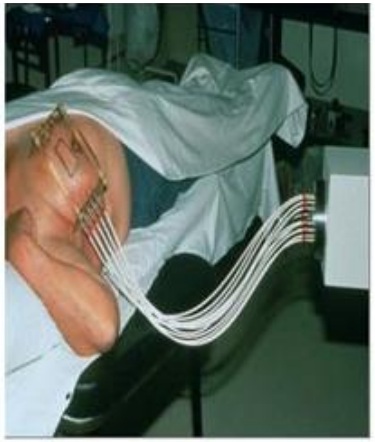
Intracavitary brachytherapy:

- It places the sources inside a pre-existing body cavity.
- Low dose rate (50cGy/h).^{137}Cs and ^{192}Ir
- Temporary.
- Gynaecological, nasopharynx applications.

Intravascular brachytherapy:

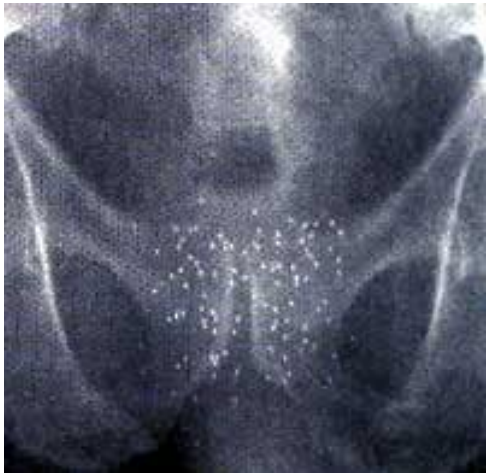
- It places a catheter with the sources inside the vasculature.
- The most common application of this method uses the beta-emitter ^{90}Sr for the treatment of coronary in-stent restenosis.

Interstitial for breast tumor ^{192}Ir



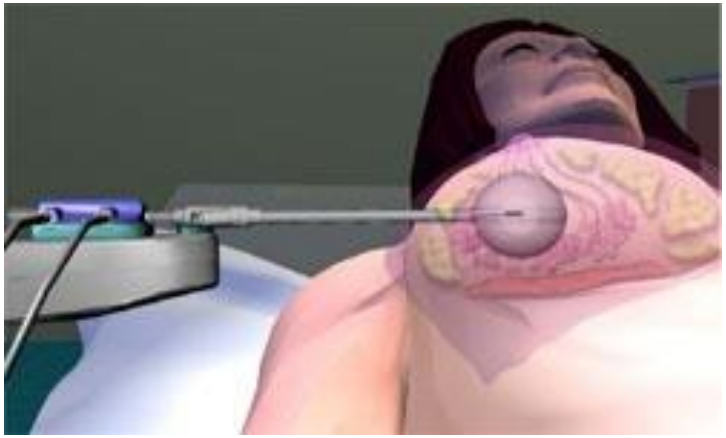
www.xoftmicrotube.com

Interstitial for prostate cancer ^{192}Ir



http://www.winterhavenhospital.org/fac/oncology/prostate.html

Intracavity for breast tumor ^{192}Ir



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Radioisotopes used in Brachytherapy

- Ideal Source Characteristics:
  - **Dose distribution around the source**
    - Photon emitters carry dose to a distance: large tumors.
    - β-emitters: small, benign tumors.
    - ^{252}Cf: γ- and n- fluxes, eliminates OER in normal tissue (damage), (OER: Oxygen Enhancement Ratio): very high LET (neutrons), good for resistant tumors.
  - **Source Construction**
    - Production of clean particle beams.
    - Encapsulation minimizes dose distribution (undesirable X-rays).
  - **Source Production**
    - High specific activity (small sources).
    - Large half-lives and production cross-section.
    - Good chemical properties for separation of radioisotopes.
    - Purity is important.

Current brachytherapy radionuclides.

Brachytherapy Source Materials						
Isotope	Max Beta Energy [MeV]	Effective or Dominant Photon Energy [MeV]	Half Life	Specific Exposure-Rate Constant [R cm²/mCi hr]	Half Value Layer [mmPb]	Theoretic Max Specific Activity [Ci/g]
Ra-226	3.17/1.17	0.83 eff (0.5 mm Pt) 1.2 eff (1.0 mm Pt)	1622 yr	8.25 [R cm²/mg hr] 7.71 [R cm²/mg hr]	12	1 (Definition)
Co-60	0.31 (99%) 1.5 (0.1%)	1.33 & 1.17	5.26 yr	13	12	1,100
Cs-137	0.51 (93%) 1.18 (7%)	0.662 (85%)	30 yr	3.26	6	100
Ir-192	0.67(46%) 0.24(8%) 0.54(41%) 0.39	0.38 eff dep. on jacket	73.8 d	4.66 or 4.60 dep. on jacket c. 4.8 naked	3	9 000
Am-241	0.054/0.022	0.06	432 yr	0.12	0.13	3
Rn-222	0.97	0.83 eff	3.83 d	8.35	12	150 000
Au-198	0.97	0.412	2.70 d	2.32	3	250 000
I-125	0.03(90%)	0.035(7%) 0.027 eff	60 d	1.45 normal 1.32 compen.	0.025	17 000
Pd-103	0.017/0.037	0.021 eff	17 d	1.48	0.008	75 000
Yb-169	0.298	0.093 eff	32 d	1.8	0.2	24 000
Ru-106	0.039/3.5	*	368 d	*		3,400
Re-186	1.07	0.137 (9%)	3.8 d	*		180 000
Sr-90,Y-90	0.6, 2.27	*	28 yr	*		140
Y-90	2.27	*	64.2 hr	*		540 000
I-131	0.61 (8%)	0.364	8 d	2.23	3	120 000
P-32	1.71	*	14.3 d	*		300 000
Sr-89	1.46	*	52.7	*		28 000
Cf-252	*	2(capture)	3.65 y			390

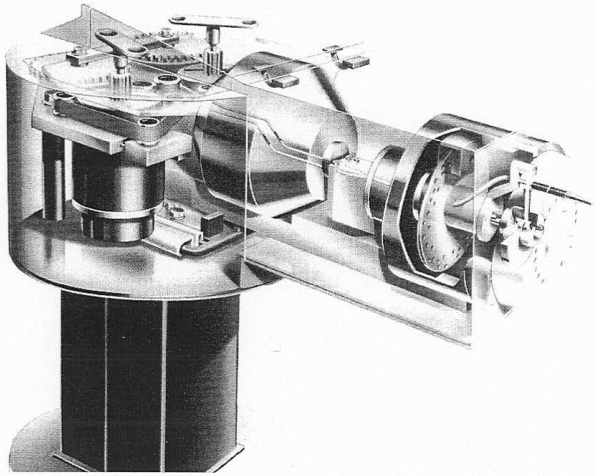
Characteristics of Brachytherapy Sources

General characteristics of brachytherapy sources.

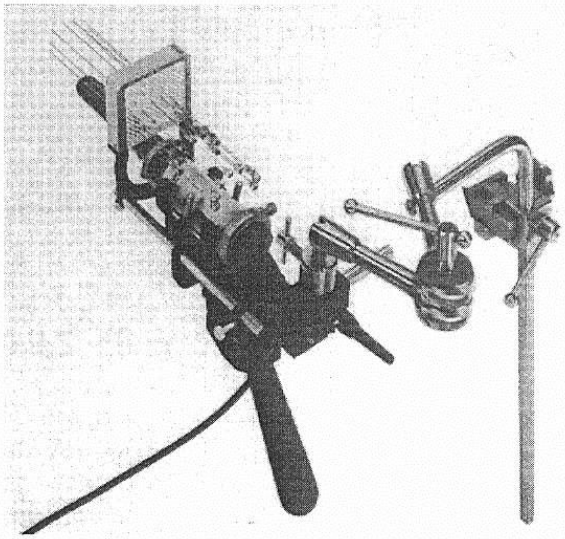
Procedure	Nature	Characteristics of Radionuclides
Interstitial implants	Permanent	Photon emitter, minimal electron contamination; low photon energy and/or short half life; small size (high specific activity); biologically inert jacket.
	Temporary low dose rate	Photon emitter, minimal electron contamination; small size (high specific activity).
	Temporary high dose rate	Photon emitter, minimal electron contamination; very high specific activity (small size); relatively long half life.
Intracavitary insertions	Temporary low dose rate	Photon emitter, minimal electron contamination; relatively high photon energy.
	Temporary high dose rate	Photon emitter, minimal electron contamination; very high specific activity (small size); relatively high photon energy; relatively long half life.
Intravascular treatments	Stents	Beta emitter, possibly with some photon component; Medium half life; able to be incorporated permanently on or in a stent; biologically inert.
	Intracatheter high dose rate	Beta emitter, probably with some photon component; very high specific activity (small size); very flexible; relatively long half life.
Surface applicators	Skin	Photon emitter.
	Eye neoplasm	Photon emitter; low photon energy; small size (high specific activity).
	Eye corneal vasculature	Beta emitter, little photon contamination; high beta energy; high activity.

Afterloading Techniques

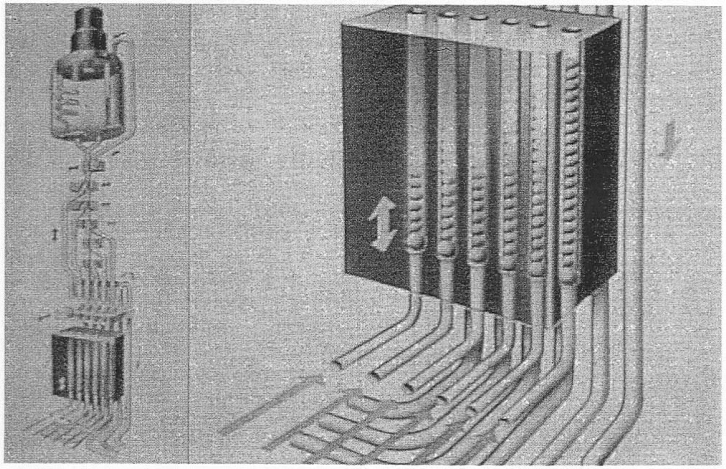
- The objective is to minimize dose to medical personnel.



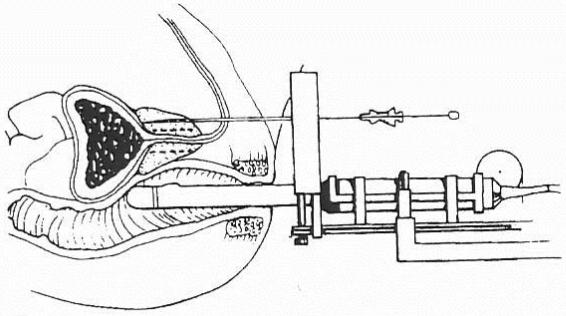
A cutaway view of a remote afterloader unit (courtesy of Nucletron Corporation).



A system for afterloading interstitial implants (courtesy of Mick Radio-Nuclear Instruments, Inc.)



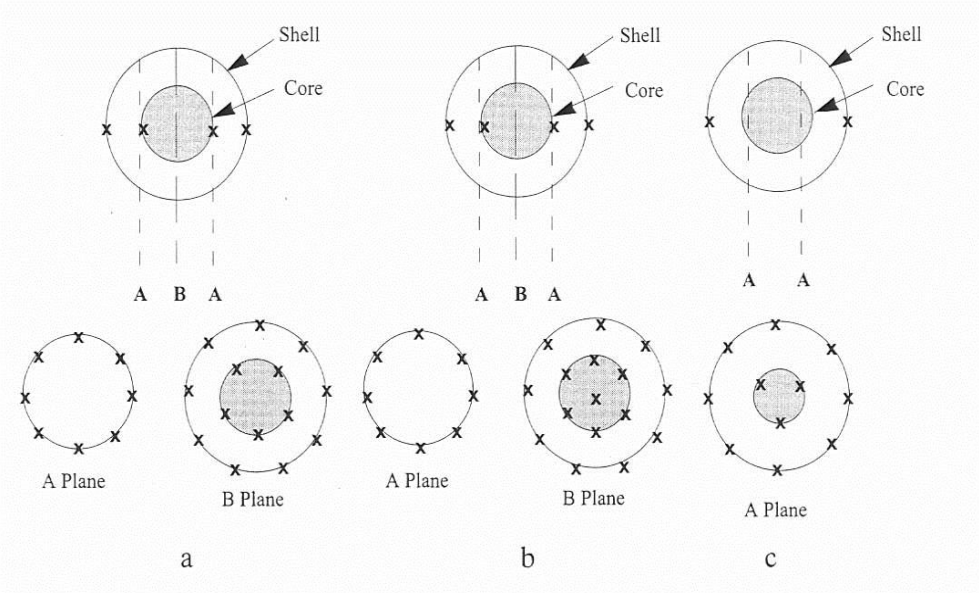
A mechanism for assembling source chains of varying active length and overall length for LDR remote afterloading (courtesy of Nucletron Corporation, Columbia, MD).



The use of a template for interstitial implantation of the prostate (courtesy of Mick Radio-Nuclear Instruments, Inc.)

Implantation Methods for Optimal Dose Distribution

- Manchester System:
  - Sets implant distribution rules.
  - Develops a uniform dose (±10%) to implanted volume.
- Quimby System:
  - Assumes a uniform distribution of radioactive material.
  - Non-uniform dose distribution.
  - Higher dose at center of implant.
- Paris System:
  - Developed for ^{192}Ir therapy and for after-loaded implants.
  - Uniform source distribution with a few volumes at high-dose.
- Kwan/Zwicker System
- Memorial System
- Computed dose distribution: greater flexibility.



A Manchester-system permanent implant using gold seeds: a) initial plan; b) plan with a single activity; c) plan with a single, more normal activity.

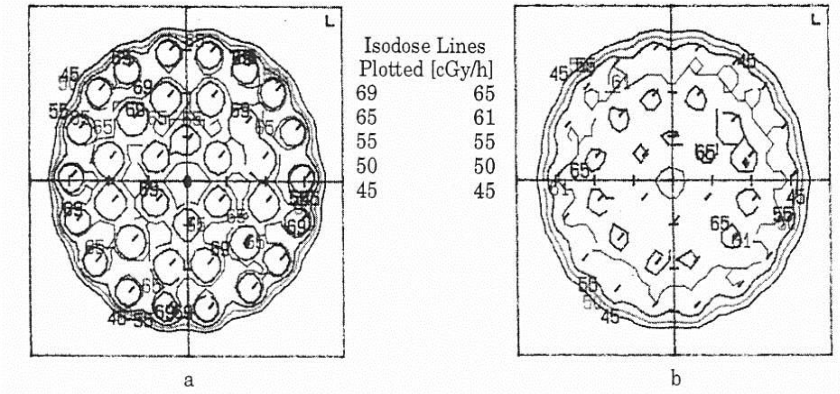


Illustration for the discussion of maximum significant dose and maximum contiguous dose: a) dose distribution through the central seed plane of an eight centimeter long template implant; b) dose distribution 0.5 cm from the plane in a) between seed planes.

Radioisotope Therapy (or Radionuclide Therapy)

- Systemic radioisotope therapy is a form of targeted therapy.
- Targeting can be achieved by:
  - chemical properties of the isotope such as radioiodine which is specifically absorbed by the thyroid gland,
  - attaching the radioisotope to another molecule, or
  - to an antibody to guide it to the target cell (Radioimmunotherapy (RIT), discussed next lecture).
- The radioisotopes are delivered through infusion (into the bloodstream) or ingestion.
- Examples of applications are:
  - infusion of metaiodobenzylguanidine (MIBG) to treat neuroblastoma,
  - oral iodine-131 to treat thyroid cancer or thyrotoxicosis, and
  - hormone-bound lutetium-177 and yttrium-90 to treat neuroendocrine tumors (peptide receptor radionuclide therapy).
- A major use of systemic radioisotope therapy is in the treatment of bone metastasis from cancer:
  - The radioisotopes travel selectively to areas of damaged bone, and spare normal undamaged bone.
  - Isotopes commonly used in the treatment of bone metastasis are ^{89}Sr and ^{153}Sm-ethylene diamine tetramethylene phosphonate.

Literature / WWW-references

- F.M. Khan, “The Physics of Radiation Therapy”, Lippincott, Williams & Wilkins, (4th edition, 2010)
- William R. Hendee (Ed.), “Biomedical Uses of Radiation”, Part B – Therapeutic Applications, Wiley-VCH (1999).
- International Commission on Radiological Protection (ICRP): http://www.icrp.org/
- International Commission on Radiation Units & Measurements (ICRU): http://www.icru.org/