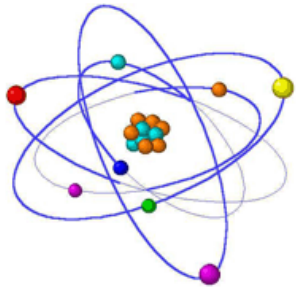
Radioisotope and Radiation Applications (FS2013)



Radiotherapy: Modern Techniques (Week 4a)

Pavel Frajtag

15.10. 2013

Radiotherapy (Modern Techniques): Outline

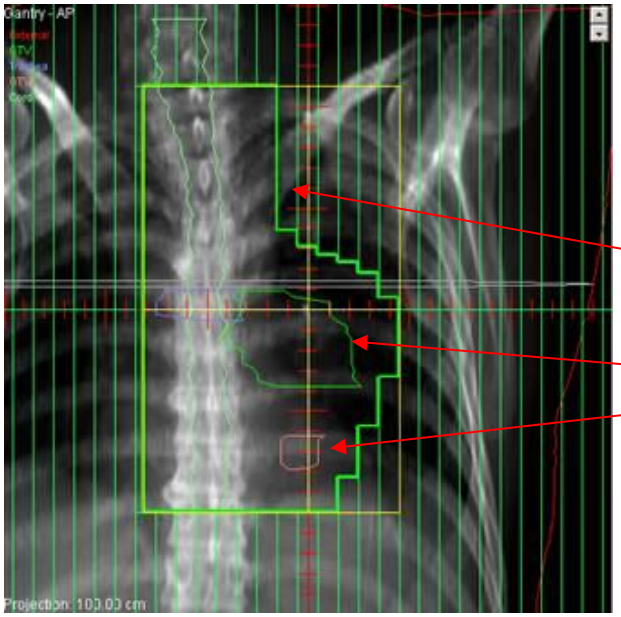
- 3-D Conformal Radiotherapy (3D-CRT)
- Intensity Modulated Radiation Therapy (IMRT)
- Stereotactic Radiosurgery (SRS, SRT)
- High Dose Rate Brachytherapy (HDR)
- Hadron Therapy (or Particle Therapy)
  - Proton Therapy
  - Light and Heavy Ions
  - Fast Neutrons
  - Boron Neutron Capture Therapy (BNCT)
- Radioimmunotherapy (RIT)

Three-Dimensional Conformal Radiotherapy (3D-CRT)

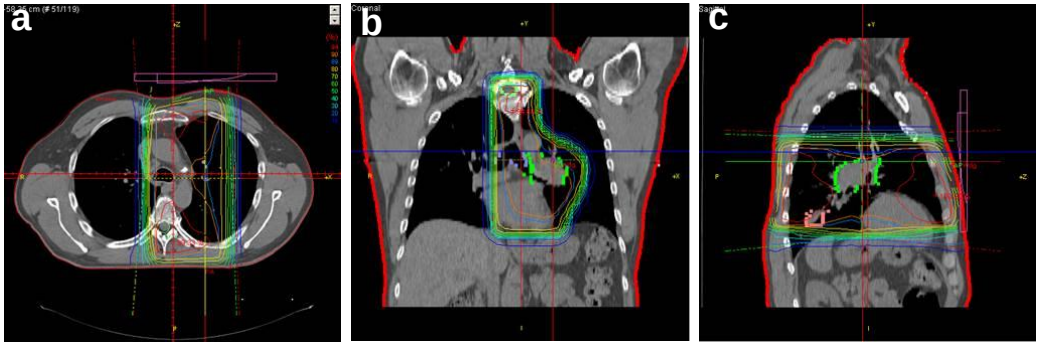
- Concept:
  - Radiotherapy treatment based on 3D anatomical information.
  - Use **dose distributions that conform as closely as possible to the target volume** with the objectives:
    - Adequate dose to the tumor: maximize tumor control probability (TCP).
    - Minimum possible dose to normal tissue: minimize normal tissue complication probability (NTCP).
  - Tries to optimize the dose distribution.
  - Often allows to deliver a higher dose to the tumor than classical methods.
- Obstacles to 3D-CRT:
  - Major limitation is the knowledge of the tumor extent: **the clinical target volume (CTV) is often not fully discernible.**
  - Potential errors due to patient motion.

3D-CRT: GTV, CTV, PTV

- **Types of target volumes to be designed:**
  - GTV: Gross Tumor/Target Volume
    - As seen in CT images.
  - CTV: Clinical Tumor/Target Volume
    - Tries to account for microscopic spread.
  - PTV: Planning Target Volume
    - Includes systematic as well as random errors (e.g. from patient motion).
- **If a portion of the diseased tissue is left untreated or receives a low dose, the treatment will be a failure!**
- Beam apertures are conformed to cover PTV (within 95-105% of prescribed dose).
- The design of conformal fields must take into account:
  - The cross-beam profile.
  - The penumbra.
  - The lateral radiation transport (scatter) as a function of depth.
  - Radial distance.
  - Tissue density.



Radiotherapy field, in heavy green, achieved by multileaf shaping for the treatment of lung cancer in light green and pink.



(a) axial, (b) coronal and (c) sagittal display of conformal dose distribution for treatment of lung cancer.

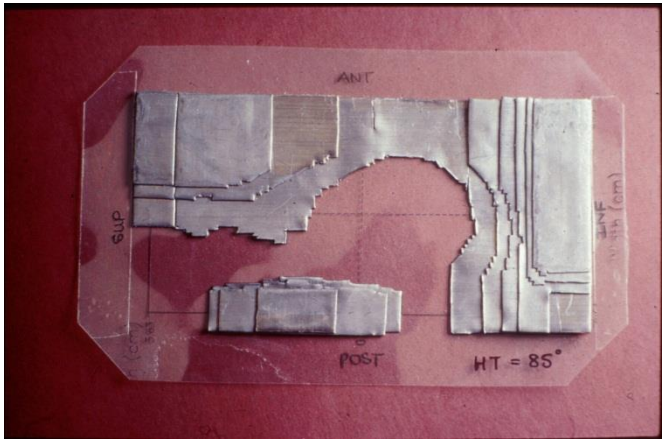
http://www.radonc.ucla.edu/clinical_programs/lung_cancer.htm

3D-CRT: Treatment Process

- Requirements:
  - 3D anatomic information, i.e., images of high quality:
    - in most cases from CT or MRI in transverse sections (slices),
    - but also from ultrasound, SPECT, and PET.
  - A treatment planning system that optimizes dose distribution according to the clinical objectives.
- Process steps in treatment planning (**forward planning**):
  - **Registration:** correlate different image data sets to identify structures.
  - **Segmentation:** outline of target volumes in each slice (PTVs).
  - **Treatment field and beam design:** using 3D treatment planning software.
    - Set field margins (distance between field edge and the PTV outline)
    - Taking account of penumbra regions cover the entire PTV with sufficiently high dose and spare the sensitive tissues.
  - **Optimization** of a treatment plan requires:
    - Design of optimal field apertures.
    - Appropriate beam directions, number of fields, and beam weights.
    - Intensity modifiers like wedges, compensators, and dynamic multileaf collimators.
- One of the most useful features in computer software supporting 3D-CRT are graphic systems that allow beam's-eye-view (BEV) visualization of the delineated targets and other structures:
  - display in a plane perpendicular to the central axis of the beam,
  - as if being viewed from the vantage point of the radiation source.

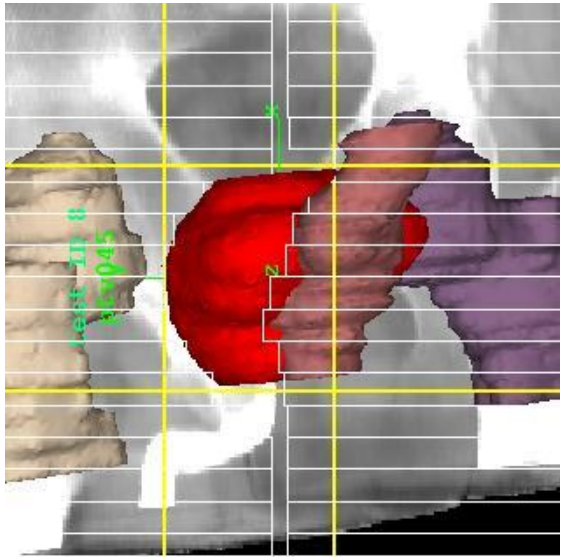
3D-CRT: Beam Shaping

- Beam shaping devices:
  - Main rectangular collimators.
  - Wedges.
  - Blocks.
  - Compensators.
  - Multileaf collimators (MLC).

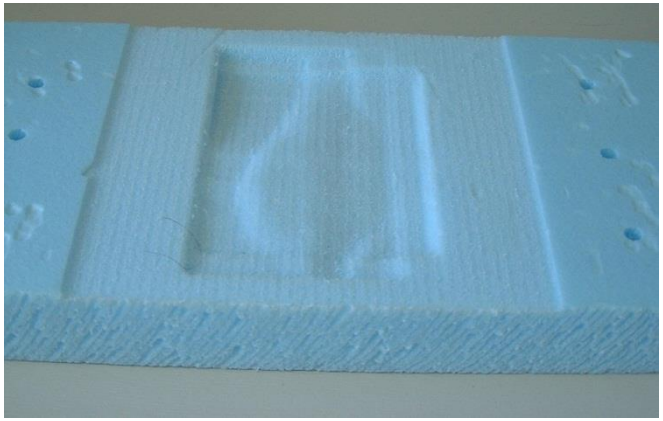


Lead compensator

- Sheets of lead 0.5 mm thick
- Used in conjunction with wedge
- Shapes to breast and shields lung



Beam conformation with a multileaf collimator

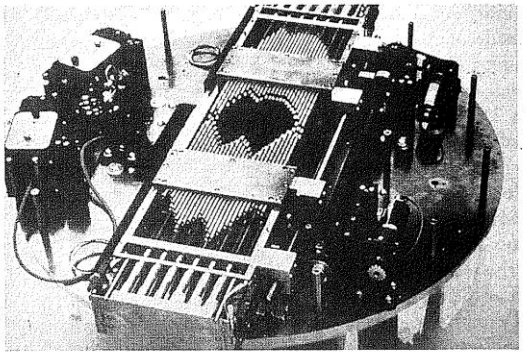


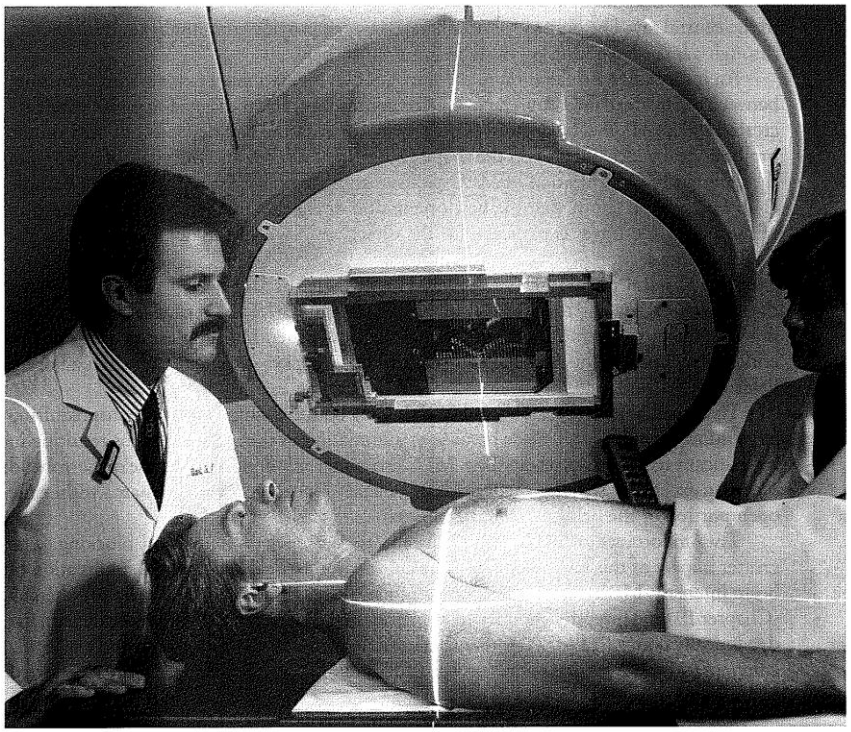
Granulate compensator

- Stainless steel granulate
- Used in conjunction with wedge
- Shapes to breast and shields lung

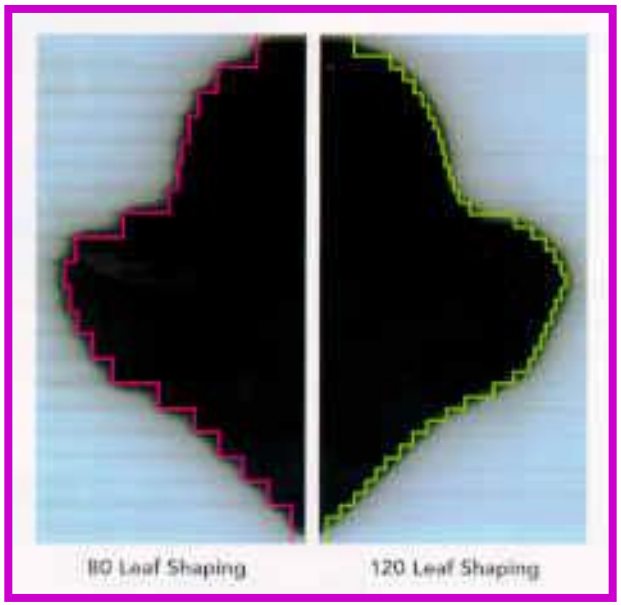
3D-CRT: Multileaf Collimators

- The quality of the field definition depends on the width of the leafs.
- There is always some interleaf leakage.
- Typically transmission through the MLC is larger than through a standard collimator.

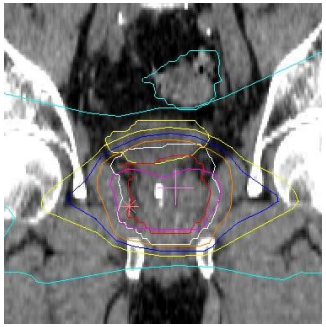


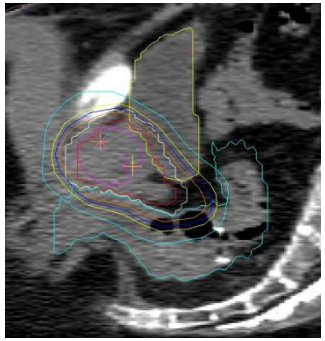


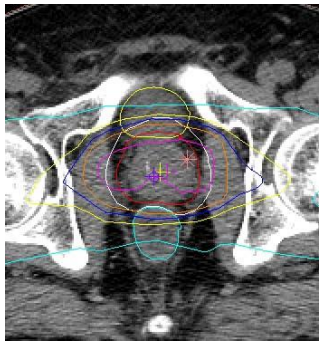
Varian multileaf collimator: (*top*) attached to accelerator and (*bottom*) with an end-on view. (Courtesy of Varian Associates, Palo Alto, CA.)



3D-CRT: "Summary"

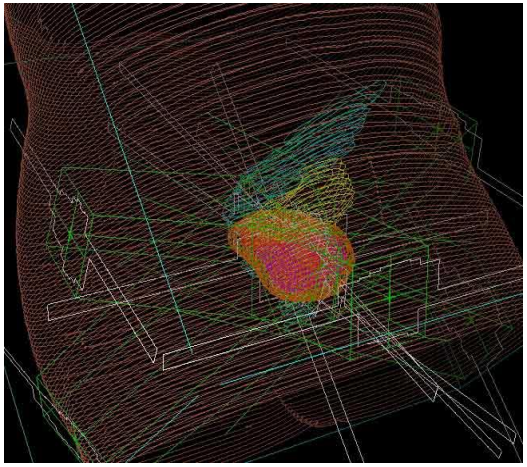


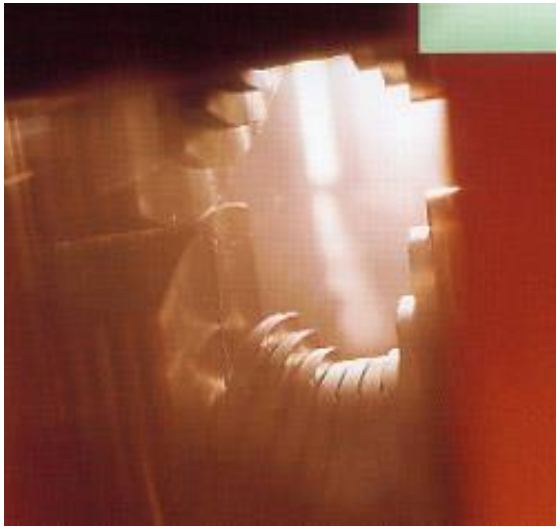




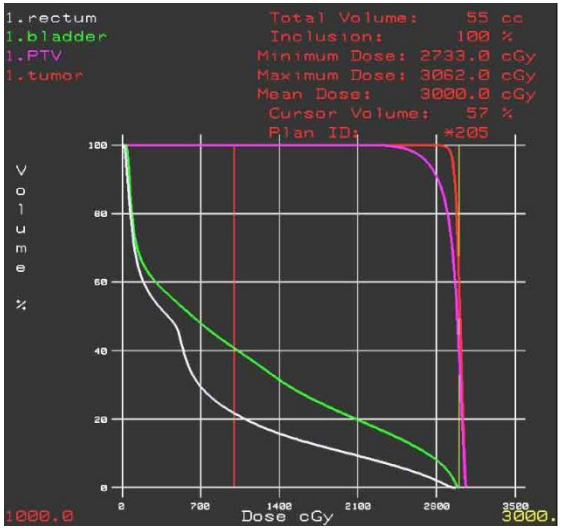
3-D conformal plan
based on 3D CT images

3-D image for PTV determination





Multileaf collimator



Dose volume histogram

Intensity Modulated Radiotherapy (IMRT)

- Concept:
  - Advanced type of high-precision radiation therapy technique in which beams with **non-uniform intensity profiles** are delivered to the patient from any given position to optimize the composite dose distribution.
- The clinical implementation is based on:
  - A **treatment planning computer system to calculate non-uniform fluence maps for multiple beams** directed from different directions.
  - A **system to deliver the non-uniform fluences** as planned, e.g., a LINAC modified for computerized beam intensity control.
  - Both systems must be tested and commissioned before clinical use.
- IMRT improves the ability to conform the high dose region to targets with concave shapes (e.g., a tumor wrapped around the spinal cord).

IMRT: Process and Treatment Planning

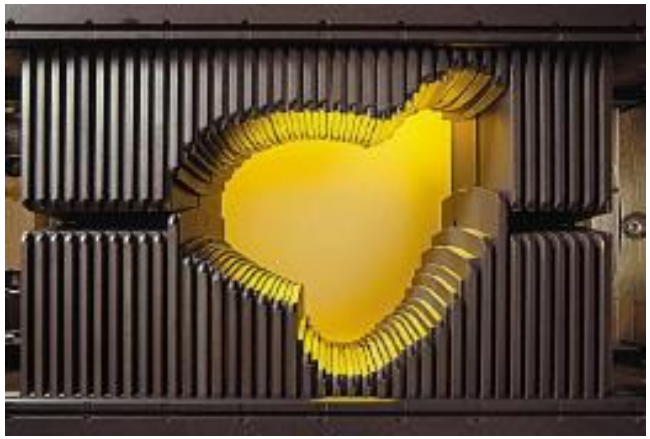
- Treat patient with beams from a number of different directions (or continuous arcs).
- Divide each beam into a large number of *beamlets*.
- The objective is to determine the optimal values of their intensities or weights.
- The optimization is done through inverse planning:
  - Beamlet intensities are adjusted to satisfy predefined dose distribution criteria for the composite plan.
  - Done using computer methods of two broad categories:
    - **Analytic**: similar to CT reconstruction, but with possibility of negative weights.
    - **Iterative**: similar to optimization methods with "cost functions" of the form:

$$C_n = \left[\left(\frac{1}{N} \right) \sum_r W(\vec{r}) \left(D_0(\vec{r}) - D_n(\vec{r}) \right)^2 \right]^{0.5}$$

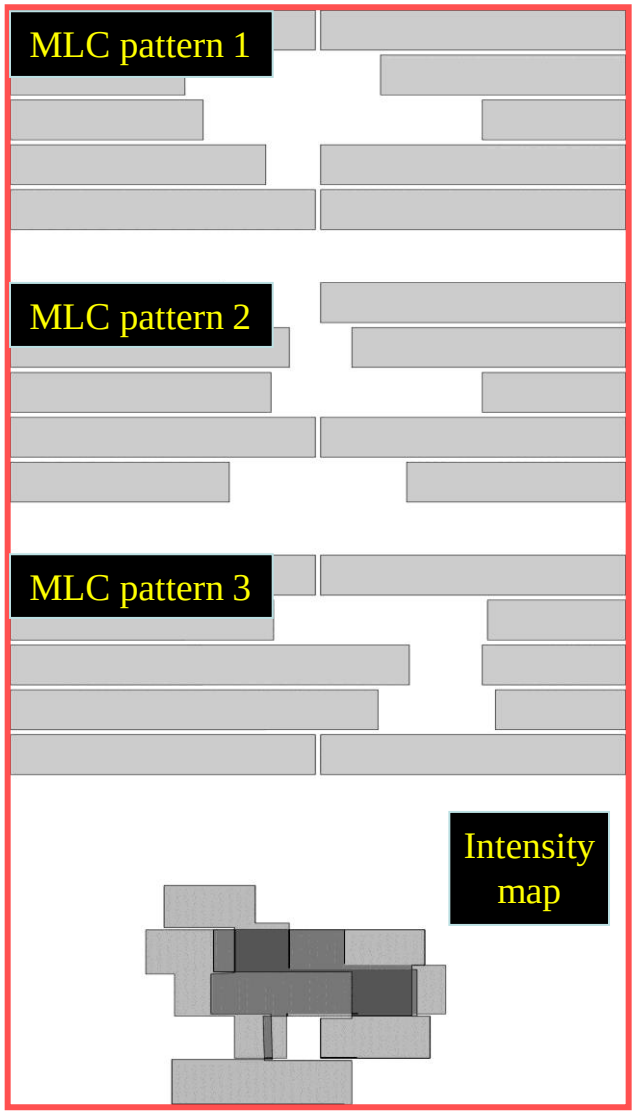
$D_0(r)$=desired dose at point r, W(r)=weight, r is mapped over target and critical structures.

IMRT: Therapy Delivery

- The IMRT plan transmits intensity profiles (fluence maps) for each beam to the treatment accelerator unit.
- The IMRT accelerator must change the given beam profile into a profile of arbitrary shape.
- For LINACs, the computer controlled multileaf collimator (MLC) is the most practical device to modulate the intensity:
  - When MLC moves during treatment, different parts of the (sub)field are shielded resulting in different overall radiation levels delivered in different parts of the beam.
- The (sub)field shape is altered step-by-step ("stop-and-shoot") or dynamically ("sliding window").

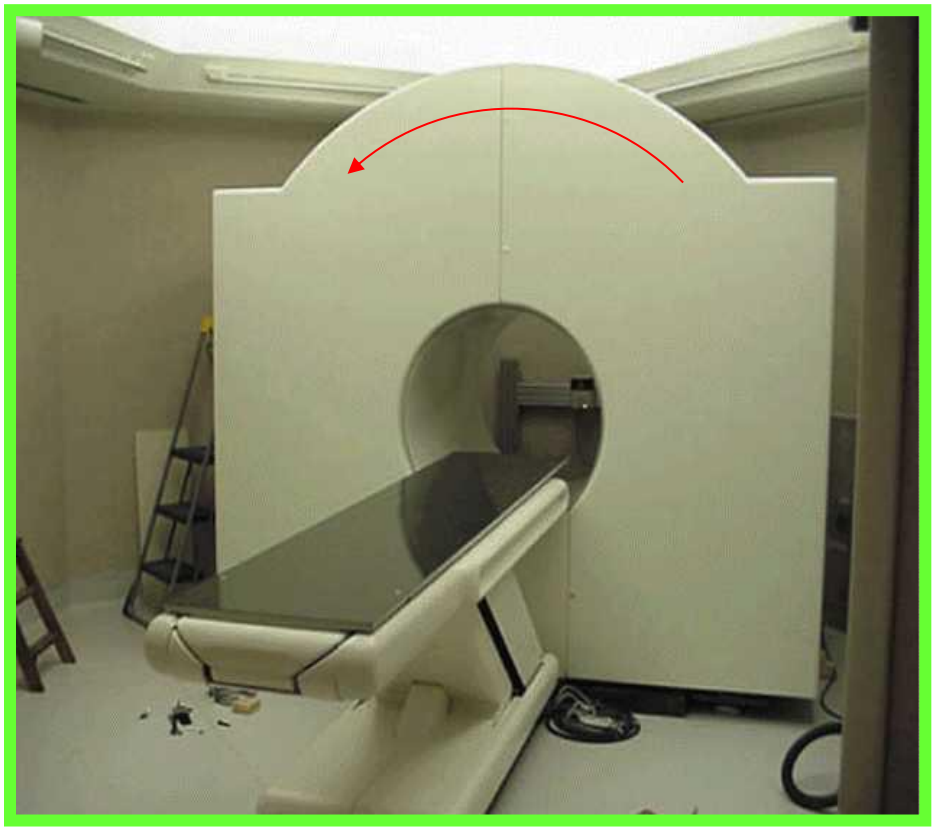


When the photon beam exits the head of the linear accelerator, it passes through the multileaf collimator (MLC). The MLC is composed of 120 computer controlled tungsten leaves that shift to form specific patterns, blocking the radiation beams according to the intensity profile from the treatment plan.

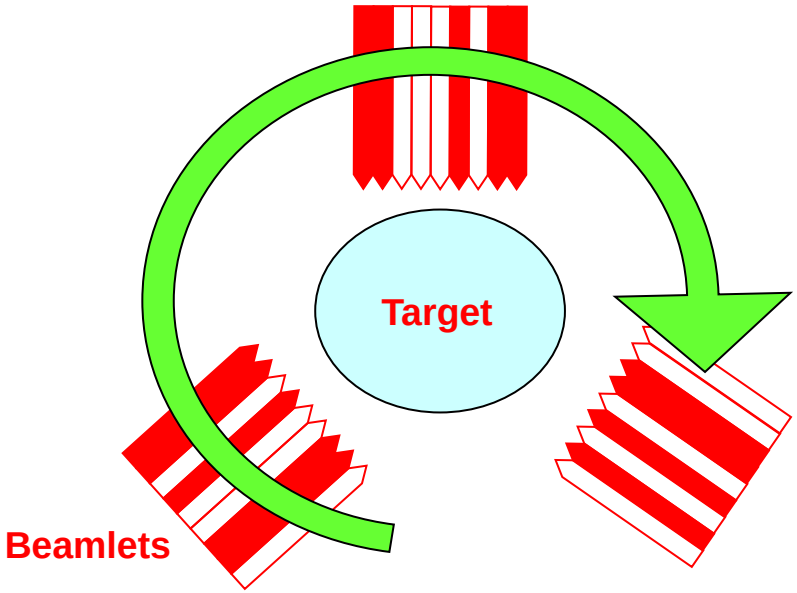


IMRT: Tomotherapy (1)

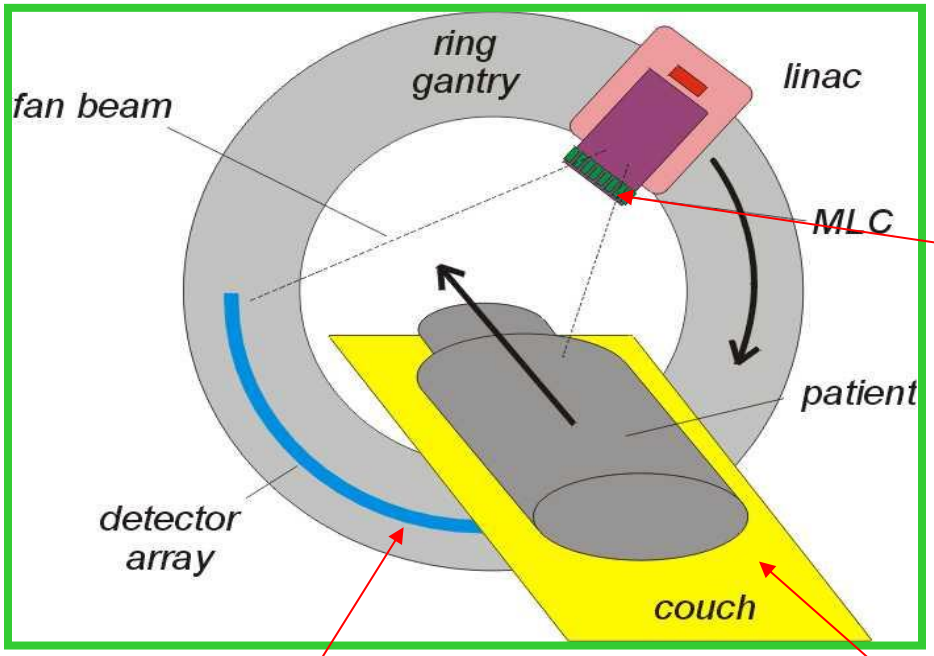
- Tomotherapy is an IMRT technique in which the patient is treated slice by slice by intensity-modulated beams in a manner analogous to CT imaging.



Continuous rotation of a one dimensional fan beam which consists of many beamlets that can be turned on or off.

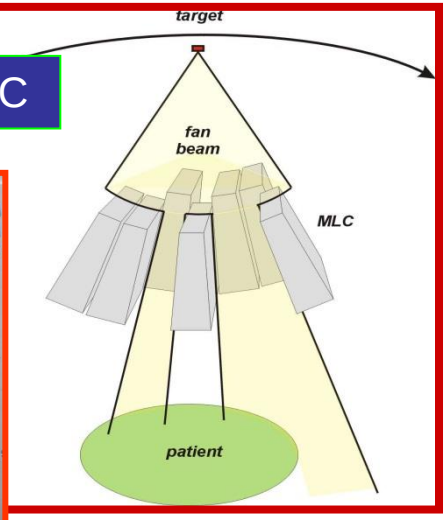


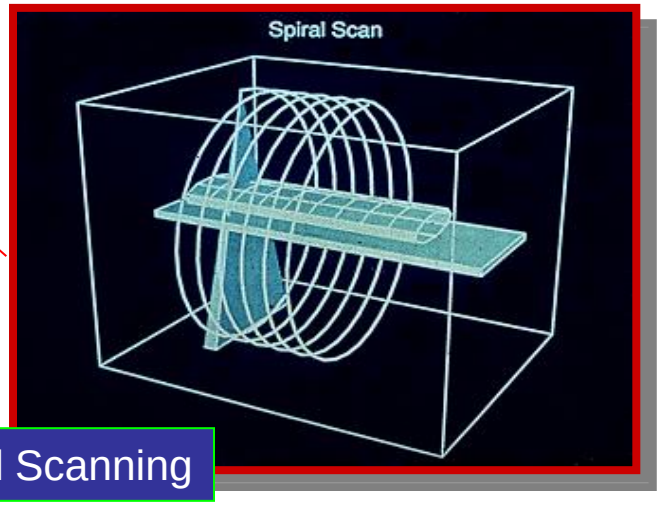
IMRT: Tomotherapy (2)



Ring detector at exit side

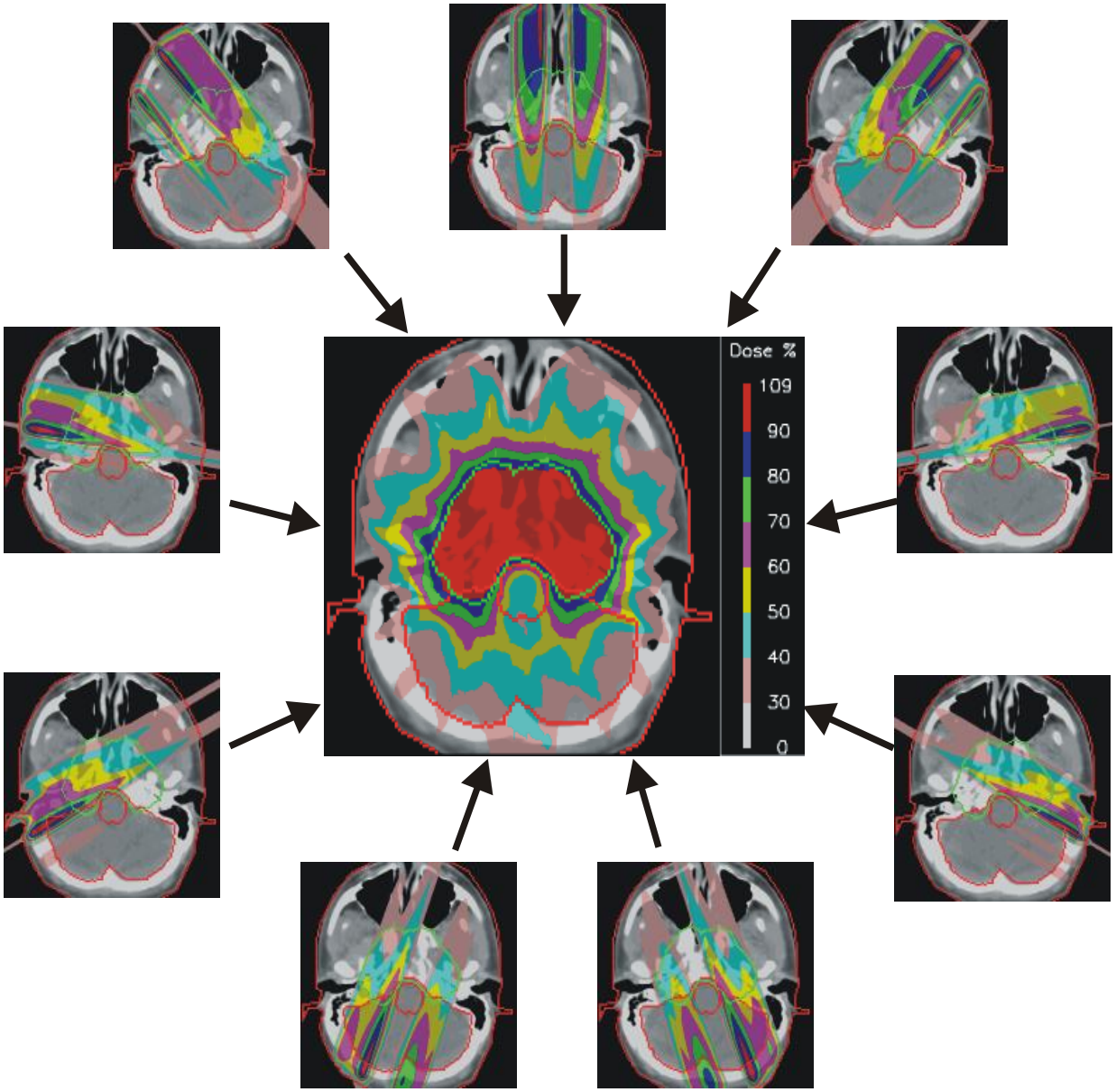
Binary MLC





Helical Scanning

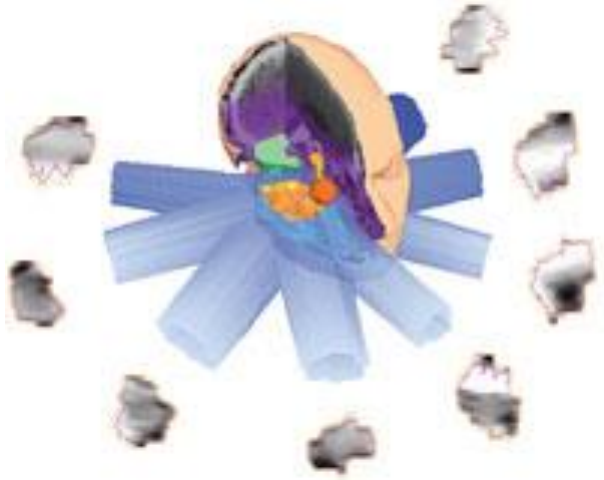
Multiple Beam IMRT



Comparison of RT Methods

Conventional radiotherapy delivers a radiation beam along a single treatment arc. It uses blocks to shape the radiation beam in a square-edged fashion.

3D conformal radiotherapy delivers radiation beams in multiple arcs at various angles. It uses collimators to shape each radiation beam in an elliptical-shaped fashion to conform the dose to the tumor (orange).



Intensity modulated radiotherapy (IMRT)
delivers radiation beams in multiple arcs, similar to 3D conformal. It uses sophisticated inverse planning software and multileaf collimators to both shape the radiation beam and change the intensity within each beam to deliver the optimum dose.

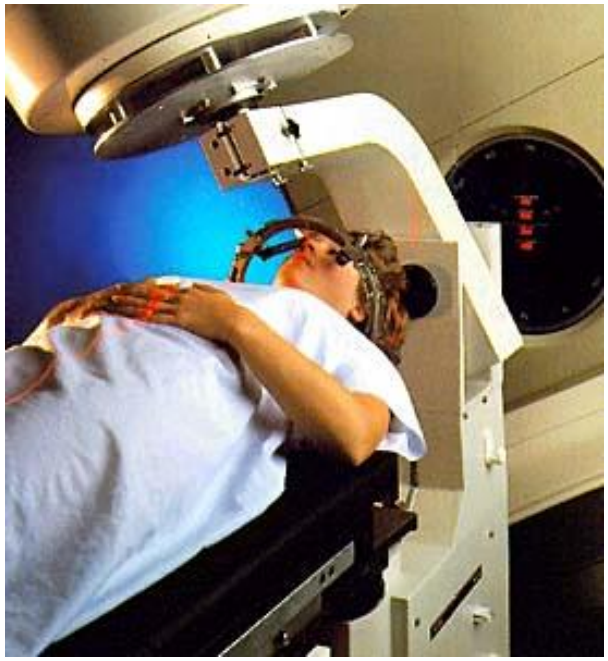
Source: www.mayfieldclinic.com

Stereotactic Radiosurgery (SRS) (1)

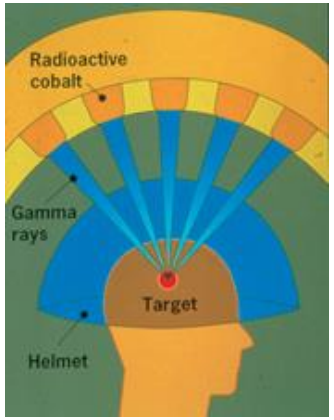
- **Single fraction** radiation therapy for treating intracranial lesions using a combination of:
  - Stereotactic apparatus.
  - Narrow multiple beams delivered through non-coplanar, isocentric arcs.
- When **multiple dose fractions** are applied to the patient the procedure is called **stereotactic radiotherapy** (**SRT**).
- Both techniques rely on 3D imaging (CT, MRI) to:
  - Localize the lesion.
  - Deliver highly concentrated, accurately positioned dose to the target volume sparing normal brain tissue.

Stereotactic Radiosurgery (SRS) (2)

- Main **characteristics of SRS**:
  - High degree of dose conformity achieved by:
    - Appropriate circular beams.
    - Optimizing arc angles and beam weights.
    - Using multiple isocenters or dynamically shaping the field with mini (or micro) MLCs.
  - High precision:
    - Achieved by stereotactic apparatus aligned with radiation generator.
    - Accuracies of 0.2 ±0.1 mm in isocenter matching target center (1mm clinical practice).
- 3 types of radiation used in SRS, SRT:
  - heavy charged particles,
  - ^{60}Co gamma rays,
  - megavoltage X-rays.
- Two most commonly used modalities:
  - X-rays produced by LINAC: X-ray knife.
  - Gammas from ^{60}Co: gamma knife.



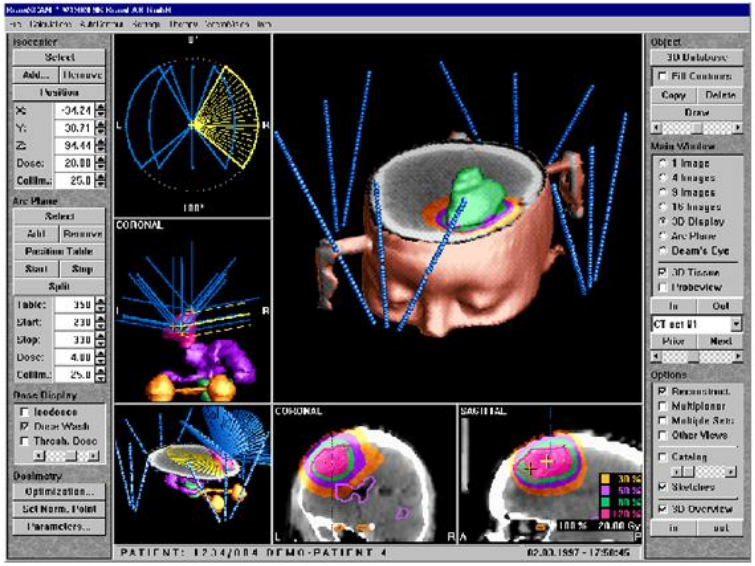
www.mc.vanderbilt.edu/surgery/neurosrg/photon.htm

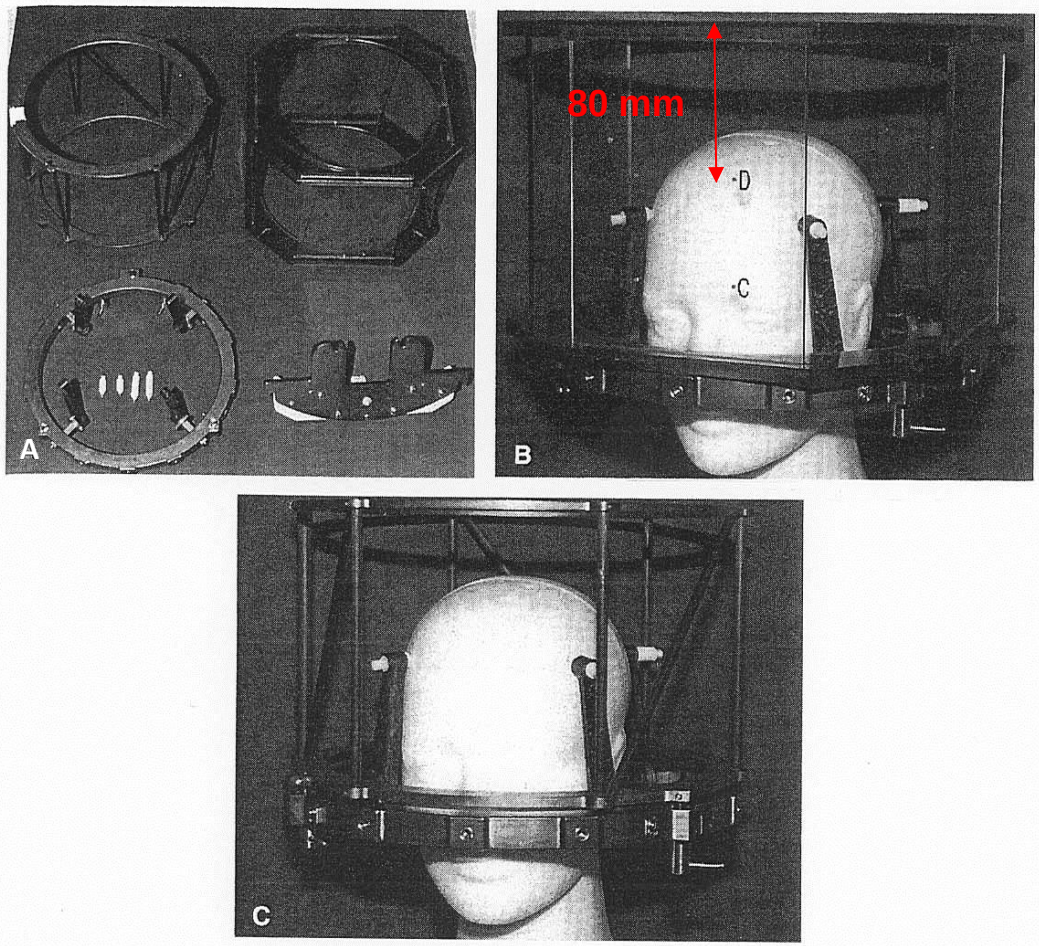


http://www.oncolink.com/types/images/brain_mets1.jpg

Stereotactic Radiosurgery: Stereotactic Frame

- Attached to:
  - Patients skull
  - SRS system frame
- Types: Leksell, Brown-Robert-Wells (BRW), etc.
- The origin of the frame (80mm below top plane) is aligned to the LINAC isocenter to within 0.2 to 1.0 mm.

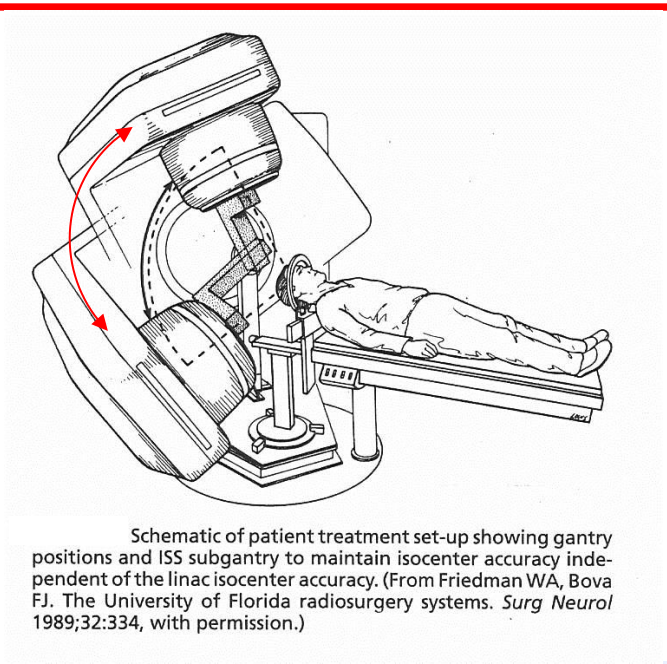




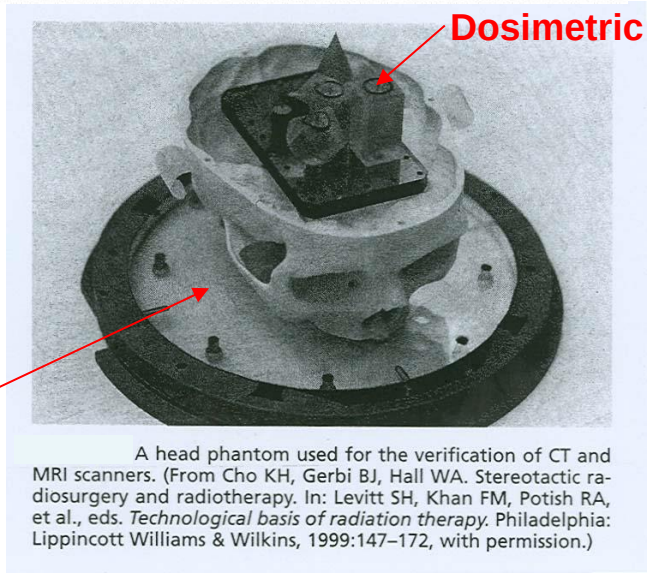
Basic stereotactic system showing **(A)** (starting clockwise from upper right) CT localizer, angiographic localizer, patient-positioning mount and head ring with posts and pins; **(B)** angiographic localizer; and **(C)** CT localizer. (From Bova FJ, Meeks SL, Friedman WA. Linac radiosurgery: system requirements, procedures, and testing. In: Khan FM, Potish RA, eds. *Treatment planning in radiation oncology.* Baltimore: Williams & Wilkins, 1998:215–241, with permission.)

Stereotactic Radiosurgery: X-Ray Knife

- LINAC based SRS (SRT).
- Consists of:
  - Multiple non-coplanar arcs of circular or dynamically shaped beams,
  - converging on the machine isocenter, which is
  - stereotactically placed at the center of imaged target volume.
- Spherical dose distribution is conformed by:
  - Shaping beam aperture dynamically with MLC.
  - Changing beam angles and weights.
  - Using more than one isocenter.
  - Combining stationary beams with arcing beams.
- Optimization is done with treatment planning software.
- QA verification using head phantoms.



Schematic of patient treatment set-up showing gantry positions and ISS subgantry to maintain isocenter accuracy independent of the linac isocenter accuracy. (From Friedman WA, Bova FJ. The University of Florida radiosurgery systems. *Surg Neurol* 1989;32:334, with permission.)

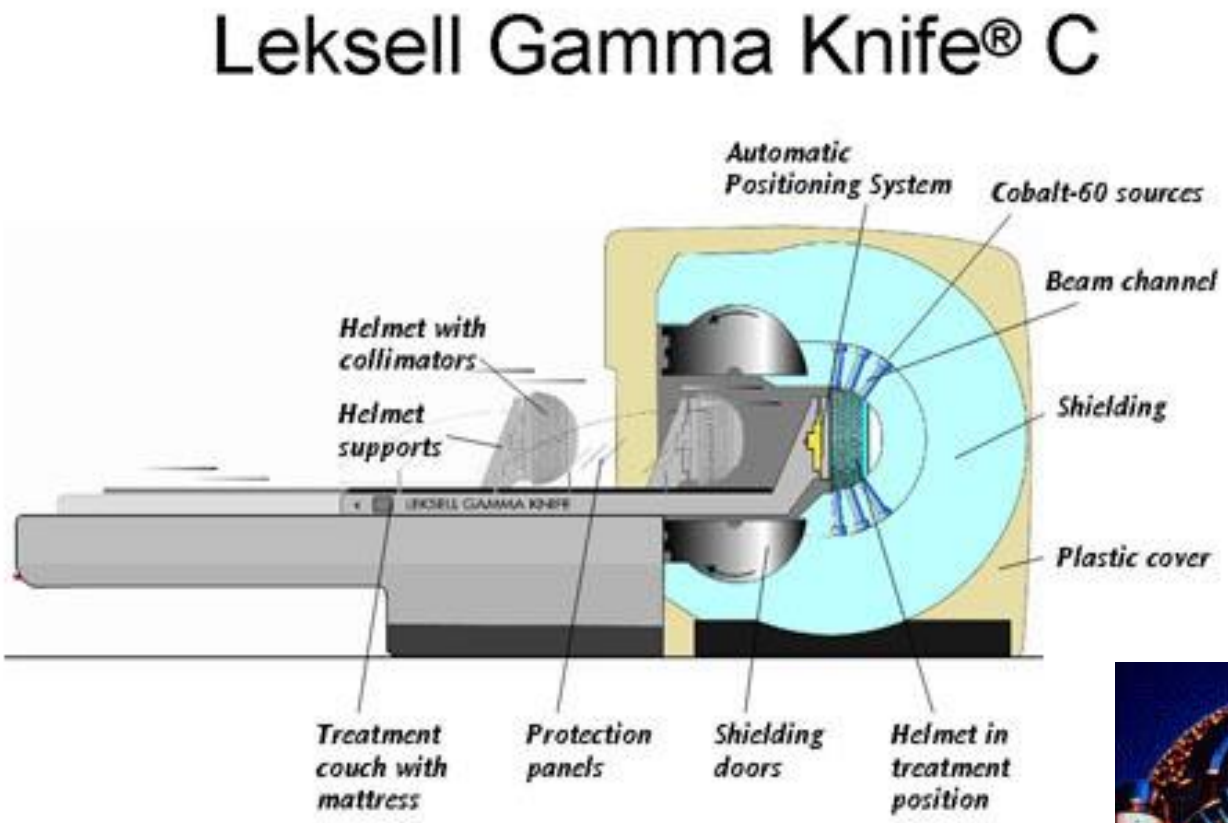


A head phantom used for the verification of CT and MRI scanners. (From Cho KH, Gerbi BJ, Hall WA. Stereotactic radiosurgery and radiotherapy. In: Levitt SH, Khan FM, Potish RA, et al., eds. *Technological basis of radiation therapy.* Philadelphia: Lippincott Williams & Wilkins, 1999:147–172, with permission.)

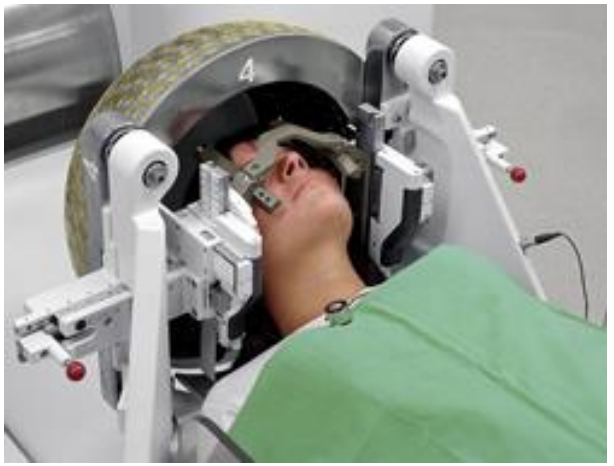
Stereotactic Radiosurgery: Gamma Knife (1)

- Uses simultaneous irradiation with a large number of isocentric γ-rays:
  - **201** ^{60}Co sources housed in a
  - hemispherical shield with collimators.
  - Sources distributed along longitudinal and transversal hemispherical arcs.
- High mechanical precision:
  - Alignment ±0.3 mm.
  - Patient helmet with collimating channels positioned with ±0.1 mm.
  - Uses the Leksell stereotactic frame.
- Clinically:
  - Only used for small lesions (18 mm max.)
  - More conformal than X-ray knife without dynamic MLC.
  - More practical than X-ray knife for multiple isocenters or targets (simplicity).
  - More expensive and can exclusively be used for SRS.

Stereotactic Radiosurgery: Gamma Knife (2)

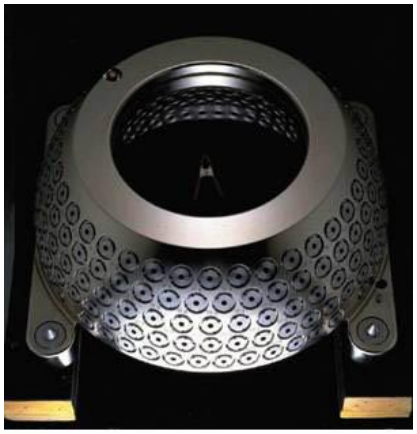


www.carolinaradiation.com/gamma.htm



Source: www.ccohta.ca

201 Beams of Focused Radiation



Helmet with Collimators

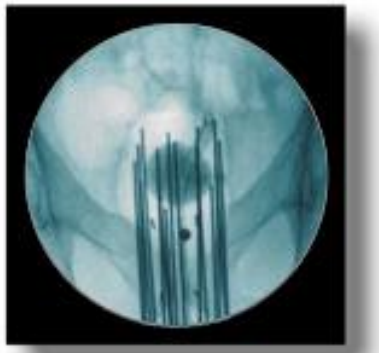
Stereotactic Radiosurgery: Clinical Applications

- Originally developed for treatment of brain benign lesions such as:
  - Arteriovenous malformations (AVM).
  - Meningiomas.
  - Acoustic neuromas.
- Use of SRS has been extended to treat:
  - many malignant tumors such as gliomas and brain metastases,
  - functional disorders, e.g., trigeminal neuralgia and movement disorders.
- Fractional SRT is applied to :
  - malignant brain tumors,
  - permits sparing of critical structures such as brain stem and optic pathways.
- Radiobiological principles:
  - of SRS are currently not well understood.
  - of SRT are well established and follow principles of radiotherapy (4-'R's).

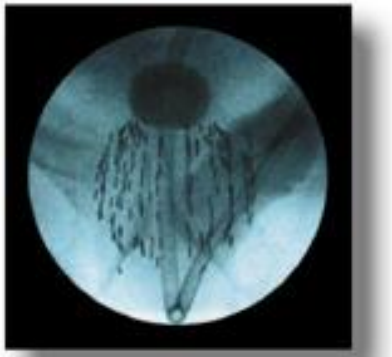
High Dose Brachytherapy (HDR)

- Doses of 20 cGy/min or above.
- Possible thanks to remote afterloading.
- Permits treatments on outpatient basis.
- Sources:
  - ~10 Ci ^{192}Ir sources (high specific activity, low half-life).
  - Line sources welded to end of flexible drive cables (d=0.3-0.6mm, l=3.5-10mm).
  - Inserted automatically in catheters implanted in patient (multiple channels).
  - Precise location of sources: accuracy ±1mm.
- Clinical applications:
  - Same as LDR Brachytherapy.
  - Endobronchial obstruction by lung cancer.
  - Post-operative treatment of endometrial carcinoma (vaginal cuff irradiation).
  - Localized prostate cancer.

http://www.npl.co.uk/ionrad



High dose rate brachytherapy (HDR) X-ray of a temporary implant



Low dose rate brachytherapy (LDR) X-ray of a permanent seed implant

www.gammawest.com/treatments.html

Hadron Therapy (or Particle Therapy): Basics

- Characterized by:
  - Superior dose localization characteristics.
  - Better differential effect between tumor and normal cells.
- Includes beams of:
  - Hadrons: neutrons, protons, π^-.
  - Light ions: He, C, Ne.
  - Heavy ions: Si, Ar.
- Energy loss per unit path (x) for Coulomb interactions of heavy particles with atomic electrons can be described by the Bohr-Bethe formula:

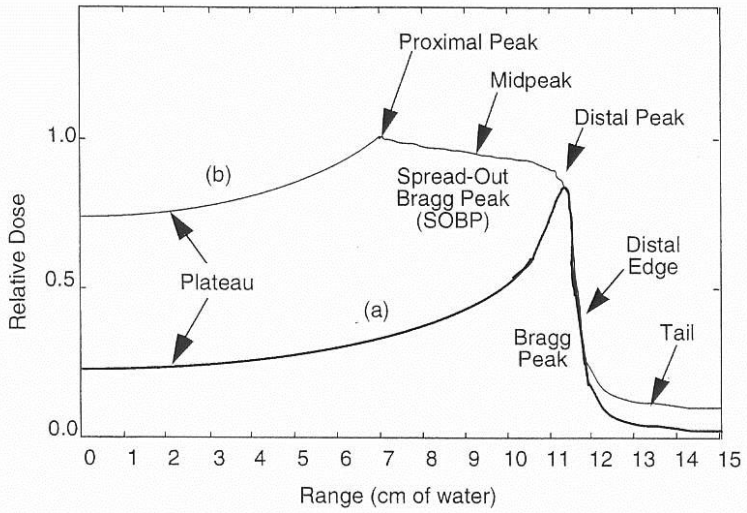


Figure 7.2. Physical dose distributions as a function of penetrating depth of (a) a pristine beam (Bragg curve) and (b) a beam whose range is modulated to widen the stopping region (spread-out Bragg peak, SOBP). The names given to several regions of the curves are labeled in the Figure.

The Bragg peak is often spread out to cover an extended target by modulating the energy of incident particles (SOBP).

$$\frac{dE}{dx} = -\frac{4\pi e^4 z^2 n_e}{m_e \nu^2}\left[\ln\left(\frac{2m_e\nu^2}{I}\right)\right]$$

Bragg peak

Range and straggling

$$R = \int_E^0 \frac{dE'}{f(E')}$$

$$S(z) = \frac{1}{\sqrt{2\pi}\sigma_z} e^{\left(-\frac{(z-R)^2}{2\sigma_z^2}\right)} \qquad \sigma_z(water) = 0.0120\frac{R^{0.961}}{\sqrt{A}}$$

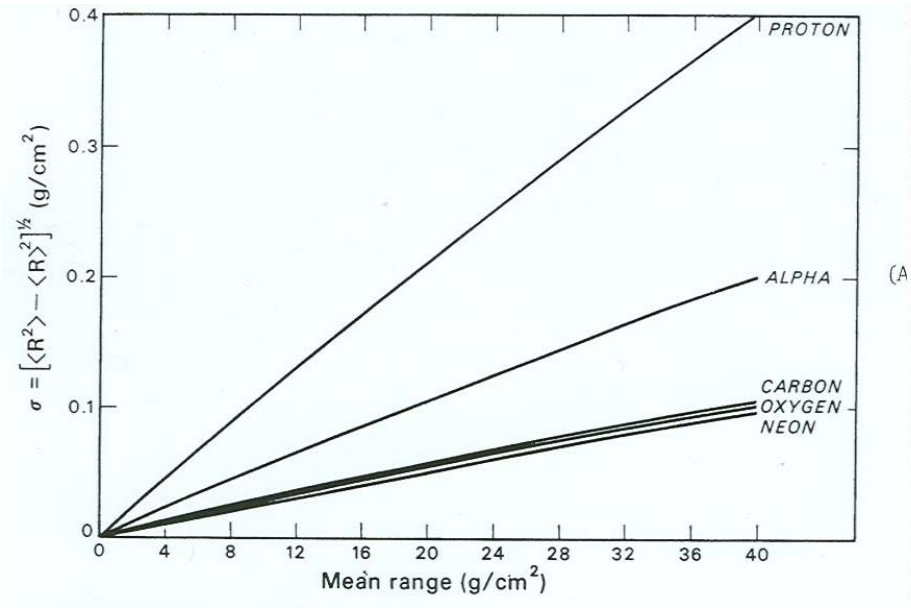
Hadron Therapy

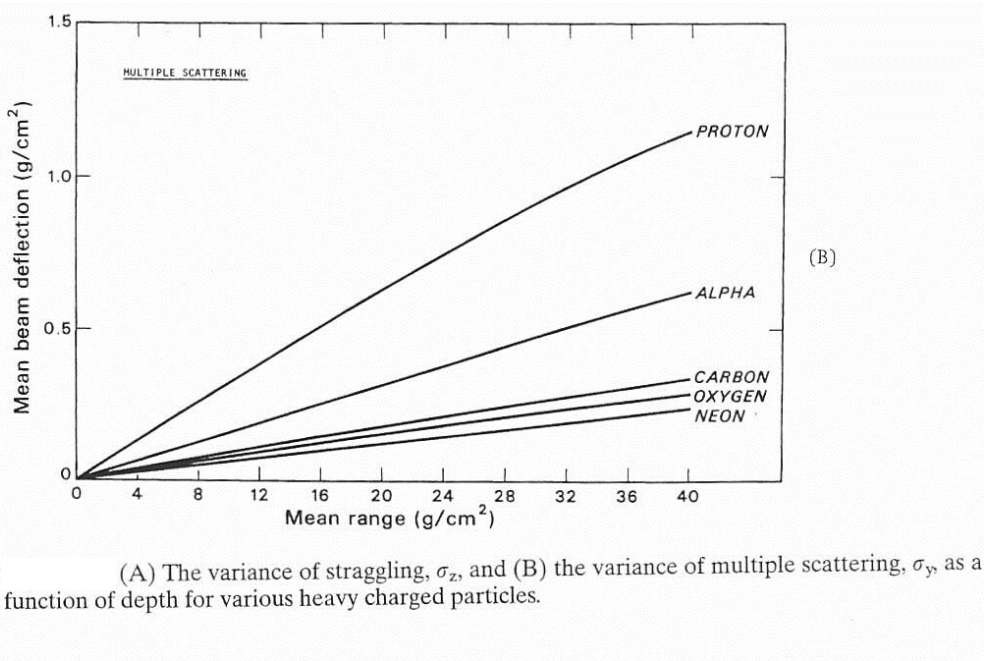
$$R = \int_E^0 \frac{dE'}{f(E')}$$

z is the penetration of the beam in the irradiated medium

$$S(z) = \frac{1}{\sqrt{2\pi}\sigma_z} e^{\left(-\frac{(z-R)^2}{2\sigma_z^2}\right)}$$

$$\sigma_z(water) = 0.0120 \frac{R^{0.961}}{\sqrt{A}}$$

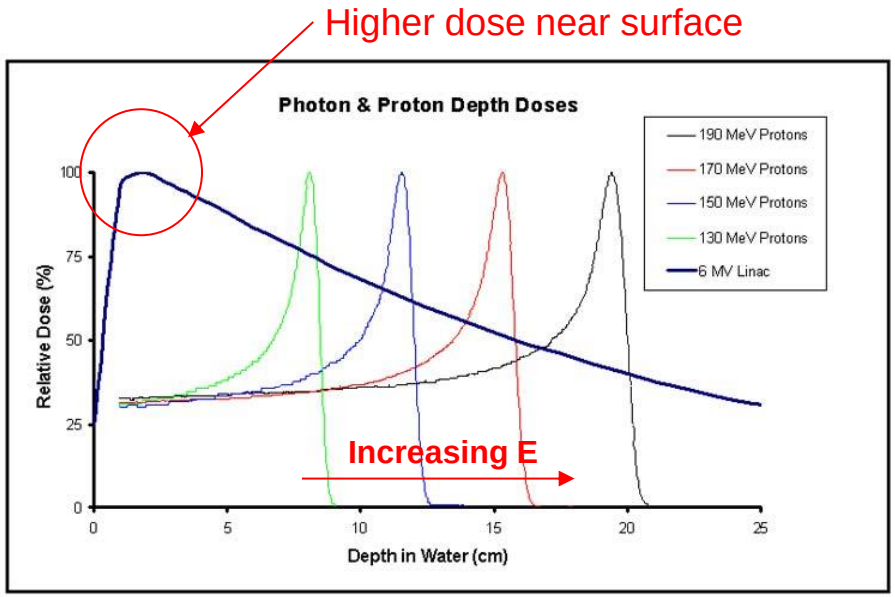




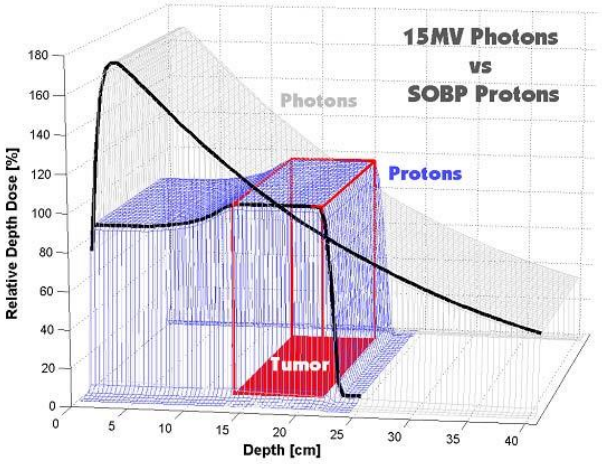
(A) The variance of straggling, σ_z, and (B) the variance of multiple scattering, σ_y, as a function of depth for various heavy charged particles.

Proton Therapy: Basics

- Irregularly shaped lesions with awkward configurations near critical structures are well suited for proton beam therapy.
- Protons have a physical advantage over gamma rays and x-rays when it comes to sparing normal tissues.
  - Protons deposit most of their radiation energy in what is known as the Bragg peak, at the point of greatest penetration of the protons in tissue.
  - The exact depth to which protons penetrate, and at which the Bragg peak occurs, is dependent on the energy of the proton beam.
  - This energy can be very precisely controlled to place the Bragg peak within a tumor or other tissues that are targeted to receive the radiation dose.
  - Because the protons are absorbed at this point, **normal tissues beyond the target receive very little or no radiation**.



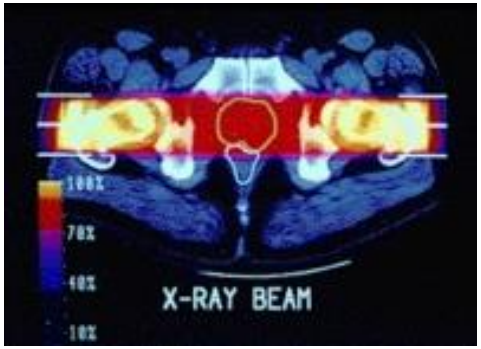
http://www2.massgeneral.org/cancer/about/providers/radiation/proton/principles.asp



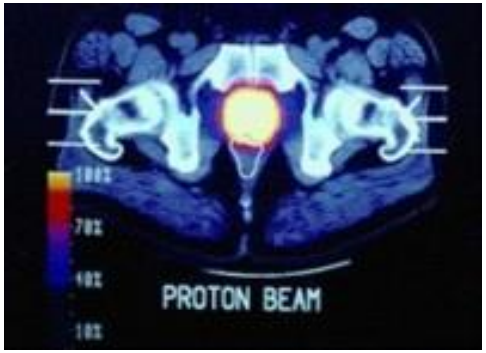
The figure on the right shows a widened proton beam as well as an x-ray beam adjusted to treat an 8 cm thick target with a maximum depth of 23 cm. The x-ray beam "spills" unnecessary dose beyond the target compared to protons.

Proton Therapy: Radiation Biology

- Proton beams transfer energy by:
  - Producing secondary electrons (δ-rays),
  - Exciting atoms and molecules in the medium (Coulomb).
- Ionization density similar to high energy photons:
  - Only increases substantially at the Bragg peak.
  - $RBE_{protons} \sim RBE_{High\text{-}E\ photons}$
  - $RBE_{protons\ Bragg} \sim 1.1$ (^{60}Co-γ ref.).
- Clinic:
  - Same Tumor Control Probability (TCP) with lower Normal Tissue Complication Probability (NTCP).



X-Ray Radiation Therapy can control many forms of cancer, however, most of the radiation is deposited on healthy tissue. Since X-rays can only be controlled in two dimensions, healthy tissue beyond the cancer (exit dose) receives high-doses of radiation as well.



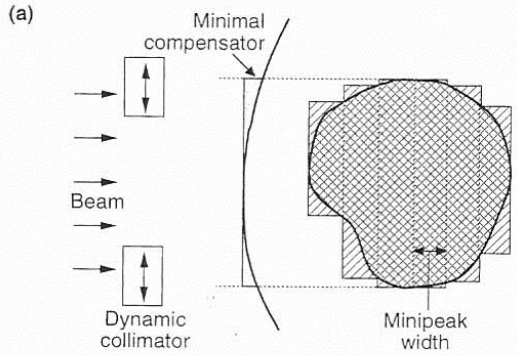
Proton Beam Therapy, unlike X-ray therapy, can be three-dimensionally conformed to the cancer's shape. It deposits the majority of it's energy at the tumor itself and spares healthy surrounding tissue. Consequently, tissues in front of the target (entrance dose) receive a very small dose, tissues adjacent to the tumor receive virtually no none.

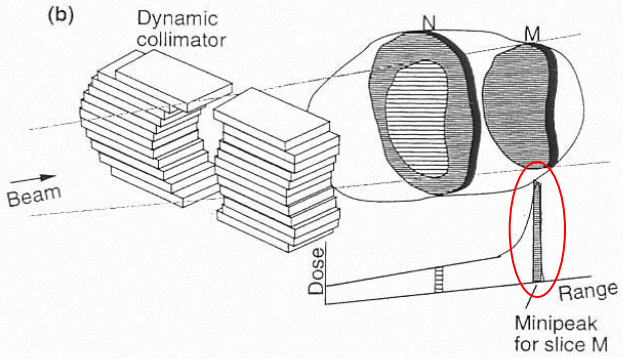
Fewer proton beams achieve same or better effect than 3-D conformal RT.

Better delivery of therapeutic dose: proton 100% isodose vs. 95% 3D-CRT

Proton Therapy: Delivery

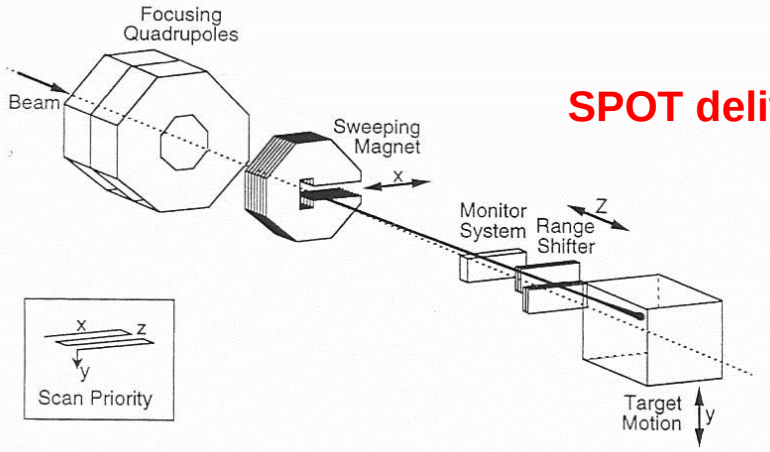
Conformal delivery





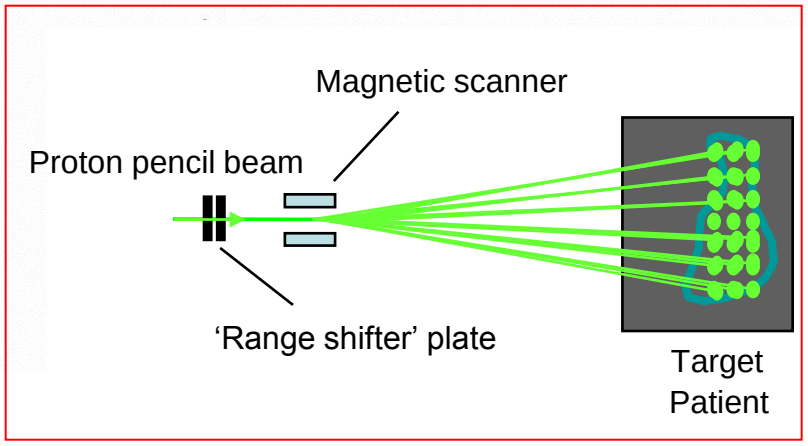
(a) The dose distribution obtained by a variable-modulation method, and (b) a schematic illustration of a three-dimensional dynamic conformal therapy delivery using a variable-speed scanner and a multileaf collimator assembly.

SPOT delivery

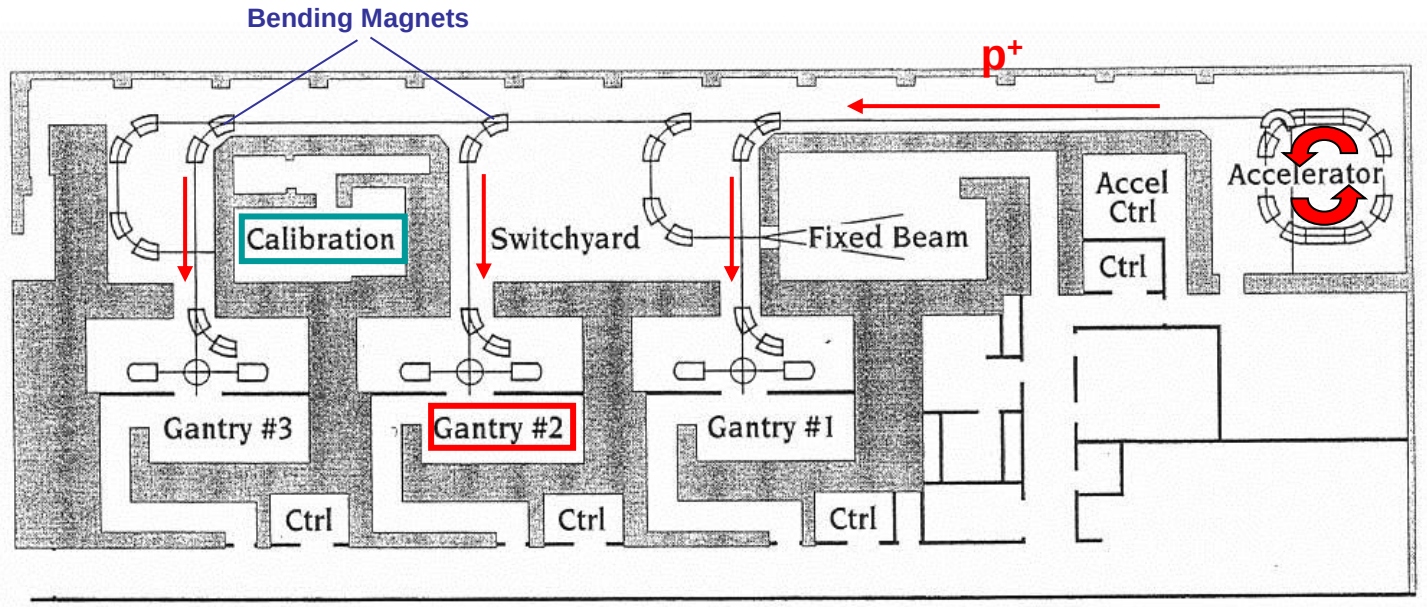


Schematic diagram showing the concept of the pixel scanning system at PSI.

Advantages of beam scanning for three-dimensional dynamic conformal therapy delivery have been discussed extensively[56]. A beam scanning system is employed to produce a prescribed dose distribution, D, in three dimensions as a convolution of the beam-profile function, p, and an occupation function, F:

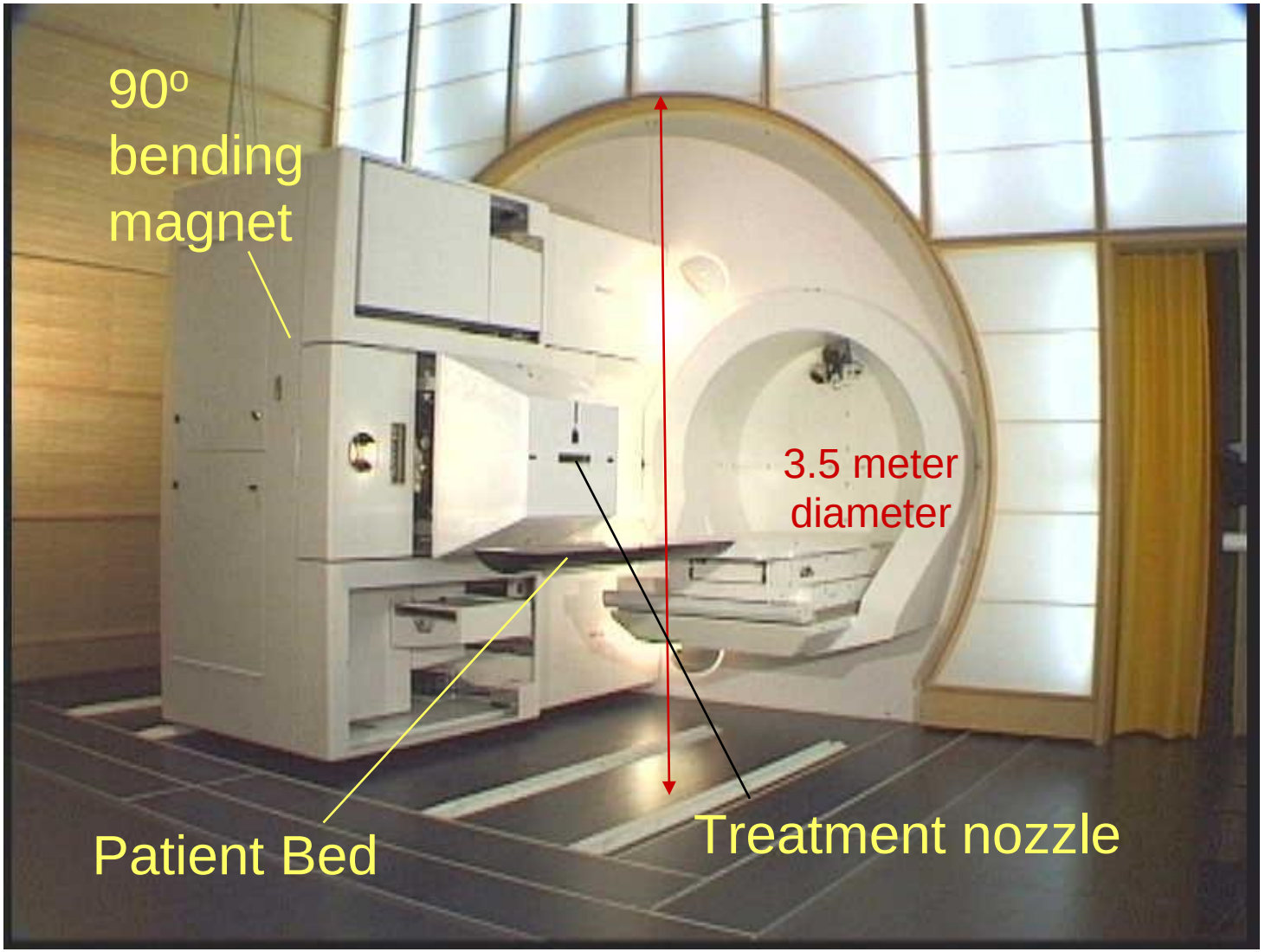


Proton Therapy: Infrastructure (1)



Schematic plan view of the proton facility at the Loma Linda University Medical Center. The synchrotron is a small part of the entire facility.

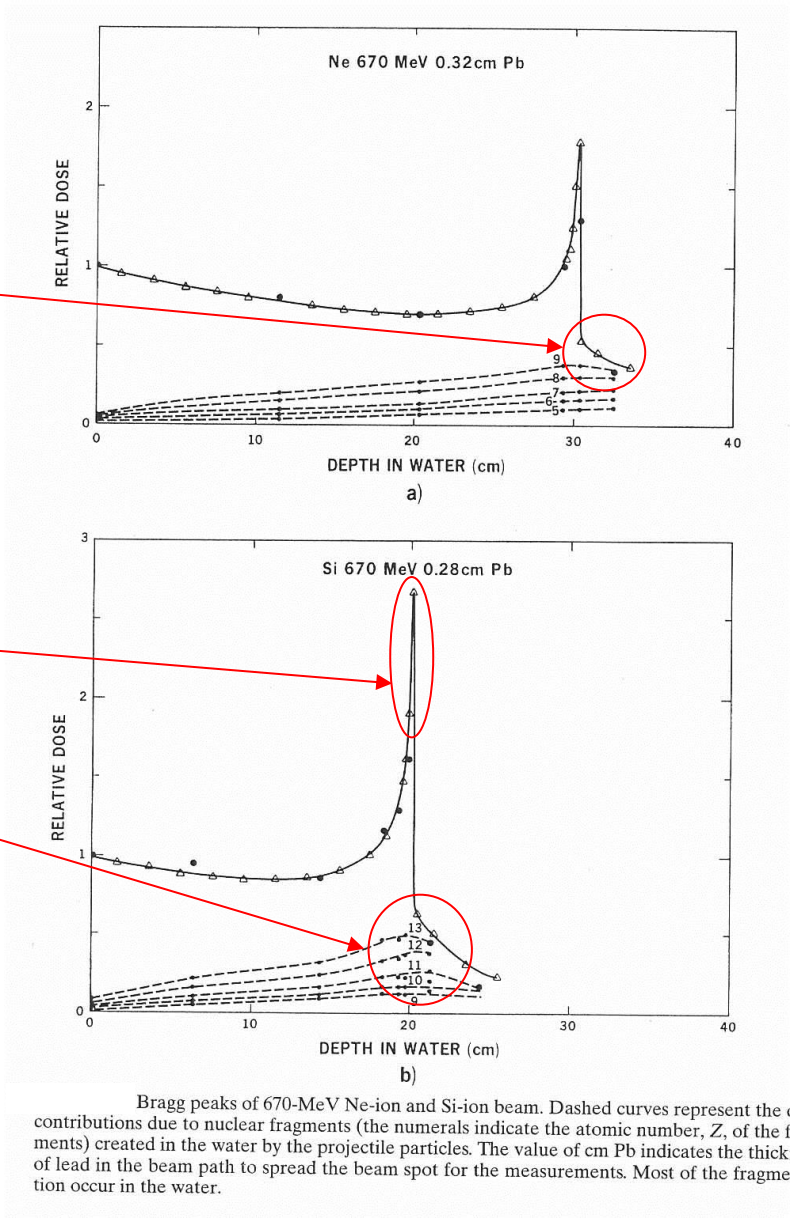
Proton Therapy: Infrastructure (2) (more in the Seminar)



PSI Gantry

Light and Heavy Ions (1)

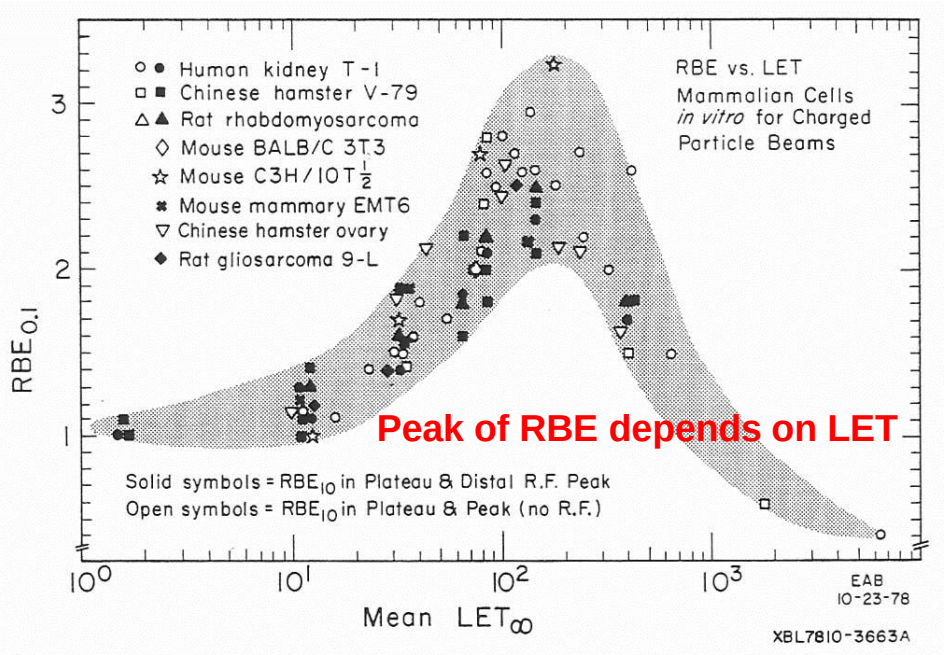
- Physics:
  - Heavier ion beams have lower straggling and less multiple scattering.
  - Useful for critically located tumors.
  - Have higher LET than p,γ.
  - Near spread-out Bragg peak RBE is large because of low velocity.
  - Secondary fragmented nuclei produce slowly decaying 'tail dose' beyond peak (10-20% entrance dose).



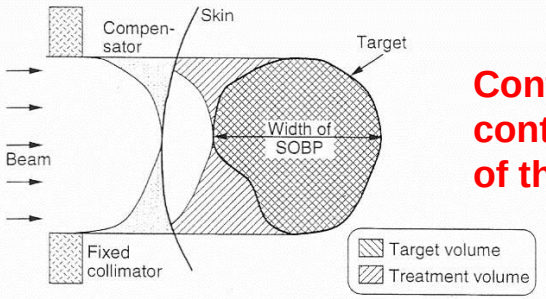
Bragg peaks of 670-MeV Ne-ion and Si-ion beam. Dashed curves represent the contributions due to nuclear fragments (the numerals indicate the atomic number, Z, of the fragments) created in the water by the projectile particles. The value of cm Pb indicates the thickness of lead in the beam path to spread the beam spot for the measurements. Most of the fragmentation occur in the water.

Light and Heavy Ions (2)

- Biology:
  - Failure of local tumor control with conventional radiation:
    - Anoxic cells are resistant to low-LET radiation.
  - High resistance of hypoxic cells is reduced when irradiated with high-LET.
  - Slowly proliferating cells are more sensitive to high-LET radiation.
  - With high LET radiation fewer fractions of higher doses are possible.
  - Heavy ion beams lead to best results for tumors with:
    - High intracellular repair.
    - Poor cell cycle redistribution.
    - Poor re-oxygenation.
    - Rapid proliferation.



A plot of *RBE* vs. LET for various cell lines. A simple relationship does not exist between the two. The shaded curve illustrates the general trend of the data.



Conformed by controlling the location of the Bragg peak

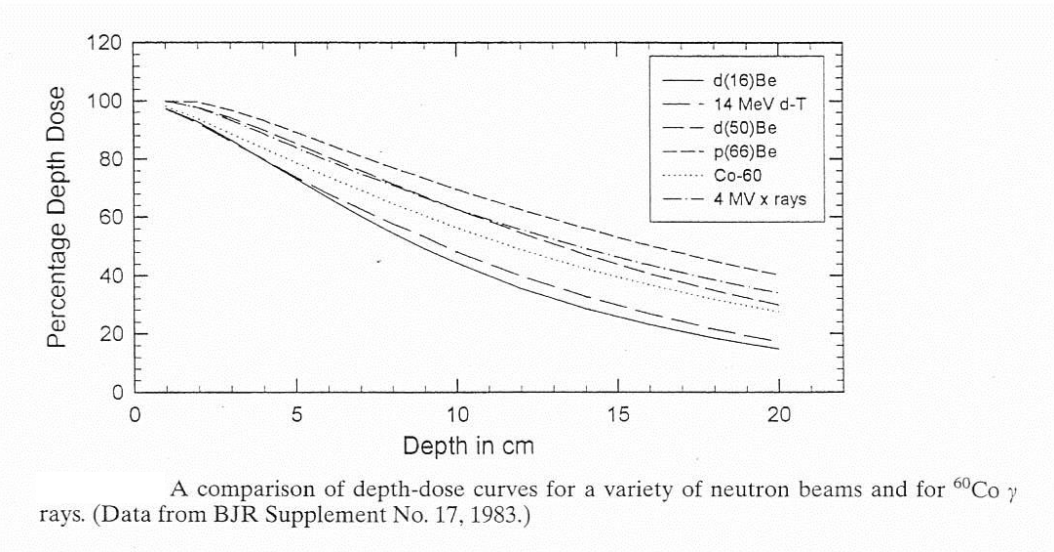
A fixed-modulation method produces a cylindrical treatment volume whose length is equal to the thickest part of the target volume. A compensator adjust the penetrating depth laterally across the target in such a way that the dose falloff region at the distal peak conform with the distal surface of the target. Much normal tissues upstream of the target are irradiated in this method. The fixed-modulation method is now employed at practically all heavy charged-particle facilities.

Fast Neutrons: Physics

- Produced via (p,n) or (d,n) reactions on Be targets.
- Depth-dose curves similar to high-E photons.
- Ionization and dose are through recoil protons from neutron collisions with H nuclei and recoil nuclei.
- Neutron beams behave as high-LET radiation:
  - Interaction through elastic scattering:
    - X(n,n)X:n+X → n+X
  - Inelastic scattering:
    - X(n,b)Y:n+X → X* → Y + b

$$^{9}\mathrm{Be}(p,n)\,^{9}\mathrm{B}: {}^{1}\mathrm{p} + {}^{9}\mathrm{Be} \rightarrow {}^{9}\mathrm{B} + {}^{1}\mathrm{n}$$

$$^{9}\mathrm{Be}(d,n)\,^{10}\mathrm{B}: {}^{2}\mathrm{d} + {}^{9}\mathrm{Be} \rightarrow {}^{10}\mathrm{B} + {}^{1}\mathrm{n}$$



A comparison of depth-dose curves for a variety of neutron beams and for ^{60}Co γ rays. (Data from BJR Supplement No. 17, 1983.)

For 15 MeV neutrons:

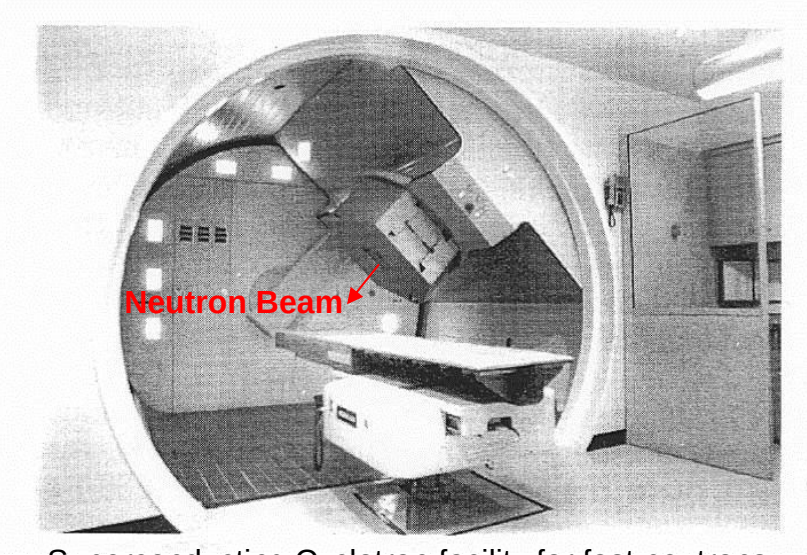
97.8% elastic : 84.1% with ^{1}H, 10.3% with ^{16}O, 2.4% with ^{12}C, and 0.95% with ^{14}N.

2.2% inelastic: ^{16}O(n,n')α, ^{16}O(n,n'), ^{1}H(n,γ) and ^{16}O(n,α)

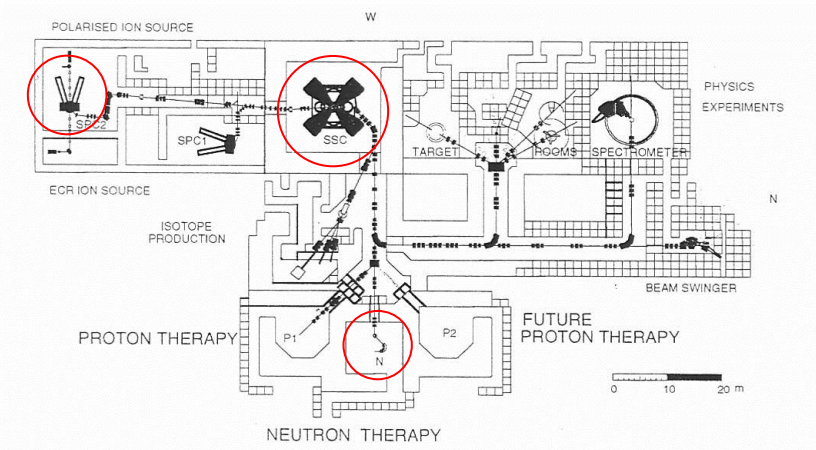
b: recoil p, α, ^{12}C, ^{14}N and ^{16}O

Fast Neutrons: Biology

- Ability to overcome the adverse effects of hypoxia in tumors.
  - Low impact on well oxygenated healthy tissue.
  - Eliminates hypoxic tumor cells better.
- Neutron RBE is very high for:
  - well differentiated slowly growing tumors.
  - tumors with high capacity for repair of SLD and PLD (melanomas).
- Clinical Applications:
  - Adenoid cystic carcinoma of salivary glands (RBE=8 for neutrons).
  - Bone and cartilage cancers.
  - Prostate adenocarcinoma.
  - Malignant melanoma.
  - Non-small cell lung cancer.



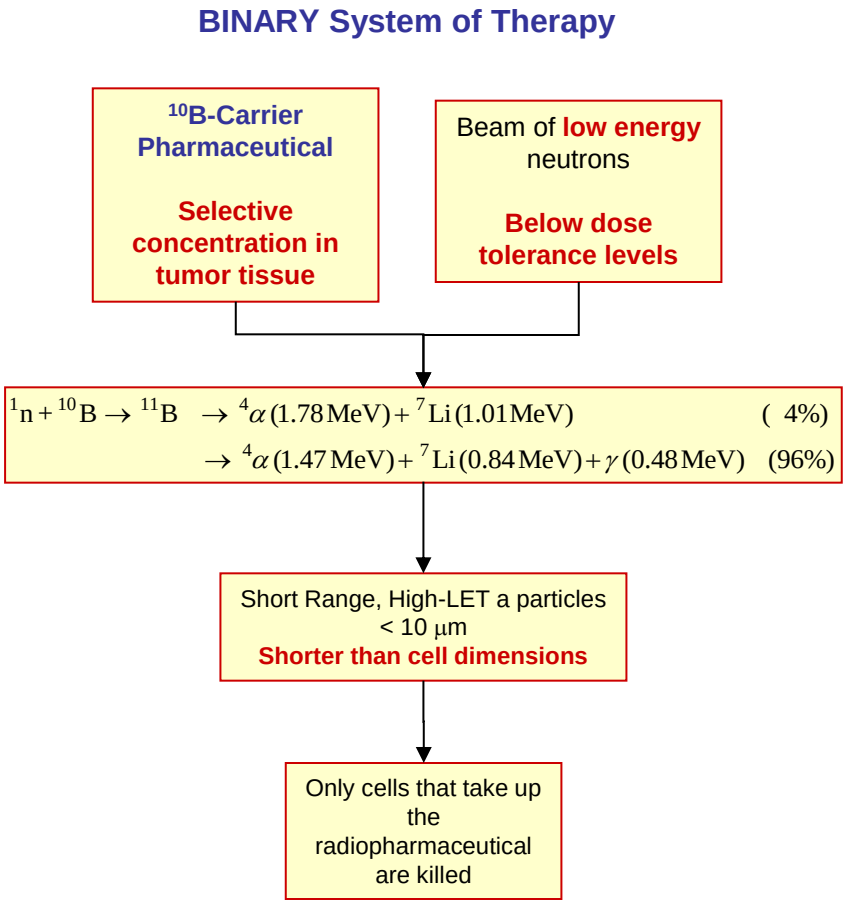
Superconducting Cyclotron facility for fast neutrons at Harpers Hospital, Detroit



National Accelerator Centre in Faure, South Africa. The accelerator facility has a fast neutron treatment room (N) with an isocentric gantry and a proton beam treatment room (P1).

Boron Neutron Capture Therapy (BNCT) (1)

- Basic idea introduced by G. Locher in 1936 !
- (Boron) Neutron Capture Therapy ((B)NCT):
  - **Teletherapy**: attempts to reach **all** cancer cells with sufficient radiation dose by irradiating a target volume.
  - **NCT (BNCT)**: The role of "finding" the cancer cells is left to the (^{10}B)-carrying pharmaceutical.
- Binary System:
  - Each component can be manipulated independently.
  - The interval between injection and irradiation is tailored so that:
    - **Highest differential** in ^{10}B concentrations in tumor and normal tissue.
    - **Collimation** of neutron beam to hit only target volume rich in ^{10}B and spare normal tissue also rich in ^{10}B.

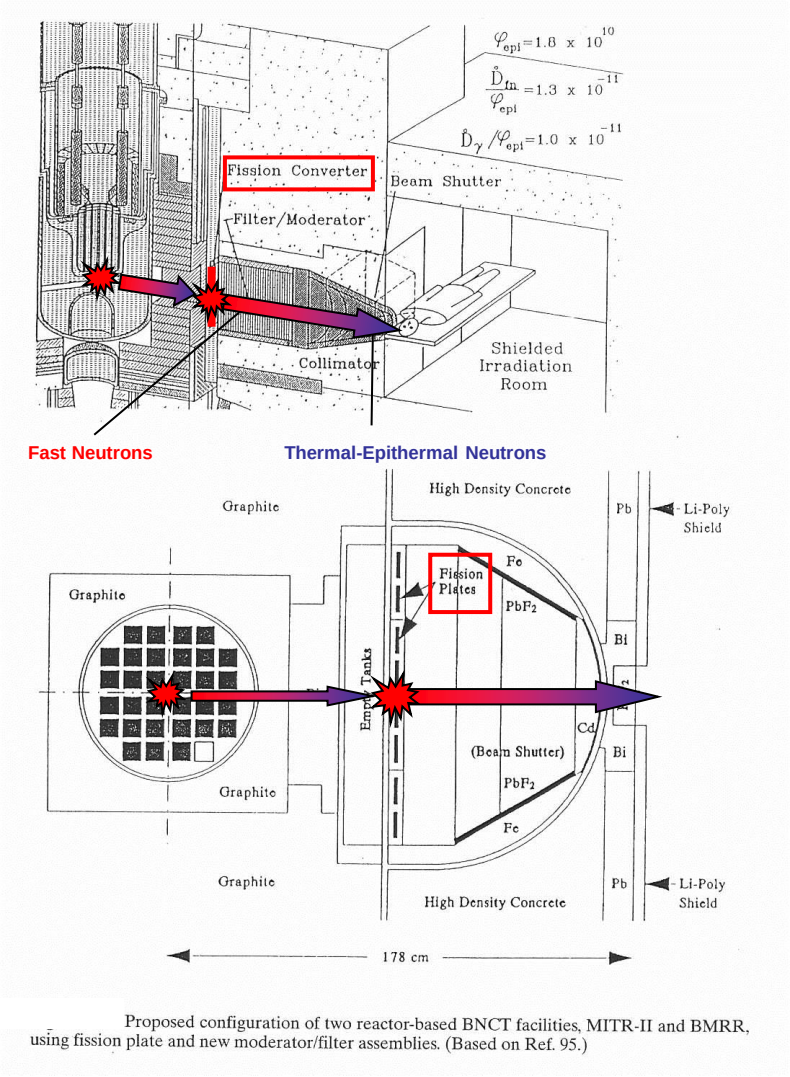


Boron Neutron Capture Therapy (BNCT) (2)

- Success depends on:
  - Tumor selectivity to the ^{10}B carrier:
    - Sodium tetraborate (borax), concentrates in the blood: NO!
    - BSH (sodium borocaptate)
    - BPA (boronophenylalanine)
  - Availability of a neutron beam of suitable energy and sufficient intensity.

Table 7.3. Concentration of ^{10}B in tumor, tumor/normal tissue ratio, and tumor/blood ratio for BSH and BPA compounds

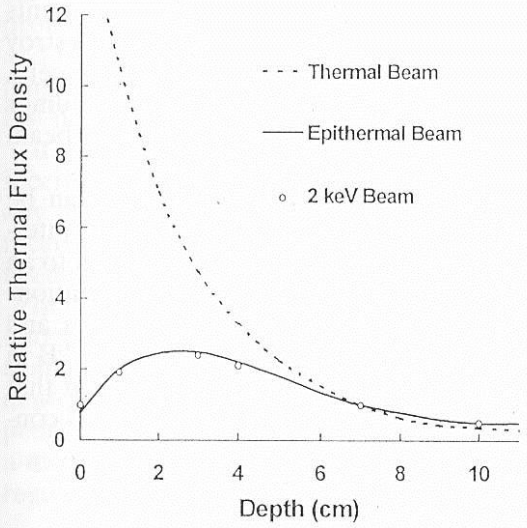
	Concentrations of ^{10}B in tumor (ppm)	Tumor/normal tissue ratio	Tumor/blood ratio
BSH	3–20	>10	~1
BPA	15–45 and higher	2–4	3–5



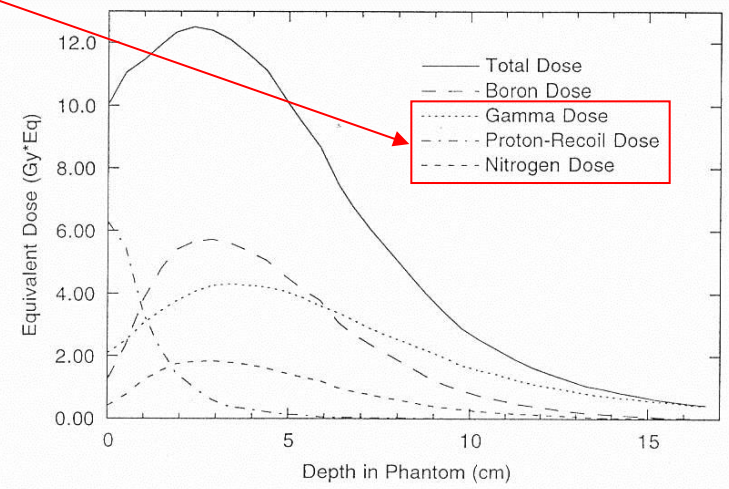
Proposed configuration of two reactor-based BNCT facilities, MITR-II and BMRR, using fission plate and new moderator/filter assemblies. (Based on Ref. 95.)

Boron Neutron Capture Therapy (BNCT) (3)

- Uses thermal and epithermal neutrons:
  - Thermal neutrons have poor penetration in tissue.
  - Epithermal neutrons can reach deeper lesions.
- Background Dose from:
  - Neutrons not captured.
  - Fast neutrons.
  - H and N neutron absorption.
- BNCT sources can be:
  - Nuclear reactors.
  - **Accelerators:**
    - $^{7}Li(p,n)^{7}Be$ with 2.5MeV p.
    - Public acceptance and energy spectrum flexibility.



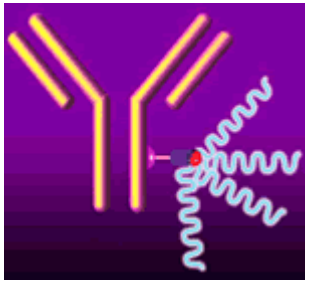
Thermal neutron flux density in head phantom for thermal and epithermal neutron beams. (From R. G. Fairchild and V. P. Bond, *Int. J. Radiat. Oncol. Biol. Phys.* **11**, 831-840, 1985.)

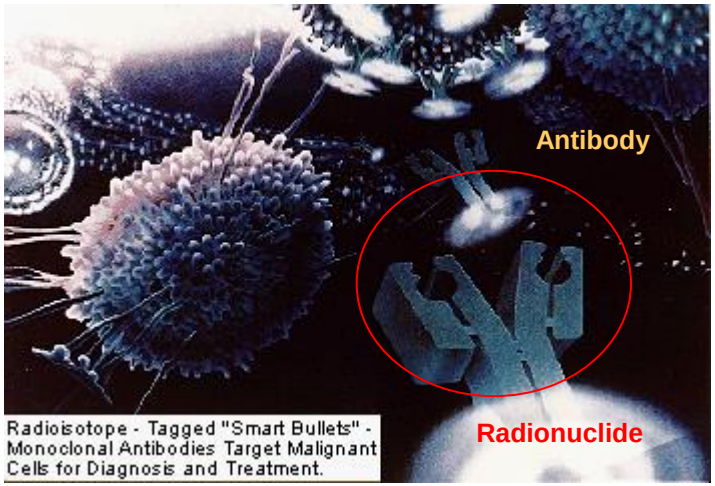


Normal-tissue depth-dose curves in a phantom for epithermal neutrons produced by $^{7}Li(p,n)$ reaction of 2.4 MeV protons and using an Al/AlF_3 moderator assembly. Boron dose, gamma dose, proton-recoil dose, nitrogen dose, and the total dose are shown as a function of the depth in phantom.

Radioimmunotherapy: Basics

- **Radioimmunotherapy** (**RIT**) utilizes an **antibody** labeled with a **radionuclide** to deliver **cytotoxic** radiation to a target cell.
- The antibody has **specificity** for a tumor-associated antigen.
  - The antibody binds specifically to a tumor-associated antigen.
  - This increases the dose delivered to the tumor cells while decreasing the dose to normal tissues.
- By its nature, RIT requires a tumor cell to express an antigen that is **unique** to the neoplasm or is not accessible in normal cells.
- Elements crucial for the success of RIT are:
  - Target antigen
  - Antibody selectivity
  - Choice of isotope
  - Stability of antibody-isotope linkage





Radioimmunotherapy (RIT) provides an opportunity to deliver more specific radiation to tumor cells while sparing normal tissue. This new medical technology capitalizes on the knowledge accumulated by microbiologists about cell-level interactions inside our bodies. The power of radiation to kill cancer cells has been known for years, but the precise science of targeting cancer cells with specific proteins and packaging the radiation for direct delivery has taken time to create. The potential for treating cancer and other diseases with RIT technology is immense. While the process itself is still in its infancy, some very promising results have been achieved.

Radioimmunotherapy: Dosimetry

- Mean dose to target organ *t:*

$$D_{t\leftarrow s}[\text{rad}] = S_{t\leftarrow s}\left[\frac{\text{rad}}{\mu\text{Ci h}}\right] A[\mu\text{Ci h}]$$

Target organ source matrix
dose from organ s on target t

Cumulated activity in organ s

- *Non-penetrating radiation:*

$$S_{np} = (1/m)\,2.13 \sum_{i=0,n} f_i E_i$$

Energy

Probability of emission

  - *np radiation cannot escape from target volume due to short range.*

- *Penetrating radiation:*

Absorbed fraction

$$S_p = (1/m)\,2.13 \sum_{i=0,n} f_i E_i \varphi_i$$

- *Pharmacokinetic data necessary to:*
  - *Estimate doses (organ-tissue accumulation).*
  - *Test distribution of radiopharmaceutical.*

A Partial List of Radionuclides Used in Internal Emitter Therapy

Radionuclide	Half Life	E_β max (MeV)	E_γ (MeV)
^{32}P	14.3 d	1.70	None
^{64}Cu	12.9 h	0.57 (β^-); 0.66 (β^+)	0.510 (38%)
^{67}Cu	61 h	0.57	0.180 (40%)
^{89}Sr	50.5 d	1.46	
^{90}Y	64.3 h	2.3	
^{117m}Sn	13.6 d	0.13; 0.16	0.158 (87%)
^{131}I	8.1 d	0.61	0.365 (81%)
^{153}Sm	1.9 d	0.81	0.103 (29%)
^{186}Re	3.8 d	1.07	0.137 (9%)
^{188}Re	17 h	2.12	0.16 (10%)
^{177}Lu	6.8 d	0.50	0.21 (6%)

Note: All beta emissions are for electrons except in the case of ^{64}Cu, which emits both electrons and positrons.

Radioimmunotherapy: Tracer Principle

Tracer Principle:

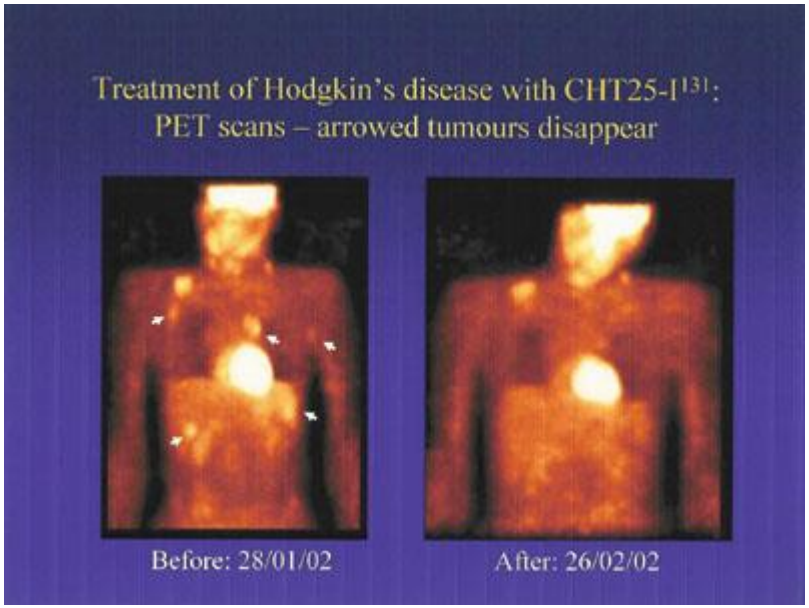
- A relatively small (tracer) amount of radiopharmaceutical can be use to predict the spatial and temporal distribution of a larger amount of the same radiopharmaceutical in the same patient.

$$\left[\frac{\text{rad}}{\text{mCi}}\right]_{therapy}^{tumor/organ} = \left[\frac{\text{rad}}{\text{mCi}}\right]_{diagnostic}^{tumor/organ}$$

- Information from the tracer study is used to compute therapy amount.

Distribution mapped through imaging techniques:

- SPECT, PET.
- Anger camera, whole body retention.

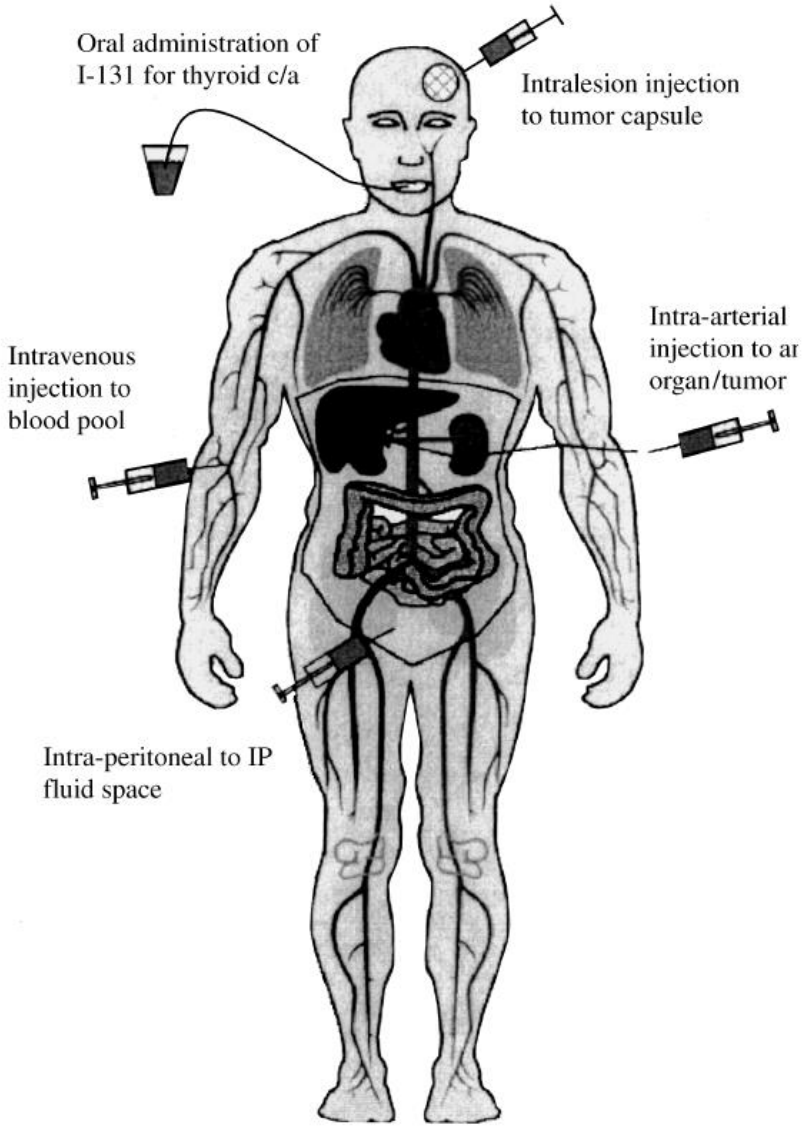


This is the PET image of the Hodgkin's patient before treatment with CHT25I131. PET images are generated using radiolabeled glucose and this is taken up by active tissues and most cancer. The very intense uptake at the top and in the middle are normal and represent the uptake in the brain and radioactivity in the heart. There are however a number of active sites. This is the pre-treatment scan

Source: www.marcfishertrust.org.uk/

Radioimmunotherapy: Clinical Aspects (1)

- Method of delivery:
  - Radiation protection measures are necessary.
  - Gloves and protective glasses.
  - Syringes in shielded pumps.
  - All couplings must be leak-proof.
  - All spills must be on absorbing pads.
  - Several routes of administration possible.
- Patient needs special handling.
  - Dosimetry estimates after administration.
  - Isolation from medical personnel.
  - Especial precautions with body fluids.
- Applications: currently, RIT (e.g. ibritumomab tiuxetan) is used to treat :
  - non-Hodgkin's lymphoma.
  - prostate cancer, ovarian cancer.
  - metastatic melanoma.
  - neoplastic meningitis.
  - leukemia, high-grade brain glioma, and metastatic colorectal cancer.



Routes for administration of radiopharmaceuticals to a therapy patient.

Radioimmunotherapy: Clinical Aspects (2)

Pre-Study Patient Evaluation for Radioimmunotherapy

- History and physical exam
- Histologically confirmed diagnosis of antigen presence on tumor by histology or imaging study. Blood assay may be used if antigen is shed.
- Chest X-Ray, Ultrasound, CT scan or MRI scan for lesion size
- Biochemical Profiles;
  - Complete blood count (CBC)
  - Chemistry Screen
  - Urine Analysis
  - Prothrombin Time (PT)
- Pregnancy test if applicable
- Signed informed consent
- Baseline Human Anti-Mouse Antibody (HAMA) or other appropriate human antibody

Radiation Safety Guidelines for Patients Receiving Radionuclide Therapy

- Admit patient to single room
- Cover floor near toilet with absorbent pads; use pads for any procedure where contamination is likely.
- Cover traffic areas with absorbent pads
- Cover door knobs, bed controls, and telephone handset with plastic wrap
- Confine patient to room except for special medical procedures
- Radiation placard on door
- Principles of time, distance, and shielding applied
- No visitors under 18 years of age.
- No pregnant visitors
- Universal precautions
- Assume all body fluids are radioactive
- Gloves and sharps disposed in container in patient's room
- Flush toilet three times after each usage
- Isolation trays used
- Contaminated non-disposable materials stored in isolation until decay (10 half-lives).
- Specimens leaving room monitored for contamination.
- No housekeeping until patient discharged and room cleared by RSO or Staff Physicist

Literature

- 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).
- L. E. Williams et al., “A Primer for Radioimmunotherapy and Radionuclide Therapy”, American Association of Physics in Medicine report No.71 (2001); http://www.aapm.org/pubs/reports/rpt_71.pdf