General Principles of Radiation Oncology

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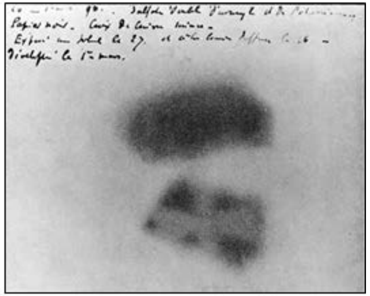
Overview

- Basics of radiation therapy
  - History
  - Mechanism
  - Particle types: photons, protons, neutrons, heavy ions
- Definition of common lingo
  - IGRT, IMRT, VMAT, SBRT, SABR, CyberKnife, Gamma Knife
- A few specific clinical points of interest
  - Palliative RT
  - Hypofractionation
  - Protons
- What’s on the frontier
  - Metastatic cancer treatment
  - MR-guided RT
  - FLASH

Radiation Oncology: A Brief History

- **1895** – Röntgen discovers x-rays (Nobel Prize 1901)
- **1896** – First patients with cancer treated with x-rays by Emil Grubbe in Chicago and Victor Despeignes in France
- **1896** – Becquerel discovers natural radioactive decay. Marie and Pierre Curie further characterize radioactive compounds. (All three win Nobel Prize in 1903)
- **1901** – First use of brachytherapy
- **1952** – First “linear accelerator” used for treatment (USA in 1957)
- **1967** – Invention of the Gamma Knife
- **1970s** – Computed Tomography (CT)
- **1980s** – Intensity modulated radiation treatment (IMRT), Proton therapy
- **2000s** – Image-guided RT (IGRT), MR-based RT



Marie Curie (1867-1934)

Radiation Oncology: A Brief History

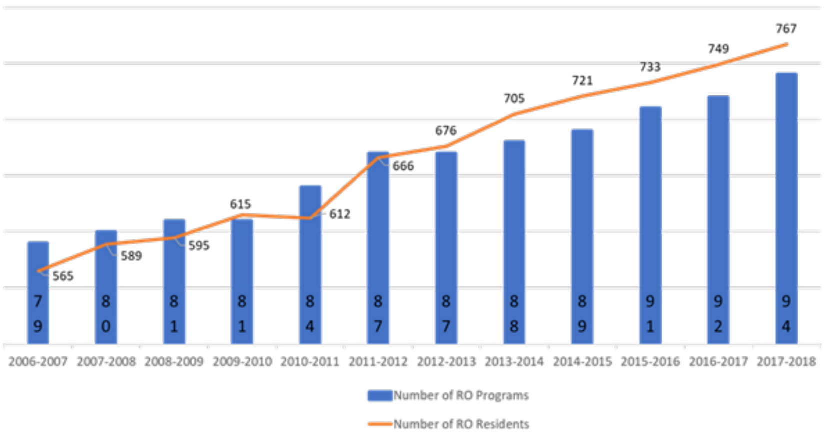
- Cyclotron (Ernest Lawrence, UC Berkeley)
- Linear Accelerator (Henry Kaplan, Stanford)

Radiation Oncology: A Brief History

- Treatment of malignant <u>and</u> non-malignant conditions
  - Tinea capitis
  - Tonsillitis
  - Enlarged thymus
  - Ankylosing spondylitis
  - Acne
  - Peptic ulcers
  - Keloids
  - Heterotopic ossification prophylaxis
  - Graves opthalmopathy
  - Orbital pseudotumor
  - Dupuytren's disease
  - Gynecomastia

Radiation Oncology: A Brief History

- Radiation oncologists initially trained as diagnostic radiologists and then pursued “Therapeutic Radiology” afterwards
- Still under American Board of Radiology, American College of Radiology, etc.
- 1970’s: dedicated radiation therapy residency programs began to proliferate



“Allied Disciplines”

One of the tines in the trident of oncology

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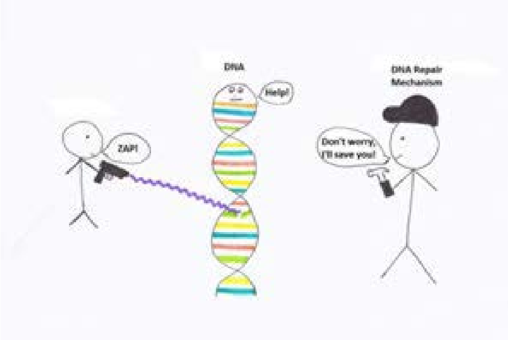
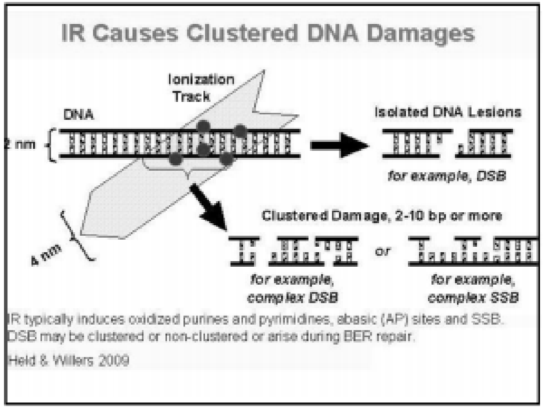
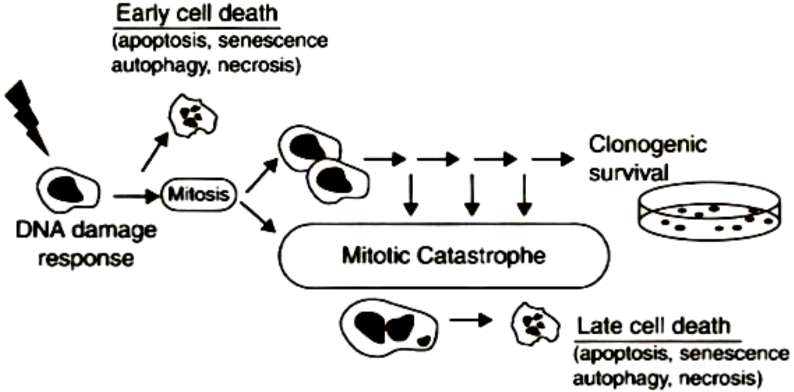
Radiation Biology 101

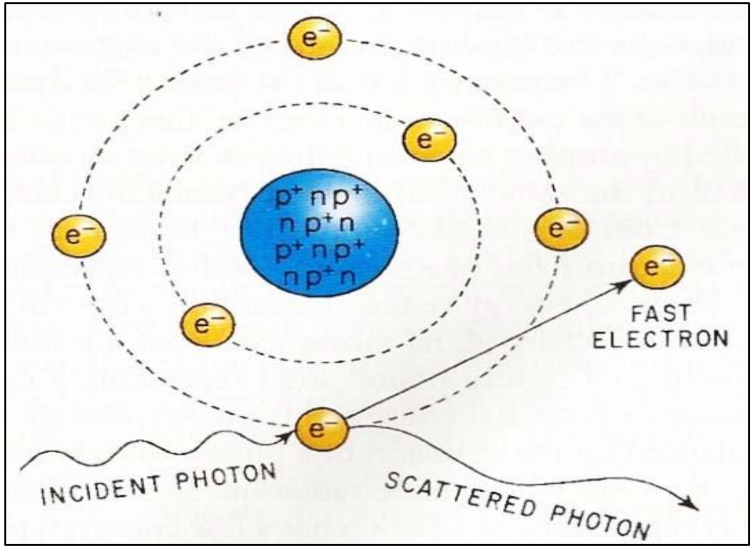


- Radiation treats cancer by directly killing tumor cells
- DNA damage → Mitotic catastrophe
- Preferentially affects rapidly proliferating cells
- Tumor Control Probability based on dose-dependent killing of all cells in a tumor

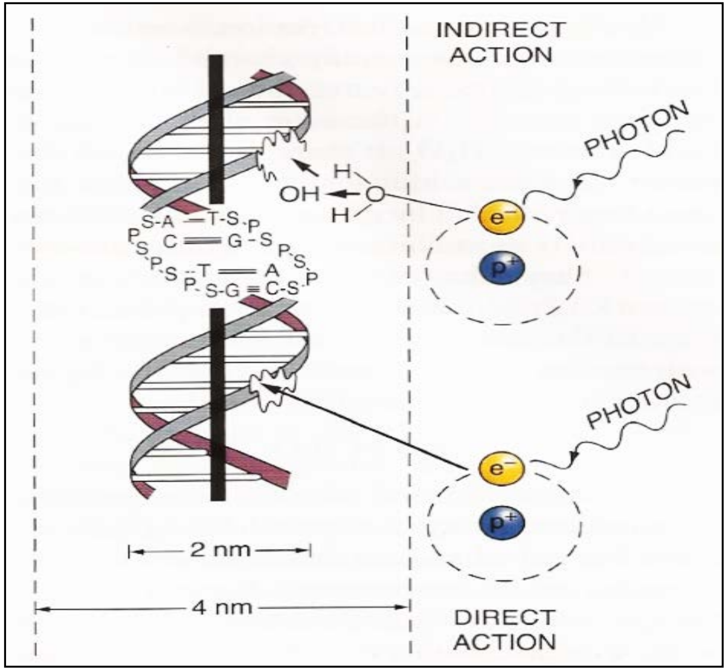




Radiation Oncology: Mechanism



Hall Figure 1.6



Hall Figure 1.8

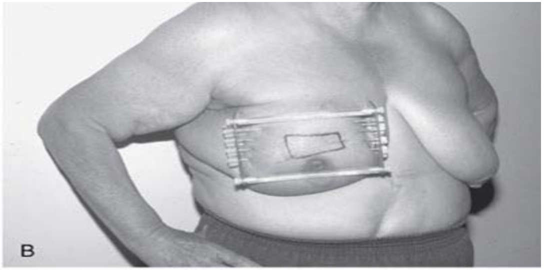
Radiation Oncology: Mechanism

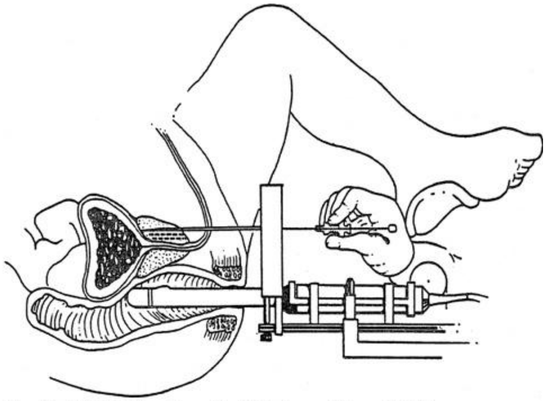
- Radiation's primary effects have been thought to be mediated by DNA damage leading directly to cell death
- However, other mechanisms may be more important than we originally realized as well...
  - Effects on vasculature, especially tumor vasculature
  - Very high dose or high LET radiation may affect cell membrane integrity and protein structures
  - Modulation of the immune response

Different RT Options and Definition of Common Lingo

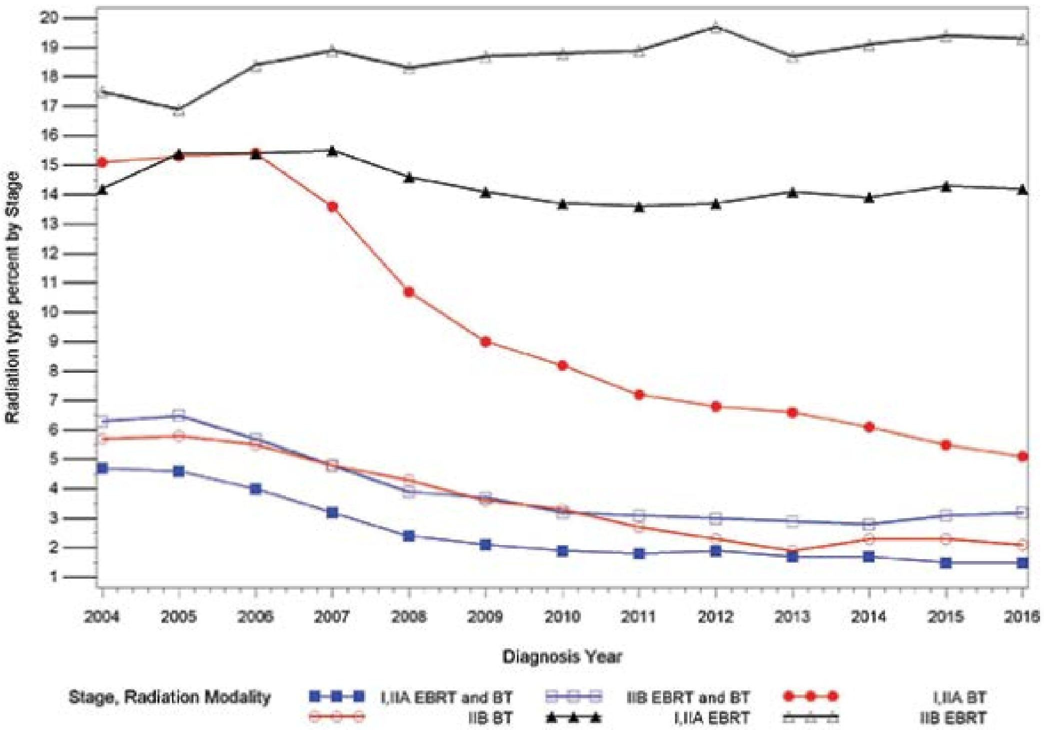
Radiation Oncology: Brachytherapy

- Brachytherapy
  - Low dose rate = < 2 Gy/hr
  - High dose rate = > 12 Gy/hr
  - Pulsed dose rate (uncommon) = 2-12 Gy/hr





Brachytherapy: A Dying Art?



External Beam Radiation Treatment Options

- The linear accelerator or LINAC

Modality	Energies
Photons	6, 10, 15, 18
MV	
Electrons	6, 9, 12, 16
MeV	

- 3DCRT, IMRT, IGRT, VMAT, SBRT, SABR, SRS
- Gamma Knife
- Cyberknife
- Tomotherapy

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Common RT Terms

3DCRT - 3-D conformal RT

IMRT - intensity modulated RT

VMAT - volumetric modulated arc therapy

IGRT - image-guided RT

SBRT - stereotactic body RT

SABR - stereotactic ablative radiation

SRS - stereotactic radiosurgery

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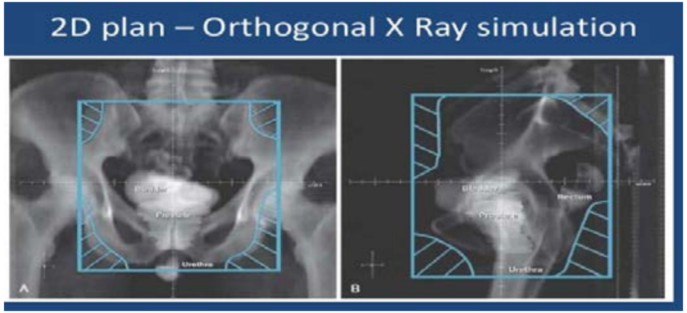

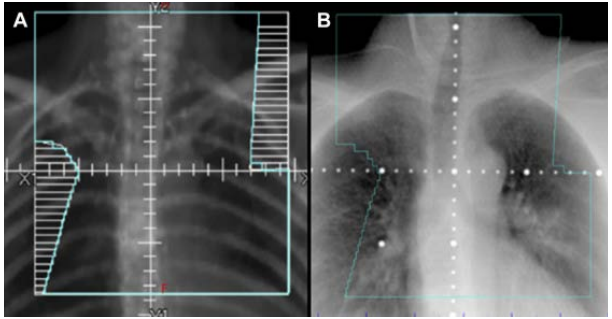

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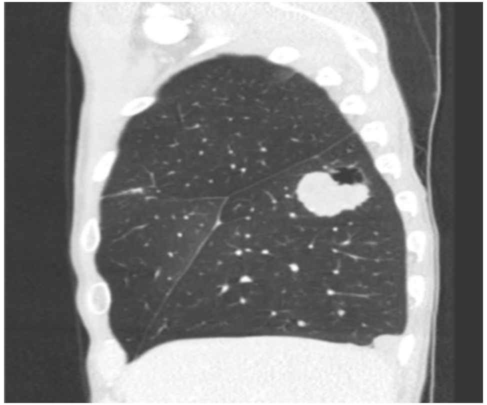

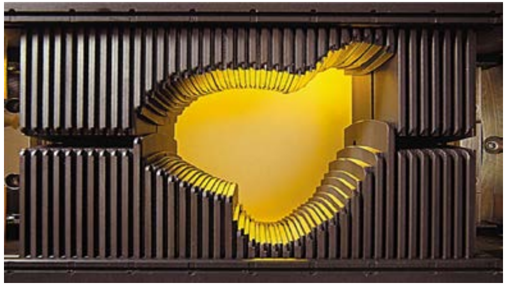

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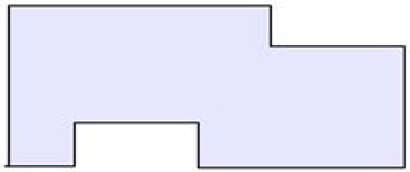
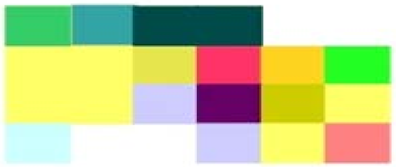


Geometrical Field shaping



With intensity modulation

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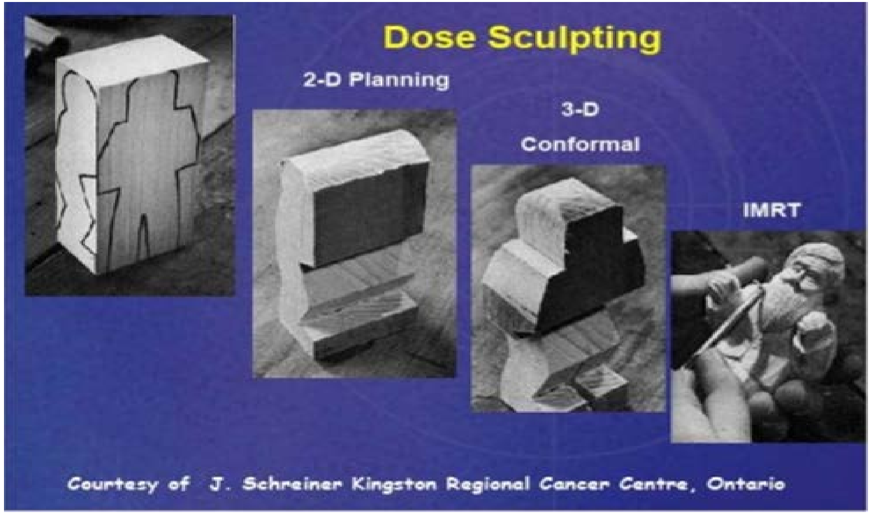

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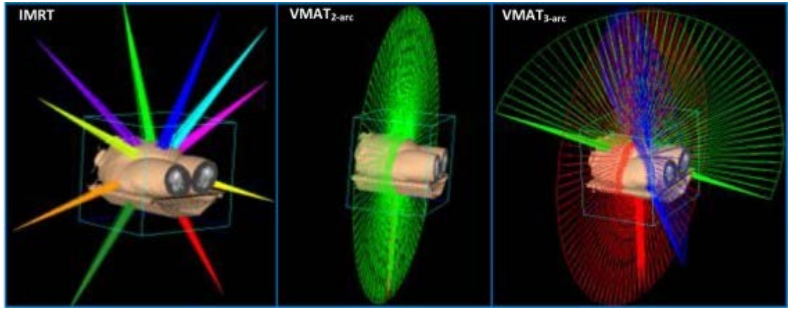

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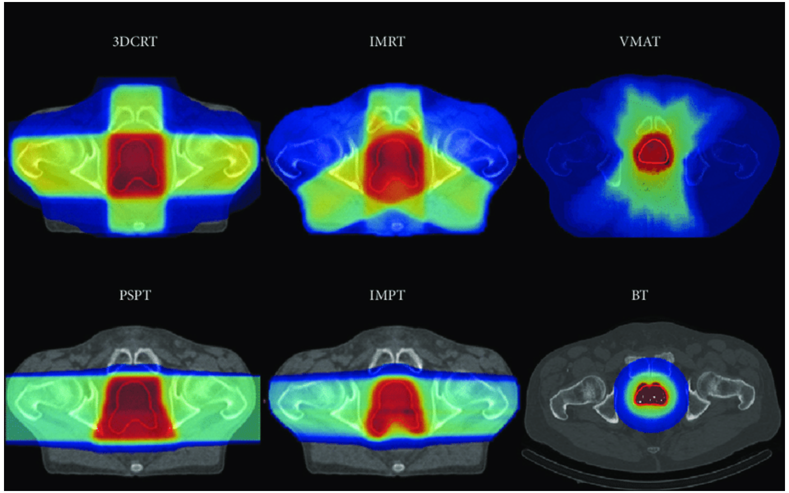

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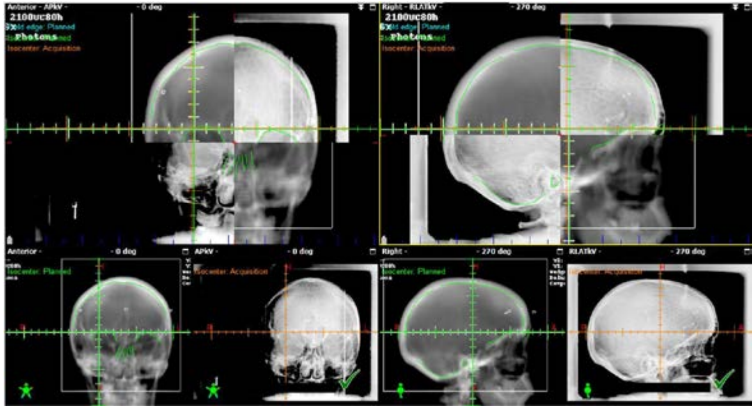

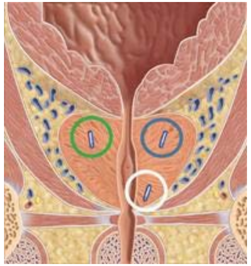

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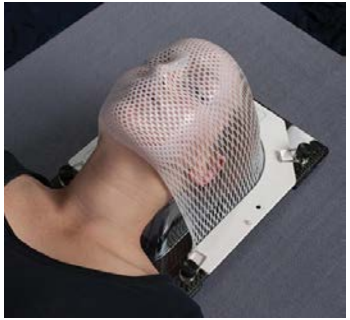
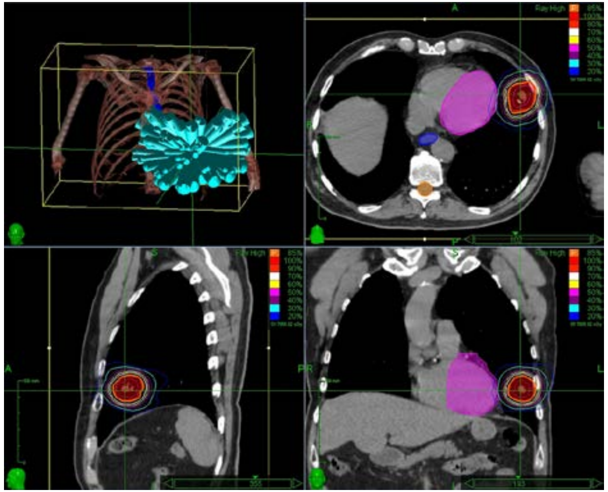
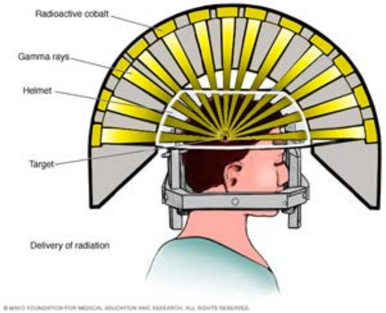
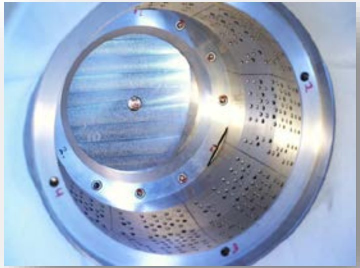




Radiation Treatment Machines: Gamma Knife

- Radiosurgery
  - Single high-dose radiation fraction
  - Very conformal (i.e. tight margins)



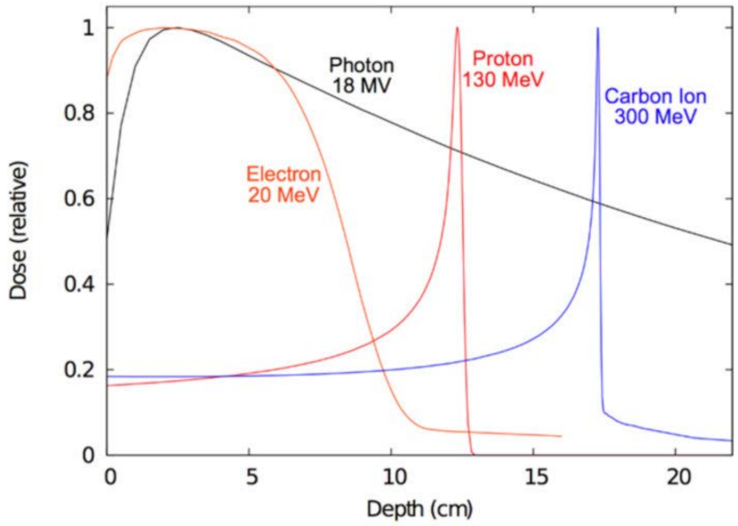


Radiation Treatment Machines: CyberKnife

Radiation Treatment Machines: Tomotherapy

Radiation Oncology: Particle Options

- Particle therapy
  - Photons
  - Electrons
  - Protons
  - Neutrons
  - Heavy ions



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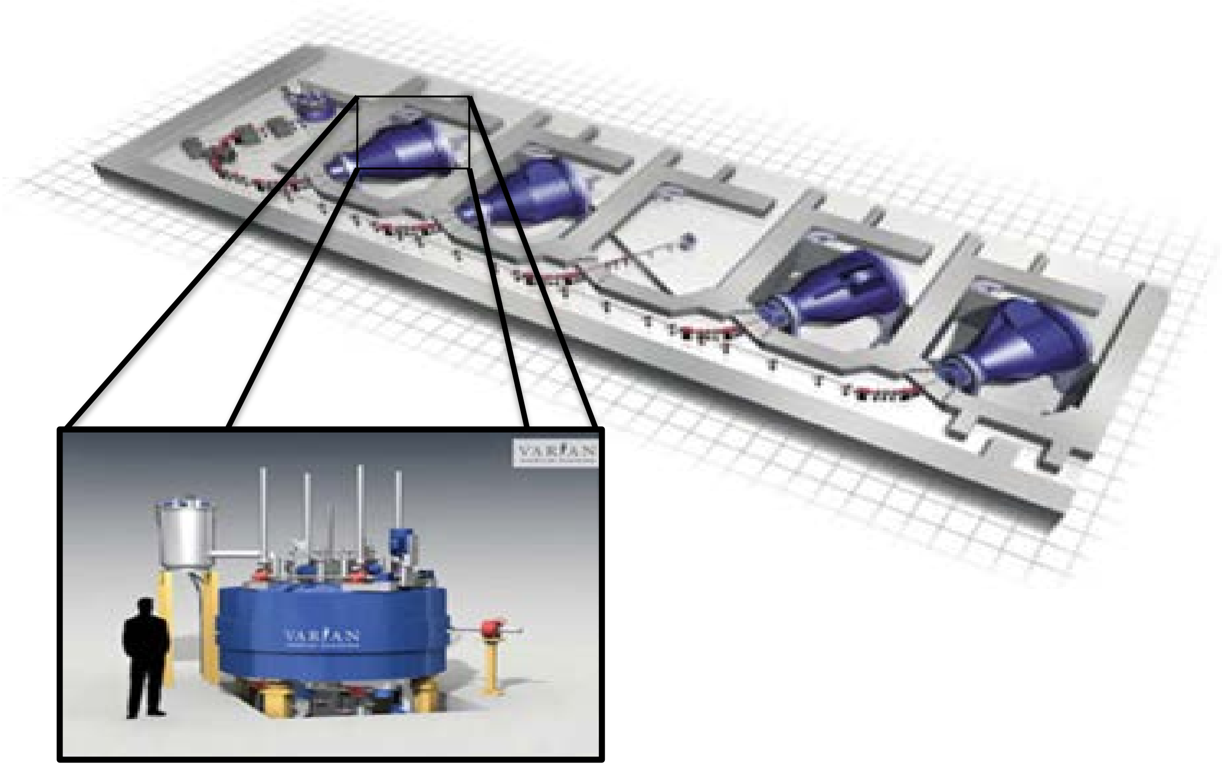
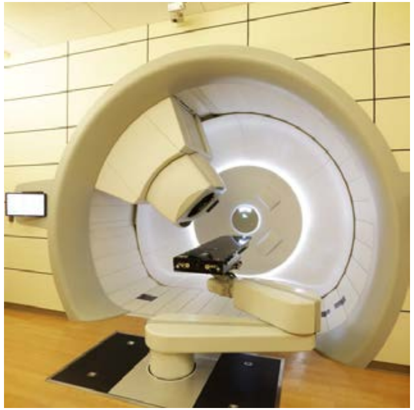
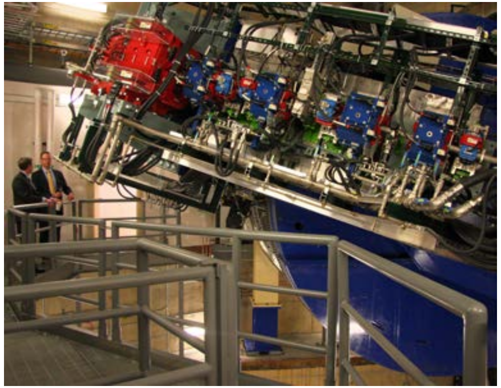
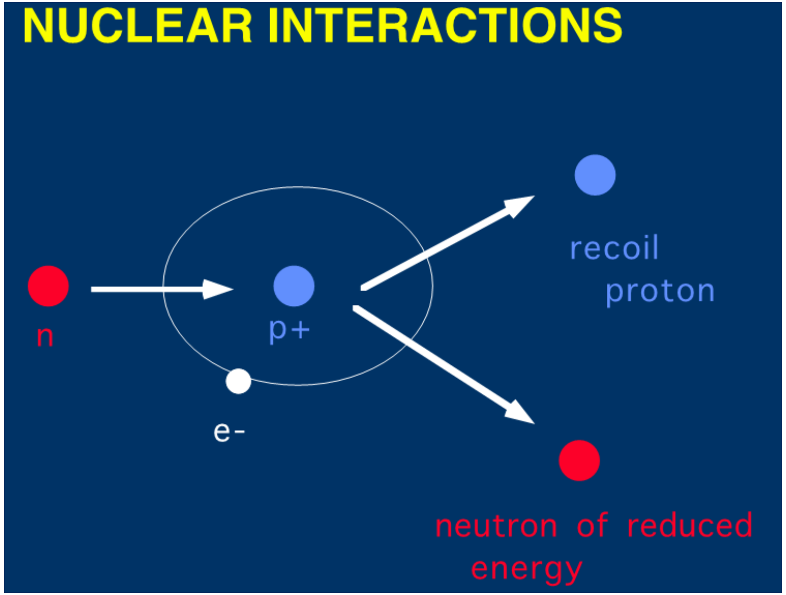






Radiation Treatment Machines: Neutrons

- Potentially lower toxicities
- Better able to kill hypoxic tumor cells
- Cells less able to repair radiation damage
- Less variation in radiosensitivity across cell cycle
- Potentially greater non-traditional anti-cancer mechanisms



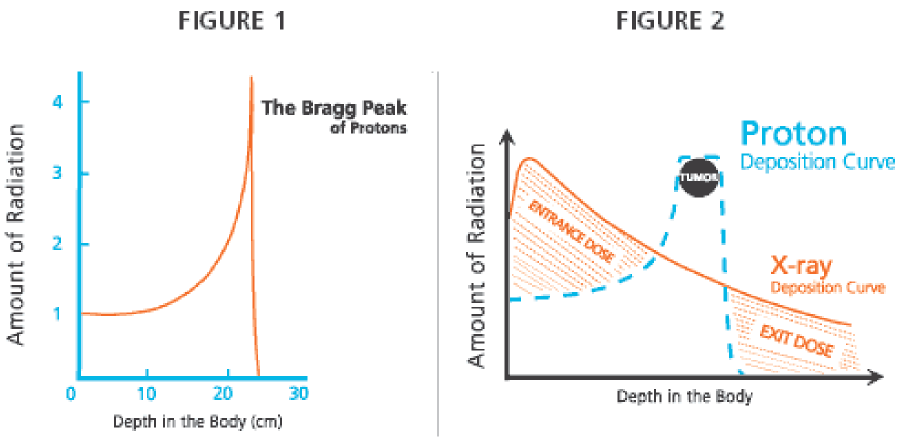
A Few Clinical Points of Interest

What is the Deal with Protons?

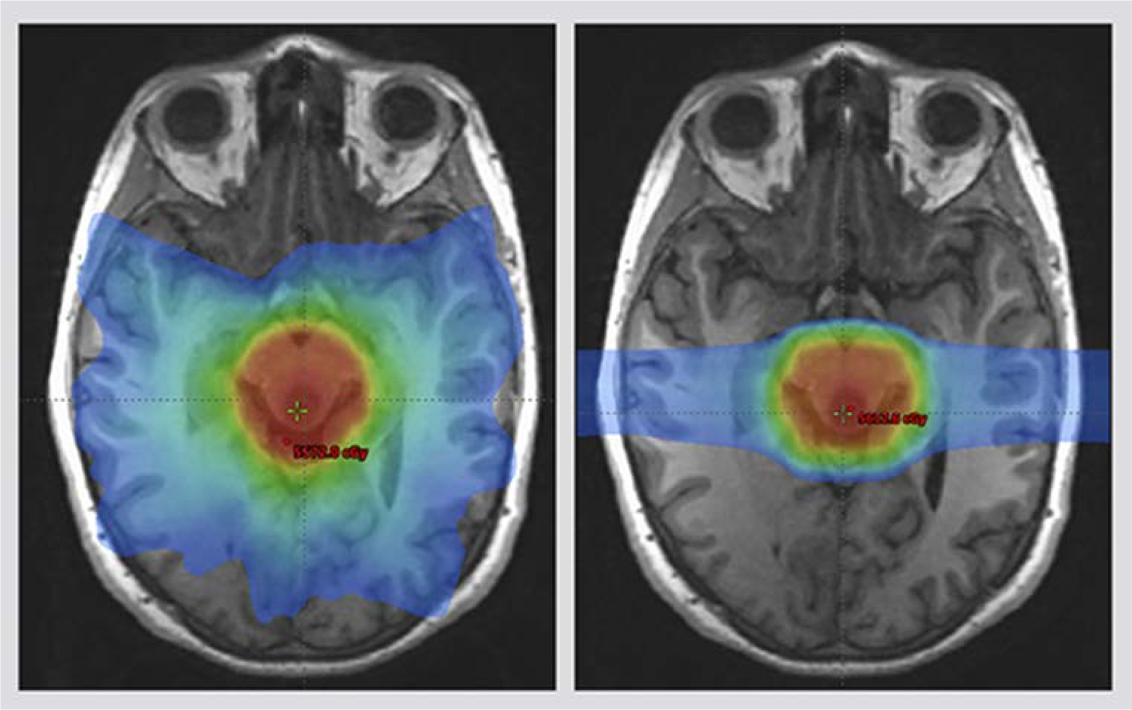
- Proton radiation is a type of radiation
- FDA approved technology 1988
- Delivers radiation to tumors while reducing radiation exposure to surrounding normal tissues
- Confers a clinical advantage for some patients compared to conventional X-ray (photon) treatment
- Another tool for the radiation oncologist
- Useful only when radiation therapy is indicated

What is the Deal with Protons?

- Unique dose depth profile due to the Bragg peak
- Spread-out Bragg peak used to treat a clinical volume (overlap individual proton beams of variable intensities)



Proton Therapy



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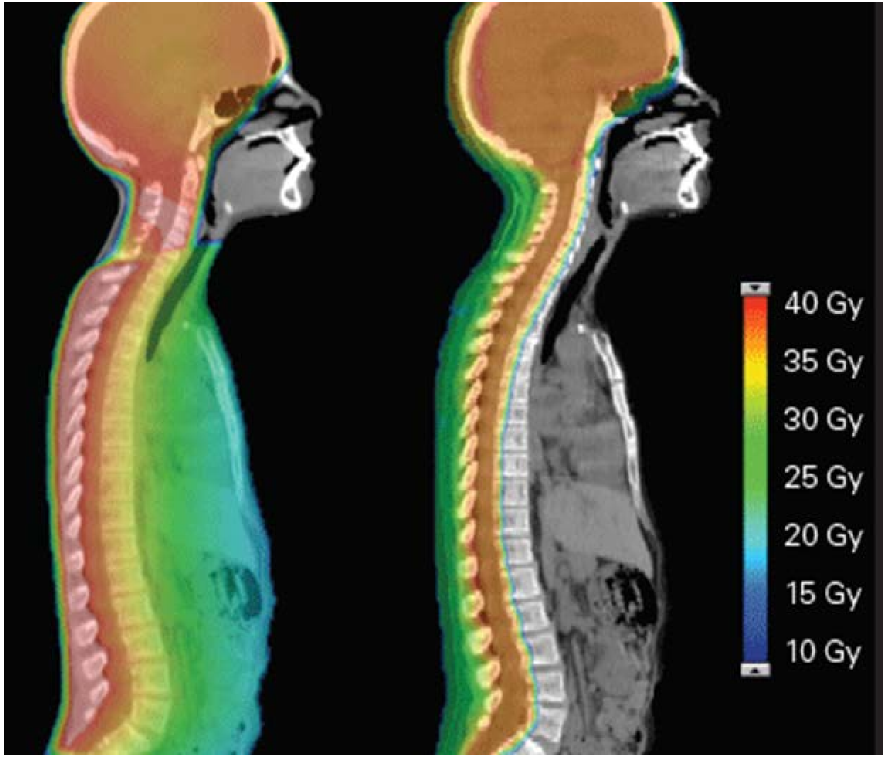

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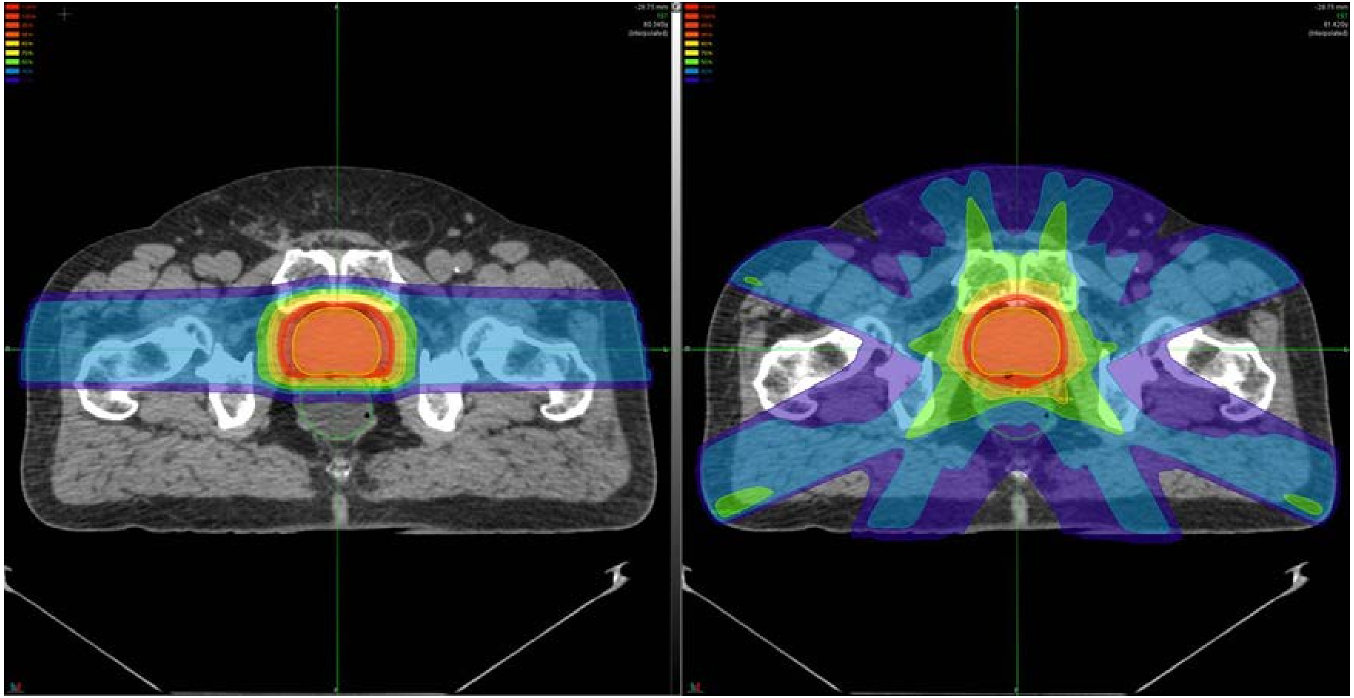


Proton Therapy

Proton Therapy

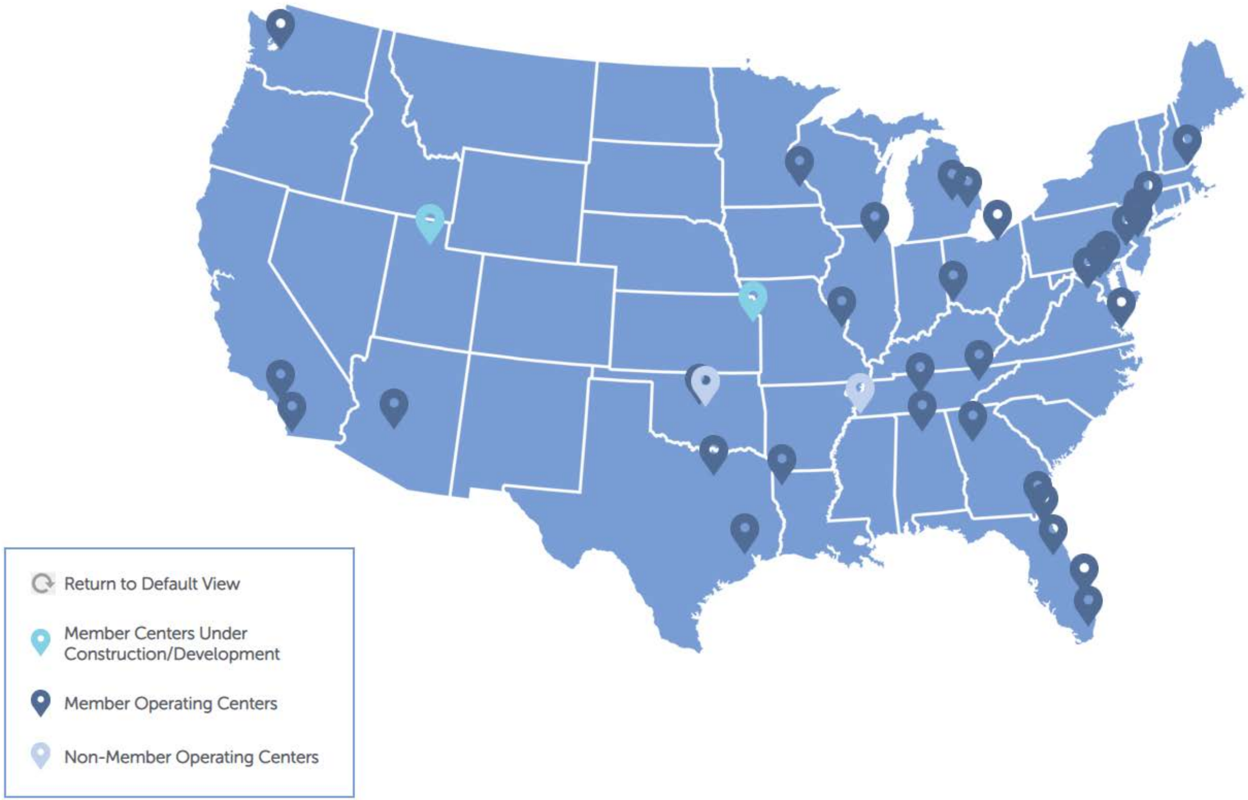
ASTRO Group 1

- Ocular tumors
- Base of skull tumors
- CNS tumors, including spinal tumors near the cord
- HCC
- Pediatric tumors
- Patients with genetic syndromes with RT hypersensitivity (e.g. NF-1, Rb)
- T4 and/or unresectable H&N cancers
- Paranasal sinus tumors
- RP sarcomas
- Re-RT

ASTRO Group 2

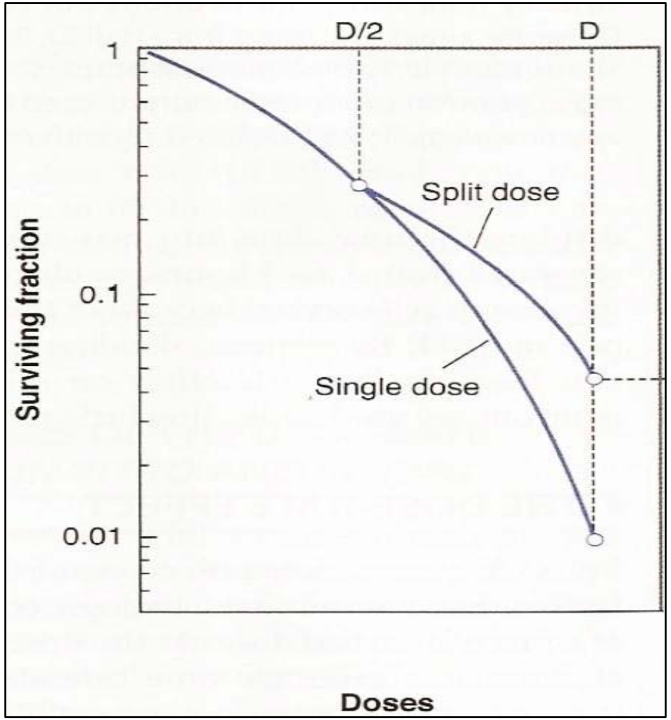
- Other H&N cancers
- Thoracic malignancies
- Abdominal malignancies
- Pelvic malignancies
- Prostate cancer
- Breast cancer

Proton Therapy Centers



Radiation Oncology: Fractionation

- Radiation therapy has traditionally been a “fractionated” treatment course spread over several weeks.
- Takes advantage of differential repair abilities of normal and malignant tissues.



Hall Figure 5.6a

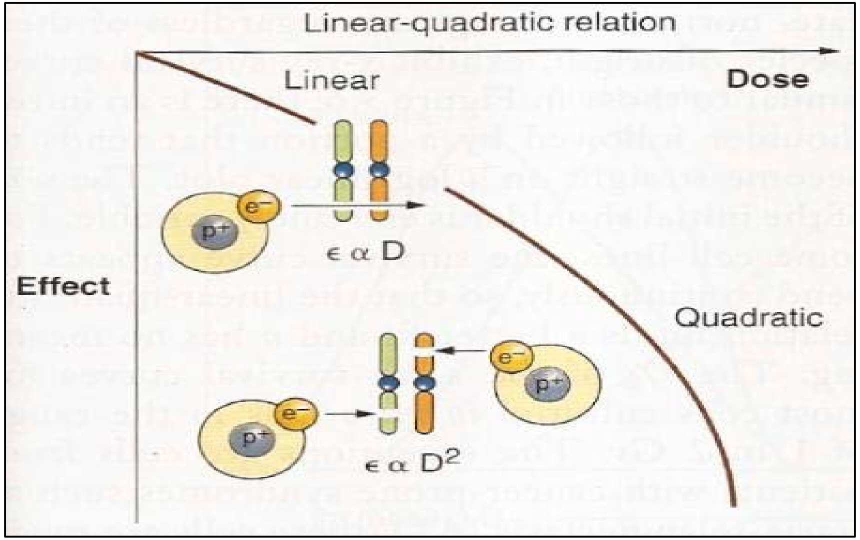
Radiation Oncology: Fractionation

- Regaud and The French Ram
  - A single dose of radiation that is sufficient to sterilize a ram also causes significant skin toxicity
  - If the same dose is delivered in several fractions, the ram is sterilized, but there is no skin toxicity
- 1920's – 1930's
  - Regaud – extended treatment time for uterine cancer improved outcomes
  - Coutard – fractionated treatment for head and neck cancer reduced toxicity with better outcomes

Hall Figure 23.1

Radiation Oncology: Fractionation

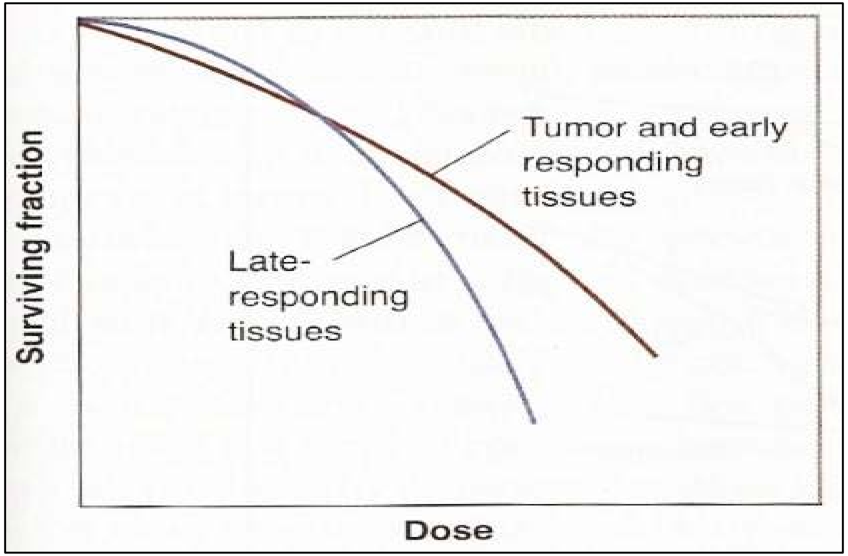
- Linear quadratic (α/β) model
  - Alpha = single hit kills
  - Beta = double hit kills



Hall Fig 3.5

Radiation Oncology: Fractionation

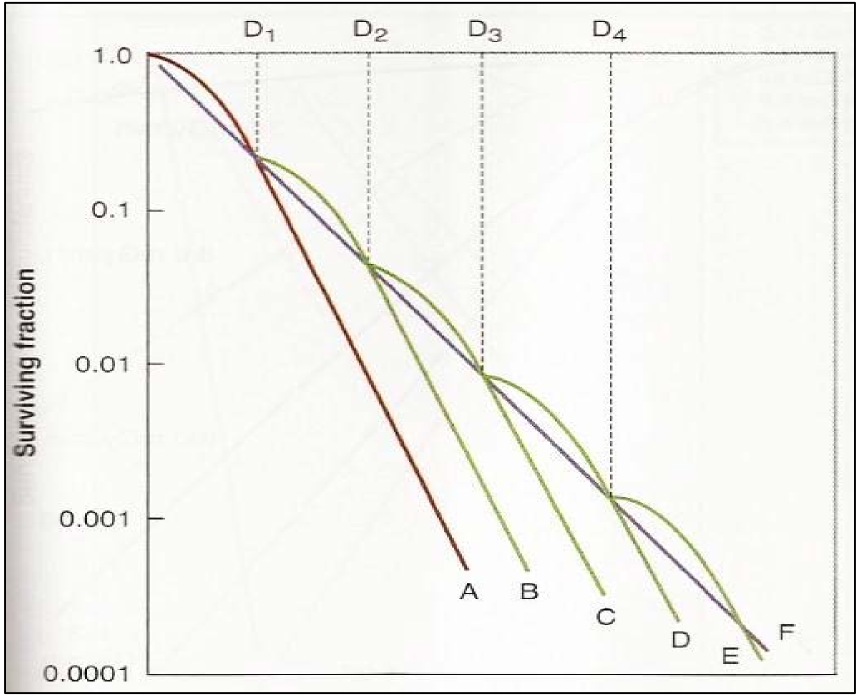
- Different cell lines, tissues, and tumors have different α/β values
  - α/β defines the dose of radiation at which the number of cells killed by a single hit equals the number killed by two hits
  - High α/β = most tumors, early responding normal tissues
  - Low α/β = late responding tissues, some tumors (eg. prostate)



Hall Figure 23.6

Radiation Oncology: Fractionation

- Radiation prescription can be modified to take advantage of different dose response curves.
  - Change number of fractions, keep same “biologically effective dose” (BED).
- BED = nd(1+d/[α/β])
  - n = number of fractions
  - d = dose/fraction



Hall Figure 5.8

Hypofractionation vs Hyperfractionation

- Hypofractionation
  - Convenience for patient
  - Potentially more effective for tumors with low a/B
  - E.g. prostate cancer, RCC
- Hyperfractionation / Accelerated
  - Potentially more favorable toxicity profile
  - May also be more effective for tumors with quick repopulation rates
  - E.g. head and neck cancers

Palliative RT

- 30 Gy in 10 fractions has been the standard for years
- 8 Gy in 1 fraction was directly compared to the standard in treating painful bone metastases
- No difference in rate of pain relief
- Higher rate of requiring re-treatment
- Other palliative situations
  - Bleeding
  - Radioresistant tumors
  - “Durable palliation”

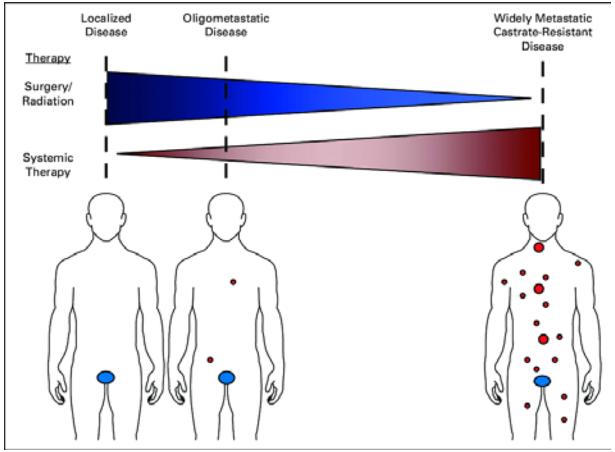
Looking to the Future

RT in the Metastatic Cancer patient

- Radiation typically restricted to palliation
- Emphasis of treatment is on systemic therapy
- Theory that cancer cells have already spread throughout the entire body, so local ablation has no curative benefit

Oligometastatic Disease

- First popularized by Hellman and Weichselbaum in 1995
- A distinct state from non-metastatic and widely metastatic disease
- Also referred to as “low metastatic burden” or “low volume disease”
- Possible benefit of definitive therapy



Can RT Do More in Metastatic Cancer?


SABR-COMET

Palma et al. (IJROBP 2018)

- Phase II multi-national study w/ patients with 1-5 mets and controlled primary
- Palliative SOC vs SOC + SABR to all mets
- Trial designed with two-sided alpha of 0.20, 1o endpoint OS
- n=99 with breast, lung, CRC, and prostate cancer
- 92/99 had 1-3 mets
- At median f/u 27 mo, median OS was 28 vs 41 mo (p=0.09), PFS was 6 vs 12 mo (p=0.001)
- Grade 2+ AEs 9% vs 30% (p=0.02), mostly fatigue, dyspnea, pain
- Three treatment-related grade 5 AEs in SABR arm

STAMPEDE

Parker et al. (Lancet 2018)

- Phase III RCT in 117 hospitals across Switzerland and the UK
- n=2061 patients w/ newly diagnosed metastatic PCa
- Median PSA 97 ng/ml
- Randomized to lifelong ADT +/- RT to prostate
- Docetaxel allowed with ADT in 2016 (18% received)
- Randomization stratified for hospital, age, nodal involvement, WHO performance status, planned ADT, and regular aspirin or NSAID use, and later docetaxel use
- RT = 55 Gy/20 fx QD or 36 Gy/6 fx weekly
- 1o endpoint: Overall Survival

STAMPEDE

Definition of “high metastatic burden” = ≥4 bone mets w/ ≥1 outside the vertebral bodies/pelvis or visceral mets

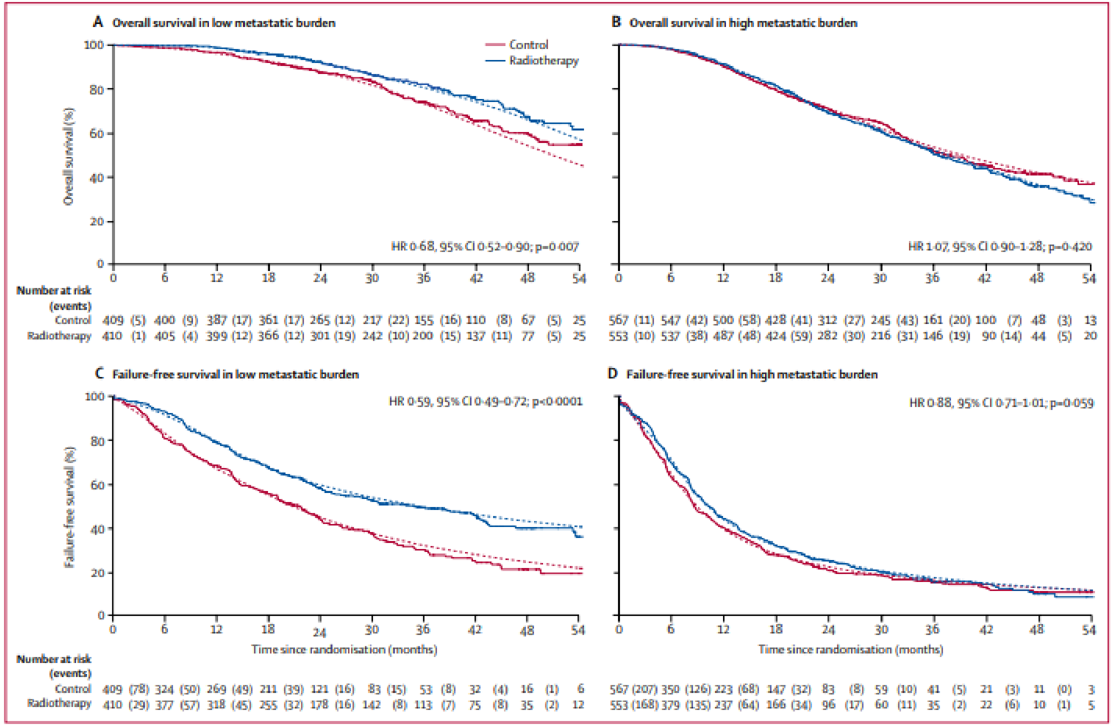


Figure 4: Overall survival and failure-free survival by treatment and metastatic burden
HR=hazard ratio. Solid lines show the Kaplan-Meier analysis and dotted lines show the flexible parametric model.

Why Does Local Therapy Help?

- Diminishes tumor burden
- Durable LC important as systemic control improves
  - Preventing morbidity/mortality from local growth
- Disrupts complex interplay between primary tumor and microenvironment of potential metastatic sites (“priming the premetastatic niche”)
- Disrupts metastasis-to-metastasis communication and spread
- SBRT may have different effects on cancer biology
- Enhances immune response

MR-Guided Radiation Therapy

- The best soft-tissue contrast
- Real-time imaging
- Automated gating
- Adapting planning

- First system launched commercially in 2014, the ViewRay MRIdian
- Other systems currently in early stages of use and testing

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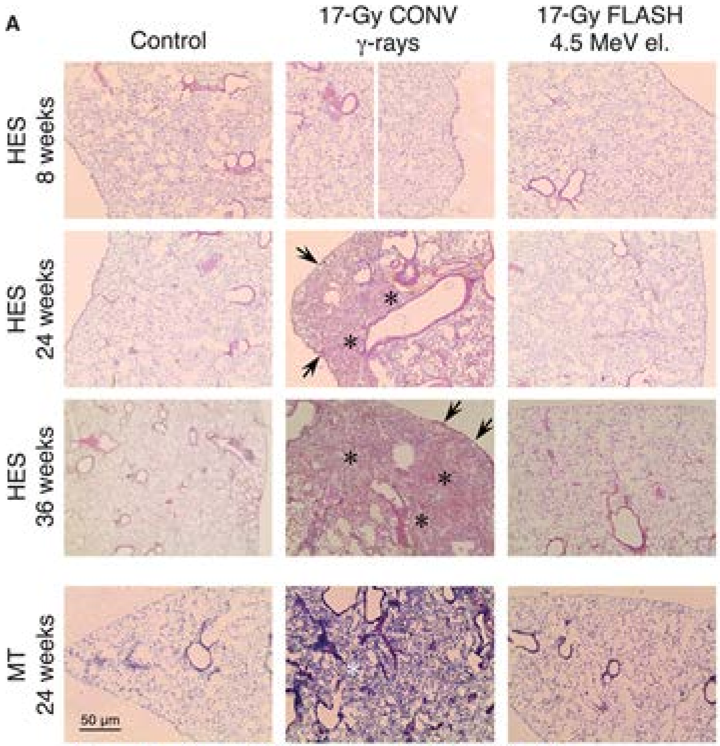
FLASH-RT

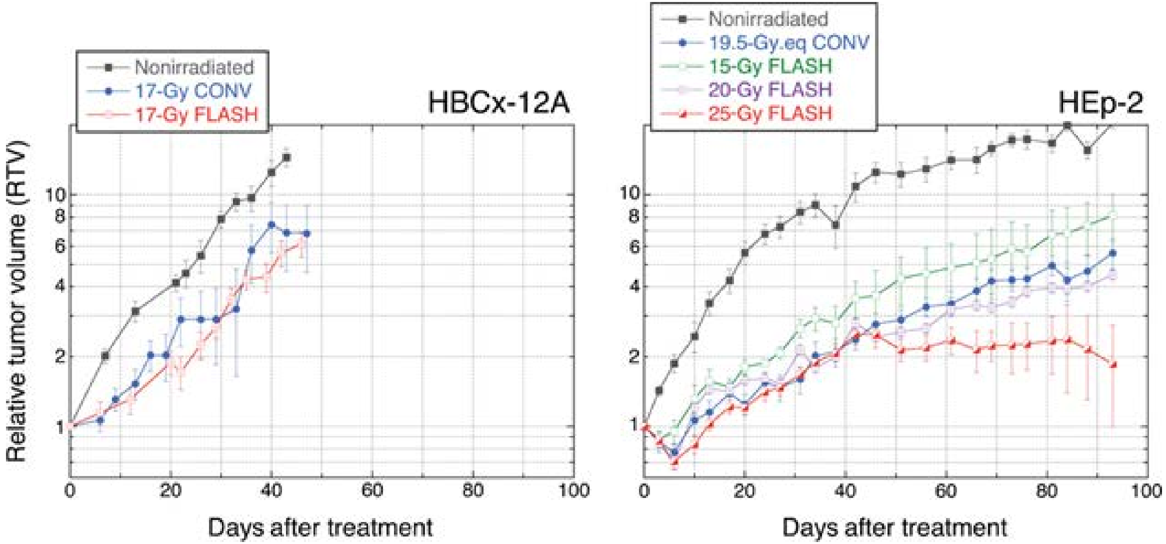
- Ultrahigh dose rate (>40 Gy/s)
  - Regular radiation treatments are typically 1-5 Gy/minute
  - Total body radiation is given 0.06-0.25 Gy/min
- Whole lung radiation in mice
  - Less pulmonary fibrosis
  - Hair depigmentation, no epilation or ulceration 36 weeks post FLASH RT



Favaudon V et al. Sci Transl Med 2014;6:245ra93.

FLASH-RT

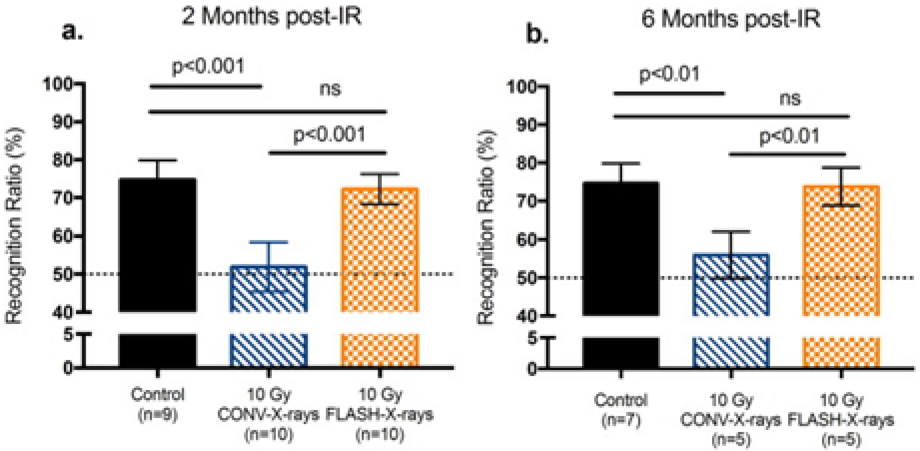
- Potentially the same or better tumor control but less toxicity



Favaudon V et al. Sci Transl Med 2014;6:245ra93.

FLASH-RT

- Similar results seen with whole brain radiation (10 Gy CONV dose rate or FLASH rate)
- Blinded assessment of mice videotaped performing Novel Object Recognition tests showed better memory skills post FLASH RT
  - Better preservation of cellular division in the hippocampus subgranular zone
  - Less astrogliosis



Montay-Gruel P et al. Radiother Oncol. 2018 Dec;129(3):582-588.

FLASH-RT at UW

- Small animal x-ray and proton radiator, beam sizes 1-40 mm, on board CT scan for positioning
- In process of being adapted to deliver proton FLASH-RT
- Existing linear accelerators cannot deliver FLASH-RT to patients, but proton centers could!

Ford E et al. Phys Med Biol. 2017 Jan 7;62(1):43-58.

Thank you for your attention!