Radiation Oncology - Basic Principles and Multidisciplinary Applications

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Things I Think Medical Oncologists Should Know about Radiation Oncology

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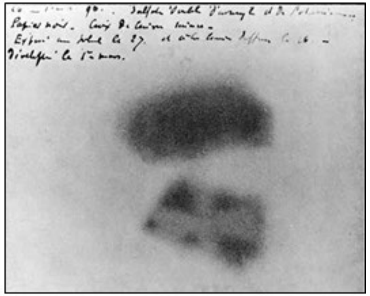
Overview

- Basics of radiation therapy
  - Mechanism
  - Particle types: photons, protons, neutrons, heavy ions
  - Definition of common parlance
- General Paradigms of Clinical Utility
- Specific site-based clinical points of interest
  - Breast
  - Prostate
  - Lung
  - Palliative RT
- 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

- 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

“Allied Disciplines”

One of the tines in the trident of oncology

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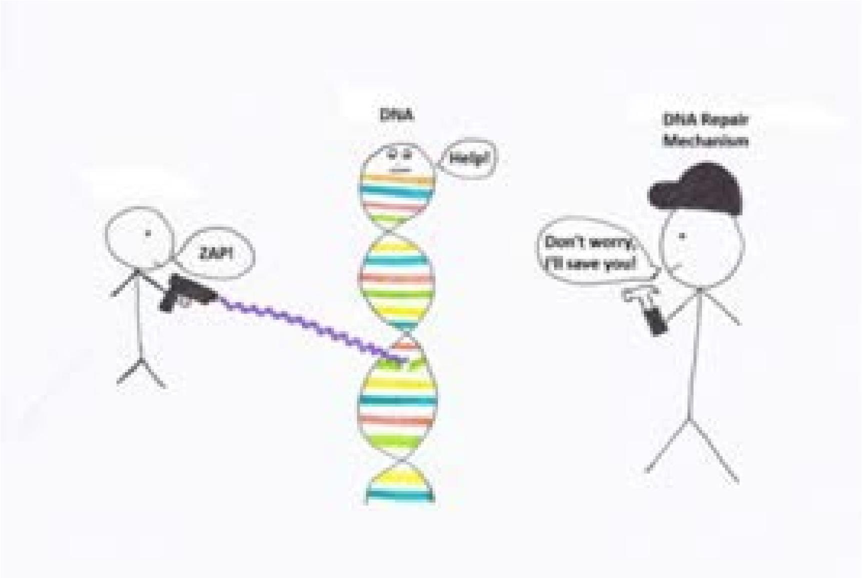
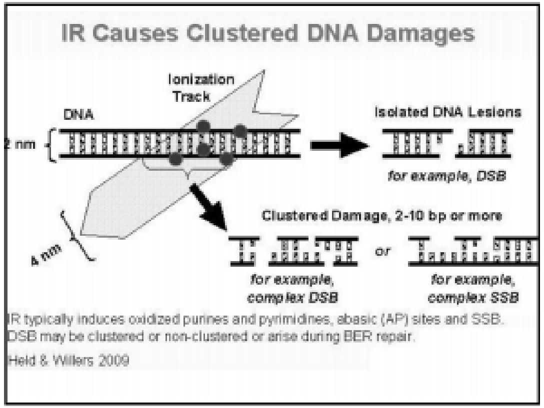
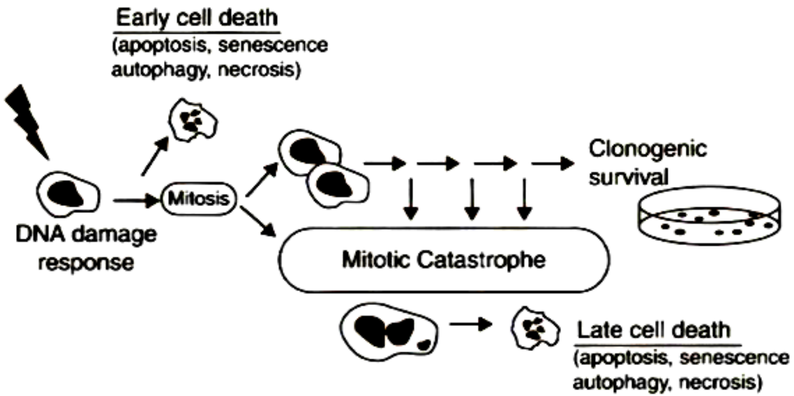
Radiation Biology 101



Radiation Biology 101

- Radiation treats cancer by directly killing tumor cells
- DNA damage → Mitotic catastrophe
- Preferentially affects rapidly proliferating cells



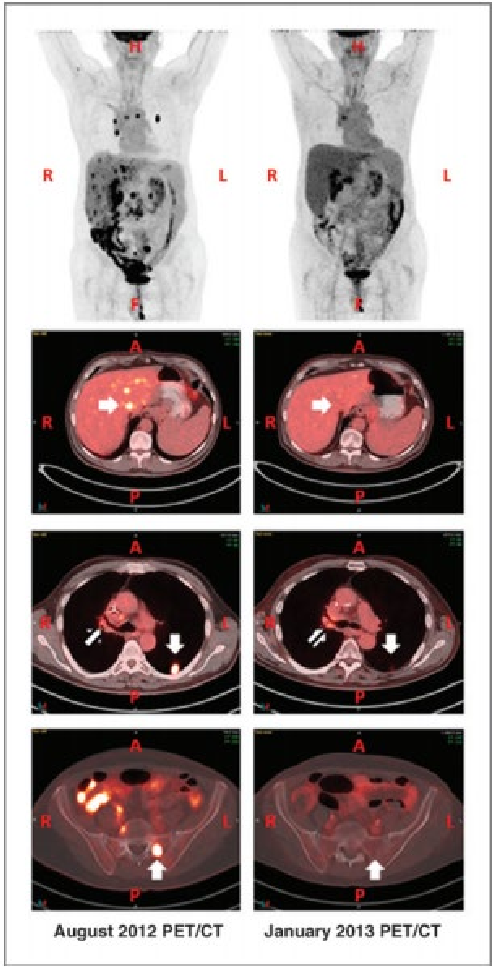


Radiation Oncology: Mechanism

- However, other mechanisms may be important as well...
  - Disruptive 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

RT and Immunotherapy

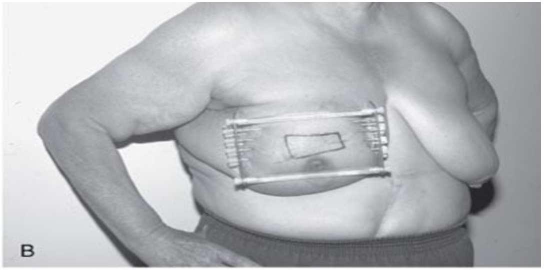
- Abscopal effects
- Combination of RT and ICI

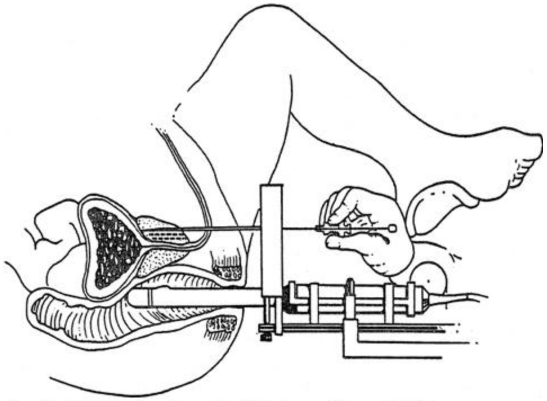


Different RT Options and Definition of Common Lingo

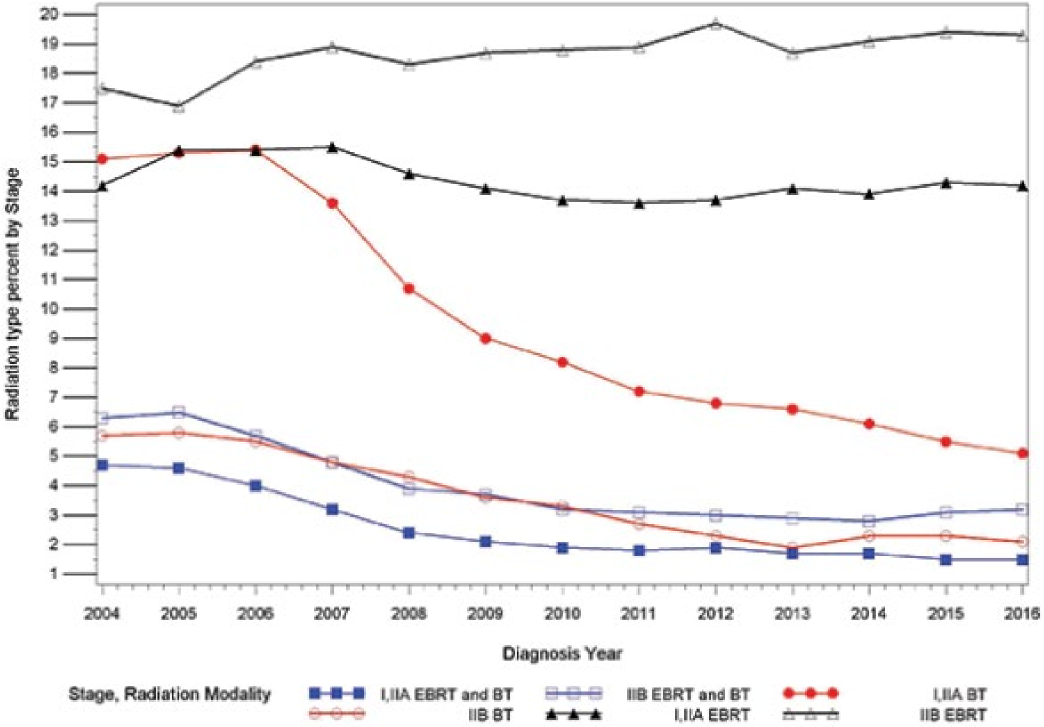
Radiation Oncology: Brachytherapy

- 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 MV	6, 10, 15, 18
Electrons MeV	6, 9, 12, 16

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

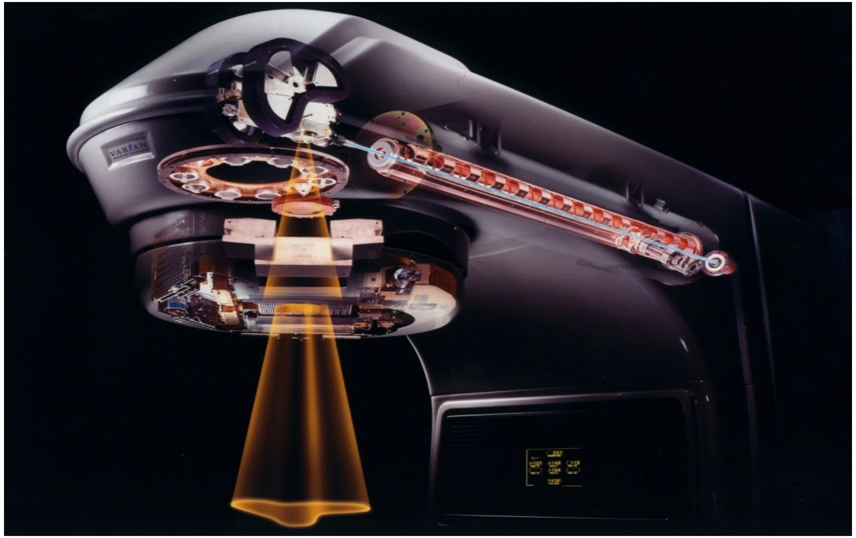


Image courtesy of Varian Medical Systems, Inc.

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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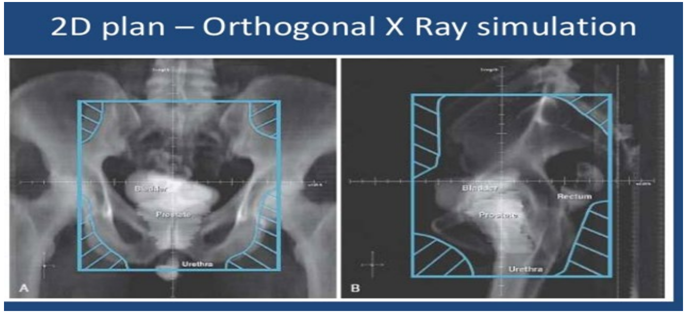

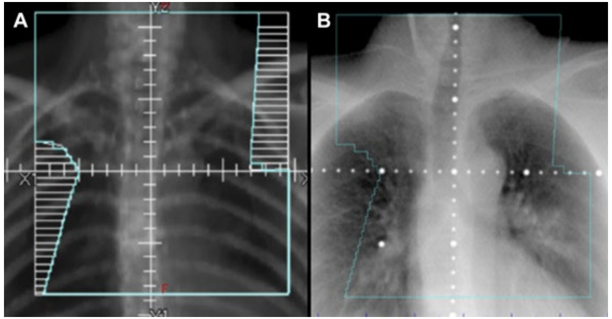

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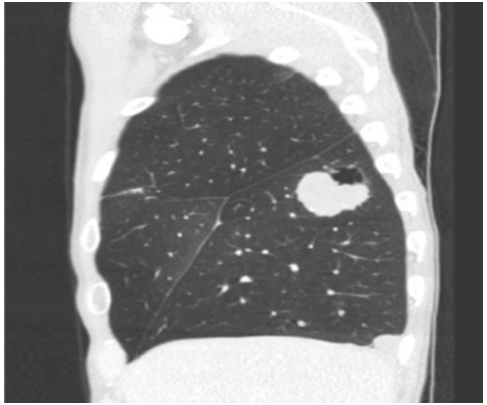

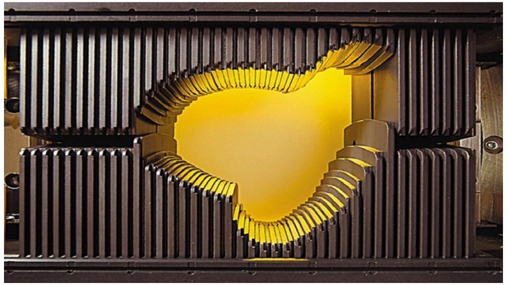

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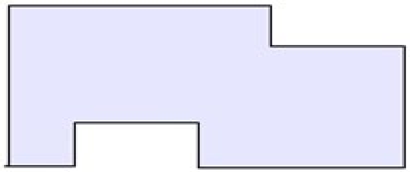
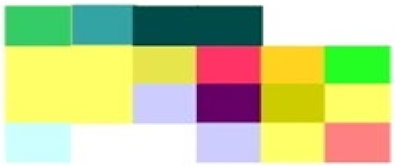


Geometrical Field shaping



With intensity modulation

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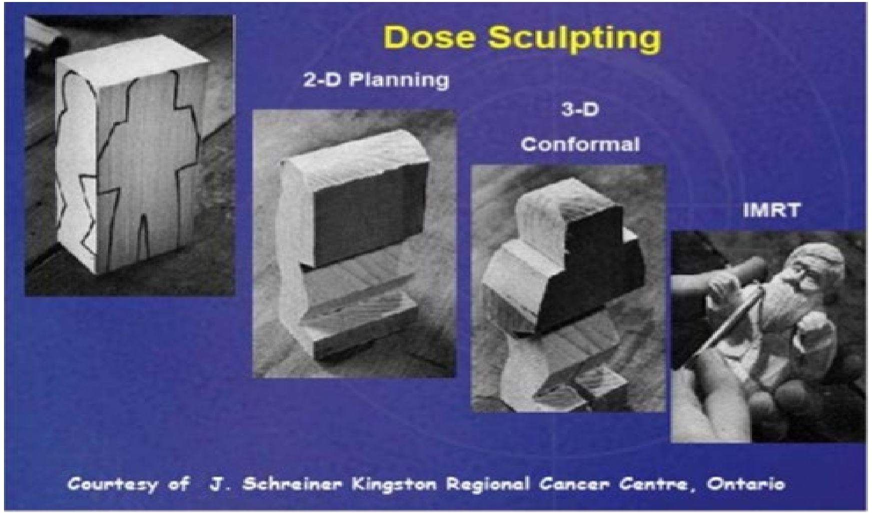

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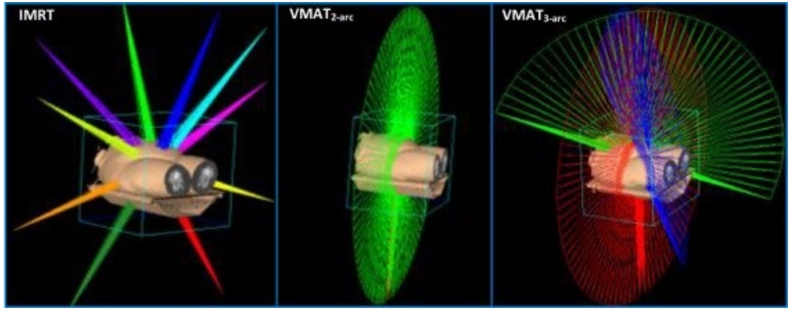

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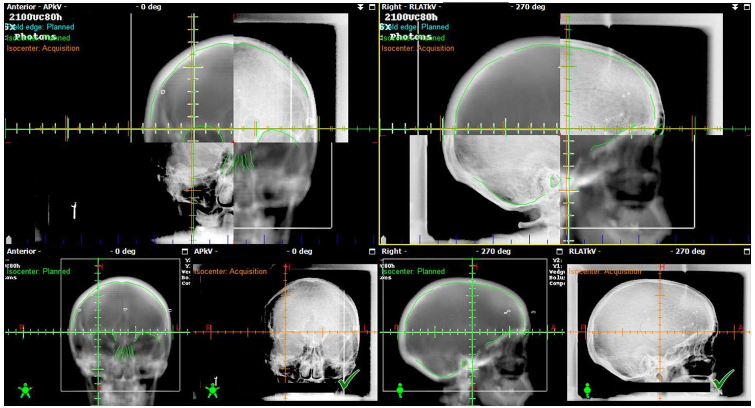

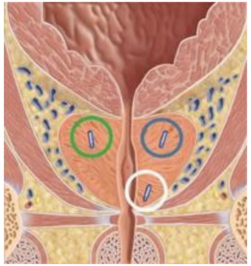

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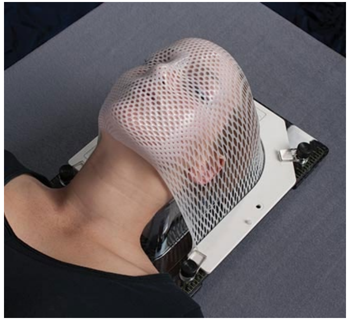
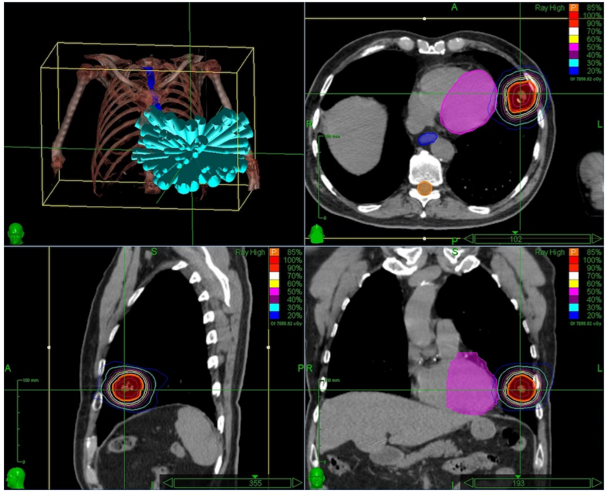
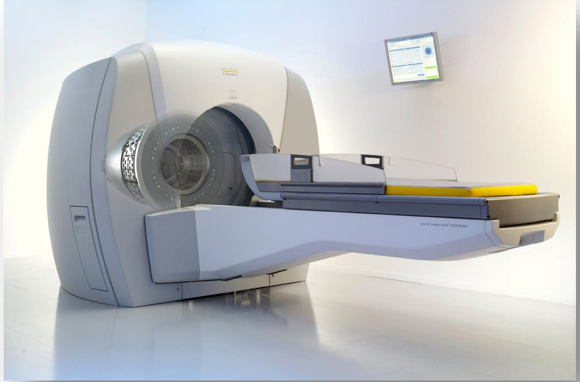
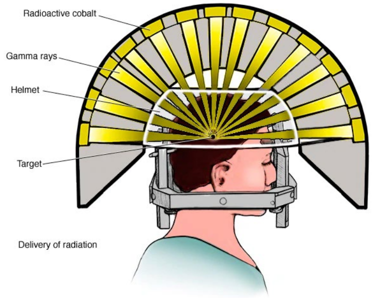


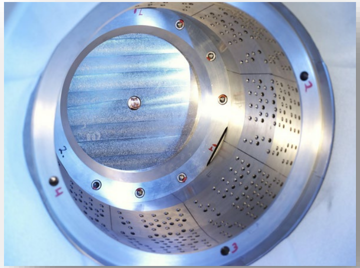


Radiation Treatment Machines: Gamma Knife

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



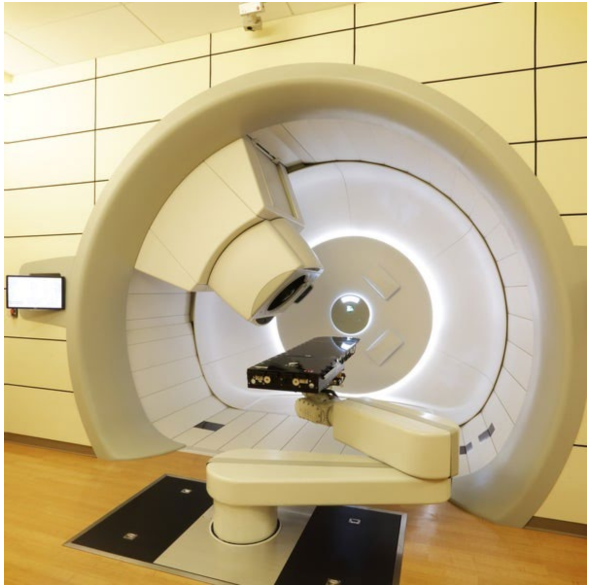




Radiation Treatment Machines: CyberKnife

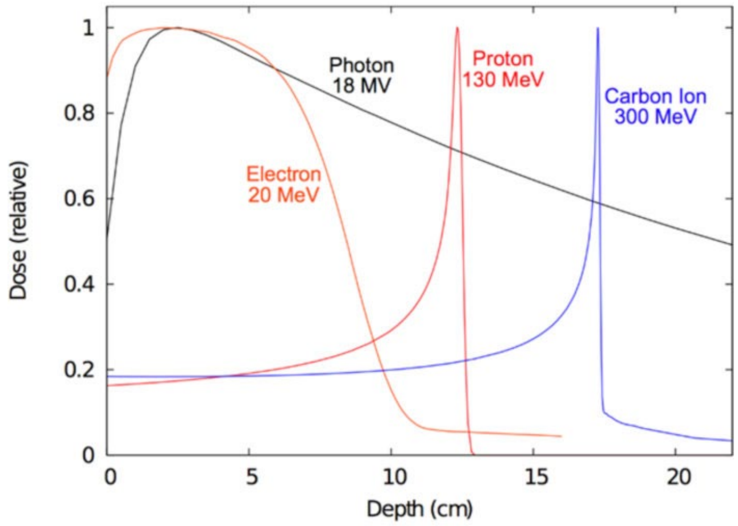
Radiation Treatment Machines: Tomotherapy

Radiation Treatment Machines: Proton Therapy

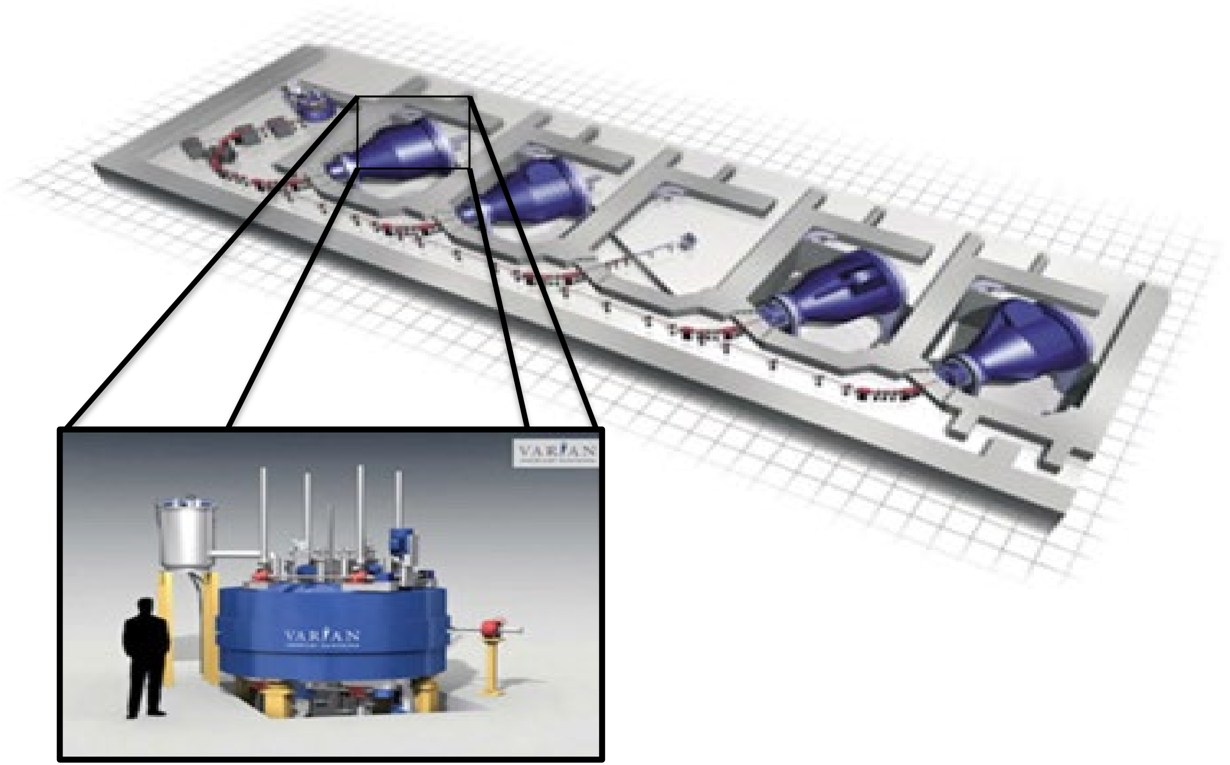


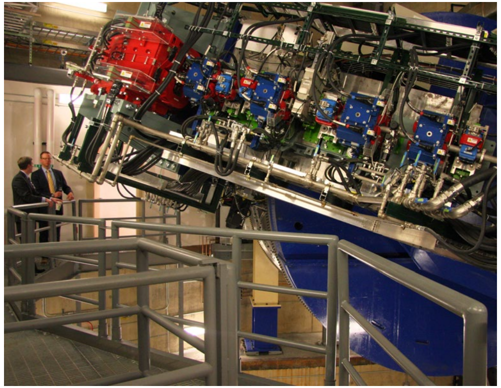
Radiation Oncology: Particle Options

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



Radiation Treatment Machines: Protons



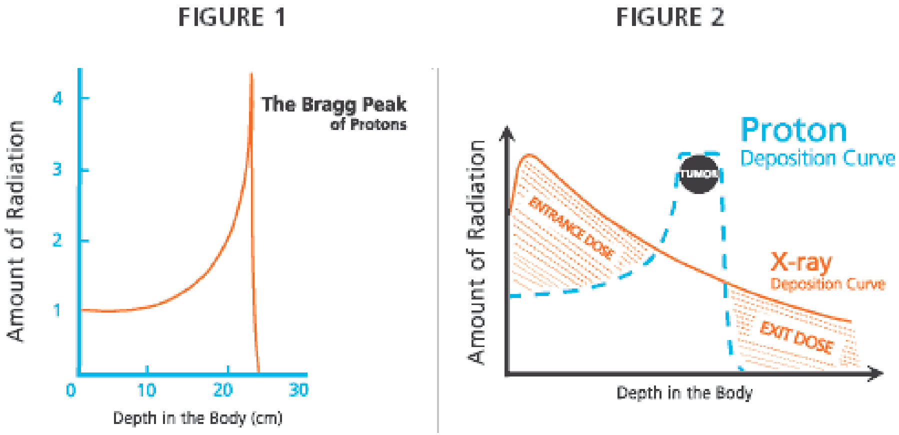


What is the Deal with Protons?

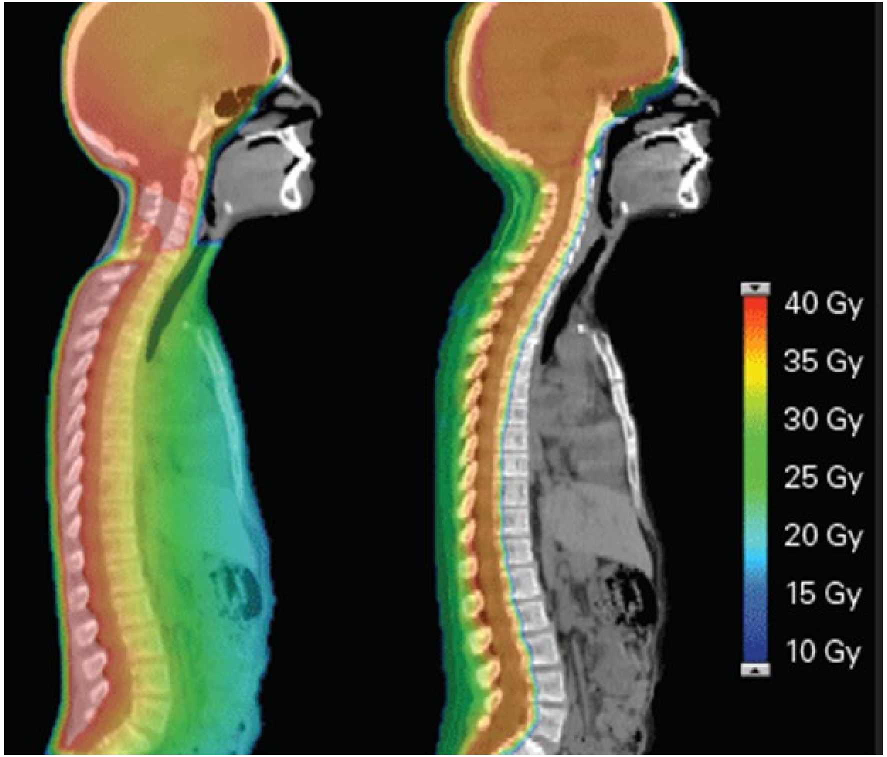
- Proton radiation is a type of external beam radiation
- FDA approved 1988
- Delivers radiation to tumors while reducing radiation exposure to surrounding normal tissues
- Confers a clinical advantage for some patients compared to conventional X-ray (photon) treatment
- Another tool for the radiation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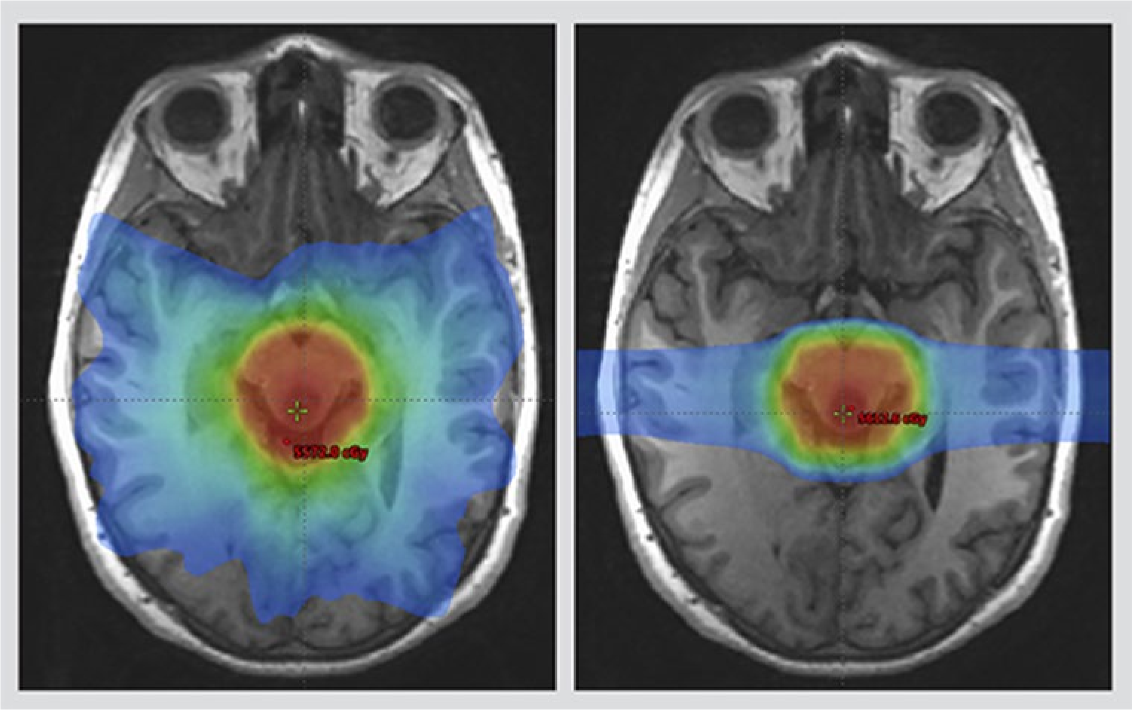

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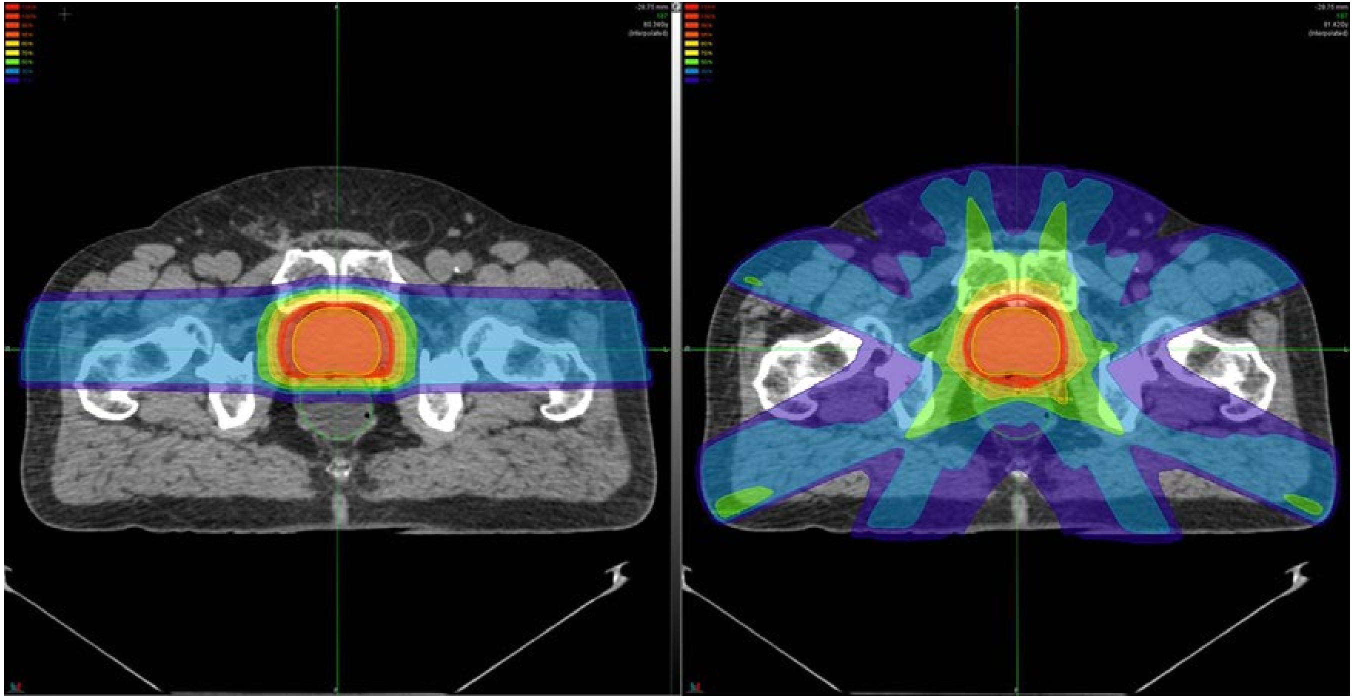


Proton Therapy: ASTRO Guidelines

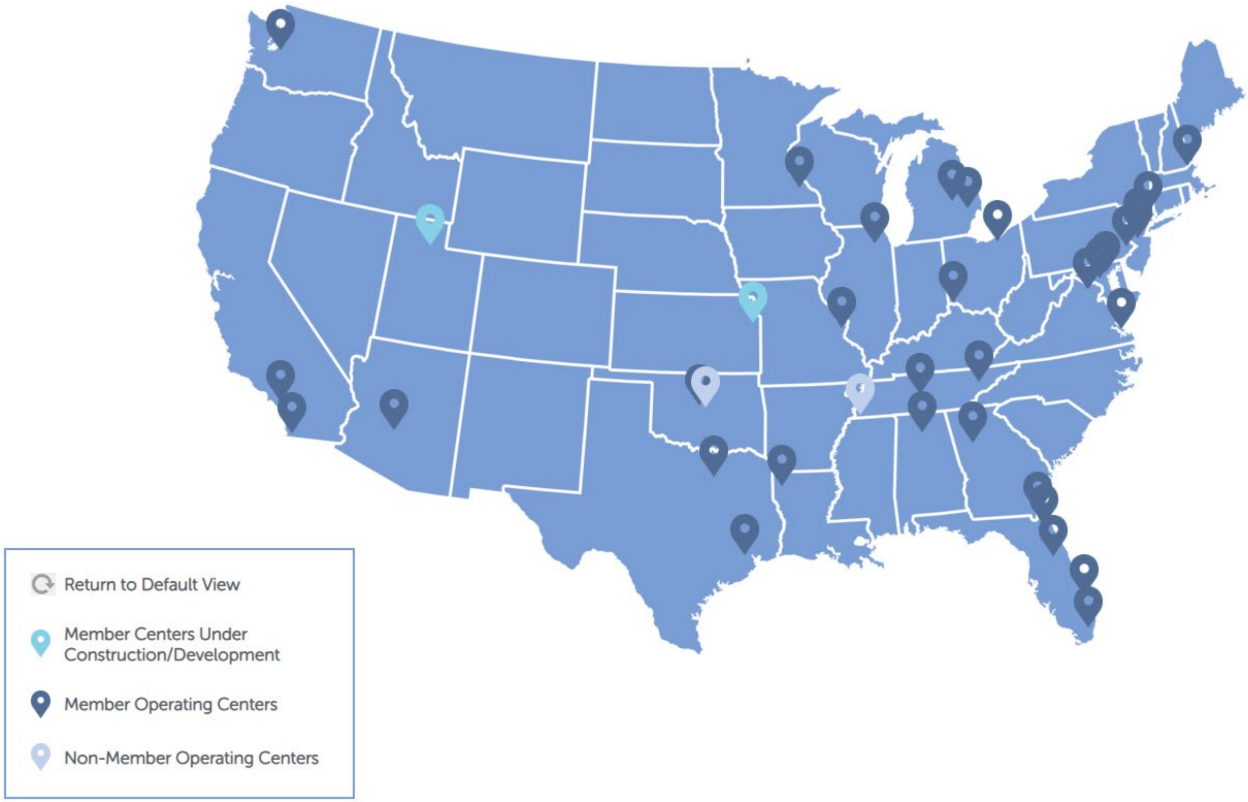
ASTRO Group 1

- 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

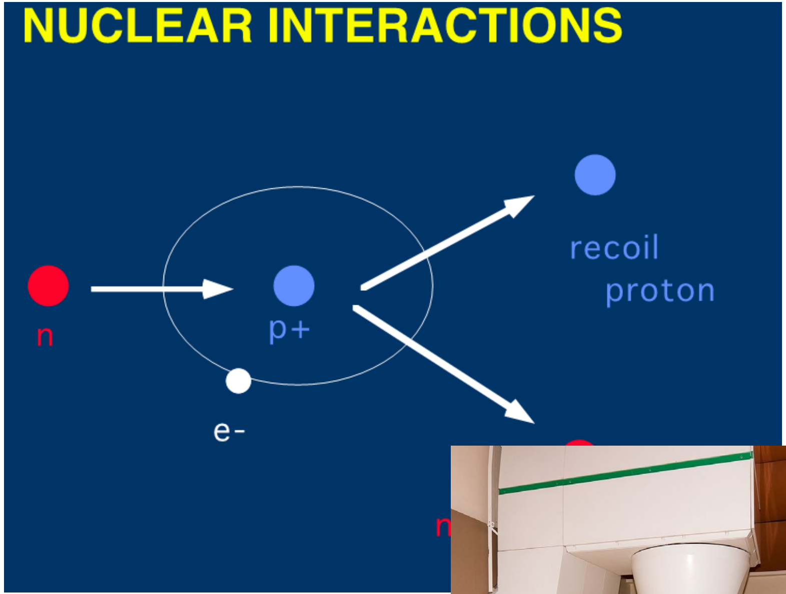
- Other H&N cancers
- Thoracic malignancies
- Abdominal malignancies
- Pelvic malignancies
- Prostate cancer
- Breast cancer

Proton Therapy Centers



Radiation 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



General Paradigms of Clinical Utility

Radiation Oncology Quick Hits

- As technology improves, so does radiation therapy
- As treatment delivery becomes more sophisticated, the planning process becomes more complex
- It takes time for it to work
- Toxicities can arise years after treatment
- Re-irradiation is not impossible, but comes with increased risks

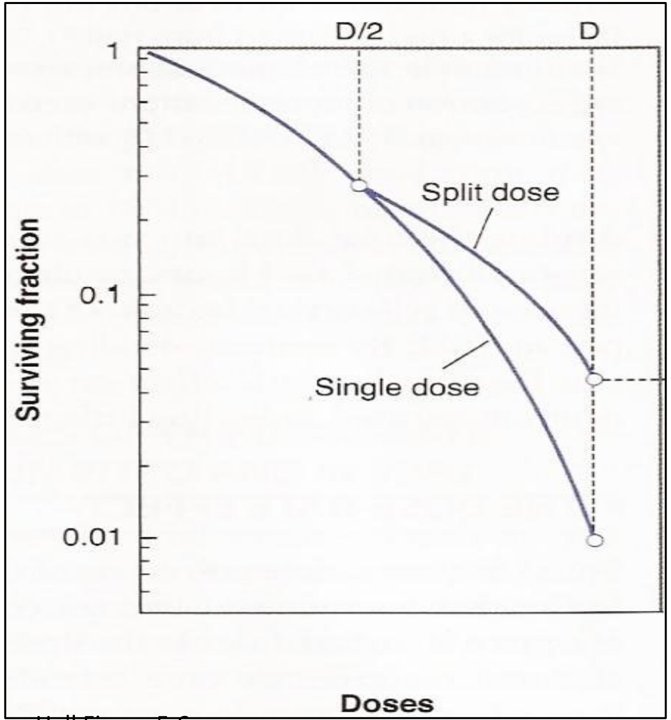
How Do We Decide on Dose?

Radiation Oncology: Dose

1. Dose needed to kill a particular type of cancer has typically been established by dose-finding studies
2. Consider the alpha/beta of the tumor
3. Consider patient safety
4. Consider patient convenience

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

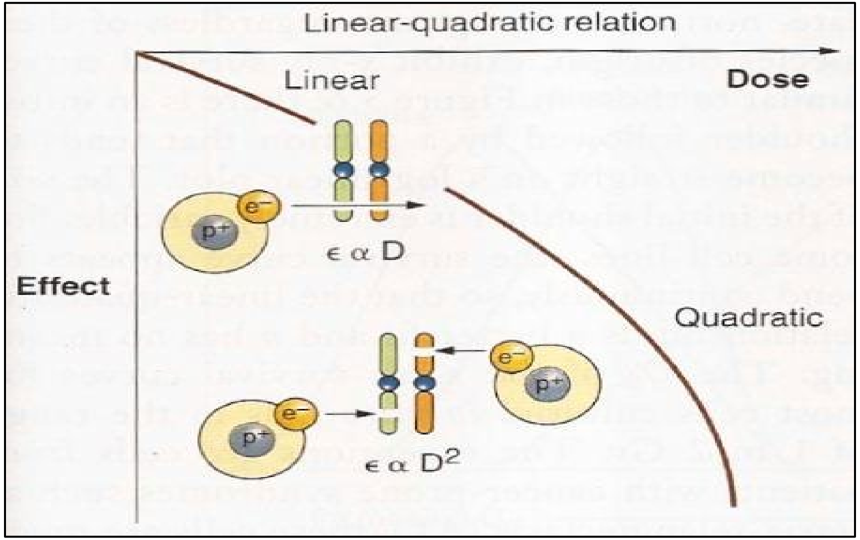
Radiation Oncology: Fractionation

- 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

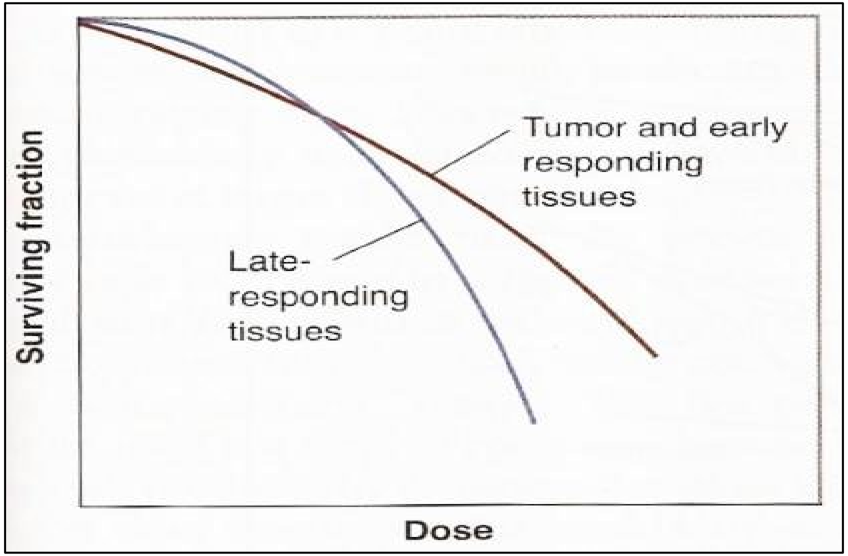
- Linear quadratic (α/β) model
  - Alpha = single hit kills
  - Beta = double hit kills



Hall Fig 3.5

Radiation Oncology: Fractionation

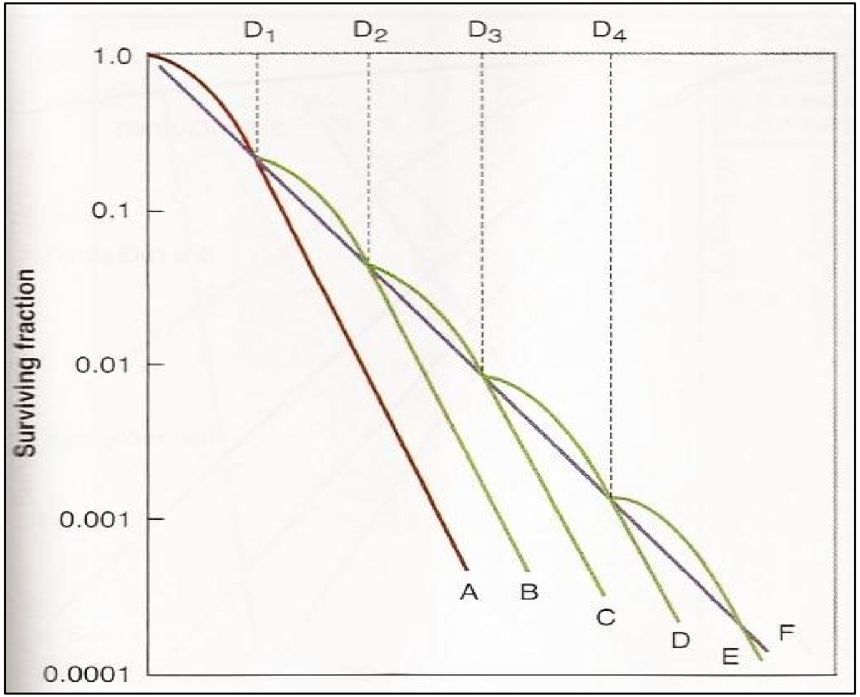
- Different cell lines, tissues, and tumors have different α/β values
  - α/β defines the dose of radiation at which the number of cells killed by a single hit equals the number killed by two hits
  - High α/β = most tumors, early responding normal tissues
  - Low α/β = late responding tissues, some tumors (e.g. 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).
- $BED = nd(1+d/[\alpha/\beta])$
  - n = number of fractions
  - d = dose/fraction



Hall Figure 5.8

Radiation Oncology: Fractionation

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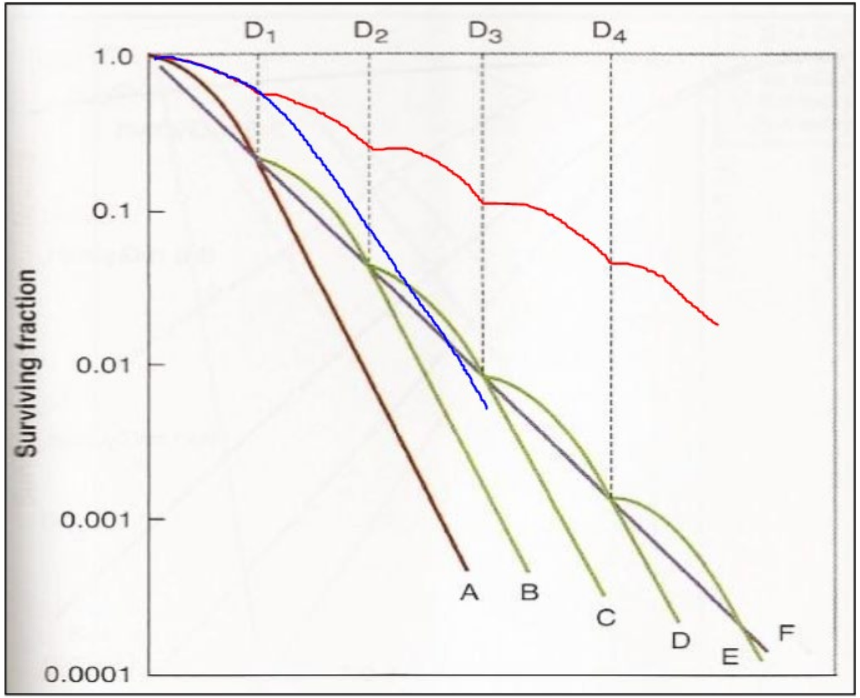


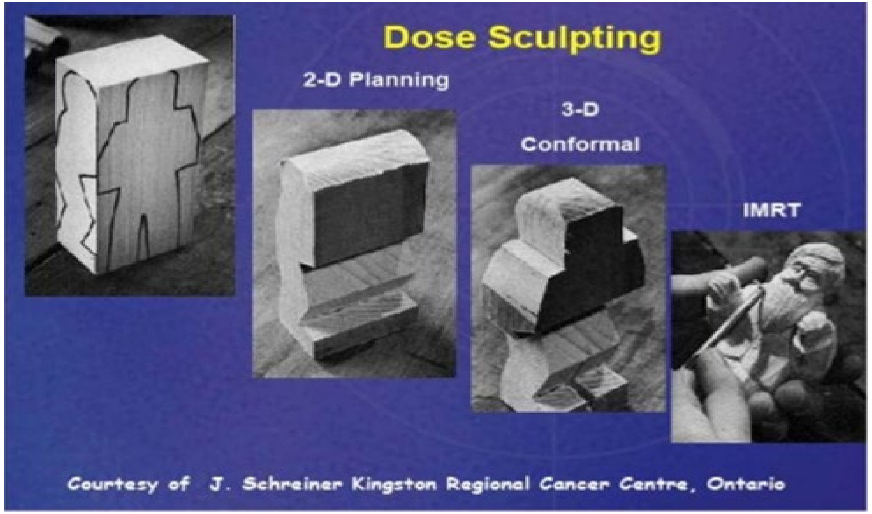
Hall Figure 5.8

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

Patient Safety vs Convenience

- Another driver of shorter treatment regimens is better targeting and accuracy allowing us to delivery the same dose faster without compromising safety
- Trend towards shorter treatments



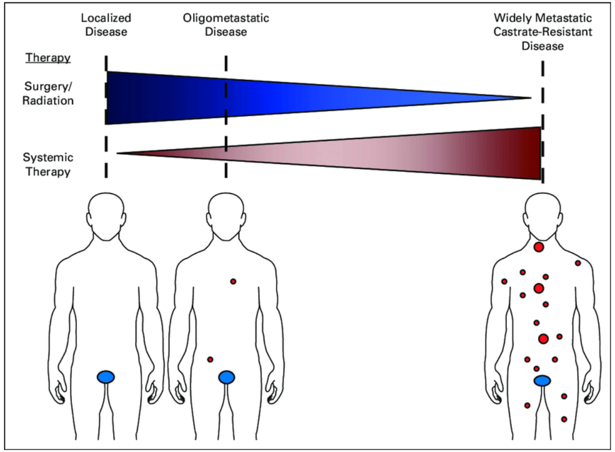
Can RT Do More in Metastatic Cancer?

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

- 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



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

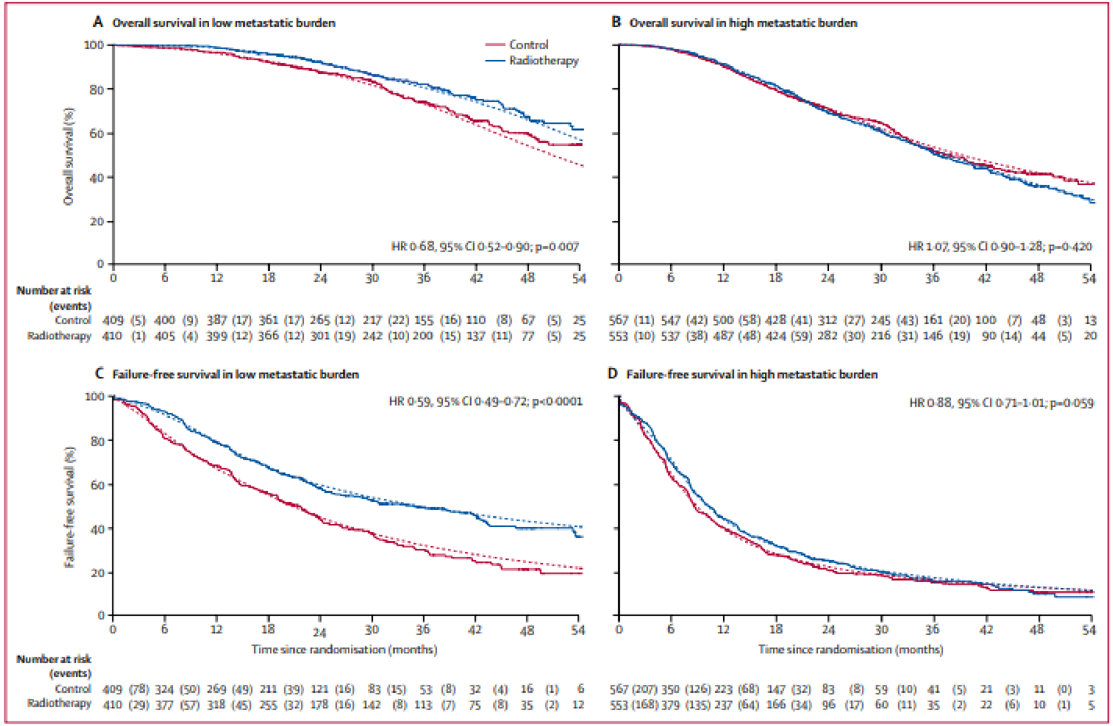


Figure 4: Overall survival and failure-free survival by treatment and metastatic burden
HR=hazard ratio. Solid lines show the Kaplan-Meier analysis and dotted lines show the flexible parametric model.

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

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

Site-Specific Clinical Points of Interest

Breast Cancer - Standard of Care

DCIS and Early Stage Invasive

- BCS → RT
- Mastectomy

+/- Systemic therapy

Locally Advanced

- BCS or Mastectomy → RT

Neoadjuvant systemic therapy for select patients

Breast Cancer - Recent Movement

RTOG 9804/CALGB 9343/PRIME II - omit RT in some patients

NSABP B39 - APBI

FAST and FAST FORWARD - shortening treatment time

Z11 - RT de-escalation to regional LNs

NSABP B51 - potentially RT de-escalation based on response to neoadjuvant chemotherapy

Prostate Cancer - Standard of Care

Localized

- Surgery
- RT +/- ADT

Metastatic

- Systemic therapy alone

Post-RP Recurrence

- Adjuvant or Salvage RT +/- ADT

Prostate Cancer - Recent Movement

ProtecT - More active surveillance

CHIIP/0415/PROFIT/HYPRO - Hypofractionation becoming more commonplace

HYPO-RT-PC/PACE-B/NRG GU005 - SBRT as ultra hypofractionation

ASCENDE-RT - combining EBRT with brachy, may allow omission of ADT

STAMPEDE - prostate RT for metastatic patients

ORIOLE/SABR-COMET - Metastasis-Directed Therapy

Lung Cancer - Standard of Care

Standard approach to treatment:

Early stage node-negative

- Surgery +/- chemo +/- PORT for N2

Stage IIIB-C

- Definitive CRT

Metastatic

- Systemic therapy only

Lung Cancer - Recent Movement

CHISEL - Increased utilization of SBRT

Treatment of oligomets and oligoprogression

Palliative RT - Recent Movement

Less focus on pure palliation, more consideration of durable LC, PFS, and possibly even OS

Increased doses → demanding more sophisticated treatment techniques

Thank you for your attention!