Radiation Oncology - Basic Principles and Updates

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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

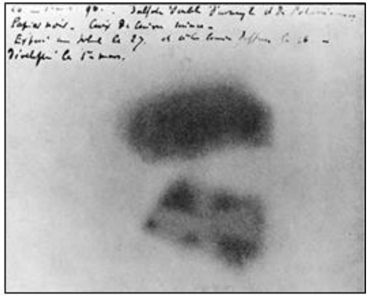
1952 – First “linear accelerator” used for treatment

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 and 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
  - AVMs
  - Benign tumors: glomus tumor, schwannomas, meningiomas, etc.

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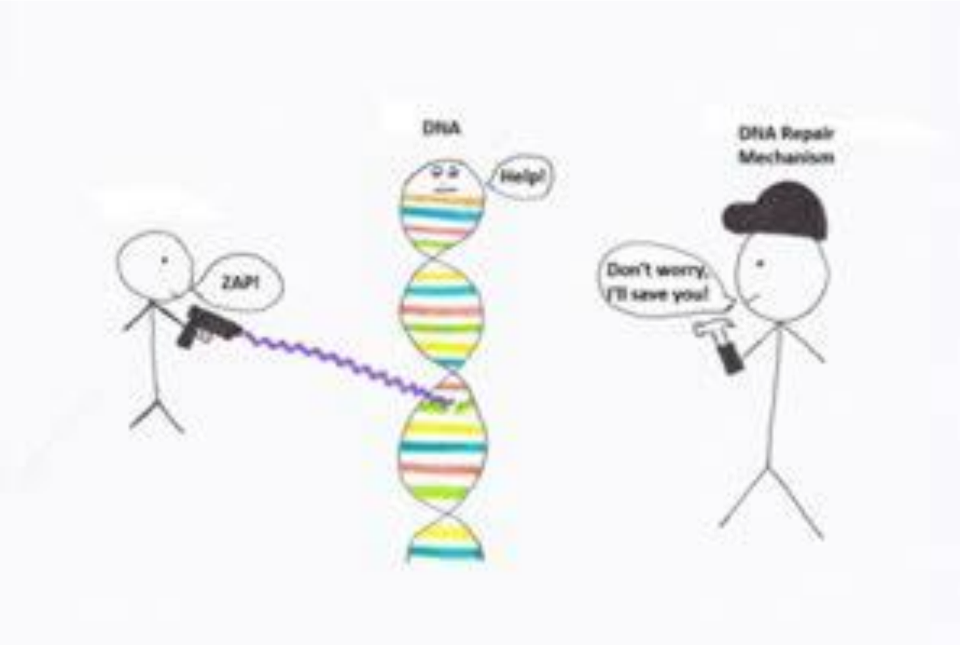
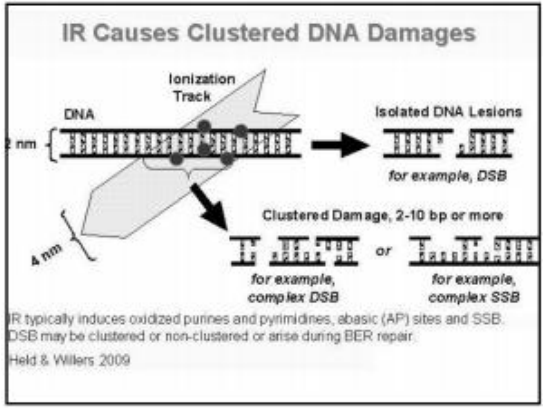
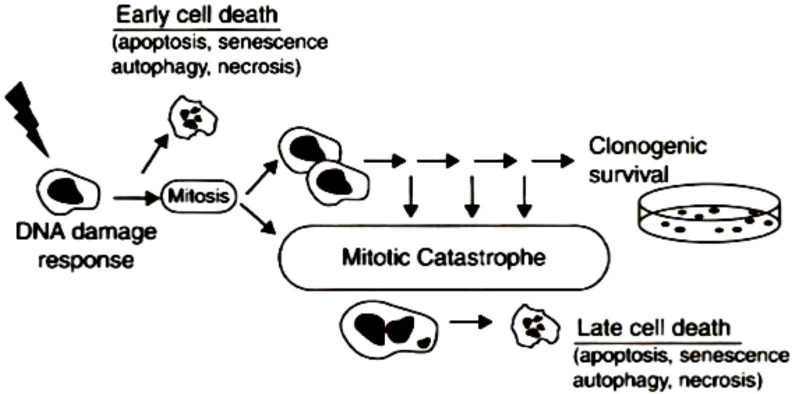
Radiation Biology 101



Radiation Biology 101

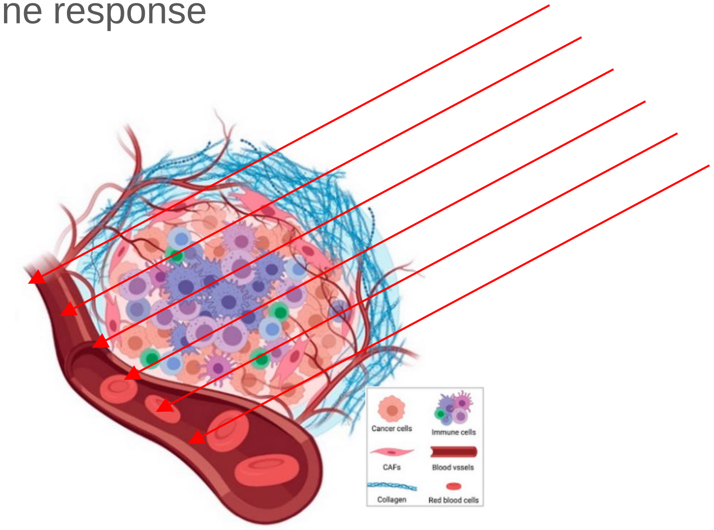
- Radiation directly kills tumor cells via DNA damage → Mitotic catastrophe
- Preferentially affects rapidly proliferating cells with impaired DNA damage repair



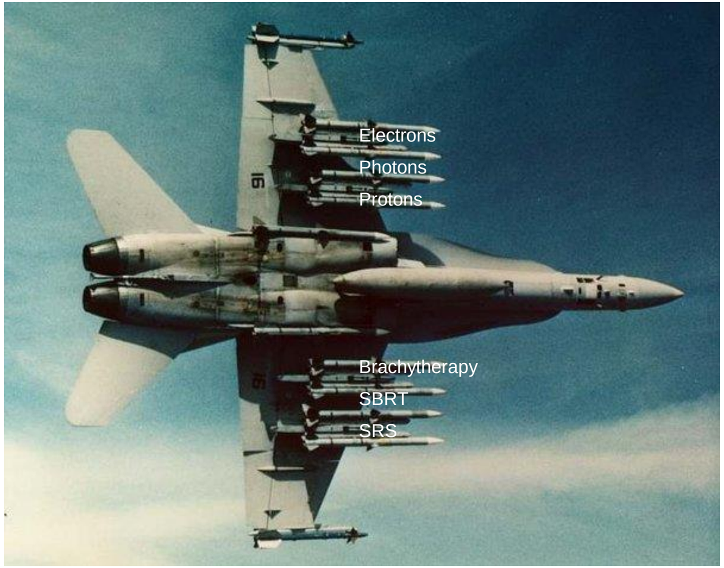


Radiation Biology 101

- Other secondary mechanisms may be important as well...
  - Disruptive effects on tumor vasculature
  - Very high dose or high LET radiation may affect cell membrane integrity and protein structures
  - Interplay with the immune response

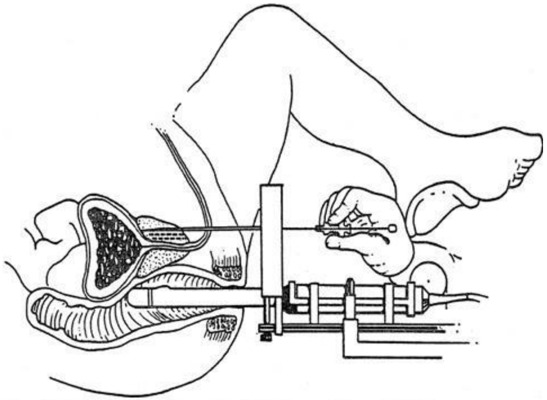


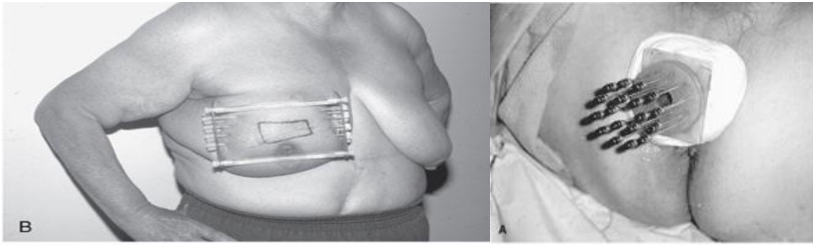
Tools in the Radiation Oncology Arsenal



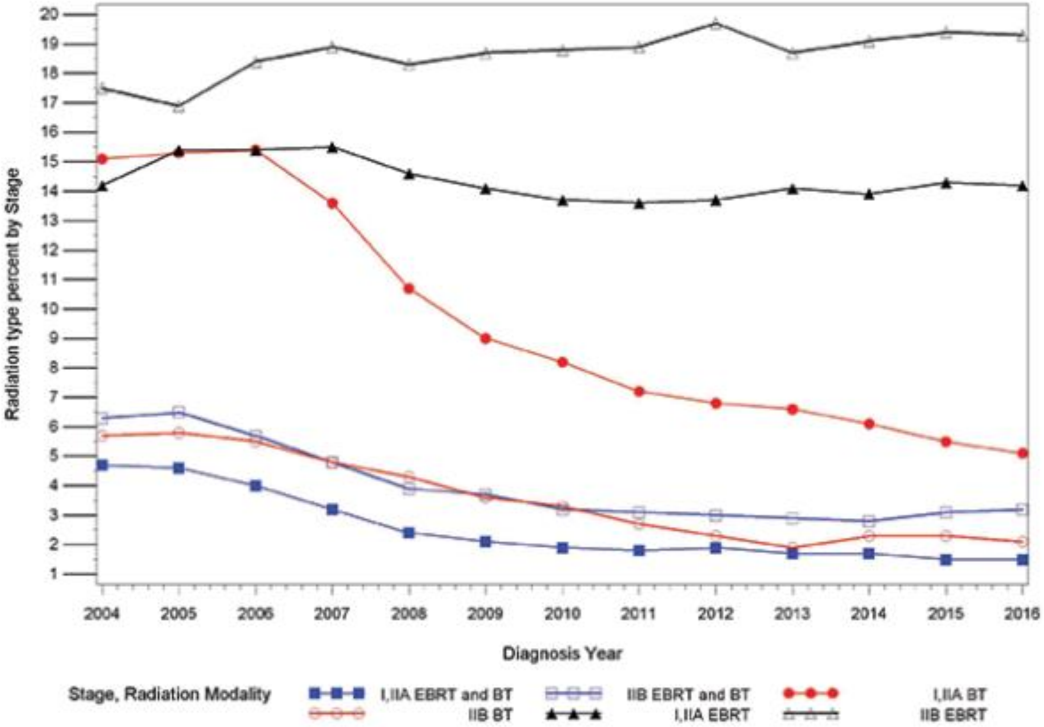
Radiation Oncology: Brachytherapy

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

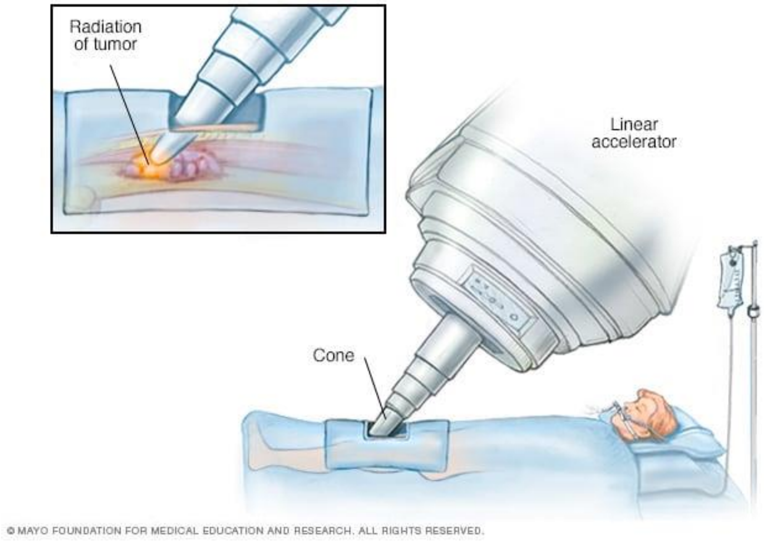




Brachytherapy: A Dying Art?



Intra-Operative Radiation Therapy



External Beam Radiation Treatment Options

Image courtesy of Varian Medical Systems, Inc. All rights reserved

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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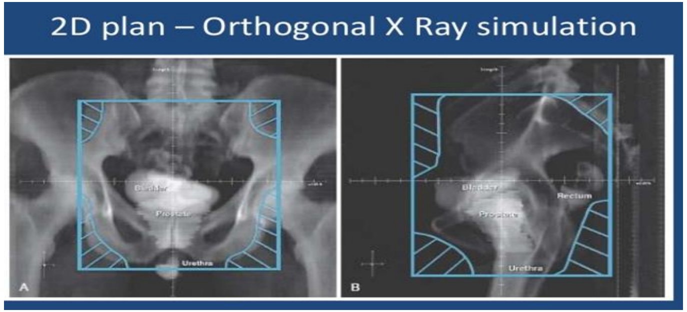

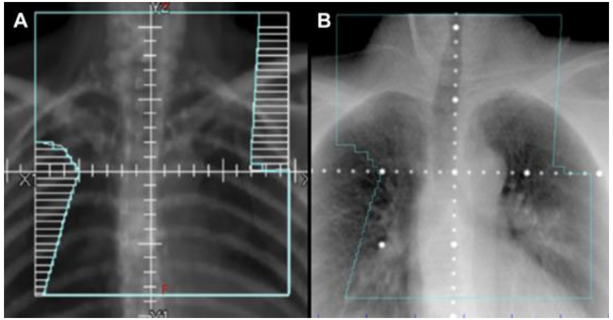

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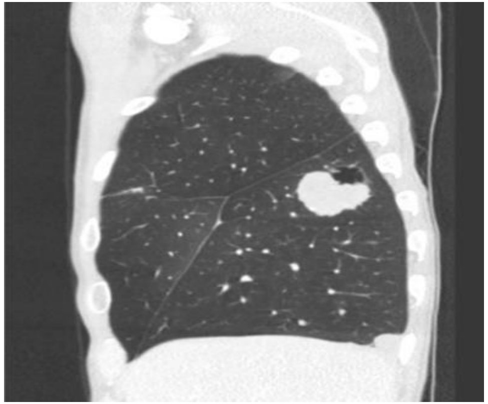

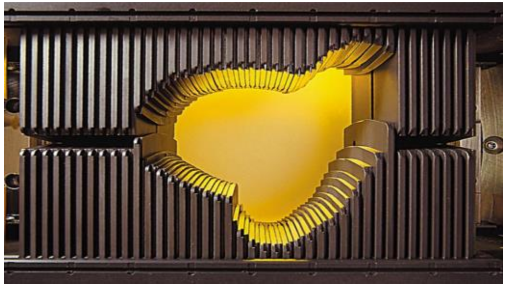

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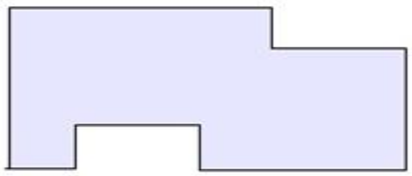

Geometrical Field shaping

With intensity modulation

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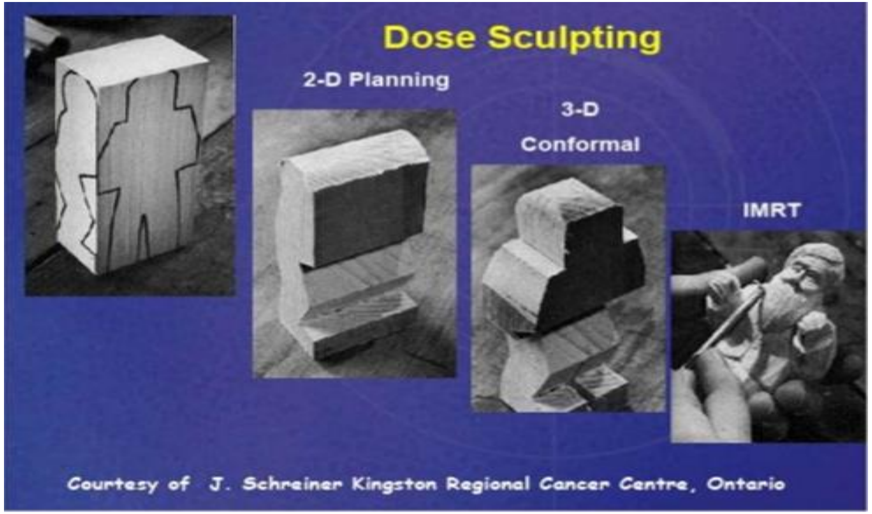

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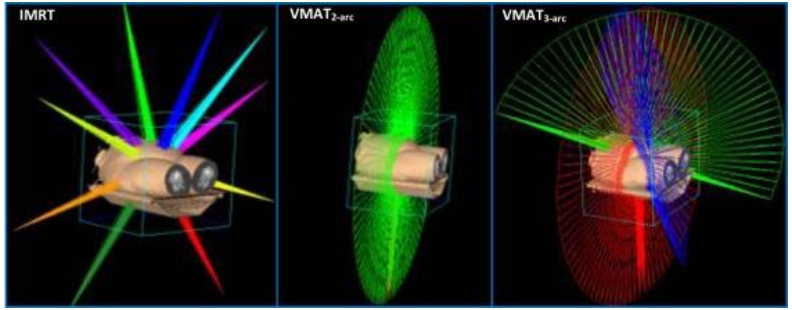

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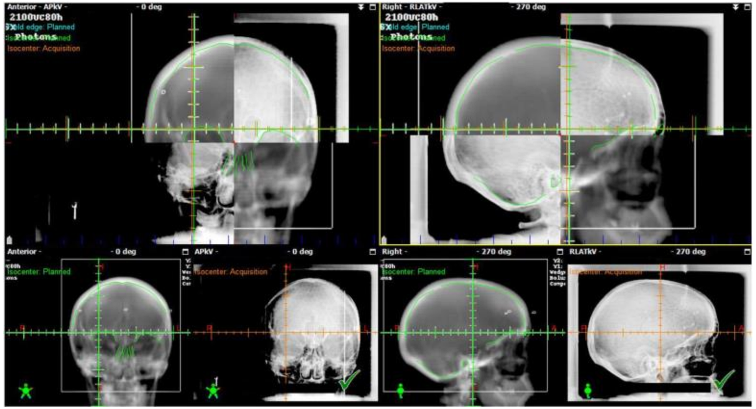

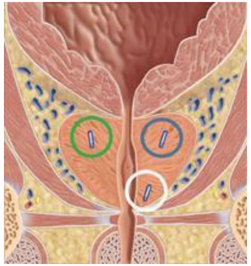

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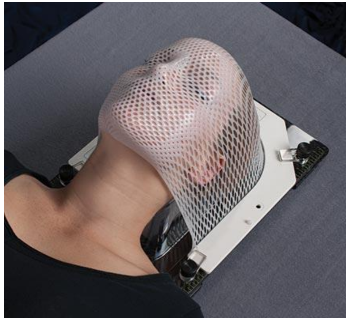
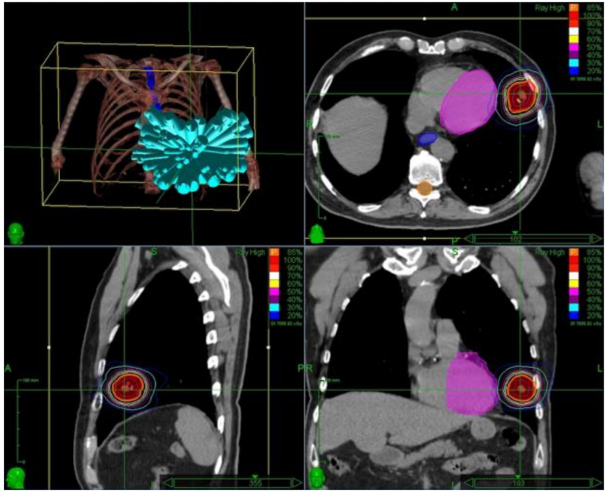


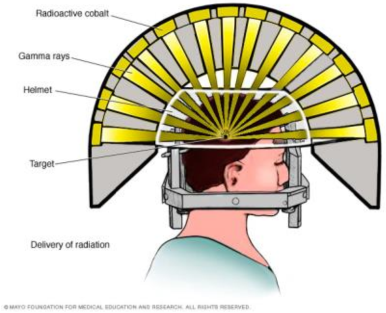


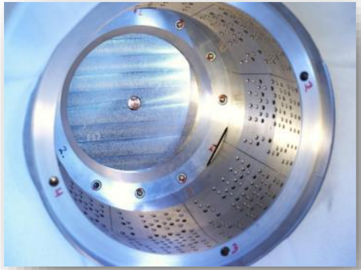
Radiation Treatment Machines: SRT

- Superficial RT
- Low energy radiation delivery machines
- Skin cancer

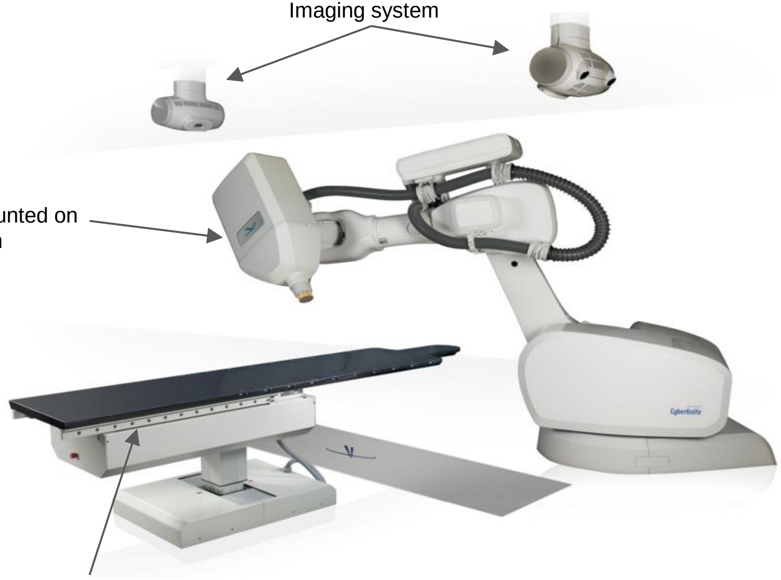
Radiation Treatment Machines: Gamma Knife

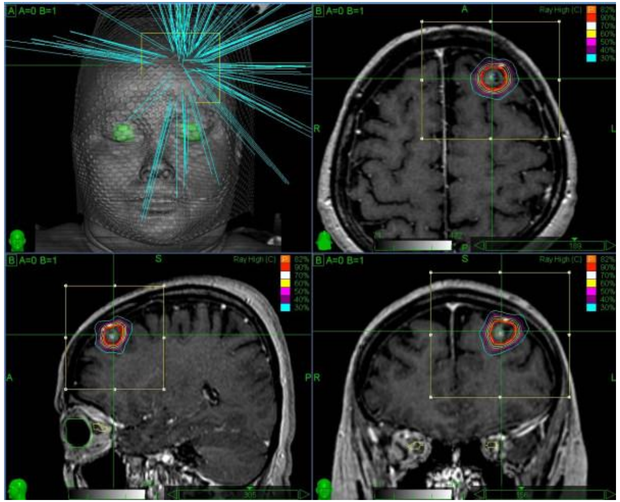
- Radiosurgery / SRS
  - Single high-dose radiation
  - Very conformal (i.e. tight margins)





Radiation Treatment Machines: CyberKnife





Radiation Treatment Machines: MR-LINACs

- The best soft-tissue resolution
- Real-time imaging
- Automated gating
- First system launched commercially in 2014

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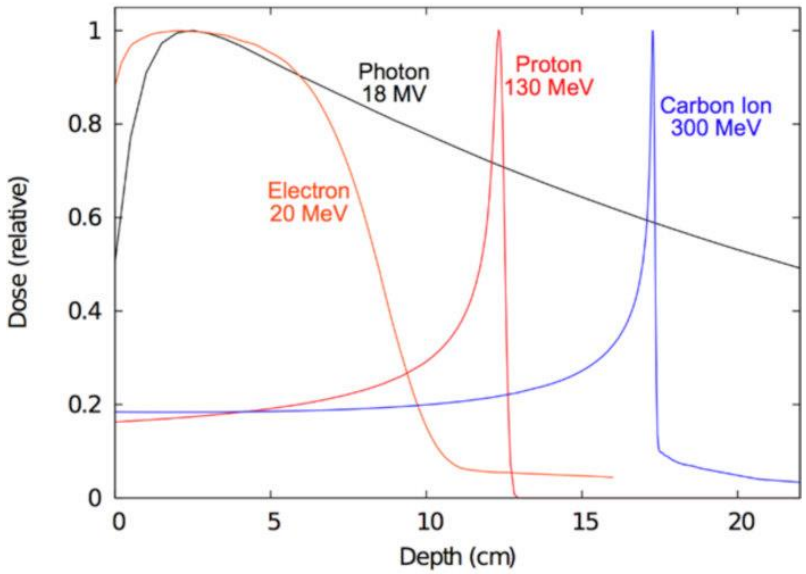
Radiation Treatment Machines: Tomotherapy

Particle Options

Radiation Oncology: Particle Options

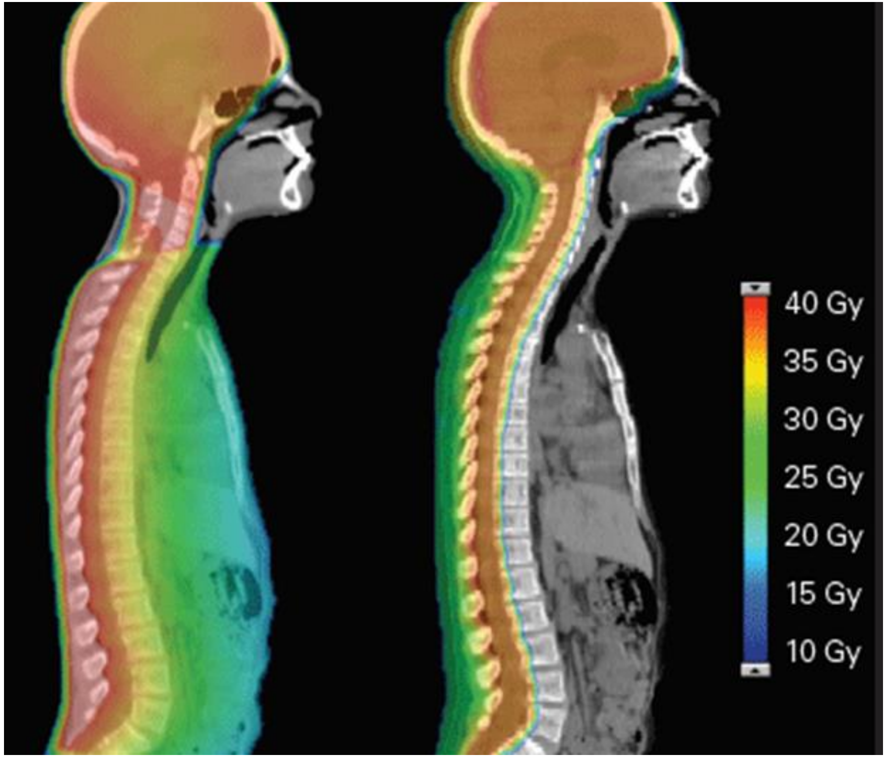
- Particle therapy
  - Photons
  - Electrons
  - Protons
  - Neutrons
  - Heavy ions



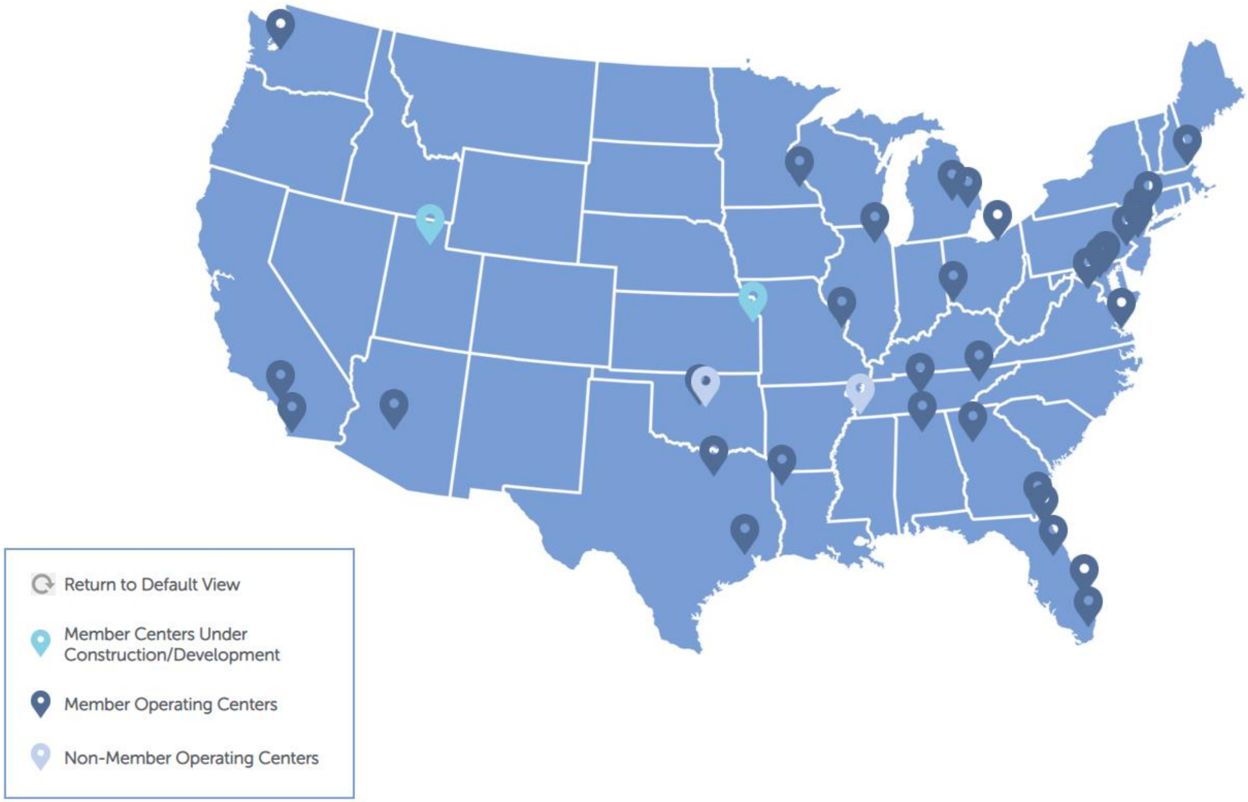
Proton Therapy

- Proton radiation is a type of external beam radiation
- FDA approved 1988
- Reduces radiation exposure to surrounding normal tissues
- Confers a clinical advantage for some patients compared to conventional X-ray (photon) treatment

Proton Therapy



Proton Therapy Centers



Proton Therapy: ASTRO Guidelines

ASTRO Group 1

- Ocular tumors
- Base of skull tumors
- Bone tumors
- CNS tumors, including spinal tumors near the cord
- CSI
- Many H&N cancers
- Esophageal cancer
- Mediastinal tumors
- Mesothelioma
- HCC and biliary cancers
- Pediatric tumors
- Patients with genetic syndromes with RT hypersensitivity (e.g. NF-1, Rb, BRCA1/2)
- RP sarcomas
- Re-RT

ASTRO Group 2

- Other H&N cancers
- Lung cancers
- Other GI malignancies
- Prostate cancer
- Breast cancer

Radiation Treatment Machines: Neutrons

- Potentially higher efficacy with radioresistant and/or hypoxic tumor cells
- Causes DNA damage that is less repairable
- Less dependent on cell cycle state

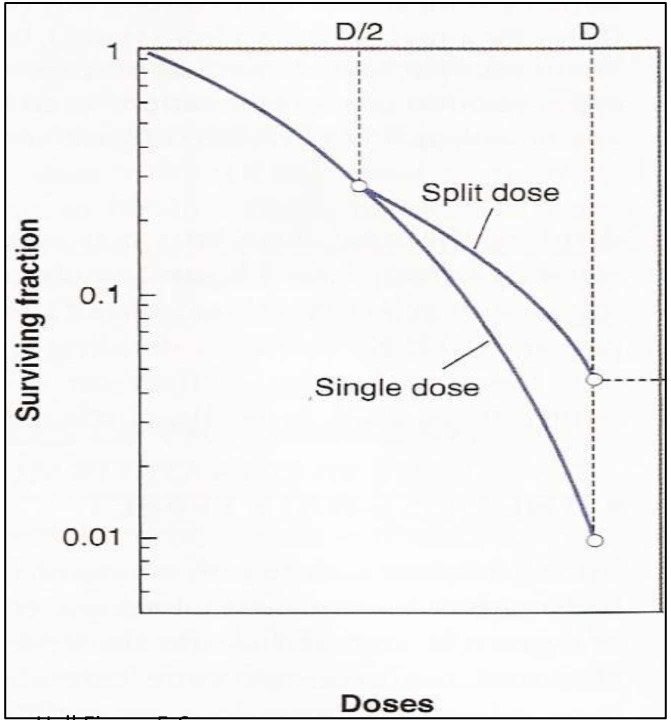
How Do We Decide on Radiation Dose and Length?

Radiation Oncology: Dose

1. Dose needed to kill a particular type of cancer has typically been established by prospective 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

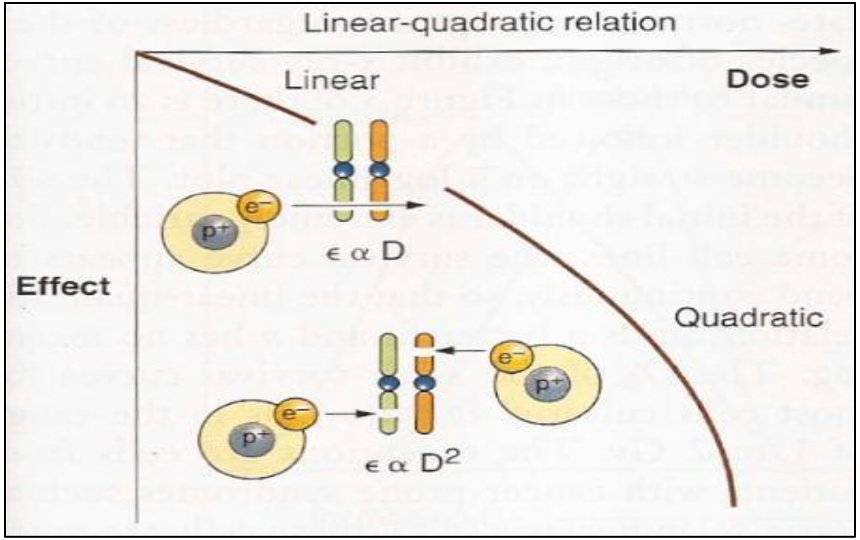
Radiation Oncology: Fractionation

- 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

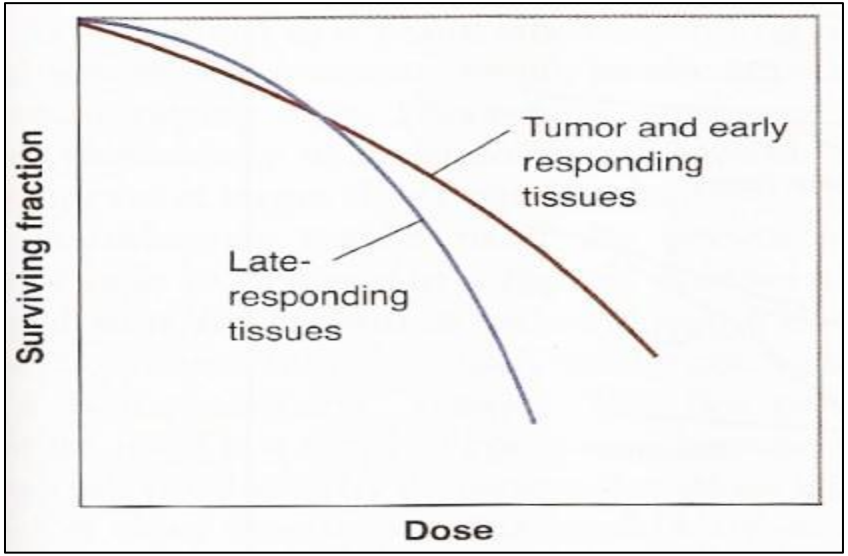
- Linear quadratic (α/β) model
  - Alpha = single hit kills
  - Beta = double hit kills



Hall Fig 3.5

Radiation Oncology: Fractionation

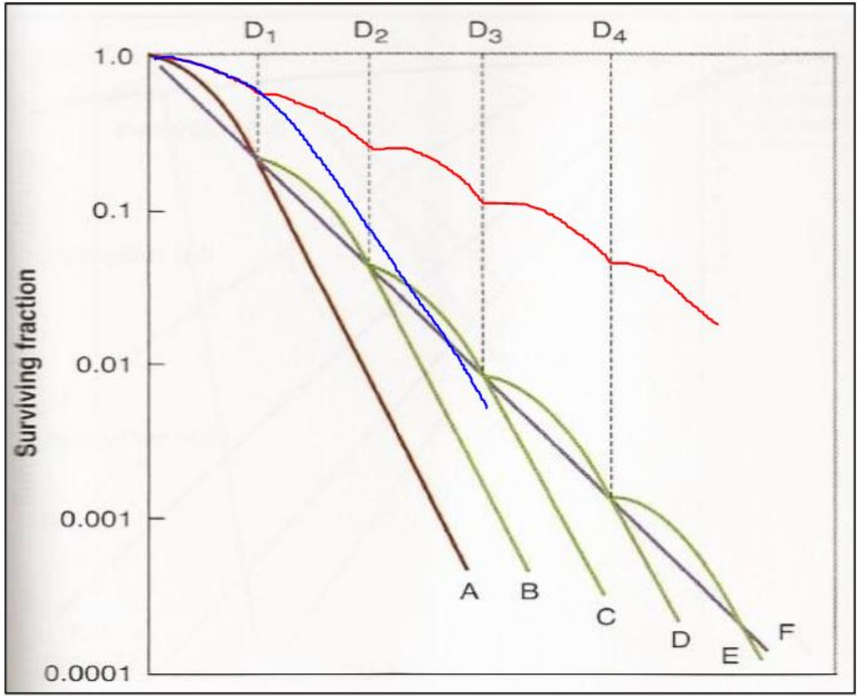
- Different cell lines, tissues, and tumors have different α/β values
  - α/β defines the dose of radiation at which the number of cells killed by a single hit equals the number killed by two hits
  - High α/β = most tumors, early responding normal tissues
  - Low α/β = late responding tissues, some 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/[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 be more effective for tumors with quick repopulation rates
    - E.g. head and neck cancers

What are some big trends in the field in recent years?

Big Trends in Radiation Oncology

- Decreasing number of treatments
- Increasing utilization of SBRT
- Expanding role in metastatic patients
- Precision radiation oncology

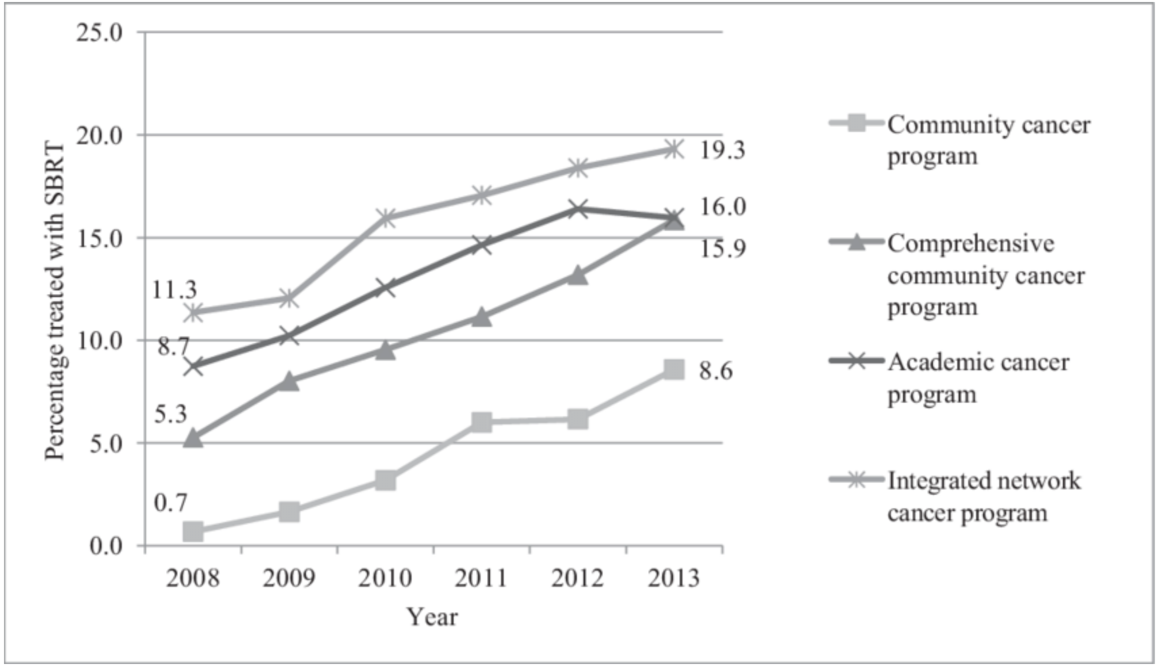
Less Treatments

- Improved technology allows for safe delivery of equi-effective doses of radiation over less time
- Breast 25 → 15 → 5
- Prostate 44 → 20-28 → 5
- Rectal 25 → 5
- Lung 30 → 5

What is SBRT?

- Billing: a certain minimum dose of radiation given in 5 or less fractions
- Technical: advanced dosimetric, imaging, and immobilization techniques to deliver radiation that is:
  - More conformal
  - More heterogeneous
  - Sharper dose penumbra
  - Allows higher doses per fraction safely

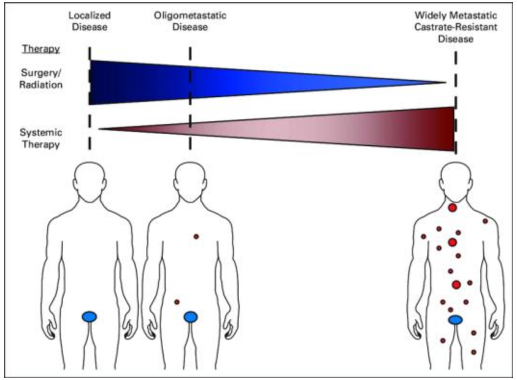
More SBRT



25.0
20.0
15.0
10.0
5.0
0.0
Percentage treated with SBRT
11.3
8.7
5.3
0.7
19.3
16.0
15.9
8.6
2008
2009
2010
2011
2012
2013
Year
Community cancer program
Comprehensive community cancer program
Academic cancer program
Integrated network cancer program

RT in Metastatic Cancer

- Radiation traditionally restricted to palliation
- Theory that cancer cells have already spread throughout the entire body, so local ablation has no oncologic benefit
- Recent studies are changing this paradigm, e.g. SABR-COMET, STAMPEDE



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 + SBRT 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

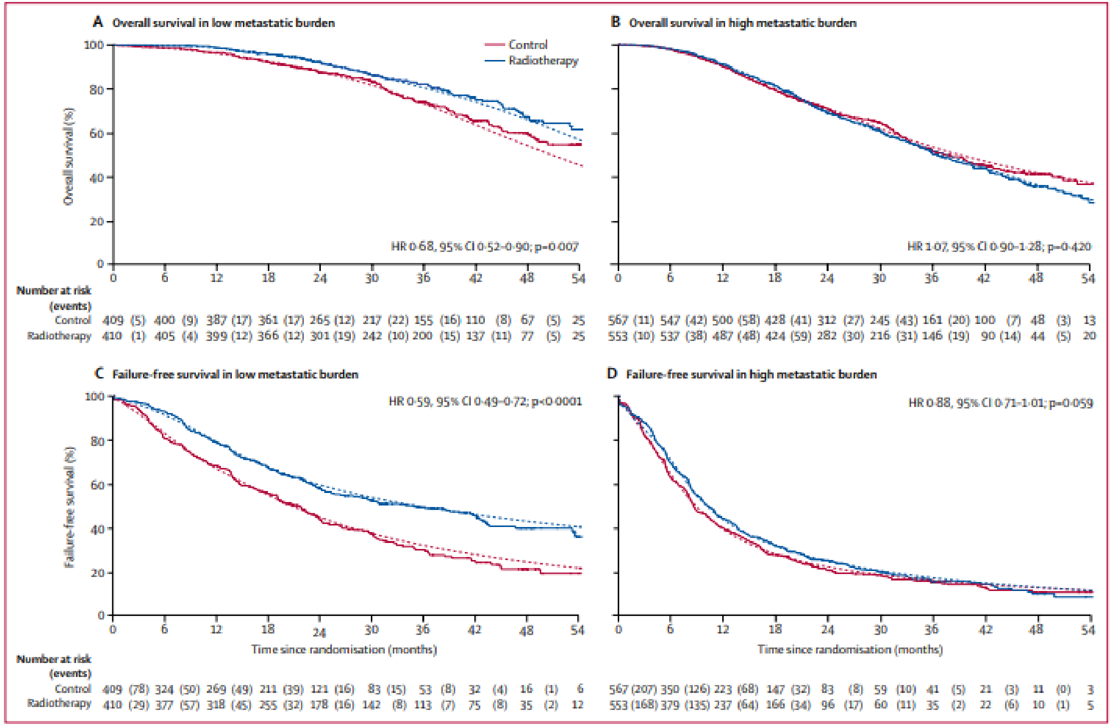


***Figure 4*: Overall survival and failure-free survival by treatment and metastatic burden**

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
- Disrupts interplay between macroscopic tumors and microenvironment of potential metastatic sites (“priming the premetastatic niche”)
- Enhancing immune response

Palliative RT Advances

- Trend to shorter regimens (8 Gy x 1)
- Increasing evidence that higher doses (SBRT) is beneficial even in palliative setting
- Research into treating mets BEFORE they're symptomatic

Precision Radiation Oncology

- Tailoring radiation treatment based on a patient’s individual factors
  - HPV status
  - Genetic/molecular tumor testing
  - Response to neoadjuvant treatment
  - Targeted radio-isotopes

Thank you for your attention!

Post-Presentation Questions

Question #1: By what mechanism does radiation therapy treat malignancy?

A. Direct cytotoxicity via DNA damage
B. Disruption of tumor vasculature
C. Impairing cell membrane integrity and denaturing proteins
D. Release of neo-antigens facilitating immune recognition
E. All of the above

Answer: E

Question #2: What characteristic of a cell indicates its sensitivity to radiation damage, and for cancers determines the optimal fractionation?

A. Oxygen enhancement ratio
B. The alpha/Beta ratio
C. Dose-depth profile
D. The Bragg peak
E. Nucleus:cytoplasm ratio

Answer: B

Post-Presentation Questions

Question #3: Why might a shorter radiation therapy treatment course be more beneficial than a longer one?

A. Patient convenience
B. Better local control based on tumor's alpha/Beta ratio
C. Widening the therapeutic window
D. Reduced cost
E. All of the above

Answer: E

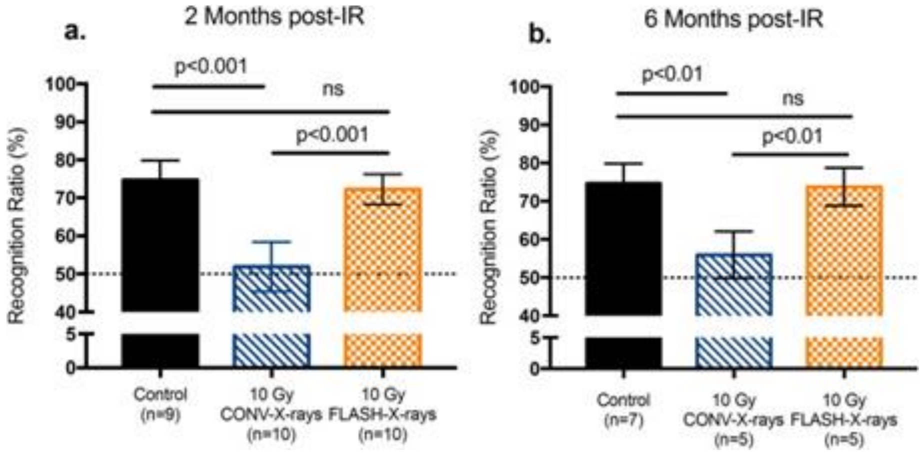
Question #4: What is the most common particle used in radiation therapy?

A. Electrons
B. Protons
C. Photons
D. Neutrons
E. Carbon ions

Answer: C

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

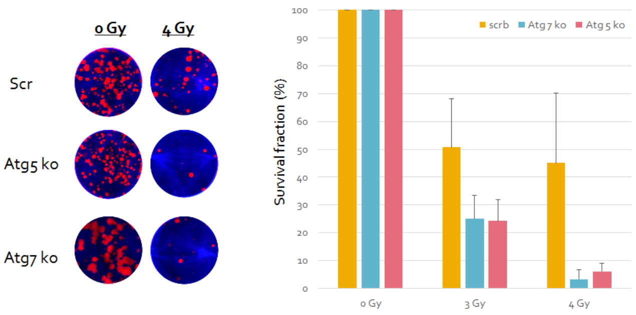


Montay-Gruel P et al. Radiother Oncol. 2018 Dec;129(3):582-588.

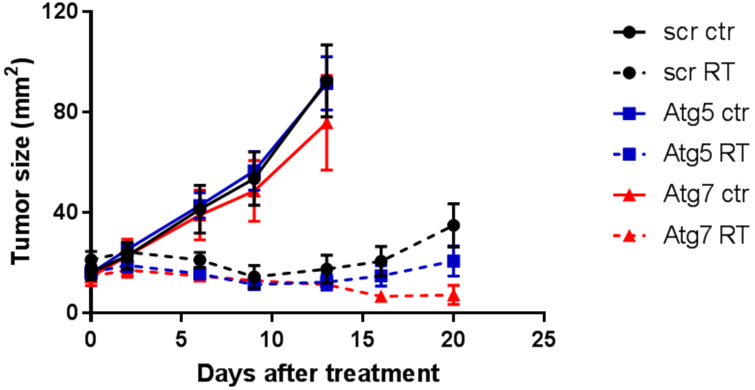
Making It Better

Can we augment the effect that RT has in metastatic cancer by modulating the way that cancer cells die?

Clonogenic response to RT



Autophagy limits efficacy of RT



Galluzzi et al., unpublished

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

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 - 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 - Recent Movement

CHISEL - Increased utilization of SBRT

Treatment of oligomets and oligoprogression

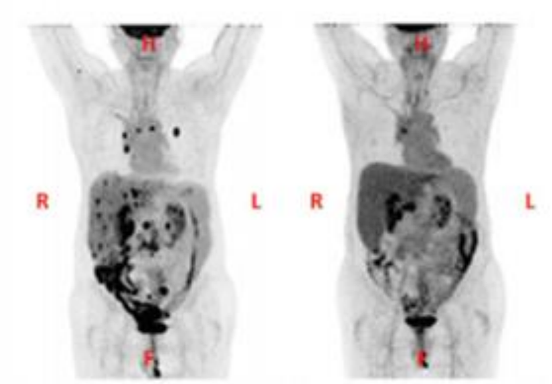
Dose escalation for SCLC (Gronberg Lancet Oncol 2021)

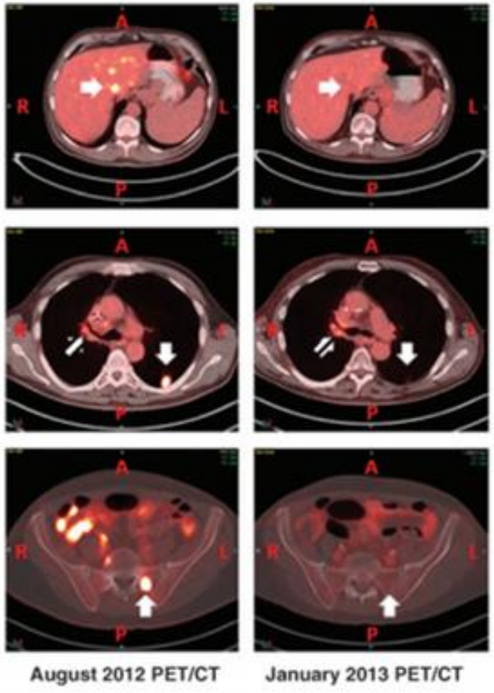
Mesothelioma

Oligomet NSCLC

The Holy Grail?

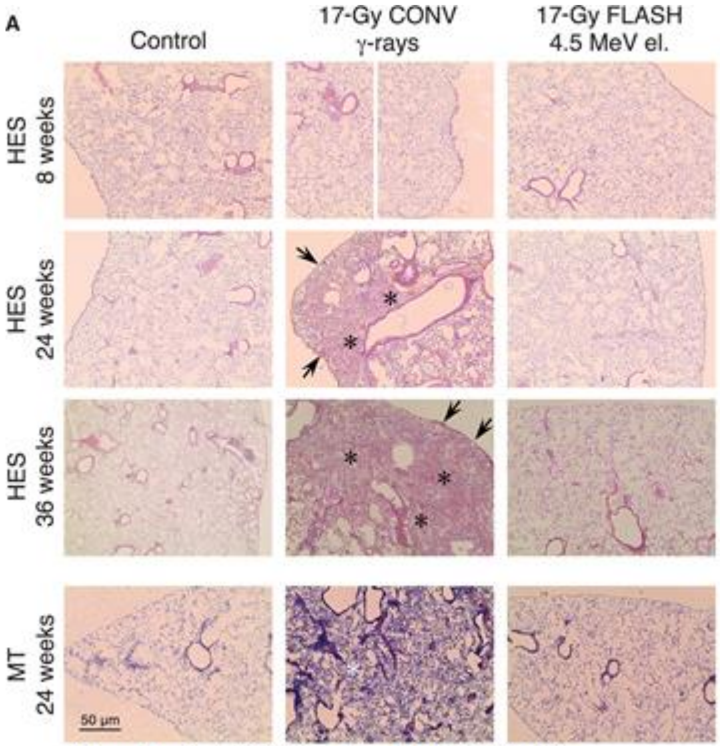
- Abscopal effects
- Synergistic combination of RT and systemic therapy





FLASH-RT

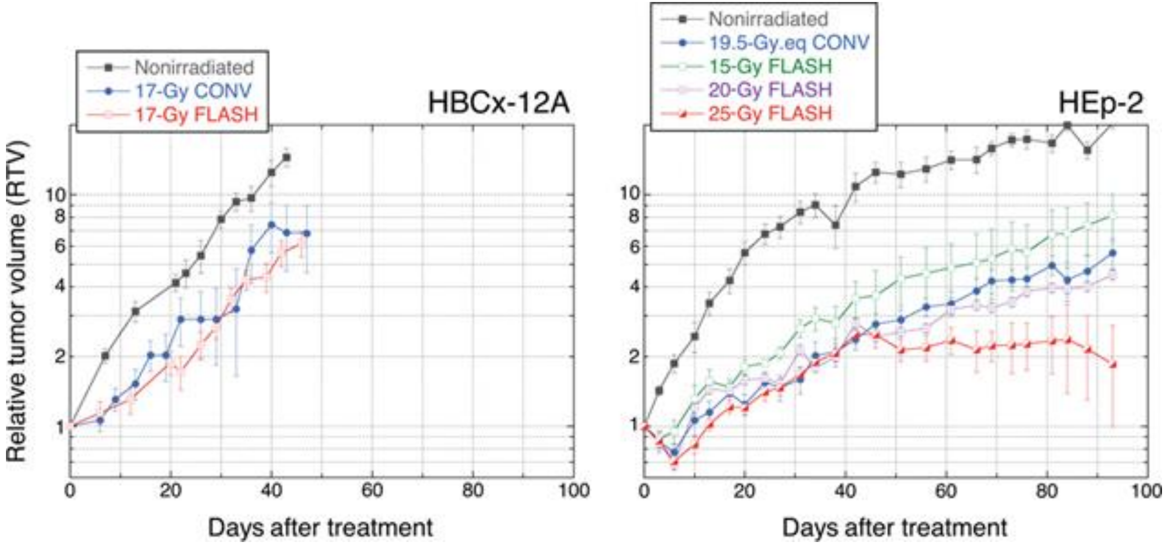
- Ultrahigh dose rate (>40 Gy/s)
  - Regular radiation treatments are typically 1-5 Gy/minute
  - Total body radiation is given 0.06-0.25 Gy/min
- Whole lung radiation in mice
  - Less pulmonary fibrosis
  - Hair depigmentation, no epilation or ulceration 36 weeks post FLASH RT



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 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.

Guidelines for this talk

45 minutes

Audience: med onc, both SCCA, local, and community. Half MDs, rest are APPs, nurses, and industry

Goal: cover some amount of rad onc for med oncs

Note: the use of RT in specific cancer types will be covered by med oncs, so the goal is not to bring up each definitive study for each cancer type, but more general background. This is the first year this topic has been added.

Chat with Andrew Coveler (co-organizer) on 7/30/20:

General Principles of Radiation Oncology

General overview of Rad Onc for med oncs - The planning process, when to use IMRT or not, advantage of protons, who really needs protons, who is it more controversial for, also a palliative focus (e.g. when to do 1 fraction vs 5 vs 10? why?), controversies in the field (e.g. short course RT in rectal cancer, hypofractionation in some sites), any use of RT in heme malignancies?

Definitely a Potpourri topic, and that’s okay