## **Complications of Radiation Therapy**





Gregg Goldin, MD BRRH Grand Rounds 2/26/19 • I have no financial disclosures relevant to this presentation

## (There aren't any)

## Many Cancer Treatments are Aggressive

- In general, to accomplish the goals of treatment we usually need to accept at least some toxicity
- Cancer is complex and requires a multidisciplinary approach (we all care for cancer patients)
  - The burden for patient and family is not only physical, but also psychosocial and financial in nature
- Seems to be general confusion about the expected side effects of a radiation treatment.
  - Many patients have comorbid issues not related to radiation; being able to differentiate between expected and non-expected side effects will allow us all to better care for our patients.

#### There will be more cancer survivors in the future...



#### **Cancer** Therapies and Early Detection Rates are Improving...



CC BY

## Objectives

- Learn basic physical, chemical, and biological principles of radiation oncology
- Learn some of the various mechanisms of radiation delivery
- Review radiation plans to understand the expected complications from some of the more common radiation treatments
  - Side effects and complications depend on total radiation dose, treatment volume, and exposed normal tissues in the near vicinity

## **Case Presentation**

#### 62 y/o M presents with new 3 month h/o back pain and Progressive lower extremity weakness/numbness

- History
  - No prior h/o cancer, otherwise was very healthy and fully functional
  - When did the pain begin?
    - 6 months ago
  - When last walking independently?
    - 3 days ago, walking with walker
  - Fever or weight loss?
    - 20 lbs in 3 months
  - Bowel/bladder symptoms?
    - Increased urinary retention and constipation

- Physical exam
  - •KPS?
    - 70
  - Raise legs against gravity?
    - 2/5 bilat.
  - •Hands sensation compared with feet sensation?
    - Worse in feet
  - •Reflexes (ankle, knee, elbow, wrist)?
    - Hyper-reflexia in lower joints

#### PSA is 1200 ng/mL

## MRI Spine: Epidural Spinal Cord Compression



#### Imaging findings

Compression of dural sac and its contents (spinal cord) by an extradural tumor mass involving 3 mid-thoracic vertebral levels

## Management

- Steroids
  - Reduce edema
  - If clinical suspicion is high, should be administered even before radiographic diagnosis
- Surgery
  - Indicated especially in young/fit patients when there is spinal instability or bony retropulsion causing the cord compression (radiation will not pull bone off nerve), as well as radioresistant tumors
  - Surgical Decompression/Stabilization
- Radiotherapy
  - indicated after surgery or in lieu of surgery
- Androgen Deprivation Therapy after staging w/u
  - to treat systemic disease as the diagnosis most likely prostate cancer based on PSA



## Introduction

- Radiation has been an effective tool for treating cancer for more than 100 years
- More than 60 percent of patients diagnosed with cancer will receive radiation therapy as part of their treatment
- Radiation oncologists are cancer specialists who manage the care of cancer patients with radiation for either cure or palliation



Patient being treated with modern radiation therapy equipment.

#### **Brief History of Radiation Therapy**

- The first patient was treated with radiation therapy in 1896, just two months after the discovery of the X-ray.
- Rapid technology advances began in the early 1950s, with the invention of the linear accelerator.
- Planning and treatment delivery advances have enabled radiation therapy to be more effective and precise, while decreasing the severity of side effects.



The linear accelerator is still used today to deliver external beam radiation therapy.

## What is Radiation?

Radiation is classified into two main categories:

- Non-ionizing radiation
- Ionizing radiation

#### **ELECTROMAGNETIC RADIATIONS**

SHORTER WAVELENGTH = HIGHER ENERGY



Photon E = hv (energy = Planck's const x frequency)

=  $hc/\lambda$  (c = speed of light,  $\lambda$  = wave length)

**ENERGY IS INVERSELY PROPORTION TO WAVELENGTH** 

#### **Non-ionizing radiation**

visible light,

microwaves, and infrared

particle or wave that has enough kinetic energy to raise the thermal energy of an outer shell electron and cause excitation with emission of low energy electromagnetic radiation (detected as heat or infrared)

#### **Ionizing** radiation

Ionizing radiation has enough kinetic energy to detach at least one electron from an atom or molecule, creating ions...

...in nature, ions are very unstable and free radicals typically result in a domino effect of utter molecular destruction

The main pertinent target in biological systems is the DNA within the cell nucleus, where irreparable damage results in cell apoptosis... leading to tumor destruction and tissue injury







### Direct and Indirect Action of Ionizing Radiation on DNA



#### **Oxygen Matters for Indirect Radiation**

- Binds H radicals forming hydrogen peroxide H<sup>·</sup> + O<sub>2</sub> → HO<sub>2</sub><sup>·</sup> (+HO<sub>2</sub><sup>·</sup>) → H<sub>2</sub>O<sub>2</sub> (+O<sub>2</sub>)
- Binds electrons to give superoxide  $e^{-} + O_2 \longrightarrow O_2^{-} + (H_2O) \longrightarrow HO_2^{-} + OH^{-}$

Oxygen <u>"fixes</u>" the radical lesions in DNA in a form that can not be easily chemically repaired and therefore is a very powerful radiosensitizer.



# What Is the Biologic Basis for Radiation Therapy?

- Radiation therapy works by damaging the DNA of cells and destroys their ability to reproduce
- Both normal and cancer cells can be affected by radiation, but cancer cells have generally impaired ability to repair this damage, leading to cell death
- All tissues have a tolerance level, or maximum dose, beyond which irreparable damage may occur



# The Aim is to Increase Therapeutic Benefit!



Normal tissue complication dose-response curves are steep!

### Latency

Different tissues take different times to express damage (latency). This depends on their turnover time.

On this basis, normal tissues can be divided into

- <u>ACUTE/TRANSIENT (clinic effects start 10-14 days after initiation of therapy and start to resolve slowly 10-14 days after radiation is completed)</u>
  - Gut
  - Skin
  - Bone Marrow
  - Mucosa
- LATE (clinic side effects start > 6 weeks after initiation of therapy, may be transient or permanent)
  - Brain
  - Spinal Cord
  - Kidney
  - Lung
  - Bladder

- Short term side effects results from destruction of some (but not all) stem cells in the compartment of rapidly dividing epithelial tissues (skin, gut, oral mucosa, bone marrow, sclera, hair follicle, and anus/rectum).
- The result is inflammation and sloughing of the epithelial tissue. The stem cells regenerate at the end of treatment (latency period of 2 weeks) and the tissue typically heals well
  - Dermatitis
  - Mucositis
  - Enteritis
  - Proctitis
  - Cystitis
  - alopecia
  - marrow suppression
  - Otitis
  - conjunctivitis
- Also, local inflammation results in leaky vessels, leading to edema, hyperemia, warmth, and occasional pain flare

## Late Effects

- Long term effects can include fibrosis and end-organ damage. There are well-described cascades of cytokines which directly injury parenchymal cells and indirectly lead to necrosis/fibrosis by causing subendothelial damange in blood vessels, eventually leading to radiation induced arteriosclerosis.
- Nearly all patients will experience some level of fatigue during and after radiation is delivered due to the pro-inflammatory cytokine cascade. Level of fatigue varies per size of the radiation field volume, individual sensitivity, activity level, and nutritional status.

#### CLASSIFICATION OF ORGANS AT RISK

o Classified as :

- Serial whole organ is a continuous unit and damage at one point will cause complete damage of the organ (spinal cord, digestive system). So even point dose is significant
- Parallel organ consists of several functional units and if one part is damaged, the rest of the organ makes up for the loss (lung, bladder). Dose delivered to a given volume or average/mean dose is considered

## **Clinical Uses for Radiation Therapy**



External beam radiation treatments are usually scheduled five days a week and continue for one to ten weeks

- Therapeutic radiation serves two major functions
  - To cure cancer
    - Destroy tumors that have not spread
    - Kill residual microscopic disease left after surgery or chemotherapy
    - Aid in organ preservation (breast, anal, certain head/neck, extremity sarcoma)
  - To reduce or palliate symptoms
    - Shrink tumors affecting quality of life, e.g., a lung tumor causing shortness of breath
    - Alleviate pain or neurologic symptoms by reducing the size of a tumor

## **Radiation** Therapy Basics

- The delivery of external beam radiation treatments is painless and usually scheduled five days a week for one to ten weeks
- The effects of radiation therapy are cumulative with most significant side effects occurring near the end of the treatment course.
  - Side effects usually resolve over the course of a few weeks



Example of erythroderma after several weeks of radiotherapy with moist desquamation

Source: sarahscancerjourney.blogspot.com

## **Common Radiation Side Effects**



Unlike the systemic side effects from chemotherapy, radiation therapy usually only impacts the area that received radiation Side effects during the treatment vary depending on site of the treatment and affect the tissues in radiation field:

- Breast swelling, skin redness
- Abdomen nausea, vomiting, diarrhea
- Chest cough, shortness of breath, esophogeal irritation
- Head and neck taste alterations, dry mouth, mucositis, skin redness
- Brain hair loss, scalp redness
- Pelvis diarrhea, cramping, urinary frequency, vaginal irritation
- Prostate impotence, urinary symptoms, diarrhea
- Fatigue is often seen when large areas are irradiated

Modern radiation therapy techniques have decreased these side effects significantly

## The Treatment Process

- Referral
- Consultation
- Simulation
- Treatment Planning
- Quality Assurance

## Simulation



- Patient is set up in treatment position on a dedicated CT scanner
  - Immobilization devices may be created to assure patient comfort and daily reproducibility
  - Reference marks or "tattoos" may be placed on patient
- CT simulation images are often fused with PET or MRI scans for treatment planning

## **Treatment Planning**

- Physician outlines the target and organs at risk
  - Sophisticated software is used to carefully derive an appropriate treatment plan
    - Computerized algorithms enable the treatment plan to spare as much healthy tissue as possible
  - Medical physicist checks the chart and dose calculations
  - Radiation oncologist reviews and approves final plan



Radiation oncologists work with medical physicists and dosimetrists to create the optimal treatment plan for each individualized patient







## Left Optic Nerve Sheath Meningioma



Isodose lines

## **Dose Volume Histogram**

- Plots dose delivered to volume of tissue exposed
- Need to meet guidelines at various doses for different tissues
  - Guidelines based on decades of collective experience
- Allows for comparison between different radiation plans (see dotted and solid lines)



Prostate radiation plan

## Safety and Quality Assurance

- Each radiation therapy treatment plan goes through many safety checks
  - The medical physicist checks the calibration of the linear accelerator on a regular basis to assure the correct dose is being delivered
  - The radiation oncologist, along with the dosimetrist and medical physicist go through a rigorous multi-step QA process to be sure the plan can be safely delivered
  - QA checks are done by the radiation therapist daily to ensure that each patient is receiving the treatment that was prescribed for them

## **Delivery of Radiation Therapy**



The type of treatment used will depend on the location, size and type of cancer.

- External beam radiation therapy typically delivers radiation using a linear accelerator
- Internal radiation therapy, called brachytherapy, involves placing radioactive sources into or near the tumor
- The modern unit of radiation is the Gray (Gy), traditionally called the rad
  - 1Gy = 100 centigray (cGy)
  - 1cGy = 1 rad
# Cyberknife Prostate SBRT – for low and favorable intermediate risk prostate ca.



CyberKnife<sup>®</sup> M6<sup>™</sup> with InCise2 Technology: A Tumor's Worst Enemy » read more on page 8



Also in this issue » Breast Health Imaging Technology: No Longer a One-Size-Fits All PAGE 5 Transcatheter Aortic Valve Replacement Surgical Method Now Offered PAGE 6







The rectum is next to the prostate complicating prostate radiation therapy.

With SpaceOAR System The SpaceOAR Spacer pushes the rectum away from the prostate, decreasing rectal injury during prostate RT.





Pre Implant









Prostate

#### Prostate seed implant



Low Dose Rate (LDR) "aka permanent seed implant"

#### High Dose Rate (HDR)

#### 2-4 treatments

a single Highly active Iridium seed moves through hollow catheters to specified points within the gland

#### **Side Effects of Prostate Radiation**



The <u>structures</u> that will get hit by radiation and have inflammation or irritation: bladder, urethra and rectum



Pelvic Nodal RT increases bowel exposure – risk for SBO and permanent low grade bowel changes



- Rectum loose/frequent stools, burning, urgency, bleeding, ulceration
- Bladder/urethra dysuria, frequency, nocturia, hesitancy, 10-20% chance of permanent low grade urinary changes, bladder outlet obstruction, bleeding/ulceration
- Large and Small Bowel enteritis, 10-20% chance of permanent low grade bowel changes, bowel obstruction,
- Pelvic Bones fractures difficult to heal
- Sexual Nerves erectile dysfunction
- Prostate and seminal vesicles dry ejaculate











6 Caplets'

100 Coated Gel Caplets\* "Capsule-Shaped Gelatin-Coated Tablets



## Skin











The images show radiation dermatitis at four different stages of severity in fair skin (A-D) and darkly-pigmented skin (E-H). Radiation dermatitis ranges from faint erythema and hyperpigmentation (A, E) to definite erythema and hyperpigmentation with dry fine desquamation (B, F) to early moist desquamation, and patchy crusting (C, G) to moist desquamation, superficial ulceration, and peeling in sheets (D, H).

• dryness, itching, burning, blistering, peeling, infection

#### • Delayed Healing:

- Areas on the extremities prone to edema
- Poor wound healing (smokers, diabetics)
- infection
- Persistent tumor





10% Calendula % Free of Toxins, Fragrance & Dyes % Iowes Easily Over Delicate Skin % Non-Gready % Non-Staining

6.3 ot (200ml)





#### Breast







Moves the heart inferiorly & posteriorly



#### **Regional lymph node Irradiation**

- Covers several lymph node basins
  - Axilla
  - Supraclavicular fossa
  - Low cervical neck
  - +/- internal mammary nodes







# Partial Breast Radiation with Balloon Catheter ("Mammosite")





## Partial Breast radiation with Accuboost Machine



Post-Radiation	Time	Complications
Early	Weeks to months	Skin thickening with breast edema
		Fat necrosis
		Dystrophic calcifications
		Radiation-induced pneumonia
		Pleural effusion
Intermediate	Months to years	Skin retraction with breast fibrosis
		Glandular atrophy
		Lactation difficulty
		Overlying bone fracture
		Pulmonary fibrosis
		Pericardial disease
Late	More than 10 years	Cardiomyopathy
		Radiation induced malignancy



Figure 1: Radiation Dermatitis—Patient's breast radiation dermatitis in the 6th week of treatment.

- 10% risk of mild pain from surgery and radiation
- Heart especially dose to the LAD
- 3% risk of pneumonitis
- Brachial plexopathy (rare) when treating lymph nodes; more of an issue in the retreatment setting
- Lymphedema

- Many women receive btw 1-3 Gy for L Breast Ca
- Relative risk may increase by 20% (7.4% per Gy)
- Average woman has 7% risk of coronary event before 80. Radiation may raise this to roughly 8 or 9%

## Risk of ischemic heart disease in women after RT for breast cancer

A population-based case control study by Darby et al. demonstrated that the risk of MCEs increased progressively with the cardiac radiation dose, by 7.4 percent for each 1 Gy of radiation to the heart



Rate of increase of major coronary events vs. mean RT dose to the Heart, as Compared with the estimated rate with no radiation exposure to the heart. (Darby et al., N Engl J Med. 2013;368(11):987-98 Radiation induced boart discass Anterior or left chest irradiation location High cumulative dose of radiation (>30 Gy) Younger patients (<50 years)

High dose of radiation fractions (>2 Gy/day)

Presence and extent of tumour in or next to the heart

Lack of shielding

Concomitant chemotherapy (the anthracyclines considerably increase the risk)

Cardiovascular risk factors (i.e. diabetes mellitus, smoking, overweight,  $\geq$  moderate hypertension, hypercholesterolaemia)

## Lung







- Rib
- Lung
- Central Airway
- Heart
- Esophagus
- Spinal cord





Radiation pneumonitis

### Rectal

· 5-6 weeks of daily (M-Fri) radiation





- Rectum
- Bladder
- Pelvic bones
- Sexual nerves
- Bowel

#### Anal Cancer



- Same as rectal
- Skin
- Anal Sphincter Muscles fecal leakage/incontinence often dependent on lifestyle factors, esp. diet



Sacral insufficiency
fracture



#### • Lymphedema





#### Brain



• Hippocampal sparing whole brain radiotherapy



- Fatigue
- Skin
- Alopecia
- 10% risk for worsening edema
  - Headaches
  - n/v
  - photophobia
  - Can be serious if ventricles obstruct or brain herniates



### Stereotactic Radiosurgery (SRS)



### SRS complications

- Radiation necrosis
- Worsening in edema



## Esophagus





#### Pancreas SBRT

Endoscopic fiducial
Markers are required

Small bowel injury is The main risk

Most patients have mild-Moderate n/v, diarrhea



#### • Radiation induced hemorrhagic duodenitis



#### Liver





 Radiation induced liver disease
# Bladder









### Cervix







#### Small bowel obstruction



### Uterus

#### Vaginal Cylinder Brachytherapy to reduce vaginal cuff recurrence







## Head and Neck Cancer











### Sarcoma



## Pediatrics

- Major Late Effects
  - Cardiotoxicity
  - Second Malignancy
- Other late effects
  - thyroid dysfunction
  - pulmonary fibrosis
  - peripheral vascular disease
  - muscle atrophy
  - Growth abnormalities

Stage III Hodgkins Lymphoma, involving neck, mediastinum, and periaortics





 Surgery followed by postoperative radiation after incisions heal (roughly 2 weeks)



30 Gy in 10 fractions AP and PA (opposed fields)

Sensitive normal tissues in field include heart spinal cord esophagus spinal bones skin

### Conclusions

- Radiation Therapy is an important tool for locoregional treatment of cancer, with either curative or palliative intent
- Radiation complications depend on a variety of factors, including
  - Total Dose
  - Volume of Field
  - Surrounding normal tissues
  - Host factors, including comorbid conditions, lifestyle, and genetics\*

 \*In the future, genetic analyses may offer potential for more-personalized radiation treatments

