Complications of Radiation Therapy

Gregg Goldin, MD
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(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...

Number of people with cancer by age, World

Total number of people with cancer, differentiated by age. This is measured across all cancer types.

Source: IHME, Global Burden of Disease
Cancer Therapies and Early Detection Rates are Improving...
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
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.
What is Radiation?

• Radiation is classified into two main categories:
  - Non-ionizing radiation
  - Ionizing radiation
Electromagnetic Radiations

Photon $E = h\nu$ (energy = Planck’s const x frequency)

$= \frac{hc}{\lambda}$ (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

**DIRECT ACTION**

- $\text{e}^-$
- $\text{OH}^-$

**INDIRECT ACTION**

- $\text{H}_2\text{O}$
- Photon

$R$: DNA molecule

4 nm and 2 nm distances indicate the range of action for direct versus indirect effects.
Oxygen Matters for Indirect Radiation

- Binds H radicals forming hydrogen peroxide
  \[ \text{H}^- + \text{O}_2 \rightarrow \text{HO}_2^- (+\text{HO}_2^-) \rightarrow \text{H}_2\text{O}_2 (+\text{O}_2) \]

- Binds electrons to give superoxide
  \[ \text{e}^- + \text{O}_2 \rightarrow \text{O}_2^- + (\text{H}_2\text{O}) \rightarrow \text{HO}_2^- + \text{OH}^- \]

- Binds organic radicals to form peroxides
  \[ \text{R}^- + \text{O}_2 \rightarrow \text{RO}_2^- \text{ (radical peroxide)} \]
  \[ \text{RO}_2^- + \text{R}' \text{ H} \rightarrow \text{ROOH} + \text{R}' \text{ (hydroperoxide)} \]
  \[ \text{RO}_2^- + \text{R}' \text{ .} \rightarrow \text{ROOR}' \text{ (peroxide)} \]

**Oxygen “fixes” the radical lesions in DNA in a form that can not be easily chemically repaired and therefore is a very powerful radiosensitizer.**
SINGLE STRAND BREAK
1000 / CELL / GRAY

BASE CHANGE (eg C - U)
BASE LOSS
1000 / CELL / GRAY
BASE MODIFICATION
(eg thymine/cytosine glycol)

INTRASTRAND CROSSLINK
0.5 / CELL / GRAY

INTERSTRAND CROSSLINK

DNA-PROTEIN CROSSLINK
1 / CELL / GRAY

SUGAR DAMAGE
(abstraction of hydrogen atom)

DOUBLE STRAND BREAK
30/ CELL / GRAY
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

• **ACUTE/TRANSIENT** (clinic effects start 10-14 days after initiation of therapy and start to resolve slowly 10-14 days after radiation is completed)
  - 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 damage 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

- 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

• 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

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

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, esophageal 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

Unlike the systemic side effects from chemotherapy, radiation therapy usually only impacts the area that received radiation.

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)
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

- *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*:
  - $1\text{Gy} = 100\text{ centigray (cGy)}$
  - $1\text{cGy} = 1\text{ rad}$

The type of treatment used will depend on the location, size and type of cancer.
Cyberknife Prostate SBRT – for low and favorable intermediate risk prostate ca.
Without SpaceOAR

- Low Dose
- High Dose
- Prostate
- Rectal Wall

With SpaceOAR

- Low Dose
- High Dose
- Prostate
- SpaceOAR
- Rectal Wall

Anatomy without SpaceOAR System

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

Post Implant

12 Months
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
The structures 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
Skin
• dryness, itching, burning, blistering, peeling, infection

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

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<th>Post-Radiation</th>
<th>Time</th>
<th>Complications</th>
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<td>Early</td>
<td>Weeks to months</td>
<td>Skin thickening with breast edema</td>
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<td>Fat necrosis</td>
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<td>Radiation-induced pneumonia</td>
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<td>Intermediate</td>
<td>Months to years</td>
<td>Skin retraction with breast fibrosis</td>
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<td>Glandular atrophy</td>
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<td>Lactation difficulty</td>
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<td>Pulmonary fibrosis</td>
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<td>Pericardial disease</td>
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<td>Late</td>
<td>More than 10 years</td>
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<td></td>
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<td>Radiation induced malignancy</td>
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**Figure 1: Radiation Dermatitis** — Patient’s breast radiation dermatitis in the 6th week of treatment.
• 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%

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**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.

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**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 heart disease

- 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, ≥moderate hypertension, hypercholesterolaemia)
• Rib
• Lung
• Central Airway
• Heart
• Esophagus
• Spinal cord
• Radiation pneumonitis
Rectal

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

- 5-6 weeks of daily (M-Fri) radiation
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 nausea, vomiting, and 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
World Health Organization’s Oral Toxicity Scale

Grade 1
- Soreness ± erythema

Grade 2
- Erythema, ulcers; patient can swallow solid food

Grade 3
- Ulcers with extensive erythema; patient cannot swallow food

Grade 4
- Mucositis to the extent that alimentation is not possible

Severe Mucositis
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