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Introduction to Radiation Oncology
Pre-clinical

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Winter 2009
Overview

Radiation Oncology depends on the fields of radiation physics, radiation biology and medicine.

The understanding and application of each is enhanced by a knowledge of the other.

In these lectures, we will review how radiation interacts with tissue physically and biologically, and then focus on how to apply these concepts to treat patients.
What is a radiation oncologist?

- An oncologist
- A specialist and a generalist (all parts of the body)
- A person expert in applications of radiation
  - Uses radiation in a clinic and in an operating room
  - Directs therapists (who place patients on the machines), dosimetrists (who do dose calculations), and physicists
- A member of a multidisciplinary team
- A teacher
Electromagnetic Spectrum

- radio
- microwave
- infrared
- near-infrared
- visible
- ultraviolet
- x-rays
- therapy rays
- cosmic rays

Source Undetermined
Kinds of radiation - Photons

- Gamma rays and x-rays
- Penetrates deeply, so that the dose to the skin is less than the deep dose ("skin sparing")
- Depth of penetration moderately dependent on the energy of the beam.
- This is the main form of radiation used because it permits us to treat deep tumors without skin damage.
Kinds of radiation - Electrons

- Electrons interact directly with tissues, so that the dose to the skin tends to be high compared to deeper tissues.
- Depth of penetration is strongly dependent on the energy of the beam.
- This type of radiation is used to treat skin cancers, or other cancers that are relatively close to the surface of the body (< 6 cm).
Kinds of radiation - Charged particles

- Charged particles (protons and carbon nuclei) have better depth dose characteristics than photons and electrons
  - Depth of penetration is strongly dependent on the energy of the beam
    - Can go deeper than electrons with more skin sparing
- Carbon nuclei can kill hypoxic cells as effectively as well oxygenated cells
- However- MUCH (at least 20x) more expensive
How radiation is produced—teletherapy

- **Teletherapy** – radiation delivered by a machine
- **Cobalt** (rarely used in the modern era)
  - Radioactive material (activated in a cyclotron) and placed in the head of a machine
- **Linear accelerator**
  - Electrons are accelerated and made very energetic
    - Can be used directly
  - Can be directed at a metal target to produce high energy photons (x-rays)
The placement of radioactive sources into or next to the tumor

Depends on the “inverse square” rule of radiation

The intensity of the radiation depends on the square of the distance from the source (2x the distance, decrease the intensity by 4x)
Brachytherapy-concepts

- **Advantage:** can permit much more radiation to be given to the tumor compared to the normal tissue
- **Disadvantage:** harder to make the dose uniform to the tumor
- **Placement can be permanent or temporary** (minutes to days)
Results of Treatment

Source Undetermined
Prostate brachytherapy

Contrast in Bladder

I-125 seeds in prostate

Trans-rectal ultrasound probe
High dose rate brachy (HDR) Example – Ring and Tandem

Used to treat cervical and endometrical cancer
Interaction of radiation with cells

- Electrons can interact directly (direct effect)
- Electrons can produce free radicals (particularly \( \text{OH}^\bullet, \text{O}^\bullet, \text{and} \ H_2\text{O}_2 \)) which then interact
NEGATIVE ION

OH

$H_2O$

20Å

photon

INDIRECT ACTION

direct action

photon

DIRECT ACTION
Effects at the cellular level

- Free radicals exist for microseconds to milliseconds after the radiation
- Biological effects occur over hours, days, and years
- Molecular and cellular targets of radiation
  - DNA
  - Cell membrane
Cellular Response
Genotoxic Stress

X-rays

0h  24h  48h  72h

Irreversible Block 24h
Apoptosis 24h
Apoptosis 48h
Mitotic Death 72h
Colony Formation
Effects of radiation on DNA

- Single and double strand breaks
- Single strand breaks are well repaired, because there is an intact (correct) template in the other strand
- Repair occurs during next 6 hours
Sublethal damage repair

Surviving fraction

Dose (Gy)

Single dose curve

Repeated fraction curve

0 1.5 3

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Fluorodeoxyuridine inhibits SLDR
Results of DNA damage

- The double strand break appears to be the lethal lesion - cell must “guess” what to put back in place.
- One double strand break can kill a cell.
- Can lead to mutations and second cancers (≈ 1/1000 patients).
Mechanisms of cell death after DNA damage-mitosis

- During mitosis, chromosomes become condensed, align, and move to the two daughter cells.
- Cells with chromosomal damage cannot perform mitosis properly and die in the attempt.
- This explains why it can take months to years for tumors to shrink.
Effect of Irradiation ± BrdUrd on Chromosomes 1 and 4
Mechanisms of cell death after DNA damage - Apoptosis

- Programmed cell death
- DNA damage can cause some cells to activate a death pathway
- Often happens during a phase of the cell cycle other than mitosis
- Mechanism for cell death of lymphocytes (lymphomas) and spermatocytes (seminoma)
Apoptosis

Control Cells

Apoptotic Cells
DNA fragmentation

[Image description: Gel electrophoresis results for A549 and UMSCC-6 cells under different conditions (standard, BJAB, dFCyd, RT, RT + dFCyd).]
Effects of radiation on the cell membrane

- The cell membrane is the origin of many “life” (growth factor receptor) and “death” (apoptotic) signals
- Radiation can activate or suppress the former and activate the latter
Effects of RT depend on biology

- Genetics
- Oxygen status
  - Hypoxic cells (in tumors) are resistant
- Cell cycle
  - S phase resistant, M is sensitive
- Chemical modifiers (protectors/sensitizers)
Effect of radiation depends on physics

• Kind of radiation (High LET vs Low LET)
  ◆ How fast radiation is given (1 Gy/min causes more effects than 1 Gy/hr)
  ◆ How many fractions
    - 30 Gy in 3 Gy fractions causes more effects than 30 Gy in 2 Gy fractions
  ◆ The total time
    - 60 Gy in 2 Gy fractions given 6 times a week causes more effects than 60 Gy in 2 Gy fractions given 5 times a week
  ◆ How much tissue is irradiated (normal tissue)
Effects at the tumor/organ level

- The 4 R’s
- Fractionation
  - Hyperfractionation
  - Accelerated fractionation
- Radiation modifying drugs
- Parallel and serial organs
- Therapeutic index
- Why does radiation cure cancers?
4 “R’s” of Radiation Biology

- Repopulation - tumor cells can grow back during a course of radiation
  - Accelerated repopulation
- Reoxygenation- tumor O2 increases as cells die
- Redistribution - cell cycle distribution changes
- Repair - cells can repair damage between fractions
Hyperfractionation

- Standard: 1.8 to 2 Gy per day
- Hyperfractionation: two treatments per day
  - Each treatment is with less dose than standard (1.1-1.2 Gy)
  - Overall treatment time about the same as standard
- Rapidly proliferating cancers (head and neck)
  - Normal cells repair damage of many fractions better than tumor
- Clinical result: for same anti-tumor effect, less late toxicity
Accelerated fractionation

- **Standard**: 1.8 to 2 Gy per day

- **Accelerated fractionation**
  - Giving 2 treatments a day (same as hyperfractionation)
  - Each treatment is about the same dose as standard
    - This means more dose per day than standard
  - Overall treatment time is shorter than standard

- **Goal**: prevent tumor from growing during treatment (accelerated repopulation)
Chemical modifiers

- Radiation sensitizers
  - Hypoxic cell sensitizers
  - Chemotherapeutic agents
  - Molecularly targeted therapies

- Radiation protectors
  - Scavenge free radicals
  - Prevent cytokine induced damage (anti-inflammatory)
Normal Tissues: Parallel and Serial Organs

- **Parallel organ**
  - Damage to small fraction has no clinical toxicity
  - Clinical toxicity occurs when pass a threshold for fraction of the organ injured
  - Examples: lung and liver

- **Serial organ**
  - Damage to a small fraction produces toxicity
  - Examples: esophagus and spinal cord
Serial Circuit

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Serial Circuit: Interruption
Parallel Circuit

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Parallel Circuit: No Interruption
Effect of radiation on normal organs

- Organs vary in radiation tolerance
  - Kidney - 20 Gy in daily 2 Gy fractions
  - Liver - 30 Gy
  - Spinal cord - 46 Gy

- Parenchyma of the organ
- Vasculature leading to the organ
Therapeutic index

Definition: selectivity of radiation for killing the cancer compared to the normal cells

The therapeutic index for a single radiation treatment is small

How can we increase the therapeutic index?
- Multiple fractions \((1.2^{30} = 36)\)
- Drugs that selectively sensitize tumor cells
- Drugs that selectively protect normal cells
Fractionation versus single fraction

- Small tumors not abutting critical structures can be treated with a single fraction
  - Usually 10-20 Gy
  - Concept is ablation
    - Metastases to brain, lung, and liver
- Larger tumors or tumors that contain normal tissues
  - Concept is therapeutic index: treatment causes at least slightly more tumor kill than normal tissue damage
  - By giving 20-40 treatments of 1.8 to 2 Gy each, this effect is multiplied
Why does radiation fail?

● Tumor size
  - Can’t give enough radiation to kill every tumor stem cell without intolerable damage to normal tissue [fractionation; tumor sensitization; normal tissue protection]
  - Genetic radiation resistance [tumor sensitization]

● Tumor physiology
  - Hypoxic cells are relatively resistant to radiation, and may reside in the center of tumors [fractionation; tumor sensitization]
  - Rapidity of tumor cell growth [accelerated fractionation; tumor sensitization]
Why does radiation cure cancers?

- Normal cells migrate back into irradiated field
- Cancer cells may not repair DNA damage correctly
  - Cancer cells often have disordered cell cycle checkpoints
  - May attempt to replicate DNA before it is properly repaired
- Greater dependence of tumor on new vasculature, which may be more sensitive to radiation
- Probably not due to initial damage from radiation
  - For same dose of radiation, cancer cells and normal cells have same number of DNA double strand breaks
Radiation affects tissues through the generation of free radicals.

Cell death is caused chiefly by DNA double strand breaks.

The effects of radiation can be modified by:

- Physical factors (fraction size, total time, total dose, dose rate, and radiation type)
- Volume of organ irradiated
- Tumor genetics
- Tumor physiology (the 4 R’s)
- Chemical modifiers
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