Principle of Radiation Therapy

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Basic sciences for residents  Aug 11, 2010
Outlines

- Basic Radiation physics
- Basic Radiobiology
- Basic Clinical Radiation Oncology

- Clinical application in different diseases
Basic Radiation Physics

- **Type of radiation delivery**
  - Teletherapy: External beam radiation therapy
  - Brachytherapy

- **Types of radiation**
  - Photon
  - Electron
  - Others: Proton, Neutron
Radiation delivery: Teletherapy

- External beam radiation therapy

Linear accelerator

Cobalt 60
**Radiation delivery : Teletherapy**

- **External beam radiation therapy**
  - >> Cobalt-60
  - >> Linear accelerator

- **Radiation : gradual fall off**

- **Application : General**
  - : wide area treated
    (primary disease and lymphatic regions)
  - : Non invasive
Basic Radiation Physics

- **Type of radiation delivery**
  - Teletherapy: External beam radiation therapy
  - Brachytherapy

- **Types of radiation**
  - Photon
  - Electron
  - Others: Proton, Neutron
**Radiation delivery: Brachytherapy**

- Intracavitary
- Interstitial
- Mold

- Radiation: Rapid fall off
  \[ \text{dose drop} \propto \frac{1}{\text{distance}^2} \]

- Limited area closed to applicators
- After loading system
  >> not expose to radiation personnel
Brachytherapy : Intracavitary
Brachytherapy: **Intracavitary**
Brachytherapy: Interstitial
Brachytherapy: Mould
Basic Radiation Physics

- **Type of radiation delivery**
  - Teletherapy: External beam radiation therapy
  - Brachytherapy

- **Types of radiation**
  - Photon
  - Electron
  - Others: Proton, Neutron
Photon vs Electron

Photon (Megavoltage)
- Deeper penetration
- Deep tumor
- Higher beam energy --> deeper penetration
- Skin sparing effect

Electron
- Less penetration
- rapid fall off
- Superficial tumor
  (<5 cm deep from skin)
- Neck nodes, skin lesions, less skin sparing effect
Radiation doses

- Absorb dose: Gy (Gray)
  
  1 Gy = 100 cGy

- Fractionation (External beam radiation therapy)
  - Conventional fractionation: 2 Gy/Fraction,
    1 Fraction/day
    5 Fractions/week
  - total dose: Microscopic & postop: 50-60 Gy
    Gross dz: 66-70 Gy
Outlines

- Basic Radiation physics

- **Basic Radiobiology**

- Basic Clinical Radiation Oncology
  - Clinical application in different diseases
  - New technologies
Basic Radiobiology

- Radiation actions: Targets of radiation
- Radiation responses
- Interactions with modifiers
  - chemotherapy
  - hyperthermia
  - biological agents
DNA as radiation targets

Radiation Interactions with DNA

1 Gy

> 1000 bases damage

1000 single strand breaks

40 Double strand break

SSB correlates poorly with cell death

DSB most relevant lesion
THE CELL CYCLE

Radiosensitive phase: G2/M

Radioresistant phase: late S

Mitosis

Single chromatid

DNA replication

S phase

G1

G2

Radiosensitive phase: G2/M

Radioresistant phase: late S
**Why do we give radiation as fractionated treatment?**

<table>
<thead>
<tr>
<th>Type</th>
<th>dosage</th>
<th>fraction (F)</th>
<th>frequency (F/day, F/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross disease</td>
<td>66-70 Gy,</td>
<td>2 Gy/F,</td>
<td>1 F/day, 5 F/wk</td>
</tr>
<tr>
<td>Microscopic dz</td>
<td>50-60 Gy,</td>
<td>2 Gy/F,</td>
<td>1 F/day, 5 F/wk</td>
</tr>
</tbody>
</table>

- **4 R**
4 R’s of Radiotherapy

(? Fractionated treatments)

- Repair
- Redistribution (Reassortment)
- Reoxygenation
- Repopulation
Normal tissues vs Tumor

Fractionated treatment

- Normal tissue
  - better repair than tumor between fraction
4 R’s of Radiotherapy

- Repair
- Redistribution (Re-assortment)
- Reoxygenation
- Repopulation
Redistribution (Re assortment)

Move to G2/M: RT sensitive phases

Figure 5.4. Survival of Chinese hamster cells exposed to two fractions of x-rays and incubated at 37°C for various time intervals between the two doses. The survivors of the first dose are predominantly in a resistant phase of the cycle (late S). If the interval between doses is about 6 hours, these resistant cells have moved to the G2-M phase, which is sensitive. (Adapted from Elkind MM, Sutton-Gilbert H, Moses WB, Alescio T, Swain RB: Radiation response of mammalian cells in culture: V. Temperature dependence of the repair of x-ray damage in surviving cells (aerobic and hypoxic). Radiat Res 25:359–376, 1965, with permission.)
4 R’s of Radiotherapy

- Repair
- Redistribution (Re-assortment)
- Re-oxygenation
- Repopulation
Hypoxic cells are radioresistant

Oxygen diffusion in tissues

- normal oxygen
- hypoxic viable
- anoxic - necrotic
Re-oxygenation: \( \rightarrow \) re-sensitive to RT

Survivors after irradiation

Re-oxygenation

Aerated cells

Hypoxic cells
4 R’s of Radiotherapy

- Repair
- Redistribution (Re-assortment)
- Re-oxygenation
- Repopulation
Repopulation

Don’t prolong overall treatment time

Figure 5.4. Survival of Chinese hamster cells exposed to two fractions of x-rays and incubated at 37°C for various time intervals between the two doses. The survivors of the first dose are predominantly in a resistant phase of the cycle (late S). If the interval between doses is about 6 hours, these resistant cells have moved to the G2-M phase, which is sensitive. (Adapted from Elkind MM, Sutton-Gilbert H, Moses WB, Alescio T, Swain RR: Radiation response of mammalian cells in culture: V. Temperature dependence of the repair of x-ray damage in surviving cells (aerobic and hypoxic). Radiat Res 25:359–376, 1965, with permission.)
Radiation responses to tumor

- **Radiosensitive tumor (RS):**
  - Leukemia, Lymphoma, Germ cell tumor

- **Relatively radiosensitive tumor (RRS):**
  - Squamous cell carcinoma

- **Relatively radioresistant tumor (RRR):**
  - Adenocarcinoma

- **Radioresistant tumor (RR):**
  - Sarcoma, Melanoma

More resistance → Surgery
Radiation response to normal tissues

1. Early responding tissues
   - radiation effect during radiation treatment course
     - skin, epithelium, mucosa, Bone marrow

2. Late responding tissues
   - long term side effect (>6 months after RT)
     - spinal cord, liver, kidney, lung, bone, cartilage
Basic Radiobiology

- Radiation actions: Targets of radiation
- Radiation responses
- Interactions with modifiers
  - chemotherapy
  - biological agents
Chemotherapy & Radiation

- **Concurrent chemoradiation**
  - chemo as a radiosensitizer
  - Inhibit sublethal damage repair after radiation

Tannock & Hill
Targeted therapy and Radiation

- **EGFR**

  Cetuximab (C-225) (anti EGFR) + RT
  - locally advanced head and neck cancer

![Histological images and survival curve diagram]

*Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.*
Radioprotectors

- Protection
  - *Amifostine* (WR 2721)
  - Via free radical scavenger
  - Head and neck cancer
    - (accumulate in kidney and salivary gland)
  - decrease xerostomia
Outlines

- Basic Radiation physics
- Basic Radiobiology
- **Basic Clinical Radiation Oncology**
  - Clinical application in different diseases
  - New technologies
**General Radiotherapy Principles**

- Higher doses for gross disease
- Lower doses for subclinical disease
- Minimize dose to adjacent normal tissues
- Early stage: Single modality
- Advanced stage: Combined modalities
Role of radiation therapy

- **Curative treatment** (Depend on cell types, size, location)
  - Definitive treatment
  - Adjuvant treatment
  - Neoadjuvant treatment

- **Palliative treatment**
  - Local: primary tumor and/or neck nodes
  - Distant: Bone, Brain metastasis
Radiation Treatment Processes

Diagnosis
- X-ray
- CT Scanner
- Ultrasound
- MRI

Simulation

Treatment Planning

Treatment Delivery

Images:
- X-ray
- CT Scanner
- Ultrasound
- MRI
Positioning and Immobilization
Radiation simulation

Conventional simulation
CT Simulator
Radiation Simulation

Conventional Simulation

CT Simulation
Target delineation

GTV : Gross tumor volume
CTV : Clinical target volume
(Microscopic dz)
PTV : Planning target volume
Radiation treatment planning

2 Dimensions
(Hand calculation)

2.5 D
Computer planning
Treatment planning

3 DCRT
(3 Dimensional conformal radiation therapy)
Radiation fields shaping

Conventional blocking

Multileafs collimator
Modified Intensity in each 3D-CRT beam = IMRT

IMRT
(Intensity Modulated Radiation Therapy)

Maximize tumor dose Minimize surrounding normal tissues
IMRT
IGRT

- **Image Guided Radiation Therapy**
  - to reduce set up error
  - to reduce treatment uncertainties
    - Bladder volume
    - Rectal volume

- **Adaptive Radiation Therapy**
  - tumor motion: Lung cancer
  - tumor shrinkage after some doses of radiation
Planning scan

Verification scan
Image analysis: comparison with reference images

Reference image (planning CT)  Localization image (cone beam CT)  Mixed image (not matched)
Disease specific sites: CNS

- **Role**: Postoperative
  - Definitive

- **Benign diseases** (46-54 Gy, in 23-27 fractions or SRS)
  - AVM
  - Pituitary adenoma
  - Meningioma
  - Acoustic neuroma
Optic n. Meningioma
50-54 Gy, 2Gy/F
Disease specific sites: CNS

- **Malignant diseases**

  - Primary brain tumor
    : Malignant gliomas (60 Gy/30F),

  - Brain metastases
    : Palliative treatment: (30 Gy/10F)
    : SRS (Stereotactic radiosurgery)
GBM

CSI Medulloblastoma
Brain metastasis

Stereotactic Radiosurgery (SRS)
Disease specific sites: Head & Neck

• **Definitive RT**
  -- Nasopharyngeal CA
  -- Oropharynx
  -- Larynx

• **Postoperative radiation therapy**
  -- oral cavity
  -- larynx, Hypopharynx
  -- Parotid
Nasopharyngeal cancer
Disease specific sites: Breast

Postoperative treatment

Indications for postoperative RT

1. All patients with breast conservative surgery

2. Post-mastectomy radiation in locally advanced

( T > 5 cm, > 4 node positive)
Disease specific sites: Thoracic

- Non small cell lung cancer
- Small cell lung cancer

Chemotherapy + Radiation therapy
Non small cell lung cancer
66 Gy, 2 Gy/F to gross disease
Disease specific sites: Pelvis

Rectal cancer (in combination with chemotherapy)

>> Locally advanced disease
   (invade through serosa, Node positive)

- Postop RT

- Preop RT: sphincter preservation
  : downstaging
  : decrease side effect from postop RT
  (small bowel trapping in the pelvis)
RT techniques for rectal cancer

50 Gy in 25 fractions
Cholangiocarcinoma

Gastric CA
Disease specific sites: GYN

- External beam RT (Pelvic ERT)
- Intracavitary brachytherapy (ICRT)
- Cervical cancer
- Endometrial cancer
- Vagina, vulva cancer
Disease specific sites: **GU**

- **Prostate CA**
  - -- Definitive treatment
  - -- Postoperative treatment

**IMRT for Prostate CA**

**Prostate Brachytherapy**
Disease specific sites: Pediatrics

- **Non CNS**
  - **Wilm’s tumor**
    - advanced stage, unfavorable histology
  - **Neuroblastoma**
    - residual dz after surgery and chemotherapy
    - advanced stage

- **CNS**
  - **Medulloblastoma: Craniospinal RT**
Oncologic emergencies & Palliative treatment

- SVC obstruction
- Brain metastasis
- Spinal cord compression: Surgery + Steroid → ERT
- Bone metastasis: RT +/- Surgical decompression
**Radiation side effects** Within RT fields

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**Acute side effects**

- During radiation treatment
- Acute responding tissues
  - (Dividing cells: Skin, mucosa)
- Transient

**Late side effects**

- Typically 0.5-6 years after RT
- Late responding tissue
  - (spinal cord, bones)
- Irreversible
Common acute side effects & managements

- **Skin: acute side effects**
  - No specific Tx
  - Steroid cream
  - Aware of superimposed infection

- **40 Gy Erythema**
- **50-60 Gy**
  - Dry desquamation
- **60-70 Gy**
  - Moist desquamation
Common acute side effects & managements

- **Mucositis, Esophagitis**: acute side effects
  - \( \sim 30 \text{ Gy} \rightarrow \) Onset
  - More dose \( ightarrow \) more severe
  - Relieve \( ightarrow \) about 2-3 wks after RT
  - Chemotherapy \( ightarrow \) enhance mucositis

**Management**
- Good mouth hygiene, treat superimposed infection
- Hydration/ Nutrition
- Xylocain viscous
- Reassure patient
Common side effects & managements

- RT induced cystitis
  
  **Onset**  acute to late effect ( > 3-6 months)
  More dose  more chance (>70-75Gy)

**Management:**

- Grade 1  Hydration
- Grade 2  Antispasmodic and treat UTI
- Grade 3  On Foley cath. & CBI
  
  Cystoscope and cauterization if possible
- Grade 4  Urinary bypass
Common side effects & managements

- RT induced proctitis

  Onset: acute to late effect
  More doses: more chance (>65-70 Gy)

**Management:**

  Grade 1: Stool softener
  Grade 2: Steroid supp.
  Grade 3: Proctoscope and cauterization if possible
  Grade 4: Bypass/ colostomy
Any Questions?
# Normal Tissue Tolerance

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Dimension</th>
<th>Dosage (Gy/wk)</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue</td>
<td>&lt; 500 cm³</td>
<td>63/6</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>&gt; 500 cm³</td>
<td>60/6</td>
<td>100</td>
</tr>
<tr>
<td>Liver</td>
<td>Whole organ</td>
<td>30/3</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>&lt; 50% of organ</td>
<td>40/4</td>
<td>66</td>
</tr>
<tr>
<td>Kidney</td>
<td>Whole organ</td>
<td>20/2</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>&lt; 1/3 of organ</td>
<td>60/6</td>
<td>100</td>
</tr>
<tr>
<td>Lung</td>
<td>Whole organ</td>
<td>30/3</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>&lt; 100 cm³</td>
<td>60/6</td>
<td>100</td>
</tr>
</tbody>
</table>
Late side effects (>6 mths after RT)

**Depend on**: Dose/ fraction, total doses, vol. of tissue

<table>
<thead>
<tr>
<th>Organ</th>
<th>volume</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>1/3</td>
<td>Clinical nephritis</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>5 cm 50</td>
<td>Myelopathy</td>
</tr>
<tr>
<td>Brain</td>
<td>60</td>
<td>Dementia, brain necrosis</td>
</tr>
<tr>
<td>Lung</td>
<td>45</td>
<td>Lung fibrosis</td>
</tr>
<tr>
<td>Heart</td>
<td>60</td>
<td>CAD risk, cardiomyopathy</td>
</tr>
<tr>
<td>Rectum</td>
<td>75</td>
<td>Proctitis, Stricture</td>
</tr>
<tr>
<td>Esophagus</td>
<td>60</td>
<td>Esophageal stricture</td>
</tr>
<tr>
<td>Small intestine</td>
<td>50</td>
<td>Perforation, stricture</td>
</tr>
<tr>
<td>Liver</td>
<td>50</td>
<td>Liver failure</td>
</tr>
</tbody>
</table>
## Acute side effects (During RT course)

Depend on: total (Accumulative) doses

<table>
<thead>
<tr>
<th>Organ</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small bowel</td>
<td>Diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td>Skin</td>
<td>Dry desquamation, Most desquamation</td>
</tr>
<tr>
<td>Mucosa</td>
<td>Mucositis</td>
</tr>
<tr>
<td>Lung</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>Brain</td>
<td>Headaches, nausea, vomiting</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Liver</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Kidney, bladder</td>
<td>Nephritis, cystitis: hematuria</td>
</tr>
<tr>
<td>Heart</td>
<td>Carditis</td>
</tr>
</tbody>
</table>