Management of Acute and Late Side Effects of Radiotherapy

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LECTURE OUTLINE

• Introduction
• Radiobiology
• Factors influencing side effects
• Types of side effects: early vs late
• Examples of side effects
• Management of side effects
• Summary
• Acknowledgement
INTRODUCTION 1
Principle of treatment

- Surgery
- Chemotherapy
- Radiotherapy
INTRODUCTION 2
Principle of treatment

DESIRABLE TREATMENT

Efficacy vs. Side Effects

FACULTY OF MEDICINE
RADIOBIOLOGY 1
Mechanism of Action

Ionising radiation

Body/tumour tissues

DNA damage

DNA repair

Cell death

DNA mutation
Figure 1 Dose-response relationships for tumour and normal tissue. For dose of 60 Gy the local control is 50% and $\gamma_{50}$ is 2.75, for dose of 50 Gy the probability of injury is 5% and $\gamma_{50}$ is 5.25. ($\gamma$ is the so called normalized dose gradient; a dose increase of one per cent on the linear part of the dose response curve will result in an increase in TCP of precisely $\gamma$ per cent). It was assumed that $\alpha/\beta$ is of 10 Gy and 2 Gy for tumour and normal tissue respectively.
The tumour response for a fixed level of normal tissue damage
Always consider tumour response and normal tissue damage
Risk-benefit ratio
For better therapeutic index: Separate the curves

RADIOBIOLOGY 3
Therapeutic Index

Response vs Radiation Dose diagram with curves for T (tumour) and NT (normal tissue)
RADIOBIOLOGY 4
Tolerance

• The maximum level of normal tissue damage produced by radiotherapy which is accepted as the clinically reasonable limit

• Usually expressed in terms of severity and time

• $TD_{5/5}$: Refers to the RT doses required to produce a severe complication rate 5% within 5 years of RT completion
  – In conventional fractionation of 2 Gy per fraction

<table>
<thead>
<tr>
<th>Organ</th>
<th>TD 5/5 Volume</th>
<th>TD 5/5 Volume</th>
<th>Organ</th>
<th>TD 5/5 Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
<td>3/3</td>
<td>1/3</td>
</tr>
<tr>
<td></td>
<td>5,000</td>
<td>3,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2,300</td>
<td>4,000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kidneys</td>
<td>8,000</td>
<td>6,500</td>
<td>8,500</td>
<td>8,000</td>
</tr>
<tr>
<td>Bladder</td>
<td>6,500</td>
<td>6,000</td>
<td>6,000</td>
<td>6,500</td>
</tr>
<tr>
<td>Femoral head</td>
<td>5,200</td>
<td>5,100</td>
<td>7,700</td>
<td>7,200</td>
</tr>
<tr>
<td>TMJ</td>
<td>6,000</td>
<td>6,000</td>
<td>7,700</td>
<td>7,200</td>
</tr>
<tr>
<td>Rib cage</td>
<td>5,000</td>
<td>5,000</td>
<td>6,500</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>100 cm²</td>
<td>100 cm²</td>
<td>100 cm²</td>
<td>100 cm²</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>50 cm³&lt;sup&gt;2&lt;/sup&gt;</td>
<td>50 cm³&lt;sup&gt;2&lt;/sup&gt;</td>
<td>50 cm³&lt;sup&gt;2&lt;/sup&gt;</td>
<td>50 cm³&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain</td>
<td>6,000</td>
<td>5,000</td>
<td>4,500</td>
<td>7,500</td>
</tr>
<tr>
<td>Brainstem</td>
<td>6,000</td>
<td>5,300</td>
<td>5,000</td>
<td>6,000</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>5,000</td>
<td>5,000</td>
<td>6,000</td>
<td></td>
</tr>
<tr>
<td>Chiasma</td>
<td>5,000</td>
<td>5,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord</td>
<td>5 cm</td>
<td>10 cm</td>
<td>20 cm</td>
<td>5 cm</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>5,000&lt;sup&gt;2&lt;/sup&gt;</td>
<td>5,000&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4,700</td>
<td>7,000</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>6,200</td>
<td>6,100</td>
<td>6,000</td>
<td>7,700</td>
</tr>
<tr>
<td>Eyes (lens)</td>
<td>1,000</td>
<td>1,600</td>
<td>1,800</td>
<td></td>
</tr>
<tr>
<td>Eyes (retina)</td>
<td>4,500</td>
<td>6,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ears (middle/external)</td>
<td>3,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4,000</td>
<td>4,000</td>
</tr>
<tr>
<td>Ears (middle/external)</td>
<td>5,500</td>
<td>5,500&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5,500&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6,500</td>
</tr>
</tbody>
</table>

*There is insufficient information for recommendations where no values are provided. Clinical judgment and experience are used in these instances, and extrapolation from available information is made.

<sup>b</sup> < 50% of volume does not make a significant change.


**TABLE 1: Normal tissue tolerance to therapeutic irradiation**

**TD 5/5 Volume**

<table>
<thead>
<tr>
<th>Organ</th>
<th>TD 5/5 Volume</th>
<th>TD 5/5 Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
</tr>
<tr>
<td></td>
<td>3,200&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3,200&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parotid</td>
<td>7,900&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7,000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Larynx</td>
<td>4,500&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4,500&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lungs</td>
<td>4,500</td>
<td>3,000</td>
</tr>
<tr>
<td>Heart</td>
<td>6,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4,500</td>
</tr>
<tr>
<td>Esophagus</td>
<td>6,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5,000</td>
</tr>
<tr>
<td>Stomach</td>
<td>6,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5,000</td>
</tr>
<tr>
<td>Small intestine</td>
<td>5,000</td>
<td>4,000&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Colon</td>
<td>5,500&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4,500</td>
</tr>
<tr>
<td>Rectum</td>
<td>6,000</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>5,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3,500</td>
</tr>
<tr>
<td>Testes</td>
<td>± 500</td>
<td>2,000</td>
</tr>
<tr>
<td>Ovaries</td>
<td>± 300</td>
<td>1,200</td>
</tr>
<tr>
<td>Vagina</td>
<td>5 cm³&lt;sup&gt;2&lt;/sup&gt;</td>
<td>9,000</td>
</tr>
<tr>
<td>Pituitary</td>
<td>4,500</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>4,500</td>
<td>7,000</td>
</tr>
<tr>
<td>Muscle</td>
<td>5,000&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5,000</td>
</tr>
<tr>
<td>Muscle</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>Cartilage (child)</td>
<td>1,000</td>
<td>3,000</td>
</tr>
<tr>
<td>Bone (child)</td>
<td>10 cm³&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10 cm³&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>TMJ</sup> = temporomandibular joint

TD 5/5 (minimal tolerance dose) and TD 50/5 (maximal tolerance dose) refer to the RT doses required to produce a severe complication rate of 5% and 20%, respectively, within 5 years of RT completion. These RT dose values are used for guidance only and are not absolute. They are modified appropriately depending on the prevailing circumstances.

1/3, 2/3, and 3/3 refer to the approximate volume of organ that is irradiated.

**PREVENTION AND MANAGEMENT OF RADIATION TOXICITY**
# Radiobiology 5

**TD$_{5/5}$**

<table>
<thead>
<tr>
<th>ORGANS</th>
<th>TD$_{5/5}$ (Partial Organ)</th>
<th>TD$_{5/5}$ (Whole Organ)</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>60</td>
<td>50</td>
<td>Necrosis/infarction</td>
</tr>
<tr>
<td>Spinal cord*</td>
<td>50</td>
<td>45</td>
<td>Necrosis/myelitis</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>62</td>
<td>60</td>
<td>Clinical nerve damage</td>
</tr>
<tr>
<td>Lungs</td>
<td>40</td>
<td>18</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>Heart</td>
<td>60</td>
<td>40</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Liver</td>
<td>50</td>
<td>30</td>
<td>Liver failure</td>
</tr>
<tr>
<td>Kidneys</td>
<td>50</td>
<td>20</td>
<td>Clinical nephritis</td>
</tr>
<tr>
<td>Rectum</td>
<td>-</td>
<td>60</td>
<td>Fistula/stenosis/necrosis</td>
</tr>
<tr>
<td>Lens</td>
<td>-</td>
<td>10</td>
<td>Cataract</td>
</tr>
<tr>
<td>Ovaries</td>
<td>-</td>
<td>±3</td>
<td>Sterility</td>
</tr>
<tr>
<td>Testis</td>
<td>-</td>
<td>±5</td>
<td>Sterility</td>
</tr>
</tbody>
</table>

Emami B 1991
FACTORS INFLUENCING RT SIDE EFFECTS

• Patient factors

• Treatment factors

• Tumour factors

• Normal tissue factors
FACTORS INFLUENCING RT SIDE EFFECTS 1

Patient Factors

Pre-existing co-morbidity

- Hypertension and diabetes mellitus are associated with end vessel disease → may increase the risk of late effects
- Inflammatory bowel disease or previous abdominal/pelvic surgery → may increased bowel side-effects in pelvic RT
- HIV infected patients are more radiosensitive than non-HIV infected individuals
FACTORS INFLUENCING RT SIDE EFFECTS 2

Patient Factors

Individual variation in sensitivity towards radiation
• Some genetically inherited conditions are associated with increased sensitivity to radiation
  • Ataxia Telangiectasia and Basal Cell Naevoid Syndrome

Smoking
• Increases side-effects and reduces tumour control in patients receiving RT for head and neck cancers.
FACTORS INFLUENCING RT SIDE EFFECTS

Patient Factors

Age
- Children
  - growth impairment/developmental problems
  - risk of a second primary in long term survivors
- Elderly patients
  - more susceptible to side-effects of RT due to poorer overall fitness and co-morbidity

Anatomy
- Thin-necked patients with head and neck cancer receiving RT to the neck area → more severe neck skin reactions
- Patients with pendulous breasts receiving RT to the affected breast → more severe skin reactions in the inframammary area
FACTORS INFLUENCING RT SIDE EFFECTS 4

Treatment Factors

Treatment intent
• Higher doses tend to be given to curable cases and increased side-effects to be expected

Treatment schedule
• Increase early effects or late effects or both if
  • Higher total dose
  • Larger dose per fraction
  • Shorter overall treatment time
  • Multiple fractions per day
FACTORS INFLUENCING RT SIDE EFFECTS 5
Treatment Factors

Type of radiation
• Lower energy X-ray irradiation → more skin side-effects
• RT with heavy particles (neutron) → increased late effects

Concurrent/combined treatment modalities
• Chemotherapy when given concurrently with RT is associated with increased side-effects.
FACTORS INFLUENCING RT SIDE EFFECTS 6

Treatment Factors

Radiotherapy technique

• Less side-effects with modern techniques
  • 3D Conformal Radiotherapy (CRT)
  • Intensity Modulated Radiotherapy (IMRT)
  • Image Guided Radiotherapy (IGRT)
FACTORS INFLUENCING RT SIDE EFFECTS 7

Tumour Factors

Size of tumour
• Less radiosensitive tumour need higher doses → greater side-effects

Site of tumour in relation to normal structures
• Closer distance → more side-effects would be expected

Tumour radiosensitivity
• Larger tumour → larger dimensions of treatment fields required → greater side-effects
FACTORS INFLUENCING RT SIDE EFFECTS 8

Normal Tissue Factors

Types of tissue
• Different types of normal structure have different tolerance to radiotherapy.

Structural organisation
• Parallel organisation: cells arranged in parallel
  – Side effects very dependent on volume irradiated
  – e.g. kidneys, lungs
• Serial organisation: cells arranged in series
  – Inactivation of a subunit can cause loss of function in the whole organ
  – Hot spots detrimental
  – e.g. spinal cord, intestines
## TYPE OF SIDE-EFFECTS 1
### Early VS Late

<table>
<thead>
<tr>
<th></th>
<th>EARLY</th>
<th>LATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>During RT or within a few weeks after RT (&lt;3 months).</td>
<td>Several months to several years post RT.</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>May last up to several months after RT. Usually reversible or self-limiting.</td>
<td>Usually irreversible or permanent.</td>
</tr>
<tr>
<td><strong>Tissue</strong></td>
<td>Tissue with rapid turnover rate e.g. epidermal layer of skin, GI epithelium and haematopoietic system.</td>
<td>Slowly proliferating tissue e.g. connective tissue or vascular cells.</td>
</tr>
</tbody>
</table>
## TYPES OF SIDE-EFFECTS 2
### Early VS Late

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Early effects</th>
<th>Late effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Erythema, desquamation, alopecia</td>
<td>Changed pigmentation, fibrosis, alopecia</td>
</tr>
<tr>
<td>Lung</td>
<td>Acute pneumonitis</td>
<td>Lung fibrosis</td>
</tr>
<tr>
<td>Brain</td>
<td>Headache, nausea &amp; vomiting, somnolence</td>
<td>Atrophy, infarction, necrosis</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Myelitis</td>
<td>Myelopathy</td>
</tr>
<tr>
<td>Gut</td>
<td>Nausea, vomiting, diarrhoea</td>
<td>Fibrosis, fistula, stricture</td>
</tr>
<tr>
<td>Bladder</td>
<td>Cystitis</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Eye</td>
<td>Epiphora, xerophthalmia, conjunctivitis</td>
<td>Epiphora, xerophthalmia, cataract, blindness</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Thick saliva, xerostomia</td>
<td>Xerostomia*</td>
</tr>
</tbody>
</table>
## TYPE OF SIDE-EFFECTS 3
### Early VS Late

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Early effects</th>
<th>Late effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td>Pericarditis, cardiomyopathy</td>
</tr>
<tr>
<td>Testes/ovaries</td>
<td>Oligospermia, amenorrhoea</td>
<td>Sterility, premature menopause</td>
</tr>
<tr>
<td>Ear</td>
<td>Otitis, tinnitus</td>
<td>Chronic otitis media, deafness</td>
</tr>
<tr>
<td>Muscle</td>
<td>Pain, sweling</td>
<td>Atrophy, fibrosis</td>
</tr>
<tr>
<td>Kidney</td>
<td>Impaired renal function</td>
<td>Nephrosclerosis</td>
</tr>
<tr>
<td>Lung</td>
<td>Pneumonitis</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Liver</td>
<td>Acute hepatitis</td>
<td>Chronic hepatitis</td>
</tr>
<tr>
<td>Bone and cartilage</td>
<td>Pain</td>
<td>Osteoradionecrosis, dwarfism in children</td>
</tr>
</tbody>
</table>
Skin erythema and alopecia
MANAGEMENT 1-14

- Prevent
- Reduce
- Patient education
- Regular review
- General self-care
- Specific side effects
- Late effects
MANAGEMENT 1

Prevent

• To prevent is better than to treat!
• Is RT necessary?
• Can the critical organs be avoided?
MANAGEMENT 2
Reduce

• Hurt the tumour a lot
• Hurt the normal tissue as little as possible
• How much dose do you need?
• Can the dose to the critical organs be reduced?
• RT simulation and planning are very important
Heart

Breast

40Gy/15#
Bladder
Prostate
55Gy/20#
Bladder

Rectum

L Head of Femur

R Head of Femur

PROSTATE

Prostate 55Gy/20#
Nasopharyngeal Carcinoma
Phase 2: 28-30 Gy/14-25
Patient Education

• Inform them
  – Well-informed patients tend to cope better
  – Informed consent
  – Joint responsibility of doctors, radiographers and nurses
MANAGEMENT 4
General Self Care

• Skin
  – Wash gently with water and mild, unperfumed soap such as baby soap
  – Pat the skin dry with a soft towel
  – If the skin very sore of peeling, do not wash at all
  – Avoid make-up, perfumes, deodorant, creams, lotions to treatment area unless otherwise directed
  – Men should use dry shave (use electric razor) rather than wet shave
  – Avoid extremes hot or cold
  – Avoid direct sunlight
    • Cover the treated area adequately
  – Wear loose cotton clothing
    • Round neck T-shirt for head and neck RT
    • Loose non-underwired bra or no bra at all for breast RT
MANAGEMENT 5

General Self Care

• Oral
  – Dental assessment
  – Good oral hygiene
    • Use saline mouthwash
    • Use soft tooth brush or soft sponge
  – Watch for signs of infection
  – Avoid hard and spicy food
  – Avoid hot food/drinks
MANAGEMENT 6
General Self Care

• Nutrition
  – Important especially for radical RT to head & neck and oesophagus areas
  – Weekly weight measurement
  – Healthy balanced diet
  – Several small meals rather than a large meal at once
  – Regular review by dietitian
    • Adequate intake
    • Dietary modifications
MANAGEMENT 7
General Self Care

• Hydration
  – Ensure adequate fluid intake 2-3 litres per day

• Others
  – To rest accordingly
MANAGEMENT 8
Regular review

• Weekly review during radiotherapy for radical treatment
  – To monitor for side-effects and start treatment early to support patient through the treatment
  – Head and neck, lung, oesophagus, breast, pelvis

• Manage as outpatient if possible

• If severe side-effects, may need admission
  – Pain control
  – IV fluids
  – Parenteral nutrition
MANAGEMENT 9
Specific Side-effects

• Skin reactions
  – Erythema or dry desquamation
    • Aqueous cream, hydrocortisone cream
  – Wet desquamation
    • Intrasite gel, liquid paraffin gel
    • Acraflavine

• Mucositis
  – Normal saline, difflam mouthwash
  – Soluble paracetamol or aspirin for gargle
  – Local anaesthetic ointment/cream for ulcers
    • Xylocaine viscous
MANAGEMENT 10
Specific Side-effects

• Laryngitis
  – Cough syrup
  – Analgesics

• Pharyngitis
  – Soft diet
  – Analgesic
  – Nutritional/fluid support as necessary
MANAGEMENT 11
Specific Side-effects

• Salivary glands
  – Thick sticky saliva
    • Steam inhalation
    • Nebulized normal saline
    • Mucosolvon
  – Xerostomia
    • Frequent sips of water, suck ice cubes, sour sweets
    • Saliva substitutes
      – Artificial saliva: *Biotene OralBalance Gel, BioXtra Gel*
MANAGEMENT 12
Specific Side-effects

• Nausea & vomiting
  – Anti-emetics

• Diarrhoea
  – Encourage fluid intake
  – Anti-diarrhoeal

• Cystitis
  – Encourage fluid intake
  – Antibiotics if urinary infection
MANAGEMENT 13
Specific Side-effects

• Analgesics
  – Depends on severity of pain
  – Start with mild analgesics like paracetamol
  – Step up to stronger analgesics later
MANAGEMENT 14
Late Side Effects

• Important to warn patients
  – Men: sterility, impotence
  – Women: Sterility, premature menopause, avoid pregnancy
  – Children: Growth, hormones, second malignancy

• Some may need surgical management
  – Cataract
  – Haematuria
  – Bowel stricture
  – PR bleeding
SUMMARY

• Radiotherapy hits both the tumour and normal tissue
• Need to balance between tumour cure/control and side effects
• Knowledge of tolerance dose is important
• RT planning is aimed at targeting the tumour and avoiding the normal tissue
• Early side effects
  – Usually manageable and reversible
  – Patient education is paramount
  – Support the patients through treatment
• Late side effects
  – Usually affect functions and irreversible
  – Prevention is the best
  – Reduce the risk is better
  – If unavoidable : inform the patients of the risk
ACKNOWLEDGEMENT

THANKS TO

• AP Dr Anita Bustam and Dr Lau Fen Nee who contributed some of the slides.
• My physicists and radiographers who helped in the preparation of some photographs.
• Patients who kindly agreed for their pictures to be taken and used for this lecture.
• The audience who have listened with great interest.