# Pathogenesis of Normal Tissue Side Effects


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# Disclosures

- **Hold'em for Life Early Career Professorship in Cancer Research**

- **AACR-AstraZeneca Career Development Award for Physician-Scientists, in Honor of José Baselga**

# Acknowledgement

14

Pathogenesis of normal tissue side effects

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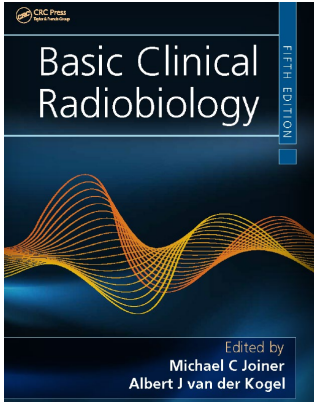


# Learning Objectives

1. Understand the pathophysiology of normal tissue response to ionizing radiation
2. Apply general radiobiologic principles to the clinical practice of radiation oncology

# Learning Objectives

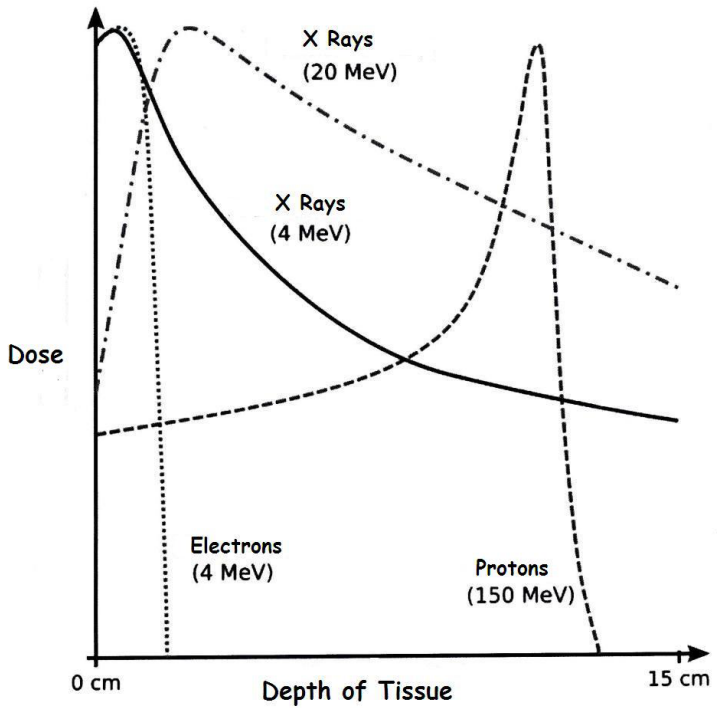
1. **Understand the pathophysiology of normal tissue response to ionizing radiation**
2. Apply general radiobiologic principles to the clinical practice of radiation oncology

# Definitions

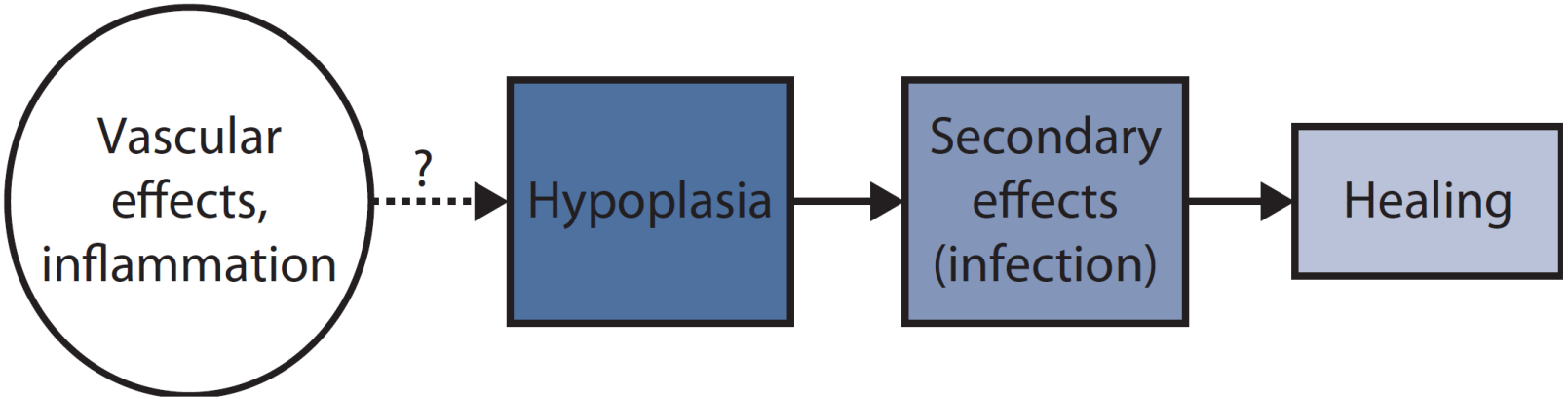
| | Time-Course Definition | Radiobiology |
|---|---|---|
| Early (Acute) Side Effects | • During or shortly after radiotherapy | • Found in tissues with high proliferative activity e.g. bone marrow, epidermis, gastrointestinal mucosa<br>• Causes imbalance in cell production vs. cell loss<br>• Results in cell depletion<br>• Recovery with proliferation and migration of stem cells into irradiated volume |
| Late (Chronic) Side Effects | • Latent clinical manifestations months to years after radiotherapy | • Found in all organs<br>• Causes a change in organ parenchyma including connective and vascular tissue changes<br>• Irreversible and progressive |

# Early Reactions

- **Dependent on:**
  - **Tissue type**
  - **Radiotherapy treatment technique**
  - **Additional traumata (e.g. chemotherapy)**



# Early Reactions
## Phases




**Humoral Response**

Paracrine secretion by vascular endothelial cells, macrophages, fibroblasts, keratinocytes, etc.

**Reduction in Cell Number**

- Epidermal/ mucosal epitheliolysis
- Leukopenia

**Breakdown of Protective Barrier**

- Septicaemia

**Stem Cell Recovery**

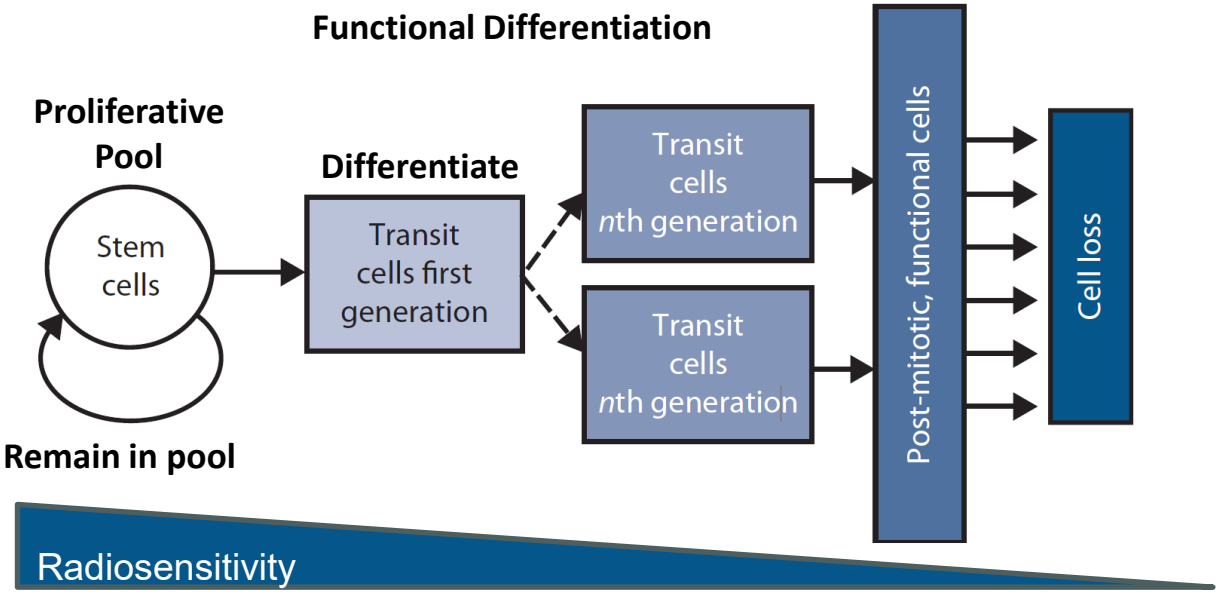
- Surviving stem cells in irradiated site
- Migration of stem cells from unirradiated sites

# Early Reactions

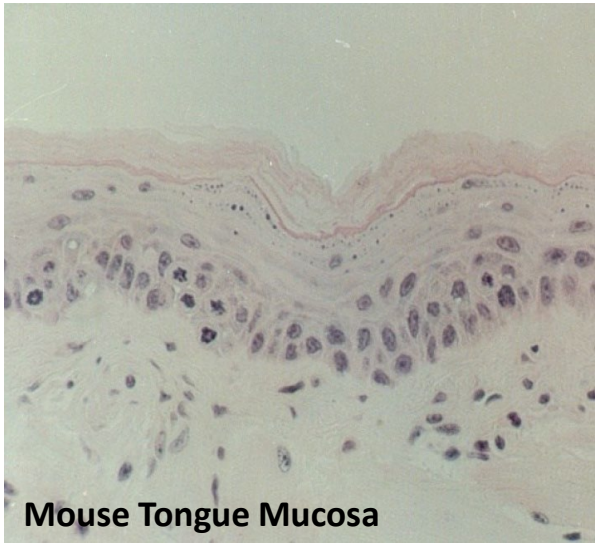
## Hierarchical Proliferative Tissue Organization

**Stem Cell Concept/ Target Cell Hypothesis**

- **Radiation tolerance depends on number and intrinsic radiosensitivity of stem cells**



# Early Reactions
# Hierarchical Proliferative Tissue Organization



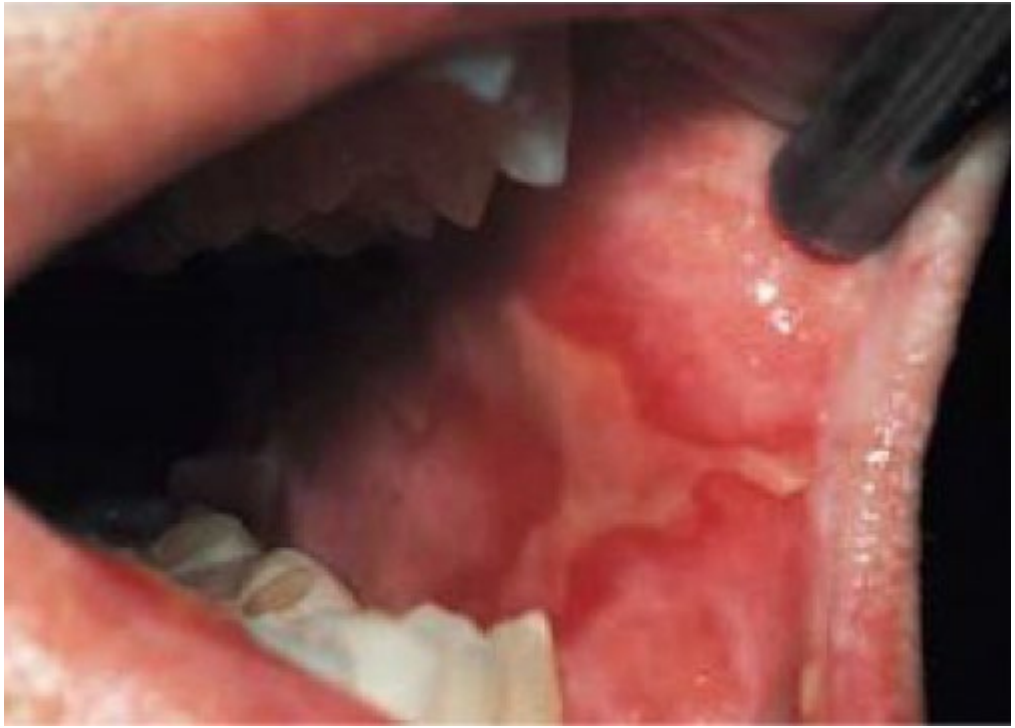

*Courtesy of Dr. Shun Wong's Lecture Slides*

**Cell loss**

**Cell production in germinal layers (basal and suprabasal)**

# Early Reactions
# Hierarchical Proliferative Tissue Organization

Oral Mucositis



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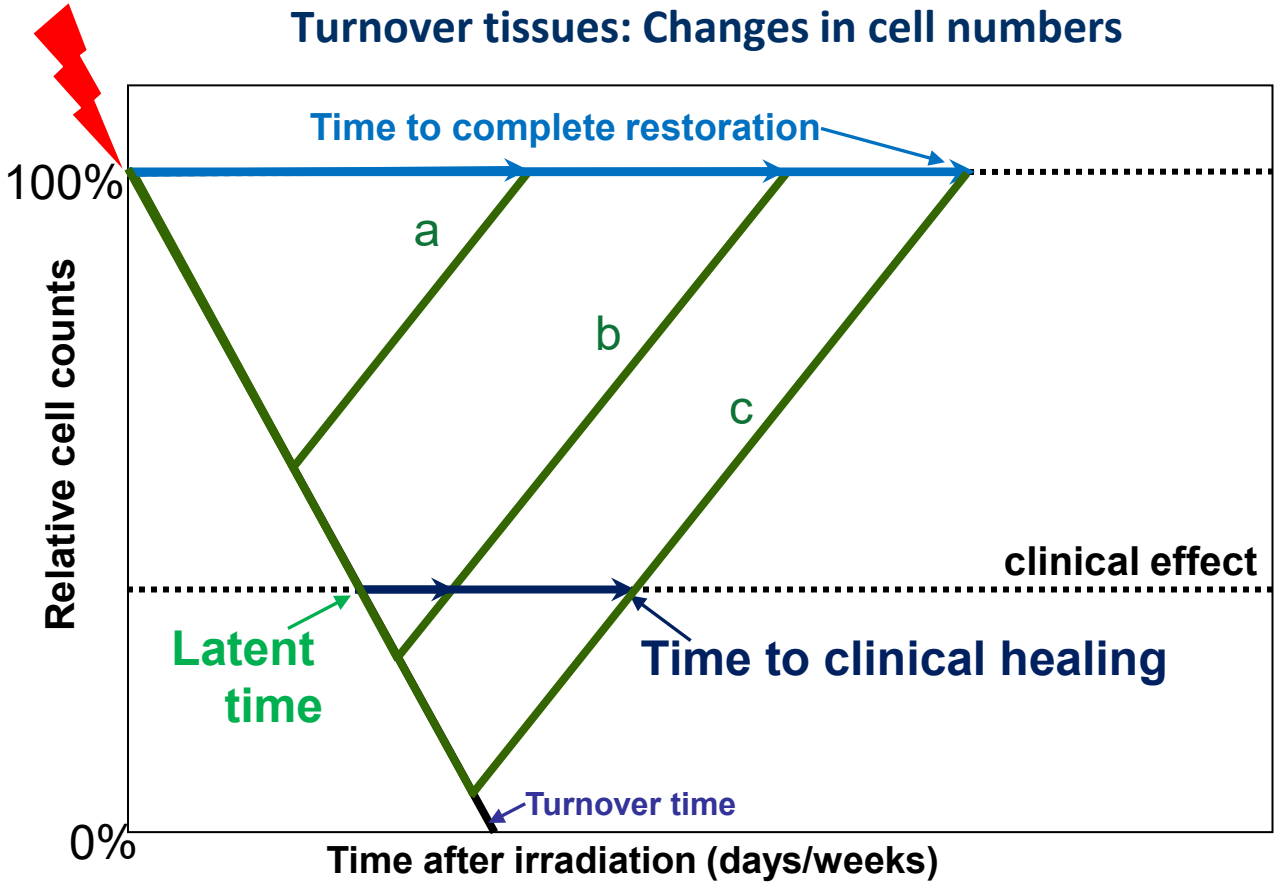
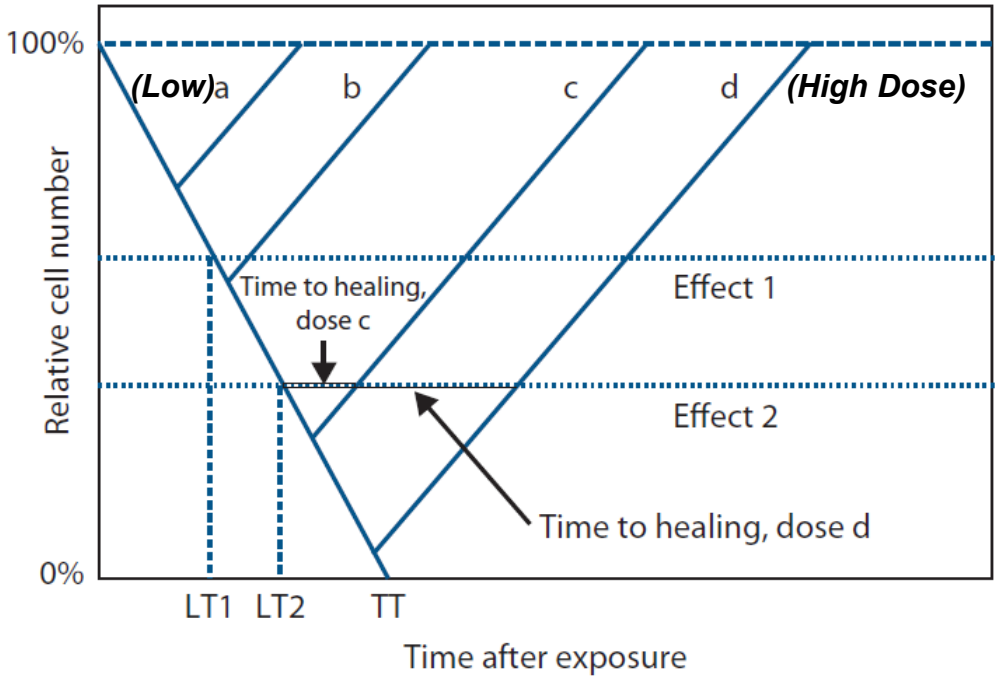
# Early Reactions

## Turnover tissues: Changes in cell numbers



# Early Reactions
## Clinical Manifestations




**Tissue Dependent**

1. Turnover Time (Rate of Cell Loss)
2. Latent Time of Clinical Manifestation

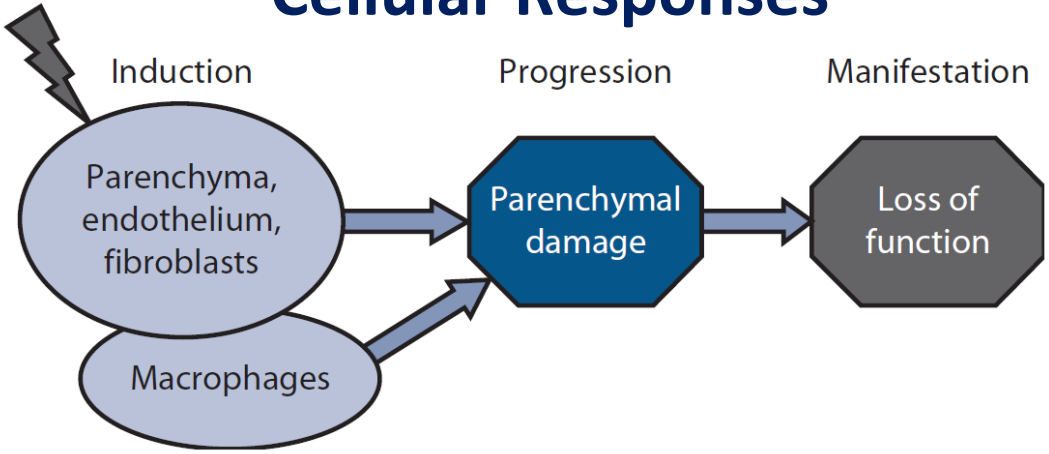
**Dose Dependent**

1. Healing Time

# Late Reactions
## Explanatory Models

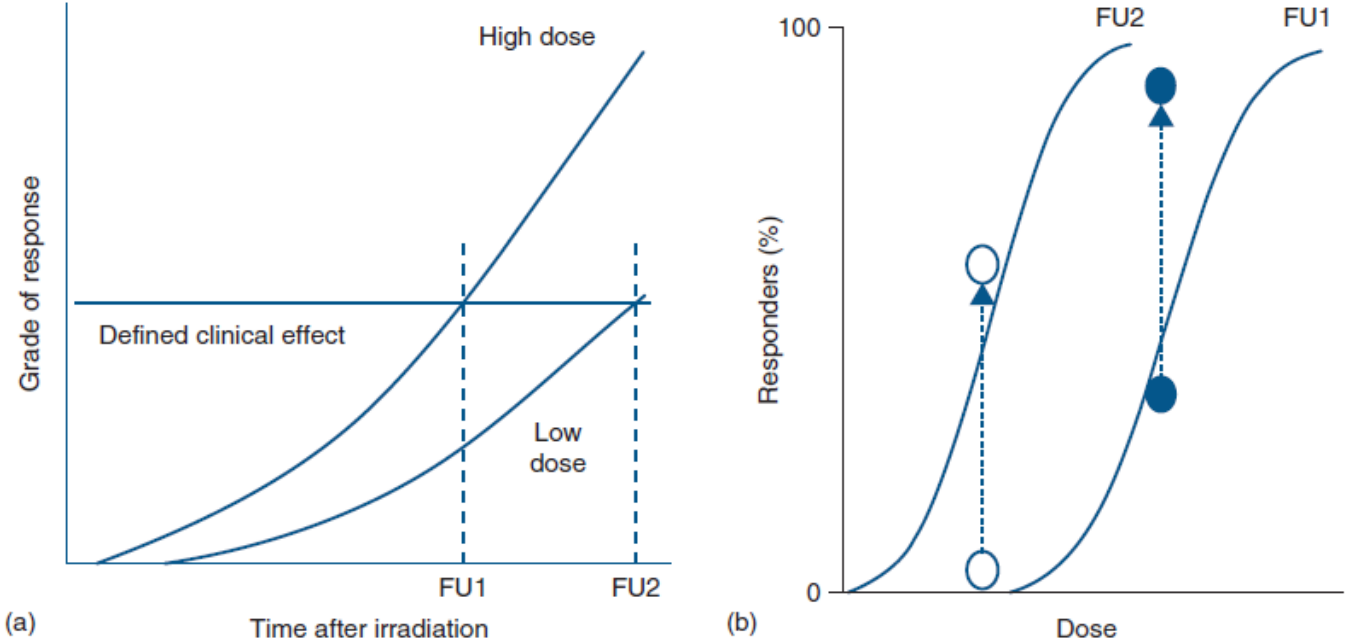
| Mechanistic Models | F-type (Flexible) Tissue Organization | Tissue-Rescuing Units (TRUs)/ Functional Sub-Units (FSUs) |
|---|---|---|
| Description | On demand recruitment of proliferating cells into functional population | Serial or parallel functional organization of stem cell-like structures |
| Clinical Manifestation of Radiation Effect When | Critical depletion of functional cells | Inactivation of TRUs/FSUs |
| Explains | Dose-response relationship | Volume-response relationship |

# Late Reactions
## Cellular Responses




| Cell Type | Response | Effect |
|---|---|---|
| Endothelium | • Cell Death<br>• Transudation and Edema<br>• Loss of Smooth Muscle | • Loss of Capillaries<br>• Thrombi and Occlusion<br>• Dilated Capillaries (Telangiectasia) & Capillary Hemorrhage |
| Fibroblast | • Differentiation | • Collagen Synthesis |
| Macrophages | • Signalling Cascades | • Reactive Oxygen and Nitrogen Species Production |

# Late Reactions
## Clinical Manifestations




**Dose Dependent**

1. Latent Time
2. Progression Rate

# Objectives

1. Understand the pathophysiology of normal tissue response to ionizing radiation
2. **Apply general radiobiologic principles to the clinical practice of radiation oncology**

# The Clinical Problem

- **The target volume in radiotherapy will include normal tissue because of:**
  - **Entrance and exit dose of radiotherapy beams**
  - **Margins of target volume**
    - **Clinical Target Volume (CTV): Includes surrounding normal tissues with suspected microscopic infiltration**
    - **Planning Target Volume (PTV): Includes setup uncertainty**

# Clinical Assessment

- **Frequency of Assessment**
  - **Early: Weekly**
  - **Late: Months to Years Post-RT**
- **Scoring System**

# Clinical Assessment
## Scoring System

Table 14.1 Systems for documentation of side effects, with examples for oral mucositis

| Grade | General | RTOG/EORTC | CTCAE (v3) | WHO |
|---|---|---|---|---|
| 0 | No change | No change | No change | No change |
| 1 | Mild | Erythema, mild soreness, painless erosions | Erythema; normal diet | Soreness, erythema |
| 2 | Moderate/clear | Painful erythema, oedema or ulcers; can eat | Patchy ulceration; can eat and swallow modified diet | Erythema, ulcers; can eat solids |
| 3 | Severe/significant | Painful erythema, enema or ulcers; cannot eat | Confluent ulcerations, bleeding with minor trauma; unable to adequately aliment or hydrate orally | Ulcers; requires liquid diet only |
| 4 | Life threatening | Requires parental or enteral support | Tissue necrosis; significant spontaneous bleeding | Alimentation not possible |
| 5 | Death due to side effects | Death due to side effects | Death due to side effects | Death due to side effects |

# Radiotherapy Constraints

- QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic)
- International Commission on Radiological Protection

# Radiotherapy Constraints

Table 14.2 Tolerance doses and fractionation response ($\alpha/\beta$ value) for early and late organ damage in humans

| Organ | Endpoint[a] | Time to manifestation during/after irradiation[b] | $\alpha/\beta$ value (Gy)[c] | Tolerance dose for total volume (Gy)[d] | Comments |
|---|---|---|---|---|---|
| Cartilage, growing | Growth arrest | Next growth spurt | 6 | 20 | |
| Cartilage, adult | Necrosis | Months–years | | 70 | Associated with vascular damage |
| Bone, adult | Osteoradionecrosis | Years–decades | | 60<br>Mandible: 40–50 | Vascular damage and trauma |
| Connective tissue | Fibrosis | Months–years | 2 | 60 | Most frequent late reaction |
| Capillaries | Capillary changes/loss | Months–years | 3 | 60 | Contribute to a variety of (late) radiation effects |
| Large vessels | Wall changes, stenosis | Years | | 70 | Resembles atherosclerotic changes |
| Heart | ECG-changes, arrhythmia | During RT | | 20 | Reversible |
| | Cardiomyopathy (Pericarditis) | Months–years | 3 | 40 | Late myocardial infraction |
| Skin | Erythema | During RT | 9–10 | | |
| | Dry radiodermatitis | During RT | 10 | 40<br>(100 cm²) | Varies with localisation (additional mechanical/chemical stress) |
| | Moist radiodermatitis | During RT | 10 | 60<br>(100 cm²) | |
| | Gangrene, ulcer | | 3 | 55<br>(100 cm²) | Vasculature! |
| Hair follicles | Hair loss | During RT<br>(4th week) | 7 | 40 | Discolouration! |
| Sebaceous glands | Dry skin | During RT<br>(2nd week) | | 12 | Transient loss of function |
| Perspiratory glands | Dry skin, loss of transpiration | During RT<br>(4th week) | | 30–40 | Long-lasting or permanent loss of function |

# Radiotherapy Constraints

| | | | | | |
|---|---|---|---|---|---|
| Oral mucosa | Ulcerative mucositis | During RT (2nd–3rd weeks) | 10 | 20 | |
| | Atrophy/fibrosis | Months–years | | 60–70 | |
| Salivary glands | Transient loss of function – xerostomia | During RT (2nd week) | | 10–20 | |
| | Loss of function – xerostomia (partially reversible) | Continuous development from the early response | 3 | 25 | 1/3 capacity is sufficient for saliva production |
| Oesophagus | Dysphagia | | | 40–45 | Early mucositis |
| | Ulcer–Fistula | During RT–months | | 55 | |
| Stomach | Atony | During RT | | 20 | 'Radiation sickness' |
| | Ulcer | Months | 4 | 50 | |
| Small intestine | Malabsorption | During RT | 8 | 30 | Reduced tolerance due to fixation of intestinal loops, e.g. post-operative |
| | Ulcer/obstruction | Months | 4 | 40 | |
| Large intestine | Diarrhoea, pain | During–post RT | | 10–20 | |
| | Ulcer/obstruction | Months–years | | 45 | Ileus-symptoms possible |
| Rectum | Proctitis | During RT | | 50 | |
| | Chronic inflammation, ulcer | Months–years | 5 | 60 | Partial irradiation of the circumference increases tolerance |
| Liver | Veno-occlusive disease (VOD) | 2–3 weeks | | 30 | Lethal after total organ irradiation; hence, late effects only after partial organ irradiation |
| | Fibrosis | Months–years | 1 | | |

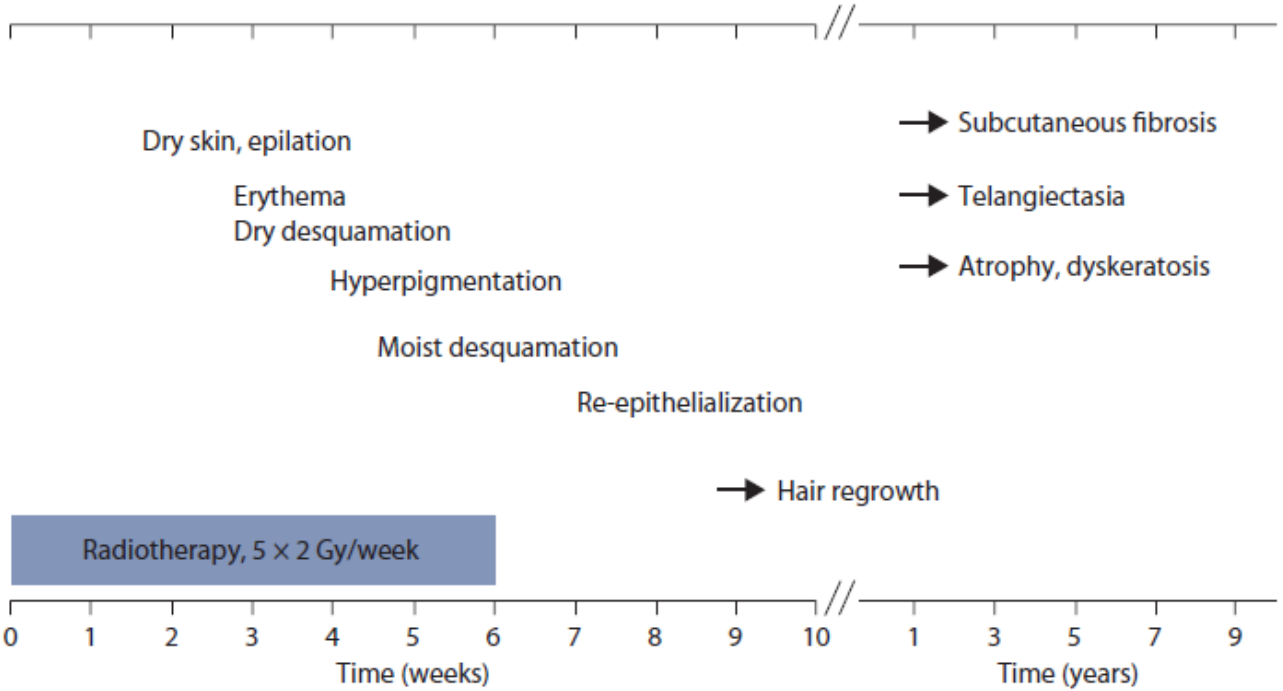
# Radiotherapy Constraints

| | | | | | |
|---|---|---|---|---|---|
| Biliary tract | Stenosis/stricture | Months–years | | | |
| Pancreas | Fibrosis | Months–years | | 50–60 | No early symptoms known, included in 'radiation sickness'? |
| Kidney | Nephropathy | 9 Months–years | 2 | 20 | |
| Ureter | Stricture | 2 years | | 60–70 | Vascular effects, potential interaction with surgery |
| Urinary bladder | Cystitis | During RT | 10 | 20–35 | Uncommon pathophysiology, no urothelial depletion |
| | Shrinkage, ulceration | Months–decades | 5–10 | 50 | Strong consecutive component |
| Urethra | Stricture | Months–years | | 60–70 | Reduced tolerance after transurethral resection of the prostate (TURP) |
| Larynx | Oedema | During RT | | 45 | |
| | Chronic enema, necrosis | Months | 2–4 | 70 | Permanent changes in voice quality, necrosis after decades |
| Lung | Pneumonitis | 2–6 weeks | 5 | 12–14 | Single-dose irradiation |
| | Pneumonitis | 4–6 weeks | 5 | 45 | |
| | Fibrosis | Months–years | 4 | | |
| Testis | Permanent sterility | Weeks–months | | 1.5 | Negative fractionation effect |
| Ovary | Permanent sterility | Weeks–months | | 2.5 | Strong inverse age dependence |
| Uterus | Atrophy | Months–years | | 100 | |
| Vagina | Mucositis | During RT | | 30 | |
| | Ulcer, fibrosis | Months–years | | 50 | |
| Breast, child | Growth arrest | At puberty | | 10 | |
| Breast, adult | Fibrosis/atrophy | Years | 2–3 | 60 | |
| Adrenal glands | Loss of function | Months–years | | 90 | |
| Pituitary gland/ diencephalon | Growth hormone deficit | Months–years | | 18–24 | Growth retardation |

# Radiotherapy Constraints

| Organ | Endpoint[a] | Time to manifestation during/after irradiation[b] | $\alpha/\beta$ value (Gy)[c] | Tolerance dose for total volume (Gy)[d] | Comments |
|---|---|---|---|---|---|
| Cerebrum, child | Somnolence syndrome | During–post RT | | 24 | Specific response in children |
| Cerebrum, adult | Necrosis | Months–years | | 55 | |
| Spinal cord | Lhermitte syndrome | Weeks–months | | 35 | Reversible |
| • Cervical/thoracic | Radiation myelopathy | Months–years | 2 | 55 | |
| • Thoracic/lumbar | Radiation myelopathy | Months–years | 2 | 55 | |
| Peripheral nerves | Functional impairment | Months–years | | 60 | Frequently associated with connective tissue fibrosis |
| Eye lens[e] | Cataract | Months–years | 1–2[e] | $<1$[e] | Surgical management |
| Lacrimal system | Dry eye, ulceration | Weeks–months | 3 | 40 | Most critical radiation effect in the eye |
| Retina | Retinopathy | Weeks–months | | 45 | |
| Optic nerve | Neuropathy | Months–years | 2 | 55 | |
| Chiasma opticum | Loss of vision | Months–years | 2 | 55 | |
| Conjunctiva | Kerato-conjunctivitis | During–post RT | | 50 | Reversible |
| Ear | Serous otitis | During–post RT | | 30 | |
| | Inner ear injury | During RT + Months | | 30 | Slight hearing loss (15 dB) frequently not recognised by patients; overlap with age effects |
| Taste | Taste impairment, loss | During RT + months | | 30 | Reversible |
| Lymph nodes | Permanent atrophy | Months–years | | 70 | |
| Lymphatic vessels | Sclerosis | Months–years | | 90 | Frequently associated with connective tissue fibrosis |
| Bone marrow | Transient hypoplasia | During RT | 10 | 2 | Total-body irradiation |
| | Lethal aplasia (1 year) | | 5 | 4 | Total-body irradiation |
| | Permanent aplasia | During–post RT | | | Compensation by unirradiated parts; post-irradiation homing of circulating stem cells possible |

# Example: Skin
## Sequence of Radiation Effects



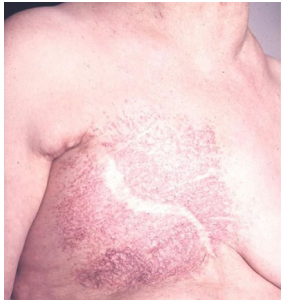
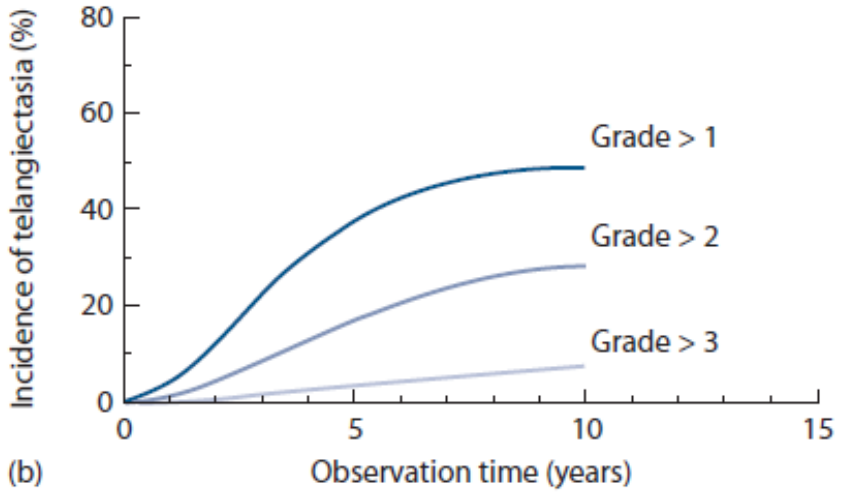



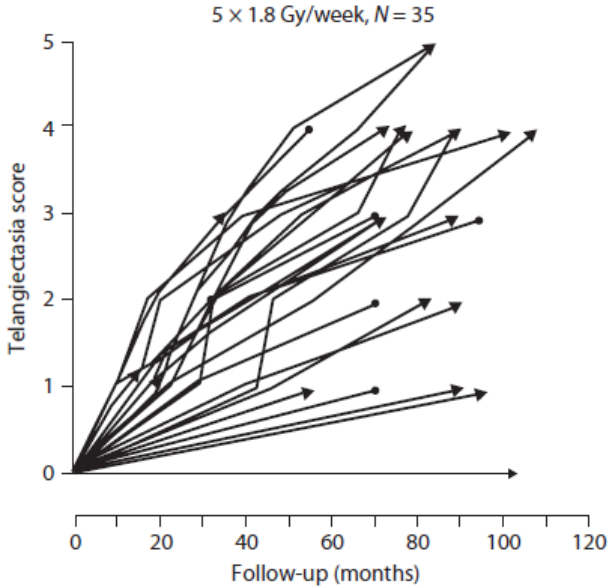
*Image Courtesy of Dr. Shun Wong's Lecture Slides*

# Example: Skin

## ↑ Incidence Over Time




## ↑ Severity Over Time



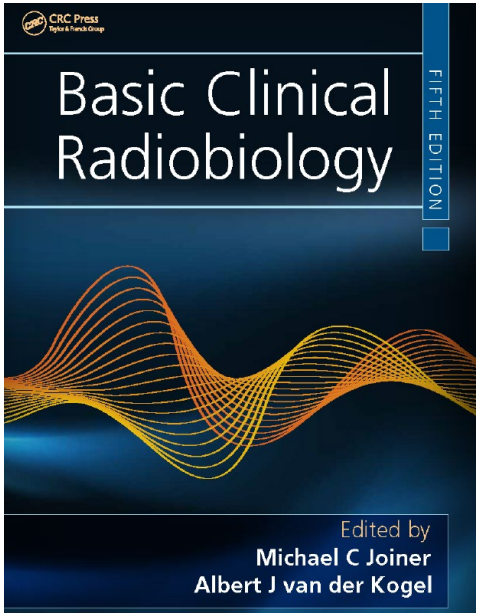
# Summary

## Key points

1. Early radiation effects, developing in turnover tissues, are dominated by tissue hypoplasia.
2. The latent time of early effects is largely independent of dose, while severity and duration/time to healing are dose dependent.
3. Additional trauma aggravates early reactions.
4. Healing of early responses, based on surviving tissue stem cells, is usually complete.
5. Late radiation sequelae, observed after months to years after therapy, are progressive and often irreversible.
6. Late effects may occur in waves, thus leading to a clear discrepancy between cumulative incidence and prevalence. Hence, both parameters need to be documented.
7. Late effects are based on a complex and interactive response of parenchymal cells, vascular endothelium and fibroblasts, with a contribution of macrophages and other cell types.
8. The latent time of chronic reactions is inversely dependent on dose.

# Resources

## Based on Chapter 14



# Questions?

# Thank you!

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