Tumor Response to Radiation

Faculty of Applied Science- Department of Radiology

Course Name: Radiobiology Course Code: MTR 211

Second Grade/ Fall Semester 2025-2026

Lecture 8/ 21st December 2025

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Outlines

- Definition of Tumor Response.
- Goals of Radiotherapy.
- Tumor Growth Kinetics.
- Tumor Control and Radiosensitivity of Tumors.
- Oxygen, Hypoxia, and Reoxygenation.
- Cell Cycle and Redistribution.
- Tumor Repopulation and Its Clinical Importance.
- Dose Fractionation and Tumor Response.
- Time Course of Tumor Regression.
- Pediatric Tissue Radiosensitivity.
- Time Course of Tumor Regression.
- Tumor Recurrence and Therapeutic Ratio.

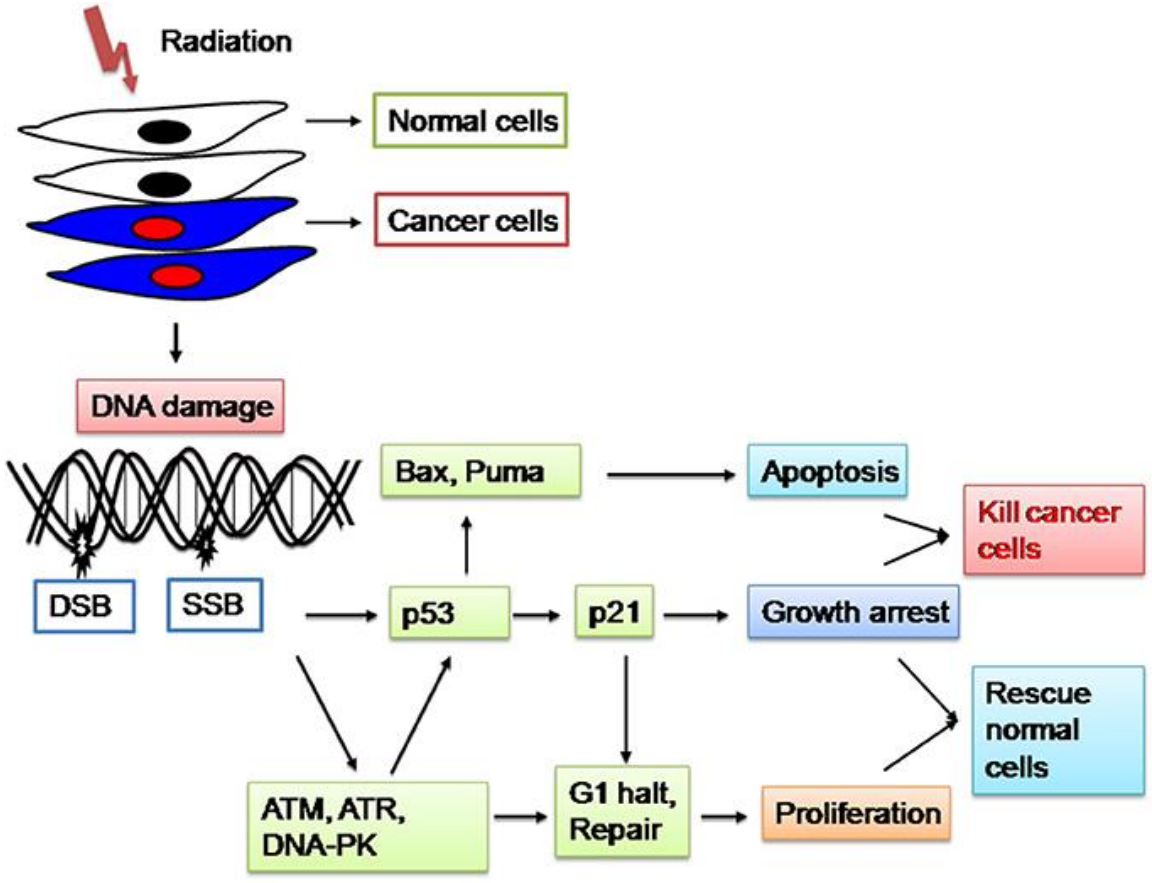
Learning Outcomes

By the end of the lecture, students should be able to:

- Define tumor response to radiation
- Explain cellular and tissue mechanisms of tumor control
- Describe factors affecting tumor radiosensitivity
- Understand the concepts of TCP and therapeutic ratio
- Differentiate early and late tumor responses
- Explain tumor repopulation and hypoxia

Introduction

- **Radiotherapy** is a major modality for **cancer treatment**.
- Approximately **50–60%** of cancer patients receive radiation therapy.
- Tumor response to radiation depends on **biological**, **physical**, and **clinical** factors.
- **Goal:** Tumor control with minimal normal tissue damage.

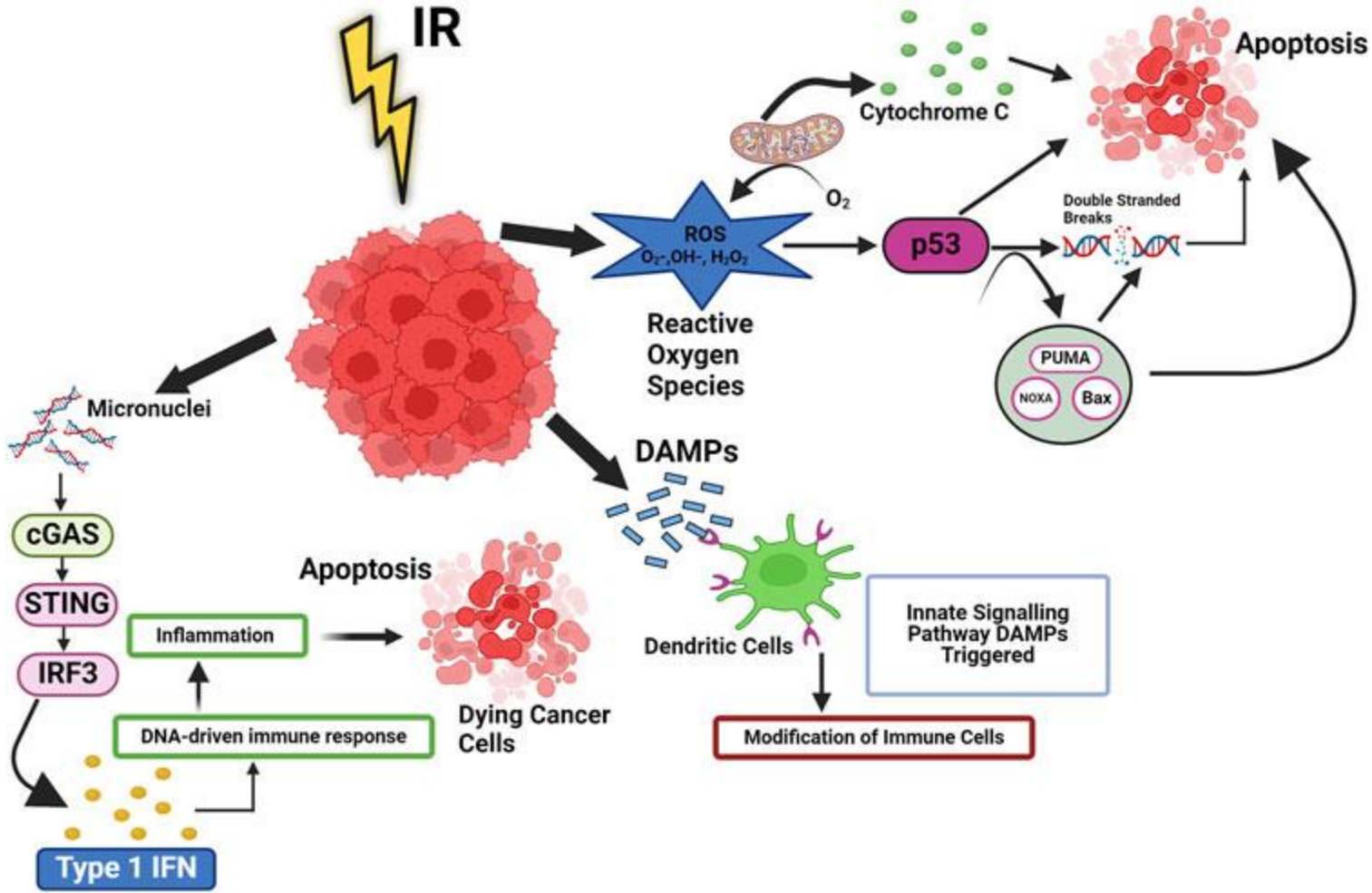


Definition of Tumor Response

- **Tumor response to radiation** refers to:
- The **biological and clinical changes** occurring in tumor cells after exposure to ionizing radiation.

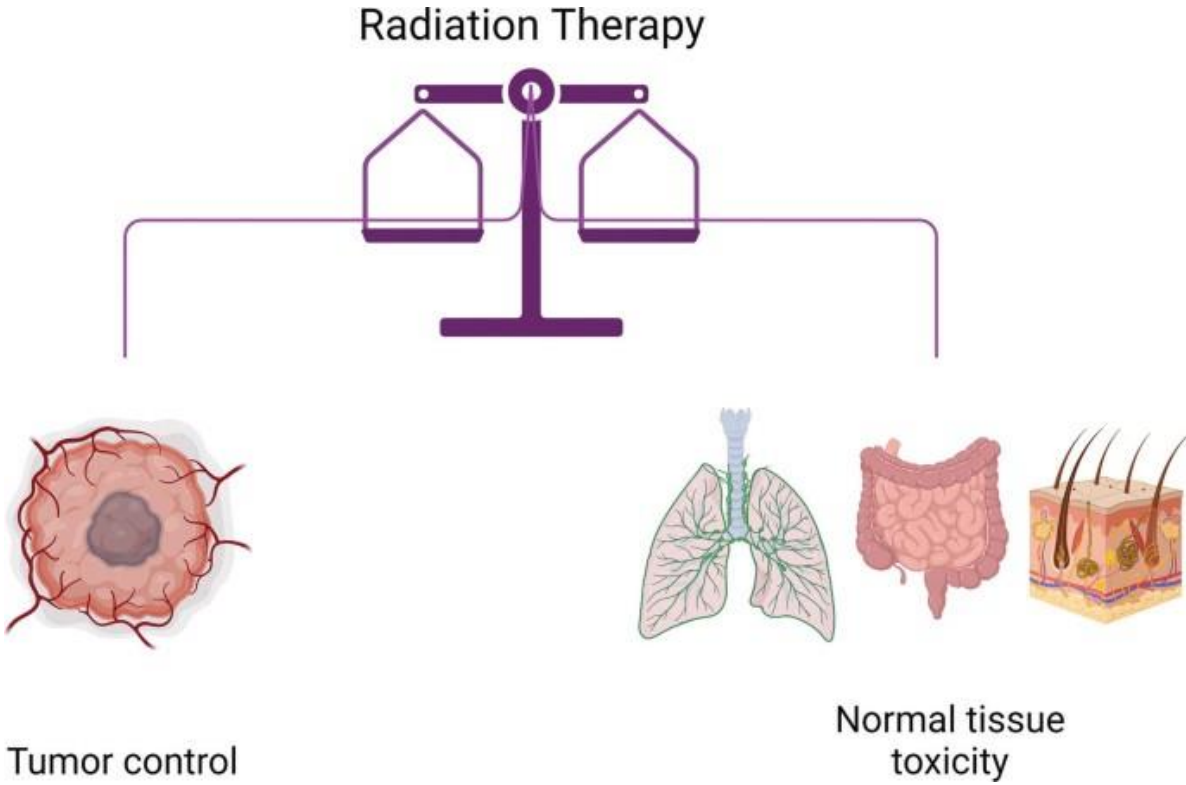
Includes:

- Cell death
- Growth delay
- Tumor shrinkage
- Local tumor control or cure



Goals of Radiotherapy

1. **Eradicate** all clonogenic tumor cells.
2. **Prevent** tumor recurrence.
3. **Preserve** surrounding normal tissues.
4. **Achieve** the best therapeutic ratio.



Types of Tumor Response

Tumor response can be:

- **Cellular response** (DNA damage, cell death).
- **Tissue response** (tumor shrinkage).
- **Clinical response** (symptom relief, imaging findings).

Cellular Mechanisms of Tumor Cell Death by Radiation

- **DNA** is the primary target of ionizing radiation.
- Radiation causes **lethal DNA damage**, especially **double-strand breaks**.

Tumor cell death mainly occurs through:

1. Mitotic (reproductive) cell death
2. Apoptosis (in some tumor types)

- Cell death may occur **immediately** or **after several cell divisions**.

Tumor Growth Kinetics

- **Tumor doubling time:** Time required for a tumor to double in size; shorter doubling time usually means better radiation response.
- **Growth fraction:** Proportion of actively dividing cells; a higher growth fraction increases radiosensitivity.
- **Cell loss factor:** Percentage of tumor cells lost due to death or poor conditions, explaining slow tumor growth despite active division.
- **Tumor growth pattern:** Tumors grow rapidly when small and slow down as size increases due to hypoxia and limited blood supply.

- **Clonogenic Cells:** are tumor cells capable of unlimited division and tumor regrowth.
- **Role in tumor control:** Radiation must eliminate **all clonogenic cells** to achieve permanent tumor control.
- **Clinical importance:** Survival of even one clonogenic cell can lead **to tumor recurrence**.

Tumor Control

- **Tumor control** refers to the complete elimination of clonogenic tumor cells.
- **Clinical meaning:** Absence of local tumor recurrence after radiotherapy indicates tumor control.
- **Goal of treatment:** Achieving tumor control is the primary objective of radiation therapy.

Tumor Control Probability (TCP): TCP is the probability that radiation eradicates all clonogenic tumor cells.

- **Dose relationship:**
  Increasing radiation dose increases TCP up to normal tissue tolerance.
- **Key determinants:**
  TCP depends on tumor radiosensitivity and the number of clonogenic cells.

Radiosensitivity of Tumors

- Radiosensitivity refers to how easily tumor cells are damaged or killed by radiation.
- **Radiosensitive tumors:** Tumors like lymphomas and seminomas respond well due to high cell division and apoptosis.
- **Radioresistant tumors:** Tumors such as melanoma and glioblastoma respond poorly and require higher doses or combined treatments.

Tumor Size and Stage

- **Small tumors:** Better oxygenation, fewer clonogenic cells → higher response to radiation.
- **Large tumors:** Poor blood supply and hypoxia → lower radiosensitivity.

Clinical relevance: Early detection and treatment improve radiotherapy outcomes.

Oxygen, Hypoxia and Reoxygenation

- **Oxygen** enhances radiation-induced DNA damage, thereby increasing the radiosensitivity of cells.
- **Hypoxic cells:** 2–3 times more resistant to radiation due to a lack of oxygen fixation.
- **Clinical implication:** Tumor oxygenation improves response, especially in fractionated radiotherapy.

- **Hypoxia** is a condition of low oxygen within the tumor.
- **Causes:** Poor blood supply, abnormal vasculature, and rapid tumor growth.
- **Effect on radiation:** Hypoxic tumor cells are more radioresistant and harder to control.

- **Surviving hypoxic tumor cells** become better oxygenated between radiation fractions.
- **Importance:** Reoxygenation increases radiosensitivity of previously resistant cells.
- **Clinical relevance:** Fractionated radiotherapy takes advantage of reoxygenation to improve tumor control.

Cell Cycle and Redistribution

- **Radiosensitivity varies by phase:** Most sensitive: **G2/M phase**; most resistant: **late S phase**.
- **Clinical relevance:** Tumors with more cells in sensitive phases respond better to radiation.
- **Implication for fractionation:** Fractionated doses allow cells to redistribute into sensitive phases, improving treatment efficacy.

- Surviving tumor cells move into more radiosensitive phases of the cell cycle between radiation doses.
- **Importance:** Enhances the effectiveness of **fractionated radiotherapy**.
- **Clinical relevance:** Allows subsequent doses to kill previously resistant cells.

Tumor Repopulation and Its Clinical Importance

- Surviving tumor cells proliferate during the course of radiotherapy.
- **Clinical significance:** Accelerated repopulation often starts after 3–4 weeks of treatment.
- **Impact on treatment:** Can reduce tumor control if treatment is prolonged or interrupted.

Clinical Importance of Repopulation

- **Effect of prolonged treatment:**
  Longer overall treatment time can decrease tumor control.
- **Treatment interruptions:**
  Gaps in radiotherapy allow tumor cells to repopulate, reducing effectiveness.
- **Management:**
  Dose compensation or accelerated schedules may be needed after interruptions.

Dose Fractionation and Tumor Response

- **Purpose:** Dividing the total radiation dose into multiple smaller fractions improves tumor control.

Advantages:

1. Allows normal tissue repair
2. Promotes tumor reoxygenation
3. Enables redistribution into sensitive cell cycle phases

Typical schedule:

1.8–2 Gy per day, 5 days a week

Fractionation and Tumor Response

- **Multiple small doses:** Improve tumor control and reduce normal tissue toxicity.
- **Reoxygenation and redistribution:** Fractionation allows hypoxic cells to become oxygenated and surviving cells to enter sensitive cell cycle phases.
- **Hypofractionation:** Fewer, larger doses can be used for selected tumors (e.g., prostate cancer).

Time Course of Tumor Regression

- **Delayed shrinkage:** Solid tumors often shrink over **weeks to months** after radiotherapy.
- **Microscopic disease:** May be eradicated without visible tumor regression.
- **Clinical relevance:** Understanding timing helps evaluate treatment response and plan follow-up.

Early Tumor Response

- **Timing:** Occurs during or shortly after radiotherapy.

Features:

  - Tumor swelling due to inflammation
  - Partial shrinkage
  - Symptom relief

- **Clinical importance:** Early changes can indicate treatment effectiveness but may not reflect full tumor control.

Time Course of Tumor Regression

Late Tumor Response

- **Timing:** Occurs **months to years** after radiotherapy.

Features:

  - Complete tumor regression
  - Fibrosis at the tumor site
  - Long-term local control

- **Clinical relevance:** Late responses indicate **permanent tumor control** and successful treatment outcome.

Tumor Recurrence and Therapeutic Ratio

Tumor Recurrence:

- Caused by surviving clonogenic cells, hypoxia, inadequate dose, or accelerated repopulation
- Most recurrences occur within 2–3 years

Therapeutic Ratio:

- Balance between tumor control and normal tissue damage
- Guides dose and fractionation to maximize tumor response while minimizing complications

Improving Tumor Response

1. **Dose escalation:** Higher radiation doses can increase tumor control if normal tissue tolerance allows.
2. **Altered fractionation:** Changing dose per fraction or treatment schedule can improve effectiveness.
3. **Radiosensitizers:** Drugs that make tumor cells more sensitive to radiation.
4. **Combined therapy:** Chemoradiotherapy or targeted therapies can enhance tumor response.
5. **Advanced techniques:** IMRT, IGRT, and other modern methods improve tumor targeting and spare normal tissue.

Questions? Comments?

Thank you!