Importance of Radiobiology in the Clinic

Scott V. Bratman, MD PhD

Clinician-Scientist & Associate Professor

Radiation Oncology & Medical Biophysics

Princess Margaret Cancer Centre

University of Toronto

April 7, 2025

Disclosures

Patents/Licensing: Roche, Adela

Ownership: Adela

Overview

Purpose: To introduce radiobiology concepts with direct clinical relevance

- A brief overview of clinical implementation of radiotherapy
- The therapeutic index
- The 5 R's of radiobiology
- Radiobiology in the 21st Century

Learning Objectives

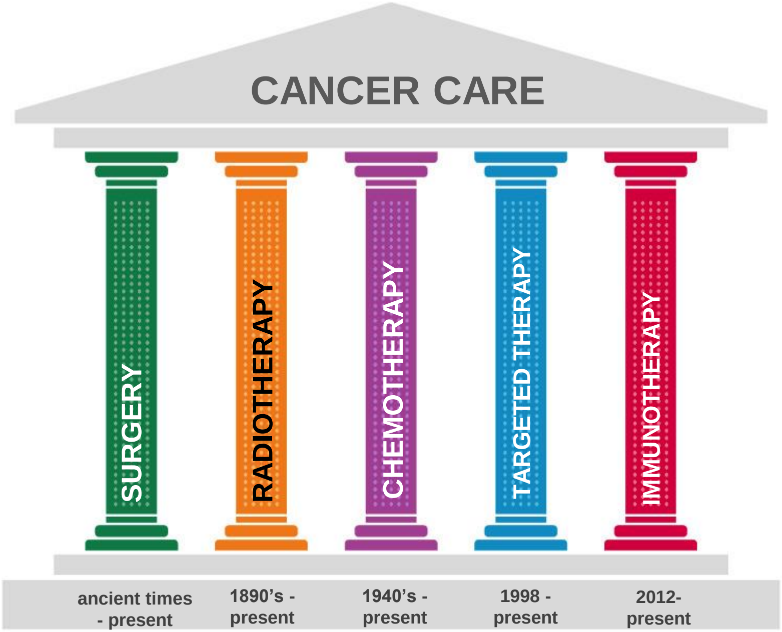
- Recognize the role of single dose and fractionated radiotherapy in cancer treatment.
- Identify the 5 R’s of radiotherapy: radiosensitivity, repopulation, re-oxygenation, repair, redistribution.
- Understand the basic concepts relating to acute and late radiotherapy toxicity.

Overview

Purpose: To introduce radiobiology concepts with direct clinical relevance

- **A brief overview of clinical implementation of radiotherapy**
- The therapeutic index
- The 5 R's of radiobiology
- Radiobiology in the 21st Century

Radiotherapy is a longstanding therapeutic pillar in oncology



Radiotherapy for Cancer

Half of all cancer patients will receive radiotherapy during their course of disease

Most common **goal is to achieve local control** or slow local tumor growth

Curative vs Palliative Intent:

- Curative: Given alone or in combination with surgery and/or systemic therapy in a clinical setting where local control can translate into cure
- Palliative: Given in clinical settings where cure is not feasible, but where local control can provide symptomatic relief (e.g., pain, bleeding)

Common Clinical Delivery of Radiotherapy

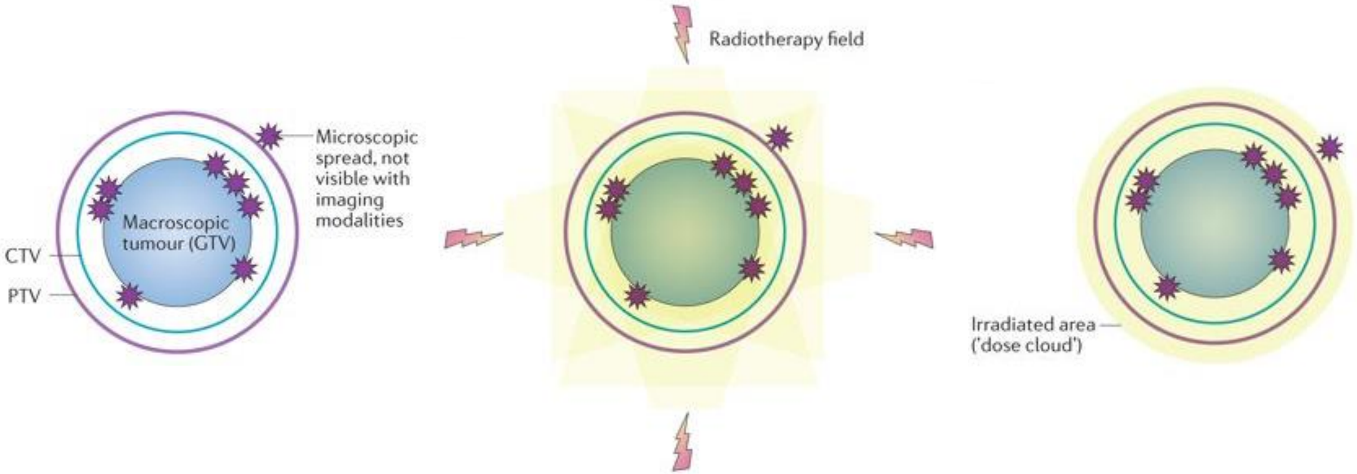
- **Fractionated External Beam Radiotherapy:** Photons (typically high-energy 6-25 MV that deposit energy deep within tissue and spare skin), electrons, or other particles (e.g., protons) given as a series of treatments/fractions over multiple days or weeks.
- **Stereotactic Radiotherapy:** One/few fraction(s) of higher doses (≥6 Gy) given as stereotactic external beam radiation to a small volume
- **Brachytherapy:** Interstitial radioactive implants given at high or low dose rate to a small volume
- **Radionuclide therapy:** Systemically administered radionuclides to treat organ-specific disease based on physiological uptake or specific cellular targets based on antibody conjugation

What is the most common direct goal of radiotherapy?

Radiotherapy for Cancer

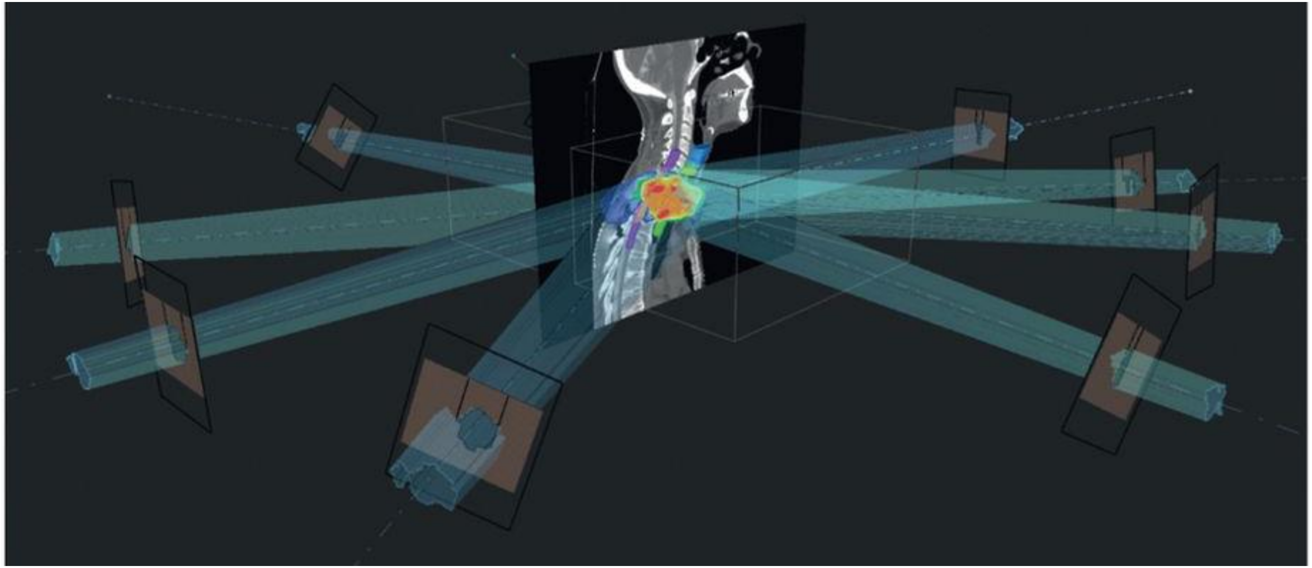
- <u>Local tumour control</u> is dictated by the eradication of all TUMOUR CLONOGENS
  - Impact of dose to the tumour
  - Impact of dose to nearby healthy tissues/organs
  - Impact of the 5 R's of radiobiology

Clinical Radiotherapy: Identifying the Target



- CT scan of the region of interest
- Radiation oncologist contours the tumour & normal structures
- A margin is added to contours to account for microscopic spread, organ motion, and uncertainty
- Dosimetrist will execute beam arrangements
- Physicist conducts QC on linear accelerator, beams, and calculated dose

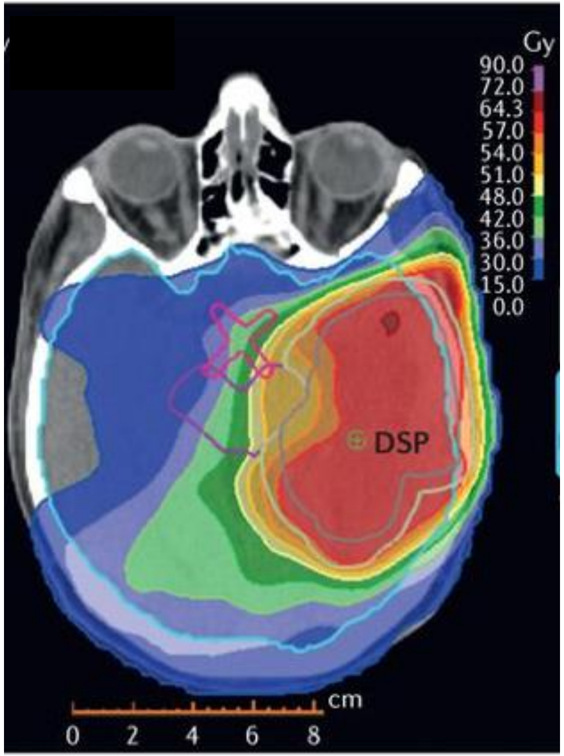
Clinical Radiotherapy: Treating the Target



Conformal techniques utilize multiple intersecting beams or arcs

Baumann, Nature Rev Cancer 2016

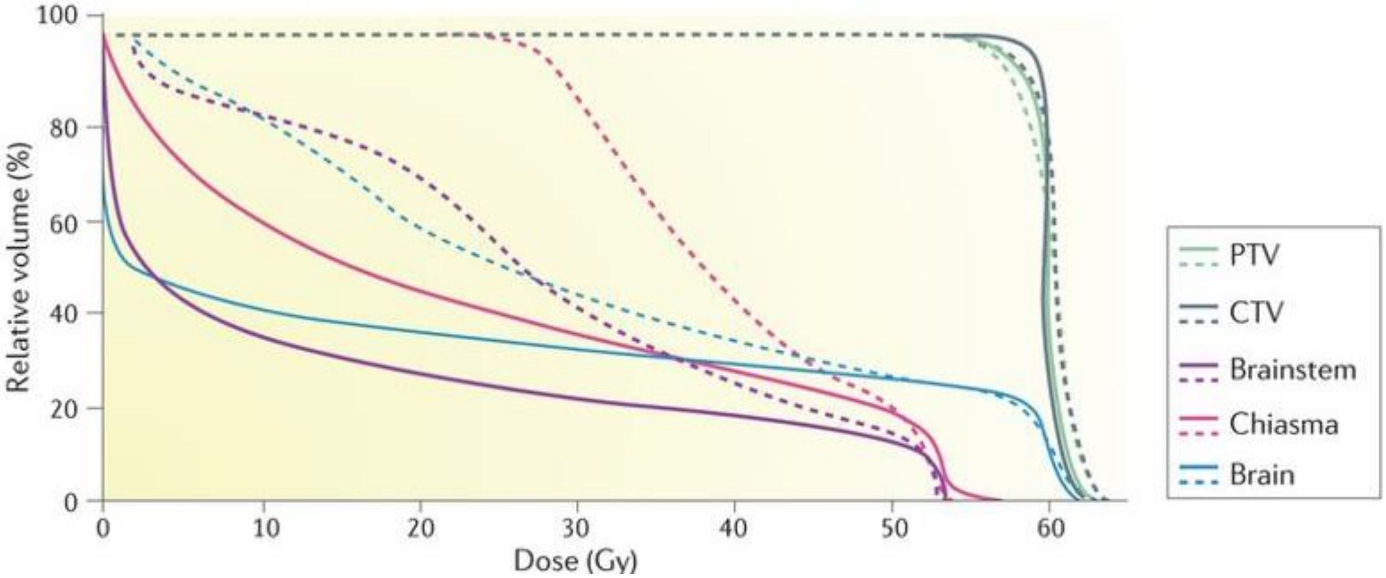
Clinical Radiotherapy: Assessing Dose Distributions



Baumann, Nature Rev Cancer 2016

Clinical Radiotherapy: Assessing Dose Distributions

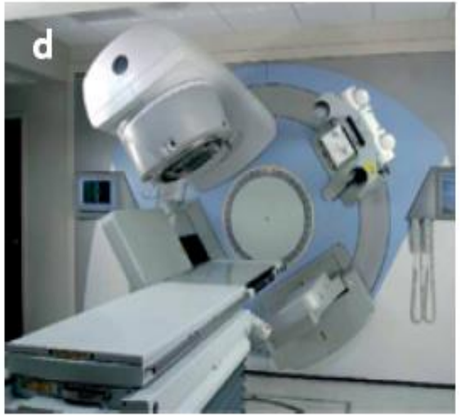
Dose-Volume Histogram (DVH):



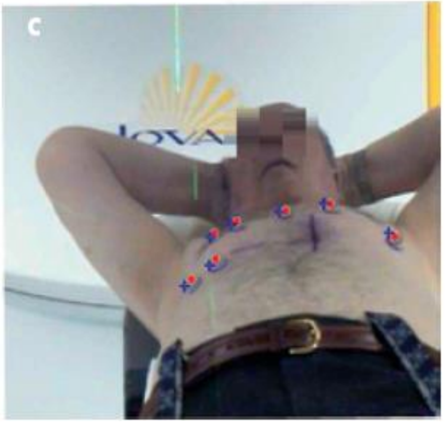
- DVH reports the radiotherapy dose to normal and tumour tissues
- OPTIMIZE TREATMENT = high dose to tumour; low dose to normal tissues

Clinical Radiotherapy: Image Guidance

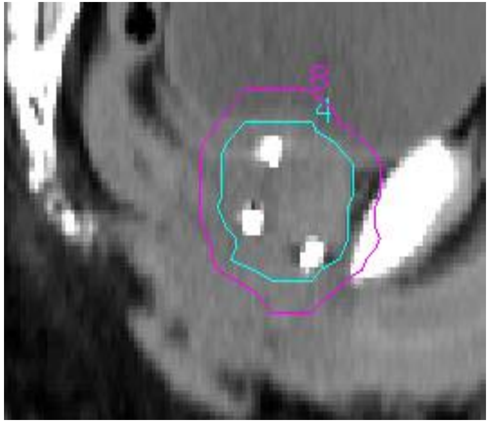
Orthogonal imaging



External Fiducials



Internal Fiducials



Verellen, 2007

Goal: Reduce uncertainty of positioning for tumor and organs-at-risk (i.e., PTV)

Overview

Purpose: To introduce radiobiology concepts with direct clinical relevance

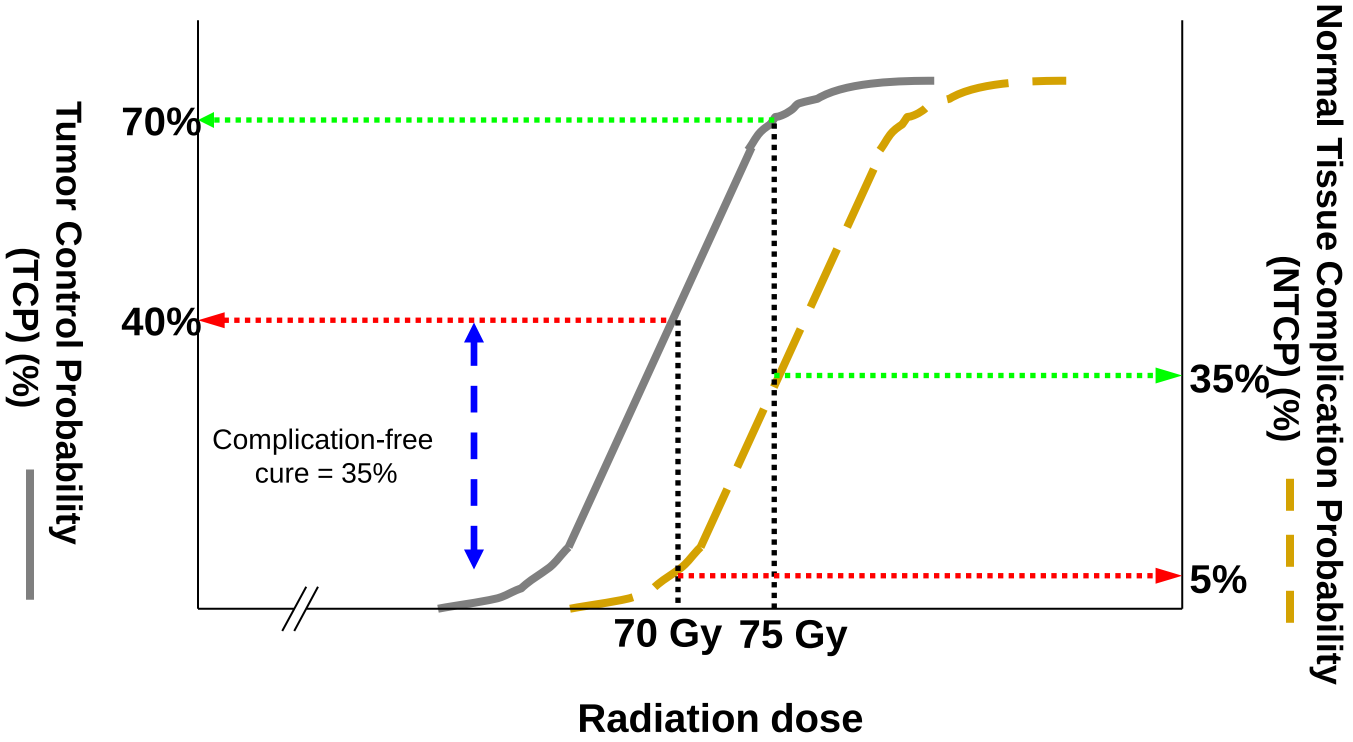
- A brief overview of clinical implementation of radiotherapy
- **The therapeutic index**
- The 5 R's of radiobiology
- Radiobiology in the 21st Century

Radiotherapy for Cancer

- Local tumour control is dictated by the eradication of all TUMOUR CLONOGENS
  - Impact of dose to the tumour
  - Impact of dose to nearby healthy tissues/organs
  - Impact of the 5 R's of radiobiology

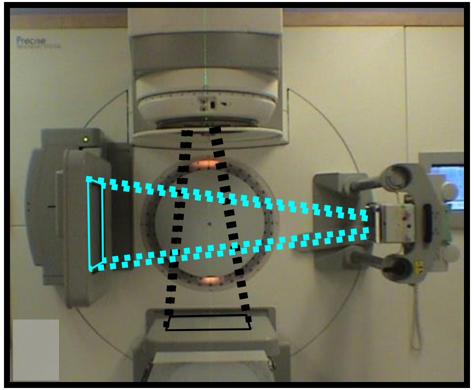
- **THERAPEUTIC INDEX** is maximized when more tumour cells than normal cells are killed
  - Physical means for maximizing
  - Radiobiological means for maximizing

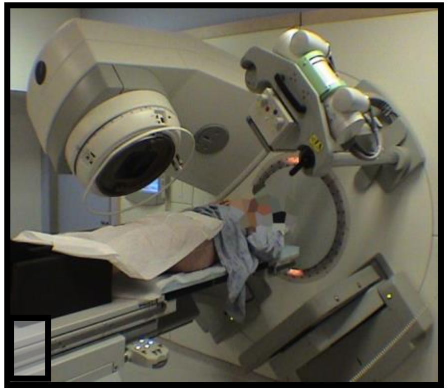
Therapeutic Index



Harrington and Nutting,
Curr Opin Investig Drugs 2002

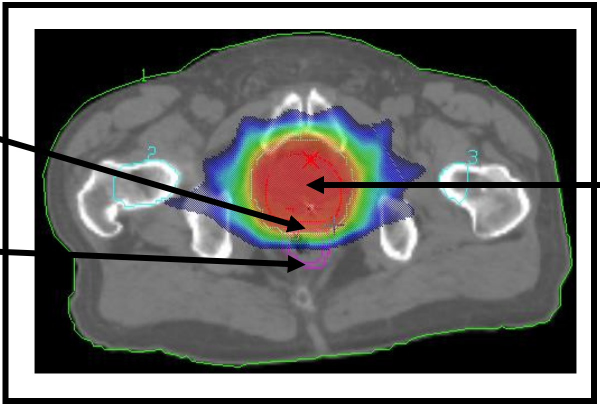
Augmenting the Therapeutic Index: Physical Precision of RT Delivery





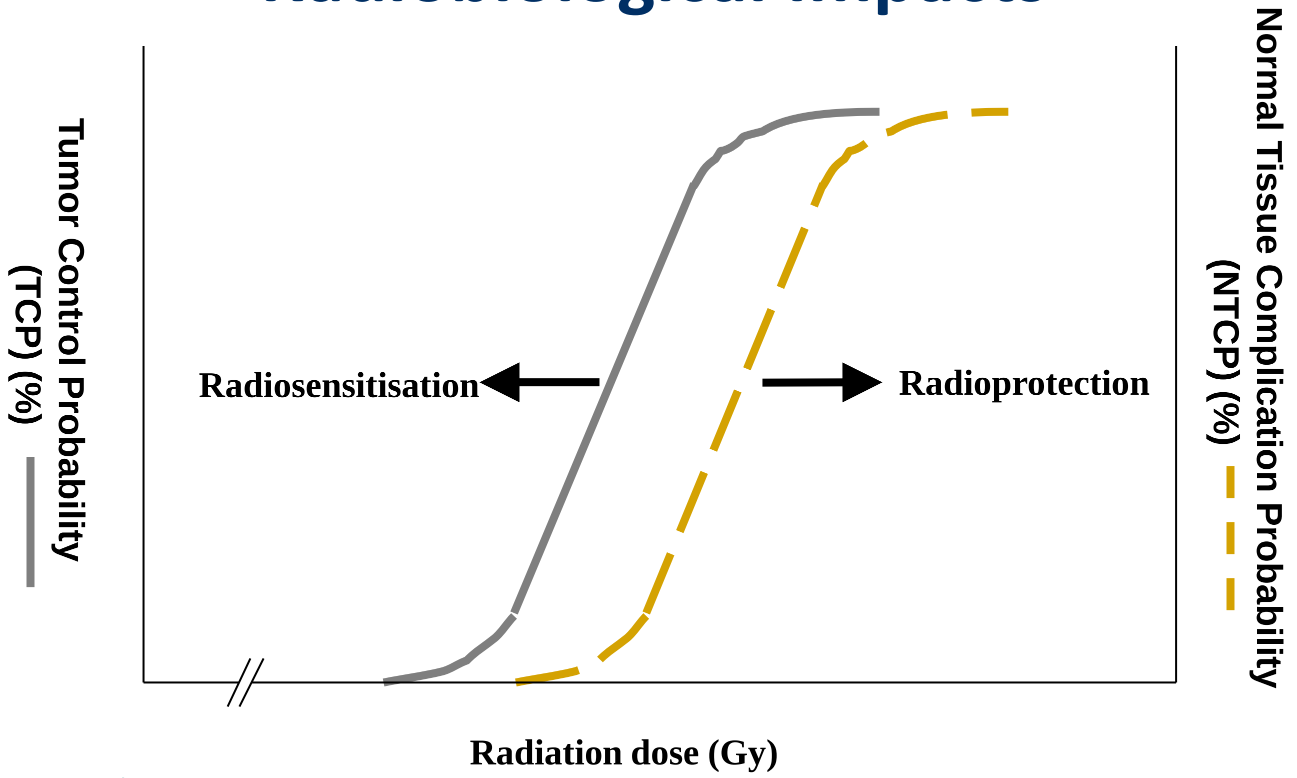
High Dose To Normal Cells

Low Dose To Normal Cells



High Dose To Cancer

Augmenting the Therapeutic Index: Radiobiological Impacts



What would a drug that radiosensitizes both tumour and normal tissue do to the therapeutic index?

Normal Tissue Effects

The time to expression of normal tissue injury depends on its turnover:

- **ACUTE RESPONDING TISSUES**
  - Are rich in stem cells and proliferative progenitor cells that differentiate into functional cells with a high turnover and a high rate of cell loss
  - Days-to-weeks
  - E.g., Gut, Skin, Bone Marrow, Mucosa
- **LATE RESPONDING TISSUES**
  - Have a slow turnover rate and stem cells play a smaller role in regeneration, which generally is from the functional cellular pools after a longer lag time
  - Months-to-years
  - E.g., Brain, Spinal Cord, Kidney, Lung, Blood Vessels

Examples of Normal Tissue Effects

Erythema

Desquamation

Telangiectasia

Overview

<u>Purpose</u>: To introduce radiobiology concepts with direct clinical relevance

- A brief overview of clinical implementation of radiotherapy
- The therapeutic index
- **The 5 R's of radiobiology**
- Radiobiology in the 21st Century

The Five R's of Radiotherapy

- Radiosensitivity
- Repair
- Repopulation
- Redistribution
- Reoxygenation

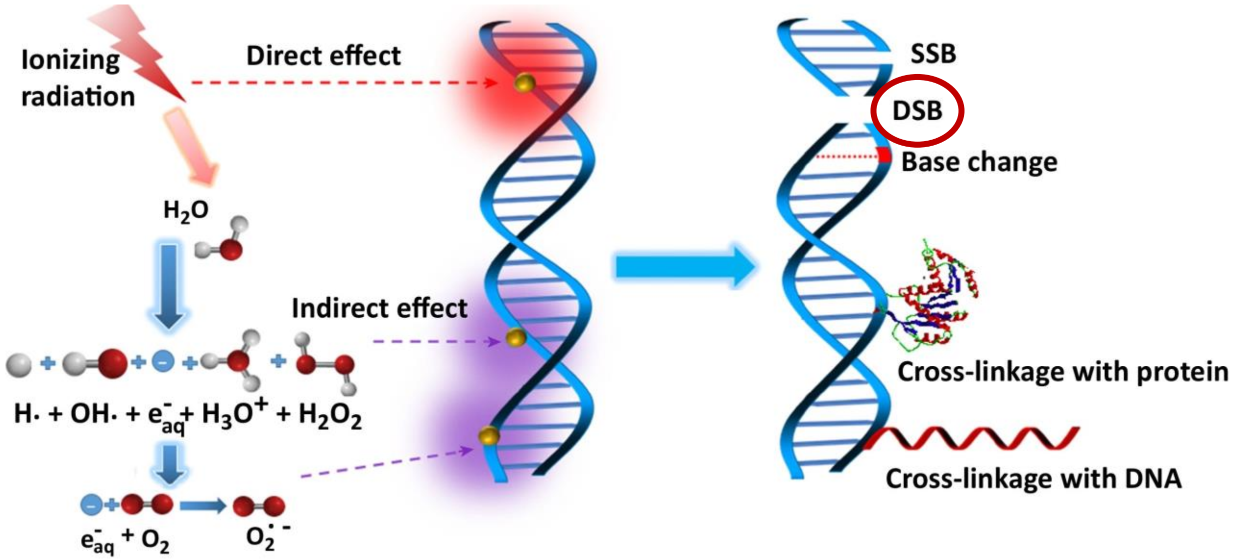
How is the use of fractionated radiotherapy affected by each of these?

Tumor Types have a Range of Intrinsic Radiosensitivities

	Example	Dose (Gy)	Tumor control probability
Sensitive	Seminoma, Lymphoma	≤ 45	$\geq 90\%$
Intermediate	Most carcinomas (e.g., squamous, adeno)	50-70	30-90% (based on number clonogens)
Resistant	Glioblastoma, Melanoma	≥ 60	<30%

Mis-Repair of DNA Damage:

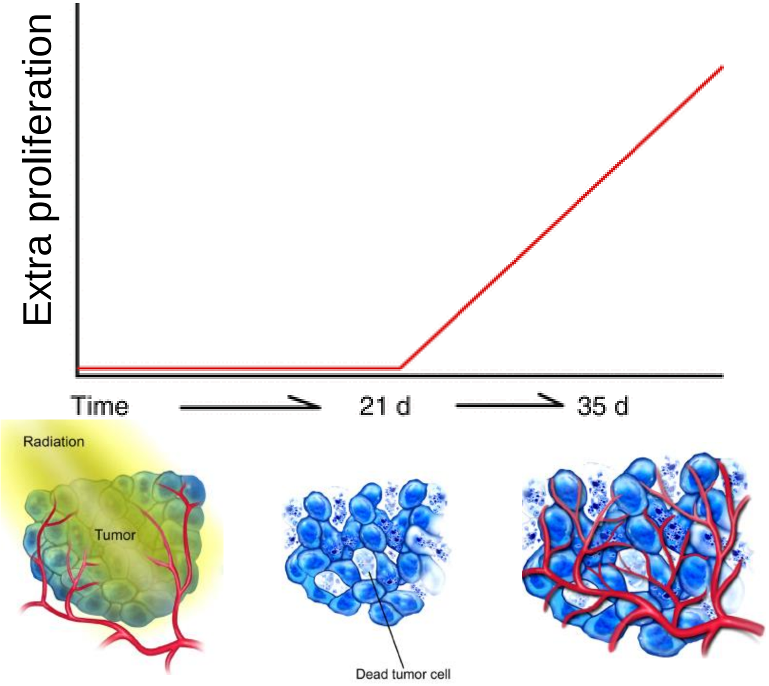
Double-strand breaks (DSBs) are the major mechanism of cell death following ionizing radiation, and repair can occur between fractions



Wang et al, Trends Pharmacol Sci. 2018 Jan;39(1):24-48.

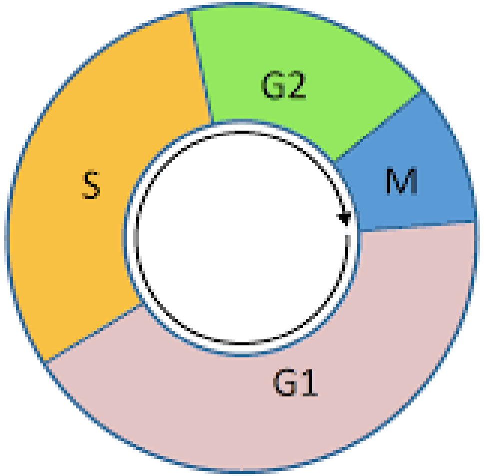
Tumor Cell Repopulation:

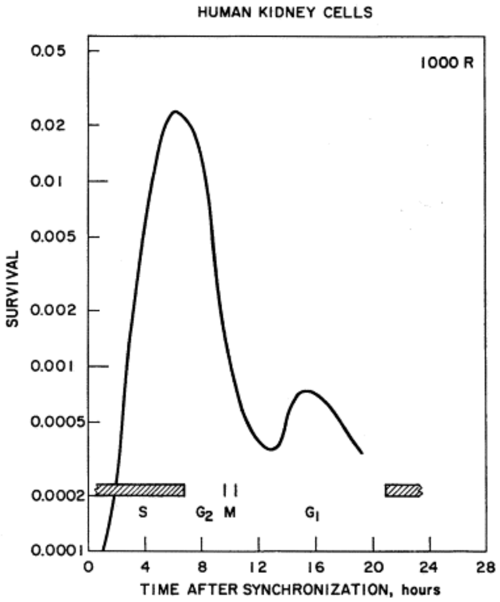
More repopulation is observed during extended courses of fractionated radiotherapy



Cell Cycle Redistribution:

Cell cycle phase affects radiosensitivity, and fractionation allows surviving cells to re-enter sensitive phases



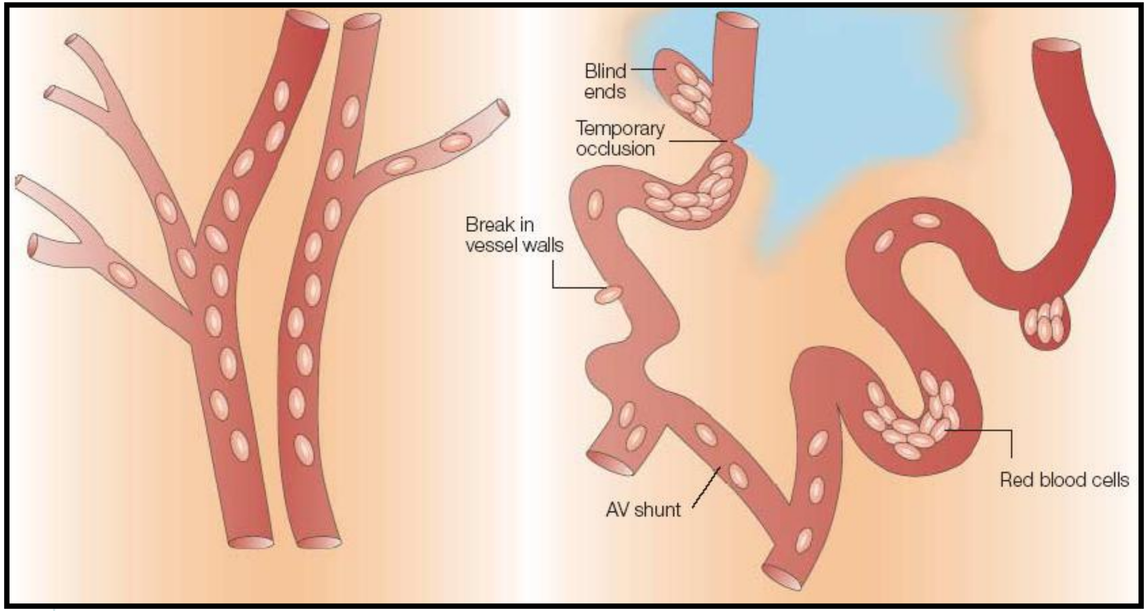


Sinclair & Morton, Radiat Res, 29 (1966), pp. 450-474

Tumor Reoxygenation:

Abnormal tumor vasculature can cause hypoxia, and fractionation can allow for re-oxygenation

Normal **Tumour**



(adapted from Brown and Wilson; Nature, 2004)

Would tumour hypoxia have a greater effect on single-fraction (e.g., SRS) or multi-fraction radiotherapy?

At the height of COVID-19, hospitals tried to reduce the number of radiotherapy fractions in order to limit exposure to patients & staff.

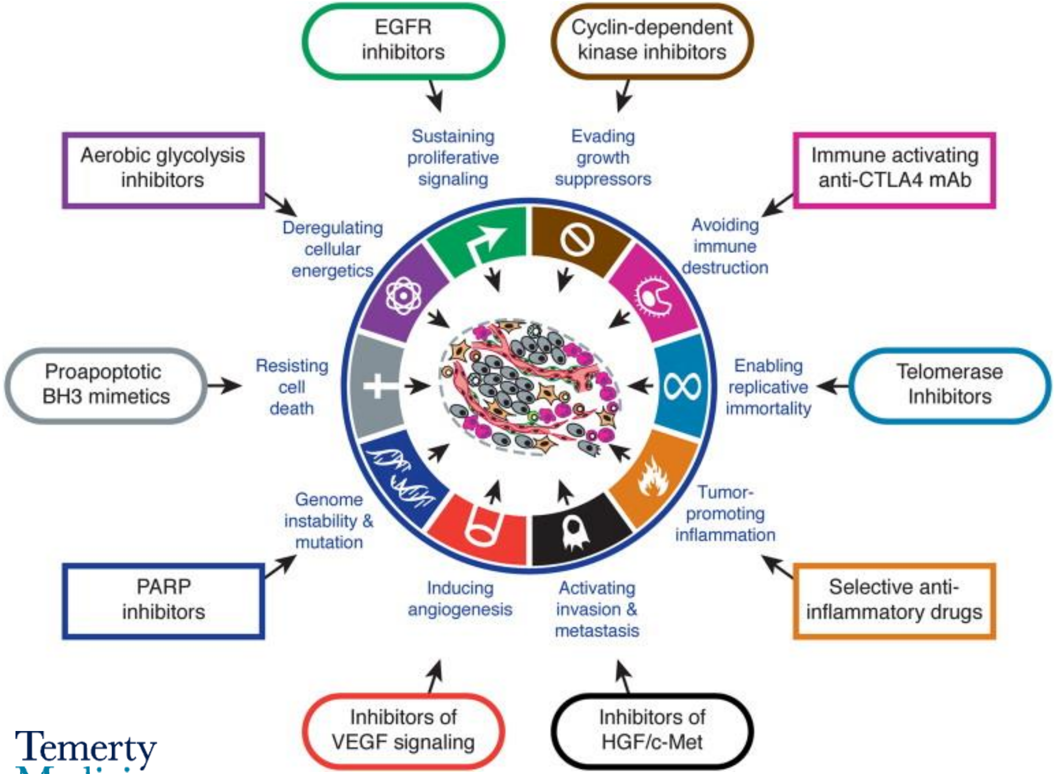
How would dose need to be adjusted to allow for equal tumour control probability?

Overview

<u>Purpose</u>: To introduce radiobiology concepts with direct clinical relevance

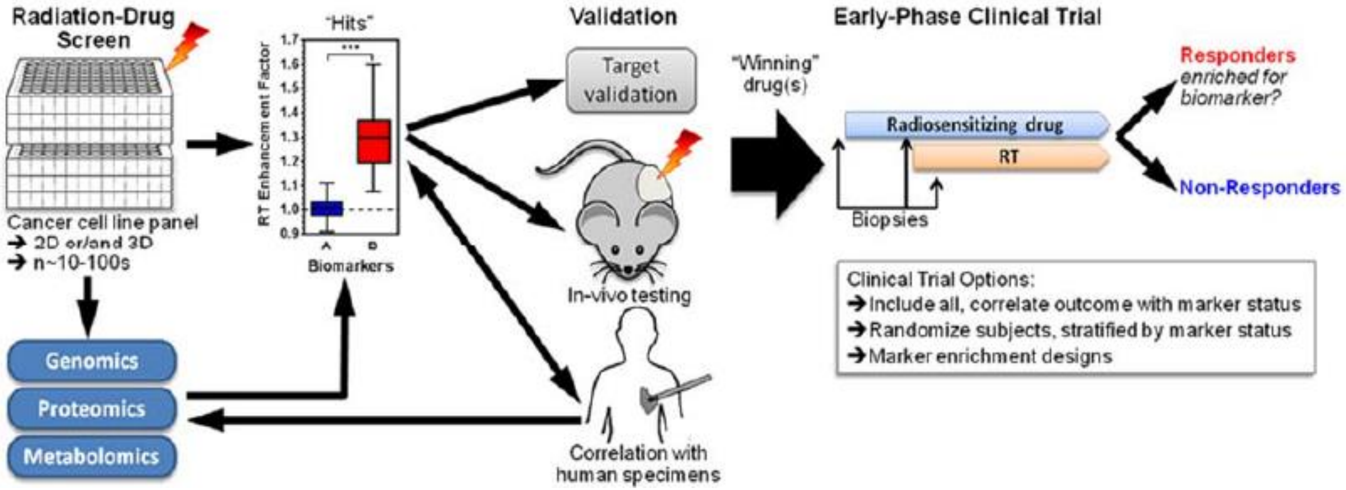
- A brief overview of clinical implementation of radiotherapy
- The therapeutic index
- The 5 R’s of radiobiology
- **Radiobiology in the 21st Century**

Opportunities for Advancing Precision Radiation Medicine



Weinberg, 2011

Opportunities for Advancing Precision Radiation Medicine



Bristow/Harari, 2018

Advancing Precision Radiotherapy in the 21st Century

- Build on Physical/Technical Precision with Biological Precision
- Optimize radiotherapy fractionation schemes to maximize therapeutic index
- Use Molecular Subtyping/Signatures for biomarker-guided individualized treatments (e.g., risk stratification, prediction, and response monitoring)
- Develop molecularly-targeted drugs and radionuclides
- Delivery of radioprotective agents to affected normal tissues
- Integrate with Immunotherapy and understand Immune Effects of radiotherapy

Questions?

Thank you!

Scott Bratman
scott.bratman@uhn.ca