Importance of Radiobiology in the Clinic

Scott V Bratman, MD PhD FRCPC
Clinician-Scientist & Assistant Professor
Radiation Oncology & Medical Biophysics
Princess Margaret Cancer Centre & U of Toronto

Clinical and Experimental Radiobiology
April 26, 2021

Radiation Oncology
UNIVERSITY OF TORONTO

UHN Princess Margaret Cancer Centre

Disclosures

- Licensing: Roche Molecular Systems, DNAMx
- Ownership: DNAMx
- Consulting: BMS, DNAMx
- Employment: DNAMx
- Research support: Nektar Therapeutics

Lecture Overview

Purpose: To introduce radiobiology concepts with direct clinical relevance

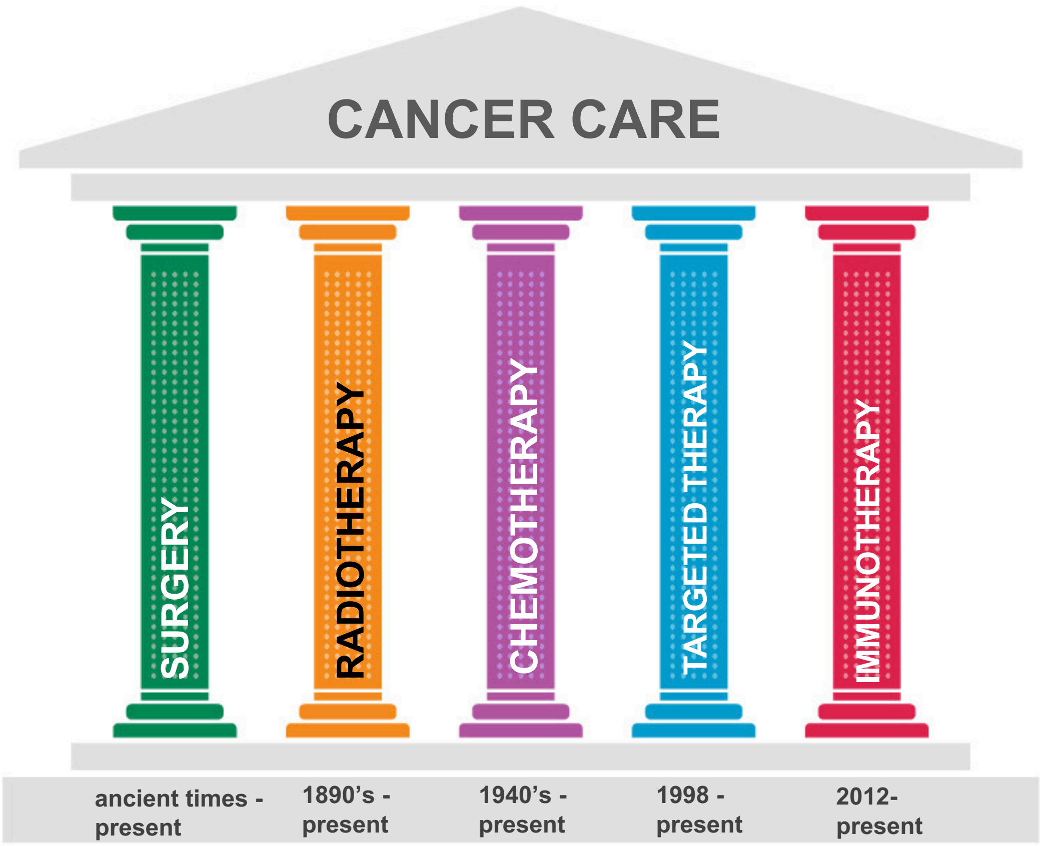
- A brief overview of clinical implementation of radiotherapy
- The therapeutic ratio
- The 5 R's of radiobiology
- Radiobiology in the 21st Century

Lecture Overview

Purpose: To introduce radiobiology concepts with direct clinical relevance

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

Radiotherapy is a longstanding therapeutic pillar in oncology



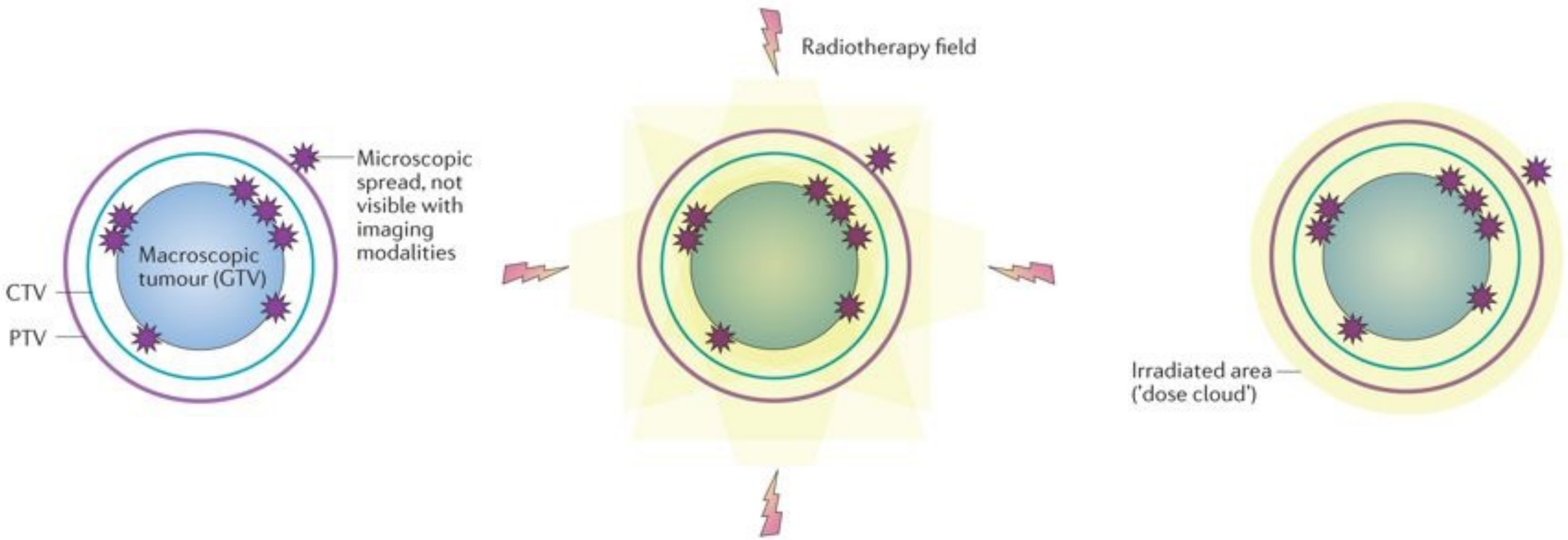
Radiotherapy for Cancer

- More than 50% of cancer patients will receive radiotherapy during their course of disease
  - Most common: high-energy (6-25 MV) photons that deposit their energy deep within tissue and spare skin
  - Alone or in combination with chemotherapy
  - Combined therapy has given another 10-15 % local control

- 1) **Curative**: Given as a series of daily treatments or "fractions" of 1.8-2.5 Gy over 6.5 to 8.5 weeks = "fractionated radiotherapy
- 2) **Palliative**: Single 8 Gy or 20 Gy in 5 fraction doses for pain control or other symptomatic end-points
- 3) **Stereotactic Radiotherapy & Brachytherapy**: High dose-per-fraction stereotactic radiation or interstitial radioactive implants ("brachytherapy") given in 1-5 high doses (6-25 Gy each) to a small area
- 4) **Radiopharmaceuticals**: Injected IV radionuclides to treat organ-specific disease based on physiological uptake or specific cellular targets based on antibody conjugation

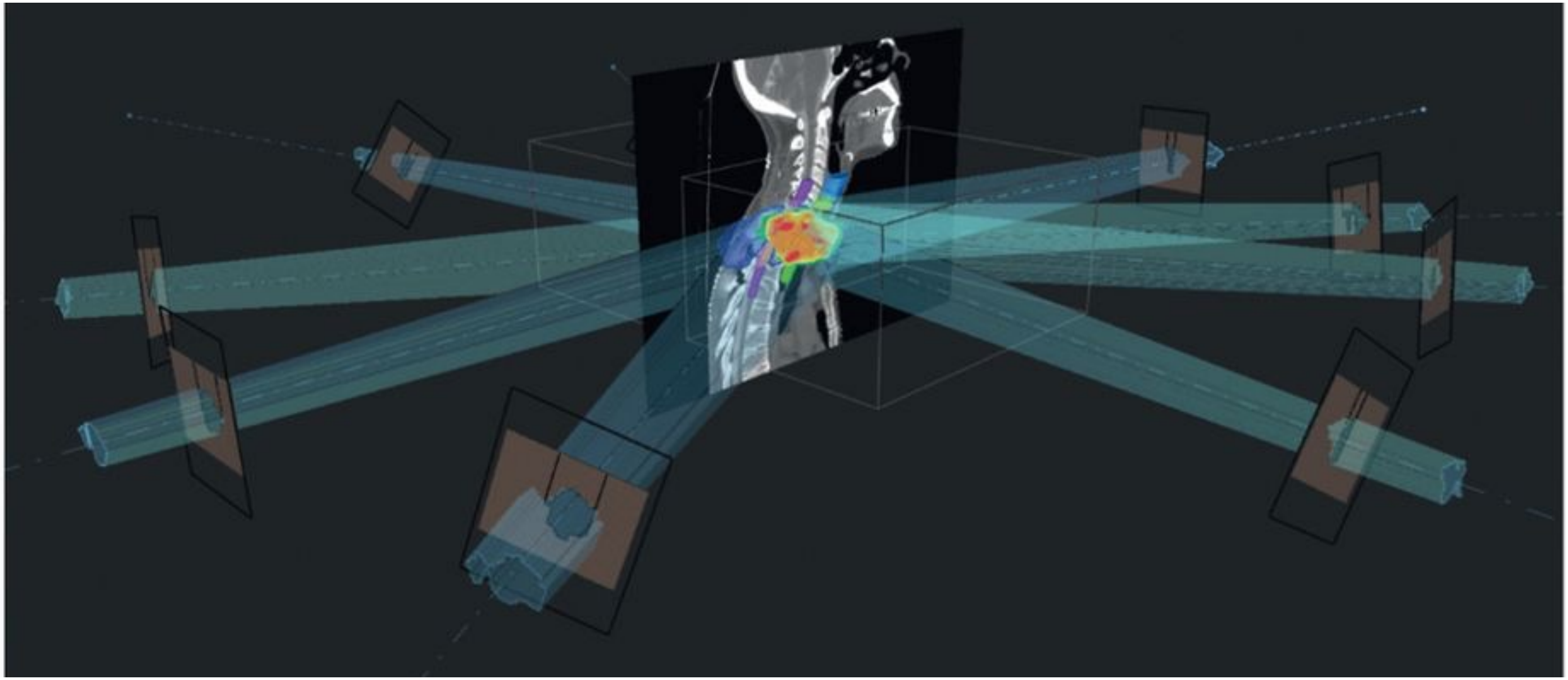
What is the most common direct goal of radiotherapy?

Clinical Radiotherapy: Identifying the Target



- **CT scan of the region of interest**
- **Radiation oncologist contours the tumour & normal structures**
- **A margin will be added to the contours to account for microscopic spread, organ motion, and uncertainty**
- **Dosimetrist will execute beam arrangements**

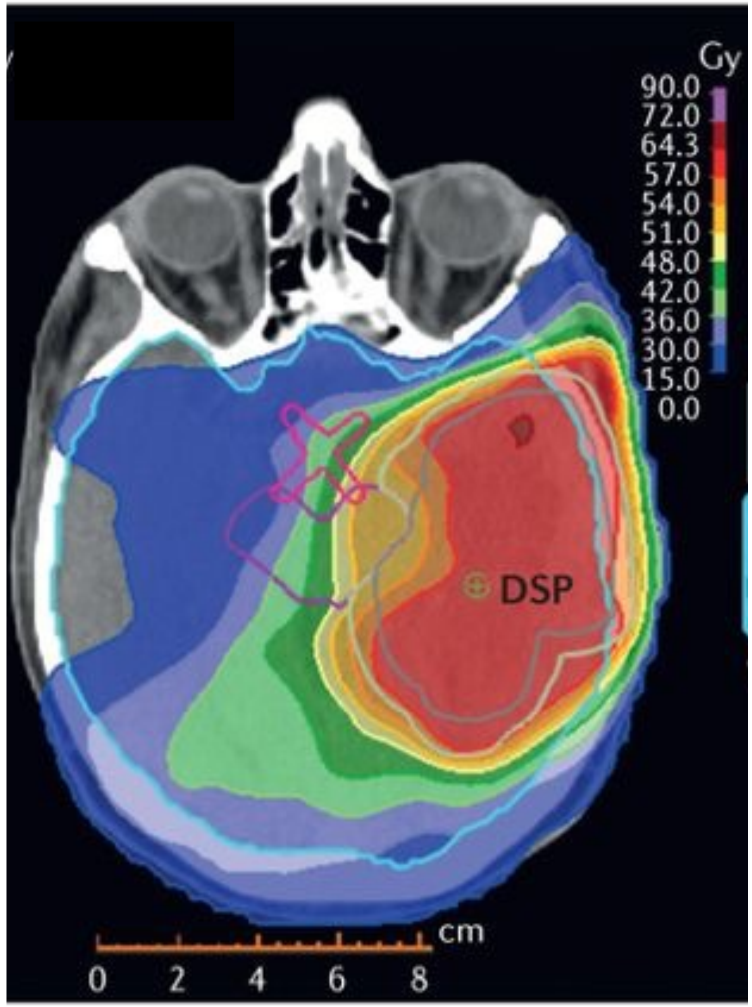
Clinical Radiotherapy: Treating the Target



- **Conformal techniques utilize multiple intersecting beams**

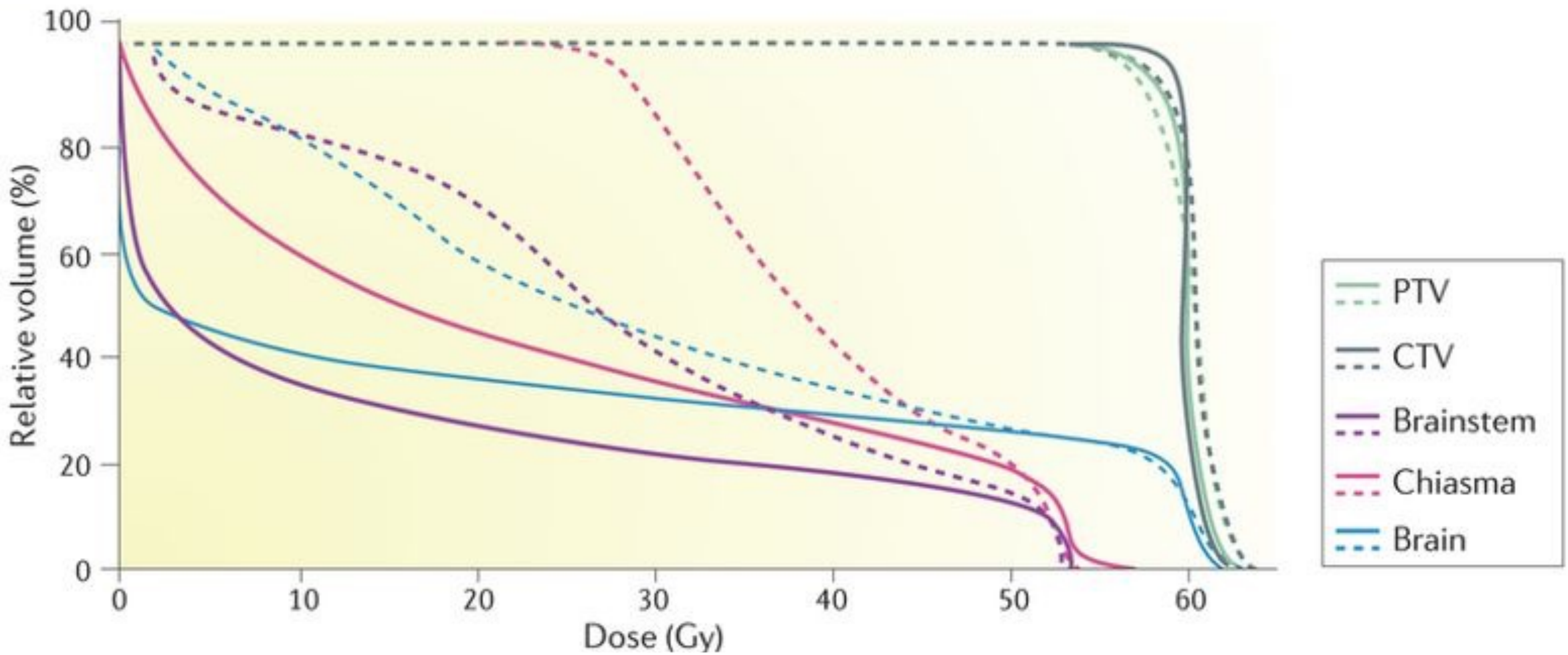
Baumann, Nature Rev Cancer 2016

Clinical Radiotherapy: Assessing Dose



Baumann, Nature Rev Cancer 2016

Clinical Radiotherapy: Dose-Volume Histogram

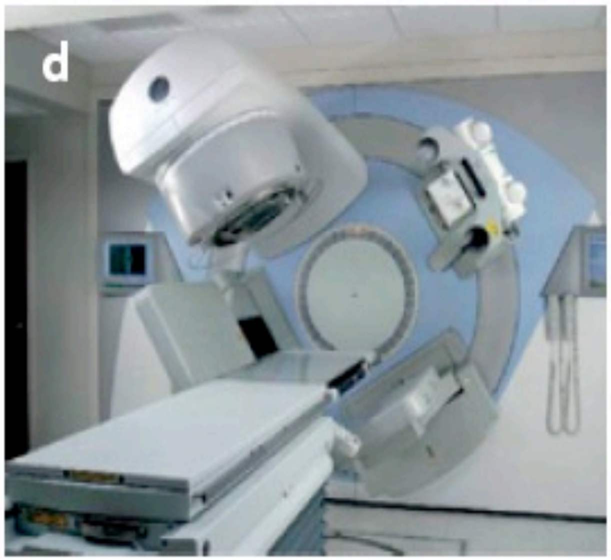


- DVH reports the radiotherapy dose to normal and tumour tissues
- OPTIMIZE TREATMENT = high dose to tumour; low dose to normal tissues

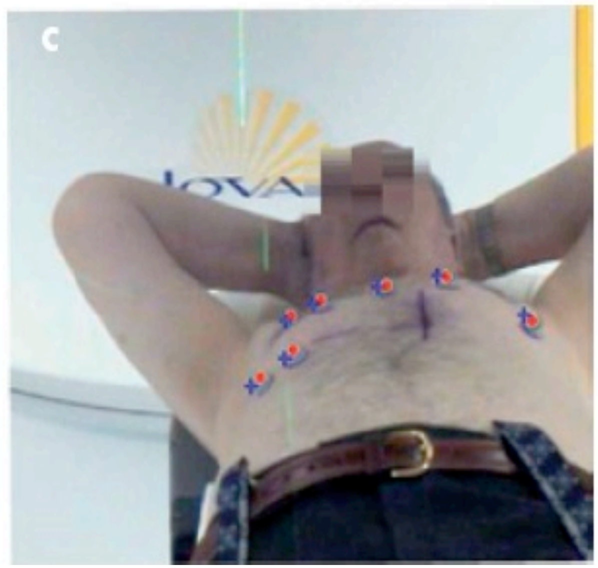
Baumann, Nature Rev Cancer 2016

Clinical Radiotherapy: Image Guidance

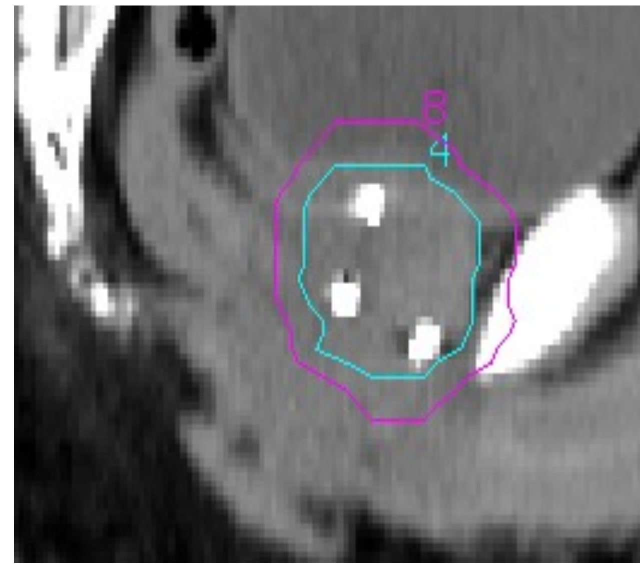
Orthogonal imaging



External Fiducials



Internal Fiducials



Verellen, 2007

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

Lecture Overview

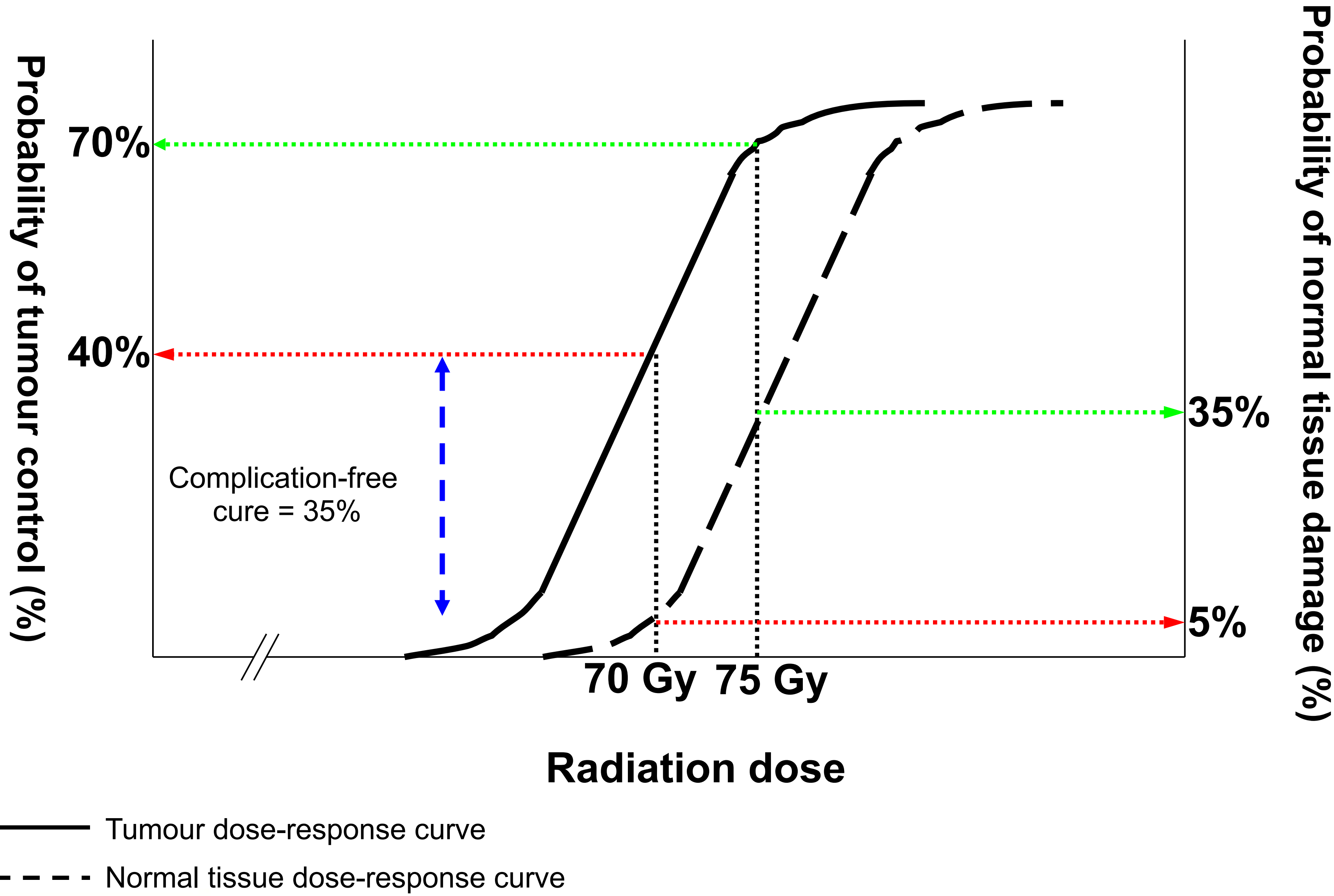
Purpose: To introduce radiobiology concepts with direct clinical relevance

- A brief overview of clinical implementation of radiotherapy
- **The therapeutic ratio**
- 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
- Fractionated radiotherapy is used to maximize the THERAPEUTIC RATIO in order to kill more tumour cells than normal cells

Therapeutic Ratio

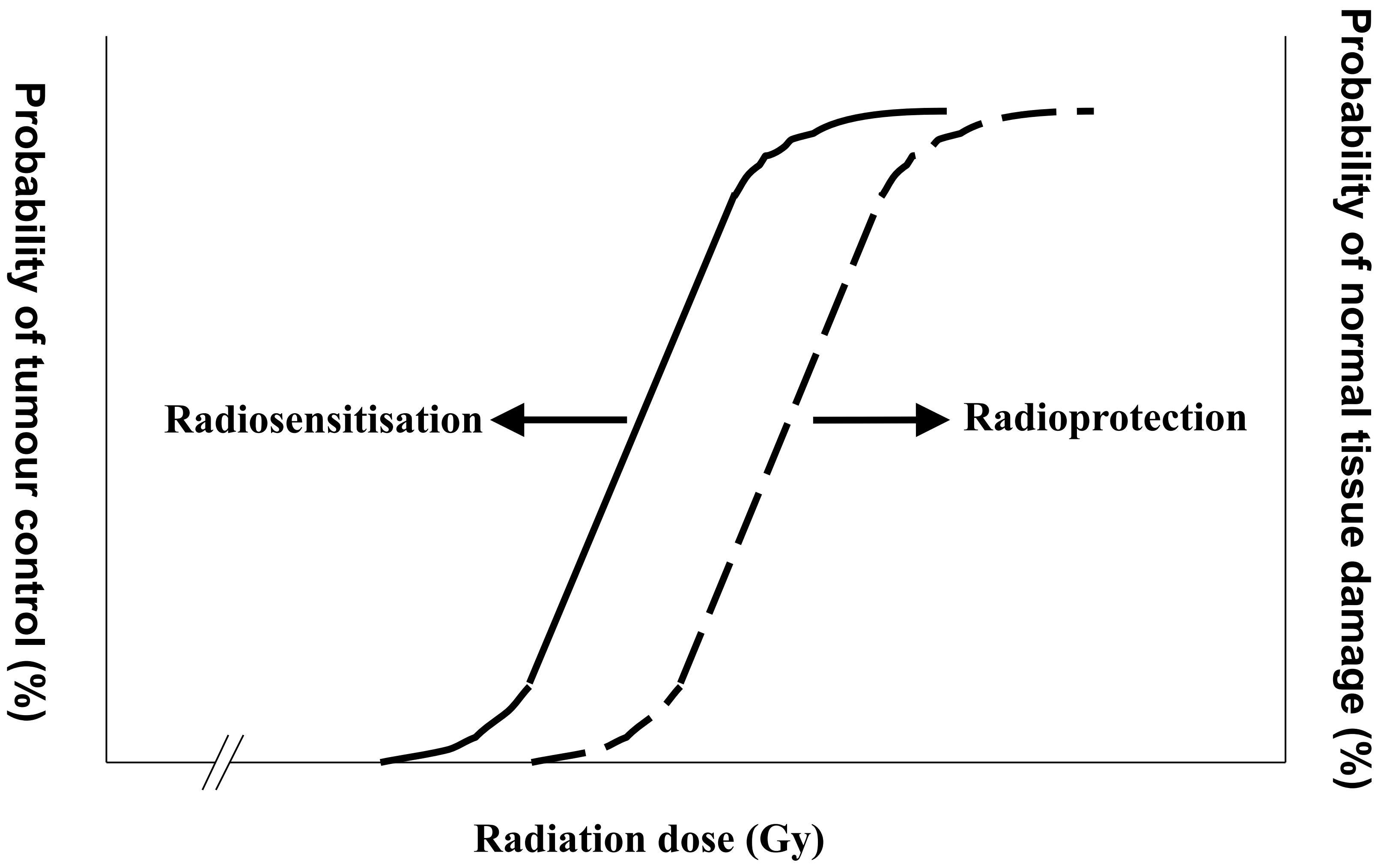


Radiation Oncology
UNIVERSITY OF TORONTO

Harrington and Nutting,
Curr Opin Investig Drugs 2002

UHN Princess Margaret Cancer Centre

Augmenting the Therapeutic Ratio



Normal Tissue Effects

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

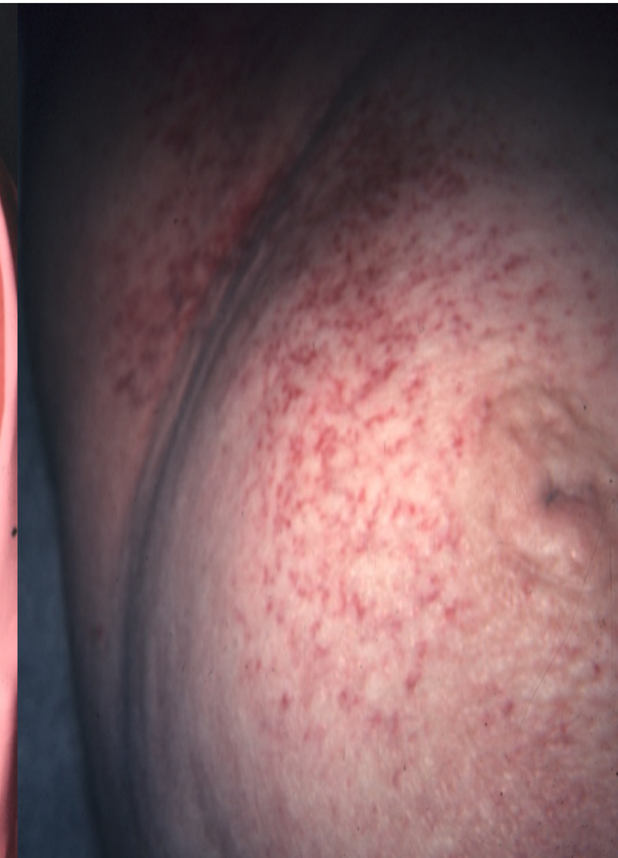
- **ACUTE RESPONDING TISSUES**
  - Are rich in stem cells and proliferative progenitor cells that differentiate into functional cells with a high turnover and a high rate of cell loss
  - Days-to-weeks
  - Eg. Gut, Skin, Bone Marrow, Mucosa
- **LATE RESPONDING TISSUES**
  - Have a slow turnover rate 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
  - Eg. Brain, Spinal Cord, Kidney, Lung, Bladder

Normal Tissue Effects

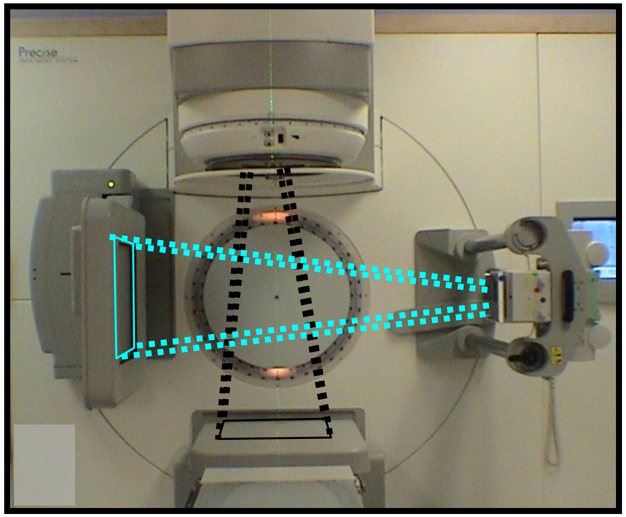
Erythema

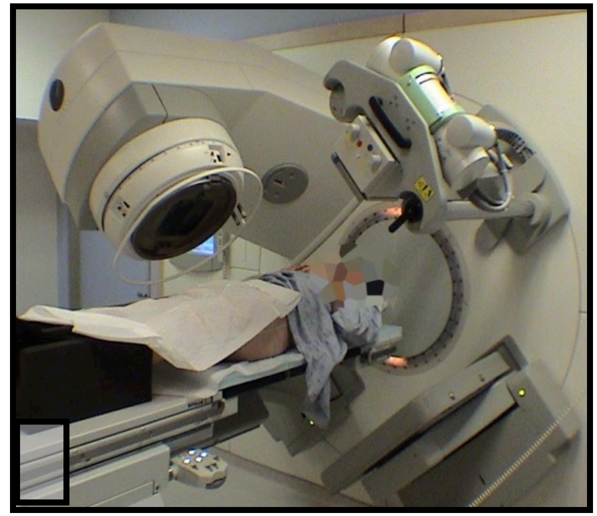
Moist Desquamation

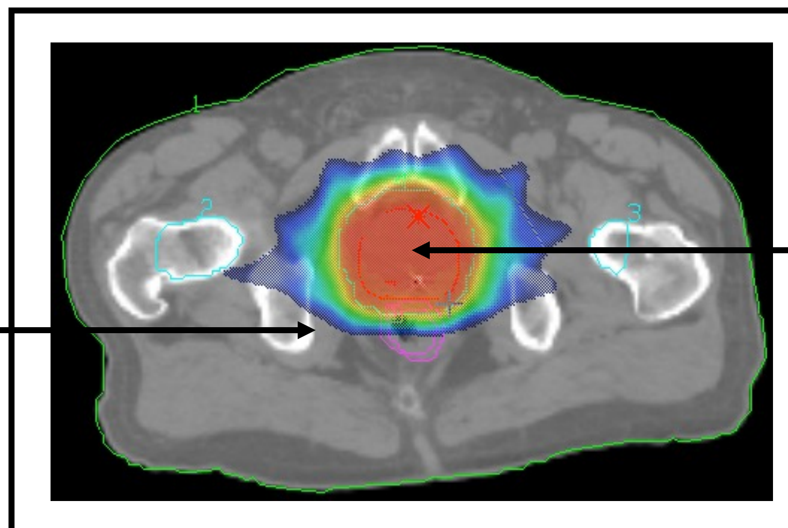
Telangiectasia



Augmenting the Therapeutic Ratio: Physical Precision of RT Delivery







Low Dose To Normal Cells

High Dose To Cancer

Radiation Oncology
UNIVERSITY OF TORONTO

UHN Princess Margaret Cancer Centre

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

Lecture Overview

Purpose: To introduce radiobiology concepts with direct clinical relevance

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

The Five R's of Radiotherapy

- Radiosensitivity
- Repair
- Repopulation
- Redistribution
- Reoxygenation

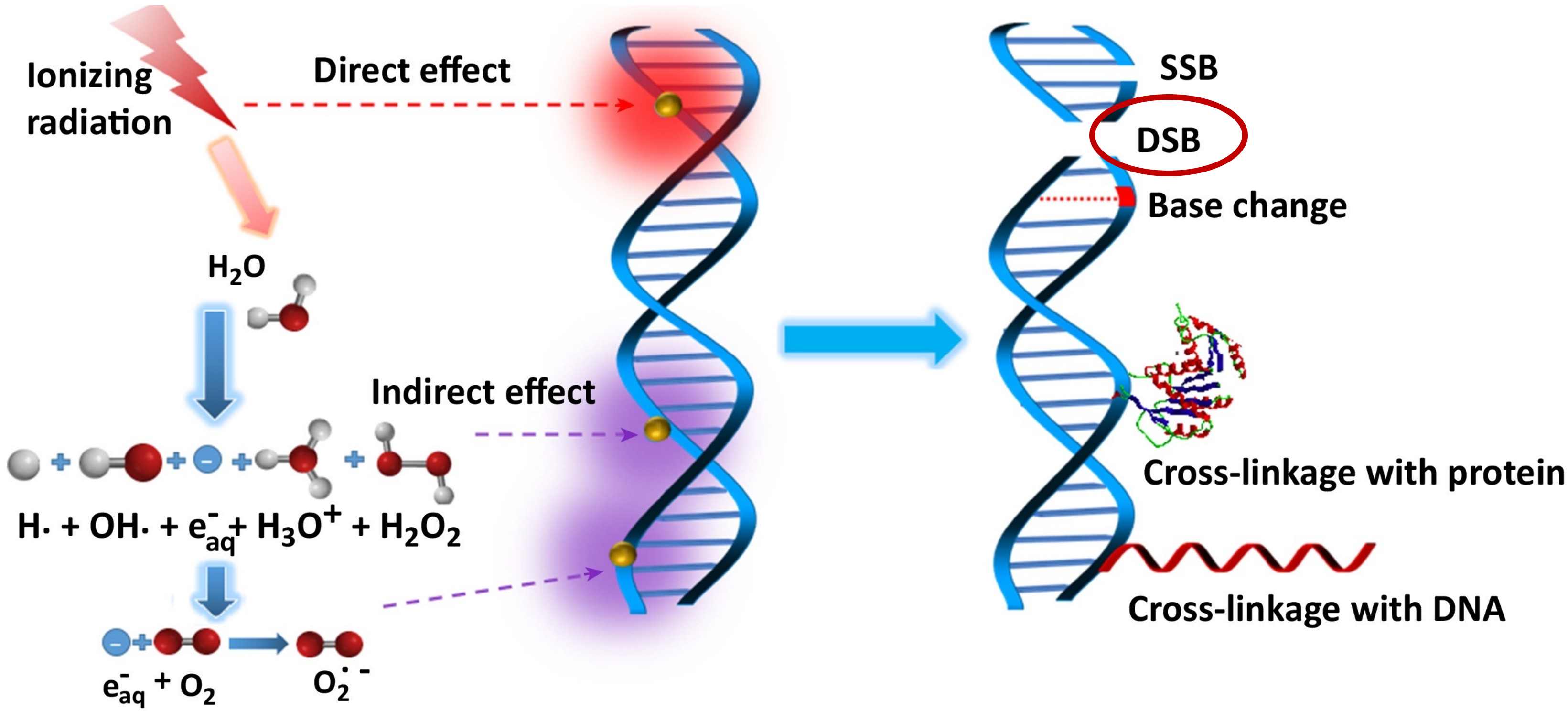
How is the use of radiotherapy affected by each of these?

Tumor Types have a Range of Intrinsic Radiosensitivities

	Example	Dose (Gy)	Tumor control probability
Sensitive	Seminoma, Lymphoma	≤ 45	$\geq 90\%$
Intermediate	SCC, Adeno-Ca	50-70	30-90% (based on number colonogens)
Resistant	Glioblastoma, Melanoma	≥ 60	<30%

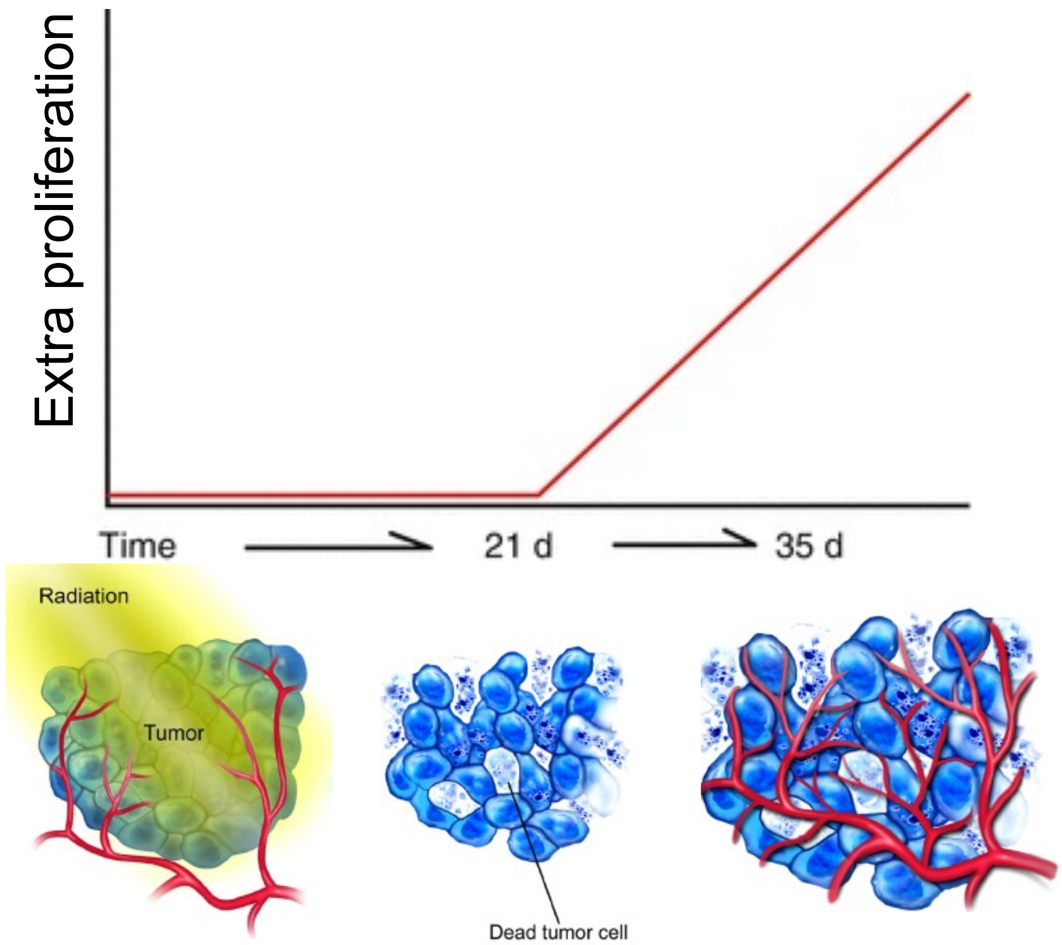
Mis-Repair of DNA Damage:

Double-strand breaks (DSBs) are the major mechanism of cell death following ionizing radiation exposure



Fractionation of radiotherapy allows normal tissues to repair DNA

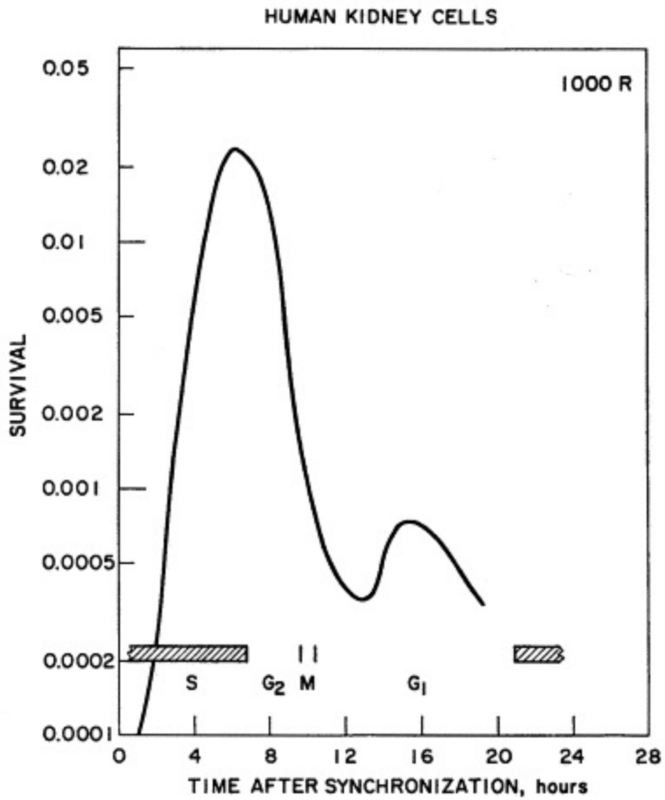
Tumor Cell Repopulation:
Competing Effect During Fractionated Radiotherapy



Longer courses of radiotherapy allow for more repopulation

Cell Cycle Redistribution

Differential radiosensitivity through the cell cycle

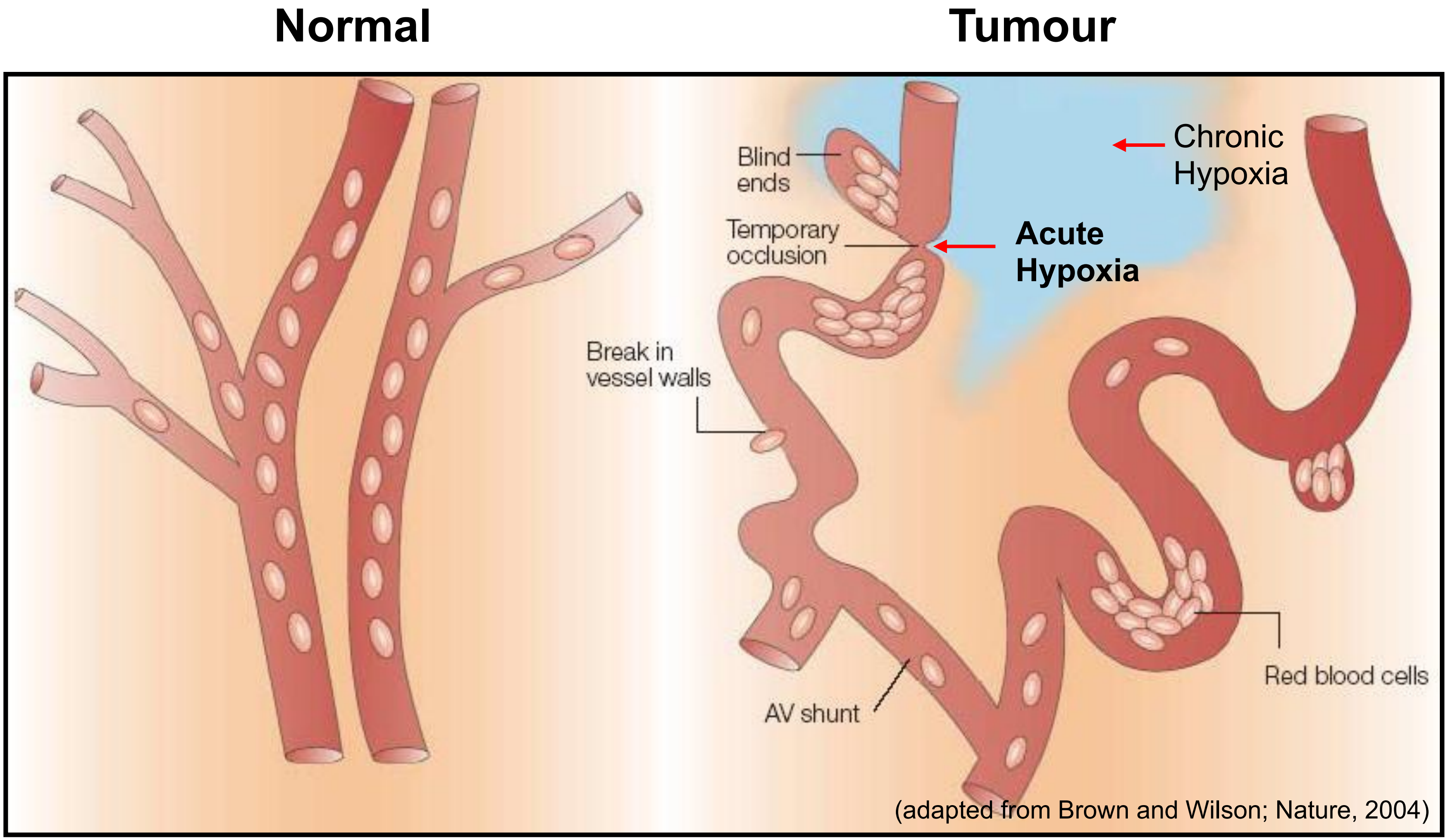


Fractionation allows surviving cells to re-enter sensitive cell cycle phases

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

Tumor Reoxygenation

Dynamic levels of O_2 in tumors during treatment



Fractionation allows regions of acute hypoxia to reoxygenate

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

With COVID-19, hospitals are trying to reduce the number of radiotherapy fractions in order to limit exposure. How would dose be adjusted to allow for equal tumor control probability?

Lecture Overview

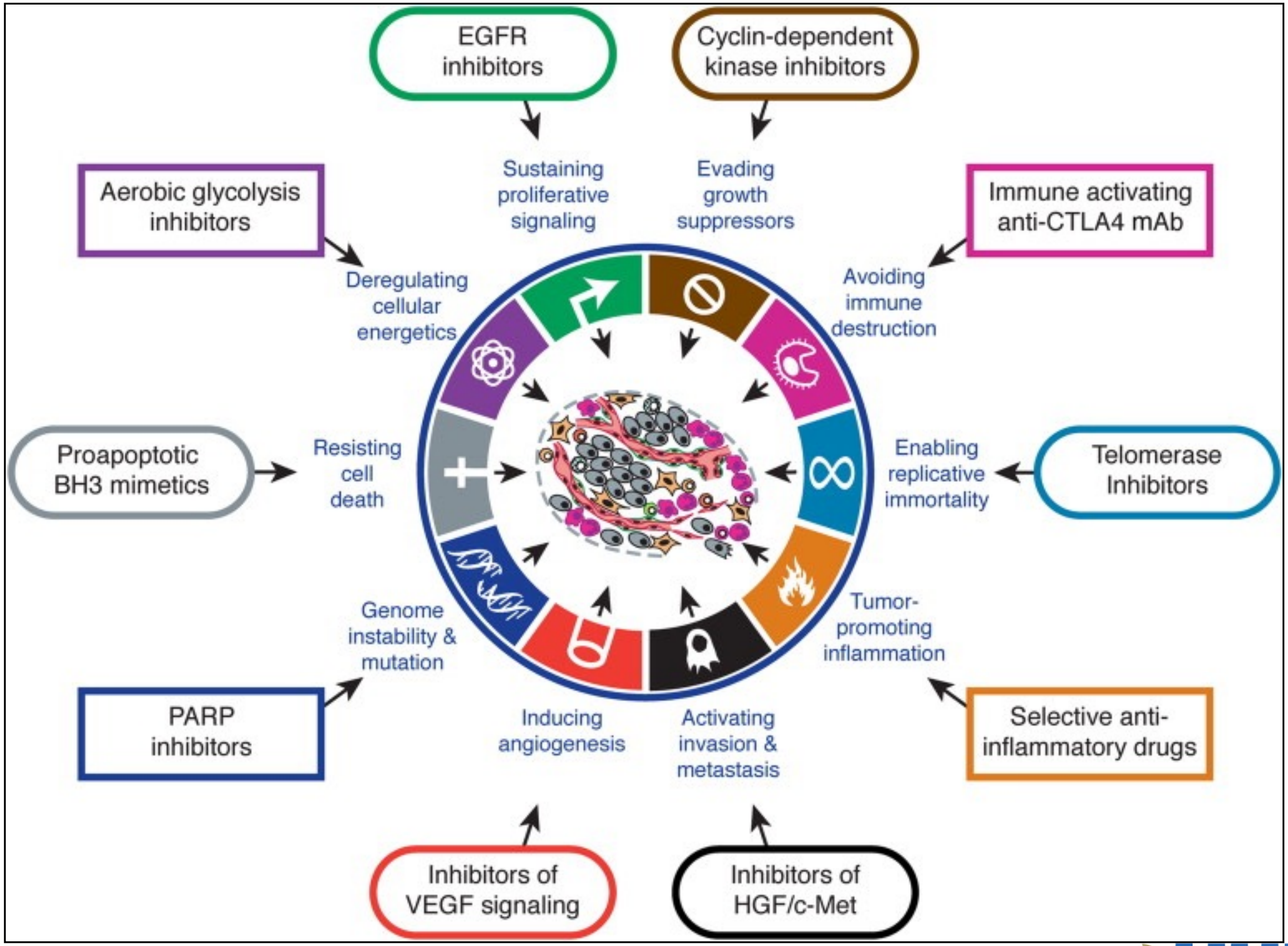
Purpose: To introduce radiobiology concepts with direct clinical relevance

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

Advancing Precision Radiotherapy in the 21st Century

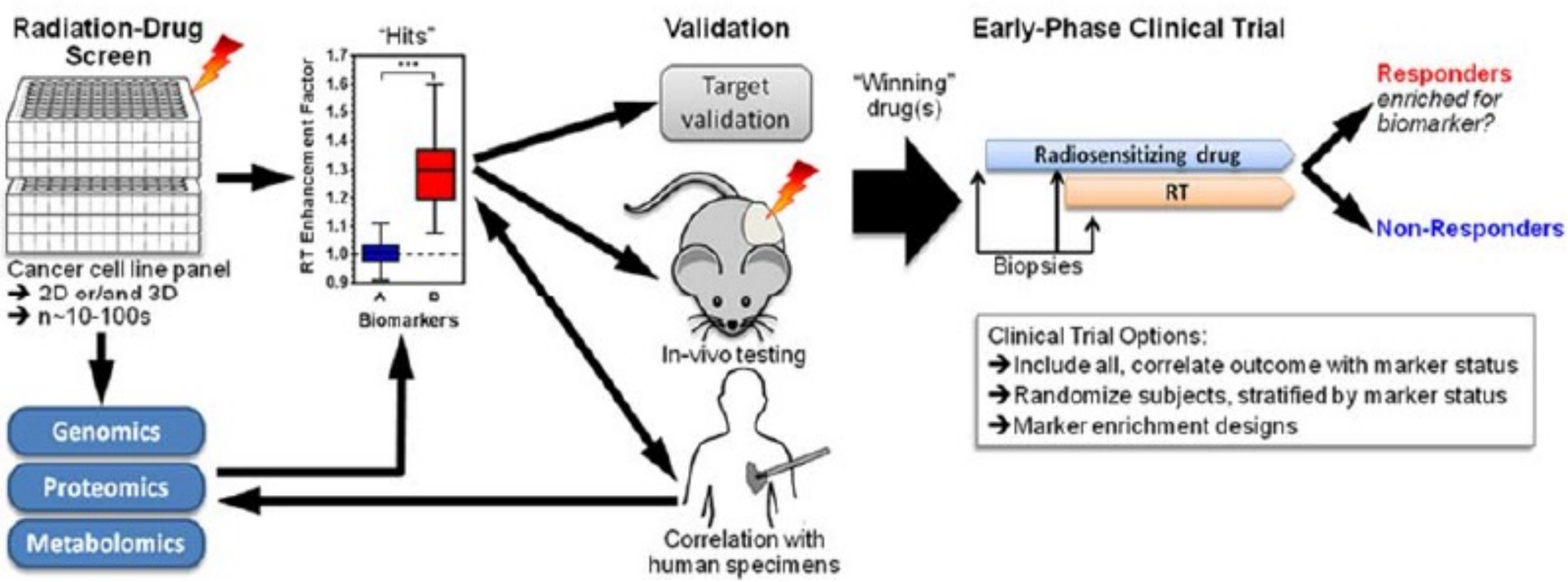
- Build on **Physical/Technical Precision** with **Biological Precision**
- Use **Molecular Subtyping/Signatures** for individualized treatment choices
- Develop **Molecular-Targeted Drugs** to add to precision radiotherapy
- Integrate with **Immunotherapy** and understand **Immune Effects** of radiotherapy

Opportunities for Advancing Precision Radiation Medicine



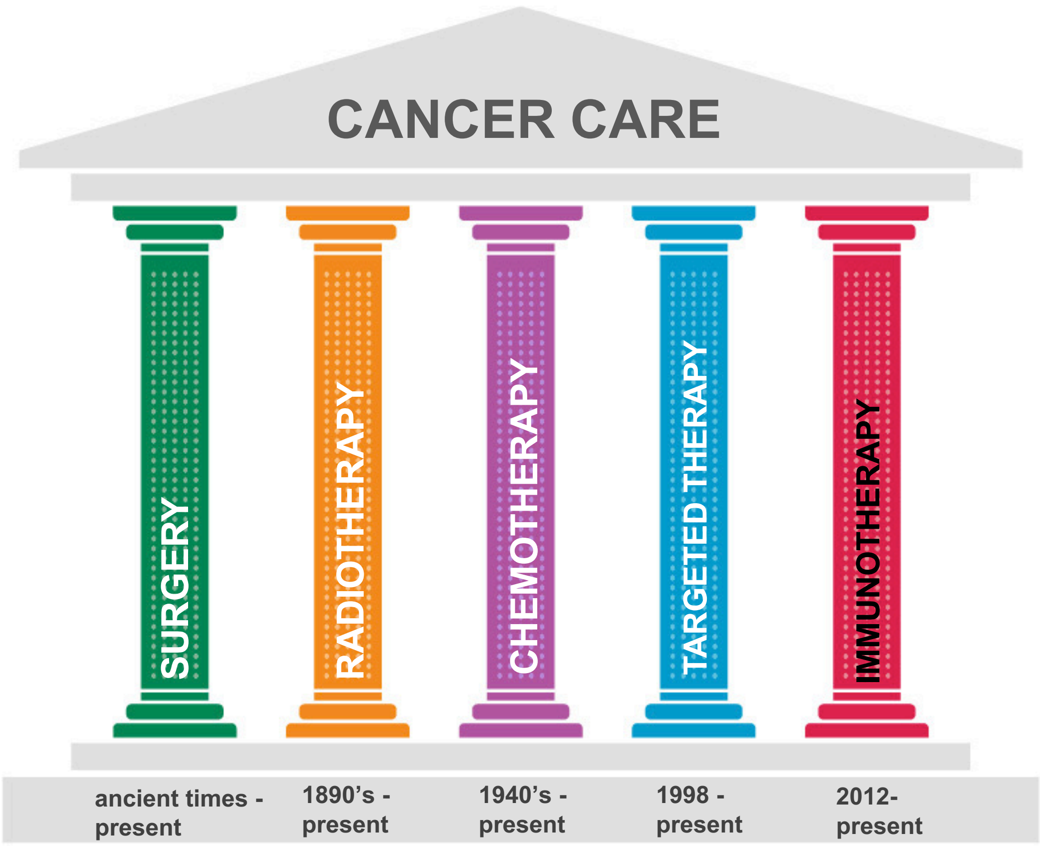
Weinberg, 2011

Opportunities for Advancing Precision Radiation Medicine



Bristow/Harari, 2018

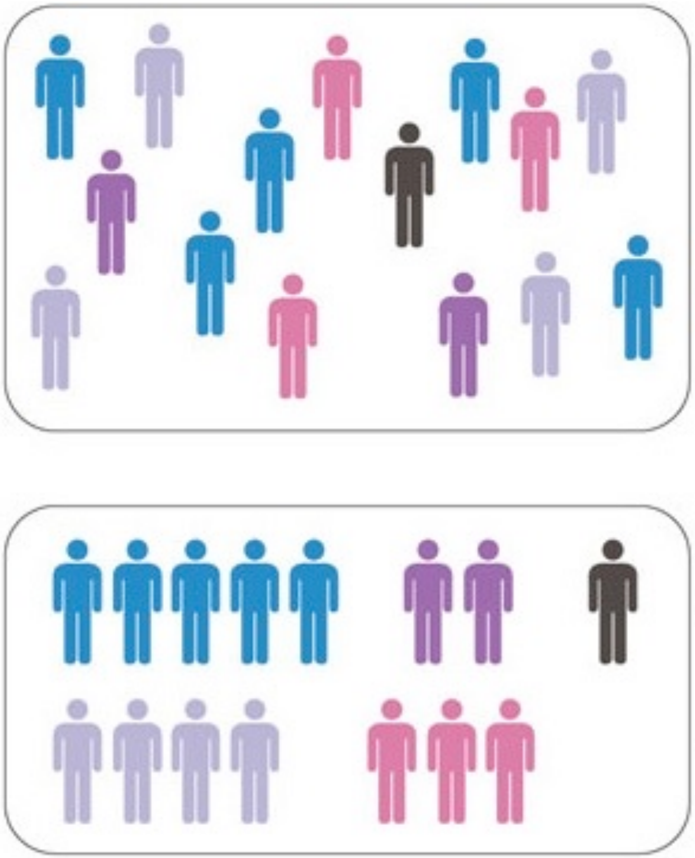
Opportunities for Advancing Precision Radiation Medicine



Opportunities for Advancing Precision Radiation Medicine

- **Optimize radiotherapy fractionation schemes to maximize therapeutic ratio**
- **Combine physical precision with biological precision**
- **Stratification of risk cohorts to enable treatment individualization**
- **New opportunities to augment the therapeutic ratio of radiotherapy by combining with other treatments**

Challenges to Implementing Precision Radiation Medicine



- Patients with the same tumour disease and stage have typically received similar treatments
- Large clinical trials possible

- Biomarkers allow stratification into small subgroups
- Trials for treatment individualization

Baumann, Nature Rev Cancer 2016