The Volume Effect in Radiotherapy

Dr. Jennifer Kwan MD PhD FRCPC

Assistant Professor, Department of Radiation Oncology, University of Toronto
Assistant Professor, Institute of Medical Science, University of Toronto
Radiation Oncologist-Clinician Scientist, Princess Margaret Cancer Centre

April 9, 2025

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

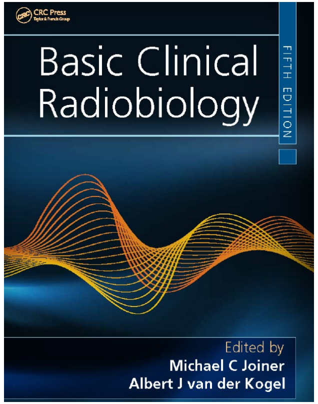
- **Dr. Albert van der Kogel**

Acknowledgement

16

Normal tissue tolerance and the effect of dose inhomogeneities

WOLFGANG DÖRR AND ALBERT J. VAN DER KOGEL



Learning Objectives

1. **Distinguish the difference between structural and functional tissue tolerance**
2. **Describe the concept of serial and parallel tissue organization**
3. **Understand the importance of cell migration from the edge of irradiated fields and their contribution to the tolerance of specific tissues**

Learning Objectives

1. **Distinguish the difference between structural and functional tissue tolerance**
2. Describe the concept of serial and parallel tissue organization
3. Understand the importance of cell migration from the edge of irradiated fields and their contribution to the tolerance of specific tissues

Organ Tolerance Dose

- **Tolerance dose = Dose at which radiation exposure of the volume induces a pathological change**
- **Considerations:**

  - Organ/tissue under consideration
  - Pathological change/symptom ('endpoint'), including the respective diagnostic procedures and the classification system applied
  - Induction probability ('risk') under consideration
  - Radiation type and quality
  - Exposure protocol
  - Follow-up period and procedures and – most importantly in the present context – also the
  - Exposed volume and dose distribution

Organ Tolerance

- **Structural tissue tolerance**
  - **Depends on cellular radiation sensitivity**
  - **Independent of volume irradiated**
  - **Local tissue damage = Significant Loss of Function**

- **Functional tolerance (“even” distribution of function)**
  - **Depends on tissue organization**
  - **Functional reserve capacity**
  - **Significant tissue damage without loss of function**

Learning Objectives

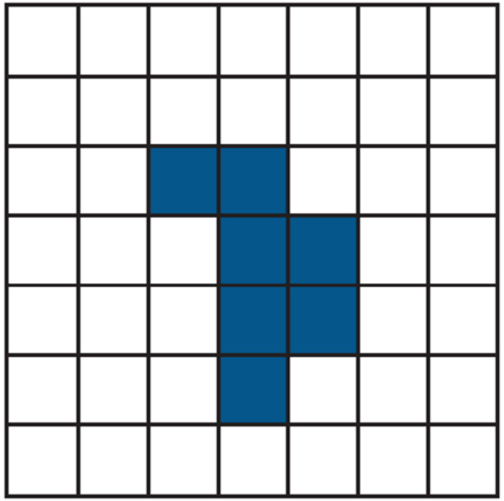
1. Distinguish the difference between structural and functional tissue tolerance
2. **Describe the concept of serial and parallel tissue organization**
3. Understand the importance of cell migration from the edge of irradiated fields and their contribution to the tolerance of specific tissues

Organ Tolerance and Tissue Architecture

- **FSU = largest tissue volume or unit of cells that can be regenerated from a single surviving clonogenic cell**
  - **Intrinsic radiosensitivity properties**
  - **Independent from other FSUs**
  - **Clinical consequences based on FSU arrangement**
    - **Serial vs. parallel**

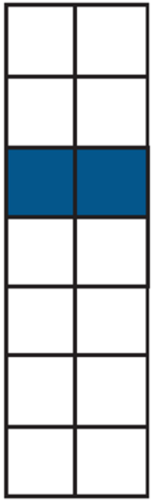
FSU Organization

Parallel
(lung, kidney, liver)



Requires "threshold damage"

Serial
(spinal cord, esophagus, intestine)

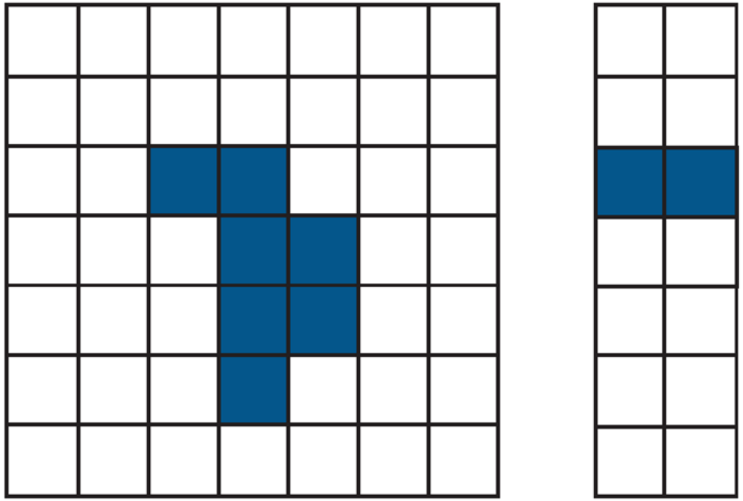


Failure of one FSU can lead to organ failure

FSU Organization

Parallel
(lung, kidney, liver)

Serial
(spinal cord, esophagus, intestine)



Requires "threshold damage"

Failure of one FSU can lead to organ failure

Most organs or tissues show both serial and parallel components

Learning Objectives

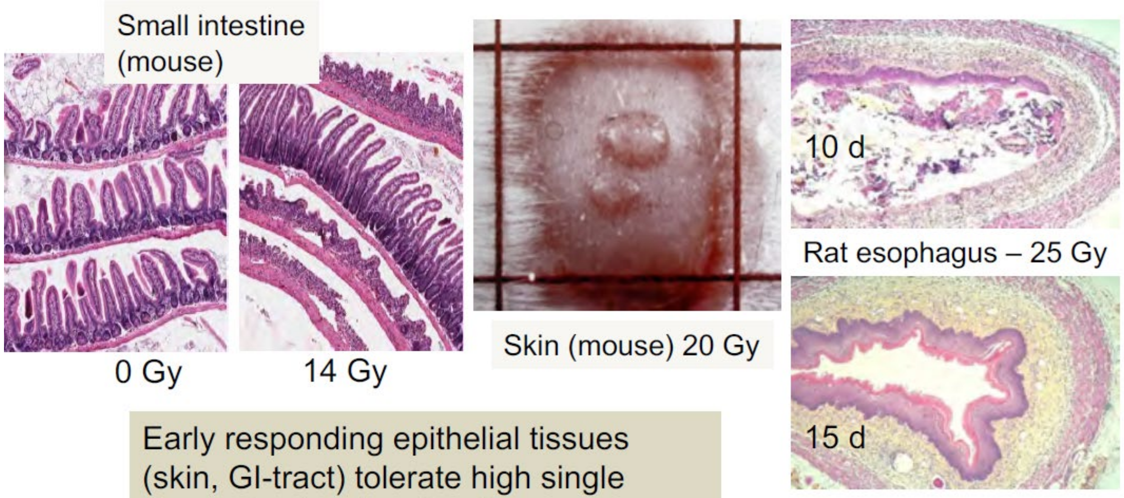
1. Distinguish the difference between structural and functional tissue tolerance
2. Describe the concept of serial and parallel tissue organization
3. **Understand the importance of cell migration from the edge of irradiated fields and their contribution to the tolerance of specific tissues**

Stem Cell Migration

- **After complete sterilisation of stem/precursor cells in an irradiated volume…**
  - **Repopulation by stem cells outside of treatment volume**
    - **Examples**
      - **Irradiated bone marrow recovery by circulating hematopoietic stem cells or un-irradiated active bone marrow**
      - **Epithelial tissues with high cellular migratory capacity (e.g. skin, oral mucosa, intestinal epithelium)**
  - **Confers tolerance to irradiation of small field sizes**

Stem Cell Migration

- **Early responding tissues: Tolerance depends largely on overall time and migration from unirradiated margins**

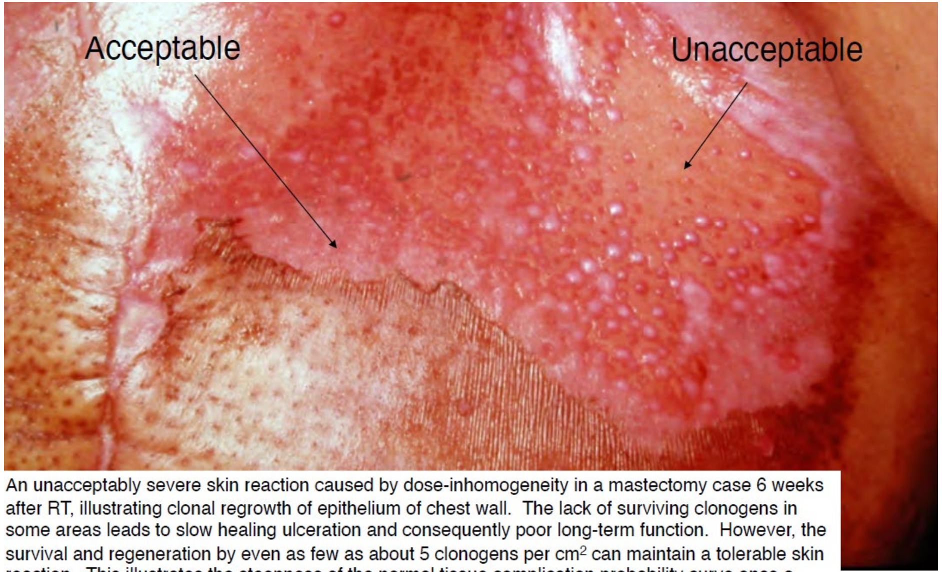


Early responding epithelial tissues (skin, GI-tract) tolerate high single doses due to migration from unirradiated partial volumes

Courtesy of Dr. Albert van der Kogel

Stem Cell Migration

- **Acute reactions in human skin: Competition between regeneration vs. tissue breakdown**

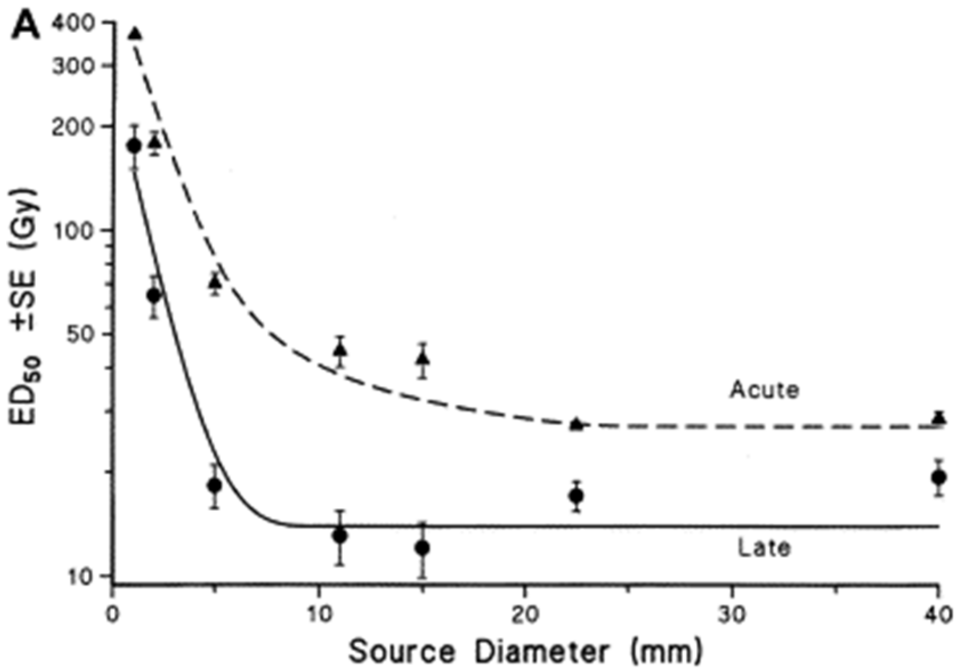


An unacceptably severe skin reaction caused by dose-inhomogeneity in a mastectomy case 6 weeks after RT, illustrating clonal regrowth of epithelium of chest wall. The lack of surviving clonogens in some areas leads to slow healing ulceration and consequently poor long-term function. However, the survival and regeneration by even as few as about 5 clonogens per cm^2 can maintain a tolerable skin reaction. This illustrates the steepness of the normal tissue complication probability curve once a certain tissue-specific threshold is exceeded.

Courtesy of Dr. Albert van der Kogel

Acute and Late Effects

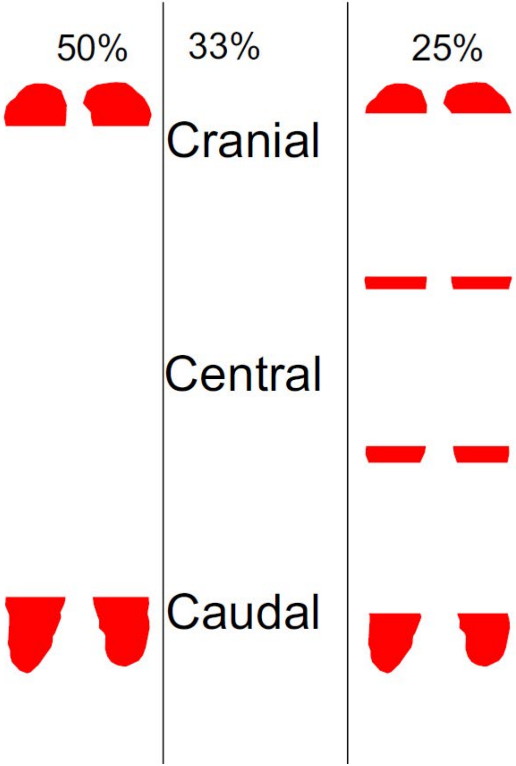
Higher doses required for small fields
due to migration of unirradiated cells into volume



Courtesy of Dr. Albert van der Kogel
Hopewell & Trott, Radiother & Oncol 2000 (Pig Skin)

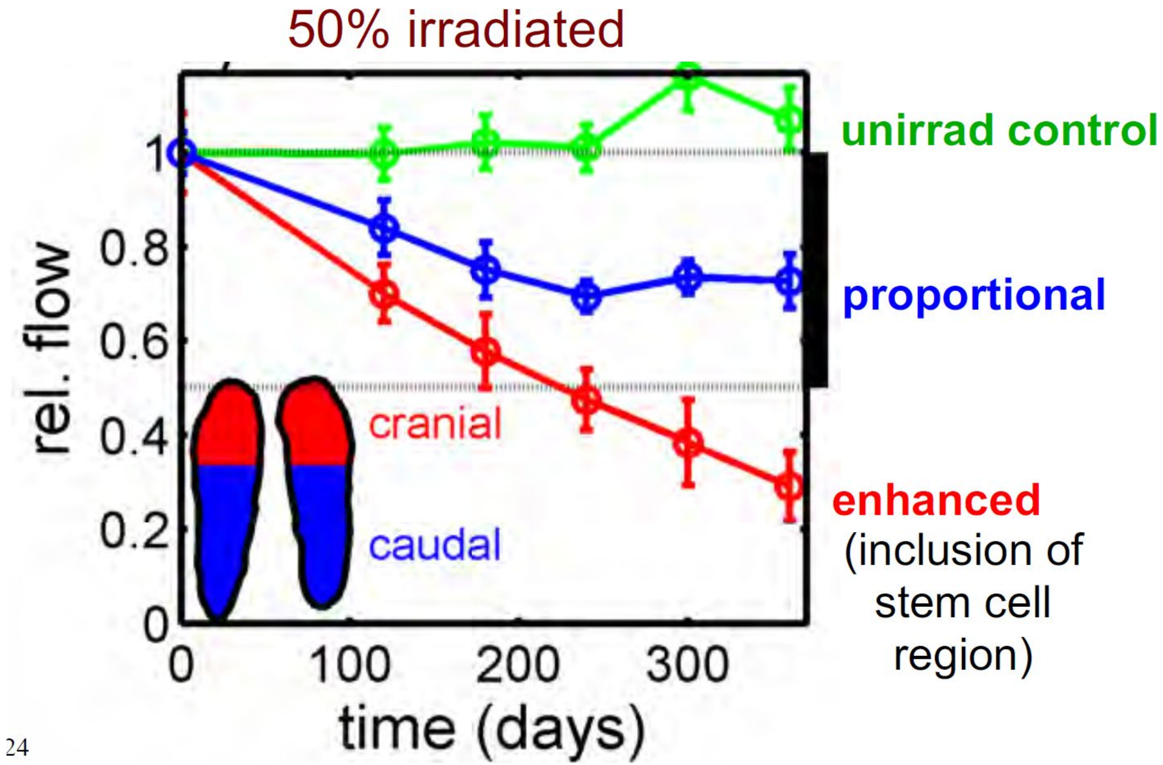
Irradiating Sub-Volumes

High-precision proton irradiation



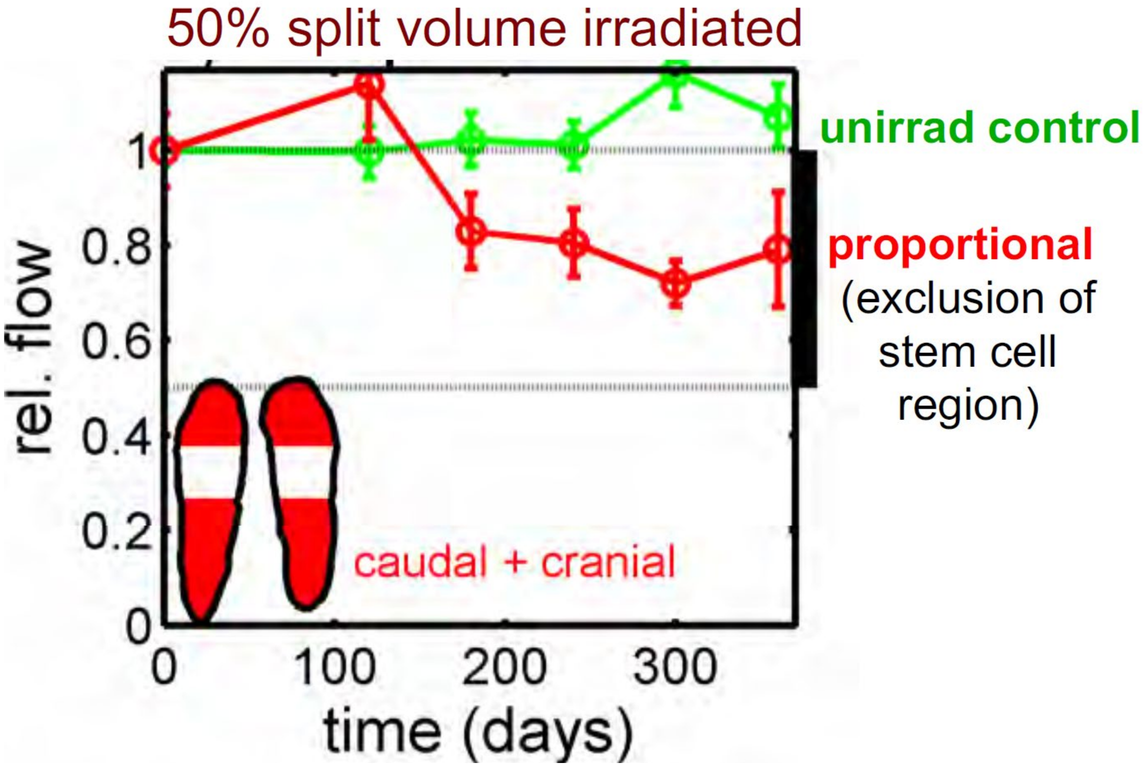
Courtesy of Dr. Albert van der Kogel
van Luijk, Coppes, et al. 2012 (Rat Parotid)

Irradiating Sub-Volumes



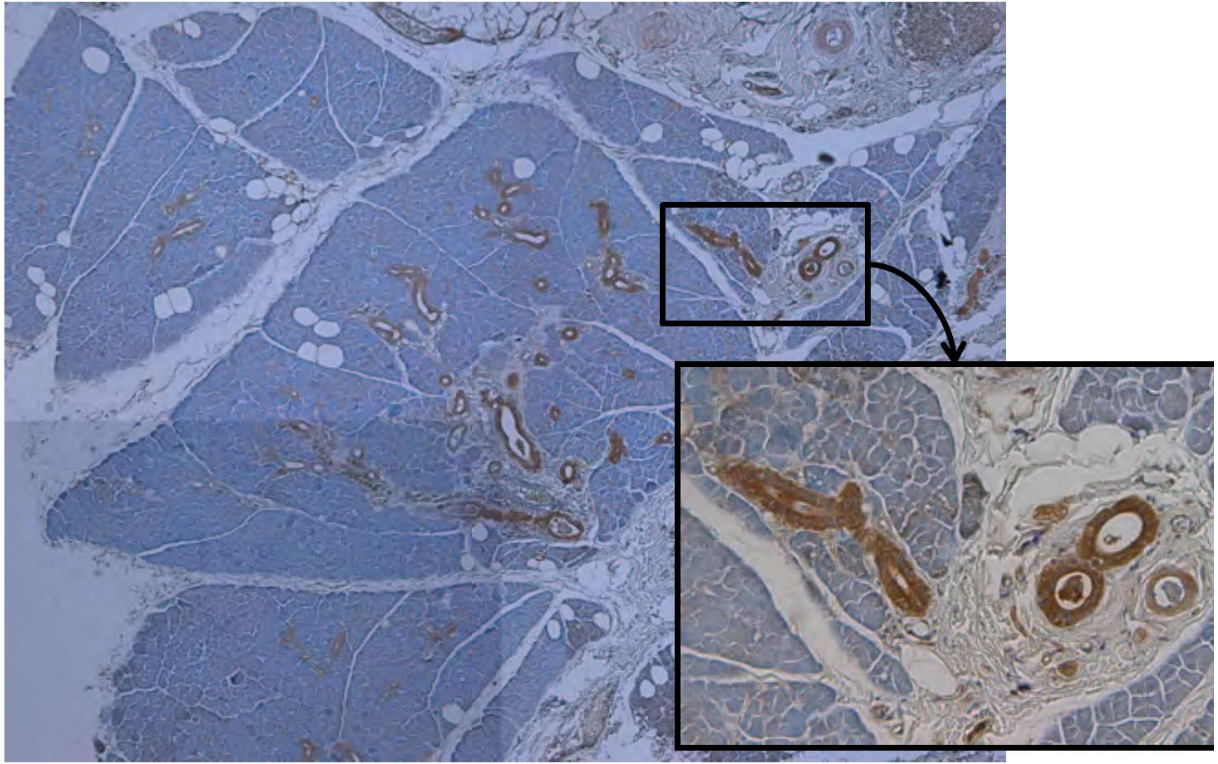
Courtesy of Dr. Albert van der Kogel
van Luijk, Coppes, et al. 2012 (Rat Parotid)

Irradiating Sub-Volumes



Courtesy of Dr. Albert van der Kogel
van Luijk, Coppes, et al. 2012 (Rat Parotid)

Irradiating Sub-Volumes

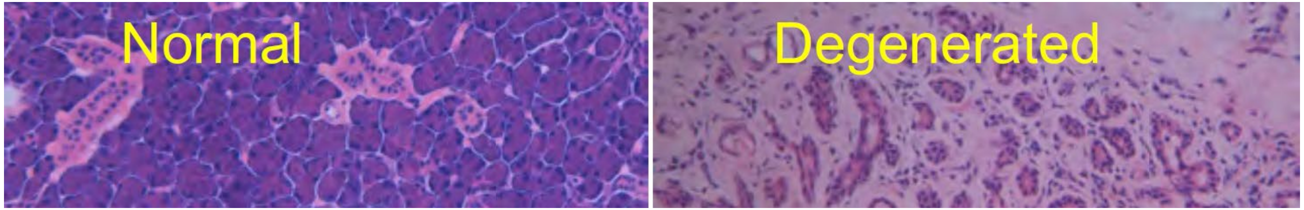


Stem cells located in ducts

Courtesy of Dr. Albert van der Kogel
van Luijk et al. Sci Transl Med 2015 (Rat Parotid)

Irradiating Sub-Volumes

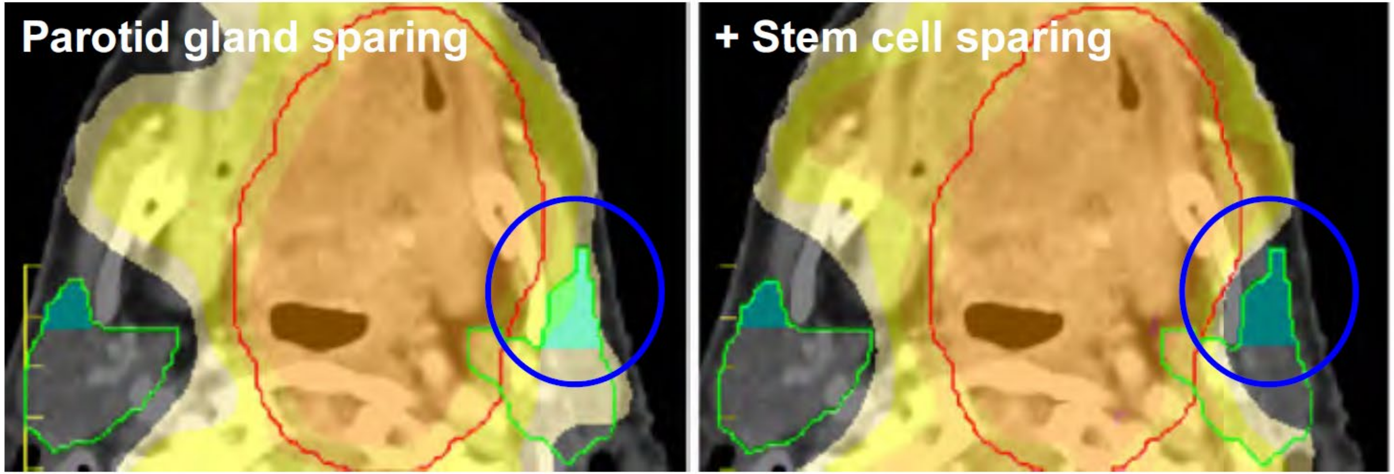
- **Two types of response:**
  - **Bulk tissue: local damage limited to irradiated volume**
  - **Critical region: global atrophy, related to dose to critical region (high concentration of stem cells)**



Courtesy of Dr. Albert van der Kogel
van Luijk, Coppes, et al. 2012 (Rat Parotid)

Parotid Stem Cell Sparing

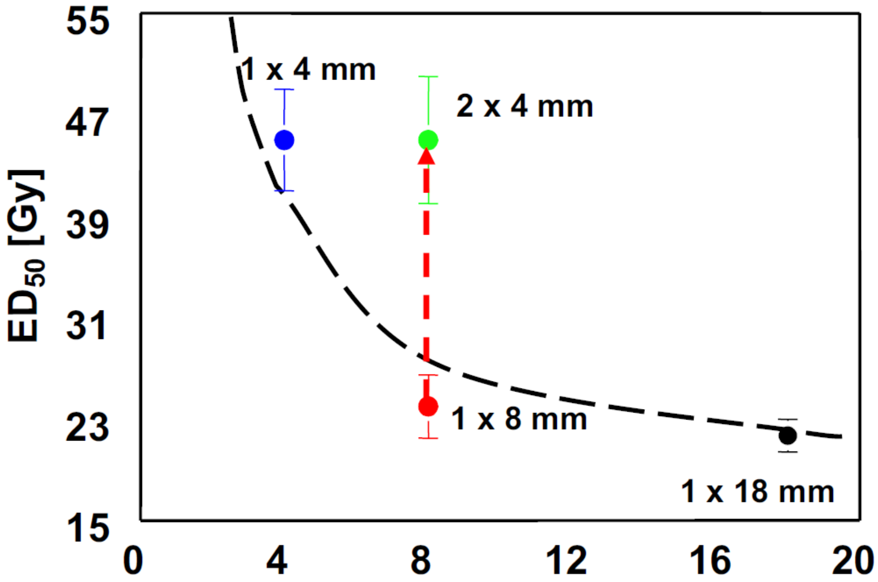
- **Reduce dose to ventral extension**
- **Maintain treatment goals**

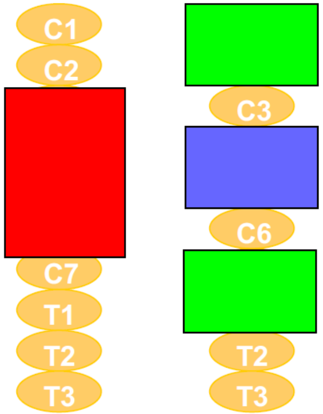


Courtesy of Dr. Albert van der Kogel
van Luijk, Coppes, et al. 2012 (Rat Parotid)

Volume Effects in Spinal Cord Tolerance

Rat spinal cord tolerance rises steeply for lengths < 1 cm



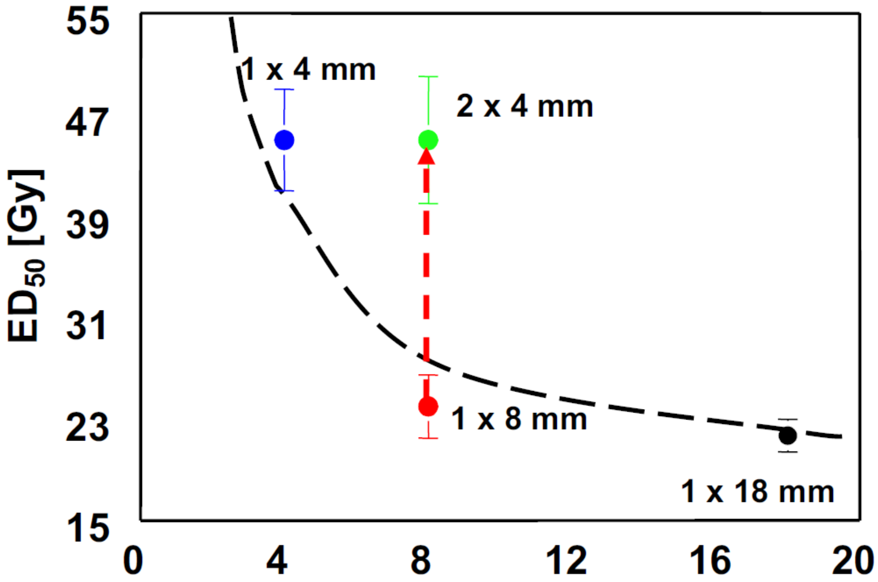


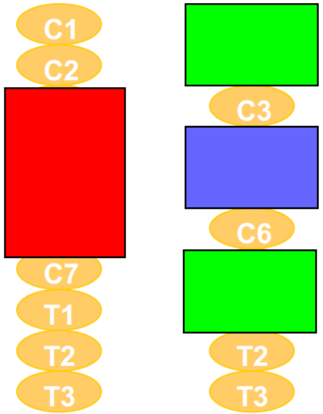
2 X 4 ≠ 8

Courtesy of Dr. Albert van der Kogel

Volume Effects in Spinal Cord Tolerance

Rat spinal cord tolerance rises with stem cell migration



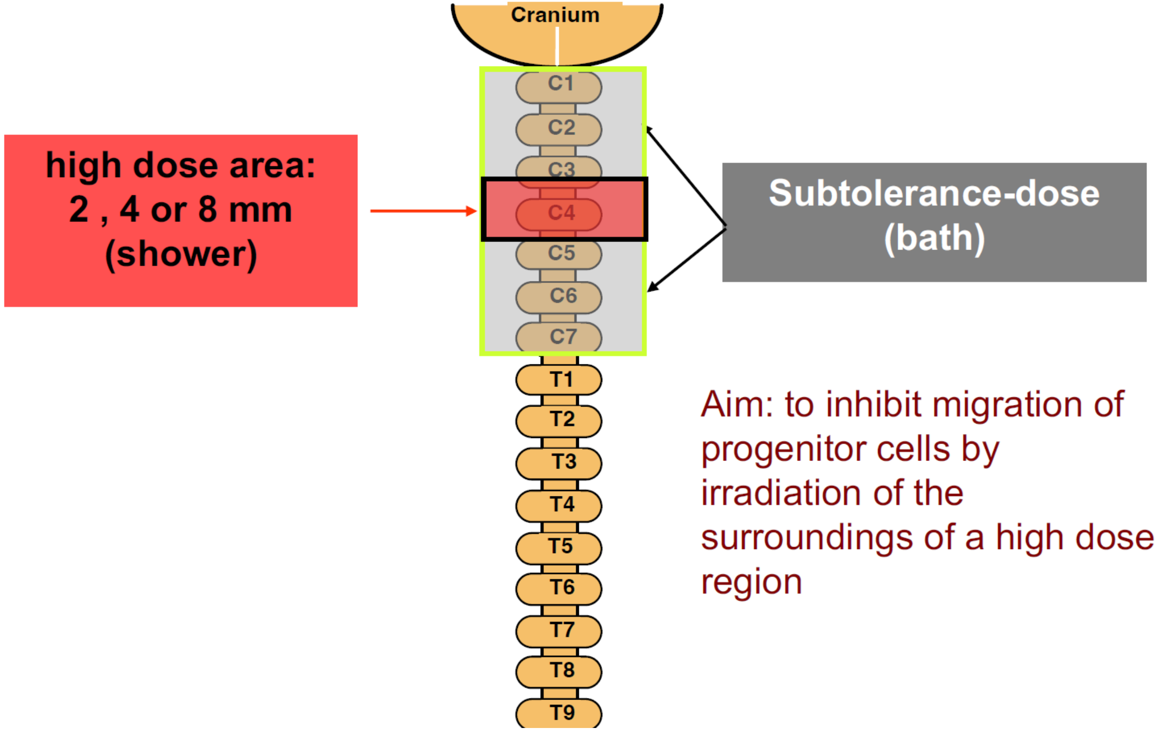


2 X 4 ≠ 8

Courtesy of Dr. Albert van der Kogel

Spinal Cord Stem Cell Regions

Tolerance reduced with bath irradiation to surrounding stem cell regions

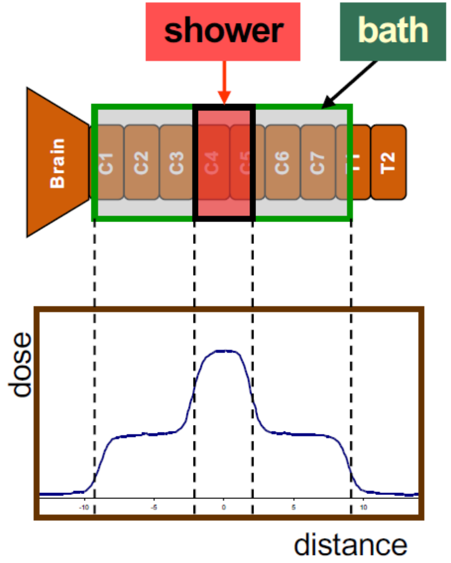


Aim: to inhibit migration of progenitor cells by irradiation of the surroundings of a high dose region

Courtesy of Dr. Albert van der Kogel

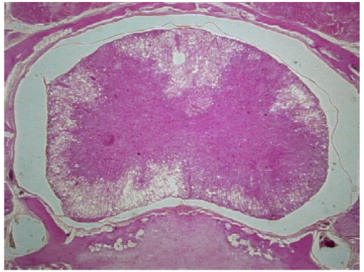
Spinal Cord Stem Cell Regions

Tolerance reduced with bath irradiation to surrounding stem cell regions



ED50 = dose (shower [4mm] + bath) causing paralysis in 50% of rats

Bath dose (Gy)	ED_{50} (Gy)
0	54
4	40
12	35
18	33

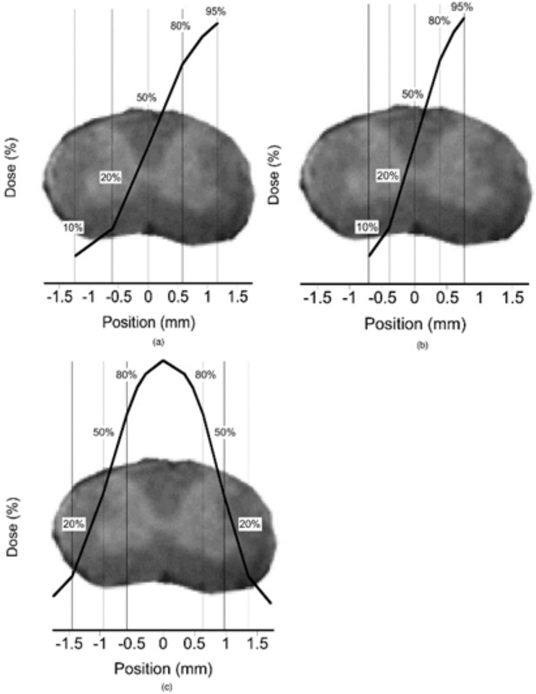


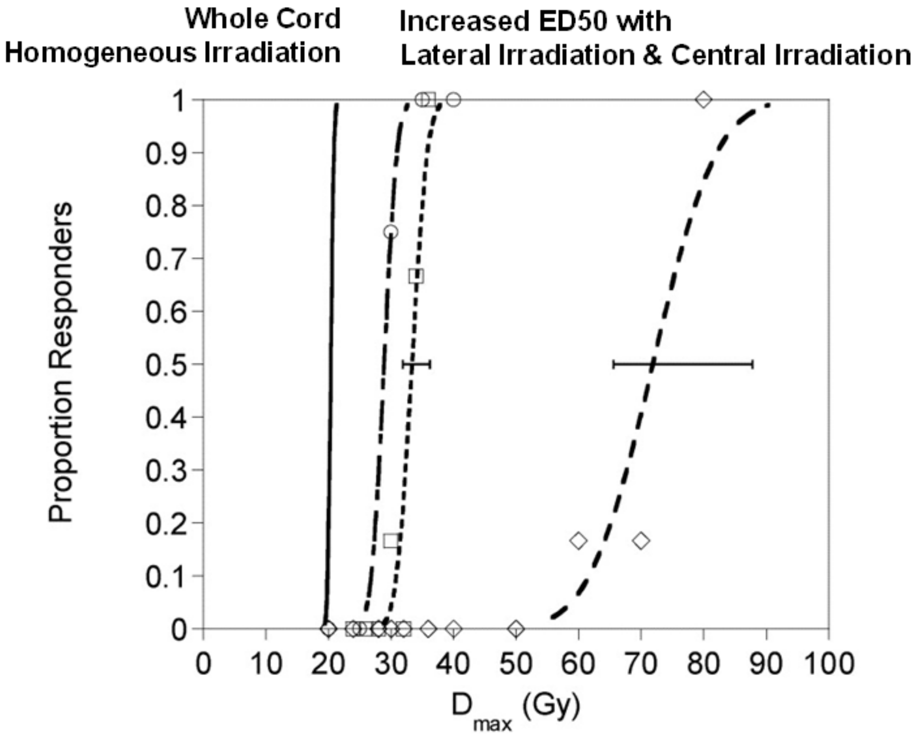
A low dose bath in adjacent regions significantly lowers the tolerance of the target volume

Courtesy of Dr. Albert van der Kogel

Spinal Cord Dose Inhomogeneity Effects

Radiosensitivity of lateral white matter > central white matter

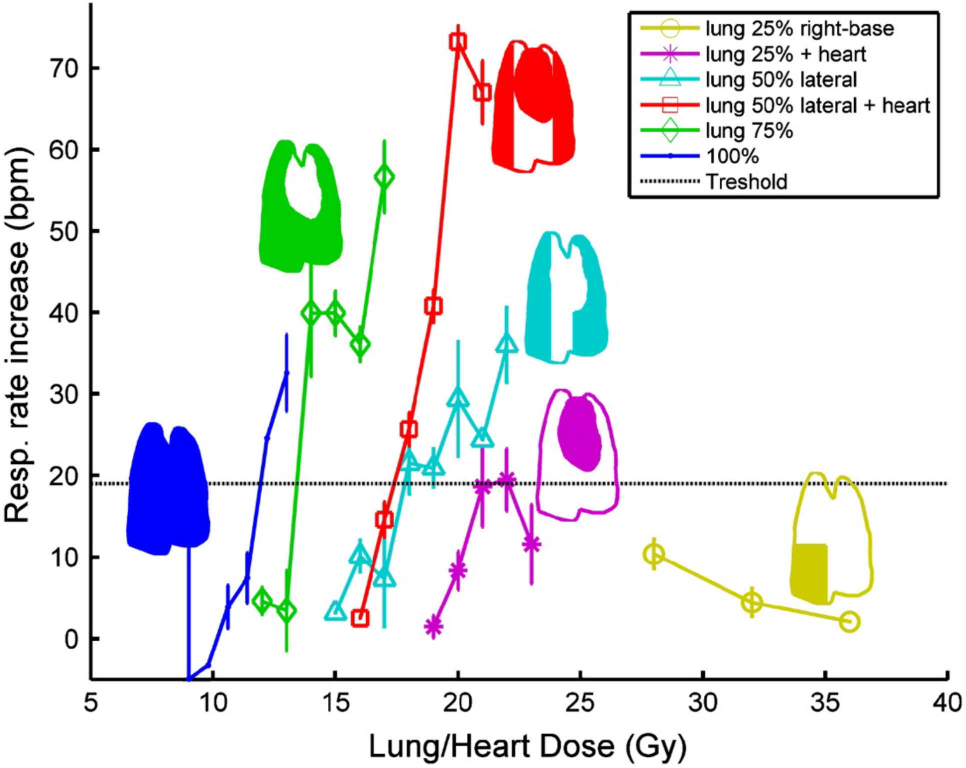




Courtesy of Dr. Albert van der Kogel
Bijl et al. IJROBP 2005 (Rat Spinal Cord)

Volume Effects in Lung Tolerance

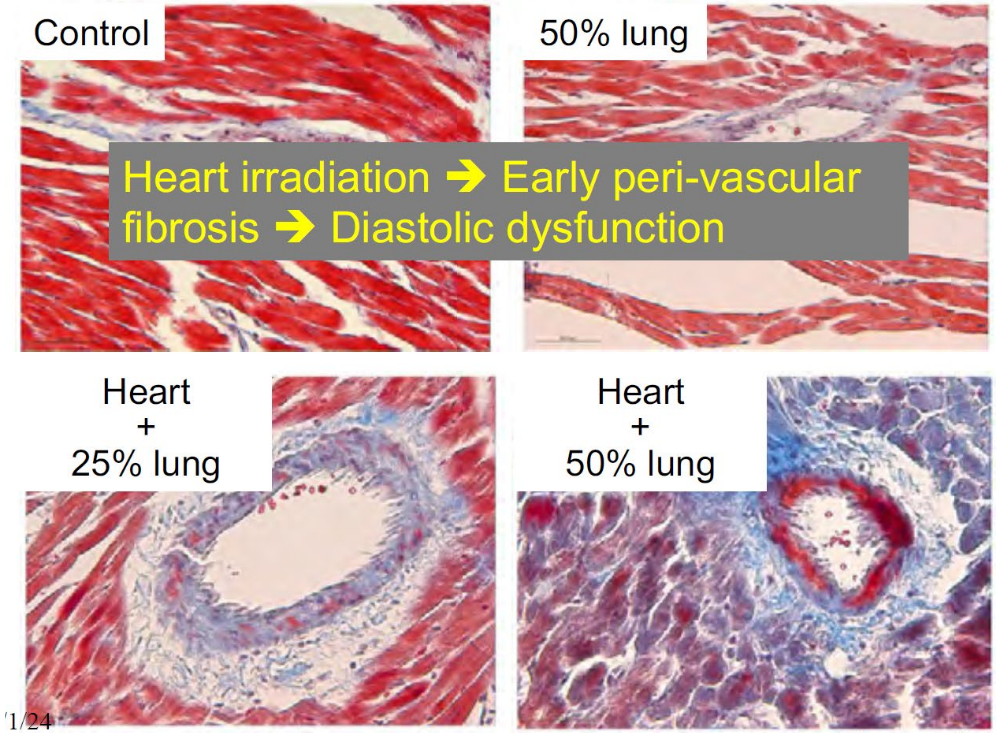
Effect of Location/ Relationship to Heart



Courtesy of Dr. Albert van der Kogel
P. Van Luijk et al IJROBP 2007 (Rat Lung)

Volume Effects in Lung Tolerance

Effect of Location/ Relationship to Heart



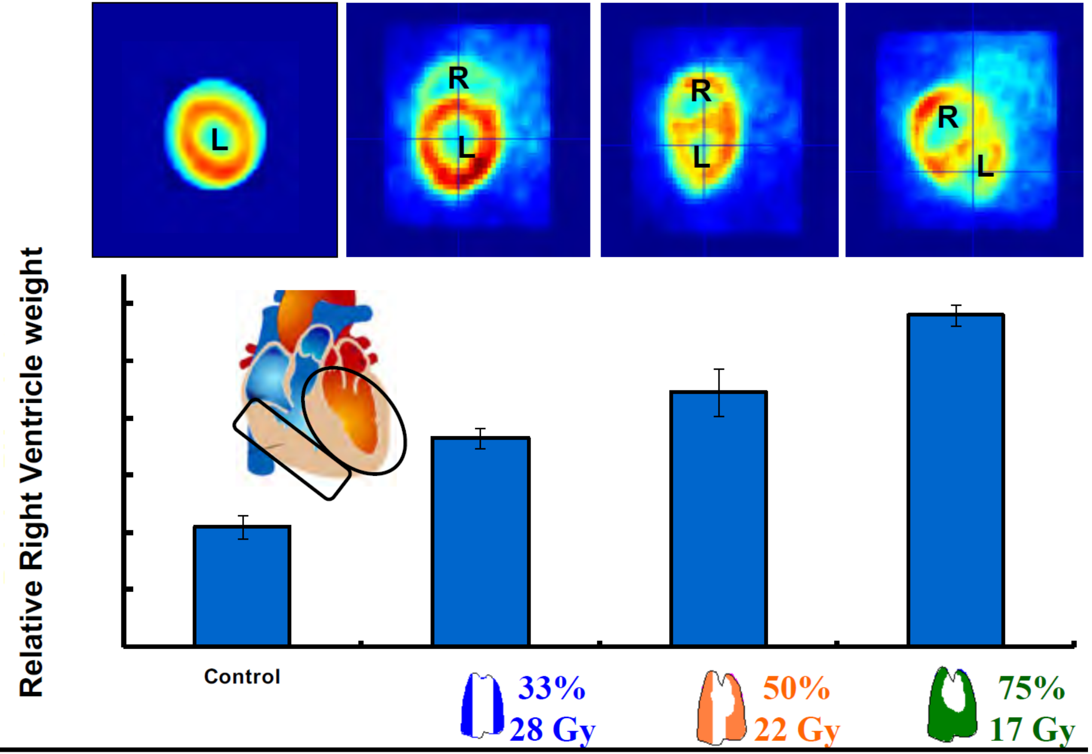
20 Gy
8 wks

Ghobadi et al. 2012

Courtesy of Dr. Albert van der Kogel

Volume Effects in Lung Tolerance

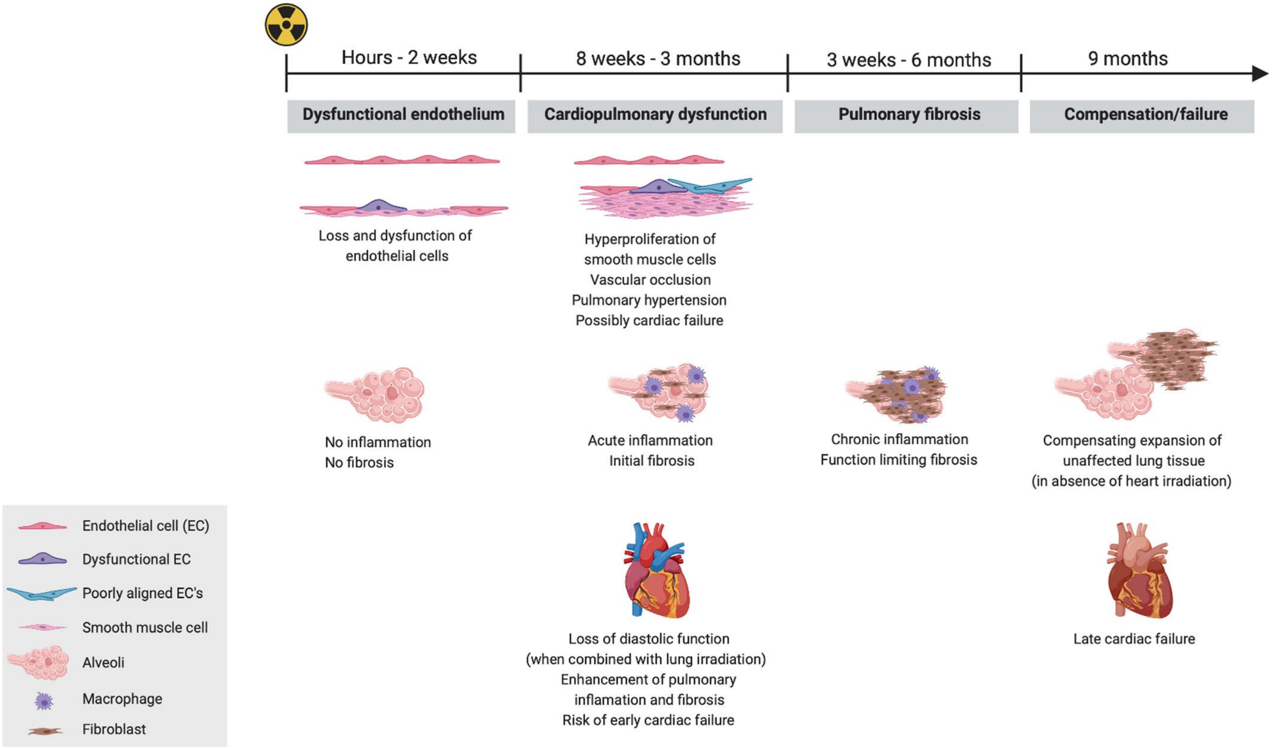
Effect of Location/ Relationship to Heart



Courtesy of Dr. Albert van der Kogel

Volume Effects in Lung Tolerance

Cardiopulmonary irradiation: Time-Course of Cellular & Tissue Events

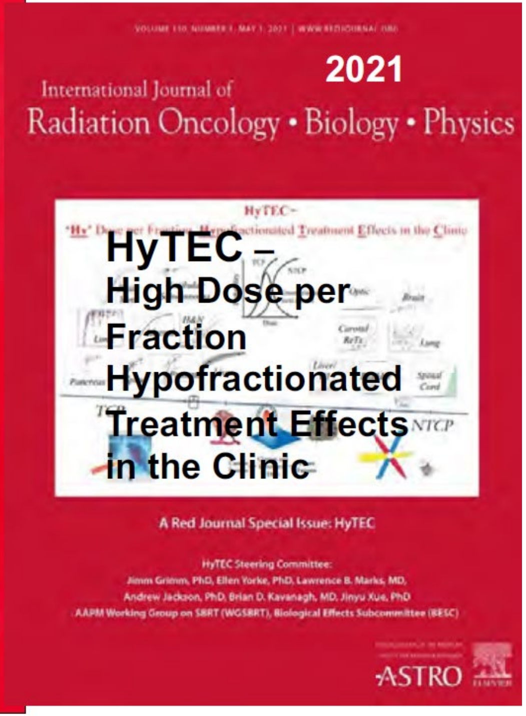


Courtesy of Dr. Albert van der Kogel
Barazzuol et al. Molecular Oncol 2024

NTCP Models

- **NTCP = Normal Tissue Complication Probability**
- **Theoretical mathematical models to estimate NTCP for:**
  - **Partial-volume irradiation**
  - **Inhomogeneous dose distributions**
- **Models have limitations/uncertainties and need to be validated against clinical data emerging from new treatment methods**

Normal Tissue Constraints



4/1/24

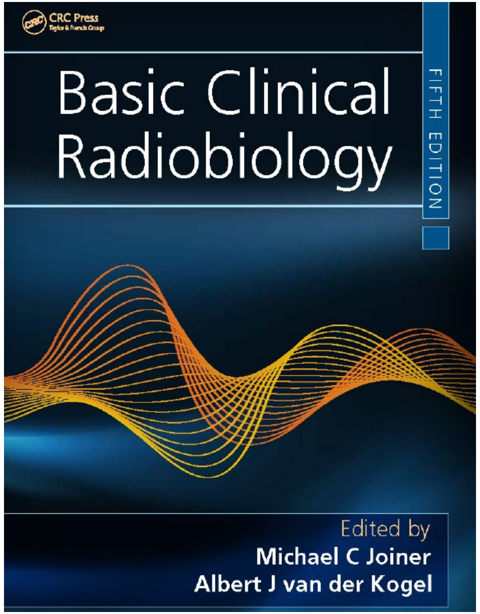
Summary

Key points

1. *Structural* tissue tolerance depends on cellular radiation sensitivity and is independent of volume irradiated. *Functional* tolerance depends on tissue organisation and functional reserve capacity.
2. Different individual endpoints related to one OAR may be based on exposure of specific target sub-volumes and follow different time course and radiobiological characteristics.
3. Tissues with a predominantly parallel organisation (e.g. lung) have a threshold volume below which functional damage does not occur. The risk of developing a complication depends on dose distribution throughout the whole organ rather than the maximum dose to a small area.
4. Tissues with a serial organisation (e.g. spinal cord) have little or no functional reserve and the risk of developing a complication is less dependent on volume irradiated than for tissues with a parallel organisation. The risk of complication is strongly influenced by high-dose regions and hot spots.
5. Migration of surviving clonogenic cells into the (margins of) irradiated volumes can lead to a steep increase in tissue tolerance for field diameters up to 20 mm in some tissues (e.g. spinal cord, intestine and skin).
6. Theoretical models have been developed to estimate NTCP for partial-volume irradiations and inhomogeneous dose distributions. Simple power-law and probability models have been expanded to incorporate parameters relating to tissue architecture and reserve capacity. These mainly phenomenological models always need to be validated against clinical data emerging from new conformal treatment schedules and new methods of delivery.

Resources

Based on Chapter 16



Questions?

Thank you!

Dr. Jennifer Kwan MD PhD FRCPC

jennifer.kwan@uhn.ca