



Proton therapy to reduce toxicity

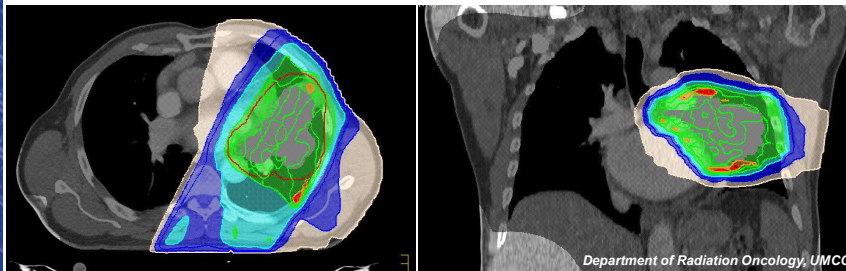
Insights from radiobiology

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Radiotherapy

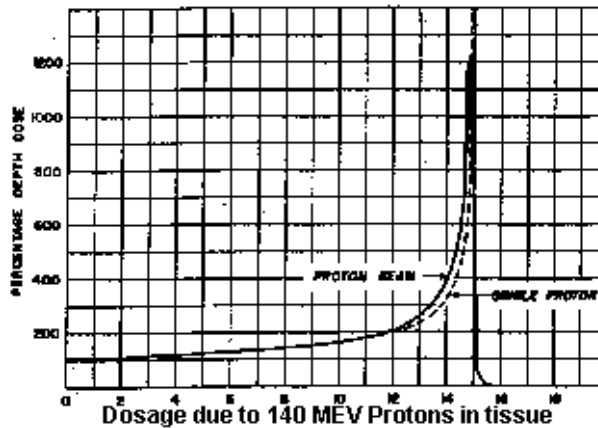


Radiotherapy: Cure ⇔ Toxicity

Radiological Use of Fast Protons

ROBERT R. WILSON

Research Laboratory of Physics, Harvard University
Cambridge, Massachusetts



Wilson RR, Radiology 1946

How to use optimally?

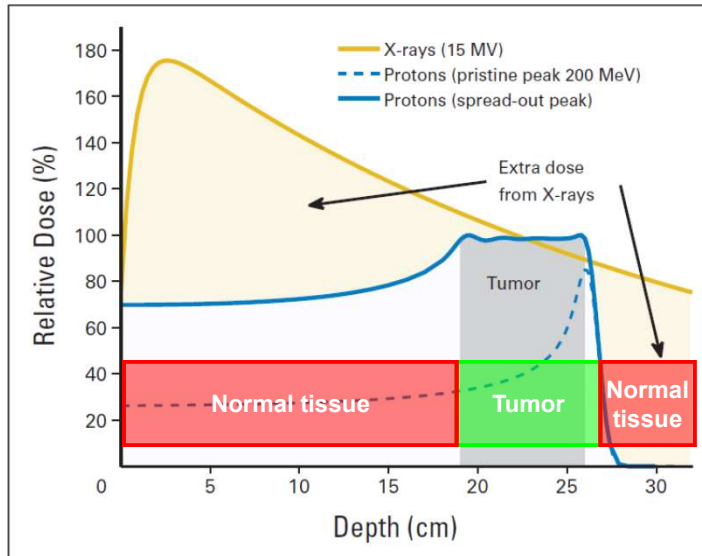


Quantec reviews of dose-volume effects in normal tissue damage

No info on protons!

Marks, ten Haken, Martel, Int J Radiat Onc Biol Phys (2010)

Protons vs. photons



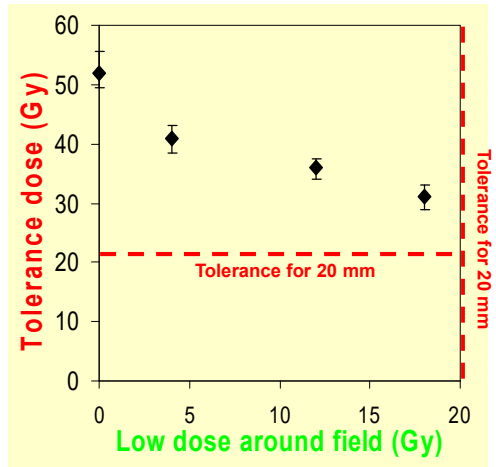
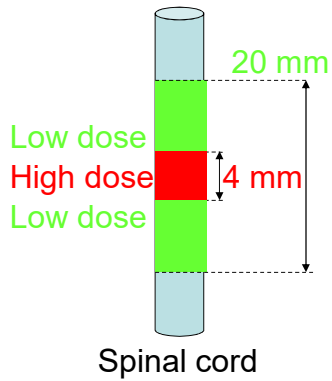
Mitin T, Zietman AL, JCO 2014

Protons vs. photons



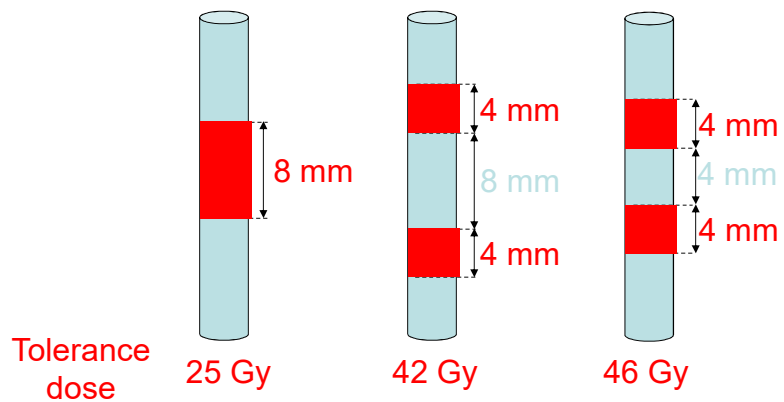
- IMRT
 - Reduce dose in high-dose regions
 - Often more beam directions: “A little to a lot”
- Protons
 - Reduce dose in high-dose regions
 - Choice: Concentrate or spread plateau dose
 - More effective sparing of smaller structures
- Information on the response to proton-specific features is not available in photon-based data
- Alternative source: normal tissue radiobiology

Spinal cord



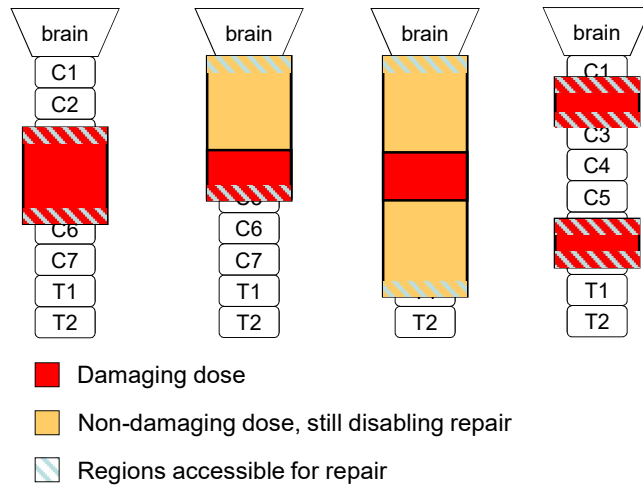
Bijl et al. Int J Radiat Oncol Biol Phys. 2003

Spinal cord



Bijl et al. Int J Radiat Oncol Biol Phys. 2003

Spinal cord



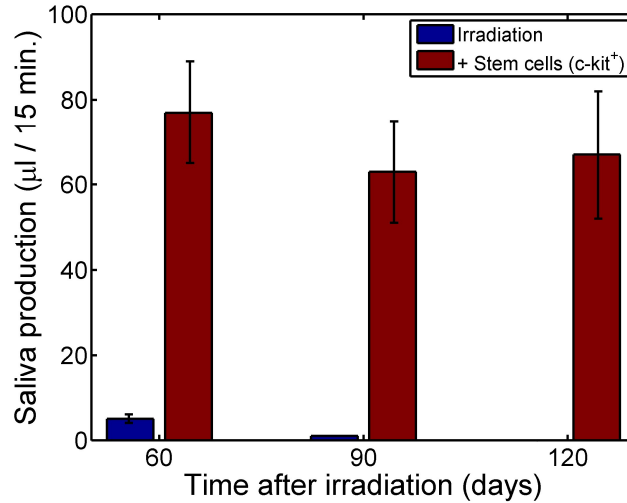
van Luijk et al. Int J Radiat Oncol Biol Phys. 2005

Conclusions



- Spinal cord
 - Low dose impairs non-local repair, critical to tolerance.

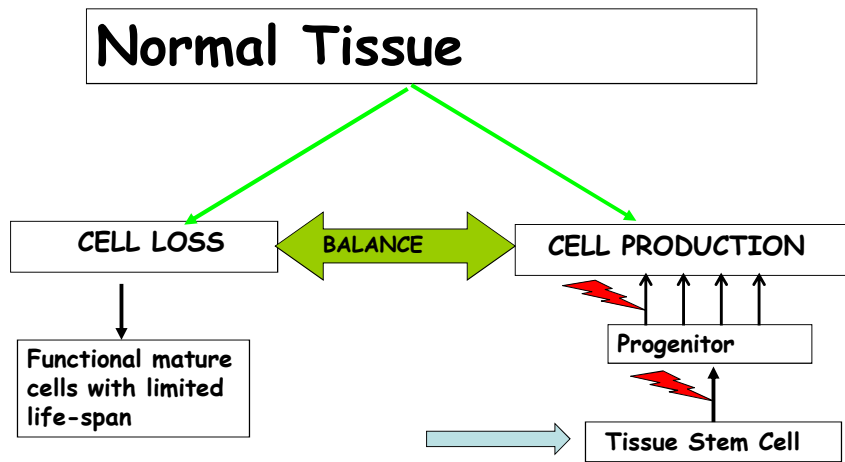
Target for dysfunction: stem cell



Stem cell transplantation rescues the gland function

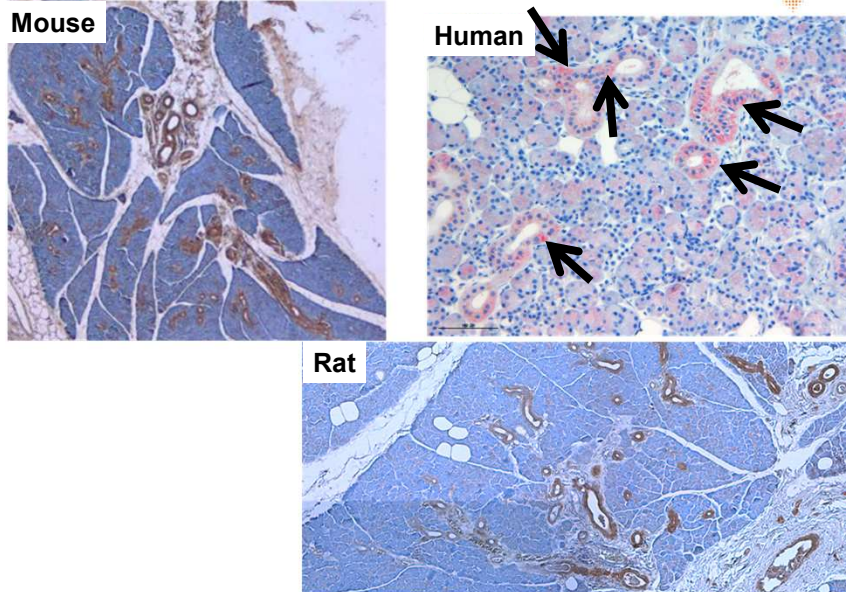
Lombaert IM et al. PLoS One. 2008 Apr 30;3(4):e2063.

Tissue Stem Cells

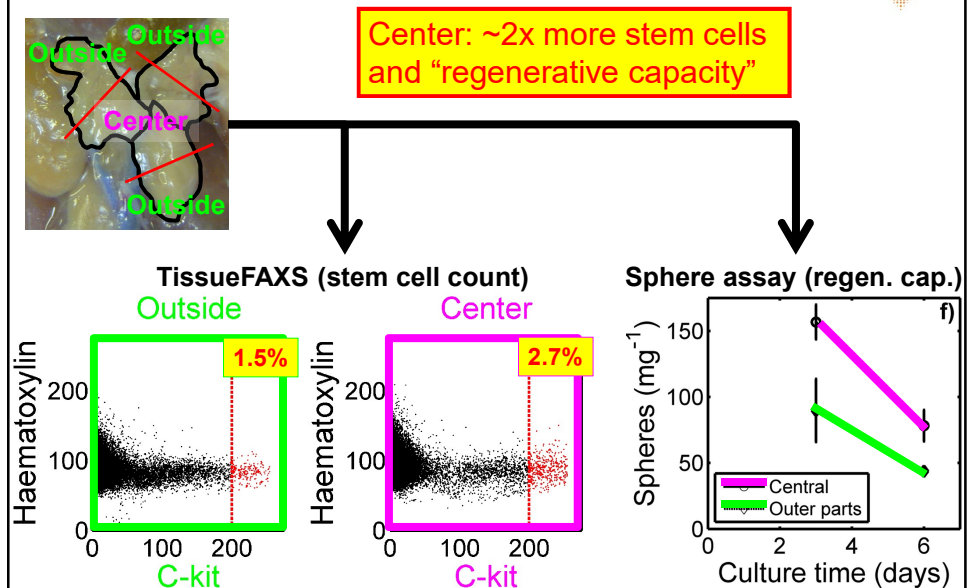


Coppes et al. Sem. Rad. Oncol. 2009

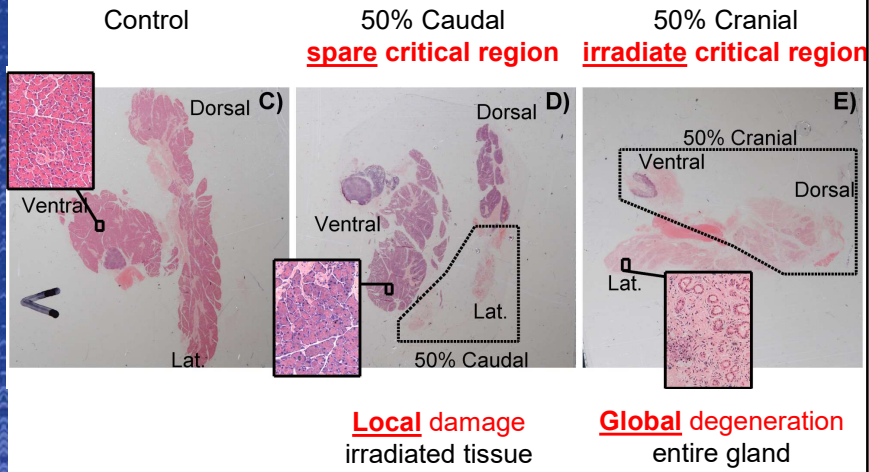
C-kit⁺ cells: in larger ducts



Spatial distribution: rat

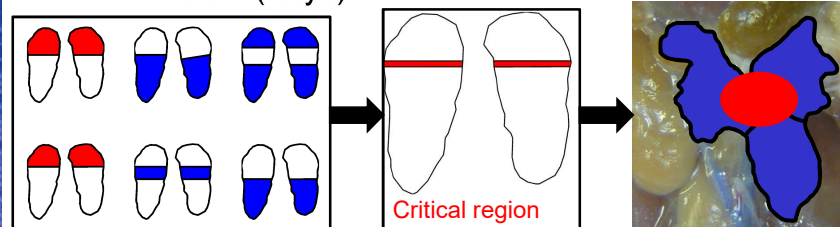
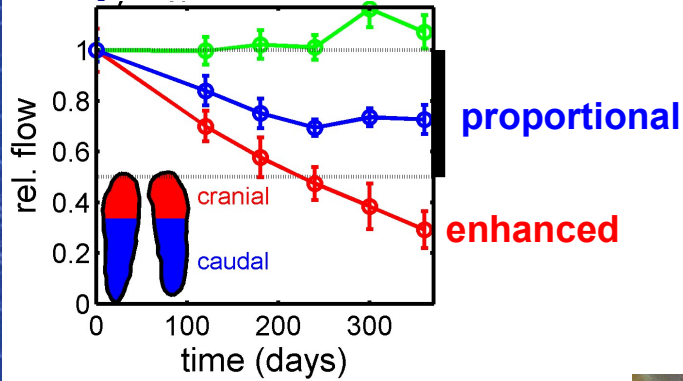


Rat morphology

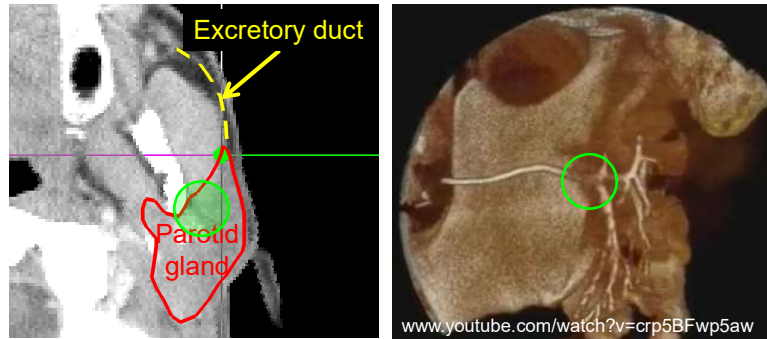


van Luijk et al. Sci. Trans. Med 2015

Impact on function



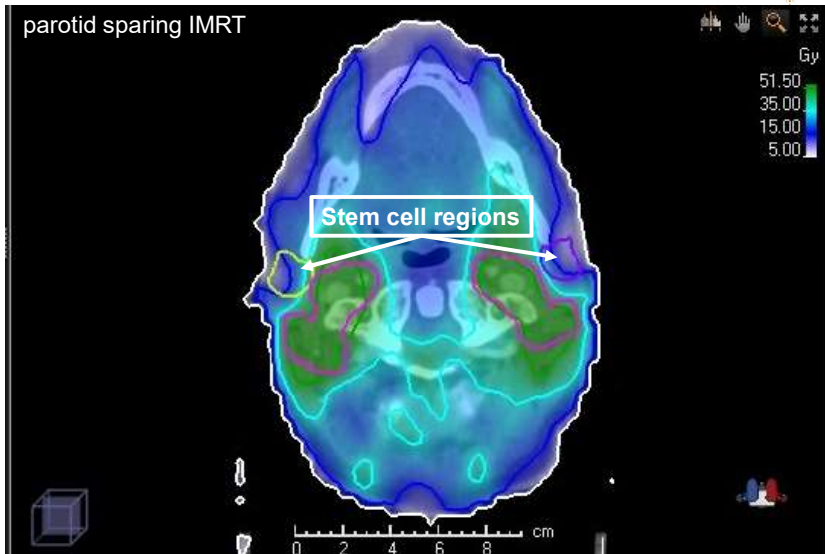
Parotid gland



Dose to major ducts best predictor of post-treatment function in patients
(cohort: British Columbia Cancer Agency - Vancouver)

van Luijk et al. Sci. Trans. Med 2015

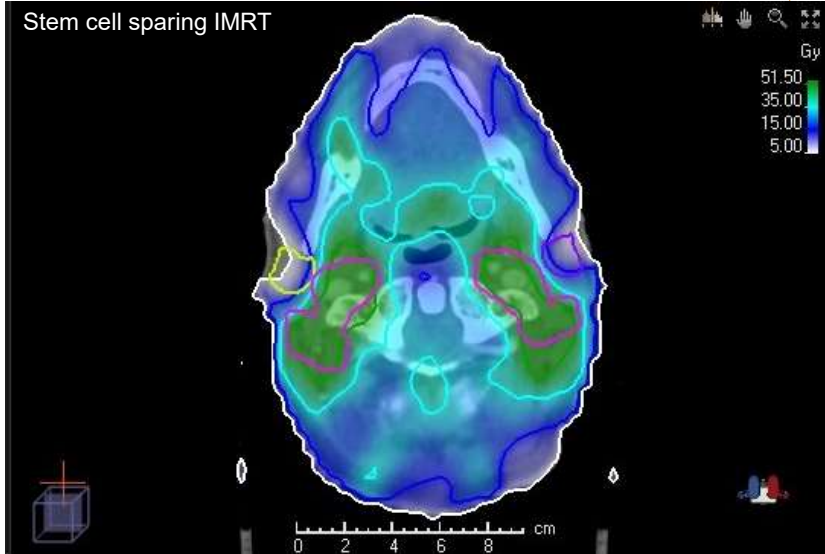
Protons vs. Photons



Protons vs. Photons



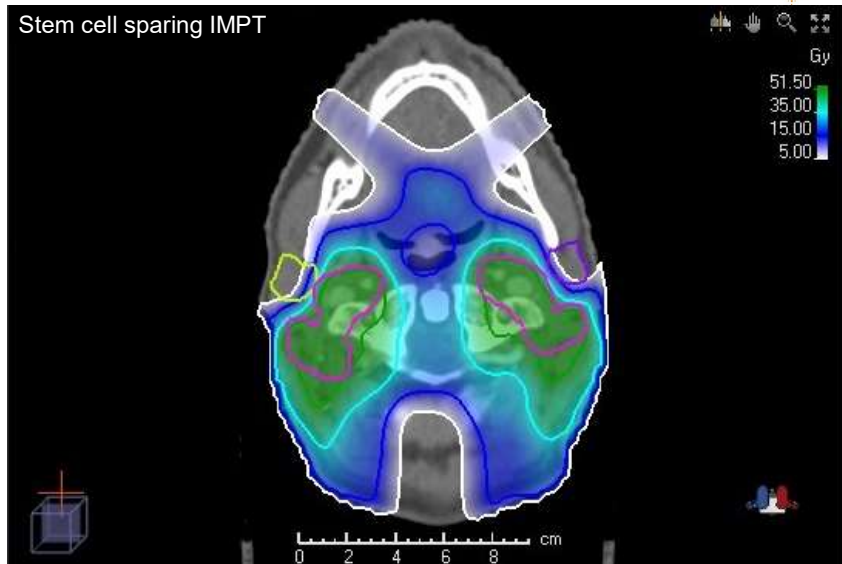
Stem cell sparing IMRT



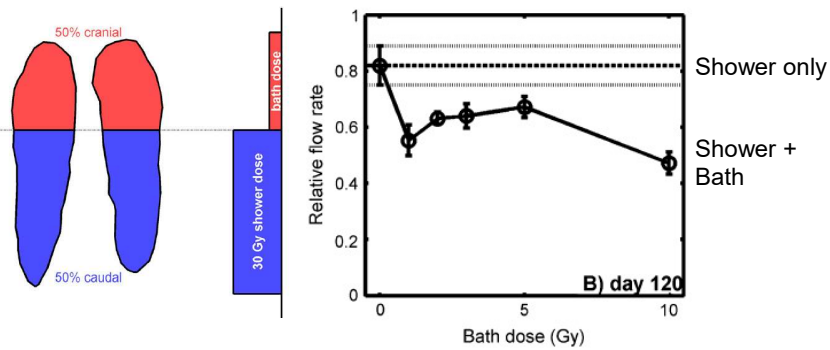
Protons vs. Photons



Stem cell sparing IMPT



Does low dose matter?



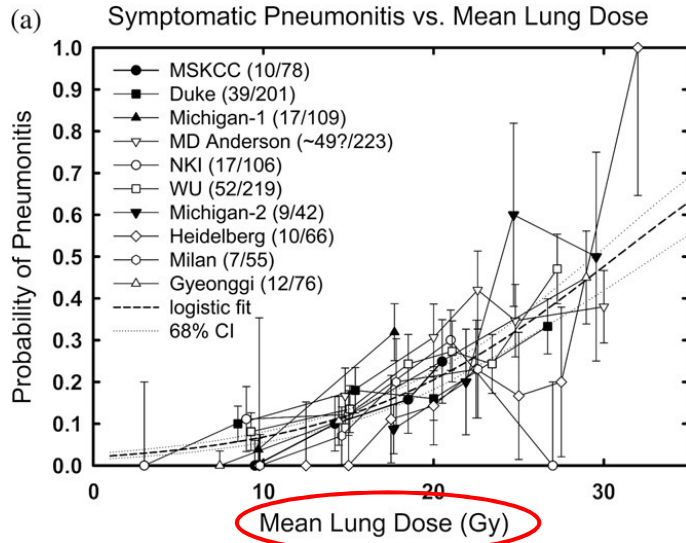
Van Luijk et al. IJROB 2009

Conclusions



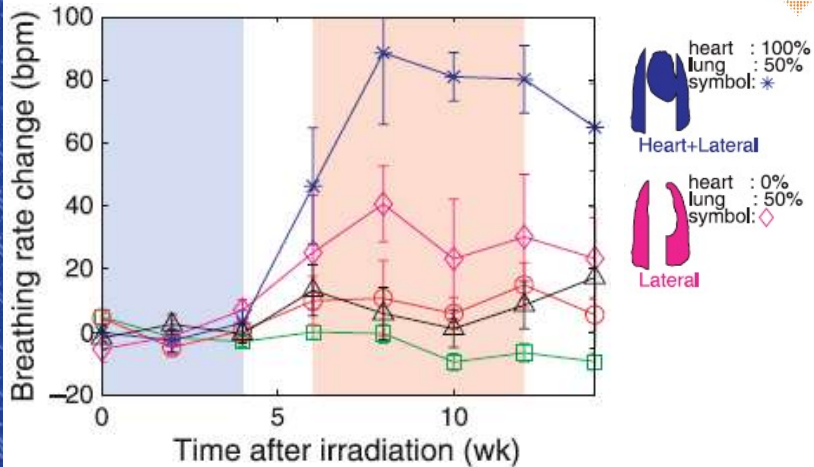
- Spinal cord
 - Low dose impairs non-local repair, critical to tolerance.
- Salivary gland
 - Response depends critically on dose a sub-volume containing its major ducts with the highest concentration of stem cells.
 - Low doses impair stem cell population.

Radiation pneumonitis



L.B. Marks et al. Int J Radiat Oncol Biol Phys. 2010 (Quantec report)

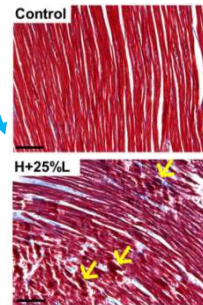
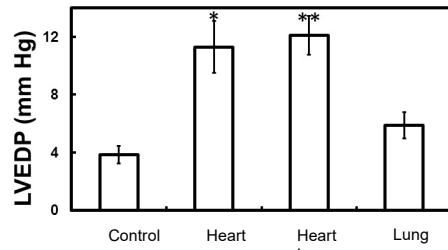
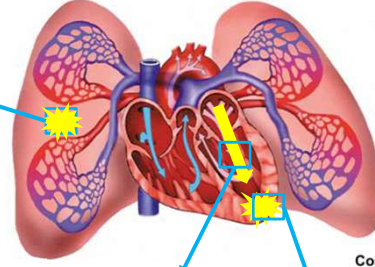
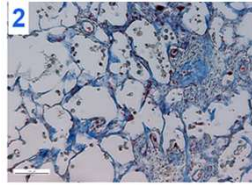
Heart and lung interaction



Dose to heart increases symptoms of radiation pneumonitis after lung irradiation

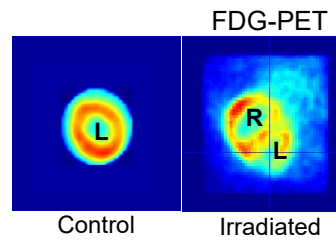
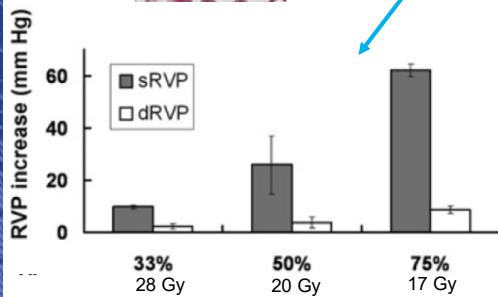
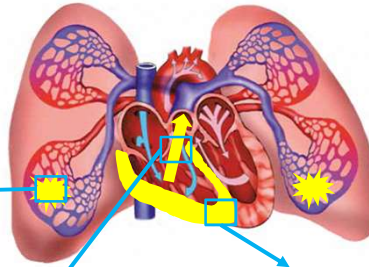
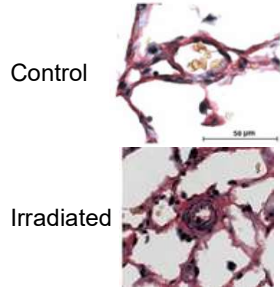
van Luijk et al. Cancer Res. 2005;65:6509-11

Toxicity: heart → lung (rat)



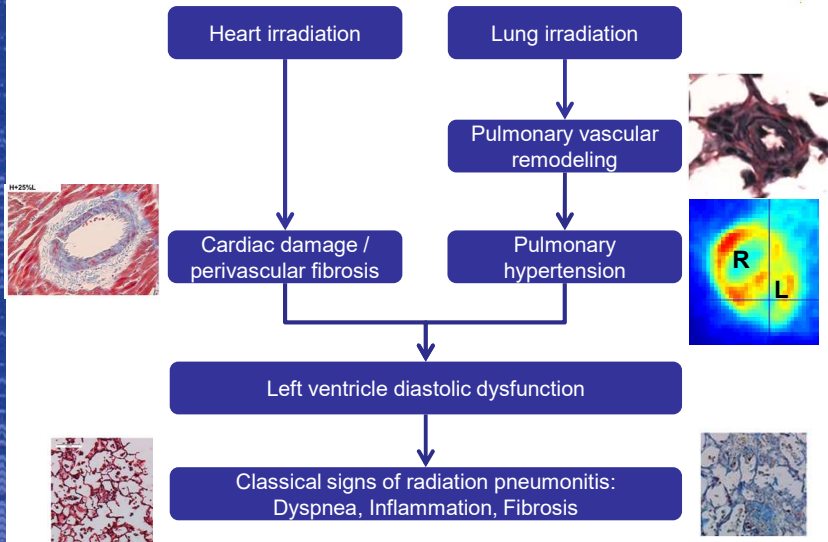
Ghobadi et al. Int J Radiat Oncol Biol Phys. 2012

Toxicity: lung → heart (rat)



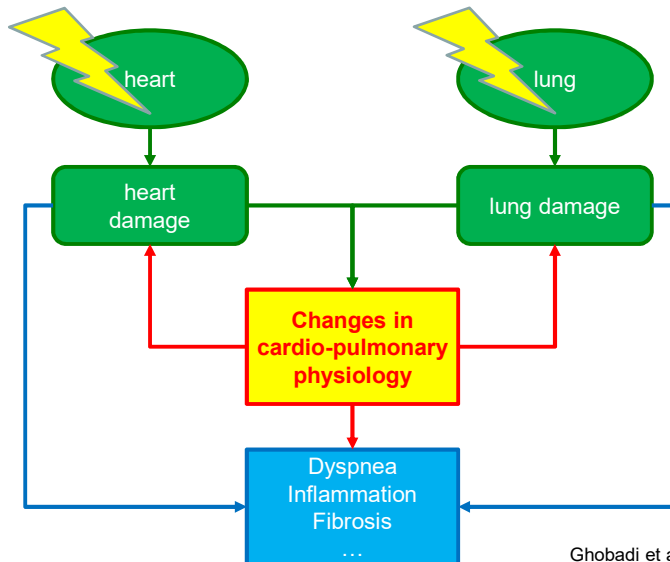
Ghobadi et al. Thorax 2012

Heart and lung interaction



Ghobadi et al. Int J Radiat Oncol Biol Phys. 2012

Toxicity: heart ↔ lung



Ghobadi et al. Thorax 2012

Ghobadi et al. Int J Radiat Oncol Biol Phys. 2012

Conclusions



- Spinal cord
 - Low dose impairs non-local repair, critical to tolerance
- Salivary gland
 - Critical target: its major ducts with the highest concentration of stem cells
 - Low doses impair stem cell population
- Lung
 - Lung? Cardiopulmonary physiology!
 - Vascular damage specifically sensitive to “a little to a lot”

Take-home



- Using unique features of protons requires
 - Information that is fundamentally not available from IMRT-based datasets
 - In vivo normal tissue radiobiology!
- Lessons already learned
 - Reducing low doses is important
 - Sparing a limited sub-volume of the parotid gland may be more feasible and effective
 - Reducing cardiopulmonary toxicity requires sparing both heart and lung



Netherlands Organisation for Scientific Research

Cancer Research Center Groningen



Netherlands Institute for Research and Innovation



**Kernfysisch Versneller Instituut -CART,
Groningen, Netherlands**
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Marc-Jan van Goethem
and many others

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Joachim Widder

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Jan de Jong

Pediatric Cardiology

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