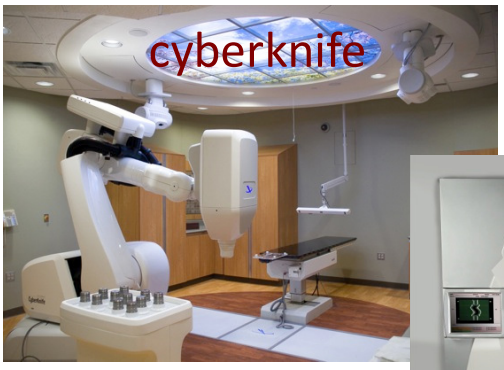
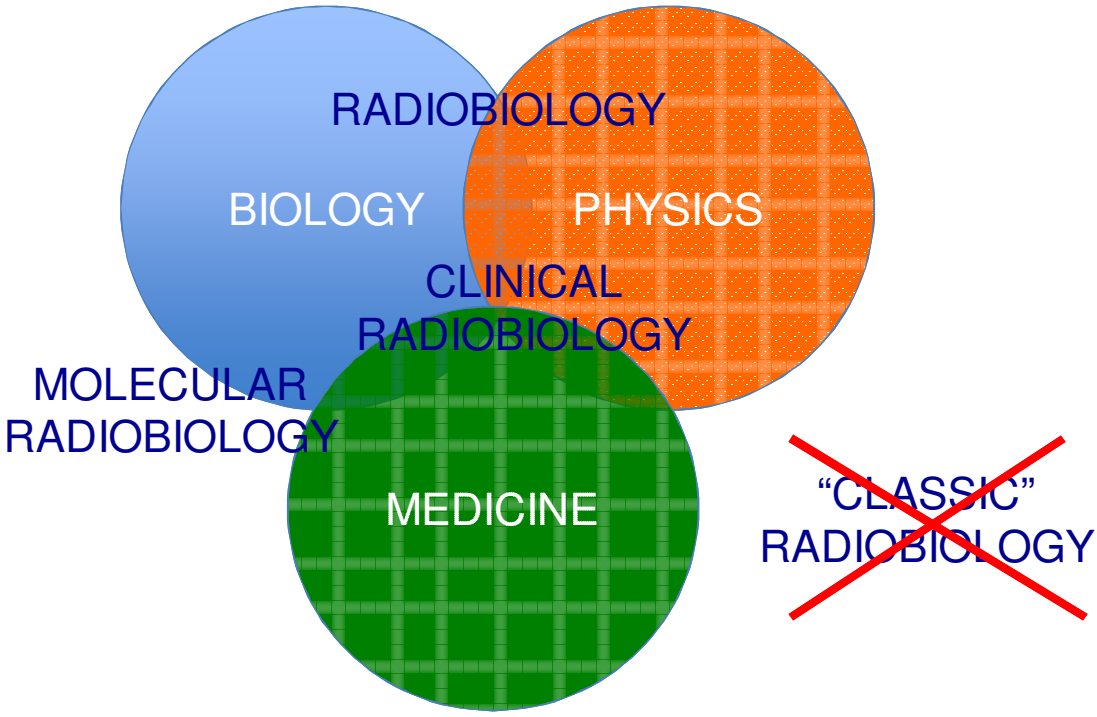
Progress in radiation oncology: is there a role for radiobiology?



What's in a name?



Two main eras in radiation oncology: differences in dose delivery

DELIVERY IN TIME (1980's – 1990's): fractionation and overall time. From NSD to Linear-Quadratic formulas.

- Emphasis on fractionation – notably hyperfractionation as a result of the radiobiological studies showing a low α/β value for late responding critical organs, a high α/β for most tumors and early mucosal effects ➞ increased therapeutic ratio when lowering the dose per fraction.

DELIVERY IN SPACE (≳2000): High precision radiotherapy Towards hypofractionation and SBRT

- Rapid developments in imaging technologies combined with high tech radiotherapy – IMRT + cone beam CT, Tomotherapy, Rapid Arc, VMAT, Cyberknife, MR-Linac, revival of Hadron therapy (protons, C^+ ions), etc.
- Hypofractionation: based on increasing knowledge of low α/β for tumors such as prostate and breast

The era of high precision radiotherapy: potential contributions by (clinical) radiobiology

Hypofractionation

- Validity of LQ model – does it hold >8-10 Gy/fx

SBRT (very high doses)

- EQD_2 / BED – irrelevant. Hypoxia?
- Increased importance of vascular effects?
- Volume effects (EUD ?, DVH?, stem cell regions?)
- Enhanced immune response?

IGRT – MR/Linac - ViewRay

- Metabolic & functional imaging (CT, PET, MR)

Protons & light-ions

- Has a proton RBE>1.1 measured *in vitro* clinical relevance?
- RBE of C+-ions in relevant tissues and tumors

The era of high precision radiotherapy: potential contributions by (clinical) radiobiology

Combined modalities

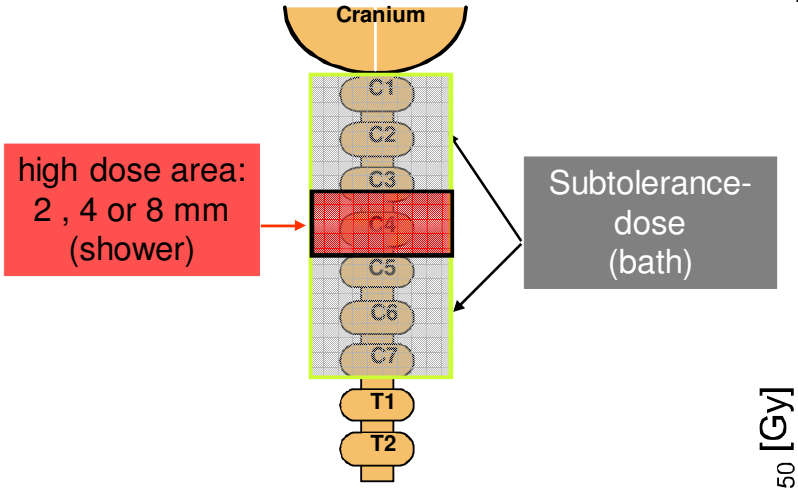
- Classic chemo: still the main stay of a few agents
- molecular inhibitors – many agents are tested, but so far little clinical impact
- metabolic inhibitors - many options with available agents

Dose-volume effects: critical observations

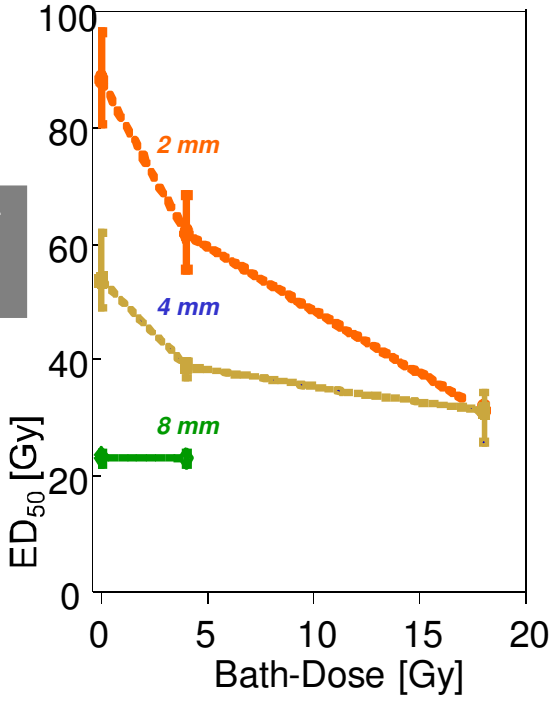
- Parallel & serial organs: the concept was important for modeling, but does not represent real organs
- Heterogeneous dose distributions are increasingly delivered:
  - Most late responding normal tissues show complex dose-volume relationships
  - Relatively low doses may have a big impact on the tolerance of a high dose volume (IMRT)
  - Steep dose gradients may impact normal tissue tolerance (SBRT)
  - Dose-volume-histograms (DVH): a clinical/physics convenience but the existence of heterogeneous tissue sensitivities and potentially critical regions are ignored (e.g.,stem-cell niches)

Impact of low dose to large volume on tolerance of high dose target:

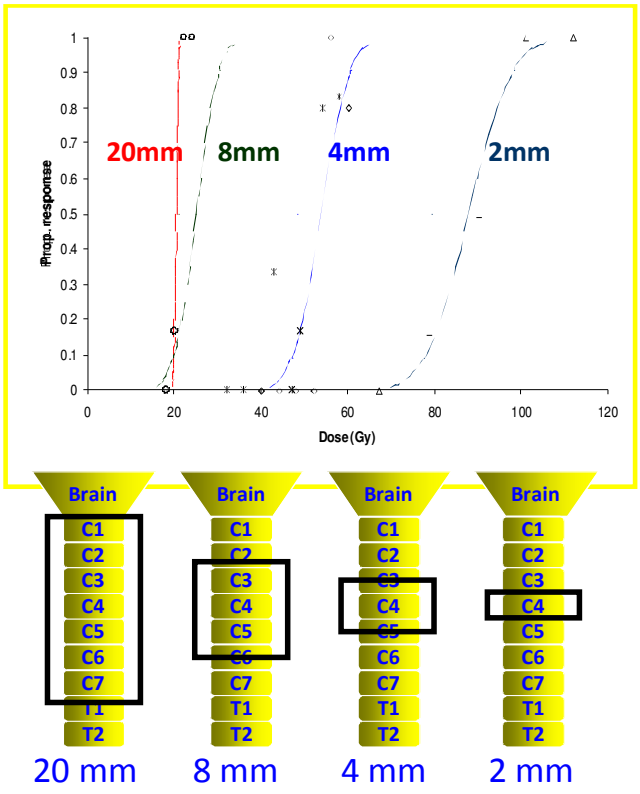
High precision protons on rat spinal cord: bath & shower



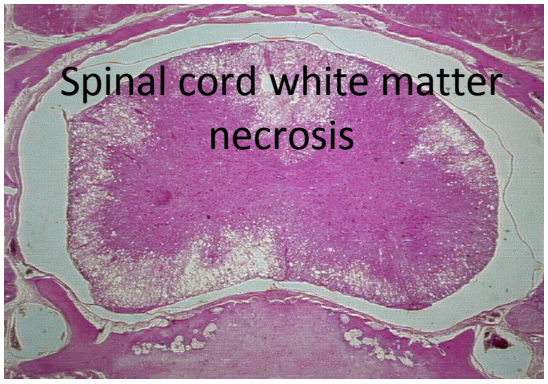
A “bath” dose as low as 4 Gy strongly reduces the tolerance of the high dose region: inhibition of migration?



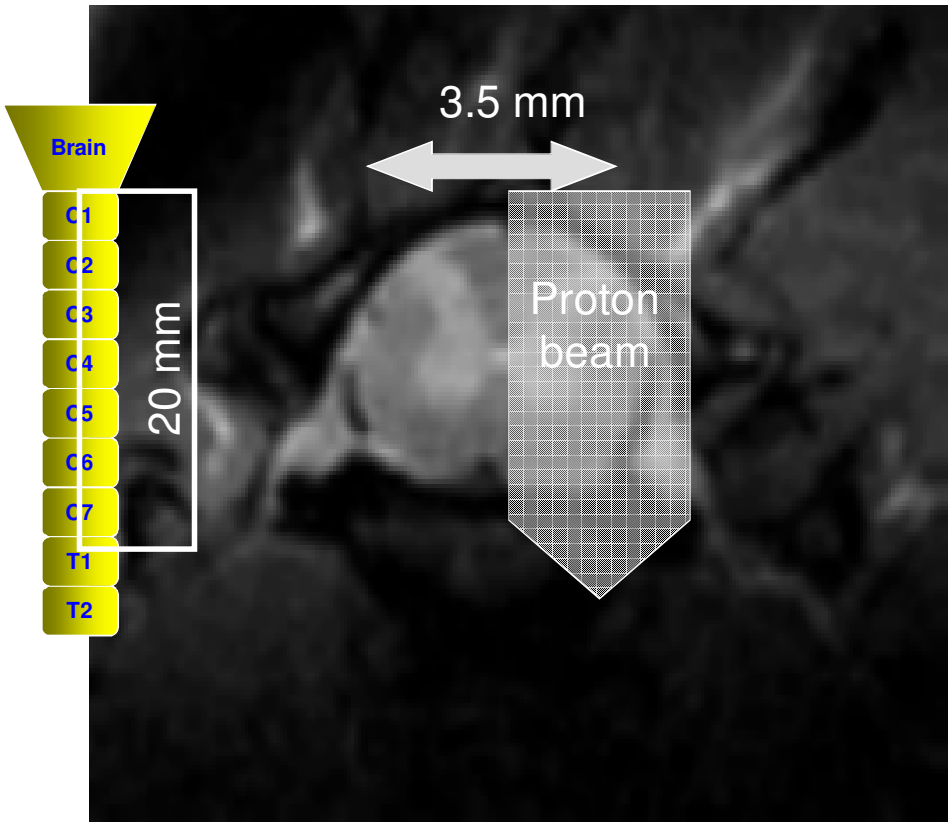
High precision partial volume irradiation of normal tissues: proton irradiation of rat spinal cord



Irradiating decreasing lengths of rat cord shows a steep rise in tolerance dose: migration of stem cells?

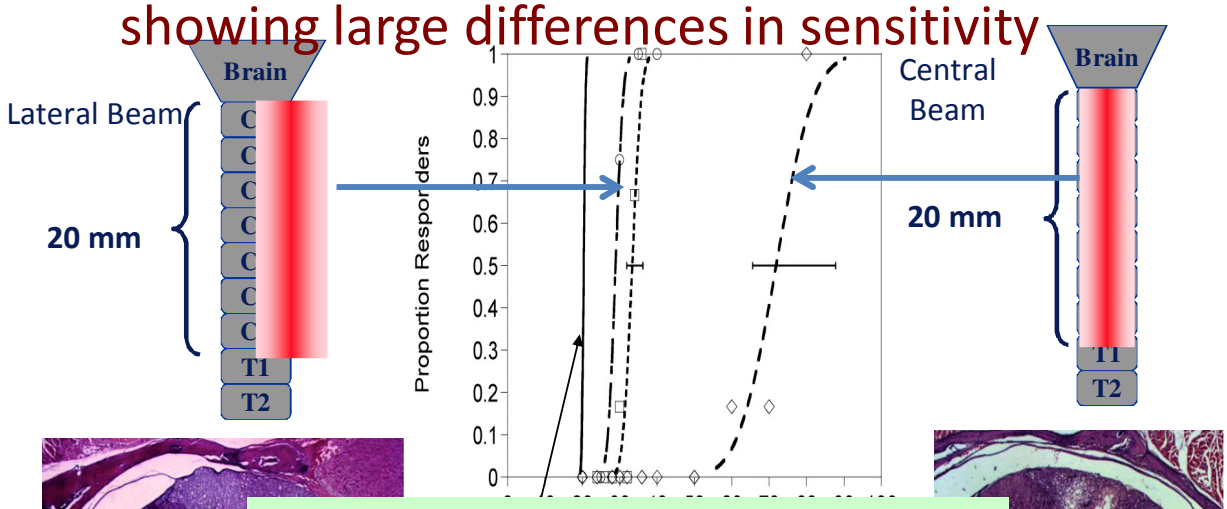


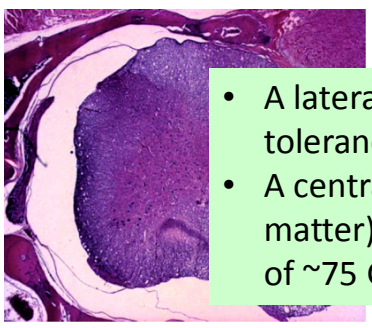
Heterogeneous dose-distributions in lateral direction across the rat spinal cord

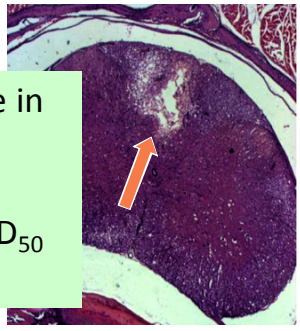


High precision partial volume irradiation of normal tissues: proton irradiation of rat spinal cord

Heterogeneous dose-distributions in lateral direction showing large differences in sensitivity

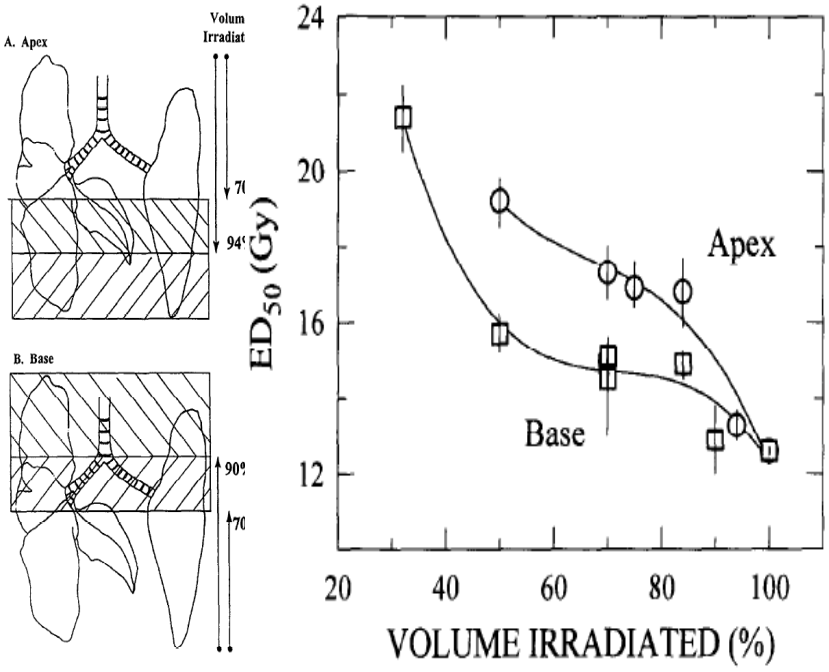






- A lateral beam shows a moderate increase in tolerance to ED_{50} of ~30Gy
- A central beam (including all of the gray matter) shows an enormous increase to ED_{50} of ~75 Gy

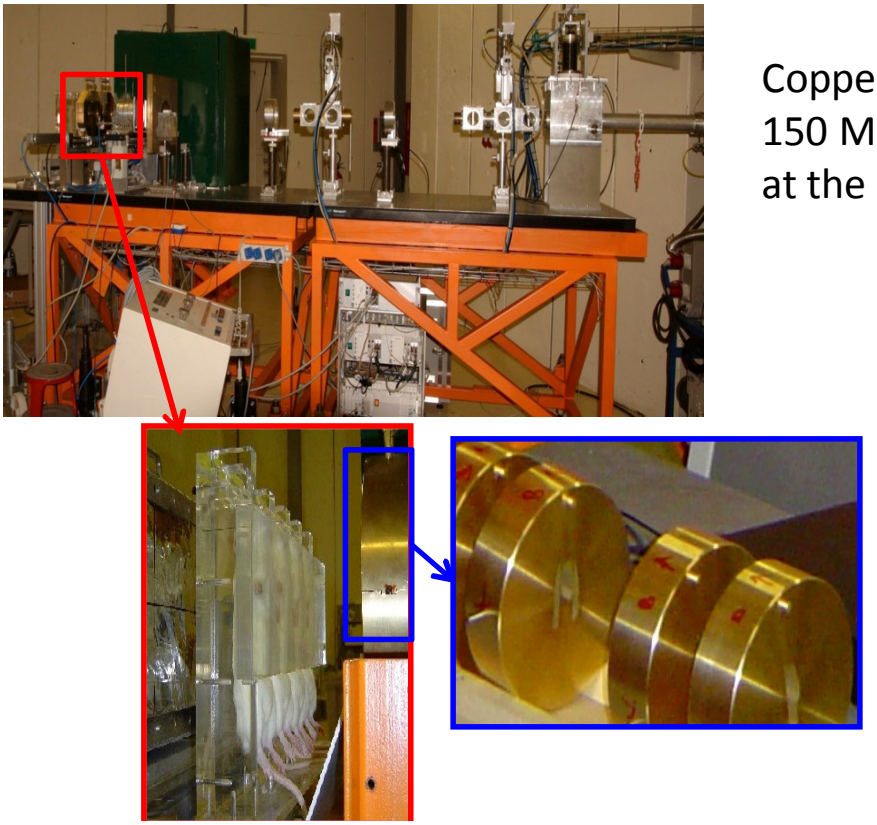
Heterogeneous response of “parallel”organs: lung



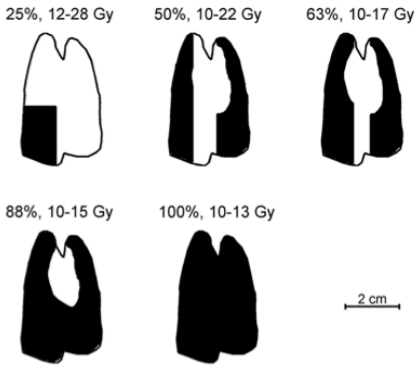
The first experimental studies showing a heterogeneous response of the lung were performed by Liz Travis at the MDACC.

Travis EL et al. Int J Radiat Oncol Biol Phys.;38:1045-54 (1997)

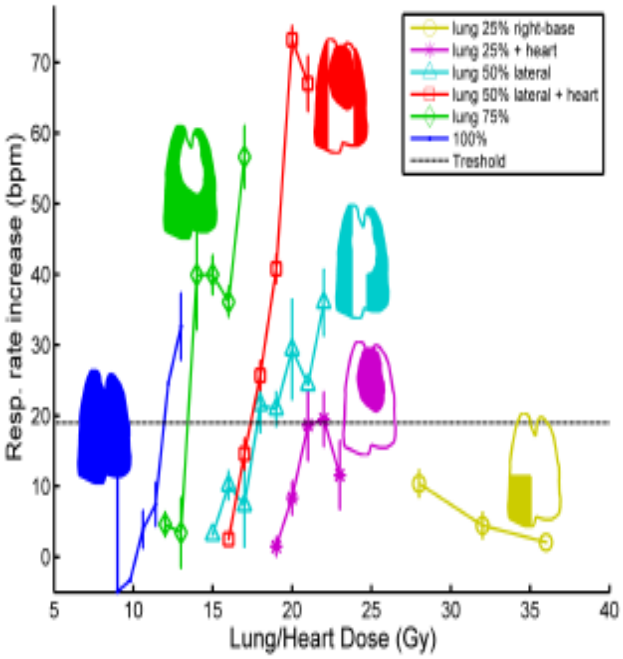
High precision partial volume irradiation of normal tissues: rat lung



Coppes, van Luijk, et al,
150 MeV proton irradiation
at the KVI in Groningen, NL



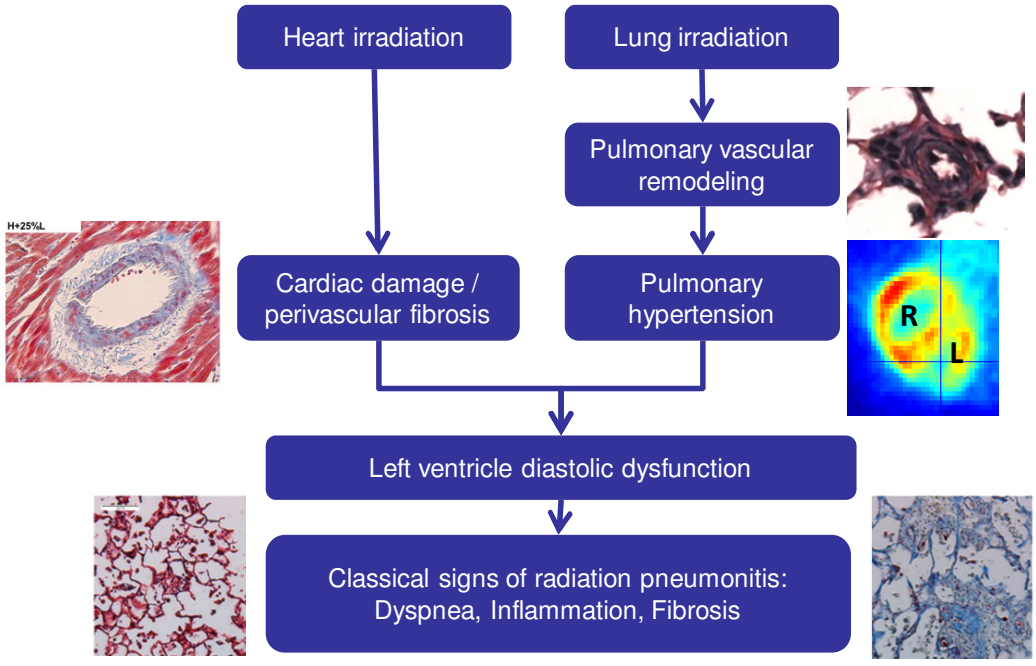
Interaction between organs: heart & lung



- High precision proton irradiation of various lung volumes, including or excluding the heart
- Inclusion of the heart significantly enhances damage to the lung, measured by respiratory frequency

van Luijk et al, IJROBP 2007

Interaction between organs: heart & lung (UMC Groningen)

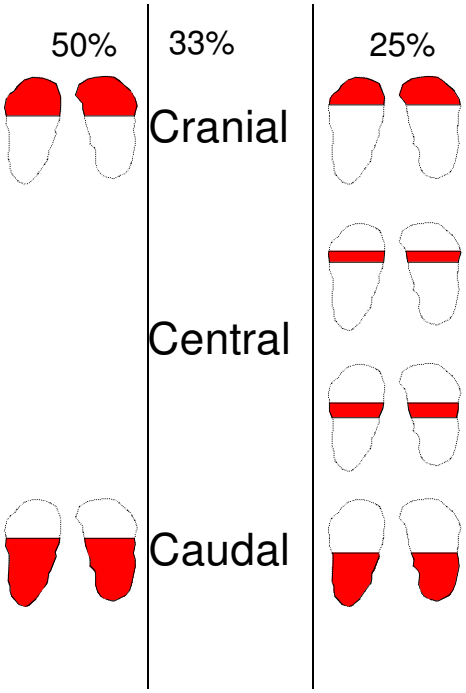


Ghobadi et al. IJROBP 2012

IBPRO

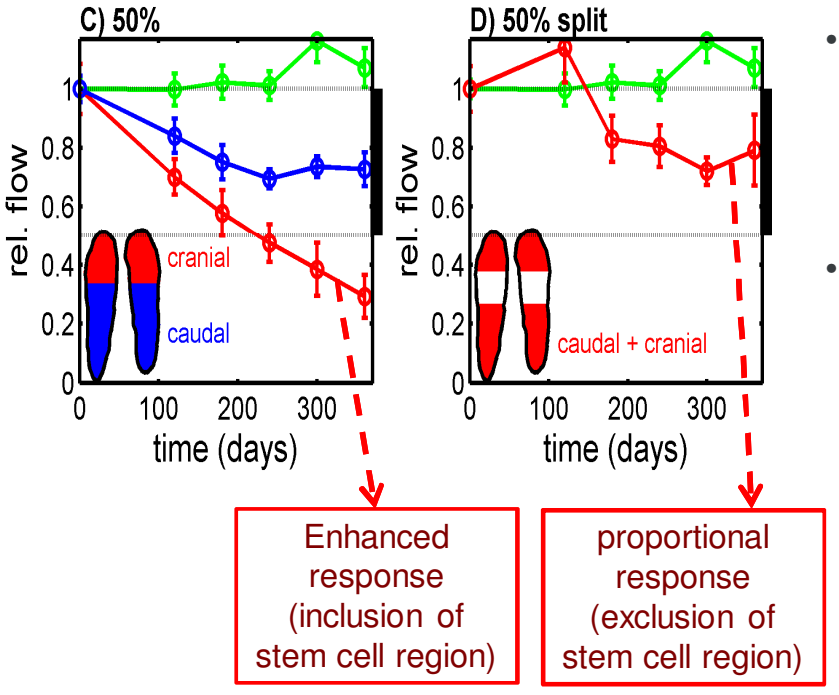
Impact of irradiation of different subvolumes of rat parotid gland on function

High-precision proton irradiation



(van Luijk, Coppes, et al, 2012)

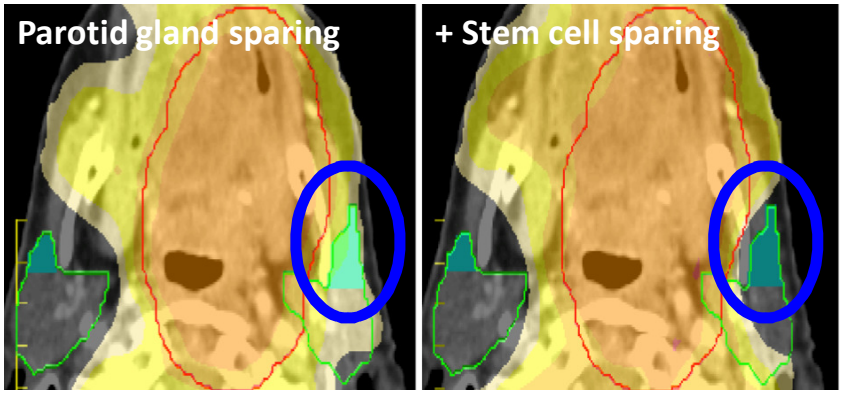
Heterogeneous response of “parallel”organs: critical regions in the parotid gland



- If the parotid gland is a parallel organ, the functional deficit should be proportional to the inactivated tissue
- Studies in rat parotid gland showed an enhanced response when a small central region was included

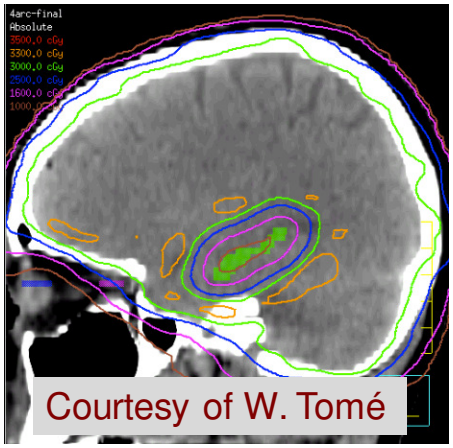
P. van Luijk et al. Sci. Transl. Med. 7, 305ra147 (2015)

New potential for IMRT: conformal avoidance of stem cell regions



Parotid gland: UMC Groningen

Brain stem cell region: hippocampus (Mehta et al, ASTRO 2013)



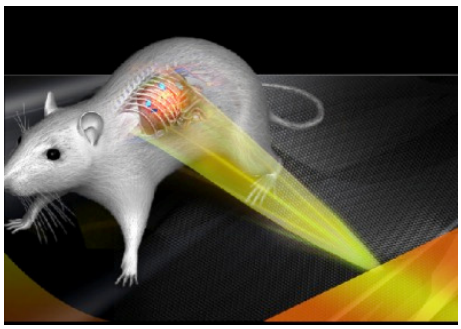
Courtesy of W. Tomé

- 95% of brain receives 30 Gy/10 fx
- Hippocampal avoidance volume 10 Gy
- RTOG 0933: reducing the radiation dose to the stem-cell niches surrounding the hippocampus during treatment was clearly associated with memory preservation

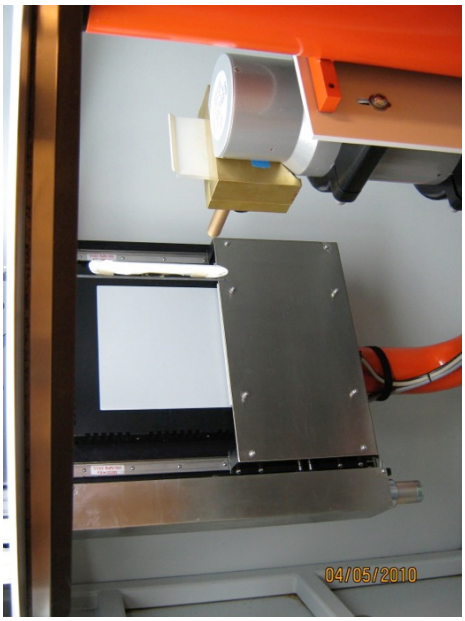
High precision small animal irradiators: Small animal radiotherapy (SmART)

Radiation Capabilities:

- X-ray energies from 0-225 kVp
- Dose rates from 0-3 Gy/min
- Beam sizes from 1-10 mm
- Short treatment scans from 5-8 minutes
- 10 cm^3 FOV



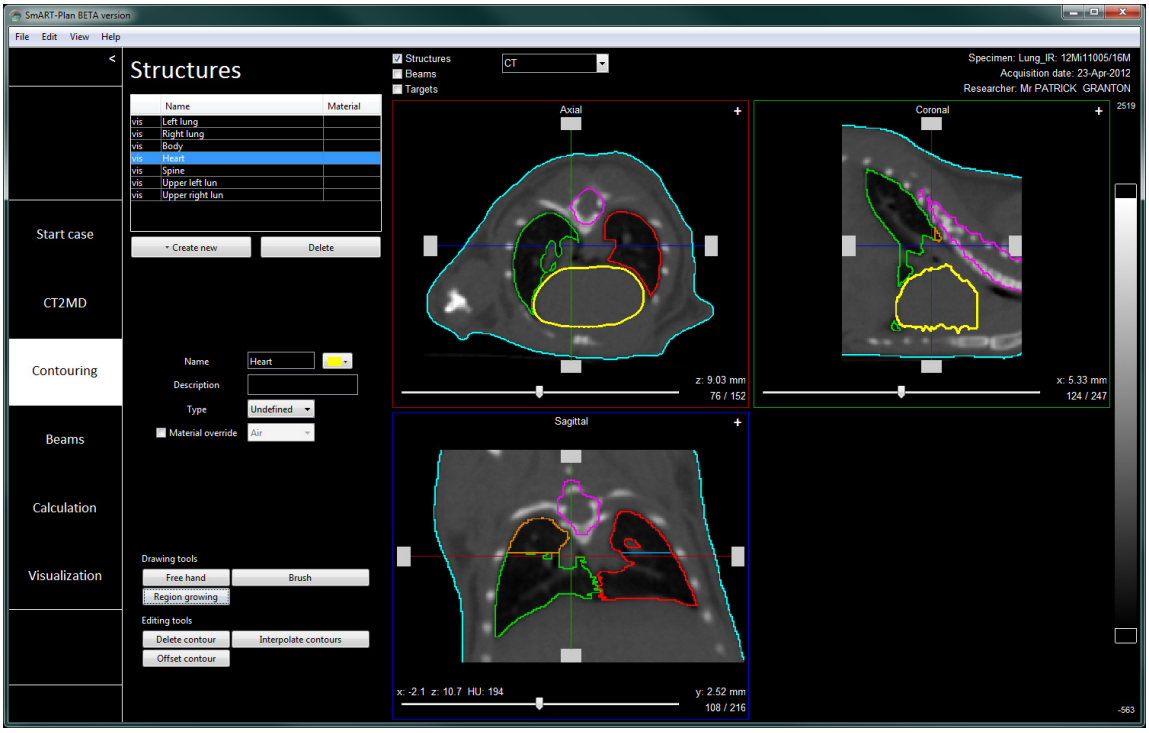
SmART collimators



SmART interior

From: Prof. Frank Verhaegen – MAASTRO Clinic – Maastricht, NL

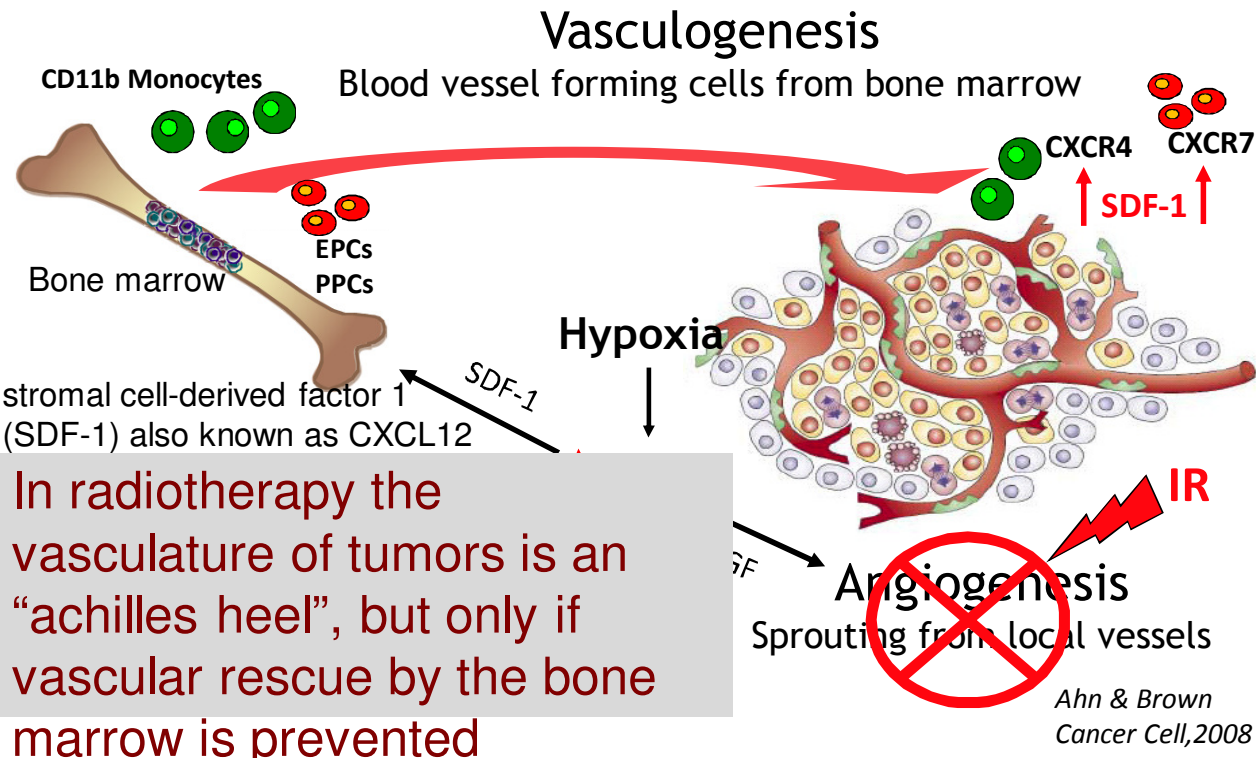
SmART-Plan: Contouring



From: Prof. Frank Verhaegen – MAASTRO Clinic – Maastricht, NL

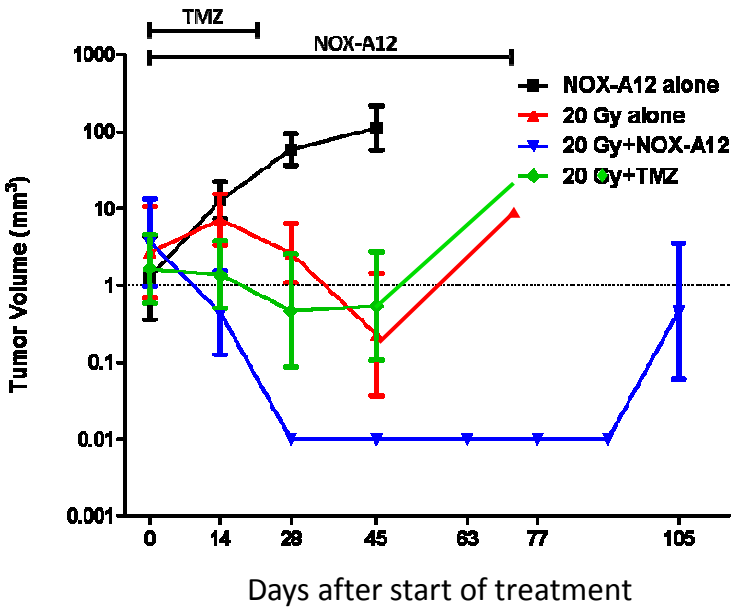
SBRT & high single doses: enhanced vascular damage?

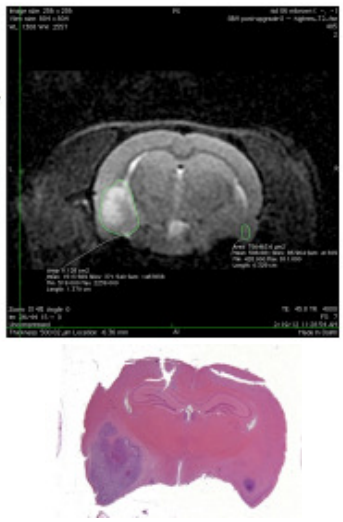
Studies on the radiation-induced influx of CD11b monocytes (J.Martin Brown lab, Stanford University)



In radiotherapy the vasculature of tumors is an "achilles heel", but only if vascular rescue by the bone marrow is prevented

Inhibition of SDF-1 following irradiation produces complete responses in ENU-induced gliomas





J.M. Brown et al, 2013

Acknowledgements

Some of the slides shown were adapted from, or inspired by, the following colleagues:

- Peter van Luijk and Rob Coppes – Groningen, NL
- Wolfgang Tomé – New York
- Frank Verhaegen – Maastricht, NL
- Martin Brown – Stanford, CA