The volume-effect in Radiotherapy: Stereotactic Radiotherapy

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Outline

- Rationale and concept of SBRT
- Normal tissue effects
  - experimental data
  - clinical data
- Tumour effects
  - experimental data
  - clinical data
- Is there a new radiobiology?

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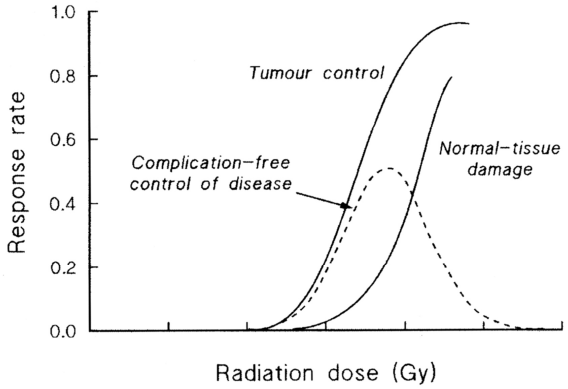
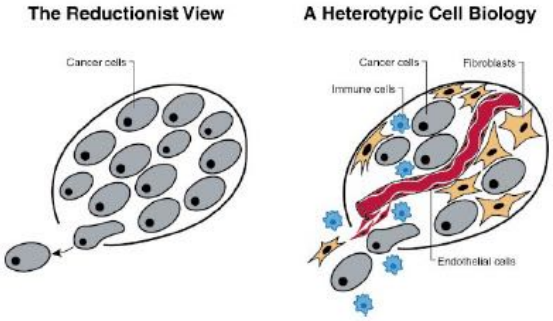
Therapeutic window – aim of RT

Balance between local tumour control and side effects



Adapted by Holthusen, Strahlentherapie 57: 254-268,1936



Hanahan and Weinberg, Cell 2000, 100:57-70

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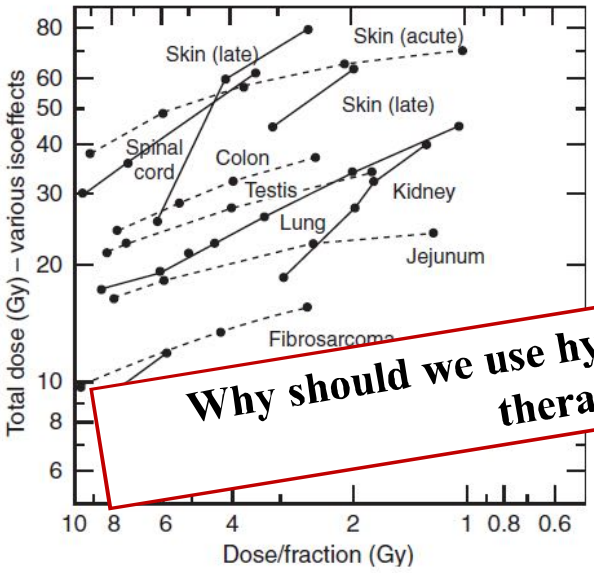
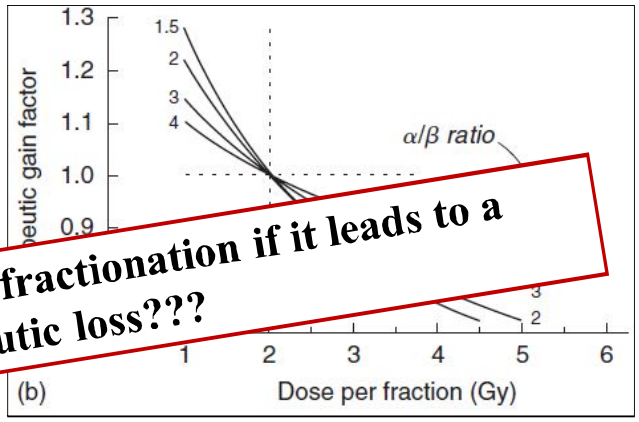
Effects of dose/fraction alteration



H. Thames et al., IJROBP 1982



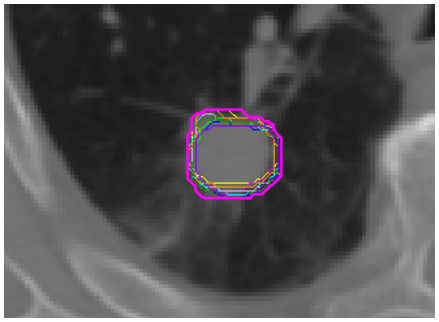
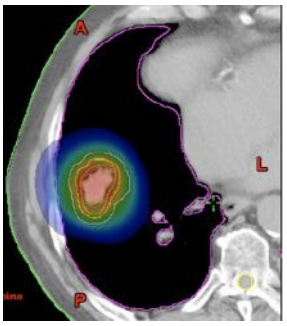
M. Joiner & A. van der Kogel, Basic Clinical Radiobiology, 4th ed. Arnold 2009

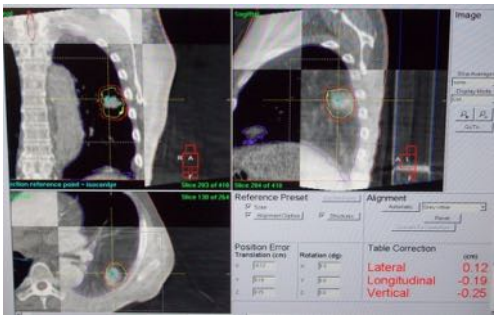
Why should we use hypofractionation if it leads to a therapeutic loss???

α/β late responding tissue (e.g spinal chord)≈ 3
α/β early responding tissue (e.g skin)≈ 10

Feasibility of SBRT: Technological advances





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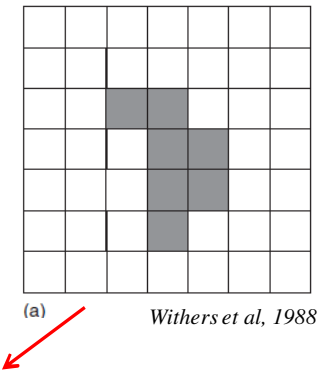
Feasibility of SBRT: The volume effect

Functional Sub Unit (FSU): the largest tissue volume that can be regenerated from a single surviving clonogenic cell

Lung
Liver
Kidney



Withers et al, 1988

Spinal Chord
Intestine
Esophagus

Parallel arrangement of the FSUs:

Threshold volume

Serial arrangement of the FSUs:

Threshold Dose

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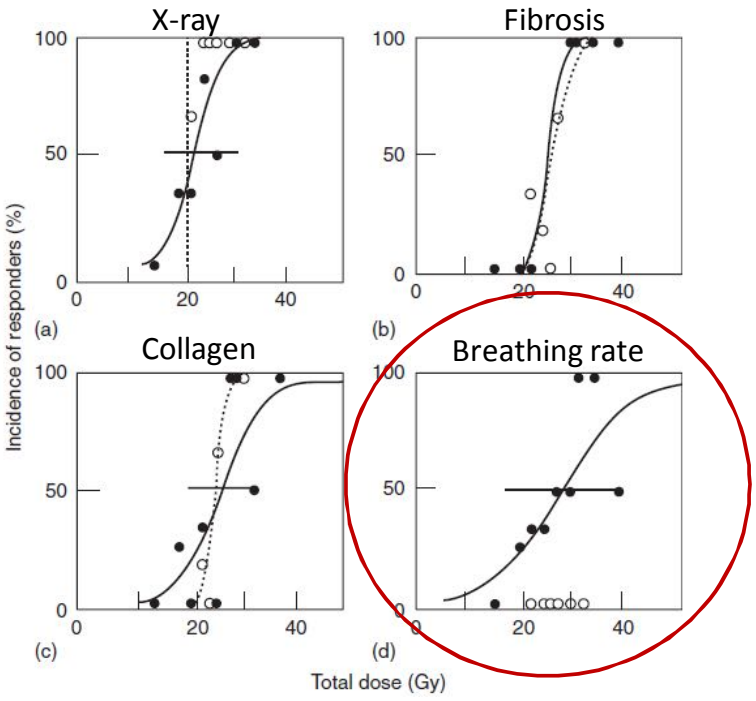
Feasibility of SBRT: The volume effect



Hermann et al., Radiother. Oncol. 1997

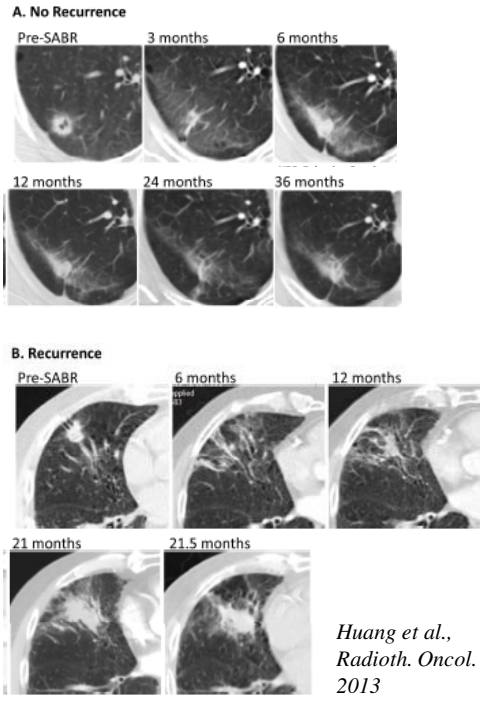
Endpoints: Structure vs function

Radiation-induced lung damage in pigs

Structural changes: independent of the IR volume

Functional changes: dependent on IR volume

SBRT: Clinical results Toxicity



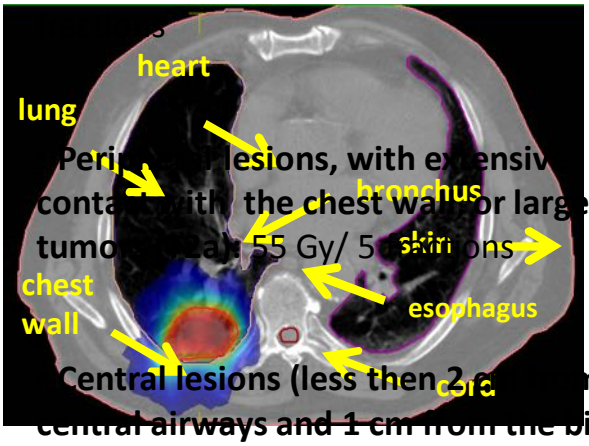
Huang et al., Radioth. Oncol. 2013

Severe Pulmonary toxicity

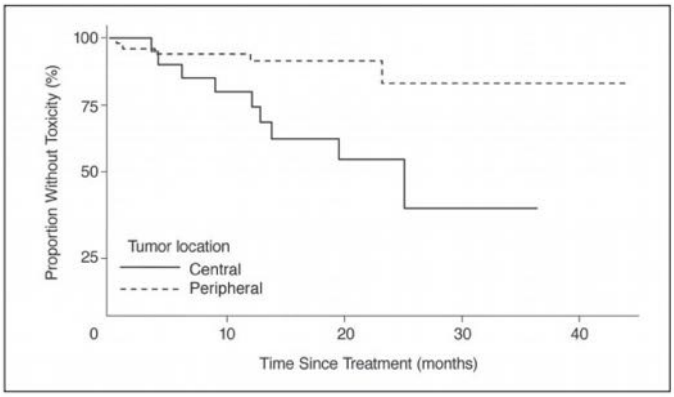
	Nº Pts	Dose	Grade ≥3 Toxicity
Uematsu, 1998	66	30-76 Gy 5-15 fx	0%
Nagata, 2005	45	40-48 Gy 4 fx	0%
Wulf, 2004	61	26-37.4 Gy 1-3 fx	0%
Onimaru, 2003	57	48-60 Gy 8 fx	0%
Whyte, 2003	23	15 Gy 1 fx	0%
Grills, 2012	505	Median BED: 132 Gy	2%
DEGRO study Guckenberger, 2013	582	Median BED: 95 Gy	7.4% G5 0.4%
Italian multicentric, Ricardi, 2014	196	Median BED: 105.6 Gy	1%

SBRT: Clinical results
Toxicity

- **Peripheral lesions (T1a-T1b):** 54 Gy/ 3



Peri lesions, with ensiv
conta with the chest wa or larg
tumo 2a): 55 Gy/ 5 ons
Central lesions (less then 2 c m
central airways and 1 cm from the big vessels): 60 Gy/ 8 fractions



Timmerman et al., JCO 2006

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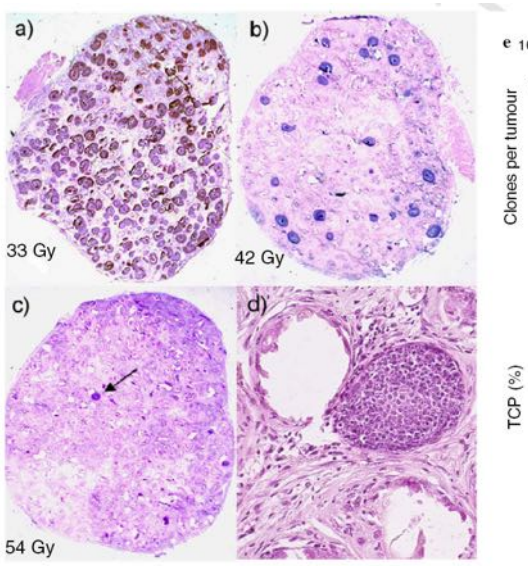
SBRT tumour effect
Experimental evidence

Evidence for clonogenic cell inactivation *in vivo*



Higher cell killing

Krause, Baumann, Kummermehr et al., Radiother Oncol 80: 112-122, 2006

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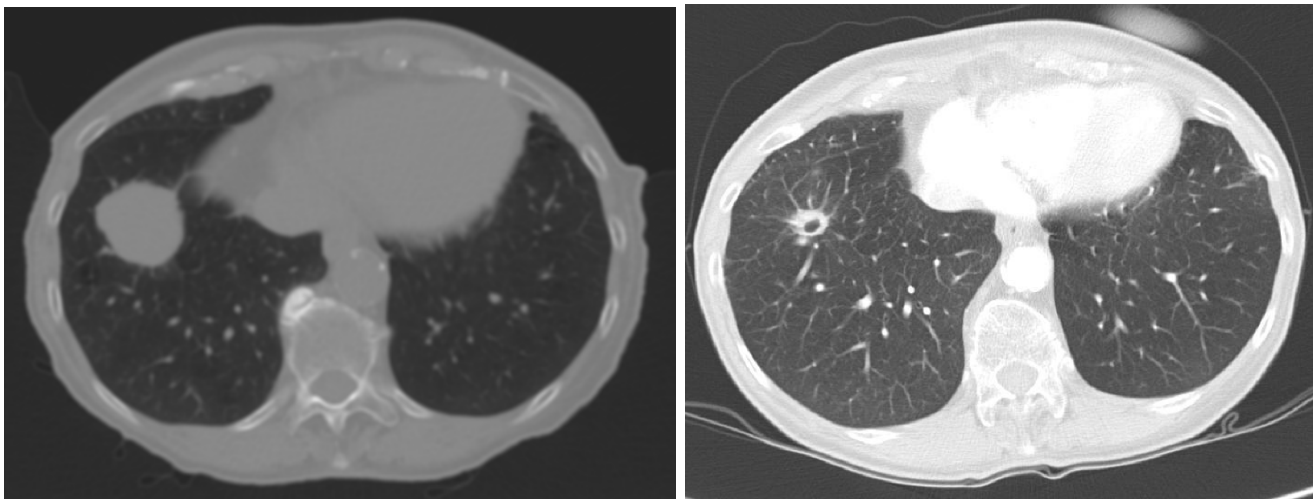
SBRT tumour effect
Clinical evidence

SABR
(Stereotactive Ablative Radiotherapy)



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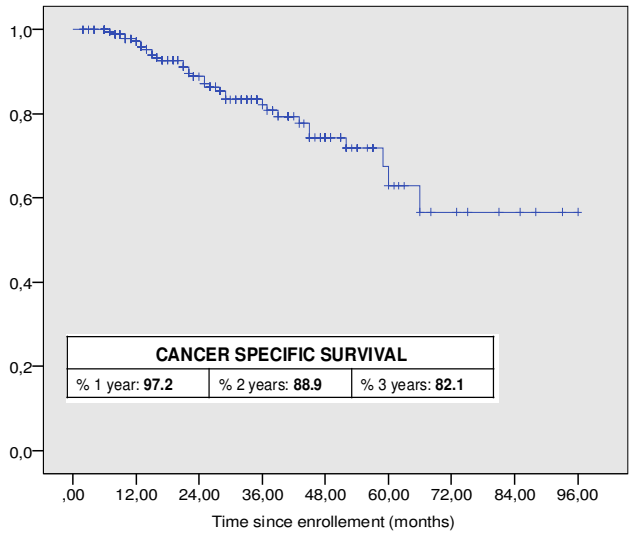
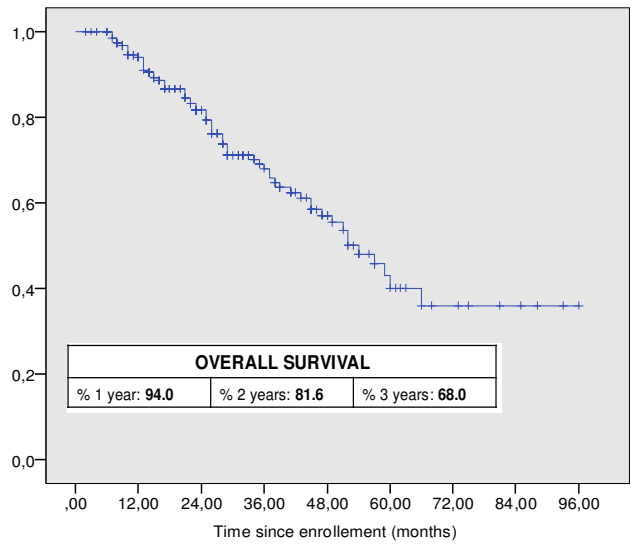
SBRT tumour effect
Clinical evidence

A



B



Ricardi et al, Lung Cancer 2014

- 196 patients, Enrollement time: 2003-2011
- 5 Italian centers (Torino, Rozzano/Milano, Genova, Bologna, Aviano)

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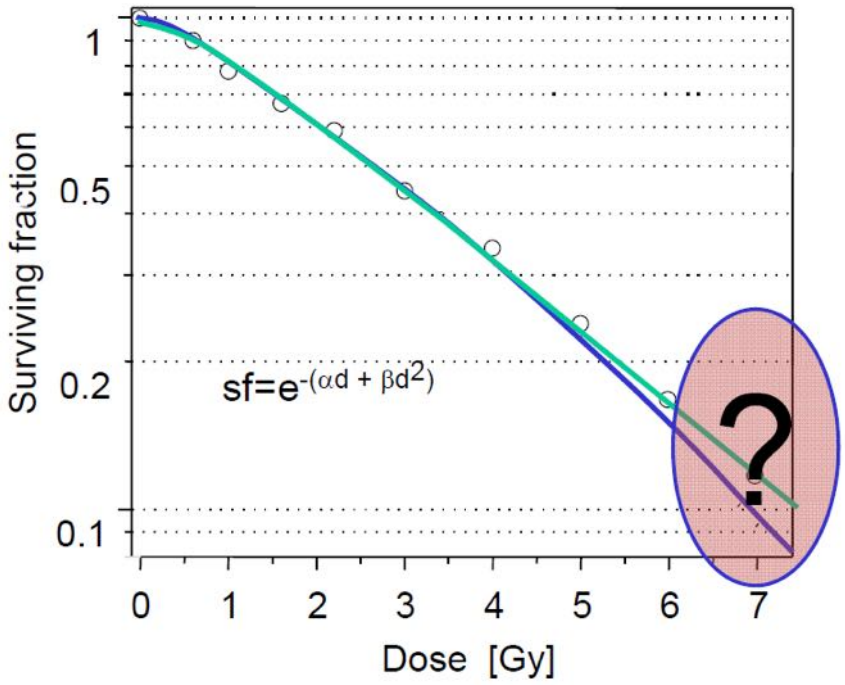
Is the LQ model still valid at high dose/fraction?



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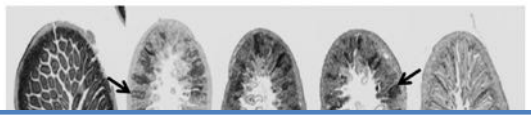
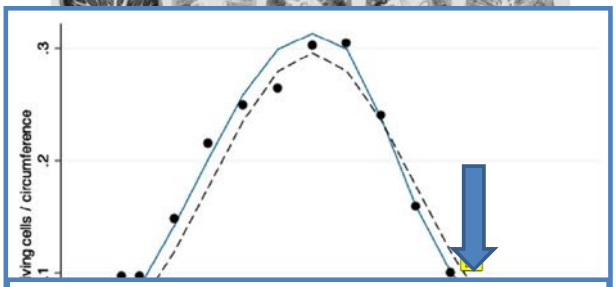
Is the LQ model still valid at high dose/fraction?

Radiotherapy and Oncology 109 (2013) 21–25
Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Modelling of fractionation

Use of the LQ model with large fraction sizes results in underestimation of isoeffect doses





The LQ model underestimates doses for isoeffective crypt-cell survival with large fraction sizes (≈ 8% of underestimation)

Radiotherapy and Oncology 109 (2013) 13–20
Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Modelling of fractionation

Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer

Matthias Guckenberger [a,*], Rainer Johannes Klement [a,b], Michael Allgäuer [c], Steffen Appold [d], Karin Dieckmann [e], Iris Ernst [f], Ute Ganswindt [g], Richard Holy [h], Ursula Nestle [i], Meinhard Nevinny-Stickel [j], Sabine Semrau [k], Florian Sterzing [l], Andrea Wittig [m], Nicolaus Andratschke [n], Michael Flentje [a]

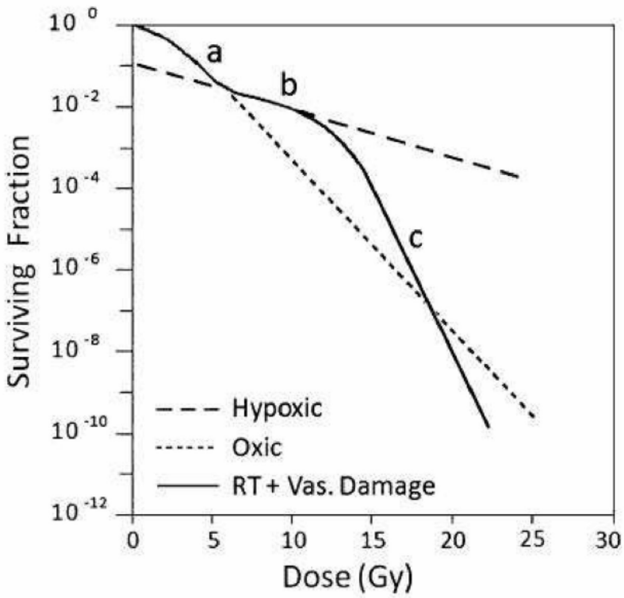
395 patients from 13 German and Austrian centers treated with SBRT for stage I NSCLC

Assuming an a/b =10 Gy, we modeled TCP as a sigmoid-shaped function of the biologically effective dose (BED).
2 Models: LQ and LQ-L

Conclusion: The LQ-L formalism did not improve the dose–effect modeling compared to the traditional LQ concept.

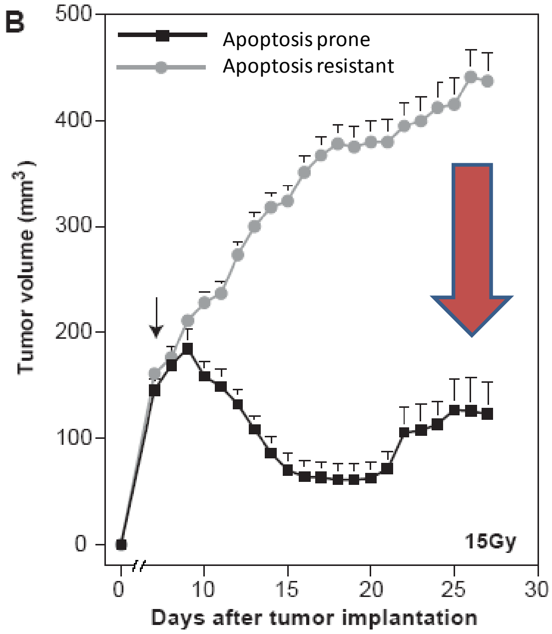
Are there more than 5Rs involved?

Vascular damage at high doses can generate secondary cell killing



Song, CW. et al., Radiobiology of stereotactic radiosurgery and stereotactic body radiation therapy. Berlin Heidelberg: Springer-Verlag; 2012.

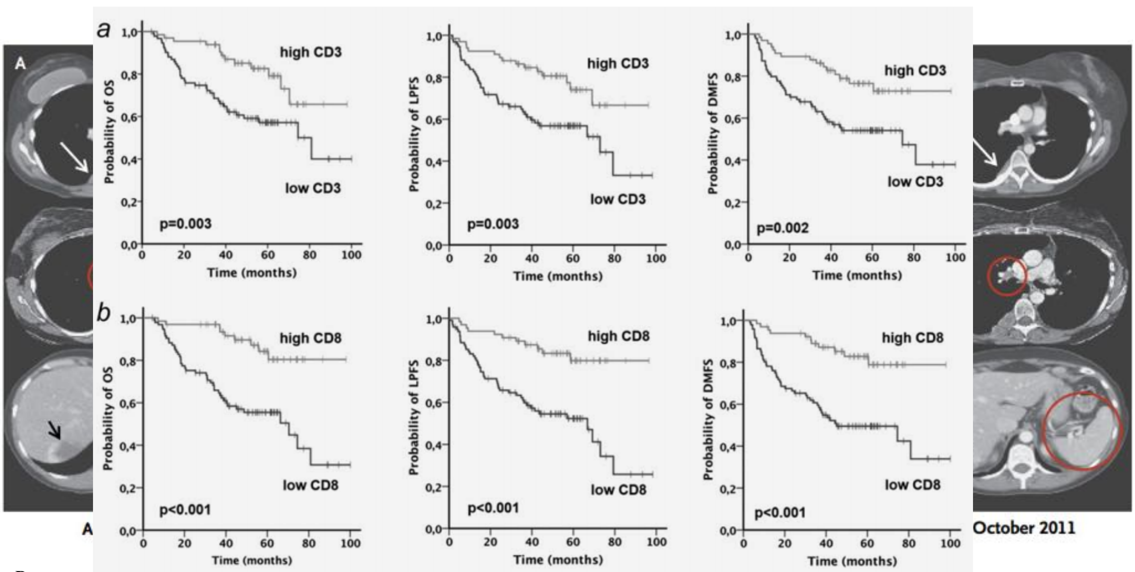
Endothelial cell apoptosis at large doses leads to a tumour growth delay



Garcia-Barros M et al., Science 2003; 300:1155-1159

Are there more than 5Rs involved?

High doses/fraction enhance anti-tumour immunity



Postow et al., NEJM 2011

Balermpas et al. (DKTK group), IJ Cancer 2015

Lugade AA, et al., J Immunol 2005;174:7516-23

Conclusions

- SBRT "narrows" the therapeutic window
- Large doses per fraction increase the biological effect of radiation to the tumour
- Win-win situation thanks to technological improvements IF performed in a (prevalent) parallel-organized organ
- Alternative models for estimation of iso-effective doses remain to be validated in the clinic
- Upcoming new radiobiology?

Thanks for your attention!