The volume-effect in Radiotherapy: Stereotactic Radiotherapy

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Outline

• Rationale and concept of SBRT
• Normal tissue effects
  o experimental data
  o clinical data
• Tumour effects
  o experimental data
  o clinical data
• Is there a new radiobiology?
**Therapeutic window – aim of RT**

Balance between local tumour control and side effects

\[
\text{Complication-free control of disease} \quad \text{Normal-tissue damage}
\]

Radiation dose (Gy)

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**

\[\alpha/\beta \text{ late responding tissue (e.g. spinal chord)} = 3\]
\[\alpha/\beta \text{ early responding tissue (e.g. skin)} = 10\]

H. Thames et al., IJROBP 1982


Why should we use hypofractionation if it leads to a therapeutic loss???
Feasibility of SBRT: Technological advances

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

Parallel arrangement of the FSUs:

<table>
<thead>
<tr>
<th>Lung</th>
<th>Liver</th>
<th>Kidney</th>
</tr>
</thead>
</table>

Serial arrangement of the FSUs:

<table>
<thead>
<tr>
<th>Spinal Chord</th>
<th>Intestine</th>
<th>Esophagus</th>
</tr>
</thead>
</table>

Threshold volume

Threshold Dose
Feasibility of SBRT: The volume effect

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

Severe Pulmonary toxicity

<table>
<thead>
<tr>
<th>Study</th>
<th>No</th>
<th>Dose</th>
<th>Grade ≥3 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uematsu, 1998</td>
<td>66</td>
<td>30-76 Gy 5-15 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Nagata, 2005</td>
<td>45</td>
<td>40-48 Gy 4 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Wulf, 2004</td>
<td>61</td>
<td>26-37.4 Gy 1-3 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Onimaru, 2003</td>
<td>57</td>
<td>48-60 Gy 8 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Whyte, 2003</td>
<td>23</td>
<td>15 Gy 1 fx</td>
<td>0%</td>
</tr>
<tr>
<td>Grills, 2012</td>
<td>505</td>
<td>Median BED: 132 Gy</td>
<td>2%</td>
</tr>
<tr>
<td>DEGRO study</td>
<td>582</td>
<td>Median BED: 95 Gy</td>
<td>7.4%</td>
</tr>
<tr>
<td>Italian multicentric, Ricardi, 2013</td>
<td>196</td>
<td>Median BED: 105.6 Gy</td>
<td>1%</td>
</tr>
</tbody>
</table>

Huang et al., Radioth. Oncol. 1997
**SBRT: Clinical results**

**Toxicity**

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

- Peripheral lesions, with extensive contact with the chest wall or larger tumors (T2a):
  - 55 Gy/5 fractions

- **Central lesions** (less than 2 cm from central airways and 1 cm from the big vessels): 60 Gy/8 fractions

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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*
SBRT tumour effect
Clinical evidence

SABR
(Stereotactic Ablative Radiotherapy)

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

Ricardi et al, Lung Cancer 2014
Is the LQ model still valid at high dose/fraction?

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

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

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

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

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