Stereotaktische Radiotherapie: Möglichkeiten und Grenzen

Matthias Guckenberger
1908: Robert Henry Clarke and Victory Horsley
Stereotactic technique based on the reproducibility of the relationships between landmarks on the skull (external auditory canals, midline) and anatomical structures within the brain

**Problem:** unsure relationship between bony landmarks and cerebral structures

- Targeting of subcortical structures only e.g. gasserian ganglion with foramen ovale as landmark
- Imaging e.g. ventriculography -> stereotactic atlas

Lars Leksell

1950s: Experiments with stereotactic proton therapy
1967: Gamma-knife radiosurgery using Co-60 for treatment of functional disorders

Since **1980s**: CT localization and linac based stereotactic radiotherapy

Since **1994**: (Lax & Blomgren): Stereotactic body radiotherapy
“Don’t routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.”
Radiosurgery for brain metastases

Prospective observational study

- SRS only for 1 – 10 brain mets
- SRS with 1 x 20-22Gy
- MRI FU every 3 months

Identical OS for 2-4 versus 5-10 brain metastases

Yamamoto Lancet Oncol 2014

Whole brain radiation as salvage treatment only?
STEREOTACTIC RADIOThERAPY OF MALIGNANCIES IN THE ABDOMEN

Methodological aspects

INGMAR LAX, HENRIC BLOMGREN, INGEMAR NÄSLUND and RUT SVANSTRÖM

A method for stereotactic high-dose radiotherapy of malignancies in the abdomen has been developed. A stereotactic frame for the body has been developed and a method for fixation of the patient in the frame is described. The reproducibility in the stereotactic system of tumours in the liver and the lung was found to be within 5–8 mm for 90% of the patient set-ups. The diaphragmatic movements were reduced to 5–10 mm, by applying a pressure on the abdomen. An analytical method is used to calculate dose distributions for a continuum of beams in an isocentric treatment technique. The advantage of a heterogeneous target dose is demonstrated and proposed for the present application. A non-coplanar treatment technique, using eight individually shaped beams is proposed and has been used for patient treatments. The dose distribution for a patient with a metastasis in the liver is shown as well as dose volume histograms for the target and the liver.
Stereotactic Body Radiotherapy

- A method of external beam radiotherapy (EBRT)
- To accurately deliver
- A high dose of irradiation
- In one or few treatment fractions
- To an extra-cranial target.
Technology for Stereotactic body radiotherapy

- Multiple dedicated devices available
- SBRT independent from technology
Stereotactic body radiotherapy (SBRT):

- Staging
- Patient selection
- 4D target volume definition
- Highly conformal treatment planning
- Image guided radiotherapy

➤ Optimization of the whole radiotherapy work-flow
STEREOTACTIC HIGH DOSE FRACTION RADIATION THERAPY OF EXTRACRANIAL TUMORS USING AN ACCELERATOR

Clinical experience of the first thirty-one patients

HENRIC BLOMGREN, INGMAR LAX, INGEMAR NÄSLUND and RUT SVANSTRÖM

A stereotactic body frame with a fixation device has been developed for stereotactic radiation therapy of extracranial targets, a precision localization and positioning system in analogy with the stereotactic head frames used for intracranial targets. Results of the first 42 treated tumors in 31 patients are presented. Most of the patients had solitary tumors in liver, lung or retroperitoneal space. Clinical target volumes ranged from 2 to 622 cm³ (mean 78 cm³) and minimum doses to the planning target volumes (PTV) of 7.7–30 Gy/fraction (mean 14.2 Gy) were given on 1–4 occasions to a total minimum dose to the PTVs of 7.7–45 Gy (mean 30.2 Gy) to the periphery of the PTV and total mean doses to the PTVs of 8–66 Gy (mean 41 Gy). The central part of the tumor was usually given about 50% higher dose compared to that of the periphery of the PTV by a planned inhomogeneous dose distribution. Some of the patients received stereotactic radiation therapy concomitantly to more than one target, in others new metastases were also treated which appeared during the follow-up period. We observed a local rate of no progressive disease of 80% during a follow-up period of 1.5–38 months. Fifty percent of the tumors decreased in size or disappeared.
Population based outcome SBRT stage I NSCLC

13 German centers: outcome between 1998 – 2011 in $n=582$

3a FFLP: 80%

3a OS: 47%

Guckenberger JTO 2013
Time trends in SBRT practice in Germany

- Biopsy confirmation
  - 1998: 89%
  - 1999: 78%

- FDG-PET Staging
  - 1998: ~55%
  - 1999: ~75%
  - 2000: >90%

- Typ B DCA
  - 1998: 25%
  - 2000: 52%

- IGRT
  - SBF
  - IGRT outside
  - IGRT inside

- Rapid implementation of modern technology
- Technology did NOT improve ANY endpoint
## Outcome of SBRT for stage I NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th># patients</th>
<th>OS @ 2-3a</th>
<th>LC @ 2-3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagata</td>
<td>2005</td>
<td>45</td>
<td>75%</td>
<td>98%</td>
</tr>
<tr>
<td>Baumann</td>
<td>2009</td>
<td>57</td>
<td>60%</td>
<td>92%</td>
</tr>
<tr>
<td>Fakiris</td>
<td>2009</td>
<td>70</td>
<td>43%</td>
<td>88%</td>
</tr>
<tr>
<td>Ricardi</td>
<td>2010</td>
<td>62</td>
<td>57%</td>
<td>88%</td>
</tr>
<tr>
<td>Bral</td>
<td>2010</td>
<td>55</td>
<td>56%</td>
<td>98%</td>
</tr>
<tr>
<td>Timmerman</td>
<td>2010</td>
<td>40</td>
<td>52%</td>
<td>84%</td>
</tr>
<tr>
<td><strong>Prospective studies</strong></td>
<td></td>
<td><strong>329</strong></td>
<td><strong>56.2%</strong></td>
<td><strong>91.2%</strong></td>
</tr>
</tbody>
</table>

- Consistent results
- No obvious progress over time
National-wide pick-up of SBRT for stage I NSCLC

New technologies:
- Improved work-flow & confidence into SBRT
Implementation of SBRT: influence on OS

Improved work-flow & confidence into SBRT

- BROAD IMPLEMENTATION

SBRT era

Pre-SBRT era

Palma JCO 2010

Graph showing overall survival probability over time since diagnosis with different eras.
Application of SBRT

Brain metastases
Primary brain tumors
Recurrent head & neck
Breast Cancer
Primary lung cancer
SBRT for locally advanced NSCLC
Lung metastases
Spine SBRT
Primary liver cancer
Liver metastases
Pancreatic cancer
Lymph node metastases
Prostate cancer
Cervical cancer
...

University Hospital Zurich
SBRT for prostate cancer
SBRT for prostate cancer: dose & fractionation

Phase I dose escalation study

<table>
<thead>
<tr>
<th>Fractionation</th>
<th>5 x 9Gy</th>
<th>5 x 9.5Gy</th>
<th>5 x 10Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Median FU</td>
<td>30 mo</td>
<td>18 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td>% with G3 Tox</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Boike JCO 2011

- Endpoint: Freedom from toxicity @ 90 days
- „Dose limiting toxicity not reached“
Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

Table 2 Worst acute and delayed rectal toxicity in patients by radiation prescription dose level

<table>
<thead>
<tr>
<th>Grade</th>
<th>All patients (n=91)</th>
<th>45 Gy (n=15)</th>
<th>47.5 Gy (n=15)</th>
<th>50 Gy (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td>Late</td>
<td>Acute</td>
<td>Late</td>
</tr>
<tr>
<td>0</td>
<td>39 (42.9)</td>
<td>38 (41.8)</td>
<td>9 (60.0)</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>1</td>
<td>33 (36.3)</td>
<td>27 (29.7)</td>
<td>6 (40.0)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>2</td>
<td>17 (18.7)</td>
<td>21 (23.1)</td>
<td>0</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>3</td>
<td>1 * (1.1)</td>
<td>3 (3.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 (1.1)</td>
<td>2 (2.2)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median Follow-up: still only 25 months

6 / 61 patients with G3+ Toxicity
5 / 61 patients required colostomy

SBRT cannot change basic radiobiology
**SBRT for metastatic disease**

<table>
<thead>
<tr>
<th>TOTAL 30 institutions</th>
<th>Practice of SBRT</th>
<th>Sufficient evidence for practice outside of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I NSCLC</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Spine Metastases</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Primary Liver Cancer</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

— Dahele Acta Oncol 2015

➢ SBRT for metastasis has become standard practice in Europe
The concept of OLIGOMETASTASES

- **Localized**: Cure with local treatment
- **Oligometastatic**: Cure with local treatment possible
- **Systemic**: Local Tx for symptom control

Hellman & Weichselbaum JCO 1995
Local surgical treatment in the metastatic setting

Colorectal liver metastases

- Long-term OS (cure?) despite metastatic stage of disease

Pulmonary metastases

Fong Ann Surg 1999

Casiraghi JTO 2011
SBRT for different histologies

<table>
<thead>
<tr>
<th>Histology</th>
<th>Study</th>
<th>Lesions</th>
<th>Local control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer</td>
<td>Hoyer 2006</td>
<td>141</td>
<td>86%</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>Svedman 2009</td>
<td>79</td>
<td>79 – 98%</td>
</tr>
<tr>
<td></td>
<td>Wersäll 2005</td>
<td>162</td>
<td>90 – 98%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Stragliotto 2012</td>
<td>136</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>Dhakal 2012</td>
<td>74</td>
<td>82%</td>
</tr>
</tbody>
</table>

➢ Local control of 80 – 90% irrespective of histology
Long-term OS: SBRT for lung metastases

n=121

6a OS 20%

Long-term OS in agreement to surgical series
Definition of oligo-metastasis

- Maximum of 3 – 5 metastases in 1 – 2 organ systems
- 80% of the patients will develop progressive disease
Biological characterization of oligometastasis

Oligometastatic lung disease

Micro-RNA expression profile predicts:

- Progression free survival
- Overall survival

➢ Selection of „truly“ oligo-metastatic patients

Lussier PLOS 2012
„targeted“
SYSTEMIC
therapy

„targeted“
LOCAL
therapy

- Anti-EGFR monoclonal antibody
- EGFR
- EGFR-TKIs
- Receptor-specific ligand
- Extracellular region
- Cell membrane
- Cytoplasm
Oligo-Metastases vs Oligo-Progression

Oligo-metastasis
- Limited number of metastases
  - Treatment of all lesions

Oligo-progression
- Multiple metastases
- Limited number of progressive metastases during systemic treatment
  - Treatment all progressive lesions
Progression under targeted systemic therapy

- **Gefitinib**
  - in mutant EGFR
  - Maemondo NEJM 2010

- **Crizotinib**
  - in ALK positive
  - Shaw NEJM 2013

- **Nivolumab**
  - in unselected patients
  - Brahmer NEJM 2015

- Substantial and clinically relevant improvement
- Still: 60 – 80% develop progressive disease after 12 months
Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

- Stage IV NSCLC
- KPS > 60
- ≤ 6 active extra-cranial lesions
- Progression during ≥1 prior chemotherapy

SBRT to all active sites + Concurrent Erlotinib
SBRT for oligo-progressive disease

Progression-free survival

- 1 / 3 of the patient remained free from any progression
- OS remarkable for patients failing to first line CT

Overall survival

Median, 14.7 months

Median, 20.4 months
Radiotherapy to enhance immune response

- Increased antigen presentation (in situ vaccination)
- T-cell mediated immune response
- Dose & fractionation dependent effect
- Local and systemic (abscopal) immune response
Proof of principle: Twyman-Saint Nature 2015

n=22
M+ Melanoma
Methodology of SRS & SBRT well established

SBRT has become guideline recommended treatment of choice for stage I NSCLC

Evaluation in other primary cancer sites ongoing

Evaluation for metastatic disease
Thanks for this invitation