Dose-intensified Image-guided Fractionated Stereotactic Body Radiation Therapy for Painful Spinal Metastases (DOSIS) versus Conventional Radiation Therapy: a Phase II Randomised Controlled Trial

Matthias Guckenberger
DOSIS: a multi-center phase II trial

Prospective phase II trial

- 54 patients with 60 vertebral metastases
- No exclusion of patients with epidural disease
- Fractionated SBRT
- SBRT using SIB concept:
  - 5 x 4 / 7Gy
  - 10 x 3 / 4.85Gy
- Selection of patients with long OS expectancy
DOSIS phase II trial – single arm trial

Guckenberger unpublished data

N=54 patients
N=60 spine mets

SBRT:
5 x 7Gy
or
10 x 4.85Gy

- Pain response at 3 months: 87%
- Reduction of opioid medication by 50%

DOSIS phase II trial – single arm trial

Guckenberger unpublished data

N=54 patients
N=60 spine mets

SBRT:
5 x 7Gy
or
10 x 4.85Gy

- Pain response at 3 months: 87%
- Reduction of opioid medication by 50%

DOSIS phase II trial – single arm trial

Guckenberger unpublished data

N=54 patients
N=60 spine mets

SBRT:
5 x 7Gy
or
10 x 4.85Gy

- Pain response at 3 months: 87%
- Reduction of opioid medication by 50%

DOSIS phase II trial – single arm trial

Guckenberger unpublished data

N=54 patients
N=60 spine mets

SBRT:
5 x 7Gy
or
10 x 4.85Gy

- Pain response at 3 months: 87%
- Reduction of opioid medication by 50%

DOSIS phase II trial – single arm trial

Guckenberger unpublished data

N=54 patients
N=60 spine mets

SBRT:
5 x 7Gy
or
10 x 4.85Gy

- Pain response at 3 months: 87%
- Reduction of opioid medication by 50%

DOSIS phase II trial – single arm trial

Guckenberger unpublished data

N=54 patients
N=60 spine mets

SBRT:
5 x 7Gy
or
10 x 4.85Gy

- Pain response at 3 months: 87%
- Reduction of opioid medication by 50%
DOSIS phase II trial – single arm trial

- Rapid, deep and durable pain reduction
However: Six (11%) and 8 (15%) patients developed progressive or new vertebral compression fractures.
DOSIS RCT

Arm A – experimental: SBRT
- High-dose PTV: 5 × 8 Gy & conventional-dose PTV 5 × 4 Gy (no epidural involvement) or
- High-dose PTV 10 × 4.85 Gy & conventional-dose PTV 10 × 3 Gy (epidural involvement)

Arm B – control: conventional radiation therapy
5 × 4 Gy or 10 × 3 Gy

3 days 1-2 weeks At least 2 years from randomization
Protocol Version 3.0 – Amendment 1

Introduction of a non-randomized part

- Oligometastatic disease (unwilling to be randomized), purely osteoblastic metastases, without pain
- Treatment according to arm A of the randomized part (5 x 8/4 Gy or 10 x 4.85/3 Gy)

Changes to inclusion criteria of randomized part

- Life expectancy ≥ 1 year according to investigator`s estimate (Modified Bauer Score)
- Osteolytic or mixed osteolytic/osteoblastic lesion (mass-type lesions)
- Pain in the affected spinal segment (pain / free of pain under medication)
- Max. 3 (cervical) or 4 (thoracic, lumber, sacral) continuous vertebrae in one target site (max 3 continuous vertebrae)
Randomized part

Arm A – experimental: SBRT
- High-dose PTV: 5 x 8 Gy & conventional-dose PTV 5 x 4 Gy (no epidural involvement) or
- High-dose PTV 10 x 4.85 Gy & conventional-dose PTV 10 x 3 Gy (epidural involvement)

Arm B – control: conventional radiation therapy
- 5 x 4 Gy or
- 10 x 3 Gy

Non-randomized part

According to arm A of the randomised part:
SBRT
- High-dose PTV: 5 x 8 Gy & conventional-dose PTV 5 x 4 Gy (no epidural involvement) or
- High-dose PTV 10 x 4.85 Gy & conventional-dose PTV 10 x 3 Gy (epidural involvement)
Protocol Version 3.0 – Amendment 1

Further changes

- Optional parts removed from protocol (blood samples, smartphone app)
- Simplification of follow-up (every 3 months for 2 years → 1m, 3m, 6m, 12m, 24m)
- Treatment time per patient reduced (3 CBCTs per fraction → 1 CBCT per fraction)
- Concomitant systemic treatments allowed (no concomitant chemotherapy)
- New wording for arm A to avoid confusions (experimental arm → investigational arm)
- Insurance for all participants provided by Clinical Trials Center at University Hospital Zurich
- Patient information sheet and informed consent form adapted
Endpoints

Primary end-point:
- Pain response - improvement by ≥ 2 points on the pain Visual Analogue Scale at 6 months post-treatment

Secondary end-points:
- Local metastasis control
- Overall survival
- Cancer-specific survival
- Quality-of-life (QoL)
- Acute and late toxicity
Treatment

Arm control

External 3-dimentional conformal radiotherapy aiming at homogeneous irradiation of the affected vertebra

Each centre has to choose one fractionation protocol and use this one consistently within this study

- 20 Gy in 5 fractions
- 30 Gy in 10 fractions
Treatment

Arm experimental

Image-guided hypofractionated SBRT using SIB to escalate radiation dose in the tumor mass (high-dose target volume) while maintaining a conventional dose in the un-involved segments of the affected vertebra (conventional-dose target volume).

In the case of no epidural involvement:
40 Gy and 20 Gy in 5 fractions --> 60Gy EQD2/10

In the case epidural involvement:
48.5 Gy and 30 Gy in 10 fractions --> 60Gy EQD2/10

- Fractionation adapted to epidural involvement
Target volume concept

High-dose TV  Low-dose TV
# Status update

<table>
<thead>
<tr>
<th>Study Sites approved by EC</th>
<th>Sites open for recruitment</th>
<th>Patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Sites with signed CTA</th>
<th>Swiss centers</th>
<th>Centers abroad</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Sides with interest</th>
<th>Swiss centers</th>
<th>Centers abroad</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>18</td>
<td>25</td>
</tr>
</tbody>
</table>
Unique features of the DOSIS trial

Inclusion criteria:

- Strict patient selection with longer-term OS
- Restriction to high risk patients with mass-like metastases
- Inclusion of epidural involvement

Treatment characteristics:

- Fractionated SBRT approach
- Fractionation adapted to epidural involvement
- SIB Concept
- Elective vertebral irradiation