Dose-intensified Image-guided Fractionated Stereotactic Body Radiation Therapy for Painful Spinal Metastases (DOSIS) versus Conventional Radiation Therapy:

a Phase II Randomised Controlled Trial

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DOSIS: a multi-center phase II trial

Prospective phase II trial

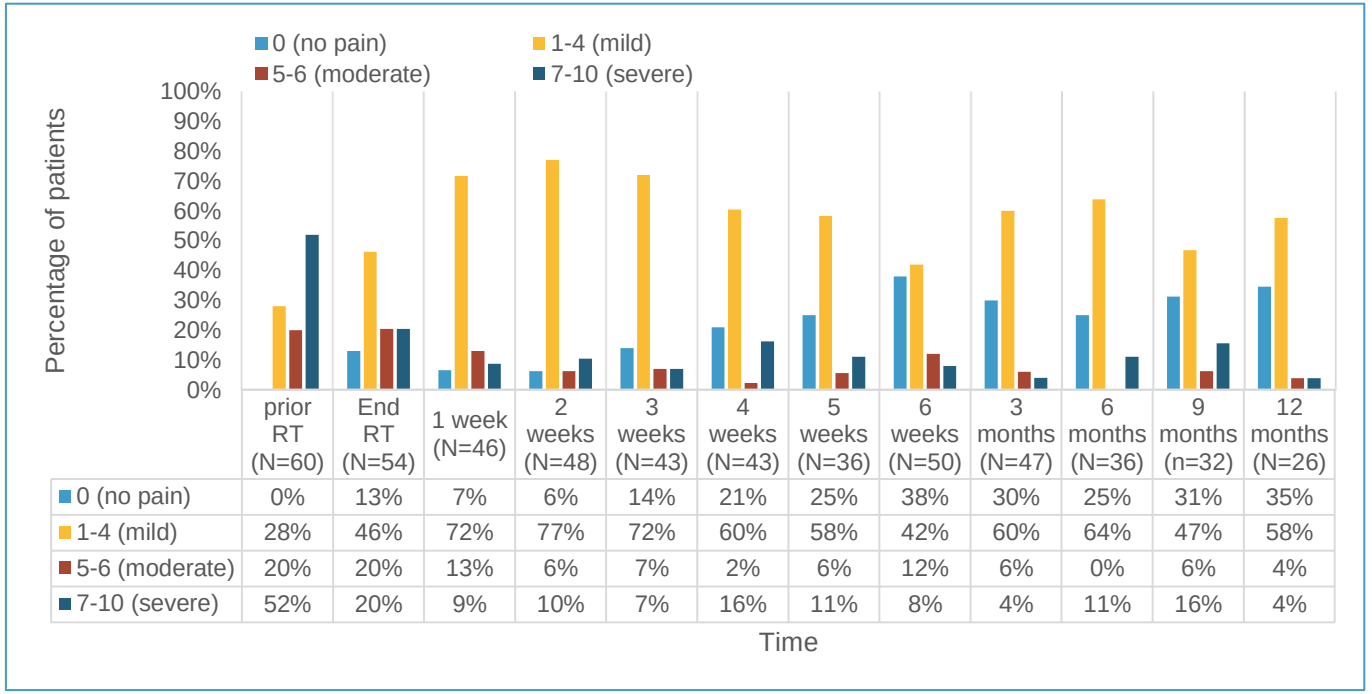
- 54 patients with 60 vertebral metastases
- No exclusion of patients with epidural disease
- Fractionated SBRT
- SBRT using SIB concept:
  - 5 x 4 / 7Gy
  - 10 x 3 / 4.85Gy
- Selection of patients with long OS expectancy

DOSIS phase II trial – single arm trial

Guckenberger unpublished data

N=54 patients
N=60 spine mets

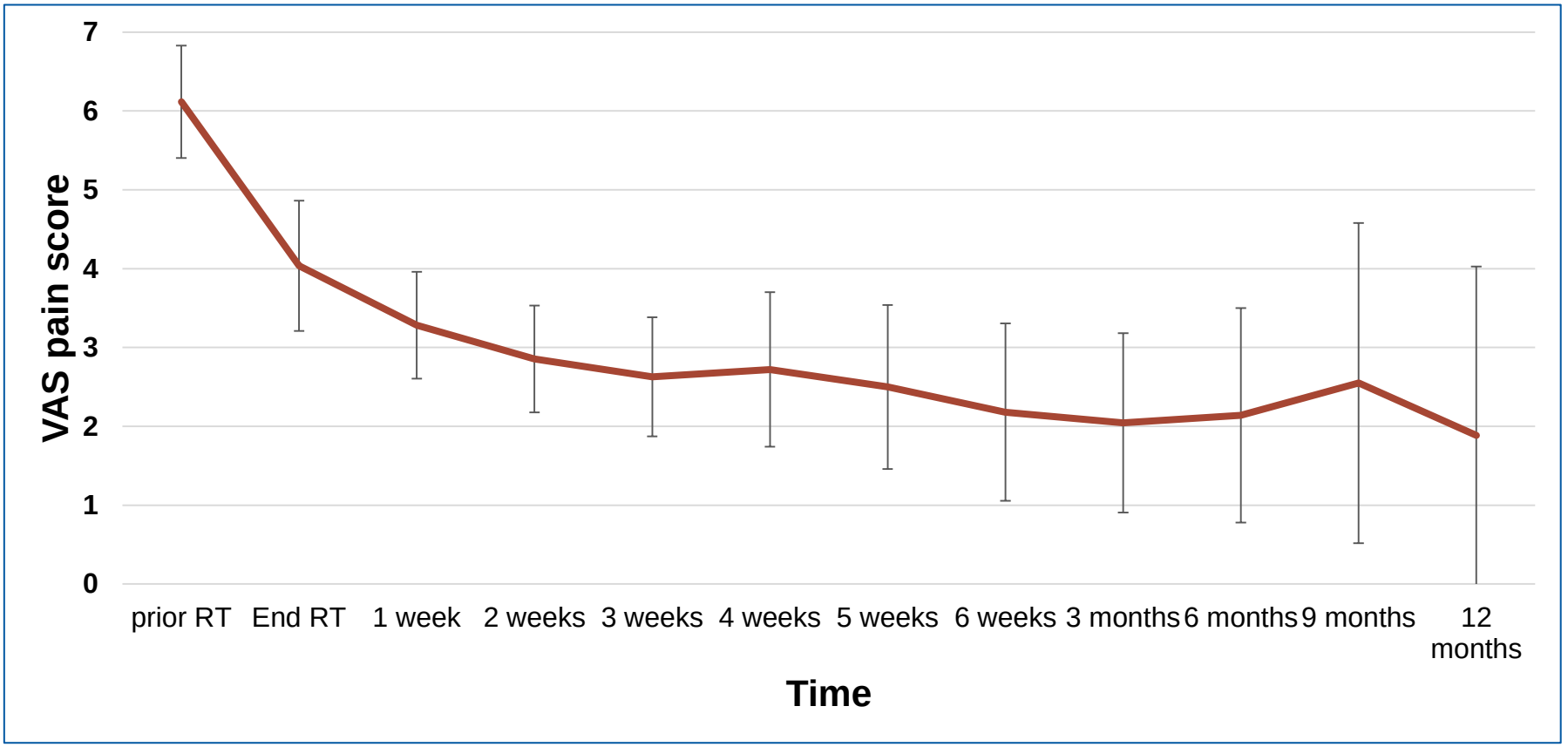
SBRT:
5 x 7Gy
or
10 x 4.85Gy



	prior RT (N=60)	End RT (N=54)	1 week (N=46)	2 weeks (N=48)	3 weeks (N=43)	4 weeks (N=43)	5 weeks (N=36)	6 weeks (N=50)	3 months (N=47)	6 months (N=36)	9 months (n=32)	12 months (N=26)
0 (no pain)	0%	13%	7%	6%	14%	21%	25%	38%	30%	25%	31%	35%
1-4 (mild)	28%	46%	72%	77%	72%	60%	58%	42%	60%	64%	47%	58%
5-6 (moderate)	20%	20%	13%	6%	7%	2%	6%	12%	6%	0%	6%	4%
7-10 (severe)	52%	20%	9%	10%	7%	16%	11%	8%	4%	11%	16%	4%

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

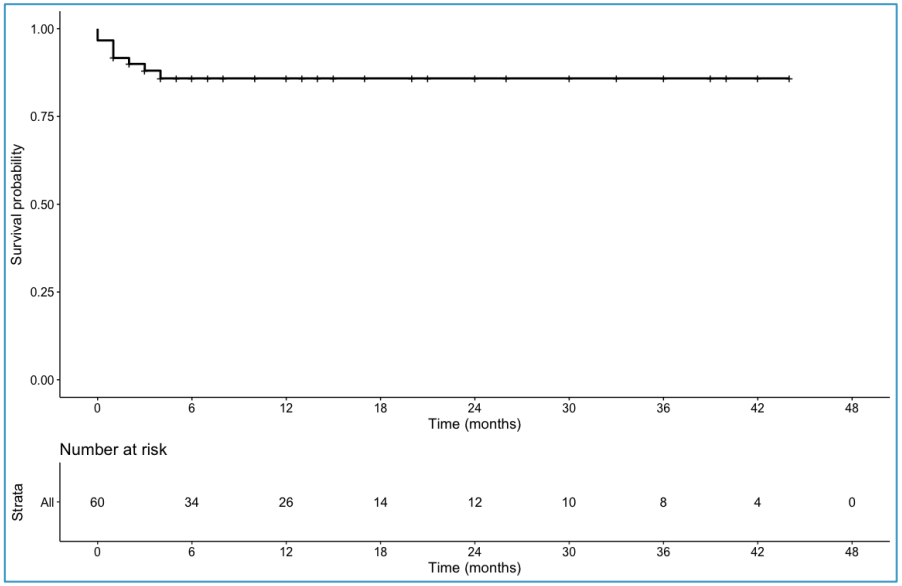
DOSIS phase II trial – single arm trial



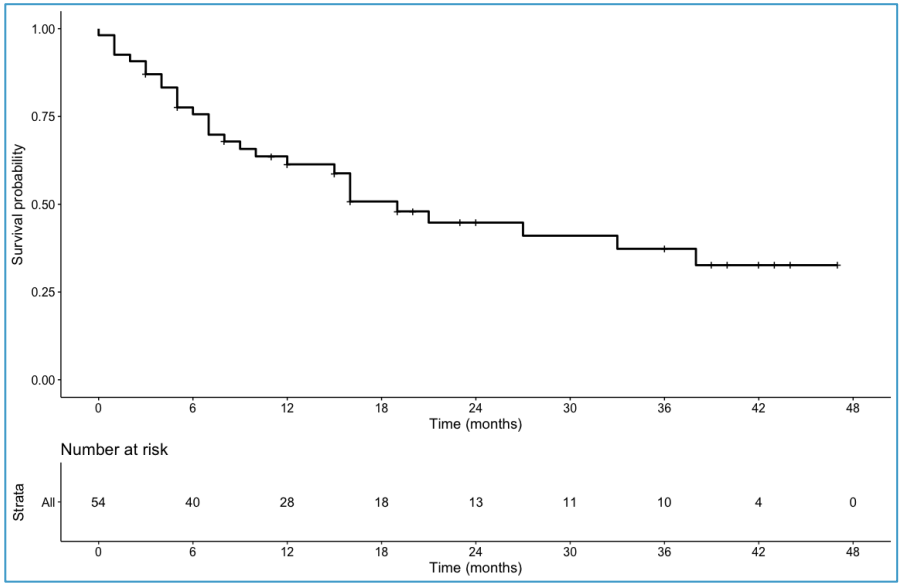
- Rapid, deep and durable pain reduction

DOSIS phase II trial – single arm trial

Local metastases control

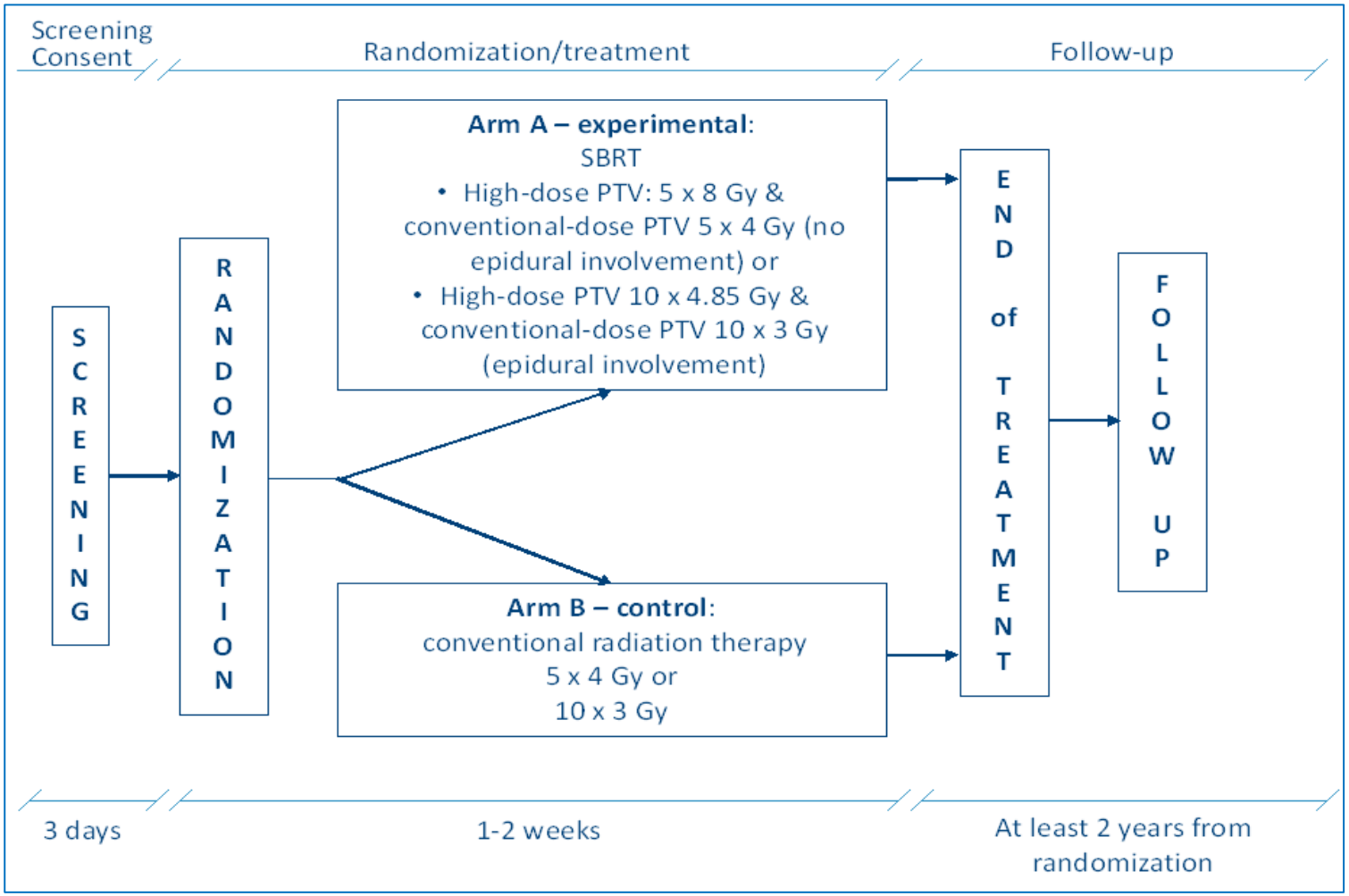


Overall survival



- However: Six (11%) and 8 (15%) patients developed progressive or new vertebral compression fractures

DOSIS RCT

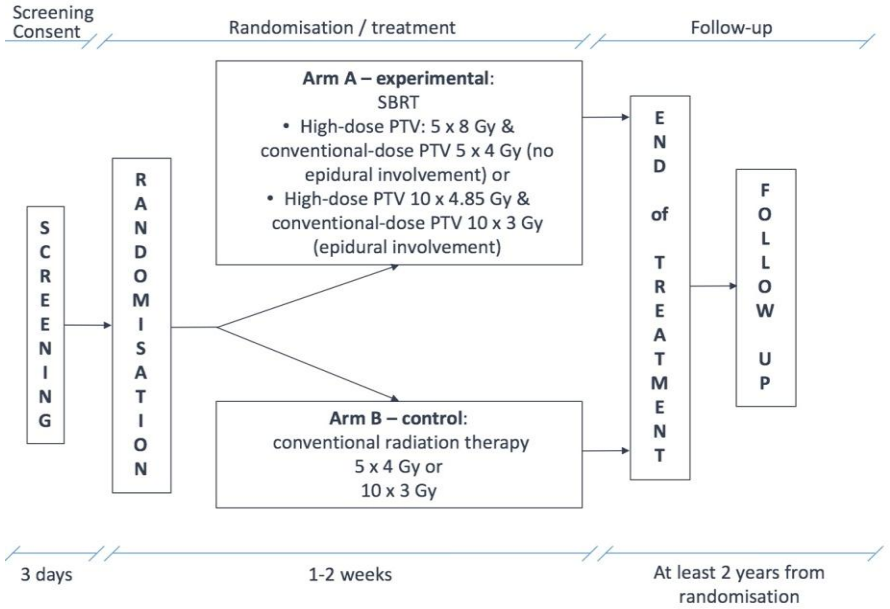

Screening
Consent
Randomization/treatment
Follow-up
SCREENING
RANDOMIZATION
Arm A – experimental:
SBRT
• High-dose PTV: 5 x 8 Gy & conventional-dose PTV 5 x 4 Gy (no epidural involvement) or
• High-dose PTV 10 x 4.85 Gy & conventional-dose PTV 10 x 3 Gy (epidural involvement)
Arm B – control:
conventional radiation therapy
5 x 4 Gy or
10 x 3 Gy
END of TREATMENT
FOLLOW UP
3 days
1-2 weeks
At least 2 years from randomization

Protocol Version 3.0 – Amendment 1

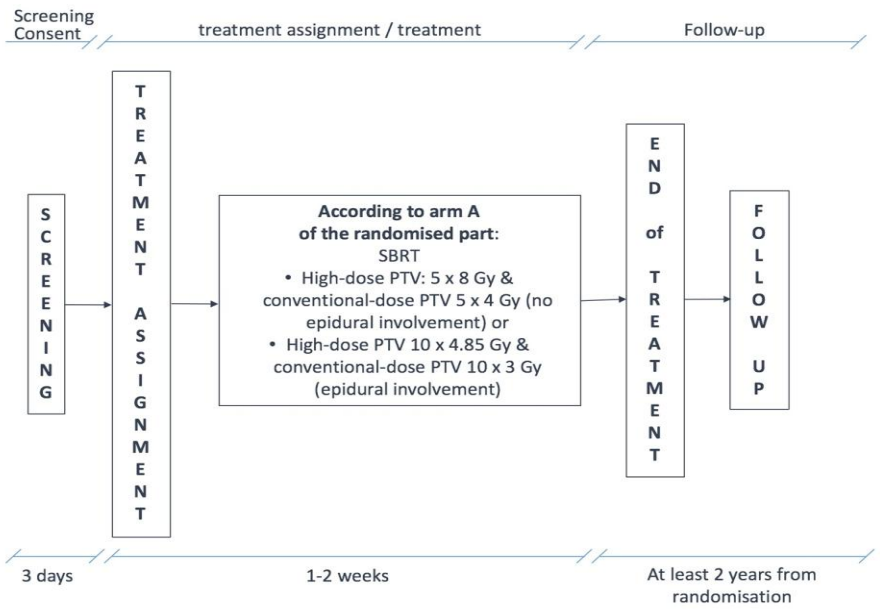
- Introduction of a non-randomized part
  - Oligometastatic disease (unwilling to be randomized), purely osteoblastic metastases, without pain
  - Treatment according to arm A of the randomized part (5 x 8/4 Gy or 10 x 4.85/3 Gy)

- 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~~)

Protocol Version 3.0 – Amendment 1



Randomized part



Non-randomized part

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**

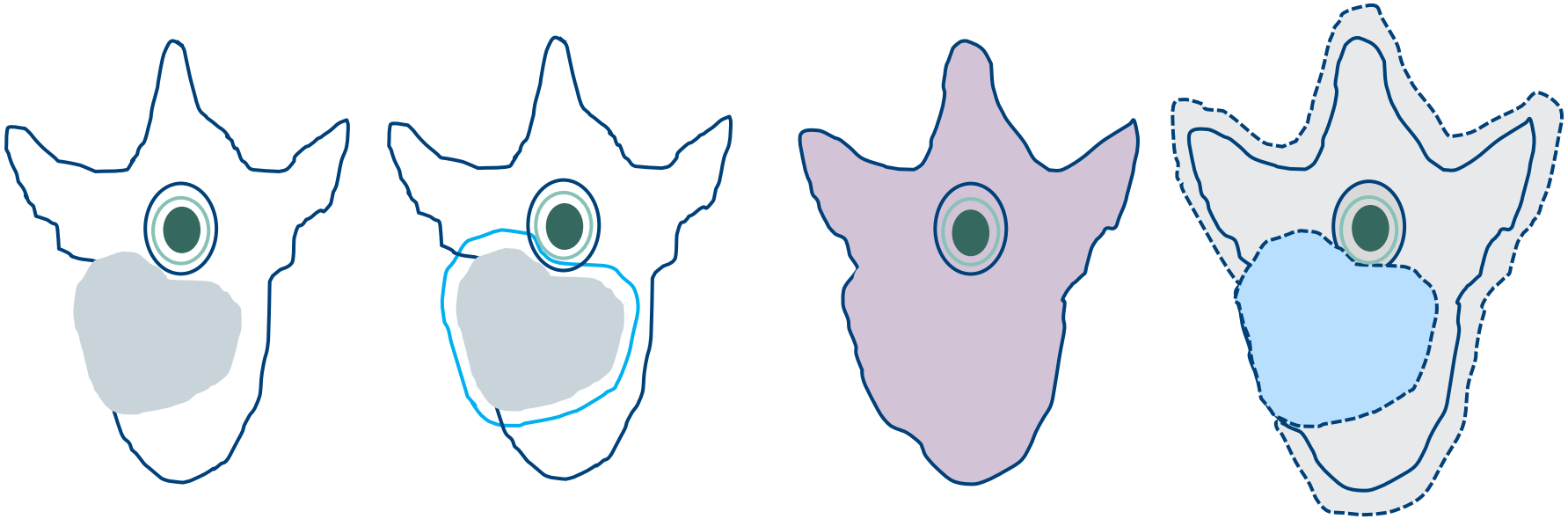
In the case epidural involvement:
48.5 Gy and 30 Gy in 10 fractions **-> 60Gy EQD2/10**

➢ Fractionation adapted to epidural involvement

Target volume concept

High-dose TV

Low-dose TV



Status update

Study Sites approved by EC	Sites open for recruitment	Patients enrolled
6	3	4

Study Sites with signed CTA		
Swiss centers	Centers abroad	Total
7	4	11

Study Sides with interest		
Swiss centers	Centers abroad	Total
7	18	25

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