



Original Article



Impact of target volume and dose concepts on the outcomes of prostate cancer patients treated with stereotactic body radiotherapy for spinal metastases – a European multicenter cohort study

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ABSTRACT

Background and purpose: The importance of metastasis-directed radiotherapy is increasing in the management of oligometastatic prostate cancer. We evaluated different target volume and dose concepts for stereotactic body radiotherapy (SBRT) of spine bone metastases (BoM) from prostate cancer in a large European cohort.

Material and methods: Data of prostate cancer patients receiving SBRT for spine BoM between 2010 and 2024 at 19 European cancer centers were retrospectively collected. Treatment volumes and dose concepts were analyzed regarding their impact on overall survival (OS), freedom from local recurrence (FFLR), biochemical recurrence-free survival (BRFS), and progression-free survival (PFS).

Results: With a median follow-up of 25.1 months (range: 1.4–77.2), 213 patients with 283 spine BoM were evaluated. 1-/3-year PFS with simultaneously integrated boost (SIB) were 85.7 %/73.9 % (BED_4 [Biologically effective dose with α/β -ratio = 4 Gy] ≥ 100 Gy) and for non-SIB concepts 81.2 %/45.5 % ($BED_4 \geq 100$ Gy), respectively. 1-/3-year BRFS for SIB-treated BoM amounted to 81.7 %/68.4 % ($BED_4 \geq 100$ Gy) and for non-SIB 78.3 %/43.6 % ($BED_4 \geq 100$ Gy). OS was not significantly different for the evaluated dose and target volume concepts. For FFLR a significant difference was observed favoring $BED_4 \geq 100$ Gy. In multivariable analysis, following factors were positively associated with both PFS and BRFS: BED_4 for GTV_{mean} dose and SIB concept. Adverse events were very low, with fracture rates of 2.2 %.

Conclusion: This multicenter cohort analysis showed that SBRT of spine BoM from prostate cancer is an effective and well-tolerated treatment. Both BED and usage of a SIB concept were associated with improved PFS and BRFS. Prospective studies are needed to confirm these findings and further standardize SBRT concepts.

Introduction

Globally, prostate cancer ranks as the second most prevalent cancer among men [1]. The increasing detection of metastatic disease at diagnosis is primarily attributable to the enhanced efficacy of screening and imaging [2]. Prostate cancer metastases have a predilection for the skeletal system, mainly presenting as osteoblastic lesions [3]. Bone metastases (BoM) are a significant cause of skeletal-related events (SREs), with approximately one-third of them being complicated lesions, resulting in pain, pathological fractures, and neurological impairments [4]. In addition to systemic treatments, palliative radiotherapy constitutes a guideline-recommended treatment for symptomatic BoM, with effective pain relief and stabilization [5,6]. Recent clinical trials revealed the clinical benefit of stereotactic body radiotherapy (SBRT) regarding local control, progression-free (PFS) and overall survival (OS), in selected cases also for oligometastatic disease [7–11]. These findings led to the publication of practice guidelines for bone SBRT [12–14]. Analysis of the STOMP/ORIOLE trials indicated a benefit of metastasis-directed therapy (MDT) over observation for patients with oligometastatic prostate carcinoma (OMPC) [15]. A recent meta-analysis revealed encouraging improvements in PFS by adding SBRT to systemic therapy for different OMPC states, with no excessive toxicities observed. However, the level of evidence was considered low or moderate, and OS comparisons remain inconclusive [16]. Also, the findings of the EXTEND and PCS 9 trials indicated a higher degree of efficacy for the combination of SBRT and androgen deprivation therapy (ADT)/systemic treatment in comparison to either systemic treatment alone or, as reported in the RADIOSA trial, SBRT alone [17–20]. The recent WOLVERINE meta-analysis demonstrated a borderline benefit even for OS [21].

SBRT enables the delivery of ablative doses to metastatic lesions with high precision, achieving superior and more durable pain control compared to conventional radiotherapy [22–24]. Nevertheless, significant uncertainties concerning the most appropriate choice between locally ablative and palliative bone radiotherapy, as well as treatment volume and dose concepts remain [12,25–28].

Target volume definition in spine SBRT is critical for treatment planning. Approaches range from contouring only the metastatic gross tumor volume (GTV) with small margins to account for setup uncertainties (expanded GTV concept), to encompassing adjacent osseous compartments or the entire involved vertebral body as a clinical target volume (CTV) [29–33]. There are two different concepts for compartmental treatments, either high-dose volumes for the BoM including the adjacent compartments (compartment concept), or high-dose volume covering only the BoM, with the entire vertebral body receiving a lower,

homogeneous dose as part of a simultaneous integrated boost (SIB concept) [34,35]. In Fig. 1, schematic dose distributions are presented to illustrate the aforementioned different target volume concepts. However, in clinical practice, considerable variability in treatment patterns is observed [36–38].

This heterogeneity extends to dose-fractionation regimes as well. International consensus guidelines recommend a prescribed dose exceeding $BED_{10} = 50$ Gy for local ablative SBRT of spine metastases, with variable fractionation schedules [12].

As SBRT becomes increasingly integrated into the multidisciplinary management of OMPC, continued efforts are needed to harmonize practice patterns with the best available evidence.

Thus, the objective of our European multicenter cohort study on SBRT for spine BoM from prostate cancer was to evaluate routinely used SBRT concepts regarding oncological outcomes and safety, depending on applied dose and target volume concepts.

Material and methods

Patient selection

As a project of the working group on radiosurgery and stereotactic radiotherapy of the German Society for Radiation Oncology (DEGRO), we performed a retrospective multicenter cohort analysis on SBRT of BoM. Individual clinical and treatment data of patients with OMPC receiving SBRT for spine BoM between 2010 and 2024 at 19 European cancer centers in Germany, Austria, Switzerland, and the Czech Republic were retrospectively collected and evaluated. The diagnosis of BoM was determined on the basis of radiographic findings revealed by computed tomography (CT), magnetic resonance imaging (MRI), prostate-specific membrane antigen positron emission tomography (PSMA PET/CT), or bone scintigraphy. According to the established European consensus criteria, the initial classification of oligometastatic disease was followed by further subclassification [39]. SBRT parameters, including target volumes, doses, and plan parameters according to the International Commission on Radiation Units and Measurements (ICRU) report 91, were analyzed [40–42]. Previous treatments, concomitant/sequential systemic therapies, and necessary salvage therapies after SBRT were recorded. Biologically effective dose (BED) was calculated with the formula $BED = n \times d \times (1 + d/(\alpha/\beta))$ with n = number of fractions, d = dose per fraction, based on an $\alpha/\beta = 10$ Gy (BED_{10}) as commonly used for tumor tissue and $\alpha/\beta = 4$ Gy (BED_4) for prostate cancer, assuming that BoM occur more frequently in high-grade prostate carcinomas [43]. BED_{10} of at least 48 Gy for the target volume

in a maximum of 10 fractions was requested as the minimal dose for bone SBRT.

This study was approved by the institutional ethics board (127/24-ek) and followed the STROBE guidelines for reporting observational studies (Supplementary Data 2) [44].

Response assessment

OS was calculated from the end of SBRT until death from any cause. PFS was defined as the time interval from completion of SBRT until death or the development of any type of imaging-confirmed cancer progression. Findings of routinely administered pre- and post-SBRT imaging examinations were analyzed retrospectively regarding local recurrence, and fractures, with local recurrence specified as imaging-confirmed progression. When patients received SBRT for multiple BoM, freedom from local recurrence (FFLR) analysis was conducted independently for each lesion. To calculate FFLR following SBRT, the occurrence of lesions was considered to be censored at the time of the most recent imaging. Given that imaging was not routinely performed during follow-up for OMPC with stable prostate-specific antigen (PSA) levels, participating centers conducted a secondary assessment of rising PSA levels after SBRT to determine biochemical recurrence and thus calculate biochemical recurrence-free survival (BRFS). Both acute (≤ 90 days post SBRT) and chronic (> 90 days post SBRT) treatment-related adverse events were documented according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [45].

Statistical analysis

All analyses were performed in Python 3.12.7 using custom scripts. Data preparation and preprocessing relied on pandas (v2.2.3) and NumPy (v2.2.1); statistical inference and survival modeling used SciPy (v1.14.1) and lifelines (v0.30.0); visualization was carried out with Matplotlib (v3.10.0). Descriptive analyses of patient demographics and clinical characteristics were performed. Median values were given as either the 95 % range or the range of the provided values, where applicable. Subgroup analyses compared cohorts defined by treatment technique and mean BED₄/BED₁₀ delivered to the GTV. The BED₄/BED₁₀ threshold for subgrouping was explored iteratively by increasing the cutoff in 1 Gy steps and recording log-rank test p-values for PFS.

Time-to-event outcomes were analyzed with Kaplan–Meier estimators and multivariable Cox proportional hazards models. Patient age, target volume concept, GTV_{mean} BED₄, and tumor volume were preselected as covariates in the Cox proportional hazards model. The proportional hazards assumption test was non-significant. Multivariable models were fitted on complete cases only. Model assumptions were assessed at $\alpha = 0.05$. Kaplan–Meier curves were compared across subgroups using log-rank tests, and survival probabilities at prespecified time points were interpolated and reported with 95 %-confidence intervals (95 %-CI).

Results

Data of 283 lesions from 213 patients treated with bone SBRT for spine BoM from OMPC were included. Detailed patient characteristics are presented in Table 1.

Target volume definition was based on multimodal imaging with PET-CT (235/283; 83 %) and/or MRI (94/283; 33 %) according to institutional standards of each center and national recommendations [46].

Target volumes were predominantly defined with the SIB concept (135/260 evaluable lesions; 51.9 %). The expanded GTV concept (BoM plus safety margins) was used in 38.5 % (100/260) of spine lesions. The minority of 25/260 spine BoM (9.6 %) was delineated as the metastasis plus adjacent osseous compartments and a small safety margin to PTV (compartment concept).

Prescribed dose for the SIB (high-dose PTV) was median 44.0 Gy (range: 35.0 Gy–48.5 Gy) in median 10 (range: 3–10) fractions, and for the expanded GTV concept 35.0 Gy (range: 18.0 Gy–40.0 Gy) in median 5 (range: 1–10) fractions, and for the compartment concept 27.0 Gy (range: 22.5 Gy–34.0 Gy) in median 3 (range: 3–5) fractions. Dose-volume parameters for the target volume and treatment parameters are shown in Table 2.

Concomitant/sequential ADT was administered in 167 of 283 lesions (59 %), whereas 101 of 283 lesions (36 %) received no additional therapy. ADT was evenly distributed among SIB (ADT: 83/283 lesions; 29.3 %; no ADT: 49/283; 17.3 %) and non-SIB (ADT: 84/283; 29.7 %; no ADT: 52/283; 18.4 %) groups.

Median follow-up time was 25.1 months (range: 1.4–77.2). A total of 30 patients died, and 19 local recurrences were reported during the follow-up period.

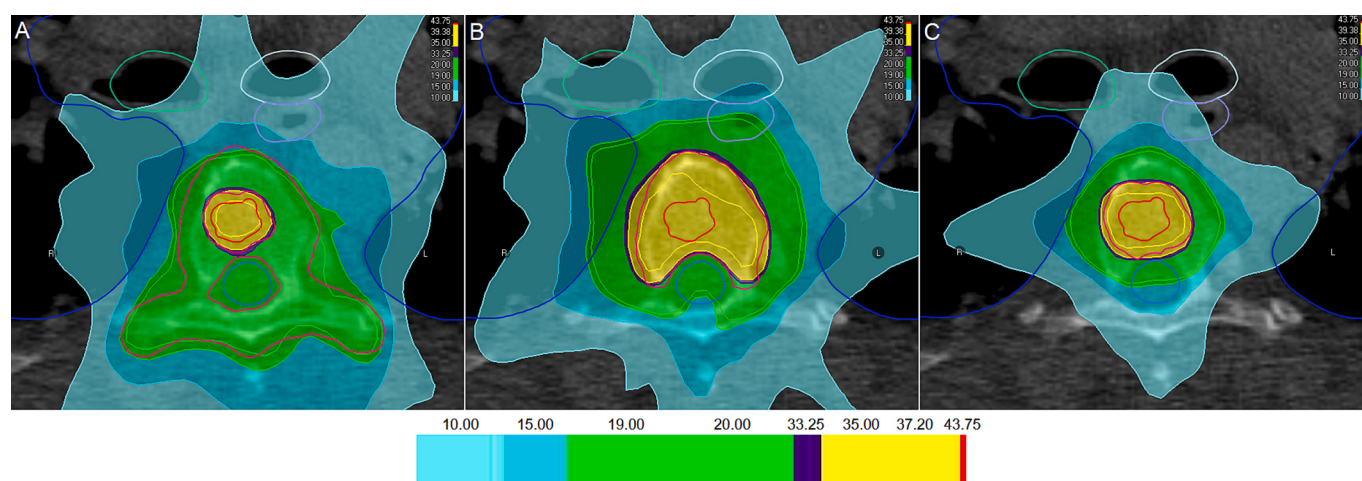


Fig. 1. Schematic dose distributions for the three different target volume concepts A) Simultaneous integrated boost (SIB) with isodoses. GTV (red) includes the metastasis plus a 2 mm margin for the high-dose planning target volume (PTV_{SIB} in pink color), and the conventional-dose PTV (outer pink contour) covers the entire affected vertebral body (CTV in orange) with a small setup safety margin in the same treatment plan. PTV_{SIB}: 5x7Gy prescribed to 80 % (inner yellow isodose), PTV_{conventional dose}: 5x4Gy (inner green isodose). B) Compartment concept. GTV (red) includes the metastasis, CTV (orange) encompassing adjacent osseous compartments plus small safety margin to the PTV (pink). PTV: 5x7Gy prescribed to 80 % (inner yellow isodose). C) Expanded GTV concept. GTV (red) includes the metastasis, CTV (orange) includes GTV with margin (2–5 mm) plus small safety margin to the PTV (pink). PTV: 5x7Gy prescribed to 80 % (inner yellow isodose). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Patient characteristics.

Variable	
<i>Patients (n = total)</i>	213
<i>Bone metastases spine (n = total)</i>	283
<i>Age</i>	
Median in years (range)	72 (48–87)
<i>Karnofsky-Index before SBRT</i>	
Median in % (95 % range)	100 (80–100)
<i>Initial therapy primary tumor (multiple treatment modalities possible)</i>	
Surgery	125 (58.7 %)
Radiotherapy	59 (27.7 %)
Systemic Therapy	32 (15.0 %)
Other	20 (9.4 %)
No information available	47 (16.6 %)
<i>Bone metastases</i>	
Time between initial diagnosis and bone metastasis, median (months)	53.6 (–4.4–177.2)
Synchronous treatment	56
Metachronous treatment	223
<i>Classification according ESTRO/EORTC [39]</i>	
Metachronous oligoprogression	65
Metachronous oligorecurrence	93
Repeat oligoprogression	16
Repeat oligorecurrence	9
Induced oligoprogression	9
Induced oligorecurrence	2
No information available	89
<i>Characteristics of bone metastases</i>	
Radiological osteolytic	45
Radiological osteoblastic	157
Mixed osteolytic/ osteoblastic	10
Soft tissue infiltration yes / no	6 / 233
Spinal canal infiltration yes / no	0 / 226
Symptomatic before SBRT yes / no	33 / 100
PSA before SBRT in ng/ml (95 % range)	7.27 (0.24–87.22)
<i>Systemic therapy</i>	
ADT concomitant / sequential	89 / 78
Cytotoxic chemotherapy	0
No systemic therapy	101
No information available	15
<i>Imaging before treatment planning:</i>	
Diagnostic CT	18
MRI	94
PET (including PSMA-PET)	235
Scintigraphy	26
No information available	9
<i>Number of treated bone metastases per patient median (range)</i>	1 (1–8)
<i>Treatment technique</i>	
LINAC (Photon FF / FFF / unknown)	106 / 112 / 43
Robotic radiosurgery (CyberKnife)	22

Abbreviations: CT: Computed Tomography, MRI: Magnetic Resonance Imaging, PET: Positron Emission Tomography, PSMA: Prostate-Specific Membrane Antigen, LINAC: Linear Accelerator, FF(F): Flattening-Filter(–Free), SBRT: Stereotactic Body Radiotherapy, PSA: Prostate-Specific Antigen, ADT: androgen deprivation therapy.

Oncological outcomes were analyzed across subgroups by target volume concept (SIB vs. non-SIB) and dose concept based on BED₄/BED₁₀ for GTV_{mean} dose.

Stratification of FFLR by target volume concept revealed no significant difference in patients treated with SIB or non-SIB. Patients receiving BED₄ ≥ 100 Gy had significantly improved FFLR compared

Table 2
Dose volume parameters according to ICRU91 Parameters presented according to the three treatment concepts.

	SIB concept	Expanded GTV concept	Compartment concept
Number of treatments	135	100	25
Mean target volume (GTV) in cc (range)	2.9 (0.4–17.8)	2.5 (0.5–27.0)	3.9 (0.7–13.7)
Prescribed dose PTV, median in Gy (range)	44.0 (35.0–48.5)	35.0 (18.0–40.0)	27.0 (22.5–34.0)
Number of fractions, median (range)	10 (3–10)	5 (1–10)	3 (3–5)
Median BED ₄ PTV (prescribed dose) in Gy (range)	107.3 (80.0–120.0)	96.2 (71.8–120.0)	87.8 (64.7–96.2)
Median BED ₁₀ PTV (prescribed dose) in Gy (range)	72.0 (56.0–72.0)	59.5 (42.6–72.0)	51.3 (39.4–59.5)
Median PTV D _{98%} in Gy (range)	39.5 (29.0–47.8)	30.0 (15.9–39.9)	25.7 (21.5–30.1)
Median PTV D _{2%} in Gy (range)	49.4 (35.8–57.1)	36.0 (22.0–49.9)	32.2 (27.3–42.6)
Median GTV _{mean} in Gy (range)	46.7 (34.8–53.4)	34.6 (22.0–49.2)	29.1 (25.7–41.3)
Median BED ₄ GTV _{mean} in Gy (range)	107.4 (80.0–152.6)	104.6 (71.7–171.3)	99.7 (80.9–128.1)
Median BED ₁₀ GTV _{mean} in Gy (range)	72.0 (55.8–91.1)	60.1 (46.3–89.8)	57.4 (47.8–75.6)
Median BED ₄ PTV D _{2%} in Gy (range)	114.2 (82.7–170.7)	112.2 (75.4–174.3)	118.6 (89.5–136.5)
Median BED ₁₀ PTV D _{2%} in Gy (range)	75.7 (57.6–97.8)	64.3 (48.2–99.6)	66.8 (52.2–79.7)

Abbreviations: SIB: Simultaneous Integrated Boost, GTV: Gross Tumor Volume, PTV: Planning Target Volume, BED: Biological Effective Dose.

with those treated with BED₄ < 100 Gy ($p = 0.02$). In patients with BED₄ ≥ 100 Gy, 1-/3-year FFLR was 97.8 % (95 %-CI: 85.3 %-99.7 %)/90.3 % (95 %-CI: 60.5 %-97.9 %) for SIB and 97.7 % (95 %-CI: 84.6 %-99.7 %)/93.8 % (95 %-CI: 76.3 %-98.5 %) for non-SIB (supplementary figure 1).

PFS was positively associated with using a SIB concept compared to non-SIB concepts ($p < 0.002$). Stratification by BED revealed that BED₄ ≥ 100 Gy as well as BED₁₀ ≥ 61 Gy were significantly associated with improved PFS compared to lower BED ($p < 0.001$). In the BED₄ ≥ 100 Gy group, a SIB concept was linked to improved PFS compared to non-SIB ($p = 0.012$). The SIB concept reached 1-/3-year PFS of 85.7 % (95 %-CI: 70.7 %-93.3 %)/73.9 % (95 %-CI: 56.5 %-85.2 %) compared to 81.2 % (95 %-CI: 67.0 %-89.8 %)/45.5 % (95 %-CI: 29.1 %-60.5 %) for non-SIB (Figs. 2 and 3, supplementary Fig. 2).

For patients with BED₄ < 100 Gy, BRFS was 73.7 % at 1 year (95 %-CI: 44.1 %-89.2 %) for SIB and 53.7 % (95 %-CI: 35.0 %-69.2 %) for non-SIB. The 3-year BRFS in this group decreased to 54.6 % (95 %-CI: 23.8 %-77.4 %) and 0 % (95 %-CI: 0 %-0%). BED₄ ≥ 100 Gy led to a 1-/3-year BRFS of 81.7 % (95 %-CI: 65.1 %-90.9 %)/68.4 % (95 %-CI: 49.7 %-81.3 %) in the SIB group and 78.3 % (95 %-CI: 63.3 %-87.7 %)/43.6 % (95 %-CI: 23.0 %-62.5 %) in the non-SIB group, respectively. Considering only the administered dose, a significantly better BRFS was shown for BED₄ ≥ 100 Gy compared to BED₄ < 100 Gy ($p < 0.001$). In patients treated with BED₄ < 100 Gy, SIB resulted in improved BRFS compared to non-SIB ($p = 0.001$) (Figs. 2 and 3, supplementary Fig. 2). Due to the small sample size of some subgroups, wide confidence intervals were evident, notably in Fig. 3.

Regarding additional ADT, we observed a positive effect on BRFS. Especially in patients with a lower BED₄ < 100 Gy administration of ADT was positively associated with BRFS ($p = 0.01$), while no significant difference was detected for BED₄ ≥ 100 Gy (supplementary Fig. 3).

There was no significant difference for OS, depending on BED or target volume concept. For BED₄ < 100 Gy, 1-/3-year OS reached 100 %

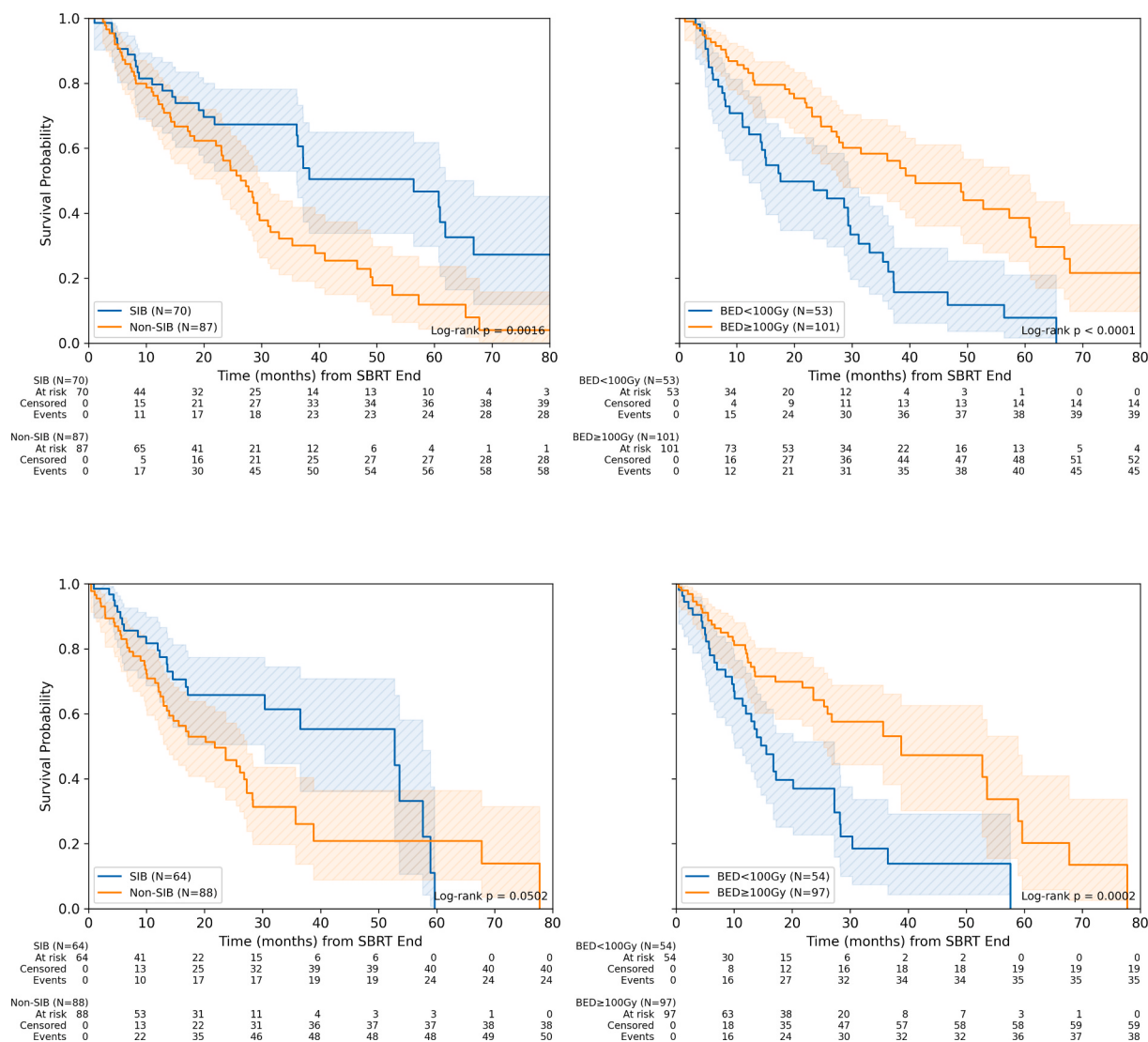


Fig. 2. Oncological outcome depending on treatment concept for SBRT of spine bone metastasis A) Comparison of PFS for simultaneously integrated boost (SIB) concept vs. non-SIB concepts B) Comparison of PFS depending on the BED₄ ($\alpha/\beta = 4$ Gy) in gross tumor volume (GTV_{mean}) C) Comparison of BRFS for SIB vs. non-SIB concepts D) Comparison of BRFS depending on the BED₄ in GTV_{mean}.

(95 %-CI: 100.0 %-100.0 %)/81.5 % (95 %-CI: 43.5 %-95.1 %) for SIB and 94.9 % (95 %-CI: 80.9 %-98.7 %)/91.8 % (95 %-CI: 76.5 %-97.3 %) for non-SIB, respectively. For BED₄ ≥ 100 Gy, 1-year OS was 96.1 % (95 %-CI: 85.2 %-99.0 %) for SIB and 98.1 % (95 %-CI: 87.6 %-99.7 %) for non-SIB, whereas 3-year OS amounted to 79.1 % (95 %-CI: 59.6 %-90.0 %) for SIB and 87.8 % (95 %-CI: 68.3 %-95.7 %) for non-SIB (supplementary Fig. 4).

In multivariable analysis, higher age was associated with worse OS (HR [hazard ratio] 1.09; 95 %-CI, 1.02–1.17; $p = 0.01$). A higher BED₄ GTV_{mean} was associated with improved PFS (HR 0.99; 95 %-CI: 0.98–0.99, $p < 0.01$) and BRFS (HR 0.98; 95 %-CI: 0.97–0.99, $p < 0.001$). Usage of a SIB concept was linked to improved PFS (HR 0.42; 95 %-CI: 0.26–0.69, $p < 0.001$). Additional administration of ADT was associated with improved BRFS (HR 0.51; 95 %-CI: 0.31–0.83, $p < 0.01$). Details are shown in Table 3.

The overall rate of adverse events was low (20.8 %, 59/283), predominantly grade 1–2 events, with fatigue grade 1 being most frequent (8.1 %, 23/283). Only 0.8 % grade 3 adverse events (2/283, 1x pain and 1x dysphagia) and no grade 4 or 5 adverse events were reported (supplementary Table 1). Fracture rates related to SBRT, without tumor progression, were 0.4 % (1/283, SIB concept) for acute and 1.8 % (5/

283: 3x compartment concept, 2x expanded GTV concept) for delayed fractures.

Discussion

To the best of our knowledge, this is the first large multicenter real-world cohort analysis investigating the impact of different treatment concepts of SBRT for spine BoM in patients with prostate cancer with a particular focus on the efficacy and safety of commonly used European practice patterns.

We found that escalation of GTV_{mean} dose to a BED₄ ≥ 100 Gy was associated with significantly improved PFS and BRFS. Additionally, our data suggest that SIB concept in our retrospective cohort had an impact on PFS and BRFS. No dependency was observed regarding OS, irrespective of target volume or dose concept. The high efficacy was accompanied by excellent tolerability and favorable safety profile with especially low fracture rates.

These findings underline the importance of high BED even for SBRT of spine BoM of prostate carcinoma, as has already been demonstrated for other metastases and primary tumors [47–51]. Our results also augment the mounting evidence that treating metastatic lesions with

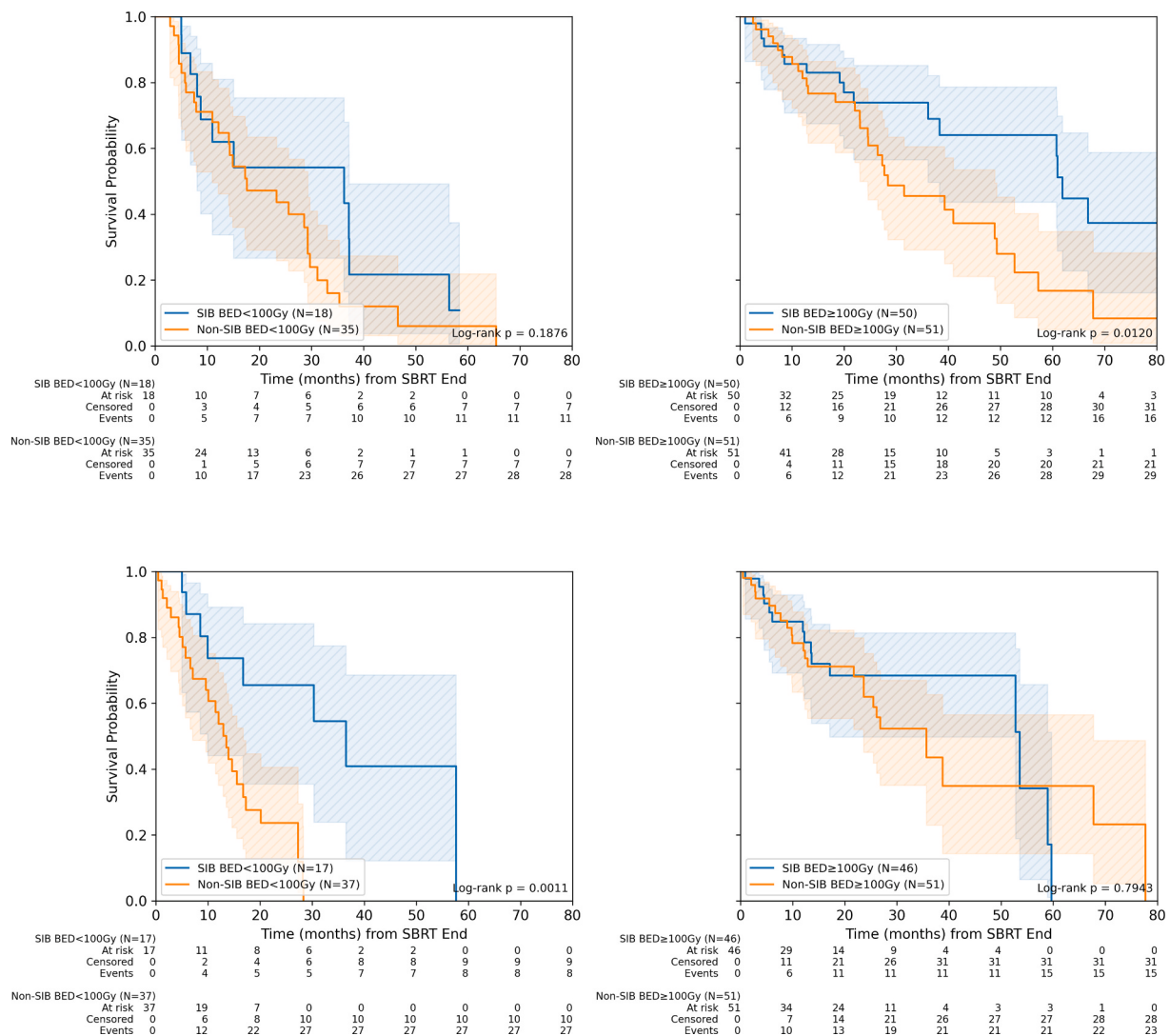


Fig. 3. Comparison of oncological outcome depending on BED₄ for different target volume concepts A) PFS for SIB vs non-SIB concept for BED₄ < 100 Gy and B) for BED₄ ≥ 100 Gy C) BRFS for SIB vs non-SIB concept for BED₄ < 100 Gy and D) for BED₄ ≥ 100 Gy.

SBRT results in a prolonged PFS in patients with OMPC [16,52,53]. A recent systematic review in OMPC reported pooled OS rates of 90.6 % and 80.1 %, and pooled PFS rates of 52.7 % and 28.4 % at 2 and 4 years, respectively [54]. In our retrospective cohort, higher BED₄ ≥ 100 Gy was associated with improved PFS, and within this high-dose-group, SIB was significantly associated with an improvement of PFS (1-/3-year: 85.7 %/ 73.9 %). PFS was worse in patients treated with BED₄ < 100 Gy, whereas the target volume concept itself did not influence PFS within this subgroup. However, underreporting of local recurrence or distant progression is a concern, as patients with OMPC often do not undergo regular imaging in the absence of PSA elevation.

Although FFLR was excellent, PFS and BRFS decreased during follow-up period, underlining the systemic nature of metastatic disease, and the need for systemic therapies [19,55]. Approximately 60 % of BoM in our cohort were treated with additional ADT, which was associated with an improvement in BRFS in the multivariable analysis. In patients who had been treated with a lower BED₄ < 100 Gy, the addition of ADT was associated with a positive effect on BRFS. At a BED₄ ≥ 100 Gy, no significant difference was observed with ADT in terms of either PFS or BRFS. In the PCS 9 trial, the addition of MDT to standard systemic therapy (ADT and enzalutamide) for patients with OMPC also improved PFS and prolonged the interval to the next line of systemic therapy [20]. As demonstrated by the EXTEND trial, the combination of MDT and ADT

improves PFS and even causes stronger activation of the systemic immune system, represented by T-cell receptor expansion and contraction [19]. This might also partly contribute to the positive effect observed in our study regarding the SIB concept with two different dose levels and the combination with systemic therapies, thus emphasizing the need for further improvements of systemic therapies as well as integration of standardized SBRT concepts within multimodal treatments.

The optimal dose for SBRT of spinal BoM is still not clearly defined and may depend on treatment indication as well as localization and underlying histology. Also, it has been indicated by a recent meta-analysis that higher SBRT doses should be used for (non)-spinal BoM to improve local control. An increase of 1 Gy in BED₁₀ was associated with a 1 % decrease in the risk of local failure [56]. According to the European Society for Radiotherapy and Oncology (ESTRO) clinical practice guideline for spinal SBRT, for de novo spine metastases, high dose SBRT practice includes 1x20–24 Gy, 2x12Gy, 3x10Gy, and 5x7Gy (BED₁₀ ≥ 50 Gy₁₀) [12]. We observed a clear dose dependency for BoM of prostate cancer, demonstrating that an escalation of GTV_{mean} dose up to BED₄ ≥ 100 Gy was associated with improved PFS, BRFS, and FFLR. For FFLR, this could not be confirmed in the multivariable analysis, suggesting that the required dose value could also be even higher. In another retrospective single-institution series for SBRT (24–28 Gy in 2 fractions) of spine metastases from prostate cancer with quarterly radiographic

Table 3

Uni- and multivariable Cox proportional hazard regression analysis for overall survival, progression-free survival, biochemical recurrence-free survival and freedom from local recurrence.

Univariable	OS		PFS		BRFS		FFLR	
Variable	p	HR (95 %CI)	p	HR (95 %CI)	p	HR (95 %CI)	p	HR (95 %CI)
Age	0.08	1.03 (1.00–1.07)	0.80	1.00 (0.98–1.03)	0.07	1.03 (1.00–1.06)	0.26	1.04 (0.97–1.11)
GTV volume	0.56	1.01 (0.98–1.04)	0.17	1.01 (1.00–1.03)	0.65	1.00 (0.97–1.02)	0.33	1.02 (0.98–1.05)
BED ₄ GTV _{Mean}	<0.01	0.98 (0.97–0.99)	<0.001	0.99 (0.98–0.99)	<0.001	0.98 (0.97–0.99)	0.22	0.98 (0.95–1.01)
SIB concept	0.78	0.91 (0.52–1.64)	<0.001	0.51 (0.35–0.75)	0.01	0.59 (0.40–0.88)	0.66	0.81 (0.31–2.11)
ADT	0.80	0.93 (0.52–1.65)	0.18	0.79 (0.55–1.12)	<0.01	0.50 (0.33–0.77)	0.86	1.08 (0.43–2.74)
Multivariable								
Age	0.01	1.09 (1.02–1.17)	0.77	1.00 (0.98–1.03)	0.11	1.02 (0.99–1.05)	0.29	1.04 (0.97–1.12)
GTV volume	0.72	1.01 (0.97–1.04)	0.57	1.00 (0.99–1.02)	0.32	0.99 (0.97–1.01)	0.47	1.01 (0.98–1.04)
BED ₄ GTV _{Mean}	0.12	0.99 (0.97–1.00)	<0.01	0.99 (0.98–0.99)	<0.001	0.98 (0.97–0.99)	0.36	0.98 (0.95–1.02)
SIB concept	0.71	1.16 (0.52–2.60)	<0.001	0.42 (0.26–0.69)	0.02	0.60 (0.39–0.94)	0.72	1.23 (0.39–3.80)
ADT	0.73	1.21 (0.42–3.42)	0.25	0.77 (0.50–1.20)	<0.01	0.51 (0.31–0.83)	0.81	0.87 (0.30–2.56)

Abbreviations: OS: overall survival, PFS: progression-free survival, BRFS: biochemical recurrence-free survival, and FFLR: freedom from local recurrence, HR: hazard ratio, CI: confidence interval, BED: Biological Effective Dose, SIB: Simultaneous Integrated Boost, GTV: Gross Tumor Volume, ADT: androgen deprivation therapy.

follow-up, local 2-year control rates up to 95 % were reported with a cumulative fracture risk of 10 % [57].

Little is known about the correlation of target volume concept and oncological outcome of patients with spine BoM. In our large multicenter cohort, SIB concept seems to improve control rates, especially in high-BED settings. It allows dose escalation within the metastatic bone lesion, comparable to the expanded GTV concept. At the same time, it enables additional irradiation of potentially microscopic disease within the whole affected vertebra with a conventional dose, accompanied by reducing risk for skeletal-related events [34,35]. In a recent analysis of SIB concepts for spinal BoM, local control appeared to be influenced by histology. Prostate cancer metastases responded particularly well, which is consistent with the radiosensitivity of prostate lesions and the longer life expectancy of these patients [58]. Multivariable analysis of a further study indicated that non-prostate histologies were associated with higher hazard of local failure and additionally, baseline osteoporosis significantly increased the hazard of post-SBRT fractures [35]. Histology may also have influenced the excellent outcome parameters in our study.

The low fracture rate of 2.2 % observed in our cohort may be explained by the fact that BoM from prostate cancer are mainly osteoblastic and hence less susceptible to fractures [59]. Hypofractionation with median 5 (non-SIB) or 10 (SIB) fractions in our cohort, as well as the median patient age of 72 years, which is younger compared to previous studies, could be other possible reasons for the low rate of vertebral fractures. A large meta-analysis, combining data on spinal BoM from different primary cancers, found 9 % total vertebral fracture rate, with 1.7 % requiring surgical stabilization [60]. Chan et al. recently described a vertebral fracture rate of 8.4 % and 12.3 % at one and two years, respectively, for spine SBRT of BoM from different primary sites. Multivariable analysis revealed that a greater BED, baseline fracture, and increasing age were associated with a higher risk of fracture [61].

Due to its retrospective design, the current study has some limitations. The substantial number of 19 participating centers resulted in an increased number of cases and, consequently, an enhancement in the informative value of the analysis. However, this also led to greater variability in SBRT protocols and significant heterogeneity in follow-up procedures across institutions. The retrospective analysis was based on

chart review and clinician reports, which may have caused underreporting of events and missing data. In consideration of these potential limitations, this study focused on a specific subgroup characterized by a distinct primary diagnosis and metastasis location in the spine. This methodological decision was made with the objective of averting any potential distortion that might be occasioned by the heterogeneity of histological characteristics of different primary tumors. Nonetheless, discrepancies emerged with regard to treatment techniques, encompassing methodologies such as linear accelerator or robotic radiosurgery, dose prescription, and target or margin definition. Additionally, the reliance on radiological reports for the assessment of local recurrence and the variability in post-SBRT imaging frequency, as this is often guided by PSA kinetics rather than systematic imaging, could have led to a possible underestimation of local recurrences.

Notwithstanding these limitations of a retrospective study with corresponding heterogeneity, our large real-world cohort shows that SBRT of spine BoM from prostate cancer was an effective and well-tolerated treatment. Higher BED was associated with an improvement of PFS and BRFS. Additionally, our data suggest that the target volume concept could influence PFS and BRFS as well. Further prospective studies are needed to confirm these results and determine standardized SBRT concepts and clarify its impact on long-term clinical outcomes such as local control, adverse events, quality of life, and survival.

Data Availability

The dataset generated during the current study is available from the corresponding author on reasonable request.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

CRediT authorship contribution statement

Isabell Seiler: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Sebastian Schäfer:** Writing – review &

editing, Writing – original draft, Visualization, Validation, Software, Formal analysis, Data curation. **Camilla von Wachter**: Writing – review & editing, Investigation. **Panagiotis Balermipas**: Writing – review & editing, Investigation. **Marek Slavik**: Writing – review & editing, Investigation. **Petr Burkon**: Writing – review & editing, Investigation. **Johannes Meents**: Writing – review & editing, Investigation. **Lena Kästner**: Writing – review & editing, Investigation. **Fabian Lohaus**: Writing – review & editing, Investigation. **Jochen Willner**: Writing – review & editing, Investigation. **Anna Sabrina Schunn**: Writing – review & editing, Investigation. **Sophia Drabke**: Writing – review & editing, Investigation. **Kenneth Klischies**: Writing – review & editing, Investigation. **Olaf Wittenstein**: Writing – review & editing, Investigation. **Priska Bank**: Writing – review & editing, Investigation. **Richard Partl**: Writing – review & editing, Investigation. **Jörg-Andreas Müller**: Writing – review & editing, Investigation. **Ahmed Gawish**: Writing – review & editing, Investigation. **Arne Grün**: Writing – review & editing, Investigation. **Andrea Baehr**: Writing – review & editing, Investigation. **Maike Trommer**: Writing – review & editing, Investigation. **Andrea Glasmacher**: Writing – review & editing, Investigation. **Thomas Mader**: Writing – review & editing, Investigation. **Richard Holy**: Writing – review & editing, Investigation. **Yvonne Dzierma**: Writing – review & editing, Investigation. **Felix Ehret**: Writing – review & editing, Investigation. **Alexander Rühle**: Writing – review & editing, Project administration. **Matthias Guckenberger**: Writing – review & editing, Conceptualization. **Christos Moustakis**: Writing – review & editing, Project administration. **Thomas Brunner**: Writing – review & editing, Conceptualization. **Oliver Blanck**: Writing – review & editing, Conceptualization. **Judit Boda-Heggemann**: Writing – review & editing, Conceptualization. **Nils H. Nicolay**: Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Franziska Nägler**: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Ethics approval

This study was reviewed and approved by the local Ethics Committee (127/24-ek). Informed consent to participate in the study was not required. All methods used in this study were carried out in accordance with relevant guidelines and regulations.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2025.111276>.

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