research article

Dose-escalated radiotherapy with simultaneous integrated boost for bone metastases in selected patients with assumed favourable prognosis

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Background. Stereotactic body radiotherapy (SBRT) concepts for dose escalation are increasingly used for bone metastases in patients with oligometastatic or oligoprogressive disease. For metastases that are not suitable for SBRT-regimens, a treatment with 30/40 Gy with simultaneous integrated boost (SIB) in 10 fractions represents a possible regimen. The aim of this study was to investigate the feasibility of this concept and the acute and subacute toxicities.

Patients and methods. Clinical records for dose-escalated radiotherapy of all consecutive patients treated with this regimen were evaluated retrospectively (24 patients with 28 target volumes for oncologic outcomes and 25 patients with 29 target volumes for treatment feasibility and dose parameters analysis). Analysis of radiotherapy plans included size of target volumes and dosimetric parameter for target volumes and organs at risk (OAR). Acute and subacute toxicities were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) V4.0.

Results. The most common localization was the spine (71.4%). The most common histology was prostate cancer (45.8%). Oligometastatic or oligoprogressive disease was the indication for dose-escalated radiotherapy in 19/24 patients (79.2%). Treatment was feasible with all patients completing radiotherapy. Acute toxicity grade 1 was documented in 36.0% of the patients. During follow up, one patient underwent surgery due to bone instability. The 1-year local control and patient-related progression-free survival (PFS) were 90.0 ± 6.7% and 33.3 ± 11.6%, respectively.

Conclusions. Dose-escalated hypofractionated radiotherapy with simultaneous integrated boost for bone metastases resulted in good local control with limited acute toxicities. Only one patient required surgical intervention. The regimen represents an alternative to SBRT in selected patients.

Key words: radiotherapy; oligometastatic disease; oligoprogressive disease; bone metastases; hypofractionated radiotherapy; simultaneous integrated boost

Introduction

Bone metastases represent one of the most frequent metastatic sites in advanced malignant disease.[1-3] This site is associated with a wide range of symptoms including pain, hypercalcemia, increased risk of pathological fracture and neurological symptoms.[1,2,4,5] Due to their complications, bone metastases can decrease the quality of life in cancer patients.[6] A significant number of patients with advanced malignant disease present with symptomatic bone metastases.[7] The analgesic effect of radiotherapy for painful bone metastases has been established for years and therefore irradiation is the preferred treatment for localized bone pain in advanced malignant disease. Approximately 70–80% of patients will respond with pain relief, up to one-third will achieve complete pain response.[1]

Significant progress in systemic and supportive therapy has increased patients' life expectancy.[2] Furthermore, beginning with Hellman and Weichselbaum in 1995, the hypothesis of the existence of an oligometastatic state of cancer, as an intermediate stage of cancer spread, has been established[8] and is nowadays differentiated from widespread metastatic disease. With improvements in diagnostic modalities, oligometastatic malignant disease is being diagnosed more frequently than before[9], resulting in earlier detection of metastases.[10] However, various definitions and different cut-offs are discussed in the literature. In most studies, oligometastatic state was defined as limited number of metastases, with 1–3 or 1–5 metastatic lesions.[9,11,12] Accumulating clinical evidence suggests that metastasis-directed local therapy for these patients might result in improved clinical response, prevent additional metastatic spread and delay the initiation of systemic therapies.[13,14] Adequate radiotherapy regimens to achieve sufficient pain relief have been discussed in the literature and different regimens in the palliative situation have been reported and summarized in various studies.[2,7,15,16] However, the optimal fractionation and dose regimen for patients with oligometastatic disease is still an unresolved issue. Considering improved survival for patients with oligometastatic disease, the goal of an aggressive metastases-directed approach is not only to achieve an optimal pain relief, but also long-term local control (LC).

To deliver high doses to the target, maximize targeting capabilities and minimize damage to organ at risk (OAR) or healthy tissue, stereotactic body radiotherapy (SBRT) has been introduced.[17] In a systematic review published in 2019 by Spencer *et al.*, the role of stereotactic radiotherapy in 1-6 fractions in the management of bone metastases from solid-organ tumours was examined. Excellent local control rates, as well as superior rates for pain relief (compared to conventional radiotherapy) were reported in this analysis.[3] However, for some bone metastases, stereotactic radiotherapy in a few fractions might be unsuitable, due to their close proximity to OAR or size or limited definability of target volumes. For this reason, many study protocols exclude tumours within a distance of < 3 mm to the spinal cord, with the aim to respect its dose limitations.[18] Various studies examined intensity modulated radiotherapy (IMRT) regimes with simultaneous integrated boost (SIB) for radiotherapy of spine metastases.[18-20] Compared to conventional IMRT, this approach should offer dose reduction in the spinal cord and dose escalation in the target volume using SIB.[21] In our institution, a higher-dose fractionated regimen for bone metastases with 30 Gy and 40 Gy radiotherapy in 10 fractions with dose escalation by SIB ("30/40 Gy") to treat patients oligometastatic and oligoprogressive malignant disease was introduced. This regimen enables not only a dose escalation in the target as an alternative to SBRT, but also a coverage of tumour-affected compartment (according to clinical assessment).

The aim of this study was to assess the feasibility concerning completion of treatment, acute toxicity and to evaluate oncologic outcomes after fractionated radiotherapy using this concept for bone metastases in selected patients with assumed favourable prognosis. In addition, dose constraints for palliative radiotherapy of the spine have been adapted to higher-dose radiotherapy.

Patients and methods

The study protocol was submitted to the Ethics Committee of the Medical Faculty in our institution and approved in 2020 (990/2020B02). This study represents a single institution retrospective analysis of all consecutive patients treated with this regimen at our institution. Clinical records of all patients treated with radiotherapy of bone metastases with intensity modulated radiotherapy (IMRT) with 30/40 Gy SIB in 10 fractions between 2017 and 2020 in were evaluated. Patients treated with the evaluated regimen were not considered for SBRT, due to close proximity of the tumour to OAR, size or limited definability of target volumes.

In most cases, patients included in the study had malignant disease in oligometastatic or oligoprogressive state. However, the evaluated treatment was also offered to patients with diffuse metastatic disease, in case of radioresistant histology (such as pheochromocytoma or renal cell carcinoma) or vertebral-body metastasis with intraspinal component, where improved LC with higher-dose fractionated regimen was desired (due to favourable prognosis and expected efficient systemic treatment). The indication for radiotherapy was mainly not palliative symptom control but local treatment of all macroscopic or progressive tumour localizations. Various definitions of oligometastatic disease have been described in the literature. Foster *et al.* reports that a definition of ≤3 metastases was used in 12/25 retrospective studies.[11] Therefore, for the purpose of this study, we defined an oligometastatic disease as 3 or less extracranial metastases. If patients had locally untreated organ metastases, disease was classified as diffuse metastatic disease. Oligoprogression was defined as progression of 3 or less extracranial metastases under systemic therapy. To determine the number of metastases, the last radiological imaging before radiotherapy was used.

Data were collected retrospectively and abstracted by chart review. Feasibility was defined as conducting radiotherapy without interruption and no toxicity ≥ grade 3 (Common Terminology Criteria for Adverse Events [CTCAE] V 4.0). Due to the retrospective study design, pain response to radiotherapy was evaluated based on clinical records and therefore not graded. Overall survival (OS) and progression-free survival (PFS) were evaluated per patient based on the follow up scans and prostate-specific antigen (PSA) measures (for prostate cancer). OS was defined as the time from the date of the end of radiotherapy to the last contact or death. LC and PFS were defined as the time from the end of radiotherapy to last follow-up or to the diagnosis of local progression for LC and local progression or distant progression for PFS. LC was calculated for each irradiated metastasis. In patients with prostatic cancer, in case of no PSA-elevation and no progression of clinical symptoms (such as pain or neurological symptoms connected to irradiated localization), no radiological imaging was performed during follow-up. PSA-level was used as a measurement to assess LC and PFS in these patients.

IMRT was planned based on a three-dimensional planning CT using 3 mm slice thickness, 4-dimensional-CT (4D-CT) was used for metastases of the ribs. Similar to the regimen described by Guckenberger *et al.*[20], we generated multiple target volumes to receive different doses per fraction and maintain the same number of fractions. Gross tumour volume (GTV), *i.e.* the macroscopic metastasis, was contoured on the planning CT by the aid (and in most cases co-registration) of diagnostic imaging. Clinical target volume (CTV) included GTV and was delineated depending on the localization: the whole vertebral body for spine, or additional assumed subclinical expansion (*e.g.* along affected ribs). Planning target volume (PTV) for the spine (PTV30) for the 30 Gy-volume was CTV plus 5 mm margin. Planning target volume (PTV40) was generated with 0-2 mm margin around the GTV for the 40 Gy-volume, depending on the localization with 0 mm next to the spinal cord. For metastases in ribs, GTV was contoured as macroscopic tumour in 4D-CT. Internal target volume (ITV) was generated by the aid of 4D-CT to incorporate all potential locations of the tumour. CTV included GTV and 2–3 mm in craniocaudal extension, as well as the whole affected rib on the metastasis level in transverse plane. Additional 6 mm margins were used on CTV to generate PTV30 for metastases in ribs. For metastases in other non-vertebrae bones (sacral bone, sternum, femur), CTV was generated to involve the whole affected bone for sacral bone and sternum (due to large metastasis-size), as well as assumed subclinical expansion along affected long bone. PTV30 was generated with different margins (5–15 mm), dependant on the size of the metastasis and considering positioning inaccuracies. Dose prescription according to International Commission on Radiation Units and Measurements (ICRU)50 was aimed at for the GTV with prioritization of limited dose to the spinal cord. Maximal tolerated dose was 107%. The PTV30 should have been covered with ≥ 90% of the prescribed dose to 98% of the contoured volume (D98) and ≤ 107% of the prescribed dose to 2% of the contoured volume (D2). An example of a treatment plan for radiotherapy with SIB with 30/40 Gy in 10 fractions is demonstrated in Figure 1. Spinal cord was limited to 34 Gy total dose, *i.e.* 50 Gy equivalent dose (2 Gy) (EQD2), estimated by the linear quadratic model with an alpha/beta = 0.87 Gy for spinal cord, according to QUANTEC.[22] An EQD2 of 60 Gy (alpha/beta = 2 Gy) was allowed for metastases localized at the level of the cauda equina. Target volumes were delineated using Monaco planning system, version 5.11.03 or Oncentra Masterplan treatment planning system 4.3 (both Elekta AB, Stockholm,

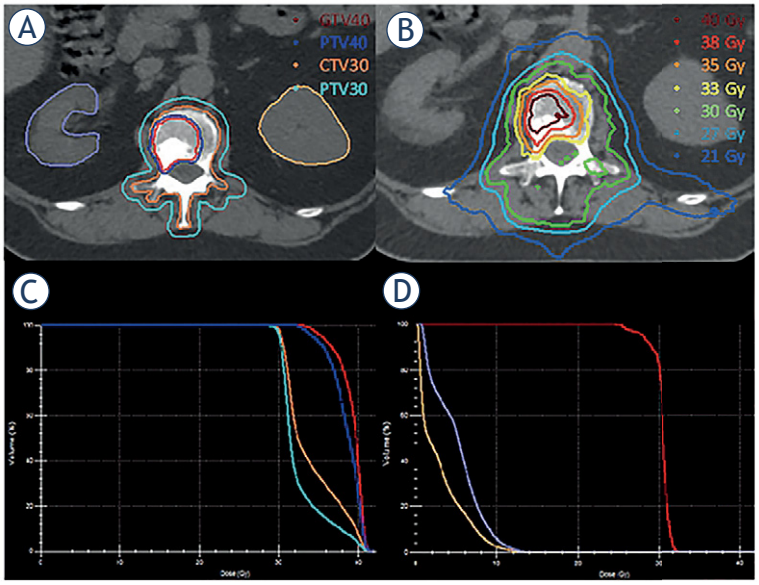

FIGURE 1. Example of a radiation plan for a bone metastasis in the first lumbar vertebra. Gross tumour volume (GTV)40 was contoured by coregistered diagnostic positron emission tomography-computed tomography (PET-CT). Clinical target volume (CTV)30 included GTV40 and the whole vertebral body. Planning target volume (PTV)40 and PTV30 were generated with 2 and 5 mm margins **(A)**. Panel **(B)** demonstrates isodose distribution. Dose-volume histograms (DVHs) PTV30, PTV40, CTV30 and GTV40 show dose coverage **(C)**. GTV40 coverage is compromised due to spinal cord sparing **(B, C)**. DVHs for both kidneys (purple and yellow), as well as spinal cord (red) are demonstrated as well **(D)**. Medical history: patient was diagnosed with high-risk prostate cancer in 2012. Initial treatment included the combination of radiotherapy (prostate and pelvic lymph node) and long-term androgen-deprivation therapy. A single metastasis in the first lumbar vertebra was diagnosed in 2018. Radiotherapy with 30/40 Gy in 10 fractions with integrated simultaneous integrated boost (SIB) was applied for better local control. By the last documented follow up in 2021, no progression was observed in the irradiated metastasis. However, the patient developed diffuse skeletal metastases (treated with secondary androgen-deprivation therapy with abiraterone and enzalutamide).

Sweden). Treatment planning (optimization) was performed by the above-mentioned version of Monaco or the inhouse product Hyperion 2.4.5, respectively. Treatment was delivered by 6 MV Elekta linear accelerators and image-guided radiotherapy (IGRT) with positioning controls using cone-beam CT and daily online corrections. No specific patient immobilisation was needed, due to daily IGRT controls and corrections.

Additionally, dose constraints for OAR and radiotherapy data were evaluated for all irradiated metastatic sites. Mean values for the volume, D2% (D2) and D98% (D98) for GTV40, CTV30, PTV40 and PTV30 were evaluated. Dose values for spinal cord were calculated for patients with metastases in the vertebral body. Mean value for the maximal point dose in the spinal cord (Dmax), D2 and D0.5ccm were reported. The mean dose (Dmean) values were analyzed for kidneys. Patients with Dmean for kidneys below 1 Gy were excluded from this part of the analysis (target volumes far away).

Statistical analysis was performed with IBM SPSS Version 26. Means were compared by two-sided Student's t-test. Survival times were examined using Kaplan-Meier estimator and compared using the log-rank test. Chi-square test was used to describe correlations between categorized variables. Significance was considered in case of $p < 0.05$ and $0.05 < p < 0.1$ was defined as a trend to statistical significance. Pearson´s correlations coefficient was used to measure the statistical relationship between two continuous variables. Pearson`s correlation coefficient $0.4 < r < 0.7$ was defined as moderate correlation, coefficient ≥0.7 was defined as a strong correlation.

Results

Patient population

A total of 25 patients with 29 irradiated metastases were included in our analysis. For oncological outcomes and patient characteristics, 24 patients with 28 irradiated localizations were evaluated. For the analyses of treatment feasibility and dosimetric parameters of all 25 patients (29 irradiated localizations) were included. One patient with non-seminomatous, extragonadal germ cell tumour with diffuse lung metastases and a single bone metastasis in a thoracic vertebral body was treated with curative therapy and therefore was excluded from the oncological outcomes-analysis (also excluded from patient characteristics table) due to specific diagnosis and curative treatment regardless of diffuse metastatic situation (high-dose chemotherapy with stem cell transplantation, resection of lung metastases and irradiation of a single bone metastasis with evaluated regimen). However, the radiation plan of this patient was included in the analyses of feasibility and radiotherapy parameter.

Median follow-up was 1.48 years (0.33–4.67 years). Follow-up data was missing for 3 patients with 4 target volumes. Median age was 67.5 years (range 28–81 years). Predominant sex was male (70.8%). Spine was the most common location (71.4%) followed by ribs (14.3%). According to histopathological reports, prostate cancer was the most frequent histology (45.8%), followed by renal cell carcinoma (12.6%), urothelial cancer (8.3%) and breast cancer (8.3%).

Staging was carried out with positron emission tomography-computed tomography (PET-CT) for 11/24 patients, but not necessarily as the last imaging before radiotherapy. In the subgroup of patients with prostate cancer (n = 11), PSMA-PET-CT was performed in 8 patients. Somatostatin-receptor-PET-CT was performed in 2 patients (pheochromocytoma and endocrine mucin-producing sweat gland carcinoma). FDG-PET-CT was performed for one patient with rectal cancer. In other patients, staging was performed depending on the histology and localization of primary disease, with whole-body CT-scan or with a combination of different imaging modalities (such as magnetic resonance imaging [MRI], skeletal scintigraphy or CT). Median time from last staging to the beginning of radiotherapy was 32 ± 20 days.

Most of the patients had oligometastatic disease in the last staging before radiotherapy (n = 16, 66.7%). In eight patients with diffuse metastases (33.3%), the indication for higher-dose radiotherapy regimen was based on oligoprogression under systemic therapy for 3 patients, radioresistent disease in 3 patients (1 pheochromocytoma and 2 renal cell carcinoma) and metastases with spinal localization and intraspinal component in 2 patients. Both patients with metastasis in the spine with intraspinal component had prostate cancer with efficient systemic therapy options and had favorable prognosis according to the prognostic score introduced by de Vin.[23]

All metastatic sites (or all progressive metastatic sites) were irradiated in 18/24 patients (75%). Two patients with prostate cancer had either synchronous oligometastatic disease at the time of primary tumour diagnosis (n = 1) or metachronous oligometastatic disease with local recurrence after initial treatment of the primary tumour (n = 1). All tumour sites were irradiated (local recurrence included) in these patients. In the group of patients with oligometastatic disease, all sites were irradiated in 15/16 patients. A very slow progression of one bone metastasis was not irradiated in 1 patient. One metastasis was irradiated with the described regimen in 20 patients, two metastases were irradiated in 4 patients. Most of the patients were treated with systemic therapy directly before, simultaneously or directly after radiotherapy (n = 20). An overview of the patient characteristics is provided in Table 1.

Pain was the main clinical symptom in the whole patient cohort (n = 13), although not the main indication for radiotherapy. Additionally, two patients had neurological symptoms, due to spinal metastasis-localization. Possible risk for pathological fracture before radiotherapy was documented in clinical records for eight patients.

TABLE 1. Patient, tumour and therapy characteristics (number of patients n = 24, number of irradiated metastases n = 28), one patient with germ cell tumour not included

Age (Years)		
Median and range	67.5 (28–81)	
Sex (n = 24)		
Female	7	29.2%
Male	17	70.8%
Histology (n = 24)		
Prostate cancer	11	45.8%
Renal cell carcinoma	3	12.6%
Urothelial cancer	2	8.3%
Other*	8	33.3%
Localization of irradiated metastasis (n = 28)		
Spine	20	71.4%
Rib	4	14.3%
Other (sternum, femur 2x, sacral bone)	4	14.3%
Oligometastatic *vs.* diffuse metastatic disease (n = 24)		
Oligometastatic disease	16	66.7%
Diffuse metastatic disease	8	33.3%
Indication for radiation therapy (n = 24)		
Oligometastatic disease	15	62.5%
Oligoprogression under systemic therapy	4	16.7%
Radiation resistant histology	3	12.5%
Intraspinal tumour component	2	8.3%
Systemic therapy (n = 24)		
No systemic therapy	4	16.7%
Chemotherapy or immunotherapy	10	41.7%
Hormonal therapy	10	41.7%

* Includes 2 patients with breast cancer, as well as one patient with rectal cancer, myxofibrosarcoma, metastatic chordoma, leiomyosarcoma, pheochromocytoma and endocrine mucin-producing sweat gland carcinoma, respectively

Feasibility

All patients (n = 25) finished all planned radiotherapy sessions. Acute toxicity grade 1 (CTCAE V4.0) was documented for 36.0% of the patients and included erythema (n = 4), gastrointestinal (n = 3), urinary (n = 2) or oesophageal toxicity (n = 2) and nausea (n = 1). No acute radiation toxicity > grade 1 was observed. One patient with metastasis in the distal femur was operated 4 months after the end of radiotherapy due to bone instability and result-

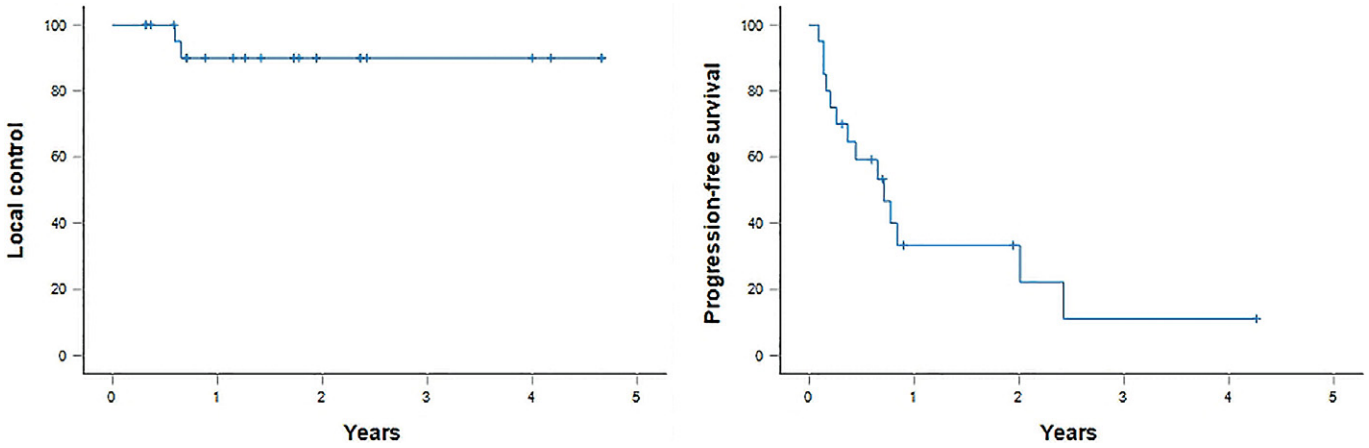

FIGURE 2. Kaplan-Maier survival curves demonstrating local control (LC) and PFS. LC-rates at 1 and 2 years (calculated per total number of irradiated metastases) was 90.0 ± 6.7% and 83.3 ± 15.2%. Estimated PFS-rates at 1 and 2 years (calculated per number of patients) were 33.3 ± 11.6% and 22.2 ± 11.9%.

ing pain during axial loading. Otherwise, no subacute toxicities were documented during follow up. No pathological fractures and no neurologic toxicity were observed with our limited follow-up. Pain relief was reported by 9/13 (69.2%) patients initially reporting pain. In one patient, no data on pain relief were available.

Oncologic outcomes

Oncologic outcomes are presented in Figure 2. During the follow-up, two local recurrences were observed (in both cases 7 months after the end of radiotherapy) in patients with spinal metastasis of clear cell renal cell carcinoma and urothelial carcinoma. In both patients, local progression was in-field. In patient with urothelial carcinoma metastasis localized in the spine (with paravertebral spread), no underdosage in target volume was observed. Tumour progression in this patient was detected in GTV area (both in the spine and in paravertebral component). In a patient treated for a renal cell carcinoma metastasis in the spine (with intraspinal and paravertebral spread), the D98 in the PTV40 was 32.31 Gy in order to respect the constraints for spinal cord. D98 of the PTV30 in this patient was 28.49 Gy. However, tumour progression in this patient seems to rather be limited to an area, where target volume coverage was sufficient.

Dependent on tumour histology and metastasis localization, LC was assessed using different imaging modalities (MRI, CT or PET-CT) or laboratory parameters (PSA). For 20/28 (71.4%) irradiated target volumes, LC was assessed using radiological imaging during follow-up. In 3 patients with 4 target volumes (14.2%), no radiological imaging was performed. However, all of these patients had prostate cancer and had no PSA-elevation nor progression of clinical symptoms during follow-up and therefore no imaging was performed. The patients were rated as locally controlled as without PSA-elevation and no symptom progression, tumour recurrence is unlikely. In 3 patients with 4 target volumes, no follow-up information was available.

Stratified by tumour histology, our analysis demonstrated significant differences in estimated 1-year PFS rates for patients with prostate cancer (66.7 ± 19.2%) vs. other malignancies (11.1 ± 10.1%), p = 0.003. However, 72.7% of patients with prostate cancer had oligometastatic disease, whereabout only 53.8% of patients with other malignancies had oligometastatic disease (not significant). No deaths were documented during follow up.

Dosimetric parameters

Dosimetric parameters and radiotherapy data were evaluated for all 25 patients (in total 29 metastatic localizations). Various parameters were evaluated for spinal cord and kidney constraints. Distribution of dose-volume histogram (DVH) derived parameters is demonstrated in Figure 3. According to ICRU prescription, good dose coverage was demonstrated for PTV30-volumes. GTV40 coverage was compromised in selected cases due to spinal cord sparing.

DVH parameters for spinal cord were calculated for 21 radiation plans for patients with metastases in the vertebral body. Respecting the dose

constraints for spinal cord had first priority, even if the GTV40 coverage was compromised. However, three patients had Dmax values above 34 Gy. To achieve improved CTV30 dose coverage, higher Dmax values were allowed in two patients due to its localization in fourth lumbar vertebra (Dmax = 34.25 Gy) and sacral bone (Dmax = 39.89 Gy), where dose constraints for cauda equina allowed higher doses than for spinal cord (max. EQD2 of 60 Gy with alpha/beta = 2 Gy). The third patient had slightly higher Dmax value (Dmax = 34.09 Gy) for spinal cord for irradiation of a metastasis in the first lumbar vertebra with intraspinal component. Mean kidney dose was limited to 12 Gy. Dose values for kidneys were calculated for 21 kidneys. Dose constraints were respected in all patients.

Radiotherapy data for the patient being operated due to painful bone instability of the distal femur were analyzed in detail. Maximal dose for GTV40 was 41.73 Gy (104% of the prescribed dose for GTV), mean dose on femoral bone was 24.7 Gy. 14.1% of delineated femoral bone received a dose of at least 40 Gy. Radiation therapy data for this patient did not exceed ICRU recommendations. Furthermore, more than 50% of the bone circumference was excluded from the PTV40. Due to the metastasis size, GTV40 (88.91 cm^3), CTV30 (534.69 cm^3) and PTV30 (1096.43 cm^3) volumes were larger than mean values in the whole cohort, also resulting in the largest PTV30 in the whole patient cohort. In multidisciplinary discussion, the bone instability was not rated as radiotherapy toxicity but rather possibly related to the size of the metastasis. Radiotherapy plan as well as follow-up MRIs for this metastasis are shown in Figure 4.

Discussion

Sufficient LC-rates were demonstrated with the evaluated regimen in our cohort, with LC at 1 and 2 years of 90.0 ± 6.7% and 83.3 ± 15.2%, respectively. SBRT regimen with SIB for patients with spinal bone metastases have been increasingly studied[18-21], and although inclusion criteria and dosing varied between studies, our 1-year LC-rate is in line with reported data.[19] In a prospective study published by Guckenberger *et al*., spinal metastases were irradiated with SBRT regimen with SIB with either 48.5/30 Gy or 35/20 Gy in 10 fractions.[20] Lubgan *et al.* reports good LC-rates after irradiation of spinal metastases using various SBRT regimen with SIB (median dose of 42.0/ 32.39 Gy in 10–12 fractions.[19] Comparable to our data, both studies

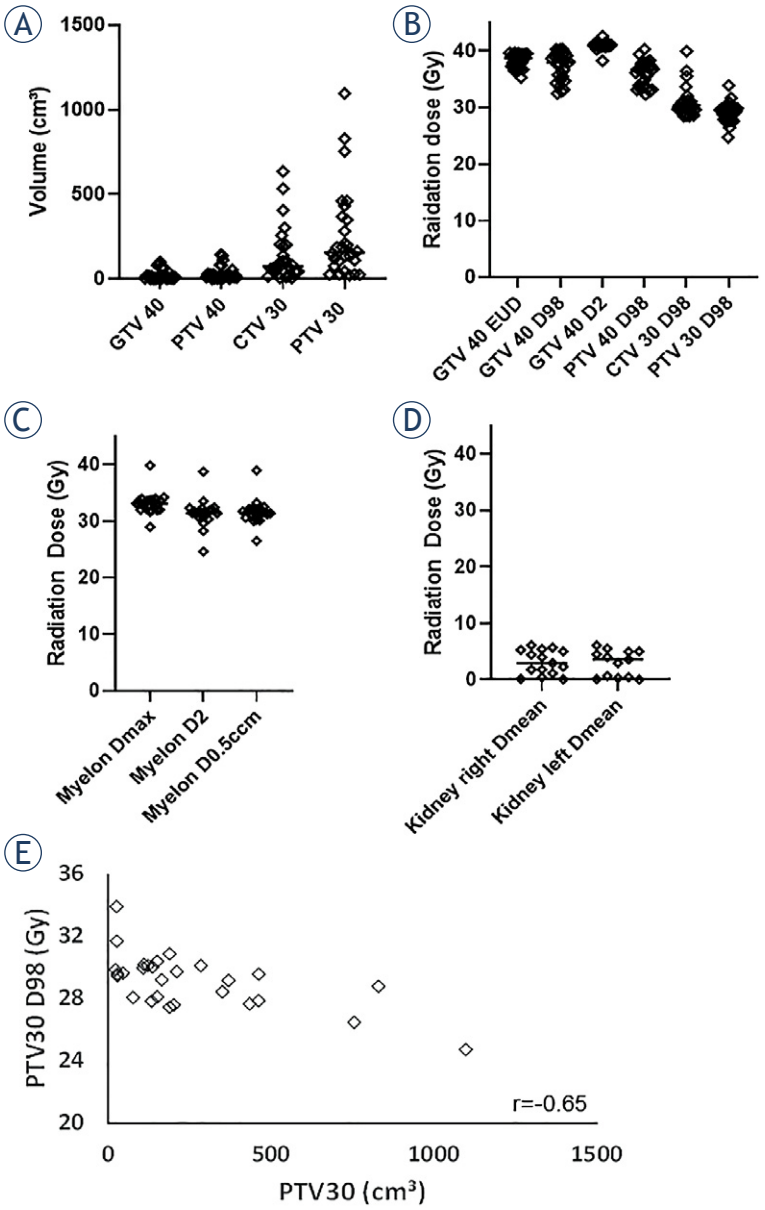

FIGURE 3. Distribution of radiation therapy parameter. Target volume size for gross tumour volume (GTV)40, clinical target volume (CTV)30, planning target volume (PTV)40 and PTV30 is shown in panel **(A)**. Mean values of the volume for GTV40, CTV30, PTV40 and PTV30 for the whole cohort were 25.90 cm^3 (range 0.11-100.74 cm^3), 140.04 cm^3 (range 5.33-635.19 cm^3), 40.43 cm^3 (range 0.11-185.43 cm^3) and 249.44 cm^3 (range 22.28-1096.43 cm^3). Panel **(B)** demonstrates target volume coverage for GTV40 minimal dose covering 98% of the target volume (D98), GTV40 maximal dose covering 2% of the target volume (D2), PTV40 D98, CTV30 D98 and PTV30 D98, as well as for GTV40 equivalent uniform dose (EUD). Mean value for D2 for GTV40 was 40.99 ± 0.65 Gy. Mean values for D98 for GTV40, CTV30, PTV40 and PTV30 were 37.26 ± 2.49 Gy, 30.94 ± 2.61 Gy, 35.75 ± 1.96 Gy and 29.10 ± 1.75 Gy. Mean value for GTV40 EUD was 38.21 ± 1.19 Gy. Panel **(C)** demonstrates radiation parameters for spinal cord (Dmax, D2 and D0.5cm). Mean values for spinal cord Dmax and D0.5ccm were 32.77 ± 1.18 Gy and 31.61 ± 2.07 Gy. Mean value for spinal cord D2 was 31.41 ± 2.36 Gy. Radiation parameter for kidneys (Dmean) are shown in panel **(D)**. Mean value for Dmean for the kidneys was 4.18 ± 1.49 Gy. Maximal kidney Dmean value was 6.14 Gy. Panel e demonstrates moderate negative correlation of the size of the target volume with PTV30 D98 coverage, showing worse target volume coverage for larger target volumes.

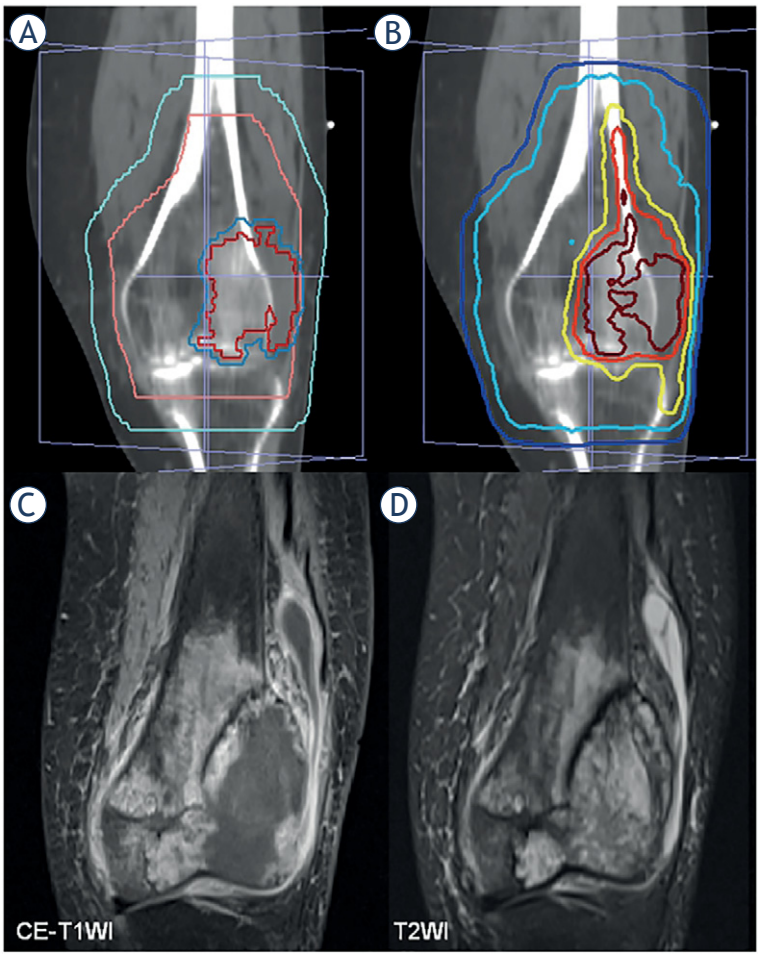

FIGURE 4. Example of the radiation plan for a metastasis in femoral bone requiring subsequent surgery. The patient was diagnosed with bladder urothelial cancer in 2007. After tumour resection in 2007, the patient was diagnosed with diffuse bone metastases in 2018. Femoral bone metastasis was the only progressive tumour localization and higher-dose radiation therapy with 30/40 Gy with simultaneous integrated boost (SIB) was applied in 2018. Four months after the end of radiation therapy, the patient developed pain during axial loading of the knee due to a bone instability. Therefore, distal femur was replaced by a prothesis. Histopathological report after surgery showed a mixture of tumour and bone necrosis without signs of progressive vital tumour. No further local tumour progression in remaining femoral bone was documented in the follow up. Panel **(A)** demonstrates target volume delineation (gross tumour volume [GTV]40 = red, planning target volume (PTV)40 = dark blue, clinical target volume [CTV]30 = orange, PTV30 = light blue). Isodose distribution is shown in panel **(B)** (dark red = 40 Gy, red = 38.3 Gy, yellow = 34.9 Gy, light blue = 29.8 Gy, dark blue = 21.0 Gy). Panel **(C)** and **(D)** present magnetic resonance imaging (MRI) 4 months after the end of radiation therapy, showing tumour metastasis and necrosis. T1-weighted contrast-enhanced MRI (CE-T1WI) sequence **(C)** demonstrates a small contrast enhanced ring with large hypointense core. T2-weighted MRI (T2WI) sequence **(D)** shows diffuse bone oedema.

reported good feasibility and no radiation-induced myelopathy as long-term side effect.[24]

Although radiotherapy for the treatment of painful bone metastases has been established[25], optimal fractionation and dose regimens for patients with oligometastatic disease seem to remain challenging and are still an unresolved issue. Various fractionation and dose schedules for palliative radiotherapy for bone metastases have been examined and can be divided broadly into two categories: short-course radiotherapy (delivered in up to five fractions) and long-course radiotherapy (delivered in 10 or more fractions).[26] Different studies found no difference in pain relief[26,27] or toxicity rates between short-course and long-course therapies.[26] However, conventional radiotherapy with 8 Gy single dose is associated with shorter pain relief (3–6 months) and can be insufficient for patients with longer life expectancy.[24] Furthermore, accumulating clinical data suggest better local control rates after irradiation of bone metastases with long-course radiotherapy. Improved 1-year local control rates for spinal metastases with spinal canal compression in patients with breast and prostate cancer were reported after long-course radiotherapy, compared to short-course palliative radiotherapy with 8 Gy in one fraction.[1] In addition, the incidence of repeated irradiation to the same metastatic site is lower in patients treated with longer fractionated schedules, compared to patients treated with 8 Gy in one fraction.[25,27]

With improved survival rates for patients with oligometastatic disease and predominant bone metastases[26], aggressive metastasis-directed therapy has been proposed to improve clinical response and eventually delay the initiation of systemic therapies.[13,14,28] In a study published in 2011 by Rades *et al*., improved local control, as well as survival benefit were demonstrated for patients with favourable survival prognoses after radiotherapy with total dose escalated beyond 30 Gy (40 Gy in 20 fractions or 37.5 Gy in 15 fractions).[29] A fractionated regimen with SIB (to escalate the dose in the target volume and reduce the dose for organs at risks) for radiotherapy of spine metastases was examined in various studies.[18,19] Various regimen for palliative radiotherapy in patients with spinal bone metastases are being evaluated in one ongoing prospective study (30 Gy in 10 fractions, 30/40 Gy in 10 fractions, 20 Gy in 5 fractions and 20/30 Gy in five fractions).[21] To increase the duration of pain relief, achieve better local control, deliver higher dose to the target volume with proper sparing of organs at risks, a higher-dose IMRT fractionated regime with 30/40 Gy with SIB was introduced in our institution. This regimen differs from stereotactic radiotherapy not only in its dose, but also in target volume delineation concept, as it integrates

two target volumes (macroscopic tumour and localized adjuvant region within the affected bone).

We included patients with favourable prognostic factors (*e.g.* number of metastases, systemic treatment options) and assumed longer life expectancy. Oligometastatic disease and oligoprogression under systemic therapy were the indication for this regimen for most of the patients (79.2%). Patients with diffuse metastatic disease were included in case of assumed radioresistant disease or vertebral metastasis with intraspinal component (if the patients had favourable prognosis and efficient systemic therapy options), where the higher-dose regime was applied to achieve better local control. This assumption was supported by a systematic literature review published in 2009 by Gerszten *et al.* They defined tumour histology as a prognostic factor in treatment response after conventional radiotherapy of spine metastases.[30]

Although the reported dataset is limited with number of patients and limited follow up, we observed sufficient LC rates using this regime. However, 83.4% of the patients received systemic therapy directly before, in parallel to or after radiation therapy, which might have influenced our LC-rates with its synergistic effect. In comparison to our results, a retrospective study published by Makita *et al.* reported a 1-year LC-rates of 60% for biological effective dose $(BED)_{10}$ < 39.0 Gy (= 1 x 8 Gy, 5 x 4 Gy, 4 x 5 Gy or 10 x 2.5 Gy) and 80% for BED_{10} = 39.0 Gy (= 10 x 3 Gy).[31] Two patients in our analysis developed local progression. In both cases, local progression seems to be limited to area with sufficient target volume coverage. These cases included radioresistant tumour histology (clear cell renal carcinoma and urothelial carcinoma) which indicates that this regimen should be evaluated in larger series for patients with radioresistant malignancies. Furthermore, feasibility of this regimen was good, with all patients completing the treatment and no patients developing acute toxicity beyond grade 1. Grade 1 acute toxicity was documented for 36.0% of the patients and included mild urinary or gastrointestinal toxicity, dysphagia and nausea. Assuming the extended life expectancy for most patients with oligometastatic disease, late side effects are much more clinically relevant than acute toxicity. Thus, one patient was operated due to painful bone instability 4 months after the end of radiation therapy. No pathological fractures and no neurologic toxicity were observed. However, these results might be limited with absence of imaging during follow-up in some patients with prostatic cancer, where no imaging was performed in case of no PSA-elevation and no progression of clinical symptoms connected to irradiated localization. We adjusted dose constraints for spinal cord using our institutional constraints for normofractionated radiotherapy for vertebral body. Respecting the dose limitation for spinal cord was priority, which led to underdosage in target volume coverage in selected cases. Thus, with this approach, clinically satisfying results were achieved regarding late neurologic toxicity as well as LC-rate.

One patient with urothelial carcinoma and metastasis in distal femur required surgery due to bone instability (rated by orthopaedic surgeons as instability due to the metastasis and not as radiotherapy-induced osteonecrosis). In our analysis, no exceed in ICRU recommendations in radiation plan for this patient was observed. This patient had the largest PTV30 in the whole patient cohort. However, this was the only metastasis in a long bone and is therefore hardly comparable to the spine and ribs volumes (where no osteonecrosis or pathological fractures were detected). This indicates that a further evaluation of this regimen for metastases therapy in long bones is needed, as there might be additional factors to be considered in radiation therapy planning for this localization (*e.g.* functional load). Pain as an initial symptom was reported in 13/25 patients. Pain relief was documented for 69.2% patients at some point during follow-up, which is comparable to another study that examined pain response after IMRT with 30 Gy in 10 fractions for spinal metastases.[32] However, due to the retrospective study design, no pain grading or accurate analyses of pain relief duration was possible.

Conclusions

In summary, higher-dose IMRT fractionated regimen with 30/40 Gy with SIB is a safe and feasible treatment regimen for selected patients with bone metastases, with all patients completing all therapy sessions with no acute radiation toxicity > grade 1. With limited number of patients and follow-up, as well as methodological limitations of a retrospective study, good LC-rates were demonstrated in our cohort. Using this treatment method, we managed to deliver a high radiation dose to the target volume and simultaneously achieve proper sparing of organs at risk. This intermediate-dose regimen represents a therapy in between clear palliative schedules and stereotactic body radiation

therapy (SBRT) in few fractions and might be the preferred option for patients with oligometastatic or oligoprogressive disease and long-life expectancy, if SBRT cannot be applied. Furthermore, this treatment can be convenient for bone metastases with intraspinal component, when improved LC-rate might be achieved using this higher-dose fractionated regime. However, late toxicity after this treatment concept and special combinations of metastasis localization and histology warrants further evaluation.

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