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PSMA-PET/CT response after metastasis-directed radiotherapy of bone oligometastases in prostate cancer

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Abstract

Objective Bone metastases are very common in advanced prostate cancer and can sensitively be detected utilizing PSMA-PET/CT. Therefore, our goal was to evaluate the suitability of PSMA-PET/CT-guided metastasis-directed external beam radiotherapy (MDT) as treatment option for patients with biochemical recurrence and oligometastatic bone lesions.

Materials & methods We retrospectively examined 32 prostate cancer patients with biochemical recurrence and PSMA-positive oligometastatic disease limited to the bone ($n = 1–3$). A total of 49 bone lesions were treated with MDT. All patients received a post-radiotherapy PSMA-PET/CT-Scan. Changes in SUV_{max}, PSMA-positive tumor volume per lesion and PSA, as well as the correlation between the PET/CT-interval and SUV_{max} response were calculated.

Results MDT lead to a SUV_{max} decrease in 46/49 (94%) of the lesions. The median relative decline of SUV_{max} was 60.4%, respectively. Based on PSMA-positive lesion volume with a SUV cut-off of 4, 46/49 (94%) of lesions showed complete response, two (4%) partial response and one lesion (2%) was stable on PSMA-PET/CT after MDT. Most of the treated patients (56.3%) showed an initial PSA decline at three months and a PSA nadir of median 0.14 ng/ml after a median time of 3.6 months after MDT. The median relative PSA change at three months after MDT was 3.9%.

Conclusion MDT is a very effective treatment modality for prostate cancer bone oligometastases and lesion response to MDT can be assessed using the (semi-) quantitative parameters SUV_{max} and PSMA-positive lesion volume with established SUV cut-offs.

Keywords Oligometastatic prostate cancer (OMPC), Prostate specific membrane antigen (PSMA), PET/CT, Metastases directed therapy (MDT), Response assessment

Background

Prostate cancer is the most common malignancy among men in Europe (Sung et al. 2021) and in advanced metastatic prostate cancer the incidence of bone metastases is 65–75% (Macedo et al. 2017). So far, no curative treatment option is available for prostate cancer which has metastasized to the bone. Patients with metastatic prostate cancer are currently treated with androgen deprivation therapy (ADT) and androgen receptor signaling inhibitors (ARSi) in the hormone sensitive state (mHSPC). Once the tumor becomes resistant to castration (mCRPC), therapy options include chemotherapy, radiotherapy and prostate specific membrane antigen (PSMA)-directed treatment (Cornford et al. 2017).

PSMA-positron emission tomography (PET)/computed tomography (CT) offers a high sensitivity and specificity for the detection of bone metastases (Zacho et al. 2018; Lawhn-Heath et al. 2019; Mingels et al. 2022). Furthermore, lesion identification is possible even at low serum prostate specific antigen (PSA) levels with a detection rate of 45% for PSA values between 0.20 and 0.49 ng/ml (Perera et al. 2020).

These imaging advancements combined with regular PSA-monitoring make a detection of metastatic prostate cancer at an early stage with limited metastatic count more likely (Lievens et al. 2020), a condition between localized and widespread metastatic disease termed oligometastatic disease (Hellman and Weichselbaum 1995). However, the definition of oligometastatic disease is inconsistent, with up to three or five metastases as frequent used cut-off values (Rogowski et al. 2022). The evolution of metastases is not unidirectional (Deek et al. 2021) and there is evidence that metastases can play a role in seeding further metastases (Gundem et al. 2015). On this ground, metastasis directed therapy (MDT), e.g. complete ablation by stereotactic body radiotherapy (SBRT) might improve clinical outcome. Several prospective studies have found MDT with SBRT to benefit patients with oligometastatic disease in respect to overall survival (OS) (Palma et al. 2020), progression-free survival (Tang et al. 2023), biochemical recurrence-free survival (Reyes et al. 2020), delaying biochemical or image based progression (Phillips et al. 2020) and ADT-free survival compared to other treatments or observation alone, while not being associated with any significant reduction in quality of life. However, MDT in oligometastatic prostate cancer is controversial and current national and international guidelines do not provide a clear recommendation for MDT or recommend it only within the context of studies (Cornford et al. 2021; Thomas and Schrader 2023).

Local control after MDT for bone oligometastases is high, with rates above 95% (Onal et al. 2021; Rogowski et al. 2021a, b). However, morphological assessment of the treatment response of osteoblastic bone metastases remains difficult on a lesion basis as hypersclerosis and tumor-related deformities often persist (Oprea-Lager et al. 2021). Hence, the current Response Evaluation Criteria In Solid Tumors 1.1 (RECIST1.1) guideline considers bone metastases without a significant soft tissue component to be unmeasurable and morphological imaging to be inadequate for assessing the response of bone metastases (Eisenhauer et al. 2009). PSMA-PET/CT, on the other hand, can (semi-)quantitatively assess PSMA-expression of bone metastases. Nevertheless, data investigating the treatment response of irradiated bone lesions based on repeated PET-imaging are scarce (Baumann et al. 2018).

Therefore, the aim of our study was to evaluate treatment response in patients treated with MDT for bone oligometastatic prostate cancer on pre- and post-radiotherapy PSMA-PET/CT.

Methods

This retrospective analysis was performed in compliance with the principles of the Declaration of Helsinki and its subsequent amendments (World Medical Associations Declaration 2013) and was approved by the local Ethics Committee of the Medical Faculty (approval number 19–361).

Patient selection

Consecutive patients undergoing MDT for bone oligorecurrent prostate cancer at the University Hospital Munich (LMU) between January 2015 and November 2022 were retrospectively identified ($n=32$). Oligometastatic disease was defined as presence of up to three bone metastases (miM1b (oligo) according to the PROMISE v2.0 framework (Seifert et al. 2023a, b). Simultaneous intrapelvic nodal disease (miN1-2) and lymph nodes in the common iliac or retroperitoneal region (miM1a) were allowed. However, patients with distant lymph nodes in other regions, visceral metastases (miM1c) and patients with oligoprogressive or induced oligometastatic disease were excluded. All patients had hormone-sensitive prostate cancer at the time of MDT. Patients with repeated PSMA-PET/CT examinations (pre- and post-radiotherapy) were considered for analysis. The reason for performing a repeated PSMA-PET/CT investigation were persisting or increasing serum PSA levels after MDT. .

PSMA ligand and PET/CT imaging protocol

Patients were imaged by [^{68}Ga]Ga-PSMA-11- or [^{18}F]PSMA-1007-PET/CT as previously described (Rogowski et al. 2021a, b). Pooling of data from different scanners (Siemens Biograph 64 and GE Discovery 690 PET/CT) was possible on the basis of phantom studies carried out by our medical physics department, resulting in a conversion factor, based on radionuclide, lesion diameter and SUV_{max}. Radiolabelling was performed in conformity with good clinical practice. In absence of contraindications, patients received 20 mg furosemide at the time of tracer injection. PSMA-PET/CT scans were acquired approximately 60 min after intravenous tracer injection. Depending on previous CT scans and contraindications, a contrast-enhanced or unenhanced diagnostic CT (120 kV, 100–400 mAs, dose modulation) was used for anatomical correlation and attenuation correction.

Image analysis

PSMA-PET/CTs were primarily interpreted in clinical routine by a junior nuclear medicine physician or radiologist and a senior nuclear medicine physician as well as a senior radiologist, the latter both with a minimum of 5 years of PET/CT experience. An independent secondary evaluation of the clinical reports and the images was carried out by another radiologist and nuclear medicine physician with 3 years of PET/CT experience. Cases of disagreement were solved in consensus. Lesion location was determined by CT. PET-positive lesions were visually identified on [^{68}Ga]Ga-PSMA-11-/[^{18}F]PSMA-1007-PET/CT as focal uptake above background not associated with the physiological uptake

(Fendler et al. 2017). Tumor delineation and an PSMA-positive volume of bone lesions was based on a 3D isocontour at 50% of a lesions maximum SUV as recommended by the European Association of Nuclear Medicine for FDG-PET imaging (Boellaard et al. 2015) and mentioned in the PROMISE V2 Supplements for PSMA-PET/CT (Seifert et al. 2023a, b).

Radiotherapy treatment

Treatment indications were approved by an interdisciplinary tumor board. Radiotherapy was administered to all PSMA-PET/CT positive lesions. The planning target volume (PTV) comprised the macroscopic bone lesion with a margin depending on the site and the expected intrafractional motion. All patients received volumetric modulated arc therapy (VMAT) and image-guided radiotherapy (IGRT). The exact dose prescription depended on the volume and the localization of the lesion. Patients diagnosed with local recurrence and / or pelvic lymph node-recurrence additional to bone metastases were treated simultaneously with radiotherapy to prostate fossa with or without whole-pelvic radiotherapy and boost to affected lymph nodes. The recommendation for concomitant ADT was based on disease burden, comorbidities and patient's preference.

Response evaluation

For the assessment of lesion response to radiotherapy SUV_{max} and PSMA-positive lesion volume of the irradiated lesions were recorded on pre- and post-radiotherapy PSMA-PET/CT-Scans and absolute and percentual changes were calculated. Based on the PSMA PET Progression framework (Fanti et al. 2020) and the consensus statements on PSMA-PET/CT response assessment criteria in prostate cancer (Fanti et al. 2021) an SUV_{max} increase of 30% was considered as progressive disease (PD), while an SUV_{max} decrease or increase below 30% was considered as non-progressive disease (non-PD).

Cut-offs for evaluation of PSMA-positive lesion volume were adopted from the RECIP framework (Gafita et al. 2022), with an increase in lesional tumor volume ≥ 20% confirming lesion progression, a decrease of ≥ 30% defining lesion regression (Fig. 1) and values

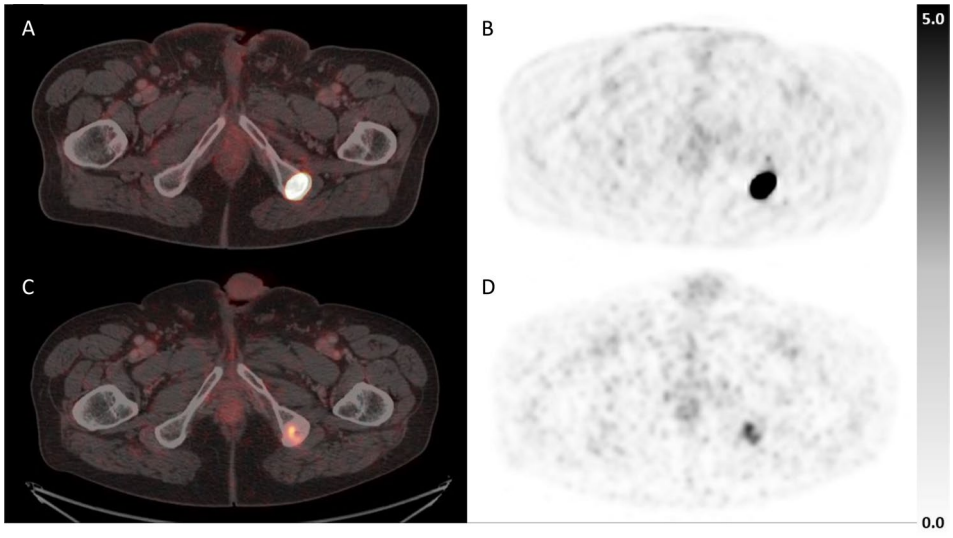

Fig. 1 Example of bone metastasis with PR, fused PET/CT and PET only prior to (**A** + **B**) and after MDT (**C** + **D**)

in between defining a stable lesion. No residual PSMA-uptake above background levels on follow-up PSMA-PET/CT was considered as complete response of a lesion (Fig. 2).

Post-radiotherapy PSA-response was also evaluated. A decrease or increase in the PSA value compared to the pre-MDT level by >0.2 ng/ml was considered as a response or progression, respectively, while values in between were considered stable.

Statistical analysis

All statistical analyses were conducted using SPSS Version 28 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe patient and treatment characteristics. Continuous measures were summarized using median and range, whereas ordinal and categorial measures were summarized using counts and percentages. Mann-Whitney-U-Test was used for univariate analyses and correlation analyses were conducted using the Spearman rank test. P-values of <0.05 were considered statistically significant.

Results

Demographics

A total of 32 patients treated with MDT for bone oligorecurrent disease had repeated PSMA-PET/CT examinations pre- and post-radiotherapy at the University Hospital Munich (LMU) between January 2015 and November 2022. PET/CT ligands were [68Ga]Ga-PSMA-11 and [18 F]PSMA-1007 in 28.1% and 71.9%, respectively pre- and 6.1% and 93.9%, respectively post-MDT. In six patients there was a switch from [68Ga]Ga-PSMA-11 pre-MDT to [18 F]PSMA-1007 post-MDT, three patients received [68Ga]Ga-PSMA-11 and 23 patients [18 F]PSMA-1007 pre- and post-MDT. The reason for the second PSMA-PET/CT was a PSA increase after MDT in all patients.

Patient characteristics at baseline and treatment characteristics are shown in Table 1. The median age at the time of MDT was 73.5 years (range 57–81). Primary therapy was radical prostatectomy in all patients. The initial tumor stage was T2 in 25%, T3 in 75% and N1 in 21.9%. The initial ISUP score was ≥4 in 71.8%. The majority of patients (62.5%)

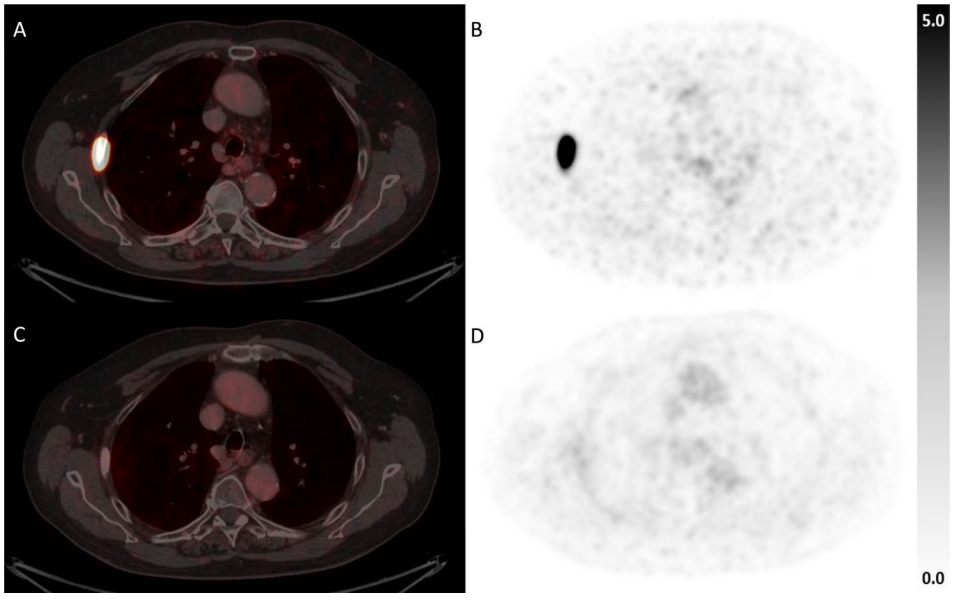

Fig. 2 Example of bone metastasis with CR, fused PET/CT and PET only prior to (**A + B**) and after MDT (**C + D**)

Table 1 Patient and treatment characteristics at baseline

Patients, *n*	32
Bone metastases, n	49
Age (years), median (range)	73.5 (61–86)
Initial tumor stage, n (%)	
T2	8 (25.0)
T3	24 (75.0)
Initial nodal stage, n (%)	
N0	23 (71.9)
N1	7 (21.9)
Nx	2 (6.3)
Initial ISUP score, n (%)	
2	5 (15.6)
3	4 (12.5)
4	6 (18.8)
5	17 (53.1)
Initial PSA (ng/ml), median (range)	11.4 (4-127)
Number of bone oligometastases, n (%)	
1	20 (62.5)
2	7 (21.9)
3	5 (15.6)
Site of bone oligometastases, n of lesions (%)	
Thorax	18 (56.3)
Spine	2 (6.3)
Pelvis	12 (37.5)
RT fractionation, n of lesions (%)	
30 Gy, 5 fractions (BED_3 = 90.0 Gy)	18 (36.7)
40 Gy, 10 fractions (BED_3 = 93.3 Gy)	24 (49.0)
other (BED_3 66.7–93.3 Gy)	7 (14.3)
Concomitant ADT, n (%)	
yes	11 (34.3)
no	21 (65.6)

Abbreviations ADT = androgen deprivation therapy; BED_3 = biologically effective dose, α/β = 3; ISUP = International Society of Urological Pathology; PSA = prostate specific antigen; RT = radiotherapy

presented with a single bone metastasis in the first PSMA-PET/CT (range one to three). Seven patients (21.9%) received additional RT to the prostatic fossa and /or a pelvic RT with a boost on positive lymph nodes simultaneously with the MDT for bone metastases due to macroscopic extraosseous recurrence. The median biologically effective dose (BED) (α/β = 3) administered to bone metastases was 93.3 Gy (range 66.7–93.3 Gy). The site of treated metastases was thorax, pelvis and spine in 56.3%, 37.5% and 6.3% of patients, respectively. Eleven patients (34.4%) received concomitant ADT at a median of four days before MDT.

PSMA-PET/CT response

The median interval between the first and the second PSMA-PET/CT was 13.2 months (range 4.4–63.3 months). The median SUV_{max} was 5.19 (range 2.3–87.4) and 1.93 (range 0,67–5.78) on pre- and post-MDT PET/CT, respectively. The median absolute and relative change of SUV_{max} was −2.97 (range −82.05 to +1.76) and −60.4% (range −98% to +54%), respectively. The median absolute change of SUV_{max} in patients with and without concomitant ADT was −12.0 (range −82.05 to +0.44) and −2.92 (range −7.32 to +1.76), respectively (p = 0.001) (Fig. 3). Based on SUV_{max} 47/49 lesions (96%) were classified as

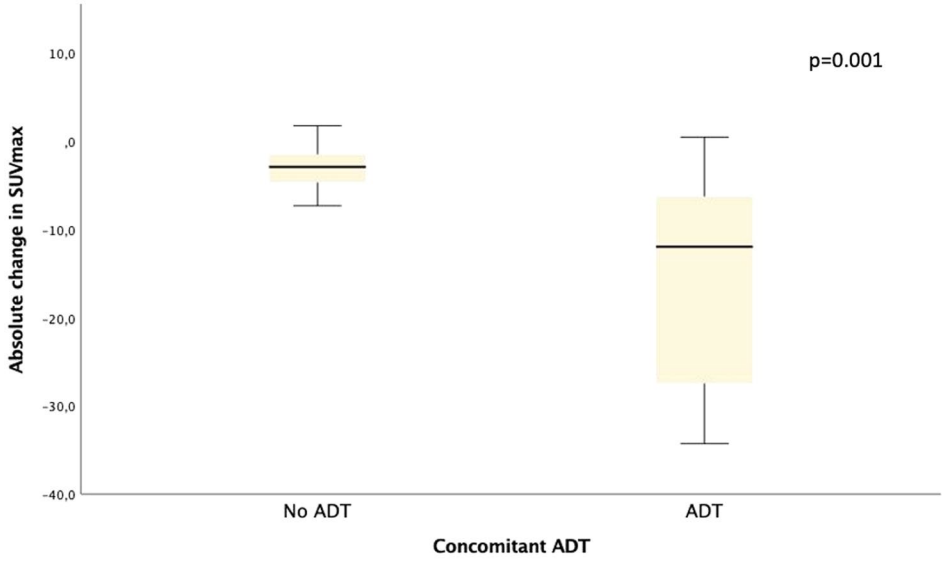

Fig. 3 Absolute change in SUV_{max} in patients with and without concomitant ADT to radiotherapy

non-progressive, of which 46 lesions had any decrease of SUV_{max} and one lesion showed an increase of only 16%. Two lesions (4%) showed an increase of SUV_{max} after MDT of 54% and 30%, respectively, and were therefore classified as non-responding lesions (non-responding lesion 1 and 2, respectively).

The median PSMA-positive lesion volume was 0.66 cm3 (range 0.2–9.4 cm3) and 0.0 cm3 (range 0.0–0.93 cm3) on pre- and post-MDT PET/CT, respectively. Based on PSMA-positive lesion volume 40/49 lesions (82%) did not have any correlate above background on post-MDT PET/CT, consistent with complete response. Seven patients showed partial response with volume decreases reaching from −66% to -95% in one lesion with a decrease of 16% was labelled as stable. When applying an SUV cut-off of 4, previously reported to be best suited to delineate the true tumor volume on [18 F] PSMA-1007-PET/CT (Mittlmeier et al. 2021), complete response was seen in 46/49 lesions (94%).

Non-responding lesion 1, which was the same lesion that was classified as stable based on PSMA-positive lesion volume, showed delayed complete response in a subsequent [18 F]PSMA-1007-PET/CT 15 months after treatment. Unfortunately there was no subsequent PSMA-PET/CT available for non-responding lesion 2, which was classified as partially responsive based on PSMA-positive lesion volume with a decrease of 94%.

Twenty-one patients (65.6%) showed new metastases on post-treatment scan. In seven patients (21.9%) no suspicious lesion could be found on PSMA-PET/CT, despite of biochemical recurrence. The rest of the patients (12.5%) had progressive lesions only apparent in hindsight ($n=2$) or local recurrence of a previously treated lesion. There was no significant correlation between the interval between the two PET/CT and the SUV_{max} response ($r=0.282$, $p=0.098$, Fig. 4).

PSA response

The median serum PSA values at the time of the pre- and post-radiotherapy PSMA-PET/CT were 1.03 ng/ml (range 0.2–39.2 ng/ml) and 1.05 ng/ml (range 0.1–10.3 ng/ml), respectively. The majority of treated patients (56.3%) showed an initial PSA decline

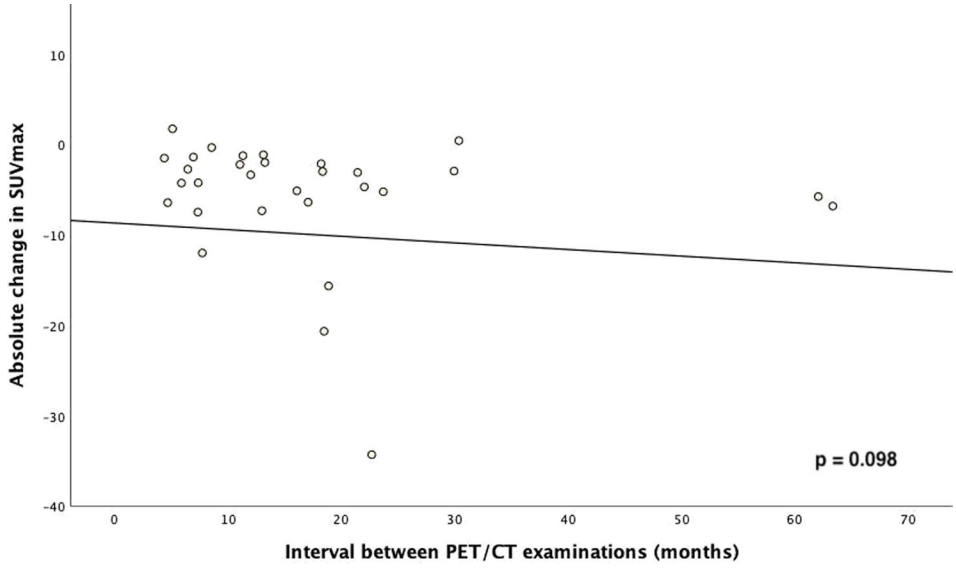

Fig. 4 Correlation between absolute change in SUV_{max} and interval between PET/CT examinations

three months after MDT and a median PSA nadir of 0.14 ng/ml (range 0.01–2.75 ng/ml) after a median time of 3.6 months (range 1.2–24.4 months) after MDT. However, after a median time of 15.7 months, all patients with an initial decline of PSA had a PSA-progression. The PSA was stable or rising at the first follow-up at three months in the remaining 14 patients. The median absolute and relative PSA change at three months after MDT was −0.2 ng/ml (range −22.9 ng/ml to +2.48ng/ml) and −3.9% (range −99.9% to +224.0%). Four patients had rising PSA values after MDT while on ADT, meeting the criteria of mCRPC.

Discussion

Bone metastases are the most frequent site of distant metastasis in prostate cancer and PSMA-PET/CT is evolving as the standard of care imaging method for metastatic prostate cancer (Zacho et al. 2018; Gandaglia et al. 2014). Several prospective trials have demonstrated that MDT in prostate cancer may prolong the initiation of systemic therapy and the time until disease progression (Tang et al. 2023; Reyes et al. 2020; Phillips et al. 2020). However, MDT is subject to critical evaluation because its impact on overall survival is still pending in trials with prostate cancer as the sole histology (Palma et al. 2020).

Current response criteria like RECIST 1.1 and PERSIST either deem bone lesions without significant soft tissue component unmeasurable or are not applicable to imaging with PSMA-PET/CT (Eisenhauer et al. 2009). We therefore aimed to investigate treatment response of MDT for bone oligometastatic disease in prostate cancer patients based on the objective parameters SUV_{max} and PSMA-positive lesion volume on pre- and post-MDT imaging with PSMA-PET/CT.

Two different PET/CT ligands were used for imaging. In January 2018 our nuclear medicine department replaced [^{68}Ga]Ga-PSMA-11 with [^{18}F]PSMA-1007 in clinical routine. Even though [^{68}Ga]Ga-PSMA-11 has been prospectively validated to have excellent sensitivity, especially for bone metastases (Lawhn-Heath et al. 2019), imaging with ^{18}F has several advantages over ^{68}Ga. The longer half-life and the possibility of large

batch production make handling easier, while the lower positron energy of ^{18}F in theory increases the resolution (Kesch et al. 2017). A potential pitfall of [^{18}F]PSMA-1007 on the other hand is the increased frequency of unspecific focal bone uptake (UBU) that has previously been reported (Grünig et al. 2021; Seifert et al. 2023a, b), which can lead to a decreased diagnostic accuracy for bone lesions (Mingels et al. 2022) and inadequate therapy. Unfortunately, there is no definitive way of differentiating between UBU and a true lesion in the retrospective setting and a standardized definition of UBU is lacking (Seifert et al. 2023a, b; Grünig et al. 2021; Phelps et al. 2023). It is therefore possible that some of the lesions we evaluated did not represent prostate cancer metastases.

We used a SUV_{max} increase above 30% to define a non-responding lesion, adopted from the PSMA PET Progression criteria (PPP) and the consensus statements on PSMA-PET/CT response assessment criteria in prostate cancer (Fanti et al. 2020, 2021) as well as volume cut-offs defined in the RECIP framework (Gafita et al. 2022) to evaluate lesion response to MDT on PMSA-PET/CT. The PPP framework by Fanti et al. defines treatment response using three different criteria, one of which is the increase in PSMA uptake of one or more existing lesions by at least 30% (Fanti et al. 2020). The RECIP framework by Gafita et al. takes into account the total PSMA-positive tumor volume and the presence or absence of new lesions (Gafita et al. 2022). Both frameworks evaluate tumor response and progression on patient basis and could therefore only be used in parts for our lesion based response assessment. While Gafita et al. propose a SUV cut-off of 3 to define PSMA-positive tumor volume on [^{68}Ga]Ga-PSMA-11, Mittlmeier et. described a SUV cut-off of 4 to be best suited to delineate PSMA-positive tumor volume on [^{18}F]PSMA-1007-PET/CT. Since some of the lesions treated with MDT were very small and already had a SUV_{max} below 3 on pre-MDT PET/CT, we utilized a relative threshold of 50% of local SUV_{max} which can be superior to fixed thresholds due to partial volume effects as also stated in the supplements of the second version of the prostate cancer molecular imaging standardized evaluation framework including response evaluation for clinical trials (PROMISE V2 (Seifert et al. 2023a, b) based on the work by Erdi et al. (1995, 1997). Morphologic imaging was not helpful in response assessment, as many lesions lacked well delineated morphologic correlates on pre- as well as post therapeutic PSMA-PET/CT. Our analysis of PET response after MDT of bone metastases showed very high response rates up to 96% based on SUV_{max} as well as PSMA-positive lesion volume, well in line with local control rates - usually defined as absence of morphological or metabolic progression - between 95% and 98% reported in literature (Onal et al. 2021; Rogowski et al. 2021a, b; Henkenberens et al. 2020). In our study the high response rate was achieved despite of a comparatively low BED_3 of median 93.3 Gy. Other studies have found that BED-values > 100 Gy and > 108 Gy, respectively, are associated with improved outcome (Ost et al. 2016; Hurmuz et al. 2020). Only two lesions showed a significant SUV_{max} progression despite of MDT. However, the interval between the pre- and post-therapeutic PSMA-PET/CT was less than six months in both cases. Baumann et al. reported a correlation between the time interval after radiotherapy and PET-response suggesting that an interval of six months or more may be required to fully estimate the efficacy of radiotherapy in PSMA-PET imaging (Baumann et al. 2018). As a matter of fact, one of the patients showed a complete response of the treated lesion on repeat PSMA-PET 15 months after MDT. The other patient could not be evaluated in this regard due to the lack of additional follow-up PET scans. We could not confirm a

correlation between the time interval and the SUV_{max} response, probably due to a long median interval of 13 months with a range of four to 63 months in our study.

SUV_{max} response was higher in patients with ADT concomitant to MDT. This might indicate a synergistic effect of radiotherapy and ADT as has been postulated before (Locke et al. 2015; Anderson and McBride 2022). This is interesting as MDT for oligometastatic disease is often investigated with the goal to defer systemic therapy (Ost et al. 2018). An increased PSMA-expression, in particular of bone metastases, has been described in patients receiving ADT and therefore could also be responsible for the difference in SUV_{max} response compared to patients not on ADT during MDT (Malaspina et al. 2023). However, the influence of ADT on PSMA-expression is complex, depending on the duration and type of ADT, and there is heterogeneity in the literature regarding the effects of ADT on PSMA expression, with some studies reporting increased PSMA uptake and others observing a decrease, particularly with long-term ADT (Vaz et al. 2020).

All patients in our study had a selection bias, since a persistent or rising PSA value after MDT was the indication for repeated PET imaging. Two thirds of the patients revealed new lesions on the second PET/CT. The informative value of the PSA response in our patient collective is thus limited by the fact that these new lesions may have already contributed to the serum PSA at the first follow-up 3 months after MDT. This underlines the importance of repeated imaging, which enables a lesion-based assessment, whereas the PSA value only provides global information about the state of the metastatic disease. Progression of some lesions may therefore be masked by the response of other lesions when looking at PSA values only (Kuten et al. 2019). Despite of this bias, most of our patients showed an initial drop of PSA levels at the first follow-up, indicating that PSMA-PET/CT-based MDT in oligometastatic prostate cancer is able to temporarily reduce the main tumor burden in the majority of patients. However, after a median time of 15.7 months all patients with an initial decline of PSA showed an increase of PSA-levels, which also has to be seen in the context of the abovementioned selection bias. In seven patients (21.9%) no suspicious lesion was found on PSMA-PET/CT at the time of biochemical recurrence after MDT (median PSA-level of 1.05 ng/ml), which matches the previously reported sensitivity of PSMA-PET/CT for biochemical recurrence (Hofman et al. 2018).

Our study has several limitations. The limited number of patients and the lack of statistical design or power make it difficult to draw a robust conclusion. Our study also has an observational nature and had no pre-defined endpoint, making it more vulnerable to bias. The different PSMA-compounds and scanners used as well as loss to follow up might also have a significant impact on the results. Furthermore, because histologic verification was not performed, we could not exclude false-positive and false-negative PSMA-PET lesions. However, sensitivity and specificity for detecting bone metastases are high (Zacho et al. 2020). Moreover, concomitant ADT was inconsistently administered, which complicated the interpretation of PSA kinetics. Nevertheless, we believe that our study adds important information to the sparse data regarding response evaluation of MDT for bone metastases of prostate cancer based on repeated PSMA-PET-imaging.

Conclusion

The ability to assess response at the lesion level is particularly important in oligometastatic prostate cancer patients treated with MDT. Serum PSA levels only provide global information on tumor burden and are therefore not suitable for response assessment in this setting, as responding lesions could compensate for progressive or even new lesions. With PSMA-PET/CT, on the other hand, it is possible to reliably assess tumor load on a lesion basis. Using SUV_{max} and PSMA-positive lesion volume, we were able to confirm an excellent response of bone oligometastases to MDT, with almost all treated lesions showing a significant if not complete response.

Abbreviations

ADT	Androgen deprivation therapy
BED	Biologically effective dose
CT	Computed tomography
IGRT	Image-guided radiotherapy
MDT	Metastasis-directed therapy
mCRPC	Metastatic castration resistant prostate cancer
mHSPC	Metastatic hormone sensitive prostate cancer
OS	Overall survival
PFS	Progression-free survival
PTV	Planning target volume
PSA	Prostate-specific antigen
PSMA-PET/CT	Prostate-specific membrane antigen positron emission tomography / computed tomography
RECIST1.1	Response Evaluation Criteria In Solid Tumors 1.1
RT	Radiotherapy
SBRT	Stereotactic body radiotherapy
SIB	Simultaneous integrated boost
SUV	Standardized uptake value
VMAT	Volumetric modulated arc therapy

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Author contributions
Gabriel T. Sheikh, Minglun Li and Paul Rogowski contributed to the study conception and design. Material preparation, data collection and analysis were performed by Gabriel T. Sheikh and Paul Rogowski. The first draft of the manuscript was written by Gabriel T. Sheikh and Paul Rogowski. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Declarations

Ethics approval and consent to participate
This retrospective analysis was performed in compliance with the principles of the Declaration of Helsinki and its subsequent amendments and was approved by the local Ethics Committee of the LMU Medical Faculty (approval number 19–361). Consent to participate was waived due to the retrospective nature of our study.

Consent for publication
Not applicable.

Competing interests
Lena M. Unterrainer received personal fees from Novartis Radiopharmaceuticals, Astellas Pharma Inc., Telix Pharmaceuticals and is on the advisory board of Telix Pharmaceuticals. All other authors declare that they have no conflicts of interest or competing interests.

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