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ORIGINAL ARTICLE

# Influence of localization of PSMA-positive oligo-metastases on efficacy of metastasis-directed external-beam radiotherapy—a multicenter retrospective study

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## Abstract

**Purpose** Approximately 40–70% of biochemically persistent or recurrent prostate cancer (PCa) patients after radical prostatectomy (RPE) are oligo-metastatic in $^{68}$gallium-prostate-specific membrane antigen positron emission tomography ($^{68}$Ga-PSMA PET). Those lesions are frequently located outside the prostate bed, and therefore not cured by the current standards of care like external-beam radiotherapy (EBRT) of the prostatic fossa. This retrospective study analyzes the influence of oligo-metastases' site on outcome after metastasis-directed radiotherapy (MDR).

**Methods** Retrospectively, 359 patients with PET-positive PCa recurrences after RPE were analyzed. Biochemical recurrence-free survival (BRFS) (prostate-specific antigen (PSA) < post-radiotherapy nadir + 0.2 ng/mL) was assessed using Kaplan-Meier survival and Cox regression analysis.

**Results** All patients were initially clinically without distant metastases (cM0). Seventy-five patients had local recurrence within the prostatic fossa, 32 patients had pelvic nodal plus local recurrence, 117 patients had pelvic nodal recurrence, 51 patients had paraaortic lymph node metastases with/without locoregional recurrence, and 84 patients had bone or visceral metastases with/without locoregional recurrence. Median PSA before MDR was 1.2 ng/mL (range, 0.04–47.5). Additive androgen deprivation therapy (ADT) was given in 35% (125/359) of patients. Median PSA nadir after MDR was 0.23 ng/mL (range, < 0.03–18.30). After a median follow-up of 16 months (1–57), 239/351 (68%) patients had no biochemical recurrence. Patients with distant lymph node and/or distant metastases, the so-called oligo-body cohort, had an overall in-field control of 90/98 (91%) but at the same time, an ex-field progress of 44/96 (46%). In comparison, an ex-field progress was detected in 28/154 (18%) patients with local and/or pelvic nodal recurrence (oligo-pelvis group). Compared with the oligo-pelvis group, there was a significantly lower BRFS in oligo-body patients at the last follow-up.

**Conclusion** Overall, BRFS was dependent on patterns of metastatic disease. Thus, MDR of PSMA PET-positive oligo-metastases can be offered considering that about one-third of the patients progressed within a median follow-up of 16 months.

**Keywords** Prostate cancer · PSMA · External-beam radiotherapy · Distribution · Recurrence

## Introduction

In 1995, Hellman and Weichselbaum hypothesized that eradicating oligo-recurrences with metastasis-directed therapy (MDT) might prevent additional metastatic spread [1]. Approximately 40–70% of biochemically persistent or recurrent prostate cancer (PCa) after radical prostatectomy (RPE) are oligo-metastatic on $^{68}$gallium-prostate-specific membrane antigen positron emission tomography ($^{68}$Ga-PSMA PET) [2].

Theoretically, metastasis-directed radiotherapy (MDR) might be curative if all recurrent disease is completely either

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covered by irradiated volumes or surgically removed, which at best is documented by biochemical recurrence-free survival (BRFS) over a prolonged period of time. From the Radiation Therapy Oncology Group (RTOG) 0534 trial, the observation can be made that recurrent disease is evidently often missed by sole irradiation of the prostatic fossa: Five-year freedom from progression was highest in patients treated with the largest clinical target volume with external-beam radiotherapy (EBRT) to the prostatic fossa and pelvic lymphatic pathways with 4–6 months of concurrent androgen deprivation therapy (ADT) (89.1%) compared with patients treated with EBRT to the former prostate only with/without 4–6 months of concurrent ADT (82.7% and 71.1%) [3]. An accurate localization of recurrent disease is critical and is currently best achieved by PSMA PET [2, 4–6]. Compared with standard of care imaging, PSMA PET has a high sensitivity and specificity in visualizing local or lymph node recurrences at low prostate-specific antigen (PSA) levels [7, 8]. This might improve EBRT outcome by firstly enabling a higher dose administration to macroscopic recurrent disease and secondly expanding target volumes to areas that are routinely not treated by RTOG consensus target volumes [9, 10]. Despite the uncertainty regarding the specific definition of oligo-metastatic disease [11, 12], MDR of these recurrences plays an increasingly important role and is frequently offered [13–16].

Until now, there are few and only retrospective analyses with PSMA PET/CT as the sole staging imaging technique reporting a 1-year BRFS ranging between 46 and 79% [17–23]. Standard of care of patients with metastasized PCa is ADT alone or in combination with abiraterone or docetaxel [24, 25]. Recently, ADT-free survival was introduced as a new endpoint in patients with oligo-metastatic PCa and so far, a prolonged ADT-free survival is reported although it is unclear whether this eventually translates into an overall survival benefit [26, 27]. Contrary to the notion to postpone ADT by MDR, there are studies explicitly using the synergistic effects of ADT with radiotherapy and reporting an improved progression-free survival for the combination of MDR with ADT in oligo-metastatic patients [28, 29]. Currently, there is lack of evidence whether ADT can be deferred or should be used concomitantly with MDR and whether even abiraterone, enzalutamide, or docetaxel should be applied additionally to MDR in oligo-metastatic patients. In this regard, oligo-metastases' localization might play a role and so far only from the pre-PSMA PET era, it is known that patients with local and pelvic nodal recurrence have a more favorable prognosis compared with those with skeletal or visceral metastases [30]. Thus, this retrospective study explicitly aims to compare the efficacy of MDR in patients with local recurrence or oligo-metastatic disease of the pelvic nodes ("oligo-pelvis") vs. MDR of distant metastases, i.e., paraaortic lymph node and/or bone/visceral metastases ("oligo-body") after RPE.

## Materials and methods

### Patient population

This retrospective multicenter study was undertaken in six university hospitals in Switzerland and Germany, was approved by the local Ethics Committee of the respective Medical Faculties (BASEC-Nr. 2017-01499), and the need for written informed consent was waived.

Patients, treated with EBRT for recurrent PCa after RPE from April 2013 until January 2018, were included. All patients were at initial diagnosis clinically without distant metastases (cM0) and had $^{68}$Ga-PSMA PET-positive macroscopic recurrent disease with evidence of nodal or distant metastases (N1 or M1a/1b/1c) or in the prostatic fossa. Any number of pelvic lymph node metastases in PSMA PET was accepted. The number of distant metastases was limited to a maximum of five sites including any of the following visceral, lymph node, or bone metastases. Ongoing ADT at time of PSA recurrence, previous chemotherapy, or prior salvage EBRT were the exclusion criteria.

### Treatment application

Imaging was performed with either $^{68}$gallium-PSMA PET/CT or PET/MRI. All recurrent lesions were irradiated using stereotactic body radiotherapy (SBRT) or conventionally fractionated EBRT often with simultaneously integrated boost or SBRT. At the discretion of the participating university hospital, total irradiation dose, irradiation of the lymphatic pathways, or concomitant ADT was applied. For comparability, the respective applied radiotherapy dose was converted to a biologically equivalent dose in 2 Gy using an $\alpha/\beta$ ratio of 1.5 Gy (EQD 2/1.5 (Gy)). A detailed description of the radiotherapy technique is given in supplemental material 1.

### PSMA ligand and PET imaging

The $^{68}$Ga-PSMA ligand was radiolabeled according to good clinical practice [31–33]. PET imaging was performed according to the joint EANM and SNMMI guidelines [34]. In brief, at the time of the PET scan, a contrast-enhanced diagnostic CT (120 kVp, 100–400 mAs, dose modulation) or a low-dose CT (120 kVp, 25 mAs/modulated) or whole-body MRI for attenuation correction was performed. Minimal prerequisite for MRI imaging were DIXON-based sequences combined with one higher resolution sequence in at least one plane (e.g., axial T2 haste) covering the whole scan for attenuation correction and anatomical localization. Furthermore, dedicated pelvic MRI with or without contrast-enhanced sequences and diffusion-weighted imaging was added.

PET scans were acquired approximately 1 h after intravenous administration of the $^{68}$Ga-PSMA ligand (mean

171 MBq; range 87–301) according to local standards. PET/CT and PET/MR images were interpreted in consensus by one nuclear medicine physician and one radiologist or by a dual-boarded nuclear medicine physician and radiologist in the sense of a clinical report-based analysis. PET-positive tumor lesions were visually identified as a focal $^{68}$Ga-PSMA ligand uptake higher than adjacent background activity, not associated with the physiologic uptake or benign lesions [34–36]. Characterization of lesions (e.g., bone lesion or lymph node) was determined on CT or MRI by reporting a corresponding lesion for the region of tracer accumulation.

## Statistical analysis

For statistical analysis, SPSS Statistics 25 (IBM, New York, USA) was used. BRFS, defined as PSA < post-radiotherapy nadir + 0.2 ng/mL from the last day of EBRT, was the primary outcome and was calculated using the Kaplan-Meier method. Follow-up examination was performed according to the respective institutional protocol with regular PSA controls. Secondary outcomes were initiation of other treatments after irradiation, overall survival, tumor-related survival, in-field control within irradiated volumes, ex-field progression, and toxicity. Acute and late toxicity was analyzed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 [37]. For the purpose of analyzing the effect of the disease recurrence patterns on the BRFS, patients were clustered in different groups like an oligo-pelvis group, defined as local and/or pelvic lymph node recurrence vs. an oligo-body group, which included patients with distant lymph node and/or visceral/bone metastases. Further stratification divided patients in subgroups with local recurrence within the prostatic fossa vs. pelvic lymph node recurrence with/without local recurrence, with local and pelvic nodal recurrence vs. pelvic nodal recurrence alone, with pelvic vs. paraaortic nodal metastases, and with paraaortic nodal vs. distant metastases. Furthermore, the association with MDR concomitant ADT use, PSA-persistence vs. recurrence, the

**Table 1** Patients' characteristics

| | Total | Oligo-pelvis | Oligo-body | *p* value |
|---|---|---|---|---|
| Patients | *n* = 359 | *n* = 224 (%) | *n* = 135 (%) | |
| Initial age (years) median (range) | 66 (46–82) | 66 (46–81) | 65 (46–82) | 0.341 |
| Initial PSA at RPE (ng/mL) median (range) | 11.19 (2.1–657.20) | 10.69 (2.10–231.00) | 12.78 (4.30–657.20) | 0.433 |
| Initial Gleason score | | | | 0.271 |
| ≤ 6–7b | 202 (56%) | 131 (58%) | 71 (53%) | |
| ≥ 8 | 155 (43%) | 91 (41%) | 64 (47%) | |
| Unknown | 2 (0.6%) | 2 (1%) | - | |
| TNM | | | | |
| Initial T-stage | | | | 0.874 |
| T2a-c | 136 (38%) | 87 (39%) | | |
| T3 | 214 (60%) | 131 (59%) | | |
| T4 | 8 (2%) | 5 (2%) | | |
| Tx | 1 (0.3%) | - | | |
| Initial N-stage | | | | 0.001 |
| N0 | 240 (67%) | 159 (71%) | 81 (60%) | |
| N1 | 107 (30%) | 53 (24%) | 54 (40%) | |
| Nx | 12 (3%) | 12 (5%) | - | |
| Number of removed LN median (range) | 14 (1–64) | 16 (1–64) | 12 (1–46) | 0.814 |
| Number of positive LN median (range) | 2 (1–20) | 2 (1–11) | 2 (1–20) | 0.501 |
| Positive surgical margins (R1) | 153 (43%) | 97 (43%) | 56 (41.5%) | 0.863 |
| Initial D'Amico classification | | | | 0.1 |
| Low | 1 (0.3%) | 1 (0.4%) | - | |
| Intermediate | 15 (4%) | 13 (7%) | 2 (1%) | |
| High | 342 (95%) | 209 (93%) | 133 (99%) | |
| Unmeasurable PSA after RPE | 181 (50%) | 110 (49%) | 71 (53%) | 0.298 |
| PSA at time of PSMA PET (ng/mL), median (range) | 1.2 (0.04–47.50) | 1.09 (0.12–40.13) | 1.58 (0.04–47.50) | 0.284 |
| Time (months) between RPE and RT start, median (range) | 34 (1–268) | 34 (1–268) | 34 (1–236) | 0.369 |

*PSA*, prostate-specific antigen; *RPE*, radical prostatectomy; *LN*, lymph node; *RT*, radiotherapy

number of PET-positive lymph nodes ≤ 2 vs. > 2 in patients with affected pelvic lymph nodes only, and/or with affected paraaortic lymph nodes and BRFS was tested. Cox proportional hazard model was performed to determine whether these disease factors influence BRFS. A $p$ value of < 0.05 was considered statistically significant.

## Results

### PSMA PET results

Overall, 342/359 (95%) of the present cohort were high-risk PCa patients at the time of RPE according to D'Amico et al. [38]. Apart from pathologic lymph nodes' (pN1) involvement, there was no other significant difference between oligo-pelvis patients compared with oligo-body patients (Table 1). Median PSA at time of PSMA PET was 1.2 ng/mL (0.04–47.5). Seventy-five patients had local recurrence within the prostatic fossa, 32 patients had local and pelvic nodal recurrence within the prostatic fossa, 117 patients had pelvic nodal recurrence, 51 patients had paraaortic nodal metastases with/without locoregional recurrence, and 84 patients had bone or visceral metastases with/without locoregional recurrence in PSMA PET. PSMA PET-positive pelvic lymph node metastases were primarily seen in the iliac lymphatic pathway (overall 310, range 1–11) followed by perirectal (73, range 1–6) and obturator region (42, range 1–4). Distant metastases were above all osseous occurring in the pelvis (63/107; 59%) and spine (22/107; 21%). Visceral metastases were treated in 19 patients (Fig. 1, Table 2).

### Management of PSMA PET-positive lesions

Patients were primarily treated with conventionally fractionated EBRT (175/359; 49%) alone or combined with simultaneously integrated boost (127/359; 35%) or SBRT (21/359; 6%). Thirty-six patients (36/359; 10%) received SBRT alone. Oligo-body patients received significantly more often SBRT compared with oligo-pelvis patients (24% vs. 2%). Median equivalent dose in 2 Gy fractions (EQD 2/1.5 Gy) delivered to the prostatic fossa was 66 Gy (range, 47.52–70.0) and to the elective pelvic and paraaortic lymphatic pathways 47.52 Gy (range, 41.96–57.70) and 47.52 Gy (range, 42.42–56.0), respectively. PSMA PET-positive local recurrences within in the prostatic fossa were treated with an equivalent dose of 70.0 Gy (range, 57.6–72/EQD 2/1.5 Gy), PSMA PET-positive pelvic lymph nodes with 60 Gy (range, 40–66.4/EQD 2/1.5 Gy), and paraaortic lymph nodes with 50.9 Gy (47.9–98.57/EQD 2/1.5 Gy). In all patients with local recurrence within the prostatic fossa, the local recurrence and prostatic fossa were irradiated (118 patients). Ninety-seven patients received elective prostate bed EBRT without evidence of local recurrence. One

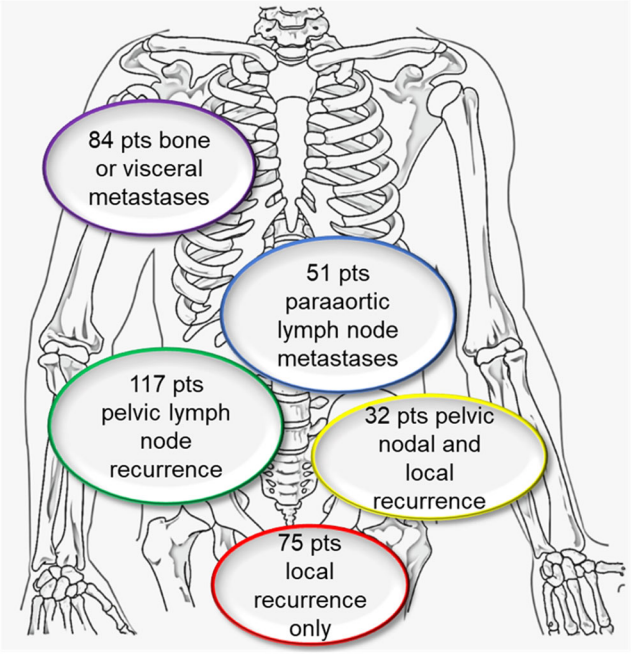



**Fig. 1** Distribution of PSMA PET-positive oligo-metastatic disease

hundred eight (108/149; 72%) patients with evidence of PET-positive pelvic lymph nodes had all of the pelvic lymphatic pathways irradiated compared with 41/149 (28%) patients in whom an involved node-based approach either by SBRT or conventionally fractionated EBRT was applied. Bone metastases were irradiated conventionally or by means of SBRT with 56 Gy (range, 40–108.57/EQD 2/1.5 Gy) and visceral metastases, primarily within lung and liver, with 93.93 Gy (range, 57.8–300/EQD 2/1.5 Gy). Most patients (234/359; 65%) had no ADT concurrently with EBRT, and there was no significant difference in the use of ADT between oligo-pelvis and oligo-body patients. ADT was applied in 125/359 (35%) patients during EBRT and discontinued in 61/125 (49%) patients after a median of 5 months (range, 1–25). Median time between the last application of ADT and last follow-up was 19 months (range 2–41). Treatment characteristics are listed in Table 3.

### Patients' outcome

Median PSA nadir after EBRT was 0.23 ng/mL (range, < 0.03–18.30). After a median follow-up of 16 months (range, 1–57), 239/351 (67%) patients had no biochemical recurrence. In the subgroup of patients without ongoing ADT at last follow-up, BRFS was 182/288 (63%). Oligo-body patients had an overall in-field control of 90/98 (91%) but at the same time, an ex-field progress of 44/96 (46%). In comparison, an ex-field progress was detected in 28/154 (18%) patients of the oligo-pelvis group with an in-field control of 149/155 (96%) (Table 4). Belonging to the group of patients

**Table 2** PSMA PET-positive oligo-metastatic disease

| All patients ($n = 359$) | | | |
|---|---|---|---|
| Oligo-pelvis ($n = 224$) | Local recurrence only within prostatic fossa | Pelvic LN recurrence + local recurrence within prostatic fossa | Pelvic LN recurrence only |
| | 75 (33%) | 32 (21%) | 117 (79%) |
| LN region (overall; range) | | | |
| Iliac | - | 39 (1–4) | 271 (1–11) |
| Obturator | - | 6 (1–2) | 36 (1–4) |
| Perirectal | - | 15 (1–2) | 58 (1–6) |
| Oligo-body ($n = 135$) | Paraaortic LN metastases ± locoregional recurrence | Distant metastases ± locoregional recurrence | |
| | 51 (38%) | 84 (62%) | |
| Distant metastases region (overall; range) | | | |
| Pelvis | - | 63 (1–2) | |
| Spine | - | 22 (1–2) | |
| Other bone | - | 22 (1–2) | |
| Visceral | - | 19 (1–4) | |

*LN*, lymph node

with oligo-pelvis relapse as compared with oligo-body was significantly associated with a higher BRFS (74% vs. 51%, $p = 0.001$) (Fig. 2). Likewise, concomitant ADT use was significantly associated with higher BRFS (83% vs. 57%, $p = 0.001$). No other predefined relapse patterns in PSMA PET were associated with a difference in BRFS at last follow-up ($p > 0.05$). Likewise, there was no association between PSA-persistence vs. recurrence and the number of PSMA PET-

**Table 3** Treatment characteristics

| | All patients | Oligo-pelvis | Oligo-body | *p* |
|---|---|---|---|---|
| | $n = 359$ | $n = 224$ | $n = 135$ | |
| ADT during/after RT | | | | 0.432 |
| Number of pts (*n*) with ADT during and after RT with discontinuation before last follow-up/duration (months) | 61 (17%)/5 (1–25) | 42 (19%)/5 (2–25) | 19 (14%)/3 (1–16) | |
| Number of pts (*n*) with ADT during and after RT until last follow-up | 64 (18%) | 36 (16%) | 28 (21%) | |
| Number of pts without ADT (*n*) | 234 (65%) | 146 (65%) | 88 (65%) | |
| Median PSA before RT (ng/mL) | 1.2 (0.04–47.5) | 1.71 (0.05–40.13) | 0.98 (0.04–47.5) | 0.311 |
| RT technique | | | | 0.001 |
| Conventionally fractionated (*n*) | 175 (49%) | 104 (46%) | 71 (53%) | |
| SBRT (*n*) | 36 (10%) | 4 (2%) | 32 (24%) | |
| Combined conventionally fractionated + SBRT (*n*) | 21 (6%) | 15 (7%) | 6 (4%) | |
| Combined conventionally fractionated + SIB (*n*) | 127 (35%) | 101 (45%) | 26 (19%) | |
| RT dose | | | | |
| Prostatic fossa (EQD 2/1.5 (Gy)) | 66 (47.52–70.0) | | | |
| Elective pelvic lymphatic pathways (EQD 2/1.5 (Gy)) | 47.52 (41.96–57.70) | | | |
| Elective paraaortic lymphatic pathways (EQD 2/1.5 (Gy)) | 47.52 (42.42–56.0) | | | |
| PET-pos. local recurrence within prostatic fossa (EQD 2/1.5 (Gy)) | 70.0 (57.6–72) | | | |
| PET-pos. pelvic LN (EQD 2/1.5 (Gy)) | 60 (40–66.4) | | | |
| PET-pos. paraaortic LN (EQD 2/1.5 (Gy)) | 50.9 (47.9–98.57) | | | |
| PET-pos. bone met. (EQD 2/1.5 (Gy)) | 56 (40–108.57) | | | |
| PET-pos. visceral met. (EQD 2/1.5 (Gy)) | 93.93 (57.8–300) | | | |

*ADT*, androgen deprivation therapy; *RT*, radiation therapy; *SBRT*, stereotactic body radiotherapy; *SIB*, simultaneously integrated boost; *met.*, metastases

**Table 4** Outcome after salvage radiotherapy

| | All patients | | | Oligo-pelvis | | | Oligo-body | | |
|---|---|---|---|---|---|---|---|---|---|
| | 359 | | | 224 | | | 135 | | |
| Median follow-up (months) | 16 (1–57) | | | | | | | | |
| PSA at last follow-up (ng/mL) | $n = 351$* | | | $n = 219$ | | | $n = 132$ | | |
| Median PSA | 0.18 (< 0.03–128.00) | | | 0.08 (< 0.03–25.8) | | | 0.39 (< 0.03–128) | | |
| PSA at last follow-up without ADT (ng/mL) | $n = 288$ | | | $n = 183$ | | | $n = 105$ | | |
| Median PSA | 0.27 (< 0.03–128.00) | | | 0.11 (< 0.03–25.80) | | | 0.81 (< 0.03–128.00) | | |
| | Clinical progress after MDR | | | | | | | | |
| | Oligo-pelvis ($n = 224$) | | | | | | | | |
| | In-field control | | | Ex-field progression | | | | | |
| Local recurrence only within prostatic fossa ($n = 75$) | 45/47 (96%) | | | 4/47 (9%) | | | | | |
| | Missing information in 28 pts | | | Missing information in 28 pts | | | | | |
| Pelvic LN recurrence + local recurrence ($n = 32$) | 18/19 (95%) | | | 3/18 (17%) | | | | | |
| | Missing information in 13 pts | | | Missing information in 14 pts | | | | | |
| Pelvic LN recurrence ($n = 117$) | 86/89 (97%) | | | 21/89 (24%) | | | | | |
| | Missing information in 28 pts | | | Missing information in 28 pts | | | | | |
| Oligo-pelvis | 149/155 (96%) | | | 28/154 (18%) | | | | | |
| | Missing information in 69 pts | | | Missing information in 70 pts | | | | | |
| | Oligo-body (n = 135) | | | | | | | | |
| | In-field control | | | Ex-field progression | | | | | |
| Paraaortic LN metastases ± locoregional recurrence ($n = 51$) | 37/41 (90%) | | | 17/40 (43%) | | | | | |
| | Missing information in 10 pts | | | Missing information in 11 pts | | | | | |
| Distant metastases ± locoregional recurrence ($n = 84$) | 53/57 (93%) | | | 27/56 (48%) | | | | | |
| | Missing information 27 pts | | | Missing information 28 pts | | | | | |
| Oligo-body | 90/98 (91%) | | | 44/96 (46%) | | | | | |
| | Missing information in 37 pts | | | Missing information in 39 pts | | | | | |
| Death | 4 | | | | | | | | |
| Tumor-related | 3 | | | | | | | | |
| Toxicity | Acute toxicity ($n = 358$) | | | | Late toxicity ($n = 358$) | | | | |
| | *n* (%) | | | | *n* (%) | | | | |
| | Grade 2 | Grade 3 | Grade 4 | | Grade 2 | Grade 3 | Grade 4 | | |
| GU | 31/359 (9%) | - | - | | 12/359 (3%) | 1/359 (0.2%) | - | | |
| GI | 49/359 (14%) | 1/359 (0.2%) | - | | 24/359 (7%) | 4/359 (1%) | - | | |
| Other | 4 (1%) | 1/359 (0.2%) | - | | 6 (2%) | 2/359 (0.5%) | - | | |

*ADT*, androgen deprivation therapy; *MDR*, metastasis-directed radiotherapy; *LN*, lymph node; *GU*, urogenital; *GI*, gastrointestinal

*Missing information in 8 pts

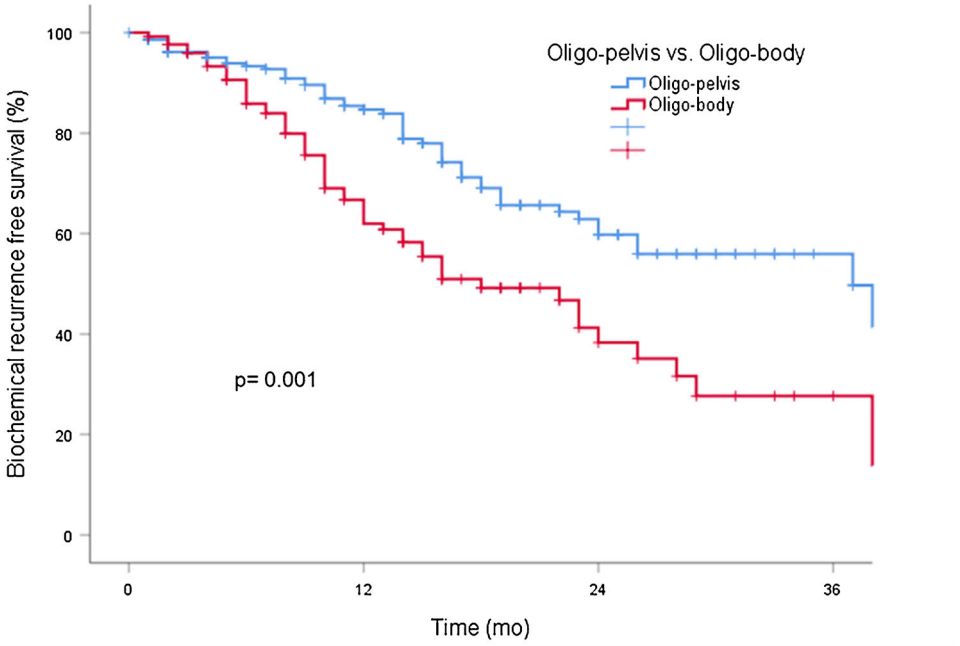
positive lymph node metastases with BRFS (Table 5). In patients with local recurrence within the prostatic fossa, a biochemical control rate of 80% was achieved compared with 48% in patients with paraaortic lymph node metastases (Table 6). Overall, 88/359 (25%) of all patients received further treatments after MDR—this was significantly higher in oligo-body patients compared with oligo-pelvis patients (38% vs. 17%, $p = 0.001$).

## Toxicity

Acute grade 3 toxicity was observed in two patients consisting of diarrhea and lymphatic edema (Table 4). Acute grade 2 gastrointestinal toxicity occurred in 49/359 (14%) patients with primarily symptoms of diarrhea and proctitis, and acute grade 2 urogenital toxicity in 31/359 (9%) patients with signs of cystitis and urinary incontinence. Late toxicity occurred overall in 49/359 (14%) patients with mainly grade 2 gastrointestinal (24/359; 7%) or urogenital toxicity (12/359; 3%). Late grade 3 toxicity was present in 7/359 (2%) patients with signs of proctitis, urinary incontinence, and erectile dysfunction. There was no significant difference in acute and late toxicity between the oligo-pelvis and oligo-body cohort.

## Discussion

Overall, an accurate assessment of metastatic disease stage using radiologic imaging techniques is in the absence of molecular predictors of metastatic state especially essential. The introduction of PSMA PET imaging has substantially improved the detection and localization of metastatic disease and possibly allows for better selection of patients who might benefit from local therapy [2, 39–41]. This has led to recent guidelines by the European Organization for Research and




| Number at risk | | | | |
|---|---|---|---|---|
| Oligo-pelvis | 213 | 114 | 39 | 9 |
| Oligo-body | 128 | 52 | 13 | 2 |

**Fig. 2** Biochemical recurrence-free survival in patients with oligo-pelvis vs. oligo-body recurrence

Treatment of Cancer (EORTC) on the use of modern imaging methods for trials of MDT in oligo-metastatic PCa [42].

As systemic therapy for patients with hormone-sensitive oligo-metastatic PCa is non-curative, MDR may improve survival outcome by delaying disease progression. This hypothesis is supported by a recent study on whole-genome sequencing in PCa that claims that metastatic lesions can possibly transform and be the origins of accelerated metastasis-to-metastasis spread [43]. Thus, with MDR to oligo-recurrent PCa after initially curative treatment of primary disease being more and more frequently offered, this retrospective analysis aims to study whether patients with the various stages of locally vs. distant recurrent disease do profit from MDR alike.

Based on its retrospective nature, this analysis has limitations due to differing institutional treatment protocols, particularly for ADT, additional EBRT to non-involved sites like the prostatic fossa or the whole of the lymphatic pathways, and follow-up procedures, as imaging strategies after MDR were not identical. A further shortcoming of the present analysis that precludes drawing final conclusions is the short follow-

**Table 5** Factors associated with biochemical recurrence-free survival after MDR

| Association with BRFS (< nadir + 0.2 ng/mL) | *p* value[a] | *p* value[b] |
|---|---|---|
| Oligo-pelvis vs. oligo-body | 0.001 | 0.001 |
| Local recurrence vs. pelvic LN recurrence ± local recurrence | 0.174 | - |
| Pelvic LN recurrence + local recurrence vs. pelvic LN recurrence alone | 0.305 | - |
| Pelvic LN recurrence ± local recurrence vs. paraaortic LN metastases ± locoregional recurrence | 0.087 | - |
| Paraaortic LN metastases ± locoregional recurrence vs. distant metastases ± locoregional recurrence | 0.444 | - |
| Number of PET-pos. LN ≤ 2 vs. > 2 (pelvic) | 0.962 | - |
| Number of PET-pos. LN ≤ 2 vs. > 2 (pelvic/paraaortic) | 0.553 | - |
| Patients with PSA-persistence vs. PSA recurrence | 0.150 | - |
| Concomitant ADT with MDR | 0.001 | 0.001 |

[a] Univariate Cox regression analysis

[b] Multivariate Cox regression analysis

*MDR*, metastasis-directed radiotherapy; *BRFS*, biochemical recurrence-free survival; *LN*, lymph node; *ADT*, androgen deprivation therapy

**Table 6** Biochemical recurrence-free survival at last follow-up

| | BRFS (< nadir + 0.2 ng/mL) |
|---|---|
| Oligo-pelvis ($n = 224$) | 74% |
| Local recurrence only ($n = 75$) | 80% |
| Pelvic LN recurrence + local recurrence ($n = 32$) | 70% |
| Pelvic LN recurrence alone ($n = 117$) | 71% |
| Pelvic LN recurrence ± local recurrence ($n = 149$) | 71% |
| Oligo-body ($n = 135$) | 51% |
| Paraaortic LN metastases ± locoregional recurrence ($n = 51$) | 48% |
| Distant metastases ± locoregional recurrence ($n = 84$) | 54% |

*LN*, lymph node

up. Hence, at best, our primary endpoint, BRFS, may serve as a surrogate marker for PCa-specific or overall survival. Nevertheless, we detected a significantly better BRFS for oligo-pelvis in comparison with oligo-body patients and for with MDR concomitant ADT use. For all other patterns of recurrence, like local vs. pelvic nodal recurrence, local plus pelvic nodal recurrence vs. pelvic nodal recurrence alone, pelvic vs. paraaortic lymph node metastases, and paraaortic lymph node vs. distant metastases, no such difference in BRFS was seen in the present study.

This is most likely due to the small number of patients in the studied subgroups. Although, neither a significant interaction between the effect of MDT and the location of metastases (i.e., with vs. without lymph node involvement) was observed in the study by Ost et al., the first randomized trial of MDT to all lesions vs. surveillance alone for patients with oligo-recurrent PCa staged with choline PET/CT [27]. Likewise, BRFS was not affected by site (bone vs. lymph node metastases) in the study by Kneebone et al. prospectively treating oligo-metastatic PCa (one to three metastases) with SBRT [20]. However, with overall only 62 and 57 patients enrolled in both studies, the small sample size used for subgroup analyses is a limiting factor.

Nevertheless, as one might expect, a reduction in biochemical control was observed once disease recurred outside the prostatic fossa. The biochemical control was 80% in patients with local recurrence confined to the prostatic fossa compared with 70%, 48%, and 54% in patients with pelvic, paraaortic lymph node, or distant bone/visceral metastases. This reduction in biochemical control is primarily explained by the progress to poly-metastatic disease in patients with distant lymph node or bone/visceral metastases: While in-field control in patients with pelvic, paraaortic lymph node, and distant metastases was with ≥ 90% high, in up to half of patients with paraaortic lymph node or distant metastases, an ex-field progress within the relatively short follow-up of median 16 months was observed. This corresponds to the results of Ost et al., equally observing a progress to poly-metastatic disease in 30% of patients within the first year [27]. Further, the high ex-field progress in oligo-body patients might reflect the fact that these patients have a more systemic than localized disease with PSMA PET/CT underestimating the true extent of disease in particular for small lymph node metastases < 3 mm [44]. Thus, MDR particularly in oligo-metastatic patients with distant lymph node, bone, or visceral metastases is controversial and one can argue that these patients might profit more from approved systemic therapies, e.g., androgen receptor antagonists like enzalutamide [45] or chemotherapy like docetaxel [46] or possibly from lutetium-177-PSMA radioligand therapy, as evaluated in the pilot study "Lutetium-177-PSMA-617 in low volume metastatic prostate cancer" [47].

Overall, a large number of patients presented with PET-positive extra-pelvic disease (38%) in the present analysis and thus would not be cured by EBRT based on standard clinical target volumes according to RTOG [9]. This was equally observed by De Bari et al. describing an even higher number of patients with extra-pelvic disease (75%) that would not be adequately covered by clinical target volume definitions according to RTOG [48]. Thus, based on PSMA PET/CT, a more individualized approach in clinical target volume definition is possible with potentially better clinical outcome by expanding target volumes to areas that are routinely not treated.

Two other prospective studies with overall small number of patients have shown a benefit of SBRT in oligo-metastatic PCa: In the POPSTAR study, SBRT was equally associated with an excellent 2-year local progression-free survival of 93% in the 33 included patients with oligo-metastatic PCa (one to three lesions) and with a 2-year distant progression-free survival of 39% [26]. So far, only interim results of the ORIOLE trial are available, in which patients with ≤ three asymptomatic metastases after primary RPE or EBRT were randomized between SBRT to all metastases vs. surveillance. Overall, progression at 6 months was lower in the SBRT vs. observation arm (33% vs. 67%) after recruitment of 36 out of a planned 54 patients [49].

Apart from EBRT, salvage lymph node dissection (SLND) is a further option in patients with pelvic and/or paraaortic lymph node recurrences after radical prostatectomy. This has been extensively studied with choline PET/CT [50, 51] with 5-year BRFS ranging from 19 to 25%, respectively. In patients who were explicitly staged with PSMA PET/CT, 1-year BRFS ranged from 23 to 64% [52]. Although such head-to-head comparisons are not without caveats due to differing patient characteristics, surgery, and EBRT approaches, e.g., limited vs. extensive SLND and SBRT vs. whole pelvis EBRT and adjuvant treatments, this rate is comparable with the present cohort with BRFS ranging from 48 to 71% in patients with paraaortic and/or pelvic lymph node recurrences. In regard to toxicity, most complications reported in patients with SLND

were of low grade with mostly lymphorrhea and symptomatic lymphoceles [52]. In contrast, the most frequent low-grade toxicity reported in the present EBRT cohort was diarrhea, proctitis, cystitis, and urinary incontinence as well as erectile dysfunction.

Overall, it is worth mentioning that the optimal treatment of oligo-recurrent PCa remains open to many questions: In patients with recurrent nodal involvement, various treatment strategies like SBRT alone vs. SLND with/without adjuvant whole pelvis radiotherapy (WPRT) vs. WPRT with/without SIB or SBRT are viable options. Furthermore, as described above, the benefit of combining MDR with systemic therapies such as first or second line ADT, like abiraterone [24, 53, 54], is not fully answered. In addition, selecting patients via circulating tumor cells/DNA to identify potentially curable metastatic disease would be desirable [55]. Despite these open questions and the so far primarily retrospective evidence based on different treatment strategies and definitions of oligo-metastatic PCa [12, 27, 56–66], approximately two-thirds of the experts at the 2017 Advanced Prostate Cancer Consensus Conference have already considered MDT a treatment option for patients with oligo-recurrent PCa [11].

In conclusion, this large, multicenter study showed that MDR of PSMA PET-positive oligo-metastases is feasible with low rates of toxicity. Overall, the outcome after MDR depended on the status of oligo-recurrent disease like oligo-pelvis as compared with oligo-body. Thus, MDR of PSMA PET-positive oligo-metastases can be offered considering that in about one-third of patients, disease progression was detected within a median follow-up of 16 months. However, further phase III trials are necessary to answer the questions, addressed above, before MDR can be considered a standard of care in oligo-metastatic PCa.

**Author contributions** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by N.-S. Schmidt-Hegemann, S.G.C. Kroeze, C. Henkenberens, M.M.E. Vogel, S. Kirste, and J. Becker. The first draft of the manuscript was written by N.-S. Schmidt-Hegemann, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committees of the respective Medical Faculties (Business Administration System for Ethics Committees Number (BASEC-Nr. 2017–01499)) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** This retrospective multicenter study was undertaken in six university hospitals in Switzerland and Germany, was approved by the local Ethics Committee of the respective Medical Faculties (BASEC-Nr. 2017–01499), and the need for written informed consent was waived.

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