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^{68}Ga-PSMA Ligand PET/CT-based Radiotherapy for Lymph Node Relapse of Prostate Cancer After Primary Therapy Delays Initiation of Systemic Therapy

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Abstract. *Aim: To evaluate ^{68}Ga-PSMA ligand positron-emission tomography–computed tomography (PET/CT)-based radiotherapy for lymph node metastases of prostate cancer after primary therapy. Patients and Methods: Twenty-three patients received radiotherapy for PSMA ligand-positive lymph node metastases. Results: The median follow-up time was 12.4 (range=6.0-28.5) months. The median pre-treatment prostate-specific antigen (PSA) decreased from 2.75 (range=0.52-8.92) ng/ml to a nadir of 1.37 (range=0.11-8.00) ng/ml (p=0.001) following radiotherapy. Except for one patient (4.4%), PSA level decreased in 22 patients (95.6%). The biochemical failure-free survival and time to initiation of systemic therapy at the median follow-up were 95.6% and 100%, respectively. Three patients (12.9%) presented with recurrent disease outside the initial radiation field. No grade III acute toxicities or late grade II toxicities were observed. Conclusion: ^{68}Ga-PSMA ligand PET/CT-based radiotherapy is a promising local treatment option for isolated lymph node metastases of prostate cancer.*

Among patients with prostate cancer, tumor relapse after primary therapy particularly occurs in high-risk groups. The standard of care for distant relapse of prostate cancer is androgen-deprivation therapy (ADT), which has a negative impact on the patient's quality of life (1). Recently alternative local treatment strategies have been proposed for patients with oligometastatic disease, who have a better prognosis than patients with extensive disease (2). Local therapies such as radiotherapy could provide effective local control, delay disease progression and therefor reduce the need to initiate systemic therapies (3). The identification of patients with oligometastatic prostate cancer is challenging due to the lack of sufficiently sensitive imaging for detection of low-volume recurrent and metastatic disease in patients with low prostate-specific antigen (PSA) levels (2). In general, positron-emission tomography–computed tomography (PET/CT) for radiotherapy has proven helpful in patient selection and target volume delineation, with promising results regarding clinical outcome and toxicity (4, 5). A new diagnostic option in this context is the use of prostate-specific membrane antigen (PSMA) ligands for PET/CT. ^{68}Ga-PSMA ligand PET/CT has been reported to have a substantially higher diagnostic accuracy for the detection of prostate cancer metastases than choline-based PET/CT, particularly in the case of lymph node metastases (6-10). Data on the effectiveness of ^{68}Ga-PSMA ligand PET/CT-based radiotherapy for prostate cancer lymph node metastases after primary therapy are limited.

The aim of the present study was to assess the clinical outcome and time of initiation of systemic therapies (ADT or chemotherapy) of patients with isolated prostate cancer lymph node metastases after primary therapy treated with ^{68}Ga-labelled PSMA ligand PET/CT-guided 3D conformal radiotherapy.

Patients and Methods

Study population. Between June 2014 and March 2016, 23 patients with biochemical failure and a PSA above 0.5 ng/ml after primary therapy of prostate cancer underwent ^{68}Ga-PSMA ligand PET/CT for restaging purposes and were treated with radiotherapy of the ^{68}Ga-PSMA ligand PET/CT-positive lymph nodes. All cases were discussed

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Key Words: PSMA-PET/CT, radiotherapy, recurrent prostate cancer, lymph node metastases, systemic therapy.

Table I. *Patient characteristics*.

Pt. no.	Age (years)	Stage	Gleason	PSA (ng/ml) iPSA	Nadir	Doubling time, months	Before PET	PET/CT result	Prior therapy	PSA (ng/ml) Nadir after RT	Final
1	79	pT2c pN0	7	8.93	<0.07	11.9	1.25	li.	RP, LAD	1.56	2.70
2	72	pT3b pN1	9	4.1	0.41	11.2	2.76	li., ri.	RP, LAD, RT-P	1.60	3.93
3	71	pT2c pN0	8	9.3	1.19	4.1	1.66	li., ri. presacral	RP, LAD, ADT	0.11	0.11
4	64	pT3b pN0	7	12.0	0.68	16.1	1.47	li., ri.	RP, LAD	0.93	3.43
5	62	pT3a pN0	7	16.8	0.42	4.5	1.67	ri.	RP, LAD, RT-P	0.19	1.35
6	68	pT2c pN0	7	3.69	<0.07	9.1	1.17	li.	RP, LAD, RT-P	0.33	3.20
7	69	cT1c cN0	6	6.7	0.1	4.8	1.09	li., ri.	RT-P	0.28	2.90
8	74	pT3b pN0	7	6.88	0.11	18.2	0.53	para-aortic	RP, LAD, RT-P,	0.23	0.23
9	65	pT2c pN0	7	16.43	0.08	0.9	3.26	li., ri. presacral	RP, LAD, RT-P, ADT	1.41	183.77
10	75	pT2a pN0	6	5.23	<0.07	1.7	8.69	retroperitoneal	RP, LAD, RT-P, ADT	8.00	8.00
11	51	pT3a pN1	9	22.25	1.91	4.7	2.75	li., ri.	RP, LAD, ADT	0.14	2.65
12	78	pT3b pN0	8	64.00	0.02	11.6	8.92	li., presacral	RP, LAD, RT-P, ADT	4.30	4.30
13	63	pT2c pN0	7	7.60	<0.07	6.6	4.60	li,	RP, LAD, RT-P, RT-Ln	6.19	0.18
14	86	pT2a pN0	8	11.40	<0.07	63.8	9.58	li., para-aortic	RP, LAD, RT-P, ADT	1.49	1.49
15	75	pT2c pN0	8	16.20	<0.07	6.9	6.33	li.	RP, LAD, RT-P	4.47	4.47
16	73	pT2c pN0	8	6.58	<0.07	9.6	2.40	li.	RP, LAD, RT-P, ADT	1.18	1.18
17	71	pT3a pN0	7	8.21	0.19	5.2	0.52	ri.	RP, LAD, RT-P, ADT	0.17	0.90
18	66	pT2c pN0	8	19.50	<0.07	5.5	2.20	ri.	RP, LAD, RT-P	1.37	1.37
19	73	pT3b pN1	7	29.00	<0.07	2.8	1.45	li., para-aortic	RP, LAD, RT-P, ADT	1.13	1.13
20	63	pT2c pN0	7	6.70	<0.07	8.1	5.70	li.	RP, LAD, RT-P	3.98	4.50
21	72	pT3b pN0	6	4.63	<0.07	9.6	2.92	li., para-aortic	RP, LAD, RT-P	0.24	0.24
22	79	pT2c pN0	8	9.10	<0.07	4.5	4.50	li., ri.	RP, LAD, ADT	3.58	3.58
23	77	pT3a pN0	7	9.70	<0.07	6.2	8.27	li., ri.	RP, LAD	4.83	4.83

Stage: Initial tumor stage; iPSA: initial PSA; PSA nadir: minimal value after primary therapy; PET/CT: ligand positron emission tomography–computed tomography; li: uptake in left iliac lymph nodes; ri: uptake in right iliac lymph nodes; ADT: androgen-deprivation therapy; RP: radical prostatectomy; LAD: pelvic lymphonodectomy; RT-P/RT-Ln: radiotherapy of prostate/pelvic lymph nodes.

and approved by the local multidisciplinary uro-oncologic team. Twenty out of 23 (86.85%) patients had high-risk cancer, one had intermediate (4.35%) and two (8.7%) presented with low-risk cancer. The median PSA at the time of ^{68}Ga-PSMA ligand PET/CT was 2.75 (range=0.52-8.92) ng/ml, with a median PSA doubling time of 6.6 (range=0.9-63.8) months. Patient characteristics are shown in Table I.

Staging. Staging included physical examination with digital rectal palpation, complete laboratory tests, ^{68}Ga-PSMA ligand PET/CT, and magnetic resonance imaging of the pelvis in the case of pelvic lymph node metastasis.

Synthesis of the PSMA-targeting ligand and PET/CT imaging. ^{68}Ga-PSMA I&T (11) was synthesized as recently reported (12) using a standardized labeling sequence with 22.5 μg (15 nmol) of PSMA I&T (Technical University of Munich, Germany). All studies were obtained on a dedicated PET/CT system (Siemens Biograph mCT 128 Flow; Siemens, Knoxville, TX, USA). The patients received an intravenous injection of median dose of 79 MBq (range=52-149 MBq) of the ^{68}Ga-PSMA ligand (13). All studies were reconstructed identically using time-of-flight and point-spread function information combined with an iterative algorithm.

TD and FMB performed PET/CT interpretation. Focally increased tracer uptake in the pelvic and retroperitoneal lymph nodes was defined as malignant lymph node relapse.

Radiotherapy. Radiotherapy planning was carried out with Oncentra® Masterplan (Elekta, Stockholm, Schweden). Image fusion was performed using the mutual information algorithm for fusion of PET/CT with planning CT images. Patients were irradiated five times weekly with 2.0 Gy up to a total dose of 50.4-54.0 Gy. The maximum dose for the intestine was kept below 50.0 Gy. The radiation dose in one patient (4.3%) was limited to 40 Gy due to former pelvic irradiation. The pathological findings in the planning CT, low-dose CT of the ^{68}Ga-PSMA ligand PET/CT and magnetic resonance imaging in cases of pelvic irradiation were defined as the gross target volume (GTV). The clinical target volume (CTV) consisted of the area with pathological tracer uptake. A 10-mm safety margin in all directions around the CTV formed the planning target volume (PTV). Overlapping PTVs were simplified in a fusion volume. Image guidance during radiotherapy was conducted twice a week with a megavoltage cone beam CT.

During radiotherapy, acute side-effects were assessed weekly by clinical examination according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (14).

Follow-up and outcome. All patients had a follow-up visit with the radio-oncologist 3 months after irradiation and annually thereafter to assess late side-effects more than 3 months after the last irradiation according to the LENT-SOMA scale (15). Uro-oncological follow-up was carried out on a 3-month basis and included clinical

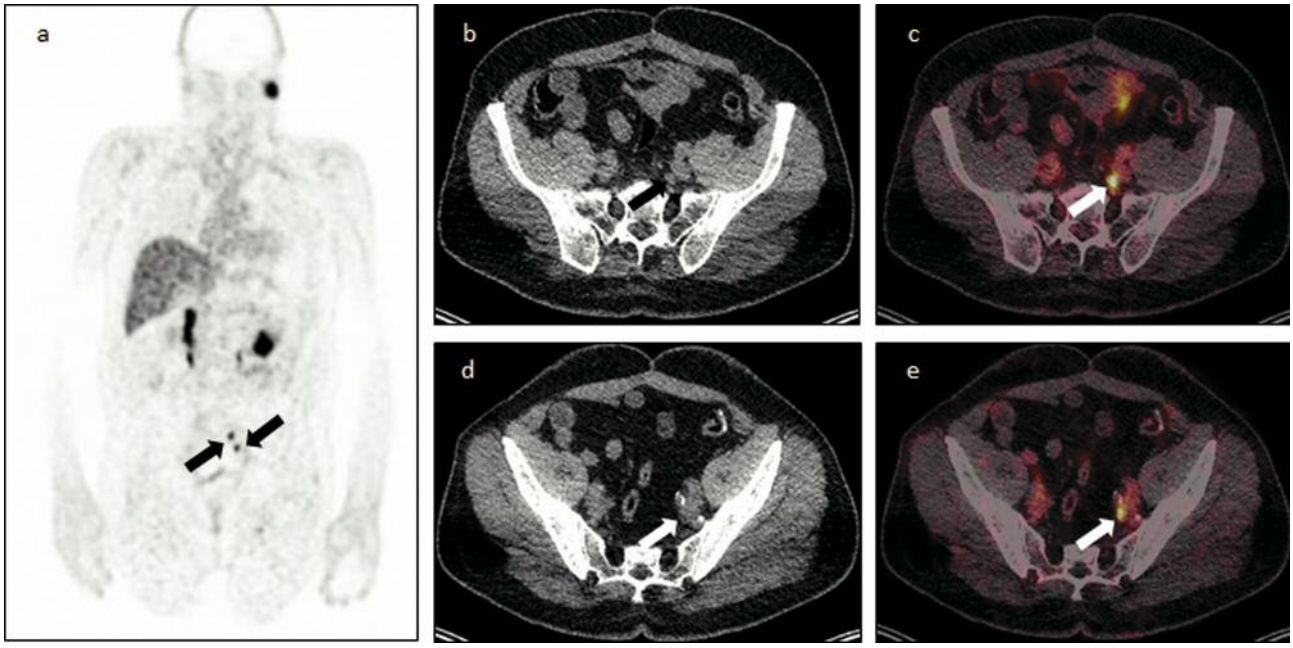

Figure 1. *^{68}Ga prostate-specific membrane antigen ligand positron-emission tomography–computed tomography in a 72-year-old patient. Coronal positron-emission tomography (a), corresponding axial computed tomography (b, d), and fused images (c, e) showing two lymph node metastases (arrows), but no evidence of disease in other localizations.*

examination and PSA measurement. A new ^{68}Ga-PSMA ligand PET/CT for re-staging of disease was performed in the case of increased PSA above baseline level prior to radiotherapy. Furthermore a bone scan was also conducted. If the PSA level was below that at baseline, neither a ^{68}Ga-PSMA ligand PET/CT nor a bone scan was performed. In cases of new metastases, a systemic therapy of the urologist's choice or local therapy was initiated. Outcomes were defined from the last day of irradiation. Biochemical failure was defined as any PSA increase after radiotherapy above the baseline PSA level prior to irradiation. Furthermore, we assessed the interval until ADT or chemotherapy was initiated.

Statistical analysis. Outcomes were defined from the last day of irradiation. Kaplan–Meier curves were used to estimate the biochemical failure-free survival (BFFS) and the time to initiation or escalation of systemic therapy (TIST). Statistical analysis was performed using commercially available software packages (SPSS 24.0 for Windows; IBM Corp., Armonk, NY, USA).

Results

^{68}Ga-PSMA ligand PET/CT. ^{68}Ga-PSMA ligand PET/CT was positive in all cases (100%). A total of 7/23 (30.4%) patients presented with unilateral and 5/23 (21.8%) with bilateral positive pelvic tracer uptake. In 9/23 (39.1%), ^{68}Ga-PSMA ligand PET/CT showed pelvic plus extrapelvic pathological tracer uptake. Two out of 23 patients (8.7%) had extrapelvic positive lymph nodes without being positive for pathological pelvic ^{68}Ga-PSMA ligand tracer uptake. Example images of lymph node metastases are shown in Figure 1 and example images of radiation treatment plans for multiple bilateral pelvic lymph node metastases are shown in Figure 2.

Efficacy and patterns of relapse. The median follow-up was 12.4 months (range=6.2-28.5) months. No patient died during the study interval, therefore overall survival was 100%. The median PSA prior to radiotherapy was 2.75 ng/ml (range=0.52-8.92 ng/ml) and the PSA nadir statistically significantly decreased to 1.37 ng/ml (range=0.11-8.00 ng/ml; p=0.001), with a decrease to 2.7 ng/ml for the last available PSA measurement (range=0.11-183.77 ng/ml; p=0.39). With the exception of one patient (4.3%), a PSA decrease was observed in the other 22 (95.7%) patients. In this patient, the dose had been limited to 40.0 Gy due to former pelvic irradiation. Eleven patients (47.8%), including the patient who did not have an initial PSA decrease, presented with a PSA increase until their last follow-up visit. One out of 11 patients (9.1%) declined PSMA-PET/CT restaging and chose ADT. In 10/11 (90%) patients, the ^{68}Ga-PSMA ligand PET/CT showed disease relapse in the form of para-aortic and retroperitoneal (6/11; 54.5%), mediastinal lymph node metastases (2/11; 18.2%) or extensive diffuse bone metastases (2/11; 18.2%) outside

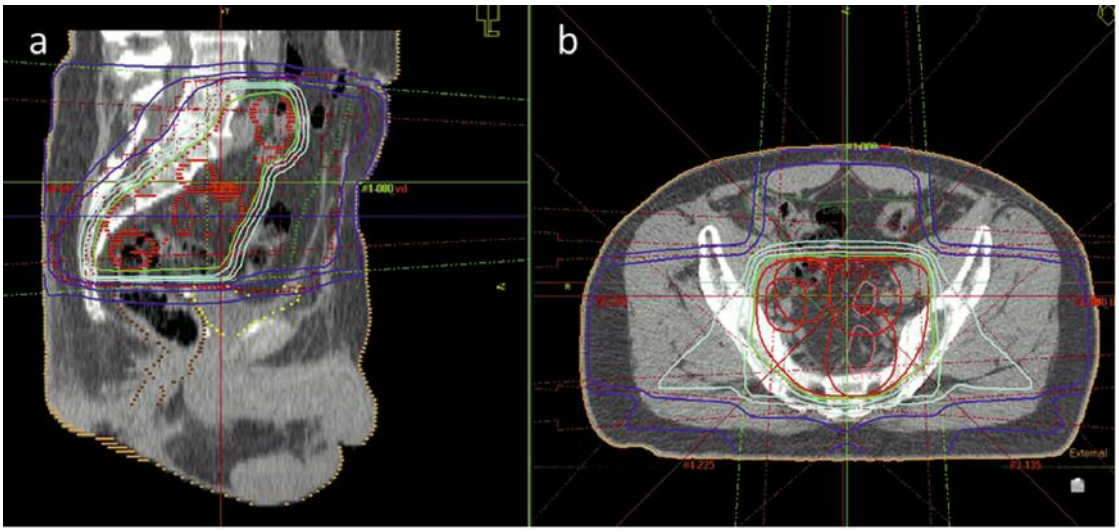

Figure 2. *Example of a radiotherapy treatment plan [sagittal (a) and axial (b)] for multiple ^{68}Ga prostate-specific membrane antigen ligand-positive pelvic lymph nodes.*

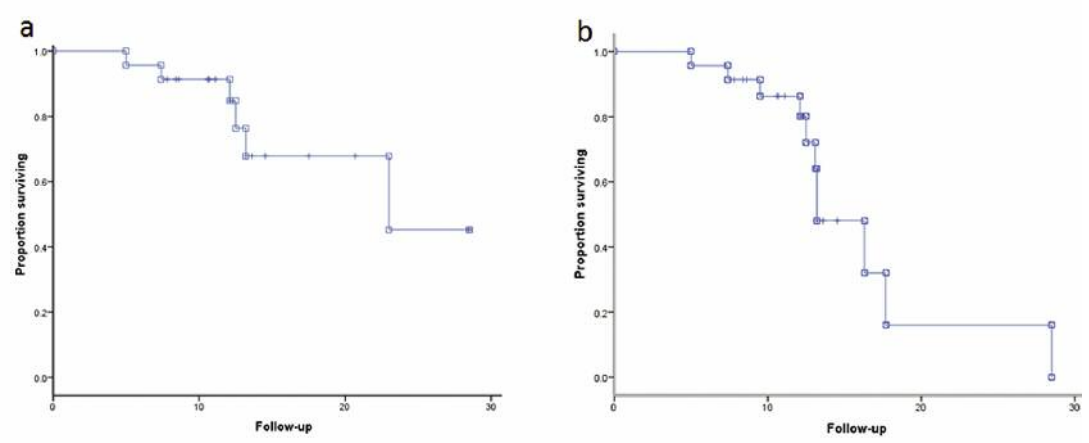

Figure 3. *Kaplan–Meier survival curves for time to initiation or escalation of systemic therapy (TIST) (a) and biochemical failure-free survival (BFFS) (b). At a median follow-up of 12.4 months, TIST was 84.8% and BFFS was 72.1%.*

the radiotherapy fields. The irradiated lymph nodes showed no pathological tracer uptake, resulting in a local control rate of at least 95.6% after a median follow-up of 12.4 months due to one unknown relapse pattern. Six out of 11 (54.5%) patients declined ADT and instead chose irradiation of the para-aortic or retroperitoneal lymph nodes, whereas ADT or chemotherapy was initiated in the two patients with mediastinal lymph node relapse (2/11; 18.2%) and the two patients with bone metastases (2/11; 18.2%), respectively. One of the six patients (16.7%) who chose re-irradiation of lymph node metastases out of the radiotherapy field presented with bone metastases 9.9 months after second irradiation and received ADT.

The BFFS was 72.1% and the TIST was 84.8% at a median follow-up of 12.4 months. The estimated mean survival durations for BFFS and TIST were 15.9 and 21.6 months, respectively (Figure 3).

Toxicity. No grade III acute toxicity according to CTCAE nor late toxicity grade II according to LENT-SOMA were observed. Furthermore, no acute or late genitourinary toxicities were observed. Five patients (21.7%) presented with grade II diarrhea according to CTCAE V. 4.0. Two patients (8.7%) reported persistent grade I diarrhea according to the LENT-SOMA criteria 3 months after radiotherapy. In addition, deterioration of urinary or fecal continence was not observed in any patient.

Discussion

The quality of imaging for biochemical failure after primary prostate cancer therapy is essential to distinguish between local relapse in the prostatic fossa, extraprostatic oligometastatic relapse and widespread extensive disease. The recent introduction of PSMA ligands for PET/CT has dramatically improved diagnostic accuracy and ^{68}Ga-PSMA ligand PET/CT is superior to all other imaging modalities, particularly in patients with a low PSA level (10), yielding a specificity >95% for resected lymph nodes (16, 17). It is therefore the most promising imaging modality for patient selection and target volume delineation for radiotherapy of prostate cancer recurrence outside the prostatic fossa (18), particularly in the context of less aggressive oligometastatic cancer spread (1). Therefore, local therapies such as radiotherapy to eradicate and control limited metastasis is a therapeutic approach to delaying disease progression and use of systemic therapies without systemic side-effects (2). This emphasizes the great importance of high imaging accuracy at low PSA levels for salvage radiotherapy in order to customize patient treatment. PSMA ligand PET imaging has proven to correlate highly with histopathological findings (16, 17, 19) and is more sensitive than computed tomographic-based 3D volumetric assessment for lymph node relapse after primary prostate cancer therapy (20). To our knowledge, there are no general recommendations for the optimal PSA detection threshold and there is always the risk of non-detection of metastases in patients with low PSA levels, although some data suggest a detection threshold of at least 0.83 ng/ml (21). In our analysis, the median PSA at the time of ^{68}Ga-PSMA ligand PET/CT was 2.75 ng/ml. Therefore, we assume that staging by PSMA ligand PET/CT was reliable, which is supported by the observed improvement of the PSA level after radiotherapy. We also show that ^{68}Ga PSMA PET/computed tomographic-based radiotherapy delayed the necessity for initiating ADT or chemotherapy in patients who had developed lymph node metastases despite ADT. In analogy to the pre-PSMA PET/CT era, this observation might offer the opportunity to prolong the duration of the prognostically important first off-treatment interval, which is the clinically relevant time to castration resistance and death in men with biochemical relapse of prostate cancer (22). Furthermore, it was already shown that multimodal primary treatment of metastatic prostate cancer with ADT and radiotherapy is safe and provides improved survival (23).

Although external-beam radiotherapy is a well-established salvage therapy in biochemically recurrent prostate cancer after prostatectomy, it achieves a better response if initiated below a PSA level of 1 ng/ml (24). The median PSA level of 2.75 ng/ml in the present analysis was much higher. Therefore, we do not know if earlier PSMA PET/CT scans at a lower median PSA level followed by radiotherapy might have resulted in better clinical outcomes.

We observed no severe acute or late radiotherapy-associated side-effects, as no grade III acute or grade II late toxicities were observed during radiotherapy nor at the periodic follow-up visits, respectively. Only two patients (8.7%) reported persistent grade I diarrhea according to the LENT-SOMA criteria 3 months after radiotherapy. Moreover, deterioration of urinary or fecal continence did not occur in any patient.

There is also the option to perform salvage lymph node dissection of the pelvis with (25, 26) or without (27, 28) adjuvant radiotherapy, taking into account that adjuvant irradiation results in delayed relapse within the treated region, but has no effect on the relapse pattern outside the treated region. Therefore, the combination of two local treatment modalities within the same anatomic region does not offer any additional benefit for patients with prostate cancer (27). In addition, surgery has the risk of common perioperative complications (25-28). To our knowledge, no prospective studies comparing salvage lymph node dissection with or without radiotherapy using PSMA-PET/CT for staging purposes have been conducted.

The biologically optimal radiation dose remains unknown due to the absence of a reliable radiobiological dose model for lymph node metastases in prostate cancer. Niyazi *et al*. published a mathematical model, based on several simplifications, assuming various PET detection rates and radiosensitivity values to estimate the effect of dose escalation on intraprostatic lesions (29). Their conclusions were cautious about the clinical relevance of that mathematical approach. Schick *et al*. reported in series of patients with fewer than five regional or distant metastases from prostate cancer that the BFFS was statistically significant dependent on a radiation dose >64 Gy (30). This is confirmed by our observation that the patient who received radiotherapy with a dose of 40 Gy showed no PSA decrease at the first PSA measurement 3 months after radiotherapy. We also cannot rule out that a higher dose of radiation, compared with the dose of 50-54 Gy in this series, may have further improved the clinical results.

Ten out of 23 patients (43.5%) developed recurrence outside of the initial radiation field. However, no recurrence within the initial radiation field was observed in this study, underlining the high efficacy of radiation therapy in the treatment of ^{68}Ga-PSMA ligand PET/CT-positive lymph node metastases. Based on this finding, one may hypothesize that combining external beam radiotherapy with ^{68}Ga-PSMA ligand radionuclide therapy for eradication of subclinical metastases not detectable with PSMA ligand PET/CT scans may be a beneficial approach in selected patients, as radionuclide therapy recently demonstrated considerable efficacy in castration-resistant metastasized prostate cancer (31).

Some limitations of this study are its retrospective character, that might have introduced a selection bias into analysis, and the small sample size, which limits the statistical power, although the observed clinical results are robust. The study assessed a selected cohort with high-risk prostate cancer (86.9%). Therefore, no general statements can be made about ^{68}Ga-PSMA ligand PET/CT-guided radiotherapy salvage radiotherapy for isolated lymph node metastases for patients with intermediate- or low-risk prostate cancer. Nevertheless, the observed clinical outcome of PSMA ligand PET-guided radiotherapy for prostate cancer relapse as lymph node metastases is promising, and clinical outcome data have not been reported before using ^{68}Ga-PSMA ligand PET-guided irradiation.

Conclusion

^{68}Ga-PSMA ligand PET/CT-based radiotherapy for isolated lymph node metastases after primary therapy showed a good risk-benefit ratio, provided effective local control, improved clinically relevant outcome parameters and thus defered the initiation or escalation of systemic treatment. Therefore ^{68}Ga-PSMA ligand PET/CT-guided radiotherapy for isolated lymph node relapse represents a viable treatment option in well-selected patients.

Conflicts of Interest

Hans-Jürgen Wester is the CEO of Scintomics. The other Authors declare that they have no conflicts of interest in regard to this study.

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