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Original Article

^{68}Ga-PSMA-PET/CT helps to select patients for salvage radical prostatectomy with local recurrence after primary radiotherapy for prostate cancer

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Objective

To investigate the diagnostic performance of gallium-68 prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) in patients with recurrent prostate cancer with regard to the presence of lymph node metastases (LNM) and local recurrences after primary radiotherapy.

Patients and methods

We retrospectively reviewed 142 patients following salvage radical prostatectomy (sRP), 50 of which had a ^{68}Ga-PSMA PET/CT performed as a preoperative staging module. Predictive clinical parameters were analysed in a multivariate Cox regression analysis. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) and the accuracy of ^{68}Ga-PSMA PET/CT were analysed with regard to LNM and local recurrence.

Results

In all, 613 lymph nodes were resected in 40 patients and 23 lymph nodes had metastatic deposits in 14 patients. In all patients local recurrence could have been found with ^{68}Ga-PSMA PET/CT. Sensitivity, specificity, PPV and NPV and accuracy on a per lymph node basis were 34.78% (16.38–57.2%), 100% (99.38–100%), 100%, 97.52% (96.69–98.15%) and 97.55% (96.00–98.62%). For detecting local recurrence, the sensitivity and PPV were both 100% with an accuracy of 100% (92.89–100%).

Conclusion

^{68}Ga-PSMA PET/CT should be the standard imaging in biochemical recurrent prostate cancer. With this imaging module one detects first local recurrence and can detect locoregional and distant metastases more precisely than standard CT and bone scan.

Keywords

prostate cancer, ^{68}Ga PSMA-PET, salvage prostatectomy, lymph node metastases, #ProstateCancer, #PCSM

Introduction

The two main local treatment options in patients with prostate cancer for local disease are radical prostatectomy (RP) and radiotherapy (RT). In cases of intermediate- or high-risk disease, androgen-deprivation therapy is also added to RT. Nevertheless, the risk of developing a biochemical recurrence after RT varies between 22% and 69% [1,2]. Salvage radical prostatectomy (sRP) is feasible and is recommended by treatment guidelines in select patients. In recent years there has been a paradigm shift in the treatment of prostate cancer recurrence after primary treatment. Recent improvements in diagnostic imaging have enabled more effective detection of potentially oligometastatic disease [1–5].

Combined integrated positron emission tomography/computed tomography (PET/CT) has played a role in this paradigm shift. The former standard method of PET/CT,

which used radiolabelled choline derivatives, has been superseded by the more accurate PET/CT using ^{68}Ga-labelled small molecule functional antagonists of the prostate-specific membrane antigen (PSMA), wherever such tracer is available [6]. Using ^{68}Ga-PSMA PET/CT, clinically useful results can be expected even with PSA levels of <0.5 ng/mL, although the clinical yield is higher in patients with higher PSA levels, shorter PSA doubling times, and higher Gleason scores [7]. For the overall detection of metastases, the sensitivity of this technique ranges from 64% to 97% and specificity from 93% to 100% [1].

For men with isolated local recurrence, sRP is a treatment option with a 10-year cancer-specific survival of 88.6% [8]. Lymph node metastases (LNM) are associated with poor tumour control and a high risk of systemic relapse [9], thus it is imperative to accurately identify these metastases to identify patients that will likely not benefit from surgery. Currently, there are no data available in the literature on the accuracy of ^{68}Ga-PSMA PET/CT in this patient group. Therefore, the aim of the present study was to investigate the role of intraprostatic tumour recurrence in relation to the diagnostic accuracy of ^{68}Ga-PSMA PET/CT for the detection of LNM.

Patients and methods

Patients

We retrospectively reviewed the charts of patients undergoing sRP for isolated local recurrence after any kind of local treatment with RT or high-intensity focussed ultrasound (HIFU). Patients underwent prostate biopsy to histologically verify local recurrence and systemic staging with a CT of the abdomen and bone scan prior to surgery. More recently patients received a ^{68}Ga-PSMA PET/CT for systemic staging. The procedures applied in the present study for the ^{68}Ga-PSMA PET/CT scan and its analysis have been described previously [6,7]. Patients with any evidence of bone or visceral metastases on staging imaging were excluded from sRP. Suspicious lymph nodes in a scan were not an exclusion criterion, comparable to primary RP.

Treatment

Salvage RP does not differ from a primary approach except the expected possible pitfalls described earlier [10]. Patients underwent an additional extended lymph node dissection (LND) in the areas of the arteria (A.) iliaca externa, interna and fossa obturatoria [10,11].

Pathological Analysis

All surgical samples were assessed macro- and microscopically by an experienced board-certified uro-pathologist. The resected lymphatic tissue was formalin-fixed and the lymph nodes were dissected and embedded in paraffin in whole. Histopathological evaluation was performed on haematoxylin and eosin-stained tissue slides and the maximum diameter of metastatic deposits was measured in millimetres. Automated immunohistochemistry (Leica Bond Max) was performed on these samples with a mouse anti-PSMA antibody (PSMA 3E6; Dako, Carpinteria, CA, USA) according to the manufacturer's protocol. For the present study, the written pathology report after surgery was used for evaluation.

Matching of ^{68}Ga-PSMA PET/CT with Histopathological Results

The surgical samples were labelled by the surgeon according to their site of origin.

After microscopic examination, the results of the prior ^{68}Ga-PSMA PET/CT scan and histology were correlated for each specimen. In the case of a discrepancy, additional slices of the corresponding specimen were immunohistochemically stained with an anti-PSMA antibody. If this failed to resolve the issue, the complete paraffin block was evaluated by serial cutting, resulting in up to 40 slices, and these slices were again microscopically assessed to rule out micrometastases.

The reported ^{68}Ga-PSMA PET/CT results were compared to the pathology reports using methods previously described [6]. The sensitivity, specificity, positive (PPV) and negative predictive values (NPV) and accuracy, as well as corresponding 95% CIs, of the ^{68}Ga-PSMA PET/CT scan were calculated on a per lymph node, per prostate lobe and per patient basis. Prognostic parameters were identified by either log-rank test or Cox regression for uni- and multivariate analysis. A $P < 0.05$ was considered to indicate statistical significance of the results.

Results

A total of 142 patients underwent sRP. The median (range) PSA level before surgery was 4.68 (2.68–8.25) ng/mL. In all, 40.85% of the patients had organ-confined disease, while 20% had at least one positive lymph node in the extended LND. Brachytherapy was used as the initial treatment in 56 cases, external-beam RT in 62 patients, HIFU in five patients, and proton therapy in one patient. The median (range) interval from RT to sRP was 59.5 (13–176) months. Androgen deprivation was introduced prior to surgery or initiated afterwards due to LNM in 18 patients. In 47 (33.1%) of the patients, biochemical recurrence was described due to PSA progression of ≥0.2 ng/mL. The clinical data for the subgroup of patients receiving ^{68}Ga-PSMA PET/CT prior to surgery was comparable to the overall patient group. More detailed information is given in Table 1. The median biochemical

Table 1 Patients' characteristics.

Characteristic	Overall	PSMA
N	160	50
Age, years, mean (range)	66 (62–71)	69 (51–84)
pT Stage, *n* (%)		
T2	66 (40.85)	23 (46)
T3a	19(10.56)	7 (14)
T3b	54 (33.8)	19 (38)
T4	4 (2.82)	
Missing	17 (11.97)	1* (2)
PSA level, ng/mL, median (range)	4.68 (2.68–8.25)	5.58 (0.2–16.56)
Time from RT to sRP, months, median (range)	59.5 (13–176)	60 (12–148)
Hormone therapy at any time, *n* (%)	18 (12.68)	5 (10)
No. of patients *N*+, *n* (%)	36 (21.83)	14 (28)
Biochemical failure, *n* (%)	47 (33.1)	4 (8)

No RP was performed in one patient.

progression-free survival at 1, 2 and 5 years was 71.0%, 59.9% and 36.2%, respectively.

Clinical parameters were analysed in a uni- and multivariate Cox regression analysis to identify independent prognostic factors. The only independent prognostic factors identified for PSA recurrence were lymph node stage, with a hazard ratio (HR) of 0.32 (95% CI 0.164–0.626; $P < 0.001$) and hormonal therapy, with a HR of 0.274 (95% CI 0.117–0.640; $P = 0.003$). In Table 2, the sensitivity, specificity, PPV and NPV and accuracy are given on a per-lymph node and per-patient basis for the patients that received a prior ^{68}Ga-PSMA PET/CT scan. For the detection of local recurrence in the prostate, the same calculations were performed in the per-lobe and per-patient analyses. In one patient, no RP was performed due to extensive fibrotic changes; however, tumour recurrence was confirmed via a biopsy prior to the surgical attempt. No lymph nodes were resected in 10 patients. In total, 613 lymph nodes were resected and 23 of these harboured metastases in 14 patients. ^{68}Ga-PSMA PET/CT correctly identified eight in four patients. There was a high specificity of 100% per lymph node and per person with a high PPV. The accuracy per lymph node was rather high at 97.55% (96–98.6). Nevertheless, due to the low sensitivity of only 34.7% per lymph node and 28.57% per person, a negative ^{68}Ga-PSMA must be interpreted with caution with regard to LNM. The median diameter of LNM correctly identified by ^{68}Ga-PSMA PET was 11.5 (4.0–20.0) mm, while the median diameter of metastases in false-negative lymph nodes was 3.5 (1.0–8.0) mm (Table 3). In the immunohistochemical analysis, all metastases demonstrated PSMA staining.

Table 2 Diagnostic value of ^{68}Ga-PSMA PET/CT in detecting (a) LNM and (b) local recurrences.

	Histology +	Histology –	%
(a) Per lymph node			
PET +, *n*	8	0	PPV 100
PET –, *n*	15	590	NPV 97.52 (96.69–98.15)
	Sensitivity, %	Specificity, %	Accuracy
	34.78 (16.38–57.27)	100 (99.38–100)	97.55 (96.00–98.62)
Per patient			
PET +, *n*	4	0	PPV 100
PET –, *n*	10	26	NPV 72.22 (65.12–78.36)
	Sensitivity, %	Specificity, %	Accuracy
	28.57 (8.39–58.10)	100 (86.77–100)	75 (58.8–87.31)
(b) Per prostate lobe			
PET +, *n*	71	4	PPV 94.67 (88.79–97.55)
PET –, *n*	17	8	NPV 32 (20.77–45.79)
	Sensitivity, %	Specificity, %	Accuracy
	80.68 (70.88–88.32)	66.67 (70.88–88.32)	79 (69.71–86.51)
Per patient			
PET +, *n*	50	0	PPV 100
PET –, *n*	0	0	NPV –
	Sensitivity, %	Specificity, %	Accuracy
	100 (92.89–100)	–	100 (92.89–100)

+, positive; –, negative. Sensitivity, specificity, PPV and NPV, and accuracy are given as percentage (95% CI) (a) per lymph node and per person and (b) per prostate lobe including seminal vesical and per patient.

All patients had positive PSMA uptake in the prostate, which resulted in 100% sensitivity and accuracy and a 100% PPV per person. These results cannot be transferred to a per-lobe analysis, as smaller lesions closer to the index tumour may be missed. The median (range) volume of correctly identified tumour in the prostate was 4 (0.1–22.75) mL. The median volume of the false-negative tumour was 0.49 (0.2–16.25) mL. Again, all the tumours demonstrated positive PSMA uptake in the immunohistochemical analysis. The pathology results from one tumour indicated a small amount of neuroendocrine component.

Discussion

There are strict guidelines for recommending sRP and the best oncological outcomes require proper patient selection. To the best of our knowledge, this is the first series of patients undergoing sRP with preoperatively performed ^{68}Ga-PSMA PET/CT. From our present analysis we learned two major lessons. The ^{68}Ga-PSMA PET/CT was able to detect local recurrent disease in all of the patients, although small lesions were missed in cases of multifocal relapse. Additionally, there is a high PPV for lymph nodes identified by ^{68}Ga-PSMA PET/CT. Unfortunately, due to the small size of metastatic deposits at the time of surgery, a many positive lymph nodes are still missed by ^{68}Ga-PSMA PET/CT.

Table 3 Volume of correctly identified and missed LNM and areas in the prostate.

	Tumour detected	Tumour missed
Tumour in lymph node length, mm, median (range)	11.5 (4.0–20.0)	3.5 (1.0–8.0)
Prostate cancer in prostate volume, mL, median (range)	3.7 (0.1–24)	0.54 (0.2–16.25)

The importance of pathological lymph node staging, and thus the urgent need for sensitive preoperative imaging modalities, has already been described by other study groups, and is also highlighted by our modern series [8,9,12].

There is a general difficulty in identifying small LNM with medical imaging modalities, which is not completely ameliorated by PET/CT. Usually the LNM at the time of surgery are small and will inevitably be missed in standard staging procedures [13]. Herlemann *et al.* [13] compared the diagnostic efficacy of ^{68}Ga-PSMA PET/CT to conventional CT in patients with primary and salvage lymph node resections. In contrast to our present results, Herlemann *et al.* [13] reported significantly higher sensitivity and accuracy, although the high PPV and specificity in both studies underline the importance of ^{68}Ga-PSMA PET/CT in the preoperative setting. In this respect, our present data are in agreement with Jilg *et al.* [14] and Rauscher *et al.* [15], who analysed the diagnostic accuracy of ^{68}Ga-PSMA PET/CT before salvage LND without local relapse in the prostate. Their calculations were mainly performed based on regional and sub-regional analyses, the latter of which best reflected our present analysis. Similar to our present results, these authors highlighted very high PPVs of 98.6% and 94.6%, respectively.

Concerning the sizes of the LNM with positive PET results, the median short axis diameter was 1.15 (0.4–2.0) mm compared to a median diameter of 0.35 (0.1–0.8) mm for LNM with false-negative PET results. The size of the LNM identified by the PET scan is similar to the size of lesions identified by conventional CT scans (1.2 cm) [13], and is in contrast to the findings in the salvage LND only setting. Jilg *et al.* [14] reported the longitudinal and short axis diameters of tumour deposits identified in false-negative lymph nodes to be 4.6 and 2.5 mm, respectively. In order to detect at least 90% of LNM on ^{68}Ga-PSMA PET/CT, the cut-off value of the longitudinal tumour size was 6 mm.

For comparison, with the primary tumour being *in situ*, there are little data regarding the initial staging of untreated prostate cancer using ^{68}Ga-PSMA PET/CT. Budäus *et al.* [16] were the first to describe their experience in 30 high-risk patients, 12 of which had LNM, of whom only one-third were positive on ^{68}Ga-PSMA PET/CT. These results are comparable to the values for sensitivity, specificity and PPV and NPV found in our present study. In a larger patient cohort, Maurer *et al.* [17] analysed the diagnostic efficacy of ^{68}Ga-PSMA PET/CT scans in patients with intermediate- and high-risk prostate cancer. Standard staging procedures were compared to ^{68}Ga-PSMA PET/CT scans and the authors reported a sensitivity of 68.3%, which is higher than in the present study. A meta-analysis summarised the diagnostic efficacy of ^{68}Ga-PSMA PET for primary staging and in recurrent disease and showed a pooled sensitivity for primary staging of 61% (95% CI 47–72%) [18]. These results accentuate that, in primary staging where the primary tumour is still present, the sensitivity is markedly lower than in patients with biochemical recurrence after RP. An Australian study [19] analysed ^{68}Ga-PSMA PET findings after RT with curative intent. The results of 107 patients were correlated to PSA level. Interestingly, ^{68}Ga-PSMA PET had already been performed in a quarter of the patients at very low PSA levels. As the PSA levels rose, the risk for lymphonodular and visceral metastases increased. At PSA levels >2 ng/mL, nodal metastases were described in 35.7% of cases. These data are comparable to our present detection rate of lymph nodes using ^{68}Ga-PSMA PET. With our pathologically confirmed analysis, we now know that the true positive rate of LNM is almost doubled.

Data on the diagnostic accuracy of ^{68}Ga-PSMA PET after RT on local recurrences are rare and mostly without pathological correlation. In the published series, different PSMA PET/CTs had been performed after biochemical failure. In a recent meta-analysis, the probability of detecting local recurrences is somewhat better than after RP, but is only 52% and dramatically less than in our report [19]. These results have been confirmed by a prospective study [20], in which 238 patients underwent conventional staging with CT and bone scan after RP (152 patients) or RT (86 patients). Of the 199 patients with normal standard imaging results, 148 (74%) had positive findings on ^{68}Ga-PSMA PET. The local detection was significantly higher after RT than RP (56% vs 10%). In their further analysis, there was no subgrouping of patients between RT or surgery. Taking the entire cohort, regional LNM, defined as pelvic nodes distal to the A. iliaca communis, were present in 42% of the patients. In the aforementioned analysis, local recurrence was described in 100% of the patients at very low PSA levels of <0.5 ng/mL. At higher PSA levels, distant metastases were found in up to 20% of cases. These high rates cannot be seen in our present patient cohort as distant metastases were a criterion for exclusion. In the future, it is probable that a combination of multiparametric MRI and ^{68}Ga-PSMA PET will have more favourable accuracy than CT. In the 18 patients with biochemical recurrence after RT, ^{68}Ga-PSMA PET/MRI was performed and the anatomical correlation with the PET findings was analysed. Concerning the lymph node analysis, the T2 sequence in particular had significantly better correlations in the sub-centimetre nodes. All of these lymph nodes could have been identified with ^{68}Ga-PSMA-PET. Local recurrences have best been identified with dynamic contrast-enhanced sequence with a sensitivity of 85% [21].

Conclusion

^{68}Ga-PSMA PET/CT has a high PPV and specificity in identifying LNM and local recurrence in the prostate. ^{68}Ga-PSMA PET/CT should be the standard procedure before

salvage local treatment. If positive lymph nodes are identified with ^{68}Ga-PSMA-PET, sRP needs to be critically discussed with the patient, as progression-free survival decreases significantly in cases of positive lymph nodes. If our present data can be validated, no further pathological investigation is needed if there is suspicion of local recurrence and a positive finding on ^{68}Ga-PSMA PET/CT.

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Conflicts of interest

All authors have no conflict of interests.

References

1 **Perera M**, **Papa N**, **Christidis D et al.** Sensitivity, specificity, and predictors of positive ^{68}Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. *Eur Urol* 2016; 70: 926–37

2 **Jereczek-Fossa BA**, **Fanetti G**, **Fodor C et al.** Salvage stereotactic body radiotherapy for isolated lymph node recurrent prostate cancer: single institution series of 94 consecutive patients and 124 lymph nodes. *Clin Genitourin Cancer* 2017; 15: e623–32

3 **Ost P**, **Bossi A**, **Decaestecker K et al.** Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. *Eur Urol* 2015; 67: 852–63

4 **Rischke HC**, **Schultze-Seemann W**, **Wieser G et al.** Adjuvant radiotherapy after salvage lymph node dissection because of nodal relapse of prostate cancer versus salvage lymph node dissection only. *Strahlenther Onkol* 2015; 191: 310–20

5 **Porres D**, **Pfister D**, **Thissen A et al.** The role of salvage extended lymph node dissection in patients with rising PSA and PET/CT scan detected nodal recurrence of prostate cancer. *Prostate Cancer Prostatic Dis* 2017; 20: 85–92

6 **Pfister D**, **Porres D**, **Heidenreich A et al.** Detection of recurrent prostate cancer lesions before salvage lymphadenectomy is more accurate with (68)Ga-PSMA-HBED-CC than with (18)F-Fluoroethylcholine PET/CT. *Eur J Nucl Med Mol Imaging* 2016; 43: 1410–7

7 **Verburg FA**, **Pfister D**, **Heidenreich A et al.** Extent of disease in recurrent prostate cancer determined by [(68)Ga]PSMA-HBED-CC PET/CT in relation to PSA levels, PSA doubling time and Gleason score. *Eur J Nucl Med Mol Imaging* 2016; 43: 397–403

8 **Pokala N**, **Huynh DL**, **Henderson AA**, **Johans C**. Survival outcomes in men undergoing radical prostatectomy after primary radiation treatment for adenocarcinoma of the prostate. *Clin Genitourin Cancer* 2016; 14: 218–25

9 **Mandel P**, **Steuber T**, **Ahyai S et al.** Salvage radical prostatectomy for recurrent prostate cancer: verification of European Association of Urology guideline criteria. *BJU Int* 2016; 117: 55–61

10 **Heidenreich A**, **Richter S**, **Thuer D**, **Pfister D**. Prognostic parameters, complications, and oncologic and functional outcome of salvage radical prostatectomy for locally recurrent prostate cancer after 21st-century radiotherapy. *Eur Urol* 2010; 57: 437–43

11 **Heidenreich A**, **Ohlmann CH**, **Polyakov S**. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. *Eur Urol* 2007; 52: 29–37

12 **Sanderson KM**, **Penson DF**, **Cai J et al.** Salvage radical prostatectomy: quality of life outcomes and long-term oncological control of radiorecurrent prostate cancer. *J Urol* 2006; 176: 2025–32

13 **Herlemann A**, **Wenter V**, **Kretschmer A et al.** ^{68}Ga-PSMA positron emission tomography/computed tomography provides accurate staging of lymph node regions prior to lymph node dissection in patients with prostate cancer. *Eur Urol* 2016; 70: 553–7

14 **Jilg CA**, **Drendel V**, **Rischke HC et al.** Diagnostic accuracy of Ga-68-HBED-CC-PSMA-ligand-PET/CT before salvage lymph node dissection for recurrent prostate cancer. *Theranostics* 2017; 7: 1770–80

15 **Rauscher I**, **Maurer T**, **Beer AJ et al.** Value of ^{68}Ga-PSMA HBED-CC PET for the assessment of lymph node metastases in prostate cancer patients with biochemical recurrence: comparison with histopathology after salvage lymphadenectomy. *J Nucl Med* 2016; 57: 1713–9

16 **Budäus L**, **Leyh-Bannurah SR**, **Salomon G et al.** Initial experience of (68)Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy. *Eur Urol* 2016; 69: 393–6

17 **Maurer T**, **Gschwend JE**, **Rauscher I et al.** Diagnostic efficacy of (68)Gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. *J Urol* 2016; 195: 1436–43

18 **von Eyben FE**, **Picchio M**, **von Eyben R**, **Rhee H**, **Bauman G**. ^{68}Ga-labeled prostate-specific membrane antigen ligand positron emission tomography/computed tomography for prostate cancer: a systematic review and meta-analysis. *Eur Urol Focus* 2018; 4: 686–93

19 **Meredith G**, **Wong D**, **Yaxley J et al.** The use of (68) Ga-PSMA PET CT in men with biochemical recurrence after definitive treatment of acinar prostate cancer. *BJU Int* 2016; 118(Suppl. 3): 49–55

20 **McCarthy M**, **Francis R**, **Tang C**, **Watts J**, **Campbell A**. A multicentre prospective clinical trial of (68)Gallium PSMA HBED-CC PET-CT restaging in biochemically relapsed prostate carcinoma: oligometastatic rate and distribution, compared to standard imaging. *Int J Radiat Oncol Biol Phys* 2019; 104: 801–8

21 **Lake ST**, **Greene KL**, **Westphalen AC et al.** Optimal MRI sequences for (68)Ga-PSMA-11 PET/MRI in evaluation of biochemically recurrent prostate cancer. *EJNMMI Res* 2017; 7: 77

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Abbreviations: (P)(N)PV, (positive) (negative) predictive value, (s)RP, (salvage) radical prostatectomy; 68Ga-PSMA PET/CT, gallium-68 prostate-specific membrane antigen positron emission tomography/CT; HIFU, high-intensity focussed ultrasound; HR, hazard ratio; LND, lymph node dissection; LNM, lymph node metastases; RT, radiotherapy.