Journal of Nuclear Medicine, published on December 14, 2018 as doi:10.2967/jnumed.118.220855

Impact of ^{68}Ga-PSMA-PET/CT on the radiotherapeutic approach for prostate cancer in comparison to CT – a retrospective analysis

Short running title: PSMA PET/CT versus CT based radiotherapeutic approach

Dr. med. Nina-Sophie Schmidt-Hegemann [1], Chukwuka Eze [1], Dr. med. Minglun Li [1], Dr. med. Paul Rogowski [1], Christian Schaefer [1], Prof. Dr. med. Christian Stief [2], PD Dr. Alexander Buchner [2], Dr. med. Constantinos Zamboglou [3], PD Dr. med. Wolfgang Peter Fendler [4], Prof. Dr. med. Ute Ganswindt [5], Prof. Dr. med. Clemens Cyran [6], Prof. Dr. med. Peter Bartenstein [7], Prof. Dr. med. Claus Belka [1,8], Dr. med. Harun Ilhan [7**]

1) Department of Radiation Oncology, University Hospital, LMU Munich (Claus.Belka@med.uni-muenchen.de, Nina-Sophie.Hegemann@med.uni-muenchen.de, Minglun.Li@med.uni-muenchen.de, Chukwuka.Eze@med.uni-muenchen.de, Paul.Rogowski@med.uni-muenchen.de, Christian.Schaefer@med.uni-muenchen.de)
2) Department of Urology, University Hospital, LMU Munich (Christian.Stief@med.uni-muenchen.de, Alexander.Buchner@med.uni-muenchen.de)
3) Department of Radiation Oncology, Medical Center – University of Freiburg, Faculty of Medicine. University of Freiburg, Germany (constantinos.zamboglou@uniklinik-freiburg.de)
4) Department of Nuclear Medicine, University Hospital Essen (Wolfgang.Fendler@uk-essen.de)
5) Department of Therapeutic Radiology and Oncology, Innsbruck Medical University, Austria (ute.ganswindt@i-med.ac.at)
6) Department of Radiology, University Hospital, LMU Munich (Clemens.Cyran@med.uni-muenchen.de)
7) Department of Nuclear Medicine, University Hospital, LMU Munich (Peter.Bartenstein@med.uni-muenchen.de, Harun.Ilhan@med.uni-muenchen.de)
8) German Cancer Consortium (DKTK). Partner Site Munich, Germany

* First author:
Dr. med. Nina-Sophie Schmidt-Hegemann
Department of Radiation Oncology, University Hospital, LMU Munich
Marchioninistr. 15, 81377 Munich, Germany
Tel: +49 89 4400 73770
Fax: +49 89 4400 76770
E-mail address: Nina-Sophie.Hegemann@med.uni-muenchen.de

** Corresponding author:
Dr. med. Harun Ilhan
Department of Nuclear Medicine, University Hospital, LMU Munich
Marchioninistr. 15, 81377 Munich, Germany
Email: harun.ilhan@med.uni-muenchen.de
Tel: 0049 89 4400 74646
Fax: 0049 89 4400 77646

ABSTRACT

^{68}Gallium-prostate-specific membrane antigen positron emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) offers unprecedented accuracy for staging of primary, persistent or recurrent prostate cancer. Thus, we hypothesized that PSMA PET/CT prior to radiotherapy significantly impacts the radiotherapeutic approach in comparison to the current standard of CT based approach. **Methods:** Between February 2014 and December 2017, a total of 172 patients received PSMA PET/CT before radiotherapy and were included in this retrospective analysis. Twenty-two (13%) patients were referred for primary definitive radiotherapy, 51% (88/172) for PSA persistence and 36% (62/172) for PSA recurrence after radical prostatectomy. An experienced radiation oncologist, blinded to the CT and PET/CT imaging results, decided on the radiation treatment management of all patients based on the clinical and pathological variables. The potential increase in diagnostic accuracy, and the subsequent change of radiotherapeutic approach was documented separately for PET/CT versus CT. **Results:** Overall detection rate was 70% (120/172) in ^{68}Ga-PSMA PET/CT. Patients with pre-PSMA PET/CT PSA-level >0.5 ng/ml (98/111; 88%) had significantly more often PET-positive results. Overall, PSMA PET/CT revealed a total of 171 lesions, PET alone 156 and CT alone 85. For all patients a continuous diagnostic increase in positive findings was observed for primary tumor/local recurrence (CT: 18% vs. PET/CT: 37%), pelvic lymph node (CT: 21% vs. PET/CT: 44%) and distant metastases (CT: 7% vs. PET/CT: 19%) when comparing CT vs. PET/CT. Compared to CT, the combination of PET/CT information resulted in a change of treatment in 107/172 (62%) patients, i.e. 8/22 (36%) patients prior to any treatment, 31/62 (50%) with PSA recurrence and 68/88 (77%) with PSA persistence. Comparing the different radiotherapy indications with each other, there was a higher change of management in postoperative patients vs. patients prior to any treatment. **Conclusion:** Compared to conventional CT, PSMA PET/CT had a remarkable impact on radiotherapeutic approach

especially in postoperative patients. Thus, considering the growing amount of data on PSMA PET/CT's impact in postoperative patients, PSMA PET/CT has recently been endorsed as an imaging modality in patients with PSA persistence/recurrence in a few cancer guidelines, for instance the German S3 guideline and the European association of urology guideline.

Key Words: prostate cancer, radiotherapy, planning, PSMA, PET/CT

INTRODUCTION

Radiotherapy is a well-established standard therapeutic approach for the curative treatment of prostate cancer. In the primary setting, both radical prostatectomy or radiotherapy with and without androgen deprivation therapy are viable options for patients with localized prostate cancer with similar oncologic outcome (*1*). So far, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis and bone scintigraphy are the standard of care in staging patients with newly diagnosed prostate cancer (*2*). Likewise, radiotherapy plays a pivotal role in achieving tumor control in patients with persistent or recurrent prostate-specific antigen (PSA) after radical prostatectomy (*3*). The current European Association of Urology - European Society for Radiotherapy & Oncology - International Society of Geriatric Oncology guidelines (*4*) concede that the diagnostic yield of common imaging techniques in staging patients after radical prostatectomy is poor and refer to MRI and choline positron emission tomography (PET)/CT as possible imaging methods in patients with PSA > 1 ng/ml. Lately, F-18 fluciclovine (Axumin) PET/CT or PET/MRI has been added to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Prostate Cancer (Version 1.2018) and is advised to be considered in the clinical workup of patients with recurrent prostate cancer. In the primary as well as in the postoperative setting dose-escalation to the primary tumor (*5,6*), local residua or recurrences within the prostatic fossa (*7-9*) and involved lymph nodes possibly correlates with a better oncologic outcome. Consequently, an accurate detection of the individual prostate cancer distribution is mandatory to select suitable patients for individualized radiotherapy dose escalation within the pelvis. So far, standard target volumes and RT planning were based on CT and MRI.

Lately, ^{68}Gallium-prostate-specific membrane antigen (^{68}Ga-PSMA) PET/CT has emerged as the imaging modality with the highest sensitivity and specificity in staging prostate cancer patients, particularly with biochemical persistence or recurrence after radical prostatectomy compared to conventional imaging like CT or MRI (*10,11*) and choline PET/CT

(*12*). Unlike conventional imaging, ^{68}Ga-PSMA PET offers the possibility of visualizing prostate cancer residual disease or recurrence already at low PSA-levels with 58.3% of PET-positive results found in a PSA range of 0.51 - 1.0 ng/ml (*13-18*). Therefore, ^{68}Ga-PSMA PET/CT might further improve oncologic outcome by modifying target volumes delineation and intended overall doses. There is increasing evidence that ^{68}Ga-PSMA PET/CT might have a major impact on radiotherapy planning in the primary (*19-21*) and postoperative setting (*21-30*).

As a standard operating procedure at our institution, evidence of PET-positive pelvic/paraaortic lymph nodes or PET-positive osseous oligo-metastases in patients scheduled for primary treatment of prostate cancer results in a change of radiotherapeutic approach. It triggers enlargement or expansion of pelvic volumes to include PSMA positive pelvic nodal disease, or adjacent para-aortic disease, with an integrated or sequential boost. Bone metastases are treated with metastasis directed radiotherapy, normally stereotactic body radiotherapy (SBRT). In postoperative patients, local macroscopic tumor residua or recurrences lead to simultaneously integrated or sequential boost volumes to the local macroscopic tumor. Likewise, PET-positive pelvic or paraaortic lymph node metastases or a limited number of bone metastases in the sense of oligometastatic disease result in an adaptation of the irradiation volume with simultaneously integrated or sequential boosts (*31,32*). In the case of poly-metastatic or visceral metastatic (M1c) disease, treatment recommendation is primary androgen deprivation therapy or systemic therapy.

Performing ^{68}Ga-PSMA PET/CT on a regular basis, the aim of this retrospective analysis was to assess the diagnostic value of ^{68}Ga-PSMA PET/CT in treatment naïve prostate cancer and post-operative patients with here detailed differentiation in patients with persistent vs. recurrent PSA and to evaluate the potential impact on radiotherapy planning.

MATERIALS AND METHODS

Study population

Between February 2014 and December 2017, 1492 patients with prostate cancer underwent ^{68}Ga-PSMA PET/CT scans at the department of Nuclear Medicine. Of this cohort, a total of 8.7% (172/1492 patients) received ^{68}Ga-PSMA PET/CT prior to radiotherapy following referral to the department of Radiation Oncology and were included in this retrospective analysis. Thirteen percent (22/172) of patients were referred for primary definitive radiotherapy, 51% (88/172) due to PSA persistence and 36% (62/172) due to PSA recurrence after radical prostatectomy. Patients were sub-grouped according to the D'Amico criteria (*33*) incorporating tumor-stage, PSA-level and Gleason Score (Table 1). All patients provided written informed consent to undergo ^{68}Ga-PSMA PET/CT. This retrospective analysis was performed in compliance with the principles of the Declaration of Helsinki and its subsequent amendments (*34*) and was approved by the local Ethics Committee (approval number 556-16). The requirement to obtain informed consent was waived.

^{68}Ga-PSMA labelling and PET/CT imaging

Radiolabelling of PSMA-HBED-CC was performed with $^{68}Ga^{3+}$ from a ^{68}Ge/^{68}Ga generator system (GalliaPharm® , Eckert & Ziegler AG, Berlin, Germany) using an automated synthesis module (GRP, Scintomics GmbH, Munich, Germany) and pre-packed cassettes (ABX GmbH, Radeberg, Germany) as described previously for a different PSMA ligand by Weineisen et al. (*35*). ^{68}Ga-PSMA PET/CT imaging was performed according to current guidelines (*36*) with a Siemens Biograph 64 or GE Discovery 690 PET/CT camera. Phantom studies based on the National Electrical Manufacturers Association NU2-2001 standard were conducted to allow valid pooling of the results, and standardized uptake value (SUV) conversion factors were calculated (*37*). ^{68}Ga-PSMA PET/CT scans were performed with a diagnostic CT scan (reference mAs,

200–240; 120 kV) and obtained with intravenous injection of iodine-containing contrast agent (Ultravist 300, Bayer Pharma AG, Berlin, Germany; or Imeron 300, Bracco, Konstanz; 2.5 mL/s; in portal venous phase) 60 min after intravenous administration of ^{68}Ga-PSMA (median 205 megabecquerel (MBq), range 87–293). In absence of contraindications, 20 mg furosemide was injected almost simultaneously with ^{68}Ga-PSMA injection and patients were implored to empty their bladder to minimize residual activity in the urinal system. PET images were reconstructed with an axial 168 × 168 matrix based on the TrueX algorithm (3 iterations, 21 subsets; Biograph 64) or on the VUE Point FX algorithm (2 iterations, 36 subsets; Discovery 690).

Image interpretation

^{68}Ga-PSMA PET/CT was interpreted by a consensus read of two nuclear medicine physicians and two radiologists and additionally evaluated by an independent observer with more than 5 years of experience in ^{68}Ga-PSMA PET/CT reading. Location of lesions was each determined by CT. PET-positive lesions were identified by ^{68}Ga-PSMA uptake visually above background beyond physiologic uptake. On CT imaging asymmetrical focal areas of mass-like contrast enhancement in the peripheral prostate detected on venous phase contrast-enhanced CT imaging or tumor penetration of prostatic capsule were considered as positive findings of primary prostate cancer. Positive nodes were defined by short axis diameter ≥ 1 cm, loss of fatty hilum, or increased contrast enhancement on CT. Bone metastases were detected by suspicious sclerotic lesions. Based on ^{68}Ga-PSMA PET/CT images and reports, stage according to PET or CT was documented in consensus. For this analysis, all PSMA PET/CT scans of the included patients were re-analyzed collecting the number of suspicious local lesions, pelvic or paraaortic lymph nodes and bone metastases by comparing each imaging modality CT vs. PET vs. PET/CT to each other.

Radiotherapy Treatment prior and post PSMA PET/CT information

An experienced radiation oncologist, initially blinded with respect to the CT and PET/CT imaging results, decided on the treatment management of all patients based on the clinical and pathological variables, like PSA, Gleason Score and TNM stage prior to the results of the CT and ^{68}Ga-PSMA PET/CT. Prior to the findings in CT and ^{68}Ga-PSMA PET/CT, prostate cancer patients referred for primary radiotherapy were stratified according to the D'Amico risk group classification in low-, intermediate- and high-risk patients (*33*). Depending on patients' D'Amico risk group and the risk for pelvic lymph node involvement according to Memorial Sloan Kettering Cancer Center Prostate Cancer Nomogram, low-risk patients are normally treated with radiotherapy of the prostate alone, intermediate-risk patients with radiotherapy of the prostate plus concomitant androgen deprivation therapy for up to six months (*38*) and high-risk patients with radiotherapy of the prostate and the pelvic lymphatic pathways plus androgen deprivation therapy for up to two years (*39,40*). Total doses applied to the prostate gland range from normo-fractionated 74 Gray (Gy) in low-risk patients to 76 - 78 Gy in intermediate- and high-risk patients. Pelvic lymphatic pathways are generally treated at our department with 50.4 Gy in 1.8 Gy daily fractions. Patients with PSA-persistence are normally treated with radiotherapy delivered to the prostatic fossa alone with 66 Gy in 2 Gy and in case of pathologic lymph nodes at the time of radical prostatectomy with irradiation of the pelvic lymphatic pathways as well (*41*). Patients with PSA-recurrence tending to have primarily local recurrences are generally treated with irradiation of the prostatic fossa only (*42*). Subsequently, the participating radiation oncologist was first unblinded with respect to CT information and assessed the change by CT information compared to standard radiotherapy target volume. Likewise, the change by PET/CT information compared to a target volume based solely on the clinical and pathological variables was assessed. The change of radiotherapeutic approach regarding CT and PET/CT information was documented separately for each patient, as well as the potential increase in diagnostic accuracy when comparing CT vs. PET vs. PET/CT.

Statistical analysis

For statistical analysis, SPSS Statistics 25 (IBM, New York, USA) was used. Descriptive analysis was performed by calculating the mean, median and range. Frequencies of CT-, PET- and PET/CT-positive cases were compared using McNemar Test. Differences in short axis diameter of lymph node metastases detected in CT and PET/CT were compared using the *t* test. A p-value of <0.05 was considered statistically significant. Logistic regression analysis was performed to identify D'Amico risk group (low-/intermediate- vs. high risk), PSA-level before PSMA PET/CT (< 0.5 ng/ml vs. ≥ 0.5 ng/ml), primary vs. postoperative status and Gleason Score (≤ 7b vs. > 7b) as potential predictors for change of management.

RESULTS

^{68}Ga-PSMA PET/CT findings

One-hundred and twenty patients (120/172; 70%) showed at least one suspicious lesion in ^{68}Ga-PSMA PET/CT (Table 1). The median PSA in these patients before ^{68}Ga-PSMA PET/CT was 1.9 (0.14-40.13) in patients with PSA persistence (77%; 68/88), 0.78 (0.27-6.24) in patients with PSA recurrence (50%; 31/62) and 13.7 (0.14-150) in patients prior to definitive radiotherapy (95%; 21/22). Fifty-two patients (52/172; 30%) had no PET-positive findings on ^{68}Ga-PSMA PET/CT. In these patients, median PSA was 0.34 (0.13-1.33) in patients with PSA persistence (23%; 20/88), 0.3 (0.15-3.24) in patients with PSA recurrence (50%; 31/62) and 0.52 in one patient prior to definitive radiotherapy. Androgen deprivation therapy was ongoing in 19 of all patients (12 of the patients with persistent PSA, 3 with recurrent PSA and 4 of the treatment naïve patients) prior to PSMA PET/CT. Eighty-four percent of all patients (146/172) and 87% (104/120) of PET-positive patients were high-risk patients according to the D'Amico classification. In the PET-positive cohort, patients with PSA persistence accounted for the

majority of patients (57%; 68/120), whereas the PET-negative cohort primarily included patients with PSA recurrence (59%; 31/52).

An overview of findings according to CT vs. PET vs. PET/CT is presented in Table 2. Overall, PET/CT revealed a total of 171 positive tumor lesions, PET alone 156 and CT alone 85. A continuous diagnostic increase in positive findings was observable for primary tumor/local recurrence [CT: 18% (31/172) vs. PET: 34% (58/172) vs. PET/CT 37% (63/172)], lymph node metastases [CT: 21% (36/172) vs. PET: 41% (71/172) vs. PET/CT 44% (76/172)] and distant metastases including non-regional lymph nodes [CT: 8% (13/172) vs. PET: 16% (28/172) vs. PET/CT 19% (32/172)] when comparing CT vs. PET vs. PET/CT with significant superiority of PET imaging compared to CT imaging alone ($p<0.05$). Compared to CT, but not to PET alone, PET/CT identified a significantly higher number of positive primary tumor/local recurrences, lymph node and distant metastases. This was equally observable for patients with definitive or postoperative radiotherapy with persistent or recurrent PSA.

In Table 3, this is specified for the detection and localization of lymph node metastases comparing CT vs. PSMA PET/CT: The detection rate of suspicious lymph nodes was significantly higher in PET/CT compared to CT imaging alone (289 vs. 85 lymph nodes, respectively; $p<0.02$). The mean short axis diameter of the smallest lymph node metastases detected in ^{68}Ga-PSMA PET/CT was significantly smaller in PET/CT imaging compared to CT imaging alone (5.8 vs. 9.9 mm, $p < 0.001$).

Impact of 68Ga-PSMA-PET imaging on change of management

Based on the above-mentioned standard operating procedure criteria, 65% (112/172) of the cohort would have been treated prior to PSMA PET/CT with irradiation of the prostate/prostatic fossa alone and 35% (60/172) with radiotherapy of prostate/prostatic fossa and lymphatic pathways, respectively (Table 4). CT information led to no change of treatment in

60% (104/172) and to intensification in 40% (68/172) of patients. PET/CT information resulted in no change of treatment in 38% (65/172) and in an intensification of treatment, e.g. enlargement of radiotherapy volume due to irradiation of lymphatic pathways with/without simultaneously integrated or sequential boosts to macroscopic local residua or recurrences, suspicious lymph nodes or bone metastases in 62% (107/172) of patients. Change of treatment according to CT- and PET/CT-information is exemplarily shown in a patient in Fig. 1 with the realized radiotherapy plan after PSMA PET/CT.

Comparing the different radiotherapy indications with each other, PSMA PET/CT vs. CT led to a higher change of management in postoperative patients than patients with definitive radiotherapy indication: Compared to CT, PSMA PET/CT intensified radiotherapeutic approach in 50% (31/62) vs. 24% (15/62) of patients with PSA recurrence and in 77% (68/88) vs. 53% (47/88) of patients with radiotherapy indication due to PSA persistence. In patients with definitive radiotherapy indication, CT led in 27% (6/22) and PSMA PET/CT in 36% (8/22) to a change of management. In Table 4 the absolute numbers of the respective radiotherapy indications for CT and PET/CT vs. standard RT target volume definition are given.

Factors predicting ^{68}Ga-PSMA PET/CT-based change of management

In the multivariate binary logistic regression analysis (Supplemental Table 1) postoperative patients with either biochemical recurrence or persistence had significantly more often a change of management than patients with definitive radiotherapy. Likewise, a Gleason Score > 7b or a PSA-level before PSMA PET/CT ≥ 0.5 ng/ml was significantly associated with a change of management. D'Amico risk group had no significant impact on change of treatment.

DISCUSSION

Recently, we reported on the clinical outcome of prostate cancer patients after PSMA PET/CT based radiotherapy (*8,9*). The main aim of the present study was to assess the impact of PSMA PET/CT in the clinical setting and whether its high detection rate compared to CT alone translates into a substantial change of management in a heterogeneous group of prostate cancer patients referred for either definitive or postoperative radiotherapy. PSMA PET/CT was performed in 172 patients and demonstrated at least one suspicious lesion in 70% (120/172) of patients.

Most studies available on the diagnostic performance of PSMA-PET/CT analyzed patients with recurrent prostate cancer: Detection rates range from 50% in patients with PSA-levels less than 0.5 ng/ml up to 73% in patients with PSA-levels between 0.51 and 1.0 ng/ml (*13-18*). In the present analysis, PSMA PET/CT was negative in 30% (52/172) of patients. Considering the relatively low median PSA in this subgroup and the fact that this subgroup consisted primarily of patients with biochemical recurrence with a known tendency to relapse within the prostatic fossa overshadowed by the SUV and radioactivity concentration within the bladder (*43*), the percentage of patients with a negative PSMA PET/CT is plausible. Of all patients with a negative PET-scan, there was only one patient with indication for primary radiotherapy.

Indeed, the implementation of PSMA PET/CT for staging at initial diagnosis prior to radical prostatectomy or definitive radiotherapy is controversially discussed at present and is not advised in current prostate cancer guidelines (*2,44*). However, compared to conventional imaging (CT, MRI) and bone scan, several groups demonstrated the superiority of PSMA PET/CT in lymph node and bone metastases staging (*10,45,46*). Overall, PSMA PET/CT was positive in 95% of patients with indication for definitive radiotherapy in our analysis. Although patients prior to definitive radiotherapy constituted the smallest subgroup of the present cohort,

there was a modest change of management (36%) compared to postoperative patients. This is in accordance with the few existing analyses on PSMA PET/CT in therapy naïve patients prior to radiotherapy (*19-21*). In a recent analysis by Calais et al. based on 73 patients with localized untreated prostate cancer, a major impact of PSMA PET/CT was noted for 16.5 % (12/73) of patients with intended irradiation of prostate, seminal vesicles and pelvic lymphatic pathways and 37% of patients when radiotherapy fields covered prostate and seminal vesicles only (*19*). Likewise, Koerber et al. presented data on the impact of PSMA PET/CT on radiotherapy planning in 50 otherwise untreated prostate cancer patients (*21*). Similar to our analysis, they compared conventional imaging to PSMA PET/CT and saw an overall increase in lymph node metastases (10% vs. 16%) and distant metastases (6% vs. 10%). An increase in diagnostic yield was equally observed in our analysis when comparing CT to PSMA PET/CT regarding lymph node (18% vs 41%) and distant metastases (5% vs. 14%). In total, PSMA PET/CT resulted in a change of radiotherapeutic management in 36% of our patients vs. 44% of treatment naïve patients included in the analysis by Koerber et al. Overall, the low number of patients intended for definitive radiotherapy is a limitation and needs further validation.

Contrary to the paucity of data on therapy naïve patients, there is growing evidence on the superiority and high impact of PSMA PET/CT vs. conventional imaging in staging patients with biochemical persistence or recurrence (*21-30*): In the present analysis, PSMA PET/CT detected in total 140 residual or recurrent disease, lymph node and distant metastases, whereas CT detected 64 lesions in postoperative patients.

Overall, there were 16% and 10% of patients with persistent or recurrent PSA with evidence of local recurrence in the prostatic fossa triggering a dose-escalation to the macroscopic tumor. This mirrors data by Habl et al. analyzing a high-risk group with biochemical failure after radical prostatectomy observing local tumor recurrence on PSMA PET/CT vs. conventional imaging in 28% of patients (*47*). Likewise, Bluemel et al. evaluated the diagnostic

performance of PSMA PET compared to CT in a smaller number of postoperative patients with elevated PSA-levels in regard to local recurrence (*27*): 1 patient (9%) only was CT positive, whereas 10 patients (91%) were positive in combined PET/CT with 5 patients (45.5%) being positive in PET imaging only.

Compared to CT, PSMA PET/CT was superior regarding the detection of pelvic lymph node metastases: In the investigated patient population, there was evidence of positive pelvic lymph nodes in 14/62 (23%) and 53/88 (60%) of patients with recurrent and persistent PSA in PSMA PET/CT vs. in 7/62 (11%) and 25/88 (28%) of patients with CT imaging only. Overall, PSMA PET/CT compared to CT imaging resulted in an upstaging of 35/150 (23%) patients with biochemical recurrence and persistence. In a similar, but smaller analysis by Sterzing et al., PSMA-PET/CT upstaged 15/29 (52%) postoperative patients from N0 to N1(*30*). In the combined analysis on PSMA PET/CT in postoperative patients with persistent or recurrent PSA by Koerber et al., a change of N-staging was observed in 20/71 (28.2%) patients compared to conventional imaging (*21*).

So far, the present analysis is one of the few (*22*) specifically addressing patients with persistent and recurrent PSA separately. In our opinion, this is of high importance as patients with biochemical persistence are mostly a subgroup with more advanced and aggressive tumor load with completely different metastatic progression patterns i.e. a high tendency to lymph node metastases compared to patients with biochemical recurrence with mostly local recurrences in the prostatic fossa. Comparing the mere numbers of upstaged patients, the diagnostic yield of pelvic lymph nodes was 2.6 times higher in patients with biochemical persistence vs. recurrence. Based on our departmental policy, evidence of pelvic lymph nodes leads to irradiation of the pelvic lymphatic basin according to the RTOG consensus recommendations on delineation of pelvic lymphatic pathways (*48*) with a simultaneous boost to the PET-positive lymph nodules and additional androgen deprivation therapy. Interestingly, there is strong controversy on the

best therapeutic approach in the case of positive lymph nodes with some centers opting for stereotactic body radiotherapy to the PET-positive lymph nodes only (*49*). Having recently presented our data on outcome in patients with biochemical recurrence treated based on the results of PSMA PET/CT (*9*), eradicating microscopic spread to surrounding lymphatic pathways, dose-escalation to macroscopic tumor burden and at least concomitant use of androgen deprivation therapy might be more favorable compared to stereotactic body radiotherapy of PET-positive nodes only.

As expected, patients with biochemical recurrence had significantly less distant metastases on PSMA PET/CT (2/62 patients), as well as on CT (1/62 patients) compared to patients with PSA persistence (27/88 in PSMA PET/CT and 11/88 in CT). Overall, a change in M-staging was present in 17/150 (11%). This is lower than the change in M-staging (22.5%) that was observed in the study by Koerber et al. (*21*) most likely due to the fact that patients in their analysis had a significantly higher PSA pre-PSMA PET/CT of 3.06 ng/ml compared to patients in the present analysis. The impact of PSA pre-PSMA PET/CT on change of therapeutic management was besides Gleason score and primary vs. postoperative status confirmed in the logistic regression analysis.

The present analysis has as limitations due to its monocentric design, a possible referral bias of patients intended for radiotherapy and an overall limited number of patients especially prior to any treatment. Thus, a larger and multicenter analysis on the impact of PSMA PET/CT on change of therapeutic management could provide further clarification. For patients with salvage radiotherapy indication, there is a currently recruiting phase III trial randomizing patients to or not to ^{68}Ga-PSMA PET/CT prior to salvage radiotherapy (https://clinicaltrials.gov/ct2/show/NCT03582774), that will further clarify the high impact of PSMA PET/CT prior to radiotherapy in the postoperative setting.

CONCLUSION

Compared to conventional CT or an approach based on clinical factors only, PSMA PET/CT had a remarkable impact on the radiotherapeutic approach especially in postoperative patients with a consecutive intensification of treatment in 31/62 (50%) of patients with recurrent PSA and 68/88 (77%) of patients with persistent PSA. Thus, considering the growing amount of data on PSMA PET/CT's impact in postoperative patients, PSMA PET/CT has been recently recommended as an imaging modality in patients with PSA persistence or recurrence in a few cancer guidelines, for instance the European Association of Urology guideline and the German S3 guideline.

DISCLOSURE

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

REFERENCES

1. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *New Engl J Med.* 2016;375:1415-1424.

2. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol.* 2017;71:618-629.

3. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. New Engl J Med. 2017;376:417-428.

4. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: Treatment of relapsing, metastatic, and castration-resistant prostate cancer. *Eur Urol.* 2017;71:630-642.

5. Zelefsky MJ, Kollmeier M, Cox B, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012;84:125-129.

6. Schlenter M, Berneking V, Krenkel B, et al. Intensity-modulated radiotherapy of prostate cancer with simultaneous integrated boost after molecular imaging with 18F-choline-PET/CT. *Strahlenther Onkol.* 2018;194:638-645.

7. King CR. The dose-response of salvage radiotherapy following radical prostatectomy: A systematic review and meta-analysis. *Radiother Oncol.* 2016;121:199-203.

8. Schmidt-Hegemann N-S, Fendler WP, Ilhan H, et al. Outcome after PSMA PET/CT based radiotherapy in patients with biochemical persistence or recurrence after radical prostatectomy. *Radiat Oncol.* 2018;13:37.

9. Schmidt-Hegemann NS, Stief C, Kim TH, et al. Outcome after PSMA PET/CT based salvage radiotherapy in patients with biochemical recurrence after radical prostatectomy: a bi-institutional retrospective analysis. *J Nucl Med.* 2018. Epub ahead of print.

10. 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;195:1436-1443.

11. Hernandez D, Salas D, Giménez D, et al. Pelvic MRI findings in relapsed prostate cancer after radical prostatectomy. *Radiat Oncol.* 2015;10:262.

12. Morigi JJ, Stricker PD, van Leeuwen PJ, et al. Prospective comparison of 18F-Fluoromethylcholine versus 68Ga-PSMA PET/CT in prostate cancer patients who have rising PSA after curative treatment and are being considered for targeted therapy. *J Nucl Medicine.* 2015;56:1185-1190.

13. Afshar-Oromieh A, Zechmann C, Malcher A, et al. Comparison of PET imaging with a 68Ga-labelled PSMA ligand and 18F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2014;41:11-20.

14. Afshar-Oromieh A, Avtzi E, Giesel F, et al. The diagnostic value of PET/CT imaging with the 68Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42:197-209.

15. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid 68Ga-PSMA-ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. *J Nucl Med.* 2015;56.

16. Giesel F, Fiedler H, Stefanova M, et al. PSMA PET/CT with Glu-urea-Lys-(Ahx)-[68Ga(HBED-CC)] versus 3D CT volumetric lymph node assessment in recurrent prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42:1794-1800.

17. van Leeuwen PJ, Stricker P, Hruby G, et al. (68) Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. *BJU Int.* 2016;117:732-739.

18. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging.* 2017;44:1258-1268.

19. Calais J, Kishan AU, Cao M, et al. Potential impact of 68Ga-PSMA-11 PET/CT on prostate cancer definitive radiation therapy planning. *J Nucl Med.* 2018; 59:1714-1721.

20. Dewes S, Schiller K, Sauter K, et al. Integration of (68)Ga-PSMA-PET imaging in planning of primary definitive radiotherapy in prostate cancer: a retrospective study. *Radiat Oncol.* 2016;11:73.

21. Koerber SA, Will L, Kratochwil C, et al. 68Ga-PSMA-11 PET/CT in primary and recurrent prostate carcinoma: Implications for radiotherapeutic management in 121 patients. *J Nucl Med.* 2018. Epub ahead of print.

22. Calais J, Fendler WP, Eiber M, et al. Impact of 68Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. *J Nucl Med.* 2018;59:434-441.

23. Calais J, Czernin J, Cao M, et al. (68)Ga-PSMA PET/CT mapping of prostate cancer biochemical recurrence following radical prostatectomy in 270 patients with PSA<1.0ng/ml: Impact on salvage radiotherapy planning. *J Nucl Med.* 2018;59:230-237.

24. Roach PJ, Francis R, Emmett L, et al. The impact of (68)Ga-PSMA PET/CT on management intent in prostate cancer: results of an Australian prospective multicenter study. *J Nucl Med.* 2018;59:82-88.

25. Hope TA, Aggarwal R, Chee B, et al. Impact of 68Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. *J Nucl Med.* 2017;58:1956-1961.

26. Albisinni S, Artigas C, Aoun F, et al. Clinical impact of (68) Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer with rising prostate-specific antigen after treatment with curative intent: preliminary analysis of a multidisciplinary approach. *BJU Int.* 2017;120:197-203.

27. Bluemel C, Linke F, Herrmann K, et al. Impact of 68Ga-PSMA PET/CT on salvage radiotherapy planning in patients with prostate cancer and persisting PSA values or biochemical relapse after prostatectomy. *Eur J Nucl Med Mol Imaging Research.* 2016;6:78.

28. Frenzel T, Tienken M, Abel M, et al. The impact of [68Ga]PSMA I&T PET/CT on radiotherapy planning in patients with prostate cancer. *Strahlenther Onkol.* 2018;194:646-654.

29. Shakespeare TP. Effect of prostate-specific membrane antigen positron emission tomography on the decision-making of radiation oncologists. *Radiat Oncol.* 2015;10:233.

30. Sterzing F, Kratochwil C, Fiedler H. (68)Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. *Eur J Nucl Med Mol Imaging.* 2016;43:34-41.

31. Steuber T, Jilg C, Tennstedt P, et al. Standard of care versus metastases-directed therapy for PET-detected nodal oligorecurrent prostate cancer following multimodality treatment: A multi-institutional case-control study. *European Urology Focus.* 2018. Epub ahead of print.

32. Tilki D, Preisser F, Tennstedt P, et al. Adjuvant radiation therapy is associated with better oncological outcome compared with salvage radiation therapy in patients with pN1 prostate cancer treated with radical prostatectomy. *BJU Int.* 2016;119:717-723.

33. D'Amico AV, Whittington R, Schultz D, et al. Outcome based staging for clinically localized adenocarcinoma of the prostate. *J Urol.* 1997;158:1422-1426.

34. Association GAotWM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Am Coll Dent.* 2014;81:14-18.

35. Weineisen M, Simecek J, Schottelius M, et al. Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer. *Eur J Nucl Med Mol Imaging. Res.* 2014;4:63.

36. Fendler WP, Eiber M, Beheshti M, et al. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging.* 2017;44:1014-1024.

37. Daube-Witherspoon ME, Karp JS, Casey ME, et al. PET performance measurements using the NEMA NU 2-2001 standard. *J Nucl Med.* 2002;43:1398-1409.

38. Pisansky TM, Hunt D, Gomella LG, et al. Duration of androgen suppression before radiotherapy for localized prostate cancer: Radiation therapy oncology group randomized clinical trial 9910. *J Clin Oncol.* 2015;33:332-339.

39. Lawton CAF, Lin X, Hanks GE, et al. Duration of androgen deprivation in locally advanced prostate cancer: Long-Term Update of NRG Oncology RTOG 9202. *Int J Radiat Oncol Biol Phys.* 2017;98:296-303.

40. Lawton CA, Michalski J, El-Naqa I, et al. RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys.* 2009;74:383-387.

41. Abdollah F, Karnes RJ, Suardi N, et al. Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol.* 2014;32:3939-3947.

42. https://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx. Accessed 01.29.2018.

43. Afshar-Oromieh A, Sattler LP, Mier W, et al. The clinical impact of additional late PET/CT imaging with 68Ga-PSMA-11 (HBED-CC) in the diagnosis of prostate cancer. *J Nucl Med.* 2017;58:750-755.

44. Wirth M, Berges R, Fröhner M, et al. *Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms*: Deutsche Gesellschaft für Urologie e. V.; 2018.

45. 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;70:553-557.

46. Pyka T, Okamoto S, Dahlbender M, et al. Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43:2114-2121.

47. Habl G, Sauter K, Schiller K, et al. 68Ga-PSMA-PET for radiation treatment planning in prostate cancer recurrences after surgery: Individualized medicine or new standard in salvage treatment. *Prostate.* 2017;77:920-927.

48. Lawton CAF, Michalski J, El-Naqa I, et al. RTOG GU radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys.* 2009;74:383-387.

49. Zschaeck S, Lohaus F, Beck M, et al. PSMA-PET based radiotherapy: a review of initial experiences, survey on current practice and future perspectives. *Radiat Oncol.* 2018;13:90.

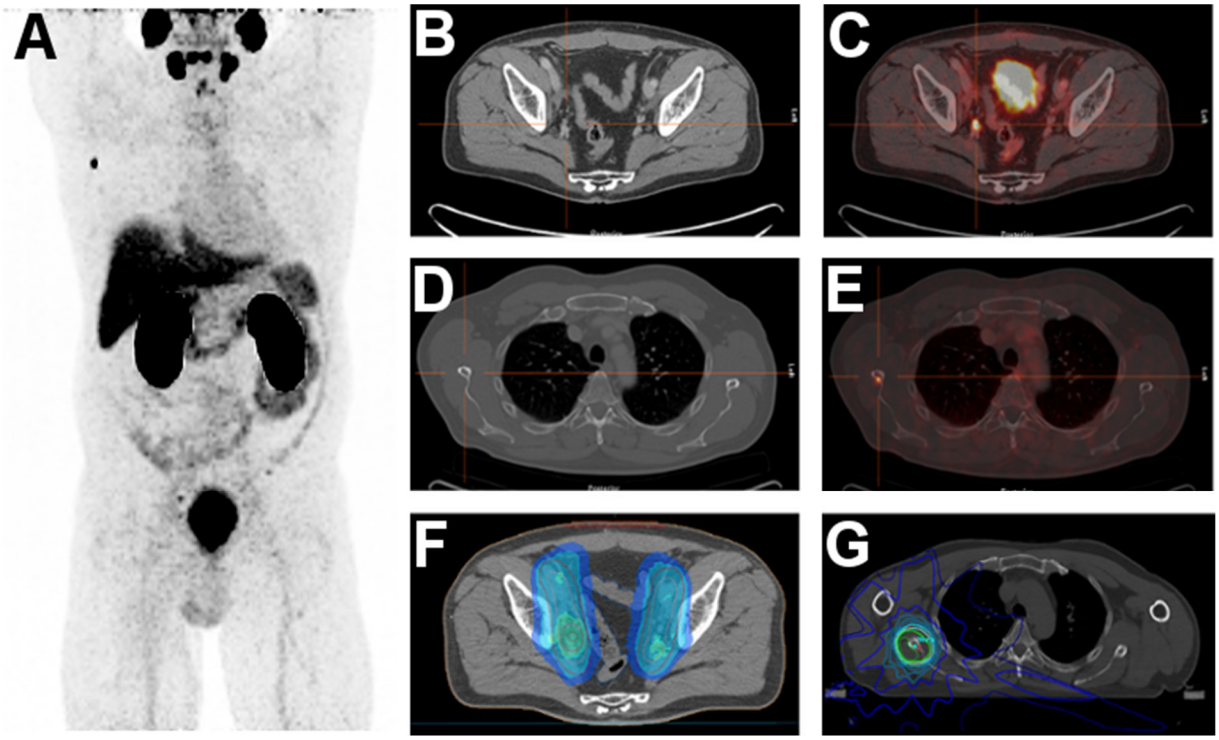

Fig. 1

59-year-old patient with Gleason 4+4=8 prostate cancer undergoing radiotherapy due to persistent PSA after radical prostatectomy. Maximum intensity projection (A) shows local residual disease (covered by the urinary bladder), a single lymphatic and a single bone metastasis with high PSMA-uptake. The right iliac lymph node metastasis with malignant PSMA uptake in PET/CT (C) was not suspicious in CT imaging (B) with just 3 mm short axis diameter. The single bone metastasis in the lateral border of the right scapula shows high uptake in PSMA PET/CT (E) but no correlate in CT imaging (D). In this patient postoperative radiotherapy of the former prostate gland (70 Gy), the pelvic lymphatic pathways (50.4 Gy) with simultaneous integrated boost to the PET-positive iliac lymph node metastasis (56 Gy) was performed (dose distribution in F). Further, this patient received stereotactic body radiotherapy (G) of the singular bone metastasis in the right scapula (30 Gy).

Table 1: Patients' characteristics

	total	PET+	PET-
Patients	172	120	52
Age (years) median (range)	70 (46-86)	70 (46-86)	70 (47-80)
PSA at PET (ng/ml) median (range)			
PSA recurrence	0.44 (0.15-6.24)	0.78 (0.27-6.24)	0.3 (0.15-3.24)
PSA persistence	1.2 (0.13-40.13)	1.9 (0.14-40.13)	0.34 (0.13-1.33)
definitive RT	13.6 (0.14-150)	13.7 (0.14-150)	0.52
Gleason Score*			
≤6	12	9	3
7a	34	21	13
7b	40	25	15
≥8	81	61	20
unknown	5	4	1
TNM			
T1c	36	26	10
T2b	2	2	0
T2c	2	2	0
T3a	5	5	0
T3b	5	5	0
Tx	122	80	42
N0	85	57	28
N1	9	9	0
Nx	78	54	24
M0	165	113	52
M1a	4	4	0
M1b	3	3	0
D`Amico classification			
low	5	3	2
intermediate	21	13	8
high	146	104	42
RT indication			
PSA recurrence	62	31	31
PSA persistence	88	68	20
definitive RT	22	21	1

PSA: Prostate Specific Antigen; RT: Radiotherapy; * data on Gleason Score obtained from biopsy in treatment naïve patients and from radical prostatectomy in postoperative patients

Table 2:

Differences in TNM staging in regard of CT vs. PET alone vs. PET/CT

		CT positive	PET positive	PET/CT positive
all patients (n=172)	**T+ (primary tumor / local recurrence)**	31 (18%)	58 (34%)*	63 (37%)*
	N1	36 (21%)	71 (41%)*	76 (44%)*
	M1a	8 (5%)	13 (8%)	17 (10%)*
	M1b	5 (2%)	15 (9%)*	15 (9%)*
PSA rec. (n=62)	**T+ (recurrence)**	6 (10%)	15 (24%)*	18 (29%)*
	N1	7 (11%)	14 (23%)*	14 (23%)*
	M1a	1 (2%)	1 (2%)	1 (2%)
	M1b	-	1 (2%)	1 (2%)
PSA pers. (n=88)	**T+ (recurrence)**	14 (16%)	25 (28%)*	26 (30%)*
	N1	25 (28%)	48 (55%)*	53 (60%)*
	M1a	6 (7%)	10 (11%)	13 (15%)*
	M1b	5 (6%)	14 (16%)*	14 (16%)*
definitive RT (n=22)	**T+ (primary tumor)**	11 (50%)	18 (82%)*	19 (86%)*
	N1	4 (18%)	9 (41%)	9 (41%)
	M1a	1 (5%)	2 (10%)	3 (14%)
	M1b	-	-	-

*p<0.05 compared to CT imaging (McNemar Test); N1: regional lymph node metastases, M1a: distant lymph node metastases, M1b: distant metastases, PSA rec. = PSA recurrence, PSA pers. = PSA persistence

Table 3:

Number and region of suspicious lymph nodes in CT compared to PET/CT

	CT	PET/CT
LN total number	85	289
mean size of smallest, LN metastasis per patient (in mm, mean ±SD)	9.9 ±2.0	5.8 ±2.0
region		
common iliac	19	51
external iliac	33	76
internal iliac	11	58
paravesical	1	6
presacral	6	16
pararectal	4	24
inguinal		7
paraaortic	11	51

LN = lymph node

Table 4:

Changes in the RT protocol due to CT and PET information

		RT indication			
		all patients (n=172)	PSA recurrence (n=62)	PSA persistence (n=88)	definitive RT (n=22)
standard RT protocol					
prostatic fossa/prostate		112 (65%)	57 (92%)	44 (50%)	11 (50%)
prostatic fossa/prostate and lymphatic pathway		60 (35%)	5 (8%)	44 (50%)	11 (50%)
change by CT information compared to standard RT target volume					
no change		104 (60%)	47 (76%)	41 (47%)	16 (73%)
change		68 (40%)	15 (24%)	47 (53%)	6 (27%)
	individual changes*:				
	SIB local recurrence	21 (12%)	7 (11%)	14 (16%)	0
	SIB lymph node	50 (29%)	9 (15%)	35 (40%)	6 (27%)
	SBRT bone	8 (5%)	0	8 (9%)	0
change by PET/CT information compared to standard RT target volume					
no change		65 (38%)	31 (50%)	20 (23%)	14 (64%)
change		107 (62%)	31 (50%)	68 (77%)	8 (36%)
	individual changes*:				
	SIB local recurrence	45 (26%)	17 (27%)	28 (32%)	0
	SIB lymph node	76 (44%)	14 (23%)	54 (61%)	8 (36%)
	SBRT bone	31 (18%)	2 (3%)	26 (30%)	0

*note: as multiple disease localizations are possible, individual changes in radiotherapy planning do not add up

RT: radiotherapy; SIB: simultaneous integrated boost; SBRT: stereotactic body radiation therapy

Supplemental Table 1: Multivariate binary logistic regression analysis of factors predicting change of management in all patients.

Association between change of management and	p-Value*
PSA PRE-PSMA PET	<0.001
D'Amico risk group	0.595
Primary vs. postoperative status	0.004
Gleason score	0.016

*p<0.05 statistically significant