



ARTICLE

The clinical consequences of routine ^{68}Ga -PSMA-11 PET/CT in patients with newly diagnosed prostate cancer, ISUP grade 5 and no metastases based on standard imaging – preliminary results

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ABSTRACT

Aim: To evaluate the clinical consequences of prostate specific membrane antigen (PSMA) PET/CT for primary staging in patients with ISUP grade 5 (Gleason score ≥ 9) prostate cancer (PCa), and no definitive distant metastases based on standard imaging.

Methods: At our tertiary referral center, PSMA PET/CT became standard of care from August 2018 for primary staging of prostate cancer given the following criteria: (1) no prior treatment for prostate cancer, (2) ISUP grade 5, (3) no definitive metastases on standard imaging (contrast enhanced CT and bone scintigraphy), and (4) deemed suitable for treatment with curative intent based on comorbidity and life expectancy. We present the preliminary results of first six months recruitment with 12 months of follow-up.

Results: Forty-eight patients (mean age 69 years, median PSA 13.0 ng/mL, 20 patients with locally advanced PCa) were included. CT was positive in pelvic lymph nodes in two patients, bone scintigraphy was equivocal in three patients. PSMA PET/CT showed pathological uptake outside the prostatic bed in 22 patients (46%) of which 13 patients (27%) showed lesions confined to regional lymph nodes, and nine patients (19%) showed nonregional lymph node metastases and/or bone metastases. PSMA PET/CT changed the treatment strategy from curatively intended treatment to palliative treatment in 18 patients (38%).

Conclusion: PSMA PET/CT revealed pathological uptake in a large proportion of high-risk patients at primary staging among patients with no definite metastases on standard imaging leading to change of patient management in 38% of the patients.

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Background

Prostate-specific membrane antigen (PSMA) PET/CT has changed the landscape of imaging in prostate cancer (PCa) in less than a decade [1–3]. It is currently the most accurate imaging modality in PCa both at primary staging [4,5] and in patients experiencing biochemical recurrence [3] and has become the recommended imaging modality in patients with recurrent PCa [6]. Despite significant improved diagnostic accuracy from diagnostic test accuracy trials [7,8], systematic reviews comparing PSMA PET/CT to cross sectional anatomical imaging for detection of lymph node metastases [4,9] and from a large randomized trial [5], PSMA PET/CT is not (yet) recommended for up-front staging of patients with PCa. Nevertheless, several institutions have implemented the clinical use of PSMA PET/CT in high-risk patients for primary staging of PCa.

At our institution, we changed clinical practice by 1st of August 2018 and conducted PSMA PET/CT in all patients eligible for treatment with curative intent and without definite distant metastases on standard imaging. The aim of the

present study was to present the preliminary data of the first six months with this new imaging strategy and evaluate the added value of PSMA PET/CT in a group of patients with newly diagnosed PCa eligible for curatively intended treatment with a particular focus on the clinical consequences in terms of change in patient management and outcome after treatment with one year of follow-up.

Methods

Patients

On the 1st of August 2018, the multi-disciplinary team (MDT) for treatment of PCa at the University Hospital in Aalborg (a tertiary referral center covering all patients with PCa in the North Denmark Region) decided to change the imaging strategy in patients with newly diagnosed PCa and ISUP grade 5 (Gleason score 9 and 10). The new imaging strategy were as follows: All patients received standard of care imaging (SoC) consisting of a contrast enhanced CT (ceCT) of thorax, abdomen and pelvis and a whole-body bone

scintigraphy as recommended by the European Association of Urology (EAU) [10]. SPECT/CT with ultra-fast acquisition and low-dose CT [11] was performed at the discretion of the nuclear medicine physician in charge.

PSMA PET/CT was conducted in all patients after SoC imaging according to the following three criteria: (1) Newly diagnosed ISUP grade 5 PCa and (2) no definite distant metastases on standard imaging and (3) eligible for curatively intended treatment either radical prostatectomy (RP) or radiation therapy (RT) based on performance status and life expectancy estimation.

The reason for not providing PSMA PET/CT as the first (and only) investigation in every high-risk patient prior to the treatment decision was due to a limited capacity for PSMA-production. The results of the PSMA PET/CT were discussed at the MDT-conference before a final treatment decision was taken. Treatment decisions were based on the European Association of Urology guideline [10] as recommended by the Danish Prostate Cancer Group (www.ducg.dk). Due to high-risk PCa in all patients, RP was conducted with extended lymph node dissection (eLND) and patients undergoing RT received 3 years of androgen deprivation therapy (ADT).

PSMA PET/CT

The PSMA-ligand used was PSMA-11, synthesized as previously described [12], a dose of 2 MBq/kg (maximum 200 MBq) was injected one hour prior to the PET/CT-scan. All patients were orally hydrated, and 20 mg of furosemide was injected shortly after injection of the tracer. Patients were scanned from base of the skull to upper thigh on a Siemens Biograph mCT Flow 64 PET/CT system (Siemens Medical Solutions, Erlangen Germany). A low dose CT was conducted and used for attenuation correction and anatomical co-registration. All PET/CT scans were conducted as part of daily clinical practice and evaluated two observers of whom at least one was considered experienced [13].

Clinical follow-up

Clinical and pato-anatomical data from all patients were retrieved from the electronic data files, including assigned treatment and follow up for at least 12 months after treatment.

Statistics

Descriptive results are summarized by their mean or median values, standard deviations and ranges. Due to the descriptive nature of the results no formal statistical analysis was conducted. STATA[®]11 (StataCorp LP, College Station, TX, USA) was used for statistical analyses.

Ethics

Due to the observational and retrospective nature of the study, no formal approval from the ethics committee was required according to our national legislation. The study was

approved by the Danish Data Protection Agency (approval number 2017-131) and the Danish Patient Safety Authority waived informed consent (file reference 31-1521-368).

Result

Patients

During the first six months of the new imaging strategy, 79 patients were diagnosed with an ISUP grade 5 PCa. Based on SoC imaging, 19 patients had definite metastatic disease. Twelve patients without metastases on standard imaging did not have a PSMA PET/CT since they were not considered eligible for curatively intended treatment based on comorbidity or too short life expectation. Consequently, 48 patients underwent PSMA PET/CT for staging (Table 1). Forty-three patients had no evidence of metastatic disease on standard imaging, whereas two patients had a single pelvic lymph nodes of 12 mm and were thus considered having regional lymph node metastasis that would not disqualify for curatively intended treatment and finally three patients had equivocal lesions on the bone scintigraphy, which would normally prompt supplementary diagnostic procedures.

PSMA PET/CT

Among the 48 patients undergoing PSMA PET/CT, avid PSMA uptake was observed in the prostatic gland in 47 patients (98%). One patient did not exhibit any PSMA uptake on the PET/CT in the prostate or outside the prostate.

PSMA uptake outside the prostate was seen in 22 of 48 patients (Table 2). In 13 patients, the PSMA uptake was seen in regional pelvic lymph nodes, in four patients the PSMA uptake was seen both in regional lymph nodes and in non-regional lymph nodes (M1a-disease). In one patient the PSMA revealed bone metastases only and finally in four patients both lymph node metastases and bone metastases were revealed by PSMA PET/CT. One patient with regional lymph node metastases also presented with multifocal PSMA

Table 1. Patient demographics for patients undergoing PSMA PET/CT.

Patients, <i>n</i>	48
Age (y), mean (range)	69 (55–78)
PSA (ng/mL), median (range)	13 (3.3–95)
Bone scan prior to inclusion	
Planar whole body	17
Planar whole body + SPECT/CT	31
Time from bone scan to PSMA-PET/CT (days), median (IQR)	19.5 (12–25)
Gleason score	
9 (4 + 5), <i>n</i>	37
9 (5 + 4), <i>n</i>	11
10, <i>n</i>	0
T-stage	
T1, <i>n</i>	12
T2, <i>n</i>	16
T3, <i>n</i>	19
T4, <i>n</i>	1
Performance status	
0, <i>n</i>	38
1, <i>n</i>	8
Unknown, <i>n</i>	2

SPECT/CT: Single photon emissions computed tomography; PSA: Prostate-specific antigen. IQR: Inter quartile range.

uptake in the liver and a biopsy revealed hepatocellular carcinoma. Twenty-six patients (61%) did not exhibit pathologic PSMA uptake outside the prostate. In both patients with SoC suggesting a single pelvic lymph node metastasis, the PSMA PET/CT revealed two respective three lymph node metastases, including the lymph node seen in ceCT. In three patients with equivocal findings on bone scintigraphy, one patient had bone metastases confirmed by PSMA PET/CT, whereas the other two patients had no PSMA uptake in the bones but PSMA uptake was seen in the regional lymph nodes (Table 2).

Impact on patient management

Based on standard imaging, 45 patients were candidates for curatively intended treatment whereas three patients had equivocal findings on bone scintigraphy which required additional diagnostic procedures anyway before treatment could be assigned. Based on the PSMA PET/CT findings, 16 of 45 patients (36%) were no longer candidates for curative treatment. If patients with equivocal standard imaging were included, PSMA PET/CT changed the patient management in 18/48 patients (38%) (Table 3, Figure 1). Among patients offered curatively intended treatment, three patients reconsidered the situation and decided not to undergo curatively intended treatment, these changes were due to personal considerations and not related to the diagnostic work-up. Ultimately, 14 patients underwent RP with eLND and 13

Table 2. Metastatic status according to PSMA PET/CT categorized by findings by standard imaging.

No metastases on standard imaging, n = 43	
No PSMA-uptake outside the prostate (N0M0)	26 (61%)
Regional LN metastases (N1M0)	8 (19%)
Regional and distant LN metastases (N1M1a)	4 (9%)
LN and bone metastases (N1M1b)	4 (9%)
Regional LN (N1M0) and other primary tumor	1 (2%)
Equivocal findings on bone scintigraphy, n = 3	
Regional LN metastases (N1M0),	2 (67%)
Bone metastasis (N0M1b)	1 (33%)
Contrast enhanced CT showing a single enlarged regional LN, n = 2	
Regional LN metastasis (N1M0)	2 (100%)

LN; Lymph node.

Table 3. Reasons for assigning nine patients with regional lymph node metastases and no distant metastases (N1M0) to palliative treatment.

	Number of regional lymph node metastases on PSMA PET/CT	Number of regional lymph node stations involved in metastatic disease	Localization of regional lymph node metastases (e.g. unresectable)
Patient 1	X	X	X
Patient 2	X	X	X
Patient 3		X	X
Patient 4		X	X
Patient 5		X	X
Patient 6		X	
Patient 7		X	
Patient 8			X
Patient 9			* *

*The patient was also diagnosed with multifocal hepatocellular carcinoma, which was the main reason for not undergoing treatment with curative intent.

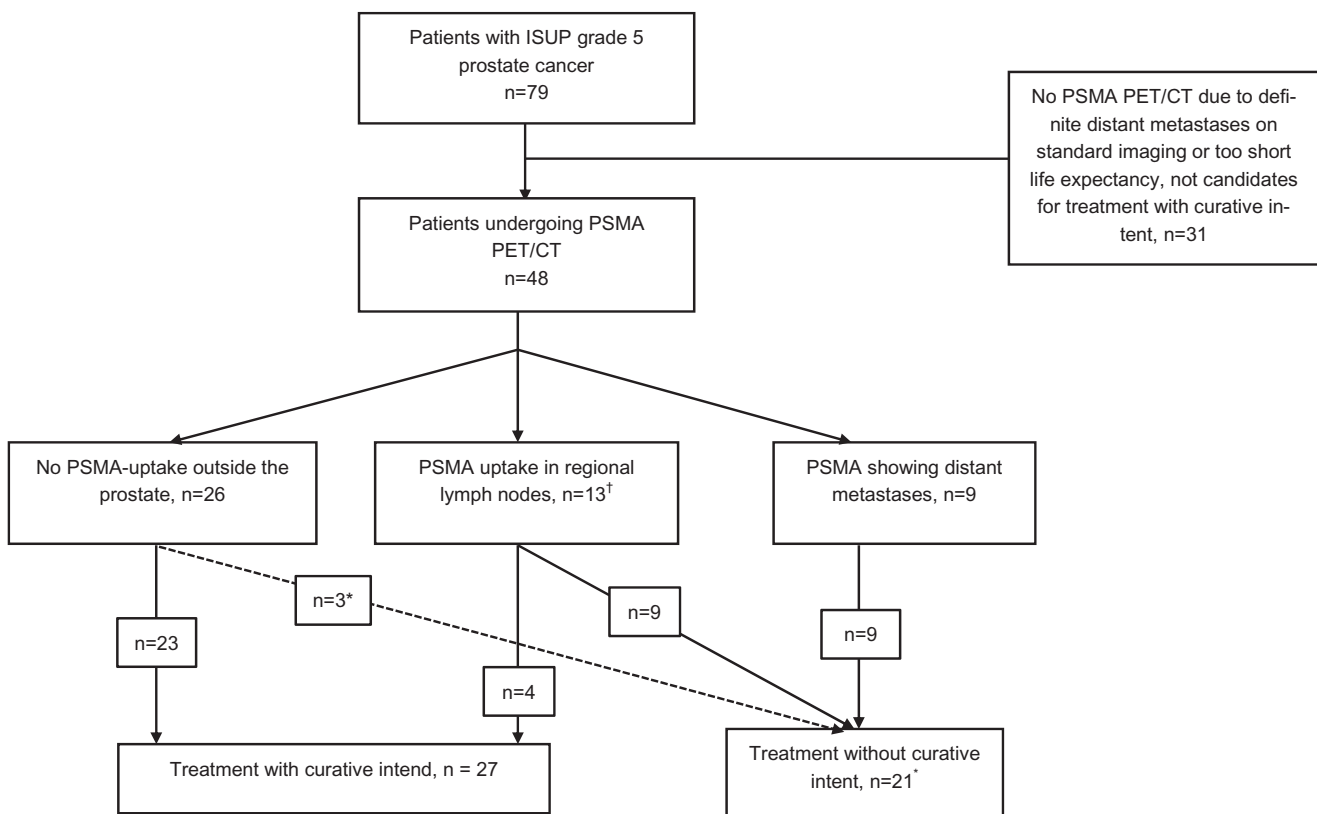


Figure 1. Flowchart of patients diagnosed with an ISUP grade 5 prostate cancer undergoing PSMA PET/CT as part of primary staging work. *Three patients with PSMA uptake in the prostate only, reconsidered the situation and decided not to undergo curatively intended treatment. †One patient with regional lymph node metastases was also diagnosed with multifocal hepatocellular carcinoma.

patients underwent curatively intended RT with 3 years of ADT.

Follow-up

At least 12 months (range 12–19 months) of follow-up was available for all patients. In patients undergoing RP, the PSMA PET/CT suggested lymph node metastases in four patients, this was verified by histology in two patients and shown to be false positive in two patients, in whom PSMA PET/CT showed one suspicious lymph node in each patient. Two lymph node metastases were diagnosed by histological examination of the operative specimen in one patient without PSMA uptake outside the prostate, the diameter of the lymph node metastases was 1 and 2 mm, respectively. Finally, the absence of lymph node metastases in PSMA PET/CT was confirmed by histology in eight patients.

Two patients undergoing RP experienced biochemical recurrence (PSA >0.1 ng/mL) during follow up, both patients had positive surgical margins. Among the 13 patients undergoing RT with 3 years of concomitant ADT; no patients experienced biochemical recurrence during follow up.

Discussion

The present preliminary study presents the clinical consequences the first six months after introducing PSMA PET/CT for primary staging in patients eligible for curatively intended treatment without definitive distant metastases on standard imaging and ISUP grade 5 PCa. The key finding was that after the addition of PSMA PET/CT to standard imaging, 38% of the patients eligible for curatively intended treatment were no longer offered this treatment. Instead, they underwent various noncurative regimens, predominantly regimens including ADT. PSMA PET/CT revealed metastatic disease in 9/48 patients without definitive distant metastases on standard imaging. Moreover, an additional eight patients had extensive PSMA uptake in regional pelvic lymph nodes rendering these patients ineligible for curatively intended treatment. Finally, PSMA PET/CT provided a definite answer in three patients with equivocal findings on bone scintigraphy.

The presence of significantly improved diagnostic accuracy for PSMA PET/CT over standard imaging have been shown in numerous studies predominantly retrospective and single-center studies but also in a recent randomized controlled trial [5]. The diagnostic superiority has been shown for the assessment of regional lymph node metastases [4,5,7] and for the diagnosis of bone metastases [14–16]. Likewise, in the present setting, PSMA PET/CT indicated regional lymph nodes in almost 40% of patients without lymph node metastases on ceCT. Among patients with regional lymph node metastases, distant metastatic disease in nonregional lymph nodes or bone were seen in 44% of the patients. Overall, PSMA revealed bone metastases in 9% of patients without metastases on standard imaging which is similar to studies comparing bone scintigraphy and PSMA PET/CT for the detection of bone metastases at the time of primary staging predominantly in patients with high-risk disease

[14–16]. These findings have been reinforced by a recent randomized controlled trial in patients with high-risk PCa by Hofman *et al.* showing that the accuracy of PSMA PET/CT to be 92% compared to 65% in conventional imaging for primary staging [5]. In addition, Hofman *et al.* investigated the incremental value of PSMA PET/CT as second line imaging and found that PSMA PET/CT had high or medium impact on patient management in 27% of the patients – which is similar to our preliminary findings. However, we only considered high impact changes in patient management – a change from curatively intended treatment to noncurative treatment – in the present study. The major reason for this was that all patients were scheduled for either RP with eLND or RT with 3 years of ADT prior to PSMA PET/CT owing to their high-risk status and in such cases a PSMA PET/CT with PSMA uptake confined to the prostate did not alter this strategy. In contrast, the impact of PSMA PET/CT on patient management in the setting of biochemical recurrence (BCR) has been reported to be around 50% [17,18]. A normal PSMA PET/CT at the time of BCR has also shown to impact patient management [19].

The use of PSMA PET/CT on top of standard imaging causes stage migration as seen in approximately 40% of the patients in the present study. Consequently, fewer patients were offered treatment with curative intent. On the other hand, patients undergoing curatively intended treatment after a PSMA PET/CT were suspected to be better selected for treatment. It is known that patients with undiscovered distant metastases are thought to experience immediate relapse following RP [20]. Likewise, patients receiving RT and ADT are prone to recurrence if distant metastases are present prior to treatment. In the present study, all patients undergoing RP experienced a PSA < 0.1 ng/mL following surgery and during follow up, except for two patients who had positive surgical margins.

The use of PSMA PET/CT improves patient selection for curative treatment, but no data exists on how patients who are deprived of curative treatment based on a PSMA PET/CT manage in terms of quality of life, morbidity and mortality. It has previously been shown that patients with lymph node metastases may benefit from RP [21,22]. It can be speculated if the withdrawal of curatively intended treatment in patients with oligo-metastatic PCa based on PSMA PET/CT findings benefits from reduced side effects from surgery or RT or if the removal of the prostate in patients might be beneficial in the long run [23].

The implementation of the new imaging strategy in our Region included patients with high-risk PCa only and was based on previous findings of few metastases in the group of patients with intermediate-risk PCa undergoing PSMA PET/CT [7,24]. Narrowing the criteria to patients without definite distant metastases and fit for curatively intended treatment reduced the need for PSMA PET/CT with almost 40% in this preliminary study. This decision was also based on the assumption that PSMA PET/CT in patients with known metastases on SoC imaging is not likely to alter patient management. The use of up-front docetaxel [25] or abiraterone [26] in patients with high volume disease and radiotherapy in

patients with locally advanced- or low volume disease [27] is assigned based SoC imaging.

The number of patients in this preliminary study is limited, and the retrospective and descriptive nature of the study is a limitation too. In addition, only patients with PSMA PET/CT indicating limited nodal disease underwent RP with lymph node dissection, no verification of lymph node metastases was conducted in the remaining patients. Similarly, only investigations deemed clinically relevant were conducted, thus no attempts to further verify evident distant metastases were conducted, which reflects the clinical reality of employing PSMA PET/CT as standard in the primary staging of selected patients with high-risk PCa.

In conclusion, the present results suggest a large effect of implementing PSMA PET/CT for up-front staging in patients with ISUP grade 5 PCa however, further studies are awaited to clarify the patient benefit of such changes in patient management.

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Author contributions

HD Zacho participated in designing the study, data collection, analysis and writing first draft of the manuscript. S Nalliah participated in data collection, analysis and critical revision of the manuscript. A Petersen participated in data collection and critical revision of the manuscript and LJ Petersen participated in design of the study, analysis, and critical revision of the manuscript. All authors approved of the final version of the manuscript prior to submission.

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