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Is 18F-FDG PET Needed to Assess 177Lu-PSMA Therapy Eligibility?
A VISION-like, Single-Center Analysis

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ABSTRACT

Introduction

18F-2-Fluoro-2-deoxyglucose (18F-FDG) in addition to Prostate Specific Membrane Antigen (PSMA) PET has been employed to assess the eligibility for PSMA-targeted therapy by some centers. However, it remains unclear, if both examinations are needed as a part of work-up in the clinical practice, or if PSMA-PET alone, as was done in the positive phase 3 VISION trial, is sufficient to identify suitable candidates. The aim was to re-analyze all patients who received both 18F-FDG- and PSMA-PET for PSMA-targeted therapy eligibility assessment using the VISION trial criteria.

Methods

Eighty-nine men with mCRPC–referred to 177Lu-PSMA therapy from June 2019 until October 2021 who received both 18F-FDG- and PSMA-PET (using either 68Ga-PSMA-11 or 18F-PSMA-1007) examinations within 2 weeks were included in this analysis. Eligibility status was determined in accordance with either (a) knowledge of both 18F-FDG- and PSMA-PET (clinical routine) or (b) VISION criteria with PSMA-PET only (study reassessment, done twice with liver only for PSMA-11 and liver/spleen as reference for PSMA-1007). A metastasis seen on 18F-FDG-PET or CT but not on PSMA-PET was denoted as a mismatch finding and led to exclusion from 177Lu-PSMA therapy. Based on clinical assessment, 52 patients received 177Lu-PSMA therapy, 37 did not; all patients were reassessed.

Results

Patients treated with 177Lu-PSMA therapy had significantly longer OS than those not treated (12.4 vs. 6.8 months, $p<0.01$). PSMA-only analysis (spleen/liver reference) and 18F-FDG/PSMA

mismatch reads had a substantial agreement (Cohen`s κ=0.73). 18% (n=16/89) of patients had a mismatch finding based on 18F-FDG/PSMA-PET. With the liver/spleen reference, a minor fraction of patients who had no mismatch finding (and were therefore treated) would have been withheld from therapy by PSMA-only analysis (3%). 3% (n=3) of all patients had an 18F-FDG/PSMA mismatch finding not detected by the PSMA-PET only (VISION-like) analysis. For patients not receiving PSMA therapy, the overall survival was not statistically significantly different comparing 18F-FDG/PSMA mismatch vs. non-mismatch (p=0.61) patients.

Conclusion

18F-FDG- and PSMA-PET provide complementary information, yet less than 5% of patients had mismatch findings not detected using PSMA-PET only. Based on our data, 18F- FDG/PSMA mismatch examination and PSMA-only analysis have a substantial level of agreement.

INTRODUCTION

Radioligand therapy targeting the prostate-specific membrane antigen (PSMA) with 177Lutetium (177Lu-PSMA) is an efficacious therapy option in patients with end-stage, metastatic castration-resistant prostate cancer (*1*). Recently, the VISION trial, an open-label international phase III trial comparing PSMA therapy against standard of care, demonstrated superiority of the additional 177Lu-PSMA therapy when compared with standard of care (SOC) only; overall survival was significantly longer when receiving 177Lu-PSMA therapy with SOC (*2*). This led to Food and Drug Administration approval in March 2022. This approval is a hallmark for nuclear medicine, as it is the first novel theragnostic treatment option available for an entity with high prevalence (in contrast to relatively rare neuroendocrine tumors).

Men with metastatic castration-resistant prostate cancer have multiple treatment options available and 177Lu-PSMA is now being tested in earlier treatment lines (*3*,*4*). Identification of patients who are most suited for PSMA therapy is critical for outcome, given the rate of non-responders of approximately 50% (RECIST response in the VISION trial) (*2*). This is relevant, as pretherapeutic PSMA-PET should allow for an improved prognostication of overall survival time and prediction of response, as it directly assesses the expression of the PSMA target (*5*,*6*). To assess eligibility, the VISION trial relied on PSMA PET in combination with diagnostic CT to exclude patients with low PSMA expression in metastases which meet specific size criteria (*7*). Patients not fulfilling the criteria had worse overall survival, which was shown by a subsequent analysis (*8*). The use of PSMA-PET only to assess 177Lu-PSMA therapy eligibility was adopted by many departments of nuclear medicine and is considered clinical standard (*9*).

In contrast, the initial prospective 177Lu-PSMA therapy trials employed both PSMA- and 18F-2-Fluoro-2-deoxyglucose (18F-FDG) Positron Emission Tomography (PET) examinations to assess

therapy eligibility, which was adopted by many departments of nuclear medicine, including ours (*10*,*11*). Dual tracer screening was implemented assuming that a PSMA-negative metastasis that is missed by PSMA-PET might heavily influence the response to 177Lu-PSMA–therapy. An 18F-FDG-positive and PSMA-negative metastasis is denoted as a mismatch finding.

However, it remains unclear if the combination of PSMA and 18F-FDG is clinically needed. Therefore, the aim of this study was to compare 18F-FDG/PSMA mismatch evaluation head-to-head with an analysis relying only on PSMA-PET. To this end, we performed a retrospective re-read of the pretherapeutic PSMA-PETs according to the VISION trial protocol.

METHODS

Patient Cohort

Among 119 patients who were referred to PSMA and 18F-FDG PET to assess 177Lu-PSMA therapy eligibility at the University Hospital Essen between June 2019 and October 2021, the patients whose image data were available and whose 18F-FDG and PSMA PETs were obtained within two weeks of each other (n=89) were included. Patient characteristics are shown in Table 1. A total number of 52 patients were treated with 177Lu-PSMA therapy, whereas 37 patients were not treated with 177Lu-PSMA therapy. Median PSA level was 176 ng/ml (IQR 32.5-526.3) in the cohort receiving 177Lu-PSMA therapy and 65.7 ng/ml (IQR 16.8-290.7) in the remaining patients. In total, 53 (59.6%) patients underwent PSMA-11 PET, whereas 36 (40.4%) patients underwent PSMA-1007 PET examination. Ethical approval for this retrospective study was present (local ethics committee approval number: 19-8570-BO).

Clinical 18F-FDG/PSMA Mismatch Analysis to Assess Therapy Eligibility

Patients with PSMA and 18F-FDG PET for PSMA therapy assessment with a maximum interval of two weeks between the PET examinations were analyzed. In our clinical routine, 177Lu-PSMA therapy eligibility was assessed based on visual analysis of PSMA PET and 18F-FDG PET to rule out clinically relevant mismatch. Inspired by the target lesion definition of the RECIST 1.1 criteria visceral metastases/soft tissue lesions with longest diameter of ≥ 10 mm and lymph nodes with short axis diameter exceeding 15 mm that have 18F-FDG uptake higher than liver and PSMA uptake lower than spleen/liver were considered as clinically relevant mismatch. In addition, for the bone lesions, more than 3 bone metastases without osteolytic correlates, which are regarded as unmeasurable in RECIST 1.1 criteria with 18F-FDG uptake higher than liver and PSMA uptake lower than liver was regarded as clinically relevant mismatch (*12*). Visual uptake generally higher than liver or spleen for all lesions on PSMA PET was necessary for therapy eligibility. All men were discussed in a multidisciplinary tumor board. A metastasis in organs or bone delineated on 18F-FDG-PET with no corresponding PSMA uptake was rated as mismatch finding and the patient was excluded from 177Lu-PSMA therapy. The mean activity administered for 68Ga-PSMA-11 and 18F-PSMA-1007 PET were 117.5±56.5 and 328.3±76.3 MBq, respectively. Supplemental Table 1 provides details on the criteria used to assess 177Lu-PSMA therapy eligibility. Clinical reads of PET images have been reassessed by two nuclear medicine physicians to ensure consistency.

Retrospective Application of the VISION PSMA-PET Only Eligibility Criteria

All PSMA PET examinations were analyzed by the same nuclear radiologist who helped design the criteria, trained the readers, and supervised the centralized eligibility analysis for the VISION

trial (P.H.K.). The reader was blinded to clinical assessment and the 18F-FDG-PET acquisition. If available, diagnostic contrast-enhanced CT was utilized as was done for the VISION trial, and if not available, the in-line CT from the PET/CT was used. Images were viewed using MIM Software 7.1.7 (Cleveland, OH, USA). Analysis was completed twice and in accordance with VISION criteria which only used PSMA-11; first, the liver was regarded as reference organ for positivity threshold. In a second approach, for patients who were imaged with PSMA-1007 and excluded due to low PSMA expression, the spleen was used as a reference organ. In summary to be VISION eligible, PSMA positive lesions above the organ threshold (liver or spleen) and no PSMA negative lesion had to be present; to ensure the latter the CT component was utilized. PSMA negativity of the following CT findings meeting these size criteria lead to exclusion: Lymph node ≥ 2.5 cm; solid organ metastases ≥ 1 cm short axis; bone metastases with soft tissue component ≥ 1 cm.

PSMA Therapy

Beside the above-described image-based criteria for therapy eligibility, the EANM procedure guidelines were followed (*9*). 177Lu-PSMA therapy was performed as previous published (*13*). Briefly, the PSMA-617 ligand (ABX GmbH, Radeberg, Germany) was conjugated with 177Lutetium (ITG Isotope Technology, Garching, Germany). A median cumulative dose of 24.4 (IQR 12.3-29.8) GBq was administered per patient, cycles were repeated every 6-8 weeks.

Statistical Analysis

R and SPSS (Version 29, IBM) used for statistical analysis, testing, and plotting. Kaplan Meier estimates were used. Cox regression analysis for analysis of censored data, and Log rank test was used to compare groups regarding survival time. Agreement between PSMA-only analysis (using

spleen/liver as a reference organ) and 18F-FDG/PSMA mismatch read was evaluated with Cohen`s kappa analysis. Difference in PSA response rate ≥ 50 % (PSA50RR) for the patients treated with 177Lu-PSMA was analyzed with chi-square test. A p value < 0.05 was regarded as statistically significant.

RESULTS

Detection of 18F-FDG/PSMA Mismatch Using PSMA PET Alone

89 out of 119 patients referred to PSMA therapy had 18F-FDG- and PSMA-PET scans within 2 weeks of each other (Figure 1). The rate of 18F-FDG/PSMA mismatch findings was 18% (n=16/89). Substantial agreement between PSMA-only analysis (in accordance to modified VISION Criteria using liver/spleen as a reference organ) and 18F-FDG/PSMA mismatch read was observed (n=81/89, 91%, Cohen`s kappa: 0.73, Figure 2). 3 % (n=3/89, denominator: total cohort) had an 18F-FDG/PSMA mismatch finding although they were deemed eligible for PSMA therapy by the PSMA-only analysis (Figure 3, Table 2). 12% (n=11/89, denominator: total cohort) had no mismatch finding and were not eligible for 177Lu-PSMA therapy according to the VISION-like analysis (of this group, not all patients were treated with PSMA therapy because of insufficient clinical parameters).

Of the 89 analyzed patients referred to PSMA therapy, 52 patients (58%) received PSMA therapy. Table 2 provides details of the reasons for exclusion from 177Lu-PSMA therapy. Of those patients treated, 7 patients (13%, n=7/52, denominator: treated patients) were treated due to the clinical assessment but would not have been eligible for 177Lu-PSMA therapy according to the PSMA-only (VISION-like) analysis. Of patients treated with 177Lu-PSMA therapy, 23f patients (44%, n=23/52, denominator: treated patients) had received PSMA-1007 PET for eligibility assessment.

VISION-like Analysis of Patients (Separated According to the PSMA Ligand Used)

This first assessment used the VISION prescribed threshold of activity greater than liver for "PSMA-positivity" and likewise activity equal or less than liver for "PSMA-negativity." In the cohort imaged with PSMA-11, 3 patients (6 %, n=3/53, denominator: patients imaged with PSMA-11) deemed eligible by the PSMA-only analysis would have been ineligible due to 18F-FDG/PSMA mismatch findings. In the PSMA-1007 cohort, no patient with a mismatch finding was rated as therapy eligible by the PSMA-only analysis. Only one treated patient (2 %, n=1/53, denominator: patients imaged with PSMA-11) without an 18F-FDG/PSMA mismatch finding was excluded in the PSMA-11 cohort though the VISION read. However, 6 treated patients imaged with PSMA-1007 (17 %, n=6/36, denominator: patients imaged with PSMA-1007) were excluded from PSMA therapy based on the PSMA-only read without a mismatch finding.

VISION-like Analysis of Patients with Adjusted Reference Organ

To adjust for the higher hepatic PSMA uptake, the eligibility of patients imaged with PSMA-1007 was reassessed using the spleen as additional reference organ (Figure 4). After this adjustment, only 3 patients (3 %, n=3/89, denominator: total cohort) of the total cohort including patients imaged with either PSMA tracer were not eligible due to the PSMA-only VISION analysis but showed no mismatch finding and were treated. For PSMA-1007, only 2 patients (6 %, n=2/36, denominator: patients imaged with PSMA-1007) were excluded without a mismatch finding and were treated.

Still, only 3 patients (3%, n=3/89, denominator: total cohort) of the total cohort had a mismatch finding, which was not detected by the PSMA-only analysis (Table 2). See supplemental Table 2 for details on mismatch and PSMA-only VISION evaluation deviations. For comparison,

supplemental Figure 1 provides the cross tables for the clinical reads (mismatch finding and/or low PSMA expression) and the VISION analysis (original and spleen adjusted) separately for the employed ligand.

Overall Survival of Total Cohort and Untreated Patients

The overall survival of patients treated with 177Lu-PSMA therapy was significantly longer compared to those not treated (12.4 [95% CI 8.6 – 25.5] vs. 6.8 [95% CI 4.2 – 9.5] months, $p < 0.01$; HR: 0.454, $p < 0.01$).

The overall survival of patients not treated with 177Lu-PSMA therapy was not statistically significantly different between those with (n=16) or without an 18F-FDG/PSMA mismatch (n=21) finding (4.7 [95% CI 2.4 – 6.8] vs. 9.2 [95% CI 3.3 – 14.3] months, $p = 0.61$; HR 1.224, $p = 0.6$), but this analysis was limited due to the low n (n=37). Patients not treated with 177Lu-PSMA therapy did not have a statistically significantly different survival time if they are VISION (spleen adjusted) eligible or not (4.7 [95% CI 2.4 – 16.1] vs. 9.2 [95% CI 3.3 – 14.3] months, $p = 0.42$; HR 0.73, $p = 0.4$) (Figure 5).

Outcome of the Patients Received 177Lu-PSMA

Of the 89 analyzed patients referred to our department, 52 patients (58%) received 177Lu-PSMA therapy. PSA50RR of all patients treated with 177Lu-PSMA was 51%. Of those patients treated, 7 patients would not have been eligible for 177Lu-PSMA therapy according to the PSMA-only (VISION-like, only liver used as reference) analysis but were still treated because of the clinical assessment. PSA50RR of those patients was not statistically significantly different from patients

who were eligible (40% vs. 52.4%, p=0.66). The overall survival time of patients who were clinically treated with 177Lu-PSMA, although they should have been excluded according to VISION re-evaluation was 7.46 months (n=7, 95% CI 5.2-18.3) in contrast to 12.4 months (95% CI 4.7-20.1) of the patients who were eligible and treated with 177Lu-PSMA; the difference was not statistically significant (p = 0.7).

DISCUSSION

In the present study, we investigated different imaging approaches to assess eligibility for 177Lu-PSMA therapy and found high agreement of PSMA-only and FDG/PSMA mismatch assessment. Specifically, we explored the need for 18F-FDG-PET in addition to PSMA-PET. Only 3% of patients were deemed ineligible for therapy in excess of a PSMA-only analysis because of 18F-FDG/PSMA mismatch findings on 18F-FDG- and PSMA-PET. Seven patients (n = 7/89; 8 %, denominator: total cohort) were excluded due to the PSMA-only VISION-like analysis but clinically treated with PSMA therapy, and only 3 patients (3 %) if the reader used the PSMA-only modified VISION criteria with liver as the reference organ for PSMA-11 and spleen for PSMA-1007.

177Lu-PSMA therapy is an emerging treatment option in prostate cancer, which builds on the theragnostics principle, meaning that the diagnostic target can be used for whole body imaging and therapeutic approaches (*14*). The assessment of PSMA expression is therefore a prerequisite to assess therapeutic eligibility (*15*). However, still the rate of non-responders is considerably high, motivating the search for additional selective examinations prior to 177Lu- PSMA therapy. The reason for this lies in the tumor biology of advanced prostate cancer. Prostate cancer has a remarkable early tendency to spread to distant organs, at the time of prostatectomy, up to 70 % of

patients have prostate cancer cells in the bone marrow (*16*). This may lead to a parallel progression of distinct cancer phenotypes and dedifferentiation throughout the course of the disease, leading to tumor heterogeneity (*17*). In fact, neuroendocrine transdifferentiation may lead to loss of PSMA expression and often occurs in liver metastases (*18*). Therefore, liver metastases are associated with worse overall survival rate and require dedicated treatment, especially when 177Lu-PSMA therapy is employed; otherwise, transdifferentiated metastases without PSMA expression would not be adequately targeted (*19*,*20*).

The assessment of tumor heterogeneity of advanced prostate cancer is challenging (*21*). Using PSMA PET alone, distinct uptake patterns can be observed that are associated with distinct rates of overall survival (*22*). Especially low PSMA expression is associated with short overall survival time (*6*,*22*,*23*). The PSMA expression is also relevant to assess the PSMA tumor volume response to systemic therapy, otherwise declining PSMA tumor volume can be erroneously assessed as response to therapy, which could also represent a reduction of differentiated tumor volume with increase of de-differentiated proportions (*24*). To this end, PSMA/18F-FDG mismatch examination may be employed; multi-tracer approaches may reveal considerable tumor heterogeneity in prostate cancer, especially in end-stage prostate cancer under PSMA therapy (*25*,*26*).

We have found a rate of patients with mismatch findings of 18 %, which is in line with previous reports (*27*). Interestingly, the overall survival rate of patients who were not treated with PSMA therapy was not different comparing patients with and without mismatch finding (4.7 months vs 9.2 months $p = 0.61$). However, a tendency to shorter OS in case of mismatch is recognizable in the cohort of patients who did not receive 177Lu-PSMA therapy. This could indicate that the tumor phenotype may not be adequately characterized by manual mismatch analysis (i.e. searching for metastases with a flip-flop phenomenon). We have presented the characteristics of patients who

have not received PSMA-therapy in supplemental Table 3 separately for those with and without a mismatch finding. There was no difference regarding the levels of PSA, LDH, ALP or hemoglobin. However, a confounding effect could still be present, causing the mismatch and non-mismatch groups to have a similar OS by disguising a potential difference. Also, the finding might partially be explained by the definition of mismatch; patients rated as mismatch could potentially also show less PSMA uptake and would therefore have been excluded from therapy in a PSMA-only VISION analysis. In contrast, *Michalski et al.* showed that patients receiving 177Lu-PSMA therapy have a significantly shorter overall survival in case of a mismatch finding (*28*). This could be in line with our finding, because we compared the implications of mismatch in a cohort not treated with PSMA therapy; therefore, the lower PSMA expression of patients with mismatch was not linked to treatment efficacy. However, the potential value of 18F-FDG PET prior to PSMA therapy start might be in assessing the prognosis of the patient. Recently, it was shown that PSMA PET was predicting response to PSMA therapy, whereas 18F-FDG PET was prognosticating the outcome (*29*). Therefore, 18F-FDG PET might have a valuable role in addition to the mismatch assessment.

In contrast to previous phase II trials, we did not require a specific SUV threshold for therapy eligibility but used visual uptake higher than liver (*10*,*11*). The TheraP study and earlier LuPSMA trial required higher PSMA positivity for eligibility (SUV_{max} of 20 in one lesion and of 10 in remaining lesions or SUV_{max} higher than 1.5 times liver activity) (*21*,*30*). This may yield in the selection of highly promising candidates for 177Lu-PSMA therapy, but also withholds therapy from many patients that would have benefitted from therapy. We found that the liver as the reference organ for PSMA-1007 may lead to the exclusion of patients who were clinically treated with 177Lu-PSMA therapy. Therefore, we proposed the spleen as alternative reference organ for patients imaged with PSMA-1007 prior to 177Lu-PSMA therapy, which is in line with previous publications. For example, the spleen was recently recommended as a reference organ for the

PROMISE framework (miTNM criteria) instead of the liver for PSMA ligands with liver dominant excretion (*31*). Also, the spleen was used as reference in a study comparing PSMA-11 and PSMA-1007 (*32*).

Conclusion

The combination of 18F-FDG- and PSMA-PET may help in the assessment of tumor heterogeneity and dedifferentiation in end stage prostate cancer, yet only a small fraction of patients was withheld from therapy due to 18F-FDG/PSMA mismatch findings not detected by PSMA-only VISION analysis. Further studies investigating the potential of 18F-FDG/PSMA imaging for predicting treatment response to 177Lu-PSMA therapy are warranted.

Disclosures:

P.H. Kuo is a consultant and/or speaker for Amgen, Bayer, Chimerix, Eisai, Fusion Pharma, General Electric Healthcare, Invicro (also prior employee), Novartis, and UroToday. He is a recipient of research grants from Blue Earth Diagnostics and General Electric Healthcare.

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The authors declare that there is no conflict of interest regarding this article.

KEY POINTS

QUESTION: Is 18F-FDG PET needed to assess 177Lu-PSMA Therapy Eligibility?

PERTINENT FINDINGS: The VISION-like analysis, which only regarded PSMA PET and CT to assess eligibility for 177Lu-PSMA therapy, resulted in a minor rate of patients who showed an 18F-FDG/PSMA mismatch finding that has been not detected; therefore, the mismatch evaluation before the start of PSMA therapy might be omitted. A spleen-adjusted threshold should be used for PSMA-1007 imaging studies to assess therapy eligibility.

IMPLICATION FOR PATIENT CARE: With careful evaluation, PSMA-PET/CT alone might be sufficient for 177Lu-PSMA therapy eligibility assessment. Still, further studies investigating the potential of 18F-FDG/PSMA for outcome prognosticating of patients treated with 177Lu-PSMA therapy are warranted.

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Figures

Figure 1: Flow chart of included patients

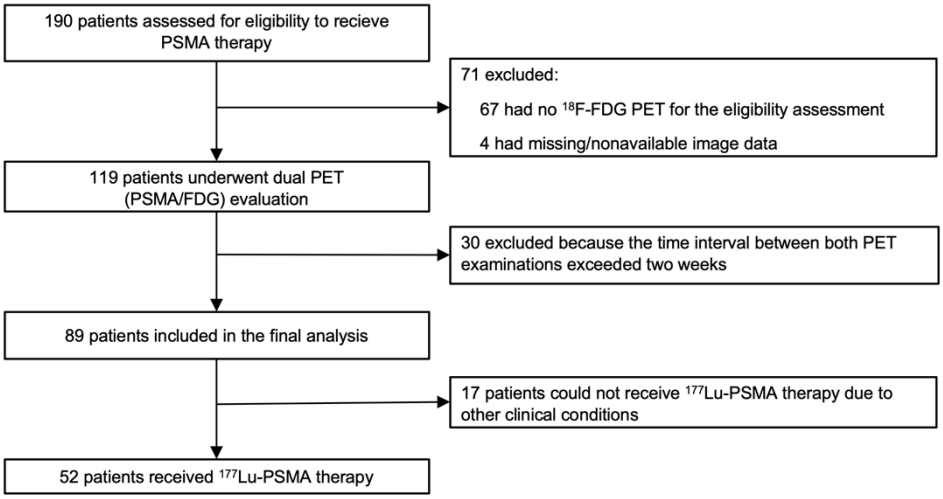


Figure 2: Exemplary patient who was ineligible for 177Lu-PSMA therapy (PSMA-only evaluation as well as 18F-FDG/ PSMA assessment)

Large osteolytic lesion in the sacrum with soft tissue component (A, yellow arrow) with low PSMA uptake (B, red arrows) and intensive 18F-FDG uptake (C, blue arrows). 18F-FDG has also shown additional liver metastases that were not detected by non-contrast enhanced CT or PSMA PET (C, arrowheads)

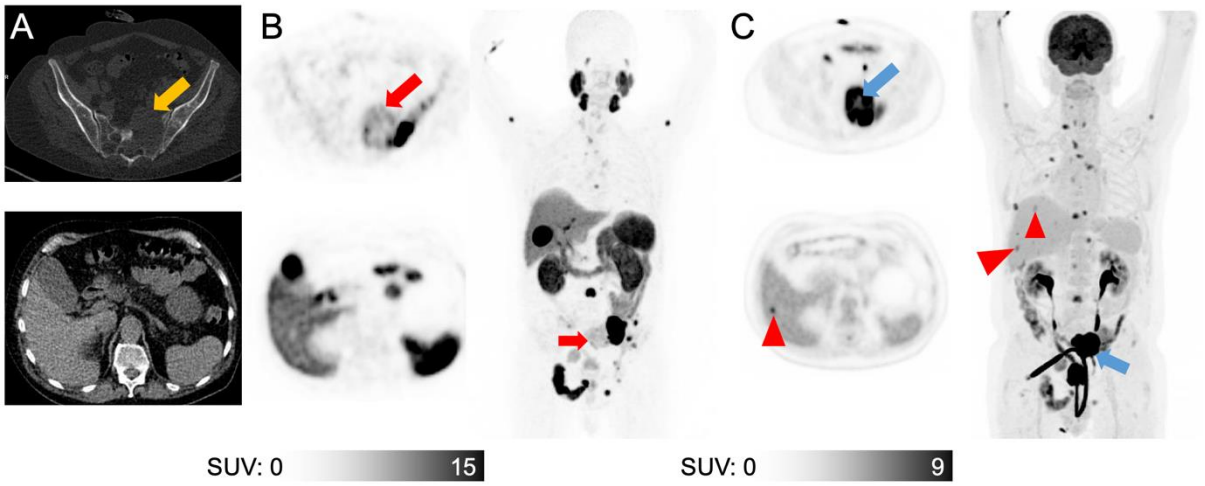


Figure 3: Exemplary patient who showed 18F-FDG/PSMA mismatch that was not detected by the PSMA-only analysis.

PSMA-11 PET/CT shows no significant CT correlate of bone lesions (A), which have a high PSMA uptake (B). However, 18F-FDG PET/CT shows more than 20 additional bone lesions (C).

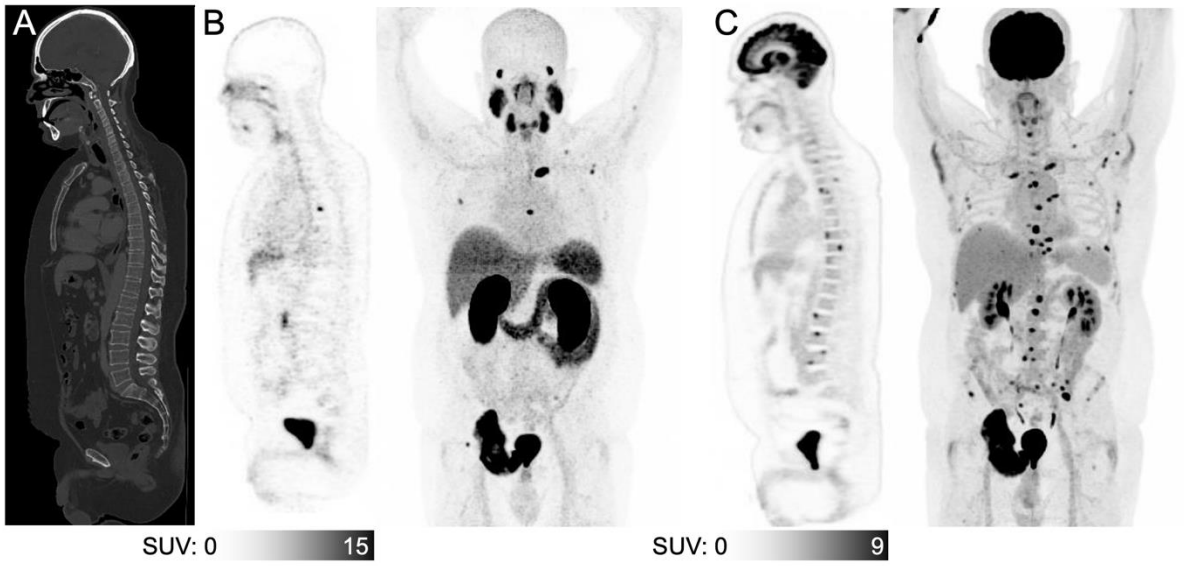


Figure 4 – Exemplary cases of patients referred to 177Lu-PSMA therapy

PSMA-11 PET imaging shows a destructive osseous metastasis with a large PSMA-negative soft tissue component is shown (dashed red circle, A). Therefore, the patient was rated as not eligible for 177Lu-PSMA therapy by the PSMA-PET only VISION analysis. PSMA-1007 PET imaging demonstrates a bone metastasis (B, arrow) with uptake lower than liver (B, blue dashed circle), and thus the VISION analysis excluded the patient from 177Lu-PSMA therapy. In the modified VISION analysis using spleen instead of liver as the threshold organ, the patient was included as the bone metastasis had higher uptake than the spleen (B, red dashed circle).

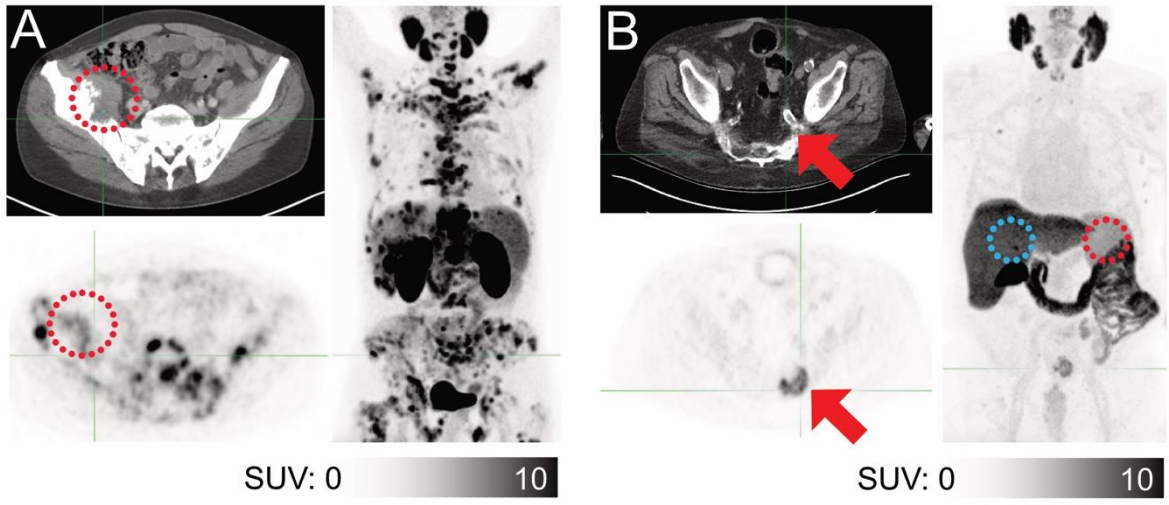
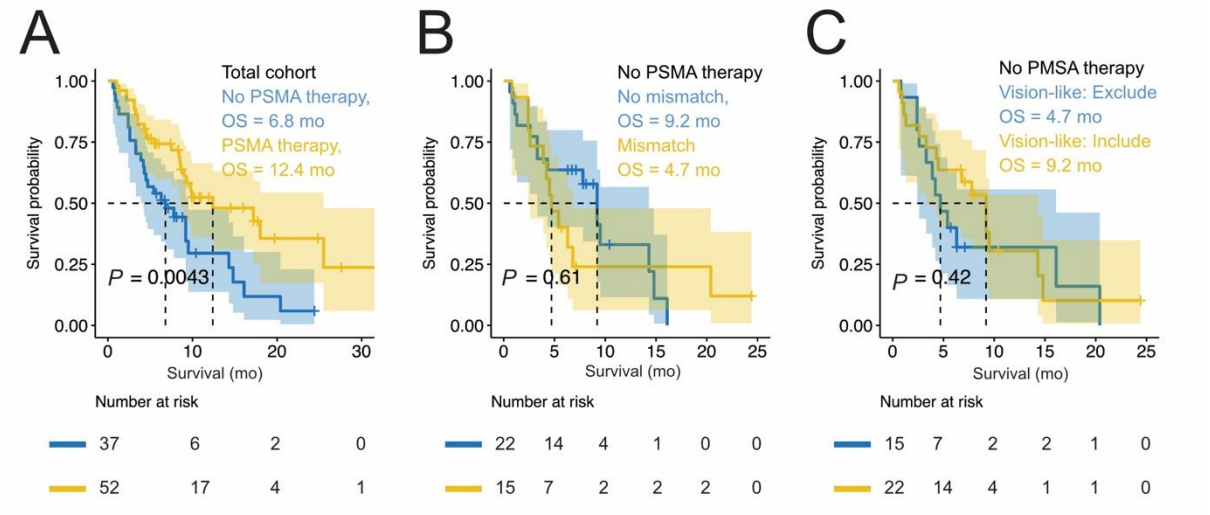


Figure 5 – Overall survival of entire cohort and patients not treated with 177Lu-PSMA therapy

Overall survival for the total cohort of patients with appropriate PET examinations is shown (A); patients treated with 177Lu-PSMA therapy have significantly longer overall survival time. Looking at patients that were not treated with 177Lu-PSMA therapy, there was no statistically significant difference in patients with a mismatch finding compared to those without (B). Likewise, patients excluded from 177Lu-PSMA therapy according to the PSMA-only VISION evaluation (spleen adjusted threshold for PSMA-1007 group) did not have shorter survival compared to excluded patients (C).



Tables

Table 1 – Patient characteristics

Parameter	Total (n=89)
Age (median (IQR))	71 (65-78)
Gleason sum Score (n (%))	n=67
≤7	11 (16.4)
≥8	56 (83.6)
Previous therapy lines (median (IQR))	4 (2-4)
Previous Therapies (n (%))	n= 86
Abiraterone	74 (86.0)
Enzalutamide	61 (70.9)
Docetaxel	77 (89.5)
Cabazitaxel	25 (29.1)
Other	23 (26.7)
ECOG PS (%)	n=53
0	20 (37.7)
1	25(47.2)
2	8 (15.1)
Treated with 177Lu-PSMA (n (%))	52 (58.4)
Cycles (median (IQR))	4 (2-4)
Cumulative dose (GBq) (median (IQR))	24.4 (12.3-29.8)
PSA (ng/ml) (median (IQR))	113 (25.4-461.5)
ALP (U/l) (median (IQR))	158.5 (91.5-330.2)
LDH (U/l) (median (IQR))	269.5 (223.7-438)
Hb (g/dl) (median (IQR))	11.4 (9.6.-12.7)
Mismatch (n(%))	16 (18.5)
Low PSMA uptake according to PSMA-only VISION evaluation (with spleen) (n(%))	18 (20.2)
Abbreviations: ALP: alkaline phosphatase, ECOG PS: Eastern Cooperative Oncology Group Performance Status, GBq: Giga Becquerel, Hb: hemoglobin, IQR: Inter-quartile range, LDH: lactate dehydrogenase, PSMA: Prostate-Specific membrane Antigen.	

Table 2 – Differences between the 177Lu-PSMA eligibility decisions made by our department (using 18F-FDG- and PSMA-PET) and PSMA-only (VISION-like) re-evaluation

		Clinical 177Lu-PSMA eligibility decisions			
		Ineligible: mismatch despite of sufficient PSMA uptake	Ineligible: low PSMA uptake and mismatch	Ineligible: low PSMA uptake	Eligible and received therapy
PSMA-only criteria (using liver)	Ineligible	0	13	4	7
	Eligible	2	1	0	45
PSMA-only criteria (using spleen/liver for PSMA-1007)	Ineligible	0	13	2	3
	Eligible	2	1	2	49

Graphical abstract