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Outcome of patients with PSMA-PET/CT screen failure by VISION criteria and treated with 177Lu-PSMA therapy: a multicenter retrospective analysis

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Abstract

The aim of the study was to assess the outcome of patients with metastatic castration-resistant prostate cancer (mCRPC) treated with 177Lu-PSMA who would have been screen failures (SF) in the VISION trial based on PSMA PET/CT criteria. **Methods**: We conducted a retrospective multicenter cohort study in 301 mCRPC patients treated with 177Lu-PSMA. The patients were classified into eligible (VISION-PET-E) and SF (VISION-PET-SF) groups based on the baseline PSMA-PET/CT. PSA response rates (decline of ≥50% (PSA50RR)), PSA-progression-free survival (PSA-PFS), and overall survival (OS) were compared. **Results**: 272/301 (90.4%) and 29/301 (9.6%) men were VISION-PET-E and VISION-PET-SF, respectively. The VISION-PET-SF patients had worse PSA50RR (21% vs. 50%; p = 0.005) and PSA-PFS (2.1 vs. 4.1 months; p = 0.023), and tended to have a shorter OS (9.6 vs. 14.2 months; p = 0.16) than the VISION-PET-E patients. **Conclusion**: The VISION-PET-SF patients had worse outcomes than the VISION-PET-E patients. Our cohort did not include pre-excluded patients (10-15%) by local sites assessments. Thus, 20-25% of the patients may be screen failures in unselected populations. Refinements in patient selection for 177Lu-PSMA are needed to optimize outcomes.

Keywords: metastatic castration-resistant prostate cancer; radionuclide therapy; PSMA PET; lutetium-177; VISION trial

Men with metastatic castration-resistant prostate cancer (mCRPC) have few alternative therapeutic options when the disease progresses after androgen-deprivation therapy (ADT), androgen receptor signaling inhibitors (ARSI), and chemotherapy. Recently, the VISION trial, an international, open-label, randomized phase 3 trial showed that prostate-specific membrane antigen (PSMA)-targeted molecular radionuclide therapy (MRT) with 177Lu-PSMA can improve the outcome of patients with advanced mCRPC. In this trial, 831 patients with mCRPC previously treated with ARSI and taxane regimens were randomized in a 2:1 ratio to 177Lu-PSMA (7.4 GBq every 6 weeks x 6 cycles; n = 551) plus best standard of care (SOC) or SOC alone (n = 280). The trial met both primary endpoints of overall survival and radiographic progression-free survival (rPFS). The median OS was 15.3 months in the 177Lu-PSMA arm versus 11.3 months in the SOC alone arm, resulting in a 38% reduction in the risk of death. The rPFS was 8.7 versus 3.4 months, respectively (*1*).

The VISION trial used PSMA-PET/CT to select patients for inclusion. The screen failure (SF) rate was "only" 12.6% (126/1003) (*1*) and some have argued that the trial could have been positive even in an unselected population (*2*). Eligibility by PSMA PET/CT scan was determined by the sponsor's central readers (criteria initially not disclosed). The VISION-PET selection criteria were released publicly at the ASCO (American Society of Clinical Oncology) 2021 meeting (see methods section) (*3*). It remains unknown whether the VISION-PET criteria were appropriate to screen for and identify the patients who will not benefit from the 177Lu-PSMA. Here, we exploited a database established retrospectively from multiple institutions to evaluate the outcome of patients treated with 177Lu-PSMA who would have been screen failure (SF) by VISION-PET criteria.

MATERIALS AND METHODS

We conducted a retrospective cohort study in our institutional database of patients treated with ≥1 cycle of 177Lu-PSMA between November 2017 and July 2021 (n = 74) and a multicenter dataset published previously (n = 230) (*4*) . Patients were treated either under compassionate use, expanded access program or clinical trials (Supplemental Table 1). All patients had a baseline 68Ga-PSMA-11 PET/CT

before 177Lu-PSMA therapy. The eligibility criteria and institutional treatment protocols are described in supplemental Table 1 and 2. Presence of "PSMA-positive" disease by PET was not consistently pre-defined and was determined by the local clinical investigators at each institution.

One dual radiology and nuclear medicine board certified reader (M.H.) blinded for patient outcomes reviewed the baseline PSMA-PET/CT scan of each patient to apply the VISION-PET criteria and define eligible (VISION-PET-E) vs screen failure (VISION-PET-SF) patients. Patients were classified as VISION-PET-E if they had at least one PSMA positive and no PSMA-negative metastatic lesions. The presence of PSMA-positive lesions was defined as PSMA uptake greater than that of liver parenchyma (*3*). The patients were classified as VISION-PET-SF if the baseline scan showed 1) absence of metastatic lesion with uptake > liver background (i.e. *low PSMA expression)* or 2) presence of ≥1 metastatic lesion measurable by CT (≥1 cm for bone lesions with soft-tissue component (M1b) and solid/visceral organs lesions (M1c), ≥2.5cm for lymph nodes lesions (N1-M1a)) with uptake ≤ liver background (i.e. *PSMA-negative lesions*) (*1*).Typical PSMA PET/CT images of " low PSMA expression" and "PSMA-negative lesions" are shown in Figure 1 and 2, respectively.

Outcome measures included prostate-specific antigen (PSA) response rates (decline of ≥ 50% (PSA50RR) and any decline (anyPSARR)), PSA-progression free-survival (PSA-PFS) and overall survival (OS). Kaplan-Meier curves with log-rank test and Cox-regression analysis were performed to compare survival outcomes. Fisher's exact test and logistic regression analysis was used for categorical variable comparisons. The UCLA IRB waived written informed consent requirements due to the retrospective design of the analysis (UCLA IRB #19-000896 and #21-001565).

RESULTS

Overall, 3/304 (1.0%) men were lost to follow-up (n = 2) or had missing DICOM CT images (n = 1) and were excluded. Among 301 men, 272 (90.4%) and 29 (9.6%) were classified as VISION-PET-E and

VISION-PET-SF, respectively. Cohort characteristics are provided in Table 1. The VISION-PET-SF patients had more visceral metastasis than VISION-PET-E patients (58.6% vs 25.4%, $p < 0.001$). The median number of cycles was lower for VISION-PET-SF patients than VISION-PET-E patients (median 2 cycles (IQR: 2-3) vs. 3 (IQR: 2-4), $p = 0.010$).

In the VISION-PET-SF group, 8/301 (2.7%) and 21/301 (7.0%) men were deemed to have "low PSMA expressing" or "PSMA-negative lesions", respectively (Summary images of these 29 patients are provided in Supplemental Figures 1-29). The PSMA-negative lesions were located in lymph nodes (n = 7), bone (n = 1), and visceral organs (liver: n = 4; lung: n = 5; pleura: n = 2; brain: n = 1; muscle: n = 1).

Our cohort of VISION-PET-E patients was fairly comparable to the cohort included in the VISION trial (analysis set used for imaging-based progression-free survival, supplemental Table 3) ***(1)***. However, the treatment history differed. All VISION patients had been treated with ARSI and taxane regimen. In contrast, only 55.1% and 80.1% of the current cohort underwent ARSI and chemotherapy before MRT, respectively. Nevertheless, the PSA response and OS were comparable between the two cohorts (PSA50RR: 50.3% vs 46.0%, anyPSARR: 71.3% vs 71.5%, OS [months]: 14.2 vs 14.6).

The median follow-up time was 22.5 months (interquartile range: 12.5-29.2, range: 2.1-62.3). The outcomes of the VISION-PET-E and VISION-PET-SF patients are shown in Table 2. The VISION-PET-SF patients had a significantly worse PSA50RR, anyPSARR, and median PSA PFS than the VISION-PET-E patients. Although not statistically significant, median OS was 4.6 months shorter in the VISION-PET-SF patients (Fig. 3).

In the VISION-PET-SF patients, the patients with PSMA-negative lesions (n = 21) had shorter OS than those with low PSMA expression (n = 8) (Supplemental Table 4). However, there was no statistical difference for the PSA50RR, anyPSARR, and median PSA-PFS between the patients with PSMA-negative lesion and those with low PSMA expression (Fig. 4).

DISCUSSION

The VISION trial used PSMA-PET as a biomarker to select patients for 177Lu-PSMA therapy. The VISION-PET-SF rate was "only" 12.6% (126/1003) (*1*). Therefore, some have argued that the trial could have been positive even in an unselected population *(2)*.

Here we report that the VISION-PET-SF patients had worse outcomes than the VISION-PET-E patients in response to 177Lu-PSMA therapy. We retrospectively identified a VISION-PET-SF rate of 9.6% in a cohort of 301 patients who were nevertheless deemed eligible for and treated with PSMA-MRT based on local assessments. Eligibility for treatment was determined by the local clinical investigators at each institution. The VISION PET criteria were released in June 2021 and were not available at the time of initial treatment. There are 2 main reasons to explain why patients with screen failure criteria by VISION PET criteria were still treated with 177Lu-PSMA. First, VISION-PET-SF patients with *PSMA-negative lesions* also had PSMA PET positive lesions. The local investigators may have considered that these PSMA-positive lesions were sufficiently suggestive of treatment response. Second, in VISION-PET-SF patients with *low PSMA expression,* the local investigators may have not considered the PSMA expression PET signal uptake as sufficiently low to exclude patients from treatment as there was no consistently predefined threshold to characterize "PSMA-positivity".

Our cohort did not include patients who were excluded upfront from PSMA-MRT by the local clinical investigators. The local SF rate was estimated at around 10-15% by contributing sites. Thus, SF numbers in our cohort is underestimated and can range from 20-25% in unselected populations. Including these patients in the analysis would further enhance the observed outcome differences.

Absent or low target expression limit the response to PSMA-targeted therapies (*5*,*6*). However, the key driving parameter of patient outcome seems to be the presence of PSMA-negative lesions that respond poorly to PSMA-targeted MRT and drive the prognostic of the patient (*7*,*8*). These lesions can be better identified with FDG-PET than with conventional imaging, as illustrated by the higher PSA-RRs and

PSA-PFS observed in the Australian trials that used FDG-PET in addition to PSMA-PET for patient selection (*9*).

Our results highlight the importance of baseline PSMA PET/CT to stratify patients unlikely to respond to PSMA-targeted therapies towards other treatment options. However, the best management of patient with PSMA-negative lesions or with low-PSMA expressing disease is unknown. Combination with SBRT to the largest and/or most glycolytic (i.e., aggressive) and/or non-PSMA-expressing lesions together with PSMA-targeted MRT may be one effective synergistic therapeutic approach. Using alternatively or in combination other non-PSMA targeted systemic therapies may be required.

Refinements in patient selection for PSMA-MRT are needed to optimize patient outcomes. More comprehensive phenotyping via PET imaging may provide the roadmap to such refinements. Not characterizing target expression prior to PSMA-targeted treatment appears now non-ethical as a predictive whole-body imaging biomarker for response to PSMA-targeted therapies is available.

CONCLUSION

Patients with low or no PSMA-expressing lesions as assessed by PSMA PET/CT have a poor response profile to 177Lu-PSMA therapy. Refinements in patient selection for 177Lu-PSMA are needed to optimize patient outcomes.

DISCLOSURE

Jeremie Calais reports prior consulting activities outside of the submitted work for Advanced Accelerator Applications, Blue Earth Diagnostics, Curium Pharma, GE Healthcare, Janssen, IBA radiopharma, POINT biopharma, Progenics, Radiomedix and Telix Pharmaceuticals. Johannes Czernin is a founder and holds equity in Sofie biosciences and Trethera Therapeutics. Intellectual property is 99 patented by the University of California and licensed to Sofie Biosciences and Trethera Therapeutics. Johannes Czernin was a consultant for Endocyte Inc. (VISION trial steering committee), Actinium Pharmaceuticals and Point Biopharma outside of the submitted work. No other potential conflicts of interest relevant to this article exist.

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KEY POINTS

QUESTION: What is the outcome of patients who would have been PSMA PET/CT screen failure in the VISION trial and who were still treated with 177Lu-PSMA therapy?

PERTINENT FINDINGS: The patients who did not meet the PSMA PET/CT criteria in the VISION trial showed worse outcomes after 177Lu-PSMA therapy than those who were eligible.

IMPLICATIONS FOR PATIENT CARE: Pre-therapy PSMA PET/CT is a biomarker of target expression that helps to predict patient response to 177Lu-PSMA therapy. Refinements in patient selection for 177Lu-PSMA are needed to optimize patient outcomes.

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TABLE 1. Patient Characteristics

	VISION PSMA PET/CT Eligible	VISION PSMA PET/CT Screen Failure	p-value
n	272	29	
Age (years) [median (IQR)]	72 (66-76)	73 (65-76)	0.91
PSA (ng/ml) [median (IQR)]	116.6 [28.4, 340.0]	74.0 [17.5, 198.3]	0.069
Treatment history			
Previous docetaxel	218 (80.1%)	25 (86.2%)	0.62
Second-line chemotherapy	95 (34.9%)	8 (27.6%)	0.54
Androgen receptor signaling inhibitor	150 (55.1%)	16 (55.2%)	1
Extent of disease on PSMA-PET/CT			
Number of metastases ≥ 20	194 (71.3%)	16 (55.2%)	0.089
Number of metastases < 20	78 (28.7%)	13 (44.8%)	
Sites of disease on PSMA-PET/CT			
Node only (N1 and/or M1a)	21 (7.7%)	1 (3.4%)	0.71
Bone only (M1b)	60 (22.1%)	3 (10.3%)	0.23
Node + bone (M1b and (N1 and/or M1a))	122 (44.9%)	8 (27.6%)	0.08
Visceral (any M1c)	69 (25.4%)	17 (58.6%)	<0.001
Number of cycles of 177Lu-PSMA received			
1	38 (14.0%)	5 (17.2%)	0.065
2	68 (25.0%)	13 (44.8%)	
3	37 (13.6%)	5 (17.2%)	
4	91 (33.5%)	5 (17.2%)	
>4	38 (13.9%)	1 (3.4%)	
Injected Activity per cycle (GBq) [median (IQR)]	7.4 (5.7-8.9)	7.4 (6.0-8.5)	0.30

IQR: interquartile range, PSA: prostate-specific antigen, PSMA: prostate-specific membrane antigen

TABLE 2. Outcomes of the VISION-PET-eligible (E) and VISION-PET-screen failure (SF) patients

	VISION-PET-E	VISION-PET-SF	p-value
n	272	29	
PSA50RR			
No. (%)	131 (50.3%)	6 (20.7%)	0.005
Odds ratio (95%CI)	1 (reference)	0.28 (0.11-0.71)	0.007
anyPSARR			
No. (%)	194 (71.3%)	12 (41.4%)	0.003
Odds ratio (95%CI)	1 (reference)	0.28 (0.13-0.62)	<0.001
PSA-PFS			
Median months (95%CI)	4.9 (4.0-5.8)	2.1 (1.4-3.3)	0.023
Hazard ratio (95%CI)	1 (reference)	1.6 (1.1-2.5)	0.025
OS			
Median months (95%CI)	14.2 (12.6-15.9)	9.6 (4.7-14.0)	0.16
Hazard ratio (95%CI)	1 (reference)	1.4 (0.89-2.3)	0.16

PSA: prostate specific antigen, PSA50RR: PSA response rates (decline of ≥ 50%), anyPSARR: any decline of PSA, OS: overall survival, PFS: progression free survival, CI: confidence interval

FIGURE LEGENDS

Figure 1

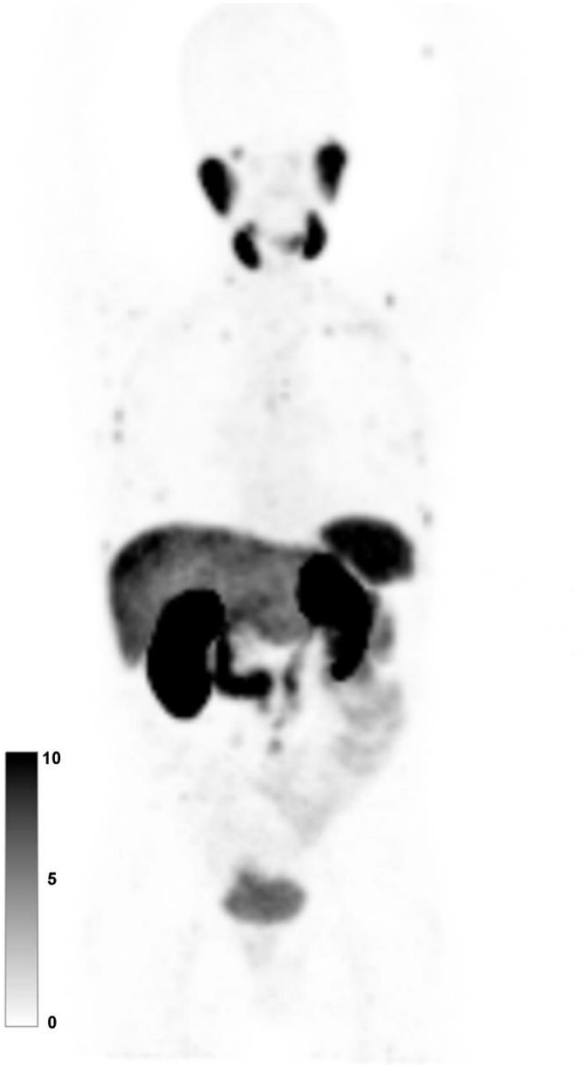


Figure 1. A baseline PSMA PET maximum intensity projection (MIP) image of the patient with mCRPC categorized as VISION-PET-SF because of low PSMA expression (i.e., No PSMA-positive (> liver) metastatic lesion). SUVmax of the liver and the highest uptake lesion were 9.6 and 6.4, respectively.

Figure 2

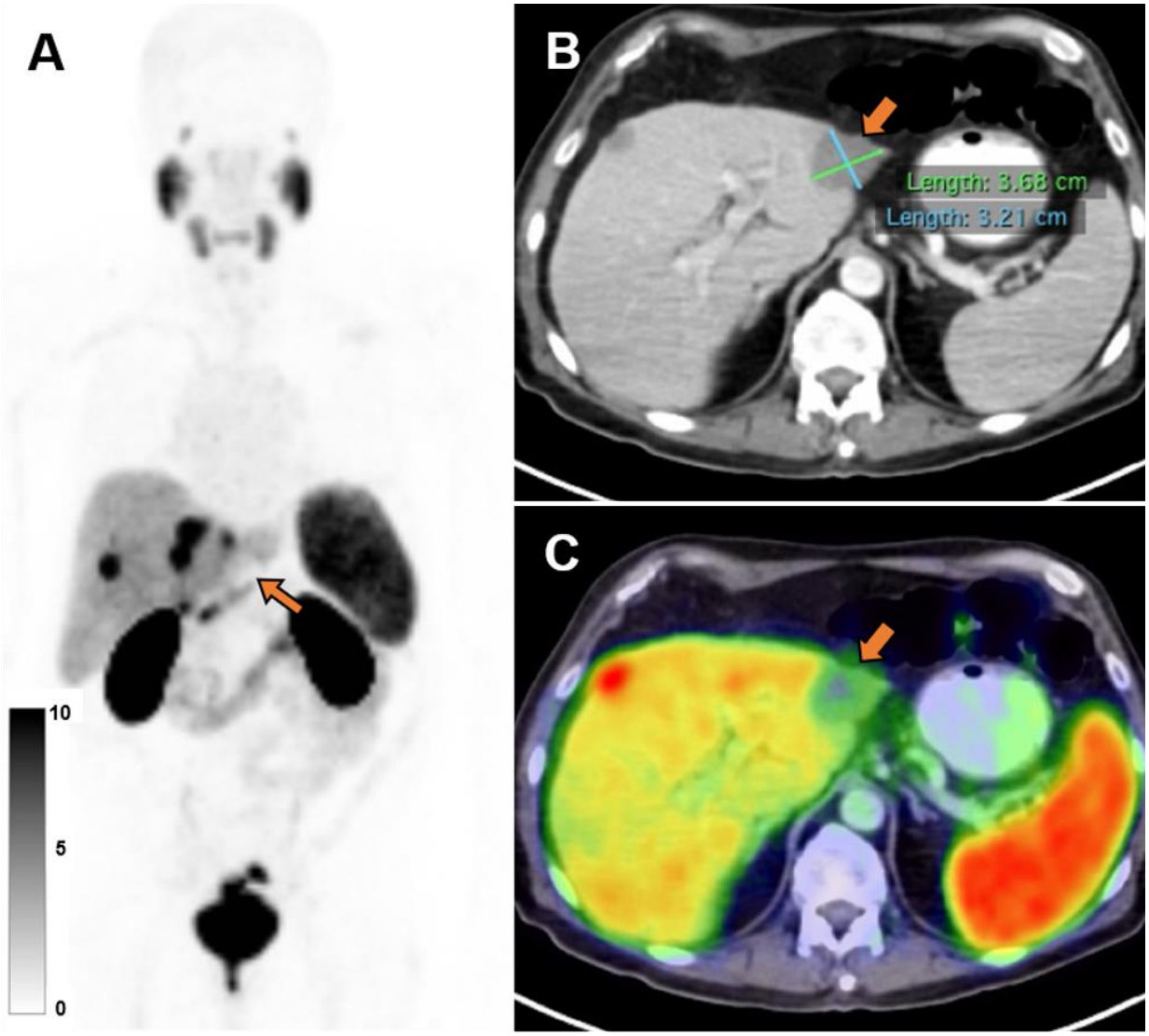


Figure 2. Baseline PSMA PET (A) MIP, (B) CT, and (C) PSMA-PET/CT images of the patient with mCRPC categorized as VISION-PET-SF because of PSMA-negative lesion (i.e., PSMA negative metastatic lesion: liver metastasis ≥ 1.0 cm, uptake ≤ liver) (A-C: arrow). One liver metastasis (A-C: arrow) showed lower uptake (SUVmax: 4.1) than the liver parenchyma (SUVmax: 6.3).

Figure 3

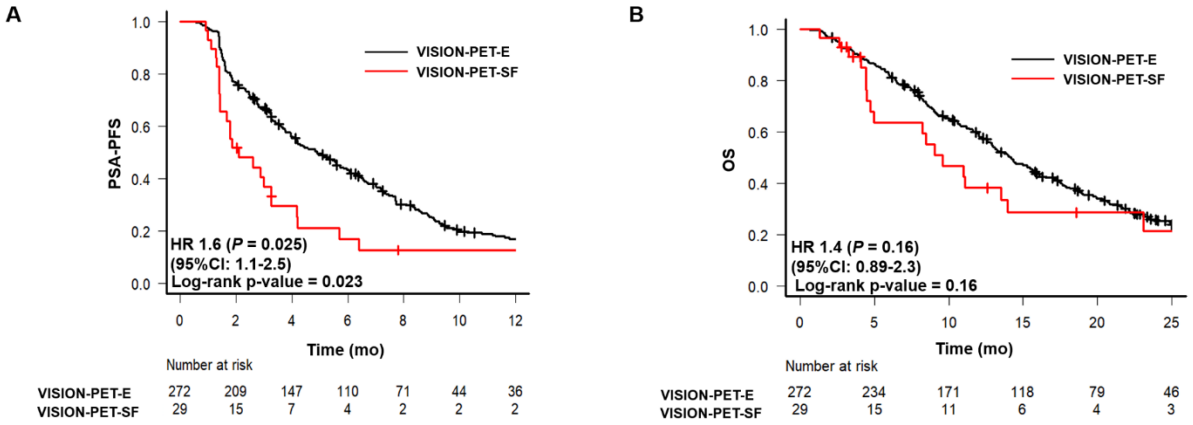


Figure 3. Kaplan–Meier curves of (A) PSA-PFS and (B) OS comparing VISION-PET-E and VISION-PET-SF patients.

Figure 4

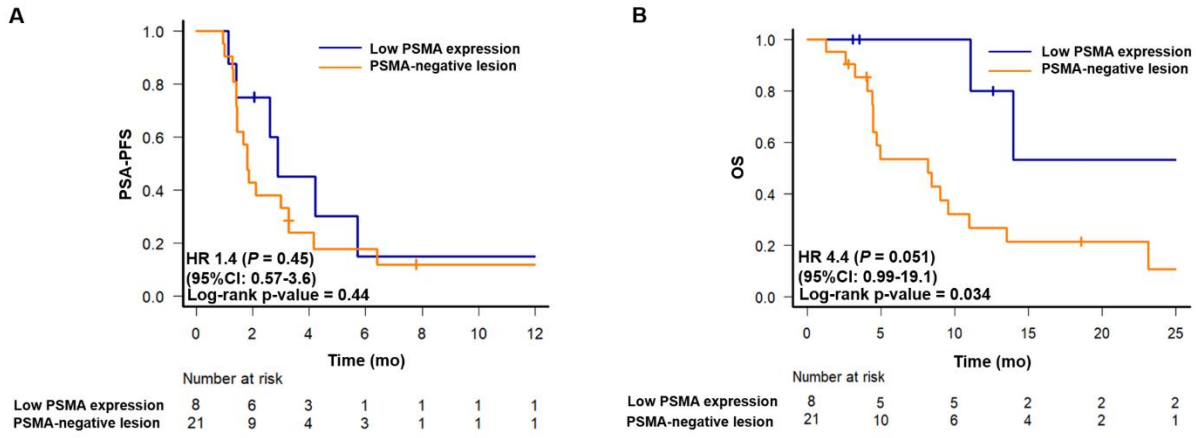
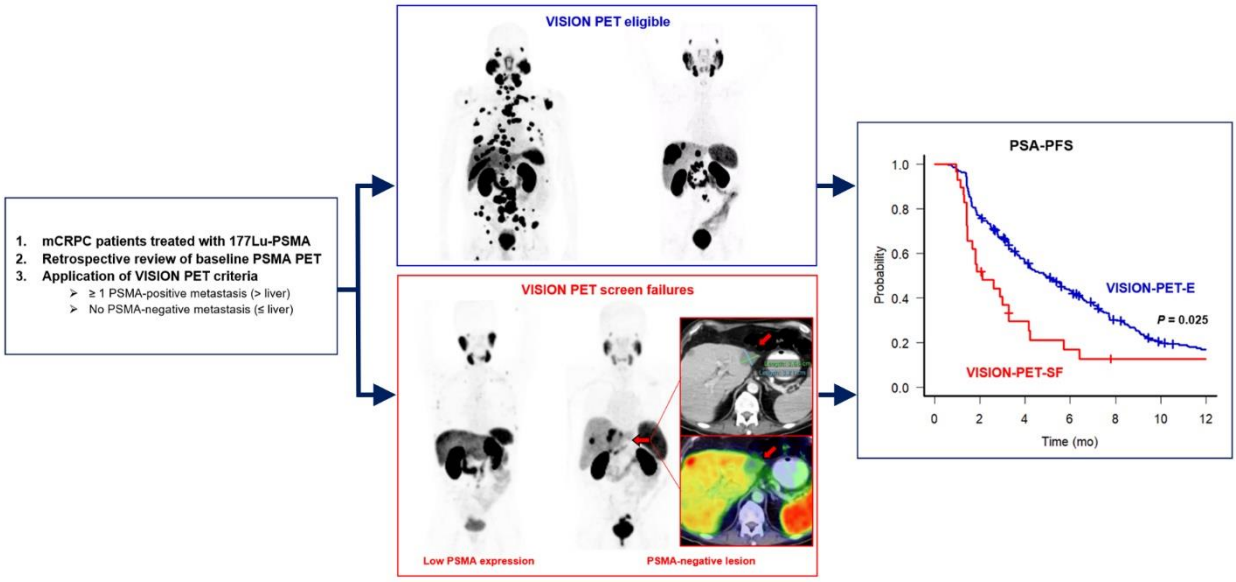
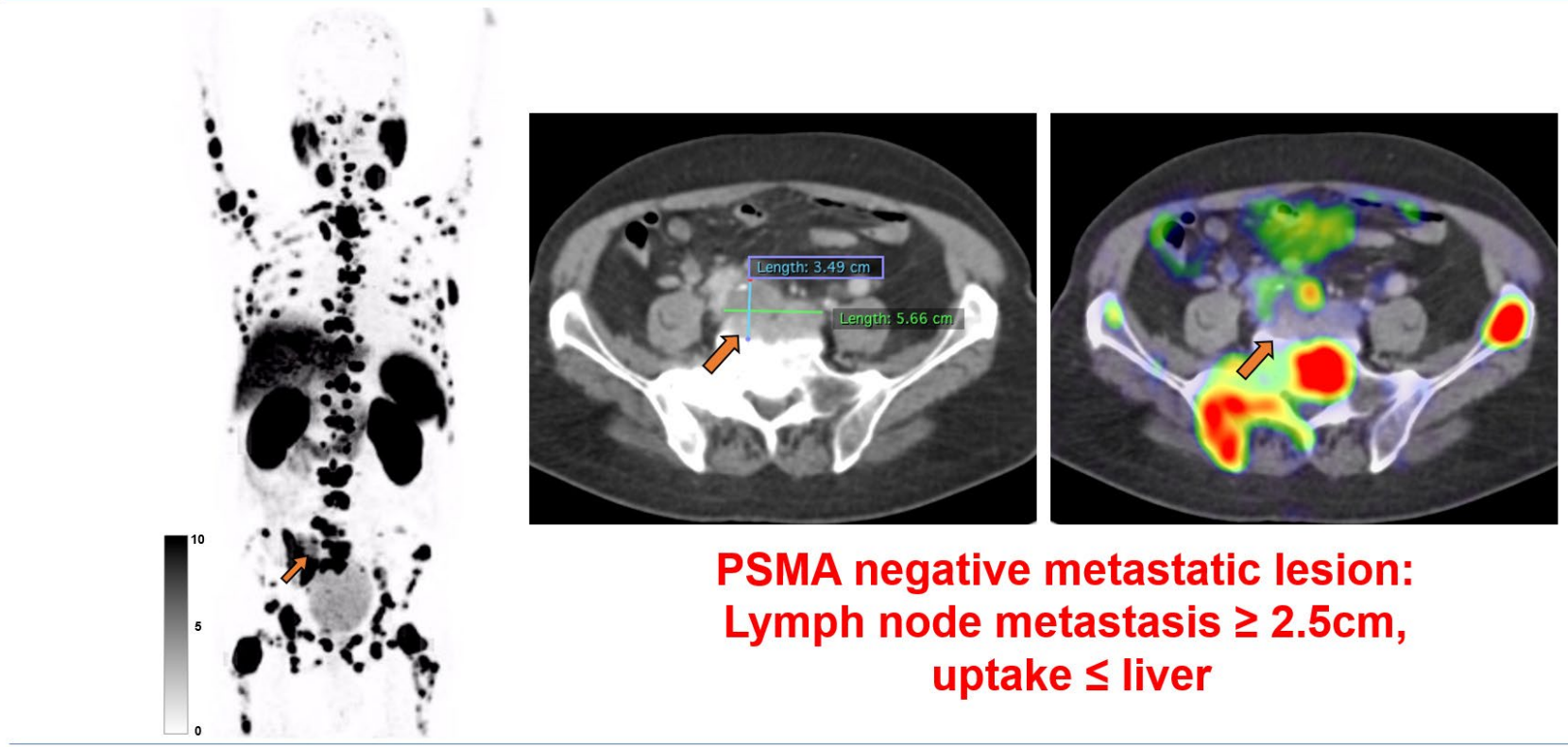


Figure 4. Kaplan–Meier curves of (A) PSA-PFS and (B) OS comparing patients with low PSMA expression and PSMA-negative lesion.

GRAPHICAL ABSTRACT

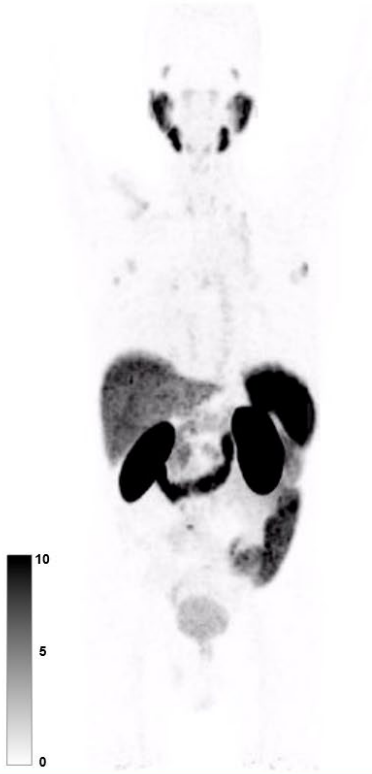


Supplemental Figure 1. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #1.



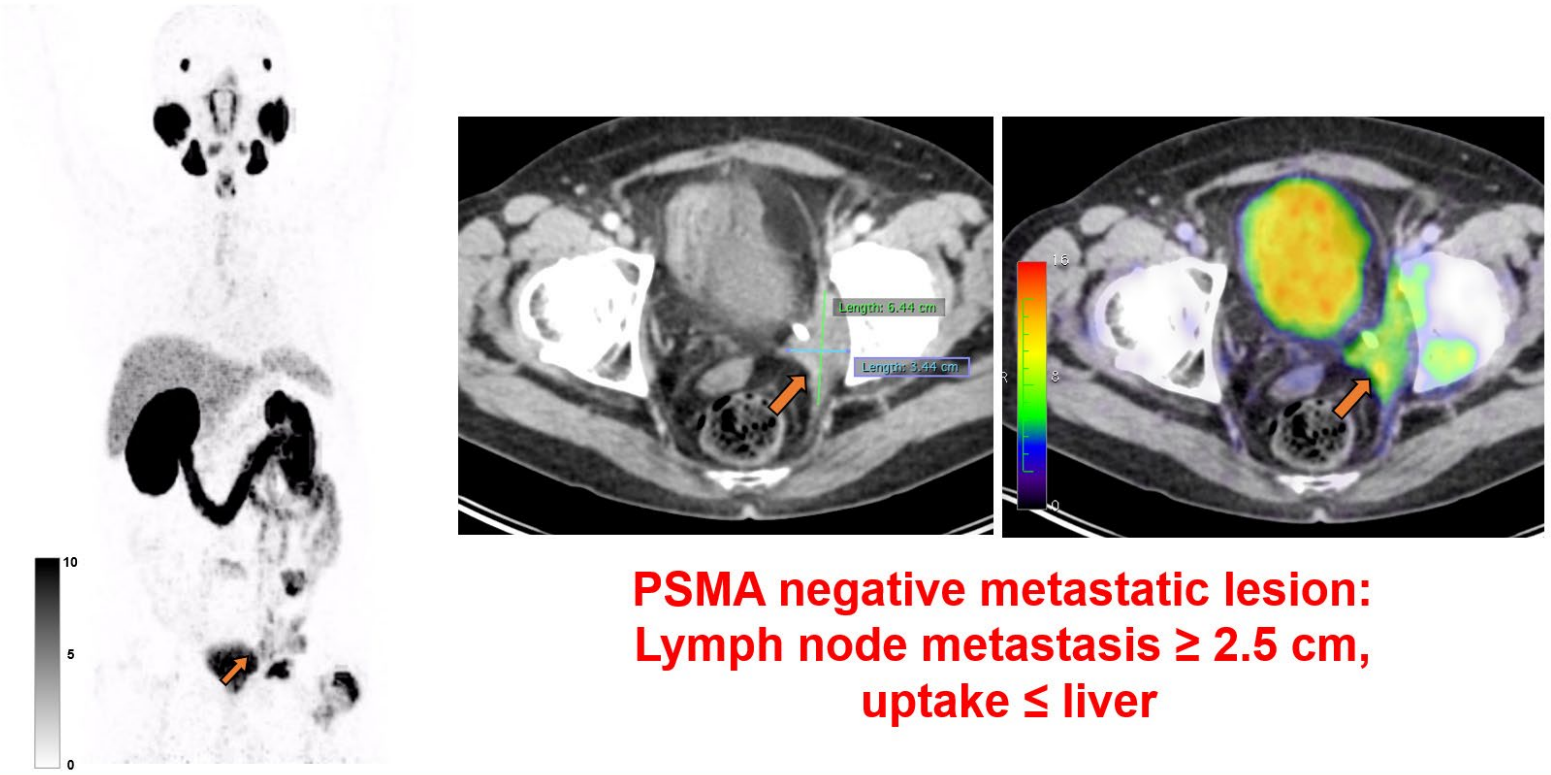
Supplemental Figure 2. Ga-68 PSMA-11 PET MIP of the VISION-PET-SF patient #2.

Patient: #2



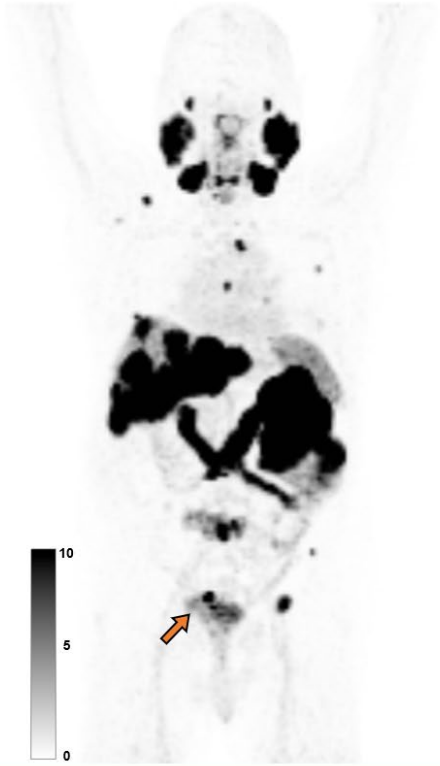
No PSMA-positive (> liver) metastatic lesion

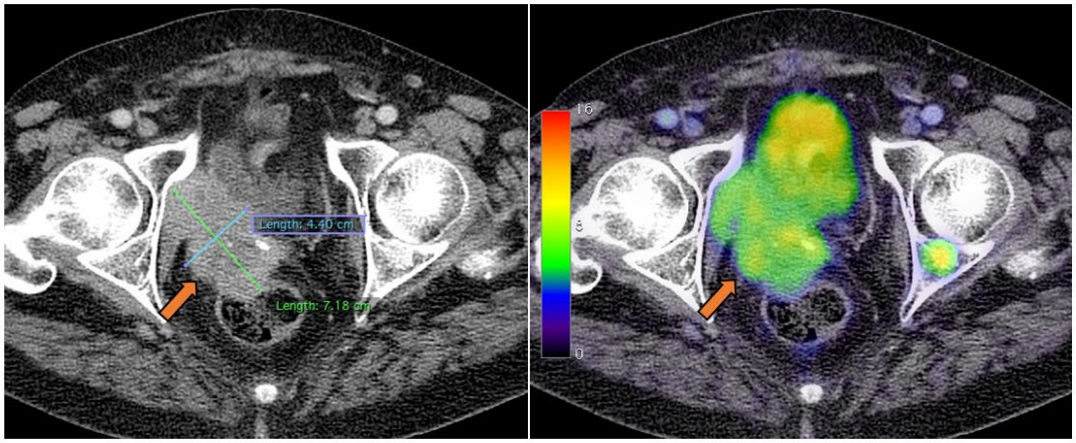
Supplemental Figure 3. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #3.



Supplemental Figure 4. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #4.

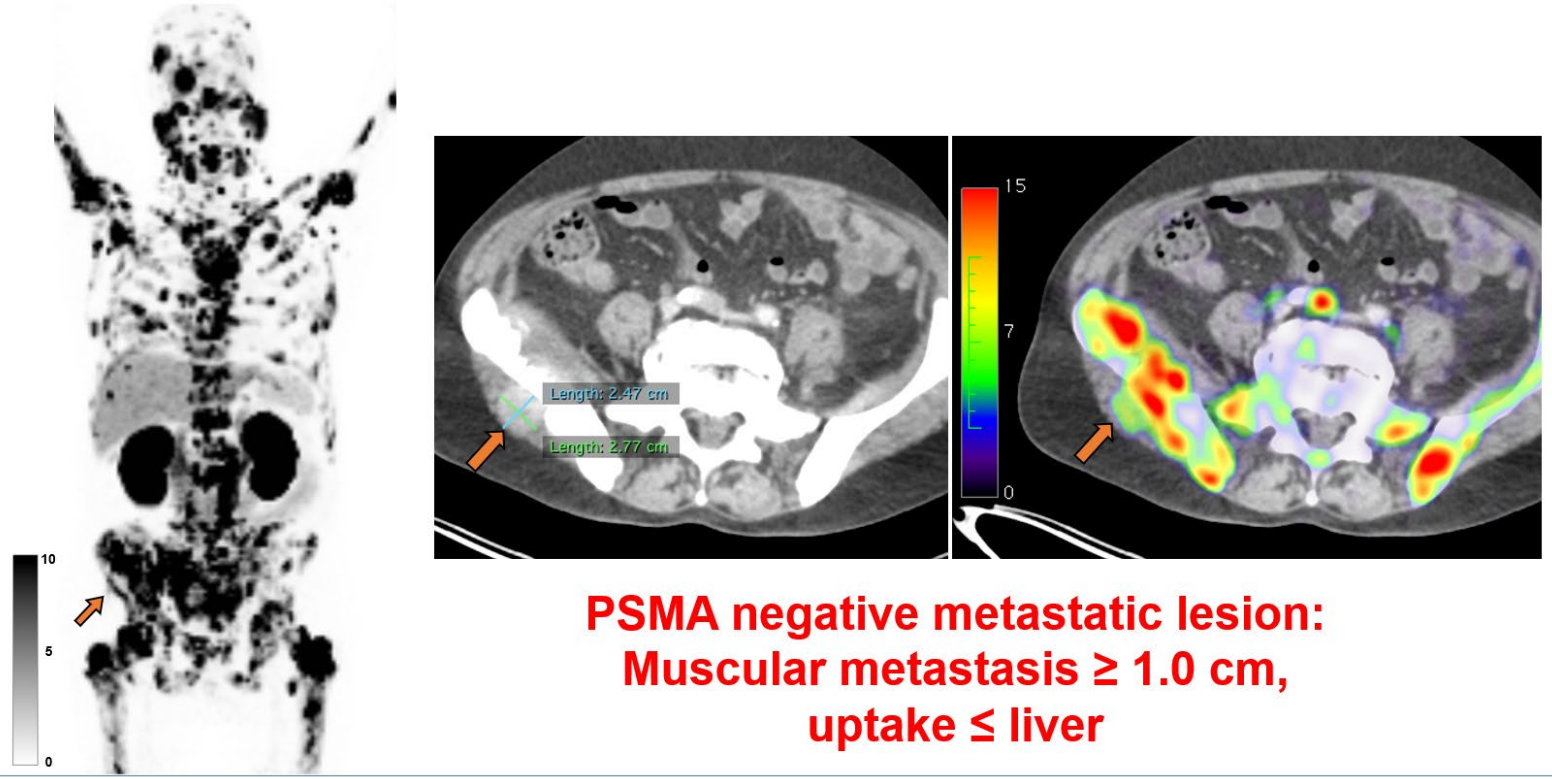
Patient: #4





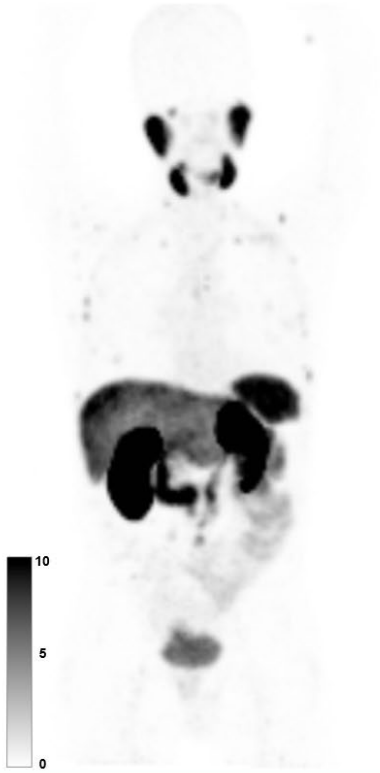
PSMA negative metastatic lesion:
Lymph node metastasis ≥ 2.5 cm,
uptake ≤ liver

Supplemental Figure 5. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #5.



Supplemental Figure 6. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #6

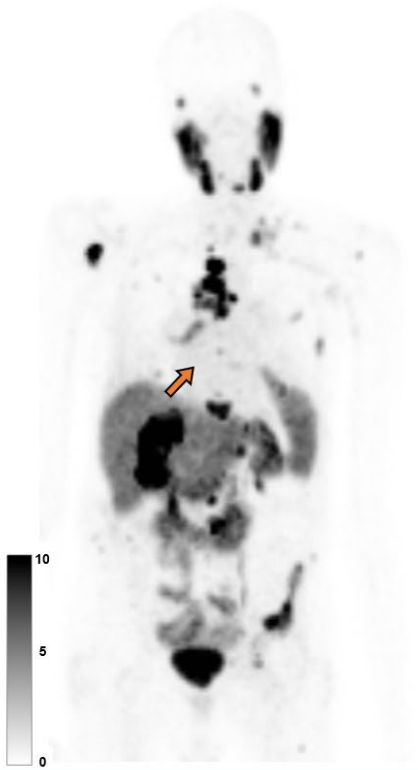
Patient: #6

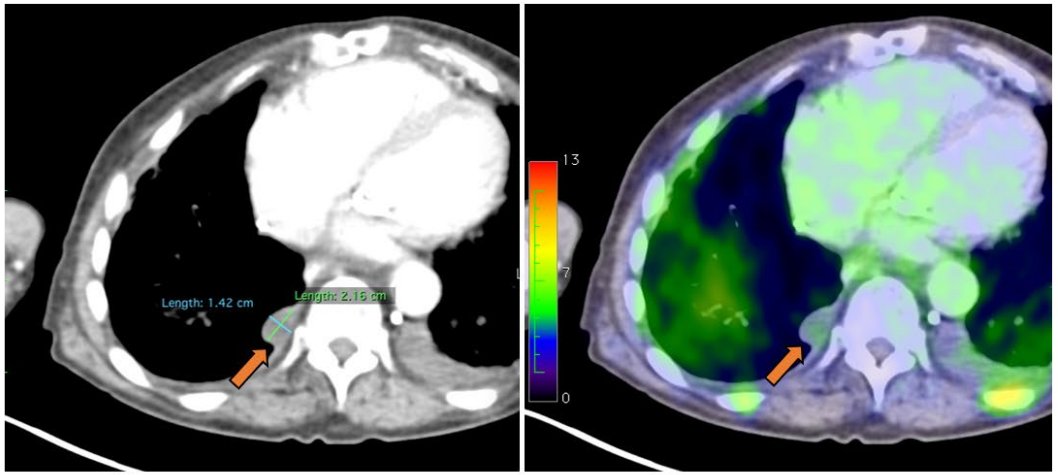


No PSMA-positive (> liver) metastatic lesion

Supplemental Figure 7. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #7

Patient: #7

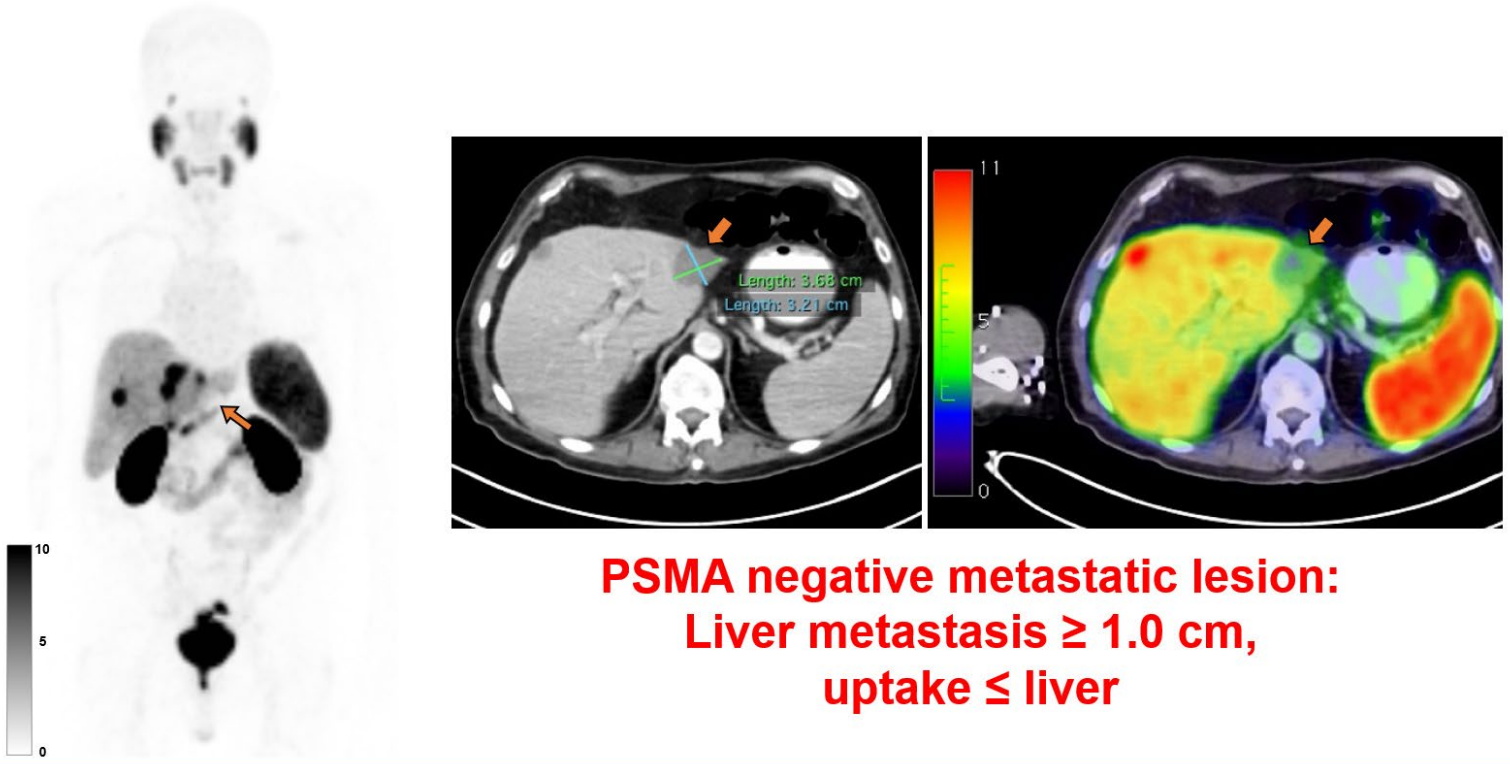




PSMA negative metastatic lesion:
Pleural metastasis ≥ 1.0 cm,
uptake ≤ liver

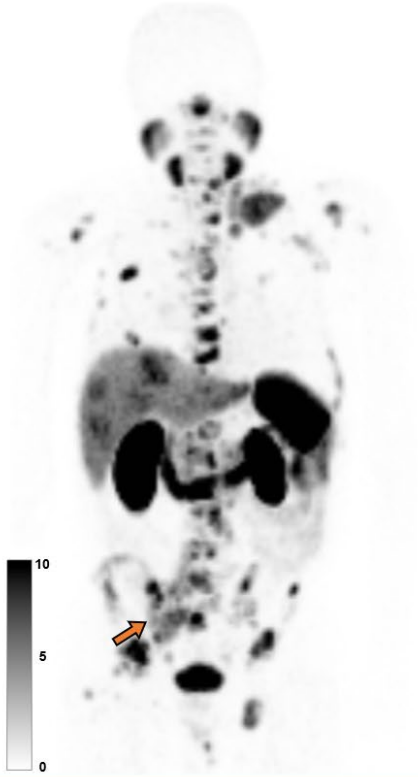
Supplemental Figure 8. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #8.

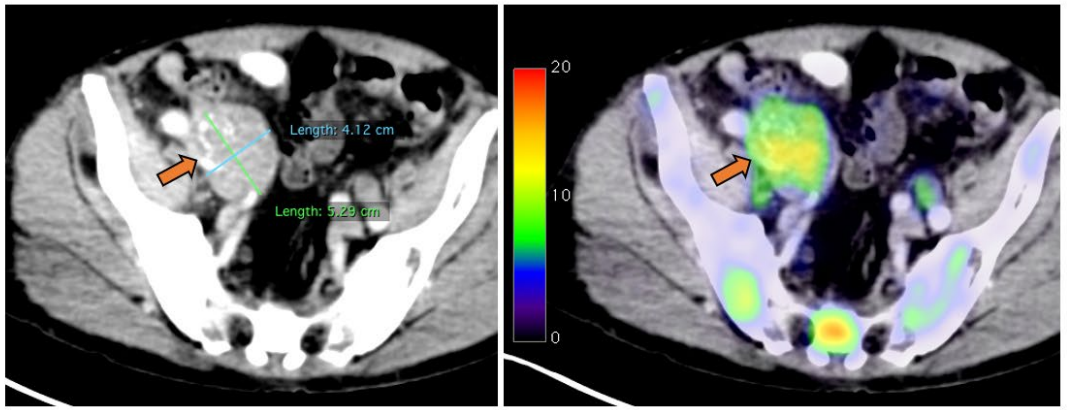
Patient: #8



Supplemental Figure 9. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #9.

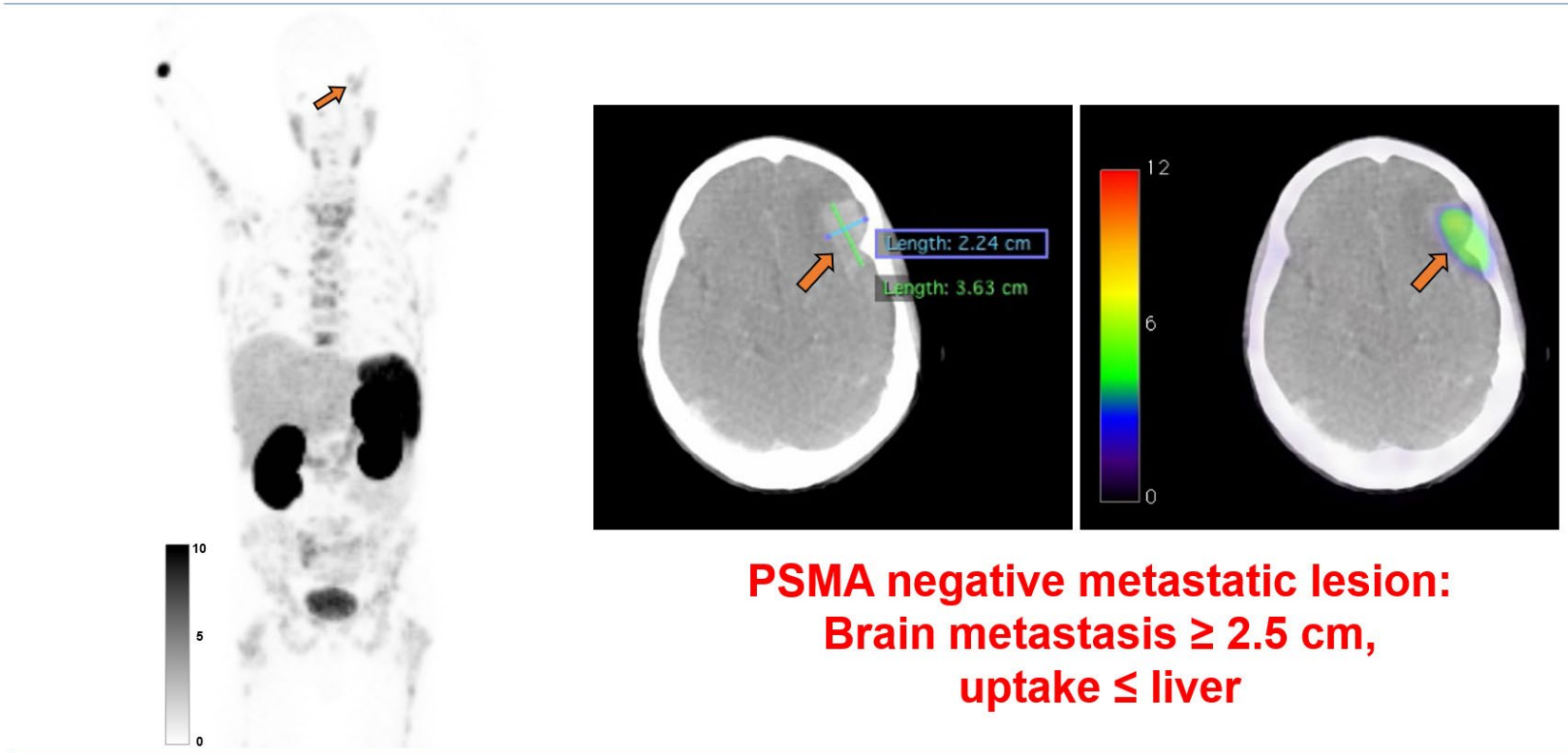
Patient: #9





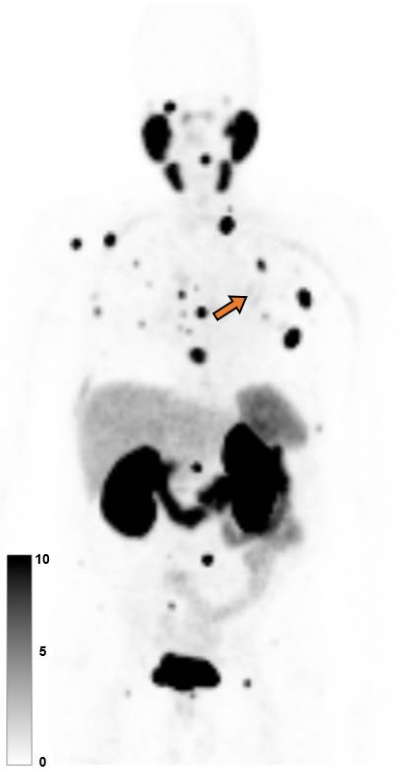
PSMA negative metastatic lesion:
Lymph node metastasis ≥ 2.5 cm,
uptake ≤ liver

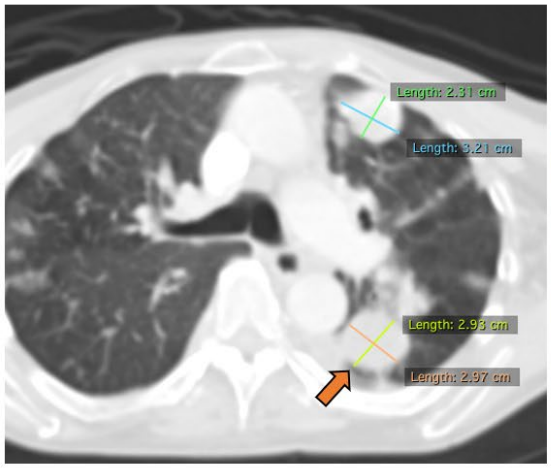
Supplemental Figure 10. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #10.

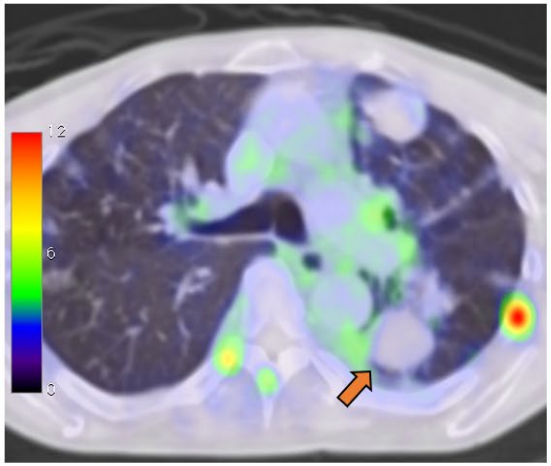


Supplemental Figure 11. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #11

Patient: #11

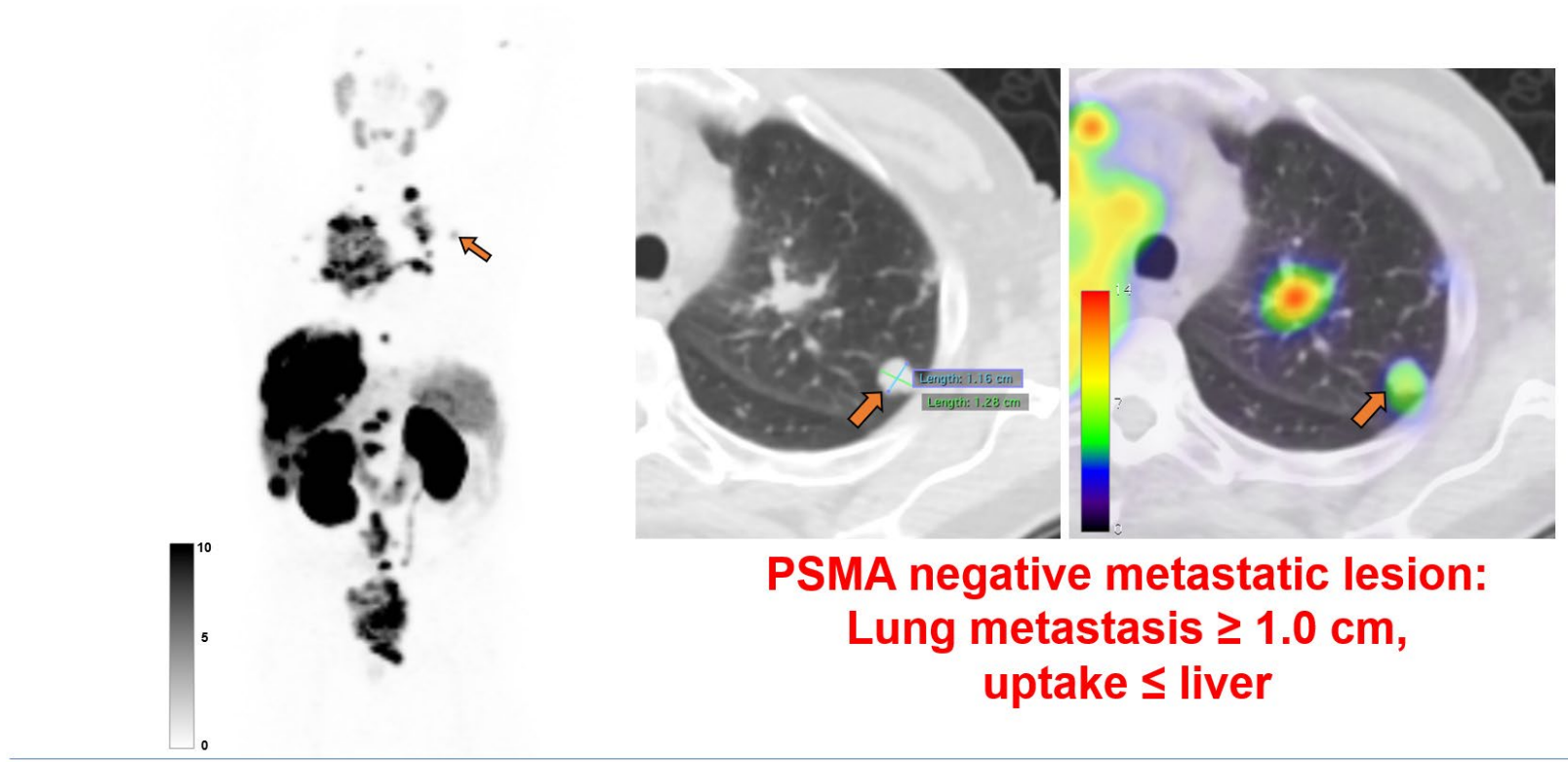




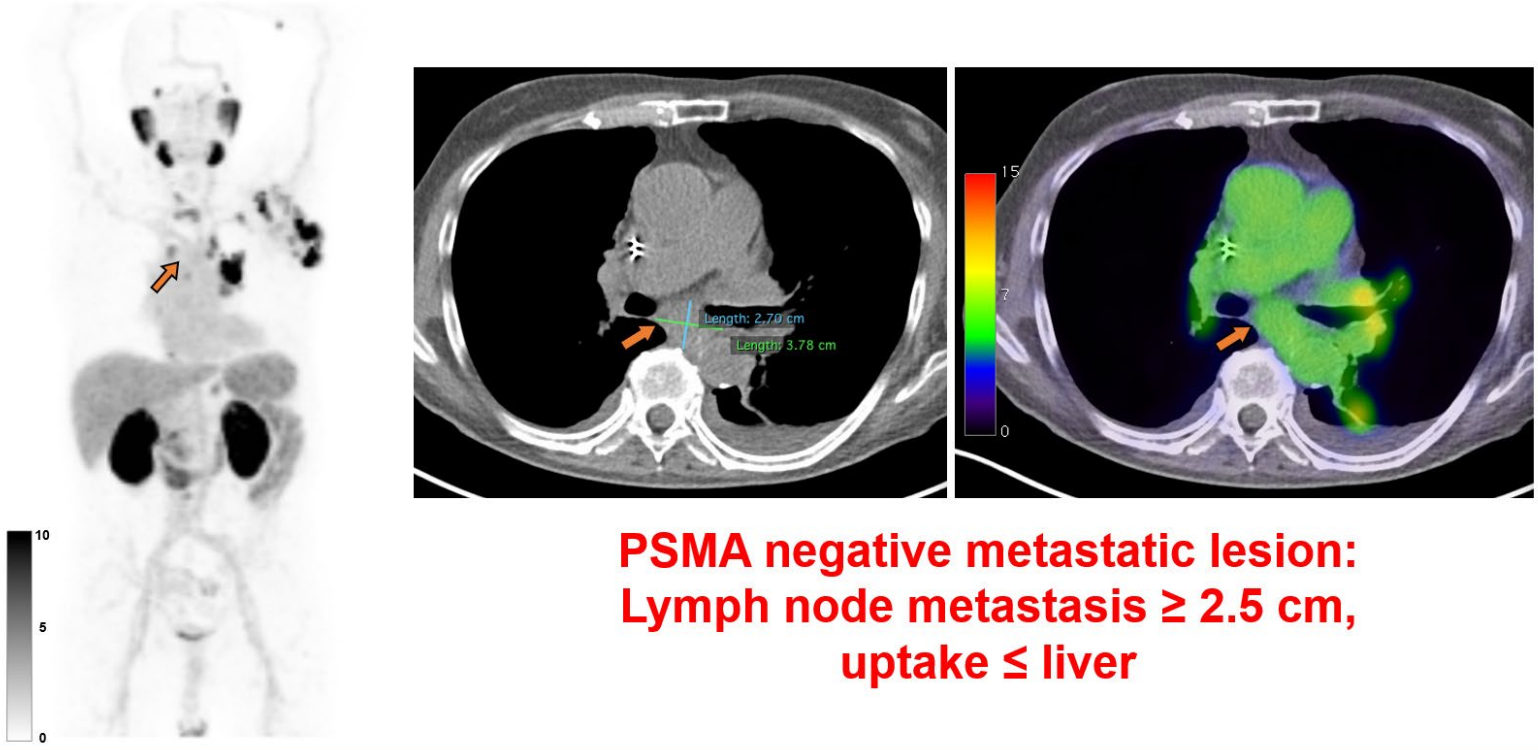


PSMA negative metastatic lesion:
Lung metastasis ≥ 1.0 cm,
uptake ≤ liver

Supplemental Figure 12. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #12

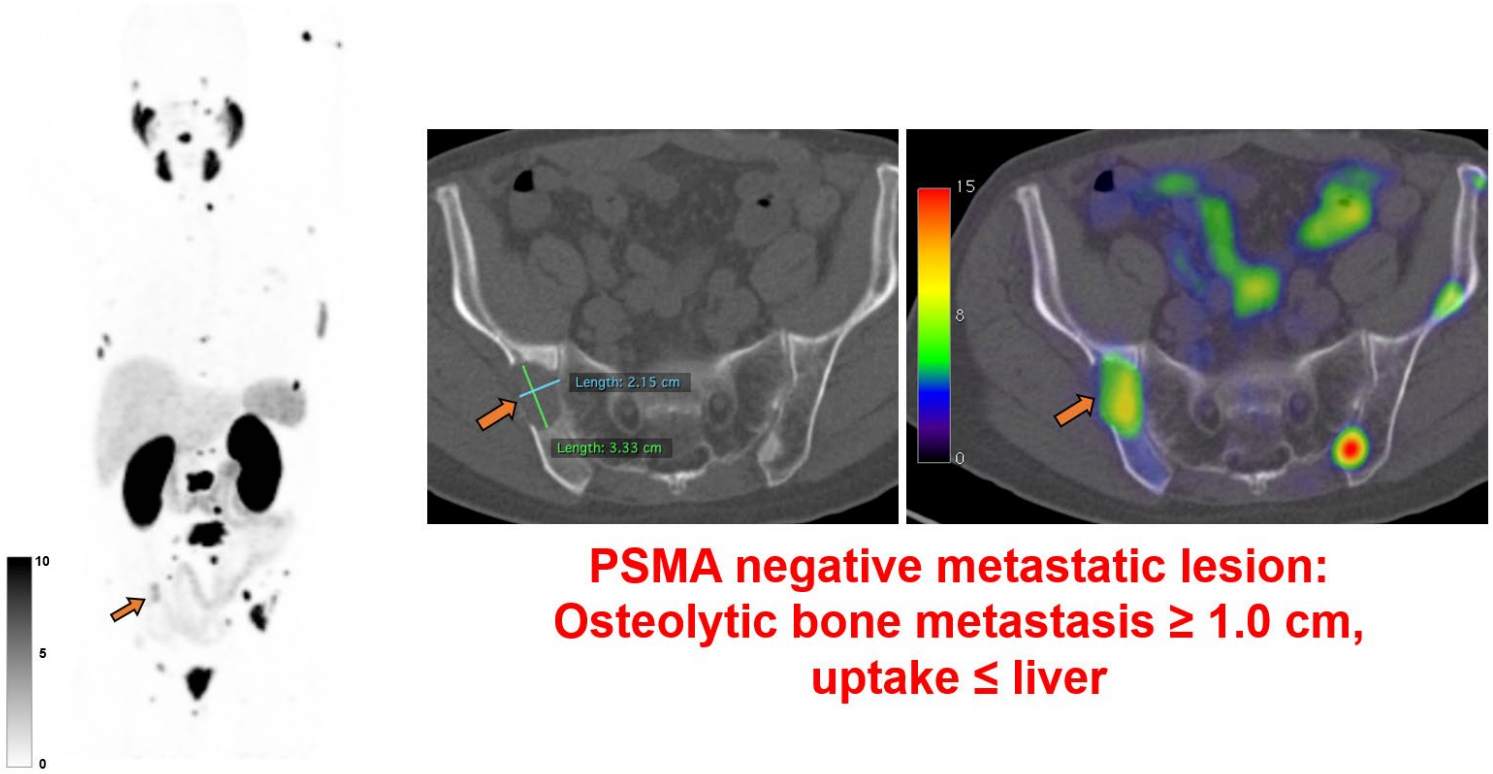


Supplemental Figure 13. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #13.

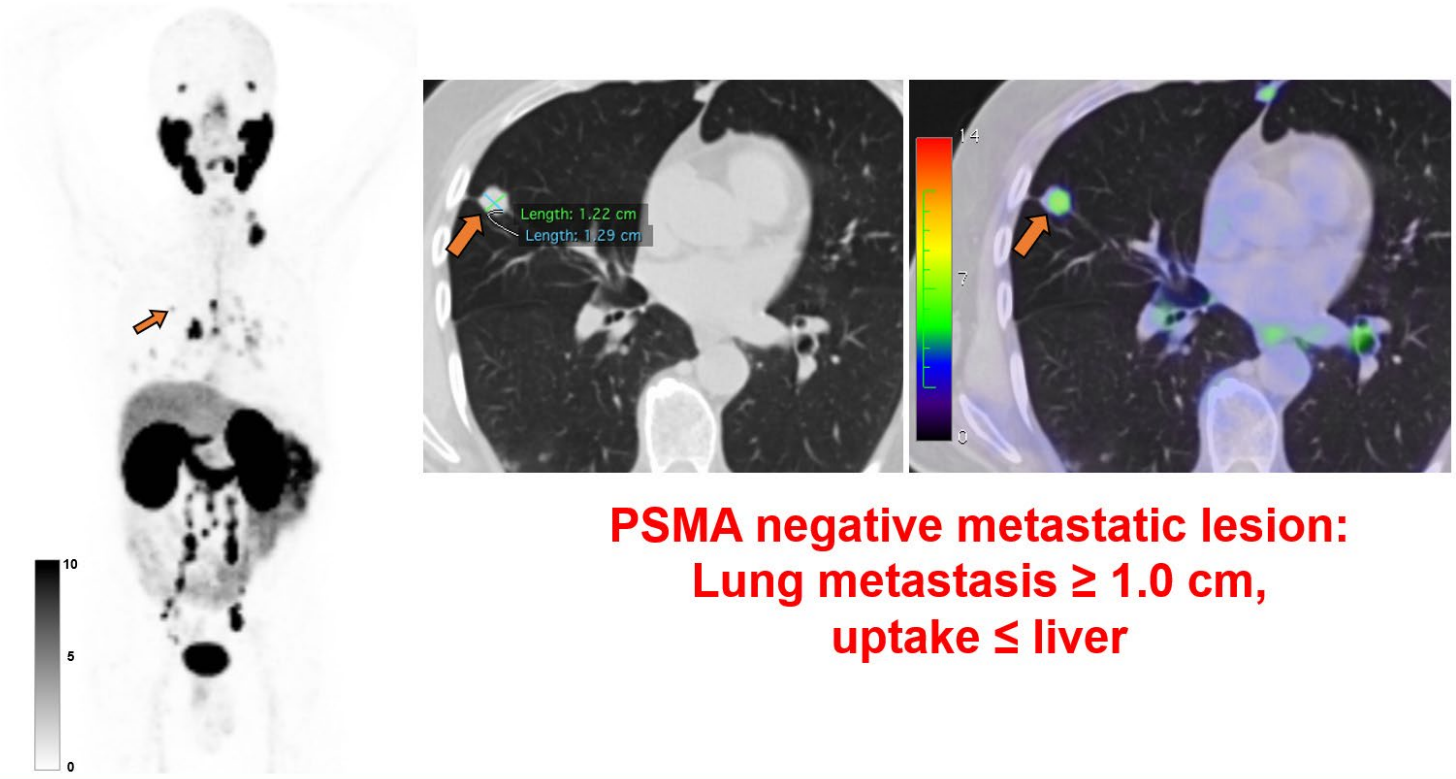


Supplemental Figure 14. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #14.

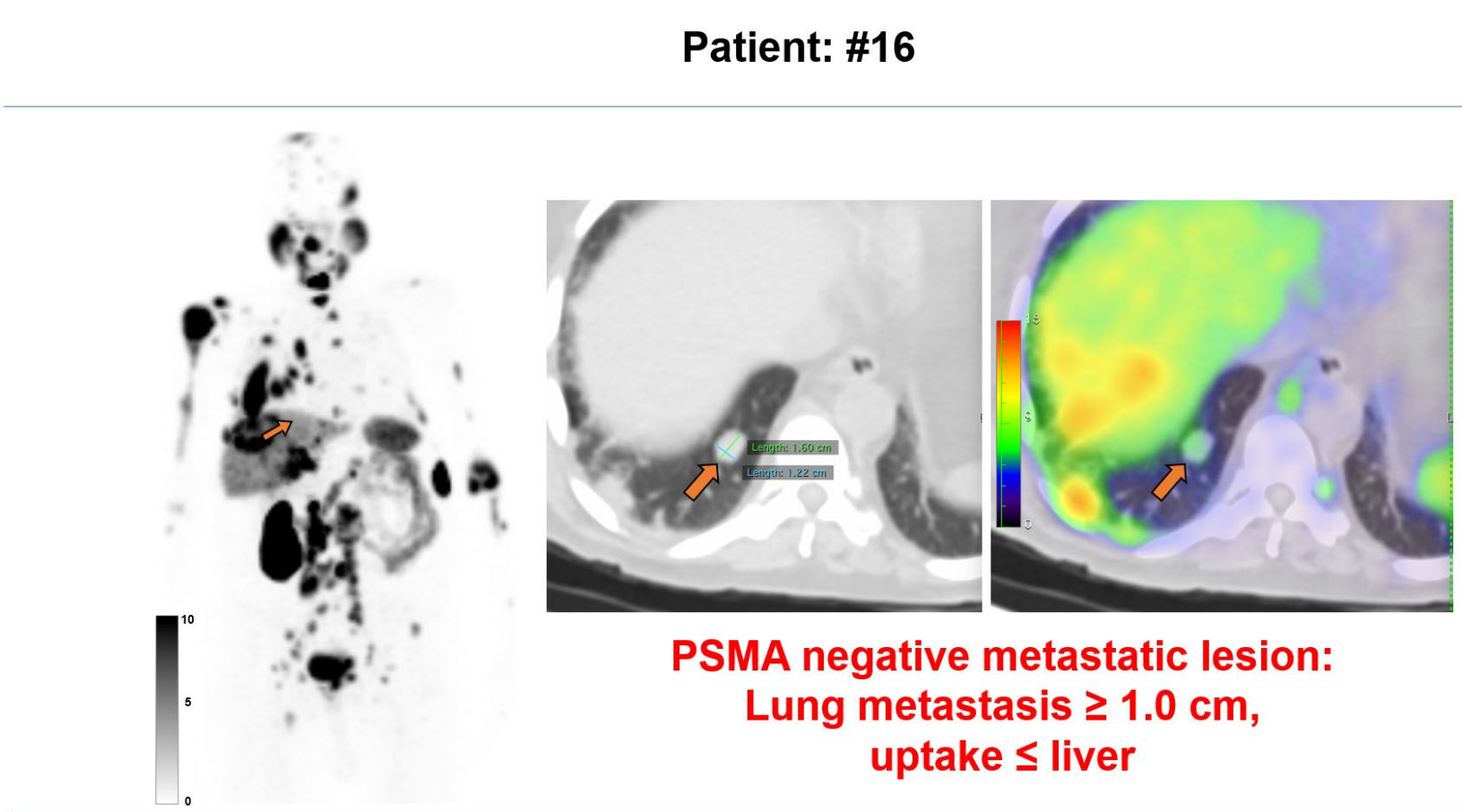
Patient: #14



Supplemental Figure 15. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #15.

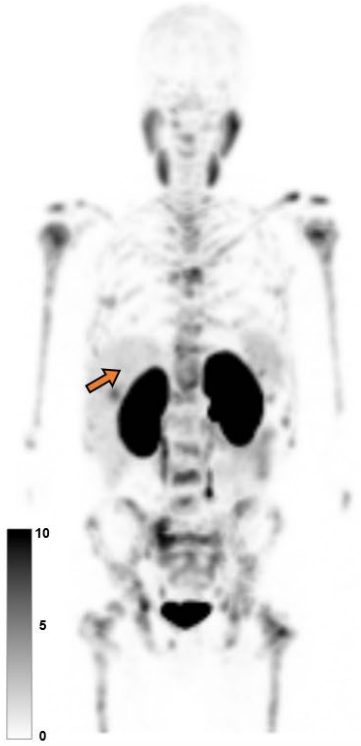


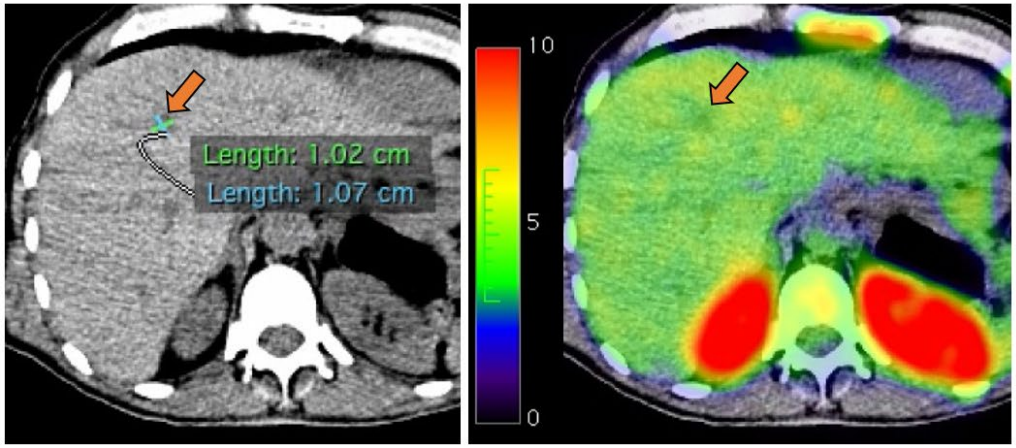
Supplemental Figure 16. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #16



Supplemental Figure 17. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #17

Patient: #17

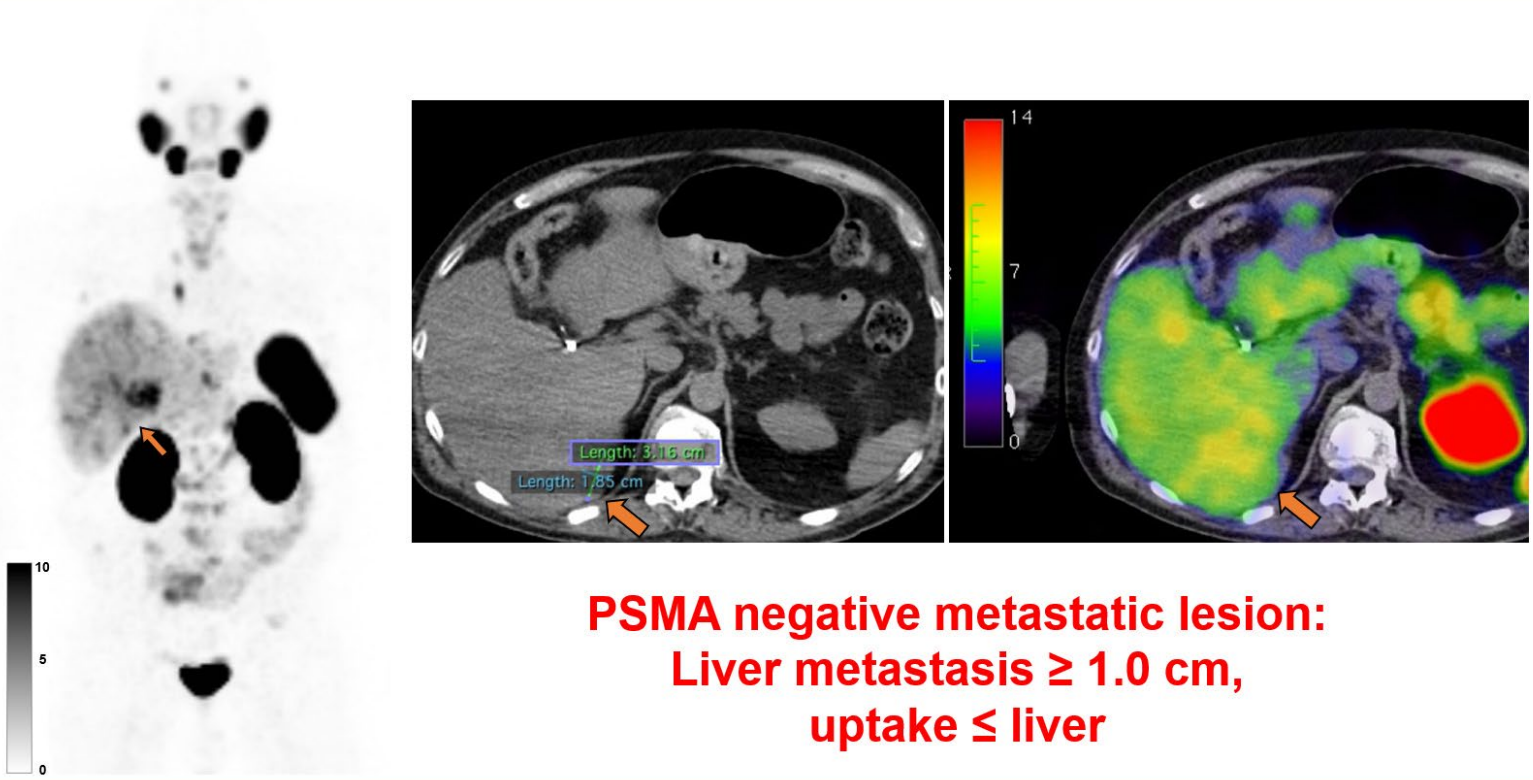




PSMA negative metastatic lesion:
Liver metastasis ≥ 1.0 cm,
uptake ≤ liver

Supplemental Figure 18. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #18

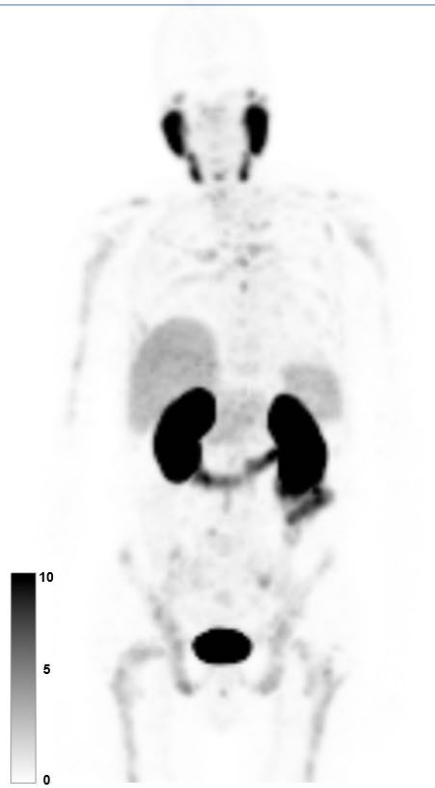
Patient: #18



PSMA negative metastatic lesion:
Liver metastasis ≥ 1.0 cm,
uptake ≤ liver

Supplemental Figure 19. Ga-68 PSMA-11 PET MIP of the VISION-PET-SF patient #19

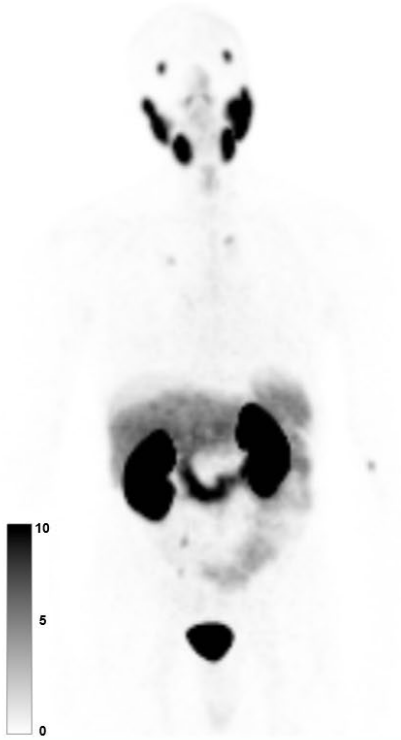
Patient: #19



No PSMA-positive (> liver) metastatic lesion

Supplemental Figure 20. Ga-68 PSMA-11 PET MIP of the VISION-PET-SF patient #20

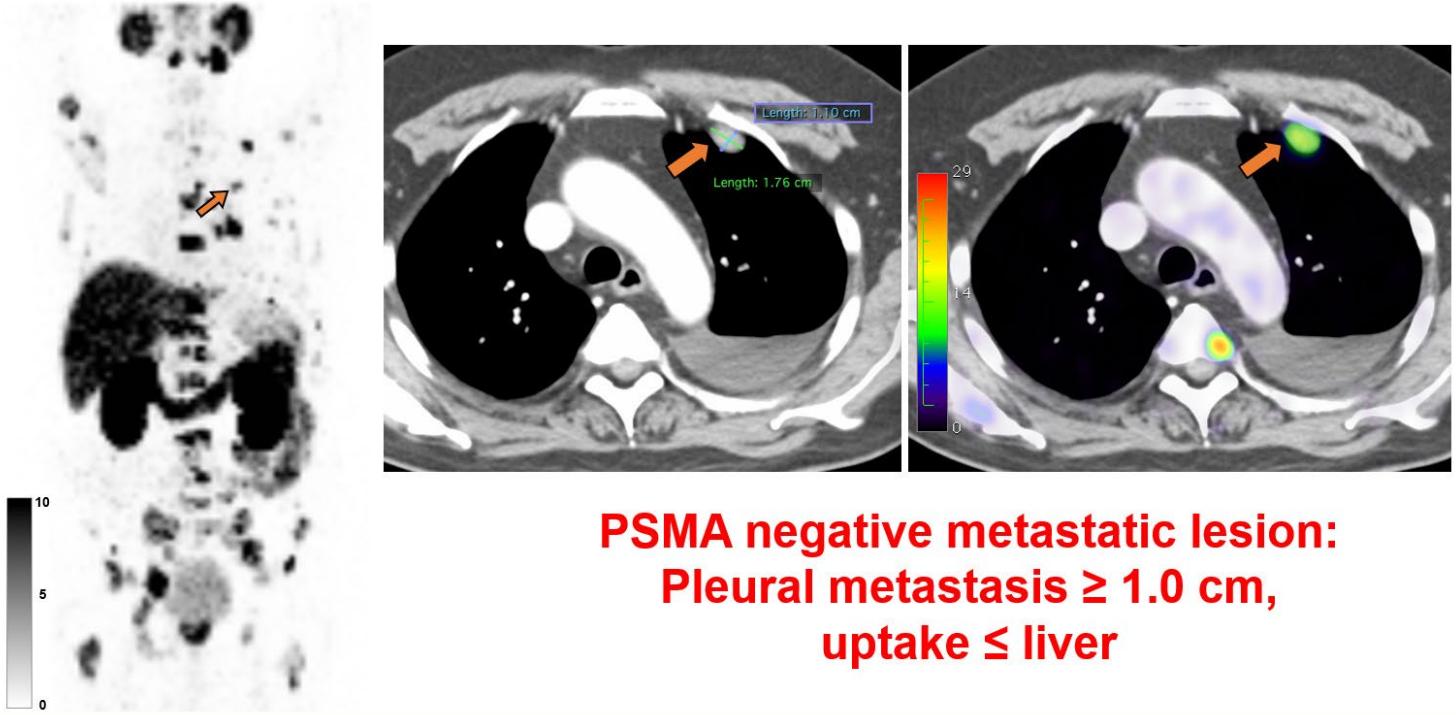
Patient: #20



No PSMA-positive (> liver) metastatic lesion

Supplemental Figure 21. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #21

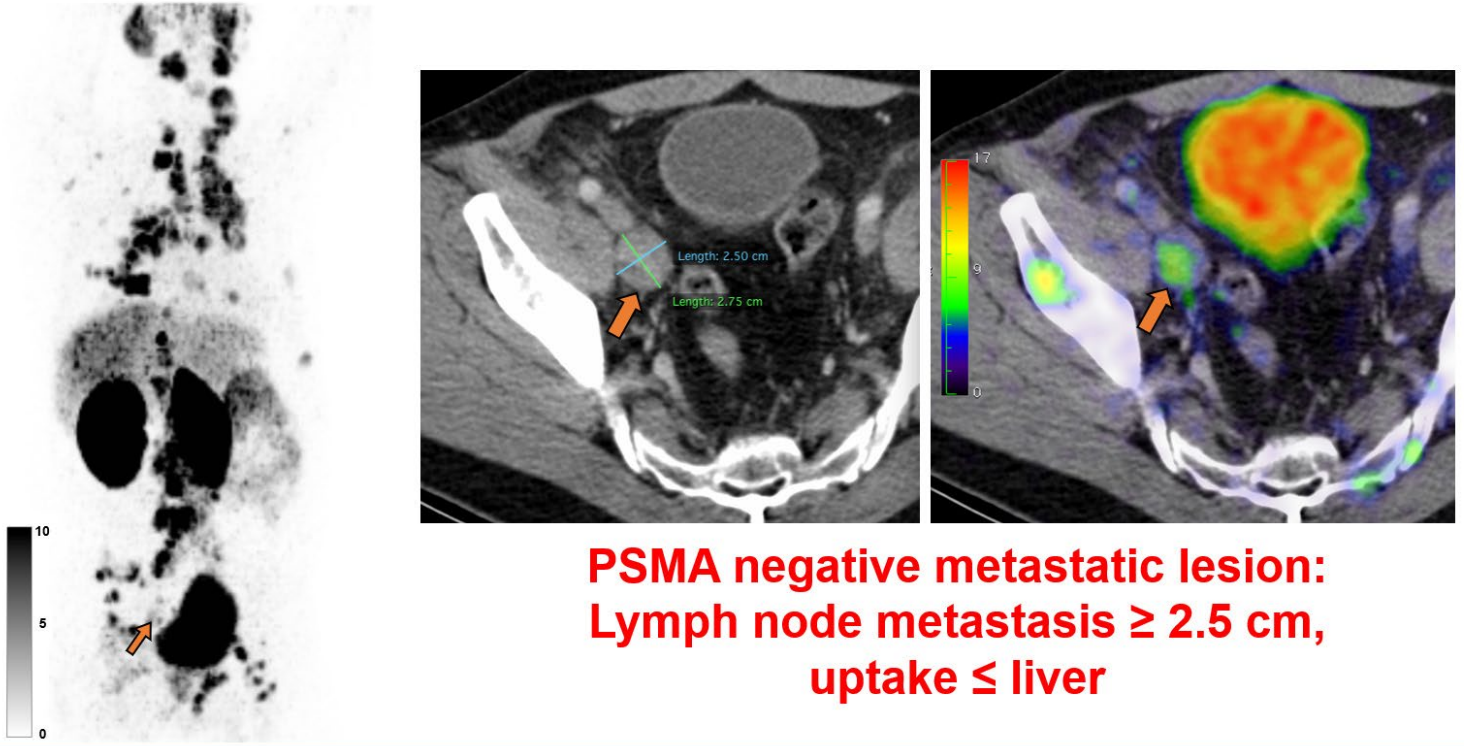
Patient: #21



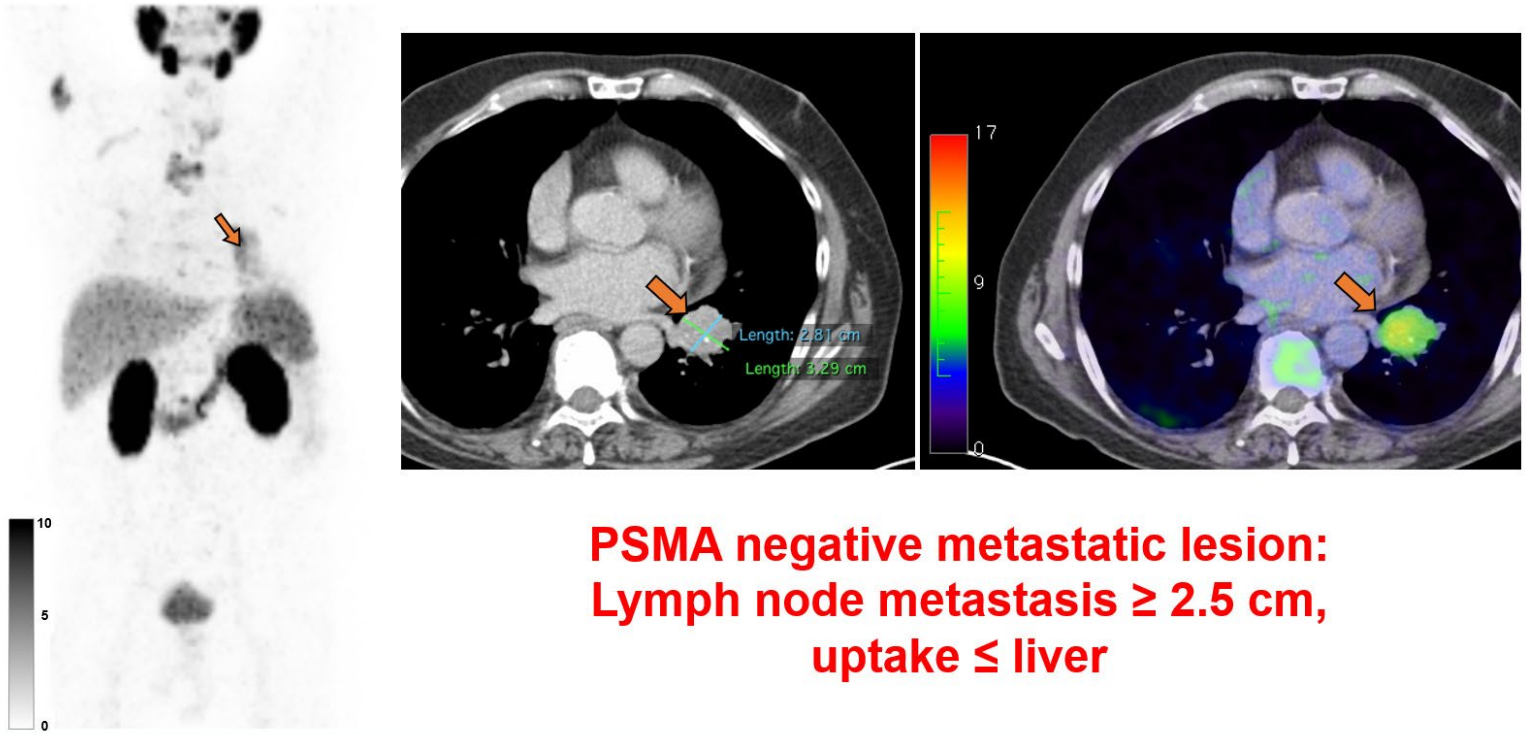
PSMA negative metastatic lesion:
Pleural metastasis ≥ 1.0 cm,
uptake ≤ liver

Supplemental Figure 22. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #22

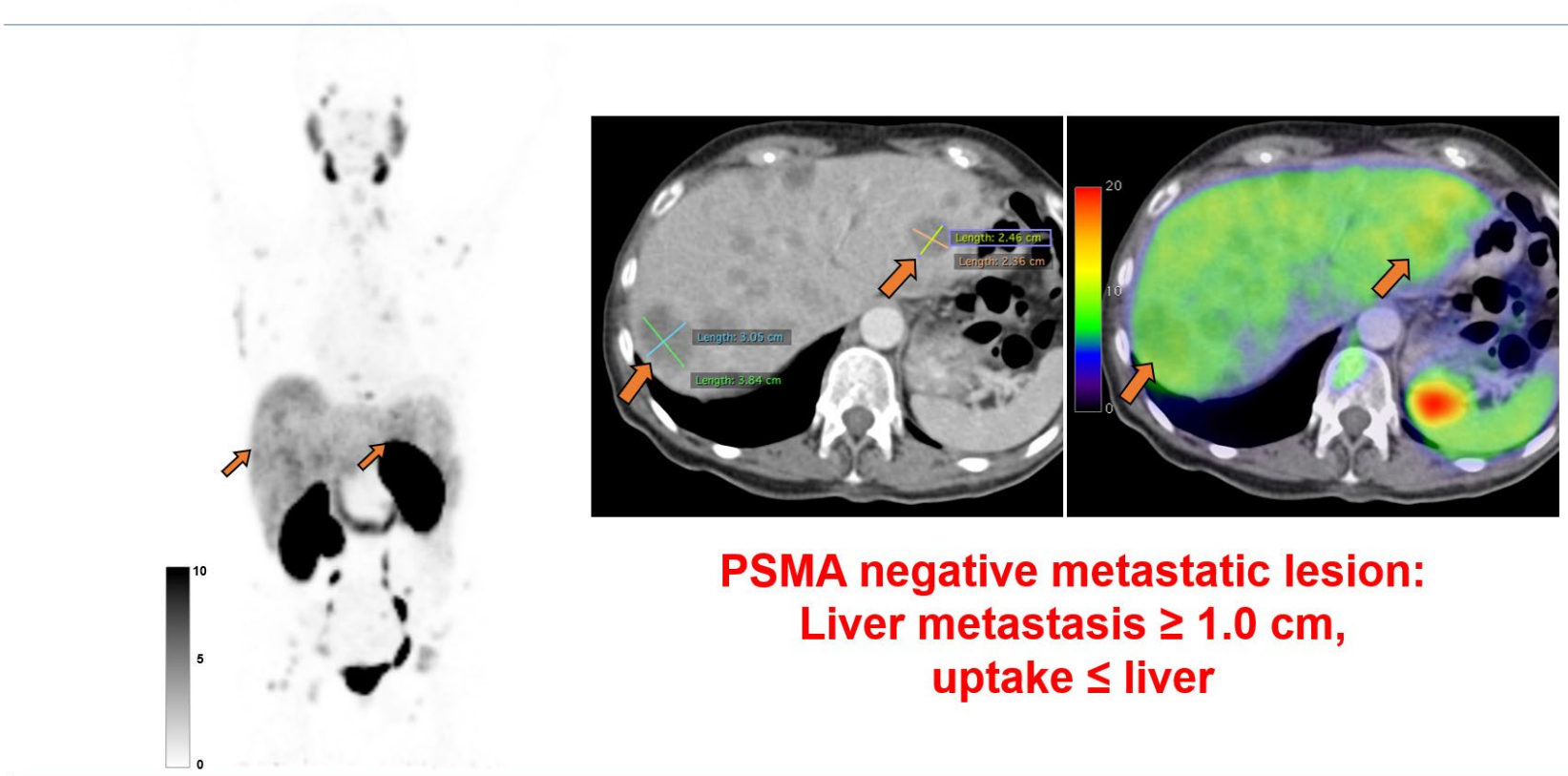
Patient: #22



Supplemental Figure 23. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #23

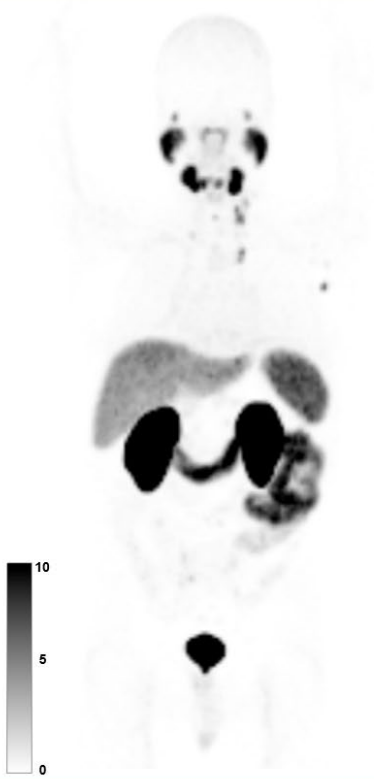


Supplemental Figure 24. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #24



Supplemental Figure 25. Ga-68 PSMA-11 PET MIP of the VISION-PET-SF patient #25

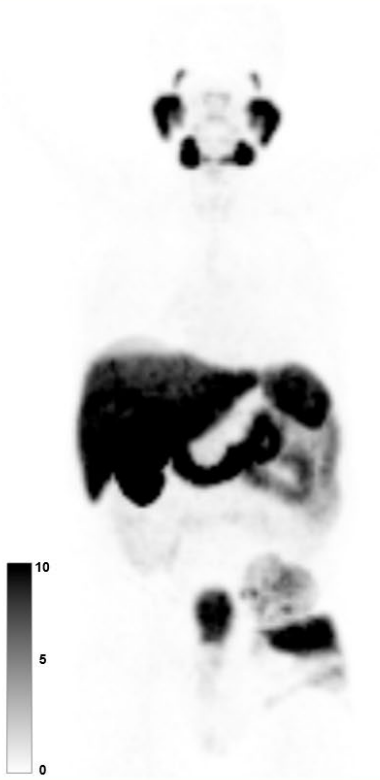
Patient: #25



No PSMA-positive (> liver) metastatic lesion

Supplemental Figure 26. Ga-68 PSMA-11 PET MIP of the VISION-PET-SF patient #26

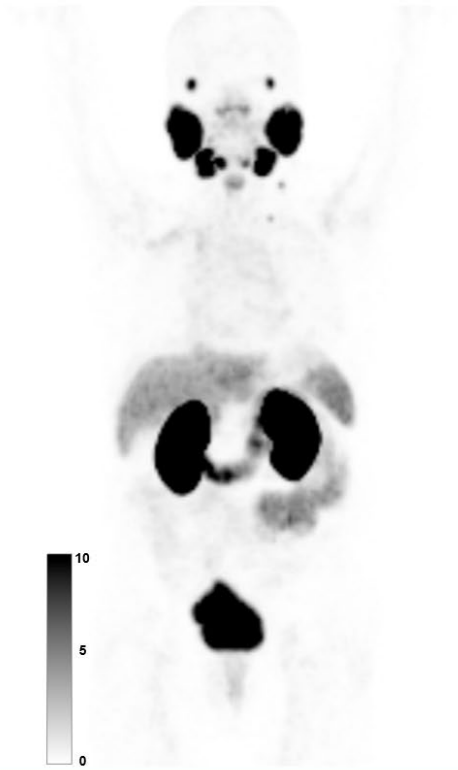
Patient: #26



No PSMA-positive (> liver) metastatic lesion

Supplemental Figure 27. Ga-68 PSMA-11 PET MIP of the VISION-PET-SF patient #27

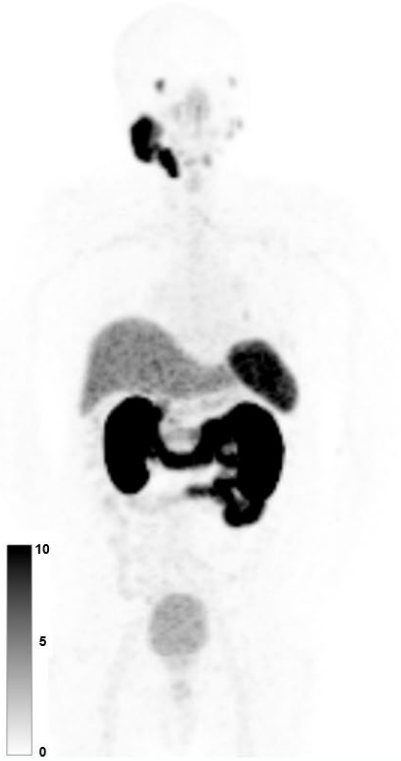
Patient: #27



No PSMA-positive (> liver) metastatic lesion

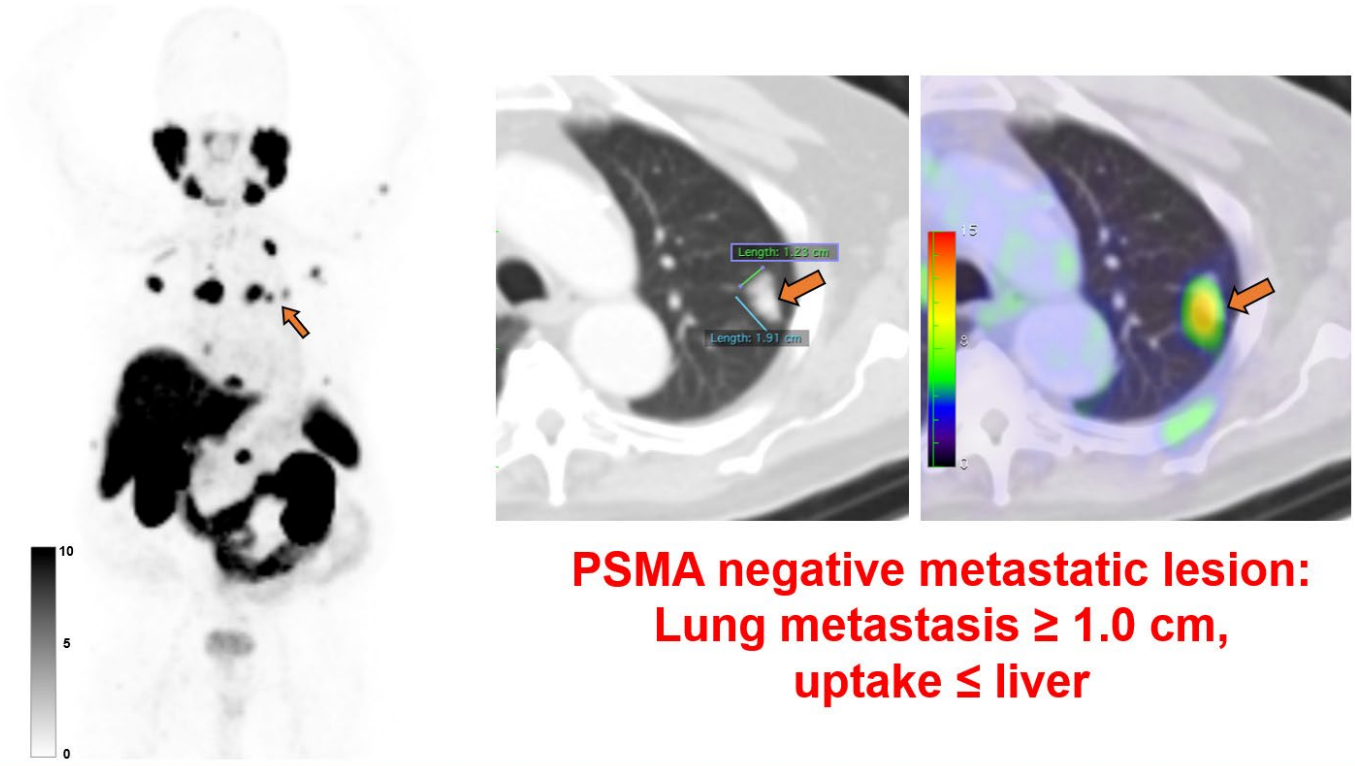
Supplemental Figure 28. Ga-68 PSMA-11 PET MIP of the VISION-PET-SF patient #28

Patient: #28



No PSMA-positive (> liver) metastatic lesion

Supplemental Figure 29. Ga-68 PSMA-11 PET/CT of the VISION-PET-SF patient #29.



Supplemental Table 1. Institutional treatment protocol

Center	Regulatory Pathway	Radiopharmaceutical	Intervals (weeks)	Activity (GBq)
UCLA	Clinical Trial Expanded access program	Lu-177 PSMA-617	8	6.0-7.4
TUM	Compassionate use	Lu-177 PSMA-I&T	6-8	7.4
PMCC	Clinical Trial	Lu-177 PSMA-617	6	6.0-8.5
UKH	Compassionate use	Lu-177 PSMA-617	8	6.0-8.5
UKE	Compassionate use	Lu-177 PSMA-617	8	7.4
EDNOC	Clinical Trial	Lu-177 PSMA-617	8	6.0-7.4

TUM: Technical University Munich, PMCC: Peter MacCallum Center Melbourne, UCLA: University of California, Los Angeles, UKH: University Hospital Heidelberg, UKE: University Hospital Essen, EDNOC: Excel Diagnostics Nuclear Oncology Center

Supplemental Table 2. Eligibility criteria

Eligibility criteria to receive Lu-177 PSMA radioligand therapy
- Histopathological confirmed adenocarcinoma of the prostate
- Confirmed metastatic castration-resistant prostate cancer (testosterone levels below 50 ng/dL)
- Failure of standard treatments, including taxane-based chemotherapy (docetaxel, cabazitaxel) and androgen-signaling- targeted inhibitor (abiraterone, enzalutamide, or both), unless patients were unsuitable or refused these standard treatment regimens
- Progressive disease by prostate-specific antigen according to Prostate Cancer Working Group 3 criteria or radiographic progression according to RECIST 1.1
- Eastern Cooperative Oncology Group performance status score of 2 or lower
- Life expectancy greater than 3 months
- Hemoglobin concentration greater than 90 g/L
- Platelet count greater than 75 x 10^9/L
- Neutrophil count greater than 1.5 x 10^9/L
- “PSMA-positive” lesions by PSMA-targeted PET imaging
Inclusion criteria for the international multicenter analysis:
- Lu-177 PSMA administered activity of 6.0-8·5 GBq
- Treatment initiation between October 1, 2014 and July 2021
- Available screening 68Ga-PSMA11 PET/CT within ten weeks of treatment
- Available survival outcome data (overall survival, PSA progression-free survival)

PSA: prostate specific antigen, RECIST: response evaluation criteria in solid tumors, PSMA: prostate-specific membrane antigen

Supplemental Table 3. Characteristics of the VISION eligible patients in the current study (VISION-PET-E) and in the intervention arm of the VISION trial (analysis set for imaging-based progression-free survival)

	***Current Study:* VISION-PET-E cohort**	***VISION Trial*: Intervention Arm cohort (Lu-177 PSMA plus SOC)**	**p-value**
n	272	385	
Median age (range) — years	72 (46-95)	71 (52-94)	NA
Median PSA (range) — ng/ml	116.6 [0, 5446]	90.7 [0, 6600]	NA
Treatment history — no. (%)			
Previous docetaxel	218 (80.1%)	385 (100.0%)	<0.001
Second-line chemotherapy	95 (34.9%)	173 (44.9%)	0.012
Androgen receptor signaling inhibitor	150 (55.1%)	385 (100.0%)	<0.001
Sites of disease — no. (%)			
Lymph node	143 (52.6%)	193 (50.1%)	0.58
Bone	182 (67.0%)	351 (91.2%)	<0.001
Visceral	69 (25.4%)	82 (21.3%)	0.22
Median OS — months	14.2	14.6	NA
PSA50RR — no. (%)	131 (50.3%)	177 (46.0%)	0.63
anyPSARR — no. (%)	194 (71.3%)	275 (71.5%)	1

SOC: standard of care, PSA: prostate specific antigen, OS: overall survival, PSA50RR: PSA response rates (decline of ≥ 50%), anyPSARR: any decline of PSA, NA: not available. The p-values of the continuous variables were not calculated because the original data of the VISION trial are not available. We compared our cohort to the analysis set for imaging-based progression-free survival (not all patients who underwent randomization: n = 551/831) in the VISION trial, because PSA responses are available only in this dataset.

Supplemental Table 4. Outcomes of the patients with PSMA-negative lesions and low PSMA expression.

	PSMA-negative lesions	Low PSMA expression	p-value
n	21	8	
PSA50RR			
No. (%)	4 (19.0%)	2 (25.0%)	1.00
Odds ratio (95%CI)	0.71 (0.11-0.71)	1 (reference)	0.72
anyPSARR			
No. (%)	8 (38.1%)	4 (50.0%)	0.68
Odds ratio (95%CI)	0.63 (0.12-3.1)	1 (reference)	0.56
PSA-PFS			
Median months (95%CI)	1.8 (1.4-3.3)	2.8 (1.1-5.7)	0.44
Hazard ratio (95%CI)	1.4 (0.57-3.6)	1 (reference)	0.45
OS			
Median months (95%CI)	8.2 (4.4-11.0)	NA (11.1-NA)	0.034
Hazard ratio (95%CI)	4.4 (0.99-19.1)	1 (reference)	0.051

PSA: prostate specific antigen, PSA50RR: PSA response rates (decline of ≥ 50%), anyPSARR: any decline of PSA, OS: overall survival, PFS: progression free survival, CI: confidence interval