Head- to head Comparison of [^{68}Ga]Ga-PSMA-11 with [^{18}F]PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as Reference-Standard

Study Protocol

Introduction:

PSMA (Prostate specific membrane antigen) is a transmembrane glycoprotein over-expressed in prostate cancer cells (1).

[^{68}Ga]Ga-PSMA-11 PET/CT, an imaging test that utilizes small molecules that bind to PSMA and internalized into the cell, was shown to be superior to other conventional and molecular imaging modalities (CT, MRI, bone-scan, choline-based PET/CT) for evaluating the extent of disease in prostate cancer patients and it's results often change therapeutic decisions (2-6). For these reasons this test was introduced to the "Israeli medical services basket" for staging intermediate- and high- risk patients as well as for evaluating the extent of disease in patients with biochemical failure.

However, [^{68}Ga]Ga-PSMA-11 PET/CT has several limitations that could be overcome by shifting to [^{18}F]-based PET/CT (7):

1. [^{18}F]-labeled agents are produced via cyclotron and enable large-scale radiosynthesis, allowing for a higher number of patient studies, as compared to the limited quantity obtained from the generator produced [^{68}Ga].
2. The longer physical half-life of the [^{18}F] radioisotope ($T_{1/2}$ = 109 min) allows for central production and distribution to satellite centers.
3. [^{18}F]PSMA-1007 may offer higher spatial resolution images than [^{68}Ga] due to the relatively low positron energy of [^{18}F] (Av. $E_{\beta+}$ = 250 keV).

Another advantage of [^{18}F]PSMA-1007 over [^{68}Ga]Ga-PSMA-11, [^{68}Ga]Ga-PSMA-617 and also the available fluorinated PSMA derivative, [^{18}F]DCFPyL, is the lack of renal excretion and the low urinary activity, as it is mostly cleared through the hepatobiliary

system, which can benefit clinical decision making in cases of local recurrence and unclear lesions in proximity to the ureter or urinary bladder (7).
[^{18}F]PSMA-1007 shares similar structural scaffold with [^{68}Ga]Ga-PSMA-617, which results in similar distribution kinetics. This makes [^{18}F]PSMA-1007 optimal for stratifying patients according to their suitability for therapy with [^{177}Lu]Lu-PSMA-617 (7).
So far, little but promising experience has accumulated in Germany, in imaging with [^{18}F]PSMA-1007 (7-10). In one published case, 17 malignant lymph-nodes were detected in a patient with biochemical failure 9 years post radical-prostatectomy that were not detected by other imaging modalities (8).

Objectives:

1. To compare the sensitivity of [^{18}F]PSMA-1007 and [^{68}Ga]Ga-PSMA-11 for detecting malignant lesions in the prostate and distant lesions, in the setting of staging intermediate- and high- risk patients.
2. Validating imaging-results with post-prostatectomy and lymph-node dissection histology.
3. To evaluate the potential influence of PET/CT results on therapeutic decisions.

Study Population:

- Men aged 18 and above
- Inclusion criteria:
    1. Untreated intermediate- and high- risk prostate cancer patients according to D'Amico classification (11) presented for staging.
    2. Patients treated in the urologic department in Tel-Aviv Sourasky Medical Center who are candidates for Radical-prostatectomy as definitive treatment.
- Exclusion criteria:
    1. Patients with a second malignancy
- Criteria for removal from the trial: None.

Duration of Study: Approximately one year or until all participants have undergone imaging.

Study details:

- This is a prospective study
- The study is done in collaboration with Prof. Eyal Mishani. The director of the cyclotron and radiochemistry unit in Hadassah Medical Center, who will provide the tracers for the study.
- Intermediate- and high- risk prostate cancer patients presented for staging, who are candidates to undergo radical-prostatectomy in Tel-Aviv Sourasky Medical Center will undergo two separate PET/CT scans on two different days, using [^{18}F]PSMA-1007 and [^{68}Ga]Ga-PSMA-11.
- A meticulous histopathological evaluation of the surgically removed-prostate will be done with identification of tumor lesion site, for validation of the accuracy of PET/CT in localizing primary lesions. Immunohistochemical analysis using PSMA staining will be done as necessary.
- Clinical follow-up will be performed by the referring urologist.

Study phases:

1. Patients will undergo routine clinical evaluation by the referring urologist prior to enrolment to the study.
2. Patients recruited to the study will receive a thorough explanation on the tests they will undergo.
3. Both PET/CT scans will be performed on the same Discovery 690 PET/CT system (GE Healthcare) in the Department of Nuclear-Medicine in Tel-Aviv Sourasky Medical Center.
4. On each day of their PET/CT scan, patients will be interviewed by a physician or a nurse, and a peripheral IV-line will be installed. Patients will be injected with 148-166.5 MBq of [^{68}Ga]Ga-PSMA-11 (12) and on the other exam-day, with 4 MBq/Kg of [^{18}F]PSMA-1007 (7).
5. During the PET/CT scan patients will be asked to lie still.

6. After completion of each scan patients will be discharged home.

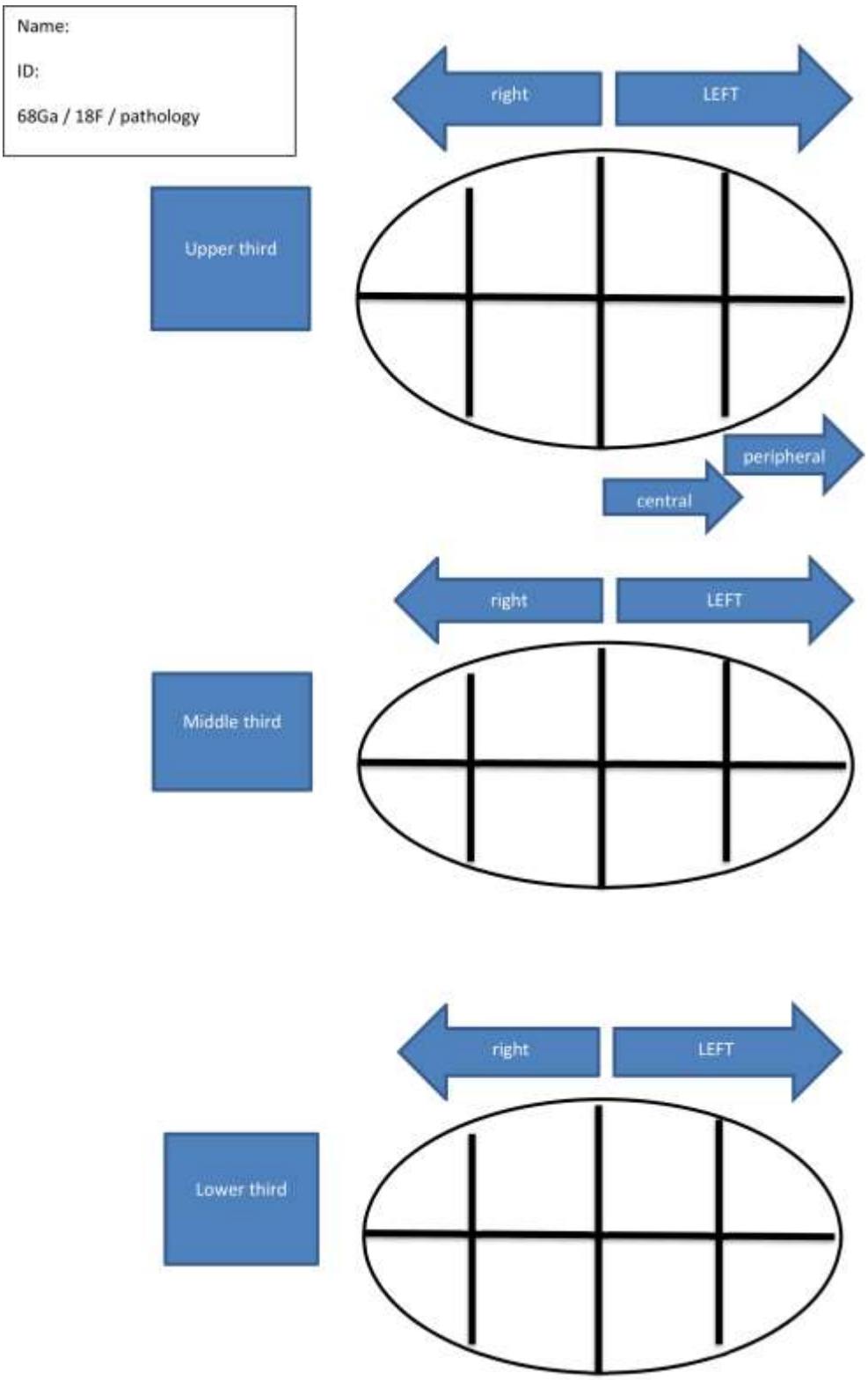
Comments:

- No contrast material will be given
- The effective-dose from each tracer is about 4.4-5.5 mSV (7, 12).

References:

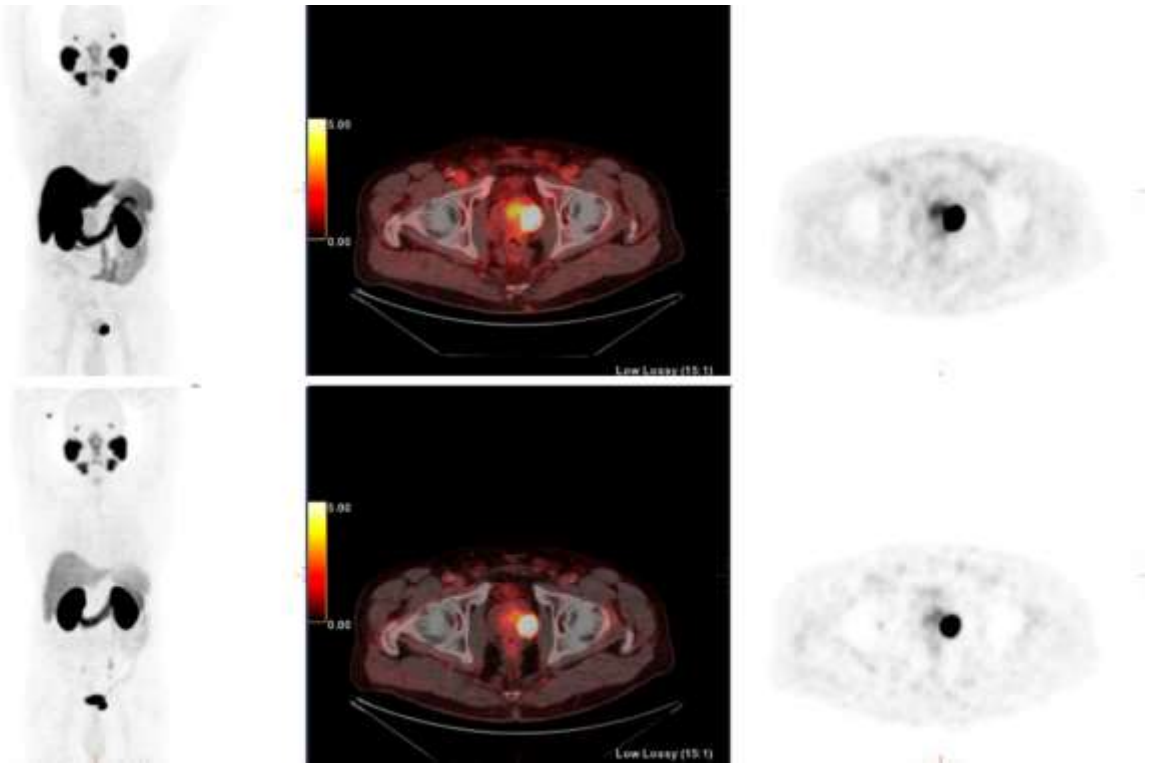
1. Afshar-Oromieh A, Babich JW, Kratochwil C, et al. The rise of PSMA ligands for diagnosis and therapy of prostate cancer. J Nucl Med. 2016;57:79S-89S.
2. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic efficacy of (68)gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol 2016; 195: 1436–1443.
3. 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.
4. Shakespeare TP. Effect of prostate-specific membrane antigen positron emission tomography on the decision-making of radiation oncologists. Radiat Oncol 2015; 10: 233.
5. 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 2017; June 23. [Epub ahead of print]
6. Fendler WP, Schmidt DF, Wenter V, et al. 68Ga-PSMA PET/CT detects the location and extent of primary prostate cancer. J Nucl Med 2016; 57: 1720-1725.
7. Giesel F.L, Hadaschik B, Cardinale J, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging 2017; 44: 678-688.
8. Giesel F.L, Kesch C, Yun M, et al. 18F-PSMA-1007 PET/CT Detects Micrometastases in a Patient With Biochemically Recurrent Prostate Cancer. Clin Genitourin Cancer 2017;15:e497-e499.

9. Kesch, C, Vinsensia M, Radtke JP, et al. Intraindividual Comparison of 18F-PSMA-1007 PET/CT, Multiparametric MRI, and Radical Prostatectomy Specimens in Patients with Primary Prostate Cancer: A Retrospective, Proof-of-Concept Study. J. Nucl. Med 2017; 58, 1805-1810.
10. Freitag MT, Kesch C, Cardinale J, et al. Simultaneous whole-body 18F-PSMA-1007-PET/MRI with integrated high-resolution multiparametric imaging of the prostatic fossa for comprehensive oncological staging of patients with prostate cancer: a pilot study. Eur. J. Nucl. Med. Mol. Imaging 2017; [Epub ahead of print].
11. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998; 280: 969-974.
12. Fendler WP, Eiber M, Beheshti M, et al. ^{68}Ga-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.

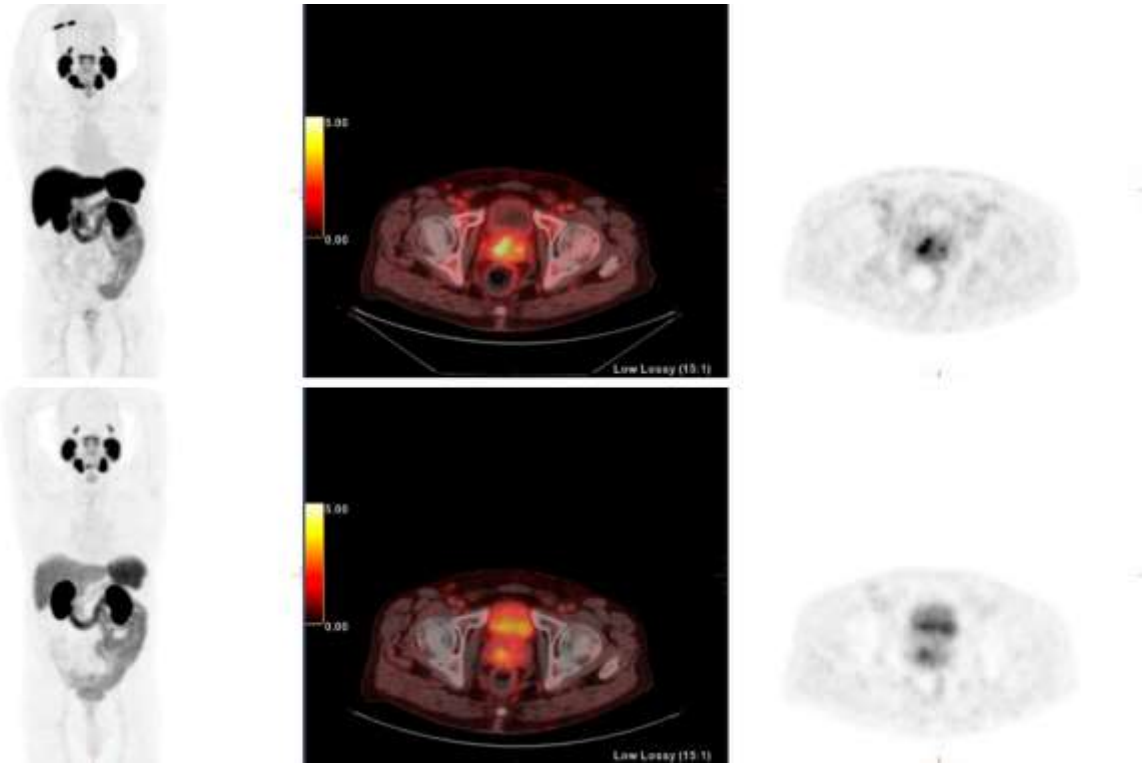


SUPPLEMENTAL FIGURE 1. Customized scheme of the prostate divided into upper, middle and lower thirds, left or right lobes, central or peripheral and anterior or posterior regions.

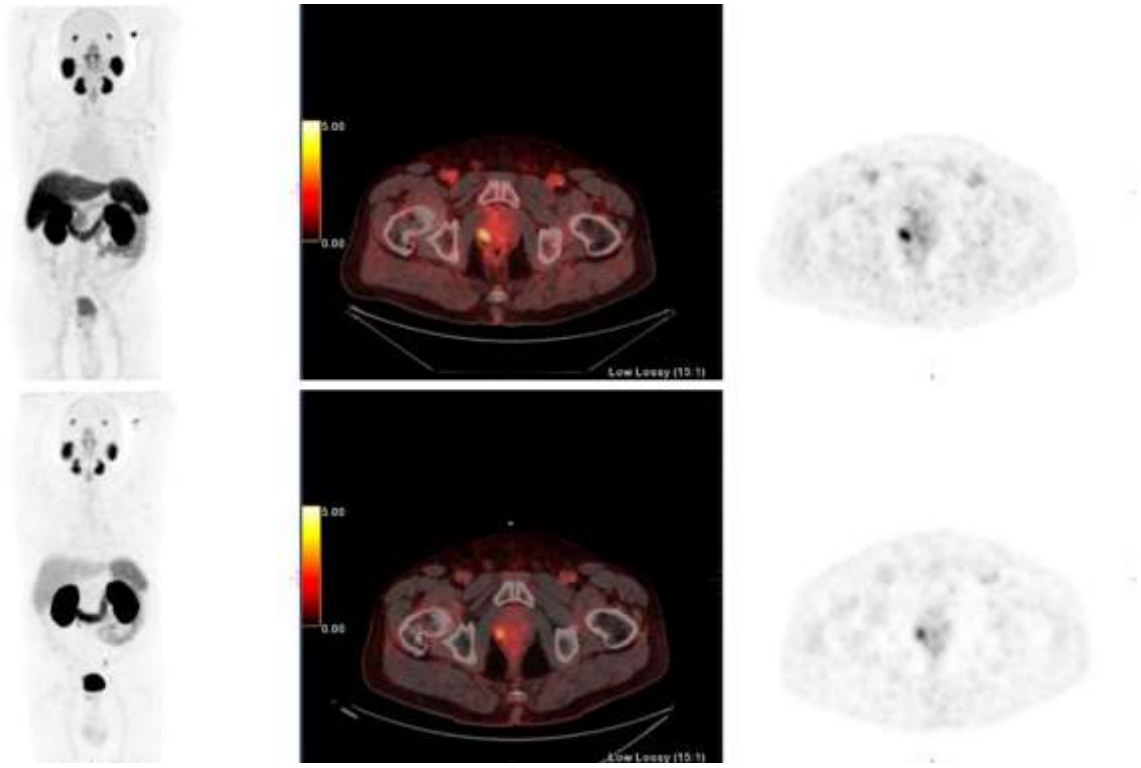
SUPPLEMENTAL FIGURES 2-17. PET/CT scans of all patients included in the study, 18F-PSMA-1007 (top row), 68Ga-PSMA-11 (bottom row), Maximum intensity projections (MIP), transaxial CT fusion and PET images at the level of the dominant prostatic lesions. Images 2-17 correspond to patients listed 1-16 in supplemental table 2, respectively.



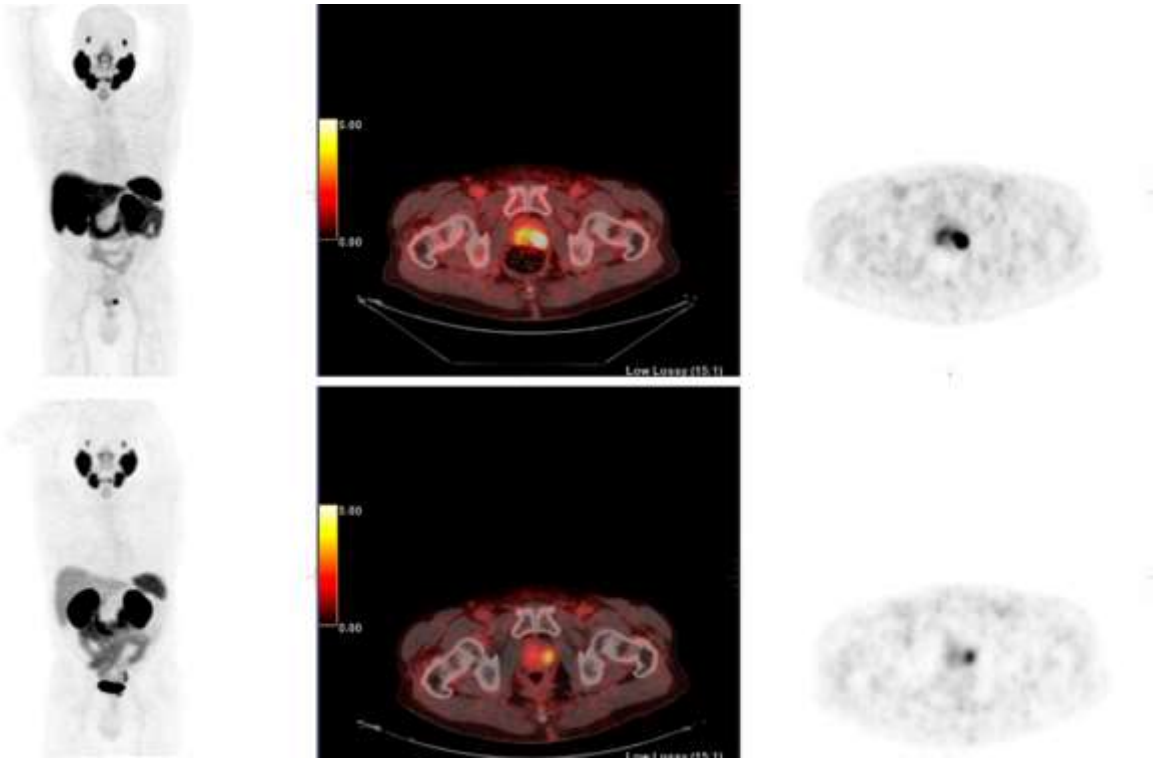
SUPPLEMENTAL FIGURE 2. Dominant lesion in left prostatic lobe.



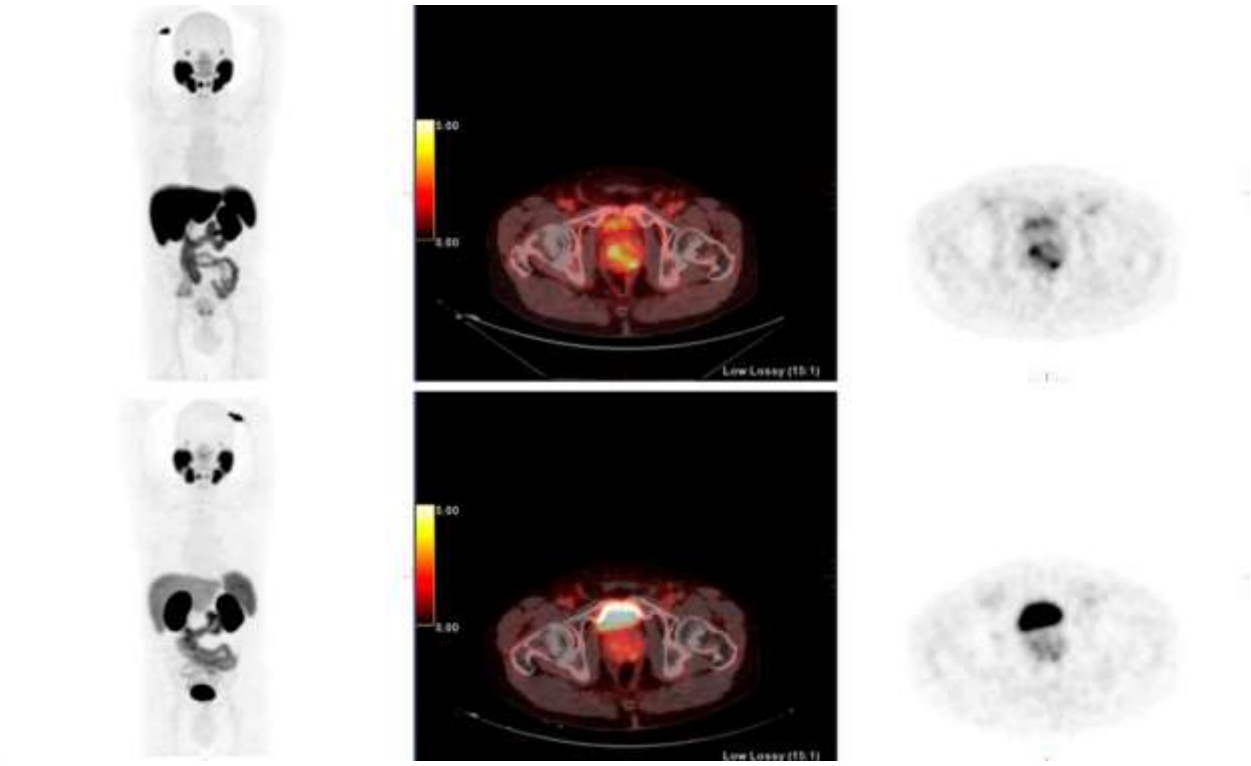
SUPPLEMENTAL FIGURE 3. Dominant lesion in right prostatic lobe. Low-intensity small contra-lateral foci noticed on 18F-PSMA-1007 scan (true positive).



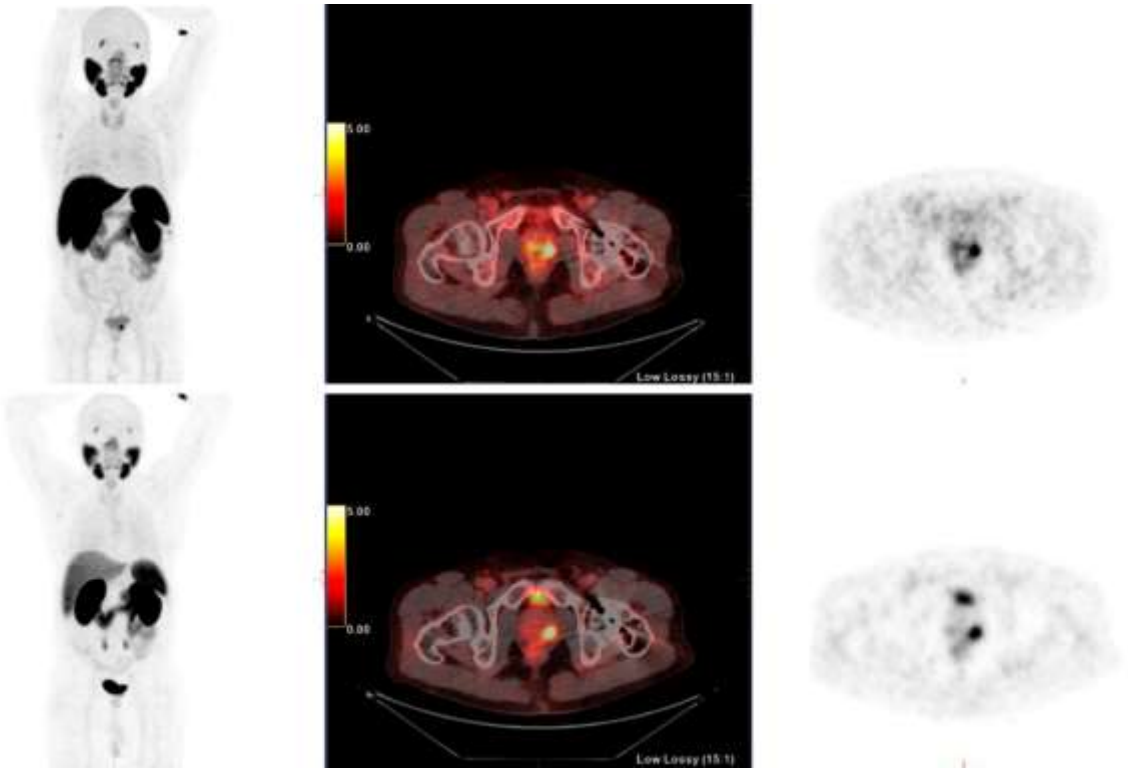
SUPPLEMENTAL FIGURE 4. Dominant lesion in right prostatic lobe.



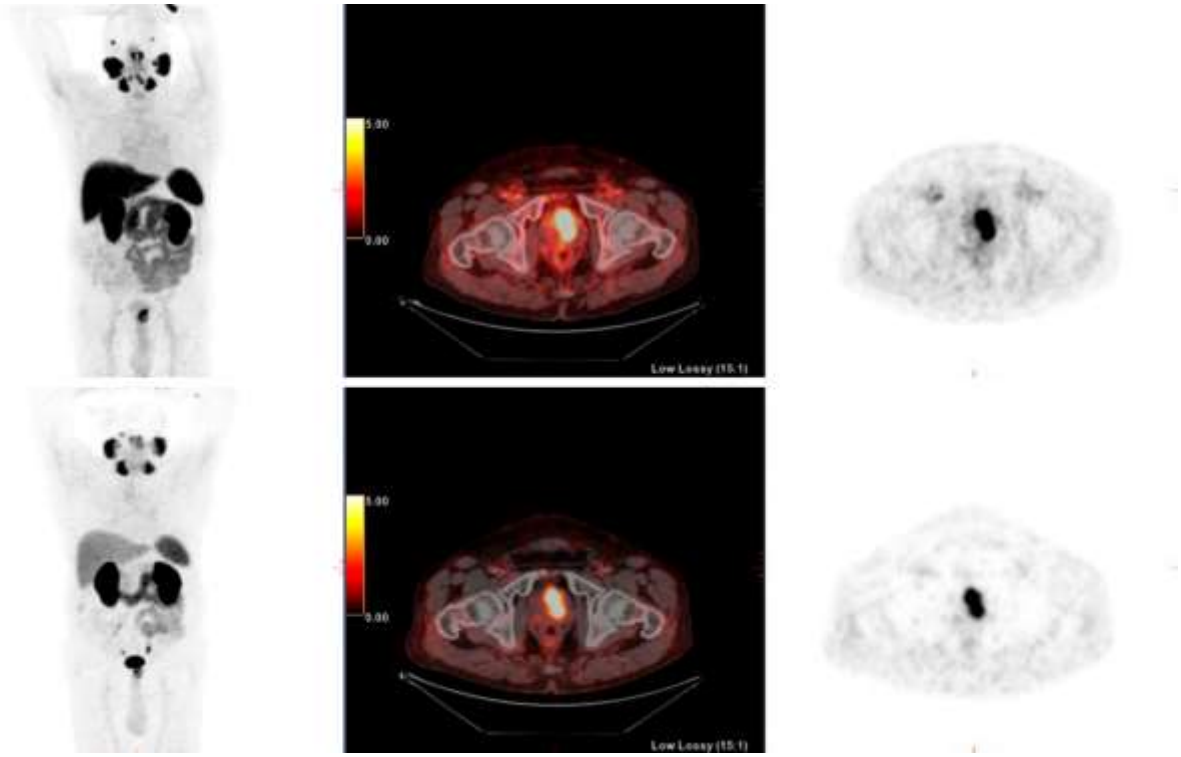
SUPPLEMENTAL FIGURE 5. Dominant lesion in left prostatic lobe. Low-intensity small contra-lateral foci noticed on 18F-PSMA-1007 scan (true positive).



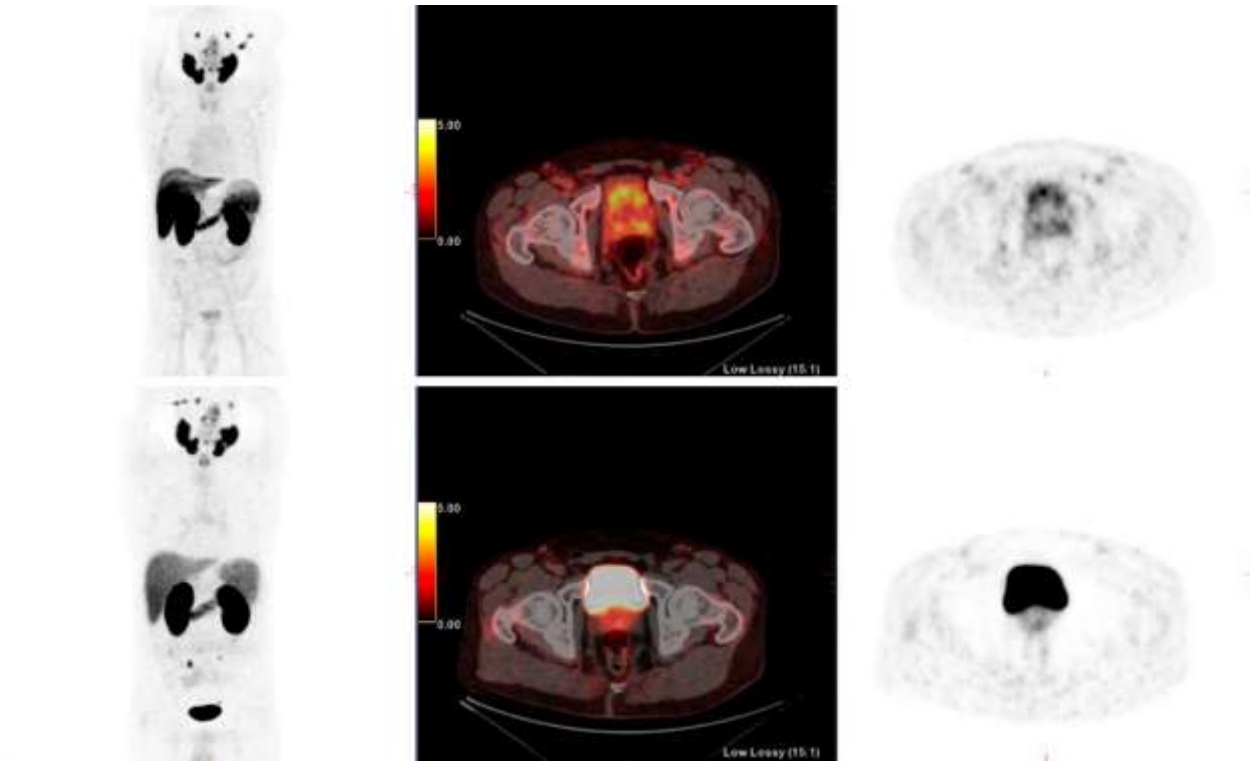
SUPPLEMENTAL FIGURE 6. Dominant lesion in left prostatic lobe. A low-intensity small contra-lateral focus was noticed on both scans (false positive).



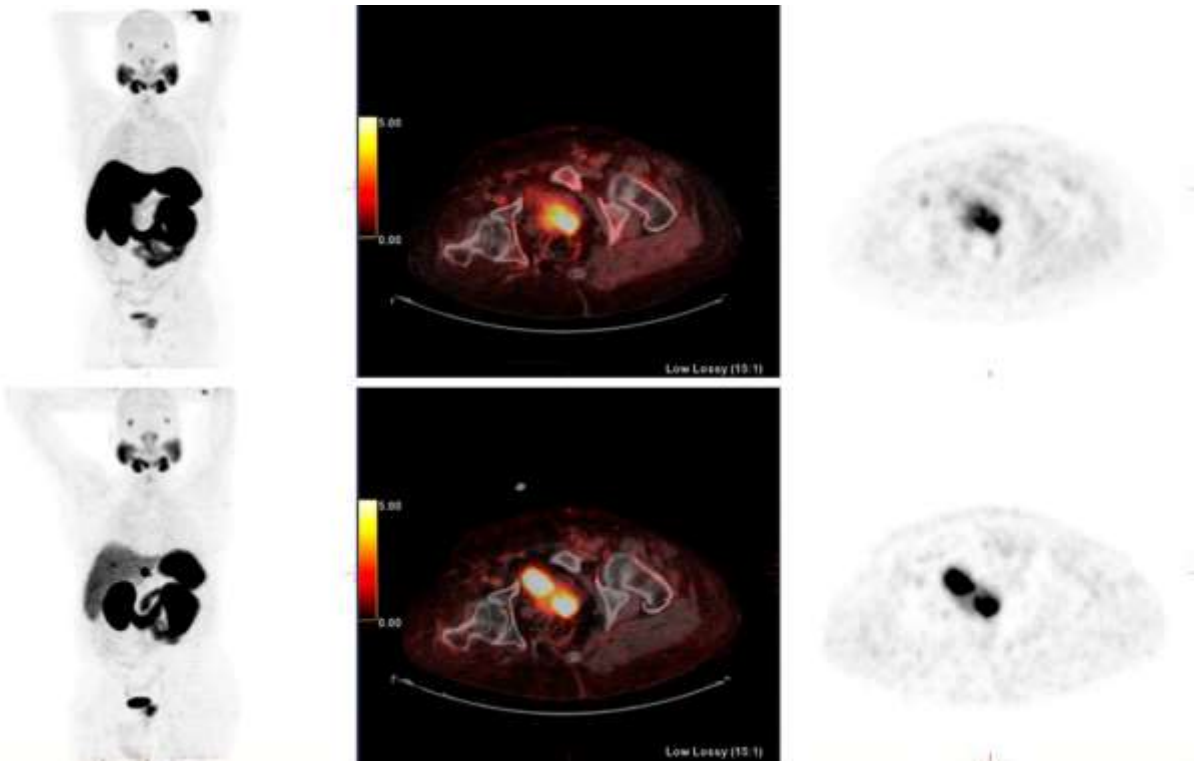
SUPPLEMENTAL FIGURE 7. Dominant lesion in left prostatic lobe.



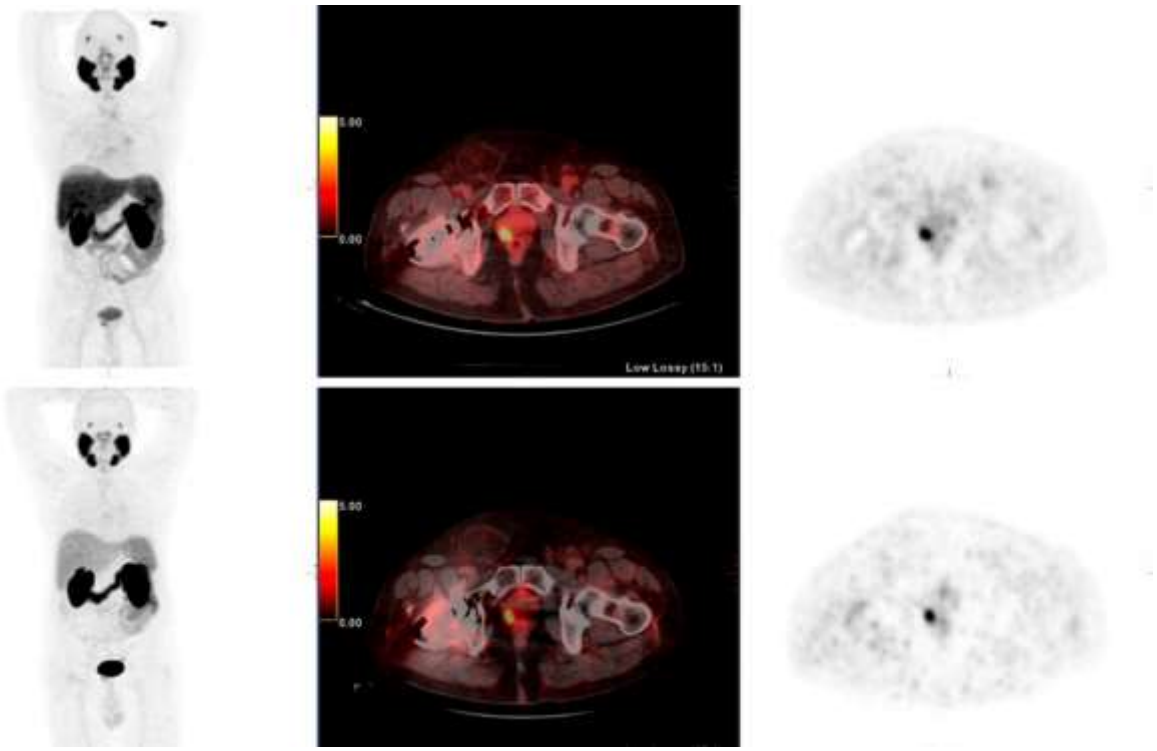
SUPPLEMENTAL FIGURE 8. Dominant lesion in left prostatic lobe.



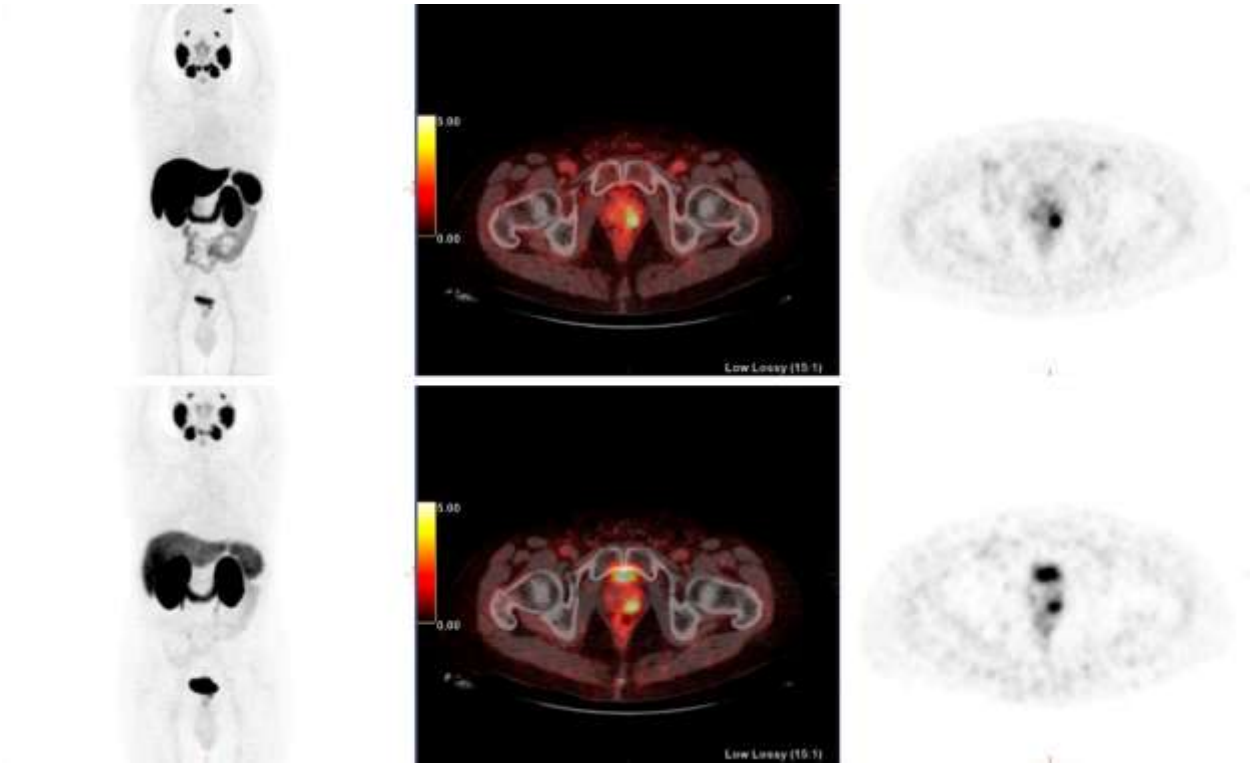
SUPPLEMENTAL FIGURE 9. Dominant lesion in left prostatic lobe.



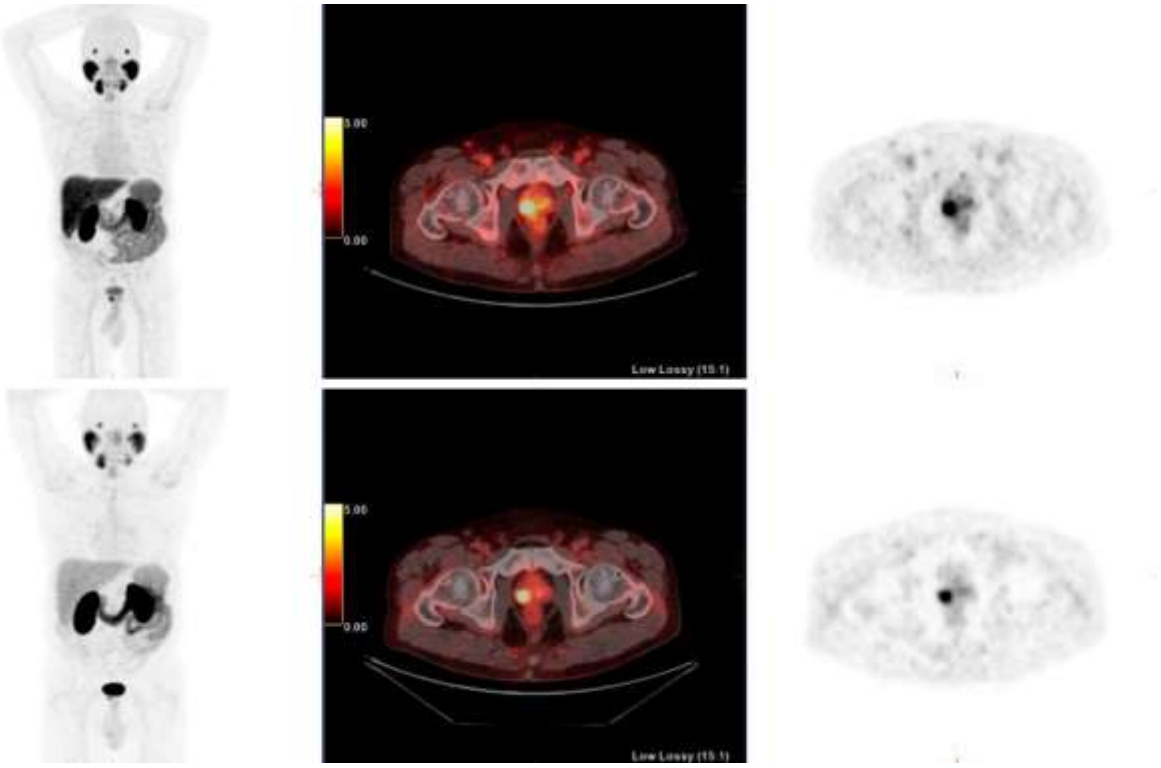
SUPPLEMENTAL FIGURE 10. Dominant lesion in left prostatic lobe.



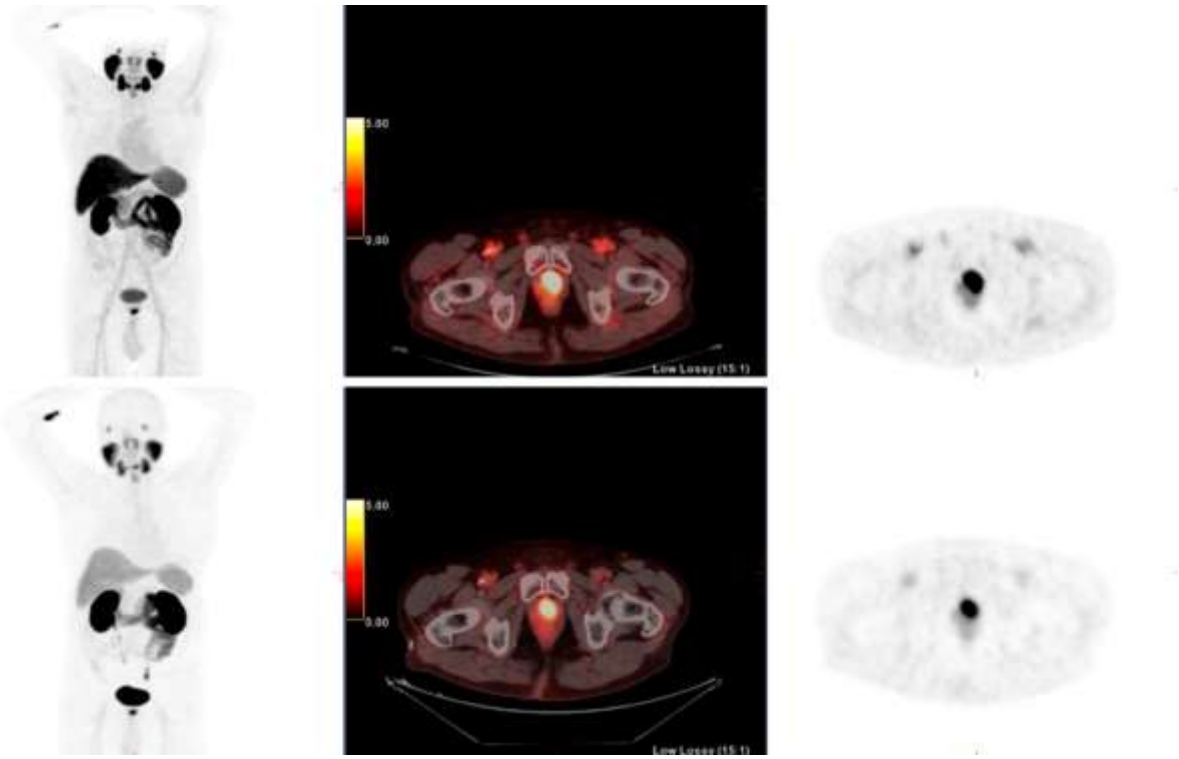
SUPPLEMENTAL FIGURE 11. Dominant lesion in right prostatic lobe.



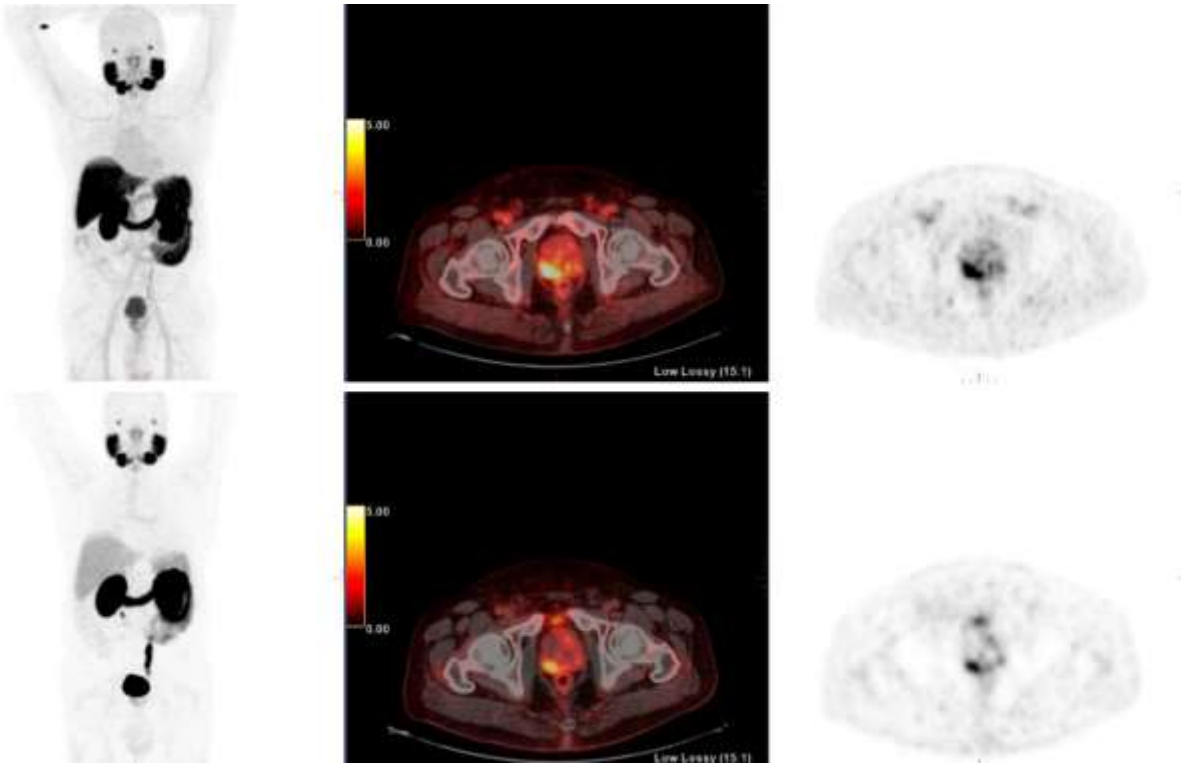
SUPPLEMENTAL FIGURE 12. Dominant lesion in left prostatic lobe.



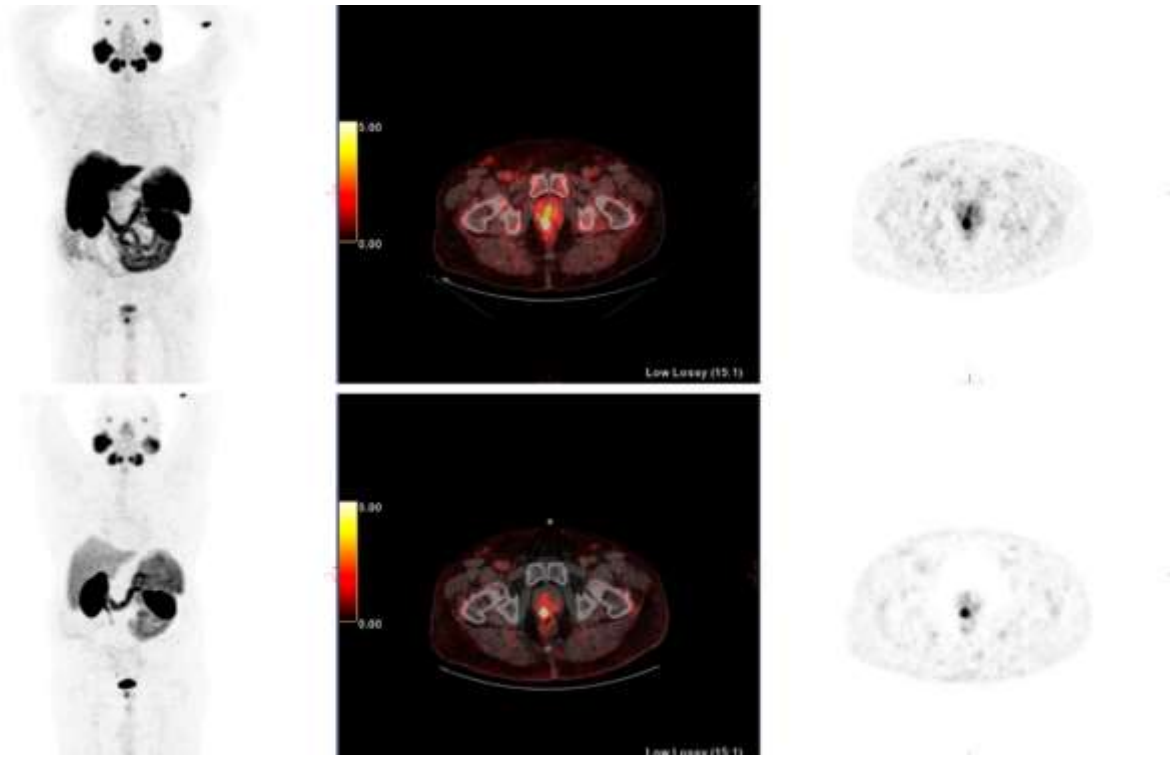
SUPPLEMENTAL FIGURE 13. Dominant lesion in right prostatic lobe. Low-intensity small contralateral foci noticed on 18F-PSMA-1007 scan (false positive).



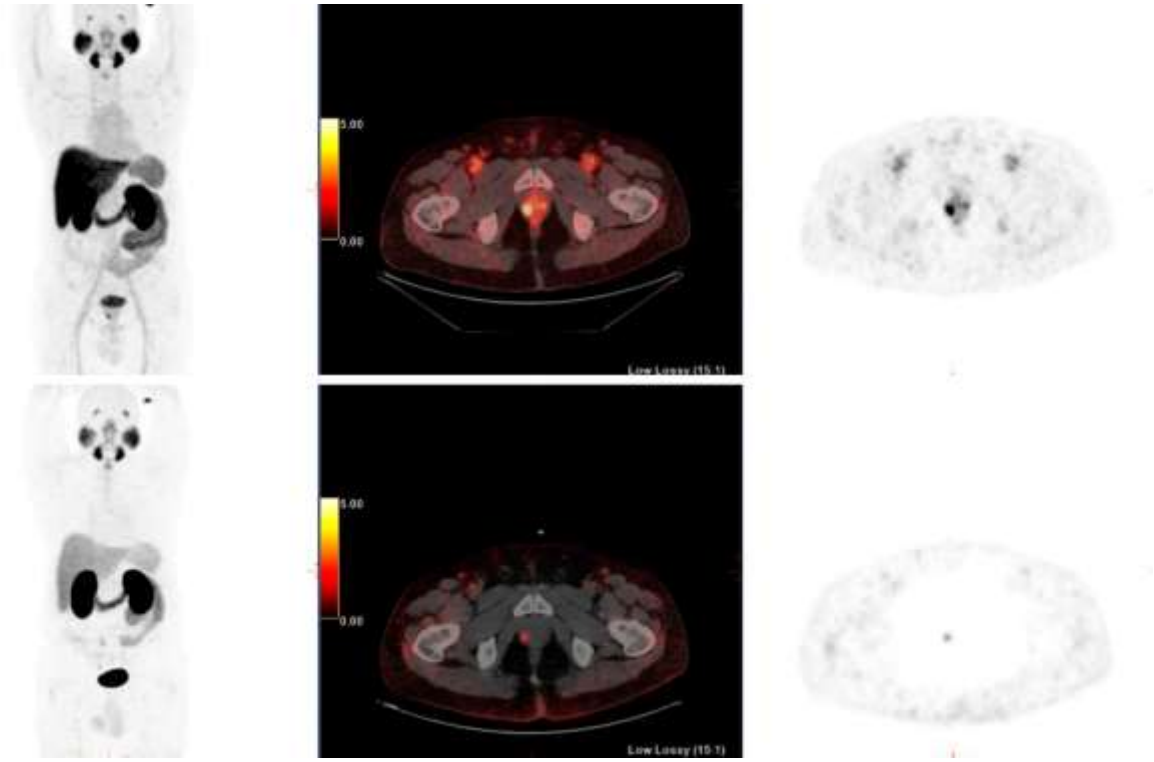
SUPPLEMENTAL FIGURE 14. Dominant lesion in left prostatic lobe.



SUPPLEMENTAL FIGURE 15. Dominant lesion in right prostatic lobe.



SUPPLEMENTAL FIGURE 16. Dominant lesion in right prostatic lobe.



SUPPLEMENTAL FIGURE 17. Dominant lesion in right prostatic lobe. Low-intensity small contralateral foci noticed on 18F-PSMA-1007 scan (true positive).

SUPPLEMENTAL TABLE 1

Characteristics of Patients (n=16)

Characteristic		
Age (yr)		
Median (IQR)	68.5 (62.7-71)	
BMI	28 (25.7-29.7)	
Median (IQR)		
PSA (ng/ml)	6.35 (5.1-10.9)	
Median (IQR)		
Biopsy Gleason score n=16, (n, %)		
	3+3	2 (12.5%)
	3+4	5 (31.3%)
	4+3	6 (37.5%)
	8	3 (18.8%)
Risk group n=16, (n, %)		
Favorable intermediate	5 (31.25%)	
Unfavorable intermediate	7 (43.75%)	
High risk	4 (25%)	
Prostatectomy Gleason score n=15, (n, %)		
	3+4	8 (53.3%)
	4+3	6 (40%)
	8	1 (6.7%)
Clinical Stage n=16, (n, %)		
	cT1c	14 (87.5%)
	cT2a	1 (6.25%)
	cT2c	1 (6.25%)
Pathological Stage n=15, (n, %)		
	pT2	10 (66.7%)
	pT3a	3 (20%)
	pT3b	2 (13.3%)

SUPPLEMENTAL TABLE 2.

Agreement between 18F-PSMA-1007 and 68Ga-PSMA-11 PET/CT for Intra-prostatic Lesions:

Area	Kappa
L Base	1
R Base	1
L Mid	0.875
R Mid	1
L Apex	0.871
R Apex	0.871

SUPPLEMENTAL TABLE 3

Intra-prostatic Lesions; PSMA PET/CT Vs. Histopathology Findings:

Area	Prev (%)	Radiotracer	Sen (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)	P(McNemar)*
L Base	46.7	^{68}Ga	100	100	100	100	100	>0.999
		^{18}F	100	100	100	100	100	>0.999
R Base	33.3	^{68}Ga	100	100	100	100	100	>0.999
		^{18}F	100	100	100	100	100	>0.999
L Mid	46.7	^{68}Ga	100	100	100	100	100	>0.999
		^{18}F	100	87.5	87.5	100	93.3	>0.999
R Mid	46.7	^{68}Ga	100	87.5	87.5	100	93.3	>0.999
		^{18}F	100	87.5	87.5	100	93.3	>0.999
L Apex	40	^{68}Ga	83.3	100	100	90	93.3	>0.999
		^{18}F	100	100	100	100	100	>0.999
R Apex	46.7	^{68}Ga	85.7	100	100	88.9	93.3	>0.999
		^{18}F	100	100	100	100	100	>0.999

*Significant values indicate non-agreement.

Prev = prevalence; Sen = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; Acc = accuracy;

SUPPLEMENTAL TABLE 4

The Ability of 18F-PSMA-1007 and 68Ga-PSMA-11 to Discriminate between Intra-prostatic Dominant Lesions and Non-diseased areas, Per Segment and Overall

Area	Median SUV (IQR)	AUC (95% CI)	*P*
L Base			
^{18}F	3 (2.58-8.64)	1 (1-1)	0.002
^{68}Ga	1.87 (1-7.34)	0.96 (0.863-1)	0.005
R Base			
^{18}F	2.75 (1.98-5.97)	1 (1-1)	0.004
^{68}Ga	2.24 (1.28-3.38)	1 (1-1)	0.004
L Mid			
^{18}F	4.2 (2.04-11.42)	1 (1-1)	0.001
^{68}Ga	2.13 (1.56-7.9)	1 (1-1)	0.001
R Mid			
^{18}F	4.15 (2-6.93)	0.964 (0.877-1)	0.003
^{68}Ga	2.7 (1.69-4.9)	0.929 (0.798-1)	0.005
L Apex			
^{18}F	3.34 (1.8-11.42)	1 (1-1)	0.001
^{68}Ga	2.13 (0.94-7.9)	1 (1-1)	0.001
R Apex			
^{18}F	3.91 (1.71-8.27)	0.964 (0.877-1)	0.003
^{68}Ga	1.87 (1.23-4.58)	1 (1-1)	0.001
All areas			
^{18}F	3.345 (2.03-8.11)	0.987 (0.971-1)	<0.0005
^{68}Ga	2.13 (1.26-4.83)	0.975 (0.949-1)	<0.0005

AUC= Area under the curve.

SUPPLEMENTAL TABLE 5

Detection of Intra-prostatic Dominant Lesions, Per Segment and Overall, Per Each Radiotracer by Optimal SUV Cutoff

Area	SUV-cutoff	Sen (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
L Base						
^{18}F	3.97	100	100	100	100	100
^{68}Ga	2.31	100	80	71.4	100	86.6
^{68}Ga*	5.33	80	100	100	90.9	93.4
R Base						
^{18}F	5.19	100	100	100	100	100
^{68}Ga	3.16	100	100	100	100	100
L Mid						
^{18}F	7.18	100	100	100	100	100
^{68}Ga	2.77	100	100	100	100	100
R Mid						
^{18}F	3.76	100	87.5	87.5	100	93.4
^{68}Ga	2.72	85.7	87.5	85.7	87.5	86.7
L Apex						
^{18}F	5.84	100	100	100	100	100
^{68}Ga	2.75	100	100	100	100	100
R Apex						
^{18}F	3.08	100	87.5	87.5	100	93.4
^{68}Ga	1.88	100	100	100	100	100
All areas						
^{18}F	3.77	100	90.9	87.5	100	94.5
^{68}Ga	3.29	85.7	98.2	96.8	91.5	93.3

*Two equally optimal cut-off values were available.

Sen = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value; Acc = accuracy

Head- to head Comparison of [^{68}Ga]Ga-PSMA-11 with [^{18}F]PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as Reference-Standard

Study Protocol

Introduction:

PSMA (Prostate specific membrane antigen) is a transmembrane glycoprotein over-expressed in prostate cancer cells (1).

[^{68}Ga]Ga-PSMA-11 PET/CT, an imaging test that utilizes small molecules that bind to PSMA and internalized into the cell, was shown to be superior to other conventional and molecular imaging modalities (CT, MRI, bone-scan, choline-based PET/CT) for evaluating the extent of disease in prostate cancer patients and it's results often change therapeutic decisions (2-6). For these reasons this test was introduced to the "Israeli medical services basket" for staging intermediate- and high- risk patients as well as for evaluating the extent of disease in patients with biochemical failure.

However, [^{68}Ga]Ga-PSMA-11 PET/CT has several limitations that could be overcome by shifting to [^{18}F]-based PET/CT (7):

4. [^{18}F]-labeled agents are produced via cyclotron and enable large-scale radiosynthesis, allowing for a higher number of patient studies, as compared to the limited quantity obtained from the generator produced [^{68}Ga].
5. The longer physical half-life of the [^{18}F] radioisotope ($T_{1/2}$ = 109 min) allows for central production and distribution to satellite centers.
6. [^{18}F]PSMA-1007 may offer higher spatial resolution images than [^{68}Ga] due to the relatively low positron energy of [^{18}F] (Av. $E_{\beta+}$ = 250 keV).

Another advantage of [^{18}F]PSMA-1007 over [^{68}Ga]Ga-PSMA-11, [^{68}Ga]Ga-PSMA-617 and also the available fluorinated PSMA derivative, [^{18}F]DCFPyL, is the lack of renal excretion and the low urinary activity, as it is mostly cleared through the hepatobiliary

system, which can benefit clinical decision making in cases of local recurrence and unclear lesions in proximity to the ureter or urinary bladder (7).
[^{18}F]PSMA-1007 shares similar structural scaffold with [^{68}Ga]Ga-PSMA-617, which results in similar distribution kinetics. This makes [^{18}F]PSMA-1007 optimal for stratifying patients according to their suitability for therapy with [^{177}Lu]Lu-PSMA-617 (7).
So far, little but promising experience has accumulated in Germany, in imaging with [^{18}F]PSMA-1007 (7-10). In one published case, 17 malignant lymph-nodes were detected in a patient with biochemical failure 9 years post radical-prostatectomy that were not detected by other imaging modalities (8).

Objectives:

4. To compare the sensitivity of [^{18}F]PSMA-1007 and [^{68}Ga]Ga-PSMA-11 for detecting malignant lesions in the prostate and distant lesions, in the setting of staging intermediate- and high- risk patients.
5. Validating imaging-results with post-prostatectomy and lymph-node dissection histology.
6. To evaluate the potential influence of PET/CT results on therapeutic decisions.

Study Population:

- Men aged 18 and above
- Inclusion criteria:
    3. Untreated intermediate- and high- risk prostate cancer patients according to D'Amico classification (11) presented for staging.
    4. Patients treated in the urologic department in Tel-Aviv Sourasky Medical Center who are candidates for Radical-prostatectomy as definitive treatment.
- Exclusion criteria:
    1. Patients with a second malignancy
- Criteria for removal from the trial: None.

Duration of Study: Approximately one year or until all participants have undergone imaging.

Study details:

- This is a prospective study
- The study is done in collaboration with Prof. Eyal Mishani. The director of the cyclotron and radiochemistry unit in Hadassah Medical Center, who will provide the tracers for the study.
- Intermediate- and high- risk prostate cancer patients presented for staging, who are candidates to undergo radical-prostatectomy in Tel-Aviv Sourasky Medical Center will undergo two separate PET/CT scans on two different days, using [^{18}F]PSMA-1007 and [^{68}Ga]Ga-PSMA-11.
- A meticulous histopathological evaluation of the surgically removed-prostate will be done with identification of tumor lesion site, for validation of the accuracy of PET/CT in localizing primary lesions. Immunohistochemical analysis using PSMA staining will be done as necessary.
- Clinical follow-up will be performed by the referring urologist.

Study phases:

7. Patients will undergo routine clinical evaluation by the referring urologist prior to enrolment to the study.
8. Patients recruited to the study will receive a thorough explanation on the tests they will undergo.
9. Both PET/CT scans will be performed on the same Discovery 690 PET/CT system (GE Healthcare) in the Department of Nuclear-Medicine in Tel-Aviv Sourasky Medical Center.
10. On each day of their PET/CT scan, patients will be interviewed by a physician or a nurse, and a peripheral IV-line will be installed. Patients will be injected with 148-166.5 MBq of [^{68}Ga]Ga-PSMA-11 (12) and on the other exam-day, with 4 MBq/Kg of [^{18}F]PSMA-1007 (7).
11. During the PET/CT scan patients will be asked to lie still.

12. After completion of each scan patients will be discharged home.

Comments:

- No contrast material will be given
- The effective-dose from each tracer is about 4.4-5.5 mSV (7, 12).

References:

13. Afshar-Oromieh A, Babich JW, Kratochwil C, et al. The rise of PSMA ligands for diagnosis and therapy of prostate cancer. J Nucl Med. 2016;57:79S-89S.
14. 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.
15. 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.
16. Shakespeare TP. Effect of prostate-specific membrane antigen positron emission tomography on the decision-making of radiation oncologists. Radiat Oncol 2015; 10: 233.
17. 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 2017; June 23. [Epub ahead of print]
18. Fendler WP, Schmidt DF, Wenter V, et al. 68Ga-PSMA PET/CT detects the location and extent of primary prostate cancer. J Nucl Med 2016; 57: 1720-1725.
19. Giesel F.L, Hadaschik B, Cardinale J, et al. F-18 labelled PSMA-1007: biodistribution, radiation dosimetry and histopathological validation of tumor lesions in prostate cancer patients. Eur J Nucl Med Mol Imaging 2017; 44: 678-688.
20. Giesel F.L, Kesch C, Yun M, et al. 18F-PSMA-1007 PET/CT Detects Micrometastases in a Patient With Biochemically Recurrent Prostate Cancer. Clin Genitourin Cancer 2017;15:e497-e499.

21. Kesch, C, Vinsensia M, Radtke JP, et al. Intraindividual Comparison of 18F-PSMA-1007 PET/CT, Multiparametric MRI, and Radical Prostatectomy Specimens in Patients with Primary Prostate Cancer: A Retrospective, Proof-of-Concept Study. J. Nucl. Med 2017; 58, 1805-1810.
22. Freitag MT, Kesch C, Cardinale J, et al. Simultaneous whole-body 18F-PSMA-1007-PET/MRI with integrated high-resolution multiparametric imaging of the prostatic fossa for comprehensive oncological staging of patients with prostate cancer: a pilot study. Eur. J. Nucl. Med. Mol. Imaging 2017; [Epub ahead of print].
23. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998; 280: 969-974.
24. Fendler WP, Eiber M, Beheshti M, et al. ^{68}Ga-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.