MRI Sequences Acquired

For in vivo MRI, the following MR sequences were acquired: axial 3D T2-weighted (T2w) fast spin echo (FSE) (3D VIEW [Philips Healthcare]; voxel size: 1.0 * 1.0 * 1.0 mm; repetition time: 2051 ms; echo time (TE): 333 ms; field of view: prostate, number of signal averages (NSA): 2), axial / sagittal / coronal T2w 2D FSE (voxel size: 0.7 * 0.9 * 3.0 mm; repetition time 4758 ms; TE 110 ms; field of view: prostate; NSA 1); axial diffusion-weighted imaging (voxel size: 2.3 * 2.4 * 3.0 mm; NSA: 6; b-factors: 0, 100, and 800 s/mm^2), axial T1w pre- and dynamic post-contrast 3D spoiled gradient echo with spectral adiabatic inversion recovery fat-saturation (dynamic contrast-enhanced (DCE); in-plane voxel size: 0.9 * 0.9 mm; slice thickness: variable by size of prostate; 53 slices; field of view: prostate; 58 dynamic scans; turbo field echo factor: 25; NSA 1). Images were reviewed on a PACS workstation (McKesson, San Francisco, CA, U.S.). An ADC map was reconstructed for all diffusion-weighted imaging sequences, and subtraction imaging was generated for all DCE sequences.

For ex vivo MRI, axial and coronal 3D T2w FSE (3D VIEW; voxel size: 0.75 * 0.75 * 0.75 mm; repetition time: 2451 ms; TE: 320 ms; NSA: 3), and axial diffusion-weighted imaging (voxel size: 0.5 * 0.5 * 3.0 mm; NSA: 2; b-factors: 0 and 800 s/mm^2) were acquired.

Radiotracer Synthesis

^{18}F-fluoromethylcholine (^{18}F-choline) was synthesized under good-laboratory-practice (GMP) conditions using no-carrier-added ^{18}F-fluoromethyl-dimethyl-2-hydroxyethyl-ammonium through the intermediate ^{18}F-fluorobromomethane. Quality control procedures were undertaken using high-pressure liquid chromatography methods ensuring radionuclide purity (> 99%) and radiochemical purity (≥ 95%).

PET Image Reconstruction

Images were reconstructed in a 200 * 200 * 56 matrix resulting in a 4 * 4 * 4 mm voxel dimension. Data were corrected for scatter, random events and decay. Images were reconstructed using an iterative ordered-subset expectation maximization algorithm (trueX, 3 iterations, 21 subsets) with a 4 mm Gaussian filter utilizing an ultra-low-dose CT (40 effective mAs, 120 keV, slice thickness 4 mm, pitch 1) without intravenous or oral contrast for attenuation correction.

Statistical Methods

Analyses were conducted using the R statistical package. Data represent mean ± standard deviation. We compared the continuity corrected odds ratio between targeted biopsy and final pathology, and standard biopsy and final pathology. The primary outcome measure was detection of Gleason ≥ 3+4 prostate cancer. We used a permutation-based test to address repeated measures within subjects (i.e., targeted biopsy and standard biopsy were obtained in each subject). We permuted within each subject the standard biopsy and targeted biopsy labels, and calculated the difference in the odds ratio for these biopsy types (i.e., targeted – standard). This was repeated 10,000 times to estimate the permutation distribution under the null hypothesis of no difference. The observed difference in odds ratios was then compared to this distribution.

To assess the value of mpMRI for the prediction of Gleason ≥ 3+4 prostate cancer, we used a logistic regression model with MRI as the only covariate. To assess the added value of PET to mpMRI, we used a logistic regression model with a variable selection procedure (forward and backward stepwise regression). Of the five ^{18}F-choline parameters evaluated, only one ^{18}F-choline variable (SUV_{mean} TBR) was selected by stepwise regression together with MRI in the final model. To determine if this PET-based measure improved identification of Gleason ≥ 3+4 prostate cancer, a likelihood ratio test was performed comparing the model with both MRI and SUV_{mean} TBR, and the model with only MRI. To determine the diagnostic performance of a hypothetical PET/MRI combination, the following rule was applied:

IF high risk lesion on mpMRI

OR low- or intermediate-risk lesion on mpMRI AND SUV_{mean} TBR > 1.583

THEN Gleason ≥ 3+4.

Contingency table and receiver operating characteristic analyses were performed to determine the value of mpMRI vs. PET vs. combined PET/MRI assessments. A paired Wilcoxon test was performed to assess the % core involvement from targeted vs. standard biopsy.

Supplemental Table 1

Patient Characteristics

Subject No.	No. of Prior Biopsy Proce-dures	Last Biopsy Proce-dure (Months)	Prior Highest Gleason Score Ever	PSA (ng/mL) at Biopsy	TRUS-MRI Regist-ration Quality Score	Standard Template Biopsy Result Regarding Gleason >3+3 Cancer	No. of Cores Positive for Cancer	Highest % Core Involve-ment	Highest Gleason Score on Standard Biopsy	Targeted Biopsy Result Regar-ding Gleason >3+3 Cancer	No. of Cores Positive for Cancer	Highest % Core Involve-ment	Highest Gleason Score on Targeted Biopsy	Definitive treatment	Highest Gleason score at Prostate c-tomy
1	2	-6	3+3	22.5	3	neg	0	0		pos	11	90	3+4		
2	6	-38	3+3	4.8	0	neg	0	0		neg	1	65	3+3		
3	1	-13	3+3	11.2	3	neg	3	25	3+3	neg	0	0		Prostatecto my	3+3
4	1	-26	3+3	9.3	2	neg	0	0		neg	0	0			
5	1	-29	3+3	4.1	3	neg	0	0		neg	0	0			

6	1	-15	neg	7.3	2	neg	0	0		neg	0	0		Prostatectomy	3+3
7	2	-15	neg	10.9	1	neg	0	0		pos	9	40	4+3	Prostatectomy	4+5
8	1	-12	3+3	4.6	3	neg	1	5	3+3	pos	1	40	3+4	Prostatectomy	3+4
9	1	-3	3+3	8.7	2	neg	0	0		neg	0	0			
10	1	-12	neg	7.9	1	pos	1	5	4+3	neg	0	0		Prostatectomy	4+3
11	2	-22	neg	3.6	3	neg	0	0		neg	0	0			
12	0		N/A	5.3	2	neg	0	0		neg	0	0			
13	0		N/A	5.8	2	neg	0	0		neg	0	0			
14	1	-15	3+3	6.0	3	neg	0	0		neg	0	0			
15	0		N/A	7.2	1	neg	1	10	3+3	neg	0	0			
16	2	-35	neg	11.7	0	neg	1	10	3+3	neg	0	0			
17	1	-28	3+3	8.9	3	neg	0	0		neg	0	0			
18	1	-96	neg	7.4	2	neg	0	0		neg	0	0			
19	2	-6	neg	32.7	0	neg	0	0		neg	0	0			
20	4	-34	neg	10.8	2	neg	0	0		neg	0	0			
21	1	-5	3+4	6.8	2	pos	2	60	3+4	pos	6	70	3+4	EBRT	
22	1	-33	neg	15.7	0	neg	0	0		pos	8	50	4+3	EBRT	
23	1	-7	3+3	6.4	3	neg	0	0		pos	4	60	3+4	EBRT	
24	3	-35	neg	15.1	0	neg	2	10	3+3	pos	6	95	3+4		
25	0		N/A	10.0	3	neg	2	15	3+3	neg	0	0			
26	2	-22	3+3	4.3	2	pos	1	85	3+4	neg	0	0		Prostatectomy	3+4
27	2	-38	neg	10.4	2	neg	0	0		neg	0	0			
28	4	-13	neg	9.4	2	neg	0	0		neg	0	0			
29	6	-36	neg	153.0	3	neg	1	5	3+3	pos	2	90	4+5	Systemic	
30	3	-11	neg	7.0	3	pos	1	25	3+4	pos	4	90	3+4		
31	1	-25	neg	4.6	3	neg	1	10	3+3	pos	5	50	3+4	Prostatectomy	3+4
32	1	-12	3+3	5.4	3	neg	2	20	3+3	neg	0	0			
33	2	-14	neg	23.0	3	pos	4	70	3+4	pos	3	100	4+4	Prostatectomy	4+3

34	2	-11	neg	8.5	3	neg	0	0		neg	0	0			
35	1	-5	3+4	3.0	2	neg	0	0		neg	2	20	3+3	Prostatectomy	3+4
36	1	-5	3+3	24.4	2	neg	0	0		pos	1	30	3+4	Prostatectomy	4+3

neg = negative, pos = positive, EBRT = external beam radiation treatment

Registration quality score: 0 = no registration, 1 = poor, 2 = adequate, 3 = excellent

Supplemental Table 2A

Target Characteristics by MRI Risk

MRI Risk Classification	N	Target Volume (cm^3)	SUV_{max}	SUV_{mean}	SUV_{mean} x Volume (cm^3)	SUV_{max} TBR	SUV_{mean} TBR
Low	19	0.28 ± 0.25	4.56 ± 3.0	3.47 ± 2.29	1.23 ± 1.43	1.46 ± 0.58	1.12 ± 0.44
Intermediate	18	0.38 ± 0.43	4.14 ± 1.99	2.95 ± 1.39	1.51 ± 2.32	1.59 ± 0.52	1.16 ± 0.47
High	15	0.71 ± 0.51	6.70 ± 4.03	4.05 ± 2.09	3.58 ± 3.73	2.57 ± 1.06	1.58 ± 0.49

Supplemental Table 2B

Target Characteristics by Pathology

Pathology	N	Target Volume (cm^3)	SUV_{max}	SUV_{mean}	SUV_{mean} x Volume (cm^3)	SUV_{max} TBR	SUV_{mean} TBR
Benign	30	0.29 ± 0.31	4.0 ± 2.57	2.89 ± 1.92	1.08 ± 1.69	1.41 ± 0.47	1.03 ± 0.37
Gleason 3+3	6	0.27 ± 0.16	4.76 ± 0.96	3.3 ± 0.64	0.95 ± 0.63	1.58 ± 0.34	1.1 ± 0.19
Gleason ≥ 3+4	16	0.79 ± 0.51	7.05 ± 3.86	4.57 ± 2.01	4.15 ± 3.51	2.7 ± 0.96	1.78 ± 0.41