

PSMA-Ligand Uptake Can Serve as a Novel Biomarker in Primary Prostate Cancer to Predict Outcome After Radical Prostatectomy

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Abstract

Background

The prostate-specific membrane antigen (PSMA) is a relevant target in prostate cancer and immunohistochemistry studies showed associations with outcome.

PSMA-ligand positron emission tomography (PET) is increasingly used for primary prostate cancer staging and the molecular imaging TNM classification (miTNM) standardizes its reporting. We aimed to investigate the potential of PET-imaging to serve as a noninvasive imaging biomarker to predict disease outcome in primary prostate cancer after radical prostatectomy (RP).

Methods

In this retrospective analysis, 186 primary prostate cancer patients treated with RP who had undergone a ^{68}Ga -PSMA-11 PET up to three months prior to the surgery were included. Maximum standardized uptake value (SUV_{max}), SUV_{mean} , tumor volume (TV) and total lesion (TL) were collected from PET-imaging. Moreover, clinicopathological information, including age, serum prostate-specific antigen (PSA) level, and pathological characteristics were assessed for disease outcome prediction. A stage group system for PET-imaging findings based on the miTNM framework was developed.

Results

At a median follow-up after RP of 38 months (interquartile range (IQR): 22-53), biochemical recurrence (BCR) was observed in 58 patients during the follow-up period. A significant association between a positive surgical margin and miN status (miN1 vs. miN0, odds ratio (OR): 5.428, $p=0.004$) was detected. miT status (miT \geq 3a vs. miT $<$ 3, OR: 2.696, $p=0.003$) was identified as an independent predictor for Gleason score (GS) \geq 8. Multivariate Cox regression analysis indicated that PSA level (hazard ratio (HR): 1.024, $p=0.014$), advanced GS (GS \geq 8 vs. GS $<$ 8, HR: 3.253, $p<0.001$) and miT status (miT \geq 3a vs. miT $<$ 3, HR: 1.941, $p=0.035$) were independent predictors for BCR. For stage I disease as determined by PET-imaging a shorter BCR-free survival was observed in the patients with higher SUV_{max} (IA vs. IB stage, log-rank, $p=0.022$).

Conclusion

Preoperative miTNM classification from ^{68}Ga -PSMA-11 PET correlates with postoperative GS, surgical margin status and time to BCR. The association between miTNM staging and outcome proposes ^{68}Ga -PSMA-11 PET as a novel non-invasive imaging biomarker and potentially serves for ancillary pre-treatment stratification. Prospective studies with larger cohort are necessary to fully determine its use including primary prostate cancer patients with different treatments and risk categories and late-stage patients.

Background

Approximately 30% to 40% of prostate cancer patients will fail primary treatment requiring further disease management [1, 2]. Traditional risk factors, including preoperative serum prostate-specific antigen (PSA) level [3-6], pathological stage [7] and Gleason score (GS) [5-9] are widely used for biochemical recurrence (BCR) prediction. However, there is growing interest in identifying novel biomarkers to improve BCR prediction accuracy of prostate cancer patients after radical prostatectomy (RP).

In the last few years positron emission tomography (PET) probes targeting prostate-specific membrane antigen (PSMA) has significantly improved detection and localization of disease in primary and recurrent prostate cancer [1, 10-12]. PSMA is a type II integral membrane glycoprotein with folate hydrolase activity, internalization after activation and is encoded by the FOLH1 gene [13, 14]. PSMA expression increases progressively in higher-grade prostate tumor cells and metastatic lesions [15, 16].

Increased PSMA expression in immunohistochemistry was more often observed in pathological stage III or IV tumors (51%) compared to stage I and II tumors (32%, $p=0.029$) [17]. High level PSMA expression in immunohistochemistry was associated with a higher risk of BCR and overall survival in several studies [16, 17]. Finally, expression of membranous PSMA is also associated with higher rates of defective deoxyribonucleic acid (DNA) damage repair gene [18].

In the last two decades, for different tumor entities results from imaging were introduced as non-invasive quantitative biomarkers. For fluorodeoxyglucose (FDG)-PET-imaging, Wieder et al. have demonstrated that mean standardized uptake value (SUV_{mean}) can be used to preoperatively predict histopathological response in esophageal squamous cell carcinoma (ESCC) patients. A decrease in SUV_{mean} of $44\pm 15\%$ from responders and $21\pm 14\%$ from non-responders ($p=0.0055$) was observed after radiochemotherapy [19]. For metastatic castration-resistant prostate cancer (mCRPC) the bone scan index (BSI) [20] and quantitative parameter from PET have been reported to serve as potential predictive biomarkers for bone tumor burden [21, 22].

To standardize reporting of PSMA-targeted PET-imaging a unified molecular-imaging TNM classification (miTNM, version 1.0) has been recently introduced [23]. It is envisioned that its system classifying tumor extent similar to the pathological TNM-system might serve as qualitative imaging biomarker potentially stratifying disease outcome.

The aim of our retrospective analysis was to investigate the potential of quantitative and qualitative parameters from ^{68}Ga -PSMA-11 PET to serve as non-invasive imaging biomarkers to predict BCR in primary prostate cancer after RP allowing for ancillary preoperative risk stratification.

Methods

Patient selection

We screened the institutions' database for all patients who underwent ^{68}Ga -PSMA-11 PET imaging maximum 3 months prior the RP between January 2013 and August 2017. All patients who received neoadjuvant therapy prior to RP, had PSA-persistence after RP or in whom follow-up data were missing were excluded. Finally, 186 patients with D'Amico intermediate- to high-risk primary prostate cancer were included in this retrospective study (Supplementary Fig. 1). Table 1 summarizes the clinical and histopathological characteristics. BCR was defined as a serum PSA level rising above 0.2 ng/ml. The primary endpoint was time to BCR. The time to BCR was calculated from the date of surgery. The retrospective analysis has been approved by the Ethics Committee of the Technical University Munich (750/20 S-KH).

Imaging protocol

The synthesis of ^{68}Ga -PSMA-11 [24] was described previously [25]. Patients were intravenously injected with a median of 139 MBq of ^{68}Ga -PSMA-11 (interquartile range (IQR): 112-156). PET acquisition was started at a median of 54 min (IQR: 49-65) after the tracer injection. Ninety-three patients underwent ^{68}Ga -PSMA-11 PET/computed tomography (CT) using a Biograph mCT flow scanner (Siemens Medical Solutions, Erlangen, Germany), and 93 patients underwent ^{68}Ga -PSMA-11 PET/magnetic resonance imaging (MRI) using an integrated whole-body PET/MRI system (Siemens Biograph mMR, Erlangen, Germany). Details on PET/CT and PET/MRI acquisition were described previously [26, 27].

Imaging analysis

^{68}Ga -PSMA-11 PET/CT and ^{68}Ga -PSMA-11 PET/MRI images were evaluated by one nuclear medicine physician blinded to the postoperative histopathological results. All lesions were reannotated by two experienced board-certified nuclear medicine physicians. Any focal or diffuse tracer uptake in the prostate or extra-prostatic lesions above the surrounding background and not associated with physiological uptake was considered suspicious for malignancy. One circular region in transaxial slices was drawn over the prostate and over every extra-prostatic lesion automatically adapted to a three-dimensional volume of interest (VOI) using Syngo.Via (Siemens Healthineers, Erlangen, Germany) at 40% isocontour. Typical pitfalls in PSMA-ligand PET including low to moderate PSMA uptake correlated with osteoblastic changes (i.e., fractures or degenerative changes), celiac, and ganglia were taken into consideration [28]. SUV_{max} , SUV_{mean} , tumor volume (TV), and total lesion (TL) of every VOI were calculated. Prostatic and extra-prostatic lesions were classified according to miTNM classification [23].

Similar to the structure of the American Joint Committee on Cancer (AJCC) Prostate Cancer Prognostic Stage Groups [29], we established a stage group system using the different grades from the miTNM staging system (Table 2). To allow the discrimination into different risk groups based on the characteristics of the primary tumor, we used a SUV_{max} cut-off of 5.4 to subgroup stage I disease into stage IA and IB. The cut-off was derived from a recent study proposing it the optimal cut-off to distinguish between $\text{GS} \leq 7a$ and $\text{GS} \geq 7b$ [30].

Table 2. Proposed miTNM stage groups for ⁶⁸Ga-PSMA-11 PET.

Stage Group	miT	miN	miM	SUV _{max}
IA	2	0	0	< 5.4
IB	2	0	0	≥ 5.4
IIA	3	0	0	Any
IIB	4	0	0	Any
III	Any	1 and 2	0	Any
IV	Any	Any	1	Any

PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SUV = standardized uptake value.

Statistical analysis

Descriptive statistics were used to display continuous variables as the median and IQR with 25th and 75th percentiles (Q1-Q3), mean ± standard deviation (SD), as well as percentages. The association between pathological results and ⁶⁸Ga-PSMA-11 PET findings was investigated with uni- and multivariate Logistic regression analyses, and the corresponding odds ratios (OR) and 95% confidence intervals (CI) were calculated. Postoperative BCR-free survival was estimated using the Kaplan-Meier method and compared between groups using the Log-rank test. Moreover, uni- and multivariable Cox regression analysis were performed to determine the ability of clinicopathological factors and ⁶⁸Ga-PSMA-11 PET findings to predict BCR after RP, and the corresponding hazard ratios (HR) and 95% CI were calculated. The multivariable model only included parameters with a significant association on univariable analysis. A *p*-value of 0.05 was used as the cut-off for statistical significance.

Given its low sample size (n=7) the miM1 subgroup was excluded for univariable and multivariable analysis.

Statistical evaluation was performed with IBM SPSS Statistics Version 20 (Armonk, NY, USA), and the figures were generated using GraphPad Prism Version 8 (San Diego, California, USA).

Results

Histopathological patient characteristics

On post-operative histopathology, a total of 133 (71.5%) patients had a GS<8, and 53 (28.5%) of the patients had a GS 8 or 9. Lymph node metastases were detected in 32 (17.2%) patients. pT3a, pT3b and pT4 disease was present in 49 (26.3%), 44 (23.7%) and 1 (0.5%) patient, respectively. Twenty-eight

(15.6%) patients had positive surgical margins (R1) (Table 1). At a median follow-up of 38 months (IQR: 22-53), BCR was observed in 58 (31.2%) patients during the follow-up period.

Table 1. Patient characteristics.

Characteristic	Patients
Age (yr), median (IQR), n=186	68 (61-72)
iPSA (ng/ml), median (IQR), n=184 ^a	9.7 (6.5-15.1)
Administered ⁶⁸ Ga-PSMA-11 activity (MBq), median (IQR), n=185 ^b	139 (112-156)
Time PET to RP (day), median (IQR), n=186	26 (13-46)
Gleason score in surgical specimen, no. (%), n=186	
6	11 (5.9%)
7a	63 (33.9%)
7b	59 (31.7%)
8	28 (15.1%)
9	25 (13.4%)
Pathological stage, no. (%), n=186	
pT status	
2a	11 (5.9%)
2b	10 (5.4%)
2c	71 (38.2%)
3a	49 (26.3%)
3b	44 (23.7%)
4	1 (0.5%)
pN status	
0	154 (82.8%)
1	32 (17.2%)
Surgical margin, no. (%), n=180 ^c	
Negative	152 (84.4%)
Positive	28 (15.6%)

^a: iPSA of two patients were unavailable; ^b: the injected dose of ⁶⁸Ga-PSMA-11 from one patient was unavailable; ^c: the status of surgical margin from six patients were unavailable.

iPSA = initial PSA; IQR = interquartile range; PET = positron emission tomography; PSA = prostate-specific antigen; RP = radical prostatectomy.

⁶⁸Ga-PSMA-11 PET findings

A. miTNM staging and miTNM stage groups

In 67.2% (n=125) of patients the primary tumor was classified as miT2, 90.3% (n=168) were classified as miN0, 3.8% (n=7) were classified as miN1, 5.9% (n=11) were classified as miN2, and 96.2% (n=179) were classified as miM0. ⁶⁸Ga-PSMA-11 PET findings (SUV_{max}, SUV_{mean}, TV, TL) of prostatic lesions were analyzed with 183 patients because three patients were reported negative PSMA prostate cancer. Table 3 lists information from ⁶⁸Ga-PSMA-11 PET.

Table 3. ⁶⁸Ga-PSMA-11 PET findings.

Characteristic	Patients
miTNM classification, no. (%), n = 186	
miT status	
2u	73 (39.2%)
2m	52 (28%)
3a	27 (14.5%)
3b	24 (12.9%)
4	10 (5.4%)
miN status	
0	168 (90.3%)
1	7 (3.8%)
2	11 (5.9%)
miM status	
0	179 (96.2%)
1a	3 (1.6%)
1b	4 (2.2%)
PSMA-PET findings of prostatic lesions, median (IQR), n = 183 ^a	
SUV _{max}	10.6 (6.4-18.9)
SUV _{mean}	6.2 (3.2-11.0)
TV	3.9 (1.7-10.5)
TL	24.7 (15.9-44.4)

^a: three patients had PSMA negative prostate cancer. miTNM of these patients were classified based on MRI images.

IQR = interquartile range; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SUV = standardized uptake value; TL = total lesion; TV = tumor volume.

Based on the proposed stage group system combining the miTNM staging by and SUV_{max} of 20 (10.8%), 96 (51.6%), 40 (21.5%), 7 (3.8%), 16 (8.6%) and 7 (3.8%) into the stage groups IA, IB, IIA, IIB, III and IV, respectively.

B. Correlation of ⁶⁸Ga-PSMA-11 PET parameters with histopathology

The sensitivity and specificity of ⁶⁸Ga-PSMA-11 PET detecting pelvic lymph nodes metastasis were 40.6% and 96.8% (13/32 and 149/154, respectively). Of 94 pT \geq 3a prostatic lesions, 45.7% (n=43) were detected (miT \geq 3a) by ⁶⁸Ga-PSMA-11 PET. 80.4% (n=74) of pT2 prostatic lesions were correctly classified as miT2. Cross tables are presented in Supplementary Table 1 and Table 2.

In the univariate analysis (Supplementary Table 3) a significant association was detected between a positive surgical margin and the following parameters: high miT status (miT \geq 3a, OR: 3.38, $p=0.004$), miN1 status (OR: 7.526, $p<0.001$), SUV_{max} (OR: 1.026, $p=0.039$) and TL (OR: 1.007, $p=0.021$). In the multivariate analysis (Table 4), miN1 (OR: 5.428, $p=0.004$) was significantly associated with a positive surgical margin. Moreover, a significant association was present between miT \geq 3a and GS \geq 8 (OR: 2.696, $p=0.003$) (Table 5).

Table 4. Multivariate analysis for the association of ⁶⁸Ga-PSMA-11 PET findings with surgical margin status.

	No. of patients	Odds ratio	95% CI	p value*
miTNM classification, no., n = 186				
miT status				
2	125	Reference		
\geq 3a	61	2.065	0.802-5.315	0.133
miN status				
No LN metastasis	168	Reference		
With LN metastasis	18	5.428	1.708-17.249	0.004
SUV _{max} of prostatic lesions	183	1.015	0.988-1.044	0.282
TL of prostatic lesions	183	1.004	0.998-1.011	0.166

*Significant associations are given in bold.

CI = confidence interval; LN = lymph node; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SUV = standardized uptake value; TL = total lesion; TV = tumor volume.

Table 5. Univariate analysis for the association of ⁶⁸Ga-PSMA-11 PET findings with Gleason Score.

	No. of patients	Odds ratio	95% CI	<i>p</i> value*
miTNM classification, no., n = 186				
miT status				
2	125	Reference		
≥ 3a	61	2.696	1.39-5.23	0.003
miN status				
No LN metastasis	168	Reference		
With LN metastasis	18	2.187	0.812-5.887	0.122
SUV _{mean} of prostatic lesions	183	1.020	0.986-1.056	0.248
SUV _{max} of prostatic lesions	183	1.017	0.995-1.040	0.138
TV of prostatic lesions	183	0.981	0.941-1.022	0.353
TL of prostatic lesions	183	1.006	1-1.012	0.056

*Significant associations are given in bold.

CI = confidence interval; LN = lymph node; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; SUV = standardized uptake value; TL = total lesion; TV = tumor volume.

Predictors of BCR-free survival

Kaplan-Meier curves for BCR-free survival with different clinicopathological and miTNM-derived parameters are shown in Fig.1-3 and Supplementary Fig.2.

The miTNM derived parameters miT2 vs. miT3 disease or higher (log-rank, $p < 0.001$, Fig. 2A), miN0 vs. miN1/2 (log-rank, $p = 0.005$, Fig. 2B) and miTNM stage group IA compared with miTNM stage group IB (log-rank, $p = 0.022$, Fig. 1) were associated with significantly different BCR-free survival rate. Lower SUV_{mean} and SUV_{max} as quantitative parameters from ⁶⁸Ga-PSMA-11 PET were also associated with longer BCR-free in patients (Fig. 3C and 3D, log-rank, $p = 0.035$, $p = 0.037$, respectively).

The following pathological features were associated with longer BCR-free survival: pT2 vs. ≥pT3a (log-rank, $p < 0.001$, Supplementary Fig. 2A). pN0 vs. pN1 (log-rank, $p < 0.001$, Supplementary Fig. 2B), lower Gleason Grades (GS < 8) (log-rank, $p < 0.001$, Supplementary Fig. 2C) and negative surgical margins (log-rank, $p < 0.001$, Supplementary Fig. 2D).

Results from a univariate Cox regression analysis investigating preoperative and postoperative risk factors for BCR is presented in Table 6. We found that following factors were significantly associated

with BCR-free survival in prostate cancer patients: clinical data including age (HR: 1.056, 95% CI: 1.018-1.096, $p=0.004$) and initial PSA (iPSA) (HR: 1.021, 95% CI: 1.007-1.035, $p=0.003$); pathological data including Gleason score (GS \geq 8 vs. GS $<$ 8, HR: 5.097, 95% CI: 3.013-8.625, $p<0.001$), pT stage (pT \geq 3 vs. pT $<$ 3, HR: 2.935, 95% CI: 1.665-5.173, $p<0.001$), pN stage (pN1 vs. pN0, HR: 3.378, 95% CI: 1.901-6, $p<0.001$) and surgical margin (positive vs. negative, HR: 3.421, 95% CI: 1.890-6.193, $p<0.001$). Imaging parameters including miT stage (miT \geq 3a vs. miT $<$ 3, HR: 2.811, 95% CI: 1.673-4.722, $p<0.001$), miN stage (miN1 vs. miN0, HR: 2.691, 95% CI: 1.311-5.527, $p=0.007$), SUV_{mean} of prostatic lesions (HR: 1.019, 95% CI: 1.002-1.036, $p=0.028$), SUV_{max} of prostatic lesions (HR: 1.015, 95% CI: 1.004-1.026, $p=0.008$) and TV of prostatic lesions (HR: 0.948, 95% CI: 0.909-0.988, $p=0.011$).

Table 6. Univariable analysis for the association of baseline factors with BCR-free survival.

	No. of patients	Hazard ratio	95% CI	<i>p</i> value*
Clinical data				
Age	186	1.056	1.018-1.096	0.004
iPSA	184	1.021	1.007-1.035	0.003
Pathological data				
Gleason score in surgical specimen, no., n = 186				
6-7	133	Reference		
8-10	53	5.097	3.013-8.625	< 0.001
Pathological stage, no., n = 186				
pT status				
2	92	Reference		
≥3	94	2.935	1.665-5.173	< 0.001
pN status				
0	154	Reference		
1	32	3.378	1.901-6.000	< 0.001
Surgical margin, no., n = 180				
Negative	152	Reference		
Positive	28	3.421	1.890-6.193	< 0.001
Imaging parameters				
miTNM classification, no., n = 186				
miT status				
2	125	Reference		
≥ 3a	61	2.811	1.673-4.722	< 0.001
miN status				
No LN metastasis	168	Reference		
With LN metastasis	18	2.691	1.311-5.527	0.007
SUV _{mean} of prostatic lesions	183	1.019	1.002-1.036	0.028
SUV _{mean} of prostatic lesions, no. n = 183				

< median	91	Reference		
≥ median	92	1.752	1.030-2.981	0.039
SUV _{max} of prostatic lesions	183	1.015	1.004-1.026	0.008
SUV _{max} of prostatic lesions, no. n = 183				
< median	91	Reference		
≥ median	92	1.744	1.025-2.968	0.040
TV of prostatic lesions	183	0.948	0.909-0.988	0.011
TV of prostatic lesions, no., n = 183				
< median	91	Reference		
≥ median	92	0.987	0.587-1.661	0.962
TL of prostatic lesions	183	1.003	1.000-1.006	0.072
TL of prostatic lesions, no., n = 183				
< median	91	Reference		
≥ median	92	0.957	0.568-1.612	0.869

*Significant associations are given in bold.

BCR = biochemical recurrence; CI = confidence interval; iPSA = initial PSA; IQR = interquartile range; LN = lymph node; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SUV = standardized uptake value; TL = total lesion; TV = tumor volume.

In the multivariate Cox regression analysis (Table 7) the following factors were independent predictors for BCR-free survival: serum PSA level (HR: 1.024, 95% CI: 1.005-1.043, $p=0.014$), advanced pathological Gleason Score (GS \geq 8 vs. GS $<$ 8, HR: 3.253, 95% CI: 1.779-5.950; $p<0.001$) and miT stage (miT \geq 3a vs. miT $<$ 3, HR: 1.941, 95% CI: 1.047-3.599, $p=0.035$).

Table 7. Multivariable analysis for the association of baseline factors with BCR-free survival.

	No. of patients	Hazard ratio	95% CI	<i>p</i> value*
Clinical data				
Age, no., n = 186				
Continuous		1.030	0.991-1.071	0.133
iPSA, no., n = 184				
Continuous		1.024	1.005-1.043	0.014
Pathological data				
Gleason score in surgical specimen, no., n = 186				
6-7	133	Reference		
8-10	53	3.253	1.779-5.950	< 0.001
pT status, no., n = 186				
2	92	Reference		
3	94	1.471	0.773-2.797	0.239
pN status, no., n = 186				
No LN metastasis	154	Reference		
With LN metastasis	32	1.027	0.418-2.525	0.954
Surgical margin, no., n = 180				
Negative	152	Reference		
Positive	28	1.539	0.716-3.305	0.269
Imaging parameters				
miT status from PSMA PET, no., n = 186				
2	125	Reference		
≥ 3a	61	1.941	1.047-3.599	0.035
miN status from PSMA PET, no., n = 186				
No LN metastasis	168	Reference		
With LN metastasis	18	1.233	0.389-3.908	0.722
SUV _{mean} , no., n = 183				
Continuous		0.743	0.491-1.123	0.159

SUV _{max} , no., n = 183			
Continuous	1.202	0.943-1.532	0.137
TV			
Continuous	0.934	0.883-0.988	0.017

* Significant associations are given in bold.

BCR = biochemical recurrence; CI = confidence interval; iPSA = initial PSA; LN = lymph node; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SUV = standardized uptake value; TV = tumor volume.

Discussion

Prognostic tools of BCR are required and essential for improving treatment management of prostate cancer patients and reducing prostate cancer-associated mortality of patients developing BCR after primary treatment [31]. With the successful application of PSMA-ligand PET for primary staging in prostate cancer patients, clinical studies are necessary to investigate its predictive value. PSMA-ligand PET is increasingly used for selection, monitoring and individualization of prostate cancer treatments.

The present analysis is the first to investigate the association of miTNM classification from preoperative ⁶⁸Ga-PSMA-11 PET imaging and postoperative histopathological findings and the potential of miTNM reporting to serve as predictors for BCR after RP. Consequently, we performed a prognostic validation of the miTNM system as a framework for PSMA-ligand PET reporting in a relatively large patient cohort. Preoperative ⁶⁸Ga-PSMA-11 PET and miTNM classification could help to stratify risk for BCR after RP and could potentially further influence the clinical patient management.

Previous studies have extensively assessed the predictors of BCR. Clinicopathological characteristics, including pathological aggressive GS [5-9], positive nerve invasion [8], pathological T stage [7] and preoperative PSA [3-6] were proven to have a strong association with BCR. Our present results are in accordance with literature data. The data from our analysis outline serum PSA level (HR: 1.024, 95% CI: 1.005-1.043, $p=0.014$) and advanced pathological Gleason score (GS \geq 8 vs. GS<8, HR: 3.253, 95% CI: 1.779-5.950; $p<0.001$) as important histopathological predictors of BCR.

In addition, and novel compared to the current literature our data indicate that also parameters from ⁶⁸Ga-PSMA-11 PET might serve as non-invasive biomarkers. We identified a miT stage \geq 3a in ⁶⁸Ga-PSMA-11 PET as surrogate for higher GS (OR: 2.696, 95% CI: 1.39-5.23, $p=0.003$) and worse BCR-free survival (HR: 1.941, 95% CI: 1.047-3.599, $p=0.035$). Notably, pelvic lymph node metastases in ⁶⁸Ga-PSMA-11 PET were not detected as an independent predictor for BCR in this study (HR: 1.233, 95% CI: 0.389-3.908, $p=0.722$). However, the BCR-free survival differed significantly between miN0 and miN1 group (log-rank, $p=0.005$). Interestingly also Raheem et al. have failed to detect lymph nodes in histopathology as an independent

predictor to BCR after RP in a study including 359 patients [4]. Of note, the sample size of miN1 group (n=18) in our cohort was relatively small. Thus, the interpretation of results should be with caution, and further studies including more miN1 patients are needed to clarify the predictive value of miN classification for BCR after RP.

Besides, our results indicate a negative association of TV with BCR-free survival (HR: 0.934, 95% CI: 0.883-0.988, $p=0.017$). Contrarily, Choi et al. have reported a significantly higher BCR-free survival rate in pT2 prostate cancer patients with percent tumor volume $\leq 7.5\%$, which was assessed using histological samples ($p<0.001$) [32]. This is partly related to the methods of obtaining tumor volume and studies are necessary to assess the standard of TV calculation from ^{68}Ga -PSMA-11 PET and pathological samples.

With this work we also introduced a stage grading system based on the recent proposed molecular staging system (miTNM staging system, version 1.0) combined with quantitative parameters. It is intended to mirror the AJCC staging system based on clinicopathological parameters which has proven to be a fundamental tool that also informs treatment decisions [33]. Bhindi et al. has confirmed the ability of the 8th edition to predict oncologic outcomes [34]. However, the AJCC staging system utilized clinical or pathological TNM stage and no parameters from imaging. With the increasing use of PSMA-ligand PET in clinical routine, a logical next step is to use information from non-invasive imaging prior to definite treatment for risk stratification.

We have shown that the miT stage is an independent predictor of BCR, and we observed a widely varying prognosis in the miT2 stage patients. Similarly, a recent study has revealed that high intraprostatic ^{68}Ga -PSMA-11 uptake ($\text{SUV}_{\text{max}}>8$) predicts short progression-free survival rate among patients with GS 3+4 on biopsy [35]. The significant difference in BCR-free survival rate has been confirmed in IA and IB stage groups. Our findings propose that a SUV_{max} cut-off extracted from literature could further stratify the group of miT2 primary disease into patients with more aggressive disease and worse prognosis. Further studies are necessary for prognostic validation of other stage groups.

The present study has several limitations. It is a retrospective analysis and includes only patients from a single center, which can introduce potential bias. Despite inclusions of a large number of patients the sample size of patients in the miM1 group was too small to conduct meaningful analysis. This is mainly related to the fact that most patients with extrapelvic metastases do not undergo primary curative RP but either get systemic treatment with or without local treatment. This explains the low number of patients in miTNM stage group III and IV. In summary, further prospective investigations with large patient numbers are necessary to fully investigate the potential of the miTNM staging and our proposed grading system to predict patient outcome after curative intent RP.

Conclusion

Our retrospective analysis indicates that the miTNM framework developed to standardize PSMA-ligand PET reported is independently associated with BCR-free survival of primary prostate cancer after RP. We

demonstrated significant associations between ^{68}Ga -PSMA-11 PET findings and histopathological parameters. In summary, our results outline that the miTNM classification and the presented further development of a miTNM based stage group system can serve as non-invasive imaging biomarkers of risk stratification for primary prostate cancer patients. However, further and prospective studies including patients with different treatments and stages are needed to fully assess the predictive value of PSMA-ligand PET imaging in the setting of newly diagnosed prostate cancer.

Abbreviations

^{68}Ga : Gallium-68; AJCC: American Joint Committee on Cancer; BCR: biochemical recurrence; BSI: bone scan index; CI: confidence interval; CT: computed tomography; DNA: deoxyribonucleic acid; ESCC: esophageal squamous cell carcinoma; FDG: fluorodeoxyglucose; GS: Gleason score; HR: hazard ratio; iPSA: initial PSA; IQR: interquartile range; mCRPC: metastatic castration-resistant prostate cancer; miTNM: imaging TNM classification; MRI: magnetic resonance imaging; OR: odds ratio; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen; RP: radical prostatectomy; SD: standard deviation; SUV: standardized uptake value; TL: total lesion; TV: tumor volume; VOI: volume of interest.

Declarations

Ethics approval and informed consent

All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki. This retrospective study has been approved by the Ethics Committee of the Technical University Munich (750/20 S-KH).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on a reasonable request

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HW was involved in study design, data acquisition, methodology and manuscript writing. TA was involved in data acquisition. CW supported statistical analysis. TL, KS, IR, TH, TM, KK, HJW, WW supported the data collection and revised the manuscript. ME was involved in study design, data acquisition and critical manuscript revising. All authors read and approved the final manuscript.

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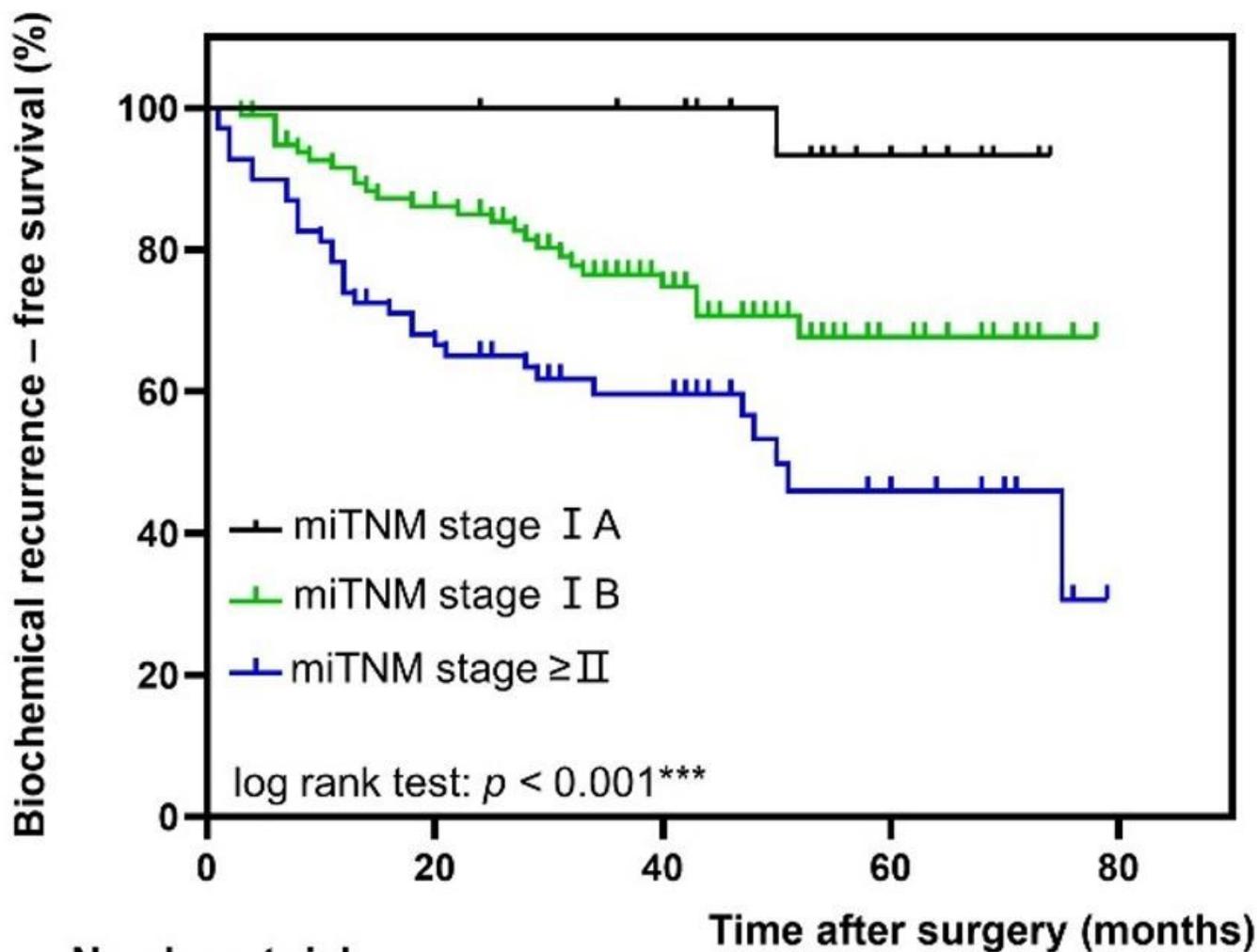
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Figures



Number at risk

miTNM stage I A

20 20 19 9 0

miTNM stage I B

97 79 47 15 0

miTNM stage \geq II

69 46 29 9 0

Figure 1

Biochemical recurrence-free survival according to miTNM stage. Pairwise comparison: miTNM stage IA vs. miTNM stage IB, $p=0.022$; miTNM stage IA vs. miTNM stage \geq II, $p=0.001$; miTNM stage IB vs. miTNM stage \geq II, $p=0.005$.

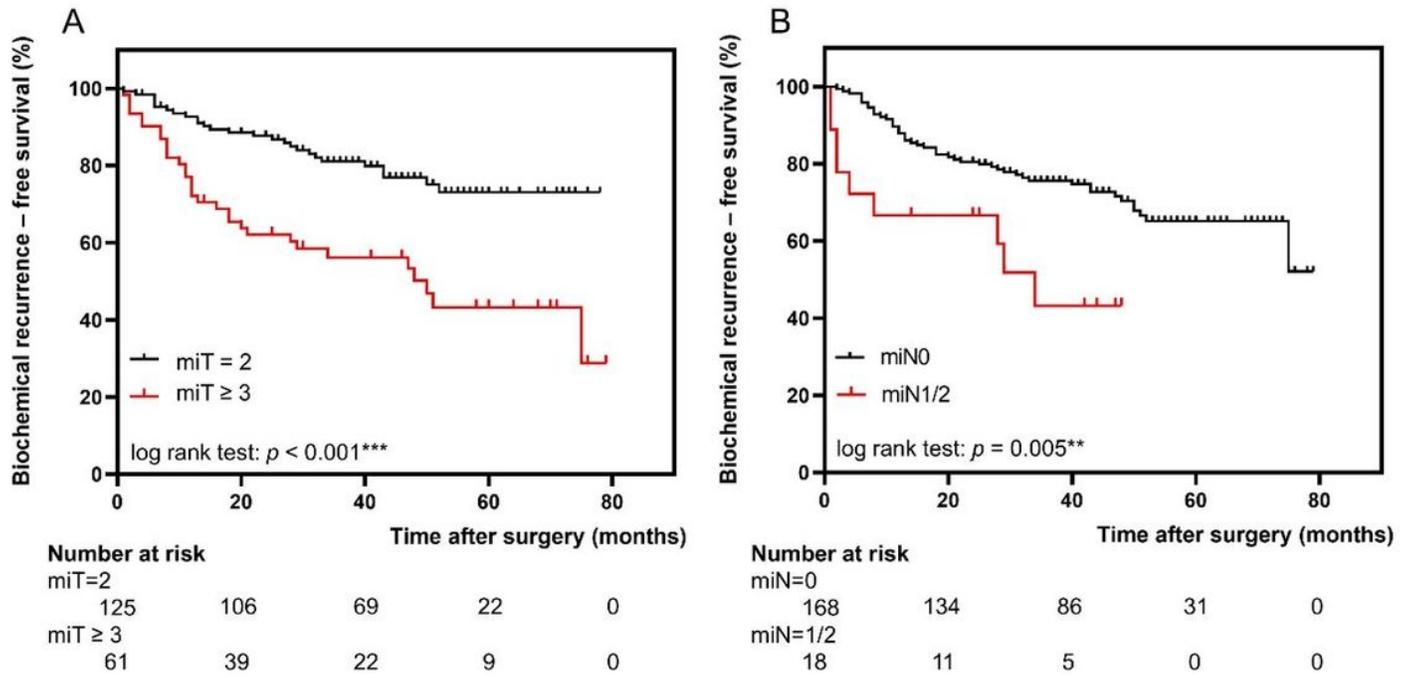


Figure 2

Longer biochemical recurrence-free survival was associated with (A) miT=2 and (B) miN=0.

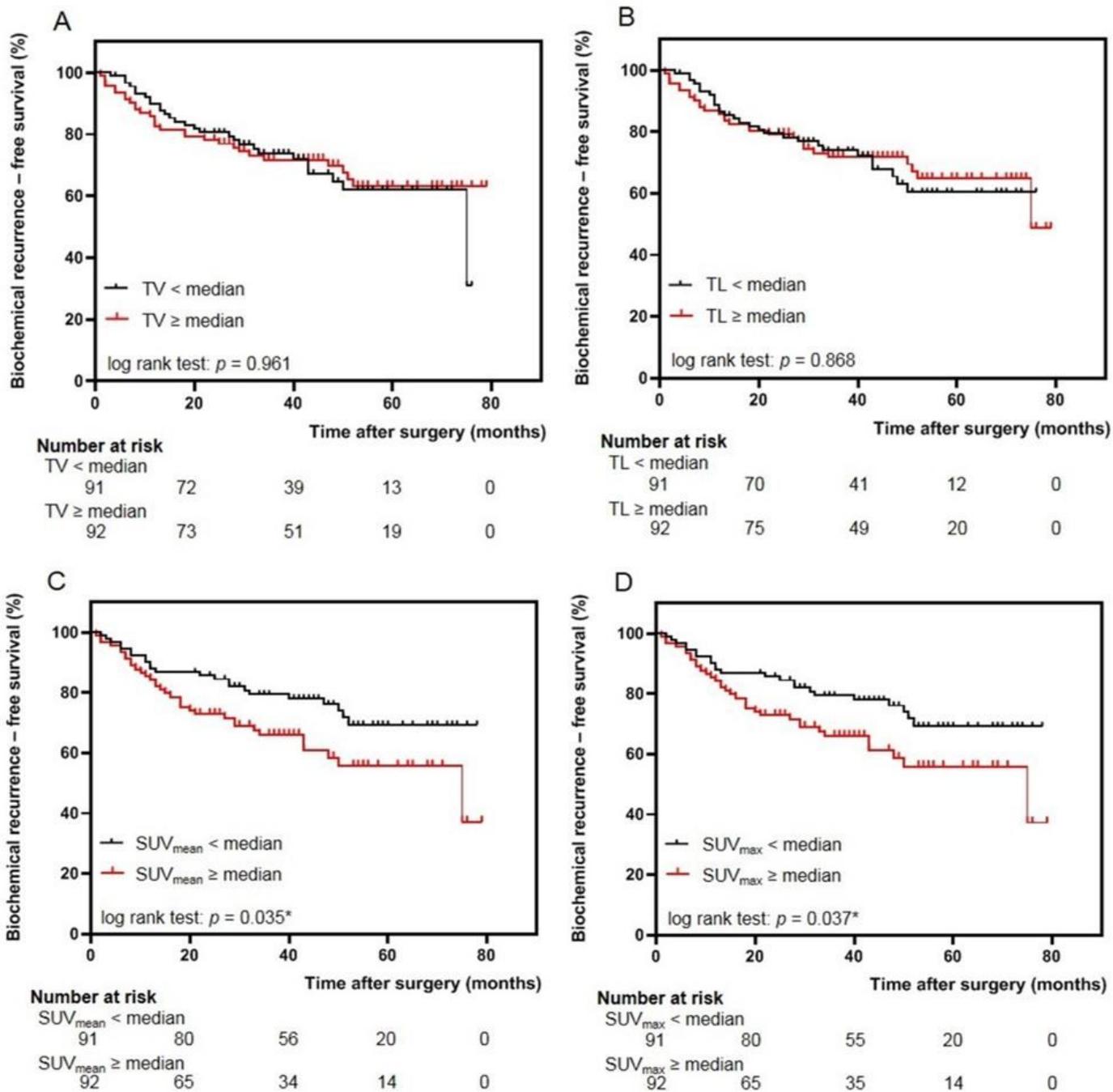


Figure 3

Kaplan-Meier curves comparing biochemical recurrence-free survival of selected patients stratified by (A) tumor volume, (B) total lesion, (C) SUVmean and (D) SUVmax. Longer biochemical recurrence-free survival was associated with lower SUVmean and SUVmax.

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