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^{68}Ga-PSMA PET/CT for primary NM staging of high-risk prostate cancer

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Short Running Title

^{68}Ga-PSMA for staging in prostate cancer

ABSTRACT

With the largest high-risk prostate cancer (PCa) cohort to date undergoing ^{68}Ga-prostate-specific membrane antigen (PSMA) PET/CT primary staging, we aimed to 1) characterize the metastatic spread of PCa in relation to tumor ^{68}Ga-PSMA-uptake and the D'Amico classification, and 2) compare ^{68}Ga-PSMA PET/CT findings with radical prostatectomy (RP) with pelvic lymph node dissection (PLND) histopathology.

Methods

A total of 691 consecutive newly diagnosed, biopsy-proven, treatment-naïve, D'Amico high-risk PCa patients primary staged by ^{68}Ga-PSMA PET/CT were included. PSMA maximum standardized uptake value (SUV_{max}) and metastatic findings were compared to PSA level, International Society of Urologic Pathology (ISUP) grade, and clinical stage as traditional risk stratification parameters. Moreover, ^{68}Ga-PSMA PET/CT findings were compared with histology in RP patients undergoing PLND. Undetected lymph node metastases (LNMs) underwent immunohistochemical PSMA staining.

Results

Advanced disease (N1/M1) was observed in 35.3% of patients (244/691) and was associated with increasing PSA levels, ISUP grades, and clinical stages. LNMs (N1/M1a) were detected in 31.4% (217/691) and bone metastases (M1b) in 16.8% (116/691). Advanced disease frequencies in patients with ISUP grade 2 and 3 were 10.8% (11/102) and 37.1% (33/89), respectively. Risk of advanced disease for cT2a/cT2b/cT2c tumors were almost equal (24.2%, 27.9%, and 22.4%, respectively). We observed a weak correlation between SUV_{max} and biopsy ISUP grade ($\rho = 0.21$; $P < 0.001$) and a modest correlation between SUV_{max} and post-prostatectomy ISUP grade ($\rho = 0.38$; $P < 0.001$). Sensitivity, specificity, positive and negative predictive value, and accuracy for LNMs detection on ^{68}Ga-PSMA PET/CT in the PLND cohort were 30.6%, 96.5%, 68.8%, 84.5%, and 83.1%, respectively. Undetected LNMs were either micrometastases located in the lymph node border or without PSMA expression.

Conclusion

In this high-risk PCa cohort, we identified advanced disease in about one-third at diagnosis. ISUP grade was the superior predictor for advanced disease at diagnosis. We found a significant difference in frequency of advanced disease between ISUP grade 2 and 3, which supports the Gleason Score 7 subdivision. Interestingly, we observed no significant differences in risk of advanced disease when comparing the different cT2 stages. The undetected LNMs were either PSMA-negative or micrometastases.

Key Words

Prostate Cancer, ^{68}Ga-Prostate-Specific Membrane Antigen PET/CT, ^{68}Ga-PSMA, primary staging, high-risk

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the fifth leading cause of cancer death among men worldwide (*1*). Accurate primary staging is one of the most important issues for clinical management of PCa patients (*2*). Prostate-specific membrane antigen (PSMA) is a promising target for personalized medicine in PCa. PSMA is a type II transmembrane glycoprotein upregulated in almost all PCa cells (97.6%) compared with its sparse distribution in benign prostate tissue (*3*). Thus, PSMA is a very attractive target for imaging and therapy with radionuclides (*4*). ^{68}Ga-PSMA PET/CT has been demonstrated to outperform conventional imaging modalities for detection of metastasis and recurrent disease (*5*,*6*). Detection of biochemical recurrence is the focus of most studies with ^{68}Ga-PSMA PET/CT (*7*), and the advantage of ^{68}Ga-PSMA PET/CT is especially evident in patients with low prostate-specific antigen (PSA) levels (<1 ng/mL) (*8*). However, ^{68}Ga-PSMA PET/CT is increasingly used for primary staging of intermediate- and high-risk PCa (*6*). In a recent review by Koschel et al. (*9*), eleven studies using ^{68}Ga-PSMA PET/CT for primary staging were included; only a single study, by Yaxley et al. (*10*) with 1253 patients including 597 high-risk, have achieved a cohort of over 200 men.

^{68}Ga-PSMA PET/CT has been used in clinical routine in PCa patients at our department since April 2016 with a high proportion of primary staging. The aim of the present, retrospective study was to characterize the metastatic spread of PCa on ^{68}Ga-PSMA PET/CT for primary staging of high-risk PCa in relation to tumor ^{68}Ga-PSMA-uptake and the D'Amico classification. Additionally, a correlative analysis of ^{68}Ga-PSMA PET/CT findings with histopathology was performed in the subgroup of patients undergoing radical prostatectomy (RP) with pelvic lymph node dissection (PLND). Finally, we described undetected lymph nodes (LNs) through immunohistochemical PSMA staining.

MATERIALS AND METHODS

Patient Population

A total of 1101 ^{68}Ga-PSMA PET/CT scans were performed at the Department of Nuclear Medicine and PET-Centre, Aarhus University Hospital, Denmark between April 2016 and March 2019. Inclusion criteria were newly diagnosed, biopsy-proven, treatment-naïve, high-risk (D'Amico classification (*11*)) PCa patients referred for primary ^{68}Ga-PSMA PET/CT staging. All 691 high-risk patients were included (Fig. 1). ^{68}Ga-PSMA PET/CT scans with extraprostatic

extension or metastasis were discussed at multidisciplinary team conferences with board-certified oncologists, radiologists, urologists, pathologists, and nuclear medicine physicians. PSA levels and clinical stages based on digital rectal examination (DRE) were available for all men. International Society of Urological Pathology (ISUP) grade group (*12*) evaluation of biopsies was available for 99.9% of patients (690/691). A total of 247 patients underwent RP with 177 patients having a PLND within the standard template of resection according to the European Association of Urology (*13*). Seventy patients did not undergo PLND as they had low preoperative risk of LN involvement (< 7%) assessed by Briganti nomogram (*14*). The number of LNs resected and the number of malignant LNs on histopathologic examinations were available in all 177 patients. ^{68}Ga-PSMA PET/CT findings were compared with histopathological findings. Pathology reports were gathered through medical records. The Central Denmark Region Committees on Health Research Ethics approved this retrospective study and the requirement to obtain informed consent was waived.

^{68}Ga-PSMA PET/CT

All ^{68}Ga-PSMA PET/CT scans were performed approximately 60 minutes following intravenous injection of 2.14 MBq ^{68}Ga-PSMA (^{68}Ga-Glu-CO-Lys(Ahx)-HBED-CC) per kilogram body weight with low-dose CT for anatomical localization and attenuation correction. All patients were scanned on a Siemens Biograph TruePoint PET/CT scanner (Siemens, Erlangen, Germany). Images were reconstructed with all available corrections applied (attenuation, scatter and Point-Spread Function) using the TrueX reconstruction algorithm (4 iterations and 21 subsets) and a 3 mm Gaussian post-filter (XYZ) and voxel size 2 x 2 x 2 mm.

Image Analysis

All PET/CT scans were analyzed by experienced, board certified specialists in nuclear medicine, knowing common pitfalls in ^{68}Ga-PSMA PET/CT (*15*). Image analysis was performed using Hybrid Viewer (HERMES Medical Solutions AB, Stockholm, Sweden). Images were interpreted according to the PSMA-RADS Version 1.0-criteria (*16*). Maximum standardized uptake values (SUV_{max}) were measured in primary prostate tumors. Primary tumors were considered ^{68}Ga-PSMA-uptake avid upon visual evaluation without pre-defined SUV threshold. Regional, ^{68}Ga-PSMA-uptaking pelvic lymph node metastases (LNMs) below the common iliac artery bifurcation were considered positive as N1 disease according to the PROMISE-criteria (*17*). Similarly, non-regional ^{68}Ga-PSMA-uptaking LNMs above the common iliac artery bifurcation were considered positive as M1a disease (extrapelvic). PSMA-avid lesions proposing bone

metastases (BMs) were reported as M1b disease. Lastly, lesions suggesting visceral metastases were considered as M1c disease. The number of metastases were recorded along with SUV_{max} for each lesion. Advanced disease was defined as having at least one extraprostatic PSMA-positive lesion (N1/M1 disease).

Immunohistochemical PSMA Staining

Fourteen formalin-fixed, paraffin-embedded tissue sections (primary tumors and LNs from RP procedures) 4.0 µm thick were used for immunohistochemical staining with monoclonal anti-PSMA (Dako, Agilent Technologies, California, United States), dilution 1:50. Antigen retrieval was done by using heat-induced epitope retrieval at pH 8.5 with Cell Conditioner 1 followed by primary antibody incubation. Sections were counterstained with hematoxylin and bluing reagent.**Data Analysis**

All variables were summarized using descriptive statistics; values without normal distribution were described as median (range) with log-transformation with 95% confidence intervals (0.95 CI) in analyses. Univariate and multivariate logistic regression analyses provided odds ratios (ORs). Sensitivity, specificity, positive and negative predictive value, and accuracy were calculated according to standard definitions. Names of utilized statistical tests are provided in the results section. *P* values < 0.05 were considered statistically significant.

RESULTS

SUV_{max} Measurements

Patient characteristics are summarized in Table 1. Focal PSMA-uptake in the prostate was observed in 97.3% of men (672/691) while 2.7% of men (19/691) had negligible ^{68}Ga-PSMA activity in the primary tumor by visual evaluation. Histopathological assessment of biopsies from patients with negligible PSMA-uptake revealed adenocarcinomas with no phenotypic deviations from the PSMA-positive patients. Likewise, PSA levels, ISUP grades, and clinical stages parameters matched those of PSMA-positive disease. Correlations between SUV_{max} and biopsy ISUP grades and post-prostatectomy ISUP grades are provided in Figure 2A and 2B, respectively. Area under the receiver operating characteristic curve for SUV_{max} to predict ISUP grade ≤2 or >2 in biopsies was 0.65 (0.95 CI: 0.56, 0.74). With an optimal cut-off of SUV_{max} of 11.4, the sensitivity and specificity were 51.2% and 77.4%, respectively. Primary tumor SUV_{max} was significantly higher in patients with at least one PSMA-positive metastatic lesion compared to patients with localized disease only with a median ratio of 1.62 (0.95 CI: 1.47, 1.80) (Fig. 2C). Median SUV_{max} values with 0.95 CI for primary

tumors in relation to ISUP grades and advanced disease are provided in Table 2. SUV_{max} and PSA values were moderately positively correlated (Fig. 2D). Median SUV_{max} values for primary tumors and different metastatic sites are accessible in Table 3. A relatively uniform PSMA-uptake across different tissues was observed with lower uptake in visceral metastases as the only exception.

Advanced Disease

Advanced disease was observed in 35.3% of patients (244/691) and increased greatly with increasing PSA levels, ISUP grades as well as clinical stages (Figs. 3A, 4A, and 5). ORs (univariate and multivariate logistic regression) of the increasing risk of advanced disease per increase in measurement (PSA level, ISUP grade, and clinical stage) are provided in Table 1.

Lymph Node Metastasis

Regional and non-regional LNMs were detected in 31.4% of patients (217/691). In these patients, 50.7% (110/217) presented with regional, pelvic LNMs alone (N1, M0) while 49.3% (107/217) had non-regional LNMs. Only a single patient (0.5%, 1/217) had non-regional LNMs without having concurrent regional LNMs (N0, M1a). Similar to advanced disease in general, increasing PSA levels, ISUP grades, and clinical stages were associated with increased risk of LNMs (Figs. 3B and 4B).

Bone and Visceral Metastasis

BMs (M1b) were identified in 16.8% of men (116/691), and only 22.5% of these men (26/116) presented with BMs exclusively. The majority of patients (77.6%, 90/116) with BMs had concurrent LNMs. BMs were present at a larger extent in patients with increasing PSA levels, ISUP grades, and clinical stages (Figs. 3C and 4C). Two percent of patients (13/691) presented with visceral metastases (M1c); 12 of these had clinical stages cT3a-cT4, and 10 of these had an ISUP grade ≥4.

Pelvic Lymph Node Dissection

RP with PLND was performed in 177 patients. All RP specimens confirmed PCa. In terms of pre-operative biopsy ISUP grades, a total of 38.1% of patients (94/247) were downgraded, and 18.2% of patients (45/247) were upgraded

following RP. More than 2,500 LNs were resected and histologically assessed. The calculated per-patient sensitivity, specificity, positive and negative predictive value, and accuracy for detection of LNMs in this subgroup on ^{68}Ga-PSMA PET/CT are provided in Table 4. The median histological size of LNMs in the 11 patients identified on PET/CT (7.0 mm (2.0-16.0)) was larger than in the 25 patients with no visible ^{68}Ga-PSMA-uptake in LNMs (3.0 mm (1.0-11.0)) with a median ratio of 2.07 (0.95 CI: 1.39, 3.10) (Wilcoxon Mann-Whitney U test; $P = 0.003$).

A true ^{68}Ga-PSMA-positive LNM and its corresponding primary tumor on PET/CT (Fig. 6, left) were immunohistochemically stained for PSMA expression (Fig. 6, left middle). In addition, this was also performed on the six histopathologically verified LNMs above 5.0 mm that went undetected on ^{68}Ga-PSMA PET/CT and their corresponding primary tumors. One undetected cancer was PSMA-negative in both primary tumor and metastasis (Fig. 6, right middle), and the remaining undetected LNMs were micrometastases characteristically located in the border of the LN cortex (Fig. 6, right).

DISCUSSION

With 691 patients, the present study constitutes the largest high-risk cohort for primary PCa staging using ^{68}Ga-PSMA PET/CT reported to date to our knowledge, and furthermore has a high proportion of patients with metastatic disease. Hence, the present study is able to characterize the metastatic spread of PCa assessed by ^{68}Ga-PSMA PET/CT and the relationship with traditional risk stratification parameters (PSA level, biopsy ISUP grade, and clinical stage).

SUV_{max} of the primary tumor in ^{68}Ga-PSMA PET/CT has previously been proposed as a surrogate marker of clinically significant PCa with higher values in higher ISUP grade tumors compared to lower ISUP grade tumors (*18*). In our cohort of high-risk patients only, we found a trend towards increasing median SUV_{max} with increasing ISUP grades in both biopsies and RP specimens as well. However, when plotting all patients, it is clear that there is a massive overlap between groups. Even the lowest SUV_{max} values can correspond to ISUP grades 4 and 5, which questions the applicability of ^{68}Ga-PSMA SUV_{max} as a marker of aggressiveness (Figs. 2A and 2B). Uprimny et al. (*19*) found greatly increased SUV_{max} in patients with ISUP grades 4-5 compared to ISUP grades ≤3 with medians of 19.5 (5.3-65) and 6.8 (2.7-35.1), respectively. In accordance with Demirci et al. (*18*), the natural separation in our cohort would be between ISUP grades 2 and 3, as the SUV_{max} values of ISUP grade 3 were as high as ISUP grade 5. Similarly, primary tumor SUV_{max} was 62%

higher in patients with advanced disease compared to patients with localized disease in our cohort (Fig. 2C). Furthermore, PSA levels correlate greatly with total metastatic burden in the body and is not solely dependent on the activity in the primary tumor as included in our analyses (Fig. 2D). This is a potential confounder in the correlation between SUV_{max} and PSA levels.

Approximately 35% (244/691) of patients presented with advanced disease. As seen in Table 1, ORs were steadily increasing for rising ISUP grades and turned out to be the far superior predictor for advanced disease at diagnosis. cT3 and cT4 disease on DRE were also apparent predictors of advanced disease. On the other hand, PSA levels were clearly inferior to the other two stratification parameters in predicting advanced disease in our cohort, which was caused by the relatively high rate of metastasis (18.5%, 37/200) in the reference group with a PSA level <10 ng/mL.

We observed a striking difference between the rate of advanced disease in patients with ISUP grade 2 (10.8%, 11/102) and ISUP grade 3 (37.1%, 33/89). This supports the subdivision of Gleason Score 7 into ISUP grades 2 and 3 (Gleason Score 3+4 and 4+3, respectively) (*20*,*21*), where ISUP grade 3 may need to be treated as a higher risk disease. According to the D'Amico classification (*11*), the subdivision of cT2 by DRE stratify patients into low-risk (cT2a), intermediate-risk (cT2b), and high-risk (cT2c) groups. Interestingly, we observed no differences in the risk of advanced disease, when comparing the different cT2 stages (Fig. 5). This gives an indication that a three-way subdivision of cT2 may not provide additional information on the risk of advanced disease once high-risk disease has already been established.

We identified LNMs (N1/M1a) in 31.4% of patients (217/691), which was markedly higher in our cohort compared to the population in the recent study by Yaxley et al. (*10*) (8.5%, 107/1253), yet they included intermediate-risk patients as well. We only observed a single patient (0.5%, 1/217) with non-regional LNMs without having concurrent regional LNMs (N0, M1a), consistent with the traditional LN spreading pattern from the pelvis and upwards via regional lymphatic vessels (*22*). With 16.8% of patients having BMs (116/691), this was by far the most common site of hematologic spread. In a recent cross-sectional study of 220 patients with newly diagnosed PCa (*23*), a total of 3.2% of patients (4/124) with a PSA level <10 ng/mL and 9.6% (5/52) of patients with a PSA level of 10-20 ng/mL displayed BMs, compared to 8.0% (16/200) and 11.3% (22/194), respectively in our high-risk only cohort.

In the sub-cohort of patients who underwent RP with concomitant PLND, we achieved a consistent, high per-patient specificity of 96.5% as reported in the majority of previous papers (>90%) (*24*). Conversely, ^{68}Ga-PSMA

PET/CT only detected 11/36 of the histologically confirmed LNMs in our population, revealing a per-patient sensitivity of 30.6%. It is important to notice that this was a highly selected subpopulation with a massive selection bias, as the patients scheduled for surgery are usually deemed free of metastatic disease by ^{68}Ga-PSMA PET/CT beforehand. Our sensitivity was on par with comparable studies (RP with PLND) reporting sensitivities spanning from 33-42% (*25*–*28*). This selection bias is illustrated by the much higher sensitivity found by Hofman et al., in their recent prospective study of ^{68}Ga-PSMA PET/CT in a less preselected group (*6*). Furthermore, we observed a large difference in median histological size of LNMs that were detected (7.0 mm (2.0-16.0)) and undetected (3.0 mm (1.0-11.0)) by ^{68}Ga-PSMA PET/CT. In a study by Budäus et al. (*28*), the median size of ^{68}Ga-PSMA PET/CT detected and undetected LNMs were 13.6 versus 4.3 mm ($P < 0.05$). On histopathology of the undetected LNMs above 5.0 mm, we observed one PSMA-negative metastasis seeded from a PSMA-negative primary tumor (Fig. 6, right middle). It was characteristic for the rest of undetected LNMs that the metastasis only infiltrated the border of LN cortex (Fig. 6, right). Even though the pathological measurement of this particular LNMs was 8.0 mm in longitudinal diameter, the actual volume of the metastasis is relatively small and hence apparently under the detection limit of ^{68}Ga-PSMA PET/CT. A recent study by Jilg et al. (*29*) has also described the importance of the volume of tumor deposits within the LN for ^{68}Ga-PSMA-positivity on PET/CT.

There are some limitations to the present study. First, the retrospective nature of the study may infer potential bias. Moreover, our population is high-risk only, and hence the findings are not valid for all PCa patients. Thirdly, many metastases reported in the present study on ^{68}Ga-PSMA PET/CT were without confirmatory biopsies, thus we solely rely on imaging with known pitfalls taken into account. However, in the subgroup with PLND histology, LNs were available.

CONCLUSION

We identified extraprostatic disease in 35.3% (244/691) of high-risk PCa patients at the time of diagnosis. As expected, the proportion of advanced disease increased with higher PSA levels, ISUP grades, and clinical stages. However, ISUP grade turned out to be the far superior predictor for advanced disease at diagnosis. We found a striking difference in the proportion of advanced disease between ISUP grade 2 (3+4) and 3 (4+3) (10.8%, 11/102, and 37.1%, 33/89, respectively), which supports a subdivision of Gleason Score 7. Interestingly, we observed no differences in the risk

of advanced disease when comparing the three different clinical T2 stages.

DISCLOSURE

This work was financially supported by The Danish Cancer Society. The authors declare no potential conflicts of interest.

KEY POINTS

QUESTION: What characterizes the initial metastatic findings of ^{68}Ga-PSMA PET/CT for primary staging of high-risk prostate cancer, and which traditional risk stratification parameters predict the risk of having advanced disease at diagnosis?

PERTINENT FINDINGS: In a retrospective study comprising 691 newly diagnosed, high-risk prostate cancer patients referred for primary ^{68}Ga-PSMA PET/CT staging, advanced disease was observed in 35% at diagnosis with ISUP grade being the superior predictor. A significant difference was observed between ISUP grade 2 and 3, yet no significant differences when comparing the different cT2 stages.

IMPLICATIONS FOR PATIENT CARE: The present study provide knowledge about risk stratification parameters, which may help improving the future prediction of advanced disease.

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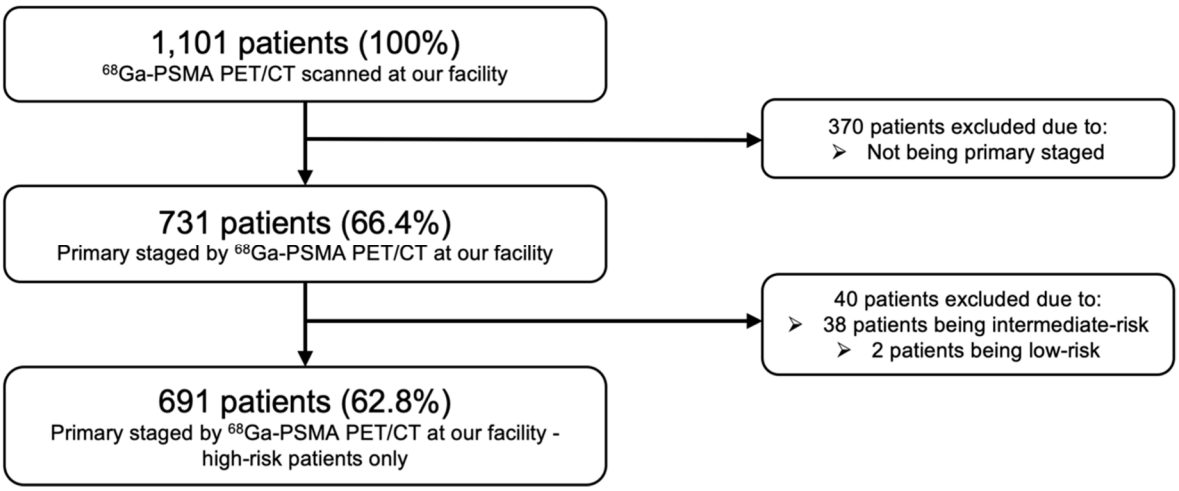

FIGURE 1: *Study flow for ^{68}Ga-PSMA PET/CT primary staging of high-risk prostate cancer patients.*

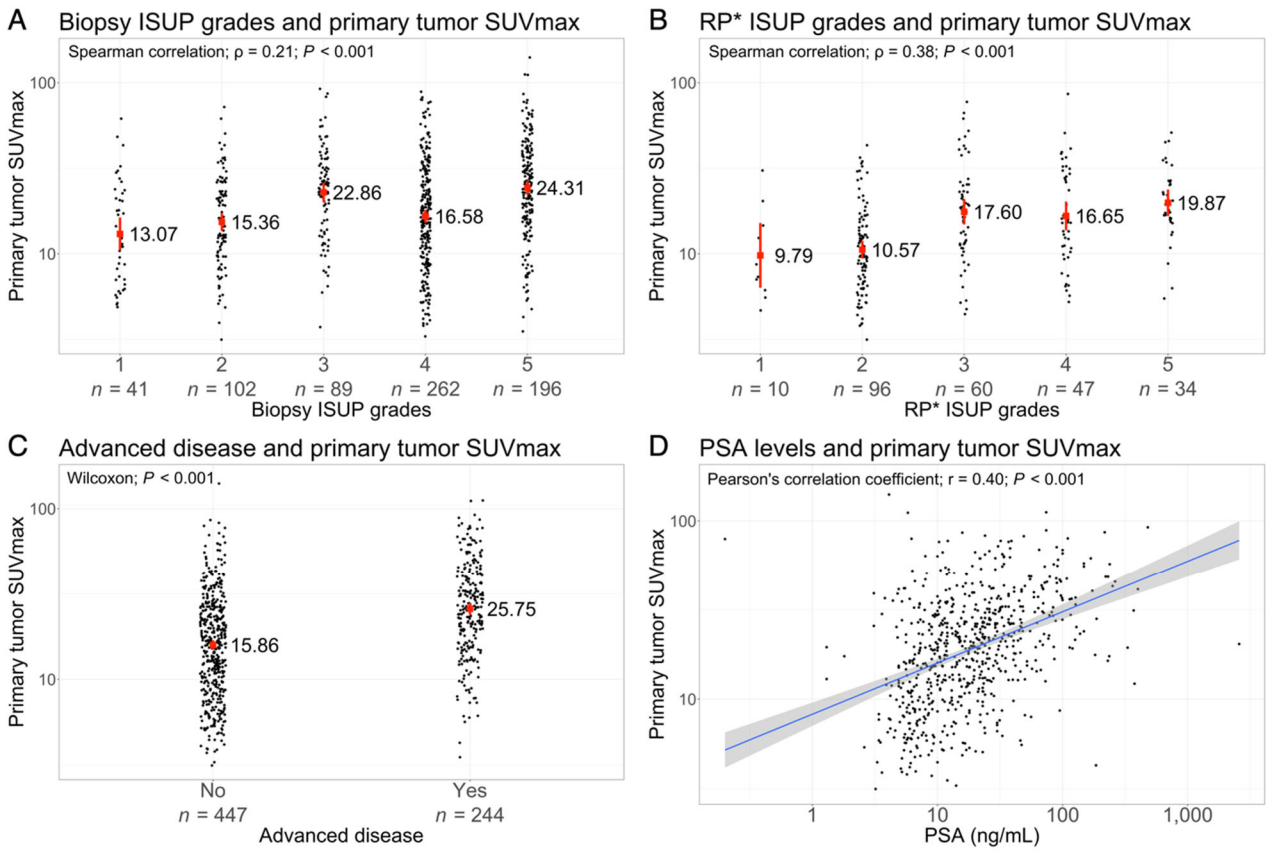

FIGURE 2: *A) Correlation between maximum standardized uptake values (SUV_{max}) of primary tumors and transrectal ultrasound (TRUS)- or MRI-guided biopsy International Society of Urological Pathology (ISUP) grades. B) Correlation between SUV_{max} of primary tumors and radical prostatectomy ISUP grades. C) Primary tumor SUV_{max} in correlation with advanced disease (N1/M1). D) Correlation between SUV_{max} of primary tumors and PSA values at diagnosis. Line of best fit (0.95 CI). *RP = Radical Prostatectomy.*

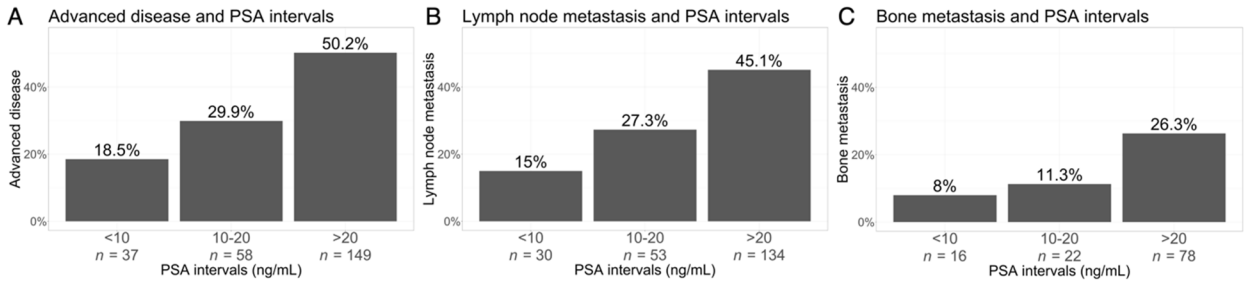

FIGURE 3: *Occurrence of A) advanced disease (N1/M1), B) lymph node metastases (N1/M1a) and C) bone metastases (M1b) according to PSA intervals.*

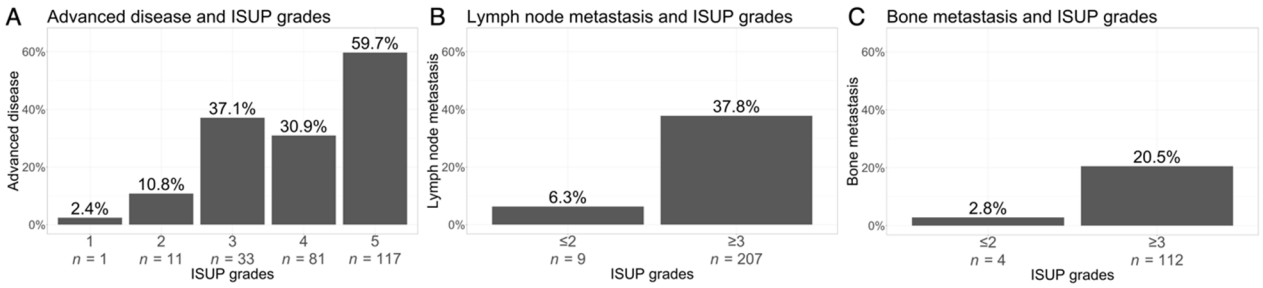

FIGURE 4: *Incidence of A) advanced disease (N1/M1), B) lymph node metastases (N1/M1a) and C) bone metastases (M1b) according to ISUP grades.*

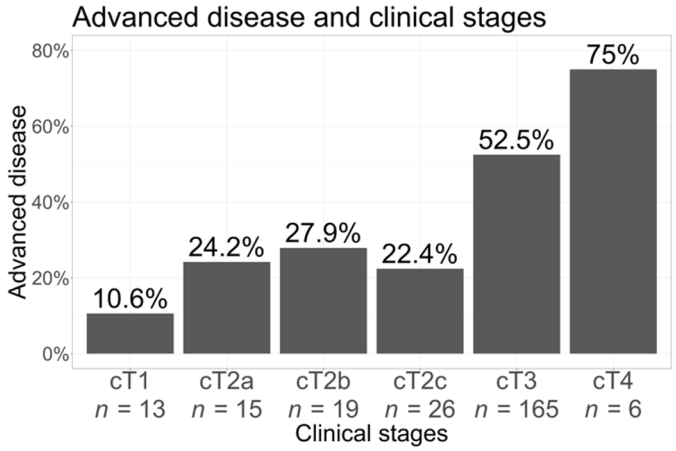

FIGURE 5: *Presence of advanced disease (N1/M1) according to clinical stages.*

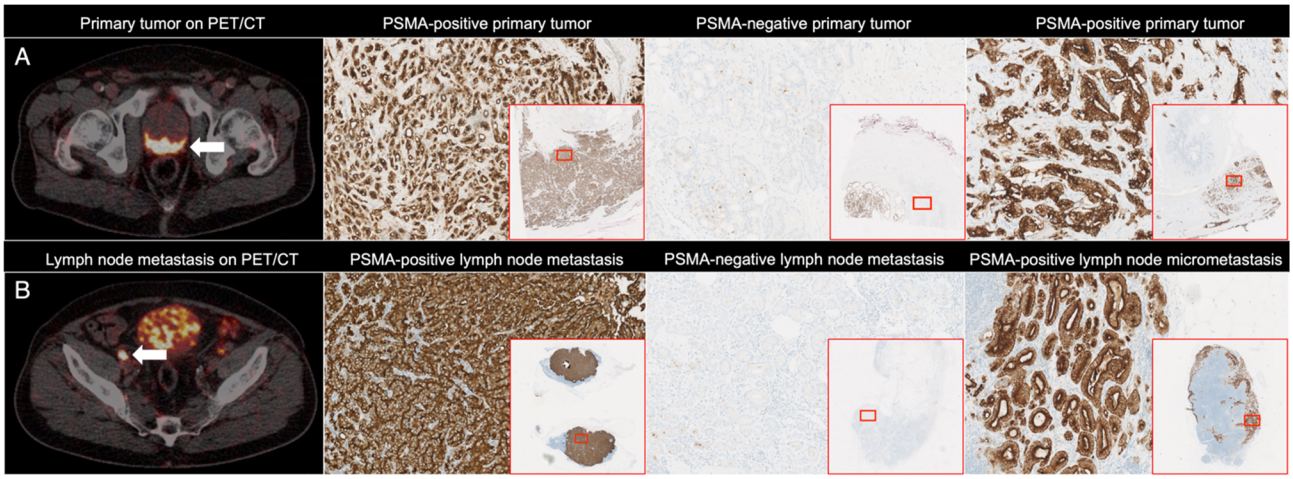

FIGURE 6: *Row A shows primary prostate tumors. From left:* ^{68}*Ga-PSMA PET/CT (white arrow), PSMA-positive immunohistochemical staining of the primary tumor from the previous image, PSMA-negative immunohistochemical staining of a primary tumor, and PSMA-positive immunohistochemical staining of a primary tumor. Row B shows lymph node metastases (LNMs) from the corresponding primary tumors in row A. From left: LNMs on* ^{68}*Ga-PSMA PET/CT (white arrow), PSMA-positive immunohistochemical staining of the true positive LNMs from the previous image, PSMA-negative immunohistochemical staining of an undetected LNMs, and PSMA-positive immunohistochemical staining of an undetected lymph node micrometastasis.*

	Study group*	Advanced disease on ^{68}Ga-PSMA PET/CT	Univariate odds ratios of advanced disease (95% confidence interval)	Multivariate odds ratios of advanced disease (95% confidence interval)
Age (years)				
Median (range)	70.4 (45.2-87.2)			
Time from biopsy to scan (months)				
Median (range)	0.7 (0.1-5.1)			
Prescan PSA (ng/mL)				
<10, *n* (%)	200 (28.9%)	37 (18.5%)	Ref. = 1	Ref. = 1
10-20, *n* (%)	194 (28.1%)	58 (29.9%)	OR_1 = 1.88 (1.17, 3.01)	OR_1 = 1.45 (0.86, 2.47)
>20, *n* (%)	297 (43.0%)	149 (50.2%)	OR_2 = 4.44 (2.90, 6.77)	OR_2 = 4.32 (2.66, 7.12)
Unknown, *n* (%)	0 (0.0%)			
ISUP grade in biopsies				
1, *n* (%)	41 (5.9%)	1 (2.4%)	Ref. = 1	Ref. = 1
2, *n* (%)	102 (14.8%)	11 (10.8%)	OR_1 = 4.84 (0.89, 89.87)	OR_1 = 3.75 (0.67, 70.51)
3, *n* (%)	89 (12.9%)	33 (37.1%)	OR_2 = 23.57 (4.76, 427.76)	OR_2 = 19.67 (3.84, 361.15)
4, *n* (%)	262 (38.0%)	81 (30.9%)	OR_3 = 17.90 (3.79, 320.27)	OR_3 = 25.55 (5.21, 462.70)
5, *n* (%)	196 (28.4%)	117 (59.7%)	OR_4 = 59.24 (12.47, 1061.62)	OR_4 = 53.17 (10.79, 964.19)
Unknown, *n* (%)	1 (0.1%)			
Clinical stage (DRE)				
cT1, *n* (%)	123 (17.8%)	13 (10.6%)	Ref. = 1	Ref. = 1
cT2, *n* (%)	246 (35.6%)	60 (24.4%)	OR_1 = 2.73 (1.47, 5.40)	OR_1 = 2.18 (1.13, 4.45)
cT3, *n* (%)	314 (45.4%)	165 (52.5%)	OR_2 = 9.37 (5.23, 18.11)	OR_2 = 7.13 (3.80, 14.29)
cT4, *n* (%)	8 (1.2%)	6 (75.0%)	OR_3 = 25.38 (5.25, 186.23)	OR_3 = 17.26 (2.82, 160.69)
Unknown, *n* (%)	0 (0.0%)			

TABLE 1: *Study group characteristics and odds ratios (OR) for having advanced disease compared with reference. *n = 691*

	Median SUV_{max} (0.95 CI) in primary tumors
ISUP grade in biopsies	
1 (*n* = 41)	13.07 (10.48, 16.31)
2 (*n* = 102)	15.36 (13.59, 17.36)
3 (*n* = 89)	22.86 (20.04, 26.07)
4 (*n* = 262)	16.58 (15.20, 18.08)
5 (*n* = 196)	24.31 (22.09, 26.75)
ISUP grade in RP specimens	
1 (*n* = 10)	9.79 (6.33, 15.15)
2 (*n* = 96)	10.57 (9.38, 11.92)
3 (*n* = 60)	17.60 (14.84, 20.87)
4 (*n* = 47)	16.65 (13.72, 20.20)
5 (*n* = 34)	19.87 (16.62, 23.75)
Advanced disease	
No (*n* = 447)	15.86 (14.87, 16.91)
Yes (*n* = 244)	25.75 (23.76, 27.91)

TABLE 2: *Primary tumor maximum standardized uptake value (SUV_{max}) with 95% confidence intervals (0.95 CI) in relation to ISUP grades and advanced disease.*

Lesion site	Number of lesions measured	Median SUV_{max} (range)
Primary tumor	*n* = 691	19.5 (3.1-140.5)
Lymph nodes (regional and non-regional)	*n* = 1222	21.1 (2.2-136.3)
Bone metastases	*n* = 386	17.3 (1.8-137.9)
Visceral metastases	*n* = 40	8.1 (3.2-48.0)

TABLE 3: *Maximum standardized uptake value (SUV_{max}) of different lesions sites.*

		Histology*		
		Positive (*n* = 36)	Negative (*n* = 141)	
^{68}Ga-PSMA PET/CT	Positive (*n* = 16)	*n* = 11 (30.6%)	*n* = 5 (3.5%)	PPV** 68.8%
	Negative (*n* = 161)	*n* = 25 (69.4%)	*n* = 136 (96.5%)	NPV** 84.5%
		Sensitivity 30.6%	Specificity 96.5%	Accuracy 83.1%

TABLE 4: *Histopathologic coherence between PSMA-positive/-negative lymph nodes and pathological verification in patients with PLND.* ***n* = 177. **PPV, NPV (positive and negative predictive value).