The association between cribriform growth and positive lymph nodes and/or metastases on PSMA PET/CT

Introduction: Cribriform growth in needle biopsies is considered as an indicator of greater risk of metastatic disease. Therefore, it is common practice to conduct a PSMA PET/CT scan to search for possible metastatic disease, without regard to the ISUP grade. However, this increasing demand poses difficulties for the Nuclear Radiology departments. Therefore, it is necessary to ascertain which patients are at greater risk of metastases.
Aim: To assess whether cribriform growth in needle biopsies is an independent predictor of a positive PSMA PET scan (N+ and/or M+)
Materials and methods: Data was collected from patients who underwent a PSMA PET/CT for primary staging between 01-01-2020 and 31-12-2021. N+ and/or M+ were considered as an outcome, and univariable and multivariable logistic regression analyses were performed.
Results: A total of 401 patients were included in our analysis. The mean age was 70.91 (± 6.5) years, mean PSA value before ^{68}Ga-PSMA PET/CT was 12.60 ng/ml (± 17.80). Cribriform growth was present in 246 (61.3%) patients. N+ was present in 126 (31.4%) patients and M+ in 90 (22.4%) which resulted in a total of 154 (38.4 %) positive PET/CT scans. In a multivariate model, cribriform growth proved to be not significant either in the entire cohort (p = 0.267) or in the ISUP 2 group (p = 0.93).
Conclusion: Cribriform growth in diagnostic needle biopsies is not an independent predictor of a positive PSMA PET scan (N+ and/or M+) in primary staging. PSAD seems to be a better predictor and should be further evaluated.

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22-11-2021 t/m 26-02-2022

Abbreviations

Ga^{68}	Gallium 68
ISUP GG	International Society of Urological Pathology Grade Group
PCa	Prostate cancer
PI-RADS	Prostate Imaging Reporting and Data systems
PSA	Prostate specific antigen
PSAD	PSA density
PSMA	Prostate Specific Membrane Antigen
PSMA PET/CT	Prostate Specific Membrane Antigen Positron Emission Tomography/Computed Tomography
SUV max	Maximum standardized uptake value

Introduction

Globally prostate cancer (PCa) is the second most diagnosed type of cancer in men. With more than 1.4 million new cases in 2020 worldwide.[1] Based on demographic developments such as an increase in population and at the same time aging of the population. In the Netherlands alone the expected rate of new PCa cases will increase by 32% in the period from 2018 to 2040.[2] Up to 4% of prostate cancer patients present themselves with distant metastatic disease at the time of initial diagnosis. [3,4] Localized or limited lymph node expanded disease can be managed with several curative treatment options. However, when metastatic disease is present at initial diagnosis, they will be treated in a non-curative setting.[5] Given the wide variation in treatment options, it is important to ascertain complete and accurate staging of newly diagnosed PCa. The Gleason score and especially the newly adapted Grade Group system by the International Society of Urological Pathology (ISUP GG) system are some of the most important tools for clinical decision-making. This system is based on the architectural growth patterns which are classified into five different grades, varying from 1 to 5. Men with a Grade Group score of 1 are in general practice eligible for active surveillance and do not require direct treatment. This is because of the negligible potential of the disease to metastasize in this large subgroup of patients.[6] Patients with a Grade Group score of 3 or higher generally require active treatment.[7] The optimal choice of treatment of patients with a Grade Group score of 2 remains challenging because of the heterogeneity of this group. Active surveillance is being increasingly considered in this group. A recent study in a tertiary cancer center showed that active surveillance can be a safe management strategy for a carefully selected group.[8] Expanding active surveillance is a favorable development to avoid or possibly delay the side effects that radical therapy entails.[9] However, it is important to gain more insight into which patients are at greater risk of metastatic disease for timely intervention. Besides the Grade Group score, clinical stage based on digital rectal examination, and the prostate-specific antigen (PSA) levels, imaging modalities are vital tools in the staging of PCa. Imaging is of special importance to determine the presence of local positive lymph nodes (N+) and/or distant metastases (M+). In the case of positive localized lymph nodes, a curative option is still possible. However, when there is locally advanced or distant metastatic disease there is no curative treatment. Quite recently positron emission tomography/computed tomography (PET/CT) using various radiological ligands of prostate-specific membrane antigen (PSMA) has been successfully introduced for detecting lymph nodes and/or distant metastases outperforming the conventional CT and bone scan.[4] A PSMA PET/CT is not performed in all PCa patients but only in those who are considered at potentially greater risk of metastatic disease. High risk for metastatic disease is defined as T3a and/or Gleason score 8–10 (translates into GG 4 and 5) and/or PSA > 20 ng/ml. Generally, patients with a

high risk of metastatic disease are always offered a PSMA PET/CT scan. Yet, intermediate-risk patients defined as T2b-T2c and/or Gleason score of 7 and/or a PSA of 10-20 ng/ml are more open to the interpretation of their own urologist.[10] Apart from these criteria, cribriform growth in diagnostic prostate needle biopsies is also considered to be an indicator of greater risk of metastatic disease. [11,12] Besides the risk of metastatic disease, it seems to be predictive of a worse general outcome, worse disease-specific survival, and a shorter disease-free survival period after radical prostatectomy.[13–16] Therefore it is the current clinical practice to perform a PSMA PET/CT in all patients who display cribriform growth in their diagnostic needle biopsies. Also, in patients that normally would not be considered at high or intermediate risk of metastatic disease. Clinicians experience an increase in the documentation of cribriform growth in biopsy results over the past few years. This consequently leads to an increase in the amount of PSMA PET/CT scans that need to be performed. However, regarding the cost-effectiveness and the strain it puts on the increasing wait time for the Nuclear Radiology department, is important to establish if this growth pattern is an independent predictor of N+ and/or M+ on PSMA PET/CT scan. Especially in Grade Group 2, because of the potential implications on decision making and cost-effectiveness. Therefore, we are conducting a study to analyze the relationship between the cribriform growth pattern, the results of imaging (PSMA PET/CT), and clinical outcome.

Objective: To assess whether cribriform growth in diagnostic needle biopsies is an independent predictor of a positive PSMA PET scan (N+ and/or M+).

Materials and Methods

2.1 Patient selection

The clinical data of 1153 consecutive Urology patients who underwent ^{68}Ga-PSMA PET/CT imaging between January 2020 and December 2021 in the St Antonius Hospital in Nieuwegein was evaluated. Patients who underwent PSMA PET/CT for primary staging and with Grade Group 2-5 in their diagnostic needle biopsies were included. Grade Group 1 was excluded because it does not contain cribriform growth by its definition. Other exclusion criteria were prior surgical, systemic, or radiotherapeutic intervention for PCa, or a lymph node dissection in a salvage setting. A total of 401 patients met the inclusion criteria for this retrospective analysis.

2.2 Clinical parameters

Clinical data such as age, clinical TNM classification, serum PSA (ng/ml), tumor grading and presence of cribriform growth based on biopsy results, SUV max of the prostate, and the presence of N+ and/or M+ were collected from the patients' file. The use of the Group Grade score to qualify the pathological samples is done with regards to the recommendations of the 2014 International Society of Urological Pathology (ISUP) consensus conference on GS grading of prostatic carcinoma. When ISUP grade was not available, the Gleason score was translated into an ISUP score according to the following model: Grade Group 1 is defined as a Gleason score of 6 or less, Grade Group 2 as Gleason score 3 + 4 = 7, Grade Group 3 as Gleason score 4 + 3 = 7, Grade Group 4 as a Gleason score of 8, and Grade Group 5 as a Gleason score of 9 or 10.[17]

2.3 Image interpretation

68Ga-PSMA PET/CTs were interpreted by one of the nuclear medicine physicians. ‘’PET-positive lesions were identified by 68Ga-PSMA uptake visually above background and not associated with the physiologic uptake. CT-positive nodes were defined by increased short-axis diameter, loss of fatty hilum, or increased contrast enhancement. Bone metastases were detected by suspicious sclerotic lesions’’.[18] Lesions were scored according to the PIP-RADS criteria, which is a locally adapted grading system based on the PI-RADS Prostate Imaging Reporting and Data System (PI-RADS) criteria. Scores 1-2 are considered not clinically suspicious, 3-4 are mildly suspicious and scores of 5-

6 are considered to be proven N+ and/or M+. When a score of 3 or 4 was assigned the level of suspicion was later discussed in a multidisciplinary meeting with a radiologist, nuclear physician, oncologist, radiation oncologist, and urologist.

2.4 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 28.[19] Data was visually inspected for invalid values and outliers by the use of boxplots. Non-normally distributed continuous parameters were analyzed by the Mann-Whitney U-test, normally distributed continuous parameters were analyzed using the independent *t*-test. Categorical parameters by the Pearson's chi-square ($\chi 2$) test.

Subsequently, logistic regression analyses were performed to assess the association between the presence of cribriform growth and a positive PSMA PET/CT while adjusting for potential confounding variables such as PSA, Grade Group, age, and SUV max of the prostate. A positive PSMA PET/CT was defined as either positive lymph node(s) and or distant metastasis. Possibly interesting variables were identified by using univariable logistic regression analysis. Variables with a *p*-value of 0.3 or lower were entered into a multivariable logistic regression analysis to determine whether they were an independent predictor of a positive PSMA PET/CT. All tests on statistical significance were performed as two-tailed and a *p*-value lower than 0.05 was considered significant.[20]

Results

Patient characteristics

The demographic and clinical characteristics of the entire cohort are summarized in table 1. The mean age of all patients was 70.91 (± 6.5) years, the mean PSA value before ^{68}Ga-PSMA PET/CT was 12.60 ng/ml (± 17.80). Cribriform growth was present in the diagnostic needle biopsies of 246 (61.3%) patients. N+ was present in 126 (31.4%) patients and M+ in 90 (22.4%) which resulted in a total of 154 (38.4 %) patients who yielded a positive ^{68}Ga-PSMA PET/CT.

Stratified by positive ^{68}Ga-PSMA PET/CT status, clinical and imaging characteristics were compared in a per-patient analysis. Only age was evenly distributed in both groups and no significant difference was found between the two groups. Other variables as PSA level, SUV prostate max, clinical TNM, ISUP Grade, and cribriform growth were significantly differently distributed among both groups. PSA values for the negative group were significantly lower than those of the positive group, which were 9.5 (±10.3) and 24.2 (±42.3) respectively (p <0.001). SUV max was significantly higher in the positive group (median 8.2 vs. 14.3, p <0.001). Especially noteworthy is the difference of distribution in ISUP grade. The PET-positive group consisted of 43.9% of Grade Group 4 versus 30.1% in the negative group. Also, the highest ISUP group 5, was far more present (20.0% vs 7.7%) in the positive group.

Table 1. Baseline characteristics

	All patients (n=401)	PSMA PET/CT negative (n= 246)	PSMA PET/CT positive (n=154)	*p*-Value
Age (years), mean (std. deviation)	70.91 (6.5)	70.27 (6.0)	71.95 (7.1)	0.11[c]
PSA before PSMA PET/CT (ng/ml), median (interquartile range)	12.60 (17.8)	9.5 (10.3)	24.2 (42.3)	<0.001[b]
SUV max prostate, median (interquartile range)	10.10 (11.1)	8.18 (8.2)	14.25 (11.2)	<0.001[b]
Clinical TNM, n (%)				
T0	49 (12.2)	38 (15.4)	11 (7.1)	<0.001[b]
T1	80 (20.0)	69 (28.0)	11 (7.1)	
T2	117 (29.2)	71 (28.9)	46 (29.7)	
T3	106 (26.4)	45 (18.3)	61 (39.4)	
T4	17 (4.2)	0 (0)	17 (11.0)	
Unknown	32 (8.0)	23 (9.3)	9 (5.8)	
ISUP Grade, n (%)				
2	99 (24.7)	80 (32.5)	19 (12.3)	<0.001[b]
3	110 (27.4)	73 (29.7)	37 (23.9)	
4	142 (35.4)	74 (30.1)	68 (43.9)	
5	50 (12.5)	19 (7.7)	31 (20.0)	
Cribriform growth, n (%)				0.004[d]
Yes	246 (61.3)	137 (55.7)	109 (70,8)	
No	154 (38.8)	108 (43.9)	46 (29.9)	
N, n (%)				
N0	274 (68.3)			
N+	126 (31.4)			
M, n (%)				
M0	311 (77.6)			
M+	90 (22.4)			

Table notes:
[a]The P-value was based on the comparison between the group with cribriform growth and the group without cribriform growth.
[b]Mann–Whitney U-test.
[c]Unpaired t-test
[d]Chi-square
PSA prostate-sspecific antigen
Pelvic lymph nodes (N+), retroperitoneal (or higher) lymph nodes, bones, and visceral organs (M+)

In the univariate analysis of the entire cohort, cribriform growth ($p = 0.004$), PSA before PET ($p < 0.001$) ISUP grade ($p < 0.001$), and the SUV max ($p < 0.001$) were all significant variables between PET-positive and PET-negative patients as listed in table 2. However, when integrated into a multivariate analysis cribriform growth was no longer of significant importance. Only the significant association between a PET-positive result and PSA level and ISUP grade persisted.

Table 2. Univariate and multivariate analysis of factors predicting 68Ga-PSMA PET/CT positive findings

Association between positive PSMA PET/CT and:	*p*-Value[a]	*p*-Value[b]
Cribriform growth	0.004	0.267
PSA before PSMA PET/CT	<0.001	0.018
ISUP Grade Group	<0.001	0.04
SUV max prostate	<0.001	0.060

Table notes: [a]univariate and [b]multivariate binary logistic regression analysis
*p < 0.05 statistically significant

Table 3 summarizes the *p*-values of the univariate and multivariate logistic regression analysis of the variables when split into Grade group 2. Cribriform growth ($p = 0.98$) and the SUV max ($p = 0.28$) were not statistically significant in the Univariable analysis, only PSA before PET proved to be significant ($p = 0.03$). In the multivariate analysis, there was no significant association between any of the variables and a positive PET result.

Table 3. Univariate and multivariate analysis of factors predicting 68Ga-PSMA PET/CT positive findings for ISUP Grade Group 2

Association between positive PSMA PET/CT and:	*p*-Value[a]	*p*-Value[b]
Cribriform growth	0.98	0.93
PSA before PSMA PET/CT	0.03	0.65
SUV max prostate	0.28	0.94

Table notes: [a]univariate and [b]multivariate binary logistic regression analysis
*p < 0.05 statistically significant

Figure 1. visualizes the amount of positive and negative PET/CT scans depending on cribriform growth. This is visualized for the entire cohort and per ISUP grade. The distribution in group 2 and 3

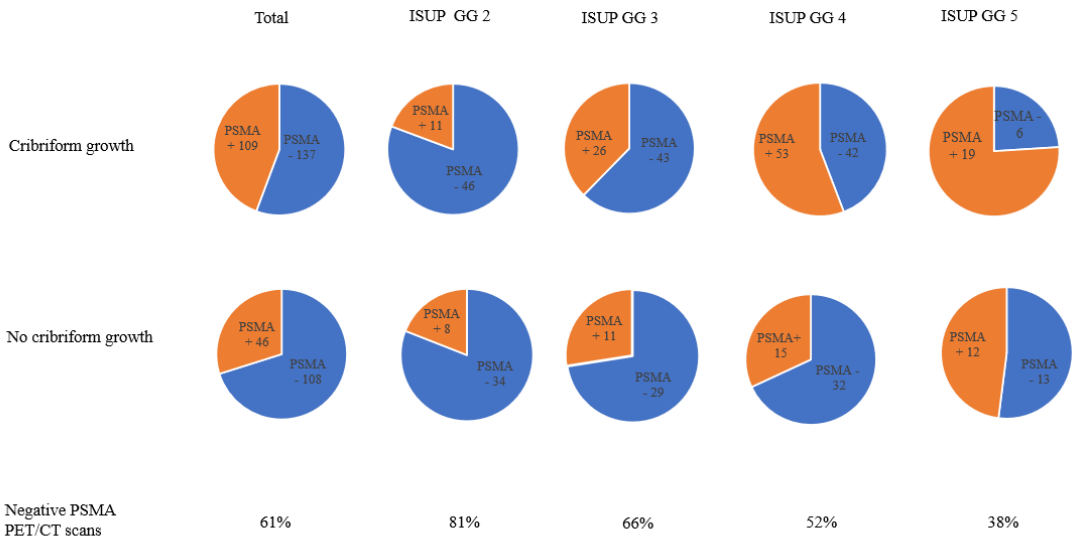

Figure 1. The distribution of PET-positive and PET-negative scans by the presence of cribriform growth of the entire cohort and per ISUP grade.

is more or less the same. In ISUP Grade Group 4 and 5 is the biggest difference between the group with and without cribriform growth and the number of positive PET/CT scans. Lastly, there is a notable decrease in the percentage of PET-negative scans as ISUP grade increases.

Discussion

Our objective was to determine whether cribriform growth is an independent predictor of a positive PSMA PET/CT.

In this study, we found that the presence of cribriform growth in the diagnostic prostate needle biopsies, of patients who underwent PSMA PET/CT in the setting of primary staging, is not an independent predictor for a positive PSMA PET/CT. Especially not in ISUP Grade Group 2.

We identified N+ and/or M+ in 38.4% of all patients (154/401). A considerably higher percentage than reported by Yaxley et al.[21] However this difference might be explained by the fact that their cohort also included ISUP Grade 1. Also, only a considerably small part of their cohort consisted of ISUP Grade 4 (9.1% versus 35.4% in our cohort). More representative and comparable numbers were reported by Klingenberg et al.[22] (31.4%) and Rogasch et al.[23] (33.3%). However, Rogasch et al. only observed N+ and organ metastases. Remarkably enough they did not report on bone metastases. In all likelihood, if they would have taken bone metastases into account their numbers would have been more comparable to ours.

We observed a striking difference in the rate of positive PET/CT scans with rising ISUP grade (fig 1.), especially in the group with cribriform growth. In Grade Group 2 only 19% of all scans were positive. Whereas, in Grade Group 4, the biggest group of our cohort. For all the scans that were made, 48% turned out positive. These findings are in line with recent studies which suggest that especially Grade Group is a significant predictor of a positive scan.[24,25] However, in Grade Group 2 both groups have an almost equal part of positive PET/CT scans, independent from cribriform growth. Moreover, still, 19% of the scans are positive. So, despite the fact, that with our results we can conclude that cribriform growth is not a statistically independent predictor for a positive scan. It is of importance for clinical implications to conclude which factors can. Because 19% positive PET/CT scans in this Grade Group 2 is still quite a substantial amount of patients that we do not want to miss. In order to make a better distinction between which patients in Grade Group 2 are at a potential higher risk of metastatic disease, we should offer clinicians better tools to pay more attention to other potential predictors. As shown in Table 3, in Grade Group 2 of our cohort, especially the PSA before the PET/CT scan seems to be of significant importance. This is in agreement with recent studies that also report on the relationship between PSA and metastatic disease. [26–28]

Moreover, in our study, we found a correlation between an elevated SUV max and a positive scan. This was not specifically an outcome we aimed for in our study but might be of interest to conduct further research into. Multiple studies already reported on the relationship between an elevated SUV max and a higher Grade Group score.[27,29,30] This in itself is already associated with a higher risk of metastatic disease as our study and multiple other studies have shown. But there is also evidence it might be directly related.[31] As promising as is it seems it must be noted that our data and also the data of Klingenberg et al. demonstrated that even low SUV max values can correspond to ISUP Grades of 4 and 5. This might question the appropriateness of its use as a suitable indicator. Therefore, further inquiry is necessary.

Strengths and limitations

To our knowledge, this is the first study to assess the independent relationship between cribriform growth and a positive PSMA PET/CT. Currently, a very relevant topic of interest because multiple centers experience an increase in the demand for PSMA PET/CT scans which poses difficulties for the

Nuclear Radiology department. Furthermore, most studies focus on the biochemical recurrence of disease instead of on primary staging. Therefore, this study contributes to acquiring new knowledge on this specific subject. Also, one of its strengths is the large sample size of this study. Moreover, the use of contemporary data is of especial use since clinicians experience a recent increase in the documentation of cribriform growth. Lastly, by using the consecutive data of the last two years of all patients who underwent a PSMA PET CT in primary staging, we tried to avert selection bias.

Limitations to our study are firstly the retrospective nature of this study. Therefore, the data collection for some patients was incomplete (missing information on PSAD levels, clinical-stage classification). Which could potentially lead to bias and loss of statistical power. This could probably be averted in possible future prospective studies. Furthermore, another possible limitation of this study might be the fact that the percentage of cribriform growth in the diagnostic needle biopsies was not determined by the pathologists. Some needle biopsies only contained focal cribriform growth whereas others were fully invaded. Because of these missing data, no distinction was made in the analysis. One might hypothesize that a bigger percentage of invasive cribriform growth, might pose a bigger risk of metastatic disease, as noted by Kweldam et al. [11] Lastly, in this study we used PSA instead of PSA density, due to too many missing values for PSA density. Yet, PSA density is more reliable because it corrects for the prostate's volume. Different studies indicate that PSA density as a predictor is superior to normal PSA values. [32,33] Therefore, prospect studies should focus on PSA density instead of PSA.

Conclusion

Cribriform growth in diagnostic needle biopsies is not an independent predictor of a positive PSMA PET scan (N+ and/or M+) in primary staging. PSA density seems to be a better predictor and should be further evaluated

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