Prostate-specific antigen density does not predict metastatic disease on PSMA-PET in high-risk prostate cancer patients with negative conventional imaging

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ABSTRACT

INTRODUCTION: The ability of prostate-specific antigen density (PSAD) to predict metastatic disease on prostate-specific membrane antigen-positron emission tomography (PSMA-PET) at initial staging in high-risk prostate cancer (PCa) for men with negative conventional imaging is unclear. We hypothesized that there might be a PSAD cutoff below which PSMA-PET would be unnecessary, as it would so rarely identify metastatic disease.

METHODS: A retrospective cohort study of all men receiving ^{18}F-DCFPyl PSMA-PET for primary staging between January 2018 and December 2022 at the University Health Network was performed. Student's t-tests or Mann-Whitney U tests were used to compare continuous variables by PSMA-PET positivity status. Receiver operating characteristic curve analysis to compare PSA and PSAD performance and Chi-squared automatic interaction detector methodologies were used to identify predictors of metastatic disease.

RESULTS: A total of 140 men with high-risk PCa and negative conventional imaging were included. The median age was 68 years (interquartile range [IQR] 63–74). Median PSA and PSAD were 13.9 (IQR 6.9–29.5) and 0.36 ng/ml^2 (IQR 0.19–0.83), respectively. PSMA-PET was positive in 40% of cases for metastatic disease. The area under the curve (AUC) to predict metastatic disease on PSMA-PET was 0.55 for PSAD (p=0.57). Patients with metastatic disease on PSMA-PET had higher Gleason grade group (GG) scores on biopsy (53 vs. 20% GG5, p<0.001) and more extraprostatic extension (19 vs. 6%, p=0.03) and perineural invasion (65 vs. 45%, p=0.03).

CONCLUSIONS: In this retrospective cohort, PSAD does not reliably predict which patients with high-risk PCa and negative conventional imaging will have metastatic disease unveiled by PSMA-PET.

INTRODUCTION

Men presenting with prostate cancer (PCa) are divided into three risk categories based on their prostate-specific antigen (PSA) level, clinical stage, and Gleason grade group (GG).[1] Patients with PSA levels >20 ng/ml, clinical stage T3a (extraprostatic tumor extension), and/or GG ≥4 on biopsy are considered high risk.[1] It is necessary to stage these patients with a computed tomography (CT) and bone scintigraphy to define the burden of disease and presence of regional and/or distant spread.

In general, patients found to have metastatic disease are offered palliative systemic therapy, whereas patients found to have localized disease are offered either radiation with or without androgen deprivation therapy or surgery with curative intent. Unfortunately, many men thought to have clinically localized disease after conventional staging will relapse after treatment. A major contributing factor to this is that CT and bone scintigraphy have modest sensitivity to detect non-localized disease.[2,3]

Prostate-specific membrane antigen (PSMA)-positron emission tomography (PET)/CT is a novel imaging modality that promises to improve outcomes by more accurately defining the extent of disease during staging. PSMA is a cell-surface glycoprotein overexpressed in PCa cells. Radiolabelled small molecules that bind with high affinity to PSMA allow for whole-body, tumor-specific imaging with PET/CT. In the

KEY MESSAGES

- PSAD does not reliably predict which men with high-risk PCa and negative conventional imaging will have metastatic disease on PSMA-PET scan.
- PSAD should not be used as a triaging tool in this setting.
- Exploratory analysis suggests higher Gleason grade group and perineural invasion may be better predictors.

multicenter, randomized pro-PSMA trial, PSMA-PET displayed better sensitivity (85% vs. 38%), specificity (98% vs. 65%), and overall accuracy (92% vs. 65%) compared to conventional imaging for the initial staging of high-risk PCa.[4] In a Best Practice Report published by the Canadian Urological Association in 2021, they recommend considering PSMA-PET scans for the primary staging of high-risk PCa when a change in management is contemplated.[5]

It should be noted, however, that in the pro-PSMA study, the addition of a PSMA-PET scan to conventional imaging for the staging of high-risk PCa only led to treatment changes in 28% of patients.[4] For the 72% of patients where no change to treatment was required, potential harm could have been incurred secondary to the delay in obtaining, interpreting, and reviewing the results of the PSMA-PET scan. Furthermore, access to PSMA-PET scans is limited in Canada, and this scarce resource must be shared with patients across the spectrum of disease, particularly those with biochemical recurrence after local treatment, where there appears to be a more pronounced benefit.[5]

In this study, we aimed to evaluate the ability of a readily available biomarker, prostate-specific antigen density (PSAD), to predict PSMA-PET positivity in patients with high-risk PCa with negative conventional imaging. We hypothesize that at lower PSAD levels, the likelihood of a positive PSMA-PET scan is low, and the test may be unnecessary. The rationale for this is that the PSA level is reflective of the prostate volume. Conversely, at higher PSAD levels, the rates of positive PSMA-PET scans increase and are more likely to be clinically beneficial. Again, this would be due to the fact that the PSA levels are not entirely explained by the prostate volume.

PSAD is currently widely used in the PCa screening setting to help decide which patients can avoid biopsy and which patients are at higher risk of harboring clinically significant disease.[6-10] Similarly, incorporating PSAD in active surveillance protocols is associated with reduced rates of upgrading and reclassification.[7,11] PSAD can also predict adverse pathology and biochemical failure after treatment;[12,13] however, the role of PSAD in triaging high-risk PCa patients with negative imaging for PSMA-PET scans has not yet been studied.

METHODS

We conducted a retrospective cohort study at the University Health Network (UHN) in Toronto, Ontario. All consecutive men who underwent ^{18}F-DCFPyl PSMA-PET for primary staging between January 2018 and December 2022 were included. Baseline demographics were recorded, including age, serum PSA level at the time of diagnosis, magnetic resonace imaging (MRI) results as per Prostate Imaging-Reporting and Data System (PI-RADS) v2, and prostate biopsy results. Prostate volume was extracted from transrectal ultrasound and/or MRI imaging. PSAD (ng/ml^2) was calculated as PSA (ng/mL) divided by the prostate volume (ml). PET/CT imaging findings were categorized according to the original reports for regional nodal (N), as well as distant metastases (M) staging: negative, positive, or equivocal. Equivocal findings were treated as negative for the analyses.

Descriptive statistics of the study sample were used to summarize relevant participant characteristics. PSMA-PET positivity was defined as non-equivocal nodal or distant metastatic disease. Student's t-tests or Mann-Whitney U tests were used for the comparison of continuous variables by PSMA-PET positivity status. Chi-square and Fisher's exact tests were used for comparison of categorical variables by PSMA positivity status. Receiver operating characteristic (ROC) curves for classifying PSMA-PET positivity were plotted as sensitivity vs. 1-specificity for all PSAD values. The area under the curve (AUC) and its 95% confidence interval were calculated. Youden's index (sensitivity + specificity - 1) was used to identify the optimal cutoff point for PSAD to be used as a predictor of PSMA-PET positivity. Classification and regression tree and χ^2 automatic interaction detection (CHAID) methods were used to divide the predictors into categories based on PSMA-PET positivity status. All tests were two-tailed, and statistical significance was defined as a $p<0.05$. Analysis was done using R.

The study was approved by the UHN Research Ethics Board (22-5993).

RESULTS

One-hundred and forty consecutive men with high-risk PCa and negative conventional imaging (i.e., CT abdo-pelvis and bone scan) were included in this study. The median age was 68 years (interquartile range [IQR] 63–74). Median PSA was 13.9 (IQR 6.9–29.5), and median prostate volume was 43.2 cc (IQR 29.6–55). Median PSAD was 0.36 ng/ml^2 (IQR 0.19–0.83). PSMA-PET was positive in 40% of men (31% oligometastatic and 9% extensive metastatic).

Table 1 summarizes the clinical and histopathological features of the men with metastatic disease on PSMA-PET vs. men without metastatic disease on PSMA-PET. Patients with metastatic disease on PSMA-PET were more likely to have higher GG scores on biopsy (53 vs. 20% GG5, p<0.001), extra-prostatic extension (19 vs. 6%, p=0.03), and perineural invasion (PNI) (65 vs. 45%, p=0.03). Patients with metastatic disease on PSMA-PET were more likely to be treated with a palliative rather than curative approach (p<0.001). PSAD was comparable between those with positive (i.e., metastatic disease) and negative PSMA-PET (median 0.41 vs. 0.33, respectively, p=0.42). No difference was detected between groups in baseline MRI findings (PI-RADS/extraprostatic extension [EPE]). In patients who underwent radical prostatectomy, it appeared that those with metastatic disease on preoperative PSMA-PET had higher pathologic T and N staging on final pathology (p<0.006 and p<0.02, respectively).

The AUC to predict metastatic disease on PSMA-PET was 0.56 for PSA and 0.55 for PSAD (p=0.57). The optimal cutoff for PSAD (which maximized the sum of the Youden index) was 0.4 ng/ml^2, with 54% sensitivity and 60% specificity for detecting metastatic disease on PSMA-PET (Figure 1).

Using the CHAID methodology, we attempted to create a decision tree analysis using PSAD, but we were unable to obtain a decision tree with a minimum of 60% sensitivity and specificity. As shown in Figure 2, PSAD is very similarly distributed between the two groups. Clearly, PSAD did not appear to meaningfully differentiate patients with metastatic disease on PSMA-PET vs. those without.

In an exploratory analysis, we were able to create a decision tree using GG group and PNI (Figure 3). The Gini index was used to determine optimal splits in the decision tree. The decision tree's accuracy, sensitivity, and specificity are 70%, 60%, and 75%, respectively. Patients with GG1–2 disease had a 15% chance of positive PSMA-PET, whereas patients with GG3–5 had up to a 62% chance of positive PSMA-PET if they also had PNI.

Table 1. Baseline characteristics

	Negative (n=83)	Positive (n=57)	p
Patient age			0.94
Mean (SD)	68.1 (8.8)	68.3 (7.6)	
Median (Q1, Q3)	68.0 (61.5, 75.5)	69 (63, 73)	
Range (min, max)	(49, 89)	(52, 88)	
PSA value within 3 months of enrollment			0.25
Mean (SD)	22.1 (23.6)	32.2 (43.2)	
Median (Q1, Q3)	13.8 (6.3, 26.4)	16.1 (8.2, 40.5)	
Range (min, max)	(0.7, 122.1)	(0.3, 251.4)	
Missing	4	2	
PSMA-PET detected new lesions not seen on conventional imaging			**<0.001**
No	45 (57.7)	5 (8.9)	
Yes	33 (42.3)	51 (91.1)	
Missing	5	1	
Prostate volume on US			0.10
Mean (SD)	45.0 (24.5)	49.0 (22.1)	
Median (Q1,Q3)	39.0 (28.0, 53.8)	45.5 (33.0, 55.9)	
Range (min, max)	(17, 155)	(15, 120)	
Missing	10	3	
Gleason grade group			**<0.001**
1	4 (4.8)	0 (0.0)	
2	35 (42.2)	7 (12.3)	
3	16 (19.3)	14 (24.6)	
4	11 (13.3)	6 (10.5)	
5	17 (20.5)	30 (52.6)	
Percent cores positive			0.14
Mean (SD)	59.6 (27.6)	66.5 (27.4)	
Median (Q1, Q3)	58.3 (37.3, 81.0)	69.2 (46.2, 91.7)	
Range (min, max)	(5.6, 100.0)	(10, 100)	

Bolded values indicate statistical significance. EPE: extraprostatic extension; IDC: intraducatal carcinoma; PSA: prostate-specific antigen; PNI: perineural invasion; PSMA-PET: prostate-specific membrane antigen-positron emission tomography; SD: standard deviation; UHN: University Health Network.

Table 1 (cont'd). Baseline characteristics

	Negative (n=83)	Positive (n=57)	p
Total cores			0.08
Mean (SD)	13.3 (3.3)	12.8 (3.1)	
Median (Q1, Q3)	13 (12, 15)	12 (12, 14)	
Range (min, max)	(4, 21)	(5, 22)	
EPE			**0.03**
No	78 (94.0)	46 (80.7)	
Yes	5 (6.0)	11 (19.3)	
PNI			**0.03**
No	46 (55.4)	20 (35.1)	
Yes	37 (44.6)	37 (64.9)	
IDC			0.06
No	62 (74.7)	33 (57.9)	
Yes	21 (25.3)	24 (42.1)	
Cribriform			0.81
No	51 (61.4)	33 (57.9)	
Yes	32 (38.6)	24 (42.1)	
Treatment approach			**<0.001**
Curative	69 (93.2)	28 (53.8)	
Palliative	3 (4.1)	21 (40.4)	
Referred out - no treatment at UHN	2 (2.7)	3 (5.8)	
Missing	9	5	

Bolded values indicate statistical significance. EPE: extraprostatic extension; IDC: intraducatal carcinoma; PSA: prostate-specific antigen; PNI: perineural invasion; PSMA-PET: prostate-specific membrane antigen-positron emission tomography; SD: standard deviation; UHN: University Health Network.

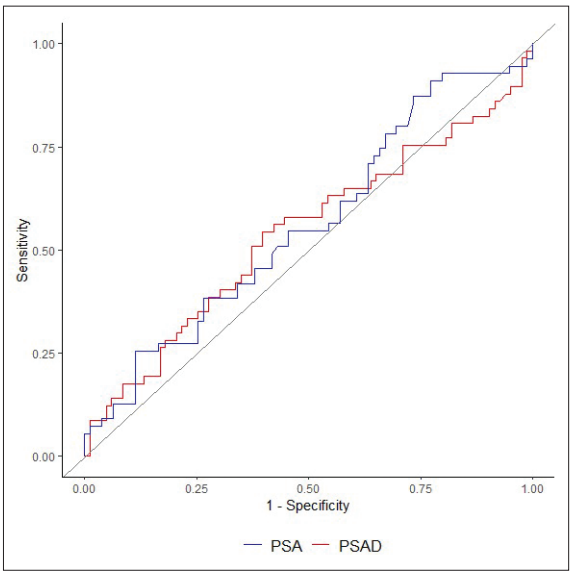

Figure 1. Predicting prostate-specific membrane antigen-positron emission tomography (PSMA-PET) positivity using prostate-specific antigen (PSA) and prostate-specific antigen density (PSAD).

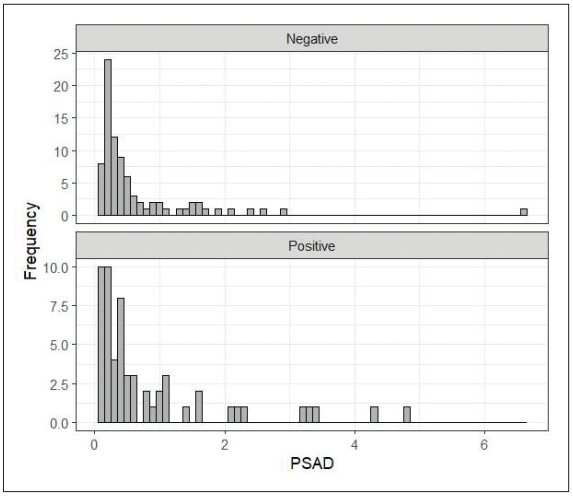

Figure 2. Distribution of prostate-specific antigen density (PSAD) by prostate-specific membrane antigen (PSMA) positivity status.

DISCUSSION

In this study, PSAD was not able to reliably differentiate which patients with high-risk PCa and negative conventional imaging should undergo PSMA-PET staging. Exploratory analysis suggests that a higher GG and the presence of PNI perturb a higher risk of harboring metastatic disease on PSM- PET.

Our hypothesis that patients with metastatic disease on PSMA-PET would have higher PSAD assumed that these patients would have higher PSAs. While there was a trend towards higher PSA in this cohort (mean 32 vs. 22, median 16.1 vs. 13.8), this was not significant (p=0.25). One explanation for this finding is that metastases detectable on PSMA-PET in the setting of negative conventional imaging secrete minimal PSA. This is supported by the fact that in the biochemical recurrent setting, PSMA-PET can detect metastases at very low levels of PSA.[5] Another explanation for the findings is that although a large percentage of patients did not have metastases on PSMA-PET scans, they did have PSMA-avid lesions localized within the prostate. With these primary tumors in situ, the relative contribution of PSA from metastasis could be negligible. Lastly, given that there were higher rates of GG4/5 disease, EPE, and PNI in the PSMA-PET-positive group, the discriminatory value of PSAD was reduced.

Another interesting finding from the study is that patients with a positive PSMA-PET scan were more likely to be treated with a palliative rather than curative approach. This is in keeping with prior studies suggesting that PSMA-PET scans result in a change in management.[4] It is important to note, however, that to date, it has not been shown that these alterations in management translate into clinical benefit for patients. It does, however, raise the risk of stage migration bias, otherwise known as the "Will Rogers phenomenon." This occurs when changes in the criteria for assigning patients to the various stages of a disease can produce spurious improvements in stage-specific prognosis, even though the outcome of individual patients has not changed.

Limitations

Limitations to consider for this study are the small sample size and the fact that it was conducted at a single institution. Furthermore, a significant proportion of patients did not have an MRI, and prostate volume estimation was based on the transrectal ultrasound, which can be imprecise.[14] Additionally, this study is limited by its retrospective nature, and may represent a biased cohort because PSAD may have already influenced clinicians' decisions on whether to obtain a PSMA-PET scan. Another limitation is that our data collection is somewhat dated, having ended in 2022; however, the outcomes should still be relevant today since overall practice and tracers are stable since that time.

Further work trying to decipher who benefits from PSMA-PET staging in the high-risk setting or improving timely access to PSMA-PET will be an important next step in improving outcomes for these men.

CONCLUSIONS

PSAD does not reliably predict which patients with high-risk PCa and negative conventional imaging will have metastatic disease on PSMA-PET. PSAD should not be used for triaging who gets PSMA-PET scans in this setting.

COMPETING INTERESTS: Dr. Kumar has received speaker honoraria from Knight Therapeutics. Dr. Fleshner is Founder and CMO of Verity Biopharma; CMO of Soricimed; has received consulting fees from Abbvie, Astellas, Bayer, Ferring, Janssen, Nucleix, and Sanofi; and has received honoraria from OICR and Movember. Dr. Hamilton has participated in advisory boards for Astellas, AstraZeneca, Bayer, Janssen, Knight, Merck, Novartis, Tersera, and Tolmar; and has participated in clinical trials supported by Janssen and Novartis. Dr. Kulkarni has participated in advisory boards for AAA/Novartis, AbbVie, Astellas, BMS, EMD Serono, enGene, Ferring, J&J, Knight Therapeutics, Merck, Pfizer, Theralase, and Verity; has received honoraria from AstraZeneca, Ferring, J&J, Merck, Photocure, TerSera, and Verity; has participated in clinical trials supported by BMS, CG Oncology, Ferring, J&J, Merck, Pfizer, Protara Therapeutics, Seagen, Theralase, and Verity; and holds a leadership position with Bladder Cancer Canada. Dr. Perlis has participated in advisory boards and educational events and has consulted for Abbvie, Focal Healthcare, Knight, Spectracure, TerSera, and Tolmar. The remaining authors do not report any competing personal or financial interests related to this work.

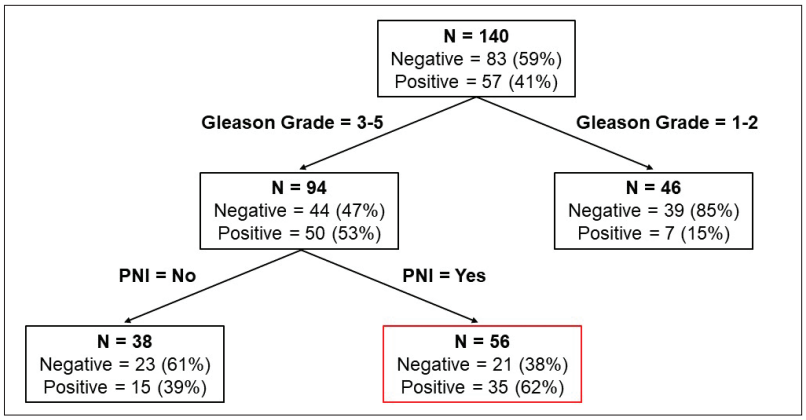

Figure 3. Decision tree analysis based on Gleason grade group and perineural invasion (PNI).

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