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SHORT COMMUNICATION

^{68}Ga-PSMA PET/CT tumour intensity pre-operatively predicts adverse pathological outcomes and progression-free survival in localised prostate cancer

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Abstract

Purpose Prostate-specific membrane antigen (PSMA) positron emission tomography (PSMA-PET) improves prostate cancer staging. Intraprostatic PSMA intensity may predict clinically relevant oncological outcomes. The aim of this study was to investigate the relationship between intraprostatic PSMA intensity and adverse pathology outcomes, including biochemical progression-free survival (PFS) after radical prostatectomy.

Methods This is a cohort study of 71 patients with MRI-guided, biopsy-proven prostate cancer and pre-operative ^{68}Ga-PSMA-11 PET/CT prior to radical prostatectomy (RP). Intraprostatic PSMA intensity was correlated to adverse pathology outcomes (Gleason score and upgrading from biopsy, pathological stage) and PFS using multivariate statistical analysis.

Results ^{68}Ga-PSMA-11 PET/CT intensity in vivo predicted all of Gleason score on RP, upgrading from biopsy to RP histopathology, pathological stage, positive surgical margins and PFS. 74.6% (53/71) of patients were free from progression at a median follow-up of 19.5 months (0.4–48 months). Predictive accuracy was particularly enhanced by PSMA among patients with biopsy Gleason score $\leq 3+4$ ($n=39$) as the most significant predictor of PFS according to Cox-proportional hazards regression. Cox-regression adjusted survival analysis predicted a 5.48-fold increase in hazard for Gleason score $\leq 3+4$ patients with high (SUVmax > 8) compared with low (SUVmax < 8) PSMA intensity.

Conclusion Intraprostatic ^{68}Ga-PSMA-11 intensity is prognostic and may be a valuable new biomarker in localised prostate cancer, especially in men with biopsy-proven Gleason 3 + 4 disease considering an initial approach of active surveillance or focal therapy.

Keywords Prostate cancer · Positron emission tomography · Magnetic resonance imaging · Prostate specific membrane antigen, PSMA · Prostatectomy

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Introduction

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is over expressed in > 90% of prostate cancers (PCa) [1]. PSMA positron emission tomography (PSMA-PET) improves PCa staging, compared with conventional imaging [1], and alters management [1, 2].

PSMA-PET accurately describes intraprostatic tumour foci with improved performance compared with multiparametric MRI (mpMRI) [3]. Increased PSMA expression ex vivo has been correlated with adverse oncologic outcomes [4]. However, the relationship between the intraprostatic intensity on PSMA PET/CT and subsequent clinically relevant oncological outcomes requires further characterisation. Hence, we sought to investigate the relationship of intraprostatic PSMA intensity with adverse pathology outcomes and biochemical progression-free survival (PFS) following definitive radical prostatectomy (RP).

Patients and methods

Study population

Patients attending our hospital who were staged with a ^{68}Ga-PSMA PET/CT following multiparametric MRI (mpMRI) prior to RP between June 2014 and July 2017 were considered (Table 1), to allow a minimum follow-up period of 2 years. Our centre uses mpMRI to triage requirement for prostate biopsy and for local staging [3]. Transperineal systematic prostate biopsies are performed, with additional cognitive target biopsies into any PI-RADS 3–5 mpMRI region of interest (median total 17 cores). Exclusion criteria included distant metastases, any prior treatment for PCa including hormone ablation or contraindication to imaging.

Imaging

^{68}Ga-PSMA-11 PET/CT and mpMRI were acquired as previously described [3]. In brief, PET images were obtained on a Siemens Biograph mCT PET/CT camera. Low-dose CT scans acquired using the 128-slice CT were used to generate CT attenuation corrected reconstructions with time of flight, scatter correction and point spread function resolution recovery (UltraHD) approximately 45 min following injection of ^{68}Ga-PSMA-11 (ABX AG, Germany) and double read independently by two experienced nuclear medicine specialists (approx. 200 reads/year). Lesions were reported positive if they demonstrated focal ^{68}Ga-PSMA-11 uptake significantly higher than background prostatic and/or mediastinal blood pool activity. Semi-quantitative analysis of PSMA intensity using an automated standardised maximum uptake value (SUVmax) was measured for identified lesions.

All men had a prostate 3 T mpMRI prior to prostate biopsy. Images were acquired and analysed by radiologists with experience in prostate mpMRI and the treating urologist, as described previously [3].

Histopathological analysis

RP histopathological analysis was reported by experienced uro-pathologists according to the 2014 International Society of Urological Pathology (ISUP) Gleason Grading Guidelines [5]. A Gleason score ≥ 3 + 4 was considered clinically significant PCa, while adverse pathological outcomes were recorded.

Outcome measures

The primary outcomes were adverse pathological outcomes (Gleason score, Gleason score upgrade from biopsy to RP, pathological stage ≥ T3a) as well as biochemical progression-free survival (PFS) following RP [6], defined as the time from RP to:

1) Biochemical recurrence (post-operative serum PSA > 0.2 ng/ml on two separate occasions at minimum 2-week intervals) OR
2) Commencement or referral for adjuvant or salvage therapies, such as radiotherapy or androgen deprivation therapy, in the absence of biochemical recurrence

Other clinically related variables, including serum PSA, PSA density, prostate volume (according to mpMRI estimation), PI-RADS score, ^{68}Ga-PSMA-11 SUVmax and biopsy outcomes (Gleason score, proportion of positive cores), were recorded.

Statistical analysis

Statistical analysis, including Mann-Whitney (MW) and Fisher's exact (exact) tests, Kruskal Wallis comparison (KW) and survival analyses, were performed using Stata 15 (StataCorp. 2017. College Station, TX) and MedCalc for Windows, Version 18 (MedCalc Software; Ostend, Belgium).

Ethical approval

The study received ethical approval from the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee (Approval Number HREC/17/QRBW/644).

Results

Demographics

A total of 71 patients met the criteria for inclusion in the study. The demographic data is listed in Table 1. Most patients presented with a PSA density ≥ 0.15 (74.6%), PI-RADS score of 4 or 5 (83.1%) and Gleason 7 (3 + 4 or 4 + 3; 83.1%) disease per RP histopathology.

PSMA intensity according to adverse pathological outcomes

^{68}Ga-PSMA-11 intensity (SUVmax) was significantly associated with Gleason score (KW(5) = 36.9, $p < 0.001$ per biopsy; KW(3) = 10.4, $p = 0.01$ per RP; Fig. 1a) and prediction of Gleason ≥ 4 + 3 (KW(1) = 10.1; $p = 0.001$) and positive surgical margins (PSM; $p < 0.001$) at RP. ^{68}Ga-PSMA-11 intensity was significantly higher among patients with Gleason ≥ 4 + 3 (10.37; IQR 8–16.06) vs Gleason ≤ 3 + 4 (6.6; IQR 4.7–10.96; MW; $p = 0.001$).

When index lesions (defined as tumour foci with highest Gleason score) were compared with additional, secondary lesions according to RP histopathology, index lesions were associated with higher SUVmax (KW(1) = 16.15; $p < 0.001$; Fig. 1b). SUVmax was not associated with tumour volume ($p = 0.22$).

Fourteen patients (19.7%) were upgraded on RP from biopsy histopathology, including 9 patients from biopsy Gleason 3 + 4 to 4 + 3 on RP histology. These men all had higher ^{68}Ga-PSMA-11 intensity compared with those not upstaged (median SUVmax 9.25 (IQR 7.13–10.54) vs. 5.53 (IQR 4.3–9.82); $p = 0.07$; Fig. 1c) and were similar to those with concordant Gleason 4 + 3 histopathology (11.77; IQR 9.23–16.06; $p = 0.2568$).

For the entire cohort, ^{68}Ga-PSMA-11 intensity was associated with stage overall (KW(2) = 6.2; $p = 0.04$; Fig. 1d) In the Gleason ≤ 3 + 4 subgroup, stage ≥ pT3a was determined with an area under the receiver operating characteristic curve of 0.774 (95% CI 0.63–0.92; $p = 0.0001$). The optimal cut-point (Youden) was 8.09 and performance was maintained at a cut-point of 8 (sensitivity 0.57, 95% CI 0.35–0.77; specificity 0.88, 95% CI 0.62–0.98; positive predictive value 0.87, 95% CI 0.63–0.96; negative predictive value 0.58, 95% CI 0.46–0.70).

Table 1 Demographic data for included patients

Patients (*n*)	71
Age, median (IQR)	64 (58–67)
PSA, ng/mL	7.4 (5.5–11)
PSA density	0.200 (0.150–0.290); ≥ 0.150 = 74.6%
Prostate volume, mL	35 (28–50)
SUVmax, median (IQR)	8.63 (5.48–13.05)
ADC, median (IQR)	573 (450–661)
mpMRI PI-RADS (%)	
2	9 (12.7)
3	3 (4.2)
4	33 (46.5)
5	26 (36.6)
Biopsy Gleason score (%)	
Benign	0
3 + 3	1 (1.4)
3 + 4	38 (53.5)
4 + 3	18 (25.4)
4 + 4	5 (7.0)
≥ 4 + 5	9 (12.7)
Whole gland Gleason score (%)	
3 + 3	0
3 + 4	41 (57.7)
4 + 3	18 (25.4)
4 + 4	1 (1.4)
≥ 4 + 5	11 (15.50)
Index tumour size, cc	1.92 (0.92–4.00)
RP stage (%)	
T2	26 (36.6)
T3a	34 (47.9)
T3b	11 (15.5)
T4	0

IQR, interquartile range; *SUVmax*, standardised maximum uptake value; *ADC*, apparent diffusion coefficient; *PI-RADS*, Prostate Imaging Reporting and Data System; *RP*, radical prostatectomy

PSMA intensity to predict biochemical progression-free survival

74.6% (53/71 patients) were free from progression at a median follow-up of 19.5 months post-RP. Stage pT3b and Gleason ≥ 4 + 3 (exact; $p = 0.013$) were strongly correlated with PFS, which was confirmed with Kaplan-Meier analysis (Fig. 2a; Supplementary Fig. 1). Among all variables, Gleason score at biopsy, presence of PI-RADS5 lesion, PSM and SUVmax (after adjustment for interaction with Gleason score; Supplementary Table 1B) were significant pre-operative predictors of PFS according to Cox-proportional hazards regression (Supplementary Table 1).

In the Gleason ≤ 3 + 4 subgroup (according to biopsy; n = 39), higher intraprostatic ^{68}Ga-PSMA-11 intensity (SUVmax > 8) predicted PFS overall. When all pre-operative variables were considered, ^{68}Ga-PSMA-11 intensity was the most significant predictor of PFS. Among patients with Gleason ≤ 3 + 4 per biopsy, Cox-regression adjusted survival analysis predicted a 5.48-fold increase in hazard for patients with high (SUVmax > 8) compared with low (SUVmax < 8) ^{68}Ga-PSMA-11 intensity, independent of PSM status (HR 4.16;

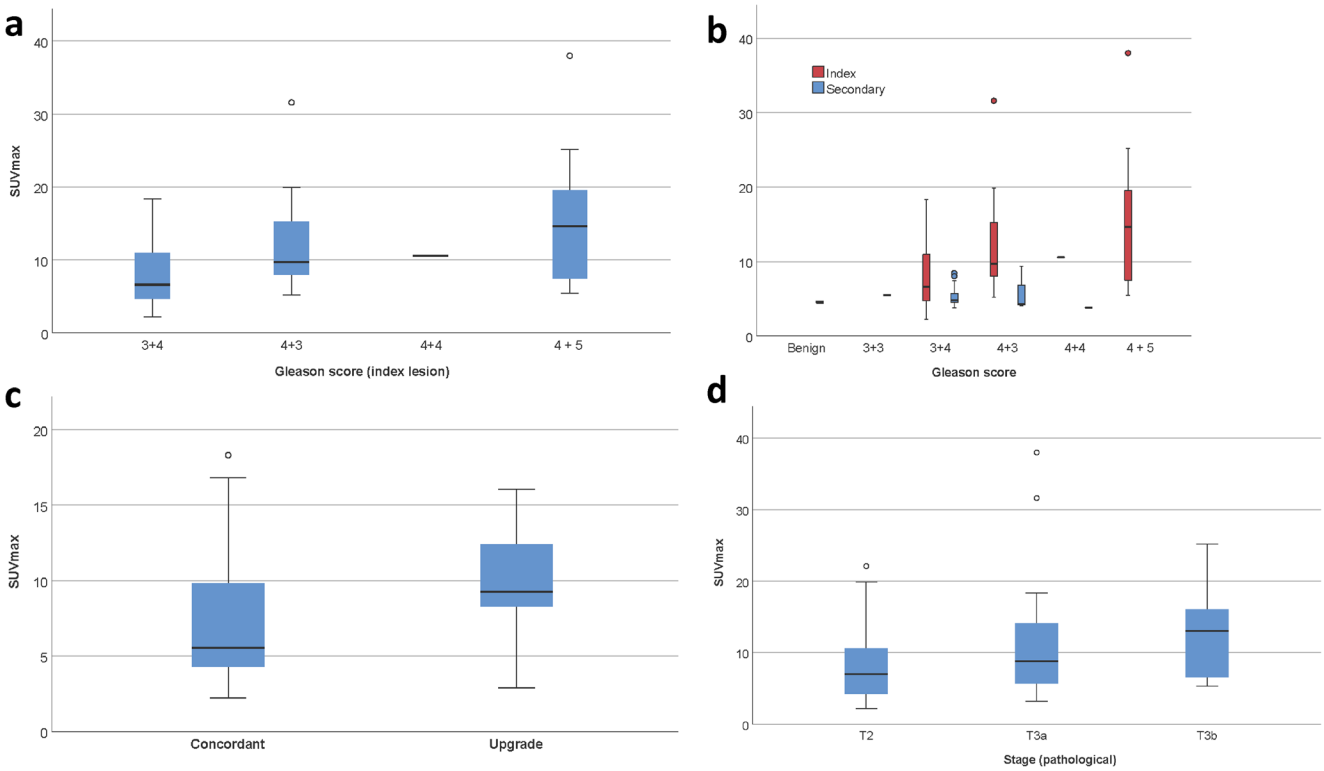

Fig. 1 Box plots of ^{68}Ga-PSMA-11 expression (SUVmax) according to RP histopathology, specifically **a** Gleason score groups of index lesion, **b** index (defined as focus with highest Gleason score; red bar) versus secondary lesion (blue bar) according to total Gleason score for each lesions, **c** upgrading of Gleason 3 + 4 to 4 + 3 at RP compared with concordant Gleason 3 + 4 histopathology and **d** stage (pathological)

Supplementary Table 2; Fig. 2b). PSM and high ^{68}Ga-PSMA-11 intensity demonstrated worst PFS (Supplementary Fig. 2).

No additive predictive benefit of SUVmax was seen in patients with higher grade (Gleason ≥ 4 + 3) disease (HR 1.94; 95% CI 0.55–6.81; Supplementary Table 2, Supplementary Fig. 3).

Discussion

Prior publications have reported a correlation between PSMA SUVmax and Gleason score [3, 7], tumour volume [8] and genomic instability [9]. However, to our knowledge, this is the first report of the prognostic potential of intraprostatic of ^{68}Ga-PSMA-11 intensity in vivo in correlating all of Gleason score, upgrading on RP, adverse surgical pathology and PFS following RP. These findings are among the first to demonstrate the prognostic potential of ^{68}Ga-PSMA-11 PET/CT in the primary staging setting.

This study demonstrated that intraprostatic ^{68}Ga-PSMA-11 intensity can provide prognostic information, particularly among patients with Gleason score 3 + 4 on biopsy. The observed strong association with PFS suggests that ^{68}Ga-PSMA-11 intensity in vivo may reflect underlying tumour biology and has potential as a meaningful biomarker in localised PCa. High ^{68}Ga-PSMA-11 expression ex vivo [4] and intensity in vivo [7] are associated with higher Gleason score and index lesion designation on RP histopathology, regardless of Gleason score and tumour volume, indicative of protein density in biologically aggressive disease [4, 9]. Thus, the association of high PSMA intensity with adverse oncological associations suggests that PSMA PET/CT detects the index lesion, the primary source of metastasis and disease progression [9].

Our findings have significant implications for management of Gleason 3 + 4 disease. There is increasing use of active surveillance and focal therapy in this cohort, however with ongoing uncertainty as to oncologic safety [3]. A SUVmax of > 8 in Gleason 3 + 4 malignancy could be a potential prognostic biological marker of more aggressive disease and have negative implications for suitability of commencing active surveillance.

Furthermore, ^{68}Ga-PSMA-11 has improved accuracy in characterisation of intraprostatic burden of disease, detecting more tumour foci than mpMRI [3, 8], supporting the increasing use of ^{68}Ga-PSMA-11 PET/CT globally for concurrent local and distant staging. Prospective assessment of the additional benefit of intraprostatic ^{68}Ga-PSMA-11 PET/CT in

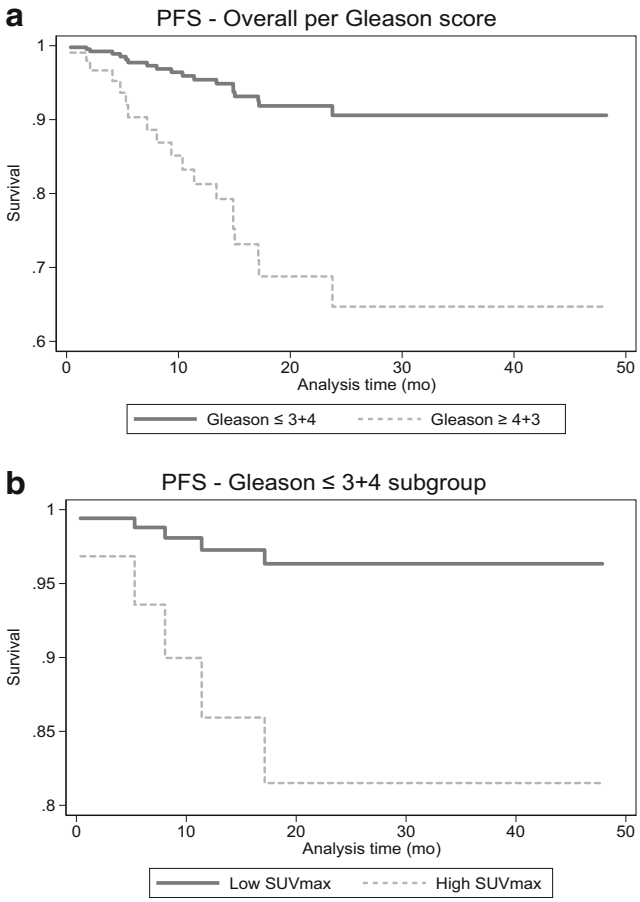

Fig. 2 Cox-regression adjusted analysis of progression-free survival (PFS) after radical prostatectomy (RP) for all patients according to Gleason score ≤ 3 + 4 or ≥ 4 + 3 (**a**) and within the Gleason score ≤ 3 + 4 subgroup according to low (SUVmax < 8) or high (SUVmax > 8) ^{68}Ga-PSMA-11 expression (**b**)

cancer detection and exclusion is underway (ANZCTR Number ACTRN12618001640291), from which intensity-related analyses are expected to reflect our findings.

The limitations of this study include the single-centre retrospective design and limited sample size. However, the observed relationship between SUVmax and Gleason score is consistent with other studies. Partial volume effect may have influenced smaller lesion detection and tumour volume associations; however, tumour volume is better characterised by PSMA PET/CT compared with mpMRI [8] while smaller tumours are less consequential [10] and unlikely to be of clinical significance.

In conclusion, intraprostatic ^{68}Ga-PSMA-11 intensity can provide prognostic information for adverse pathological outcomes and PFS, particularly among patients with Gleason score 3 + 4 on biopsy. Consideration of ^{68}Ga-PSMA-11 intensity information may further aid clinicians in patient selection during treatment planning and patient counselling for subsequent oncological outcomes. Multi-centre and prospective studies, with comparison to late imaging, are in preparation to further validate findings presented here.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The study received ethical approval from the Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee (Approval Number HREC/17/QRBW/644).

References

1. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multi-centre study. Lancet. https://doi.org/10.1016/S0140-6736(20)30314-7.
2. Emmett L, Tang R, Nandurkar R, Hruby G, Roach PJ, Watts J, et al. 3 year freedom from progression following 68GaPSMA PET CT triaged management in men with biochemical recurrence post radical prostatectomy. Results of a prospective multi-center trial. J Nucl Med. 2019.
3. Donato P, Roberts MJ, Morton A, Kyle S, Coughlin G, Esler R, et al. Improved specificity with (68)Ga PSMA PET/CT to detect clinically significant lesions "invisible" on multiparametric MRI of the prostate: a single institution comparative analysis with radical prostatectomy histology. Eur J Nucl Med Mol Imaging. 2018. https://doi.org/10.1007/s00259-018-4160-7.
4. Hupe MC, Philippi C, Roth D, Kümpers C, Ribbat-Idel J, Becker F, et al. Expression of prostate-specific membrane antigen (PSMA) on biopsies is an independent risk stratifier of prostate cancer patients at time of initial diagnosis. Front Oncol. 2018;8. https://doi.org/10.3389/fonc.2018.00623.
5. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016;40:244–52. https://doi.org/10.1097/PAS.0000000000000530.
6. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet. 2012;380:2018–27. https://doi.org/10.1016/S0140-6736(12)61253-7.
7. Uprimny C, Kroiss AS, Decristoforo C, Fritz J, von Guggenberg E, Kendler D, et al. 68Ga-PSMA-11 PET/CT in primary staging of prostate cancer: PSA and Gleason score predict the intensity of tracer accumulation in the primary tumour. Eur J Nucl Med Mol Imaging. 2017;44:941–9. https://doi.org/10.1007/s00259-017-3631-6.
8. Spohn S, Jaegle C, Fassbender TF, Sprave T, Gkika E, Nicolay NH, et al. Intraindividual comparison between (68)Ga-PSMA-PET/CT and mpMRI for intraprostatic tumor delineation in patients with primary prostate cancer: a retrospective analysis in 101 patients.

Eur J Nucl Med Mol Imaging. 2020. https://doi.org/10.1007/s00259-020-04827-6.

9. Kesch C, Radtke JP, Wintsche A, Wiesenfarth M, Luttje M, Gasch C, et al. Correlation between genomic index lesions and mpMRI and (68)Ga-PSMA-PET/CT imaging features in primary prostate cancer. Sci Rep. 2018;8:16708. https://doi.org/10.1038/s41598-018-35058-3.
10. Mouraviev V, Villers A, Bostwick DG, Wheeler TM, Montironi R, Polascik TJ. Understanding the pathological features of focality, grade and tumour volume of early-stage prostate cancer as a foundation for parenchyma-sparing prostate cancer therapies: active surveillance and focal targeted therapy. BJU Int. 2011;108:1074–85. https://doi.org/10.1111/j.1464-410X.2010.10039.x.