

68Ga-PSMA PET/CT-avid Tumour Volume: A Potential Prognostic Biomarker in Metastatic Hormone Sensitive Prostate Cancer

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Abstract

Background Prostate-specific membrane antigen (PSMA) PET/CT provides sensitive whole-body assessment in prostate cancer, yet the prognostic role of total tumour volume (TTV) is not fully defined in metastatic hormone-sensitive disease and needs further exploration.

Methods We retrospectively reviewed patients with de novo metastatic prostate cancer undergoing baseline PSMA PET/CT at Royal North Shore Hospital between 2014-2019. TTV was quantified using a standardized Standard Uptake Value (SUV) threshold, and patients were stratified by median TTV. Associations between TTV, progression-free survival (PFS), and overall survival (OS) were assessed using Kaplan–Meier and Cox regression analyses.

Results Fifty-nine patients were included in the study. Patients in the high-TTV group demonstrated reduced OS but no significant difference in PFS. Higher PSMA-derived TTV correlated with increased prostate-specific antigen (PSA) at diagnosis and higher rates of skeletal related events. Higher SUVmax was not associated with longer PFS or OS, nor was it associated with increased skeletal related events.

Conclusion Baseline PSMA PET/CT-derived tumour volume is an independent prognostic biomarker in metastatic hormone-sensitive prostate cancer, associated with inferior overall survival. Incorporating TTV into existing risk models may refine patient selection for treatment intensification.

Key words: prostate, PSMA, tumour volumes, prognostic biomarker, hormone sensitive

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Introduction

Prostate Cancer (PC) is the most commonly diagnosed cancer amongst men in Australia, accounting for 28% of male cancer diagnoses, with 25,500 new cases diagnosed in 2023 [1]. Whilst imaging with CT and Bone Scans has conventionally been used for Prostate Cancer staging, Prostate Specific Membrane Antigen (PSMA) PET/CT imaging is increasingly used in the metastatic disease settings. 68Ga-PSMA PET/CT (PSMA PET/CT) demonstrates increased sensitivity when compared to conventional cross-sectional imaging [2] as well as FDG PET scans [3]. Increased PSMA avidity is correlated with higher grade disease and poorer prognosis, but the role of PSMA-avid tumour burden in predicting survival and other clinical outcomes remains unclear [4].

PSMA PET Scans have also been increasingly used to guide the use of radiopeptide therapies such as lutetium-177 (177Lu)-PSMA-617. The VISION trial showed that this novel treatment improved overall and progression-free survival in patients with metastatic castrate resistant prostate cancer [4]. As PSMA avidity is required for effective delivery and efficacy of 177Lu-PSMA, PSMA PET/CT scans will be increasingly employed to select patients for this exciting therapy.

There has been some published data for patients with metastatic castrate resistant prostate cancer (mCRPC) examining the role of total tumour volumes (TV) in PSMA PET/CT. Higher PSMA-TV was associated with poorer overall survival (OS) in patients receiving 177Lu-PSMA [5], and decreased OS and progression-free survival (PFS) for those treated with cabazitaxel chemotherapy [6-7]. Similarly, a substudy of ENZA-p, which

looked at Lu-PSMA-617 plus enzalutamide in patients with mCRPC demonstrated that higher baseline PSMA-TV was associated with poorer overall survival [8]. There is, however, little data regarding the prognostic correlation between tumour volumes and outcomes in the setting of metastatic hormone sensitive prostate cancer (mHSPC), as well as its relationship to established prognostic markers such as the Gleason score and PSA. Given the evolving landscape of treatment for metastatic prostate cancer including novel anti-androgen therapies and chemotherapy in the upfront setting for high-risk hormone-sensitive metastatic patients, examining this cohort and being able to accurately assess risk has become more relevant than ever before.

We therefore sought to investigate the role of PSMA PET scans as a prognostic biomarker in patients with metastatic hormone sensitive prostate cancer, with a particular focus on the relationship between parameters such as tumour volume and SUVmax and outcome measures such as progression free survival (PFS) and overall survival (OS), which may help guide treatment decisions and individualization of systemic therapy choice.

Methods

We performed a single-centre retrospective study at Royal North Shore Hospital (RNSH), Australia from 1 January 2015 to 31 December 2020. Included patients had histologically confirmed metastatic prostate cancer and underwent [68Ga] Ga-PSMA-11 PET/CT within 3 months of initiating Androgen Deprivation Therapy (ADT) at RNSH (2014-2019). Patients were collected as two cohorts; patients in Cohort 1 received ADT + further systemic therapy (docetaxel, enzalutamide or abiraterone); Cohort

Table 1. Clinicopathologic characteristics of the cohort (n = 59).

Characteristic	Value
Age, y	Median 72 (range, 48-88)
Baseline PSA, µg/L	Median 7.9 (range, 0.19-282)
Gleason score, n (%)	
6-7	24 (41)
8-10	32 (54)
Unknown	3 (5)
Systemic therapy, n (%)	
ADT alone	39 (66)
ADT + enzalutamide	11 (19)
ADT + abiraterone	6 (10)
ADT + docetaxel	2 (3)
ADT + other	1 (2)
PSMA-avid tumour volume, mL	Median 13.8 (range, 0.27-479.3)
SUVmax of overall tumour burden	Median 27.7 (range, 4.6-98.9)

ADT = androgen deprivation therapy; CT = computed tomography; mHSPC = metastatic hormone-sensitive prostate cancer; PSMA = prostate-specific membrane antigen.

2 consisted of those receiving ADT alone.

PET/CT images were acquired on a scanner with Time-of-Flight capabilities and extended axial field of view (Biograph mCT.S/64 PET/CT, Siemens Healthcare, Hoffman Estates, USA). Injection of [⁶⁸Ga] Ga-PSMA-11 at a dosage of 200–250 MBq was followed 60 minutes later by PET/CT acquisition.

Images were analysed using MIM software (version 6.8.3) applying a flat SUV threshold of 4 using a semi-automated algorithm with removal of areas of false positive avidity (e.g. bladder). These contours were subsequently reviewed by expert nuclear medicine physicians with >10 years expertise to ensure veracity of measurements. Following finalization of contours, PSMA avid tumour burden (total, primary, metastatic) was collected along with SUVmax/SUVmean.

Relevant clinicopathologic variables including age, sites of metastatic disease, baseline PSA and Gleason score, as well as clinical outcomes (progression-free and overall survival) were collected through retrospective chart review.

The primary end point was progression-free survival (PFS), with secondary end points being overall survival (OS) and time to first skeletal related event (TSRE). Both PFS and OS were censored at time of last follow-up, 9 years and 6 months. As per standard practice, progression-free survival was judged as time to a composite of radiological progression, initiation of new systemic therapy, a rise in PSA of >2 ng/mL confirmed by two tests a minimum of two weeks apart, or death. Overall survival was defined as time from treatment initiation to death from any cause. Patients were censored at date of last known follow-up where relevant. Skeletal related events were defined as: pathological

fracture, spinal cord compression, necessity for radiation to bone for either pain or impending fracture, or surgery to bone.

Clinicopathological variables were presented descriptively. The patient cohort was dichotomised by median total PSMA-avid tumour volume, and Gleason score (6-7 vs 8-10), PFS, OS and TSRE were compared between such cohorts using the log-rank test.

This study received ethical approval from the NSLHD HREC, approval number 2020/ETH0059.

Results

In total, 59 patients were included in this study. The median age was 72 years (range, 48–88). Over half of the cohort (54%) had a Gleason score of 8–10. The median baseline PSA was 7.9 µg/L (interquartile range, 3.3–20.7). All patients received androgen deprivation therapy (ADT): 66% received ADT alone and 34% received additional systemic therapy (19% enzalutamide, 10% abiraterone, 3% docetaxel, and 2% other). Median follow-up for surviving patients was 39.9 months. Clinicopathologic characteristics are summarized in **Table 1**.

The median PSMA-avid tumour volume (TV) was 13.8 mL (range, 0.27–479.3), and the median SUVmax of overall tumour burden was 27.7 (range, 4.6–98.9). Patients were dichotomized into high- and low-volume groups using the median TV cutoff (**Figure 1**). Median PFS did not differ significantly between groups (26.5 vs 43.0 months; HR, 0.59; 95% CI, 0.31–1.14; *p* = 0.118). In contrast, median OS was significantly shorter in the high-TV group than in the low-TV group (56.6 vs 82.3 months; HR, 0.29; 95% CI, 0.11–

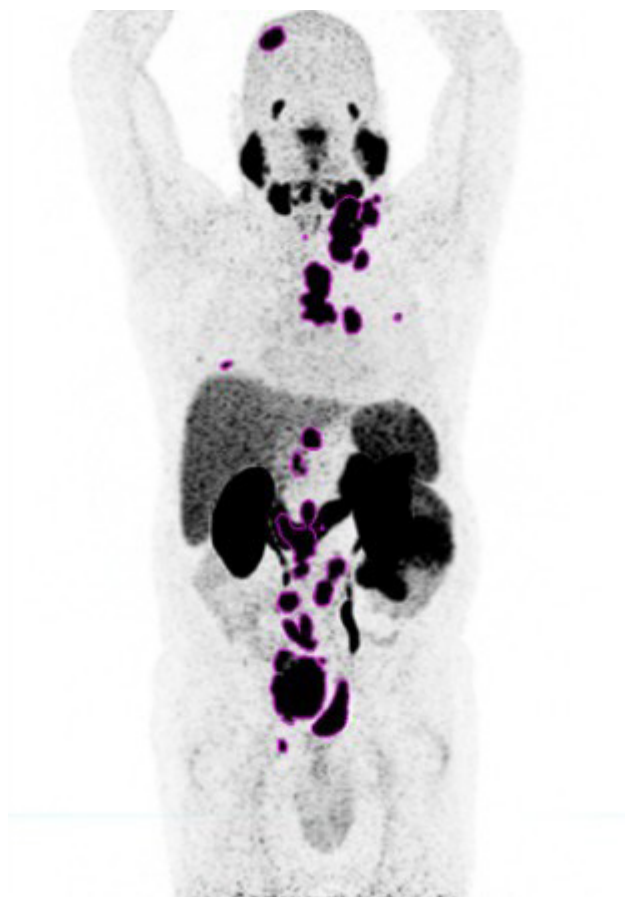


Figure 1. Indicative [⁶⁸Ga] Ga-PSMA-11 PET/CT image, maximal intensity projection (PSMA-avid lesions outlined in blue).

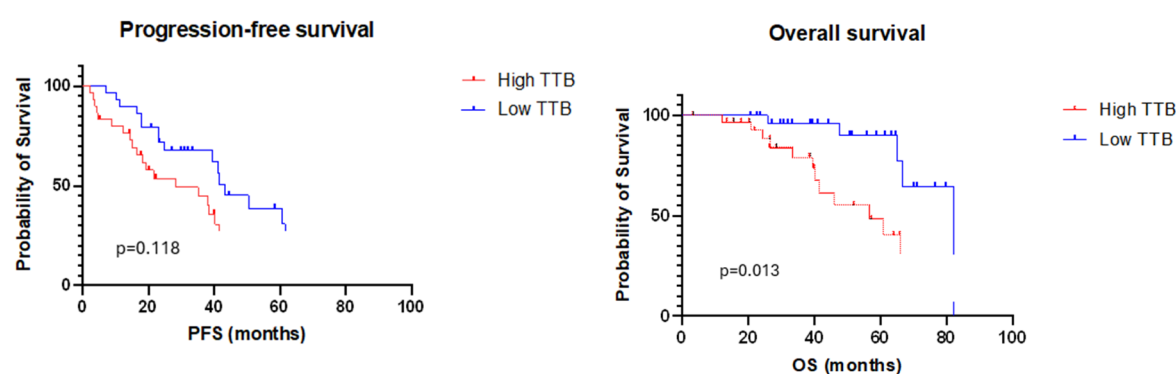


Figure 2. PFS and OS in in high-TV group and the low-TV group.

0.77; $p = 0.013$) (**Figure 2**).

There was no difference in overall survival between patients in cohort 1 (ADT alone) and those in cohort 2 (ADT with additional therapy, either chemotherapy or targeted therapy) (median OS 66.6mo vs NR), HR 0.62 95% CI 0.0-1.79, $p = 0.38$). OS was numerically higher for patients on ADT alone, likely reflecting the more indolent biology of this group resulting in their selection for ADT alone. There was also no significant difference when comparing patients with ADT alone and those who had ADT + targeted therapy (i.e. excluding those who had ADT + chemotherapy) - (median OS 66.6mo vs 41.6mo, HR 0.62, 95% CI 0.19-2.02). Detailed analyses for overall survival by univariate analyses are shown in **Table 2**. Multivariate analyses were not performed due to the small size of the patient cohort.

Finally, we investigated the prognostic value of SUVmax in our cohort, appreciated the relative lack of data linking SUVmax to survival outcomes to date. SUVmax on PSMA PET was not significantly associated with PFS (HR, 1.01; 95% CI, 0.99-1.02; $p = 0.264$), OS (HR, 1.02; 95% CI, 0.99-1.04; $p = 0.120$), or skeletal-related events (SREs) (HR, 1.01; 95% CI, 0.99-1.04; $p = 0.260$).

As expected, patients with Gleason score 6-7 disease had improved survival compared with those with Gleason score 8-10. Median OS was 82.3 vs 64.8 months (HR, 0.35; 95% CI, 0.12-0.93; $p = 0.036$), and median PFS was 57.0 vs 21.6 months (HR, 0.34; 95% CI, 0.17-0.64; $p = 0.002$). Tumour burden was also

significantly lower in the Gleason score 6-7 cohort (mean, 32.7 vs 77.7 mL; $p = 0.030$).

Twelve skeletal-related events occurred: 8 patients required radiotherapy for painful or unstable bony lesions, 2 sustained pathological fractures, 1 developed spinal cord compression, and 1 underwent surgery for pain or impending cord compression. Time to skeletal-related event (TSRE) was shorter in the high-TV group compared with the low-TV group (HR, 4.6; 95% CI, 1.33-15.97; $p = 0.030$), although the median TSRE was not reached in either cohort.

Discussion

The current study demonstrates for the first time the use of PSMA PET tumour volumes as a prognostic biomarker in patients with metastatic hormone-sensitive prostate cancer. Current risk stratification of mHSPC patients in the de novo setting relies on the ARASENS/CHAARTED/LATITUDE definition (**Table 3**), which defines high risk patients as >4 metastatic sites of disease on conventional imaging [9-12] and often guides treatment recommendations. We would argue that a patient with a high PSMA-TV, which captures the total tumour burden, may be at higher risk than a patient with 4 small bone metastases (e.g. tumour volume <5 mL), highlighting the potential usefulness of tumour derived metrics as a more precise assessment of disease

Table 2. Univariate analysis for overall survival.

Category	Median OS (months)	Hazard Ratio (HR)
Cohort 1 (ADT + Additional Tx)	Not reached	
Cohort 2 (ADT alone)	66.6	HR 0.65 (95% CI 0.23-1.8); $p=0.38$
Gleason Score ≥ 8	64.8	
Gleason Score ≤ 7	82.3	HR 0.35 (95% CI 0.12-0.93); $p=0.036$
High Tumour Volume	56.6	
Low Tumour Volume	82.3	HR 0.29 (95% CI 0.11-0.77); $p=0.013$

ADT = androgen deprivation therapy; CT = computed tomography; mHSPC = metastatic hormone-sensitive prostate cancer; PSMA = prostate-specific membrane antigen.

Table 3. Definitions of high-volume and high-risk disease in landmark mPC trials.

Study	Setting and treatment	Definition of high volume / high risk disease
CHAARTED	Metastatic hormone-sensitive prostate cancer; docetaxel + ADT	Presence of visceral metastases and/or ≥ 4 bone metastases with ≥ 1 beyond the vertebral column and pelvis High risk: ≥ 2 of the following—
LATITUDE	Metastatic hormone-sensitive prostate cancer; abiraterone + prednisone + ADT	• Gleason score ≥ 8 • ≥ 3 bone metastases (on bone scan/CT) • Measurable visceral metastases High volume: Visceral metastases and/or ≥ 4 bone metastases with ≥ 1 beyond the vertebral column/pelvis
ARASENS	Metastatic hormone-sensitive prostate cancer; darolutamide + docetaxel + ADT	High risk: ≥ 2 of the following— • Gleason score ≥ 8 • ≥ 3 bone metastases (on bone scan/CT) • Measurable visceral metastases
Proposed definition		High PSMA tumour volume cutoff ≥ 14 mL

ADT = androgen deprivation therapy; CT = computed tomography; mHSPC = metastatic hormone-sensitive prostate cancer; PSMA = prostate-specific membrane antigen.

burden and prognostication. This is echoed by Unterrainer et al., who compared conventional imaging (CI) disease volume criteria to PET-based volume definitions (>107 mL) and found that 22% of patients with low volume disease (LVD) on CI were upstaged to high volume disease (HVD) and 5.9% of HVD patients on conventional imaging were downstaged to LVD [12]. This reinforces the use of PSMA-PET scans in this setting as providing the most useful and accurate information to inform treatment choice.

The median tumour volume of 14 mL in the current study was used to dichotomize our study cohort, and a statistically significant difference in overall survival was observed between the high TV and low TV cohorts. We do note that studies examining the prognostic and predictive value of PSMA-TTV in the metastatic castrate resistant setting had much higher median tumour volumes [13, 16]. Interestingly, whilst OS was significantly lower in the high TV group compared to the low TV group, the difference in PFS between the two groups was not statistically significant. The finding with regards to OS is consistent with existing literature [5-6], and the lack of significance with regard PFS may potentially be explained by the heterogeneity of patients included in the current study, or the small cohort. This finding may also potentially suggest that treatment is effective in early lower volume disease but less so in higher volume disease. Other variables which were considered in our analysis also need to be taken into account, for example the difference in overall survival between the different treatment arms of Cohort 1 and Cohort 2, as well as OS differences by Gleason score. Of note, 1 patient with histological evidence of neuroendocrine differentiation was included in our study, which was an exclusion criteria for LATITUDE.

Interestingly the SUVmax on PSMA PET was not significantly associated with improved survival or skeletal related events. This is concordant with prior studies that demonstrated a statistically significant correlation with PSA levels as a surrogate marker of tumour burden, whereas SUVmax and SUVmean did not correlate to OS in early stage or biochemically recurrent disease [14-15]. The relationship between PSMA PET scan as potential biomarker and other existing biomarkers needs to be further explored in the metastatic hormone sensitive setting.

It is also notable that there is no widely accepted voluming

method for PSMA PET. Contouring using both relative (percentages of SUVmax) and absolute (flat) thresholds have been investigated. Whilst prior studies have suggested SUVmax cutoffs of 5.30 [13] and 3 [16], we adopted a SUV cutoff of 4 based on review of locally acquired imaging to strike a balance between identifying disease effectively and minimising identification of physiological uptake. The European Association of Nuclear Medicine (EANM) recommends the use of percentage-based thresholding of SUVmax for assessment of tumour volume in 18F-FDG PET/CT [17], however there is no recommendation to date regarding contouring of 68Ga-PSMA PET/CT imaging. Studies have demonstrated the limitations of both relative and absolute thresholding [18-19]. We opted for a flat cutoff in the current study in an aim to establish a time-efficient, reproducible thresholding approach. There is a pressing need to define the best tumour voluming method to provide a quantitative imaging biomarker that can be used for prognostication, as well as to measure response.

We adopted an innovative semi-automated workflow in the current study, with contour verification by an experienced nuclear medicine physician to confirm accuracy. This paves the way to efficient generation of tumour volumes for potential clinical translation, as well as annotation of datasets for large-scale radiomic analysis and training of machine learning models. There has however been prior studies examining the accuracy of semi-automated methods for analysing PSMA PET tumour volumes with concern between variability between difference platforms which may limit clinical comparability [20-22]. It has been noted that assessment of volumetric parameters was time and labour intensive [14], again emphasizing the importance of generating an accurate and reproducible semi-automatic voluming method.

The strengths in this study lie in the robust imaging analysis which utilised semi-automated software to improve efficiency. To our knowledge it is the first data looking at prostate cancer in the metastatic castrate sensitive setting, and complements the existing literature on tumour volumes in more advanced disease, as well as that published regarding lutetium therapy. We acknowledge the relatively small numbers in this single centre, retrospective study. There is a need to investigate the prognostic value of tumour volumes in an expanded multicentre retrospective study, as well

as validation of our findings in prospective clinical trial settings to translate it to clinical practice. Prospective studies will also allow for the protocolised collection of prognostic variables such as performance status, PSA and histopathological variables.

Conclusion

We have identified PSMA-TV as a potential novel imaging biomarker that can be used not only as a prognostic tool but also to help guide treatment choice for patients with mHSPC, although noting the limitations of a small cohort. This adds to the existent evidence for patients with mHSPC, and potentially can help risk stratification in the setting of initially diagnosed metastatic disease. We hope that this study will prompt further investigation into the role of automated software to reduce physicians' workload and improve outcomes for patients.

Author contributions

GB drafted the manuscript and analysed the data, AY assisted with drafting the manuscript and collecting data, DC assisted with drafting the manuscript, statistical analysis and developed the design of the study. MT and WHC assisted with data collection. EH analysed images. JC, TE, GH, AK, AG and AL assisted with study design and coordination, All authors read and approved the final manuscript.

Competing interests

All authors declare no competing interests.

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