An Audit of the Patterns of Prostate Carcinoma Metastases in Patients Referred for PSMA PET/CT Imaging at Charlotte Maxeke Johannesburg Academic Hospital

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Declaration

I, Mbali Nonhlanhla Matyeshana, declare that this research report is my own work. It is being submitted for the degree of MMed (Nuclear Medicine) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

_____
Dr Mbali Nonhlanhla Matyeshana
On this 30th day of July 2025

DEDICATION

This thesis is dedicated to my family: my husband and our two precious daughters for their unwavering support, patience, and encouragement throughout this journey.

To my parents, who instilled in me the values of perseverance and lifelong learning, and to my mentors and colleagues, whose guidance and wisdom have shaped my path in nuclear medicine.

I dedicate this work to every patient who has inspired my pursuit of knowledge in medical research.

May this contribution serve as a step toward improving the lives of those we care for.

Publications and presentations

This work has never been published.
This work has never been presented at a congress.

Abstract

INTRODUCTION: Prostate cancer (PCa) remains a significant global health concern, with accurate staging being key for effective management and prognostication.

AIM:

This study aimed to audit the findings from Prostate Specific Membrane Antigen (PSMA) PET/CT reports and describe the patterns of metastases in patients referred for initial staging at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), while investigating associations between serum index Prostate Specific Antigen (iPSA) levels, Gleason Scores (GS), and disease burden.

METHODOLOGY:

A retrospective analysis was conducted on 108 PSMA PET/CT reports performed between January 2018 and December 2020. Patient data, including demographics, serum iPSA levels, GS, and PSMA-avid disease sites, were analyzed.

RESULTS:

The majority of patients (84.3%) had biopsy-confirmed adenocarcinoma, with 40.7% presenting with an iPSA ≥20 µg/L. Metastatic patterns included locoregional nodal disease (23.2%), distant nodal disease (12%), and distant organ involvement (15.7%), primarily in bone (88.2%). Statistically significant findings included the association of locoregional ($p=0.002$) and distant nodal disease ($p=0.013$) in high-risk patients, and extra-pelvic nodal involvement with iPSA >20 µg/L ($p=0.018$). Higher GS (≥8) was significantly linked to locoregional ($p<0.001$) and distant nodal metastases ($p=0.001$).

CONCLUSIONS: These findings demonstrate the utility of PSMA PET/CT in the staging of all 3 risk categories of PCa, providing evidence for its role in guiding personalized treatment approaches.

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List of Abbreviations and Terminology

- ADT: Androgen Deprivation Therapy
- AJCC: American Joint Committee on Cancer
- BPH: Benign Prostatic Hyperplasia
- CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
- DRE: Digital Rectal Examination
- EANM: European Association of Nuclear Medicine
- EAU: European Association of Urology
- FDA: Food and Drug Administration
- ^{18}F-PSMA: Flourine-18 Prostate Specific Membrane Antigen
- ^{68}Ga-PSMA: Gallium-68 Prostate Specific Membrane Antigen
- ISUP: International Society of Urological Pathology
- miTNM: molecular imaging TNM
- MRI: Magnetic Resonance Imaging
- NCCN: National Comprehensive Cancer Network
- NPV: Negative Predictive Value
- PCa: Prostate Carcinoma
- PET/CT: Positron Emission Tomography / Computed Tomography
- PLND: Pelvic Lymph Node Dissection
- PPV: Positive Predictive Value
- PSA: Prostate Specific Antigen
- RP: Radical Prostatectomy
- SNMMI: Society of Nuclear Medicine and Molecular Imaging
- SUVmax: maximum Standardized Uptake Value
- TRUS: Trans-rectal Ultrasound
- TURP: Trans-urethral Resection of the Prostate

1. Introduction

1.1. Introduction

Prostate carcinoma (PCa) is the 5th most common cause of mortality due to cancer, with a worldwide incidence estimated at 1.4 million cases diagnosed worldwide in 2020 (1,2). A number of Sub-Saharan countries (including South Africa) have shown an annual increase in mortality rates ranging from 2 -10% during the period of 1995 – 2018 (1). The mortality rates from PCa vary considerably worldwide, with a noted decrease in developed countries over the last decade (2). In the African context, PCa showed age-standardized incidence and mortality ratios of 29.7 per 100 000 and 16.3 per 100 000, respectively in 2020 (2). Southern Africa was reported to have a 60% increased incidence of PCa from 2002 – 2018 (3). In South Africa specifically, all 11 South African provinces reported PCa as the leading cancer amongst males, with incidence rates of 61.8 per 100 000 men as per the National Cancer Registry; this figure having doubled in 10 years (2007-2017) (4). South African mortality rates account PCa for 13% of male deaths (5).

Factors contributing to the rising PCa statistics in Africa in the past decade have been cited as: improved life expectancy, hereditary predisposition in black males, inconsistent screening or diagnostic programs as well as limited access to healthcare and treatment (4,5).

The majority of PCa demonstrate a slow progression in disease course which can be well monitored using Prostate Specific Antigen (PSA) screening and/or active surveillance. These measures are not without pitfalls, as they can result in over-diagnosis and/or over-treatment. Early detection is associated with prolonged survival with a reported 5-year survival of almost 100%, while the presence of metastases has shown a significant reduction in the survival rate (6). Primary staging of the disease has become crucial in the accurate characterization of the overall disease burden, to allow a more personalized and targeted approach to the management strategy.

The Food and Drug Administration (FDA) approved Gallium-68 Prostate Specific Membrane Antigen-11 (^{68}Ga-PSMA-11) for clinical use in December 2020, the first radiopharmaceutical specifically targeting PSMA-avid PCa on PET/CT imaging (7). However, its global implementation remains variable due to regional differences in availability and cost. Furthermore, the distribution patterns of prostate cancer metastases in South African patients may differ from global trends due to differences in genetic and environmental factors. There is,

therefore, a need for continued research on PSMA PET/CT imaging of PCa in the local context to inform local guidelines, policy and clinical practice.

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) is a quaternary level hospital in South Africa serving a diverse population with a high burden of cancer in the greater Johannesburg region. It is the only hospital with a PET/CT unit in this region and, as such, receives patients from surrounding hospitals (e.g. Chris Hani Baragwanath Hospital and Helen Joseph Hospital) for specialized healthcare services.

The current study aims to determine the patterns of disease identified on PSMA PET/CT imaging at our institution.

1.2. PSMA Ligands

PSMA (or glutamate carboxypeptidase II), is a transmembrane glycoprotein made up of 3 distinct segments, (namely, 19 amino acid internally, 24 amino acids located in the membrane and 707 amino acids externally). It lies in the cell membrane of normal prostate tissue, with 100-1000 fold increased expression in neoplastic prostate tissue (specifically associated with the tumour neovasculature) (8,9). It has been suggested that the neoplastic over-expression of PSMA is mediated by cellular folate metabolism, where the external component of the molecule aids in processing of the folate metabolites from tumour cells and contributes to their propagation (9).

PSMA ligand refers to the radiopharmaceuticals which specifically target or bind the PSMA on cell surfaces. They include: ^{68}Ga-PSMA -11, ^{18}F-PSMA-1007, ^{68}Ga-PSMA -I&T and ^{18}F-DCFPyL. Of these, ^{68}Ga-PSMA -11 is the most extensively researched and used today (10). These ligands have different properties and practical limitations based on their production, binding characteristics, half-life of the labelling isotope and route of excretion (11).

1.3. Histological confirmation

A histological diagnosis of PCa can be obtained from a prostate biopsy (ideally, transrectal ultrasound or multiparametric MRI-guided) sample or radical prostatectomy specimen (12). The 2016 World Health Organisation (WHO) Classification modified the histopathological staging of PCa to include the Gleason Score and Grade Group in all pathology reports (2,13). This provides a comprehensive assessment of the tumour subtype, quantified extent of positive

cores in the sample, dimensions of involved tumour cores, pathological staging and the involvement of surgical resection margins by tumour (2).

1.4. Classification and staging of PCa

1.4.1. TNM Classification

The purpose of staging is to evaluate for disease spread beyond the borders of the prostate gland, prior to selection of management approaches (14).

The latest TNM staging system of the American Joint Committee on Cancer (AJCC) has both clinical (cTNM) and pathological (pTNM) components. In the cTNM, the Tumour, lymph node (N) and Metastatic status are based on findings detected by digital rectal examination (DRE) (2) and are provided in Figure 1.1. pTNM is based on histopathological findings following prostate biopsy or resection together with the findings on conventional (CT/MRI) and functional (SPECT/CT and PET/CT) imaging. The American Joint Committee on Cancer (AJCC) 8th edition incorporation of serum PSA levels, TNM staging and Group Grade into a comprehensive and dynamic prognostic Stage Group is provided in Figure 1.2.

The pathways of metastatic spread in prostate cancer mainly involve regional lymph nodes (pelvic and para-aortic) and the bones (10). Extra-nodal visceral metastatic sites occur in the lung and liver. Malan & Vangu described the most common metastatic sites in the skeleton (84%), lymph nodes (10.6%) and liver (10.2%) (10).

T - Primary Tumour (stage based on digital rectal examination [DRE] only)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour that is **not palpable**
T1a	Tumour incidental histological finding in 5% or less of tissue resected
T1b	Tumour incidental histological finding in more than 5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate
T2a	Tumour involves one half of one lobe or less
T2b	Tumour involves more than half of one lobe, but not both lobes
T2c	Tumour involves both lobes
T3	Tumour extends **palpably** through the prostatic capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional (pelvic) Lymph Nodes[1]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M - Distant Metastasis[2]	
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
M1b	Bone(s)
M1c	Other site(s)

[1] *Metastasis no larger than 0.2 cm can be designated pNmi.*

[2] *When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.*

Figure 1.1: cTNM staging system for prostate cancer (2)

1.4.2. Gleason Score (GS) and ISUP Grading Groups

The GS is made up of the most extensive pattern in the biopsy sample (primary grade) added to the second most extensive pattern (secondary grade), with each grade scored out of 5 (2). In the presence of only 1 pattern, the score is doubled to give the summed GS. PCa grading systems have been incorporated into the overall assessment of the patient's disease burden as per the International Society of Urological Pathology (ISUP) Consensus Conference in 2014. The following Grade Groups (1 to 5) are endorsed (15):

- **Grade Group 1**: Gleason score ≤6; only individual discrete well-formed glands
- **Grade Group 2**: Gleason score 3+4=7; predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
- **Grade Group 3**: Gleason score 4+3=7; predominantly poorly formed/fused/cribriform glands with lesser component of well-formed glands
- **Grade Group 4**: Gleason score 4+4=8; 3+5=8; 5+3=8

- **Grade Group 5**: Gleason score 9–10; lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands

WHEN T IS...	AND N IS...	AND M IS...	AND PSA IS...	AND GRADE GROUP IS...	THEN THE STAGE GROUP IS...
cT1a-c, cT2a	N0	M0	<10 ng/mL	1	I
pT2	N0	M0	<10 ng/mL	1	I
cT1a-c, cT2a	N0	M0	≥10, <20 ng/mL	1	IIA
pT2	N0	M0	≥10, <20 ng/mL	1	IIA
cT2b-c	N0	M0	<20 ng/mL	1	IIA
T1-2	N0	M0	<20 ng/mL	2	IIB
T1-2	N0	M0	<20 ng/mL	3	IIC
T1-2	N0	M0	<20 ng/mL	4	IIC
T1-2	N0	M0	≥20 ng/mL	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any	M1	Any	Any	IVB

Abbreviation: PSA indicates prostate-specific antigen. [a]Note that, when either PSA or grade group is not available, grouping should be determined by T category and/or either PSA or grade group, as available.

Figure 1.2: AJCC PCa Prognostic Stage Groups (15)

1.5. Risk Stratification

Risk stratification for the probability of disease recurrence is done using criteria updated by the European Association of Urology (EAU) and National Comprehensive Cancer Network (NCCN). Traditionally, these were: low, intermediate and high-risk. The latest NCCN guideline (14) further sub-divides the intermediate risk group into two separate entities categorized as favourable and unfavourable, which have been shown to have different tumour characteristics from each other and thus warrant separate management. The favourable risk group demonstrates low-risk characteristics, while the unfavourable group demonstrates high-risk pathological course. The favourable intermediate-risk group fulfills 3 criteria: 1 intermediate-risk factor, Gleason Score of 3+4=7 (or less), <50% of biopsy cores positive for cancer. The unfavourable group comprises any of the following 4 criteria: 2 or more intermediate-risk factors, GS of 4+3=7 (ISUP Grade 3+), PSA >20, >50% positive biopsy cores (14).

1.6. Imaging modalities in the work-up of newly-diagnosed PCa

1.6.1. Magnetic Resonance Imaging (MRI) and Computed Tomography (CT)

Imaging with multi-parametric MRI (mpMRI), using T2 weighted, diffusion-weighted and contrast-enhanced, offers accurate characterization of the primary tumour in the prostate gland

at a sensitivity and specificity of 91% (95% CI: 83–95%) and 37% (95% CI: 29–46%), respectively (2). In addition, tumour aggressiveness and risk of biochemical recurrence can be predicted. Within the pelvic field of view, enlarged loco-regional lymph nodes (>1cm) commonly seen in unfavourable intermediate and high-risk PCa (ISUP grade 2+) can also be assessed (2). There is, however, poor sensitivity (<30%) for very small (<0.5cm) nodal metastases in the pelvis which are associated with low- to intermediate-risk PCa (2). mpMRI imaging is superior to bone scintigraphy in the detection of skeletal lesions (16). Similarly, CT of the abdomino-pelvis evaluates lymph node morphology and size (short axis diameter >0.8 - 1cm) to determine locoregional nodal involvement of malignancy. A poor sensitivity (<1%) for sub-centimeter lymph nodes likely results in missed nodal lesions, particularly in low-risk PCa (2).

1.6.2. Bone Scintigraphy

In the South African context, a wholebody bone scan using the bone-targeting Single Photon Emission Computed Tomography (SPECT) tracer, ^{99m}Tc-Methylene Disphosphonate (MDP) is routinely used for patients with Gleason score >7 or PSA > 20 ng/mL and yields a good detection rate for osteoblastic skeletal metastases, with demonstrated sensitivity and specificity of 79% (95% CI: 73–83%) and 82% (95% CI: 78–85%), respectively (2).

1.6.3. Positron Emission Tomography/Computed Tomography (PET/CT)

Earlier guidelines from the EAU and the NCCN recommend the use of PSMA PET/CT imaging for initial staging of high-risk PCa; however, in practice, findings remain inconclusive (2).

The bulk of clinical research on PSMA PET/CT has mainly focused on its role in detecting biochemically recurrent or persistent disease (17). The 2023 joint guideline from the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine & Molecular Imaging (SNMMI) endorses routine investigation with PSMA PET/CT for intermediate- and high-risk PCa (8). Several studies have shown good performance of PSMA PET/CT in the staging of PCa. In the context of limited resources or availability, the 2017 South African Prostate Cancer Guidelines do not recommend PET/CT for initial staging of PCa, but rather for re-staging or suspected recurrence following definitive therapy (18). Tsechelidis et al (11) described an important clinical scenario where there is strong clinical suspicion for metastatic PCa based on markedly elevated serum PSA. PSMA PET/CT will not alter management and may sometimes be deferred in these patients. When PSMA Radioligand Therapy (PRLT) is

available, a staging PSMA PET/CT is indicated in metastatic PCa to assess eligibility for targeted therapy. PSMA-avidity is determined by the intensity of tracer uptake compared to physiological accumulation in the liver and spleen (which are used as reference sites for background uptake) (8). Donswijk et al (16) demonstrated N stage changes in 33% and M stage changes in 36% with change in management in 36% of cases. This study demonstrated a sensitivity of 66% and specificity of 99% for the detection of lesions in the staging of intermediate and high risk PCa (16).

1.7. Treatment planning of prostate cancer

1.7.1. Hormone-sensitive disease

Castration using ADT is predominantly used as 1st line therapy in these patients, which can consist of medical treatment (e.g. LHRH agonists/antagonists) or surgery (i.e. orchidectomy). In the E3805 CHAARTED trial published in 2015, high volume disease is defined as the presence of visceral metastases or more than 4 skeletal foci of metastases (1 or more being in the extra-axial skeleton) (19,20). In addition to ADT, these patients are treated with chemotherapy (i.e. Docetaxel) (18).

1.7.2. Castrate-Resistant Pca (CRPC)

CRPC is defined as disease progression despite adequate suppression, as evidenced by serum testosterone levels < 50 ng/mL, rising serum PSA levels or presence of new metastases. This scenario occurs in patients with failed hormonal treatment (described above) or treatment naïve patients. Treatment aims are primarily to improve overall survival (OS) and symptom control. First line therapy comprises chemotherapy with Docetaxel in combination with corticosteroids (i.e. Prednisone). Second-line therapy, in this regard, includes androgen receptor pathway inhibitors: Abiraterone Acetate (in patients post-chemotherapy) or Enzalutamide. Strategies for symptom control range from chemotherapeutic agents to bone-targeting therapies for predominant skeletal metastases (including radionuclide therapies such as Radium-223) (18).

1.8. Image Interpretation

The normal biodistribution of the tracer is ligand dependent. In our setting: when ^{68}Ga-PSMA -11 is used, physiological uptake of the tracer (ie. biodistribution) is seen in the lacrimal glands,

salivary gland, liver, spleen, and duodenum with excretion via the renal system (10,21). ^{18}F-PSMA-1007 on the other hand, has shown superior characteristics of larger tracer production with a longer half-life, smoother workflows, improved spatial resolution and better detection of genitourinary involvement, due to its predominantly hepatobiliary excretion (11). A standardized system of reporting during image interpretation aids in uniformity of findings as well as improved reporter confidence (2). Current Nuclear Medicine guidelines endorse several PSMA PET/CT reporting systems, including: EANM Delphi, the PSMA Reporting and Data System (PSMA-RADS), miTNM, E-PSMA, 5-point PRIMARY score and the Response Evaluation Criteria in PSMA imaging (RECIP) (8). Whole-body PET/CT images should be assessed by at least 1 qualified Nuclear Medicine physician. Special attention is given to: prostate gland or prostate bed as well as surrounding regional structures of the seminal vesicles, vas deferens and regional lymph nodes. Extra-pelvic nodal, skeletal, pulmonary and hepatic metastases are also evaluated (7). Malignant lesions demonstrate increased focal uptake of tracer compared to surrounding normal structures, i.e. high target-to-background ratio (7).

1.9. Pitfalls of PSMA PET/CT imaging

There are numerous pitfalls to the use of PSMA which impact image interpretation in patients with PCa. Benign PSMA uptake has been demonstrated in prostatitis, BPH, autonomic ganglia as well as in benign conditions such as Paget's disease, sarcoidosis, stroke and skeletal fractures (21). Well-established radiopharmaceuticals, such as ^{18}F-FDG, have a recognised maximum Standardized Uptake Value (SUVmax) cut-off (typically SUVmax >2.5) to assist reporting clinicians in assessing lesions as benign vs worrisome lesions – a clinically useful parameter for which consensus has not yet been reached for PSMA imaging (13). Ulas Babacan et al (22) reported an SUVmax ≥ 8.75 to have sensitivity of 78.9%, specificity of 59.05% and NPV of 82.4% in metastatic lesion detection, while the PRIMARY study proposed an SUVmax ≥12 with 100% specificity for clinically significant disease burden (23). Further investigation is required to determine potential SUVmax values for consensus. Tracer uptake in sympathetic ganglia mimicking lymph node involvement is an important cause of false positive findings and can be reasonably excluded based on location (e.g. cervical, caeliac or sacral) or shape (usually linear or comma-shaped) (8). Increased PSMA expression is also seen in other neoplasms such as breast, thyroid, lung and colorectal cancer due to uptake in tumour neovasculature (21). A photopaenic circumference or "halo" artifact may be visualized in patients with increased residual renal activity following micturition. This may obscure visualization of involved structures near the renal system (10). In approximately 5% of cases, malignant lesions can have

minimal or absent PSMA expression (i.e. not PSMA avid) and, thus, be poorly detected on PSMA PET/CT. Causes include absent PSMA expression or tumour de-differentiation (8). In such cases, the use of alternative radiotracers with a different mechanism of tracer localisation on to tumour cells is helpful, including: ^{11}C-Choline (cell membrane metabolism), ^{18}F-Fluciiclovine (amino acid synthesis), ^{18}F-FDG (tumour de-differentiation) (8). In our context, patients are often initiated on ADT prior to imaging and associated upregulation of PSMA receptor expression in malignant lesions may result. This increased PSMA uptake is highest during the first few weeks of ADT treatment, with gradual decrease over time as tumour reduction response occurs (8). Radiation exposure from injection of the radiotracers mentioned above and from CT acquisition are additional pitfalls (8).

Research studies reviewed showed some variability in the role of PSMA PET/CT and several authors recommended that further research needs to be conducted on PSMA PET/CT for initial staging of PCa.

1.10. Aim & Study objectives

The aim of this study was to conduct an audit of findings on PSMA PET/CT reports and describe the patterns of prostate cancer metastases in patients referred for initial staging at CMJAH. Furthermore, the presence and absence of primary disease and metastases was compared amongst the 3 defined risk group categories. We also investigated the association between serum iPSA levels and Gleason Score with the reported disease burden. Lastly, we investigated iPSA as a predictor of metastasis at initial staging.

2. Materials and Methods

2.1. Research paradigm

The study was conducted in the Nuclear Medicine PET/CT unit at CMJAH in Johannesburg, South Africa. We conducted a retrospective case analysis of patients with prostate cancer referred to the Nuclear Medicine department at CMJAH for ^{68}Ga-PSMA PET/CT as part of initial staging work-up.

2.2. Sample

From the CMJAH Nuclear Medicine digital archives, data was selected from 108 reports of PSMA PET/CT scans conducted from 1 January 2018 to 31 December 2020.

2.2.1. Inclusion and exclusion criteria

Patients who underwent ^{68}Ga- or ^{18}F-PSMA PET/CT scan for initial staging work-up during the study period. Patients with either a biopsy-confirmed diagnosis or a clinical index of suspicion for malignancy were included in the study sample. And those with missing relevant data in the PSMA PET/CT report were excluded from the study.

2.3. Data collection

PET/CT reports were retrieved from the Nuclear Medicine department's digital archiving system to extract data regarding demographics, namely: age, serum iPSA level, Gleason Score and PET/CT findings. There were no scans performed using ^{18}F-PSMA in our study sample. Data was collated and coded on Microsoft Excel datasheets. Each patient report was allocated a unique study number to maintain anonymity. The report findings were captured according to sites of PSMA-avid disease, namely:

- Prostate gland (primary)
- Invasion into locoregional structures (namely, the seminal vesicles and rectum)
- Regional lymph adenopathy (from the pelvis up to the level of the common iliac arteries)

- Distant lymph adenopathy (extra-pelvic nodes beyond the level of the common iliac arteries)
- Distant organ involvement

2.4. Data analysis and statistics

Continuous variables were assessed for normality using the histogram plot with a superimposed normal curve and the Shapiro Wilk test. Variable's that were normally distributed were summarized using mean (standard deviation (SD)) while variables that deviated from the normal curve were summarized using median (interquartile range (IQR)). Categorical variables were summarized using frequencies and percentages. Histogram plots and box plots were used to show a pictorial distribution of the continuous variables.

Risk groups were defined based on Gleason Score (GS) and/or serum index PSA (iPSA) levels. The low-risk category was defined by a GS of ≤6 **or** serum iPSA <10 ug/L. The intermediate-risk category was determined by GS of 7 **or** serum iPSA of 10-20 ug/L. The high-risk category was defined by GS of ≥8 **or** serum iPSA of >20 ug/L. When both the serum iPSA and the Gleason score were available in a single case report, the risk group was assigned to the higher of the two parameters. Where there was only a serum iPSA or Gleason score provided, then the risk group was assigned based only on that available variable.
A comparison was done of the metastatic disease burden against risk groups, GS and serum iPSA; the Chi-square test was used. A P-value less than 0.05 was considered statistically significant.

2.5. Ethics

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, approval number: M231166 M240513-G-0002. This certificate is attached as Appendix A. Patient consent was waived because this study was a retrospective analysis of previously collected clinical data from PSMA PET/CT scan reports archived in the Nuclear Medicine Department's database. The data was anonymized prior to analysis to ensure patient confidentiality. No direct patient contact or intervention occurred during the study.

Additionally, the study posed no risk to the patients, as it involved only the evaluation of existing records in our archives.

3. Results

3.1. Patients' characteristics

A total of 117 PSMA PET/CT reports were reviewed (all referred for staging of PCa); of these, 9 reports were excluded from the study due to missing data, with the remaining 108 reports being included in our study analysis. The mean (SD) age of the patients was 64.2 (7.7) years. The youngest patient was 39-years old and the oldest patient was 86-years-old. Figure 3.1 shows the age distribution of the patients on a Whisker box plot.

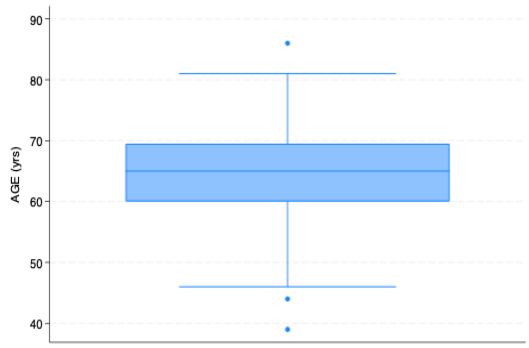

Figure 3.1: Age distribution of participants

Table 3.1 shows the characteristic summary of the patients. Majority of the patients (84%) had biopsy-confirmed adenocarcinoma, with the remaining patients having negative biopsies (but still having a high index of clinical suspicion for PCa). Overall, there was predominant GS of 7 (42%), ISUP grade group of 2 (17%) and serum iPSA levels of ≥20 ug/L for almost half of the patients (41%). There was information missing from some PET/CT reports, namely: Gleason score in 19% and serum iPSA levels in 14% of our sample reports. As mentioned earlier in this report, these patients remained in the study sample as there was either a Gleason score or an iPSA available to allow analysis.

Table 3.1: Clinical characteristics of the patients

Variable	Categories	Frequencies	Percentages
Histology	AdenoCa	91	84
	Negative	4	4
	Missing	13	12
Gleason score	6	16	15
	7	45	42
	≥8	26	24
	Missing	21	19
ISUP grade group	1	8	7
	2	18	17
	3	11	10
	4	3	3
	5	8	7
	Missing	60	56
Index/initial PSA (µg/L)	<10	2	20
	10-20	27	25
	More than 20	44	41
	Missing	15	14

ISUP: Internation Society of Urological Pathology. PSA: Prostate Specific Antigen

Table 3.1 tabulates the characteristics of the patient sample: 84% of patients were referred with biopsy-confirmed adenocarcinoma, with the remaining patients had negative biopsies (with a high index of clinical suspicion for PCa)

Figure 3.2 displays the risk groups of the patients, categorized into low-risk, intermediate-risk and high-risk. Our study results showed risk distribution of 11.9%, 32.7% and 55.5%, respectively. There were 7 case reports without a Gleason score or serum iPSA available and assignment of risk group could not be done in these patients.

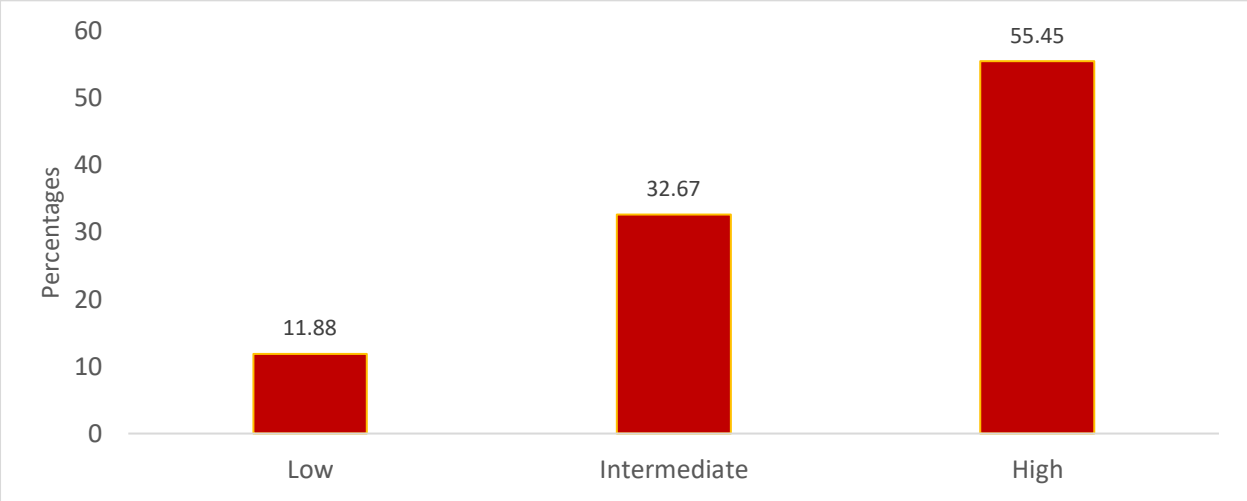

Figure 3.2: Risk group distribution

3.2. Metastatic disease patterns on PSMA PET/CT at initial staging

Table 3.2 shows the metastatic disease pattern of the patients. Overall, out of 108 cases reported to have PSMA-avid disease, 75% had primary disease in the prostate gland, 5% with locoregional (i.e. seminal vesicle or rectal invasion) disease, 23% had locoregional nodal disease, 12% had distant nodal disease and 15.7% had distant organ disease. Among the 17 patients with distant organ disease, the most common disease sites were: bone, liver and lungs, as demonstrated on Figure 3.3. Skeletal metastases to the spine showed almost equal distribution of thoracic and lumbar lesions, with only 1 lesion identified in the cervical spine. There was also a case reported to have "foci in virtually all the bones of the skeleton", including the spine.

Table 3.3 and Figure 3.4 show the distribution of the highest SUVmax reported in PSMA-avid lesions. For those with avid disease in the prostate gland, the SUVmax range was 3.8 to 61.0 with a median (IQR) of 15.1 (IQR: 9-19.3). The reported distant organ disease had an SUVmax range of 3.0 to 74.0 with a median (IQR) of 13.7 (IQR: 8.3-20.6).

Table 3.2: Distribution of PSMA-avid disease patterns

PSMA-avid disease on scan	Categories	Frequencies	Percentages
Avid disease in prostate gland	No	27	25
	Yes	81	75
Seminal vesicles or rectal invasion	No	103	95
	Yes	5	4
Locoregional nodal disease	No	83	77
	Yes	25	23
Distant nodal disease	No	95	88
	Yes	13	12
Distant organ disease	No	91	84
	Yes	17	16

Table 3.2 depicts the distribution of PSMA-avid disease patterns on scan: 75% had primary disease in the prostate gland, 5% with locoregional (i.e. seminal vesicle or rectal invasion) disease, 23% had locoregional nodal disease, 12% had distant nodal disease and 16% had distant organ disease.

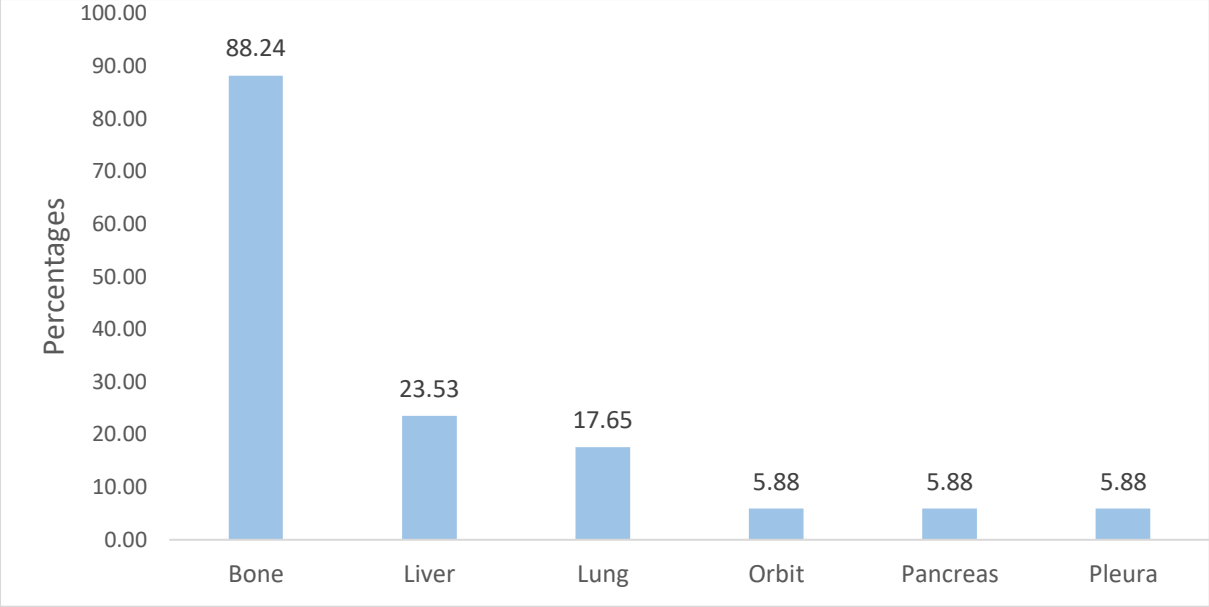

Figure 3.3: Distal organ disease sites (total patient number 17)

Table 3.3: Highest SUVmax measurements for regions of disease

PSMA-avid disease on scan	N	Min	Max	Mean	median	L-IQR	U-IQR
Prostate gland	81	3.8	61.0	17.2	15.1	9.0	19.3
Locoregional structures	5	3.5	59	16.0	4.8	3.7	9.0
Locoregional nodal disease	25	2.4	64.2	21.5	17.2	10.0	29.3
Distant nodal disease	13	4.3	57.0	21.9	17.5	9.7	26.3
Distant organ disease	17	3.0	74.0	17.6	13.7	8.3	20.6

Table 3.3 tabulates the highest PSMA intensities reported in different disease regions: the highest intensity reported was in a distant organ site (SUVmax 74) followed by locoregional lymph nodes (SUVmax 64.2) and primary disease in the prostate gland (SUVmax 61).

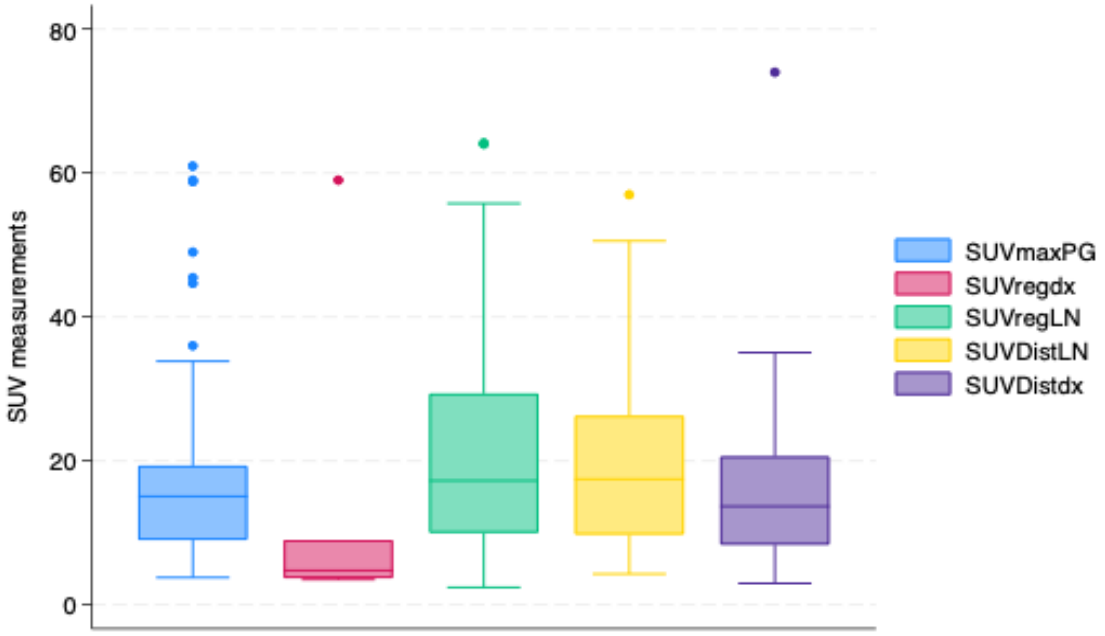

Figure 3.4: Box plots distribution of SUVmax measurements

SUVmaxPG: highest SUVmax measured in the prostate gland. SUVregdx: highest SUVmax measured where there was seminal vesicle or rectal invasion. SUVregLN: highest SUVmax measured in regional (pelvic) lymph nodes. SUVDistLN: highest SUVmax measured in distant (extra-pelvic) lymph nodes. SUVDistdx: highest SUVmax measured in distant organ disease.

3.3. Burden of disease amongst the defined risk groups (N = 101)

In total, 101 patients had both iPSA levels and GS available. The metastatic disease patterns stratified by the disease risk based on serum iPSA levels and Gleason score combined are shown in Table 3.4. Locoregional nodal disease was reported in 23 patients and 20 of these were categorized as high-risk; this was highly significant (p=0.002). Almost all 13 patients with distant nodal disease were from the high-risk group (92%), with only 1 patient in the low-risk group and, this was statistically significant (p=0.013). Distant organ disease was reported in 16 patients, 13 of which were in the high-risk group (81.3%); this was not statistically significant (p=0.076).

Table 3.4: Patterns of disease involvement stratified by risk group

PSMA-avid disease on scan	Low risk n(%)	Intermediate risk n(%)	High risk n(%)	P-value
Prostate gland				
No	6(50)	9(27)	12(21)	0.127
Yes	6(50)	24(73)	44(79)	
Locoregional structures				
No	12(100)	33(100.0)	51(91)	0.121
Yes	0	0	5(9)	
Locoregional nodal disease				
No	11(92)	31(94)	36(64)	**0.002**
Yes	1(8)	2(6)	20(36)	
Distant nodal disease				
No	11(92)	33(100)	44(79)	**0.013**
Yes	1(8)	0	12(21)	
Distant organ disease				
No	11(92)	31(94)	43(77)	0.076
Yes	1(8)	2(6)	13(23)	

Table 3.4 outlines the patterns of disease involvement stratified according to risk groups:
Locoregional nodal disease was reported in 23 patients and 20 of these were categorized as high-risk; this was highly significant (p=0.002). Almost all 13 patients with distant nodal disease were from the high-risk group (92%), with only 1 patient in the low-risk group and, this was statistically significant (p=0.013). Statistically significant P-values are in "bold."

3.4. Association between serum iPSA levels with disease burden (N=93)

The disease patterns found on our PSMA scans as stratified by serum iPSA levels are shown in Table 3.5. In total, 93 patients had serum iPSA levels available in the PET/CT report. There was extra-pelvic nodal involvement reported in 12 patients, of which 83.3% had iPSA > 20 ug/L, and this was statistically significant (p=0.018). Almost three-quarters (73.3%) of the patients reported with distant organ disease had iPSA > 20 ug/L, which was not statistically significant (p=0.057). The scan findings based on iPSA had a positive predictive value (PPV) of 80% (CI: 72-88%) and a negative predictive value (NPV) of 27% (CI: 18-36%).

Table 3.5: Association between serum iPSA levels and disease burden

	PSA <10 ug/L n(%)	PSA 10-20 ug/L n(%)	PSA >20 ug/L n(%)	P-value
Avid disease in prostate gland				
No	7(28)	7(28)	11(44)	0.833
Yes	15(22)	20(29)	33(49)	
Locoregional structures				
No	21(24)	26(30)	41(47)	0.836
Yes	1(20)	1(20)	3(60)	
Locoregional nodal disease				
No	20(27)	22(30)	31(43)	0.147
Yes	2(10)	5(25)	13(65)	
Distant nodal disease				
No	20(25)	27(33)	34(42)	**0.018**
Yes	2(17)	0	10(83)	
Distant organ disease				
No	19(24)	26(33)	33(42)	*0.057*
Yes	3(20)	1(7)	11(73)	

Table 3.5 depicts the association between serum iPSA levels and disease burden: there was extra-pelvic nodal involvement reported in 12 patients, of which 83% had iPSA > 20 ug/L, and this was statistically significant. Statistically significant P-values are in "bold."

3.5. Association between Gleason score and disease burden (N=87)

The PSMA-avid disease patterns stratified by the Gleason score are shown in Table 3.6. A total of 87 patients had Gleason Score reported. Of the 66 patients with avid disease in the prostate gland, approximately half had a GS of 7 (53%), which was not statistically significant (p=0.103). Of the 5 patients with locoregional disease, 3 had GS ≥ 8, however, this was not statistically significant (p=0.256). More than two-thirds of the 21 patients with locoregional nodal disease had GS ≥ 8 (66.7%), and this was very highly significant (p<0.001). Three-quarters of patients with distant nodal disease had GS ≥ 8 (75%), and this was highly significant (p=0.001). Over one-third of patients with distant organ disease had GS of 7 (40%), and this was not statistically significant (p=0.075). The findings on scan based on GS had a PPV of 86% (CI: 79-93%) and a NPV of 34% (CI: 27-48%).

Table 3.6: Association between Gleason score (GS) and disease burden

	GS ≤ 6 n(%)	GS = 7 n(%)	GS ≥ 8 n(%)	P-value
Avid disease in prostate gland				
No	7(33)	10(48)	4(19)	0.103
Yes	9(14)	35(53)	22(33)	
Locoregional structures				
No	16(20)	43(52)	23(28)	0.256
Yes	0	2(40)	3(60)	
Locoregional nodal disease				
No	15(23)	39(59)	12(18)	**<0.001**
Yes	1(5)	6(29)	14(67)	
Distant nodal disease				
No	16(21)	42(56)	17(23)	**0.001**
Yes	0	3(25)	9(75)	
Distant organ disease				
No	15(21)	39(54)	18(25)	*0.075*
Yes	1(7)	6(40)	8(53)	

Table 3.6 outlines the association between Gleason score (GS) and disease burden: 67% of the 21 patients with locoregional nodal disease had GS ≥ 8, and this was very highly significant (p<0.001). 75% of patients with distant nodal disease had GS ≥ 8 and this was highly significant (p=0.001). Statistically significant P-values are in "bold."

3.6. Overall disease burden on PSMA scan

Figure 3.5 shows results of the positive findings on PSMA PET/CT at initial staging. Local disease encompasses PSMA avid foci confined to the prostate gland. Locoregional disease has invasion of seminal vesicles / rectum as well as spread to pelvic lymph nodes and, lastly, distant disease involves extra-pelvic lymph nodes as well as distant organ sites.

Three-quarters of the patients had local disease (n=81, 75%), while 23% (n=25) had local regional disease and 19% (n=25) had distant disease.

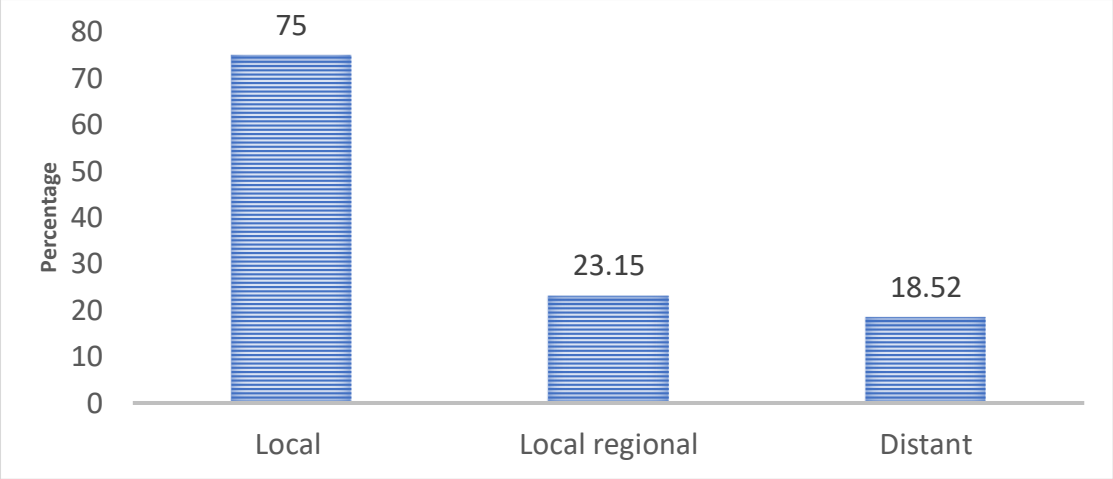

Figure 3.5: Bar chart of overall disease burden on scan findings

The patterns of disease reported on our PSMA scans are shown in Table 3.7, as categorized according to regional involvement. Out of the sample population of 108 cases, 80% were reported to have PSMA-avid disease. Approximately half of the patients had local disease at the primary site (prostate gland), with 12% having a combination of disease in the primary site with locoregional and distant involvement.

Table 3.7: Combinations of disease patterns on PSMA scan

PSMA-avid Disease	Frequency	Percentage
No disease	22	20
Local (prostate gland only)	56	52
Locoregional only (seminal/rectal)	0	0
Distant only	3	3
Local + Locoregional	10	9
Local + Distant	2	2
Locoregional + Distant	2	2
Local + Locoregional + Distant	13	12

Table 3.7 shows the combinations of disease patterns found on PSMA scan: Approximately half of the patients had local disease at the primary site in the prostate gland, followed by 13 patients (12%) having a combination of disease in the primary site with locoregional and distant involvement.

3.7. Serum PSA as a predictor of disease burden on scan (at initial staging)

Of the 93 patients with serum PSA levels available, 79% were reported to have disease on PSMA PET/CT scan (Figure 3.6). In the category with PSA <10 ug/L, disease was reported in 73%, while 78% of those with serum PSA of 10-20 ug/L were reported with disease and 81% for those with serum PSA >20 ug/L had disease involvement. The prediction of serum PSA on the presence of metastatic disease (i.e. extension beyond the primary prostate site) was determined using calculation of odds ratio's for the three iPSA groups. Where the iPSA was <10 ug/L, 10-20 ug/L or >20 ug/L, the odds ratios were 1, 1.02 and 2.57, respectively.

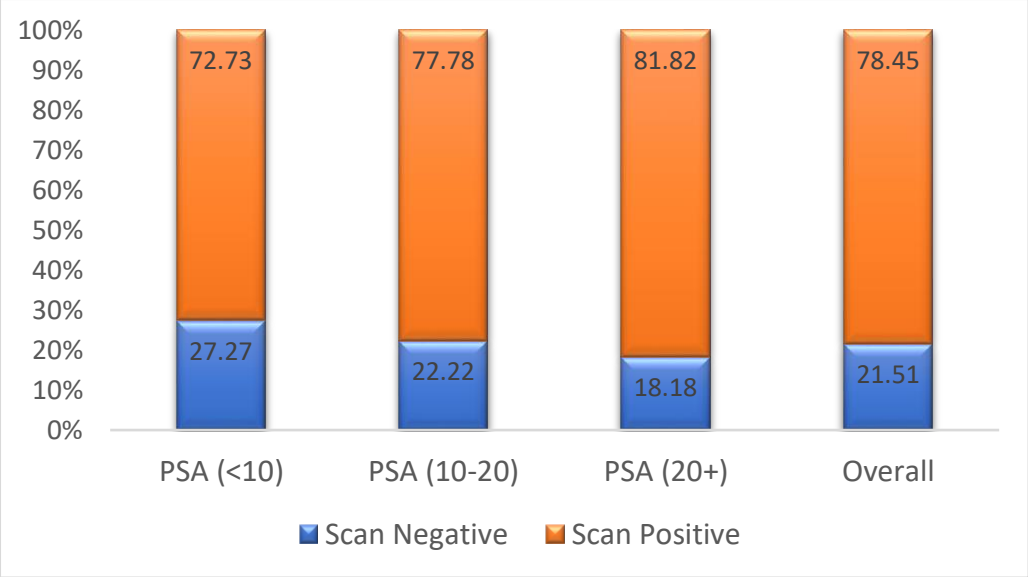

Figure 3.6: Stacked bar chart of disease burden on scan

Overall, our study demonstrated some significant findings and correlations in the metastatic patterns of prostate cancer (PCa). Locoregional nodal disease was significantly associated with high-risk patients, with 87% of cases reported in this category (p=0.002). Distant nodal involvement was predominantly seen in high-risk patients, accounting for 92% of cases, which was also statistically significant (p=0.013). Extra-pelvic nodal involvement showed a significant association with serum iPSA levels >20 µg/L (83%, p=0.018), supporting the predictive utility of elevated iPSA for distant lymph node metastases. Additionally, GS ≥8 was strongly associated with locoregional nodal disease (67%, p<0.001) and distant nodal disease (75%, p=0.001).

4. Discussion

Research on the role of PSMA PET/CT in Prostate carcinoma (PCa) has largely focused on detection of biochemical recurrence and restaging. The bulk of studies evaluating the utility of PSMA PET/CT in initial staging of newly-diagnosed PCa highlight its value in intermediate-risk and high-risk patient categories. Our study undertook to evaluate the role of PSMA PET/CT in disease detection in 3 risk group categories, low-, intermediate- and high-risk. A study of 40 Chinese patients by Zang et al (6) demonstrated 100% sensitivity of ^{68}Ga-PSMA 11 in the detection of primary prostatic lesion in treatment-naïve patients with GS 6-9. The metastatic distribution involved: bone (72.5%), lymph nodes (37.5%), lungs (12.5%) and liver

(10%). Klingenberg et al (24) conducted a retrospective study of 691 patients for primary staging of PCa using PSMA PET/CT, which demonstrated primary lesion detection in 97.3% of patients. There was regional lymph node involvement in 50.7% of patients and distant nodal involvement in 49.3%. Distant organ metastases involved: bone (16.8%) and other sites found in 2% of patients. In a retrospective study of 438 patients with intermediate and high risk PCa by Keidar et al (21), re-evaluation of ^{68}Ga-PSMA PET/CT images showed disease involvement in 72% of patients, with primary lesion detection in 43% of patients. Metastatic sites included: locoregional structures - such as the seminal vesicles, adjacent fatty tissue, bladder, and rectum (11%), regional lymph nodes (30%) and distant sites (46%). The distant nodal distribution included: mediastinal (45%), neck (31%), axillae (7%) and thoracic (16%) nodes. In a study of 49 males by Aghaee et al (25), the relationship between serum PSA levels and GS with PSMA PET/CT findings at 3 time points (early pelvic, 1-hour wholebody and 3-hour pelvic) was evaluated and findings showed a higher metastatic burden amongst the higher risk groups as well as positive correlation between GS and SUVmax in all 3 scan phases. Maserumule et al (26) evaluated the differences in the metastatic burden between 148 (black and white) South African males with PCa. PSMA PET/CT for initial staging in these patients with ISUP grades 1 and 2 PCa showed 52.7% patients with loco-regional disease involving the seminal vesicles; nodal disease was found in 20.9% of patients and skeletal involvement in 10.1%. Visceral metastases were detected in 3.4% of patients; of these: 60% were in the liver, 40% in the lungs and 20% in the brain.

The current study aimed to evaluate the metastatic patterns in PCa patients found on ^{68}Ga-PSMA PET/CT scans in our center. The relationships between serum iPSA levels, GS and disease burden were also evaluated. From our sample of 108 patients, 91 patients (84.3%) had biopsy confirmed adenocarcinoma while 17 patients (15%) were referred for PET/CT based on a high clinical index of suspicion for malignancy despite a negative result on prostate biopsy or even without a biopsy being performed. This is in keeping with clinical practice in resource-limited settings where biopsy may be deferred due to advanced disease, lack of availability or logical constraints, as highlighted by Maserumule et al. (26) in similar regional studies. Prostate biopsy may sometimes miss the site of tumour during needle sampling, giving a false negative result on histology; with a reported false negative rate of 20-40% (12,27) for TRUS-guided biopsy. From available histology results in our study, A GS 7 (41.7%) and ISUP Grade Group 2 (16.7%) were the most common, though ISUP grading was often omitted from reports. Serum iPSA levels were >20 ug/L in more than one-third of the patients, reflecting the proportion of high-risk patients. This was consistent with prior studies, including Klingenberg et al (24),

demonstrating elevated iPSA levels which correlated with aggressive disease findings. As per the D'Amico classification, risk stratification based on GS and iPSA levels categorized the majority of patients into intermediate (42.6%) and high-risk groups (31.5%), emphasizing the known utility of these parameters in predicting disease burden. The lack of histological confirmation of GS and iPSA in 19.4% and 13.89% of our cases, respectively, is identified as a limitation in overall risk assessment.

While PSMA PET/CT is currently recommended for staging high-risk PCa, our study population had more than half of the patients referred being low- and intermediate risk patients. These may have been patients with equivocal findings on 1st line conventional imaging (namely, bone scan or CT scan) or rising tumour markers (i.e. serum PSA) after diagnosis.

4.1. Avid Disease Patterns

In a study of 203 treatment-naïve patients, Ulas Babacan et al demonstrated significant correlation between risk classification, GS, ISUP group grade and metastatic burden (22). The majority of patients (75%) in our study demonstrated local disease confined to the prostate, with 23.2% showing locoregional nodal involvement and 15.7% exhibiting distant organ metastases. Among distant metastases, bone was the most common site (88.2%), followed by the liver (23.5%) and lungs (17.7%). This pattern is in agreement with the literature, including Fendler et al (8), Malan and Vangu (10), Zang et al (6) and Klingenberg et al. (24), who also reported a predominance of skeletal metastases. Locoregional disease (seminal vesicle or rectal invasion) was observed in 4.6% of our cases, predominantly in high-risk patients. Although not statistically significant, this trend supports findings in prior studies by Keidar et al. (21) and Ulas Babacan et al (22), which highlighted the association between advanced disease and higher risk categories.

4.2. Correlation with Serum iPSA Levels

Our study revealed significant associations between higher iPSA levels (>20 µg/L) and advanced metastatic disease. For instance, categorisation based on PSA levels showed that 83.3% of patients with extra-pelvic nodal involvement and 73.3% of those with distant organ metastases had elevated iPSA levels >20 µg/L, the latter approaching statistical significance ($p=0.057$). These findings align with Maserumule et al. (26), who found similar correlations in a South African cohort and demonstrating iPSA's role as a predictive biomarker for metastatic

disease burden. Interestingly, while iPSA was predictive of distant disease, its association with locoregional spread (pelvic nodal involvement) and primary prostate lesions was not statistically significant. This could be attributed to variability in PSA kinetics or PSMA expression in different tumour microenvironments in the prostate gland and warrants further investigation.

4.3. Correlation with Gleason Score

A strong correlation was observed between GS ≥8 and metastatic disease, consistent with findings by Ulas Babacan et al (22). Locoregional nodal involvement ($p<0.001$) and distant nodal disease ($p=0.001$) were significantly associated with higher Gleason Scores, consistent with previous findings by Klingenberg et al. and Zang et al (6,24). However, the association between GS and distant organ metastases was not statistically significant ($p=0.075$) in our study.

The finding of 6 out of 15 patients (40%) with distant organ disease having a GS of 7 (similar to findings by Ulas Babacan et al) suggests heterogeneous metastatic potential among patients with intermediate-risk disease (22). This reinforces the importance of integrating GS with other biomarkers (such as: iPSA, molecular profiling) to optimise risk stratification.

4.4. Overall Disease Burden

Three-quarters of patients presented with disease confined to the prostate gland, while 18.5% had distant metastases. Our results showed a stepwise increase in the odds ratios for metastatic disease across iPSA categories (<10 ug/L, 10–20 ug/L, >20 ug/L), which highlights the incremental risk associated with rising PSA level. Similarly, findings by Keidar et al. (21) demonstrated the prognostic value of serum PSA in predicting metastastic involvement in PCa staging.

4.5. Limitations of the Study

There are some limitations identified in our study. Missing data on GS and iPSA levels (i.e. not documented in reports) in a subset of patients restricted comprehensive risk stratification. The retrospective study design introduces potential selection and information bias, particularly

regarding report variability and non-standardisation in reporting. Our findings highlight the challenges of staging PCa in resource-limited settings, where incomplete clinical data may compromise data quality and accurate risk stratification. Reliance on reported imaging findings alone, without follow-up with histopathological confirmation of metastases, may have influenced the reported disease burden; therefore, confounding variables should be considered in interpretation of our results. The strength of our predicitive values could also be improved by histologial confirmation of Additionally, our study represents a single institution, limiting the generalisation of our findings. Future multicentre studies are needed to validate these results and explore potential differences in PCa presentation, particularly in the South African context.

5. Conclusion

Current guidelines recommend PSMA PET/CT in high-risk PCa patients. Our study findings support the utility of PSMA PET/CT in the context of staging newly-diagnosed malignancy in all 3 defined risk groups. There were notable findings in low-risk patients where PET/CT showed disease detection with some – albeit a minority – having distant metastases. Intermediate-risk patients were found to have both local and distant metastatic disease patterns. The findings, therefore, suggest the potential for future research into the role of PSMA PET/CT in the staging of lower risk PCa patients as well. Multi-centre trials with larger cohorts of patients are recommended in this regard.

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Appendix A: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Mbali Nonhlanhla Matyeshana

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M231166 M240513-G-0002

NAME: (**Principal Investigator**)	Dr Mbali Nonhlanhla Matyeshana
DEPARTMENT:	Nuclear Medicine Charlotte Maxeke Johannesburg Academic Hospital PET/CT Unit
DEGREE:	MMed (Nuclear Medicine)
PROJECT TITLE:	An Audit of the Patterns of Prostate Carcinoma Metastases in Patients referred for PSMA PET/CT Imaging at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	24-Nov-2023
DECISION:	Approved unconditionally
CONDITIONS:	N/A
NOTE:	Application Number: MED23-11-017.
SUPERVISORS:	Dr K. Purbhoo and Prof M. Vangu
APPROVED BY:	Prof P. Ruff, Chairperson, HREC (Medical)
DATE OF APPROVAL:	13-May-2024 **EXPIRY DATE:** 12-May-2029

This clearance certificate is valid for 5 years from data of approval. Extension may be applied for.

DECLARATION OF INVESTIGATOR(S)

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in the month date of convened meeting each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Email a signed copy of ethics clearance certificate to HREC-Medical.ResearchOffice@wits.ac.za

Signature of Principal Investigator

13/05/2024
Date

Appendix B: CMJAH CEO Final Approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries: *Ms N. Mzila*
Email: Nolwazi.Mzila@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 06 June 2024

GP 202311061

Dear Dr Mbali Matyeshana

Re: Final Approval of Study

Title: An Audit of the Patterns of Prostate Carcinoma Metastases in Patients referred for PSMA PET/CT Imaging at Charlotte Maxeke Johannesburg Academic Hospital.

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/ ~~Not Supported~~

Signed by:Patricia Nokukhanya Africa
Signed at:2024-06-06 15:37:32 +02:00
Reason:Witnessing Patricia Nokukhanya

Dr. P.N. Africa
Acting Clinical Director

Approved / ~~Not Approved~~

Ms G. Bogoshi
Chief Executive Officer: CMJAH

Appendix C: TURNITIN Result

FinalTurnitin MMed-3.docx

ORIGINALITY REPORT

32%	6%	14%	24%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	23%
2	"Annual Congress of the European Association of Nuclear Medicine October 13 – 17, 2018 Düsseldorf, Germany", European Journal of Nuclear Medicine and Molecular Imaging, 2018 Publication	3%
3	"EANM'17", European Journal of Nuclear Medicine and Molecular Imaging, 2017 Publication	1%
4	Pat Price, Karol Sikora. "Treatment of Cancer", CRC Press, 2025 Publication	1%
5	www.mdpi.com Internet Source	<1%
6	www.jrmds.in Internet Source	<1%
7	Anna Rebecca Lisney, Conrad Leitsmann, Arne Strauß, Birgit Meller, Jan Alexander Bucerius, Carsten-Oliver Sahlmann. "The Role of PSMA PET/CT in the Primary Diagnosis and Follow-Up of Prostate Cancer—A Practical Clinical Review", Cancers, 2022 Publication	<1%
8	www.medrxiv.org Internet Source	<1%

9	Hui Sze Wong, John Leung, Dylan Bartholomeusz, Peter Sutherland, Hien Le, Michelle Nottage, Ivan Iankov, Joe H Chang. " Comparative study between Ga-prostate-specific membrane antigen positron emission tomography and conventional imaging in the initial staging of prostate cancer ", Journal of Medical Imaging and Radiation Oncology, 2018 Publication	<1 %
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11	link.springer.com Internet Source	<1 %
12	Mina Swiha, Narjess Ayati, Daniela E. Oprea-Lager, Francesco Ceci, Louise Emmett. "How to Report PSMA PET", Seminars in Nuclear Medicine, 2023 Publication	<1 %
13	Scott R Gerst, Abdelkrim K Touijer, Bertrand Guillonneau, Hikmat Al-Ahmadie, Amir Mehdizade. "The importance of MRI evaluation in the preoperative work-up of prostate cancer", Nature Clinical Practice Urology, 2005 Publication	<1 %
14	J. Krammer, A. Schnitzer, C. G. Kaiser, K. A. Buesing et al. "18 F-FDG PET/CT for initial staging in breast cancer patients – Is there a relevant impact on treatment planning compared to conventional staging modalities?", European Radiology, 2015 Publication	<1 %
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Appendix D: TURNITIN Letter

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

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RE: TURNITIN result

The TURNITIN programme is detecting similar words from the title of previously conducted research between the Nuclear Medicine and Urology departments. However, the 2 studies are completely different in the aims, objectives and design.
Clearly, automated function of the tool used (Turnitin) simply picks up similar words from the prompt without deep analysis.

Signed

Dr MN. Matyeshana
Author

Date: 07/03/2025

Dr K. Purbhoo
Supervisor

Date: 07/03/2025

Prof. MDTHW Vangu
Supervisor

Date: 07/03/2025

Appendix E: Data Collection Spreadsheet (sample)

PSMA DATA CAPTURING SHEET						
PatientID	AGE (yrs)	HISTO	Gleason	ISUP Grade	indexPSA	RiskGroup
1	63	AdenoCa	7	2	18.7	IR
2	76	AdenoCa	9		27	HR
3	71	AdenoCa	7	3	800	HR
4	70	AdenoCa	8	4	2.1	HR
5	70	AdenoCa	9			HR
6	67	AdenoCa			134.3	HR
8	75	AdenoCa	6		6.9	LR
9	66	AdenoCa	6			IR
10	75	AdenoCa	9		12.02	HR
11	66	AdenoCa	9	3	17.7	HR
12	66	AdenoCa	7	3	89.9	HR
13	66	AdenoCa	7		25.3	HR
14	52	AdenoCa	6	1	133	HR
15	71	AdenoCa	9		30	HR
16	55	AdenoCa	7		9.3	IR
17	61	AdenoCa	7		276.9	HR
18	57	AdenoCa	7	2	10.42	IR
19	64	AdenoCa	6	1	40.5	HR
20	59	AdenoCa	7	2	6.9	IR
21	67	AdenoCa	7		106	HR
22	61	AdenoCa	9	4	27.73	HR
23	63	AdenoCa	9	5	452.21	HR
24	64	AdenoCa	9	5	61	HR
25	65	AdenoCa	7	2	7.4	IR
26	67	AdenoCa	7	3	23.86	HR
27	56	AdenoCa	7	3	49.9	HR
28	71	AdenoCa	6	2	11.72	IR
30	64	AdenoCa	7	3	18.63	IR
31	70	AdenoCa	7	3	21.3	HR
32	67	AdenoCa	6		23.37	HR
33	58	AdenoCa	10		4.55	HR
34	58	AdenoCa	7	2	70	HR
36	61	AdenoCa	7	2	17.81	IR
37	49	AdenoCa	7	2	19.8	IR
38	60	AdenoCa	7	3	154.16	HR
39	66	AdenoCa	7	2	14.2	IR
40	62	AdenoCa	8	4	8.1	HR
41	54	AdenoCa	6		16.1	IR
42	65	AdenoCa			40.4	HR
43	68	AdenoCa	7		23.6	HR
44	61	AdenoCa	9	5	23.15	HR
45	55	AdenoCa	7		22.3	HR

Prostate dx	SUVmaxPG	locoregdx	SUVregdx	Locoreg LN	SUVregLN	DistLNdx
Y	8.98	N	NA	N	NA	N
Y	6.46	N	NA	Y	24.08	Y
Y	59	Y	59	Y	20	Y
N	NA	N	NA	N	NA	N
Y	14	N	NA	Y	36	N
Y	10.61	N	NA	Y	14.9	N
Y	9.34	N	NA	N	NA	N
N	NA	N	NA	N	NA	N
Y	15.18	N	NA	Y	3.71	N
Y	49	N	NA	Y	64	N
N	NA	N	NA	N	NA	N
Y	24.69	N	NA	Y	64.15	Y
N	NA	N	NA	N	NA	N
Y	15.57	N	NA	N	NA	N
Y	13.22	N	NA	N	NA	N
Y	20.59	N	NA	N	NA	N
Y	4.42	N	NA	N	NA	N
Y	44.66	N	NA	N	NA	N
N	NA	N	NA	N	NA	N
Y	13	N	NA	N	NA	N
N	NA	N	NA	Y	42.34	N
Y	33.83	N	NA	Y	19.04	Y
Y	45.45	N	NA	Y	55.76	Y
Y	7.92	N	NA	N	NA	N
Y	15.06	N	NA	N	NA	N
Y	17.9	N	NA	N	NA	N
Y	10.92	N	NA	N	NA	N
N	NA	N	NA	Y	4.6	N
N	NA	N	NA	N	NA	N
Y	19.32	N	NA	N	NA	N
Y	5.7	Y	3.49	Y	2.93	Y
Y	16.41	N	NA	N	NA	N
Y	15.43	N	NA	N	NA	N
N	NA	N	NA	N	NA	N
Y	15.3	N	NA	N	NA	N
Y	7.53	N	NA	N	NA	N
Y	15.17	N	NA	N	NA	N
Y	15.95	N	NA	N	NA	N
Y	27.02	N	NA	N	NA	N
N	NA	N	NA	N	NA	N
Y	11.51	N	NA	N	NA	N
Y	33.04	N	NA	N	NA	N

Appendix F: Note on referencing style

Please note that the referencing in this thesis is a modification of the Vancouver Referencing style, done according to the Faculty of Health Sciences Style Guide as set out by the Wits Health Sciences Library.

The information on this WHSL Vancouver Citation Style Guide for Theses, Dissertations and Research Reports is available from http://libguides.wits.ac.za/whsl-vancouver updated on 8 August 2017.