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THE CORRELATION BETWEEN PSA, GLEASON SCORE AND BONE SCAN FINDINGS

DR KGOMOTSO MOSIDI GOITSIMANG MOKOALA

692233

A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Master of Medicine in the branch of Nuclear Medicine

Johannesburg

November 2016

Candidate's declaration

I, Kgomotso Mosidi Goitsimang Mokoala, declare that this research report is my own work. This research report is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



Dr. Kgomotso Mokoala

Novemeber 2016

Master of Medicine in the branch of Nuclear Medicine

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November 2016

To whom it may concern:

Re: Dr. Kgomotso Mokoala
Student number: 692233
Staff number: A0028309
MMed Nuclear Medicine

This letter is to certify that dr. Kgomotso Mokoala has done her research in Nuclear Medicine. Her topic is "The correlation between PSA, Gleason score and bone scan findings" She compiled and analyzed the data herself and followed the protocol for her study accordingly.
The entire research article was written by herself with assistance from her supervisor.

Kind regards,

Prof MDTHW Vangu
Head of Radiation Services
Head of division Nuclear Medicine

Dedication

To God Almighty: For providing me with the ability and strength to complete this MMed project.

My husband, Rapula Joseph Mokoala: A very special thank you for your support and understanding, which allows me to pursue my goals. You are God's greatest gift to me. You were my greatest strength, always provided me with endless support and the will to continue despite any adversity.

My children, Omphile Sechaba and Reneilwe Masego Mokoala: you are my greatest blessings. Never doubt my dedication and love for you.

My mother, Dikeledi Mokoena: Thank you for your support and numerous sacrifices throughout my life. I am who I am because of you.

My sister and brother, Dipolelo and Kagiso Mokoena: Thank you for believing in me.

My new family, the Mokoala's: Thank you for your prayers and your support. Thank you for understanding my absence during this time.

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- To my friends and colleagues at Charlotte Maxeke Johannesburg Academic Hospital for the endless support.

- To Dr L. Louw for her invaluable input and constant words of motivation.

- Sincere gratitude is extended to all the people who have helped me complete this report.

- To all our patients, without whom medicine and research would not be possible.

Abstract

Prostate cancer is one of the leading cancers in males worldwide. Osseous metastases are very common in prostate cancer and represent the main metastatic site in the majority of patients, with a significant impact in the prognosis of the disease. Early detection of bone metastases is critical in the management of patients recently diagnosed with a high-risk prostate cancer. Bone scintigraphy that is commonly known as bone scan, is of great importance in the management of these patients. In this study we wanted to correlate the PSA levels, Gleason score and bone scan findings.

We enrolled all patients with prostate cancer that were referred to our institution for bone scans from January 2010 – December 2014. A total of nine hundred and forty (940) patients were included. The PSA, Gleason score, ALP and calcium were recorded whenever available.

The median age of the cohort was 71 years (range 49 – 94). We found metastasis in 243 (26%) patients. Four hundred and forty-three scans were for staging and 25 % in this group had evidence of metastases on bone scan. There was a significant relationship between PSA and bone scan findings ($p = 0.0001$). For patients with a PSA ≥ 20ng/mL there was a positive risk of developing metastases with an OR of 1.253 (95 % confidence interval CI: 0.843 – 1.862). Using a cut-off of 20ng/mL for PSA levels, the measured sensitivity, specificity, NPV and PPV for predicting metastases were 73.3%, 74%, 87.1% and 54.1%, respectively. In 237 patients with a Gleason score > 7, eighty-seven (71.9%) had positive bone scans. When the Gleason score was > 7, patients were at risk of developing metastases with an OR 1.322 (95% CI: 0.838 – 2.086). Using a cut-off of 7 on the Gleason score, the sensitivity, specificity, NPV and PPV for predicting metastases were 78.8%, 26.8%, 77.8% and 28.1% respectively. Furthermore we analyzed the ALP levels and bone scan findings. The Pearson Chi-square test indicated a significant association with a p-value = 0.0001. Seventy-nine (63.7%) patients with a raised ALP had evidence of bony involvement on scintigraphy. When assessing the calcium levels, there was a weak association between calcium levels and bone scintigraphy. Direct logistic regression revealed that PSA (OR = 1.001; 95% CI: 1 – 1.003; $p = 0.017$) and ALP (OR = 1.013; 95% CI: 1.007 – 1.018; $p = 0.0001$) were the independent predictive

factors for bone metastases.

Patients with a PSA > 20 and Gleason score > 7 should have a bone scan. For patients with PSA < 20, the decision for a bone scan should be taken in view and consideration of other clinical parameters. PSA and ALP were found to be independent predictive factors for the presence of bony metastases on logistic regression.

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Nomenclature and Abbreviations

ACR – American College of Radiology

AJCC – American Joint Committee on Cancer

ALP – Alkaline Phosphatase

AUA – American Urological Association

AUC – Area Under the Curve

B-ALP – Bone Specific Alkaline Phosphatase

BPH - Benign Prostatic Hyperplasia

BS – Bone scan / scintigraphy *

CEO – Chief Executive Officer

CMJAH – Charlotte Maxeke Johannesburg Academic Hospital

DRE – Digital Rectal Examination

EAU – European Association of Urology

GS – Gleason Score

HREC – Human Research Ethics Committee

MANOVA – One-Way Between Groups Multivariate Analysis of Variance

M0 – Metastases absent

M1 – Metastases present

ng/mL – nanograms / millileter

N category – Lymph node assessment

NCR – National Cancer Registry

NHLS – National Health Laboratory Services

NPV – Negative Predictive Value

OR – Odds Ratio

PAP – Prostatic Acid Phosphatase

PCA3 – Prostate Cancer Antigen 3

PCa - Prostate Cancer

PIN – Prostatic Intraepithelial Neoplasia

PSA – Prostate Specific Antigen

PPV – Positive Predictive Value

ROC – Receiver Operator Curves

TNM – Tumour Node Metastasis

T-ALP – Total Alkaline Phosphatase

UICC – International Union for Cancer Control

UCa/Cr – Urinary Calcium / Creatinine ratio

UK – United Kingdom

VACURG – Veterans Administration Cooperative Urological Research Group

^{99m}Tc MDP – 99 metastable Technitium Methylene Diphosphonate

95% CI – 95 % Confidence Interval

* Please note that the words bone scan, bone scintigraphy and skeletal scintigraphy are used interchangeably in this research report.

CHAPTER 1

1.1 Introduction

1.1.1 Background

Prostate carcinoma (PCa) is on the list of the leading cancers in males worldwide [1]. Older men are primarily affected and the median age at diagnosis is 72 years [1]. In white South African males it has been found to be the second most prevalent cancer. When looking at recent statistics, it is evident that black males are increasingly at risk of prostate carcinoma and often this group develops an aggressive type of prostate cancer [2].

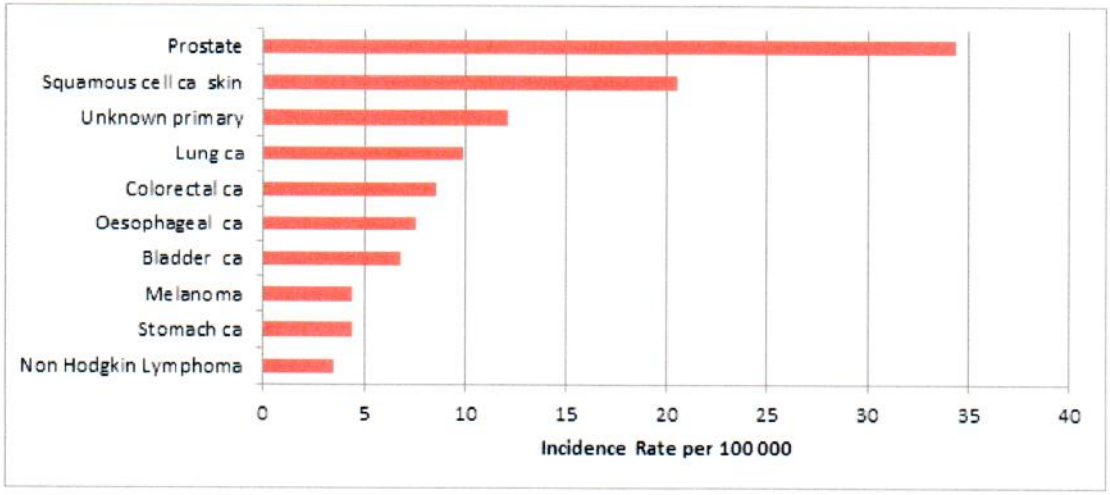


Figure 1.1 Incidence of Prostate cancer in South Africa in 2004 from the National Cancer Registry

Source: http://www.afcrn.org

According to the National Cancer Registry (NCR) statistics for 2010, there were 4652 (17.15% of all carcinomas) new prostate carcinoma cases recorded in South Africa with a lifetime risk of 1:27 (1 in 27 men) [3]. The incidence of prostate carcinoma is influenced largely by testing and, where testing is common practice with subsequent biopsy, prostate carcinoma rates are likely to increase. Prostate specific antigen (PSA) assay has been introduced in many countries as a means of detecting PCa and this has been related to the increase in the number of cases being diagnosed.

Within the scope of prostate cancer there are many different histological subtypes and different parts of the prostate gland may be invaded / affected by tumour. Prostatic intraepithelial neoplasia (PIN) is thought to be the precursor to prostate cancer [1,2]. Histologically, adenocarcinoma has been found in an immense number (± 95 %) of prostate cancer biopsy specimen [1,2]. Since adenocarcinoma is the most widespread form of prostate cancer it has become tantamount with the term prostate cancer [1,2]. The other types of prostate cancer are small cell carcinoma and squamous cell carcinoma; with sarcomas and transitional cell carcinoma being the more rare forms of prostate cancer [1,2].

1.1.2 Etiology

There is no single causative factor known to cause prostate carcinoma, however certain elements have been identified that increase the risk of developing prostate carcinoma.

There are many known risk factors for prostate cancer and these include [1,2,4,5]:

1. Age
2. Family history
3. Inheritance of prostate cancer
4. Lifestyle
5. High alcohol intake
6. Race

1.1.3 Screening and diagnosis

Population or mass screening is the methodical investigation of men who are asymptomatic but have risk factors for Pca, and it is customarily initiated by health authorities. One of the principal endpoints of screening is a decline in mortality from prostate carcinoma and an improved quality of life [6].

The issue of prostate carcinoma screening is controversial. Most guidelines do not advocate for prostate carcinoma screening in men below the age of 40 years [7,8,9]. In the recently published new guidelines for the early detection of PCa, the American Urological Association (AUA) stresses the following [7]:

1. prostate-specific antigen (PSA) screening is not advised in: men below the age of 40 years and in men between the ages of 40 – 54 years at average risk

2. advises that there should be shared decision making for men between the ages of 55–69 years

3. advocates a screening interval > 2 years, and

4. discourages PSA screening in men older than 70 years of age or in men with a life expectancy of less than 10 to15 years.

The European Association of Urology (EAU) however does not use a definite linear age as a limit for screening. They highlight the need to cautiously isolate the patients likely to benefit most from individual timely diagnosis, after weighing the prospective harms against the benefits. They advocate for screening of well-informed men at risk with a good performance status with a risk-adapted strategy. Similarly, they do not recommend screening in men with a life expectancy < 10 – 15 years [8].

A drawback of PSA testing is the possibility of over-diagnosis and subsequent negative biopsies due to the poor specificity [6,7,8].

Screening and diagnosis of prostate carcinoma includes digital rectal examination, urine tests, and measurement of prostate specific antigen (PSA) and Prostate Cancer Antigen 3 (PCA3) [1,2,4,5,6,9].

- Digital rectal examination (DRE): the prostate gland is examined with a finger that is inserted into the rectum. The peripheral zone of the prostate is the commonest site for prostate cancers and these may be discovered by DRE when the volume of the tumour ± 0.2 mL or larger. A less likely site of origin is the anteromedial prostate, the transition zone, which is distant from the rectal surface and is usually the location of benign prostatic hyperplasia (BPH). The presence of nodules, asymmetry, irregularity and tethering of the overlying mucosa are in keeping with an abnormal DRE. It must however be noted that a normal DRE does not excluded malignancy [9,10].

- Urine tests: to determine the presence of blood that could be a sign of cancer, but it is non-specific.
- Prostate specific antigen (PSA): a protein secreted by the prostate gland in trace amounts. A level that is high may allude to a problem with the prostate, which may be infection, cancer or a prostate that is enlarged.
- PCA3: this is a urine test that has the advantage over PSA in that it is prostate cancer specific and not found in other conditions such as prostatitis and benign prostatic hyperplasia. The recommendation is that it should not be used in place of PSA testing.

1.1.4 Staging:

It is predicted that the community health load of prostate cancer will certainly escalate as a result of the ageing population and the greater usage of diagnostic techniques. The chief objective of clinical staging of prostate carcinoma is to safeguard that the patient has the most relevant treatment modality.

To date, the tumour, node and metastases (TNM) staging system remains the most clinically useful system and most widely used. The American Joint Committee on Cancer (AJCC) system and Union for International Cancer Control (IUCC) incorporate the clinical and pathological features of malignancy into the staging to facilitate clinical management. It has been recently revised [10]. Staging of prostate carcinomas according to the AJCC system are described in detail in Appendix 4.

1.1.5 Prognosis:

The prognosis is dependent on the extent of the carcinoma at the time of diagnosis; therefore, it is extremely important to accurately identify the prostate cancer stage because the optimal treatments as well as the prognosis are determined from this [2,4,9].

Regardless of the treatment regimen, it has been found that patients with a great tumour load do worse than patients with a tumour load that is low. The prognosis is usually poor for patients with distant metastases, with a survival that averages 24 to

48 months. In order to prognosticate the patient, the burden of disease at diagnosis is taken into account. This could be illustrated as elevated PSA concentration, more metastases on bone scintigraphy or abnormal (high) concentrations of skeletal tumour markers [11,12,13].

Prognostic risk groups are currently used frequently for patients with localized prostate carcinoma. Variables such as PSA, clinical T-stage and biopsy / GS (available before treatment has been initiated) are what the prognostic risk groups are based on. Subsequent to various therapeutic treatments such as radiotherapy or surgery, post-treatment outcome is established using the risk groups [14,15,16]. Table 1.1 below describes the risks group classification defined by clinical stage, PSA concentration and Gleason score.

Table 1.1 Risk group classification based on clinical T-stage, PSA and Gleason score

	Clinical T-stage	**PSA concentration**	**Gleason score**
Low risk	**T1c – T2a**	**≤ 10ng/mL**	**≤ 6**
Intermediate risk	**T2b**	**> 10ng/mL but < 20ng/mL**	**7**
High risk	**T2c**	**≥ 20ng/mL**	**≥ 8**

An alternative way to utilize these broadly available clinical variables is as endorsed risk calculators or nomograms for which the 5-year outcome following diverse treatment modalities can be correlated to each patient's clinical characteristics (risk factors) [17].

1.1.6 Management:

Numerous publications describe types of existing treatment modalities of prostate carcinoma that may be summarized consisting of the following [2,4,7,8,9,11,12,13,14,15,16,17]:

- Active surveillance
- Surgery
- External radiation therapy
- Internal radiation therapy (brachytherapy)

- Hormone therapy
- Chemotherapy

1.2 Literature review

According to surveillance the most commonly diagnosed carcinoma in men is prostate cancer and it forms an important health concern in most countries [1,2,3,4,5]. On the other hand, the bulk of prostate cancer cases are considered clinically insignificant and certainly not lethal. These inconsistencies emphasize the necessity for early detection of specifically those cases that are aggressive in nature and call for early and drastic intervention [2,3,4,5].

In patients with prostate carcinoma, it is imperative to identify patients with metastatic (M1) disease as this has a significant prognostic value [2,4,9,11-13]. Additionally it influences the choice of therapy. The AJCC and UICC recommend the T category from the TNM staging to evaluate the local degree of the tumour. This is conventionally done by DRE, which is conducted by clinicians and urology specialists. To assess lymph node involvement (N category), lymph node dissection surgery is required. This may not be easy to perform; therefore this is not routinely recorded. The commonest location of distant metastases from prostate carcinoma is the skeleton, namely the long bones and axial skeleton and infrequently to the liver and the lung [10]. To establish the metastatic status (M0 or M1) of the tumour, radiological investigations as well as radionuclide bone scans are performed to assess for spread to the organs (lungs and liver) and the skeleton, respectively [18].

1.2.1 PSA

Prior to Wang et al isolating a glycoprotein that is known today as prostate specific antigen (PSA), prostatic acid phosphatase (PAP) and alkaline phosphatase (ALP) existed as the only valuable markers in prostate carcinoma [19]. PSA is a serine protease of the Kallikrein family [19]. It is found in the cytoplasm of malignant and benign prostatic cells [19,20,21]. The molecular mass is 34000 daltons as contrasted with 100000 daltons for PAP. Due to the weight of the PSA protein, it can seep into the general circulation by passing through the basement membrane considerably earlier than PAP. The increased sensitivity, relative stability with temperature and time, and fewer diurnal variations makes PSA a more dependable marker than PAP in diagnosing prostate carcinoma [19].

While PSA is produced primarily by prostatic epithelial cells, PSA has also been noted to be detected in trace amounts in the peri-urethral glands, normal breast tissue, endometrium, breast milk, breast tumours, female serum, renal cell

carcinomas, and adrenal neoplasms [22,23,24]. However quantifiable levels used in clinical practice essentially make PSA organ-specific, leading to its use as an important marker of prostatic disease. A limiting factor of PSA is its organ specificity, and the fact that it is not specific to prostate cancer. As a functional product of normal prostatic epithelial tissue, PSA levels will thus not merely reveal changes due to carcinoma, but additionally alterations due to trauma, inflammation, or benign proliferation [20,22,23,24]. The universal cut-off for the PSA value is 4.0 ng/mL. When this cutoff is utilized, the cancer detection rate varies from 35% to 42.3% for 10- to 12-core biopsy [25,26].

Even though PSA levels increase with progressing disease, there is no direct correlation between pathologic stage and PSA levels [19,27]. In an effort to determine if an association exists between the clinical stage and PSA level, Myrtle and coworkers assessed 553 patients with different stages of prostate carcinoma in a multi-institutional analysis [28]. They discovered that the number of patients with a high serum PSA concentration reached a total of 447 (81%), and the proportion of patients with elevated values of serum PSA expanded progressively with stage of carcinoma [28]. Therefore they concluded that, PSA concentration escalates correspondingly with stage; however, assigning a clinical stage based on the PSA concentration alone may be challenging due to the significant overlap in values of the PSA between stages [28,29].

1.2.2 Gleason score

In order to measure the prostate cancer grade, Gleason examined the histological slides of 5000 Veterans Administration Cooperative Urological Research Group (VACURG) trial patients and devised a scoring system [30]. The Gleason sum score is broadly acknowledged as a "gold standard" for grading of prostate cancer owing to its simplicity and reproducibility with less subjective variation [30]. Gleason grade, Gleason sum, combined Gleason grade and category score are selected synonyms for Gleason score [30]. To calculate the Gleason score the two principal histological grades, from grade 1 (well differentiated) to grade 5 (very poorly differentiated) are used. In order to derive this score the two most prevalent patterns are added together with total scores ranging from 2 to 10 [30,31]. A pattern (grade) must occupy above five percent of the biopsy specimen to be considered [30,31].

It is considered the single most important prognostic factor in prostate cancer

[30,31,32,33]. While some prostate cancers are biologically indolent, patients with Gleason scores between 8 and 10 cancers often have early spread of the disease, significant morbidity and eventual mortality because these tumours are so aggressive [30,32,33]. Figure 2.1 shows the different patterns seen when assessing the Gleason score.

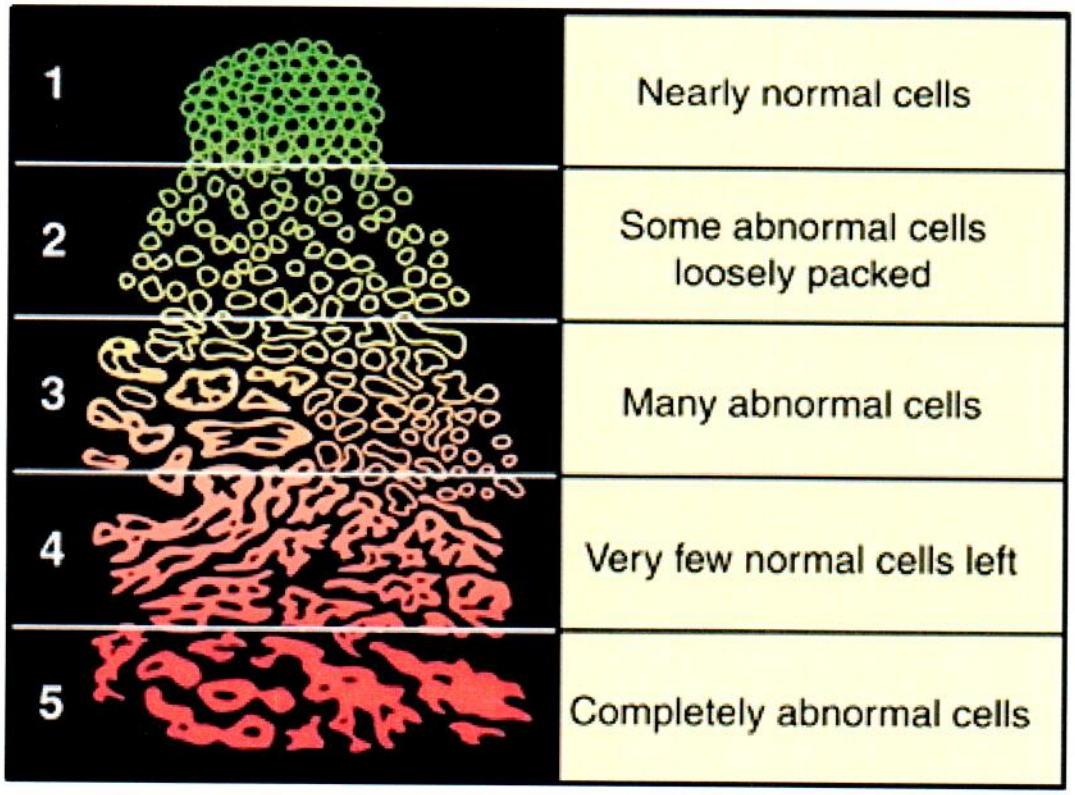


Figure 1.2 Gleason grades: standard drawing free image adapted from http://www.cancer.ie/sites/default/files/styles/large/public/gleason_score.jpg?itok=7sx1UqGA

1.2.3 Bone metastases

Prostate cancer, like other carcinomas has an incredible ability to spread outside the prostate gland. This is a result of numerous molecular processes. These mechanisms lead to invasion of surrounding structures and passage and establishment of metastases at secondary locations, typically in the bone, liver, or lung [34]. The possibility of having the tumour spread to distant sites even when the lesion within the prostate is small exists. In 1940, Batson described a plexus of vertebral veins that formed rich anastomotic networks with veins of the brain, skull,

neck, ribs, shoulder girdle, viscera and vertebral column. These veins are valveless and have low pressures. They allowed retrograde blood flow when either thoracic or intra-abdominal pressures were raised. He suggested that this forms the basis of metastatic spread of the two most common malignancies (breast and prostatic carcinoma) to the axial skeleton via the haematogenous route [35,36]. A wealth of observations has supported this hypothesis [37].

When performing histopathologic analysis of bone that has been invaded by prostate cancer, a great number of bone forming cells, namely osteoblasts, are seen neighboring prostate cancer cells [37].

The texture of bone tissue deposited in bone metastases of prostatic origin is mainly made of woven bone that is characterized by a higher mineral appositional rate and an osteosclerotic appearance than the lamellar structure of normal bone. Often at the site of the lesion, there is increase in bone mass as well as associated increase in osteoid surface area and volume [38,39].

One of the first few radiopharmaceuticals to be used and documented for the identification of skeletal metastases utilizing radionuclide bone scans was Strontium [40,41,42,43,44,45]. Over the years, many agents have undergone extensive evaluation and comparison, but Technetium labelled methylene diphosphonate (^{99m}Tc MDP), developed by Subramanian et al, remains the most widely used agent [40,41,42,43,44,45,46]. Since then, skeletal scintigraphy has become the standard examination for detecting skeletal metastases from prostate carcinoma, which are mainly osteoblastic [40,41,42,43,44,45]. Bone scanning is ideal because it is readily available and is a sensitive modality for detecting bone metastases, particularly osteoblastic metastases [45].

The localization of the ^{99m}Tc complexes in the bone is dependent upon sufficient blood flow to the bone and the smooth, unobstructed passage from blood to the surface of the bone. It is believed that these anionic Tc^{99m} labeled phosphate and phosphonate complexes interact with bone by attaching to calcium ions in bone crystals. This interaction has been termed chemisorption. Localization occurs primarily in the mineral phase of bone. This radiopharmaceutical gained popularity because of more rapid blood clearance and higher skeletal affinity [40,41,42,43,44,45,46].

There are many patterns of uptake on the bone scan, however the most common appearance of osteoblastic metastases is a focal area of increased uptake of tracer, frequently in the axial skeleton, linked to the patient's osteoblastic bone reaction to invasion by tumour [40,41,42,43,44,45,46]. Figure 1.3 – 1.6 are images retrieved from our archives demonstrating the different patterns seen on bone scintingraphy.

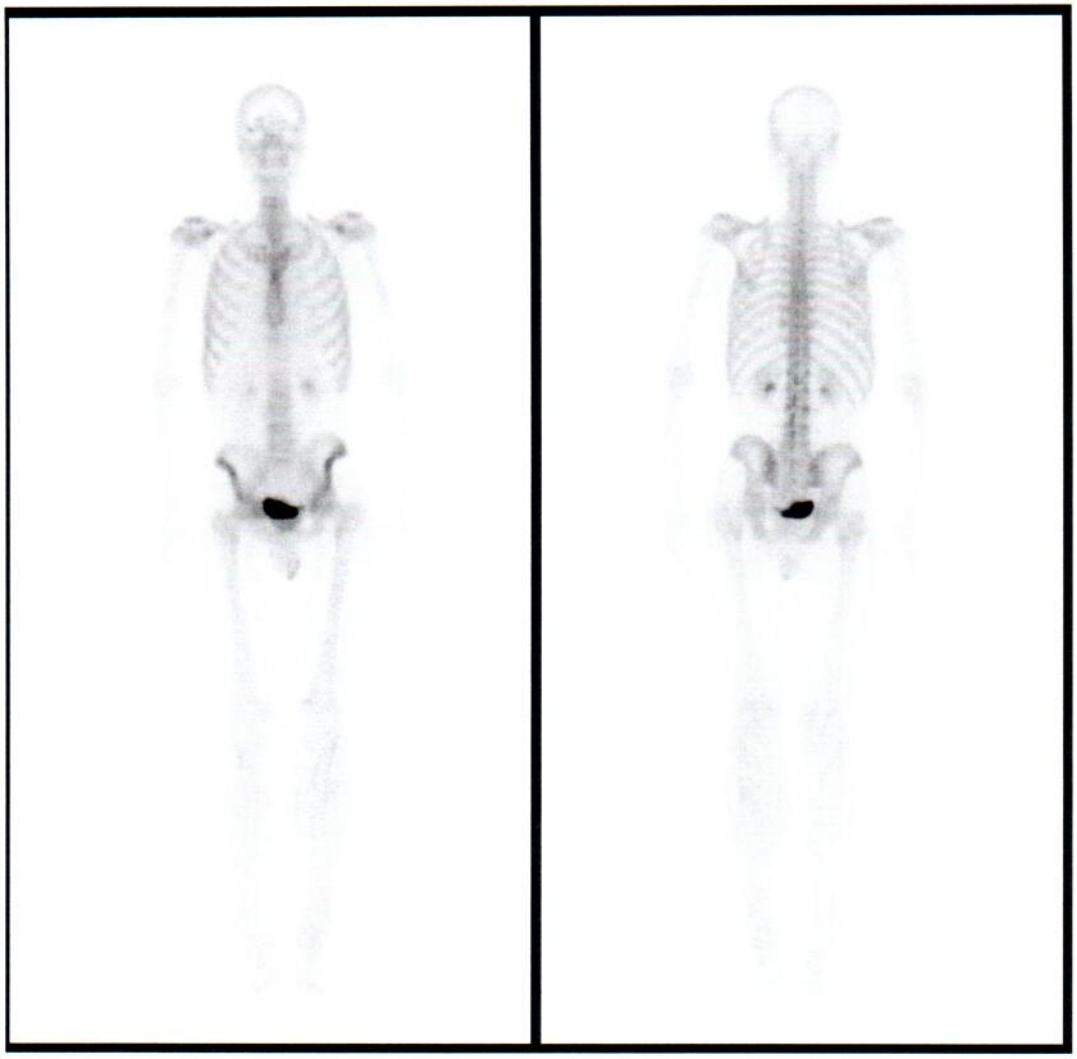


Figure 1.3 A 72 year old newly diagnosed with PCa. PSA = 25ng/mL; Gleason score = 7. The bone scan is within normal limits with normal bio-routing of tracer and no focal abnormal uptake. This scan is considered negative for metastatic disease.

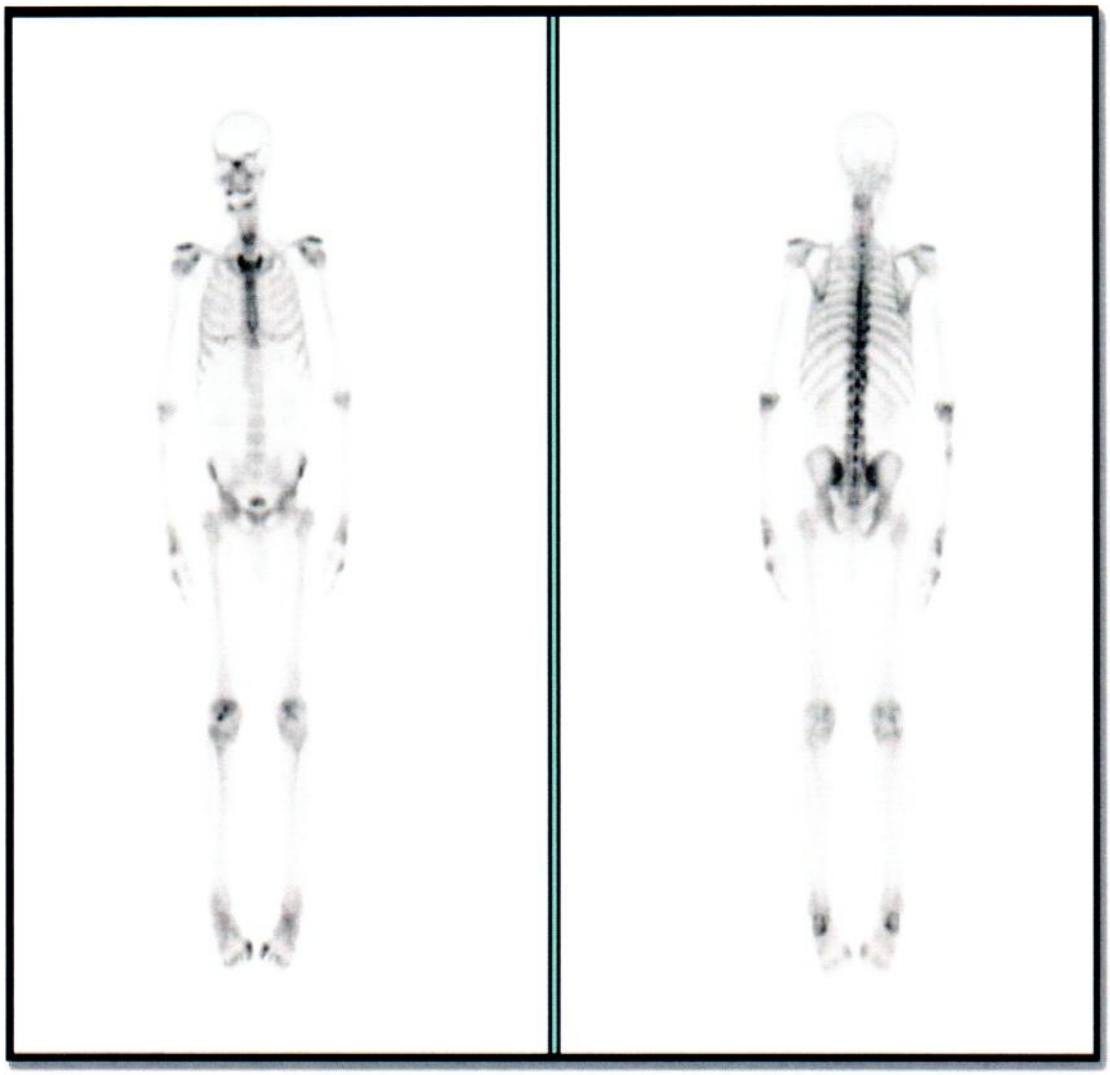


Figure 1.4 A 72 year old male with PCa diagnosed in 2014. Had brachytherapy. Now presenting with rising PSA = 10.95ng/mL; Gleason score = 7. Similar to the previous case, the bone scan was considered negative for metastatic disease, however the patient has inflammatory / degenerative disease of the small and large joints. The findings in this scan must not be confused for metastatic disease.

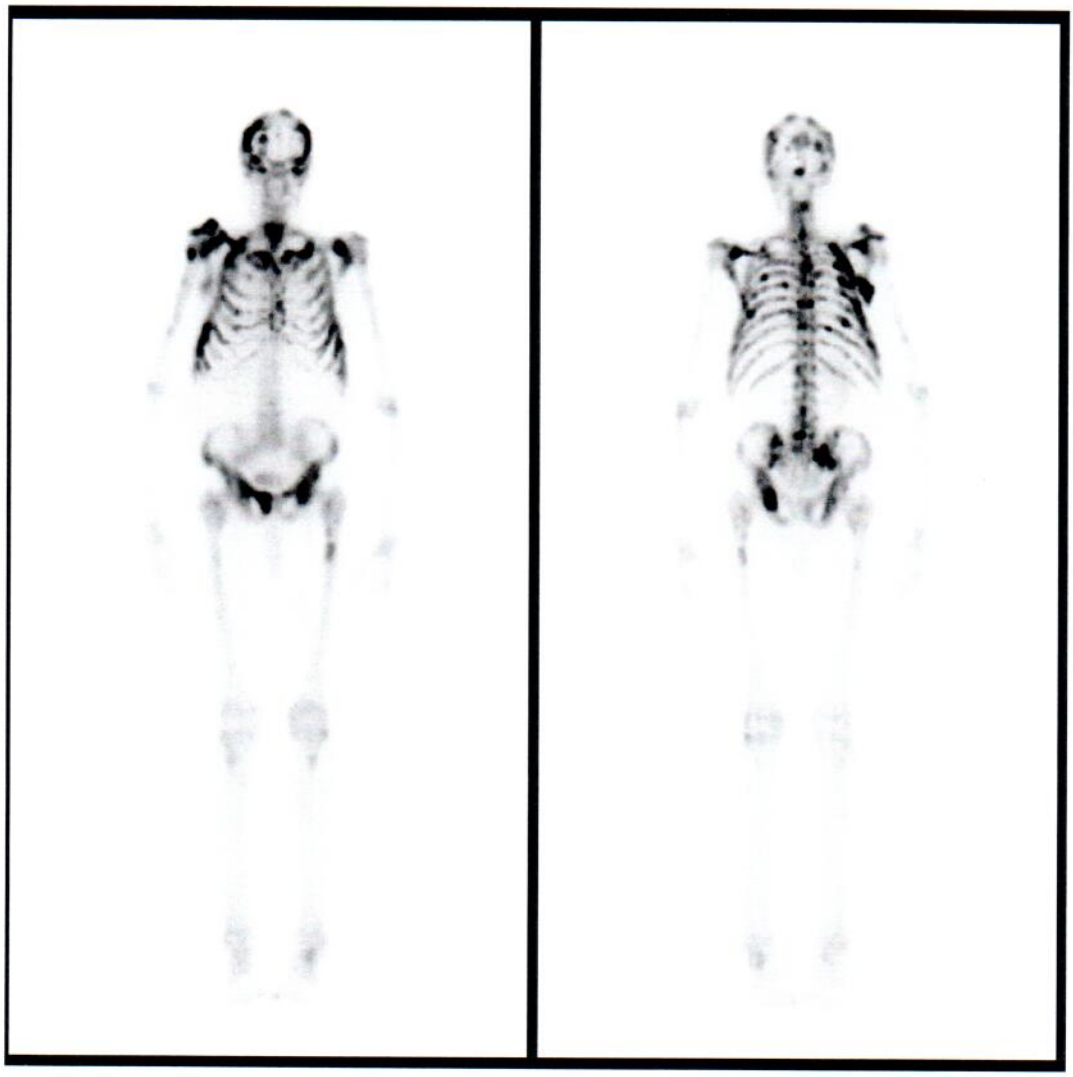


Figure 1.5 An 84 year old newly diagnosed with PCa. PSA = 8952ng/mL; Gleason score = 7. The bone scan revealed widespread osteoblastic metastases involving the axial and appendicular skeleton.

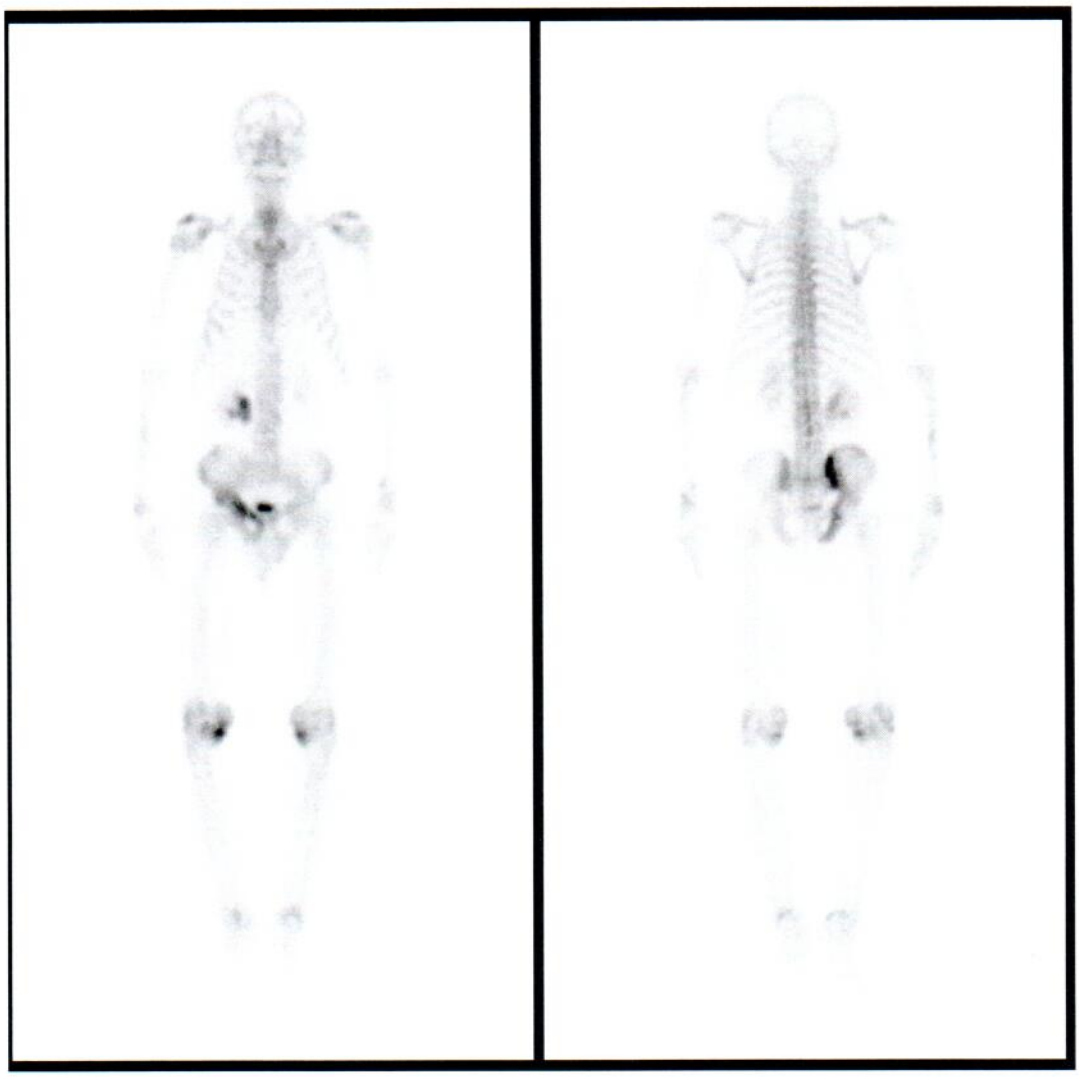


Figure 1.6 A 68 year old newly diagnosed PCa. PSA = 19.66ng/mL; Gleason score = 6. Bone scintigraphy showed abnormal increased uptake in the right hemi-pelvis, intense in the sacro-iliac joint and the acetabulum. This finding is highly suspicious for metastasis. Other structural imaging modality is needed to confirm metastasis at this site. This scan may be considered equivocal.

Palmer *et al* demonstrated that bone scanning was 28% more sensitive than conventional radiographs in detecting bone metastases [47]. Bone scanning continues to be the initial modality of choice for evaluating skeletal involvement in cancer patients due to the superior sensitivity and the ability to survey the entire skeleton [47].

The degree of skeletal metastases is also linked with survival, but there has not been any clinically valuable system of quantifying the skeletal tumour load and incorporating this information in the risk assessment. The prospect of positive bone scans differs with the histological score, clinical stage, PSA and PAP levels. Studies

have indicated that in patients with PSA levels < 20 ng/ml, the incidence of a positive bone scan at initial diagnosis is below 1% [41,44,48]. For patients with PSA levels < 10 ng/ml, staging bone scintigraphy is not recommended except if there are identified preexisting conditions that might interfere with scan interpretations or the patient has symptomatology or suspicion of malignancy radiographically [41,44,48].

1.2.4 ALP and Calcium

The nature of bone metastases is that they release several biochemical markers into the bloodstream, which reflect bone remodelling, and these may be monitored as an indirect assessment of disease activity. When contrasted with imaging studies / investigations, biochemical investigations have the advantage of being easy to perform and economical. Their shortcoming is that, they do not detect the location of metastatic deposits. Often in clinical practice the assessment of bone formation involves the use of regular biochemical investigations, such as blood levels of alkaline phosphatase (ALP) and calcium assays [49]. The total serum ALP activity in the circulation also depends on the gastrointestinal tract, liver, tumours and placenta, therefore when it is increased, it does not unequivocally reflect bone function [49].

In a study comparing sensitivity, specificity, and efficiency of new and "traditional" biochemical serum markers of osteoblastic and osteoclastic activity in the detection of bone metastases, Plebani et al found that the ALP and bone specific ALP (B-ALP) gave serum values that are more increased in patients with skeletal metastases than in age-matched controls [49].

Interestingly, the total ALP (T-ALP), which remains the most commonly used parameter for evaluating bone metastases, was as sensitive as B-ALP. This means that this non-specific bone turnover indicator is a valuable marker of osseous formation in this condition [49,50]. However, others reported a higher diagnostic value of B-ALP compared to T-ALP especially for stratifying the degree of bone metastases [51,52].

In a study by Wymenga and colleagues that investigated the role of ALP and PSA in predicting bone metastases, there was a trend suggesting ALP values correlated better with anomalous bone scintigraphy than did PSA, although not significantly so [53].

Radiologically bone metastases from prostate cancer appear sclerotic, however histologically, these metastases have a more multifaceted picture composing of zones of both increased bone formation and substantial bone resorption. The urinary levels of calcium are dependent on the phase of bone activity. When the bone is undergoing osteolysis, calcium is liberated into the bloodstream and excreted in urine, while during the phase of osteoblastosis there is a demand for calcium and this may result in a decline in excretion of calcium in the urine [38]. To explore the variations in bone turnover in metabolic bone diseases, changes in urinary and serum calcium balance are regularly utilized. These deviations have never been recommended as a method of monitoring bone metastases from prostate cancer [38,54,55].

Francini et al investigated various indicators of both bone formation (ALP and b-ALP) and resorption (urinary calcium / creatinine ratio). The blood levels of calcium of the bulk of the patients approached the lower limit of normal, certainly, their urinary calcium / creatinine (UCa/Cr) ratios were significantly less than the recognized cutoff level. In patients with extensive sclerotic / osteoblastic osseous metastases as is seen with prostate carcinoma, there is a incessant requirement for calcium as this is essential for new bone creation (the bone-hunger syndrome) and this may result in both hypocalcaemia and hypocalcuria. Due to the complexity of prostatic cancer bone metastases, there is usually a discrepancy between formation of bone and bone resorption in favour of the former and this may explain the low levels of UCa/Cr [38,56].

1.2.5 Bone Scans in Prostate Cancer

Several international guidelines and societies suggest bone scintigraphy for patients with newly diagnosed prostate cancer only if PSA values are raised, clinical T staging is high and Gleason histological scores are above a certain level.

A meta-analysis published in the Journal of Urology 2004 stated that patients with low risk prostate cancer are less likely to have metastatic disease demonstrated by bone scintigraphy. However, patients with PSA ≥20 ng/ml, clinical stage T3 or T4, or Gleason score ≥8 are at greater risk for bone metastases and ought to be considered for bone scan [57].

The American Urological Association specifies in their Prostate Specific Antigen Best Practice Statement: 2009 Update that: "Routine use of a bone scan is not required

for staging asymptomatic men with clinically localized prostate cancer when their PSA level is equal to or less than 20.0 ng/mL." They do go on to suggest that metastatic prostate cancer is considerably more common in advanced local disease (≥T3 clinical stage) or in high-grade (Gleason ≥8) disease. In patients with a PSA <10.0 ng/mL, bone scintigraphy should be considered at the time of diagnosis when the Gleason score is ≥8 or the clinical stage is ≥T3. This is due to the fact that some high-grade prostate cancers have lower PSA values [58].

The American College of Radiology ACR Appropriateness Criteria®: Pretreatment Staging Prostate Cancer guideline agrees with the above-mentioned recommendations and both associations refer to the meta-analysis by Abuzallouf *et al* [18,57].

This meta-analysis of Abuzallouf correlated PSA, Gleason score and clinical staging with the likelihood of metastases detected using bone scans.

The detection rates in patients with PSA<10ng/ml, PSA 10 to 19.9ng/ml, PSA 20 to 49.9ng/ml, PSA 50 to 99.9ng/ml and PSA >100 ng/ml were 2,3%, 5.3%, 16.2%, 39.2% and 73.4% respectively [57].

In this meta-analysis seven studies resolved that bone scans could be omitted in patients with PSA levels < 20 ng/ml [53,59,60,61,62,63,64]. Ten studies recommended omitting bone scans for PSA less than 10ng/ml [65,66,67,68,69,70,71,72,73,74]. A negative predictive value (NPV) of less than 90% for PSA less than 20 ng/ml was found in only 5 studies [53,64,68,73,75]. Only 2 studies concluded that bone scan is indicated in all patients [76,77].

The detection rates of metastases on bone scans in patients with Gleason score ≤7 and Gleason score ≥8 were 5.6% and 29.9% respectively [57].

The detection rates of metastases on bone scans for localised (T1 to T2) disease were 6.4% and locally advanced (T3 to T4) cases, 49.5% [57].

When the initial / baseline bone scan is normal or even equivocal, follow-up bone scans are not routine, although when the patient presents with unexplained bone pain or a rising PSA level, they may be a helpful investigation. In recognized skeletal involvement serial bone scans can monitor the effectiveness of therapy.

1.3 Rationale for the study

According to the American Cancer Research, patients with PSA < 20ng/ml and Gleason score < 8 have a 1% to 13% rate of positive bone scans [18]. They recommend that patients with PSA > 20 ng/ml (with any T stage or Gleason score), locally advanced disease (T3 or T4 with any PSA level or Gleason score), or Gleason score > 8 (with any PSA level or T stage) should undergo radionuclide bone scans [18].

Unnecessary bone scanning is costly and leads to additional resource strain on our public health sector. No local data exists regarding the negative predictive value of PSA values and/or Gleason scores for bone metastases on bone scanning in newly diagnosed prostate cancer patients.

This retrospective study was conducted to establish if existing published guidelines can be applied in our environment.

CHAPTER 2

Materials and methods

Ethics clearance was obtained from the University of Witwatersrand's Human Research Ethics Committee (HREC), ethics clearance number M140232 (Appendix 1).

Permission was obtained from the CEO of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) for the use of hospital patients' information (Appendix 2).

Permission from National Health Laboratory Services (NHLS), School of Pathology, Division of Anatomical Pathology for the use of blood and histology results was obtained (Appendix 3).

2.1 Study Design

In our institution, Charlotte Maxeke Johannesburg Academic Hospital, we receive numerous referrals for bone scans amongst which the majority is for prostate cancer. Our practice is to perform bone scintigraphy in all patients, regardless of PSA, Gleason score and symptomatology. There are no defined guidelines in our institution as to which patients are sent for this imaging modality.

This was a retrospective, cross-sectional descriptive study to assess if we can apply existing published guidelines and develop an appropriateness use criteria for bone scans in prostate cancer patients in our environment.

2.2 Study Objectives

The aim of this study was to ascertain if it is feasible to apply or adopt existing recommendations for the selective use of bone scintigraphy in only intermediate and high risk patients in our institution. This would improve the cost effective and clinically appropriate use of bone scintigraphic investigations in prostate carcinoma patients.

2.2.1 Primary Objective:

- To determine the percentage of skeletal scintigraphy studies that we do for patients with a new diagnosis of prostate cancer
- To determine the correlation between PSA value, Gleason score and ^{99m}Tc-MDP bone scan findings.

2.2.2. Secondary Objective:

- To determine if a case can be presented for a change in the current management of bookings for bone scans and follow-up of prostate cancer patients in our institution
- To determine the correlation with other principle blood markers such as ALP and calcium

2.3 Study Population

Study Population

All patients with diagnosed and histologically confirmed prostate carcinoma that had been referred to the Nuclear Medicine department at Charlotte Maxeke Johannesburg Academic Hospital for a bone scan from the period January 2010 – December 2014 were included in the study.

All age ranges of the adult population (> 18 years old) were included.

A total of 940 patients, aged 49 to 94 years were included for data analysis.

2.3.1 Inclusion criteria

- Patients referred for ^{99m}Tc-MDP bone scan
- Patients with histologically proven prostate cancer

2.3.2 Exclusion criteria:

- Patients with double cancers or
- Recent history of trauma (particularly multiple of multiple nature)

2.4 Data collection and data processing

The patients' request forms and bone scans reports were assessed to determine the eligibility of patients for the study. Age and hospital number, PSA values and Gleason scores in the identified patients as well as the results of bone scan (bone metastases present, absent or equivocal) were collected.

The patients' blood results were collected to assess the recorded levels of the ALP and the calcium.

2.5 Data analysis

PSA values:

Blood results were retrieved from the archive of the National Health laboratory service (NHLS).

The serum PSA determination within 3 months of the bone scan was used.

Normal values are between 0 – 4ng/mL.

PSA values were grouped as follows:

- < 10 ng/L (less than ten)
- 10 – 19.9 ng/mL
- ≥ 20 ng/mL (more than twenty)

Gleason score:

The histology results were also retrieved from the archive of the NHLS with the permission from the clinical department of anatomical pathology.

On pathological analysis, the specimens were graded from Grade 1 - Grade 5 based on the universal grading system for PCa (Gleason system). The General Rules for Clinical and Pathological Studies on Prostate Carcinoma guided the histological grading.

The sub-type of prostate carcinoma was also recorded where available.

The Gleason score was grouped as follows:

- Gleason grade 2 – 6
- Gleason grade 7
- Gleason grade 8 – 10

Bone scan analysis:

Tc-99m methylene diphosphonate (MDP) radionuclide bone scans were performed upon request from referring physicians.

Bone scans were reported by local nuclear medicine physicians with varying number of years of experience.

The bone scans were categorized as negative, positive or equivocal.

- Negative scan: this was reported as having no typical evidence of metastases and it was defined when there were no focal abnormal areas of tracer uptake
- Positive scan: this was reported as findings consistent with metastases and it

was defined when either a solitary area or multiple irregular areas of increased tracer uptake were seen, however this excluded uptake of tracer in sites usually associated with inflammatory and or degenerative diseases of the skeleton

- Equivocal scan: this was reported as neither having metastases or not. It was reported as suspicious for metastases with further imaging (x-ray, CT or MRI) required

ALP and Calcium values:

Blood results were retrieved from the NHLS.

The serum ALP and calcium determination within 3 months of the bone scintigraphy was used.

ALP:

The normal range for this in our laboratory is: 53 – 128

The normal range for the bone specific ALP is: 14 – 41.3

The ALP levels were categorized as follows:

- Low (below 53)
- Normal (between 53 – 128)
- High (above 128)

Calcium:

The normal range of the calcium in our laboratory is: 2.15 – 2.50

For the analysis the calcium levels were categorized as follows:

- Low (below 2.15)
- Normal (between 2.15 and 2.50)
- High (above 2.50)

2.6 Statistical analysis

Data were analyzed using the IBM SPSS statistical analysis package, version 22.
For continuous variables the descriptive results were presented as medians and range. Categorical variables were summarized as frequencies and percentages.
Univariate and multivariate logistic regression analyses were used to assess the predictors of patients with positive bone scans.

Mann- Whitney's U-test was used to compare the continuous parameters and Pearson chi square test were used to compare the patients ages with positive bone scintigraphy with those with negative bone scintigraphy. A p-value of <0.05 was considered to indicate statistical significance.

Crosstables were generated to evaluate a relationship between categorical variables using the Fisher's probability exact test and Pearson Chi square test.
The strength or magnitudes of associations / relationships were evaluated using the Phi and Cramer's V tests.

CHAPTER 3

Results

Table 3.1 shows the clinical characteristics of patients included in the study.

Table 3.1 – Patient characteristics and descriptive statistics

VARIABLES	ALL PATIENTS
Age, yr Mean (median) Range	 71.17 (71) 49 – 94
PSA Mean (median) Range	 227.49 (14.34) 0.01 – 14226
PSA, ng/mL, No (%) 0 – 9.9 10 – 19.9 >20	 295 (39.3) 138 (18.4) 317 (42.3)
Gleason score Mean (median) Minimum Maximum	 7.56 (7) 4 10
Gleason score, No. (%) 2 – 6 7 8 – 10	 110 (21.5) 165 (32.2) 237 (46.3)
ALP Mean (median) Range	 167.24 (94) 34 – 2389
ALP, No. (%) Low Normal High	 9 (1.9) 347 (72.7) 121 (25.4)
Calcium Mean (median) Range	 2.32 (2.31) 1.75 – 2.79
Calcium, No. (%) Low Normal High	 51 (9.8) 438 (84.2) 31 (6)
Bone scan findings, No (%) Negative Positive Equivocal	 502 (53.4) 243 (25.9) 195 (20.7)

A total of 940 radionuclide bone scans were perfomed and were included in the study.

3.1 Correlation between Age and Bone Scan results

The median age of the cohort is 71 years ranging from 49 to 94 years. The age group with the highest frequency of positive bone scans was noted between 60 – 69 year age group with 94 (38.7%) patients. The highest frequency of negative bone scans were found in the 70 – 79 year old age group with 206 (41 %) of patients. Table 3.2 below gives the frequencies and percentages of negative, positive and equivocal bone scans in each age group.

Table 3.2 Frequencies and percentages of negative, positive and equivocal bone scans in different age groups

	AGE	FREQUENCY	PERCENTAGE
NEGATIVE BONE SCAN	40 – 49 years	4	0.8
	50 – 59 years	54	10.8
	60 – 69 years	177	35.3
	70 – 79 years	206	41.0
	80 – 89 years	55	11.0
	90 – 99 years	5	1.0
POSITIVE BONE SCAN	50 – 59 years	20	8.2
	60 – 69 years	94	38.7
	70 – 79 years	90	37.0
	80 – 89 years	33	13.6
	90 – 99 years	4	1.6
EQUIVOCAL BONE SCAN	40 – 49 years	1	0.5
	50 – 59 years	14	7.2
	60 – 69 years	70	35.9
	70 – 79 years	77	39.5
	80 – 89 years	29	14.9
	90 – 99 years	3	1.5

3.2 Analysis of Staging bone scans

We were able to determine whether a scan was requested for staging or not in 633 cases. Of the 633, four hundred and fourty three (70%) were staging bone scans while 190 were not. Twenty-five percent of the bone scans that were for staging revealed bone metastases on scintigraphy.

3.3 Correlation between PSA and Bone Scan results

The association between the PSA level and osseous metastases was evaluated in 750 (79.8%) patients, 195 (26%) of whom bone metastases were detected. The association between PSA level and BS result is shown in Table 3.3.

Table 3.3. Association between PSA level and bone scan results

Scan findings	PSA, ng/mL			
	0 – 9.9	10 – 19.9	> 20	Total
Negative, No. (%)	196 (48.4)	88 (21.7)	121 (29.9)	405 (54)
Positive, No. (%)	30 (15.4)	22 (11.3)	143 (73.3)	195 (26)
Equivocal, No. (%)	69 (46)	28 (18.7)	53 (35.3)	150 (20)
Total	295 (39.3)	138 (18.4)	317 (42.3)	750

A Chi-square test for independence indicated a significant association ($p = 0.0001$) between PSA and positive bone scans. Odds ratios (OR) were used in an attempt to correlate PSA levels and metastases as an outcome. In this particular analysis, we only looked at positive versus negative bone scans (excluding the equivocal results on bone scan) in the 3 categories for PSA levels (< 10, 10 -19.9 and ≥ 20). The results are found in the Table 3.4. below.

Table 3.4 Odds ratios and Confidence intervals for PSA categories

PSA subcategories	Odds Ratio	95% CI
0 – 9.9	1.155	0.794 – 1.681
10 – 19.9	1.099	0.668 – 1.810
≥ 20	1.253	0.843 – 1.862

Patients with a PSA <10 were found to have an insignificant risk of developing osseous metastases with an OR =1.155 (95%CI: 0.794 – 1.681). There was also no risk of developing metastases in patients with PSA between 10 and 20 (OR = 1.099). In patients with a PSA value ≥ 20ng/mL, there was a positive risk of developing bone metastasis with an OR of 1.253 (95% CI: 0.843 – 1.862). Using a cut-off of 20ng/mL for PSA levels, the measured sensitivity, specificity, NPV and PPV for predicting metastasis were 73.3%, 74%, 87.1% and 54.1%, respectively.

3.4 Correlation between Gleason score and Bone Scan results

The pathological analysis for Gleason scores were available in 512 (54.5%) patients. The number of patients in the GS groups <7, 7 and >7 were 110, 165 and 237 respectively. About 11 (9.1%) patients with a GS of < 7 had positive bone scans. There were 23 (19 %) patients with a GS equal to 7 who had positive skeletal scintigraphy and in all 87 (71.9 %) patients with a GS > 7 had positive bone scintigraphy. Using the Gleason score as the only criterion for bone scan imaging 9.1% of patients with osseous metastases would have been missed. Figure 3.1 demonstrates the relationship between Gleason score and bone scan findings.

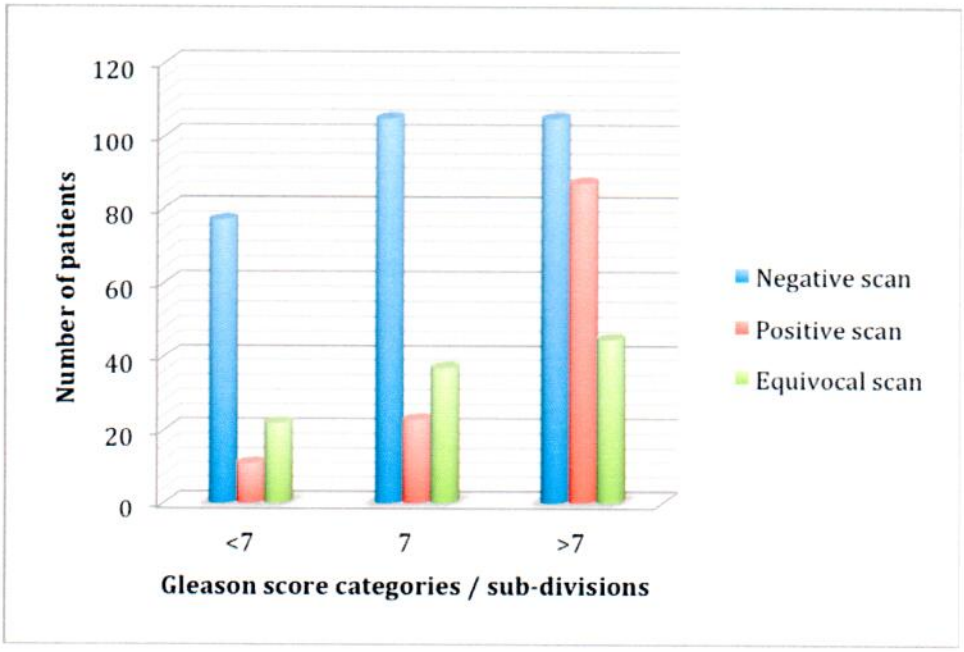


Figure 3.1 Negative vs positive vs equivocal scans in each Gleason bracket

Similar to PSA analysis, we used a Gleason of 7 for the OR calculation because most of the positive bone scans were seen above this level. Therefore, we wanted to

see if we could use Gleason 7 as a cut-off for predicting the presence of metastatic bone disease. Patients with a GS < 7 were unlikely at risk of developing metastases (OR = 1.367; 95% CI = 0.798 – 2.341). Similarly, for those with GS = 7 were also unlikely at risk of developing skeletal metastases with an OR = 1.045 (95% CI = 0.654 – 1.668). When the GS was > 7, patients were at risk of developing metastases with an OR of 1.322; 95% CI = 0.838 – 2.086). Using a cut-off of 7 on the scorring of Gleason, the sensitivity, specificity, NPV and PPV for predicting metastases were 78.8%, 26.8%, 77.8% and 28.1%, respectively.

3.5 Correlation between ALP and Bone Scan results

There were only 477 patients with ALP results at the laboratory. Only 1 (8%) patient with low ALP had a positive bone scan. Forty four (35.5%) patients with normal range of ALP had positive scans while 79 (63.7%) patients with ALP above the upper limit had positive bone scans. The Pearson Chi-Square indicated a significant relationship with a p-value of 0.000.The Cramer's V test showed a medium effect on this relationship.

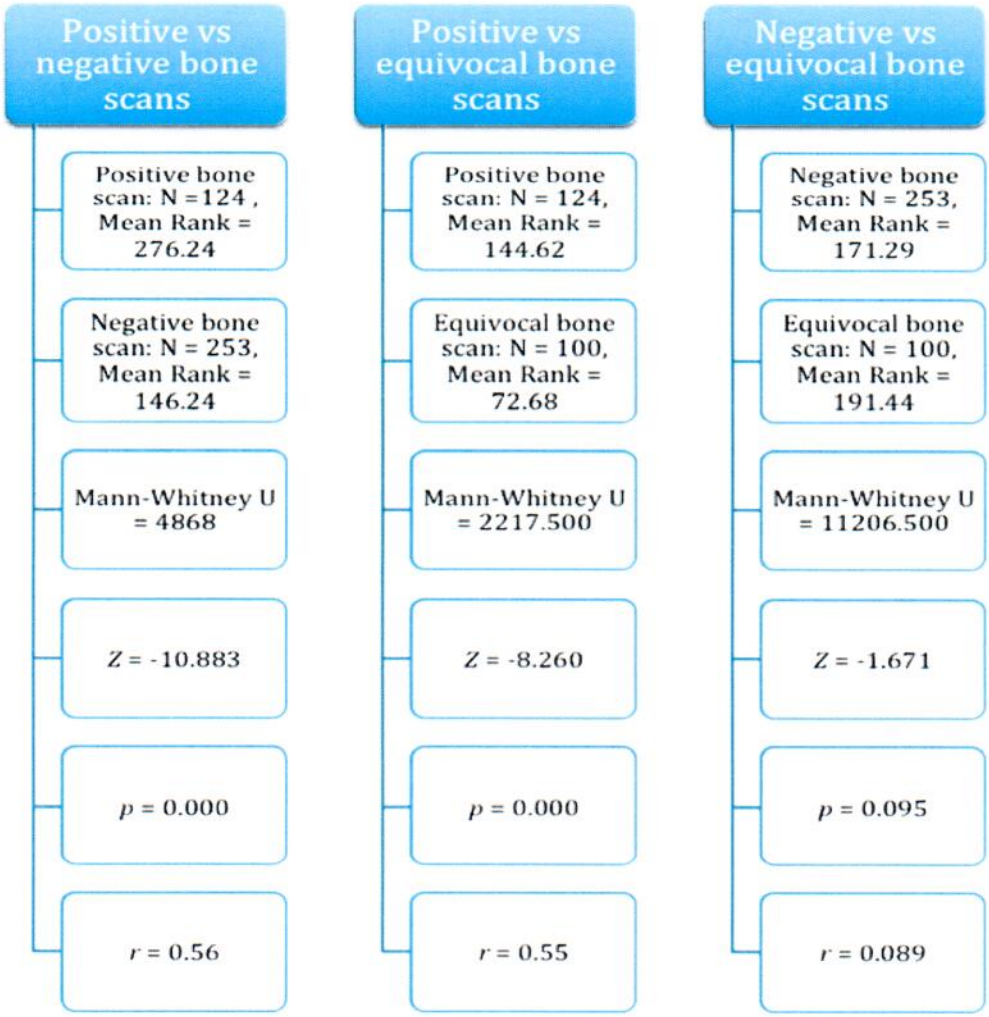
A Kruskal-Wallis test was done to assess if there is a variance in ALP levels across the different bone scan groups. This revealed a statistically substantial difference in bone scan findings for the different ALP groups (negative bone scans, n = 253; positive bone scans, n= 124; equivocal bone scans, n= 100), X^2 (2, n=477) = 127.65, p = 0.000. The positive bone scans recorded a higher mean rank (Mean Rank = 358.35) than the other 2 groups (negative and equivocal bone scans) which recorded Mean ranks of 190.54 and 213.61,respectively.

A Mann Whitney *U*-test was done as a post-hoc test to see in which 2 groups was there a significant difference. This revealed a significant difference in the ALP levels of patients with positive (Mean Rank = 276.24, N= 253) versus negative bone scans (Mean Rank = 146.24, N = 253), U = 4868, z = -10.883, p = 0.000, r = 0.56 as well as positive (Mean Rank = 144.62, N= 124) versus equivocal bone scans (Mean Rank = 72.68, N = 100), U = 2217.50, z = -8.260, p = 0.000, r = 0.55. However there was no significant difference in the ALP levels of patients with negative versus equivocal bone scans with a p = 0.095. Table 3.5 and 3.6 show some of the above results.

Table 3.5 Kruskal Wallis Test results

SCAN FINDINGS	N	MEAN RANK
Negative bone scan	253	190.54
Positive bone scan	124	358.35
Equivocal bone scan	100	213.61
Total	477	

Table 3.6. Mann-Whitney Tests of bone scan findings from the ALP results



3.6 Correlation between Calcium and Bone Scan results

The calcium blood results of 520 patients were available for analysis. Table 3.7 displays the association between bone scintigraphy findings and calcium levels.

Table 3.7. Association between bone scan findings and calcium levels

	CALCIUM CODED			
SCAN FINDINGS	Low	Normal	High	TOTAL
Negative, No. (%) **Positive, No. (%)** **Equivocal, No (%)**	18 (6.5) 25 (17.2) 8 (8)	243 (88.4) 112 (77.2) 83 (83)	14 (5.1) 8 (5.5) 9 (9)	275 (52.9) 145 (27.9) 100 (19.2)
Total	51 (9.8)	438 (84.2)	31 (6)	520 (100)

A Pearson Chi-Square test showed a significant association between calcium levels and bone scan findings with a $p = 0.005$, however the Cramer's V test showed a weak association (0.119).

A Kruskal-Wallis test to assess if there was a substantial difference in the calcium levels in the different groups for bone scan findings revealed that there was a difference in calcium levels of patients with negative, positive or equivocal bone scans ($p = 0.038$).

The post-hoc Mann-Whitney test revealed that there was a difference in calcium levels in patients with positive bone scans versus negative bone scans ($p = 0.021$) and positive versus equivocal bone scans ($p = 0.034$). Similar to the ALP results, there was no significant difference in the calcium blood levels of patients with negative versus equivocal bone scans ($p = 0.669$).

There were too few numbers of patients in each category of the ALP and Calcium to calculate odds ratios.

3.7 Logistic regression

Direct logistic regression analysis was performed to evaluate which, amongst serum PSA, Gleason score, serum calcium and ALP were independent predictors for bone metastases on scan. The full model containing all predictors was statistically significant, X^2 (4, N = 225) = 118.585, $p < 0.001$, indicating that the model was able to discriminate patients with and without skeletal metastases. The model as a whole explained between 41% (Cox and Snell R square) and 58% (Nagelkerke R squared) of the variance in bone scan findings, and correctly classified 87 % of cases. Only serum PSA (odds ratio = 1.001; 95% CI = 1 – 1.003; p 0.017) and serum ALP (odds

ratio = 1.013; 95% CI = 1.007 – 1.018; $p < 0.001$) were the predictive factors for detecting bone metastases. These results are found in Table 3.8 below.

Table 3.8 Results from the logistic regression

VARIABLE	p-value	ODDS RATIO	95% CI
Gleason score	0.07	1.38	0.973 – 1.957
PSA	0.01	1.001	1 – 1.003
Calcium	0.59	2.186	0.126 – 37.892
ALP	0.0001	1.013	1.007 – 1.018

3.8 MANOVA

A one-way between groups multivariate analysis of variance (MANOVA) was perfomed to explore bone scan findings in patients with both PSA and GS results available. The independent variable was the bone scan findings while the two dependent variables were the serum Gleason score and PSA. There was a statistically significant difference on bone scintigraphy findings on the combined dependent variables, F (2, 370) = 42.04, $p < 0.001$; Wilks' Lambda = .82; partial eta squared = .19. An inspection of the means revealed that for Gleason score, there was not a large difference in the mean of those patients with negative (7.29) or positive (8.18) bone scans, while for PSA there was a large difference in the means of patients with positive (737.79) versus negative (58.37) bone scintigraphy.

A MANOVA test was also perfomed in patients who had results for all 4 variables ie. Serum PSA, Gleason score, serum calcium and ALP. This result also revealed a statistically noteworthy difference in the bone scan findings on the combined variables, F (4, 220) = 33.69, $p < 0.001$. Upon further investigation, bone scan findings differed for Gleason score, serum PSA and ALP. They did not however differ for serum calcium. See table 3.9 below.

Table 3.9 Descriptive statistics from the MANOVA analysis

VARIABLES	BONE SCAN FINDINGS	MEAN
Gleason Score	Negative bone scan	7.244
	Positive bone scan	8.275
PSA	Negative bone scan	61.05
	Positive bone scan	868.18
ALP	Negative bone scan	97.295
	Positive bone scan	404.09
Calcium	Negative bone scan	2.311
	Positive bone scan	2.283

CHAPTER 4

4.1 Discussion

The occurrence of prostate cancer in the male population has increased over the years and currently it is the highest frequently detected cancer in males. Detection of locoregionally advanced and distant metastases determines the treatment options offered to patients. The commonest location for metastases from carcinoma of the prostate is the skeleton. Bone scintigraphy ranks high amongst the investigations ordered in nuclear medicine. Bone scanning is readily available and is a sensitive modality for identifying bone metastatic lesions, particularly osteoblastic metastases [45]. Many studies have evaluated the correlation between clinical staging, PSA and GS with the likelihood of metastases detected using bone scans [53,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77]. In this study we correlated PSA and Gleason score with bone scan findings.

We observed bone metastases in 25.1% of newly diagnosed PCa and 26% bone metastases in total (all our cases including patients that had BS after therapy had been initiated). This figure is higher than that reported in the Unites States (14%) [79] and Europe 8% [78] and similar to that reported in Japan (22.2% and 20.6%) [74, 80]. The reasons for the differences may be multifactorial related to: late presentation of patients to seek health care due to low levels of awareness and PSA screening being not widely available. The percentage of affirmative bone scans in patients with PSA <10 was 15.4% a value higher than that cited in most of the previous studies, which range from 0% to 8.7% [60,63,64,65,66,67,68,69,70,71,73,75,76,77], however it is similar to value given by Wymenga et al. of 15.7% [53]. This discrepancy most likely reflects that we could be possibly dealing with a different, more aggressive type of cancer in Southern Africa. The frequency in patients with PSA between 10–19.9 at 11.3% is not comparable to the work of other authors, which ranges from 0 - 33.3% with an average of 5.3%, of which most are lower or higher than our value. This difference is in keeping with the literature which states that in this PSA group, results and rate of positivity on scan is variable. This may account for the differences in guidelines with some suggesting a cut-off of 10ng/mL as an indication for an initial bone scan, while others use a PSA of 20ng/mL. The rate in patients with a PSA ≥ 20 was 73.3%.

Looking at a bit more than two thousand (2064) patients, Oesterling *et al.* found that

the likelihood for skeletal scintigraphy to be positive in patients who are clinically without symptoms and having a serum PSA below 20 ng/mL was lower than 1% [66]. The authors also reported a negligible number of abnormal BS (3) or indeterminate (1) result in 561 patients with a blood PSA concentration of 10 ng/mL or less. As an outcome, PSA's value ability to predict the findings on BS was not enhanced by other variables such as GS and clinical stage of the disease.

In another study that correlated PSA and Gleason score with results of BS in patients who were newly diagnosed with the disease in the UK, McArthur *et al.* studied 672 participants who had their ages ranging from 39 to 93 years [78]. Eight percent of these study participants were found to have spread disease into the skeleton. Interestingly as opposed to what Oesterling and colleagues found, when they considered which of the variables were independent predictors for a positive BS, Gleason score and PSA were found not only to be independent but also had a significant additive predictive value ($p < 0.01$). In 357 patients with a PSA less than 20 and a Gleason score below 8, none of them had a positive BS. They concluded that bone scan can be omitted safely in patients who met this criteria, with a NPV = 100% [78]. They also looked at the age and found that it was not a predictive factor.

Lee *et al* studied 631 patients newly diagnosed with PCa [79]. Of the six hundred and thirty one successive patients, 88 (14%) had positive bone scintigraphy. In their analysis, they sub-divided the PSA into 3 groups, namely PSA 0 - 15, 15.01 – 50 and PSA > 50. This differs slightly from other published results. The multivariate analysis of their data showed almost similar outcome as from the study by McArthur and colleagues. Statistical analysis revealed that the GS, PSA as well as the clinical stage were independent predictors for the presence of metastases with $p < 0.002$, $p < 0.001$, $p < 0.001$, respectively. The ORs and 95% confidence intervals (95 % CI) were as follows (table 4.1):

Table 4.1 Odds ratios and 95 % CI for PSA, GS and clinical T-stage

PSA level	OR	95 % CI
0 - 15	1	
15 - 50	0.47	0.28 – 0.78
> 50.01	5.25	3.43 – 8.04

Gleason score	OR	95% CI
2 – 6	1	
7	1.02	0.62 – 1.67
8 - 10	2.25	1.43 – 3.54

Clinical T-stage	OR	95% CI
T1a – T2b	1	
T2c – T4	2.15	1.54 – 2.99

We could not compare our results to the work of this group because we had different sub-divisions for our PSA levels and for our GS results we only looked at GS = 7 or GS > 7. In the patients with a Gleason score between 2–7, PSA ≤ 50, and clinical stage of ≤ T2b, only 3 / 308 (1 %) had skeletal metastases on scan. Fifty percent of patients with a PSA > 50, had metastases on BS. They recommended that bone scan could be omitted in low-risk patients, namely, Gleason score between 2 – 7, PSA of ≤ 50 and clinical stage of ≤ T2b. All other patients outside this bracket and especially patients with PSA > 50, skeletal scintigraphy ought to be considered. One could argue that the cut off of 50 ng/mL is not the traditional way of looking at the PSA levels. Looking at that study in that angle, different authors may decide on different cut-off levels to fit their results thus reducing the power of studies in terms of the accuracy on the likelihood of the test to predict bone metastases as per acceptable international consensus.

A multicenter retrospective study of 1294 patients from Japan by Kosuda *et al.* assessed if PSA values may be used to disregard bone scintigraphy in Japanese men with recent diagnosis of PCa [74]. Two hundred and eighty seven (22.2%) of the patients had skeletal involvement as detected by BS and the remaining the remaining 1007 patients (77.8%) had negative BS. Three hundred patients had PSA levels ≤ 10ng/mL and 4 (1.33% of positive BS) of these had bone metastasis. Receiver operator curves (ROC curves) were used in this analysis and generated an area under the curve of 0.870 for serum PSA levels to detect skeletal metastasis. Patients with GS ≥ 7 had a higher fraction of positive BS than patients with Gleason score ≤ 6. They concluded that an initial BS should not be considered in patients with PSA ≤ 10ng/mL, GS ≤ 6 and Gleason grade ≤ 2. Conversely patients with Gleason grade 5 or GS ≥ 7 ought to be offered an initial BS even when their PSA values are ≤ 10ng/mL, because probability of having a positive BS is high. This study was flawed in that it was a multicenter study therefore it was not so well standardized with regards to PSA kits, pathologists and radiologists.
A study by Ishizuka *et al.* also found a 20.6% positivity rate for bone metastases on BS in Asian men [80]. These figures are higher than those quoted from studies from Europe and America. Perhaps there is some truth in the speculation by Koshuda and colleagues; that this may be due to the limited accessibility of PSA screening for PCa in Japan paralleled to other considerably screened populations.

A meta-analysis by Abuzallouf and colleagues of 23 studies with a total of 8644 patients found that the most documented prognostic factor is the PSA. The frequencies of detection in patients with PSA < 10, 10 – 19.9, 20 – 49.9, 50 – 99.9 and ≥ 100 ng/mL were 2.3%, 5,3%, 16.2%, 39.2% and 73.4%, respectively. In this meta-analysis seven studies established that bone scintigraphy could be omitted in men with PSA levels < 20 ng/ml [53,59,60,61,62,63,64]. Ten studies recommended omitting BS for PSA less than 10ng/ml [65,66,67,68,69,70,71,72,73,74]. A negative predictive value (NPV) of less than 90% for PSA < 20 ng/ml was found in only 5 studies [53,64,68,73,75]. Only 2 studies concluded that BS is indicated in all patients [76,77].

The detection rates of metastases on BS in those patients with Gleason score ≤7 and Gleason score ≥8 were 5.6% and 29.9% respectively [57].

There are a number of publications that address the findings on BS with regard to both the PSA and Gleason score, however the serum ALP has been assessed in a only a few.

Wymenga *et al.* evaluated the necessity for skeletal scintigraphy as a routine first line investigation in the patients with a recent diagnosis of cancer of the prostate in relation to the ALP and PSA levels [53]. ALP results were available for 119 patients with PSA values < 20ng/mL. They found a positive scan in 7 (7%) patients with ALP levels that were within normal limits, while 8 (44%) of 18 patients with an abnormal ALP had metastases detected on BS [53]. Their results showed that ALP was found to be the variable that correlated best with metastases [area under the curve (AUC) 0.83], whilst for the PSA, the AUC was 0.76. However, there was no statistically significant ($p = 0.26$) difference between these curves. The role of PSA and ALP in relation with skeletal metastatic process was also found to be significant ($p=0.007$) using the ROC curves analysis. The AUC were 0.445 for PSA and 0.734 for ALP. They concluded that ALP as a biomarker had better correlation with bone scintigraphy results than PSA levels. In our study we grouped the ALP results into 3 groups (low, normal and high) whereas in this study they had normal and abnormal. We also had 3 groups for the BS findings (negative, positive and equivocal). In their study they found that fifty-nine (63%) of 94 patients with skeletal metastases also had elevated ALP. Our study revealed similar findings in that 79 (63%) of patients with positive BS had high ALP while 44 (36%) of patients with a normal ALP had positive bone scans. Unlike Wymenga *et al.* we did not look specifically to see what the ALP levels were for patients with PSA < 20ng/mL. Our findings are in agreement with theirs as we also found that ALP and PSA were independent predictive factors for the presence of bony metastases from logistic regression and that ALP was superior to PSA in predicting for the presence of skeletal metastases on bone scintigraphy, with $p = 0.017$ and $p < 0.001$ for PSA and ALP, respectively.

In 1996, Lorente *et al.* researched the effectiveness of bone specific ALP and PSA to predict bone scan evidence of metastases [81]. They analyzed serum concentrations of B-ALP and PSA in 350 men. They had a control group of 150 (presumably healthy) men, 100 men with BPH and 100 with PCa (52 staged as M0 and 48 with bone metastases). They found that the difference in concentration of B-ALP between patients with and without bone metastases was substantial. They also measured the effects of B-ALP enzyme and PSA levels on the magnitude of skeletal metastases.

They grouped the extent of metastases into 4 groups, M1 to M4. A statistically noteworthy difference was found among all groups ($p < 0.001$), except between those with stage M1 and M2 disease. Using an upper limit of 30ng/mL, they obtained 87.5% sensitivity, 100% specificity, with a high PPV of 100%, NPV of 89.6% and clinical effectiveness of 93.7%. In 48 patients that had both analyzed simultaneously, 46 (95.8%) had B-ALP > 30ng/mL and/ or PSA > 100ng/mL. 33 (71.7%) patients had both substances greater than the cut-off values. The sensitivity for the association between a PSA > 100ng/mL and a B-ALP > 30ng/mL is 95.8%, for the diagnosis of skeletal metastases in patients with PCa. Their conclusion was that B-ALP plays a complementary role to PSA level in the diagnosis of bone metastases [81].
In another study, this same group of authors looked at the clinical value of PSA in addition to B-ALP in the staging of patients with recently diagnosed PCa. They analyzed the results of 295 men and found that the combination of PSA and B-ALP, with a cut-off value of 20ng/mL resulted in a 100% NPV [82].

The report of Kamiya *et al.* evaluated the investigative precision of bone turnover markers in blood to identify skeletal metastasis in PCa patients and the assessment of their efficacy as possible predictors of death from this carcinoma [83]. They, like the previous authors found that both t-ALP and B-ALP were notably raised in patients with skeletal metastases, and these levels correlated ominously with the tumour burden as seen on BS.

In another study that investigated several factors, namely the T-stage (clinical), histological grade of tumour, PSA, PAP and acid phospatase to predict the outcome of skeletal scintigraphy, Chybowski and colleagues observed that these factors were able to predict for a positive scan. They also discovered that PSA alone performed better than all the other parameters. They reported a NPV of 99.7% for a PSA < 20ng/mL [65]. This outcome is comparable to that of the work by Oesterling et al. In our study however, the value of PSA < 20ng/ml as a negative test for the presence of metastases was lower (87.1%) than the one from the above mentioned studies. The difference on the percentage value between our two studies could be due to the numbers of studies' participants as we had more than twice the number but also in the design of the studies as they recruited only newly diagnosed patients. Their results almost exclude using BS in patients that have PSA levels below 20 ng/mL, which in our environment would mean missing bone metastasis in a non-negligible

number of patients. As opposed to conclusion made from the work of Chybowski et al, our study revealed that ALP was the best at predicting the findings on BS.

4.2 Limitations

There are a few limitations identified in this research report.

The first limitation is in the study design. As this was retrospective, we might have introduced potential bias and we also could not ascertain that all the relevant data (history, histology, blood results) is available.

Secondly, the skeletal lesions detected on bone scintigraphy were not confirmed histologically, as this is the "gold standard". Due to the lack of specificity of this modality, there is room for inaccuracy.

Thirdly, although a lot of studies have correlated clinical stage with bone scan findings, we decided to exclude this variable from our analysis after previously identifying challenges with data collection in our institution.

Lastly, the number of patients with calcium measurements in each sub-category was insignificant to draw robust conclusions on the role of this bio-marker in prostate carcinoma patients in our setting.

Several publications have recruited only newly diagnosed patients in their studies, however we adopted a different approach and collected data from all patients including those patients that had had surgery or commenced hormonal therapy.

The imaging was performed at a single institution and this may provide some form of standardization.

The other aspect of the study that was indirectly standardized is the biochemical (PSA, ALP and calcium) and pathology (GS) results. These were collected from the NHLS laboratory, which provides its services to all state / government hospitals in our province.

4.3 Conclusion

In this study, we found that two-thirds (70%) of scans that are referred to our institution are for staging and a quarter (25%) of them are found to have bone metastases as compared to other studies. Measuring the ORs, a Gleason score of up to 7 and a PSA level up to 20 were not the risk factors for the development of bone metastases, where as a GS above 7 and a PSA level more than 20 put the patients at risk of developing bone metastases. In fact, the overall analysis found that ALP and PSA were independent predictive factors for the presence of bony metastases from logistic regression. However, neither the lower Gleason (up to 7) and PSA (up to 20) nor the PSA level nor GS at risk (GS > 7 and PSA > 20) could either protect patients from developing bone metastases or expose all patients to the risk of developing osseous metastases.

The ALP may be used in conjunction with the PSA and GS in assessing for skeletal metastases in prostate cancer.

In conclusion, patients with PSA > 7 and GS > 20 should have skeletal scintigraphy. When the PSA is less than 20, deciding on a bone scan should be in conjunction with other clinical parameters, keeping in mind the high rate of bone metastases at presentation in our environment. A GS that is below 7 shouldn't be used as a factor to decide on BS.

Our results may serve as a guide to clinicians when deciding on bone scintigraphy for patients with PCa. This may have an impact on the number of requests that we receive and hence the waiting times for a bone scan.

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R14/49 Dr KMG Mokoala

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140232

NAME: (Principal Investigator) Dr KMG Mokoala

DEPARTMENT: Radiation Sciences
Charlotte Maxeke Johannesburg Academic Hospital

PROJECT TITLE: Correlation between PSA, Gleason Score and Bone Scan Findings

DATE CONSIDERED: 28/02/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof MDTHW Vangu

APPROVED BY:
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 05/03/2014

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned 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**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

GAUTENG PROVINCE
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REPUBLIC OF SOUTH AFRICA

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Date: 29th November 2013

Dr. K.M.G. Mokoala
Nuclear Medicine Department
CMJAH

Re: "The correlation between PSA, GLEASON SCORE AND BONE SCAN FINDINGS"

Please note that permission to conduct the above mentioned study is provisionally approved. Your study can only commence once ethics approval is obtained. Please forward a copy of your ethics clearance certificate as soon as the study is approved by the ethics committee for the CEO's office to give you the final approval to conduct the study.

Approved/not approved

Ms. G. Bogoshi
Chief Executive Officer
Date: 2/11/2013

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

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November 17, 2015

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Mokoala with her study entitled "The correlation between PSA, Gleason score and Bone scan findings".

Notwithstanding the requirement that research projects should comprise the researchers work only, it is recognized that publication of such work is encouraged. In the event that the information used comprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Mokoala will be in contact with the Department of Anatomical Pathology in respect of this.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Professor MJ Hale
Head: Department of Anatomical Pathology

17/11/2015
Date

American Joint Committee on Cancer

Prostate Cancer Staging

7th EDITION

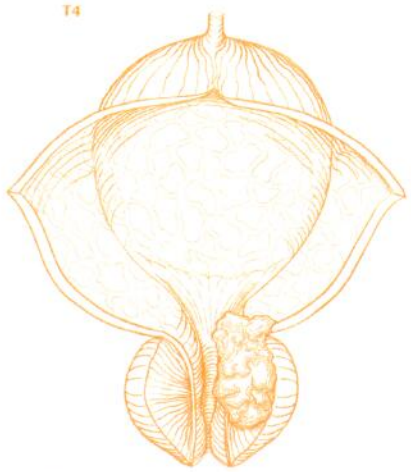


Figure A. T4 tumor invading adjacent structures other than seminal vesicles, such as bladder, rectum, levator muscles, and/or pelvic wall.

ANATOMIC STAGE/PROGNOSTIC GROUPS[6]					
Group	T	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA <20	Gleason 7
	T1a–c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

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Definitions

Primary Tumor (T)

CLINICAL

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **T1** Clinically inapparent tumor neither palpable nor visible by imaging
- **T1a** Tumor incidental histologic finding in 5% or less of tissue resected
- **T1b** Tumor incidental histologic finding in more than 5% of tissue resected
- **T1c** Tumor identified by needle biopsy (for example, because of elevated PSA)
- **T2** Tumor confined within prostate[1]
- **T2a** Tumor involves one-half of one lobe or less
- **T2b** Tumor involves more than one-half of one lobe but not both lobes
- **T2c** Tumor involves both lobes
- **T3** Tumor extends through the prostate capsule[2]
- **T3a** Extracapsular extension (unilateral or bilateral)
- **T3b** Tumor invades seminal vesicle(s)
- **T4** Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall (Figure A)

Pathologic (pT)[3]

- **pT2** Organ confined
- **pT2a** Unilateral, one-half of one side or less
- **pT2b** Unilateral, involving more than one-half of side but not both sides
- **pT2c** Bilateral disease
- **pT3** Extraprostatic extension
- **pT3a** Extraprostatic extension or microscopic invasion of bladder neck[4]
- **pT3b** Seminal vesicle invasion
- **pT4** Invasion of rectum, levator muscles, and/or pelvic wall

Regional Lymph Nodes (N)

CLINICAL

- **NX** Regional lymph nodes were not assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in regional lymph node(s)

PATHOLOGIC

- **pNX** Regional nodes not sampled
- **pN0** No positive regional nodes
- **pN1** Metastases in regional node(s)

Distant Metastasis (M)[5]

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Nonregional lymph node(s)
- **M1b** Bone(s)
- **M1c** Other site(s) with or without bone disease

Notes

[1] Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

[2] Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

[3] There is no pathologic T1 classification.

[4] Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

[5] When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced.

[6] When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available.

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Appendix 5

Data Collection Sheet

Code	Age	PSA	ALP	Calcium	Gleason score	Symptomatology	Newly diagnosed	Bone scan finding	e of adenocar

CorrelationbetweenPSAGleasonscoreandbonescanfindings..

ORIGINALITY REPORT

%19	%12	%16	%2
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