UTILISATION OF STANDARDIZED UPTAKE VALUE MAXIMUM (SUVMAX) IN SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY/ COMPUTED TOMOGRAPHY (SPECT/CT) TO DIFFERENTIATE BETWEEN METASTATIC VS DEGENERATIVE JOINT DISEASE OF THE SPINE IN BONE SCAN FOR PROSTATE CANCER PATIENTS

BY

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DECLARATION

I hereby declare that this research has been sent to Universiti Sains Malaysia for the Degree of Master of Medicine (Nuclear Medicine). It is also not to be sent to other universities. With that, this research might be used for consultation and will be photocopied as reference.

Mohd Fazrin Bin Mohd Rohani

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ABBREVIATIONS

SUV	Standardized Uptake Value
SUVmax	Standardized Uptake Value Maximum
SPECT	Single Photon Emission Computed Tomography
SPECT/CT	Single Photon Emission Computed Tomography acquisition combined with Computed Tomography using integrated CT scanner
^{99m}Tc-MDP	Technetium-99 metastable methylene diphosphonate
DJD	Degenerative joint disease
PSA	Prostate specific antigen
WBBS	Whole body bone scan
CT	Computed tomography
ROC	Receiver operating characteristic
AUC	Area under the curve
CI	Confidence interval
^{18}F-NaF	Fluorine-18 sodium fluoride
PET/CT	Positron emission tomography combined with Computed Tomography using integrated CT scanner
DRE	Digital rectal examination
MRI	Magnetic resonance imaging
DWI	Diffusion weighted imaging
TNM	Tumor-node-metastasis
AJCC	American Joint Committee on Cancer
ADT	Androgen deprivation therapy
SRE	Skeletal related event

ABBREVIATIONS (CONTINUED)

ALP	Alkaline phosphatase
ROI	Region of interest
^{223}Ra	Radium-223
bsa	Body surface area
lbm	Lean body mass
bw	Body weight

SYMBOLS

g	gram
mg/ml	milligram per milliliter
mCi	millicurie
MBq	megabecquerel
cm/min	centimeter per minute
s	seconds
mAs	milliampere-seconds
kV	kilovoltage
mm	millimeter
ng/ml	nanogram per milliliter
g/ml	gram per milliliter
U/L	units per litre
kBq/ml	kilobecquerel per milliliter

ABSTRAK

Objektif. Analisa secara kualitatif menggunakan skan tulang sering kali di rumitkan dengan kewujudan penyakit degeneratif sendi tulang belakang lebih-lebih lagi pada pesakit yang sudah berusia. Tujuan utama kajian ini adalah untuk membandingkan secara semi-kuantitatif akumulasi pengesan ^{99m}Tc-MDP di antara penyakit degeneratif sendi dan metastatik kanser pada tulang belakang menggunakan SPECT SUV.

Subjek dan Kaedah. Skan tulang dengan SPECT/CT menggunakan ^{99m}Tc-MDP telah di lakukan pada 34 pesakit kanser prostat. SPECT/CT di lakukan berdasarkan garis panduan institusi kami. Pengiraan standardized uptake value maximum (SUVmax) berdasarkan berat badan pada 238 vertebra normal yang di lihat pada SPECT/CT telah di lakukan sebagai asas. Sebanyak 211 lesi telah di kenal pasti pada skan tulang. Morfologi lesi telah dicirikan berdasarkan pemerhatian gambar pada CT skan dos rendah. Analisa secara semi-kuantitatif telah di buat menggunakan SUVmax terhadap 89 lesi untuk penyakit degeneratif sendi dan 122 untuk metastatik.

Keputusan. Mean SUVmax untuk vertebra normal adalah 7.08 ± 1.97, 12.59 ± 9.01 untuk penyakit degeneratif sendi dan 36.64 ± 24.84 untuk metastatik kanser pada tulang belakang. SUVmax untuk metastatik kanser pada tulang belakang adalah lebih tinggi daripada penyakit degeneratif sendi dengan ketara (nilai $p < 0.05$). Untuk menganalisa ketepatan diagnosis, kurva ciri operasi penerima (ROC) telah dibuat dan didapati kawasan di bawah lengkung (AUC) adalah agak tinggi pada 0.874 (95% CI: 0.826-0.921). Nilai SUVmax ≥ 20 dapat membezakan antara metastatik kanser pada tulang belakang daripada penyakit degeneratif sendi dengan sensitiviti sebanyak 73.8% dan spesifisiti 85.4%.

Kesimpulan. SPECT SUVmax pada metastatik kanser pada tulang belakang adalah lebih tingggi secara ketara daripada penyakit degeneratif sendi. Analisa secara semi-kuantitatif menggunakan SUVmax boleh menjadi pelengkap pada analisa secara kualitatif. Nilai SUVmax $\geq$ 20 boleh di gunakan untuk membezakan antara metastatik kanser tulang belakang dan penyakit degeneratif sendi. Namun begitu, nilai tersebut tidak sesuai di gunakan secara klinikal kerana terdapat pertindihan yang besar antara nilai SUVmax pada penyakit degeneratif sendi dan metastatik kanser tulang belakang.

ABSTRACT

Objective. Qualitative interpretation in bone scan is often complicated by the presence of degenerative joint disease (DJD) especially in the elderly patient. The aim of this study is to compare objectively ^{99m}Tc-MDP tracer uptake between DJD and osseous metastases of the spine using semi-quantitative assessment with SPECT SUV.

Subjects and Methods. Bone scan with SPECT/CT using ^{99m}Tc-MDP were performed in 34 patients diagnosed with prostate carcinoma. SPECT/CT were performed based on our institutional standard guidelines. SUVmax based on body weight in 238 normal vertebrae visualized on SPECT/CT were quantified as baseline. A total of 211 lesions in the spine were identified on bone scan. Lesions were characterized into DJD or bone metastases based on its morphology on low dose CT. Semi-quantitative evaluation using SUVmax were then performed on 89 DJD and 122 metastatic bone lesions.

Results. The mean SUVmax for normal vertebrae was 7.08 ± 1.97, 12.59 ± 9.01 for DJD and 36.64 ± 24.84 for bone metastases. The SUVmax of bone metastases were significantly greater than DJD (p value <0.05). To assess for diagnostic accuracy, receiver operating characteristic (ROC) curve was performed. The area under the curve (AUC) was found to be fairly high at 0.874 (95% CI: 0.826-0.921). The cut-off SUVmax value ≥ 20 gave a sensitivity of 73.8% and specificity of 85.4% in differentiating bone metastases from DJD.

Conclusion. SPECT SUVmax was significantly higher in bone metastases than DJD. Semi-quantitative assessment with SUVmax can complement qualitative analysis. A cut-off SUVmax of ≥ 20 can be used to differentiate bone metastases from DJD. However, it is not feasible to be applied clinically due to the considerable overlap of SUVmax between DJD and bone metastases.

INTRODUCTION

1.0 INTRODUCTION

Early diagnosis of bone metastasis is essential in prostate cancer to aid the referring physician in choosing the appropriate therapy, assessing the extent of bony involvement, monitoring of treatment response and assessing for possible complications (McLoughlin *et al*., 2016). In general, bone is the 3rd most common site of cancer metastasis after lung and liver (Macedo *et al.*, 2017). In prostate cancer, bone metastases are seen in up to 65-75% of patients and commonly involved the axial skeleton, the site of active bone marrow (Langsteger *et al.*, 2016 ; Macedo *et al.*, 2017 ; O'Sullivan, 2015). It also represents the initial and main site of metastases in approximately 80% of cases (Tombal, 2012).

Whole body bone scan (WBBS) is widely used for the assessment of bone metastasis in prostate cancer owing to its high sensitivity, availability and affordability (Macedo *et al.*, 2017). Often it is used for staging in the early stage of prostate cancer in order to decide on the appropriate treatment or making decision on change of therapy in patient with advanced disease (Donohoe *et al.*, 2017). In spite of its high sensitivity, planar WBBS has low specificity due to the accumulation of the radiotracer in traumatic, degenerative and inflammatory lesions which may cause false positive findings (Langsteger *et al.*, 2016). In addition, increased in tracer uptake in degenerative joint disease of the spine is also common in men more than 50 years old (Muzahir *et al.*, 2015 ; O'Sullivan, 2015).

Single photon emission computed tomography (SPECT) which shows axial slices of radiopharmaceutical uptake (O'Sullivan, 2015), performed in limited regions of the body is used to clarify indeterminate lesions by identifying certain patterns of radiotracer accumulation that is more indicative of either benign or malignant disease (Helyar *et al.*, 2010 ; Love *et al.*, 2003). Compared to planar bone scan, SPECT of the spine has shown to detect 20 to 50% more lesions (Sapir, 2005) and has higher sensitivity and specificity (Love *et al.*, 2003).

The introduction of hybrid single photon emission computed tomography/ computed tomography (SPECT/CT) has further enhanced the sensitivity and specificity of bone scan (Kuwert, 2014). SPECT/CT enables anatomical correlation, characterizing morphologic changes and attenuation correction of radiotracer uptake on CT which led to significant increase in diagnostic accuracy especially in assessing indeterminate lesions on planar WBBS (McLoughlin *et al.*, 2016). SPECT/CT has been shown to define more than 90% indeterminate lesions on bone scan (Römer *et al.*, 2006).

In clinical practice, disease progression or regression in bone metastases is commonly characterized by increase or decrease in number of bone lesions. Qualitative interpretation of bone scan with SPECT and SPECT/CT is subjective and interpreter dependent (Beck *et al.*, 2016). This poses difficulty in differentiating between malignant and degenerative changes both of which will give rise to increased tracer uptake on bone scan. There is no defined, standardized value or cut-off point to differentiate between degenerative joint disease and bone metastases objectively. An objective semi-quantitative analysis was proposed in a similar manner to positron emission (PET) standardized uptake value (SUV) as this could be useful in determining treatment response.

To date, there is little data available on the usage of semi-quantitative measurement with SPECT SUV in differentiating degenerative joint disease (DJD) from metastatic bone disease. Furthermore, the clinical utility of SUV in SPECT based radiotracers are not well established and not widely used in clinical practice. The aim of this study is to evaluate the utility of semi-quantitative assessment with SPECT SUV in differentiating DJD from bone metastasis of the spine in prostate cancer patients who underwent bone scan in Hospital Universiti Sains Malaysia (HUSM).

LITERATURE REVIEW

2.0 LITERATURE REVIEW

2.1 NORMAL ANATOMY OF PROSTATE

The prostate is a small gland which is a part of the male reproductive system. It has the shape and size of a walnut. It weighs from 7 to 16g with a mean of 11g in adult and surrounds the urethra at the neck of urinary bladder (Kumar, 1995). It is located anterior to the rectum and in between the urogenital diaphragm and bladder. The urethra runs through the prostate gland centrally from the urinary bladder to the penis, allowing urine and semen excretion from the body.

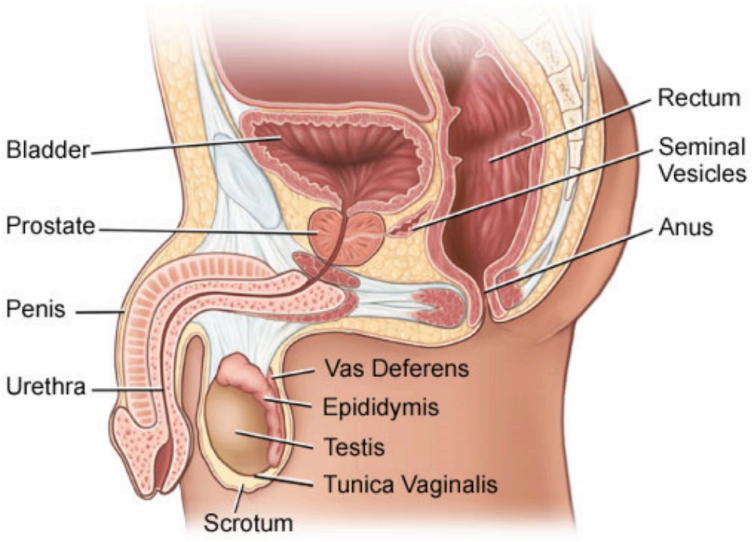

Figure 2.1: Anatomy of prostate

(adapted from https://www.hopkinsmedicine.org/healthlibrary/conditions/prostate_health/anatomy_of_the_prostate_gland_85,P01257 accessed on 13th February 2019)

The function of prostate gland includes the control of urine excretion from the bladder, seminal fluid transmission, reduction of urethral activity via secretion of prostatic fluids and also aids in testosterone metabolism. The main male hormone testosterone is being produced by the testes. Histologically, the prostate gland can be

divided into lobes (two laterals, anterior, posterior and median) and three zones, namely the peripheral, transitional and central zone (Kumar, 1995).

2.2 EPIDEMIOLOGY

Prostate cancer is the 2nd most frequent malignancy in male and the 4th most common cancer for both male and female worldwide. In 2012, an estimate of 1.1 million prostate cancer cases were diagnosed which accounts for 15% of cancer diagnosed in men. The incidence however varied across the region worldwide with 70% of cases occurring in more developed countries (Ferlay *et al.*, 2015). High incidence of prostate cancer can be found in North America and Australia/ New Zealand while the lowest incidence is seen in the Asian population (Ferlay *et al.*, 2015 ; Zhou *et al.*, 2016 ; Gjertson, 2011). This is primarily attributed to the prevalence of PSA testing which was followed by biopsy of the prostate gland in the developed regions especially in men aged 50 years or older (Zhou *et al.*, 2016 ; Tombal, 2012). In terms of mortality, prostate cancer represents 6.6% (or 307,000 deaths) of the total cancer mortality in male and is the 5th highest cause of death from cancer in men. The mortality rate is however high in the African population, intermediate in Oceania and Americas and low in Asian population (Ferlay *et al.*, 2015).

Based on the Malaysian National Cancer Registry 2007-2011 (Manan *et al.*, 2007-2011), prostate cancer is the 5th most frequent malignancy in Malaysian men and ranked 11th overall in Malaysia. Cancer of the prostate accounts for 6.7% of all cancers in the Malaysian male population with a lifetime risk of 1 in 117. The incidence of prostate cancer is at 6.7 per 100,000 and increased with advanced age. The highest incidence of

prostate cancer is seen in Penang (at 13.8 per 100,000) while the lowest incidence is seen in Wilayah Persekutuan Labuan (at 2.8 per 100,000). The state of Kelantan however has an incidence of 5.9 per 100,000. In Malaysia, prostate cancer is most common in the Chinese, followed by the Indian and Malay race. It is often diagnosed late as 41.6% of prostate cancer patients presents to the tertiary center with stage IV disease.

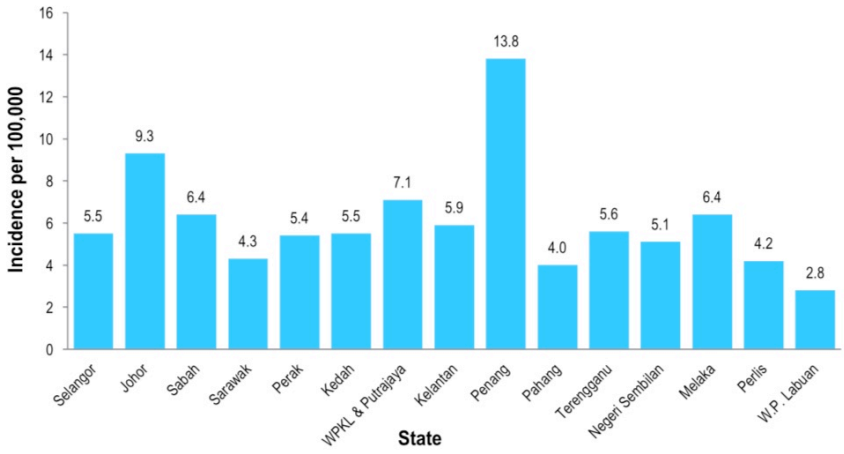

Figure 2.2 Incidence of prostate cancer per 100,000 males according to states in Malaysia. Adapted from (Manan *et al.*, 2007-2011)

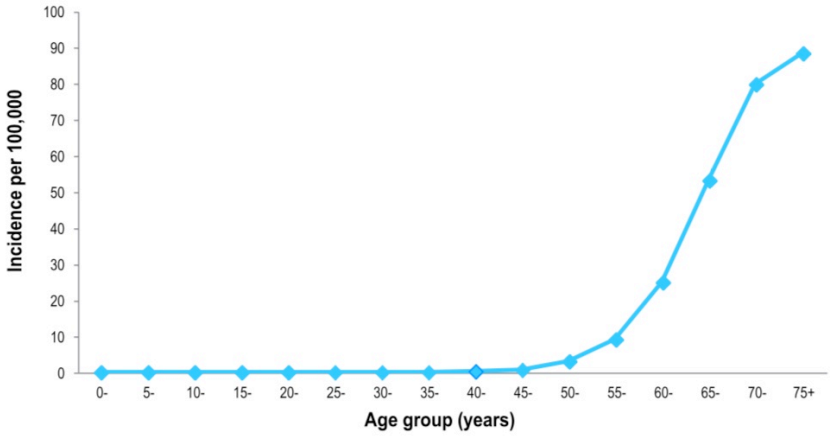

Figure 2.3 Incidence of prostate cancer per 100,000 males in Malaysia based on age group. Adapted from (Manan *et al.*, 2007-2011)

2.3 SYMPTOMS & DIAGNOSIS OF PROSTATE CANCER

Prostate cancer is often multifocal and commonly found in the peripheral zone (80 to 85%) followed by transitional zone (10-15%) and central zone (5 to 10%). Adenocarcinoma is the most common histology which represents more than 95% of prostate cancer. Growth of prostate cancer follows a multistep process starting from prostate intraepithelial neoplasia, which is a precursor for carcinoma. Initially, the prostate cancer cells are confined to the normal gland. Further cell mutation leads to disease progression and metastasis. Prostate cancer cells are sensitive to androgen receptor activation and with progression of disease, there is upregulation and mutation of the androgen receptors (Strauss *et al.*, 2017).

Prostate cancer is generally slow growing, and patient is often asymptomatic for a number of years. The disease often affect urination owing to its vicinity to the urethra. Symptoms of prostate cancer includes an increased in urinary frequency, nocturia, hematuria, poor stream and dysuria. Sexual function can also be affected, manifested by painful ejaculation or difficulty in attaining erection. Clinically, abnormalities of the prostate can be assessed by digital rectal examination (DRE). The prostate can be felt as hard and craggy in the presence of cancer. Often however, prostate may feel normal in spite of the presence of cancer cells. It is recommended that men aged more than 50 years have yearly DRE and prostate specific antigen (PSA) test (Zhou *et al.*, 2016). DRE is used to determine whether patient need further investigation.

The serum PSA is a glycoprotein synthesized by the prostate epithelial cells. Its function is to dissolve seminal clot post ejaculation which facilitates the transport of sperm along the female reproductive tract. The concentration of PSA is found to be high in seminal fluid with a range of 0.5 to 2.0 mg/mL, but is much lower in blood. Its elevation

in the blood in disease states have been postulated to be caused by the disruption of prostate gland cellular architecture (Gretzer, 2002). Elevation of PSA may indicate prostate cancer. However, serum PSA is not a specific prostate cancer marker as its rise can also be seen in prostatic trauma, inflammation and benign proliferation (Gretzer, 2002 ; Gjertson, 2011). The normal values of PSA for men over the age of 40 is equal or less than 4.0 ng/mL (Gretzer, 2002). In prostate cancer, elevation of PSA cannot differentiate between low grade and high grade cancer (Gjertson, 2011). Nonetheless, higher PSA level signifies advanced disease (Donohoe *et al.*, 2017).

Transrectal ultrasound is being used to measure the prostate size and density. Biopsy for histological confirmation is done with guidance from ultrasound where 10 to 12 tissue samples or cores are being taken for histopathological confirmation. CT scan on the other hand can assess for cancer spread to regional lymph nodes. Magnetic resonance imaging (MRI) uses magnetic field which is a non-ionizing radiation that creates a clear picture of the prostate gland. It is also the imaging modality used to assess metastases in the bone marrow cavity before osteoblastic lesion manifest as a focal of uptake in skeletal scintigraphy (O'Sullivan, 2015).

2.4 STAGING AND RISK ASSESSMENT

The tumor-node-metastasis (TNM) system, developed by the American Joint Committee on Cancer (AJCC) is used for pre-therapy staging in prostate cancer. For the T (tumor) staging, it is based on DRE, cancer involvement in prostate on biopsy and radiological imaging such as CT scan and MRI. Nodal metastases are assessed based on anatomic enlargement of lymph nodes on CT scan or MRI. PET/CT tracers are however able to identify nodal metastases prior to enlargement of the lymph nodes. Metastases on the other hand is also evaluated by CT scan and MRI with the addition of bone scintigraphy as bone is the commonest site for distant metastasis in prostate cancer.

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

Figure 2.4 AJCC TNM criteria for prostate cancer 7th edition (Adapted from https://cancerstaging.org/references-tools/quickreferences/Pages/default.aspx accessed on 25th September 2018).

Histologic grading is essential in disease prognostication of clinically localized prostate cancer. Over the years, the Gleason score has been the widely accepted standard for prostate cancer grading where the cancers are scored based on its appearance under the microscope. The Gleason grading system practically assess the architectural pattern of the prostate cancer. It scores both the primary grade or dominant patterns (>50%) and non-dominant or secondary patterns (5 to 50%) of cancer from 1 to 5, where 1 is well differentiated and 5 is poorly differentiated. The Gleason score is the total score of the dominant and non-dominant pattern (Parker *et al.*, 2015).

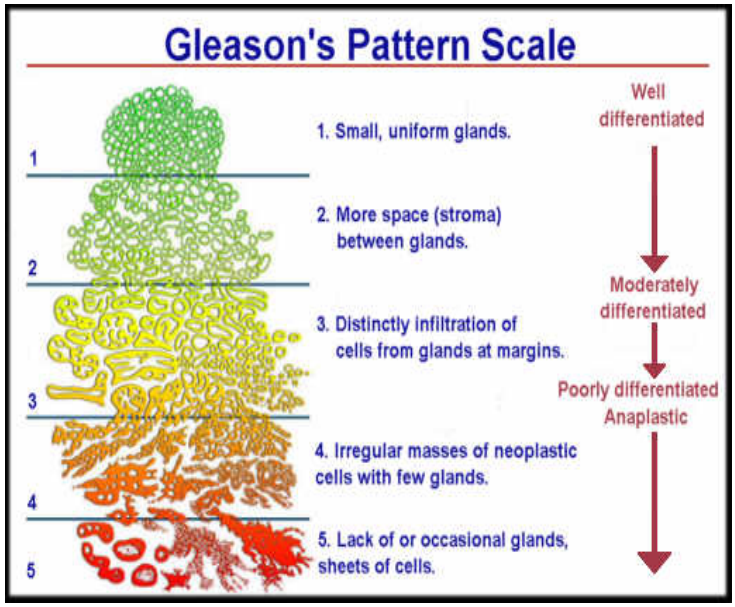

Figure 2.5 Gleason's Pattern Scale. (Adapted from https://www.prostateconditions.org/about-prostate-conditions/prostate-cancer/newly-diagnosed/gleason-score accessed on 25th September 2018)

Localized disease with Gleason sum of 8, 9 or 10 can progress to metastasis which can lead to death in a short time span. Those with low grade cancer (Gleason sum of ≤6) however, may not demonstrate disease progression in spite of not having any treatment. In terms of mortality, patients with Gleason sum of 7 and 8 to 10 has a higher rate of

death. On the contrary, patient with Gleason score of ≤6 is at low risk of cancer related death (Gjertson, 2011).

2.5 TREATMENT OF PROSTATE CANCER

The treatment of prostate cancer is risk adjusted and patient specific. Early stage prostate carcinoma is often treated with the aim of cure. Therapy includes active surveillance, radical prostatectomy, radiotherapy and seeds implant (Parker *et al.*, 2015). Local therapy is indicated for localized low or intermediate risk disease while bone metastases patients are generally treated with systemic therapy (Tombal, 2012).

Hormonal therapy is commonly used in prostate cancer that has spread beyond the prostate gland and also in cases of cancer recurrence post radiotherapy or radical prostatectomy. Prostate cancer needs fuel to grow and survive which is mainly provided by the hormone testosterone. It is known that androgen deprivation therapy (ADT) by using drug or surgery, limit or slow the growth of prostate cancer by reducing the levels of androgen. Most of the prostate cancer cells will respond to ADT but some may become independent and thus resistant to hormonal therapy (Strauss *et al.*, 2017). Chemotherapy with docetaxel is reserved for metastatic prostate cancer that is resistant to ADT (Strauss *et al.*, 2017 ; Parker *et al.*, 2015). A change in therapy is often considered based on symptoms, PSA elevation, presence of metastasis or progression of disease (Donohoe *et al.*, 2017).

2.6 BONE METASTASES IN PROSTATE CANCER

Prostate cancer has a high tendency for bone metastases. The occurrence of skeletal metastases correlates with PSA level and Gleason scoring. The incidence of bone metastases is approximately 2% in patient with PSA of <10 ng/ml, while the likelihood of bone metastases is at 16% for PSA of >20 ng/ml. In terms of Gleason score, bone metastases are seen in 6% of patients with a score of <6 compared to 30% in patient with Gleason score of >7 (Donohoe *et al.*, 2017).

More than 90% of bone metastases are found in the axial skeleton, the site of active red marrow which can lead to skeletal complications. Skeletal metastases occur most commonly via hematogenous spread, mainly through the venous pathway. The tumor cells detached from its primary site and enters the blood circulation. It then survived the host immune response and vascular resistance (Maccauro *et al.*, 2011 ; Sapir, 2005). Entry of tumor cells to the well vascularized active bone marrow is facilitated by its sluggish and slow blood flow (O'Sullivan, 2015).

After bone colonization, tumor cells released cytokines and growth factors which disrupt normal bone turnover. Parathyroid-related hormone protein, tumor necrosis factor alpha and cytokines such as interleukin-1 upregulates the osteoclast by increasing the production of receptor activator of nuclear kappa B ligand (RANKL) causing osteolysis. On the other hand, insulin-like growth factors, epidermal growth factor and transforming growth factor alpha causes osteosclerosis from upregulation of osteoblasts (O'Sullivan, 2015 ; Maccauro *et al.*, 2011). In bone metastases, there is a disruption in the balance between osteoblast mediated bone formation and osteoclast mediated bony destruction (So *et al.*, 2012 ; Maccauro *et al.*, 2011) .

In the marrow, as the tumor cells enlarge, the adjacent bone underwent osteoblastic and osteolytic changes. The radiographic appearance of bone metastases can be lytic, sclerotic or a mixture of both lytic-sclerotic lesion depending on the balance between osteolytic and osteoblastic processes. Aggressive bone metastases tend to be lytic while sclerosis signifies slower tumor growth (Sapir, 2005). In prostate cancer, there is a characteristic association between osteoblastic response to the presence of metastatic cancer cells.

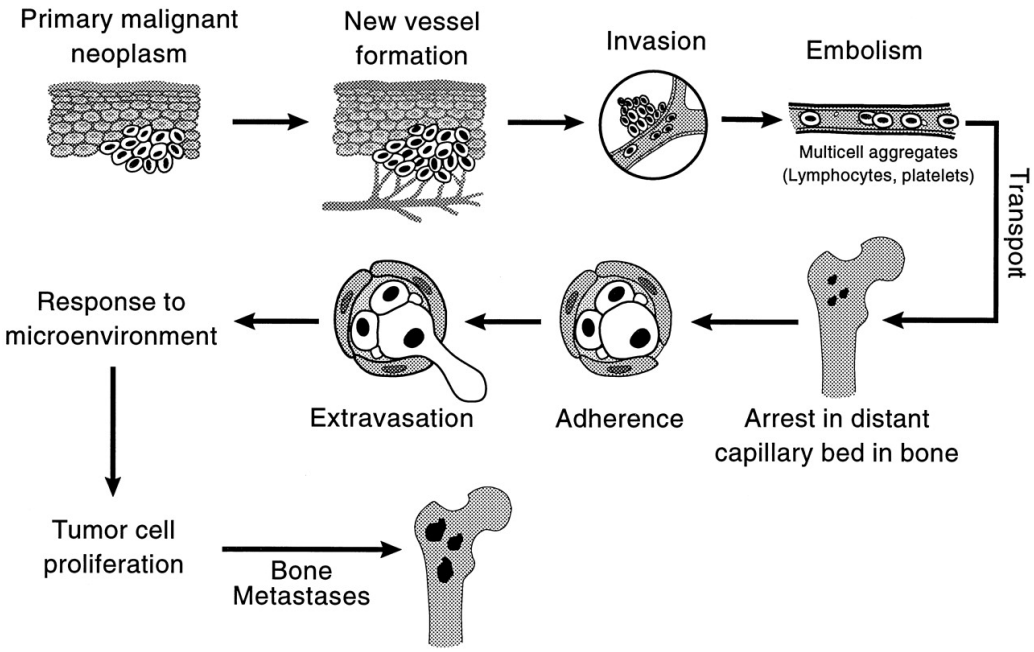

Figure 2.6 Mechanism of tumor metastases to the skeletal system in prostate cancer. (Adapted from https://academic.oup.com/edrv/article/19/1/18/2530783 accessed on 25th September 2018)

2.7 MANAGEMENT OF BONE METASTASES IN PROSTATE CANCER

Bone metastases commonly caused skeletal related events (SRE), complications that are associated with significant morbidity (Cook *et al.*, 2011). By definition, SRE encompassed pathological fracture, hypercalcemia, spinal cord compression and the necessity for patient to undergo radiotherapy or surgery to the bone (So *et al.*, 2012 ; Coleman *et al.*, 2014 ; Klaassen *et al.*, 2017). Replacement of bone marrow hematopoietic cell by prostate cancer cells can also lead to anemia (Tombal, 2012). If left untreated, up to 50% of advanced prostate cancer patients will experienced SRE within 2 years (So *et al.*, 2012) and it is associated with significant loss of mobility, reduction in quality of life and increased in cost of treatment (Coleman *et al.*, 2014 ; Klaassen *et al.*, 2017). Presence of 3 or more lesions on bone scan also increased the risk of SRE (So *et al.*, 2012).

Treatment modalities include analgesics, bisphosphonates (like zoledronic acid), receptor activator of nuclear factor kappa-B ligand (RANK-L) inhibitor and bone targeted radionuclide therapy such as Radium-223 (^{223}Ra) (So *et al.*, 2012). ^{223}Ra has been shown to improve the survival of patients diagnosed with bone metastases and delays skeletal related event (Parker *et al.*, 2015 ; Klaassen *et al.*, 2017). In spite of the advancement of bone targeted therapies, bone metastases are still considered incurable (Tombal, 2012 ; Coleman *et al.*, 2014). Mortality from prostate cancer is often due to complications from bone metastases (Klaassen *et al.*, 2017).

2.8 IMAGING MODALITIES IN BONE METASTASES

Plain radiographs are widely available and often used in the initial assessment of bone metastases. However, it has limited contrast between cortical and trabecular bone. Unlike plain radiographs, CT scan offers excellent resolution between cortical and trabecular bone and enables bone visualization in multiple planes resulting to an increased in sensitivity without the effect of superposition. However, both plain radiographs and CT scan requires 50 to 70% of bony destruction for lesion detection, reveals only structural bony alterations and unable to fully differentiate between sclerotic lesion from progression of disease from those caused by bone remodeling in treatment response (O'Sullivan, 2015 ; Heindel *et al.*, 2014).

MRI is the imaging of choice for assessment of bone metastases in the marrow cavity due its good resolution in soft tissue with a sensitivity and specificity of 95% and 90% respectively. It has the added advantage of detecting intramedullary bone metastases prior to cortical bone destruction and before the manifestation of radiotracer uptake from osteoblastic process in a bone scan. However, MRI has poor visualization of bone with low marrow volume due to its short T2 relaxation time (O'Sullivan, 2015 ; Heindel *et al.*, 2014).

Radionuclide bone scan either with SPECT [like ^{99m}Tc-methylene diphosphonate (MDP)] or PET [like ^{18}F-sodium fluoride (NaF)] tracer is commonly used in nuclear medicine procedure in the assessment of skeletal metastasis. In comparison to SPECT, PET has superior spatial and image resolution. Uptake of radiotracer relies on blood flow, osteoblastic process and its extraction efficiency. The radiotracer concentrates at bone diphosphonates which is chemiabsorbed by the osseous matrix into the hydroxyapatite crystal on the surface of bone. The advantage of bone scan is from its ability to image the

whole skeleton, high sensitivity and early detection of skeletal metastasis with as little as 5 to 10% of bone alteration exhibiting abnormal tracer accumulation. Its limitation lies in its low specificity, where non-metastatic lesions such as degenerative joint disease and fracture may display abnormal tracer accumulation, assess osteoblastosis rather than cancer proliferation and little or absent tracer uptake seen in osteolytic lesions (O'Sullivan, 2015 ; Heindel *et al.*, 2014).

Compared to ^{99m}Tc-MDP, ^{18}F-NaF is superior with increased in sensitivity and specificity in detecting skeletal metastasis. However, ^{18}F-NaF limited availability and cost restrict its usage. ^{18}F-fluorodeoxyglucose (FDG) is a glucose analog where its uptake reflects tumor metabolism and is superior than both ^{99m}Tc-MDP and ^{18}F-NaF in detecting lytic and purely bone marrow metastasis (Bastawrous *et al.*, 2014).

Technological advancement enables the usage of hybrid imaging such as SPECT/CT, PET/CT and PET/MRI which allows morphological correlation from functional imaging with the added advantage of quantitative assessment with SUV (O'Sullivan, 2015 ; Heindel *et al.*, 2014).

2.9 MONITORING OF BONE METASTASES

Monitoring of treatment response in bone metastases is laborious. In practice, assessment is based on clinical examination, biochemical markers such as PSA and alkaline phosphatase (ALP) which is a serum marker for osteoblastic proliferation (Tombal, 2012) and imaging modalities. Nonetheless, these methods are not sensitive and non-specific (Cook *et al.*, 2011).

Visually counting the number of lesions on bone scan has been a commonly used method to assess extent of bone metastases. Bone scan image interpretation based on changes of lesion intensity and size is subjected to inter-observer variation which will cause difficulty in comparing images in the long term (Zafeirakis, 2014). An objective quantitative tool is thus essential to monitor the progression of bone metastases.

With the improvement of therapy of bone metastases, better methods are needed to characterize disease burden at the initial stage and to assess treatment response (Zafeirakis, 2014). In addition, radiographic changes in treatment response takes a couple of months to occur (Cook *et al.*, 2011 ; O'Sullivan, 2015). MRI can be used to assess treatment response in skeletal metastases based on number and size of lesions. Further studies are however needed to ascertained T1 and diffusion weighted imaging (DWI) characteristics in the evaluation of therapy response (O'Sullivan, 2015). Comparing qualitative analysis with semi-quantitative analysis using SUV in bone scan have demonstrated almost perfect inter-observer agreement between interpreters compared to visual analysis alone (Beck *et al.*, 2016). Lei Mao *et al.* (2015) has concluded that SUV SPECT can be used as an absolute quantitative parameters in the follow up of prostate cancer patients with bone metastases. Hence, quantification of tracer uptake ensures consistency in monitoring of treatment response.

2.10 STANDARDIZED UPTAKE VALUE (SUV)

SUV is a commonly used semiquantitative parameter to calculate accumulation of tracer in PET studies especially in ^{18}F-FDG PET/CT. Its clinical application lies in measuring the relative change in SUV to assess treatment response. The measured radiotracer within a region of interest (ROI) is normalized to the average accumulation of radiotracer in the body which is estimated by the radiopharmaceutical injected dose divided by the body size. The measurement of body size can be based on body surface area (bsa), lean body mass (lbm) and body weight (bw). However, SUV based on body weight is commonly used (Adams *et al.*, 2010).

Based on the study by Keramida *et al.* (2015) in relation to SUV in ^{18}F-FDG PET/CT, all three body size measurements has its own advantage and disadvantages. SUVbw commonly concentrates less ^{18}F-FDG than lean tissue but is easily calculated. SUVbsa calculation on the other hand are not gender specific and in relation to body mass, is found to be lower in larger patients. It also correlates negatively with body weight. SUVlbm has the possibility of underestimating the SUV and there is no standard formula in measuring lean body mass.

There are two methods in calculating SUV based on body weight, SUVmean and SUVmaximum, which is commonly used. SUVmean integrates the information from multiple voxels causing it to be varied based on the voxels included in the average. Hence, it is ROI dependent and subjected to both inter- and intraobserver variability. Unlike SUVmean, SUVmax measures the value in the highest voxel within an ROI making it to be independent of the ROI size, is more reproducible and has less observer variability. SUVmax however is more susceptible to image noise compared to SUVmean. In addition, there is also SUVpeak which incorporates the average SUV values in a group

of voxels around the voxel with highest activity. The idea is to maintain the SUV's reproducibility and to reduce image noise. However, SUVpeak is not widely used in clinical practice (Adams *et al.*, 2010).

2.11 QUANTITATIVE BONE SCAN WITH SPECT SUV

Compared to SPECT, PET system has the capability in generating cross sectional images in the unit of kBq/ml. Moreover, dual photon coincidence detection and photon attenuation correction in PET allows quantitative assessment. On the contrary, SPECT system detects single photon and in general, is not susceptible to photon attenuation correction. However, the introduction of hybrid SPECT/CT imaging coupled with technological advancement has enabled quantitative assessment in SPECT especially SUV calculation due to the improvement in detector performance, development in image reconstruction algorithms and the presence of co-registered CT image which allows attenuation and scatter correction (Bailey, 2014).

Quantification in SPECT based radiotracer such as ^{99m}Tc-MDP uptake is basically a process of calculating the osseous radioactivity concentration expressed in SUV. Two studies have been performed utilizing SPECT SUV with SPECT/CT on bone scintigraphy involving the normal spine. Both studies involved quantification of radiopharmaceutical in the healthy vertebrae. Cachovan *et al.* (2013) measures the SPECT SUV of the healthy lumbar spine in a population of 50 female patients whereas Kaneta *et al.* (2016) measures the SUV of normal vertebrae using SPECT/CT in a population of 21 men and 8 women with cancer or joint disorders. Both studies advocate further studies in clinical application of SPECT SUV. Compared to SUVlbm and SUVbsa, SUVmax has been shown to have

the lowest variability in SPECT SUV (Kaneta *et al.*, 2016). In SPECT/CT, there is no standard cut off SUV value to differentiate an uptake on bone scan as benign or malignant. Hence, SUV measurement has the potential of being a diagnostic tool. The clinical utilization of SUVmax has been reported in both ^{18}F-NaF PET/CT and ^{99m}Tc-MDP SPECT/CT by Muzahir *et al.*(2015) and Kuji *et al.*(2017) respectively.

OBJECTIVES

3.0 OBJECTIVES OF THE STUDY

3.1 GENERAL OBJECTIVE

To compare between degenerative joint disease and bone metastases lesions semi-quantitatively using SPECT SUV.

3.2 SPECIFIC OBJECTIVES

3.2.1 To determine the SUVmax value in normal vertebra, degenerative joint disease and bone metastases.

3.2.2 To determine the difference in SUVmax value between degenerative joint disease and bone metastases.

3.2.3 To determine the sensitivity and specificity of SUVmax in differentiating degenerative joint disease and bone metastases

3.3 RESEARCH HYPOTHESIS

3.3.1 Null hypothesis: There is no significant difference in SUVmax between degenerative joint disease and bone metastases.

3.3.2 Alternative hypothesis: There is a significant difference in SUVmax between degenerative joint disease and bone metastases.

MATERIALS AND METHODS