THE UTILITY OF EARLY GALLIUM-68 PSMA PET/CT IMAGING IN LOCOREGIONAL DISEASE DETECTION RATE IN PROSTATE CANCER: A SINGLE CENTRE EXPERIENCE

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Advanced Medical and Dental Institute

Universiti Sains Malaysia

Dissertation submitted to

Advanced Medical and Dental Institute (AMDI),

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in partial fulfilment of the requirement for the Degree of

MASTER OF MEDICINE (NUCLEAR MEDICINE)

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DECLARATION

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

KAVITA ARUMUGAM

P-IPM0030/19

Date: 28/11/2023

DISCLAIMER

I hereby certify that the work in this dissertation is my own. I declare that I have no financial of interest in the instruments or materials used in this study.

KAVITA ARUMUGAM

Q-IPM0030/19

Date: 28/11/2023

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LIST ABBREVIATIONS SYMBOLS OR NOMENCLATURE

Abbreviations

^{68}Ga	Gallium-68
^{11}C	Carbon-11
^{18}F	Fluorine-18
^{68}Ge	Germanium-68
AJCC	American Joint Committee on Cancer
CT	computed tomography
EANM	European Association of Nuclear Medicine
FDG	Flurodeoxyglucose
GS	Gleason score
IKN	Institut Kanser Negara
LN	lymph node
min	minute
mpMRI	multiparametric magnetic resonance imaging
p.i.	post-injection
PCa	prostate cancer
PET/CT	positron emission tomography/ computed tomography
PSA	prostate specific antigen
PSMA	prostate-specific membrane antigen
ROI	region of interest
RP	radical prostatectomy
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SOP	Standard Operating Procedure
SUVmax	maximum standardised uptake value

Symbols

g/ml	gram per milliliter
kBq/ml	kilobecquerel per milliliter
MBq	Megabecquerel
ng/ml	nanograms per milliliter

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ABSTRAK

Pengenalan: Pengimejan ^{68}Ga-PSMA PET/CT telah menunjukkan hasil yang memberangsangkan dalam menentukan tahap kanser prostat (PCa). Banyak literatur yang diterbitkan menunjukkan bahawa ^{68}Ga-PSMA PET/CT mempunyai ketepatan diagnostik yang lebih baik jika dibandingkan dengan pengimejan konvensional. Protokol pengimejan seluruh badan rutin ^{68}Ga-PSMA PET/CT dilakukan pada selang 60 minit selepas pemberian ubat radioaktif. Penilaian kelenjar prostat / batas prostat dan/atau penglibatan organ berdekatan (iaitu pundi kencing, rektum, vesikel mani) serta nodus limfa serantau pada skan ^{68}Ga-PSMA PET/CT seluruh badan mungkin sukar untuk dikesan disebabkan bacaan radioaktif yang tinggi di dalam pundi kencing (air kencing). Beberapa kajian telah mencadangkan pengimejan pelvis awal untuk membantu meningkatkan kadar pengesanan PCa di kawasan ini. Walaupun begitu, data yang sedia ada tidak mencukupi dan tanpa konsensus yang pasti untuk menerapkannya ke dalam garis panduan PET/CT ^{68}Ga-PSMA yang tersedia ada. Oleh itu, kajian ini dijalankan untuk menilai kadar pengesanan perebakkan setempat ("locoregional") PCa dalam pengimejan ^{68}Ga-PSMA PET/CT seluruh badan standard berbanding dengan pengimejan pelvis awal.

Metodologi: Kajian retrospektif telah dijalankan ke atas pesakit PCa yang dirujuk ke Institut Kanser Negara untuk imbasan PET/CT ^{68}Ga-PSMA dari Februari 2020 hingga Disember 2021. Protokol imbasan melibatkan pengimejan pelvis awal (sejurus selepas

suntikan radiotracer) dan pengimejan seluruh badan (kira-kira 60 minit selepas suntikan radiotracer). Penilaian dilakukan di kawasan pelvis berdasarkan analisis visual dan nilai SUVmax patologi “locoregional” yang dikesan di dalam pengimejan pelvis awal berbanding pengimejan standard.

Keputusan: Sebanyak 210 pesakit PCa yang menjalani imbasan PET/CT ^{68}Ga-PSMA telah dinilai. Patologi “locoregional” yang dikesan dalam pengimejan pelvis awal ialah 68.6% (144/210), manakala, dalam pengimejan standard ialah 70.5% (148/210). Pengimejan standard mempunyai kadar pengesanan yang lebih tinggi berbanding dengan pengimejan awal, namun ini tidak mencapai statistik yang signifikan (p=0.344).

Kesimpulan: Tiada perbezaan statistik dalam kadar pengesanan “locoregional” antara kedua-dua protokol ini. Oleh itu, penggunaan pengimejan pelvis awal mungkin tidak bermanfaat untuk semua pesakit dan tidak praktikal dilakukan di negara ini kerana beban kerja yang tinggi.

ABSTRACT

Introduction: ^{68}Ga-PSMA PET/CT imaging have shown promising results in staging and restaging of prostate cancer (PCa) patient. Many published literatures have shown, ^{68}Ga-PSMA PET/CT has greater diagnostic accuracy when compared to conventional imaging. Standard whole-body imaging protocol of ^{68}Ga-PSMA PET/CT is performed at approximately 60 minutes interval after radiotracer administration. Standard imaging involves the assessment of whole-body ^{68}Ga-PSMA uptake, however, high physiological tracer excretion in the urinary bladder may obscure locoregional lesions in the pelvis, specifically in prostate gland / prostatic bed, adjacent organs (i.e., urinary bladder, rectum, seminal vesicles) as well as regional nodes. Some studies have proposed early pelvic imaging to help improve the detection rate of PCa in this region. Nevertheless, the data is sparse with no definite consensus of implementing it into available ^{68}Ga-PSMA PET/CT imaging guidelines. Therefore, this study was conducted to evaluate the locoregional detection rate of PCa in standard whole-body ^{68}Ga-PSMA PET/CT imaging compared to early pelvic imaging.

Methodology: A retrospective study was conducted on PCa patients who were referred to Institut Kanser Negara for ^{68}Ga-PSMA PET/CT scans from February 2020 to December 2021. The scan protocol involved early pelvic imaging (immediately post radiotracer injection) and whole-body imaging (approximately 60 minutes post radiotracer injection). Assessment was done at the pelvic region based on visual

analysis and SUVmax values of pathological locoregional lesions in early and standard imaging.

Results: A total of 210 PCa patients who underwent ^{68}Ga-PSMA PET/CT scans were assessed. Locoregional lesions detected in early pelvic imaging was 68.6% (144/210), whereas, in standard imaging was 70.5% (148/210). Standard imaging has a higher detection rate as compared to early imaging, however this did not reach statistical significance (p=0.344).

Conclusion: There is no statistically significant improvement in the locoregional detection rate of PCa by including early pelvic imaging. Therefore, routine application of early pelvic imaging may not have added value for all patients and is impractical in the local settings given the heavy workload.

CHAPTER ONE: INTRODUCTION

1.1 **Overview**

Prostate cancer (PCa) is the third most common cancer among men globally with more than 1.4 million new cases and 375304 related deaths, reported in 2020 (Sung *et al.*, 2021). Age-standardised mortality rates in Asia are as high as 4.1% in 2022, trailing behind continents like Africa, Australia, Europe, and America (Wang *et al.*, 2022). PCa is typically localized (80%) at diagnosis, followed by regional nodal metastasis (15%) and less frequently distant metastases (5%) (Rebello *et al.*, 2021).

The locoregional disease is defined as disease within the prostate gland / prostatic bed (post operatively) or involvement of the adjacent organs (i.e. urinary bladder, rectum, seminal vesicles) as well as lymphatic spread to pelvic nodes located below the bifurcation of the common iliac arteries extending to inguinal nodes. A comparison between localised and metastatic disease of prostate cancer, showed that the 5- year survival rate in the localised disease was 100%, while the latter showed only 85% (Pascale *et al.*, 2017).

Lymph node staging (N) of TNM classification of prostate cancer plays a cardinal role in curative intent surgery. Often, the presence of regional lymph node metastasis is associated with poorer prognosis (Prendeville and Van Der Kwast, 2016). Therefore, early detection, risk stratification, or restaging by the means of biopsy, monitoring the level of PCa biomarker (serum prostate specific antigen , PSA) together with various

imaging modalities such as ultrasound, computed tomography (CT), multiparametric magnetic resonance imaging (mpMRI), or positron emission tomography/computed tomography (PET/CT) scan are imperative in prostate cancer staging and restaging (Sarkar and Das, 2016). MRI is often used in the initial staging of PCa compared to CT. This is mainly because MRI have superior soft tissue resolution which can offer additional information regarding invasion of the nerve or to nearby structures as well as in detection of lymph node metastasis. Furthermore, MRI has added bonus because of no radiation risk to patient.

The role of nuclear medicine imaging in staging and restaging of PCa is emerging since the last decade. There are only a handful of radiotracers, which are available for the detection of PCa and its recurrence, such as ^{18}F-flurocholine, ^{11}C-choline, ^{68}Ga-prostate specific membrane antigen (^{68}Ga-PSMA) and ^{18}F-PSMA, in which recent publication has reported ^{68}Ga-PSMA performed better in overall detection rate than choline- based radiotracers (Uprimny *et al.*, 2017b). According to Hofman *et al.*, 2020, ^{68}Ga-PSMA PET/CT when compared to conventional imaging methods like CT and bone scan, has shown to have greater diagnostic accuracy (92% versus 65%), as well as higher sensitivity (85% versus 38%) and specificity (98% versus 91%).

In a retrospective analysis, molecular imaging using ^{68}Ga-PSMA PET/CT detected more lesions compared to CT alone (156 versus 85) with an indispensable role in the change of management in postoperative patients than for pre-treatment patients (Schmidt-Hegemann *et al*., 2019). A non-randomised study was conducted to assess the sensitivity and specificity of locoregional staging for intermediate and high risk PCa at

an institution in India, using ^{68}Ga-PSMA-11 PET/CT, and mpMRI. A total of 35-biopsy proven PCa patients who had undergone both imaging modality were then compared with their post radical prostatectomy histopathological report, in which ^{68}Ga-PSMA PET/CT yield higher sensitivity and specificity (86% and 95%) compared to mpMRI (69% and 89%) in lesion detection thus proving superior locoregional preoperative staging (Un *et al*., 2019).

^{68}Ga-PSMA PET/CT has exceptional sensitivities and specificities for detecting intraprostatic disease, typically ranging from 87-98% and 91-96%, respectively (Bouchelouche and Choyke, 2018). Compared to CT and MRI, which had sensitivities ranging from 27.3% to 43.9%, ^{68}Ga- PSMA PET/CT was more effective at detecting lymph node metastases with specificity of 98.9% and sensitivities ranging from 65.9% to 68.3% (Zhang *et al.,* 2017, Maurer *et al.,* 2016). Similarly Wang *et al.*, 2021 discovered that ^{68}Ga-PSMA outperformed MRI in identifying lymph node metastasis prior to radical prostatectomy in PCa with a sensitivity of 70% as opposed to 40% with similar specificity (92% versus 92%). In terms of detection of the size of locoregional or metastatic lymph node disease, various studies (Maurer *et al*., 2020; De Visschere *et al.*, 2019; Jilg *et al*., 2017; Hövels *et al*., 2008) have found that ^{68}Ga-PSMA PET/CT's detection rates were more than 50% and 90% respectively when the short-axis diameter of the metastatic lymph node lesion was more than 2.3 and 4.5 mm and clearly outperformed conventional CT or MRI, which could detect lymph node metastases only if their size exceeded 8–10 mm.

According to the Joint European Association of Nuclear Medicine and Society of Nuclear Medicine and Molecular Imaging's (SNMMI) ^{68}Ga-PSMA PET/CT procedure guideline for prostate cancer imaging (version 1.0), the recommended time for PET CT imaging post-injection (p.i.) of radiotracer was standard 60 minutes (acceptable range 50-100 minutes), and optional delay imaging at 3 hours was suggested for indeterminate findings to increase the detection rate (Fendler *et al.*, 2017). Normal physiological biodistribution for ^{68}Ga-PSMA radiotracer are at lacrimal glands, salivary glands, liver, spleen, and urinary system (kidneys, ureters, and urinary bladder), in which the latter is the route of excretion of the radiotracer and contributes to the highest activities on PET/CT images. Intense physiologic urinary excretion of radiotracer at the standard imaging (60 minutes p.i.), may mask small PSMA avid prostatic (primary or recurrence) lesions, or small regional nodes surrounding the prostatic bed. This may potentially lead to underestimation of locoregional disease in patients (Maurer *et al.*, 2016) .

Hence, early pelvic imaging is suggested to improve the locoregional disease detection as no significant radiotracer excretion has occurred into the urinary bladder at early imaging. This can eventually affect patient prognosis as well as clinical management. This theory was supported by Uprimny *et al.*, 2017b in which detection rate of locoregional ^{68}Ga-PSMA avid lesion was found significantly higher on early pelvic imaging as opposed to standard whole-body imaging of ^{68}Ga-PSMA PETC/T (24.6% versus 12.8%). Another published report from the University of Beirut Medical Centre, also supported this claim revealing higher rate of locoregional disease in early ^{68}Ga-PSMA in PET/CT as opposed to standard imaging protocol (4.8% versus 0.6%) in PCa (Barakat *et al.,* 2020). Furthermore, Perveen *et al.*, 2018 demonstrated that all

pathologic lesions including regional nodes were able to show radiotracer uptake within the first 3 minutes of post radiotracer injection.

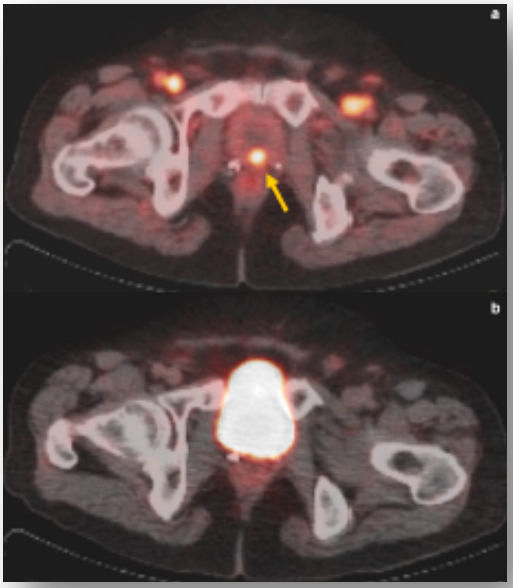

Figure 1: (a) Fused axial images of early imaging and (b) standard imaging of ^{68}Ga-PSMA PET/CT scan at the pelvic region. A focal PSMA avid lesion was seen at the prostate gland (yellow arrow) during early imaging which was not visible during standard imaging due to radiotracer activity within the urinary bladder. (Images sourced from Barakat *et al.*, 2020)

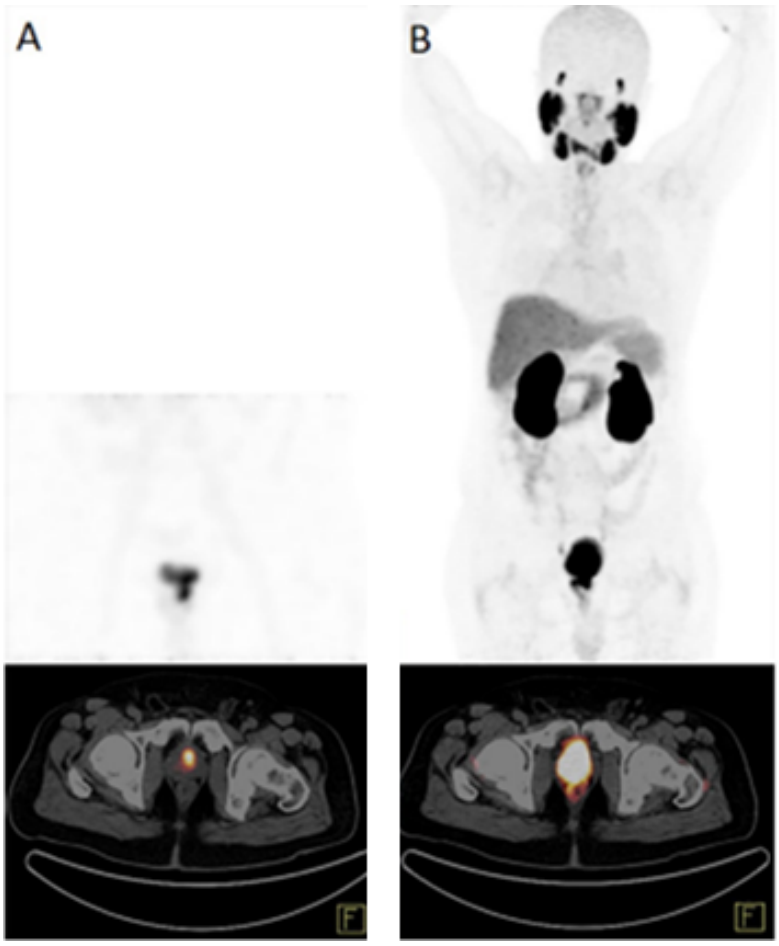

Figure 2: (A) MIP and fused axial images of early imaging and (B) standard imaging of ^{68}Ga-PSMA PET/CT scans at the pelvic region. The early scan detected a PSMA avid lesion (local recurrence) that was masked by bladder activity in standard scan. (Images sourced from Dadgar *et al.*, 2021)

1.2 LITERATURE REVIEW

The role of prostate-specific membrane antigen (PSMA) in PCa has been studied since the 1990s, and ^{68}Ga-PSMA PET radiotracer has been utilized clinically for PCa imaging since 2011(Afshar-Oromieh *et al.*, 2017). ^{68}Ga is produced by ^{68}Ge/^{68}Ga generator system. It has a half-life of 67.6 minutes. The ligand that is commonly used for tagging with ^{68}Ga are either PSMA-11, PSMA-617 or PSMA I&T, which all demonstrate similar biodistribution on PET-CT (Fendler *et al*., 2017). In our centre, ^{68}Ga is conjugated with Glu-urea-Lys(Ahx) (Glu-NH-CO-NH-Lys(Ahx) HBED-CC PSMA-11 ligand.

^{68}Ga-PSMA binds specifically to a PSMA antigen, which are often over expressed in de-differentiated, metastatic, or hormone-refractory PCa (Fendler *et al.,* 2017). PSMA is a trans-membrane protein found within the apical epithelium of secretory ducts in prostatic tissue and its expression often increased by 100-1000 times in PCa compared to normal prostate cells (Han *et al.,* 2018). This renders ^{68}Ga-PSMA radiotracer as an effective tool in assessing PCa, either for primary staging or for restaging. Benign prostate pathologies such as prostatitis and benign prostatic hyperplasia may also show ^{68}Ga-PSMA avidity but in lesser intensity due to weaker expression of PSMA. Other than that, non-prostatic malignancies such as non-small cell lung carcinoma, gastric and colonic adenocarcinoma, renal cell carcinoma, neuroendocrine tumours, glioma, and breast carcinomas have also shown to demonstrate varying degrees of PSMA expression in their tumour's neovasculature (Shetty *et al*., 2018).

There are number of factors responsible for guiding treatment in PCa based on the National Comprehensive Cancer Network (NCCN) guidelines such as serum prostate specific antigen (PSA) values and Gleason score (GS). Serum PSA is not only beneficial for initial staging of PCa, but it is also frequently utilized to detect biochemical recurrence in patients who have had PCa treatment (post radiation or prostatectomy). Rising blood PSA levels in PCa patients after treatment may generate physician's concerns about recurrence. Biopsy of the disease recurrence is not always possible, therefore imaging modalities ofter an alternate option.

Conventional imaging modality such as transrectal ultrasound able to detect <50% of local recurrence when PSA level was <0.5 ng/ml, however PET tracer such as ^{68}Ga-PSMA, ^{11}C-choline and ^{18}F-Fluciclovine appeared to outperformed the conventional imaging in detecting biochemical recurrence (Shaikh *et al.*, 2020). Evans *et al*., 2018 showed that ^{68}Ga-PSMA PET/CT, was able to detect potential sites of recurrence in a 51.5% of patients when PSA level is <1.0 ng/mL, 74% of patients when PSA level was 1.0 to 2.0 ng/mL, and as many as 90.5% of patients when PSA level was >2.0 ng/ml. The same study showed ^{68}Ga-PSMA outperformed other PET radiotracers such as ^{11}C-choline and ^{18}F-Fluciclovine in the detection of local recurrence for each respective PSA cohort, despite having similar operational characteristics to PSMA-based imaging. In fact, in a meta-analysis study conducted by Han *et al*., 2018, the management had been altered in 54% of PCa patients management following ^{68}Ga-PSMA PET/CT scan. In line with this findings, the U.S. Food and Drug Administration has approved the usage ^{68}Ga-PSMA-11 in December 2020, for the purpose of staging and restaging of

PCa patients. The previously used radiotracers such as ^{18}F-Fluciclovine and ^{11}C-choline PET tracer were approved by FDA for patients suspected of tumour recurrence only.

The Gleason score (GS) is another strong contributing factor to the prognosis of PCa patients. Based on NCCN guidelines (2021), PCa patient were stratified into GS risk groups, which are low risk (GS 6 and below), intermediate risk (GS 7), and high risk (GS 8 and above). The architecture of the malignant cells inside the tumor, as well as the degree of differentiation, determine the Gleason grade. The GS is always the product of two numbers: the Gleason grade of the dominating pattern added by the grade of the next most prevalent pattern. Lower scores (6 and below) are mostly indolent and have a better prognosis, while scores of 8 or above are often linked to poorly differentiated tumors and bad prognosis (Munjal and Leslie, 2023).

Few literature reviews have looked into relationship between SUVmax of ^{68}Ga-PSMA radiotracer with GS and serum PSA. Curr Med *et al.*, 2021 have demonstrated positive correlation between SUVmax with total PSA levels. Furthermore, it was noted that PCa patients with GS >7 have a higher range of SUVmax and PSA values than the lower GS. Similarly, Vongvanichvathana *et al*., 2023 discovered higher SUVmax values in higher GS risk groups among PCa patients who were referred for primary staging. This finding was also consistent with similar studie conducted by Fajardo-Ordóez *et al.,* 2019.

Based on guidelines by EANM and SNMMI Guideline for Prostate Cancer Imaging 1.0 (Fendler *et al.*, 2017), the indications of ^{68}Ga-PSMA PET/CT are as stated below :

i. Localisation of tumour tissue in recurrent prostate cancer (PSA 0.2-10ng/ml) and guide salvage therapy. It is more sensitive in shorter serum PSA doubling time and higher Gleason grade.

ii. Primary staging in high-risk disease before surgical procedures or planning external beam radiation.

iii. Other emerging indications are staging before and during PSMA-directed radioligand therapy in castration-resistant prostate cancer, targeted biopsy after previous negative biopsy (in high suspicion patient), and monitoring systemic treatment in metastatic treatment even though its superiority has-not been proven yet.

Extensive research has been undertaken in recent years to increase the efficacy of ^{68}Ga-PSMA PET/CT scan in PCa patients for staging and restaging. In line with this, new discovery of early pelvic imaging in addition to standard imaging, has been found to be beneficial in improving locoregional detection rate of PCa (Uprimny *et al.,* 2017b, Barakat *et al*., 2020, and Perveen *et al*., 2018). Hence, early pelvic ^{68}Ga-PSMA PET/CT has been incorporated into the standard operating protocol at the Nuclear Medicine Department in Institut Kanser Negara, Malaysia as of February 2020.

The early pelvic imaging, involves acquisition of the pelvic region immediately p.i. for 5 minutes. This is followed by a standard whole-body PET scanning, 60min p.i. (acceptable range 50-100 minutes p.i.) and has an acquisition time of approximately 25 minutes. Both early and standard imaging requires a low dose CT scan for anatomical

localisation purposes which do not contribute to significant radiation exposure to the patients. The average effective radiation dose for ^{68}Ga-PSMA PET scan is 4.6mSV (ARSAC, 2023). Low dose CT scan to the pelvis ranges from 3-6 mSv (Akin and Washington, 2017), whereas whole-body low dose CT effective radiation dose approximately 15.9 mSv (Xia *et al.*, 2012). Average effective dose for CT pelvis for PCa patients in IKN is 2.3 mSv and as for whole-body is 11.4 mSv, making the average total effective dose of ^{68}Ga-PSMA PET/CT scan approximately 18mSv.

1.3 Problem Statement

Intense physiologic ^{68}Ga-PSMA activity in the urinary bladder may hinder the detection of PSMA avid small prostatic lesions (primary or recurrence), or small regional nodes surrounding the prostatic bed. To overcome this problem, various studies have shown that early imaging ^{68}Ga-PSMA PET/CT has led to improved locoregional detection rates. Uprimny *et al*., 2017b showed an improved detection rate of 24.6% for early imaging compared to 12.8% for standard 60min p.i. ($p < 0.001$) in the European population. These values have yet to be validated among the South East Asian population and this study will be among the first to do so.

1.4 Justification / Aim / Benefits

Justification of study

Locoregional disease detection is important in the management of patient with prostate cancer. However, detection by standard ^{68}Ga PSMA PET/CT could be hindered by intense physiologic radiotracer excretion in the urinary bladder. Few studies abroad have shown the advantage of early imaging in addition to standard imaging. This study was proposed to evaluate this finding as currently there is no such study from our local setting which improve on recommendations of future local and national guidelines for ^{68}Ga-PSMA PET/CT scan.

Aim of study

The aim of this study is to evaluate the role of early pelvic imaging using ^{68}Ga-PSMA PET/CT scan (immediately p.i.) in improving the locoregional detection rate of PSMA avid PCa lesions.

The locoregional disease is defined as disease within the prostate gland / prostatic bed (post operatively) or involvement of the adjacent organs (i.e urinary bladder, rectum, seminal vesicles) as well as lymphatic spread to pelvic nodes located below the bifurcation of the common iliac arteries extending to inguinal nodes.

Benefit of study

This study shall provide comprehensive and accurate information on the disease status and shall potentially improves subsequent clinical management of the patients.

CHAPTER TWO: OBJECTIVES

2.1 General Objective

To evaluate the role of early imaging ^{68}Ga-PSMA PET/CT in improving the locoregional detection rate in PCa patients.

2.2 Specific Objective

i. To determine the locoregional detection rate for early pelvic imaging compared to standard imaging of ^{68}Ga-PSMA PET/CT scans in prostate cancer patients.

ii. To assess the association between the total number of patients with locoregional lesions detected in early pelvic imaging compared to standard imaging with serum PSA values and Gleason scores, respectively.

iii. To correlate highest SUVmax of PSMA avid lesions in early pelvic imaging compared to standard imaging with serum PSA values and Gleason scores, respectively.

2.3 Null Hypotheses

There is no difference in the detection rate of locoregional ^{68}Ga-PSMA avid lesions between early pelvic imaging (immediately p.i.) and standard imaging (60 min p.i.) in prostate cancer patients.

2.4 Alternative Hypotheses

There is a significant difference in the detection rate of locoregional 68Ga-PSMA avid lesions between early pelvic imaging (immediately p.i.) and standard imaging (60 min p.i.) in prostate cancer patients.

CHAPTER THREE: METHODOLOGY

3.1 Study Location

PET/CT unit, Department of Nuclear Medicine, Institut Kanser Negara (IKN).

3.2 Study Design

This is a retrospective cross sectional study.

3.3 Sampling

3.3.1 Target Population

All prostate cancer patients who were referred to the Department of Nuclear Medicine, PET/CT IKN for ^{68}Ga-PSMA PET/CT scan for staging and restaging during the period of February 2020 to December 2021.

3.3.2 Population Sample

Patients who underwent ^{68}Ga-PSMA PET/CT scan (early pelvic and standard imaging) for either staging or restaging of prostate cancer from the period of February 2020 to December 2021.

3.3.3 Sample Frame

Retrospective sample collection was taken from electronic medical records (EMR) from February 2020 to December 2021.

3.3.4 Sampling Method

The method used for sampling is universal sampling.

3.3.5 Sample Size

Sample size (number of patients) estimation was calculated using two correlated proportions formulae. Prior data indicate that the proportion of detection rate of locoregional lesions on early imaging was 0.3 and the proportion of detection rate of locoregional lesions on standard imaging was 0.13. Thus, a minimum sample size of 116 samples (number of patients) to be able to reject the null hypothesis with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

McNemar test was used to evaluate the null hypothesis. With an additional 20% dropout rate, the sample size (number of patients) was calculated to be 145 samples. (Reference based on the study conducted by Uprimny *et al*., 2017b).

3.4 Inclusion and Exclusion Criteria

3.4.1 Inclusion Criteria

All patients who were referred for ^{68}Ga-PSMA PET/CT, for the purpose of either staging or restaging of prostate cancer irrespective of serum PSA level and GS.

The GS was stratified into three risk groups based on the National Comprehensive Cancer Network (NCCN) prostate cancer 2021 guidelines, which are low risk (GS 6 and below), intermediate risk (GS 7), and high risk (GS 8 and above).

3.4.2 Exclusion Criteria

Missing important data in the electronic medical records (i.e. serum PSA, GS, information regarding treatment and absence of early imaging).

3.5 Data Collection

Retrospective analysis of clinical information of patients who had undergone early and standard imaging of ^{68}Ga-PSMA PET/CT from the duration of 1st February 2020 to December 2021, based on standard operating protocol of Department of Nuclear Medicine, IKN (as shown in Appendix D) were retrieved from electronic medical records (Hospital Information System; FiSiCien, Radiological Information System, RIS and Patient Archiving and Communication System, PACS). Patient's details including the age, gender, race, date of diagnosis, histopathology, serum PSA, GS and treatment done was recorded. Image data of ^{68}Ga-PSMA PET/CT of patients retrieved from the electronic medical records archives and independently reviewed by primary investigator on GE ADW 4.7 workstation using PETVCAR application. All data retrieval was performed according to the principles of the Declaration of Helsinki and national regulations.

3.5.1 Radiotracer preparation

Certified ^{68}Ga-PSMA-chloride was eluted from ITG (Isotope Technologies Garching, Munich Germany) ^{68}Ge/ ^{68}Ga generator. PSMA HBED CC (PSMA 11) was purchased from ABX (Advanced Biochemical Compound) from Germany. The radiolabelling was done in the radiopharmaceutical PET preparation facility in Institut Kanser Negara, Putrajaya Malaysia. The preparation was done following good manufacturing practice standard and quality (GMP). It is administered as a single bolus intravenously, 1.8-2.2 MBq per kilogram body weight based on EANM and SNMMI Guideline for Prostate Cancer Imaging 1.0 (Fendler *et al*., 2017).

Radiopharmaceutical agent, activity, patient's body weight and time of tracer injection will be recorded. PET/CT scan was performed immediately (p.i.) for early pelvic imaging and 60 minutes (p.i.) with acceptable range of 50-100 minutes for standard whole-body imaging, in accordance with Standard Imaging Protocol of ^{68}Ga-PSMA PET/CT in the department.

3.5.2 Image Acquisition

^{68}Ga-PSMA PET/CT imaging was performed using a dedicated GE PET/CT system, equipped with LBS-Lutetium based scintillator with extended FOV(70cm). Low dose non-enhanced CT using "GE smart mA dose modulation" (100kV, 15-250 mA modulated, and pitch 1.5, reconstructed axial slice 3.75mm, reference noise index 28.50) were performed for attenuation correction of PET acquisitions.

Imaging acquisition was carried out according to Standard Operating Procedure (SOP) in the Nuclear Medicine Department IKN. Patient was asked to void 5 minutes prior to injection and instructed to remove all metallic objects.

Early pelvic imaging: Dynamic imaging procedure was performed with frame centred on the pelvis (prostate bed) at 1-minute per frame, acquired immediately p.i. of radiotracer for a duration of 5 minutes. A composite image from the dynamic images was constructed to generate the early image of the pelvis.

Standard imaging : Whole-body PET images were performed using continuous bed motion acquired 60 minutes p.i. with acceptable uptake time range of 50-100 minutes (2 mins per bed position for 6-8 bed positions, slice thickness 3.75mm), which took approximately 20-25 mins acquisition time per patient. After completion of scan, all patients were advised to maintain good oral hydration and void.

All studies were reconstructed identically with ordered subset expectation maximization algorithm (OSEM), 3 iterations and 18 subsets.

3.5.3 Image analysis

All early pelvic and standard imaging of ^{68}Ga-PSMA PET/ CT scan were assessed qualitatively and quantitatively (SUVmax value) by two nuclear medicine physicians using a dedicated workstation as per departmental protocol. The images reviewed using GE ADW 4.7 workstation equipped with PETVCAR applications. All lesions suspicious of primary or locoregional recurrence of PCa at the pelvic region were noted.

The locoregional disease is defined as disease within the prostate gland / prostatic bed (post operatively) or involvement of the adjacent organs (i.e. urinary bladder, rectum, seminal vesicles) as well as lymphatic spread to pelvic nodes located below the bifurcation of the common iliac arteries extending to inguinal nodes.

Early pelvic imaging (immediately p.i.)

- Any patient who had at least one positive PSMA avid lesion in the prostatic bed or regional nodes was classified as positive.
- Positive PSMA avid lesion was defined as any abnormal lesion in the prostatic bed or regional nodes with SUVmax of 2.0 and above (the reference for cut off value for early pelvic imaging was taken based on Barakat *et al.*, 2020).
- Lesion was considered negative if the radiotracer uptake less than SUVmax of 2.0.

Standard imaging (60 minutes p.i. with acceptable range of 50-100 minutes)

- Background activity was noted by drawing a region of interest (ROI) in the right lobe of liver (the reference was based on the PROMISE criteria, Eiber *et al.*, 2018).
- Any patient who had at least one positive PSMA avid lesion in the prostatic bed or regional nodes was classified as positive.

- Positive PSMA avid lesion was defined as any abnormal lesion in the prostatic bed or regional nodes, that was higher than the background activity and that did not correspond to physiological tracer uptake.
- Lesion was considered negative if the radiotracer uptake was less than background activity.

For each suspicious lesion, corresponding SUVmax will be noted using a 3D box volume of interest covering the whole lesion volume. The number of detected abnormal lesions and SUVmax of those lesions at the prostatic bed and regional nodes at early pelvic imaging and standard imaging were recorded.

3.6 Data extraction and Analysis

The ^{68}Ga-PSMA PET/CT images were extracted from the imaging database at our centre. Other research data's that were extracted from the hospital database and clerking sheet: age, indication for PET (primary staging/recurrent disease staging), Gleason score, PSA levels and record of previous therapies. The measured injection activity, lesions detected and SUVmax values of these lesions were recorded. These extracted data were recorded in an Excel workbook (Microsoft Corporation, USA) and the data analysis was performed using SPSS 28.0 (IBM Corp).

3.7 Statistical analysis

Statistical analysis was performed using SPSS version 28.0 (IBM Corp). The categorical and demographic data were presented in number, percentage and mean according to the distribution of data. Descriptive analysis for continuous variables were presented as standard deviation, whereas frequency and percentages were used for categorical variables.

Each variable of interest for analysis has been inspected for its fitness for type of analysis. Data on the number of abnormal locoregional lesions, PSA, GS, and SUVmax were assess for normality of distribution. By using Kolmogorov-Smirnov, it was found all values were not normally distributed; therefore non-parametric tests were used for all statistical analyses.

For objective (1):

McNemar‘s test was applied for determination of locoregional detection rate between two protocols (early pelvic and standard imaging) and $p<0.05$ was considered significant.

For objective (2 & 3):

The relationship between the total numbers of patients with locoregional lesions or SUVmax of locoregional lesions with serum PSA during early pelvic and standard imaging were assessed using Spearman’s rho correlation.

The p value range and strength for Spearman's rho correlation are defined as follows:

p = 0.00-0.20 indicates negligible strength,

p = 0.21-0.40 indicates weak strength,

p = 0.41-0.60 indicates moderate strength,

p = 0.61-0.80 indicates strong strength, and

p = 0.81-1.00 indicates very strong strength.

Independent-sample Kruskal-Wallis Test was used to investigate the differences of number of locoregional lesions / SUVmax of locoregional lesions during early pelvic or standard imaging protocol with GS risk groups (low, intermediate, and high). P-value < 0.05 was considered significant.

In PCa patients that showed statistically significant results based on the Independent-sample Kruskal-Wallis Test, further Post hoc analysis using Pairwise comparison was done to find the correlation, and p value <0.05 was considered significant.