THE ROLE OF FDG PET-CT IN DETECTION OF RECURRENT COLORECTAL CANCER IN NATIONAL CANCER INSTITUTE, PUTRAJAYA, MALAYSIA

BY:

DR WONG TECK HUAT

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DECLARATION

"I hereby declare that the dissertation entitled **The Role Of FDG PET-CT In Detection Of Recurrent Colorectal Cancer In National Cancer Institute, Putrajaya, Malaysia** is a result of my own work, except for the work that have been cited clearly in the references"

Signature:

Name: Dr Wong Teck Huat

Date:

SUPERVISOR'S RECOGNITION

This Dissertation Report has been read and certified by

Signature:

Name: Dr Mahayuddin bin Abdul Manap

Date:

Signature:

Name: Dr Siti Zarina binti Amir Hassan

Date:

ACKNOWLEDGEMENT

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LIST OF ABBREVIATIONS

1. ASR: Age Standardized Rate

2. CEA: Carcinoembryonic antigen

3. CECT: Contrast-enhanced computed tomography

4. CI: Confidence interval

5. CRC: Colorectal cancer

6. FDG PET-CT: ^{18}F-Fluorodeoxyglucose Positron Emission Tomography – Computed Tomography

7. MRI: Magnetic resonance imaging

8. OR: Odds ratio

9. SD: Standard deviation

10. SUVmax: Maximum standardized uptake value

11. TNM: American Joint Committee on Cancer Tumour, Node and Metastasis staging system

UNITS

keV: kiloelectron volt

kg: kilogram

kVp: kilovoltage peak

mAs: miliampere second

MBq: megabecquerel

ABSTRAK

Kajian ini bertujuan untuk menentukan peranan ^{18}F-Fluorodeoxyglucose FDG PET-CT untuk mengesan kanser kolorektal yang berulang serta mengkaji faktor yang mungkin mempengaruhi prestasi diagnostik PET-CT. Satu kajian retrospektif yang diluluskan oleh lembaga etika daripada University Sains Malaysia dan Jawatankuasa Etika & Penyelidikan Perubatan (MREC) telah dijalankan di Institut Kanser Negara Putrajaya di antara Januari hingga Disember 2014, melibatkan kesemua pesakit kanser kolorektal yang pernah dirawat dan dirujuk untuk ujian PET-CT atas sebab disyaki penyakit berulang berdasarkan paras CEA atau pengimejan CT skan. Imej-imej PET-CT dinilai oleh seorang pakar perunding perubatan nuklear. Histopatologi, pengimejan atau susulan klinikal sekurang-kurangnya enam bulan diguna sebagai standard rujukan untuk mengenalpasti diagnosis akhir. 16 daripada 85 pesakit dikecualikan daripada analisis sebab maklumat susulan tidak diperolehi. Daripada 69 pesakit yang dianalisa (lelaki: perempuan = 41:28), kanser berulang dikesan dalam 39.1%. Sensitiviti, spesifisiti, nilai ramalan positif, nilai ramalan negatif dan ketepatan PET-CT ialah 92.6%, 88.1%, 83.3%, 94.9% dan 89.9% masing-masing. PET-CT mempunyai prestasi diagnostik yang tinggi untuk menilai pesakit dengan paras CEA tinggi dan pesakit dengan penemuan mencurigakan pada CT skan. Ia lebih tepat daripada CT skan dalam mengesan lokasi benar kanser berulang dan dapat mengesan lebih banyak lokasi metastasis. Pesakit dengan tahap CEA semakin meningkat tetapi masih dalam had normal dan CT skan normal mempunyai risiko kanser berulang yang rendah (0% dalam kajian ini) dan kemungkinan pengimejan PET-CT adalah tidak diperlukan. Kesimpulannya, PET-CT adalah sensitif dan spesifik dalam mengesan kanser kolorektal berulang.

ABSTRACT

Title: The Role Of FDG PET-CT In Detection Of Recurrent Colorectal Cancer In National Cancer Institute, Putrajaya, Malaysia

This study aimed to determine the role of ^{18}F-Fluorodeoxyglucose (FDG) PET-CT in detection of recurrent colorectal cancer in our institution as well as to correlate factors which may influence diagnostic performance of PET-CT. An Ethics Board (from Universiti Sains Malaysia and Medical Research & Ethics Committee, MREC) approved retrospective study was performed in National Cancer Institute, Putrajaya from January to December 2014, recruiting all consecutive patients with treated colorectal cancer and was suspected to have recurrence based on CEA levels or CT imaging. PET-CT images were reviewed by a dedicated senior nuclear medicine consultant. Histopathology or clinical and imaging follow up for at least six months were used as reference standard to confirm the final diagnosis. 16 of 85 patients recruited were excluded from analysis due to unavailability of follow up data. In the other 69 patients (M:F = 41:28), recurrence was diagnosed in 39.1%. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of PET-CT in detecting recurrent colorectal cancer in this study were 92.6%, 88.1%, 83.3%, 94.9% and 89.9% respectively. PET-CT had high diagnostic performance to evaluate patients with elevated CEA levels and with suspicious CT findings. It was more accurate than CT in detecting the true locations of recurrence and could detect more sites of recurrence. Patients with rising CEA level but still within normal limit and normal CT imaging had low risk of recurrence (0% in this study) and were likely not indicated for PET-CT imaging. In conclusion, PET-CT is sensitive and specific in detecting recurrent colorectal cancer.

CHAPTER 1

INTRODUCTION

1.1 EPIDEMIOLOGY OF COLORECTAL CANCER:

Colorectal cancer (CRC) is a major global health problem. It is the third most common cancer in men after lung and prostate cancers and the second most prevalent cancer in women following breast cancer. According to GLOBOCAN database 2012, the highest incidence of CRC in Australia/ New Zealand (Age Standardized Rate, ASR of cancer incidence 44.8 and 32.2 per 100,000 in men and women) is almost ten times the incidence in South Africa (4.5 and 3.8 per 100,000 in men and women). In general, CRC is two to three folds more prevalent in the well developed nations than in developing nations. ASR in developing countries is 13.6 and 9.8 per 100,000 in men and women (Ferlay *et al.*, 2015). Being a developing country, Malaysia has ASR of 13.4 and 10.2 per 100,000 in men and women respectively (based on Malaysia Cancer Statistics 2007) which is very similar to the global data.

A very interesting change in the incidence rate of CRC has been observed over the last few decades. While many countries are enduring annual increase of CRC burdens, the incidence rate of CRC is actually decreasing in many developed countries such as United States of America, Western European countries and Japan. In fact, the incidence rate of CRC in USA declines by an astonishing rate of 3% each year from 2000 to 2010 (Siegel *et al.*, 2014). This achievement is attributable to extensive availability of colonoscopy facilities and timely treatment of premalignant polypoidal lesions, which has been shown to prevent CRC (Winawer *et al.*, 1993).

Consistent with higher incidence rate of CRC, the ASR of CRC mortality is also higher in more developed regions of the world (14.4 and 9.3 per 100,000 in men

and women respectively) as compared to the less developed regions (7.8 and 5.6 per 100,000 in men and women) (Ferlay *et al.*, 2015). Nevertheless, more than 50% of these cancer deaths occur in developing countries.

Malaysia Cancer Statistics 2007 reveals that our ASR of CRC mortality is 9.39 per 100,000. The patient survival is highly dependent on the TNM staging. Proportions of Malaysian patients presenting in Stage I to Stage IV cancers are 9%, 28%, 31% and 32% respectively and 5-year survival of each successive stage is 79%, 65%, 44% and 9.3% respectively (Kong *et al.*, 2010).

Risk factors leading to development of CRC in a patient has been extensively researched. In the oncogenesis of CRC, environmental factors play a more dominant role than genetic mutations, which are mostly sporadic with minority of patients having hereditary disorders. The culprit environmental risk factors that have been identified include sedentary lifestyles, obesity, excessive red meat consumption, smoking and diabetes (Watson and Collins, 2011).

1.2 OVERVIEW OF MANAGEMENT OF COLORECTAL CANCER:

The optimal treatment for CRC aims at curative surgical resection of the primary tumour and the regional draining lymph nodes that could harbour metastatic tumour cells. Complete mesocolic resection with removal of at least 12 lymph nodes is recommended as the standard surgical procedure for all patients (Benson *et al.*, 2014). Post-surgical treatments involving adjuvant chemotherapy and radiotherapy may be required depending on histopathology of the tumour, TNM staging and other risk factors such as bowel obstruction on presentation, DNA microsatellite instability (MSI) and chromosomal instability.

Recurrence is a major issue following curative treatment determining ultimate survival of the patients. The reported overall recurrence rate ranges 25 – 40% and it is more common in the first two to three years post treatment (Steele *et al.*, 2015). International guidelines that are published by American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) recommend routine use of clinical examination, colonoscopy, carcinoembryonic antigen (CEA) measurement and CT imaging for surveillance post treatment but recommended intervals to perform these tests are slightly different among these guidelines.

Evidence supporting use of these routine investigations is provided by a study which showed that 63% of recurrences were first detected by rising CEA levels, 25% by imaging and 8% by clinical symtopms alone (Jochmans *et al.*, 2008). Another study also demonstrated that follow up using CT imaging and frequent CEA measurements enabled earlier detection of recurrence by 8.5 months (p < 0.001) and improved detection rate of isolated local recurrence (p = 0.011) (Renehan *et al.*, 2002). In a randomised controlled trial, CEA measurement 3-monthly for 2 years followed by 6-monthly for 3 years detected recurrences with a median lead time of 6 months (range 1 – 30 months) (McCall *et al.*, 1994).

Early detection of recurrence by active surveillance strategy has positive impact on patients' survival. Reduction of all-cause mortality (combine risk ratio 0.81, p = 0.007) was shown in a study (Renehan *et al.*, 2002) whereas improvement of overall survival (OR=0.73; 95% CI 0.59 to 0.91) was demonstrated in another meta-analysis (Jeffery *et al.*, 2007). The improved survival is due to increased likelihood of curative surgery in patients owing to early detection of recurrence. A randomised controlled trial assigned 1202 participants to 1 of the 4 groups for follow-up: CEA

only, CT only, CEA and CT or minimum follow up. After mean follow up of 4.4 years, recurrences detected in the first 3 groups were at least 3 times more likely to be amenable to surgical treatment with curative intent compared with minimum follow up group (Primrose *et al.*, 2014).

Even though it is without doubt that surveillance is beneficial to CRC patients post treatment, sometimes inconsistent tests results may make the clinical decision of recurrent disease difficult. The examples include elevation of CEA when all other investigations are negative or CT findings suspicious of recurrence while CEA level is normal. These are common scenario in our local setting and ^{18}F-Fluorodeoxyglucose PET-CT is often utilised for further assessment.

Management of recurrent colorectal cancer is best done in multi-disciplinary approach. Curative resection may be performed for locoregional recurrence and limited liver metastasis. Non-resectable metastatic disease may be treated with chemotherapy or biological targeted agents (monoclonal antibodies against vascular endothelial growth factor, VEGF or epidermal growth factor receptor, EGFR) (Van Cutsem *et al.*, 2014).

1.3 FUNDAMENTALS OF ^{18}F-FLUORODEOXYGLUCOSE PET-CT:

Positron emission tomography (PET) is one of the nuclear medicine imaging modalities that provides functional and molecular imaging. PET technology first emerges in 1950s due to contributions by Gordon Brownell and others in Massachusetts General Hospital. Development of ^{18}F-Fluorodeoxyglucose (FDG) by Al Wolf and Joanna Fowler in Brookhaven Laboratory, United States is another important milestone in PET imaging.

Unlike other nuclear medicine imaging utilising gamma emission radionuclides, PET uses positron emiting radioisotopes which include commonly used ^{18}Fluorine, ^{11}Carbon, ^{13}Nitrogen, ^{15}Oxygen and ^{82}Rubidium. In PET, radioactivity of administered radiotracer is localised by coincidence detection of 511keV annihilation photons directing at 180° apart along the line of response. In recent years, image quality has been improved by using photon detector with higher spatial and timing resolutions (e.g. LYSO) as well as more sophisticated processing using time of flight technology (TOF). Hybrid imaging combining PET with CT or even MRI is another major breakthrough in PET imaging (Lewellen, 2008). CT and MRI images provide attenuation correction for PET images and improve accuracy of PET by providing anatomical correlations.

The physical half-lives of PET radioisotopes that range from few seconds to several hours, have huge impact on their availability and usage in various nuclear medicine centres across the world. ^{18}F with its physical half-life of 110 minutes is the ideal radioisotope that can be produced in a regional cyclotron facility and subsequently be distributed to several nuclear medicine centres. This has helped to contain the cost of running PET imaging facilities, making PET imaging more affordable for the patients.

PET radiopharmaceuticals are used to target various biological processes of interest, such as metabolism of glucose, amino acid, phospholipid, nucleic acid as well as expressions of various receptors and hormones. Among them, glucose metabolism is the most studied metabolic pathway with its wide indications in both oncologic and non-oncologic diseases. ^{18}F-Fluorodeoxyglucose (FDG) is a glucose analogue, which is taken intracellularly through glucose transporters (GLUT) via facilitated diffusion. Once the FDG is within the cytoplasm, it is phosphorylated by

hexokinase but unlike glucose FDG is not further metabolised along the glycolytic pathway. Hence, the phosphorylated FDG is trapped intracellularly and its bio-distribution can be visualised by PET imaging.

Abnormal glucose metabolism in pathological conditions has been described as Warburg effect, in which there is overexpression of GLUT-1 and hexokinase resulting in increased glucose uptake by various oncogenic cells as well as activated leucocytes. Specifically for cancer cells, it has been discovered that increase in glucose metabolism is only part of the complex oncogenesis process which involves but not limited to oncoprotein expression, activation of tyrosine kinase activity, mitochondrial dysfunction, activation of proliferative cascades, angiogenesis, inhibition of apoptosis pathway and so forth. (Hagland *et al.*, 2013)

1.4 CLINICAL USE OF PET-CT:

Direct imaging of pathological glucose metabolism, which occurs in various diseases, provides useful clinical information. Hence, PET-CT has been used widely for many clinical indications, which include staging of malignancy, restaging after neoadjuvant therapy, monitoring of treatment response and detection of recurrence. In some malignancies such as lymphoma, PET-CT has surpassed CT imaging as the imaging modality of choice for staging and monitoring of treatment response. Early treatment response monitoring provided by PET-CT enables individualised treatment strategy so that treatment efficacy is optimised while minimising treatment related complications (Johnson *et al.*, 2015).

In the management of CRC, the currently recommended indications of PET-CT is to investigated unexplained elevation of CEA when other imagings are negative

or equivocal, as well as restaging of patients before surgical resection of limited liver metastasis (*Evidence-based indications for the use of PET-CT in the UK*, 2012).

However, in our local experience the degree of CEA elevation when PET-CT should performed is variable, which may be influenced by the individual institution protocol, clinicians' and also patients' preferrences. It is also done when CEA is increasing trend but still within the normal range.

1.5 RATIONALE OF THIS STUDY:

Characteristics and risk of recurrence of patients with suspected recurrent CRC who are referred for PET-CT in our institution may be different from other study populations. Hence, diagnostic performance of PET-CT in our institution may also be different from other studies. Information about diagnostic performance of a test is essential to guide clinicians in selecting appropriate test for their patients.

Besides that, when the clinical suspicion of recurrent CRC is based on rising trend of CEA levels, there is limited data from previous studies with regards to appropriate CEA threshold when PET-CT should be performed. As the result, we have observed considerable variation of CEA levels in patients referred for PET-CT in our institution.

In addition, correlation between diagnostic performance of PET-CT with various demographic and clinical characteristics of patients are also studied with the intention to find more criteria that could assist in patient selection for PET-CT when recurrent CRC is suspected.

CHAPTER 2

LITERATURE REVIEW

2.1 FDG PET-CT IN DETECTION OF RECURRENT COLORECTAL CANCER:

PET-CT is useful in detection of local recurrence of CRC as well as regional or distant metastasis. With regards to its role in detection of local recurrence, a study has shown that PET-CT can diagnose peri-anastomotic recurrence with high sensitivity and specificity of 100% and 97.1% respectively and in this study local recurrence was associated with peri-anastomotic or eccentric mass on CT (Shyn *et al.*, 2010). However, results of specificity of PET-CT are not consistent across the previous studies. Kau et al. (2009) has demonstrated in their cohort of 341 rectal cancer patients that even though PET/CT can detect local recurrence with high sensitivity of 100%, specificity is limited with the result of 64% (Kau *et al.*, 2009).

Direct comparison of PET-CT and CT has shown that PET-CT detects more lesions in patients with recurrent colorectal cancer. In a study by Yoon et al. (2011), PET-CT detected 27 additional lesions in 8 patients, comprising 9 seeding peritoneal nodules and 18 lymph nodes while both PET-CT and CECT successfully identified other 38 lesions in 12 patients; PET-CT was also superior to CECT in detecting subcentimeter lesions in pelvic cavities (Yoon *et al.*, 2011).

Diagnostic performance of PET-CT and CT is also compared in several other studies. In a retrospective study of 50 post treatment CRC patients with elevated CEA levels to compare performance of PET-CT and contrast-enhanced CT (CECT) in detection of recurrent disease, the result revealed that PET/CT has higher sensitivity

than CECT (97.3% and 70.3% respectively) (Metser *et al.*, 2010). In this study, lesions correctly identified by PET-CT and missed by CECT were local recurrence in presacral space, metastasis in subcentimeter lymph nodes, peritoneal deposits and recurrence at periphery of radiofrequency ablated metastatic hepatic lesions.

Han et al. (2011) performed another study in 66 patients and also showed superiority of PET-CT as compared to CT in detection of recurrence (sensitivity, specificity of 96.3%, 94.9% and 70.4%, 82.6% respectively) (Han *et al.*, 2011). In this study, it was also demonstrated that mean SUVmax for malignant and benign lesions were 8.06 and 2.82 respectively.

Another study of 170 patients also demonstrated that PET-CT had higher sensitivity than CECT (98% versus 82%) in detection of recurrent CRC, particularly in detecting local recurrence (100% versus 35%) and lymph nodes metastasis (100% versus 39%) (Deleau *et al.*, 2011).

High diagnostic performance of PET-CT to detect recurrent or metastatic CRC in patients with elevated CEA was confirmed by a meta-analysis of 11 studies that showed pooled sensitivity and specificity of 90.3% and 80.0% respectively (Lu *et al.*, 2013). A more recent meta-analysis combining data from 26 individual studies to ascertain diagnostic performance of PET-CT in detecting local recurrence showed high pooled sensitivity and specificity of 94.0% and 94.0% respectively, with overall diagnostic accuracy index of 0.9329 (Yu *et al.*, 2015).

MRI is another clinical imaging modality that has advantages of avoiding ionising radiation and confering high soft tissue contrast. With advancement of technology such as parallel imaging which significantly reduces image acquisition

time, whole-body MRI has emerged as a valuable alternative in screening and detecting recurrent cancers.

In a retrospective study to compare diagnostic accuracy of whole-body MRI and PET-CT to detect recurrent CRC, it was demonstrated that both whole-body MRI and PET-CT are equally sensitive to detect local recurrence and organ metastases; however PET-CT is more sensitive than whole-body MRI to detect lymph node metastasis (93% versus 63%) (Schmidt *et al.*, 2009).

A separate study comparing diagnostic accuracy of whole-body diffusion-weighted MRI with 3.0 T and PET-CT in detecting primary and metastatic neoplasms also demonstrated similar sensitivities of both modalities (Akay *et al.*, 2013). Even though whole-body MRI is an attractive alternative to detect recurrent CRC, it also suffers from significant drawback of high cost and limited availability.

2.2 CORRELATION OF PET-CT AND FACTORS AFFECTING ITS DIAGNOSTIC PERFORMANCE:

Several studies have been done to investigate relationship between CEA and PET-CT in detection of recurrent CRC. A study conducted by Choi et al. (2005) observed a significant positive linear correlation between CEA and metabolic tumour volume on PET-CT (Choi *et al.*, 2005). Besides that, Kyoto et al. (2010) also demonstrated that CEA levels significantly correlated with the tumour volumes ($r = 0.500$, $p < 0.001$) (Kyoto *et al.*, 2010).

Due to the relationship between CEA and tumour volume on PET-CT, it is expected that PET-CT would have higher sensitivity to detect recurrent disease in patients with higher CEA levels. This is substantiated by a study of 73 post-operative CRC patients with various degrees of CEA elevation and the study result revealed that sensitivity of PET-CT increased from 53% in the group with CEA of 3 to 5 ng/ml to 100% in the group with CEA of > 50 ng/ml (Mittal *et al.*, 2011).

A lesion-based analysis study of 106 post-operative patients with suspected recurrence found that PET-CT had sensitivity, specificity, and accuracy of 97.8%, 82.6%, and 95.6% for patients with abnormal CEA levels, compared with 81.3%, 80%, and 80.6% for patients with normal CEA levels and the difference was statistically significant (Zhang *et al.*, 2014).

However, there are also two studies which showed similar performance of PET-CT in detecting recurrence irrespective of the CEA levels. In one of the study, 235 patients were subdivided into normal CEA (< 5 ng/ml) and elevated CEA (> 5 ng/ml) groups and the result revealed that PET-CT had similar sensitivity, specificity of 100%, 84% and 97.1%, 84.6% respectively in the two groups (Sanli *et al.*, 2012).

However, in this study, both groups had high percentage of recurrence, 64.4% for normal CEA group and 88% for elevated CEA group.

In the other study, 69 patients were grouped according to CEA levels (5 to 9.9 ng/ml, 10 to 14.9 ng/ml and > 15 ng/ml) and the results showed that sensitivity, specificity of PET-CT in each group were 100%, 60%; 100%, 75% and 95%, 62% respectively and the difference between the groups was not statistically significant (Ozkan *et al.*, 2012b).

Extensive literature search did not find studies that attempt to correlate other possible factors that may influence diagnostic performance of PET-CT. Hence, this study would have added value in attempting to determine whether the diagnostic performance would differ in accordance to patients' demographic and clinical characteristics.

CHAPTER 3

STUDY OBJECTIVES

3.1 GENERAL OBJECTIVE:

This study intends to evaluate the role of PET-CT to detect recurrent CRC in National Cancer Institute, Malaysia.

3.2 SPECIFIC OBJECTIVES:

1. To determine diagnostic performance of PET-CT in detecting recurrent CRC.

2. To correlate factors affecting diagnostic performance of PET-CT in detecting recurrent CRC.

CHAPTER 4

METHODOLOGY

4.1 PATIENT:

This study included all consecutive patients with stage I to III (based on American Joint Committee on Cancer, AJCC TNM staging system) histologically proven CRC patients with no age limit and completed primary treatment with curative intent, which included compulsory surgery with or without chemotherapy and radiotherapy. Patients with distant metastases at presentation, recent chemotherapy or surgery less than 1 month, recent radiotherapy less than 3 months, history of other primary malignancies were excluded. Post therapy follow-up and surveillance were undertaken by their respective attending surgeons or oncologists and suspected recurrences were based on increasing or elevated CEA levels and/ or suspicious findings on follow-up CT imaging.

The surveillance CECT imaging as well as CEA measurement were performed in the patients' respective hospitals. All CECT scans were reported by qualified radiologists and the CEA measurement were performed using immunoassay method with the normal values ranging from < 2.5 to 5.0 ng/ml (in this study, normal value was taken as $\leq$ 3.0 ng/ml). CEA and CECT investigations were performed at the intervals of 5 to 12 weeks before PET-CT, with mean durations of 10 weeks.

4.2 STUDY DESIGN:

A retrospective observational study was designed and performed in Department of Nuclear Medicine, National Cancer Institute, Putrajaya, Malaysia from January to December 2014 to recruit all consecutive patients who fulfilled the inclusion and exclusion criteria. The patients were referred from all states in Malaysia except for the northern states of Pulau Pinang, Kedah and Perlis.

Patients who were involved in this study did not require additional procedure other than the routine PET-CT imaging, which was conducted in accordance to standard operative procedure of the department. Data collection was done and kept in a computer database that was accessible solely by the study investigators. This study received ethical approval from Medical Research and Ethics Committee (MREC), National Institute of Health, Malaysia as well as Jawatankuasa Etika Penyelidikan (Manusia) JEPeM, Universiti Sains Malaysia to access the patients' clinical data.

Sample size calculation was performed using the following equation for dichotomous endpoints, one sample study (Rosner, 2011).

$$N = \frac{p_0 q_0 \left\{ z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1 q_1}{p_0 q_0}} \right\}^2}{(p_1 - p_0)^2}$$

$q_0 = 1 - p_0$

$q_1 = 1 - p_1$

p_0 = proportion (incidence) of population

p_1 = proportion (incidence) of study group

N = sample size for study group

α = probability of type I error (usually 0.05)

β = probability of type II error (usually 0.2)

z = critical Z value for a given α or β

Proportion (recurrence rate) of this study group was 40.6%; proportion (recurrence rate) of Malaysian population from previous study was 26% (Rashid *et al.*, 2009). Hence, the calculated sample size was 76 subjects in order to yield study power of 80%. Post-hoc calculation using the following equation demonstrated that power of current study (with sample size of 69 subjects) was 76.4%.

$$Power = \Phi \left\{ \frac{\sqrt{N * \frac{(P_1 - P_0)^2}{(P_0 * Q_0)}} - z_{1-\alpha/2}}{\sqrt{\frac{P_1 * Q_1}{P_0 * Q_0}}} \right\}$$

$Q_0 = 1 - P_0$

$Q_1 = 1 - P_1$

P_0 = proportion (incidence) of population

P_1 = proportion (incidence) of study group

N = sample size for study group

α = probability of type I error (usually 0.05)

z = critical Z value for a given α or β

Φ() = function converting a critical Z value to power

4.3 PET-CT IMAGING:

Patients were instructed to reduce strenuous exercise for 24 hours and to fast for at least 6 hours prior to the procedure. Fasting glucose testing was performed using capillary blood and the preferred glucose level to perform PET-CT scans was < 8.3 mmol/L. If glucose was > 8.3 but < 11.0 mmol/L, subcutaneous rapid acting insulin (Actrapid) would be injected but the FDG injection would be delayed for 2 hours. PET-CT would be postponed if fasting glucose level exceeded 11.0 mmol/L. Diabetic patients on insulin therapy were required to omit the morning dose on the day of procedure. Once ensuring acceptable glucose level, FDG activity of 5 MBq/kg was administered intravenously by a trained technologist while the patients rested in a warm, dimly lit room. Imaging was done after a lead-time of 45 to 60 minutes and it was performed without intravenous or oral CT contrast.

An integrated PET-CT system (Discovery ST, GE Medical System, Milwaukee, USA) was used for imaging all the patients. Whole-body PET-CT acquisition was started with CT scan from the head to the mid-thighs (60mAs, 140kV) during current breathing. This was followed immediately by two-dimensional PET scan from head to the mid-thighs as well (7 fields of view, 15cm per field, 4 minutes emission scan per table position, 3.3mm slice thickness). PET data with and without CT attenuation correction was reconstructed by filtered back-projection and ordered-subset expectation-maximization (OS-EM) (two iterations, 15 subsets and matrix of 128×128).

Attenuation corrected PET, CT and combined PET-CT images were displayed on a dedicated workstation running Advantage version 4.2 software (GE Medical System, Milwaukee, USA). The images were reviewed by an experienced nuclear medicine physician using visual assessment and semiquantitative measurement of

FDG uptake using maximum standardized uptake values (SUVmax). The physician was not blinded to patients' clinical history.

4.4 REFERENCE STANDARD:

After six months of PET-CT studies, patients' clinical diagnosis was retrieved through the referring physicians from the respective hospitals.

1. Recurrence was defined as positive clinical diagnosis of recurrent lesions, which was based on histopathology or clinical, and imaging follow up. In patients without histopathology confirmation, progression of disease or response of disease to treatment was considered as confirmatory of recurrence.
2. No recurrence was defined as absence of clinical evidence of recurrence based on histopathology or clinical and imaging follow up.
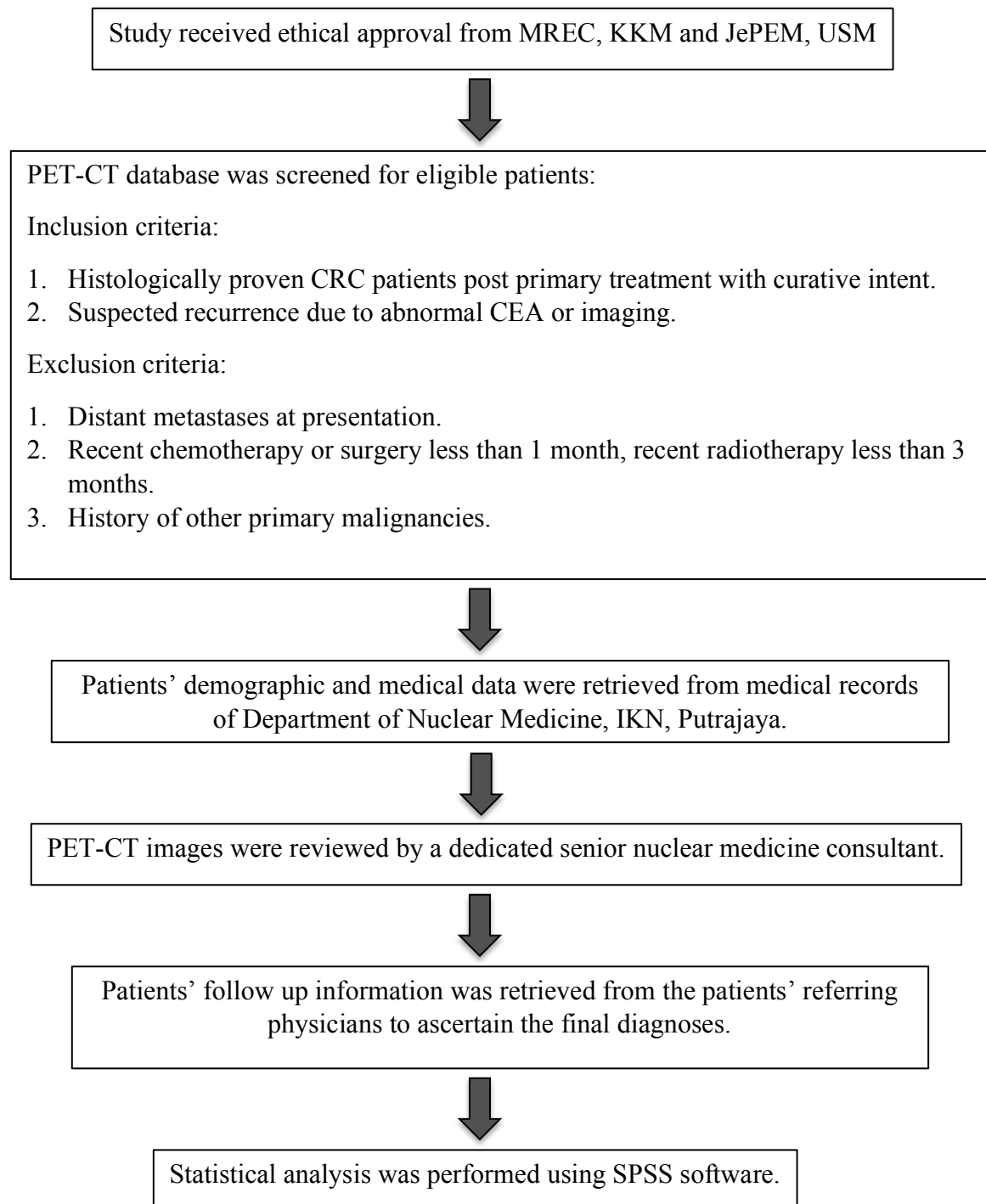
4.5 STATISTICAL ANALYSIS:

The data was analysed with IBM SPSS Statistics software version 22.0. Mean CEA levels were compared using independent T-test. P-value of < 0.05 was considered to be statistically significant.

4.6 DEFINITION OF VARIABLES:

1. Positive PET-CT: Non-physiological focal FDG uptake more intense than background FDG activity that is suggestive of recurrent colorectal cancer. Liver FDG activity was considered as background activity to differentiate benign from malignant lesions. CT appearance of the lesions was also considered in distinguishing benign from malignant lesions.

2. Negative PET-CT: Physiological FDG metabolism in various organs such as brain, heart, liver, urinary tract and diffuse bowel uptake. FDG hypermetabolism that was due to inflammatory process or other alternative diagnoses as evidenced by CT characteristics of the lesions, was also considered negative.

3. True positive PET-CT: Positive PET-CT results that were substantiated by positive clinical diagnosis of recurrent CRC.

4. False positive PET-CT: Positive PET-CT results but recurrence was excluded by histopathology, clinical or imaging follow-up.

5. True negative PET-CT: Negative PET-CT results with no evidence of disease recurrence at the end of follow-up period.

6. False negative PET-CT: Negative PET-CT results but recurrence was confirmed subsequently by histopathology, clinical or imaging follow-up.

4.7 FLOW CHART OF STUDY METHODOLOGY

Study received ethical approval from MREC, KKM and JePEM, USM

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PET-CT database was screened for eligible patients:

Inclusion criteria:

1. Histologically proven CRC patients post primary treatment with curative intent.
2. Suspected recurrence due to abnormal CEA or imaging.

Exclusion criteria:

1. Distant metastases at presentation.
2. Recent chemotherapy or surgery less than 1 month, recent radiotherapy less than 3 months.
3. History of other primary malignancies.

⬇

Patients' demographic and medical data were retrieved from medical records of Department of Nuclear Medicine, IKN, Putrajaya.

⬇

PET-CT images were reviewed by a dedicated senior nuclear medicine consultant.

⬇

Patients' follow up information was retrieved from the patients' referring physicians to ascertain the final diagnoses.
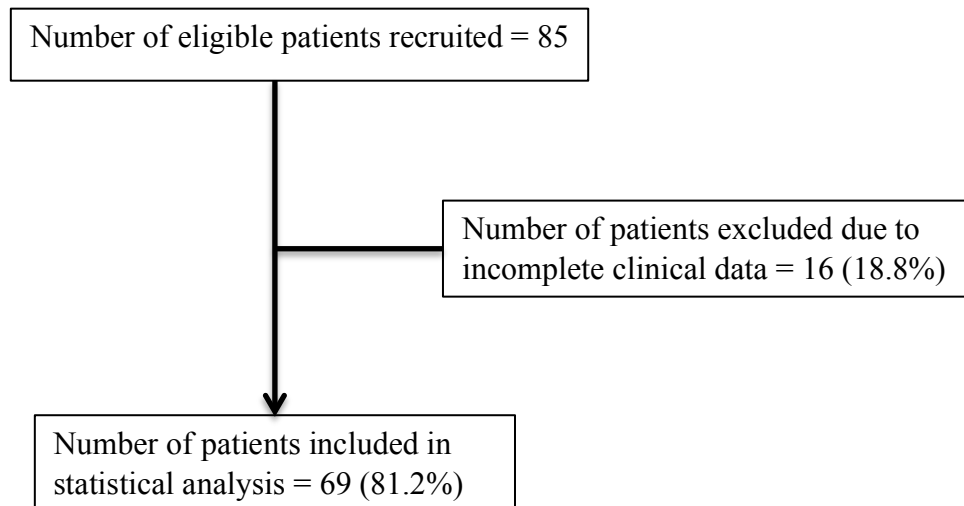
⬇

Statistical analysis was performed using SPSS software.

CHAPTER 5

RESULTS

5.1 PATIENT RECRUITMENT:

Total of 85 eligible patients were recruited, however 19 patients were excluded from data analysis because their medical records were unavailable to the investigator or the patients had discontinued their follow up at their respective hospitals.

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┌─────────────────────────────────────────┐
│ Number of eligible patients recruited = 85 │
└─────────────────────────────────────────┘
            │
            │          ┌──────────────────────────────────┐
            ├─────────→│ Number of patients excluded due to │
            │          │ incomplete clinical data = 16 (18.8%) │
            │          └──────────────────────────────────┘
            ↓
┌──────────────────────────────────┐
│ Number of patients included in    │
│ statistical analysis = 69 (81.2%) │
└──────────────────────────────────┘
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At the end of at least six months of follow-up period, 28/69 patients (40.6%) were diagnosed to have recurrent CRC based on either histopathology or clinical and imaging follow-up.

5.2 DEMOGRAPHIC CHARACTERISTICS:

The mean age of the patients was 59.6 years old (range 38 – 79 years old). There was slight male preponderance (male: female ratio of 1.46: 1). Percentages of Malay and Chinese patients were similar (40.6% and 42.0% respectively). The patients' demographic information was summarised in Table 5.1.

Table 5.1 Summary of patients' demographic characteristics.

Age, years (mean, SD)	59.57 (11.29)
Gender (N, %)	
Male	41 (59.4%)
Female	28 (40.6%)
Ethnic Group (N, %)	
Malay	28 (40.6%)
Chinese	29 (42.0%)
Indian	12 (17.4%)

SD, standard deviation.