END OF CHEMOTHERAPY RESPONSE IN LYMPHOMA PATIENTS: THE PREDICTIVE VALUE OF DUAL TIME POINT IMAGING OF MINIMAL RESIDUAL UPTAKE LESIONS DURING INTERIM PET-CT

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 any other universities. With that, this research might be used for consultation and will be photocopied as reference.

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PIPM 0009/12

DEDICATION

This dissertation is dedicated to my beloved parents for their unconditional support, encouragement, understanding and sacrifices.

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ABBREVIATIONS AND SYMBOLS

ABVD	Adriamycin, Bleomycin, Vinblastine, Dacarbazine
BEACOPP	Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin (Vincristine) , Procarbazine, Prednisalone
BFM	Berlin-Frankfurt-Munster chemotherapy
CVAD	Cyclophosphamide, Vincristine, Adriamycin, Dexamethasone
DLBCL	Diffuse large B-cell lymphoma
DTPI	Dual time point imaging
F-18 FDG	Fluorine-18 Fluorodeoxyglucose
FDG	Fluorodeoxyglucose
FL	Follicular lymphoma
HL	Hodgkin lymphoma
MRU	Minimal residual uptake
MTV	Metabolic tumour volume
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography-Computed Tomography
PFS	Progression free survival
R-CHEOP	Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Etoposide, Oncovin, Prednisalone
R-CHOP	Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisalone
R-EPOCH	Rituximab, Etoposide, Prednisalone, Oncovin, Cyclophosphamide, Hydroxydaunorubicin

RI	Retention Index
SUVmax	Maximum Standardised Uptake Value
SUVmax change	Maximum Standardised Uptake Value change

UNITS

kg	kilogram
MBq	Mega Becquerel
mmol/l	millimol per litre

ABSTRAK

Pengenalan Penilaian peringkat awal tahap keberkesanan rawatan kemoterapi yang diberikan kepada pesakit limfoma adalah penting kerana ia membolehkan pesakit yang tidak bertindak balas dikenal pasti lebih awal. Imbasan interim Fluorine-18 Fluorodeoxyglucose (F-18 FDG atau FDG) Positron Emission Tomografi – Komputer Tomografi (PET-CT) adalah pengimejan imbasan yang masih di peringkat kajian dari segi kegunaannya dalam menilai tahap awal keberkesanan rawatan limfoma. Semasa menilai tahap keberkesanan rawatan pada peringkat awal, kewujudan lesi yang menunjukkan tahap pengambilan sederhana (lesi MRU) menimbulkan kesukaran dalam menentukan keberkesanan rawatan sama ada ia perlu dikategorikan sebagai rawatan yang berkesan atau tidak. Bagi mendapatkan maklumat yang lebih lanjut berkaitan lesi MRU, kaedah pengimejan imbasan dwi-masa (DTPI) dan analisis semikuantitatif digunakan. Tujuan kajian ini adalah untuk menilai kaedah DTPI yang dibuat ke atas lesi MRU semasa peringkat awal rawatan sama ada ianya boleh meramal keberkesanan rawatan di akhir sesi kemoterapi.

Metodologi Satu kajian prospektif telah dijalankan di Jabatan Pengimejan Molekul dan Perubatan Nuklear, Hospital Canselor Tuanku Muhriz bermula daripada April 2014 sehingga Ogos 2015 melibatkan 28 orang pesakit limfoma dengan 67 lesi MRU. Pesakit yang terlibat dikenalpasti semasa menjalani sesi imbasan interim FDG PET-CT. Semasa sesi imbasan interim FDG PET-CT, kaedah DTPI telah dilaksanakan ke atas lesi MRU dan nilai perubahan pengambilan terpiawai maksimum (SUVmax perubahan), perubahan isipadu tumor metabolik (MTV perubahan) serta indeks penahanan (RI) dikira. Selepas pesakit menjalani sesi imbasan interim FDG PET-CT, pesakit akan menjalani satu lagi imbasan FDG PET-CT yang dibuat setelah sesi kemoterapi tamat. Pada peringkat ini, pesakit akan dibahagikan kepada dua kumpulan iaitu kumpulan

‘responder’ dan kumpulan ‘non-responder’ mengikut tahap keberkesanan rawatan berdasarkan Klasifikasi Lugano. Maklumat yang diperolehi daripada kedua-dua imbasan iaitu semasa imbasan interim dan imbasan pada tamat sesi kemoterapi kemudiannya dianalisa.

Keputusan Imbasan interim PET-CT berjaya meramal keberkesanan rawatan untuk sesi akhir imbasan PET-CT dengan ketepatan 95%. SUVmax bagi kumpulan ‘responder’ adalah lebih rendah jika dibandingkan dengan kumpulan ‘non-responder’. Bagaimanapun hasil analisa data yang diperolehi menunjukkan tiada perbezaan yang ketara dari segi analisa statistik di antara median SUVmax perubahan (p=0.422) dan median MTV perubahan (p=0.933) bagi lesi MRU dalam kumpulan ‘responder’ dengan kumpulan ‘non-responder’. Begitu juga tiada perbezaan yang ketara dari segi analisa statistik di antara median indeks penahanan (RI) bagi lesi MRU dalam kumpulan ‘responder’ dan kumpulan ‘non-responder’ (0.862). Lesi MRU dengan nilaian Deauville 3 semasa imbasan interim PET-CT memberi kesukaran dalam meramal tahap keberkesan rawatan di akhir sesi kemoterapi.

Kesimpulan Kaedah DTPI terhadap lesi MRU ketika imbasan interim FDG PET-CT tidak memberi manfaat dalam meramal status keberkesanan rawatan di akhir sesi kemoterapi.

ABSTRACT

Introduction Early treatment response assessment in lymphoma is important as it allows physicians to identify patients with poor response to treat earlier. Interim Fluorine-18 Fluorodeoxyglucose (FDG) Positron Emission Tomography – Computed Tomography (PET-CT) scan is currently regarded as an investigational imaging tool in evaluating early treatment response in lymphoma as clinical trials evaluating it's use are still on-going. The presence of minimal residual uptake (MRU) lesion in interim PET-CT scan possess uncertainty in interpreting early treatment response whether MRU lesion should be considered as representing poor treatment response. To characterize MRU lesions in interim FDG PET-CT scan, dual time point imaging (DTPI) technique with semi-quantitative analysis is used. This study is aimed to determine the predictive value of DTPI technique in predicting the end chemotherapy response of lymphoma patients with MRU lesions identified on interim FDG PET-CT scan.

Methodology Prospective study was performed at the Department of Molecular Imaging and Nuclear Medicine, Hospital Canselor Tuanku Muhriz from April 2014 to August 2015 recruiting 28 lymphoma patients with 67 MRU lesions. DTPI technique was applied to interim FDG PET-CT scan to characterize MRU lesions by measuring their early and delayed maximum standardized uptake values (SUVmax) and calculating the SUVmax change, changes in metabolic tumour volume (MTV) as well as the retention index (RI). Upon completion of chemotherapy, patients underwent end treatment FDG PET-CT scan. Patients were divided into responder and non-responder group based on Lugano's Classification for end treatment response assessment.

Results Interim PET-CT predicted the end-treatment PET-CT findings with accuracy of 95%. SUVmax of responders was significantly lower than that of non-responder. However, there was no statistical significant difference between the median SUVmax

change (p= 0.422) and median MTV change (p= 0.930) of MRU lesions in responder and non-responder groups. There is also no statistical significant difference between RI in responder and non-responder groups (p = 0.862). MRU lesions with Deauville 3 at interim PET-CT were less predictable end-treatment response.

Conclusion DTPI technique applied during interim PET-CT has no predictive role in indicating end chemotherapy response in lymphoma patients with MRU lesions.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Positron emission tomography – computed tomography (PET-CT) with Fluorine-18 Fluorodeoxyglucose (FDG) has become an essential imaging investigation in the management of lymphoma. It is used for disease staging and treatment response assessment. In terms of assessing treatment response, PET –CT scan performed during treatment (interim PET-CT scan) has the potential to be used to assess chemosensitivity of tumour and to predict the treatment outcome (Valls et al., 2016). Information obtained from interim PET-CT scan is helpful in guiding clinicians in planning the chemotherapy with the aims of achieving a better quality of life by minimizing side effects as well as prolonging survival. Interim PET-CT scan is considered at present as a research tool. Its use in response adapted-chemotherapy trials in lymphoma are currently under evaluation.

In order to improve the response assessment interpretation in interim PET-CT scan, Deauville criteria was introduced in 2009 (Moghbel et al., 2016) . With the introduction of Deauville criteria, a term called minimal residual uptake (MRU) lesion which refer to lesion with Deauville score of 2 to 3 was re-defined. The presence of MRU lesions in interim PET-CT scan cause a considerable uncertainty in predicting the outcome of chemotherapy as well as early response interpretation. In one study involving interim FDG PET-CT scan in NHL patients, early stage NHL patients with MRU lesions have different outcome compared to advanced stage NHL (Mikhaeel et al., 2005). In response adapted-chemotherapy trials, MRU lesion in interim FDG PET-CT scan is assigned to a different treatment strategy.

In order to further assess MRU lesions, apart from Deauville criteria which is based on visual interpretation of FDG PET-CT scan images, semi-quantitative analysis with application of dual-time point imaging (DTPI) technique, could be used. Maximum standardised uptake value (SUVmax) is an example of semi-quantative analysis in which it offer information on quantitative aspect of FDG uptake. DTPI technique in PET-CT scan is often used to study tracer kinetics. It has been used in investigation of lymphoma and has significantly improved the specificity and sensitivity of PET imaging (Michihiro et al., 2013). DTPI technique has been shown to produce higher accuracy rate in diagnosis, staging of malignant lymphoma and also in predicting the histological grades of malignancy (Takayoshi et al., 2012).

This study is designed to evaluate the significance of MRU lesions in interim FDG PET-CT by application of DTPI technique. Semi-quantitative analysis of FDG uptake by measuring the maximum standardised uptake value (SUVmax) of the MRU lesions in order to study its kinetic behaviour. Retention index (RI) and metabolic tumour volume (MTV) of MRU lesion are also calculated to give added value to the analysis. The aim of this study is to look for any association between the change of SUVmax value, the change of MTV value and RI of MRU lesions obtained during interim FDG PET-CT scan with end of treatment response based on FDG PET-CT scan results performed after completion of therapy.

CHAPTER 2

LITERATURE REVIEW

2.1 General overview of lymphoma

Lymphoma is a type of neoplasm involving the lymphatic system (Swerdlow et al., 2016). It is a diverse group of diseases that occurs as the result of a clonal expansion of lymphocytes. Each types of lymphoma is a disease with a distinct clinical manifestation. This biologic diversity gives rise to prominent differences among the lymphomas in terms of clinical presentation, pathological characteristics, epidemiology and overall management.

Based on the World Health Organisation (WHO) classification of lymphoma which was published in 2008, lymphoma is divided into several major groups with each groups consists of various types and certain types are further divided into sub-types. The WHO classification is based on combination of morphology, immunophenotype, genetic features, molecular characteristics and clinical presentation. Among these major groups, only Hodgkin's lymphoma (HL), the abnormal lymphocyte is the Reed-Sternberg cell. This particular lymphocyte is not found in other groups of lymphoma. All other groups of lymphoma are called non-Hodgkin lymphoma (NHL) and there are about thirty types of NHL. Lymphoma can also be classified based on the rate of growth, areas of presentation and by lymphocyte type (Swerdlow et al., 2016).

NHL is more common than HL. According to the National Cancer Registry 2003 and 2007, lymphoma is the sixth most common cancer among Malaysians. Based on gender, lymphoma is the sixth most common cancer in males and the eighth most common cancer in females. The cancer incidence per 100,000 population for HL is 0.7 for male and 0.6 for female, and for NHL is 4.7 and 3.4 in male and female,

respectively. Among the NHL, the two commonest types of NHL are diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) (Armitage et al., 1998). Of all NHL cases, DLBCL make-up of 30-58% cases (Tilly et al., 2015) and FL accounting for about 20% of all lymphomas (Luminari et al., 2012).

Staging for lymphoma is used to identify disease location and extent, offers prognostic information, allows useful comparisons among studies and this will give the opportunity to assess disease progression or response to treatment. Both HL and NHL were staged based on Ann Arbor classification system (Cheson et al., 2007). The Ann Arbor staging system was originally published in 1971. In 1989 the 'Cotswold modifications' was added subsequently to extend the definitions of stage IV disease, and also adding the suffix 'X' for description of bulky disease (Cheson et al., 2007). In 2014, the International Conference on Malignant Lymphomas published guidelines for the evaluation, disease staging and treatment response assessment of patients with malignant lymphomas. The staging system is known as the Lugano Modification of the Ann Arbor staging system (Cheson et al., 2014).

Chemotherapy options for HL are based on the stage of HL. In general, the main chemotherapy regimes used is a combination of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). Other chemotherapy regime is used in advanced stage HL which is combination of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisalone (BEACOPP). Radiotherapy is used after completion of chemotherapy in limited and intermediate stage of HL. In general, advanced stage HL is commonly treated with chemotherapy alone. Radiotherapy treatment is confined to patients having large residual masses after chemotherapy (Eichenauer et al., 2011).

Chemotherapy options for NHL groups vary because of its heterogenous nature. In DLBCL, the combination chemotherapy with rituximab, cyclophospamide,

doxorubicin, vincristine and prednisolone (R-CHOP) is the standard chemotherapy regime used (Tilly et al., 2015). In FL, the chemotherapy may include a single agent, for example rituximab, or multi-agent chemotherapy, like R-CHOP (Luminari et al., 2012).

2.2 Positron Emission Tomography in staging and end-treatment response in lymphoma

Positron emission tomography (PET) is a three-dimensional, noninvasive functional imaging tool that has become an important and essential imaging modality in clinical oncology. It was first introduced in the early 1950s for brain imaging. In 2001, positron emission tomography/X-ray computed tomography (PET-CT) hybrid imaging system became commercially available. This has improved the detection and localisation of lesions (International Atomic Energy Agency, 2008).

Fluorine-18 Fluorodeoxyglucose (FDG), a glucose analog, is the commonest PET tracer used in clinical oncology. After injection, FDG is taken up by cells. Subsequently it is phosphorylated in the same process as glucose. However, the phosphorylated product is not further metabolized. It remains trapped in the cells for extended periods of time (Weiss et al., 2012). This process of FDG accumulation is detected by PET-CT scan, and provides visualisation of glucose consumption by different cells in the body. In cancer cells, there is increased in the number of the membrane glucose transporters, known as GLUT-1 and GLUT-3, as well as increased in enzyme hexokinase and with overall augmented glucose metabolism, making FDG the most suitable tracer for measuring viability of malignant cells. When the anatomical imaging tool CT is combined with PET, the hybrid PET-CT scan will deliver more precise images that can discriminate between physiological and pathological FDG

uptake. PET-CT scan is also able to differentiate between necrotic masses and viable tumours (Kinahan et al., 2010).

FDG PET scan is a useful functional imaging tool which has a higher sensitivity and specificity than conventional imaging in evaluation of lymphoma (Spaepen et al., 2001). For example, up to 64% of lymphoma patients are found to have residual or remaining lesional abnormalities following chemotherapy treatment as a result from the development of tumour fibrosis or necrosis. Conventional imaging alone cannot reliably differentiate between these abnormalities with active residual tumour.

In general, most of malignant lymphomas are FDG-avid, including both aggressive and indolent subtypes. Examples include HL, Burkitt lymphoma, mantle cell lymphoma, anaplastic large T-cell lymphoma, marginal zone lymphoma (nodal), lymphoblastic lymphoma, angioimmunoblastic T-cell lymphoma, plasmacytoma, natural killer/T-cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma and peripheral T-cell lymphoma. A few examples of low FDG avid lymphoma include small lymphocytic lymphoma, enteropathy-type T-cell lymphoma, MALT marginal zone lymphoma, lymphomatoid papulosis and primary cutaneous anaplastic large T-cell lymphoma (Sagie et al., 2010).

PET-CT scan with FDG has been utilised extensively in managing malignant lymphoma. It is a recommended imaging modality in disease staging and chemotherapy response assessment in FDG avid lymphoma (Cheson B., 2014). Information obtained is used to monitor disease progression and guide clinician in management of the disease. Lugano Classification, which was introduced in 2014 as an updated version of the 2007 Revised Response Criteria for malignant lymphoma, recommends FDG PET-CT scan for pretreatment staging assessment and end-treatment response assessment after completion of treatment.

Based on Lugano Classification, the end-treatment FDG PET-CT scan is interpreted using a five-point visual scale known as Deauville criteria, also known as the London criteria which was introduced in 2009 (Moghbel et al., 2016). The Deauville criteria initially proposed as a guideline in interpretation of findings in treatment response assessment in interim FDG PET-CT scan (Barrington et al, 2010). FDG uptake in the nodal/lesion is compared visually with two reference sites, the mediastinal blood pool and the liver, and score from 1 to 5 is given based on the comparison (Table 2.0).

Table 2.0 Deauville Criteria.

Deauville Criteria	
Point scale	Description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum ≤ liver
4	Uptake moderately more than liver uptake, at any site
5	Markedly increased uptake at any site and new sites of disease

Source: Valls, L., et al. (2016). 'FDG-PET imaging in haematological malignancies', *Blood Review*, vol.30, no.4, July, pp323.

The Deauville criteria is now recommended as guideline in interpretation of treatment response assessment in both interim and end-treatment FDG PET-CT scan. Four categories of response have been outlined (Cheson et al,. 2014) as follows: (a) complete metabolic response – score of 1, 2 or 3; (b) partial metabolic response – score of 4 or 5 with reduced FDG uptake; (c) no metabolic response – score of 4 or 5 without significant change in FDG uptake; and (d) progressive metabolic disease – score of 4 or 5 with increased FDG uptake or with new lesions.

2.3 Interim FDG PET-CT scan in lymphoma

FDG PET-CT scan has been utilised as a monitoring tool in FDG avid lymphoma especially in assessing response to treatment given (Johnson et al., 2015). Information obtained could be used to alter the treatment for a better outcome. As mentioned earlier, FDG PET-CT scan in FDG avid lymphoma is performed before initiation of treatment for staging assessment and at the end of treatment for end treatment response assessment (Cheson et al,. 2014).

Interim FDG PET-CT scan refers to scan that is performed during a schedule course of chemotherapy, prior to completion. Interim FDG PET-CT scan, at the time of this writing, is still considered as an investigational imaging modality and has not yet been implemented in clinical practice (Cheeson et al,. 2014). It has a promising role for assessment of chemosensitivity and offers prognostic value in predicting end of treatment response (Itti et al., 2009). The key interests of interim PET-CT scan in lymphoma are to assess its capability in term of predicting the outcome of treatment and in assessing chemotherapy sensitivity with the aim of modifying treatment given.

Interim FDG PET-CT scan has a potential use in response-adapted therapy, whereby treatment could be de-escalated in intensity in the setting of a satisfactory early response or escalated if early response is inadequate based on interim FDG PET-CT scan findings (Hutching et al,. 2009). Deauville criteria, which was mentioned earlier, is used to interpret interim FDG PET-CT scan as recommended by Lugano Classification.

2.4 Minimal residual uptake lesion in interim FDG PET-CT scan

In 10% of patients diagnosed with HL, whom undergoing interim FDG PET-CT scan, a persistent faint residual FDG uptake often observed in a site with previous bulky disease and it is interpreted as minimal residual uptake (MRU). MRU was first defined

as a FDG uptake just above background, which was unlikely to represent persisting disease (Huching et al., 2005). In order to improve interim FDG PET-CT scan interpretation and with the introduction of Deauville criteria, the definition of MRU has changed and based on Deauville criteria it is defined as lesion or lymph node with score 2 or 3 (Barrington et al., 2010).

High grade NHL patients with MRU lesion in interim FDG PET scan after two to three cycles of chemotherapy were found in a study done by Mikhaeel et al., to have a different progression free survival (PFS) and overall survival (OS). In this study, which was done before introduction of Deauville criteria, recruited one hundred and twenty one patients with high grade NHL and underwent interim FDG PET scan. PET-negative scan was interpreted as non-visualisation of all abnormal disease-related FDG uptake. PET-positive scan was interpreted as presence of persistent FDG uptake sites or appearance of new sites of increased FDG uptake, related to lymphoma. MRU was defined in this study as a focus of low grade FDG uptake within an area of previously noted disease, interpreted by the nuclear medicine physicians as likely due to inflammatory process but possibility of small volume disease could not be totally excluded. Fifty interim FDG PET scans were considered PET-negative, 19 scans were with MRU and 52 scans were PET-positive. Early stage NHL patients with MRU lesion showed PFS and OS similar to PET-negative NHL patients and advanced stage NHL with MRU lesion showed PFS and OS similar to PET-positive NHL patients. The estimated 5 year PFS from this study was 88.8% for PET negative group, 16.2% for the PET positive group and 59.3% for the MRU group (Mikhaeel et al., 2005). Results from this study demonstrate that MRU lesions require further assessment as to explain the reason behind the findings.

An international study to validate the prognostic role of interim FDG PET-CT scan in ABVD-treated, advanced-stage HL, using Deauville criteria and to assess the concordance rate among reviewers was carried out involving 260 patients. In this study, patients underwent FDG PET-CT scan at baseline and at interim post 2 cycles of ABVD chemotherapy. MRU lesions with Deauville score 2 to 3 were considered as negative for presence of disease in interim PET-CT scan. They found the sensitivity, specificity and accuracy of interim PET-CT were 73%, 94% and 91%, respectively. Negative predictive value and positive predictive value were 0.94 and 0.73, respectively. There were only 12 false-negative results (6% of interim FDG PET-negative patients) in which 7 of these were MRU lesions with Deauville score 3. The researchers in this study concluded that Deauville criteria is precise, reproducible and reliable to be recommended as standard reporting criterion in clinical practice and for clinical trials (Biggi et al., 2013).

There are several on-going clinical trials that are looking into the response-adapted chemotherapy in advanced HL utilizing interim PET scan with the aim is to reduce chemotherapy side effects by changing the chemotherapy. In these clinical trials, the MRU lesion is interpreted as negative for presence of disease and the scan is considered negative (Cheson et al., 2014). Based on Lugano classification recommendation which was introduce in 2014 for treatment response assessment, the interpretation of MRU lesion is often based on the intention of the therapy. For example, MRU lesion with Deauville score 3 in interim PET scan is considered as negative scan if the intention of subsequent treatment is to escalate chemotherapy. However if the intention is to de-escalate chemotherapy, MRU lesion with Deauville score 3 is considered as positive scan. This is to prevent under treatment (Cheson et al., 2014). Study performed by Southwest Oncology Group S0816 in which the researchers

escalate therapy from ABVD to dose escalated BEACOPP in stage III-IV HL patients with interim PET-positive scan. In this study, interim PET-positive scan was defined as scan which has lesion with Deauville score 4 and 5. Patients with interim PET-negative scan will continue with ABVD therapy. The results from this study showed response-adapted therapy based on interim PET scan after two cycles of ABVD seems promising with a 2-year PFS of 64% for PET-positive patients, which is much higher than expected 2-year PFS of 15% to 30%. However despite these results, there were 58 patients experiencing treatment failure in the interim PET-negative group, and the 2-year estimate of PFS for 271 patients with interim PET-negative group was 82% (Press et al., 2016).

2.5 Maximum Standardised Uptake Value (SUVmax), Dual Time Point Imaging (DTPI) technique and Retention Index (RI)

FDG PET-CT scan demonstrates the FDG uptake distribution in the body. Certain organs in the body utilised the FDG higher than others. It is important to be able to recognised the physiological FDG uptake distribution in the body in order to avoid misinterpretation of the scan. As described earlier, once FDG is in the cells, it is phosphorylated by enzyme hexokinases. FDG cannot be further processed and is trapped intracellularly as FDG-6-phosphate. Thus, FDG accumulates in areas with high levels of metabolism and glycolysis, for example at sites of inflammation, active tissue repair, sites of hyperactivity and also in cancer cells. In neoplastic cells, these increases in glucose demands lead to increase uptake of FDG and increased intracellular accumulation of FDG-6-phosphate in neoplastic cells relative to normal cells (Weiss et al., 2012). With this differentiation of FDG uptake, the areas of higher FDG uptake is visualised on the image and with the knowledge of normal physiological FDG

distribution in the body, areas of abnormal FDG uptake can be identified. This is the basic principle used behind the FDG PET scan visual analysis (Weiss et al., 2012).

Standardised uptake value (SUV) is a semi-quantitative analysis of FDG uptake in the body. SUV refers to a ratio of FDG uptake in a region of interest to the FDG uptake of the rest of body and it is dimensionless. The basic expression for SUV is

$$SUV = \frac{r}{(a'/w)}$$

where r is the radioactivity concentration (kBq/ml) measured by the PET scanner within a region of interest, a' is the decay-corrected amount of injected radiolabeled FDG (kBq), and w is the weight of the patient (g). Maximum SUV (SUVmax) refers to maximum SUV measured in the region of interest.

Visual analysis of PET images for treatment response assessment is considered adequate and sufficient for a positive or negative decision of overall response (Juweid et al., 2007). However, evaluation of therapy response during interim FDG PET-CT scan especially in clinical trials, some form of semi-quantitation of FDG uptake may be helpful (Lin et al., 2007). SUV is helpful in assessing treatment response by comparing its value during baseline, interim and at end of chemotherapy assessment of FDG PET scan (Kinahan et al., 2010).

As mentioned earlier, increased FDG uptake in the body is a non-specific process. FDG uptake can increase in various disease processes either due to benign inflammatory process or due to malignant cells with high metabolism. To differentiate between benign and malignant processes that produce increased in FDG uptake, dual time point imaging (DTPI) technique has been introduced (Houshmand et al., 2016). DTPI is an imaging technique that is used to study tracer kinetics. DTPI refers to scan procedure that is performed twice on the same subject at a different time point within

the same day. With this technique, SUV of a region of interest can be measured on both occasion and comparison can be made (Houshmand et al., 2016).

DTPI FDG PET-CT scan has been utilised in predicting the histological grades of malignancy in lymphoma and the SUVmax on 2-hours delayed scan were significantly higher than those on 1-hour early scan for all histological grades of malignant lymphoma during initial staging (Takayoshi et al., 2012). DTPI PET scan also been used for differentiating the lymph nodes between malignant lymphoma and benign lesions in which the malignant lymphoma demonstrates higher SUVmax during delayed scan (Michihiro et al., 2013).

DTPI technique has also been used to study the significant of retention index (RI) in various disease entities. Retention index is calculated by using this formula:

$$\text{Retention index} = \frac{\text{SUVmax delayed} - \text{SUVmax early}}{\text{SUVmax early}}$$

In general, retention index reflects the capability of retaining the FDG. High RI reflects the capability of the cells in retaining FDG which may indicate association with malignancy. In one study, it was shown that the high RI of FDG correlate with the expression of hexokinase type II which it is increased in malignant cells (Higashi et al., 2002). In another study, it was shown that RI of FDG in undifferentiated breast cancer was higher than differentiated breast cancer. From this study, high RI indicates aggressive disease (Vicente et al., 2012).

The FDG uptake in malignant cells was associated with low glucose-6-phosphatase enzyme activity, and increased glucose uptake through glucose transporter proteins, in particular GLUT-1 and GLUT-3, in these cells. Malignant cells also demonstrate longer duration of FDG uptake as compared to benign lesions and normal tissues (Kumar et al., 2005). Tumours had average SUVmax increase of 12% between

early and delayed scan (Takayoshi et al., 2012). In patients with malignant lymphoma, there were increased FDG uptake in lymphoma lesions on delayed scans (Takayoshi et al., 2012). These findings demonstrate the usefulness of DTPI PET scan in assessing tracer kinetics. Consequently, DTPI technique on FDG PET-CT scan could be used to evaluate tracer kinetics of MRU lesions in lymphoma patients during interim treatment assessment by measuring the change in SUVmax and RI.

2.6 Metabolic tumour volume (MTV)

Metabolic tumour volume (MTV) represents the volume of tumour tissues showing avid FDG uptake. It combined the dual characteristics of three dimensional volumetric data and the metabolic activity of tumour. MTV has been investigated for it use as a prognostic factor in lymphoma and also in various other solid tumours. MTV has been shown in one study as an independent predictor of progression free survival in HL (Kanoun et al., 2014). Another study has shown that MTV was a better predictor of progression free survival compared with SUVmax reduction in diffuse large B-cell lymphoma (Malek et al., 2015). In solid tumours, MTV has been shown to be useful in predicting short-term outcome to radiotherapy in pharyngeal cancer (Chung et al., 2009) and in other study involving oral cavity squamous cell carcinoma treated with primary surgery, MTV was found to be an independent adverse prognostic factor for death and disease recurrence (Zhang et al., 2014).

The combination of MTV and semi quantitative measurement are useful in assessing chemoresponse and in predicting the outcome. The fact that there are multiple prognostic factors which influencing the chemotherapy response and outcome in lymphoma, the combination of these prognostic factors will further increase the accuracy of treatment response prediction. Currently the use of MTV in lymphoma chemotherapy response is being evaluated and is not yet included of its application in

the latest guidelines (Cheson et al., 2014). In this study, to assist in evaluating the tracer kinetics of MRU lesions, the MTV changes of MRU lesions during interim PET-CT will be assess using DTPI as a secondary parameter whether it can differentiate between responder and non-responder in order to predict the end chemotherapy response.

CHAPTER 3

OBJECTIVES AND HYPOTHESES

3.1 Justification of the study

Interim FDG PET-CT scan in lymphoma is currently considered as an investigational tool. Information gathered from interim FDG PET-CT for early treatment response evaluation has the potential to guide physicians in response adaptive chemotherapy. However the presence of minimal residual uptake (MRU) lesion during interim PET-CT has created uncertainty in the treatment response assessment whether this finding should be considered as a poor response (positive PET) or a good response (negative PET) to chemotherapy. Since introduction of Lugano's classification in 2014 with recommendation of Deauville criteria to be used as guidelines in image interpretation of response assessment in interim and end treatment FDG PET-CT, MRU lesion with Deauville score 2 or 3 has been considered as a negative finding which translates as a good chemotherapy response (Cheson et al., 2014). At present, various clinical trials in response adaptive chemotherapy involving interim FDG PET-CT adopting Lugano's classification are on-going and results are being validated. Further study is required to assess MRU lesions characteristics particularly its kinetics behavior in interim FDG PET-CT by application of DTPI technique and semi-quantitative analysis.

3.2 Benefits of the study

1. Early identification of patients with poor response to chemotherapy, allowing a change in chemotherapy planning.

2. Benefit to patients in term of reducing chemotherapy side effects associated with ineffective treatment.

3. Reducing patient's anxiety associated with uncertainty in the treatment outcome.

3.3 General objective

To evaluate the predictive value of dual time point imaging (DTPI) of minimal residual uptake (MRU) lesion in interim FDG PET-CT scan in predicting the end post chemotherapy response in lymphoma patients.

3.4 Specific objectives

1. To compare the median of SUVmax changes and median MTV changes between responder and non-responder groups.

2. To compare the median SUVmax changes between 4 groups based on revised response criteria.

3. To evaluate any association between demographic factors and end of chemotherapy response.

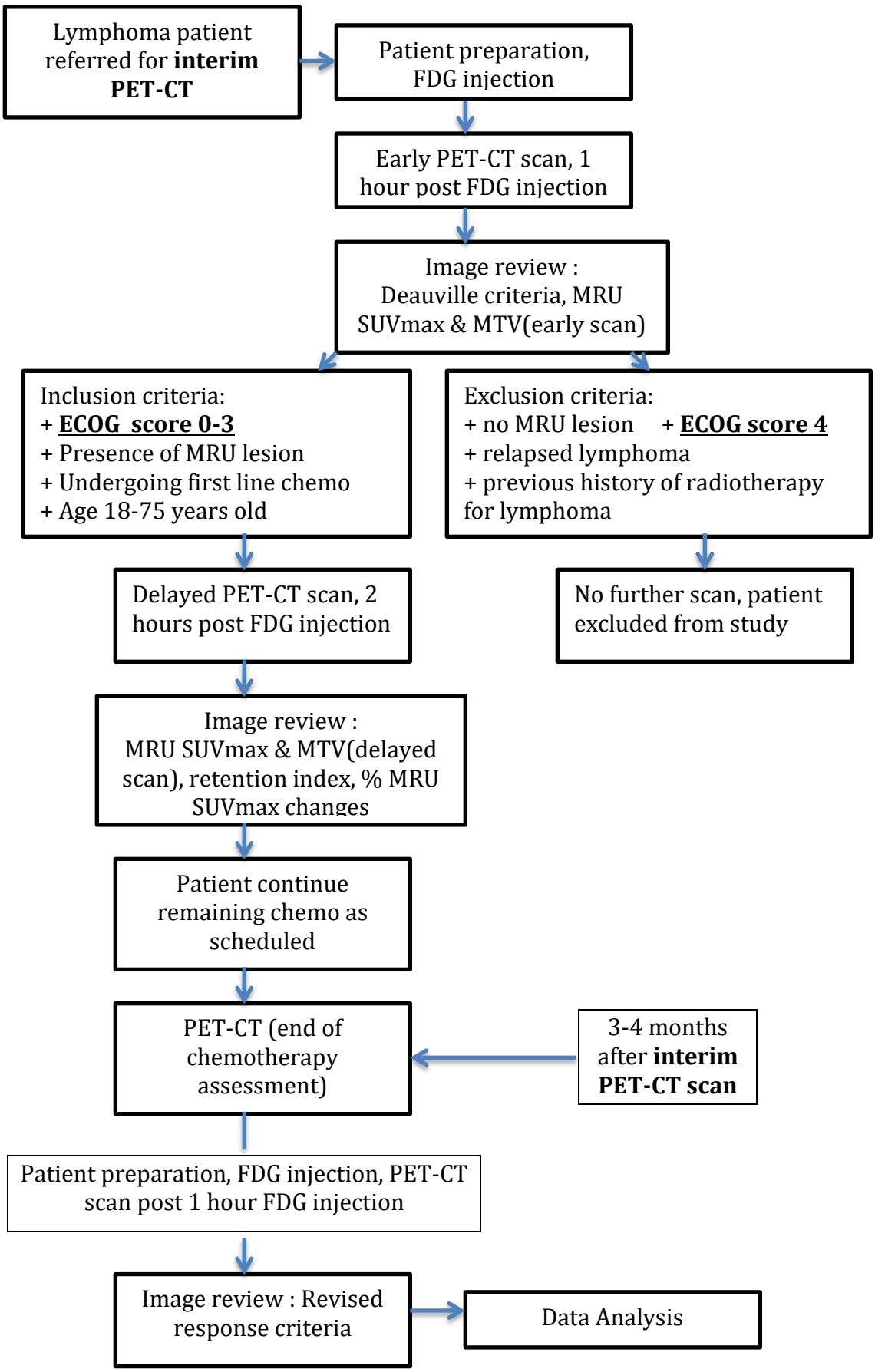
3.5 Research hypothesis

Increased in SUVmax change of MRU lesion during interim PET-CT assessment is associated with poor response at the end of chemotherapy.

3.6 Null hypothesis

Increased in SUVmax change of MRU lesion during interim PET-CT assessment does not associated with poor response at the end of chemotherapy.

3.7 Research framework



CHAPTER 4

METHODOLOGY

4.1 Research location

Department of Molecular Imaging and Nuclear Medicine, Hospital Canselor Tuanku Muhriz (HCTM), Bandar Tun Razak, Cheras, Kuala Lumpur.

4.2 Research design

This is a prospective cohort study.

4.3 Research period

The study was conducted from April 2014 to August 2015.

4.4 Sampling

4.4.1 Target population

Patients with histopathologically proven lymphoma.

4.4.2 Population sample

Lymphoma patients that were subjected to interim FDG PET-CT investigations and noted to have MRU lesions following the image review.

4.4.3 Sample size and dropout rate

Sample size was calculated using independent t-test. Parameters used are estimated from previous study (Itti et al., 2009) with the same population.

$$\text{Formula (t-test for two means):} \quad n = \frac{2\sigma^2}{\Delta^2}(Z_\alpha + Z_\beta)^2$$

where $Z_\alpha = 1.96$ $Z_\beta = 0.84$

Δ difference = 3.6 power = 0.8 (80%) SD, $\sigma = 5$ $\alpha = 0.05$