Malaysian Joint Recommendations of Reporting Format for FDG PET-CT in Lymphoma.

Teik Hin Tan[1], Teck Huat Wong[2], Alex Chin Hoe Khoo[3], Thanuja Mahaletchumy[4], Chen Siew Ng[5], Mohd Wajdi Ghazali[6], Nor Salita Ali[7], Mahayuddin Abdul Manap[8], Soo Min Lim[9], S Fadilah S Abdul Wahid[10], Jameela Sathar[11]

1 Nuclear Medicine Centre, Sunway Medical Centre, No 5, Jalan Lagoon Selatan, Bandar Sunway, 47500 Selangor, Malaysia.

2 Department of Nuclear Medicine, Hospital Umum Sarawak, Jalan Hospital 93586 Kuching, Sarawak, Malaysia.

3 Penang Adventist Hospital, 465, Jalan Burma, Taman Selamat, 10350 Pulau Pinang, Malaysia.

4 Department of Molecular Imaging and Nuclear Medicine, Universiti Kebangsaan Malaysia Medical centre, Selangor, Malaysia.

5 Department of Nuclear Medicine, Hospital Sultanah Aminah, Johor Bahru, Malaysia.

6 Department of Nuclear Medicine, Hospital Pulau Pinang, Pulau Pinang, Malaysia.

7 Department of Nuclear Medicine, Institut Kanser Negara, Putrajaya, Malaysia.

8 Institut Perubatan dan Pergigian Termaju, University Sains Malaysia, Bertam Pulau Pinang.

9 Department of Medicine, Hospital Sultanah Aminah, Johor Bahru, Malaysia.

10 Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia.

11 Department of Haematology, Hospital Ampang, Selangor, Malaysia.

Abstract

Over the past decade, 18F-Fluorodeoxyglucose (FDG) PET-CT has emerged as an important imaging modality in the management of lymphoma. Since the introduction of Deauville scoring

system (2009) and the Lymphoma Response Assessment Criteria (2014), clinicians are now sharing a common language in the management of lymphoma. In Malaysia, nearly a third of PET-CT request is related to lymphoma imaging. Though there are extensive publications regarding these scoring systems and assessment criteria for lymphoma, there is hardly any literature on the reporting format for the 18F-FDG PET-CT in this disease. The variable reporting formats have on many occasions caused confusion not only to the referring clinicians but also to nuclear medicine physicians. Thus, a working committee comprising of experienced nuclear medicine physicians and hematologists in Malaysia has made a joint recommendation on the standard reporting format for 18F-FDG PET-CT in Lymphoma. This recommendation will minimize inter-observer discrepancies in reporting, facilitate the referring clinicians' understanding of the report as well as facilitate counseling between patients and clinicians in the management of the disease.

Keywords lymphoma . 18F-Fluorodeoxyglucose . FDG; PET-CT . positron emission tomography . Report

Introduction

Lymphoma ranked fourth in males and sixth in females for the most common cancer among Malaysians according to the Malaysian National Cancer Registry Report 2007-2011[1].

Over the last two decades, 18F-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) has emerged as an important imaging modality in lymphoma management [2]. PET-CT has been shown to improve the accuracy in staging, treatment response assessment, surveillance, detection of transformation and, as a surrogate marker in new drug development in assessing FDG-avid lymphoma [3,4].

Since the introduction of Deauville five-point (5-PS) at the first International Workshop on PET in Lymphoma in 2009, PET-CT has been recommended, as an imaging biomarker, in the risk-adapted strategies in the management of lymphoma [5]. In 2011 and 2013, following the 11th and 12th International Conferences on Malignant Lymphoma in Lugano, a consensus was reached among haemato-oncologists and nuclear medicine physicians to accept PET-CT in lymphoma evaluation and harmonisation in PET reporting [6].

The Deauville (5-PS) scoring system was adopted in Malaysia shortly after the publication of Lugano Criteria in 2014 [6]. Nevertheless, there is still a lack of standardised format for PET-CT reporting in lymphoma cases using the published guideline. Therefore, there is a need to harmonize the reporting format by outlining the minimum expectation in reporting the findings for the local population.

Aim of this consensus

The aim of this paper is to harmonise the FDG PET-CT reporting format for lymphoma in Malaysia. This will (i) minimise inter-personal discrepancies in reporting; (ii) facilitate the reading and understanding of the reports by the referring clinicians; (iii) facilitate counselling of patients in planning the subsequent therapeutic management; and (iv) standardise clinical trial.

In this review, a multidisciplinary panel was established with representation from nuclear medicine physicians and clinical haematologists from public, private and university hospitals. The initial draft was prepared by the nuclear medicine physicians based on the existing guidelines [7,8]. Subsequently, the draft was presented and discussed with clinical haematologists according to local clinical settings.

Of note, in order to adapt to the local needs and for practicality reasons (e.g. regions without the availability of the PET-CT service), it is important to note that some of the recommendations are based on the committee's consensus based on the current accepted practice in Malaysia.

Preparations for FDG PET-CT imaging

The recommended timing for performing PET-CT is summarized in Table 4. Optimal patient preparation for PET-CT examination is essential to obtain good-quality images for accurate interpretation. Patients are required to fast for at least 4 hours before the procedure with only plain water permitted. Serum glucose need to be assessed prior PET-CT examination. The optimal glucose level prior to FDG injection is below 11.1mmol/l. In diabetic patients, anti-diabetic medication may need to be adjusted at the discretion of the attending physician. Re-schedule the procedure may be necessary if the glucose level is too high (for example >18mmol/l).

In addition to the dietary restrictions, patients are required to avoid strenuous exercise a day before the procedure. Physiological brown fat uptake can occur when patients are exposed to the cold environment during the procedure. Medications such as oral propranolol and benzodiazepine can be used to minimise this problem.

Lymphoma uptake, physiological distribution and pitfalls of FDG PET-CT

Lymphomas comprise a heterogenous group of histological subtypes with various genetic, molecular characteristics and biological behaviours. Most of the common lymphoma subtypes demonstrate high FDG avidity but particular attention should be paid to a few less common subtypes with variable FDG avidity as illustrated Table 1.

It is important to take note of the patterns of normal physiological FDG uptake in the brain, nasopharynx, liver, spleen, bone marrow and brown fat [9]. Brown fat activity, due to cold stimulation, is commonly seen at bilateral neck, shoulder, mediastinal, perirenal and paraspinal areas [10,11]. The uptake in these organs may occasionally mask small nodal and extranodal lesions. Therefore, CT component of PET-CT images should be scrutinised for any potential lesions. Specific measures such as drug administration (propranolol or benzodiazepine) or keeping the patients warm should also be undertaken to reduce brown fat activity and improve image quality [10,11].

Diffuse splenic FDG uptake is physiological but if the intensity is higher than the liver, it is suggestive of splenic involvement [9].

Focal uptake in the BM is highly predictive of lymphoma infiltration, which has been validated by various studies [13]. Therefore, it is suggested that definite FDG uptake in the marrow can help to obviate the need for bone marrow biopsy (BMB) in Hodgkins' lymphoma (HL) and to a certain extent, diffuse large B cell lymphoma (DLBCL) [13]. For HL, in the absence of B symptom and negativity in PET-CT, BMB can be omitted. For DLBCL, BMB may still be required when PET-CT shows no evidence of marrow involvement but identification of low volume disease is clinically important for subsequent treatment planning [14-17]. BMB is still recommended for the staging of other histological types [4]. On the other hand, diffuse intense bone marrow uptake in DLBCL patients, especially following institution of therapy, is usually attributable to hyper-reactive marrow (result of disease or treatment related factors) and should not be reported as definitive lymphomatous involvement. *As summary, bone marrow biopsy should be performed in any*

case when confirmation of marrow involvement is clinically important for treatment planning.

Diagnosing lung involvement in lymphoma is a challenge [18]. Lung lymphomas may present as nodules, consolidation or interstitial infiltrates with moderate to high FDG uptake. False positive findings due to bacterial pneumonia, granulomatous disease such as tuberculosis or sarcoidosis and bleomycin-induced pneumonitis have been well-documented [19]. Clinical, histopathological correlation, or follow-up study may be needed to establish the diagnosis. Lymphomatous infiltration and extension from adjacent mediastinal or hilar adenopathy (E lesion) should be differentiated from non-contiguous lymphomatous involvement of the lung parenchyma (Stage IV).

Increased FDG activities in the activated lymphoid tissues are another common pitfalls in PET-CT scans [19,20]. Rebound thymic hyperplasia can be observed in children and younger adults after chemotherapy, and thus needs to be distinguished from the residual mediastinal lymphoma. FDG uptake in the reactive lymph nodes especially at upper jugular chains are often seen on the end-of-treatment PET-CT scan. Comparison of these findings with the baseline study and recognition of the specific patterns are useful to derive the accurate conclusion [21].

False positive can also occur due to the presence of concurrent infection, inflammation during PET-CT examination or the patient receiving the immunotherapy. Referring clinicians should inform any conditions that may result in false positive results in the request form. Reporting doctors should also be aware of these conditions.

Recommendation: *FDG uptake should be interpreted in conjunction with CT morphology when writing a PET-CT report. Indeterminate lesion should be clearly stated. Clinical and histopathological correlation should always be taken into consideration when reading and interpreting the PET-CT report.*

Use of standardized uptake value (SUV) and Deauville criteria

FDG uptake is commonly presented semi-quantitatively by the SUV [9,23]. However, SUV may vary as it is subjected to injected FDG dose, time-to-image, scanner and other

factors [21]. To avoid such variations and to ensure consistencies in reporting, it is recommended that serial studies are performed on the same PET-CT scanners [9].

Despite standardization of PET-CT imaging techniques, inter-observer agreement of PET response in lymphoma treatment was not satisfactory, leading to concerted efforts for improvement, known as the International Harmonization Project. The previous shortcoming was partly due to lack of a reliable SUV cut-off value in differentiating active versus non-active lesions, especially in the category of 'minimal residual uptake' [3,6]. This problem has been overcome by the five-point scale grading or Deauville Criteria, which has been shown to be more reproducible by incorporating the use of mediastinum blood pool and liver as "reference tissues" and normalization of lesion/target SUV measures to the selected reference tissues [3,5,6].

Deauville criteria is recommended for response assessment at interim as well as end of treatment PET [5]. Score 1 and 2 represent complete metabolic response (CMR). When a target lesion demonstrates score 4 and 5 during interim or end-of-treatment study, a SUV of more than 30% reduction from baseline study represents partial metabolic response (PMR); whereas more than 30% increment from baseline study is considered progressive metabolic disease (PMD). Change of SUV that does not meet the above criteria is considered no metabolic response (NMR). In additional, any new metabolically active lesions represent progressive metabolic disease (PMD) (Table 3) [3,6].

In order to avoid missing small residual disease, Score 3 should be interpreted with anticipated prognosis, lymphoma subtype, clinical findings, other markers (such as CT size reduction) and decision on escalation/ de-escalation of treatment. For instance, score 3 is likely to represent CMR in interim PET in HL receiving standard induction therapy. However, score alone should not be used to decide on de-escalation of treatment.

For the lesion occurring in the regions with high physiological FDG uptake (i.e. bowel, spleen and bone marrow), a reduction of previous uptake to the level not exceeding the current surrounding normal tissue activity can be regarded as a CMR.

Recommendation: *Deauville score should be provided together with SUV when reporting FDG PET-CT in lymphoma. Although Deauville Criteria is useful when comparing serial studies, it is recommended to state the Deauville score in the baseline study. If there are*

multiple lesions in a particular nodal region, the highest Deauville score lesions should be provided at each region.

NOTE: *Deauville criteria provides the metabolic response of the target lesions. Morphologic (tumour size and volume) response and other blood parameters should be taken in consideration when assessing overall clinical response.*

Indications of FDG PET-CT in Lymphoma

PET-CT is considered the standard-of-care imaging for staging, response assessment and surveillance of lymphomas (Table 3). When the initial PET-CT demonstrates low FDG avid nodes, subsequent diagnostic CT should be used to monitor morphological response.

Recommendation: *FDG PET-CT should not be used to diagnose lymphoma in suspected case. Histopathological results remain the gold standard. However, PET-CT maybe useful to map the distribution of active lesions and identify the optimal biopsy site for histopathologic confirmation.*

Terminology such as “baseline scan”, “interim scan” and “end-of-treatment scan” are widely used in our clinical practice. (Table 4) However, some clinicians prefer terminology like “pre-treatment scan” and “post-treatment scan”. It is important that both the referring clinicians as well as the reporting nuclear medicine physicians share the same understanding of the terminology used.

Structured FDG PET-CT report for lymphoma

The report usually contains the following sections:

Sections of the Report	Details of the Content
Demographics	Patient’s identifiers, the referring doctor’s name, date of the study and type of the examination (FDG PET-CT).

Clinical summary	Histologic subtype of lymphoma, the primary sites of disease, initial staging and treatment history (including dates of last cycle of chemotherapy, immunotherapy, or radiotherapy, stem cell transplant), recent investigation results (tumour markers), recent procedures, past or co-existing medical illnesses and drug history (GCSF administration, metformin etc), previous imaging studies.
Study indication	Baseline, interim, end-of-treatment or surveillance scan (specify the purpose of the surveillance study).
Procedure	Name of the radiopharmaceutical, the administered activity (total activity or per body weight), anatomical site of injection (optional), time from injection to imaging, pre-injection blood glucose level, oral or intravenous CT contrast (if given), other medication administered e.g. diuretics, benzodiazepines, propranolol (if given), additional regional or delayed scanning (if performed).
Findings	• There are two ways of reporting the findings of PET/CT: arrange the findings in descending order of clinical importance (preferred by majority of the clinicians) or according to successive structured anatomical regions. Both reporting styles are acceptable and endorsed by International Atomic Energy Agency (IAEA) [23]. • When comparing two or more studies, it should be clearly stated *"Comparison was made with previous PET-CT(s) dated ....."*. • Potential limitations such as intense brown fat uptake and patient's motion artefact should be stated. Non-FDG avid

	proven or suspicious lymphoma lesions should also be included. • Lymphoma typically involves multiple groups of lymph nodes at multiple regions. The reporting nuclear medicine physicians should specify each regional involvement (e.g. unilateral/ bilateral cervical, mediastinal, axillary, retroperitoneal, pelvic, inguinal regions) and any extra-nodal or bone marrow involvement • In each region (cervical, mediastinal, retroperitoneal, etc), SUV with Deauville score of the representative lymph node (typically the most metabolically active one) should be stated. Tumour size, and if possible tumour volume, should be stated together with SUV. *For example:* *"Intense FDG uptake is demonstrated at large lobulated mediastinal mass (SUVmax 15.7 (Deauville 5), measuring 123.4ml in tumour volume)".* • In assessment of the therapy response, changes of uptake intensity and CT size of the target lesions should be clearly stated. For example: *"Previous mediastinal mass has markedly reduced in hypermetabolic intensity and CT size (current SUVmax 4.0 (Deauville 4), measuring 40.5ml in tumour volume; previous SUVmax 15.7 (Deauville 5), measuring 123.4ml)".* • CT component should be examined. Any bulky lymph nodes or lesions compromising critical structures must be stressed to the referring physicians.

	• Non-oncologic incidental findings e.g. pneumonia, chemotherapy/ radiation-induced lung fibrosis, vascular aneurysm, thromboembolism, obstructive uropathy, gynaecological masses etc. should be reported.
Conclusion	• A brief conclusion to answer the clinical questions of the referral. For example: *"Current study demonstrates active lymphoma at bilateral cervical and right axillary regions (Ann Arbor stage II). No demonstrable bulky disease or extra-nodal lesion."* • In response assessment, it may be concluded that: *"The findings are consistent with complete metabolic response/ partial metabolic response/ stable metabolic disease/ progressive metabolic disease."* • If baseline study is not available for comparison, the term *"residual active lymphoma"* if presence of active disease. • It is advisable to avoid the term of *"mixed response"* which may result in confusion. • The strength of evidence indicative of active lymphoma present on the current study can be reflected by using the terms such as *"highly suggestive of", "suggestive of" or "less likely"*. • If there is an indeterminate lesion *"suggestive of"* residual lymphoma, the nuclear medicine physician should suggest an appropriate subsequent action(s) such as a suitable site for biopsy. If active lymphoma is *"less likely"*, then an alternative differential such as infection should be given.

	• Verbal communication of the critical finding e.g. airway compromise, cord compression, thrombosis or impending fracture to the referring doctor must be recorded.
Addendum	Following the issuance of the initial official report, any discrepancies, variation in findings and/or conclusions, additional amendment, comments or feedbacks should be recorded in this section.

Conclusion

This document provides essential elements and standardized terminology used in PET-CT reporting in lymphoma. It is intended to provide a practical guide to Malaysian physicians involving in lymphoma management in reporting, interpreting and understanding the PET-CT report. We hope that these joint statements will lead to more collaboration and cross-disciplinary input among all parties in optimising better care in lymphoma management in future. In view of rapid progress in lymphoma imaging and therapy, these recommendations will be reviewed within 5 years.

Conflict of interest

All author declares no conflict of interest.

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Table 1: 18F-FDG avidity of various subtypes of lymphoma [4,6]

		FDG avidity (%)
High avidity		
	Hodgkin Lymphoma	97-100
	Diffuse Large B Cell Lymphoma	97-100
	Follicular Lymphoma	97-100
	Mantle-cell lymphoma	100
	Marginal zone lymphoma, nodal	100
	Lymphoblastic lymphoma	100
	Sezary syndrome	100+
	Anaplastic large T-cell lymphoma	94-100*
	Natural Killer/ T-cell lymphoma	83-100
	Mycosis fungoides	83-100
	Angioimmunoblastic T-cell lymphoma	78-100
	Enteropathy-type T-cell lymphoma	67-100
	Peripheral T-cell lymphoma	86-98
Moderate to High Avidity		
	MALT marginal zone lymphoma	54-81
	Small lymphocytic lymphoma	47-83
Mild to Moderate Avidity		
	Subcutaneous panniculitis-like T-cell lymphoma	71
	Marginal zone lymphoma, unspecified	67
	Marginal zone lymphoma, splenic	53-67
	Primary cutaneous anaplastic large T-cell	40-60
	Lymphomatoid papulosis	50
Poor FDG Avidity		
	Cutaneous B-cell lymphoma (n=2)	0

Note: + *only 62% of cutaneous sites*

* *only 27% of cutaneous sites*

Table 2: The definitions of Deauville five-point scale

Score	Definition
1	No uptake
2	Uptake < mediastinal blood pool
3	Uptake ≥ mediastinal blood pool but < liver
4	Moderately increased uptake compared to the liver (<3 × SUV liver)*
5	Markedly increased uptake compared to the liver (>3 × SUV liver)* or new lesion
X	New areas of uptake unlikely to be related to lymphoma

Note: ** The 3 times SUV of liver as the cut-off to classify Deauville Score 4 and 5 is recommended by our working committee based on our expert opinions.*

Table 3: The definitions of metabolic response criteria based on Lugano Classifications [3,6]

Categories of response	Definition
Complete metabolic response (CMR)	• Score 1, 2 or 3 in the nodal or extranodal sites, with or without residual mass(es).
Partial metabolic response (PMR)	• Score 4 or 5, with reduced uptake compared with baseline and residual mass(es) of any size. • SUV of the baseline target lesion^{+} is reduced by > 30%.$^{\#}$ • None of the other less active non-target lesions showing SUV increment of >30%.$^{\#}$ • Bone marrow metastases uptake > normal marrow but reduced compared with baseline scan. • At interim scan, PMR may suggest responding disease but at the end-of-treatment scan it indicates residual active lymphoma.
No metabolic response (NMR)	• Score 4 or 5 on the interim or end-of-treatment scan, with no significant change in target lesion uptake from baseline. • None of the other less active non-target lesions showing SUV increment of >30%.$^{\#}$
Progressive metabolic disease (PMD)	• Score 4 or 5 on the interim or end-of-treatment scan, with an increase in uptake from baseline. • New FDG-avid foci consistent with lymphoma. • SUV of the baseline target lesion is increased by > 30%.$^{\#}$ • Any of the other less active non-target lesions showing SUV increment of >30%.* $^{\#}$

Note: [+] *Target lesion is the most metabolically active lymphoma lesion*

[#] *The 30% cut-off value is based on the expert opinions of our working committee*

***** *The increase in FDG uptake may be due to inflammation, thus biopsy may be necessary to confirm PMD*

Table 4: Terminology of indication of PET-CT scan in lymphoma

Baseline scan: It is performed prior to institution of the definitive therapy to provide information about the staging and the prognosis. It also enables comparison with the subsequent study to facilitate evaluation of treatment response.

Interim scan: It is the mid-treatment scan frequently done after the second or third cycle of therapy, at a timing just before the start of the following cycle. It must be performed at least 14 days after the previous chemotherapy cycle. It is useful to predict the response to the current regime so that early treatment adaptation can be performed.

End-of-treatment scan: It is used to evaluate response following the completion of the predefined treatment regime, usually within 6 months after treatment. The scan is recommended to be performed at the following time frame to avoid false positive flare reaction:

- At least 2 weeks after GCSF
- At least 4 weeks post-surgery
- At least 6 weeks post chemotherapy including immunomodulator
- At least 8 weeks after PD-1/ PDL-1 immunotherapy
- At least 12 weeks post radiotherapy

Surveillance scan: It refers to the follow-up scan which is done:

i) to assess the equivocal findings on the end-of-treatment scan, or
ii) more than 6 months after completion of the definitive treatment with the purpose of screening to ensure remission, or
iii) to evaluate the suspicion of relapse after achieving complete remission