Chapter 9
F-18 FDG PET Tests in Malignant Lymphoma

Norifumi Tsukamoto

9.1 Introduction

Malignant lymphomas, which are a heterogeneous group of diseases that arise from the cells of the immune system, are classified as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The HL group mainly involves the lymph node, and has been subdivided into nodular lymphocyte predominant HL and classic HL (cHL). The latter group has been further divided into four histological subtypes: (1) nodular sclerosis cHL, (2) lymphocyte-rich cHL, (3) mixed-cellularity cHL, and (4) lymphocyte depleted cHL [1]. In contrast, NHL often involves up to 40% extranodal sites, and based on the phenotype, is divided into the B cell lymphoma and NK/T cell lymphoma groups. Diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL) are the common subtypes, with the former type being aggressive, while the latter is indicative of an indolent clinical course [1].

Accurate staging and post-therapy evaluation are essential for the improvement of lymphoma treatment. Imaging plays a key role in the management of lymphoma, as comparison of the images before and after treatment is objective and reproducible [2]. When the Cotswold classification [2], which is based on the Ann Arbor classifications [3, 4], is used for evaluation of computed tomography (CT) images, this makes it possible to visualize the lymph node and organs. The 1999 National Cancer Institute Working Group published an evaluation of lymphoma lesion by CT, which was also adopted for the staging and response criteria for NHL as well as HL [5]. These criteria involve complete (CR) and partial response (PR), stable, progressive, and relapsed disease (RD), and CR undetermined (CRu), in which the tumor mass persists with a size reduction following treatment due to tumor fibrosis rather than residual disease.

N. Tsukamoto (✉)
Oncology Center, Gunma University Hospital, Maebashi, Gunma, Japan
e-mail: tsukamoto@gunma-u.ac.jp

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Due to the high sensitivity of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in the detection of the disease, this methodology has become the standard procedure for the evaluation of lymphomas [6–8]. Furthermore, the 2007 International Working Group (IWG) also incorporated this technique into the revised response criteria due to both the superior sensitivity and specificity in HL and DLBCL, along with the elimination of the CRu [9]. The collection of sufficient additional information that supported the usefulness of PET/CT in other histologies, especially FL, subsequently led to the publication of the Lugano classification in 2014 [10, 11]. This classification recommended using PET/CT as the standard method for staging and response criteria in most of the FDG-avid lymphoma. In addition, this classification has also incorporated the Deauville 5-point scale method [12], which is a standardized criteria for the interpretation of scans. The recent introduction of immune checkpoint inhibitors has helped to elucidate a different clinical course named "pseudo-progression," which documents the presence of progressive disease despite the contrary evidence of clinical benefit [13, 14]. The provisional recommendation was introduced in 2016 in order to address this phenomenon in the guidelines [14].

9.2 Role of PET in Staging at the Time of Diagnosis

Staging is important not only for treatment decisions but also for predicting the lymphoma prognosis. This staging process is based on the Ann Arbor staging system, which differentiates the lymphoma lesion into four stages [3, 4]. Although CT scans and gallium scintigraphy were commonly used modalities for staging, PET/CT has proved to be a more sensitive and specific imaging method than a CT scan by itself. Moreover, the PET/CT methodology is advantageous as it can detect metabolic changes in the areas involved with lymphoma before the structural changes become visible. In the Lugano classification [10, 11], PET/CT was included as a way to evaluate the lymphoma lesions seen in most of the subtypes. These are recognized based on the increased FDG uptake in the lymph node, spleen, liver, and other extranodal sites, which includes the bone marrow (Table 9.1) (Fig. 9.1). Extension from a nodal lesion into extranodal tissues such as the lung, pericardium, and pleura, which may occur in stages I–III, does not cause the stage to develop into stage IV.

In the Ann Arbor classification, patients were subdivided according to the absence (A) or presence (B) of disease-related symptoms such as fever, weight loss, or sweating [3, 4]. However, these features do not confer unfavorable prognosis in NHL; the presence of disease-related symptoms correlates only in HL. Therefore, it is recommended that the description of the disease-related symptoms A or B are only needed in HL; it can be omitted in NHL [10].

In contrast, although FDG avidity is variable in small lymphocytic lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphomas, and mycosis fungoides, CT scans can still be used for detection of lymphoma lesions [10].

Table 9.1 Staging system for lymphoma (the Lugano Classification)

Stage	Nodal Involvement	Extranodal Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky	II as above with "bulky" disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm: Nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

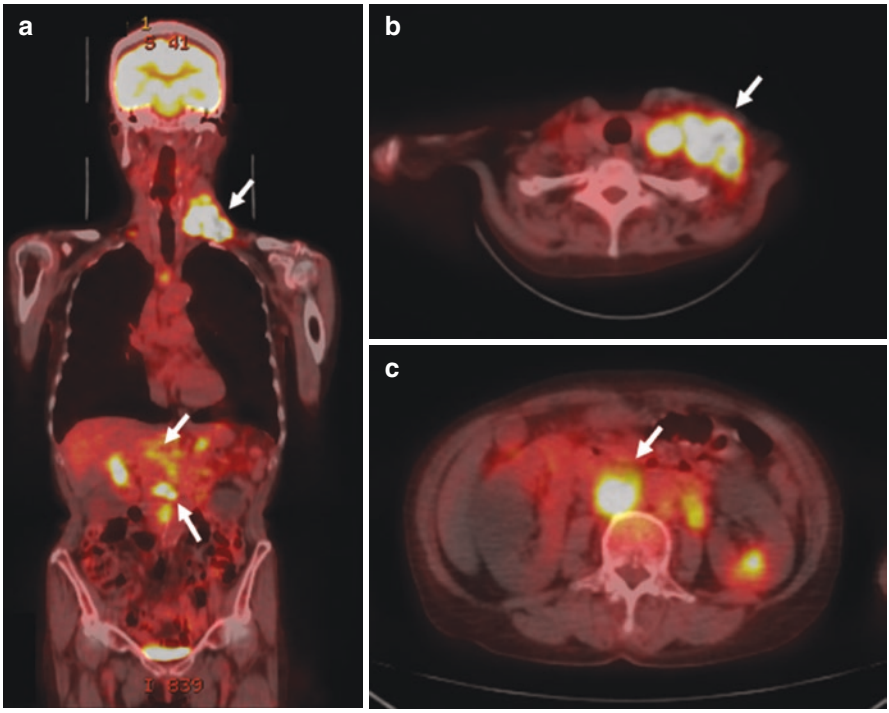

Fig. 9.1 Initial staging with ^{18}F-fluorodeoxyglucose (FDG) PET/CT in Hodgkin Lymphoma. (**a**) Coronal image shows accumulation of FDG in left cervical, mesenteric and para-aortic lymph nodes (arrows). Axial images of left cervical lymph node (**b**) and para-aortic lymph node (**c**) with SUVmax 12.5 and 10.5, respectively

PET/CT improves the accuracy of the lymphoma lesion detection, with mainly upstaging occurring in 10–30% of cases [10]. This can potentially help to avoid overtreatment as well as undertreatment. Upstaging has especially been reported to be more common in FL versus the other subtypes. However, since an enhanced CT scan can identify a nodal mass more clearly as compared to PET/CT, enhanced CT is considered to be suitable for accurately measuring the tumor size. When the size of the spleen exceeds 13 cm, this classification recommends that this condition be defined as splenomegaly. Furthermore, diffusely increased or focal uptake of FDG in the liver is recognized as liver involvement [10].

The presence of bulky disease is a negative prognostic factor in some lymphomas. In fact, the longest diameter of the largest lymphoma lesion is used as one of the factors in the FL International Prognostic Index 2 [15]. Although a variety of sizes have been proposed, such as 6 cm in FL, 6–10 cm in DLBCL, and 10 cm in HL, these sizes have yet to be definitively validated. The Lugano classification recommends recording of the longest measurement by CT in order to determine the presence of bulky disease [10].

The role of bone marrow biopsy has changed during the current PET/CT era. In HL and DLBCL, PET/CT sensitivity surpasses that for bone marrow biopsy when detecting bone marrow involvement [16, 17]. However, since the use of a bone marrow biopsy can still be important when evaluating hematopoietic function, performing a bone marrow biopsy prior to treatment is preferable in all cases.

The degree of the FDG uptake can be expressed quantitatively by the standardized uptake value (SUV). SUV is defined as the concentration of radioactivity in the tissue or lesion (MBq/mL) × patient body weight (g)/injected dose (MBq) [18], while the maximum uptake of ^{18}F-FDG in the tumor is represented by the SUVmax. SUVmax is correlated with the activity of the lymphoma lesion. HL and aggressive lymphoma such as DLBCL exhibited a higher FDG uptake as compared to indolent lymphoma [19, 20], with a SUVmax > 10 suggestive of aggressive lymphoma [19, 21]. These values can also potentially be used to identify the foci of the aggressive transformation in those patients who were initially diagnosed as indolent lymphoma.

Staging is an important component of a predictive model for newly diagnosed patients with lymphoma. For example, the five factors that affect the prognosis in aggressive lymphoma include age, serum lactate dehydrogenase (LDH), performance status (PS), stage, and extranodal involvement [22]. Likewise, the presence of an advanced stage (stages III–IV) is also an important risk factor for other lymphomas, such as the follicular lymphoma prognosis index (FLIPI) for FL [23], and the international prognosis score for advanced HL [24].

9.3 End of Treatment Evaluation

Since complete remission is a prerequisite for a cure, the major objective in patients with lymphoma is to achieve complete remission. The therapeutic response is assessed based on clinical manifestation, blood tests, and imaging. A decrease in the

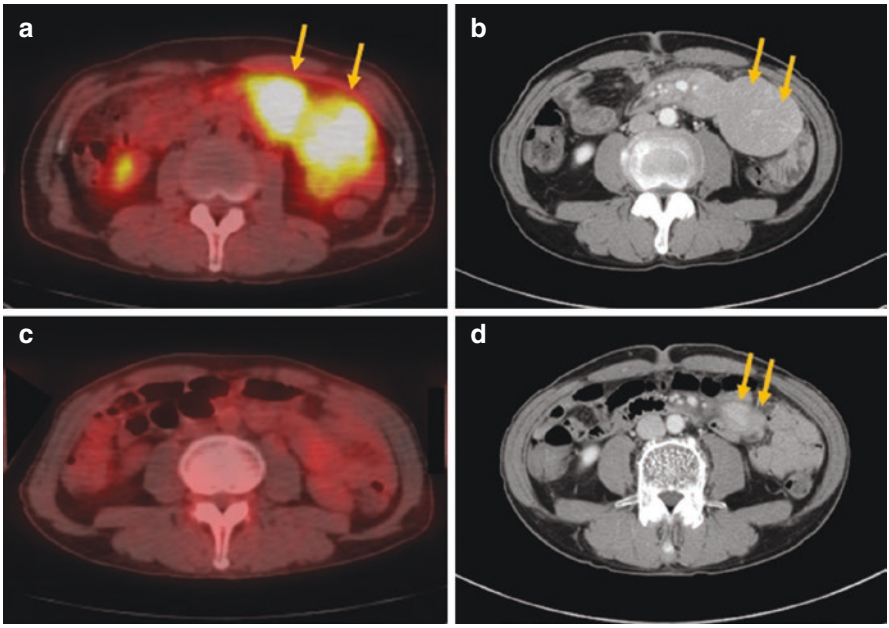

Fig. 9.2 Pretreatment and posttreatment images in a patient with follicular lymphoma. Pretreatment PET/CT (**a**) and CT scan (**b**) shows large mesenteric lymph nodes (arrows). Posttreatment PET/CT (**c**) demonstrates no uptake of FDG, but residual mass on CT scan (arrows) (**d**)

size of the tumor mass has been the cornerstone for a good therapeutic response in lymphoma. However, when CT finds a residual mass, this can be ambiguous, as it is not always metabolically active. Therefore, performing PET/CT at the end of treatment for lymphoma proved to be effective in discriminating residual active disease from fibrotic masses [10]. Thus, the value of PET/CT determined for the end of treatment assessments can be established for DLBCL, HL, FL, and other FDG-avid lymphomas (Fig. 9.2). In these subtypes, a positive PET/CT after treatment is strongly predictive of residual disease, whereas a negative PET is predictive of the absence of residual disease [10, 25, 26]. To minimize false-positive results, PET/CT needs to be performed at 6–8 weeks after the administration of chemotherapy, and at 8–12 weeks after completion of irradiation [27]. As PET/CT reflects glucose metabolism, evaluation of the CR indicates complete metabolic remission (CMR), whereas the PR indicates the partial metabolic response (PMR) [10].

For the 2007 IWG criteria, PET/CT evaluations were based on visual interpretations that used the mediastinal blood pool as the standard portion [9]. To assure reproducibility, a 5-point scale was recommended as the standard criteria for the scoring system used to assess the residual FDG uptake in the Lugano classification [10, 11]. The system is defined as follows [12]:

- Score 1: no uptake.
- Score 2: slight uptake, but below the mediastinum (blood pool).

- Score 3: uptake above the mediastinal, but below or equal to uptake in the liver.
- Score 4: uptake slightly to moderately higher than liver.
- Score 5: uptake markedly higher than liver and/or new lesions (on response evaluation).

The results of the PET/CT are interpreted as follows [10, 11] (Table 9.2):

- Complete response (CR): scores of 1, 2, or 3 together with the absence of any FDG-avid bone marrow lesion(s), irrespective of a persistent mass seen on CT.
- Partial response (PR): Deauville score of 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size.
- Stable disease (SD), also referred to as no response: Deauville score of 4 or 5 without any significant change in the FDG uptake from baseline.
- Progressive disease (PD): Deauville score of 4 to 5 with increasing intensity compared to baseline or any interim scan and/or new FDG-avid foci consistent with malignant lymphoma.

Score 3 should be interpreted according to the clinical context and the treatment, but in many patients indicates a good prognosis. A score of 4 or 5 indicates the presence of a residual lymphoma lesion even if the FDG uptake decreased from baseline [10].

In patients with relapsed or refractory HL or NHL, PET/CT can also determine prognostic information after salvage chemotherapy and high-dose chemotherapy followed by autologous stem cell transplantation. Three-year progression-free survival (PFS) in patients who were PET negative was more than 75%, which was superior to the 30–40% PFS in the PET positive patients. Thus, PET/CT findings may be useful in the final decision as to whether a patient should undergo high-dose chemotherapy followed by ASCT [11, 28, 29].

For the variable PET-avid subtypes, the assessment of the response needs to be done using a CT. CR is defined as follows: all of the target lesions, which includes up to six of the largest lesions at baseline, need to regress to a longest diameter of $\leq$1.5 cm after completion of the treatment. PR is defined as a decrease of more than 50% of the sum of the product of the long axis diameter and the short axis diameter for up to six of the target lesions. If the mass decreased in size but still persisted, it was defined as the best PR without the demonstration of the absence of lymphoma by biopsy [10, 11].

The results of the post chemotherapy evaluation by PET/CT is also part of the decision for the radiotherapy. Patients who were PET/CT negative had a far better PFS than that of patients who were PET/CT positive. In the posttreatment PET/CT positive patients, PFS of patients receiving radiotherapy was superior to those not receiving radiotherapy. Thus, the end of treatment PET/CT could potentially be used in the decision for using additional radiotherapy [30, 31]. With regard to radiotherapy planning, post-therapy PET/CT can more precisely determine the localization of the lymphoma lesion. In addition, PET/

Table 9.2 Response criteria for patients with FDG-avid lymphoma proposed in the 12th ICML Conference (Lugano 2013)

Response assessment	Evaluation by PET-CT	Lymph nodes and extralymphatic sites	Nonmeasured lesion	Organ enlargement	New lesion	Bone marrow
CR	Complete metabolic response (CMR)	Score 1, 2, or 3 with or without a residual mass on CT	NA	NA	None	No evidence of FDG-avid disease in marrow
PR	Partial metabolic response (PMR)	*Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size (but no new lesions)	NA	NA	None	Residual uptake higher than uptake in normal marrow but reduced compared with baseline
SD/NR	No metabolic response (NMR)	Score 4 or 5 with no significant change in FDG uptake from baseline	NA	NA	None	No change from baseline
PD	Progressive metabolic disease (PMD)	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma	None		New FDG-avid foci consistent with lymphoma rather than another etiology	New or recurrent FDG-avid foci
		*At end of treatment; residual disease, At interim; responding disease	NA: not applicable			

Table 9.3 Refinement of the Lugano classification lymphoma response criteria in the era of immunomodulatory therapy

Response assessment	Definition
CR	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
PR	≥50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart (as measured bidimensionally)
PD	≥25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart, where Tumor Burden = SPD index lesions + SPD new, measurable lesions

CT yields better consistency of the target volume delineation as compared to the CT scan [32–34].

Recently, immune checkpoint inhibitors have been added to lymphoma therapy. These agents are sometimes associated with the progression of the lymphoma lesion despite the evidence of clinical benefit. This is referred to as "pseudo-progression" and its occurrence is well-known in solid tumors [13, 14]. To address this issue, a workshop proposed the creation of provisional response criteria, which led to the concept of "indeterminate response." In order to confirm an evaluation, consecutive assessment for at least 4 weeks after the first documentation is required, after which either PD or pseudo-progression can be determined [14] (Table 9.3).

9.4 Interim PET (iPET)

In spite of the introduction of molecular target chemotherapy using agents such as rituximab or brentuximab vedotin, relapse is still the most important concern when treating the disease. In this respect, assessment of early response becomes an important factor. Since PET/CT makes it possible to perform early evaluation of metabolic changes during induction therapy, PET/CT is now recognized as a useful method for assessing the therapeutic response during the chemotherapy course. In most chemotherapy responders, the PET/CT becomes negative after 2 cycles of chemotherapy [35, 36]. In HL, iPET has proven to be a powerful predictor of treatment outcome. Patients who were PET/CT negative after 2–3 cycles of chemotherapy (ABVD) had a remarkably better PFS and overall survival (OS) than those who were PET/CT positive, while patients who were iPET positive had a poor prognosis [36–38]. Thus, it would be of interest to know whether an iPET-adaptive strategy based on early chemotherapy escalation could perhaps improve the prognosis in patients who are iPET positive. Gellamini et al. examined iPET positive patients after 2 cycles of ABVD and found that the PFS and OS improved after the administration of BEACOPP chemotherapy [39]. Besides achieving a cure for the disease, one of the other major goals of treatments is to reduce the toxicity. In early stage

HL, iPET negative patients were shown to be able to reduce the cycles of chemotherapy [40, 41]. Likewise, in advanced stage HL, patients who were iPET negative were able to omit bleomycin without any effect on the survival [42].

However, conflicting results have been reported for DLBCL. In the recent report by Burggraaff et al., a meta-analysis of 18 studies found there was a predictive value for iPET [43]. Likewise, Gouill et al. also reported iPET can assist the clinician in predicting patients' outcome [44]. On the contrary, Mamot et al. reported the results of a prospective trial in 138 patients with DLBCL who were treated with R-CHOP-14. In these patients, iPET was performed after two (PET-2), four (PET-4), and six (PET-6) cycles of R-CHOP with results revealing that PET-2 and PET-4 had a less predictive value than PET-6 (=end of treatment) [45]. Dührsen et al. also reported finding limited prognostic value in patients treated with R-CHOP. In their analysis, although they used a semi-quantitative method based on the SUVmax and SUVmax variation (ΔSUVmax) to improve the sensitivity, the prediction capability of prognosis was not high, and iPET-guided therapy did not improve outcome [46]. These data seem to suggest that iPET has a limited prognostic value for DLBCL. Furthermore, these findings showed that iPET-guided treatment did not improve the treatment outcome.

9.5 Post-Therapy Surveillance

In HL and DLBCL, approximately two-thirds of the patients are expected to achieve long-term remission with first-line chemotherapy. Among the patients achieving remission from first-line chemotherapy, relapse is commonly seen within 2 years [47]. Thus, surveillance imaging is conducted in order to detect relapse as early as possible, as salvage chemotherapy can be effective if the tumor burden is low. However, many studies have reported finding that a relapse was identified before the scheduled follow-up visit. As a result, surveillance imaging was only able to detect relapse before clinical manifestations in a minority of these patients. Furthermore, relapses detected by imaging, which included PET/CT were not associated with an improved survival even when the relapse was only in the early stage [11, 47, 48].

These studies suggest current imaging approaches such as PET/CT and CT are not able to detect most relapses prior to the presence of clinical signs and symptoms, and thus they do not contribute to an improved survival.

Summary and Key Points

In this chapter, we overviewed the important roles of PET/CT in staging at the time of diagnosis in the first half. In the latter half, we described the role of PET/CT in evaluation of post- and mid- therapy evaluation. PET/CT has high sensitivity in detecting lymphoma lesions compared to CT and it has become standard procedure for staging and end of treatment evaluation in most of the lymphoma subtypes. Whereas significance of Interim PET in predicting treatment outcome is limited.

The following are key points to understand the contents of this review.

- PET/CT has high sensitivity in detecting lymphoma lesion compared to CT scan. This methodology has become the standard procedure for the evaluation of lymphomas.
- In staging at the time of diagnosis, PET/CT is regarded as a standard method to evaluate the lymphoma lesions in most of FDG-avid subtypes. In contrast, in small lymphocytic lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphomas, and mycosis fungoides, CT scans can still be used.
- The value of PET/CT determined for the end of treatment assessments is established for DLBCL, HL, FL, and other FDG-avid lymphomas.
- A 5-point scale is recommended as the standard criteria for the scoring system used to assess the residual FDG uptake.
- Interim PET (iPET) is a powerful predictor of treatment outcome in Hodgkin lymphoma, but its role in other subtypes is controversial. Furthermore, the value of iPET-guided therapy is not established.
- Surveillance imaging by PET/CT does not contribute to an improved survival.

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