

PET/CT: appropriate application in lymphoma

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Abstract: Positron emission tomography (PET) integrated with computed tomography (CT) (PET/CT) provides both metabolic and morphologic information, and becomes the most sensitive and specific imaging armamentarium in patients with non-Hodgkin lymphoma (NHL) and HL. This multimodality is being routinely used in staging, response assessment, and end-of-treatment evaluation for most lymphoma subtypes with convincing data. However, there are still controversial issues in the clinical management of patients with lymphoma. This comprehensive review addresses the latest information regarding the appropriate application of Fluorine 18 fluorodeoxyglucose (^{18}F -FDG) PET/CT, discusses the current dilemma in the prognostic value of interim PET/CT, and tries to clarify questions existing in PET/CT-navigated application.

Keywords: Positron emission tomography (PET); computed tomography (CT); lymphoma

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Introduction

Fluorine 18 fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET), and more recently PET-computed tomography (PET/CT) is a very useful and powerful tool in evaluating most lymphoma subtypes. Co-registering functional and morphologic data, this multimodality can accurately diagnose the lymphoma lesion, monitor the treatment response, and predict the prognosis (1). Nowadays, the National Comprehensive Cancer Network (NCCN) guidelines recommend the use of ^{18}F -FDG PET/CT for primary staging, early or final response evaluation, and prognosis in patients with lymphoma. Many risk-adapted therapies based on interim ^{18}F -FDG PET/CT have been currently carried out globally to improve the management and outcome of patients (2,3). However, the optimal application of ^{18}F -FDG PET/CT scans in lymphoma remains problematic because of several variables, such as the standardization of PET/CT interpretation, the meaning of positive PET results, and so on. Thus, the present article reviewed the last decade of publication concerning PET data in lymphoma patients,

selected key clinical trials, and discussed the new guidelines to provide an evidence-based approach for the utility of ^{18}F -FDG PET in staging, treatment planning, response assessment, and prognosis evaluation of these patients.

Mechanism of ^{18}F -FDG PET/CT

^{18}F -FDG is a surrogate biomarker for glucose metabolism *in vivo* and is the most commonly clinical used PET radiotracer (4,5). ^{18}F -FDG is transported into metabolically active cells via glucose transporter proteins, and subsequently phosphorylated in a manner similar to glucose. Phosphorylated ^{18}F -FDG cannot typically dephosphorylate and then trap in the cell (6). Numerous malignant tumors express higher numbers of specific membrane transport proteins, with greater affinity for glucose than normal cells, which permits increased glucose flow into the cancerous cells (7). The positron emitted from ^{18}F bumps into an electron in tumor cells, generates two 511 KeV photons (called the annihilation radiation) emitted in nearly opposite direction that are detected by the PET detector and reconstructed into a metabolic functional

Table 1 Standard protocol of ^{18}F -FDG PET/CT scan

| Parameter | Recommendation |
|---|--|
| Patient preparation | Fast overnight, or at least 6 hours No exercise previous to the exam Hydrate with >500 mL post-FDG injection Mild sedation as needed |
| Blood glucose | Not to exceed 200 mg/dL |
| Patient imaging | Regular scan: 60±10 min after ^{18}F -FDG injection Delay scan: 180 min postinjection of ^{18}F -FDG |
| Reconstruction | Three-dimension |
| Timing of PET scan | Pretreatment scans required if post-treatment to be performed within 2 weeks of therapy Post-treatment scans at least 6-8 weeks after chemo(immuno)therapy or 8-12 weeks after radiotherapy |
| FDG dose | 3.7-7.4 MBq/kg (0.1-0.2 mCi/kg) body weight, minimum 185 MBq |
| Acquisition | Base of skull to mid-thigh unless other areas of concern |
| ^{18}F -FDG, Fluorine 18 fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography. | |

imaging of malignant tumor. The low-dose CT images co-registered make the attenuation correction of metabolic imaging, and add the anatomic information *in vivo* in one scanning session. To date, the success of PET/CT in the oncology domain still relies on the use of ^{18}F -FDG, and some recommendation of conduct of ^{18}F -FDG PET/CT are listed in *Table 1* (5).

Histopathologic lymphoma subtypes

Since lymphomas are a heterogeneous group of neoplastic disease of lymphocyte origin, ^{18}F -FDG avidity of lymphoma lesion correlates better with the histopathologic subtype than with clinical characteristics (8). Most malignant lymphomas, such as HL, diffuse large B cell lymphoma (DLBCL), Burkitt, mantle cell lymphoma (MCL), are shown as generally moderate to high ^{18}F -FDG uptake with a sensitivity of 85-100% (*Table 2*). While, some indolent NHLs including marginal zone lymphomas (MZL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and lymphoplasmacytic lymphoma (LPL) have no established role for the clinical usefulness of ^{18}F -FDG PET because of the limited and variable ^{18}F -FDG-avidity (*Figure 1*). Most of T-cell origin lymphoma is FDG-PET avid, except for the Enteropathy-type T-cell lymphoma (67%) and primary cutaneous anaplastic large cell lymphoma (36%) (*Figure 2*) (8,10).

Several reports revealed the transformation rate from indolent lymphomas to aggressive NHL is about 3% per year, up to 15 years after diagnosis, in patients with

lymphoma. Despite their recognition and intensification of treatment, the prognosis is poor, with death within less than one year in most patients (11). ^{18}F -FDG PET/CT can reveal the suspicious sites of transformation due to the different avidity between the aggressive lymphomas and the indolent ones. The standardized uptake value (SUV) exceeding ten yields 80% certainty for the identification of aggressive behavior, particularly, in Richter's transformation for patients with CLL/SLL. These suspicious sites of transformation should be confirmed via the histopathologic biopsy (12).

Staging of lymphomas

^{18}F -FDG PET/CT has demonstrated a better and accurate diagnostic yield, with 97% of sensitivity and 100% of specificity, than contrast-enhanced CT (CECT), especially for normal-sized lymph nodes and extranodal sites (13-17). The finding of the multimodality can upstage the lymphoma (20% to 40% of patients) by detecting more avid-lesions than CECT; while it exhibits no pathological uptake of the morphological lesion identified by CECT, causing downstage of disease (5% to 15% of patients) (14). The current NCCN guidelines recommend initial/baseline PET imaging as an essential test in HL, DLBCL, acquired immune deficiency syndrome (AIDS) related B-cell lymphomas, and as a useful test in selected cases in follicular lymphoma (FL), MZL, MCL, but not recommend it in CLL/SLL because of low-to-moderate ^{18}F -FDG uptakes (18). CECT is still a powerful modality in evaluating no FDG-avid histologies, distinguishing bowels or vessels from lymphadenopathy,

| Table 2 The uptake of ¹⁸ F-FDG PET/CT of the different subtype of lymphoma (9) | | |
|---|------------------------|------------------|
| Type of lymphoma | % patients with uptake | Uptake intensity |
| Hodgkin's disease | | |
| Classical HD | 100 | High |
| Nodular HD with lymphocytic predominance | 100 | Moderate-high |
| Aggressive NHL | | |
| Diffuse large B-cell lymphoma | 97 | Moderate-high |
| Burkitt lymphoma | 100 | High |
| Peripheral T-cell lymphoma | 90 | Low-high |
| Anaplastic large T-cell lymphoma | 100 | High |
| Mantle cell lymphoma | 100 | Moderate |
| Indolent NHL | | |
| Follicular lymphoma* | 95 | Low-high |
| Lymphoplasmacytic lymphoma | 100 | Low-moderate |
| Marginal zone lymphoma, nodal | 100 | Null-high |
| marginal zone extranodal lymphoma (MALT) | 54 | Null-high |
| Small lymphocytic lymphoma | 83 | Null-high |
| Cutaneous anaplastic large T-cell lymphoma | 40 | Null-moderate |

*, take the cytological grade of follicular NHL into account, grade III follicular NHL is considered as aggressive, presenting moderate-high avidity for FDG. However, grades I and II (considered to be indolent) present low-moderate uptake. ¹⁸F-FDG, Fluorine 18 fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; NHL, non-Hodgkin lymphoma.

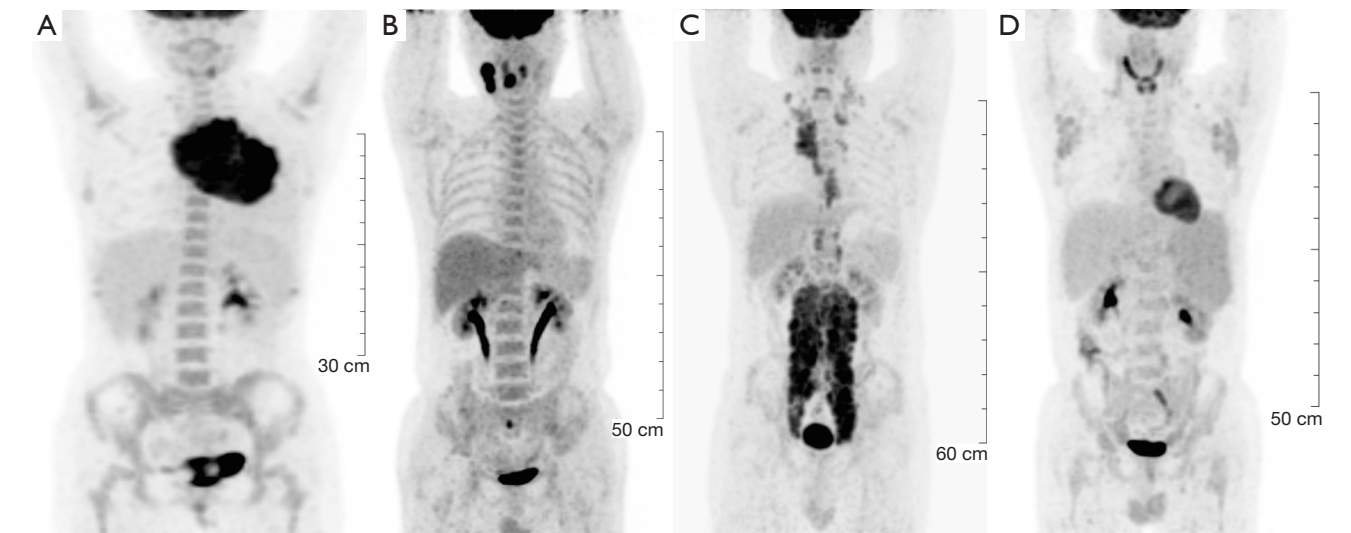


Figure 1 ¹⁸F-FDG PET/CT for the initial staging of lymphomas and different grades of FDG uptake according to histologic subtype. (A) A 23-year-old woman diagnosed with HD; (B) a 45-year-old male diagnosed with DLBCL; (C) a 52-year-old man diagnosed with FL; (D) a 48-year-old male diagnosed with SLL/CLL. ¹⁸F-FDG, Fluorine 18 fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; DLBCL, diffuse large b cell lymphoma; SLL, small lymphocytic lymphoma; CLL, chronic lymphocytic leukemia.

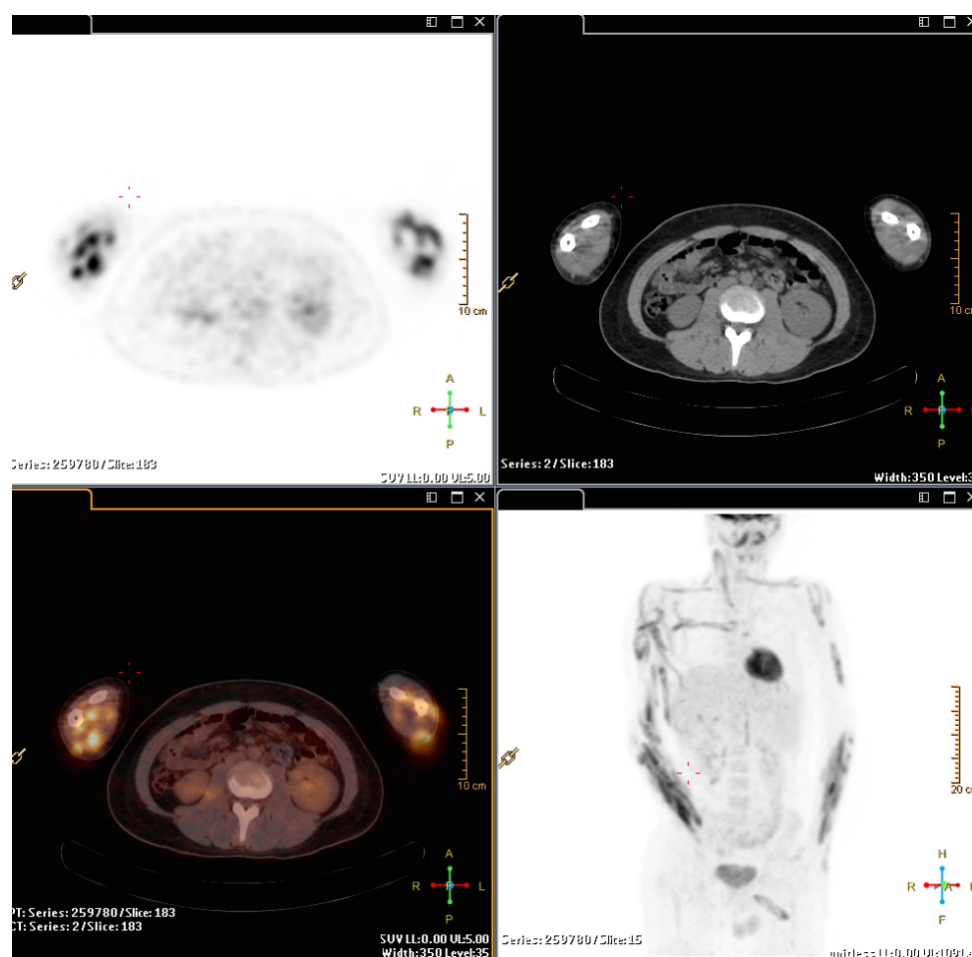


Figure 2 Primary cutaneous T-cell lymphoma. Axial PET and fused imaging shows multiple foci of abnormally high FDG uptake in muscles, while CT failed to show abnormal. PET, positron emission tomography; FDG, fluorodeoxyglucose; CT, computed tomography.

and in the setting of compression/thrombosis of mediastinal vessels. Because of the intense physiologic FDG uptake in the brain vortex, detection of intracranial lymphomatous involvement (especially leptomeningeal infiltration) is difficult. Moreover, steroid therapy, which is given to most patients with suspected brain involvement, may interfere with the uptake of FDG and possibly lead to false-negative results (19,20). Magnetic resonance imaging (MRI) is preferred to assess suspected central nervous system (CNS) involvement.

Even though the correction of the stage normally changes in the treatment of lymphoma (5-15% of patients), no evidence revealed that outcome is improved as a result of these data (21-23). However, improving staging accuracy ensures that fewer patients are undertreated or overtreated (24). ^{18}F -FDG PET/CT is particularly important for staging before consideration of radiation therapy.

The increased use of systemic and multimodality

approaches has made Ann Arbor stage less relevant in directing the choice of therapy (24). Thus, the Ann Arbor classification is recommended to modify for anatomic description of disease extent by the recent Lugano Classification. According to the revised staging system (Table 3), the patients with the primary nodal lymphoma can be divided into two categories, the limited stage (Ann Arbor stage I and II, nonbulky) and the advanced stage (stage III or IV). Stage II bulky disease is considered as the limited or advanced stage depended on the histology and several prognostic factors. The extranodal disease is only relevant for the limited stage, not for the advanced-stage, including a single extranodal lesion without nodal involvement and Stage II disease with direct extension to a non-nodal site. Now only patients with HL need be assigned the absent or presence of disease-related symptoms because treatment in HL is still directed by symptoms (24,25).

| Table 3 Revised Ann Arbor staging system (24) | | |
|---|---|--|
| Stage | Nodal | Extranodal |
| Limited | Lymph nodal groups on the same side of the diaphragm | Single extranodal lesion without nodal involvement or nodal lesions involving the contiguous extranodal tissue |
| II bulky | Limited stage with “bulky” disease | No applicable |
| Advanced | Lymph nodes group on the both side of the diaphragm; additional noncontiguous extralymphatic involvement | No applicable |

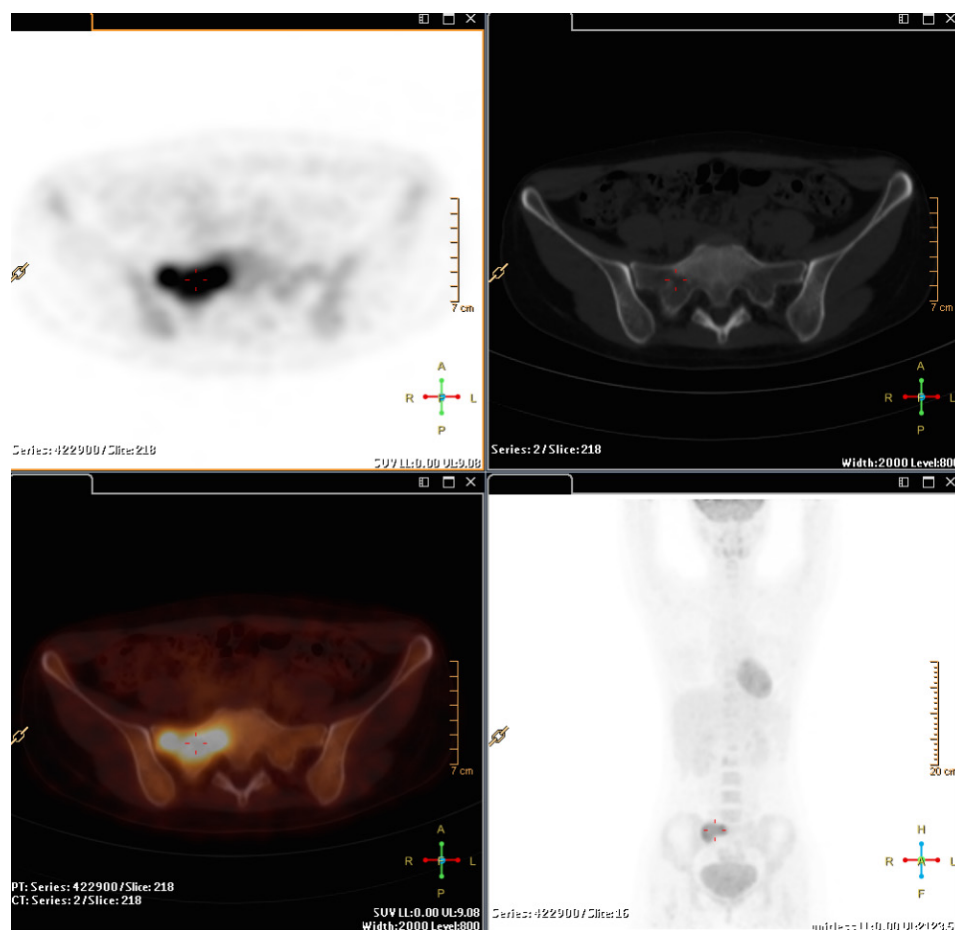


Figure 3 Sacrum involvement of primary diffuse large B-cell lymphoma with intense FDG activity. FDG, fluorodeoxyglucose.

Bone marrow involvement (BMI)

Routine bone marrow biopsy (BMB), usually sampled the posterior iliac crest, may not be representative of the whole disease involvement (26). ^{18}F -FDG PET/CT robustly detects BMI of whole body in lymphoma patients with avid lesions, especially those with a negative iliac crest BMB (*Figure 3*) (27). The sensitivity and positive predictive value (PPV) in detecting BMI are about 90% and 75%,

100% and 96%, respectively, in HL and DLBCL (28,29). The high sensitivity of ^{18}F -FDG PET/CT scans brought the debate whether the BMB could be obviated in FDG patients already undergone the scan (24). Many recent studies revealed that routine BMB added limited useful clinical information in newly diagnosed patients with HL and DLBCL staged by ^{18}F -FDG PET/CT scans, and the prognosis of these patients with systemic therapy is more

Table 4 Visual assessment of FDG PET/CT scans according to Deauville 5-point scale

| Score | Grade of uptake |
|-------|---|
| 1 | No uptake |
| 2 | Uptake \leq mediastinum |
| 3 | Uptake $>$ mediastinum and \leq liver |
| 4 | Uptake moderately increased above liver at any site |
| 5 | markedly increased uptake above liver and/or new sites of disease |

FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

related to early interim-PET activity than to the BMB result (29-32). Furthermore, patients with a positive BMB generally have other factors consistent with advanced stage or poor prognosis. Consequently, the Lugano Classification stated that a BMB is no longer required for the routine evaluation of patients with HL and aggressive NHL if an ^{18}F -FDG PET/CT is performed (24,25).

The sensitivity and specificity of ^{18}F -FDG PET/CT for detecting BM involvement in indolent lymphomas are 46% and 93%, respectively (28). Patients with most indolent lymphomas (especially SLL/CLL) may have high percentage of the absence of avidity or the diffuse uptake in the scan, and still need a BMB to detect the involvement of lymphoma.

Bulky lymphoma

The definition of bulky lymphoma is a single nodal mass of 6-10 cm, depended on the histology of lymphoma, or greater than a third of the transthoracic diameter at any level of thoracic vertebrae. The presence of bulky disease is considered a negative prognosis factor in early stage-HL but not in advanced HL. In DLBCL, bulk is predictive of inferior survival in favorable-prognosis disease but not in poor-prognosis disease, probably because the prognosis is determined by multiple adverse factors, not a single one, in the advanced lymphoma (25). However, none of the proposed sizes have been validated in the current therapeutic era; volumetric measurement for tumor bulk and total tumor burden, including methods combining metabolic activity and anatomic size or volume, may be a potential prognostic factor and worth the further investigation.

Response evaluation criteria

The most common anatomic imaging modality used for assessment of treatment response in lymphoma is CECT. The international prognostic index and the FL international prognostic index are currently used clinical prognostic indices for DLBCL and FL, respectively, and the International Prognostic Score is used for HL (33-36). It mainly base on a morphological evaluation with a reduction in tumor size, definitely cannot differentiate tumor from necrosis or fibrotic tissue, and result in false negative results.

^{18}F -FDG PET/CT imaging can provide the metabolic and morphological information of the lesion, and improve the capability of diagnosis and differentiation in the patients with lymphoma. Furth *et al.* reported in children with HL that ^{18}F -FDG PET/CT diagnosed an early response to therapy with a sensitivity of 100% and a specificity of 68%, and late response to therapy with 100% sensitivity and 78% specificity (37).

However, the definition of 'negative' or 'positive' of lesion are a matter of ongoing debate. There is variability in interpretation of PET scans among center or even within the same institution. In current clinical practice, visual inspection of ^{18}F -FDG PET or PET/CT images is usually adequate for image interpretation, especial for staging. However, if comparison of ^{18}F -FDG PET/CT images was obtained from different center, the final results will be profoundly influenced by many reasons, especially dada analysis method. To standardize the interpretation criteria and make rigorous quality control, the International Harmonization Project (IHP) subcommittee developed consensual criteria of the imaging interpretation for lymphoma, which was set the mediastinal blood pool uptake as a reference background to define FDG PET/CT positivity for a residual mass of 2 cm and greater (38). Although the IHP criteria are useful for the analysis at completion of therapy, it is preferable to have a higher level of uptake (such as liver) as background reference for interim FDG PET/CT because of false-positive rate.

Further refinement of the evaluation criteria led to the Deauville criteria, which have been initially proposed for the assessment of ^{18}F -FDG PET/CT imaging after one or more cycles of therapy (Table 4). The criteria use a five-point scale to determine the FDG uptake in the involved sites relative to that of the mediastinum and the liver (39). ^{18}F -FDG PET scans with scores 1-2 were considered negative; scores 4-5 were considered positive (Figure 4). Normally, score 3 is considered negative, while it's better

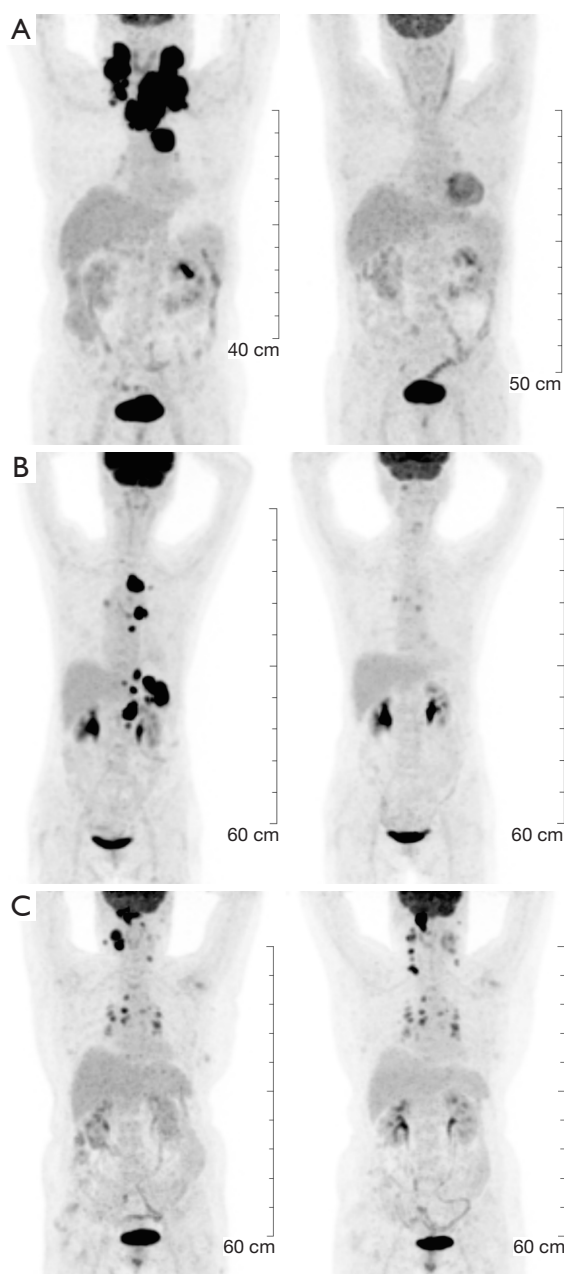


Figure 4 ^{18}F -FDG PET/CT for the evaluation of response to treatment. (A) Pretreatment and example of score 1: complete metabolic response with no uptake in both cervical-supraclavicular nodes with the normal size (nonspecific uptake of bilateral cleidomastoid muscles); (B) pretreatment and example of score 4: residual uptake of intensity > liver in residual mediastinal mass; (C) pretreatment and example of score 5: residual uptake in necks, supraclavicular sites, and mediastinum with intensity markedly higher than normal liver. ^{18}F -FDG, Fluorine 18 fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

to be a threshold for positivity for de-escalation of therapy based on interim PET scan. The criteria have been validated in international multicenter trials for ^{18}F -FDG PET/CT-guide interim response assessments, and the recent NCCN guidelines have set the criteria as standard protocols for the interpretation of the interim and end-of-treatment in HL patients (40,41). Also, these criteria are agreeable for interpreting therapy responses in DLBCL and FL (42-44).

Semi quantification of FDG uptake using the maximum SUV (SUV_{max}) at baseline and midtherapy allows evaluation of the lymphoma metabolic changes during induction treatment, so percentage change in the SUV_{max} ($\Delta\text{SUV}_{\text{max}}$) in tumor before and after treatment has been adopted as an interpretation criteria to reduce false-positive of interim PET/CT and to improve prognosis value in NHL. Receiver operator curve in patients with DLBCL identified optimum thresholds for $\Delta\text{SUV}_{\text{max}}$ as 66% for predicting event-free survival (EFS) in retrospective studies (45-47). Even though many studies accepted 66% as the threshold, the reported cut-off values of $\Delta\text{SUV}_{\text{max}}$ range from 66% to 91%, suggesting that consistency in scanning protocols, matching conditions for serial scans, and proper calibration and scanner maintenance are mandatory for general application (25,47-49). No validated cut-off value was reported yet.

The metabolic tumor volume (MTV), as a reflection of the disease burden and prognostic factor, is measured on ^{18}F -FDG PET/CT images by the select tumor lesion with uptake above SUV_{max} 2.5 or using a threshold of liver or mediastinum as a reference organ. Some researches were performed in patients with DLBCL and extranodal natural killer/T cell lymphoma (ENKTCL) (50-52). The total lesion glycolysis (TLG) is also an accurate volume measure to determine disease burden by accounting for the tumor volume and intensity using sophisticated software systems (53,54). These automated volumetric methods may possess better prognosis values, and is one of future directions investigated in patients undergoing interim PET.

End-of-treatment ^{18}F -FDG PET/CT

End-of-treatment FDG PET/CT is used to evaluate the efficacy and monitoring of residual tumor, and to provide the basis for selecting treatment with or without high intensity chemotherapy, radiotherapy or transplantation (55,56). The sensitivity and specificity of ^{18}F -FDG PET/CT for follow-up HL patients were reported to be 94% and 100% and for NHL patients 90% and 88%, respectively.

Patient with negative ^{18}F -FDG PET/CT has an excellent prognosis in posttreatment follow-up, in contrast to a positive scan where the risk for disease to relapse increases. Spaepen *et al.* reported that 56 of 67 NHL patients with negative ^{18}F -FDG PET/CT scan after first-line chemotherapy remained in complete remission (CR) at a median follow-up of 653 days compared to all 26 patients with positive ^{18}F -FDG PET/CT scan who experienced relapse at a median of 73 days (57). In HL patients, several studies demonstrate significantly shorter progression-free survivals (PFS) for PET-positive patients (0-4%) compared with 85-95% for those with a negative scan (1,58-61). However, the therapeutic responses of some indolent lymphomas, such as SLL/CLL, should still be assessed in terms of anatomical relief because of variable or no FDG uptake (38,62).

A complete metabolic response (CMR) represents a good indicator of clinical CR (cCR) leading to less intense therapy or only routine surveillance, whereas persistent abnormal ^{18}F -FDG uptake in residue require a clinical decision whether continuing or switching therapy or considering stem cell transplantation. It is necessary and important to make the histopathological confirmation of positive PET finding before further treatment.

To avoid equivocal interpretation, the scan should ideally performed 6-8 weeks, or at least 3 weeks, after completion of chemotherapy and 8-12 weeks after radiation therapy because of radiation-induced hypermetabolic inflammatory changes (55). Some physiologic uptake often occur after treatments, such as reactive diffuse bone marrow hyperplasia and diffuse splenic uptake (typically 2-4 weeks after therapy); an intense bone marrow hyperplasia after the administration of marrow-stimulating factors; thymic hyperplasia in children and adolescents (2-6 months post-therapy persisting for up to 12-24 months).

Response evaluation during therapy

^{18}F -FDG PET/CT imaging can sensitively detect the metabolic changes of tumor as early as several days after the therapy, and has been recognized as a surrogate marker of chemosensitivity and prognosis (Figure 4) (63-66). In a meta-analysis, interim ^{18}F -FDG PET/CT yielded an overall sensitivity of 81% and a specificity of 97% for advanced-stage HL, and a sensitivity of 78% and a specificity of 87% for DLBCL (67).

Gallamini *et al.* reported the predictive value of ^{18}F -FDG PET/CT scan in HL patients posttreated with two cycles

of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). The data showed the 2-year probability of failure-free survivals for PET-2 negative and for PET-2 positive patients were 96% and 6%, respectively (66). The German Hodgkin Study Group (GHSG) evaluated ^{18}F -FDG PET/CT after four cycles of escalated or every-14-day bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) chemotherapy in 50 patients with advanced-stage HL and found an NPV of 97%, allowing omission of radiotherapy in 36 patients, none of whom experienced progression. Of the 14 with a positive scan, seven underwent radiotherapy (a PPV of only 14%), and no difference in PFS was found between the PET-negative and PET-positive groups (68). More recently, the best predictive value for interim PET imaging was reported by Zinzani *et al.* in a retrospective study (n=304) on a subgroup of 147 I-IIA HL patients treated with standard therapy followed by IFRT (69). They found that 97.6% of patients with a negative PET-2 result were in continuous CR (CCR) (median follow-up, 45 months) whereas only 21% of PET-2-positive patients had a CCR (median follow-up, 28 months). The 9-year PFS for PET-2-negative and PET-2-positive patients were 95% and 31% respectively.

However, in an analysis of early-stage HL, Hutchings *et al.* reported a PPV for interim ^{18}F -FDG PET after 2-3 cycles of ABVD chemotherapy of only 30% whereas the NPV was maintained at 95% (3). In this group, the 2-year PFS in the interim PET-negative and PET-positive patients were 97-100% and 70-80%, respectively. Barnes *et al.* showed that interim PET did not predict outcome in ninety-six patients with nonbulky limited-stage HL patients, with PFS in positive and negative patients 87% *vs.* 91%, respectively, whereas the end-of-treatment PET result was predictive of outcome, with a PFS of 94% for PET-negative *vs.* 54% for PET-positive patients (70). More results revealed that the role of FDG-PET in the prediction of ultimate outcome is clearer in advanced-stage than early stage HL (1,71,72).

The interim PET/CT scan can predict the outcome of patients of NHL undergoing the systematic chemotherapy, but the prognosis value is somewhat less convincing than that of HL (73). Initial retrospective studies in DLBCL suggested a difference in outcome for patients with positive and negative findings on interim PET (64,74), while more recent studies have demonstrated good NPV but more variable PPV. PFS for the PET-positive groups has ranged from 18% to 74% (1,25). The difference in PET results may be related to evaluating criteria, variable duration

of follow-up, patient populations, and different types of treatment adapted, different number of chemotherapy cycles, and timing of scanning during the chemotherapy cycle, and so on. The lower PPV is partial related to the higher risk of infections among patients treated with higher dose-density and intensity strategies and among typically older patients. In addition the use of rituximab may produce a high incidence of false positive results by inducing an inflammatory response by activation of antibody dependent cellular cytotoxicity and complement dependent cytotoxicity. Moskowitz *et al.* treated 98 patients with DLBCL using a dose-dense R-CHOP-like regimen, with ^{18}F -FDG PET/CT after four cycles. The biopsy data of FDG-positive residue proved 87% of patients were false positive. PFS of interim PET-positive/biopsy-negative patients was identical to that in patients with a negative interim PET scan (73).

The use of quantitation to improve on visual assessment has been explored in DLBCL. Lin *et al.* assessed the prognostic value of early ^{18}F -FDG PET/CT in 92 patients with DLBCL with the $\Delta\text{SUV}_{\text{max}}$ criteria, and yielded an accuracy of 76.1% to predict event free survival (EFS). The 2-year estimate for EFS was 21% in patients with SUV_{max} reduction $\leq 65.7\%$ compared with 79% in those with reduction $>65.7\%$ (45). Now, the $\Delta\text{SUV}_{\text{max}}$ criteria are being prospectively applied in several multicenter studies exploring response-adapted treatment with immunochemotherapy. Changes in the MTV and TLG are additional exploratory quantitation measures. However, some preliminary reports have suggested changes in the MTV and TLG are not predictive in DLBCL.

Since several criteria exist in the response evaluation system, it will definitely affect the prognosis value of ^{18}F -FDG PET/CT in patients with NHL. Many researchers suggested that the prospective studies should be performed in homogenous populations receiving the same treatment to determine the optimal one (75). Itti *et al.* and Casasnovas *et al.* compared the Deauville criteria and $\Delta\text{SUV}_{\text{max}}$ criteria for assessing the prognostic value of interim PET/CT in DLBCL, and results showed that $\Delta\text{SUV}_{\text{max}}$ leads to slightly better performance and interobserver reproducibility than the Deauville criteria (42,47). While, Manohar *et al.* insisted that 5-point scale is preferentially over other criteria because of simplicity in interpretation and reproducibility when assessed end-of-treatment ^{18}F -FDG PET/CT in 69 patients with aggressive NHL (61). More investigation need to be explored in the future's clinical trials. Anyway, standardization of PET

methods is mandatory for the use of quantitative approaches and desirable for routine clinical practice.

PET-directed treatment

To date, there is no direct evidence that altering therapy on the basis of interim PET findings improves patient outcome. More the 80-90% of early-stage lymphoma patients are cured with standard therapy. However, a substantial number of early-stage lymphoma patients are subject to some amount of overtreatment, and this is an argument for using early PET/CT to identify good-risk, early-stage patients eligible for less-intensive treatment. Multiple PET-directed randomized studies were initiated to determine the outcome of therapy de-escalation in patients who achieve an early CR as well as escalation in non-responding patients. But only few have reported interim results. The Hay *et al.* investigated the prognosis of patients, with nonbulky stage IA-IIA HL, treated with combined modality therapy (CMT) using ABVD plus radiotherapy, or ABVD alone. The results showed that 8-year PFS was 87% and overall survival 96% in patients who achieved CR/unconfirmed complete response (CRu) after two cycles of ABVD. In contrast, among those without CR/CRu after two cycles of ABVD, 8-year PFS was 88% and overall survival 95% (76). In the HD15 trial of the GHSG, a subset of 69 HL patients (stages IIB, III, IV) with a large mediastinal mass or extranodal disease were treated with either 8 or 6 cycles of escalated BEACOPP or with 8 cycles of BEACOPP14. Those with a residual mass of at least 2.5 cm underwent an ^{18}F -FDG PET/CT scan. Patients with a negative study were not further treated, whereas those with a positive scan received involved field radiation. The frequency of consolidative radiotherapy was only 11% compared with 70% in prior studies antedating the use of PET scans, with no difference in overall survival (1,77).

Kasamon *et al.* used a risk-adapted approach in 59 newly diagnosed patients with various histologies of aggressive NHL. ^{18}F -FDG PET/CT was performed after two to three cycles of therapy. Of those 33 patients, 28 underwent ASCT and experienced a 2-year EFS of 75% (67% for all PET-positive patients), which was better than the anticipated 20% that was based on historical controls (78). Mostly recently, a phase II clinical trial was conducted by using interim PET as a guide to risk-adapted therapy in high-risk patients with newly diagnosed DLBCL (79). Patients achieving negative FDG-PET continued receiving three additional cycles of R-MegaCHOP (rituximab,

cyclophosphamide, doxorubicin, vincristine, prednisone), whereas PET-positive patients received two courses of R-IFE (rituximab, ifosfamide, etoposide) followed by BEAM (BCNU, etoposide, cytarabine, melphalan) and autologous stem-cell transplantation. Patients in CR after interim PET had significantly better 3-year PFS than those with partial response (81% *vs.* 57%) but not a statistically significant longer OS. Three-year PFS (81% *vs.* 33%) and OS (95% *vs.* 33%) were significantly better for negative than for positive interim PET patients.

In summary, on the basis of the available data, midtreatment clinical trials addressed important clinical questions and should not be performed as standard practice yet.

Surveillance ¹⁸F-FDG PET/CT scan

The utility of ¹⁸F-FDG PET/CT in the follow-up is not recommended because the published data failed to prove its clinical value (80,81). More than 60% of relapses of patients with HL and aggressive NHL were diagnosed clinically, especially in aggressive NHL in cases with extranodal involvement. Jerusalem *et al.* showed doubtful cost-benefit profitability of follow-up with ¹⁸F-FDG PET/CT since the appearance of an important number of false positive required the performance of complementary tests to determine possible relapse (82). Meanwhile, the false-positive result of ¹⁸F-FDG PET/CT scan may cause possible and unnecessary radiation exposure and patient anxiety. In clinic, CECT and laboratory examinations, such as serum lactate dehydrogenase, are recommended to follow up the relapse of lymphoma. The frequency of examinations depends on the histologies. For example, patients with HL or DLBCL should visit hospital every 3 months during the first 2 years, to every 6 months for the next 3 years, and then annually thereafter to monitor for late relapse and treatment-related adverse effect; while patients with FL should be observed every 3 to 6 months (24). When patients are suspicious of the relapse of lymphoma, ¹⁸F-FDG PET/CT scan should be performed at the first instance.

PET/CT in stem cell transplantation

Compare to standard chemotherapy, treatment with high doses of chemotherapy followed by stem cell transplantation offer long-term disease free survival in more than 50% of transplanted patients (83). ¹⁸F-FDG PET/CT has demonstrated to be an effective tool to differentiate between responders and non-responders to this treatment,

with a sensitivity of 69% and a specificity of 81% (84). In addition, PET-positive prior to transplantation was associated with a 3-fold greater risk of progression and a 4-fold greater risk of death than patients presenting a negative result in the functional study (85,86). Qiao *et al.* noted that post-transplantation PET/CT scan might also be considered as a prognostic factor in terms of survival comparing to pre-transplantation scan (87).

Conclusions

¹⁸F-FDG PET/CT scan has become an important part of the management of lymphoma, and been recommended for staging, detection of recurrence, evaluation of response to treatment, and prediction of response in patients with lymphoma due to the high sensitivity and specificity rates. Even though an interim PET scan possesses the predictive value, its role in directing treatment remains investigational. Any alteration during the treatment should be confirmed by the biopsy.

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