FDG-PET Imaging for Hodgkin Lymphoma: Current Use and Future Applications

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Abstract: A significant amount of data has been published over the past decade regarding the clinical utility of F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the diagnosis and management of Hodgkin lymphoma (HL). This includes studies examining interim FDG-PET, which has been shown to be a strong tool for predicting relapse and survival, especially in advanced-stage HL. Despite progress, a number of questions remain regarding the precise role and value of FDG-PET in the diagnosis, risk stratification, and management of HL. These questions include the need for concomitant contrast enhanced computed tomography with FDG-PET, reproducibility and interpretability of FDG-PET, optimal imaging for the treatment surveillance of HL following definitive treatment, and the use of FDG-PET for patients with relapsed/refractory disease, including stem cell transplantation. In this review, these issues are critically examined and the study designs and results of observational and prospective FDG-PET response-adaptive clinical trials in HL are described in detail. In addition, novel techniques and future applications of FDG-PET, such as metabolic tumor volume, tumor proliferation via 3′-deoxy-3′-18F-fluorothymidine, and integrated PET/magnetic resonance imaging are discussed.

Introduction

New treatment paradigms have been developed over the last several decades in Hodgkin lymphoma (HL). Staging of HL remains a critically important component of the management of patients. The widely used Ann Arbor staging system relies primarily on computed tomography (CT)-based evaluation, which was incorporated in the Cotswold's recommendations in 1989.[1] There are a number of limitations of CT imaging, which include understaging or overstaging in an appreciable number of cases.[2-6] Functional imaging has been utilized, in particular F-fluorodeoxyglucose positron emission tomography (FDG-PET), as a complementary tool in the management of HL patients. Several studies have shown that FDG-PET more accurately identifies the correct pretreatment stage in HL compared with

contrast-enhanced CT (CECT). Furthermore, FDG-PET is able to distinguish viable/active tumor cells from fibrosis or necrosis in a residual mass after treatment.

The great majority of patients with HL will achieve complete remission (CR) and cure; however, a subset of patients will experience relapse and ultimately die of the disease. Efforts have been made to identify high-risk groups earlier in the disease course in order to institute modified and/or intensified therapy, which could theoretically improve outcomes. In contrast, significant efforts recently have been made to decrease the amount and type of therapy for patients in order to mitigate acute and long-term treatment-related toxicities, which remain problematic in the treatment of HL. Contemporary clinical trials have begun to examine these questions through the use of response-adapted treatment strategies that harness the results of interim FDG-PET.

Numerous studies have been published over the past decade regarding the clinical utility of FDG-PET in the diagnosis and management of HL. Despite progress, a number of questions remain regarding the precise role and value of FDG-PET in the diagnosis, risk stratification, and management of HL. This includes the need for concomitant CECT and FDG-PET, the reproducibility and interpretability of FDG-PET, and the use of FDG-PET in patients with relapsed/refractory disease, including stem cell transplantation (SCT). These issues are examined in this review, along with the details of observational, completed, ongoing FDG-PET adaptive clinical trials. In addition, the novel techniques and future applications of FDG-PET are discussed.

The Impact of PET/CT on Staging

A multitude of FDG-PET studies have been conducted in HL.[3-9] A meta-analysis demonstrated that FDG-PET leads to more accurate staging compared with CECT; the median sensitivity and specificity of FDG-PET were found to be 93% and 88%, respectively.[7] More recent data have further proven the superior sensitivity of FDG-PET, which is achieved without diminished specificity.[4]

FDG-PET/CT as a Potential Replacement for CECT Staging. Imaging with both CECT and low-dose FDG-PET/CT is often done for HL patients. It is not clear, however, whether a combination of these modalities provides additional benefit vs FDG-PET/CT alone. Moreover, this approach increases patient radiation exposure by 1.5- to 2-fold.[10] At initial staging, FDG-PET/CT is a highly sensitive modality and detects more disease sites than CECT in 25% to 30% of the HL cases.[3-9] Several studies have reported that the sensitivity of FDG-PET/CT is superior to CECT for both nodal disease (92% -94% vs 83%-88%) and extranodal disease (73%-88% vs 37%-50%).[4,9] In a systematic review, Kwee and coinvestigators noted that the sensitivity and specificity in the initial staging of lymphomas were 88% and 100%, respectively, for FDG-PET, vs 88% and 86% for CT.[11] Despite its high sensitivity, FDG-PET upstages disease from early to advanced stage in only 10% to 15% of patients in whom treatment is modified.[3-5,8,9,12-15] It is not universally accepted that FDG-PET/CT can easily replace CECT for staging, in part owing to concerns about expense and an unknown survival benefit yielded from detection of additional disease sites.

PET/CT in Association With Staging CECT. It can be argued that the addition of CECT to FDG-PET/CT imaging improves HL outcomes. Several series have disputed the benefit of the addition of CECT to FDG-PET/CT in HL, whereas there is substantial evidence that FDG-PET/CT findings result in a management change in almost half of the cases.[16-18] Only 1 study suggested a marginal survival benefit with simultaneously acquired CECT and FDG-PET/CT compared with each test alone (event-free survival, 95% vs 81%; P=.002).[17] However, the results of this study have not been reproduced in larger series, and definitive proof of a survival benefit is currently lacking.

Available data that show significant differences for the use of FDG-PET/CT combined with CECT are minimal. It may be reasonable to avoid CECT in patients with primary chest involvement, whereas a combined FDG-PET and CECT may be preferred in cases with abdominal and pelvic involvement. CECT may identify additional findings with respect to visceral organs, such as the liver, pancreas, and bowel. It can also help distinguish lymph nodes from bowel loops and other vasculature,[9,16,18-21] thus improving lesion detection and characterization in patients with abdominal/pelvic disease.[9,16,20] Further consideration for the use of both FDG-PET and CECT includes patients who are to undergo radiation therapy for planning purposes. Some centers acquire a CECT in the same session as the FDG-PET/CT to allow the companion CT to be diagnostic and to avoid a repeat examination. This approach would seem to be the most practical practice from the standpoint of time and radiation exposure. Furthermore, the tumor standardized uptake value (SUV) overestimation that would arise from overcorrection of attenuation maps by the intravenous contrast is reportedly insignificant.[17,22-24]

Nodular Lymphocyte-Predominant HL. Nodular lymphocyte-predominant HL is an uncommon HL subtype that accounts for approximately 5% to 10% of HL cases. Patients usually present with supradiaphragmatic early stage HL, and extranodal involvement is rare. In a preliminary study, FDG-PET/CT imaging showed similar trends, detecting approximately 30% more disease

sites compared with CECT.[25] In this study, FDG-PET led to upstaging in 7 of 31 patients, and changed radiation fields in 3 patients.

FDG-PET for Extranodal Disease. The most common extranodal sites involved in HL are the bone marrow and the spleen. Bone marrow involvement indicates stage IV disease and significantly changes disease management.[26] Bone marrow biopsy is the mainstay for the detection of bone marrow involvement despite the inaccuracy rate for focal infiltration distal to the biopsy site. Notwithstanding the superior sensitivity of magnetic resonance imaging (MRI), it is not practical to routinely assess the entire bone marrow, given the time needed and the cost. FDG-PET/CT imaging is able to detect focal bone marrow involvement.[4,27] Diffusely increased bone marrow uptake, however, is nonspecific and can be observed in cases with reactive bone marrow hyperplasia induced by erythropoietin or colony-stimulating factors.[27] In a systematic review of 32 studies, FDG-PET/CT was found to have a high pooled sensitivity and specificity—92% and 90%, respectively—compared with corresponding values of 90% and 76% for MRI.[28] The sensitivity in FDG-PET/CT studies, however, was highly heterogeneous, which affected the diagnostic value of FDG-PET/CT in diagnosis of bone marrow involvement in lymphoma. Nonetheless, FDG-PET/CT data should be compared with that of whole-body MRI rather than to limited-field MRI, which offers an advantage to FDG-PET/CT imaging. A recent study of 454 HL patients with a staging bone marrow biopsy and FDG-PET/CT showed no value of routine bone marrow biopsy when FDG-PET/CT was used as a staging tool.[29] Consequently, although a consensus is yet to be established, there should be consideration of FDG-PET/CT as the first test to be pursued in staging HL. In those cases with a PET-positive bone marrow finding, bone marrow biopsy should be pursued for confirmation if the therapy decision is likely to be influenced.

Approximately one-third of patients with lymphoma have splenic involvement regardless of its size, whereas only up to 10% HL patients have hepatic involvement.[30] The sensitivity and specificity of FDG-PET/CT in the detection of splenic involvement by lymphoma exceed that of CECT, at greater than 90%.[31] In a recent prospective study, 3 times more patients were found to have hepatic and splenic involvement when FDG-PET/CECT was performed compared with staging using each test alone.[31]

Influence of Staging FDG-PET on HL Management. Upstaging of HL from early to advanced stage is of clinical consequence, owing in part to the significant change in therapeutic plans from short courses of chemotherapy or combined-modality therapy to more extended courses of chemotherapy with or without radiation therapy. Recently introduced sophisticated radiotherapy techniques may decrease therapy-related complications. The frequent involvement of the mediastinum in HL patients, however, makes it difficult to completely avoid radiation exposure to the heart, great vessels, and breasts. Therefore, the accuracy of staging plays a significant role in enabling decisions to either reduce the intensity of therapy or omit radiotherapy in low-risk, limited-stage patients, or to escalate therapy in high-risk, advanced-stage patients. Furthermore, staging FDG-PET/CT provides a baseline scan against which subsequent scans can be compared; this is important in light of the recent trends toward therapy deintensification, which requires more accurate information on anatomic disease extent. Better definition of involved sites is even more important in the setting of involved-field and involved-node radiotherapy planning in HL.[6,25,32]

Risk Stratification

Limited-Stage HL: Clinical Definition/Stratification. Limited-stage HL is frequently subdivided into "favorable" and "unfavorable" (or intermediate) early-stage disease based on the presence or absence of several adverse prognostic factors (Table 1). This has been especially important for the design and interpretation of homogenous patient populations in large, prospective clinical trials. As detailed in Table 1, the German Hodgkin Study Group (GHSG) and the European Organization for Research and Treatment of Cancer (EORTC) differ slightly; EORTC considers age 50 years or older a risk factor for unfavorable disease and GHSG considers extranodal disease to be a risk factor. Additionally, EORTC considers having more than 4 involved nodal regions to be a risk factor, whereas GHSG sets the cutoff at 3 or more involved nodal regions.[33-36]

The National Cancer Institute of Canada (NCI-C) and the Eastern Cooperative Oncology Group (ECOG) subdivided patients into risk categories with "low risk" and "high risk" in a prior randomized early-stage HL trial.[37,38] The classification incorporated histology and utilized a low age cutoff (ie, age 40 years). In the GHSG, all disease that is stage III or IV, or is stage IB to IIB with bulky mediastinal mass or extralymphatic extension of the disease, has been designated as "advanced stage." More recently, the North American and United Kingdom groups have combined all early-stage patients into a single category, singling out only "bulky disease" as an adverse risk factor.

Advanced-Stage HL: Is IPS a Good Risk Stratification System in The Current Era? An international effort involving more than 5000 HL patients treated prior to 1992, led by Hasenclever and Diehl, identified clinical adverse prognostic factors for advanced-stage HL.[39] Seven prognostic factors were recognized on multivariate analysis, each of which contributed approximately a 7% reduction in freedom from

Table 1. Clinical Risk Stratification of Early-Stage Hodgkin's Lymphoma, by Research Group

Clinical Risk Factors		
GHSG	**EORTC/GELA**	**NCI-C/ECOG[b]**
Large mediastinal mass	Large mediastinal mass	Bulk >10 cm or ≥1/3 chest wall diameter
Elevated ESR[a]	Elevated ESR[a]	Elevated ESR[a]
3 or more involved nodal regions	4 or more involved nodal regions	4 or more involved nodal regions
Extranodal disease	Age ≥50 years	Age ≥40 years
—	—	MC or LP histology
Early-stage, favorable: I-II with no risk factors Early-stage, intermediate: I-IIA with 1 or more risk factors or I/IIB with elevated ESR and/or 3 or more involved nodal regions Advanced stage: III/IV or I/IIB with large mediastinal mass and/or extranodal disease	Early-stage, favorable: I-II (supradiaphragmatic only) with no risk factors Early-stage, intermediate: I-II (supradiaphragmatic only) with 1 or more risk factor Advanced stage: III/IV	Early-stage, favorable: I-II (supradiaphragmatic only) with no risk factors Early-stage, intermediate: I-II (supradiaphragmatic only) with 1 or more risk factor Advanced stage: III/IV

[a] ESR: ≥50 mm per hour without B-symptoms or ≥30 mm per hour with B-symptoms.
[b] Low-risk patients excluded from early-stage studies (ie, stage IA with a single node and all of the following: LP or NS histology, bulk <3 cm, ESR <50 mm per hour, disease involving high neck or epitrochlear only).
ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; LP, lymphocyte predominant; MC, mixed cellularity; NCI-C, National Cancer Institute Canada; NS, nodular sclerosis.

progression at 5 years: stage IV disease, male sex, age greater than 45 years, hemoglobin less than 10.5 g/dL, white blood cell count greater than 15,000 per µL, lymphocyte count less than 600 per µL, and albumin less than 4 g/dL (Table 2). More recently, the British Columbia Cancer Agency (BCCA) analyzed 740 HL patients to reexamine the prognostication of the International Prognostic Score (IPS) in a modern cohort (most patients were treated after 1990). Although the IPS was still prognostic for freedom from progression (P<.001) and OS (P<.001), the survival rates between low- and high-risk groups were much narrower compared with the initial IPS data (ie, 5-year OS rates ranged from 73% to 98% for patients aged <66 years). Thus, in the modern era, better prognostic models and analytic tools are needed to predict HL outcomes.

Table 2. International Prognostic Score for Advanced-Stage Disease: Original Hasenclever and Diehl Model and Recent Prognostic Analysis by the British Columbia Cancer Agency (BCCA)

Number of Risk Factors[a]	Percent of Population: Original (BCCA)	Freedom From Progression at 5 Years: Original (BCCA)
0	7 (8)	84 (88)
1	22 (26)	77 (85)
2	29 (26)	67 (80)
3	23 (21)	60 (74)
4	12 (12)	51 (67)
5+	7 (7)	42 (62)

[a]Risk factors: stage IV disease; male sex; age >45 years; hemoglobin <10.5 g/dL; white blood cell count >15,000/µL; lymphocytes <8% or absolute lymphocyte count <600/µL; albumin <4 g/dL.

Prediction of Response to Therapy

FDG-PET/CT Interpretation Criteria. Because of the nonspecific nature of low- to moderate-grade residual uptake within a tumor mass during therapy, the interpretation of FDG-PET/CT images has undergone an evolutionary period to increase the specificity of FDG-PET/CT readings.[40-42] The first standardization initiative was adopted in 2007 for the end-of-therapy FDG-PET/CT interpretation by the imaging subcommittee of the International Harmonization Project (IHP) in Lymphoma.[43,44] According to these criteria, uptake greater than that seen in the mediastinal blood pool in residual masses measuring 2 cm or larger was considered positive for residual lymphoma (Figure 1). The addition of FDG-PET/CT imaging to the evaluation algorithm used after therapy eliminated the CR/unconfirmed response category by enhancing the ability to differentiate between patients attaining a complete or partial remission and those with stable or progressive disease. These criteria, however, were based on a retrospective study of 54 diffuse large B-cell lymphoma patients treated with an anthracycline-based regimen[45] and were not validated in HL multicenter studies. Moreover, these criteria were not recommended for interim FDG-PET/CT evaluation

Deauville 5PS Criteria (interim PET)

Negative Scan
Score 1: no uptake
Score 2: uptake ≤mediastinum
Score 3: uptake >mediastinum but ≤liver

Positive Scan[a]
Score 4: moderately ↑ uptake >liver
Score 5: markedly ↑ uptake >liver

IHP Criteria (End-Therapy PET)

Positive Scan
Uptake >mediastinal blood pool in residual masses measuring >2 cm

Uptake >background in lymph nodes measuring <2 cm

Figure 1. The Deauville 5 point system (5PS) criteria for interpretation of interim F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) studies (top panel), and the interpretation for end-therapy FDG PET/CT studies recommended by the International Harmonization Project (IHP) for response criteria in lymphoma (lower panel).

[a] A Deauville score >3 is most optimal for advanced-stage interim PET to increase PPV, whereas a cutoff <3 is desirable for limited-stage HL in order to enhance NPV.

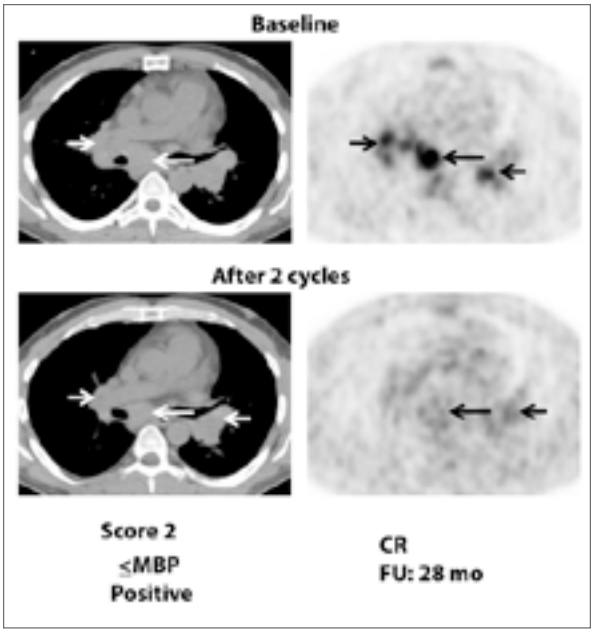

Figure 2. A 45-year-old man with classical Hodgkin lymphoma underwent F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) for staging and after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) to evaluate for response to therapy. At baseline (upper panel), axial FDG-PET/CT images demonstrate multiple prominent lymph nodes in the subcarinal and bilateral hilar (arrows) with increased FDG uptake, consistent with lymphoma involvement. After 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD; lower panel), axial FDG-PET/CT images demonstrate FDG uptake in the corresponding regions (arrows) that equals that seen in the mediastinal blood pool. This qualifies for a score of 2 by Deauville 5 point system criteria. These findings are consistent with complete response (CR). Note the residual posttherapy masses in the respective regions.

FU, follow-up; MBP, mediastinal blood pool; mo, months.

because in this setting, a higher cutoff is preferable given that the goal is to measure chemotherapy sensitivity rather than response during therapy.[46-49] Setting the threshold at the level of mediastinal blood pool activity may lead to an unacceptable rate of false-positive results.[50] A high positive predictive value (PPV) using a higher cutoff (eg, liver uptake) may be preferred for interim assessment of response. Furthermore, a better fit for measuring the response as a continuous variable would be a categorical scoring system, such as the Deauville 5 point system (5PS), rather than a dichotomous data set (Figure 1). A high PPV using a higher cutoff (eg, liver uptake) may be preferred for therapy intensification to minimize overtreatment and toxicity, whereas a high negative predictive value (NPV) using a lower cutoff (eg, mediastinal blood pool) can be used to decrease the intensity of therapy in order to prevent undertreatment. To satisfy this need, Deauville 5PS was proposed to serve as a categorical reading scheme that is suitable for different positivity thresholds to adjust for the intended treatment endpoints (Figures 1-5).[40-42]

In a study by Le Roux and colleagues, a better prognostic value was confirmed using a higher threshold for positivity even after 4 cycles of chemotherapy.[50] These results showed that the NPV was encouragingly high regardless of the criteria applied, but that the use of a higher threshold for a positive interim PET led to an increase in the PPV. The best PPV was obtained using Deauville 5PS: it increased from 19% to 45% using various criteria, including IHP criteria. Interim PET/CT was best correlated with PFS using 5PS criteria (P<.0001). The reproducibility of Deauville 5PS was also confirmed in an international multicenter study of a retrospective cohort of 260 advanced-stage HL patients imaged after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), with no treatment change based on PET-2 results.[51] The sensitivity, specificity, NPV, and PPV were 73%, 94%, 94%, and 73%, respectively. After a mean follow-up of 27 months, the 3-year failure-free survival was 28% for PET-2–positive patients and 95% for PET-2–negative patients (P<.0001). The binary concordance between paired reviewers was high (Cohen κ=0.84).[51]

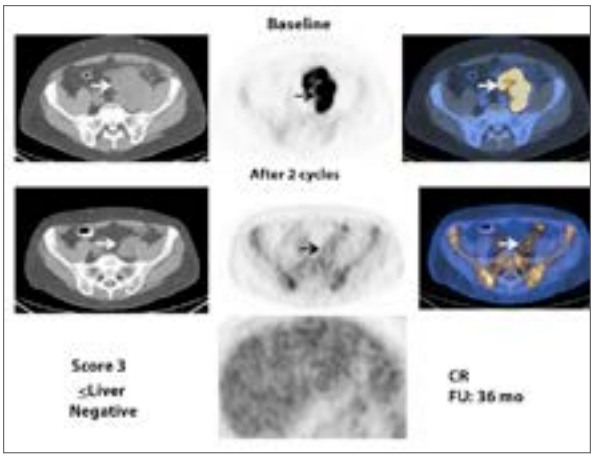

Figure 3. A 40-year-old woman with classical Hodgkin lymphoma underwent a F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) study for staging and after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) to evaluate for therapy response. At baseline (upper panel), axial FDG-PET/CT images demonstrate a conglomerate mass in the left pelvis with increased FDG uptake (arrow), consistent with lymphoma involvement. After 2 cycles of ABVD (lower panel), axial FDG-PET/CT images demonstrate FDG uptake in the corresponding region (arrow) that equals to that seen in the liver (axial image at the lowest panel) that qualifies for a score of 3 reading by Deauville 5 point system criteria. These findings are consistent with resolution of disease activity.

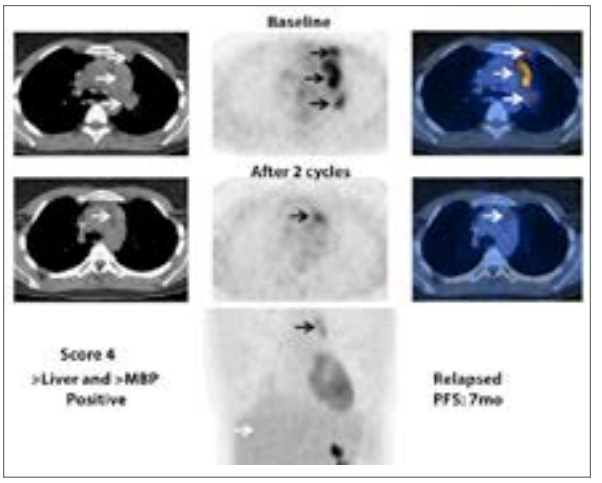

Figure 4. A 41-year-old woman with classical Hodgkin lymphoma underwent a F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) study for staging and after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) to evaluate for therapy response. At baseline (upper panel), axial FDG-PET/CT images demonstrate multiple prominent lymph nodes in the prevascular and left hilar as well as left internal mammary regions (arrows) with increased FDG uptake, consistent with lymphoma involvement. After 2 cycles of ABVD (lower panel), axial FDG-PET/CT images demonstrate persistent FDG uptake in the prevascular mass that exceeds the uptake seen in the liver (white arrow) (coronal PET image in the lowest panel) that qualifies for a score of 4 reading by Deauville 5 point system criteria. These findings are consistent with residual lymphoma. Note the excreted FDG activity in the left kidney on the coronal image.

MBP, mediastinal blood pool.

The PPV of PET-2 needs to be improved further to better guide management even after the introduction of Deauville 5PS criteria. There are data suggesting that PET-2–positive patients have larger lesions after cycle 2 of therapy.[52] In a study of 88 patients with stages I to II, non-bulky HL, IHP and Deauville 5PS criteria, the percentage decrease in the sum of the products of the perpendicular diameters after 2 cycles strongly correlated with PFS.[52] The combined analysis of PET-2 with CECT-2 data suggested an improvement in prediction of PFS compared with each test alone. In the PET-2–positive group, a negative diagnostic CT—defined as a decrease in the size of a mass greater than 65%—decreased the false-positive PET results. This increased the predictive value for PFS by 27% to 35%. Some confidence intervals were not reliable because of small sample sizes, however. Therefore, these results should prompt further study of the combination of PET-2 and diagnostic CT.

Interim PET/CT in Limited-Stage HL. Given the excellent survival rates with first-line therapy for HL, reduced-intensity treatment has been proposed to retain the favorable prognosis while reducing acute and long-term treatment–related adverse effects.[53] Hence, omission of consolidative radiotherapy and/or shorter courses of chemotherapy such as ABVD may be tenable for continued optimization of therapy for limited-stage HL. Recommended therapy for limited-stage patients with a favorable risk profile involves combined-modality therapy consisting of 2 cycles of ABVD followed by 20 Gy of involved field radiotherapy (IFRT). Recommended therapy for limited-stage patients with an unfavorable risk profile includes chemotherapy plus 30 Gy of IFRT or 4 to 6 cycles of chemotherapy without radiation.[54,55]

Most of the observational studies reporting on the potential value of interim FDG-PET/CT as a response predictor included mixed-profile HL patients with divergent risk factors for relapse (Table 3).[46-49,55,57] The predictive value of interim PET is well documented in advanced-stage and unfavorable limited-stage HL[48,57-59] but the results are not as clear in favorable limited-stage HL.[46,47,56-62] In limited-stage HL, Hutchings and coinvestigators reported no differences in 2-year PFS for interim FDG-PET–negative and FDG-PET–positive patients,[42,47] suggesting a low predictive value for PET in this population. In line with these results, Barnes and colleagues reported similar PFS for interim FDG-PET–positive and FDG-PET–negative groups (P=.57) in nonbulky limited-

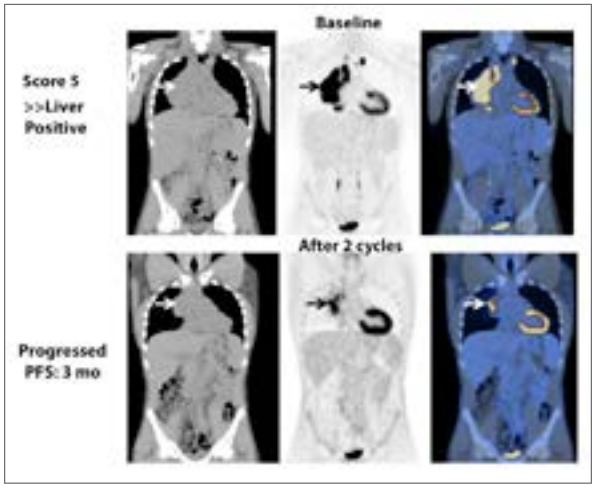

Figure 5. A 31-year-old man with classical Hodgkin lymphoma underwent a F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) study for staging and after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) to evaluate for therapy response. At baseline (upper panel), coronal FDG-PET/CT images demonstrate multiple lymph nodes in the left mediastinal and hilar lymph nodes, as well as left paratracheal regions (arrows) with increased FDG uptake, consistent with lymphoma involvement. After 2 cycles of ABVD (lower panel), coronal FDG-PET/CT images demonstrate persistent FDG uptake in the right parahilar region that significantly exceeds the uptake seen in the liver that qualifies for a score of 5 reading by Deauville 5 point system criteria. These findings are consistent with residual lymphoma.

stage HL patients treated with standard therapy,[60] while end-of-therapy FDG-PET was predictive of outcome (PFS was 94% for negative FDG-PET vs 54% for positive FDG-PET [*P*<.0001]). This study, however, was limited by its retrospective design and variable FDG-PET timing intervals of 2 to 4 therapy cycles. Other investigators corroborated these results in limited-stage HL.[61,62] Sher and coauthors reported a 2-year failure-free survival of 92% for patients undergoing consolidation radiation therapy vs 69% for those not undergoing consolidation radiation therapy for residual FDG-PET avidity after completion of ABVD, indicating the efficacy of radiation of the residual mass after chemotherapy.[62] It should be highlighted that the efficacy of treatment is a crucial factor that contributes to the predictive value of FDG-PET/CT. In a prospective study of 88 patients with limited stage nonbulky HL treated with a nonstandard regimen, doxorubicin, vinblastine, and gemcitabine (AVG), 2-year PFS rates were 88% and 54% for FDG-PET-2–negative and FDG-PET-2–positive groups, respectively (*P*=.0009).[52,63] Although the PPV (50%) was better, the NPV (86%) appeared to be inferior to previously published early-stage HL data (95%-100%),[42,47,56,57] in part owing to the lower CR rate achieved with the AVG regimen (81%) compared with standard ABVD therapy (94%).

In summary, the published results on interim PET for limited HL confirm a consistently high NPV and a low to moderate PPV in relation to treatment outcome. The high incidence of inflammatory processes, particularly in those with bulky disease, contributes to a significant number of false-positive PET results. An additional consideration is that with the use of a PET-response–adapted strategy, the benefits of therapy de-escalation and omission of consolidative radiation therapy in those with a negative interim FDG-PET/CT should be weighed against the risk of disease relapse and the ability to salvage the individual patient.

Recent Clinical Trials Using a Response-Adapted Strategy in Limited-Stage HL. With a premise that treatment can be tailored according to the results of interim FDG-PET imaging, various FDG-PET–adapted clinical trials have been initiated. Several trials have been presented and/or published, while others are awaiting mature data of long-term follow-up.

Le Roux and colleagues reported results in early- and advanced-stage HL patients undergoing treatment with an interim response-adapted strategy after 4 courses of ABVD therapy (PET-4; Table 4).[50] In the limited-stage favorable HL group (n=26), PET-4–negative patients with no progressive disease on CT or patients with CR on CT regardless of FDG-PET/CT findings received only IFRT. In patients with limited-stage unfavorable HL and advanced-stage disease (n=44), those with PET-4–negative findings received 4 more cycles of ABVD. The remaining 28 patients with a positive PET-4 result and no CR on CT underwent autologous SCT. The NPV and PPV for PET-4 for predicting 2-year PFS were 95% and 16%, respectively (*P*<.0001). The low PPV for PFS likely reflects the negative impact of the efficacy of therapy intensification on the predictive value of interim FDG-PET results. The delayed interim PET timing deviates from other studies performed earlier during the course of therapy (PET-4 vs PET-2).

Recently completed and ongoing response-adapted studies that have incorporated early FDG-PET/CT into the clinical trial design for limited stage HL are detailed in Table 5.[53,64-68] The United Kingdom (UK) National Cancer Research Institute (NCRI) RAPID trial enrolled 602 patients with early-stage HL.[53] Thirty-three percent of patients had stage IA HL and 67% had stage IIA HL, while 62% had a favorable prognosis according to EORTC criteria. This was a noninferiority trial whereby all patients received 3 cycles of ABVD, which was followed by FDG-PET/CT scanning (ie, PET-3); a negative PET was defined as Deauville 5PS of 1 or 2 (Tables 5 and 6). Patients with a positive PET-3 result received an additional cycle (fourth) of ABVD followed by IFRT, while PET-3–negative patients were randomized to IFRT vs no IFRT. Of the initial 602 patients, 571 underwent PET-3; PET-3 was negative in 75% of patients. At a

Table 3. Observational Studies (Nonadaptive) Using Interim PET as a Surrogate for Chemosensitivity in HL

Author	Prospective?	No.	Stage	Chemo	Cycle # iPET	PET+, %	PPV, %	NPV, %	2-y PFS, %, PET+	2-y PFS, %, PET–	Med FU, mo
Friedberg,[2] 2004	Yes	22	I-IV, 28% III-IV	ABVD	3	23	80	94	—	—	24
Hutchings,[46] 2005	No	85	I-IV, 33% III-IV	ABVD	2-3	15	62	94	46	97	40
Hutchings,[47] 2006	Yes	77	I-IV, 36% III-IV	ABVD	2	21	69	95	0	96	23
Gallamini,[48] 2006	Yes	108	IIA[rf], IIB-IV 46% III-IV	ABVD	2	19	90	97	6	96	20 (mean)
Gallamini,[49] 2007	Yes	260	IIA[rf], IIB-IV, 47% III-IV	ABVD	2	19	86	95	13	95	26
Sher,[a,62] 2009	No	46	I-II	ABVD-based	2-4	43	15	96	85	96	41
Barnes,[60] 2011	No	96	I-II, 22% IIB	ABVD	2-4	18	12	92	87 (4 y)	91 (4 y)	46
Zinzani,[57] 2012	No	304	I-IV, 51.5% III-IV	ABVD	2	17	92	72	13	95	45
Cerci,[59] 2010	No	104	I-IV, 59% III-IV	ABVD	2	29	53	92	53 (3 y)	90 (3 y)	36
Kostakoglu,[52] 2012	Yes	88	IIB, 20% IIB	AVG	2	27	46	84	50	89	39

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AVG, doxorubicin, vinblastine, and gemcitabine; cycle # iPET, number of chemotherapy cycles before interim PET study; HL, Hodgkin lymphoma; med FU, median follow-up; No., patient number; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; rf, risk factor(s); 2-y PFS, 2-year progression-free survival.

[a] The majority of patients with positive PET at interim or end-of-therapy evaluation received consolidative radiotherapy.

Table 4. Completed Prospective PET-Adapted Trials in Hodgkin Lymphoma

Author	No.	Stage	Chemo	Cycle # iPET	PET+, %	PPV, %	NPV %	4-y PFS, %, PET+	4-y PFS, %, PET–	Med FU, mo
Le Roux,[50] 2011	90	I-IV 50% III-IV	ABVD	4	34	16	95	—	—	49
Dann,[71,72] 2007	108	IIB-IV 93% III-IV	BEACOPP-esc × 2, then ABVD	2	29	17	93	87	87	89
Avigdor,[73] 2009	45	IIB-IV 93% III-IV	BEACOPP-esc × 2, then ABVD	2	29	45	87	53	87	48

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; cycle # iPET, number of chemotherapy cycles before interim PET study; esc, escalated; med FU, median follow-up; MRU, minimal residual uptake; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; 2-y PFS, 2-year progression-free survival.

median follow-up of 49 months, the PFS rate was 95% for PET-3–negative patients who received IFRT compared with 91% for the no-IFRT arm (P=.23). A "per protocol" analysis excluded 26 patients who were allocated to IFRT but did not receive it and 2 patients allocated to no IFRT who received it; 3-year PFS was 97% for the IFRT arm compared with 91% for no IFRT (P=.03). OS at 3 years was 97% in the IFRT arm and 99% in the no-IFRT arm. The 3-year PFS and OS rates for the patients with a positive PET-3 result were 85% and 94%, respectively. The 4% to 6% difference in PFS without difference in OS may be considered acceptable; however, longer follow-up is warranted prior to making definitive conclusions.

EORTC has completed accrual for a large response-adapted study in patients with limited-stage HL.[64] As detailed in Table 5, the H10F and H10U studies randomized patients with favorable and unfavorable HL to PET-based and non–PET-based treatment strategies. The initial study designs for the non–PET-based strategy included consolidative involved-node radiation therapy (INRT) for all patients, while the

Table 5. Limited-Stage (I-II) Hodgkin Lymphoma: Prospective Response-Adapted Studies

Trial	Patient Characteristics	Treatment Regimens	Current/ Projected Enrollment[a]	Preliminary Results
Phase 2				
CALGB 50604[67]	Stage I/IIA-B (no bulk)	ABVD × 2: If PET–, 2 ABVD If PET+, 2 BEACOPP-esc + 30-Gy IFRT	160/160[b]	Accrual completed February 2013; preliminary results expected 2014
CALGB 50801[68]	Stage I/IIA-B bulky	ABVD × 2: If PET–, 4 ABVD If PET+, 4 BEACOPP-esc + 30-Gy IFRT	*43/123*[c]	NA
Phase 3				
UK NCRI (RAPID)[53]	Stage I/IIA (no bulk or B symptoms)	ABVD × 3: If PET–, 30-Gy IFRT vs no RT If PET+, 1 ABVD + 30-Gy IFRT	602/602[b]	3-year PFS for PET– no RT vs IFRT: 91% vs 95% by ITT (*P*=.23) and 91% vs 97% by protocol (*P*=.03); 3-year PFS for PET+ 85%
EORTC/ GELA H10F[d,64]	Favorable group	ABVD × 3 + INRT vs PET directed: ABVD × 2: If PET+, BEACOPP-esc × 2 + INRT If PET–, ABVD × 1 + INRT	761/761[b]	Accrual completed June 2011[d]
EORTC H10U[e,64]	Intermediate group	ABVD × 4 + INRT vs PET directed therapy: ABVD × 2: If PET+, BEACOPP-esc × 2 + INRT If PET–, ABVD × 2 + INRT	1191/1191[b]	Accrual completed June 2011[e]
GHSG HD16[65]	Favorable group	ABVD × 2 + 20-Gy IFRT vs PET directed: ABVD × 2: If PET+, 20-Gy IFRT; if PET–, no further treatment	*686/1100*[c]	NA
GHSG HD17[66]	Intermediate group	BEACOPP-esc × 2 + ABVD × 2: If PET–, 30 Gy vs no further treatment If PET+, 30-Gy IFRT vs 30-Gy INRT	*283/1100*[c]	NA

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CALGB, Cancer and Leukemia Group B; EORTC, European Organisation for Research and Treatment of Cancer; esc, escalated; GELA, Groupe d'Etude des Lymphomes de l'Adulte; GHSG, German Hodgkin Study Group; Gy, Gray; IFRT, involved field radiation therapy; INRT, involved nodal radiation therapy; ITT, intent-to-treat; MRU, minimal residual uptake; PET+, PET-positive; PET–, PET-negative; PFS, progression-free survival; RT, radiation therapy; UK NCRI, United Kingdom National Cancer Research Institute.

[a] Enrollment as of August 2013.

[b] Enrollment has been completed to these studies.

[c] Italicized enrollment numbers indicate clinical trials that remain open for patient accrual.

[d] Initial study design had PET– patients receiving 2 ABVD without RT (ie, 4 total ABVD, no RT); study amended on interim/early analysis (August 2010) by Data and Safety Monitoring Committee to current design owing to increased relapse rate in no RT arm.

[e] Initial study design had PET– patients receiving 4 ABVD without RT (ie, 6 total ABVD, no RT); study amended on interim/early analysis (August 2010) by Data and Safety Monitoring Committee to current design owing to increased relapse rate in no RT arm.

PET-based approach obviated INRT for a negative PET-2 result and escalated therapy to bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) for a positive PET-2 result. With early follow-up, interim analyses were performed. In the H10F study, approximately 190 patients had been randomized to each study arm; at that point, 1 event had occurred in the INRT arm compared with 9 events in the PET-based (no INRT) arm. Thus, the data safety and monitoring committee amended the study to include INRT in all treatment arms; similar results and modifications were made for the H10U.

GHSG is also examining the strategy of response-adapted therapy for favorable and unfavorable HL in the HD16 and HD17 studies, respectively (Table 3).[65,66] HD16 is similar to the EORTC design in randomizing patients to a standard non–PET-based treatment (ie, ABVD × 2 + 20-Gy IFRT) vs a PET response-adapted therapeutic strategy (ie, no IFRT with negative FDG-PET). For HD17, all patients receive 2 cycles of escalated BEACOPP and 2 cycles of ABVD; PET-4–negative patients are randomized to IFRT vs no IFRT, while PET-4–positive patients are randomized to IFRT vs INRT.

Table 6. Advanced-Stage (III/IV) Hodgkin Lymphoma: Prospective Response-Adapted Studies

Trial	Treatment	Current/ Projected Enrollment[a,b]	Outcomes
Phase 2			
SWOG-S0816[74]	ABVD × 2 cycles (PET-2): If PET–, ABVD × 4 (arm 1) If PET+, BEACOPP-esc × 6 (arm 2)	371/371	18% with +PET-2; arm 1 ORR 100% (96% CR), arm 2 ORR 85% (49% CR); HIV-negative: 2-year PFS 76%, 2-year OS 95%
COG AHOD0831[75]	ABVE-PC × 2 cycles (PET-2): If PET–, ABVD × 2 (arm 1) If PET+ IV × 2, then ABVE-PC × 2 (arm 2)	165/165	Accrual completed January 2012; preliminary results expected mid-2014
Phase 3			
RATHL (UK-NCRI)[76]	ABVD × 2 cycles (PET-2): If PET–, ABVD × 4 vs AVD × 4; if PET+, BEACOPP-14 × 4 (RT if PET+ after BEACOPP)	1214/1214	16% +PET-2 (higher CR rate with lower PET score); 76% of +PET-2 converted to PET– with BEACOPP
HD0607 GITIL[77]	ABVD × 2 cycles (PET-2): If PET–, ABVD × 4: PET–: randomize to RT vs no RT If PET+, randomize BEACOPP-esc vs BEACOPP-esc + rituximab	627/627	Preliminary results expected to be presented October 2013 at the Cologne International Hodgkin Lymphoma meeting
HD0801 IIL[78]	ABVD × 2 cycles (PET-2): If PET–, ABVD × 4: PET–: randomize to RT vs no RT If PET+, autologous SCT	300/300	Accrual completed June 2013; preliminary results expected to be presented October 2013 at the Cologne International Hodgkin Lymphoma meeting
GHSG HD18[79]	BEACOPP-esc × 2: If PET–, BEACOPP-esc × 2 vs BEACOPP-esc × 6; if PET+, BEACOPP-esc + rituximab vs BEACOPP-esc × 6	1758/1758	NA

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; COG, Children's Oncology Group; CR, complete remission; esc, escalated; GHSG, German Hodgkin Study Group; GITIL, Gruppo Italiano Terapie Innovative nei Linfomi; HD, Hodgkin disease; IIL, Intergruppo Italiano Linfomi; ORR, overall response rate; OS, overall survival; PET+, PET-positive; PET–, PET-negative; RATHL, A Randomised Trial to Assess Response Adapted Therapy Using FDG-PET Imaging in Patients With Advanced Hodgkin Lymphoma; RT, radiation therapy; SCT, stem cell transplantation; SWOG, Southwestern Oncology Group; UK NCRI, United Kingdom National Cancer Research Institute.

[a] Enrollment as of August 2013.

[b] Enrollment has been completed to these studies.

Interim PET/CT in Advanced-Stage HL. Interim FDG-PET/CT has high sensitivity and specificity in advanced-stage disease, and it has been shown to more accurately predict patient outcomes compared with the IPS (Table 3).[46-49,56-59] Most often, a "positive" interim FDG-PET result in advanced-stage HL is defined as a Deauville score of 4 or 5 (Figure 1). Consequently, a response-adapted therapeutic strategy based on interim FDG-PET results might distinguish high-risk patients (ie, interim FDG-PET–positive) who may benefit from altered/escalated treatment regimens. Conversely, low-risk patients (ie, interim FDG-PET–negative) could potentially have treatment de-escalated in an attempt to decrease acute and long-term adverse effects.

In a seminal analysis of FDG-PET in newly diagnosed advanced-stage HL, Gallamini and colleagues reported in 2007 on the prognostic importance of interim PET following 2 of 6 planned cycles (PET-2) of ABVD.[49] Among 260 patients (190 with advanced-stage disease), the 2-year PFS for patients with a positive FDG-PET/CT after 2 cycles of ABVD therapy was 13%, compared with 95% for patients with a negative FDG-PET/CT.[1] Several factors were prognostic in univariate analysis (including IPS); however, in multivariate analysis, interim PET was the only significant prognostic factor. Moreover, interim PET-2 status essentially abrogated the prognostic importance of IPS. In an additional meta-analysis of 13 studies that included 360 untreated advanced-stage HL patients, FDG-PET had an overall sensitivity of 81% and specificity of 97%; this analysis was partly limited in that there were few high-risk (IPS 4-7) patients included in the associated trials.[58]

In a recent retrospective study of 304 newly diagnosed ABVD-treated HL patients, a positive PET-2 result was

associated with a continuous CR of 25%, whereas 92% of PET-2–negative patients achieved a continuous CR at a median follow-up of 31 months.[57] In a multicenter prospective trial of 260 patients either with unfavorable stage IIA (n=70) or stages IIB to IVB (n=190) disease, the 2-year PFS was 13% for PET-2–positive patients vs 95% for PET-2–negative patients (*P*<.0001) after ABVD treatment with or without IFRT. In multivariate analyses, only PET-2 was found to be significant as a prognostic indicator (*P*<.0001), overshadowing the prognostic value of IPS. In another prospective cohort of 104 HL patients, Cerci and colleagues reported a 3-year event-free survival of 55% and 94% for PET-2–positive and PET-2–negative patients, respectively (*P*<.001).[59]

A recent retrospective analysis of 160 early-stage unfavorable or advanced-stage HL patients examined outcomes for ABVD-treated patients with a positive PET-2 result who had therapy intensified to BEACOPP therapy (4 cycles escalated followed by 4 cycles of baseline).[69] Patients with a negative PET-2 who remained on ABVD therapy had a 2-year failure-free survival of 95%. Patients in the PET-2–positive group, who had therapy intensified, had a 2-year failure-free survival rate of 62%; this appeared to be higher than the rate found in historical controls. By multivariate analysis, PET-2 was the only prognostic factor associated with failure-free survival (*P*=.001). These findings suggest that in advanced-stage HL with positive interim PET-2, early intensification with BEACOPP may improve patient outcomes. This is important in the context of limiting undue toxicity of aggressive chemotherapy to only those patients who would require treatment intensification.

Recent Clinical Trials Using a Response-Adapted Strategy in Advanced-Stage HL. Several studies have reported outcomes incorporating PET-adapted treatment strategies (Table 4).[50,69-73] In the GHSG HD15 trial, a subset of 69 patients with untreated stage III, IV, or IIB HL with a large mediastinal mass or extranodal disease were treated with either 8 (n=35) or 6 (n=24) cycles of escalated BEACOPP or with 8 cycles of BEACOPP-14 (n=10). Interim PET after 4 cycles proved to have a high NPV for PFS[68]; only 1 out of 51 PET-4–negative patients relapsed (NPV=98%). Interestingly, in the PET-4–positive group (n=18), only 4 patients progressed or relapsed within 1 year (PPV, 22%). The 4-year PFS for PET-4–negative and PET-4–positive patients were 96% and 78%, respectively (*P*=.016). There are several potential explanations for the low PPV, including a conservative threshold using IHP criteria (Figure 1) for PET positivity; a late time for the interim PET scan (after the fourth cycle), when most patients could be already considered cured; the absence of a baseline PET scan as a reference for interim PET reporting; and the efficacy of the escalated BEACOPP regimen, possibly rescuing the few patients with a positive interim PET result.

In the previously cited study by Le Roux and colleagues, a limited cohort of 54 patients with early, unfavorable, or advanced-stage HL were treated with a PET-adapted strategy after 4 ABVD courses (refer to the *"Recent Clinical Trials Using a Response-Adapted Strategy in Limited-Stage HL"* section).[50] Only 6 of 31 patients with a positive PET-4 result (19%) and 7 of 59 with a negative PET-4 result (12%) had treatment failure, resulting in a high NPV (96%), but a relatively low PPV (16%). Limitations of this study include the combined criteria based on both of the CT and PET results, the relatively late timing of PET during therapy, and the incomparability of the criteria used for interim PET interpretation. The fact that the PPV of PET cannot be determined in a treatment escalation setting would negate the predictive value of PET positivity.

In advanced-stage HL, an adaptive treatment based on a response-adapted (interim PET) and risk-adapted (high vs low IPS) therapeutic strategy was prospectively examined by the Haifa group in a cohort of 124 advanced-stage HL patients.[71,72] Patients with IPS scores of 0 to 2 or 3 to 7 were treated with 2 cycles of baseline or escalated BEACOPP, respectively. Interim[67] gallium scintigraphy or PET determined subsequent therapy with continuation of the escalated BEACOPP (test-positive) regimen or de-escalation to baseline BEACOPP. With a median follow-up of 89 months, 10-year PFS and OS in the entire cohort were 87% and 88%, respectively, yielding similar PFS and OS in both arms. The 10-year PFS was 83% in patients with a positive interim PET result, compared with 93% for those with a negative interim result (*P*=not significant). As in the trial reported by le Roux and colleagues,[50] the PPV was substantially low (17%), as noted in Table 3.

In a similar study by Avigdor and colleagues, 45 newly diagnosed HL patients with stages IIB to IVB HL and an IPS of at least 3 were treated with 2 courses of escalated BEACOPP.[73] Both interim PET and a CECT scan determined the response and treatment arms. Patients in CR or partial remission (PR) according to IHP criteria underwent de-escalation with ABVD × 4, and patients with less than PR proceeded to autologous SCT. Of 44 patients in CR or PR, 70% had a negative PET-2 and 30% had a positive PET-2 result. In patients with PET-2–negative and PET-2–positive results, 97% and 69% achieved a CR, respectively. PPV and NPV were 45% and 87%, respectively. After a median follow-up of 48 months, 98% of patients were alive. The 4-year PFS was 87% for PET-2–negative patients and 53% for PET-2–positive patients (*P*<.01). The weaknesses of this study were its low power and the combined use of PET and CT to guide treatment, as well as the exclusion of patients who had less than PR, making the results difficult to compare with those of other studies.

Several clinical trials in advanced-stage HL have recently been completed, and a number are ongoing, examining

response-adapted therapy via the incorporation of early PET scan (Table 6).[74-79] The US Cooperative Groups recently reported preliminary results from a large prospective phase 2 clinical trial (Table 6).[74] After 2 cycles of ABVD, PET-2–negative patients continued for 4 cycles of ABVD (without radiation), while PET-2–positive patients had therapy intensified to escalated BEACOPP. The study included HIV-positive patients who were treated with baseline BEACOPP who had a positive PET-2 result. There were 371 stage III/IV patients who enrolled; the PET-2 was negative in 82% of patients. Two-year PFS and OS for all patients were 76% and 90%, respectively. The 2-year PFS for PET-2–negative patients was 78%, while 2-year PFS for PET-2–positive patients was 61%. The latter appeared increased compared with historical controls, which thus far has met the predefined study criteria/goals (ie, projected 2-year PFS for PET-2–positive patients were 48%). Of the 13 HIV-positive patients enrolled, 11 had a negative PET-2; 12 were progression-free, and all are alive. Continued follow-up is needed for this study. The Children's Oncology Group (COG) has also completed accrual to a recent phase 2 study.[75] They utilized a similar design as SWOG-S0816, though with different chemotherapy. All patients received doxorubicin, bleomycin, vincristine, and etoposide (ABVE) plus prednisone and cyclophosphamide (PC); PET-2–negative patients received 2 further cycles of ABVE-PC, while PET-2–positive patients received 2 cycles of chemotherapy followed by 2 ABVE-PC cycles. Results from this study are awaited.

A large randomized phase 3 study for advanced-stage HL completed accrual and preliminary results were recently reported. The RATHL (Response-Adjusted Therapy for Hodgkin Lymphoma) study, led by the UK NCRI, enrolled 1241 advanced-stage HL patients.[76] All patients were treated with 2 cycles of ABVD and repeat PET/CT was done; the Deauville scores were 4 or 5. Notably, all PET/CT scans were ready centrally by each participating country. Eighty-five percent of patients had a negative PET-2; these patients were randomized to continued ABVD or doxorubicin, vinblastine, and dacarbazine (AVD). PET-2–positive patients had their therapy increased to BEACOPP-14. Patients who were PET-2 positive at diagnosis were more likely to have B symptoms, bulky disease, and a higher IPS. After BEACOPP therapy, 76% of patients converted to a negative PET. Outcomes, especially for the noninferiority component of the study for PET-2–negative patients, are anticipated in 2014. In addition, there are several ongoing phase 3 randomized advanced-stage HL studies as detailed in Table 6. Results from these studies are eagerly awaited.

The Role of End-of-Therapy PET

End-of-treatment FDG-PET/CT results serve as a sensitive tool to distinguish between fibrotic tissue and residual viable disease. In 1 prospective study, a negative end-of-treatment FDG-PET had a NPV of 96% for progression or early relapse in advanced-stage disease.[80] This result is clinically relevant in the context of determining the necessity of further treatment because radiotherapy could potentially be omitted in advanced-stage HL patients with a residual mass but a negative end-of-treatment FDG-PET result. In limited-stage HL, several investigators found that end-of-treatment PET was highly predictive of PFS and OS, regardless of interim PET results.[60,62] For example, Sheret and coinvestigators found that the end-of-treatment PET result was predictive of PFS in a cohort of 73 limited-stage HL patients (a 31% rate of relapse in PET-positive patients vs a 5% rate of relapse in PET-negative patients),[62] although 70% of PET-positive patients were successfully treated with consolidative IFRT with durable remissions. In fact, according to the results of the GHSG HD10 trial (without the guidance of an interim PET), the combination of 2 ABVD cycles and 20-Gy IFRT led to 5-year PFS rates of 91%, suggesting that an interim PET as a marker of chemotherapy sensitivity may not be necessary when the disease has limited burden conferring a high likelihood of success for the subsequent consolidative therapy.[81]

FDG-PET has been adopted in the revised response criteria for lymphoma, which require a negative scan to classify a patient in CR and allow residual masses as long as they are not FDG-avid.[44] It is crucial to recognize, however, that the PPV of PET is less reliable than its NPV because of infection, inflammation, and reactive changes after treatment. Thus, to ascertain whether disease relapse/progression has occurred, histologic evidence remains the standard of care (ie, tissue biopsy) to confirm persistent or relapsed disease compared with FDG-PET/CT alone.[82] It should also be highlighted that once HL patients enter remission, continued FDG-PET/CT scanning is not recommended during postremission surveillance, owing mainly to low specificity and poor PPV.

Additional Considerations and Challenges. The results of interim PET studies should be reviewed with the understanding of some limitations for their generalizability and the interpretation criteria. The high percentage of false-positive interim PET results (~30%) remains a significant shortcoming of this modality with respect to its potential role in response-adapted therapy.[46-49,56] The residual low- to moderate-grade uptake in HL masses is usually caused by an inflammatory component of the tumor mass. HL has an idiosyncratic tumor architecture, with only 1% of the total cell count of the neoplastic tissue being constituted of the malignant Reed-Sternberg and Hodgkin cells, and the remainder being a functional network of non-neoplastic mononuclear bystander cells.[83] These inflammatory cells are likely partially responsible for the high FDG uptake within the tumor stroma. The paradoxical phenomenon of a persis-

tent mass associated with no metabolically active tumor cells, termed "metabolic complete remission," supports a high NPV for interim PET in predicting treatment outcome.[46-49]

The inflammatory response peaks around 10 to 15 days after therapy administration.[84] Consequently, interim PET studies should be scheduled at least 2 weeks after the initiation of therapy[43,85] and/or 3 to 4 days before the start of the subsequent therapy cycle. The timing of end-of-therapy FDG-PET studies allows for more flexibility: a 3-week window after the completion of therapy suffices to avoid the inflammatory period. Importantly, the interval between radiation therapy and FDG-PET imaging should be at least 6 to 8 weeks to allow for the inflammation caused by tissue radiation to subside.

Novel Applications and Techniques

Metabolic Tumor Volume. Alternative quantitative imaging biomarkers of disease response are needed to identify more sensitive markers of change in tumor response than the current linear measurement-based methods. Better prognostic indicators would include the comparison of linear measurements vs volumetric analyses, as well as metabolic tumor volume/burden. Although disease bulk at staging is an established risk factor for an unfavorable prognosis, no universal method has been adopted to measure disease bulk. The ratio of the mediastinum to the thoracic diameter and the maximum size of the largest mass are the existing methods. However, the threshold values for size vary across groups (Table 1). There are ongoing efforts to develop a PET-based methodology to measure tumor metabolic volume, and thereby disease burden, for both limited- and advanced-stage lymphoma patients using sophisticated software systems.[86-88] These methodologies are demanding, however, as they require strict adherence to PET protocols for all imaging periods considering the dependence of metabolic activity measurements on multiple variables. These variables include interval after injection, blood glucose level, body weight, and technical PET parameters. Preliminary data in HL patients suggest a better role for Deauville 5PS for interim analysis.[89] In another preliminary data set, PET parameters from pretreatment scans including metabolic tumor volume (MTV) and SUVmax did not significantly correlate with outcomes, but the change in MTV between interim and baseline studies was associated with PFS (P=.01), along with SUVmax (P=.02).[90] Additional novel imaging biomarkers will include measures of heterogeneity, which is emerging as an important factor in imaging analyses.[91] Tumor quantitative metabolic measurements may provide predictive information and may identify patients at high risk of treatment failure, but further supporting data and validation of these methodologies are warranted to define the potential role of PET based quantitative approach for HL in adaptive strategies.

Imaging Tumor Proliferation. Proliferative capacity is an important hallmark of cancer. The noninvasive assessment of tumor proliferative activity may provide a critical tool for individualized treatment. The 3'-deoxy-3'-^{18}F-fluorothymidine (FLT) is the most extensively investigated functional imaging probe for measurement of cancer cell proliferative capacity.[92, 93] The role of FLT-PET will depend in part in its ability to predict early response during treatment, rather than determining the extent of disease involvement at initial staging. FDG, which has tumor uptake that is at least twice that of FLT, will probably maintain its role as initial staging for lymphoma, including HL. Moreover, the overall lower uptake in tumors and higher background activity in the liver and bone marrow further dampens the enthusiasm to use this tracer as a staging tool. FLT is a promising probe, however, to determine therapy response with the expectation of a lower false positive rate. The temporary rise in inflammatory cells during therapy does not seem to influence FLT uptake.[94-96] The clinical utility of FLT as an early response surrogate has been demonstrated by several investigator in preliminary clinical studies in non-Hodgkin lymphoma.[97-99] A significant tumor SUV decline was noted at 1 week (77%) and at 6 weeks (85%) after initiation of therapy. More recently, in a prospective study of 66 patients with aggressive NHL treated with R-CHOP, the initial mean SUV was significantly higher in patients who showed progressive disease and partial response than in patients who achieved a CR (P=.049).[99] Despite these early data in non-Hodgkin lymphoma, there are thus far no published data in HL.

Integrated PET/MRI. Conventional contrast-enhanced MRI with contrast administration is able to display a snapshot of tumor enhancement, but does not provide functional information. Multiparametric MRI, which combines anatomic T2-weighted (T2W) imaging with dynamic contrast-enhanced MRI (DCE-MRI), evaluates perfusion characteristics, and diffusion-weighted imaging (DWI) evaluates diffusion characteristics. DCE-MRI provides assessment of tumor angiogenesis and enables the depiction of physiologic alterations as well as morphologic changes.[100,101] One preliminary study reported improvement in detection of splenic involvement in HL when T2-weighted imaging was complemented by DCE-MRI.[102] However, quantitative analysis of MRI data using DCE-MRI is still in evolutionary phase. Furthermore, it is unclear what the optimal set of values should be and how parameters should be adjusted according to tumor type and site, all of which influence apparent diffusion coefficient (ADC) values.

DWI sensitizes the brightness of an image to the net displacement of water molecules over a given time.[98,99] Water movement can be quantified as the ADC. In patients with lymphoma, an increase in cellular density is correlated

with an elevated signal (reduced ADC) on DWIs. Several studies comparing DWI with FDG-PET/CT for staging lymphoma have shown reasonable diagnostic accuracy for DWI.[102-107] In a pilot study, whole-body DWI with ADC quantification enabled early assessment of treatment in aggressive NHL.[107] Furthermore, the data suggested a strong inverse correlation between ADC and PET SUV in lymphoma.[106] Another potential area of interest is the use of MR imaging in combination with FDG-PET/CT as a noninvasive means of visualizing the bone marrow throughout the entire body. If this combination approach is sufficiently sensitive with a high NPV, it may be used to exclude lymphoma involvement of the bone marrow and prevent unnecessary bone marrow biopsies. Only a limited number of small sample studies have evaluated the value of whole-body MRI in this setting so far,[107-110] although 1 study reported unfavorable results for whole-body MRI at staging bone marrow biopsy in 116 patients with newly diagnosed lymphoma. The sensitivity of whole-body MRI was significantly higher in aggressive lymphoma than in indolent lymphoma (90% vs 23%) and was equal to FDG-PET in both entities.[111] A pilot study also reported the prognostic value of DWI with ADC mapping in evaluation of the efficacy of chemotherapy in non-Hodgkin lymphoma.[110] With the advent of integrated PET/MRI platforms,[109] the potential complementary nature of MRI and PET will undergo continued investigation.

Conclusions

FDG-PET/CT is an important component of pretreatment staging in HL. Further analyses are warranted to see if FDG-PET/CT alone may be sufficient in the initial staging of HL vs performing FDG-PET/CT concomitantly with CECT. Interim FDG-PET has been shown to be a highly prognostic tool, especially in advanced-stage HL. Numerous studies are evaluating the possibility of using interim FDG-PET/CT for response-adapted approaches in order to diminish toxicity and improve patient outcomes through minimization of therapy or via intensification of treatment for low- and high-risk HL populations, respectively. Results of these studies are eagerly awaited; in the interim, modification of therapy based on interim FDG-PET/CT in HL is not advocated in routine clinical practice. Additionally, once HL patients achieve CR, FDG-PET/CT scanning should not be continued during postremission surveillance, owing mainly to challenges with PPV. Finally, there are a number of new and exciting applications and novel techniques of functional imaging, such as metabolic tumor burden/volume, tumor proliferation via FLT, and integrated PET/MRI, that continued to be explored for enhanced staging, characterization, and prognostication of HL.

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