The Role of Interim FDG-PET in Defining Prognosis of Hodgkin Lymphoma for Early Stage Disease

Andrew M. Evens, DO, MSc¹ and Lale Kostakoglu, MD, MPH²

¹Division of Hematology-Oncology, Tufts Medical Center, Boston, Massachusetts; ²Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, New York

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F-fluorodeoxyglucose positron emission tomography, FDG-PET/CT, Hodgkin lymphoma, response-adapted therapy, prognosis

Correspondence:
Dr. Andrew M. Evens
Professor of Medicine and Chief
Division of Hematology-Oncology
Director, Tufts Cancer Center
Tufts Medical Center
Boston, MA, USA 02111
Phone: 1-617-636-6227
Email: aevens@tuftsmedicalcenter.org
Abstract

Given the excellent survival rates for early-stage Hodgkin lymphoma (HL), the young age of many patients, and continued concerns regarding acute and late treatment-related toxicities, there is a desire to have a predictive tool that enables therapy to be tailored towards the individual patient. Early (or interim) 18F-fluorodeoxyglucose positron emission tomography with computerized tomography (FDG-PET/CT), as a test of tumor sensitivity to ongoing/planned therapy, has been shown to be prognostic for survival in HL. Based on results of interim FDG-PET/CT, therapy may be subsequently modified through minimization or via intensification of therapy for low- and high-risk patient populations, respectively (i.e., response-adapted therapy). Important data have been generated to standardize the interpretability and reproducibility of interim FDG-PET/CT (i.e., Deauville 5 point system) and observational and non-controlled prospective studies have produced evidence supporting the hypothesis that response-adapted therapy may potentially serve as a predictive tool. Moreover, results from non-inferiority, phase III clinical trials randomizing early-stage HL patients with negative interim FDG-PET/CT to combined modality therapy (CMT) versus chemotherapy alone have recently been reported. The current collective data from these latter studies have shown that interim FDG-PET/CT has thus far been unable to discriminate a group with equivalent acute disease control rates in early-stage HL. Additional randomized response-adapted studies are ongoing and novel FDG-PET/CT applications involving quantitative techniques and innovative imaging modalities are being investigated to identify more robust imaging biomarkers. Altogether, treatment of early-stage HL remains a clinical management choice for physicians and patients to decide with consideration of acute and long-term outcomes.
Introduction

The high majority of patients with early-stage Hodgkin lymphoma (HL) will achieve complete remission (CR) and be cured with current treatment paradigms. A common treatment strategy for early-stage HL involves combined modality therapy (CMT) sequencing consolidative radiotherapy after induction chemotherapy, although chemotherapy alone is a viable option with the number of chemotherapy cycles (i.e., 2-6) and radiation dose (i.e., 20-30 Gy) being dependent in part on clinical risk factors. Despite disease-specific survival rates of 90-95% for early-stage HL with current treatment paradigms, treatment-related toxicities remain a concern. This includes increased risk of late effects including second cancers and arterial disease as well as negative impact on quality of life. Significant efforts have been made to decrease the amount and intensity of therapy in order to potentially mitigate acute and long-term toxicities. Conversely, a small subset of early-stage patients will have primary refractory disease or experience relapse and ultimately die of the disease.

There is an interest to identify these high-risk groups earlier in the treatment course to potentially institute modified and/or intensified therapy, which may lead to improved outcomes. In both clinical scenarios, it is desirable to have a prognostic tool that may predict patient outcome and allow therapy to be tailored towards the individual patient.

18F-fluorodeoxyglucose positron emission tomography with computerized tomography (FDG-PET/CT) is a functional imaging modality that has become a standard tool complementing contrast enhanced CT (CECT) scans in the diagnosis and management of HL. A number of studies have shown that FDG-PET/CT more accurately identifies the correct pretreatment stage in HL compared with CECT though FDG-PET/CT upstages disease from early to advanced stage in only 10-15% of patients where treatment is ultimately modified. After completion of intended treatment, FDG-PET/CT is also usually able to distinguish viable tumor cells from fibrosis or necrosis in a residual mass. FDG-PET/CT may have its greatest impact, however, in the prediction of patient outcome with use of early (interim) imaging. Results from non-controlled studies of interim FDG-PET/CT (e.g.,
following 2 cycles of chemotherapy) as a test of tumor sensitivity of planned/ongoing therapy have been shown to be prognostic of survival.\textsuperscript{12-18}

Significant amounts of data have been published over the past decade regarding the clinical utility of FDG-PET/CT in the management of HL.\textsuperscript{14-22} This includes important data that have been produced regarding the standardization of the reproducibility and interpretability of FDG-PET/CT, which are critical for the appropriate incorporation of this modality into routine clinical practice. In addition, observational and non-controlled prospective studies have generated hypotheses supporting the concept of early (interim) risk assessment utilizing FDG-PET/CT imaging for prognostication and prediction of outcome. Moreover, results of randomized phase III clinical trials that have incorporated response-adapted treatment strategies based on interim FDG-PET/CT to guide treatment decisions have recently been completed in an attempt to answer the question: is interim FDG-PET/CT a compass for a safe navigation in HL?\textsuperscript{19} There are also multiple novel FDG-PET/CT applications involving quantitative techniques and future imaging modalities are being investigated for the potential incorporation into the clinical care for better management of HL patients.

**FDG-PET Interpretation and Reproducibility**

The first initiative for standardization 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.\textsuperscript{23} According to these criteria, uptake greater than that seen in the mediastinal blood pool in residual masses measuring $\geq 2$ cm was considered positive for residual lymphoma. It is important to note that these criteria were not recommended for interim FDG-PET/CT evaluation. A more accurate method for measuring response versus a dichotomous data set would be a continuous variable with a categorical scoring system, such as the Deauville 5 point system (5PS) (\textit{Figure 1}).\textsuperscript{24-26}
A scoring system that enables different cutoffs (i.e., thresholds for positive versus negative) is desirable to assess tumor chemotherapy sensitivity versus response. Such a scoring system is also adaptable as study goals and endpoints change. A high positive predictive value (PPV) using a higher background/threshold (i.e., liver uptake) is preferred for therapy intensification to minimize overtreatment and toxicity and decrease the rate of false positives, whereas a high negative predictive value (NPV) using a lower background/threshold (i.e., mediastinal blood pool) may be used to decrease intensity of therapy in order to minimize under treatment. To in part satisfy this need, the Deauville 5PS was developed to serve as a categorical reading scheme that is suitable for different positivity thresholds to adjust for the intended treatment endpoints (Figure 1). In addition, by using the patient as his or her own control with a reference organ with relatively consistent metabolic activity (e.g., mediastinal blood pool and liver), it minimizes inter-reader subjectivity and reduces inter-device inconsistency.

In a study by Le Roux and colleagues, the improved prognostic value of the Deauville 5PS was confirmed. The study showed that the NPV was high regardless of the criteria applied, but that the use of a higher threshold for a positive interim FDG-PET/CT led to an increased PPV. The best result was obtained using Deauville 5PS criteria, which increased the PPV from 19% to 45%. Furthermore, interim FDG-PET/CT correlated strongest with progression-free survival (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 of 6 intended cycles (i.e., PET-2) of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), with no treatment change based on PET-2 results. The sensitivity, specificity, NPV, and PPV for PET-2 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 \(\kappa=0.84\)). It should also be noted that the NPV and PPV of FDG-PET/CT in HL may be disease- and treatment-specific.
and the aforementioned results should not be automatically applied to diseases or therapies other than HL and ABVD, respectively.

**Current Treatment Paradigms for Early Stage HL**

A common current treatment recommendation for early-stage HL patients with a *favorable* risk profile involves CMT consisting of 2-3 cycles of ABVD followed by 20-30 Gray (Gy) of involved field radiotherapy (IFRT) or involved node RT (INRT). Commonly recommended therapy for early-stage patients with an *unfavorable* (intermediate) risk profile includes 4 cycles of chemotherapy followed by 30 Gy IFRT/INRT. In addition, chemotherapy alone for 4 to 6 cycles (without radiation) has been identified as a valid option for the treatment of early-stage HL.8

From 2002 to 2005, there were 4 published randomized clinical trials that compared CMT versus chemotherapy alone for the treatment of adult early-stage HL.30-33 In each of these studies, disease control (i.e., freedom from disease progression, freedom from treatment failure, or event free survival) was better with CMT versus chemotherapy with absolute improvements ranging from 3% to 7%. Overall survival (OS) rates were similar in each study, although final analysis of the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) Eastern Cooperative Oncology Group (ECOG) HD.6 study showed superior OS for chemotherapy alone at 12 years due to increased late events/toxicity in the CMT arm.34 A recent analysis that combined individual patient data from the NCIC-CTG HD.6 and German Hodgkin Study Group (GHSG) HD10/HD11 studies showed that disease control (i.e., 8-year time to treatment progression) was improved by 6% with CMT versus chemotherapy alone, while OS rates were identical at 95%.35 Similar data regarding the improvement in disease control (i.e., event-free survival) with similar OS was seen in a pediatric HL study randomizing patients who achieved CR on CT to IFRT or no radiotherapy.36

As noted above, improvement in acute disease control (e.g., PFS) is well documented for CMT versus chemotherapy alone early-stage HL patients who receive, however this has not translated to an improvement in OS. In addition, there are late adverse effects due to therapy such
as arterial disease and second cancers that occur. Thus, the preferred treatment of HL patients with early-stage disease continues to be strongly debated in part given the overarching goal of long-term OS with preserved quality of life. New scientific advances have been sought in order to identify select low risk patients whereby radiation may be obviated and/or less chemotherapy delivered. The functional imaging modality, FDG-PET/CT, has been examined as a tool to direct when treatment should be de-intensified or escalated based on interim results.

**Interim PET/CT in Early-Stage HL**

*Observational and prospective studies without treatment modification.* FDG-PET/CT may provide prognostic information at the individual patient level allowing early in vivo evaluation of chemotherapy sensitivity. It should be highlighted that most initial observational studies reporting on the potential value of interim FDG-PET/CT as a response predictor included mixed profiles of HL patients with divergent risk factors. Furthermore, there is comparatively much less data regarding the predictive value of interim PET in early-stage HL versus advanced-stage, especially in favorable early-stage HL. In the observational study by Gallamini and Hutchings that ignited an intense interest into response-adapted therapy in HL, only a minority of patients had early-stage disease and most of these patients had adverse risk factors (i.e., unfavorable/intermediate early-stage HL).

In a retrospective analysis of 85 HL patients who had interim FDG-PET/CT after 2-3 cycles of ABVD, the predictive power of FDG-PET/CT was much less robust for early-stage versus advanced stage HL patients (*Figure 2a and 2b*). Interim FDG-PET/CT was prognostic for 2-year PFS among the 57 early-stage HL patients (P=0.003), but only two of seven interim FDG-PET/CT-positive patients with early-stage relapsed. Interestingly, Ann Arbor stage retained strong prognostic significance on multivariate analysis with interim FDG-PET/CT included as a covariate. In a subsequent prospective analysis of patients with early- and advanced-stage HL, extranodal disease and a positive interim FDG-PET/CT were found to be predictive of outcome. Among patients with
early-stage disease, none with a negative PET-2 progressed (0/26) and only 1 of 5 with positive PET-2 experienced progression.

Other investigators have reported similar PFS differences for interim FDG-PET/CT–positive and FDG-PET/CT–negative groups \((P=0.57)\) in non-bulky limited-stage HL patients treated with standard therapy.\(^6^0\) This study was limited by its retrospective design and variable FDG-PET/CT timing (intervals of PET 2-4), though these results have been corroborated.\(^6^1\),\(^6^2\) Sher and colleagues reported a 2-year failure-free survival (FFS) of 92% versus 69% for patients undergoing consolidation radiation therapy (RT) versus no RT for residual FDG-PET/CT avidity after completion of ABVD, indicating the potential efficacy of RT to a residual mass after chemotherapy.\(^6^2\) It should be highlighted that the efficacy of treatment is a crucial factor that may significantly alter the predictive value of FDG-PET/CT. In a prospective study of 88 patients with early-stage non-bulky HL treated with a non-standard regimen of 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 \((P=.0009)\) (Figure 2c).\(^3^8\) Although PPV was better, the NPV (86%) appeared to be inferior to previously published early-stage HL data (95%-100%) in part due to the lower CR rate achieved with the AVG regimen (81%) compared with standard ABVD (94%).

Collectively, initial reports of interim FDG-PET/CT for early-stage HL demonstrated 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, may contribute to a significant number of false-positive FDG-PET/CT results. The primary use of a PET-response–adapted strategy in early-stage HL is likely de-escalation of therapy (e.g., omission of consolidative radiation therapy) for those with negative interim FDG-PET/CT, while modified and/or escalated therapy may be more challenging due to the modest PPV of positive interim FDG-PET/CT.

**Phase II clinical trials using response-adapted strategies in early-stage HL.** There have been only a handful of phase II clinical studies completed using a response-adapted strategy with interim FDG-PET/CT for early-stage HL. Le Roux and colleagues reported results in patients with
early- and advanced-stage HL patients undergoing treatment with a response-adapted strategy after 4 cycles of ABVD (i.e., PET-4) (Table 1). In stage I/II non-bulky patients (n=26), PET-4 negative patients without progressive disease on CT or patients with CR on CT regardless of FDG-PET/CT findings received only IFRT. In patients with bulky stage I/II and advanced-stage disease (n=44), those with negative PET-4 received 4 more cycles of ABVD. The remaining 28 patients with positive PET-4 and no CR on CT underwent autologous stem cell transplant (SCT). The NPV and PPV with PET-4 for 2-year PFS were 95% and 16%, respectively (P<.0001). The low PPV reflects the likely negative impact that therapeutic intensification had on the predictive value of interim FDG-PET/CT results.

Dann and colleagues reported preliminary results from an ongoing phase II study examining response-adapted therapy that included early-stage HL (Table 1), while other phase II prospective studies have contained only a small minority of early-stage patients. Two US CALGB-led early-stage response-adapted studies await long-term follow-up and completion of patient accrual (Table 1). CALGB 50801 (NCT01118026) is an important clinical trial in that it is one of the few prospective response-adapted studies in early-stage HL that is studying patients with bulky disease.

**Completed phase III clinical trials using response-adapted strategies in early-stage HL.**

Recently completed response-adapted randomized studies are detailed and depicted in Table 2 and Figure 3. The European Organisation for Research and Treatment of Cancer (EORTC)-led H10F and H10U studies randomized patients with favorable and unfavorable early-stage HL (according to EORTC definitions) to FDG-PET-based versus non-PET-based treatment strategies in non-inferiority trials with the former representing the experimental arm(s). FDG-PET/CT negativity was defined as Deauville 5PS of 1 or 2; early-stage patients in both the H10F and H10U studies with negative PET-2 received chemotherapy alone versus CMT with involved-node radiation therapy (INRT) in the control (non-PET-based) treatment arm (see Table 2 and Figure 3). Patients with positive PET-2 in the experimental arms of H10F and H10U had treatment intensified to bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP)-escalated and
INRT. With relatively early follow-up, pre-planned interim analyses were performed for H10F and H10U.

In H10F, approximately 190 patients had been randomized to each study arm; the PET-2 negative rate was 86%. At that point, 1 event had occurred in the INRT arm versus 9 events in the PET-based (no INRT) arm. In the H10U study, approximately 260 patients had been randomized to each study arm with a PET-2 negative rate of 75%; 7 events had occurred in the INRT arm versus 16 in the PET-based (no INRT) arm. Despite the low absolute number of events, statistical analyses in both H10F and H10U showed that the null hypotheses of inferiority of the experimental PET-based treatment arms would not be rejected and futility was declared for both studies (P=.017 and P=.026, respectively). In other words, if accrual continued to the original number of planned study patients, it was unlikely that equivalence would be shown between the control and experimental arms. Thus, the data safety and monitoring committee amended the study adding INRT to all treatment arms. In addition, patient enrollment was increased in the PET+ arms to improve statistical power for the planned objectives. The study completed overall enrollment June 2011 with 1,952 total patients; results from the interim PET+ treatment groups are awaited.

Results from the United Kingdom (UK) National Cancer Research Institute RAPID study have been presented in abstract form. This was a phase III non-inferiority randomized study that enrolled 602 patients with stage I/II non-bulky HL. All patients (i.e., favorable and unfavorable groups) were included/studied in one cohort. All patients received 3 cycles of ABVD, which was followed by FDG-PET/CT (i.e., PET-3); negative FDG-PET/CT was also defined as Deauville 5PS of 1-2 (Table 2). Patients with positive PET-3 result received an additional cycle (fourth) of ABVD followed by IFRT, while PET-3 negative patients were randomized to IFRT versus no IFRT. The study was powered to exclude ≥7% difference in PFS (lowest acceptable 3-year PFS of 88% in the no IFRT arm). Of the initial 602 patients, 571 underwent PET-3 with 74.6% of patients being negative.

At a median follow-up of 49 months from randomization, the 3-year PFS rates on intent to treat (ITT) for PET-3 negative patients who received IFRT versus not were 94.5% (91.3%, 97.7%)
versus 90.8% (86.8%, 94.7%), respectively (hazard ratio (HR)=1.51, P=NS). Notably, this 3-year absolute risk difference yielded 95% CIs of 1.2% to -9.9% with the -9.9% limit exceeding the pre-specified non-inferiority boundary. It is important to highlight that, 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 (personal communication, John Radford). It should be noted that of the 5 early deaths on study, all occurred in patients prior to receiving allocated IFRT. Further, all 5 of these patients were ages >60 years with 3 deaths being due to apparent treatment-related toxicities and at least 2 of these deaths were due to pneumonitis. On the per protocol analysis, 3-year PFS was 97.0% for the IFRT arm compared with 90.7% for no IFRT (P=.03). This would suggest that non-inferiority is not present for 3-year PFS. OS at 3 years was 97.1% in the IFRT arm and 99.5% in the no-IFRT arm (ITT analysis, P=NS). Three-year PFS and OS rates from registration for the patients with a positive PET-3 were 86.2% and 94.3%, respectively. Final analysis and publication of this study is awaited.

**Non-inferiority study analyses.** There are several salient considerations when examining results from a non-inferiority trial. In a superiority trial, ITT analysis leads to more conservative analyses and robust conclusions by reducing bias in order to help ensure that post-randomization circumstances (e.g., non-compliance or contamination of prescribed therapy) do not confound the compared populations in a systematic way. For non-inferiority studies, these factors have the reverse impact. An ITT brings the results of a comparative study closer together and may “hide” a truly inferior comparator treatment arm. Thus, one should perform a “per protocol” analysis in non-inferiority studies. Furthermore, the expectation is that the per protocol analysis yield the same result as ITT, otherwise this may lead to uncertainty and instability regarding the ultimate correct study conclusion.

**Ongoing phase III clinical trials using response-adapted strategies in early-stage HL.** The GHSG is examining the strategy of response-adapted therapy for favorable and unfavorable HL in the HD16 and HD17 non-inferiority randomized trials, respectively (Table 2).
(NCT00736320) and HD17 (NCT01356680) are similar to the EORTC design in randomizing patients to a standard non–PET-based treatment versus a PET response-adapted therapeutic strategy (i.e., no IFRT with negative FDG-PET/CT) as shown in Figure 3. A notable difference in treatment is the use of BEACOPP escalated as a component of therapy in HD17. Further, the non-inferiority margins for these studies are set at 5%. It may be anticipated that similar results of “inferiority” for PFS will be identified for the non-RT arms, however the treatment groups are defined differently for GHSG versus the EORTC studies and a non-ABVD regimen is being examined for the unfavorable group in HD17. Results from these studies are eagerly awaited.

FDG-PET Considerations, New Imaging Techniques, and Novel Therapeutic Agents

Additional FDG-PET considerations. The results of interim FDG-PET/CT studies should be reviewed with the understanding of limitations for their generalizability and the interpretation criteria. The PPV of PET-2 in HL needs to be further improved to better guide management even after implementation of the Deauville 5PS criteria. There are data suggesting that PET-2 positive patients have larger lesions after cycle 2 of therapy. 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 2-year PFS. The combined analysis of PET-2 with CECT-2 data suggested an improvement in prediction of 2-year PFS compared with each test alone. In the PET-2–positive group, a negative diagnostic CECT-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%, although some confidence intervals were not reliable due to small sample sizes. These findings were supported by recent data after chemotherapy in advanced stage HL patients treated in the HD15 GHSG trial. In a subgroup of 54 PET-positive patients after completion of chemotherapy with a reduction in tumor size of <40%, the risk of progression or relapse within the first year was 23% versus 5% for patients with a larger
reduction. These results should prompt further examination of the combination of PET-2 and diagnostic CECT towards a fusion of qualitative and quantitative analyses.

**New techniques.** There are ongoing efforts to develop PET-based and other quantitative methodologies that measure tumor metabolic volume (MTV) or total lesion glycolysis (TLG), which may be a more accurate assessment of disease/tumor burden. In a recent study, pre-treatment PET parameters metabolic tumor volume (MTV) and maximum standardized uptake value (SUVmax) did not correlate with outcome, however change in MTV between interim and baseline studies was associated with median PFS ($P=0.01$) as was SUVmax ($P=0.02$).46 In addition, a recent analysis examined the prognostic importance of baseline (pre-treatment) total MTV in untreated HL patients.47 Baseline total MTV more accurately predicted outcome than tumour bulk and it was prognostic in multivariate analysis for PFS.

Novel imaging biomarkers include measure of tumor heterogeneity, which is emerging as an important factor in imaging analyses.48 The noninvasive assessment of tumor proliferative activity may also provide a 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.49 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 staging. The clinical utility of FLT as an early response surrogate to date has been demonstrated in preliminary clinical studies in non-Hodgkin lymphoma.49

Multiparametric MRI, which combines anatomic T2-weighted (T2W) imaging with dynamic contrast-enhanced MRI (DCE-MRI), and diffusion-weighted imaging (DWI) evaluating perfusion and diffusion characteristics, respectively.50 DCE-MRI provides assessment of tumor angiogenesis and enables the depiction of physiologic alterations as well as morphologic changes. A preliminary study reported improvement in detection of splenic involvement in HL when T2-weighted imaging was complemented by DCE-MRI.51 However, quantitative analysis of MRI data using DCE-MRI is still in
evolution. With the advent of integrated PET/MRI platforms, the potential complementary nature of MRI and PET will undergo continued investigation.

**Novel therapeutic agents.** Brentuximab vedotin (BV) is an antibody drug conjugate with significant activity for patients with relapsed/refractory HL and clinical studies are ongoing that incorporate this agent earlier in the treatment course of HL patients, including frontline. It will be important to determine the impact of FDG-PET/CT with BV alone as well as in combinations with standard chemotherapy. There are recent FDG-PET/CT data in relapsed/refractory and newly diagnosed HL. Using Deauville 5PS as visual analysis, investigators analyzed the prognostication of interim FDG-PET/CT with single-agent BV for a small cohort of relapsed/refractory HL patients. After a median of 3 BV doses, 67% were interim-PET positive (5PS 4-5); 1-year PFS rates were 100% and 38%, respectively, for patients with negative and positive interim FDG-PET/CT, respectively (P=.033).

Additional FDG-PET/CT data using sequential BV followed by ICE chemotherapy prior to autologous SCT have been reported; the PET negative rate (5PS 1-3) using concurrent BV and ABVD or AVD chemotherapy for newly diagnosed HL was 96%. The prognostic impact of FDG-PET/CT with incorporation of novel therapeutic agents should continue to be examined.

**Conclusions**

FDG-PET/CT is an important tool for clinicians in the diagnosis and management of patients with HL. Standardization of the interpretation and reproducibility of FDG-PET/CT (e.g., Deauville 5PS) have been critical in the routine application of this imaging modality in clinical practice. Prospective and randomized clinical studies evaluating the impact of FDG-PET/CT for response-adapted approaches have been completed. In terms of the question: is interim FDG-PET/CT a compass for a safe navigation in HL? The current answer with existing techniques and available data is: no. Based on present data, FDG-PET/CT has not been able to discriminate a low-risk early-stage HL group whereby RT maybe be obviated with respect to acute disease control. The type or modification of therapy based on interim FDG-PET/CT in early-stage HL is not advocated in routine
clinical practice at this time. It should also be considered that the currently available results from response-adapted studies do not dictate that RT should be recommended for all early-stage HL patients. In part since the primary goal in treating most HL patients is long-term OS, it remains a clinical management choice for physicians and patients to decide. Figure 4 depicts personal recommendations for the treatment of early-stage HL based on currently available data.

In addition, there should not be a rush towards final judgment regarding FDG-PET/CT response-adapted data in HL. We must await longer follow-up of reported trials and the outcomes of recently completed and ongoing FDG-PET/CT response-adapted studies in early-stage HL are eagerly awaited especially towards potential longer-term OS differences that may be gleaned. We also await data from the treatment arms with ‘positive’ interim FDG-PET/CT whereby in most cases treatment was escalated to more intensive therapy. Further, there are multiple important ongoing response-adapted clinical trials in advanced stage HL where the prognostic impact of FDG-PET/CT is much more pronounced. We should also continue to explore new and novel techniques of functional imaging and innovative applications such as metabolic tumor burden/volume, tumor proliferation via FLT, and integrated PET/MRI. Finally, the examination of the prognostic impact of FDG-PET/CT with new/targeted therapeutic agents is needed and the integration of biologic biomarkers in combination with functional imaging modalities should be investigated in order to identify the most robust predictive markers of patient outcome.

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Table 1. Prospective Non-Controlled Response-Adapted Studies in Adult Early-Stage (I-II) Hodgkin Lymphoma.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Treatment</th>
<th>Number</th>
<th>Interim PET+</th>
<th>PPV</th>
<th>NPV</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Roux, 2011</td>
<td>Stages I-IV</td>
<td>ABVD x 4 (FDG-PET): I/II non-bulky: PET- and/or CR on CT IFRT; PET+ SCT II bulky/III/IV: PET- ABVD x 4; PET+ SCT</td>
<td>90 (45 stage I/II)</td>
<td>34% (all pts)</td>
<td>16% (all pts)</td>
<td>95% (all pts)</td>
<td>NA</td>
</tr>
<tr>
<td>Dann, 2013</td>
<td>Stage I-IIA-B non-bulky</td>
<td>ABVD x 2 (FDG-PET): F: PET- INRT; PET+ ABVD x 2 + INRT (PET 4)a U: PET- ABVD x 2 + INRT; PET+ ABVD x 4 + INRT (PET 4)a</td>
<td>350/350b</td>
<td>13%</td>
<td>26%</td>
<td>93%</td>
<td>2-year PFS 94%</td>
</tr>
<tr>
<td>CALGB 50604</td>
<td>Stage I-IIA-B non-bulky</td>
<td>ABVD x 2 (FDG-PET): PET- ABVD x 2 PET+ BEACOPP-esc x 2 + 30Gy IFRT</td>
<td>160/160</td>
<td></td>
<td></td>
<td></td>
<td>Accrual completed February 2013; preliminary results expected late 2014</td>
</tr>
<tr>
<td>CALGB 50801</td>
<td>Stage I-IIA-B bulky</td>
<td>ABVD x 2 (FDG-PET): PET- ABVD x 4 PET+ BEACOPP-esc x 4 + 30Gy IFRT</td>
<td>53/123b</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; esc, escalated; CR: complete remission; CT, computerized tomography; SCT, stem cell transplantation; F: favorable; U: unfavorable; INRT, involved nodal radiation therapy; IFRT, involved field radiation therapy; Gy, Gray; NPV, negative predictive value; PPV, positive predictive value; PFS, progression-free survival; NA, not available.

aBiopsy done if PET-4 is +; patients receive same therapy as PET-4 negative for negative biopsy and salvage therapy for positive PET-4 biopsy.

bEnrollment as of June 2014.
Table 2. Randomized Phase III Response-Adapted Studies in Adult Early-Stage (I-II) Hodgkin Lymphoma.*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Enrollment(^a)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC/LYSA/FIL H10F(^41)</td>
<td>Favorable group</td>
<td>761/761(^a) (381 PET- pts)</td>
<td>1-year PFS rates 100.0% and 94.9% in standard and experimental arms, respectively; estimated HR 9.36 (79.6% CI, 2.45 to 35.73)</td>
</tr>
<tr>
<td>EORTC/LYSA/FIL H10U(^41)</td>
<td>Unfavorable/intermediate group</td>
<td>1191/1191(^a) (519 PET- pts)</td>
<td>1-year PFS rates 97.3% and 94.7% in standard and experimental arms, respectively; estimated HR 2.42 (80.4% CI, 1.35 to 4.36)</td>
</tr>
<tr>
<td>UK NCRI RAPID(^42)</td>
<td>Favorable and unfavorable/intermediate groups combined (non-bulky)</td>
<td>602/602</td>
<td>3-year PFS for no RT versus IFRT in PET– pts: 91% versus 95% by ITT ((P=.23)) and 91% versus 97% by protocol analysis ((P=.03)); 3-year PFS for PET+ 85%</td>
</tr>
<tr>
<td>GHSG HD16 (NCT01356680)</td>
<td>Favorable group</td>
<td>686/1100(^b)</td>
<td>NA</td>
</tr>
<tr>
<td>GHSG HD17 (NCT00736320)</td>
<td>Unfavorable/intermediate group</td>
<td>283/1100(^b)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; EORTC, European Organisation for Research and Treatment of Cancer; esc, escalated; LYSA, Lymphoma Group and the Lymphoma Study Association; FIL, Fondazione Italiana Linfomi; pts, patients; GHSG, German Hodgkin Study Group; PET–, PET-negative; PFS, progression-free survival; RT, radiation therapy; UK NCRI, United Kingdom National Cancer Research Institute; NA, not available.

*See Figure 3 for study designs.

\(^a\) Interim/early analysis performed and study amended based on these results adding radiation to all arms

\(^b\) Enrollment as of April 2014.
Figure Legends.

Figure 1. The Deauville 5 point system (5PS). These are the criteria for interpretation of interim F-fluorodeoxyglucose positron emission tomography (FDG-PET/CT). A Deauville score >3 is the most optimal cutoff for interim PET with advanced-stage HL to increase positive predictive value, whereas a cutoff <3 is desirable for non-bulky early-stage HL in order to enhance negative predictive value. Abbreviations: HL, Hodgkin lymphoma; ES, early-stage; AS, advanced stage.

Figure 2. Prognostication of FDG-PET/CT in early-stage HL. Progression-free survival (PFS) according to the result of interim FDG-PET/CT (status-post 2-3 ABVD cycles) of (A) 57 early-stage and (B) 28 advanced-stage HL patients. Treatment was continued regardless of FDG-PET/CT result. Reprinted with permission from Hutchings M, Mikhaeel NG, Fields PA, Nunan T, Timothy AR. Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. Ann Oncol. 2005;16(7):1160-1168. (C) PFS for 88 patients with early-stage non-bulky HL treated on a US Cooperative group phase II study using doxorubicin, vinblastine, and gemcitabine (AVG) frontline therapy. Abbreviations: Incl, including; MRU, minimal residual uptake. Reprinted with permission from Straus DJ, Johnson JL, LaCasce AS, et al. Doxorubicin, vinblastine, and gemcitabine (CALGB 50203) for stage I/II nonbulky Hodgkin lymphoma: pretreatment prognostic factors and interim PET. Blood. 2011;117(20):5314-5320.

Figure 3. Clinical trial designs of recently completed and ongoing phase III randomized studies of response-adapted therapy for adult early-stage HL. (A) EORTC/LYSA/FIL H10F study; *none of the following present: a) large mediastinal mass; b) age ≥50 years; c) high ESR; or d) 4 or more areas; (B) EORTC/LYSA/FIL H10U study; *any of the following present: a) large mediastinal mass; b) age ≥50 years; c) high ESR; and/or d) 4 or more areas; (C) UK-led RAPID study; all PET-3 + patients received a 4th cycle of ABVD followed by 30 Gray of involved field radiotherapy; (D) GHSG HD16 favorable trial; *none of the following present: a) large mediastinal mass; b) extranodal disease; c) high ESR; or d) 3 or more areas; (E) GHSG HD17 unfavorable trial; *any of the following present: a) large mediastinal mass; b) extranodal disease; c) high ESR; and/or d) 3 or more areas. High ESR for all of above defined as: >50mm without B symptoms or ESR <30mm with B symptoms. Abbreviations: HL, Hodgkin lymphoma; EORTC, European Organisation for Research and Treatment of Cancer; esc, escalated; LYSA,
Lymphoma Group and the Lymphoma Study Association; FIL, Fondazione Italiana Linfomi; pts, patients; UK, United Kingdom; GHSG, German Hodgkin Study Group.

**Figure 4. How I treat early-stage adult Hodgkin lymphoma in 2014.** These are treatment strategies as advocated by Dr. Evens based on current clinical data. Based on available data, treatment should not be modified based on results of interim FDG-PET/CT; however, continued follow-up is needed of ongoing studies including results from studies examining changes/intensification based on ‘positive’ interim FDG-PET/CT. The treatment algorithms are separated by different early-stage subgroups (i.e., favorable, unfavorable (non-bulky), bulky, and older patients).
Figure 1. Deauville 5PS Criteria (Interim PET)

Score 1: No uptake

Score 2: Uptake ≤ mediastinum

Score 3: Uptake > mediastinum but ≤ liver

Score 4: Moderately ↑ uptake > liver

Score 5: Markedly ↑ uptake > liver
Figure 3

A. Stage I/II Favorable*
   - Standard Arm
     - 2 x ABVD PET (+/-)
     - 1 x ABVD 30 Gy INRT
   - Experimental Arms
     - 2 x ABVD PET-
     - 2 x ABVD PET+
     - 2 x BEACOPP esc INRT 30 Gy

B. Stage I/II Unfavorable*
   - Standard Arm
     - 2 x ABVD PET (+/-)
     - 2 x ABVD 30 Gy INRT
   - Experimental Arms
     - 2 x ABVD PET-
     - 4 x ABVD
     - 2 x BEACOPP esc INRT 30 Gy

C. Stage I/II (non-bulky)
   - 3 x ABVD
     - *PET –
     - Standard Arm
       - 30 Gy IFRT
     - Experimental Arm
       - No further treatment

D. Stage I/II without RF*
   - Standard Arm
     - 2 x ABVD PET (+/-)
     - 20 Gy IFRT
   - Experimental Arms
     - 2 x ABVD PET-
     - Follow-up
     - 20 Gy IFRT

E. Stage I/II without RF*
   - Standard Arm
     - 2 x ABVD PET (+/-)
     - 20 Gy IFRT
   - Experimental Arms
     - 2 x ABVD PET-
     - Follow-up
     - 20 Gy IFRT
Figure 4. How I Treat Early-Stage Hodgkin Lymphoma in 2014.

- **Favorable***
  - Younger women (i.e., ages <35 years) with chest disease and/or other risk factors (e.g., arterial disease): 3-4 cycles ABVD
  - All others: 2 x ABVD followed by 20 Gy IFRT

- **Unfavorable (non-bulky)**
  - 4-6 x ABVD

- **Bulky**
  - 6 x ABVD followed by 30 Gy IFRT

- **Older patients (>65 years)**
  - Similar as above except with *a priori* exclusion of bleomycin (i.e., AVD)

*As determined by German Hodgkin Study Group criteria (i.e., none of the following): a) large mediastinal mass; b) extranodal disease; c) high ESR; d) 3 or more areas
The role of interim FDG-PET in defining prognosis of Hodgkin lymphoma for early stage disease

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