Published in final edited form as:

Curr Opin Oncol. 2008 March ; 20(2): 206–219. doi:10.1097/CCO.0b013e3282f5123d.

FDG PET and risk-adapted therapy in Hodgkin's and non-Hodgkin's lymphoma

Yvette L. Kasamon^a and Richard L. Wahl^b

^aDepartment of Oncology and Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA

^bDepartment of Oncology and The Russell H. Morgan Department of Radiology and Radiological Science, Division of Nuclear Medicine, Johns Hopkins University, Baltimore, Maryland, USA

Abstract

Purpose of review—The prognostic utility of midtreatment fluorine-18 fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) has become widely appreciated in aggressive B-cell non-Hodgkin's lymphoma and, more recently, in Hodgkin's lymphoma. Outcomes based on midtreatment FDG PET performed during primary and salvage therapy are reviewed and management strategies considered, with a focus on treatment intensification for poor-risk disease as identified by metabolic imaging.

Recent findings—PET, when performed after as few as two cycles of primary chemotherapy, is strongly prognostic in certain aggressive lymphomas and provides information independently from validated prognostic indices. What constitutes a positive or negative scan is not always clear, particularly if there is minimal tracer uptake, and the causes of false positive and false negative scans must be considered. How to tailor therapy based on the midtreatment PET result is the focus of current trials and is presently being defined for both Hodgkin's and non-Hodgkin's lymphoma.

Summary—Early PET has the strong potential to improve clinical outcomes by sparing good-risk patients from overly aggressive treatments, and by more accurately identifying poor-risk patients so as to guide changes in management. Treatment modifications on the basis of midtreatment PET are presently best made in clinical trial settings.

Keywords

FDG PET; Hodgkin's lymphoma; non-Hodgkin's lymphoma; prognosis; transplantation

Introduction

Metabolic imaging with fluorine-18 fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) is rapidly changing how patients with a variety of lymphomas are staged, restaged, risk-stratified and managed. FDG PET complements computed tomography (CT) scans in initial staging evaluation, in many histologies offering superior diagnostic accuracy by detecting subcentimeter lesions missed on CT [1–3]. FDG PET can also help to differentiate viable tumor from fibrosis in masses that persist after chemotherapy, translating into fewer posttreatment false positive results [4]. The recently proposed, revised response criteria for lymphoma clinical trials integrate metabolic and conventional anatomic imaging

[5••,6••]. These criteria are based upon the recognition that the size of a residual mass correlates poorly with prognosis, and that the posttreatment FDG PET result is a powerful indicator of outcome in both Hodgkin's lymphoma and aggressive B-cell non-Hodgkin's lymphomas [7,8]. FDG PET, when performed during chemotherapy, however, is at least as prognostic and has the potential to help tailor treatment based upon individual patient risk and response. We focus upon how FDG PET, when performed early during treatment, can guide risk-adapted strategies in patients with newly diagnosed or relapsed aggressive B-cell lymphoma.

Categorizing risk with midtreatment metabolic imaging: newly diagnosed lymphoma

As discussed next, PET performed after as few as two cycles of chemotherapy has reasonably consistently predicted outcome in patients with newly diagnosed aggressive B-cell lymphoma, with a positive midtreatment PET scan being associated with a significantly inferior prognosis than a negative midtreatment scan [9,10••]. The findings in aggressive non-Hodgkin's lymphoma and Hodgkin's lymphoma are reproducible despite the mixture of prospective and retrospective studies, histologies, treatments, scanning techniques and methods of FDG PET assessment - qualitative (by visual assessment) or semiquantitative (with standardized uptake values). The data suggest that what defines prognosis is not simply whether the PET becomes negative during treatment, but how quickly this occurs.

What might the midtreatment PET result signify? In an idealized setting, chemotherapy acts by first-order kinetics (killing the same fraction rather than the same number of tumor cells with each cycle) [11]. Thus, assuming no interval regrowth of resistant tumor, one would expect most of the tumor burden to be eliminated early during the treatment course - as early as the first two cycles (Fig. 1) [12]. According to this model, the true midtreatment PET result implies a certain rate of tumor cell kill, which is either adequate or inadequate for achieving cure by the time that therapy is completed (Fig. 1) [13]. Indeed, in both Hodgkin's lymphoma and aggressive non-Hodgkin's lymphoma, cycle 4 PET has not added prognostic information to PET obtained after cycle 2 [14,15]. 'Slow' metabolic response portends an inferior prognosis, and PET after only one cycle has been reported to have prognostic significance [16,17]. Having a baseline PET scan can be very helpful to determine how much cell kill has occurred as well as how FDG-avid the tumor was at the outset of therapy.

A negative PET does not necessarily mean absence of disease. The lower limit of PET detection in lymphoma is a mass of approximately 0.5–1cm depending on tumor avidity [1,18], which translates roughly into 10^8 to 10^9 tumor cells. As such, one could have no, or many millions, of viable tumor cells remaining in the context of a negative PET scan.

Newly diagnosed non-Hodgkin's lymphoma

Numerous studies have confirmed the strong prognostic significance of FDG PET performed after 2–4 cycles of first-line chemotherapy for aggressive non-Hodgkin's lymphoma [9,14,19–24]. In these studies, the PET result is most commonly designated as 'negative' or 'positive', wherein 'negative' is defined as having no evidence of malignant disease, with any uptake being limited to that expected for an anatomic site; and 'positive' is defined as having focal or diffuse uptake in an area incompatible with normal anatomy and consistent with malignant disease [9]. The exact criteria for a positive PET scan can vary by study, but typically represent tumor tracer activity well above the background uptake levels.

In representative series of newly diagnosed non-Hodgkin's lymphoma, in which early PET did not influence scheduled therapy, relapse or disease progression has been consistently noted in 71–100% of patients with positive midtreatment PET scans, associated with a 2-

year progression-free or event-free survival (EFS) of 0-30% (Table 1). A more promising 2-year EFS of 43% in patients with positive cycle 2 PET included a subset that received consolidative high-dose therapy and autologous blood or marrow transplantation (BMT) as part of planned therapy [14]. In contrast, negative midtreatment PET after two or more cycles has predicted failure rates of 0-36%, translating into an estimated 2-year EFS of 72-93%. The median time to treatment failure is also significantly shorter in patients with a positive midtreatment PET (1.5 months vs. 35 months if PET-negative, in the original series by Spaepen *et al.*[9]). The median follow-up in these series is relatively short, in the order of 2-3 years; however, the divergence in outcome based on metabolic imaging results is marked between the PET-positive and PET-negative groups.

Newly diagnosed Hodgkin's lymphoma

Recently, the prognostic significance of midtreatment PET in newly diagnosed Hodgkin's lymphoma has also become widely appreciated [10•,15,23,25-28] (Table 2). After 2-3 cycles of first-line chemotherapy, PET has been highly specific, with negative predictive value of 94-100% on relatively short (generally 2-year) follow-up. Whereas a negative PET has been associated with a 2-year EFS of 95-100%, a positive PET has been associated with a 2-year EFS of 0-13%.

The majority of patients with Hodgkin's lymphoma are cured with first-line chemotherapy; as such, the number of treatment failures (and the proportion having positive early PET results) is low compared with aggressive non-Hodgkin's lymphoma. Correspondingly, the positive predictive value of cycle 2-3 PET in Hodgkin's lymphoma is based on relatively small numbers (from as low as four, to 50 in the largest series), and has varied from 61.5% to 100% (Table 2). Hodgkin's lymphoma also deserves special consideration with regard to histology. Except in the rare lymphocyte-depleted subtype, most of the tumor in classical Hodgkin's lymphoma is composed of an intense, benign inflammatory infiltrate, with interspersed malignant Hodgkin/Reed-Sternberg cells usually constituting only about 1% of the mass. This contrasts with other lymphomas. As such, although midtreatment and end-of-treatment PET scans have clear prognostic significance in both Hodgkin's lymphoma and non-Hodgkin's lymphoma, the source of the FDG uptake in Hodgkin's lymphoma is likely both benign and malignant cells. This should particularly be kept in mind when reviewing a borderline or positive scan in Hodgkin's lymphoma, and may, along with the small numbers, explain some of the variability noted in positive predictive value of midtreatment PET [29,30]. Certainly, the approach to image interpretation (a sensitive or a more specific one) can also influence both the negative and positive predictive value of the test.

FDG PET in relation to prognostic indices

Validated prognostic indices, such as the International Prognostic Index (IPI) [31] in aggressive non-Hodgkin's lymphoma and the International Prognostic Score (IPS) [32] in Hodgkin's lymphoma, provide valuable information that guides the design and interpretation of clinical trials, as well as patient management. These are population-based parameters, however, and they also do not provide information about the quality of the treatment response as they are determined prior to treatment. In contrast, midtreatment metabolic imaging permits an individualized, early assessment of response and risk and has strong prognostic significance independent of the IPI [9,21] or IPS [10•]. For example, Spaepen *et al.*[9] found that, in a series of 70 patients with aggressive non-Hodgkin's lymphoma treated with anthracycline-containing therapy, midtreatment PET more strongly predicted progression-free ($P < 0.0000001$) and overall ($P < 0.000009$) survival than did the IPI ($P = 0.11$ and $P = 0.03$).

The IPS (consisting of seven pretreatment factors that independently predict outcome) [32] has been widely applied for risk assessment in advanced Hodgkin's lymphoma, and has been the basis for planning risk-stratified clinical trials. The estimated 5-year failure-free survival ranges from 84% in patients with a risk score of 0, to 42% in those with a risk score of 5 or greater. In a potentially paradigm-shifting paper by Gallamini *et al.* [10••] (Table 2), 260 Hodgkin's lymphoma patients with newly diagnosed, stage II-IV disease were prospectively evaluated with PET after two cycles of mostly doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) without change of therapy on this basis. On median 2.2-year follow-up, there was a stark divergence in outcome, with 2-year progression-free survival of approximately 13% in PET-positive patients vs. 95% for PET-negative patients as determined by visual assessment. Univariate analysis identified a number of significant factors including cycle 2 PET and the IPS score, and patients with a higher IPS were more likely to have a positive midtreatment PET (38% PET-positive if IPS 3–7, and 13% if IPS 0–2). On multivariate analysis, however, the IPS as a continuous variable dropped out, and only cycle 2 PET ($P<0.0001$) and stage IV disease had independent prognostic value. Although reproducibility of PET readings is always an issue (particularly in cases of 'borderline' scans), the implications for clinical trial design and for managing individual patients are substantial.

High-dose therapy for lymphoma and the significance of FDG PET

High-dose therapy with autologous BMT is the standard approach for relapsed aggressive diffuse large B-cell lymphoma, provided that the lymphoma is sensitive to salvage therapy [33]. Chemoresistant relapse is a particular problem, however, with poor outcomes regardless of the treatment modality. The overwhelming majority of patients with resistant non-Hodgkin's lymphoma will have disease progression despite BMT, which in this setting confers a 3-year EFS of approximately 20% at best [34,35]. As only about 60% of cases of relapsed aggressive non-Hodgkin's lymphoma are chemosensitive (defined by achievement of at least a partial anatomic response to salvage chemotherapy), numerous clinical trials have examined early (preemptive) BMT as part of front-line therapy. Results have however been mixed: some studies suggest a benefit [36], while others suggest no benefit or even a disadvantage [37] to early BMT. The divergent results are in part explained by the heterogeneity of induction regimens, induction cycles (short course vs. full course) and patient features. As such, the role of upfront BMT remains controversial, with the published data used both to support and refute its appropriateness.

What is evident, however, is that the benefit of early BMT is most pronounced in patients who have poor-risk features [36,38•,39,40]. Furthermore, although the IPI has traditionally been used to determine which patients may warrant early BMT, the prognostic significance of midtreatment PET has highlighted the limitations of using the IPI and conventional anatomic response criteria in risk-stratifying individual patients. This is likely one reason for the heterogeneous outcomes of studies of early BMT. The PET data raise the interesting possibility of using midtreatment metabolic imaging, rather than pretreatment parameters such as the IPI, to select patients for early treatment intensification. As discussed later, this strategy has begun to be investigated [13].

For newly treated or relapsed disease, the results of midtreatment metabolic imaging expand the definition of chemosensitive and chemoresistant disease [41]. In relapsed or refractory lymphoma patients, multiple studies have demonstrated the prognostic significance of the FDG PET result after salvage chemotherapy, prior to high-dose therapy and BMT [41–45,46•,47–51] (Table 3). With exceptions, many of these studies are relatively small and are heterogeneous in terms of timing of transplant (front-line, relapsed, refractory), histology (including combined analyses of non-Hodgkin's lymphoma and Hodgkin's lymphoma),

transplant procedure, metabolic response criteria, and length of follow-up, which is generally short (Table 3). What can be concluded, however, is that patients who have positive PET scans at the time of BMT have a substantially inferior prognosis compared with patients whose PET scans become negative. Relapsed patients who respond to salvage therapy by CT criteria may very well have an inadequate response by metabolic criteria; FDG PET in this setting helps to distinguish who is 'chemosensitive' or 'chemorefractory' [45]. Indeed, a prognostic score for relapsed/refractory lymphoma patients, which combines a clinical risk score with the results of prehigh-dose therapy metabolic imaging, more accurately distinguishes outcomes in non-Hodgkin's lymphoma and has the potential to improve patient selection for BMT [46•].

The data have understandably generated lack of enthusiasm about transplanting relapsed patients with residually PET-positive tumors. Nonetheless, the limitations of these studies must be considered. As indicated above, while most PET-positive patients have poor outcomes, the prognostic power of PET is imperfect. Another consideration is that, among patients with positive interim PET who go on to salvage therapy, prognosis might differ depending on the intensity of abnormal FDG uptake. Studies incorporating an FDG scale, which differentiates 'moderate' from 'strong' tumor FDG uptake [13,45], should help address this question. Given the present amount of data and a defined (albeit far from optimal) salvage rate with BMT, one should not deny BMT to an otherwise appropriate candidate solely because of a residually positive PET scan. In the absence of disease progression, some of these patients may in fact stand to benefit most from transplantation. Whether allogeneic rather than autologous BMT is more advantageous in this setting (because of a potential graft-versus-lymphoma effect, and not reinfusing tumor with the graft) is not yet known and is worthy of investigation.

Progress with risk-adapted therapy based on FDG PET

Risk-adapted and response-adapted approaches based on the results of midtreatment FDG PET have recently begun to be investigated in non-Hodgkin's lymphoma and Hodgkin's lymphoma. As this is a relatively new research focus, the optimal strategy is not yet defined. Nonetheless, such studies clearly have the potential to define ways to minimize toxicity in good-risk patients, while reserving more intensive therapies for patients who stand to benefit most from them.

Approaches investigated in non-Hodgkin's lymphoma

Clinical trials in which therapy is modified based on the results of midtreatment PET are now ongoing or recently completed. For example, promising outcomes were seen in a recently completed phase II, risk-adapted trial at Johns Hopkins for newly diagnosed aggressive non-Hodgkin's lymphoma [13]. Investigators hypothesized that early FDG PET would identify those patients who stood to benefit most from preemptive BMT vs. continued conventional-dose chemotherapy. In the absence of disease progression, patients with poor-risk disease, defined by a positive FDG PET performed after two or three cycles of first-line chemotherapy, received rituximab, etoposide, methylprednisolone, cytarabine and cisplatin (R-ESHAP) or rituximab, ifosfamide, carboplatin and etoposide (R-ICE) followed by high-dose therapy and autologous BMT; whereas those with a negative midtreatment PET completed full-course, standard rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). Equivocal PET results (tumor FDG uptake equal to mediastinal blood pool) were scored as negative. Of 58 evaluable patients (most with large B-cell lymphoma), 32 (55%) had a positive midtreatment PET and 28 of these proceeded to BMT regardless of stage or IPI. Biopsies of PET-positive foci were not performed. On preliminary analysis, the estimated 2-year EFS after BMT was promising at 67%, compared with 86% in the PET-negative cohort treated with R-CHOP alone.

A different, promising strategy was preliminarily reported by the Memorial Sloan-Kettering group for newly diagnosed, advanced diffuse large B-cell lymphoma with risk factors [52]. After four cycles of dose-dense R-CHOP, patients with a negative PET or those with a positive PET (defined as activity above background) but negative biopsy received ICE for three cycles; whereas patients with a positive PET who had biopsy confirmation of residual disease received ICE for two cycles, then R-ICE, as a bridge to BMT. Of 86 patients, 31 had a positive midtreatment PET scan, but interestingly only four of these (13%) had a positive biopsy and received BMT. In contrast to other experiences to date, there was no significant difference in EFS in those with a positive or negative midtreatment PET, with an estimated EFS of 88% overall on median 20-month follow-up.

The Memorial Sloan-Kettering investigators [52] concluded that the false positive rate of midtreatment restaging PET was 87% in this interim report. Details of the criteria used to interpret the PET images are awaited. Notably, however, the prognostic value of both midtreatment and posttreatment PET was established without the use of rebiopsies. Furthermore, false negative biopsy results due to sampling error are possible, and biopsy may be impractical or risky. The literature on the pathology of midtreatment lymphoma lesions appears limited and not as well established as for posttreatment biopsy. For example, in a study of 27 Hodgkin's lymphoma patients who had abnormal PET within 2 months after completion of first-line therapy, 23 had active Hodgkin's lymphoma documented on biopsy and only four biopsies were benign [53]. The excellent preliminary outcome of this particular PET-positive non-Hodgkin's lymphoma cohort treated with ICE contrasts with the poor outcomes seen consistently in other studies of PET-positive patients treated with standard anthracycline-based therapy (Table 1). The contribution of ICE to these promising outcomes warrants investigation. An ongoing Eastern Oncology Cooperative Group trial (E3404) of risk-adapted therapy will help to address this question. In this study, patients with newly diagnosed stage II bulky, III or IV diffuse large B-cell lymphoma receive PET after three cycles of R-CHOP; those who are PET-positive receive one additional cycle of R-CHOP followed by four cycles of R-ICE, whereas those who are PET-negative complete a total of six cycles of R-CHOP.

As another example of risk-adapted therapy, Canadian investigators recently reported on a strategy for limited-stage non-Hodgkin's lymphoma based on midtreatment metabolic imaging [54]. Patients with stage I or IIA, nonbulky diffuse large B-cell lymphoma who had a negative PET after three cycles of R-CHOP completed a fourth cycle, whereas those with a positive PET received involved-field radiation therapy [54]. On median 17-month follow-up of the first 50 patients, the estimated 2-year EFS was 97% if PET-negative and 67% if PET-positive. More mature results are awaited but these data support, as do many other studies, the prognostic value of the midtreatment PET scan.

An important question requiring further study is the contribution of biologic therapies, and rituximab in particular, to the midtreatment or posttreatment FDG PET result. One could imagine that antibody therapies could induce a local inflammatory response, leading to a false positive signal on FDG PET. In an analysis of B-cell lymphoma patients treated with iodine-131 anti-CD20 radioimmunotherapy, the standardized uptake volume measured 6 or 7 days after the tracer dose rose transiently compared with baseline values in one out of six responders, declined in the remainder [55]. In addition, clinical exams in some patients showed evidence of tumor warmth following infusions of anti-CD20 antibodies, suggesting immunological reactions could be contributing to the PET signal observed. Most of the studies of midtreatment PET in non-Hodgkin's lymphoma have involved heterogeneous regimens that either did contain, or variably contained, rituximab. In the prospective study by Haioun *et al.* [14], however, midtreatment PET had prognostic significance regardless of whether patients had received rituximab. Likewise, in an analysis of prehigh-dose therapy

metabolic imaging in non-Hodgkin's lymphoma using either gallium-67 scintigraphy or FDG PET, the metabolic imaging result and treatment with high-dose rituximab were independent predictors on multivariate analysis [51] (Table 3). Prospective studies such as the Cancer and Leukemia Group B 50303 phase III trial of R-CHOP vs. dose-adjusted rituximab, etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone (R-EPOCH) for diffuse large B-cell lymphoma, which incorporates cycle 2PET/CT without change in therapy, will further inform the rituximab question [56].

Approaches investigated in Hodgkin's lymphoma

Risk-adapted strategies based on early metabolic imaging are also being investigated in Hodgkin's lymphoma. Efforts to lower toxicity while preserving or improving cure rates are a major research focus, as Hodgkin's lymphoma is typically a disease of younger individuals wherein late treatment toxicities are a dominant concern.

As a leading example, in early-stage Hodgkin's lymphoma (which is standardly treated with combination chemotherapy plus involved-field radiation), concerns about the late toxicities of radiation have led to recent randomized studies of extended-course chemotherapy alone for nonbulky disease [57–59]. Chemotherapy alone has emerged as a viable option, but the topic has generated intense debate [60,61]. There are patients who stand to benefit from the addition of radiation, but how best to identify them is not known. PET scans performed during or after chemotherapy promise to guide this decision, although there are not yet published clinical trials in this regard. In a phase III study of early stage Hodgkin's lymphoma by the European Organization for Research and Treatment of Cancer – Groupe d'Études des Lymphomes de l'Adulte (EORTC-GELA), the standard arm of ABVD plus radiation is being compared with a risk-adapted strategy based on PET performed after two cycles of ABVD; PET-negative patients receive ABVD alone for a total of 4–6 cycles, whereas PET-positive patients are switched to an intensified combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (escalated BEA-COPP) and radiation. Similarly, a phase III trial in the UK is investigating the omission of involved-field radiation therapy in early stage Hodgkin's lymphoma patients who achieve PET negativity after three cycles of ABVD.

Another area of uncertainty, and a matter of ongoing debate, is the optimal chemotherapy regimen for advanced Hodgkin's lymphoma, for which ABVD is the present standard. In a randomized phase III study by the German Hodgkin Study Group [62,63], escalated BEACOPP produced a statistically significant advantage in 5-year and 10-year failure-free survival compared with baseline BEACOPP and cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, vinblastine and dacarbazine (COPP-ABVD). The benefit was statistically significant across IPS groups but was most pronounced in patients with four or more risk factors. Escalated BEACOPP, however, is also more toxic, with a greater incidence of acute toxicities, infertility, and potentially secondary myelosuppression and acute leukemia [62]. The question, then, is how best to identify patients for these effective but more toxic regimens, while sparing the majority of better-risk patients who can be cured with ABVD. Studies that incorporate early and posttherapy metabolic imaging are certain to address this question. For example, Dann *et al.* [64••] recently published a prospective multicenter trial in which 108 patients with newly diagnosed Hodgkin's lymphoma received either standard or escalated BEACOPP depending on pretreatment risk factors, with subsequent escalation or deescalation of therapy based on cycle 2 FDG PET/CT or gallium scintigraphy. With this strategy, disease progressed in only 21% of the 54 patients with interim positive scintigraphy (27% in PET-positive patients). A number of other trials of risk-adapted therapy are in progress or planned. In advanced Hodgkin's lymphoma, for example, the German Hodgkin Study Group will conduct a trial in which initial therapy is based on the IPS, and therapy then escalated or deescalated on the

basis of cycle 2 PET/CT. Another multicenter European trial for advanced Hodgkin's lymphoma will investigate risk-adapted therapy based on PET/CT after two cycles of ABVD. Both of these studies will also restrict consolidative radiotherapy to residual PET-positive tumor foci, rather than to any mass of a predetermined size.

Considerations in performing and interpreting PET

When performing PET or PET/CT for lymphoma, some leading considerations include the type of imaging modality, how one defines metabolic response, potential causes of false negative and false positive results, and the timing of the metabolic imaging.

Type of imaging modality

In the past 14 years, PET has moved beyond being a diagnostic method, to being both a diagnostic and management tool for lymphoma. While the use of PET has changed and grown in lymphoma, there have been major technological changes. From 1993 to 2002, almost all PET imaging was done using scanners which were PET only, with fusion of PET and CT being done by software methods, if at all. Since the introduction of commercial PET/CT scanners and their wide dissemination beginning in approximately 2001, only PET/CT scanners have been manufactured. The CT portion of a PET/CT scan is required to measure the body thickness, help localize the tumor, and make PET quantitative. A wide range of CT scan types is possible, however, ranging from low-power CT scans for attenuation correction and localization only, typically performed without intravenous contrast, to fully diagnostic CT with intravenous contrast and a much greater photon flux. Interestingly, where directly compared in small studies, the lower-power CT has been strongly correlated with the higher-powered diagnostic CT and has provided similar information at a lower radiation burden to the patient [65,66]. As much of the data using PET are based on the PET and not on the CT scan, and cumulative radiation burden is a health issue [67], some efforts are ongoing to determine the actual contribution of the CT portion of the PET/CT, and whether the 'lower-power', 'attenuation correction and localization' CT scan is adequate for clinical decision making [65,66]. In some instances, lower-quality CT may be adequate when coupled with PET to make the major diagnostic determinations required for FDG-avid lymphomas. Particularly for pretreatment assessment, however, a dedicated contrast-enhanced CT scan is strongly advised in order to measure tumor size accurately (particularly with neck, abdominal, or pelvic disease) and evaluate extranodal disease [68].

Definition of metabolic response

The intensity of radiotracer uptake on FDG PET is a continuous variable reflecting the absolute concentration of F-18 (as FDG-6-phosphate in the tumors). Dichotomizing a continuous variable can be reasonable if all values of activity are at either extreme. If the activity levels are distributed more broadly, however, dichotomization is problematic as a cut-off point between positive and negative must be determined. Furthermore, lesion size has some influence on the 'apparent' tracer uptake, with smaller lesions of biologically high tracer uptake appearing less 'hot' because of the limited resolution of the PET scanner; thus their signal is contaminated by lower uptake nearby normal tissues that are not FDG-avid, resulting in an overall lower signal. As PET scanners are developed with higher resolution, this becomes less problematic, but remains an issue. Further, not all tumors are intrinsically as glycolytically active as others, meaning that 'positive' in a lower-uptake tumor may be biologically and prognostically different from 'positive' in a higher-uptake tumor.

As tumor glucose utilization and FDG uptake is a continuous variable, any attempt to dichotomize the data into 'positive' or 'negative' inherently reduces some of the potentially

prognostic information in the scan. Thus, how much FDG uptake defines a positive PET? In other words, how 'positive' is 'positive'?

Clinically, FDG PET is most commonly assessed visually and as such, there is a subjective component. While cases of absent or very intense metabolic activity in sites of previous tumor are usually clear-cut, FDG uptake is not truly binary. Thus, where to define the 'cut-off' can be nebulous. This potentially problematic issue is illustrated by an observer variation study of FDG PET in lymphoma [68], in which scans were independently reviewed by a panel of variably experienced nuclear medicine physicians. Only about 60% of scans were read in accordance with expert readers; while there was agreement upon the 'positive' scans in 82–94% of cases, there was only 45% concordance with the 'negative' readings. There has been a higher agreement rate in limited observer studies of quantitative tracer uptake, but quantitation has some challenges as well [69].

The qualitatively vague PET result is not infrequently encountered, and cases of 'minimal' uptake which might represent inflammation or viable residual tumor pose a particular challenge. This is captured by the category of 'minimal residual uptake' (MRU), defined as low-level FDG uptake that potentially represents inflammation but that may also represent residual tumor [21]. In a series of aggressive non-Hodgkin's lymphoma, approximately 15% of cycle 2-3 PET scans had MRU, associated with a prognosis intermediate between 'negative' and 'positive' cases [21]. Similarly, in an analysis of PET performed prior to high-dose therapy and BMT [46•], relapsed/refractory non-Hodgkin's lymphoma patients achieving a 'partial metabolic response' by visual assessment had a prognosis in between those achieving 'complete' or 'no' metabolic response (Table 3). A partial metabolic response was defined as FDG uptake above background in the site of previous tumor, and therefore is similar to the concept of MRU [46•]. The difference in failure-free survival was statistically significant ($P < 0.001$) among the three metabolic response categories in non-Hodgkin's lymphoma ($n = 78$), but not in Hodgkin's lymphoma ($n = 23$). The latter might reflect differences in biology, or simply small numbers.

When results have been dichotomized as positive or negative, MRU has generally been analyzed as negative [10••]. In the new proposed criteria for response assessment in lymphoma clinical trials, mild, diffuse FDG uptake that is equal to or less than mediastinal blood pool structures is considered negative [5••,6••]. Modest uptake slightly greater than mediastinal background activity, however, may well not be associated with a poor prognosis, and a higher cut-off value relative to background is being used in some prospective studies. Although some of these patients may have prognoses inferior to those with 'completely' negative scans, a conservative approach seems reasonable, i.e. reserving a 'positive PET result' for patients whose PET scans are quite intensely positive.

The variability in outcome, depending on how one scores the PET result, was also illustrated in a recent comparison of semiquantitative and visual analyses of cycle 2 PET after first-line therapy of diffuse large B-cell lymphoma [22]. In this study, the optimal cut-off value for 'good metabolic response' was determined, by receiver operating characteristic analysis, to be an approximately two-thirds reduction in maximum standardized uptake volume. In newly-diagnosed patients treated with anthracycline-containing regimen with or without upfront BMT, the estimated 2-year EFS was 79% in 'responders' compared with 21% in nonresponders. On visual assessment, a negative cycle 2 PET was also associated with a 2-year EFS of 79%, while the 2-year EFS in patients with a positive PET was 51%. Fourteen of 92 'good responders' (15%) by semiquantitative analysis could have been 'positive' by visual analysis [22]. Thus, as in any diagnostic test, how a cut-off between positive and negative is made is very important. To facilitate appropriate decision making in our own center, we provide more gradations of reporting than the dichotomous values.

False positives and negatives

The potential causes of false negative and false positive FDG signals must be considered. Hyperglycemia is a common factor that may sometimes cause false negative results. In most centers performing PET studies with frequency, serum glucose levels are measured before the FDG injection to avoid studying hyperglycemic patients. In addition to inflammation and infection, supraclavicular brown fat [70], 'rebound' thymic hyperplasia (particularly in patients with mediastinal tumors), and bone marrow uptake (and potentially uptake in bony lesions) after growth-factor colony stimulating factors [71] can be mistaken by inexperienced observers for viable tumor. For example, lung uptake appearing in a patient with non-Hodgkin's lymphoma who did not previously have lung FDG uptake and who is otherwise responding, likely represents false positive tracer uptake. Occasionally, contracting muscles can also cause false positive uptake, but have a rather typical appearance anatomically. In bony lesions due to lymphoma, the kinetics of FDG uptake during therapy are not yet well defined; as such, caution is advised when assessing bony lesions by midtreatment or posttreatment PET in patients who do not have concomitant nodal masses. Recent data have however shown that bone marrow lesion response in lymphoma is highly correlated with the response of regional lymph nodes to treatment, and appears reasonably reliable [72]. In practice, the most common cause of false positives is probably inflammation at the tumor site, especially in Hodgkin's lymphoma.

Histology is also relevant. The biological aggressiveness of the lymphoma does not necessarily correlate with its being FDG-avid [73], and nor does the intensity of FDG uptake accurately distinguish indolent from aggressive histologies [74]. For example, although Hodgkin's lymphoma, large B-cell lymphoma and mantle cell lymphoma are PET-positive in about 98-100% of cases, peripheral T-cell lymphoma (also aggressive) is less reliably so (2/5 cases in the series by Elstrom *et al.* [73]). Whereas follicular lymphomas are FDG-avid in approximately 98% of cases, only 8/12 cases (67%) of (low-grade) marginal zone lymphoma were detected on PET in this series [73]. None of 10 cases of extranodal marginal zone lymphoma were detected by PET in another series [75]. Small lymphocytic lymphoma/chronic lymphocytic leukemia is also only variably FDG-avid, although a maximum standardized uptake value greater than 5 may raise suspicion for a large cell transformation [76]. For these reasons, in cases of the appropriate histology in which midtreatment or end-of-treatment PET scans will be performed, we favor a baseline PET scan when feasible to determine lesion FDG avidity as well as the locations of FDG-avid tumors.

Timing

Combined with considerations about kinetics of tumor kill (Fig. 1), the clinical data suggest that PET performed after two or three cycles of first-line chemotherapy is optimal for prognostication. The optimal interval between chemotherapy or radiation and PET scanning is uncertain. A minimum 10-day interval may be desirable after chemotherapy, in order to allow the treatment to take effect and to avoid capturing transient fluctuations in metabolic activity (metabolic 'stunning' in the first hours to days after chemotherapy [77], and tumor 'flare'). The International Working Group response criteria guidelines suggest a minimum 3-week interval between PET and last chemotherapy or chemoimmunotherapy, and an 8-12-week interval after radiation because of postradiation inflammation [6••]. After radioimmunotherapy in one small series, FDG PET performed at 1-2 months was found to correlate best with response [55].

Management outside of a clinical trial

Risk-adapted therapy based on metabolic imaging is a new investigative focus. As such, many questions remain about how best to manage a midtreatment or posttreatment PET result. Midtreatment FDG PET is increasingly being performed. Recent phase II trials have explored different possibilities in non-Hodgkin's lymphoma [13,52], but how best to manage an abnormal result is not yet defined (short of being concerned). Treatment modifications on the basis of early FDG PET, whether for non-Hodgkin's lymphoma or Hodgkin's lymphoma, are therefore best made in the context of a clinical trial.

For patients with negative midtreatment PET, early truncation of therapy is not advised outside of a clinical trial, as negative PET does not necessarily mean eradication of all disease (Fig. 1). Given the risks and costs of chemotherapy, however, it is reasonable to consider exploring the possibility of abbreviated chemotherapy in a trial. In patients with aggressive non-Hodgkin's lymphoma who have residual FDG-avid tumor after completion of six courses of chemotherapy, but otherwise appear to have responded on CT, a conservative strategy is advised. Giving two additional courses of the same chemotherapy is unlikely to produce cure (as whatever cancer cells remain are probably resistant to that regimen), but it may increase therapeutic toxicity. BMT on the sole basis of a positive posttherapy PET is not advised in an otherwise 'responding' patient, because of the possibility of a false positive result. Rather, depending on the location, FDG avidity and size of the tumor, one should either confirm the presence of viable tumor by biopsy, or perform short-term radiographic (CT or PET/CT) and clinical follow-up to assess for objective evidence of disease progression.

In patients with limited stage Hodgkin's lymphoma, for whom chemotherapy vs. chemoradiation are contemplated, early PET may ultimately guide the decision; patients who have residual FDG-avid tumor midtreatment may be more likely to benefit from consolidative radiation than those who appear to be responding optimally. Similarly, patients with limited-stage disease who have residual PET positivity after 4–6 cycles of chemotherapy might also be more likely to benefit from radiation. The possibility of false positives, however, is again raised, particularly due to inflammation. Secondly, lymphoma that is chemoresistant is also more likely to be radioresistant [78]. As such, radiation is not necessarily the next best step for some of these patients.

Conclusion

There is clear potential to optimize treatment of lymphoma based on early metabolic imaging, with likely impact on the type and duration of chemotherapy, the decision whether and where to radiate, and whether and when to consider high-dose therapy with BMT. The optimal strategy is not yet defined, however, and mid-treatment PET is best performed on a clinical trial. Before making treatment decisions based on midtreatment or posttreatment FDG PET, reviewing the study with the radiologist or nuclear medicine specialist is of utmost importance especially in the setting of borderline or positive scans. Temporization seems prudent, particularly in borderline cases or in cases where the PET result is at great variance with the other clinical findings. Critical management questions about risk-adapted therapy based on early FDG PET will be addressed by ongoing and upcoming clinical trials.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 241–242).

1. Tatsumi M, Cohade C, Nakamoto Y, et al. Direct comparison of FDG PET and CT findings in patients with lymphoma: initial experience. *Radiology*. 2005; 237:1038–1045. [PubMed: 16304117]
2. Allen-Auerbach M, Quon A, Weber WA, et al. Comparison between 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography and positron emission tomography/computed tomography hardware fusion for staging of patients with lymphoma. *Mol Imaging Biol*. 2004; 6:411–416. [PubMed: 15564152]
3. Schiepers C, Filmont JE, Czernin J. PET for staging of Hodgkin's disease and non-Hodgkin's lymphoma. *Eur J Nucl Med Mol Imaging*. 2003; 30(Suppl 1):S82–S88. [PubMed: 12719922]
4. Juweid ME, Wiseman GA, Vose JM, et al. Response assessment of aggressive non-Hodgkin's lymphoma by integrated International Workshop Criteria and fluorine-18-fluorodeoxyglucose positron emission tomography. *J Clin Oncol*. 2005; 23:4652–4661. [PubMed: 15837965]
- 5••. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007; 25:579–586. In contrast to previous CT-based criteria, these new standardized response criteria for Hodgkin and non-Hodgkin's lymphoma, proposed for use in clinical trials and for facilitating the evaluation of new drugs, integrate the results of FDG PET into the assessment of the treatment response. [PubMed: 17242396]
- 6••. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol*. 2007; 25:571–578. These consensus recommendations from an expert panel discuss interpretation of FDG PET for response assessment in lymphoma. Included are guidelines on interpreting minimal residual uptake in previous sites of tumor, evaluation of extranodal disease, and timing of metabolic imaging. [PubMed: 17242397]
7. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [18F]FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol*. 2001; 19:414–419. [PubMed: 11208833]
8. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood*. 1999; 94:429–433. [PubMed: 10397709]
9. Spaepen K, Stroobants S, Dupont P, et al. Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. *Ann Oncol*. 2002; 13:1356–1363. [PubMed: 12196360]
- 10••. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. *J Clin Oncol*. 2007; 25:3746–3752. This prospective analysis of cycle 2 PET in newly diagnosed Hodgkin's lymphoma is the largest in this disease to date. On multivariate analysis, the International Prognostic Score was no longer an independent prognostic factor when the cycle 2 PET result was included. [PubMed: 17646666]
11. Skipper HE, Schabel FM Jr, Wilcox WS. Experimental evaluation of potential anticancer agents. Xiii On the criteria and kinetics associated with 'curability' of experimental leukemia. *Cancer Chemother Rep*. 1964; 35:1–111. [PubMed: 14117037]
12. Kasamon YL, Jones RJ, Wahl RL. Integrating PET and PET/CT into the risk-adapted therapy of lymphoma. *J Nucl Med*. 2007; 48(Suppl 1):19S–27S. [PubMed: 17204717]
13. Kasamon YL, Wahl RL, Ziessman HA, et al. Risk-adapted therapy of aggressive lymphoma based on FDG-PET performed after 2 or 3 cycles of initial chemotherapy. *Blood*. 2007; 110(11):1894. abstract.

14. Haioun C, Itti E, Rahmouni A, et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. *Blood*. 2005; 106:1376–1381. [PubMed: 15860666]
15. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. *Blood*. 2006; 107:52–59. [PubMed: 16150944]
16. Kostakoglu L, Goldsmith SJ, Leonard JP, et al. FDG-PET after 1 cycle of therapy predicts outcome in diffuse large cell lymphoma and classic Hodgkin disease. *Cancer*. 2006; 107:2678–2687. [PubMed: 17063502]
17. Romer W, Hanauske AR, Ziegler S, et al. Positron emission tomography in non-Hodgkin's lymphoma: assessment of chemotherapy with fluorodeoxyglucose. *Blood*. 1998; 91:4464–4471. [PubMed: 9616140]
18. Humm JL, Rosenfeld A, Del Guerra A. From PET detectors to PET scanners. *Eur J Nucl Med Mol Imaging*. 2003; 30:1574–1597. [PubMed: 14579100]
19. Mikhaeel NG, Timothy AR, O'Doherty MJ, et al. 18-FDG-PET as a prognostic indicator in the treatment of aggressive non-Hodgkin's lymphoma – comparison with CT. *Leuk Lymphoma*. 2000; 39:543–553. [PubMed: 11342337]
20. Jerusalem G, Beguin Y, Fassotte MF, et al. Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. *Haematologica*. 2000; 85:613–618. [PubMed: 10870118]
21. Mikhaeel NG, Hutchings M, Fields PA, et al. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in highgrade non-Hodgkin lymphoma. *Ann Oncol*. 2005; 16:1514–1523. [PubMed: 15980161]
22. Lin C, Itti E, Haioun C, et al. Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. *J Nucl Med*. 2007; 48:1626–1632. [PubMed: 17873129]
23. Querellou S, Valette F, Bodet-Milin C, et al. FDG-PET/CT predicts outcome in patients with aggressive non-Hodgkin's lymphoma and Hodgkin's disease. *Ann Hematol*. 2006; 85:759–767. [PubMed: 16871391]
24. Zhao J, Qiao W, Wang C, et al. Therapeutic evaluation and prognostic value of interim hybrid PET/CT with (18)F-FDG after three to four cycles of chemotherapy in non-Hodgkin's lymphoma. *Hematology*. 2007 Epub ahead of print.
25. Friedberg JW, Fischman A, Neuberger D, et al. FDG-PET is superior to gallium scintigraphy in staging and more sensitive in the follow-up of patients with de novo Hodgkin lymphoma: a blinded comparison. *Leuk Lymphoma*. 2004; 45:85–92. [PubMed: 15061202]
26. Hutchings M, Mikhaeel NG, Fields PA, et al. Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma. *Ann Oncol*. 2005; 16:1160–1168. [PubMed: 15939713]
27. Zinzani PL, Tani M, Fanti S, et al. Early positron emission tomography (PET) restaging: a predictive final response in Hodgkin's disease patients. *Ann Oncol*. 2006; 17:1296–1300. [PubMed: 16766583]
28. Gallamini A, Rigacci L, Merli F, et al. The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease. *Haematologica*. 2006; 91:475–481. [PubMed: 16585014]
29. Meany HJ, Gidvani VK, Minniti CP. Utility of PET scans to predict disease relapse in pediatric patients with Hodgkin lymphoma. *Pediatr Blood Cancer*. 2007; 48:399–402. [PubMed: 16514616]
30. Levine JM, Weiner M, Kelly KM. Routine use of PET scans after completion of therapy in pediatric Hodgkin disease results in a high false positive rate. *J Pediatr Hematol Oncol*. 2006; 28:711–714. [PubMed: 17114956]
31. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993; 329:987–994. [PubMed: 8141877]
32. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med*. 1998; 339:1506–1514. [PubMed: 9819449]

33. Gianni AM, Bregni M, Siena S, et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. *N Engl J Med*. 1997; 336:1290–1297. [PubMed: 9113932]
34. Aksentijevich I, Jones RJ, Ambinder RF, et al. Clinical outcome following autologous and allogeneic blood and marrow transplantation for relapsed diffuse large-cell non-Hodgkin's lymphoma. *Biol Blood Marrow Transplant*. 2006; 12:965–972. [PubMed: 16920563]
35. Stiff PJ, Dahlberg S, Forman SJ, et al. Autologous bone marrow transplantation for patients with relapsed or refractory diffuse aggressive non-Hodgkin's lymphoma: value of augmented preparative regimens - a Southwest Oncology Group trial. *J Clin Oncol*. 1998; 16:48–55. [PubMed: 9440722]
36. Milpied N, Deconinck E, Gaillard F, et al. Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support. *N Engl J Med*. 2004; 350:1287–1295. [PubMed: 15044639]
37. Gisselbrecht C, Lepage E, Molina T, et al. Shortened first-line high-dose chemotherapy for patients with poor-prognosis aggressive lymphoma. *J Clin Oncol*. 2002; 20:2472–2479. [PubMed: 12011124]
38. Greb A, Bohlius J, Trelle S, et al. High-dose chemotherapy with autologous stem cell support in first-line treatment of aggressive non-Hodgkin lymphoma - results of a comprehensive meta-analysis. *Cancer Treat Rev*. 2007; 33:338–346. This useful meta-analysis of preemptive BMT for aggressive non-Hodgkin's lymphoma places the studies of early BMT for non-Hodgkin's lymphoma, which have mixed results, into perspective. [PubMed: 17400393]
39. Strehl J, Mey U, Glasmacher A, et al. High-dose chemotherapy followed by autologous stem cell transplantation as first-line therapy in aggressive non-Hodgkin's lymphoma: a meta-analysis. *Haematologica*. 2003; 88:1304–1315. [PubMed: 14607760]
40. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol - a Groupe d'Etude des Lymphomes de l'Adulte study. *J Clin Oncol*. 2000; 18:3025–3030. [PubMed: 10944137]
41. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of pretransplantation positron emission tomography using fluorine 18-fluorodeoxyglucose in patients with aggressive lymphoma treated with high-dose chemotherapy and stem cell transplantation. *Blood*. 2003; 102:53–59. [PubMed: 12609836]
42. Cremerius U, Fabry U, Wildberger JE, et al. Pretransplant positron emission tomography (PET) using fluorine-18-fluoro-deoxyglucose (FDG) predicts outcome in patients treated with high-dose chemotherapy and autologous stem cell transplantation for non-Hodgkin's lymphoma. *Bone Marrow Transplant*. 2002; 30:103–111. [PubMed: 12132049]
43. Becherer A, Mitterbauer M, Jaeger U, et al. Positron emission tomography with [18F]2-fluoro-D-2-deoxyglucose (FDG-PET) predicts relapse of malignant lymphoma after high-dose therapy with stem cell transplantation. *Leukemia*. 2002; 16:260–267. [PubMed: 11840293]
44. Svoboda J, Andreadis C, Elstrom R, et al. Prognostic value of FDG-PET scan imaging in lymphoma patients undergoing autologous stem cell transplantation. *Bone Marrow Transplant*. 2006; 38:211–216. [PubMed: 16770314]
45. Schot BW, Pruim J, van Imhoff GW, et al. The role of serial pretransplantation positron emission tomography in predicting progressive disease in relapsed lymphoma. *Haematologica*. 2006; 91:490–495. [PubMed: 16533726]
46. Schot BW, Zijlstra JM, Sluiter WJ, et al. Early FDG-PET assessment in combination with clinical risk scores determines prognosis in recurring lymphoma. *Blood*. 2007; 109:486–491. This analysis combines the results of PET, performed after two cycles of reinduction for relapsed/refractory lymphoma, with a clinical risk score in patients undergoing autologous BMT, and in so doing predicts prognosis more accurately. The distinction between no metabolic response, partial metabolic response, and complete metabolic response is helpful and has prognostic significance in the non-Hodgkin's lymphoma cases. [PubMed: 17003382]
47. Jabbour E, Hosing C, Ayers G, et al. Pretransplant positive positron emission tomography/gallium scans predict poor outcome in patients with recurrent/refractory Hodgkin lymphoma. *Cancer*. 2007; 109:2481–2489. [PubMed: 17497648]

48. Filmont JE, Gisselbrecht C, Cuenca X, et al. The impact of pre and post transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation. *Cancer*. 2007; 110:1361–1369. [PubMed: 17623832]
49. Filmont JE, Czernin J, Yap C, et al. Value of F-18 fluorodeoxyglucose positron emission tomography for predicting the clinical outcome of patients with aggressive lymphoma prior to and after autologous stem-cell transplantation. *Chest*. 2003; 124:608–613. [PubMed: 12907550]
50. Schot B, van Imhoff G, Pruim J, et al. Predictive value of early 18F-fluoro-deoxyglucose positron emission tomography in chemosensitive relapsed lymphoma. *Br J Haematol*. 2003; 123:282–287. [PubMed: 14531910]
51. Alousi AM, Saliba RM, Okoroji G, et al. The influence of PET/gallium (P/G) status and high-dose rituximab (HDR) in patients (pts) with aggressive, large, B-cell lymphoma (LBCL) receiving autologous stem cell transplants (ASCT). *J Clin Oncol*. 2006; 24(18 Suppl):6518. abstract.
52. Moskowitz C, Hamlin PA, Horwitz SM, et al. Phase II trial of dose-dense R-CHOP followed by risk-adapted consolidation with either ICE or ICE and ASCT, based upon the results of biopsy confirmed abnormal interim restaging PET scan, improves outcome in patients with advanced stage DLBCL. *Blood*. 2006; 108(11):532. abstract.
53. Schaefer NG, Taverna C, Strobel K, et al. Hodgkin disease: diagnostic value of FDG PET/CT after first-line therapy – is biopsy of FDG-avid lesions still needed? *Radiology*. 2007; 244:257–262. [PubMed: 17581905]
54. Sehn LH, Savage KJ, Hoskins P, et al. Limited-stage diffuse large B-cell lymphoma (DLBCL) patients with a negative PET scan following three cycles of R-CHOP can be effectively treated with abbreviated chemoimmunotherapy alone. *Blood*. 2007; 110(11):787. abstract. [PubMed: 17606766]
55. Torizuka T, Zasadny KR, Kison PV, et al. Metabolic response of non-Hodgkin's lymphoma to 131I-anti-B1 radioimmunotherapy: evaluation with FDG PET. *J Nucl Med*. 2000; 41:999–1005. [PubMed: 10855624]
56. Kelloff GJ, Sullivan DM, Wilson W, et al. FDG-PET Lymphoma Demonstration Project Invitational Workshop. *Acad Radiol*. 2007; 14:330–339. [PubMed: 17307666]
57. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2005; 23:4634–4642. [PubMed: 15837968]
58. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood*. 2004; 104:3483–3489. [PubMed: 15315964]
59. Eghbali H, Brice P, Creemers G, et al. Comparison of three radiation dose levels after EBVP regimen in favorable supradiaphragmatic clinical stages (CS) I-II Hodgkin's lymphoma (HL): preliminary results of the EORTC-GELA H9-F trial. *Blood*. 2005; 106(11):814. abstract.
60. Yahalom J. Don't throw out the baby with the bathwater: on optimizing cure and reducing toxicity in Hodgkin's lymphoma. *J Clin Oncol*. 2006; 24:544–548. [PubMed: 16446326]
61. Canellos GP. Chemotherapy alone for early Hodgkin's lymphoma: an emerging option. *J Clin Oncol*. 2005; 23:4574–4576. [PubMed: 15837972]
62. Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med*. 2003; 348:2386–2395. [PubMed: 12802024]
63. Diehl V, Franklin J, Pfistner B, Engert A. Ten-year results of a German Hodgkin Study Group randomized trial of standard and increased dose BEACOPP chemotherapy for advanced Hodgkin's lymphoma (HD9). *J Clin Oncol*. 2007; 25(18 Suppl):8015. abstract.
64. Dann EJ, Bar-Shalom R, Tamir A, et al. Risk-adapted BEACOPP regimen can reduce the cumulative dose of chemotherapy for standard and high-risk Hodgkin lymphoma with no impairment of outcome. *Blood*. 2007; 109:905–909. This is the first published study of risk-adapted therapy based on midtreatment metabolic imaging in lymphoma. [PubMed: 17018856]

65. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging - do we need contrast-enhanced CT? *Radiology*. 2004; 232:823–829. [PubMed: 15273335]
66. Rodriguez-Vigil B, Gomez-Leon N, Pinilla I, et al. PET/CT in lymphoma: prospective study of enhanced full-dose PET/CT versus unenhanced low-dose PET/CT. *J Nucl Med*. 2006; 47:1643–1648. [PubMed: 17015900]
67. Brenner DJ, Hall EJ. Computed tomography - an increasing source of radiation exposure. *N Engl J Med*. 2007; 357:2277–2284. [PubMed: 18046031]
68. Zijlstra JM, Comans EF, van Lingen A, et al. FDG PET in lymphoma: the need for standardization of interpretation. An observer variation study. *Nucl Med Commun*. 2007; 28:798–803. [PubMed: 17728610]
69. Minn H, Zasadny KR, Quint LE, Wahl RL. Lung cancer: reproducibility of quantitative measurements for evaluating 2-[F-18]-fluoro-2-deoxy-D-glucose uptake at PET. *Radiology*. 1995; 196:167–173. [PubMed: 7784562]
70. Cohade C, Osman M, Pannu HK, Wahl RL. Uptake in supraclavicular area fat ('USA-Fat'): description on 18F-FDG PET/CT. *J Nucl Med*. 2003; 44:170–176. [PubMed: 12571205]
71. Sugawara Y, Fisher SJ, Zasadny KR, et al. Preclinical and clinical studies of bone marrow uptake of fluorine-18-fluorodeoxyglucose with or without granulocyte colony stimulating factor during chemotherapy. *J Clin Oncol*. 1998; 16:173–180. [PubMed: 9440740]
72. Goudarzi, B.; Kowalski, J.; Tsa, H., et al. Measuring tumor response in unmeasurable disease involving bone marrow in lymphoma: comparison to measurable disease. *Proceedings of the RSNA Annual Meeting*; 25-30 November 2007; Chicago, IL. p. 440abstract SSJO8-01
73. Elstrom R, Guan L, Baker G, et al. Utility of FDG-PET scanning in lymphoma by WHO classification. *Blood*. 2003; 101:3875–3876. [PubMed: 12531812]
74. Schoder H, Noy A, Gonen M, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2005; 23:4643–4651. [PubMed: 15837966]
75. Hoffmann M, Kletter K, Diemling M, et al. Positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose (F18-FDG) does not visualize extra-nodal B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT)-type. *Ann Oncol*. 1999; 10:1185–1189. [PubMed: 10586335]
76. Bruzzi JF, Macapinlac H, Tsimberidou AM, et al. Detection of Richter's transformation of chronic lymphocytic leukemia by PET/CT. *J Nucl Med*. 2006; 47:1267–1273. [PubMed: 16883004]
77. Engles JM, Quarless SA, Mambo E, et al. Stunning and its effect on 3H-FDG uptake and key gene expression in breast cancer cells undergoing chemotherapy. *J Nucl Med*. 2006; 47:603–608. [PubMed: 16595493]
78. Fox KA, Lippman SM, Cassady JR, et al. Radiation therapy salvage of Hodgkin's disease following chemotherapy failure. *J Clin Oncol*. 1987; 5:38–45. [PubMed: 3806158]

Figure 1. Kinetics of tumor cell kill and relation to FDG PET

Line B represents the minimum rate of tumor cell kill that, in an idealized setting, would lead to cure with six cycles of chemotherapy for lymphoma. Line A represents a brisker tumor response that would produce cure after only four cycles. Both scenarios would be associated with a negative PET scan after two cycles. In contrast, line C represents a rate of tumor cell kill that that would be associated with a negative PET scan after 4–6 cycles, but would not produce cure. The PET scan for line C would notably be positive after two or three cycles. Reprinted with permission from the Society of Nuclear Medicine from Kasamon *et al.*, Figure. 4 [12].

Table 1
Fluorodeoxyglucose positron emission tomography during first-line therapy of non-Hodgkin's lymphoma

Study	Type	Histology	Cycles before PET	Treatment	Number of pts	Number PET+	PPV	NPV	EFS, PET+	EFS, PET-	Median follow-up	TTF
Mikhaeel <i>et al.</i> 2000 [19]	Retrospective	Mostly aggressive	2-4	First-line	23	8 (35%)	88%	100%	-	-	30 mo	-
Jerusalem <i>et al.</i> 2000 [20]	Prospective	Aggressive or indolent	2-5 (median 3)	First-line or salvage	28	5 (1 8%)	100%	67%	20% (1 y), 0% (2 y)	81% (1 y), 62% (2 y)	17.5 mo	-
Spaepen <i>et al.</i> 2002 [9]	Retrospective	Aggressive	2-4	First-line	70	33 (47%)	100%	84%	4% (2 y) ^a	85% (2 y) ^a	36 mo	Median 1.5 mo if PET+, 35 mo if PET-
Mikhaeel <i>et al.</i> 2005 [21]	Retrospective	Aggressive	2-3	First-line	102 ^b	52 (51%)	71%	90%	30% (2 y), 16% (5 y)	93% (2 y), 89% (5 y)	24 mo ^c	Average 10 mo if PET+, 7 mo if MRU, 24 mo if PET -
Haoun <i>et al.</i> 2005 [14]	Prospective	Aggressive	2	First-line, with or without BMT ^{d,e}	90	36 (40%)	-	-	43% (2 y)	82% (2 y)	24 mo	
Kostakoglu <i>et al.</i> 2006 [16]	Retrospective	Aggressive	1	First-line	47 (24 NHL, 23 HL)	16 (34%) ^f	87.5%	100%	1 2.5% (2 y)	1 00% (2 y)	21 mo ^a	Median PFS 5.5 mo if PET+, not reached if PET-
Zhao <i>et al.</i> 2007 [24]	Retrospective	Aggressive or indolent (31%)	3-4	First-line	61	28 ^g	79%	64%	23% (2 y)	72% (2 y)	27 mo	-

BMT, blood or marrow transplantation; EFS, event-free survival; HL, Hodgkin's lymphoma; mo, months; MRU, minimal residual uptake; NHL, non-Hodgkin's lymphoma; NPV, negative predictive value; PPV, positive predictive value; pts, patients; SUV, standardized uptake value; TTF, time to treatment failure; y, year. Definition of EFS variably represents freedom from disease progression/relapse, incomplete remission, disease-related death, and/or any death. Table modified from Kasamon *et al*[12].

^aEstimated from data.

^bAn additional 19 patients with MRU were analyzed separately with a 2-year and 5-year EFS of 59%.

^cTwenty-four months for all patients, 28.5 months for surviving patients.

^dForty percent received autologous BMT as part of planned therapy, irrespective of PET results. Results published for the group as a whole.

^ePET interpreted visually. SUV-based analysis later published by Lin *et al*[22].

^fSix of 23 HL PET+, 10/24 NHL PET+.

^gEight patients with MRU were analyzed separately; four relapsed with a 2-year EFS of 56%.

Table 2
Fluorodeoxyglucose positron emission tomography during first-line chemotherapy of Hodgkin's lymphoma

Study	Type	Stage	Cycles before PET	Number of pts	Number PET+	PPV	NPV	EFS, PET+	EFS, PET-	Median follow-up	Comments
Friedberg <i>et al.</i> 2004 [25]	prospective	I-IV; most I-II	3	22	5 (23%)	80%	94%	-	-	24 mo	-
Hutchings <i>et al.</i> 2005 [26]	retrospective	I-IV; 28% III-IV	2-3	85	13 (15%) ^a	61.5%	94%	46% (2 y), 38.5% (5 y)	97% (2 y), 91.5% (5 y)	40 mo	Median TTF 24 mo if PET+, 9 mo if PET-
Gallamini <i>et al.</i> 2006 [28]	prospective	IIA unfavorable-IV; 46% III-IV	2	108	20 (18.5%)	90%	97%	60/o (2 y)	96% (2 y)	20 mo (mean)	13/20 PET+ pts progressed during therapy
Hutchings <i>et al.</i> 2006 [15]	prospective	I-IV; 36% III-IV	2	77	16 (21%) ^a	69%	95%	0% (2 y)	96% (2 y)	23 mo	-
Zinzani <i>et al.</i> 2006 [27]	prospective	MB —IV; 47.5% III-IV	4	64	13 (20%)	85%	96%	1 9% (2 y)	96% (2 y)	23 mo	-
			2	40	8 (20%) ^b	100%	100%	0%	-	18 mo	7/8 PET+ pts progressed during therapy
Querellou <i>et al.</i> 2006 [23]	retrospective	IIA-IV; 62.5% III-IV	3-4	24 ^c	4 (16%)	75%	95%	50% (1 y) ^d	100% (1 y) ^d	18 mo for PET-	-
Gallamini <i>et al.</i> 2007 [10•] ^e	prospective	IIA-IV; 47% III-IV	2	260	50 (19%) ^a	86%	95%	13% (2 y)	95% (2 y)	26 mo	-

mo, months; MRU, minimal residual uptake; PPV, positive predictive value; pts, patients; NPV, negative predictive value; TTF, time to treatment failure; EFS, event-free survival; y, years. Definition of EFS variably represents freedom from relapse/progression, incomplete remission, disease-related death, and/or any death. Table modified from Kasamon *et al.* [12].

^aMRU cases were regarded as PET-negative.

^bMRU cases were analyzed separately. Four had MRU after cycle 2 PET, three had MRU after cycle 4 PET, one relapsed.

^cAmong 24 non-Hodgkin's lymphoma patients with PET after 2-4 cycles.

^dEstimated from data.

^eIncludes previously reported patients [15,28].

Table 3
Examples of fluorodeoxyglucose positron emission tomography prior to high-dose therapy for lymphoma

Study	Type	BMT indication and type	Timing of PET	Number of pts	PPV	NPV	EFS, FI+	EFS, FI-	Median PFS	Median follow-up
Cremierus <i>et al.</i> 2002 [42] ^a	Prospective	Consolidation of front-line therapy, or relapse; ABMT	Before HDT	22 NHL	86%	67%	29% (2 y)	67% (2 y)	5 mo if < PMR, vs. not reached if MR	30 mo in surviving pts
Becherer <i>et al.</i> 2002 [43] ^b	Retrospective	Consolidation or relapse/refractory; 94% ABMT	8 weeks before HDT	16 (10 NHL, 6 HL)	73%	100%	1.8% (1 y)	100% (1 y)	-	13 mo
Spaepen <i>et al.</i> 2003 [41]	Retrospective	Relapse/refractory; 90% ABMT	8 weeks before HDT	60 (41 NHL, 19 HL)	87%	90%	23% (2 y)	96% (2 y)	13 mo if PET +, vs. not reached if PET-	50 mo for PET-
Alousi <i>et al.</i> 2006 [51]	Retrospective	Chemosensitive disease; ABMT	Before HDT	41 NHL	90%	90%	-	-	-	-
				19 HL	78%	90%	-	-	-	-
Svoboda <i>et al.</i> 2006 [44]	Retrospective	Relapsed/refractory; ABMT	Before HDT	188 NHL, with either gallium or PET	83% without HDR, 54% with HDR ^d	65% without HDR, 78% with HDR	17% (4.5 y) without HDR, 45% with HDR	55% (4.5 y) without HDR, 75% with HDR	-	44 mo
				50 (31 NHL, 19 HL)	94%	53%	13% (1 y) ^e	55% (1 y) ^e	5 mo if PET +, vs. 19 mo if PET-	19 mo for pts not progressing
Schot <i>et al.</i> 2006 [45]	Prospective	Relapsed/refractory; ABMT	After 2 salvage cycles	39 (28 NHL, 11 HL)	73% ^f	71%	27% (2 y)	71% (2y)	-	22 mo
Schot <i>et al.</i> 2007 [46] ^{g,h}	Prospective	Relapsed/refractory; ABMT	After 3 salvage cycles ^c	22	82%	60%	1.8% (2 y)	60% (2 y)	3 mo if PET +, vs. >50 mo if PET-	-
			After 2 salvage cycles	78 NHL	87% if NMR, 61% if PMR	74% if CMR, 39% if PMR	1.0% (2 y) if NMR	72% (2 y) if CMR, 380/o if PMR	-	22 mo for nonrelapsing NHL or HL pts
Jabbour <i>et al.</i> 2007 [47]	Retrospective	Relapsed/refractory; ABMT	After 2 salvage cycles	23 HL	60% if NMR, 70% if PMR	75% if CMR, 30% if PMR	40% (2 y) if NMR	73% (2 y) if CMR, 370/o if PMR	-	-
			Before HDT	211 HL, with either PET or gallium	74% ^d	68%	23% (3 y)	69% (3 y)	-	34 mo for nonrelapsing pts

Study	Type	BMT indication and type	Timing of PET	Number of pts	PPV	NPV	EFS, FI+	EFS, FI-	Median PFS	Median follow-up
Filmon <i>et al.</i> 2007 [48]	Prospective	Consolidation or relapsed/refractory with at least PR	Before HDT	68 HL, with PET 60 (50 NHL, 10 HL)	72% 62.5%	77% 82%	- 43% (1 y)	- 80% (1 y)	- -	- 15 mo

ABMT, autologous blood or marrow transplantation; CMR, complete metabolic response; EFS, event-free survival; FI, functional imaging; HDR, high-dose rituximab; HDT, high-dose therapy; NMR, no metabolic response; NPV, negative predictive value; mo, month; PMR, partial metabolic response; PPV, positive predictive value; PR, partial response; pts, patients; TTF, time to treatment failure; y, year. Definition of EFS variably represents freedom from relapse/progression, incomplete remission, disease-related death, and/or any death.

^aScans were scored as less than a PMR (<25% reduction in serial standardized uptake values), PMR, or CMR. PMR and CMR are here grouped as PET-negative.

^b'Weakly', 'moderately', and 'strongly' positive scans are here grouped as PET-positive.

^cCycle 3 PET performed if cycle 2 PET was abnormal.

^dOutcomes represent combined data for pre-HDT PET and gallium scans.

^eEstimated from data.

^fFor any vs. no abnormal FDG uptake. The authors also analyzed outcomes for complete or partial vs. no metabolic response.

^gIncludes previously reported patients [45,50].

^hFor PPV/NPV and EFS, subgroup outcomes statistically significant in NHL but not HL.