
Integrating PET and PET/CT into the Risk-Adapted Therapy of Lymphoma

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Imaging with ¹⁸F-FDG PET is increasingly accepted as a valuable tool for lymphoma management. A recent shift in the use of PET and PET/CT in medical practice has become evident. We selected aggressive lymphomas as a platform for the discussion of these imaging modalities in oncology patients and the resulting management questions. **Methods:** On the basis of our clinical experience and a review of the literature, we evaluated the emerging role of ¹⁸F-FDG PET in staging, response assessment, risk stratification, and tailored therapy. We explored the biologic meaning of true-positive or true-negative PET results in assessing tumor killing and the implications for risk-adapted therapy of lymphoma. **Results:** PET/CT improves the accuracy of staging and response assessment over that of conventional anatomic imaging. The strong prognostic value of PET for aggressive lymphomas is established, whether the imaging is performed at the end of therapy or after only a few cycles of chemotherapy. How to modify therapy on the basis of PET results is not yet established, although it is clear that high-risk patient subsets can be reliably identified. **Conclusion:** PET/CT improves the accuracy of staging and response assessment over that of CT alone. A negative midtreatment PET result does not indicate the absence of a viable tumor or that therapy can be abbreviated or reduced in intensity. Similarly, a positive PET result does not necessarily indicate a viable tumor or that extending or intensifying treatment will benefit the patient. In assessing response, it is possible that prognosis rests not only on whether the PET result is positive or negative but also on the intensity of the signal. Although the prognostic value of PET for lymphoma is now clear, how to tailor therapy accordingly is a separate matter that requires further investigation.

Key Words: PET; PET/CT; lymphoma; prognosis; response

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Metabolic imaging with ¹⁸F-FDG PET has recently come to the forefront of cancer management. This change has been quite pronounced for both Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL).

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In patients with lymphoma, the size of a mass is only somewhat indicative of the number of viable tumor cells, especially after therapy. Metabolic imaging with ¹⁸F-FDG PET provides a more reliable measure of cancer burden, as the intensity of uptake reflects the number of viable cancer cells (1,2). PET addresses this and other limitations of anatomic methods of staging and response assessment. Accordingly, in the past few years, the clinical applications of PET and PET/CT for lymphoma have evolved from staging to response assessment and now to response-adapted therapy.

STAGING

¹⁸F-FDG PET improves the detection of occult splenic disease (3), bony lesions, and small tumor foci over that of CT and is superior to ⁶⁷Ga scintigraphy for the detection of infradiaphragmatic disease (4). However, because of partial-volume effects, PET may fail to detect tumors that are smaller than the spatial resolution of the scanner and may incorrectly estimate their sizes (5,6). As a functional imaging tool, PET also may not permit the precise localization of lesions. Consequently, nontumoral ¹⁸F-FDG uptake (e.g., that attributable to physiologic uptake, infection, or inflammation) may be less readily distinguishable from and may be misinterpreted as tumor.

PET combined with CT, however, provides complementary information. PET/CT allows more precise anatomic localization as well as more reliable tumor measurements. Such images have usually been acquired separately, but dedicated fusion scanners are becoming more widely available. CT generates anatomic maps or full-quality diagnostic scans and attenuation correction data for PET (7), thereby improving diagnostic accuracy (8,9). For example, in an analysis of 48 discordant sites on dedicated combination scans, PET was determined to be correct in 83% of cases, of which 78% involved a site with positive PET but negative CT results often attributable to small lesion size (7).

The contribution of PET to the primary staging of lymphoma has been established (10). PET complements but cannot replace bone marrow biopsy for lymphoma (11,12). Compared with anatomic imaging, metabolic imaging often correctly leads to either upstaging or downstaging in approximately 10%–40% of patients with Hodgkin's lymphoma or

NHL, variably influencing management (Fig. 1) (7,10). For lymphoma, metabolic imaging is particularly important in distinguishing disseminated disease from localized disease that might be amenable to irradiation. It cannot be over-emphasized, however, that one should not defer urgent treatment initiation (such as that for symptomatic or highly aggressive lymphomas) to obtain a PET or PET/CT scan.

RESPONSE ASSESSMENT

Residual, even bulky masses after therapy completion are frequent in both Hodgkin's lymphoma and NHL but correlate poorly with survival (13). Masses often do not regress completely after adequate (curative) treatment because of fibrosis and necrotic debris. The anatomic response categories of "complete remission unconfirmed" or "clinical complete remission" were created in recognition of the problem that, particularly in patients with lymphoma, anatomic response criteria often underestimate the chemotherapeutic effect. However even patients described as having stable disease by conventional anatomic criteria may be cured. It has been demonstrated that adding PET to post-therapy CT is especially useful in identifying which of these patients have achieved satisfactory functional remission (5,14).

It therefore makes sense to adopt a response classification for lymphoma that integrates tumor size and metabolic response. The reasons are many and include the improved accuracy of PET/CT over that of CT alone (8,9), the ability of metabolic imaging to help differentiate viable tumor

from fibrosis or necrosis in residual masses (15), and the prognostic and potential therapeutic implications. Additionally, changes in tumor size can be slow and may not reflect the real-time treatment effect.

Such a classification was recently proposed for aggressive NHL (5). This classification combines traditional (largely anatomic) response definitions with the PET result, which is scored as "completely negative" or "positive." On retrospective analysis, these new criteria predicted progression-free survival more accurately than traditional anatomic response criteria (5). These criteria are an important step forward and require validation in prospective studies. Integrated response criteria are similarly needed for Hodgkin's lymphoma.

However, a central and as-yet-unresolved question is how and when to best define a metabolic response. Conventional response criteria can be easily standardized because they are based on relatively straightforward tumor measurements (16). However, ^{18}F -FDG uptake is not binary but lies on a continuum, as does tumor size (Fig. 2). The prognostic implications were illustrated in an analysis of midtreatment PET for NHL (17), in which patients with minimal residual uptake had survival outcomes intermediate between those of patients with positive scan results and those of patients with negative scan results (Table 1).

An arbitrary designation of positive or negative results is attractive for formulating standardized metabolic response criteria as well as for planning clinical trials in which treatment is modified on the basis of the PET result.

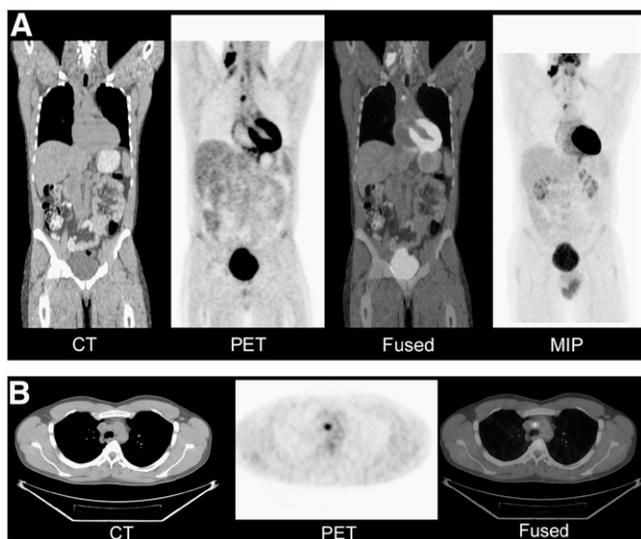


FIGURE 1. PET/CT for staging of Hodgkin's lymphoma. CT showed involvement only in right neck. PET/CT (A: coronal views; B: transverse views; MIP = maximum-intensity projection) showed that normal-size (9-mm) upper mediastinal lymph node was clearly metabolically active, changing stage from I to II. This finding is relevant if consolidative radiation after chemotherapy is planned. Incidental normal scalene muscle uptake was noted on coronal PET.

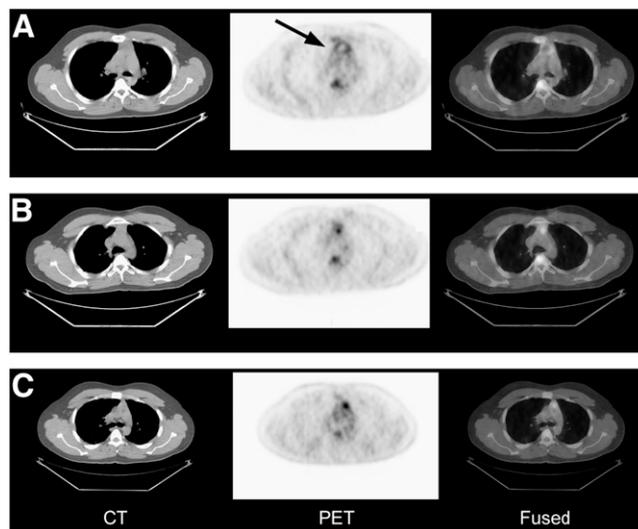


FIGURE 2. Defining positive PET results after treatment. After 3 cycles of chemotherapy for NHL, midtreatment PET/CT showed persistent, metabolically active disease in mediastinum (enhancing rim with central necrosis [arrow] in A; nodular pattern in B). After BMT in clinical trial, PET/CT showed decreased but persistent metabolic activity (C) compatible with either inflammation or residual malignancy, raising questions about management and prognosis. Uptake was in location of prior residual mass and was cephalad and distinct from thymus.

TABLE 1
Midtreatment ¹⁸F-FDG PET for NHL

Study	Type	Cycles before PET	Treatment	No. of patients	No. of patients with positive PET results	PPV (%)	NPV (%)	% EFS (no. of y) for patients with the following PET results:		Median follow-up (mo)	Median TTF (mo)
								Positive	Negative		
Mikhaeel et al. (18)	Retrospective	2-4	First line	23	8	88	100	—	—	30	—
Spaepen et al. (19)	Retrospective	2-4	First line	70	33	100	84	4 (2)*	85 (2)*	36	1.5 if PET positive, 35 if PET negative
Jerusalem et al. (20)	Prospective	2-5	First line or salvage	28	5	100	67	20 (1), 0 (2)	81 (1), 62 (2)	17.5	—
Kostakoglu et al. (21)	Prospective	1	First line or salvage	30 (17 with NHL, 13 with HL)	15	87	87	20 (1)*	85 (1)*	19	—
Mikhaeel et al. (17)	Retrospective	2 or 3	First line	102†	52	71	90	16 (5)	89 (5)	24‡	10 if PET positive, 7 if MRU, 24 if PET negative
Haïoun et al. (22)	Prospective	2	First line, with or without BMT§	90	36	—	—	43 (2)	82 (2)	24	—

*Estimated from Kaplan-Meier curves.

†Nineteen additional patients had MRU and were analyzed separately, with 5-y EFS of 59%.

‡Value of 24 mo was for all patients; value for surviving patients was 28.5 mo.

§Forty percent of cohort received autologous BMT as part of planned therapy, irrespective of PET results. Results were reported for whole group.

PPV = positive predictive value; NPV = negative predictive value; EFS = event-free survival; TTF = time to treatment failure; — = no data; NHL = non-Hodgkin's lymphoma; HL = Hodgkin's lymphoma; MRU = minimal residual uptake; BMT = blood or marrow transplantation. Definition of EFS variably represents freedom from disease progression, relapse, incomplete remission, disease-related death, or death from any cause.

However, the reproducibility of the response designation may be compromised if it is based on qualitative (visual) criteria. Quantitative or semiquantitative measures, such as standardized uptake values, although more complex and time-consuming, are potentially highly reproducible (23). A clear cutoff for an adequate (clinically meaningful) reduction in the standardized uptake value remains to be defined in large trials (24) and may vary on the basis of tumor histology and type of treatment. It should be noted, however, that conventional anatomic response definitions are also quite arbitrary and are not based on strong outcome data (6).

RISK STRATIFICATION AND RESPONSE ASSESSMENT

Midtreatment (interim) ^{18}F -FDG PET has emerged as a powerful prognostic tool that complements and is more informative than established prognostic indices for lymphoma (19,25).

PET and PET/CT have clearly enhanced the ability to risk stratify patients. Independent groups have established that ^{18}F -FDG PET, whether performed after treatment (at the completion of all therapy) (18,26) or midtreatment (after only a few cycles of chemotherapy) (17,19) for aggressive NHL, is highly predictive of progression-free and overall survival. In patients with newly diagnosed NHL, representative studies have demonstrated disease progression rates of 71%–100% if the midtreatment PET scan result is regarded as positive but only 8%–16% if the midtreatment PET scan result is regarded as negative (Table 1). Time to treatment failure also tends to be significantly shorter in patients with a persistently abnormal midtreatment PET result (Table 1). For example, in patients with NHL, the median times to treatment failure have been found to be 1.5–10 mo in patients determined to have a positive midtreatment PET result and 24–35 mo if the midtreatment PET result is determined to be negative (17,19).

More recently, dedicated studies of midtreatment PET for Hodgkin's lymphoma were also published (Table 2). The negative predictive value of midtreatment PET (i.e., the probability of patients with negative PET results achieving durable remission) has been consistently high (at least 94%). Notably, however, the positive predictive value (i.e., the probability of patients with positive PET results having disease progression) has been quite variable (approximately 62%–90%).

Survival outcomes depend not simply on whether the PET result becomes negative but also on the rapidity with which it happens. Of particular clinical significance is that most patients who have lymphoma and who achieve durable remission will have negative PET results after the first few (2–4) chemotherapy cycles. In fact, the kinetics of the metabolic response during even the first week of chemotherapy have been found to be prognostic (29). PET thus permits the earlier identification of high-risk patients (Fig. 3) and could shape individualized, response-adapted therapy.

RESPONSE-ADAPTED THERAPY

It has become increasingly clear that PET, whether performed midtreatment or after therapy completion, brings new meaning to the definition of an adequate therapeutic response. The management implications are many. However, to better understand the role of PET as a measure of lymphoma treatment effectiveness, a brief discussion of the biology underpinning the clinical observations is in order.

Meaning of Midtreatment or Posttreatment PET Results

Cancers are usually not diagnosed until they reach a size of 10–100 g, or 10^{10} – 10^{11} cells (Fig. 4). In the idealized setting, external-beam radiation and cytotoxic chemotherapy kill cancer cells by first-order kinetics; that is, a given treatment dose will kill the same fraction, not the same number, of cancer cells regardless of the size of the tumor (30). Thus, a dose of therapy that produces a 90% (1-log unit) reduction in tumor mass will have to be repeated at least 10 times to eliminate a newly diagnosed cancer (obviously ignoring immunologic effects that could potentially improve treatment efficacy or resistant subpopulations of cancer cells that would worsen it). Moreover, cure of lymphoma with 6 cycles of therapy, assuming no interval regrowth, requires at least 1.5 log units of tumor cell killing per cycle, or a 99.9% reduction in the number of viable cancer cells after 2 cycles. The limit of resolution of ^{18}F -FDG PET for detecting lymphoma generally ranges between 0.5 and 1.0 cm (7,31), which translates to a tumor size of approximately 0.1–1.0 g, or 10^8 – 10^9 cells. It therefore follows that PET likely can only measure the first 2–3 log units of tumor cell killing, depending on the initial size of the tumor (Fig. 4).

Accordingly, a true-positive PET scan result at the end of 6 cycles of therapy likely signifies that the cancer is resistant because probably fewer than 2 or 3 log units of tumor cells have been eliminated. Conversely, a true-negative PET scan result at the end of therapy might be expected to have less predictive value because the tumor cell killing could be quite heterogeneous, including patients whose tumors were completely eliminated and those whose tumor cell killing was as small as 2 log units. Whereas a negative PET scan result at the end of treatment is probably not able to distinguish between 2 and 10 log units of tumor cell killing, a midtreatment scan may be able to do so. Because a true-positive PET scan result at the end of 2 cycles of therapy suggests that fewer than 2 or 3 log units of tumor cells have been eliminated, it is unlikely that the 10 or 11 log units needed for cure will be eradicated by 6–8 cycles. A true-negative PET scan result after 2 cycles of therapy implies the opposite; that is, the rate of tumor cell killing for this lymphoma is sufficient to produce cure (Fig. 4).

False-Positive Results

Relatively common potential causes of false-positive readings on ^{18}F -FDG PET for lymphoma patients include inflammation, infection, supraclavicular adipose tissue

TABLE 2
¹⁸F-FDG PET During Initial Therapy for Hodgkin's Lymphoma

Study	Type	Cycles before PET	No. of patients	No. of patients with positive PET results	PPV (%)	NPV (%)	% EFS (no. of y) for patients with the following PET results:		Median follow-up (mo)	Median TTF (mo)
							Positive	Negative		
Friedberg et al. (3)	Prospective	3	22*	5	80	94	—	—	24	—
Gallamini et al. (27) [†]	Prospective	2	61	10	90	98	10 (3)	98 (3)	19	—
Hutchings et al. (28)	Retrospective	2 or 3	85 [‡]	13	61.5	94	46 (2), 38.5 (5)	97 (2), 91.5 (5)	40	24 if PET positive, 9 if PET negative (including MRU)
Hutchings et al. (25)	Prospective	2	77	16	69	95	0 (2)	96 (2)	23	—
Hutchings et al. (25)	Prospective	4	64 [§]	13	85	96	19 (2)	96 (2)	23	—

*Thirty-six additional patients had PET scans after therapy completion; results for 8 were positive, with PPV of 50% and NPV of 96%.

[†]Interim data.

[‡]Nine patients had MRU; for analysis, their PET results were considered negative.

[§]PET was also performed after therapy completion for 65 patients; results for 9 were positive, with PPV of 78% and NPV of 96%.

PPV = positive predictive value; NPV = negative predictive value; EFS = event-free survival; TTF = time to treatment failure; — = no data; MRU = minimal residual uptake. Definition of EFS variably represents freedom from relapse, progression on therapy, incomplete remission, disease-related death, or death from any cause.

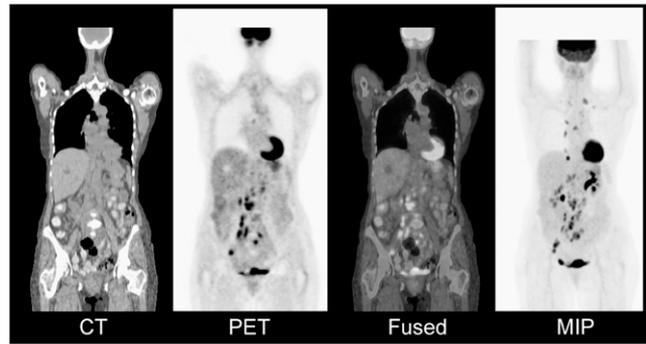


FIGURE 3. PET/CT for early risk stratification. Midtreatment PET/CT after 3 cycles of chemotherapy for diffuse large B-cell lymphoma showed dramatic anatomic response (baseline imaging not shown) but persistent metabolic activity in multiple mediastinal and para-aortic lymph nodes. Despite modification of chemotherapy in clinical trial, 2 mo later patient developed abdominal pain and was found to have fulminant disease progression (not shown). MIP = maximum-intensity projection.

(brown fat) (32), thymic hyperplasia (thymic rebound), and bone marrow uptake attributable to granulocyte colony-stimulating factors. Experienced interpreters and the use of PET/CT likely can reduce but not totally eliminate false-positive readings on initial imaging or imaging after therapy.

Timing of Metabolic Imaging

The optimal number of cycles before midtreatment PET and the optimal interval between last treatment and PET are matters of debate. After chemotherapy, a minimum 10-d window has been advised to permit the chemotherapeutic effect and to bypass transient fluctuations in ¹⁸F-FDG

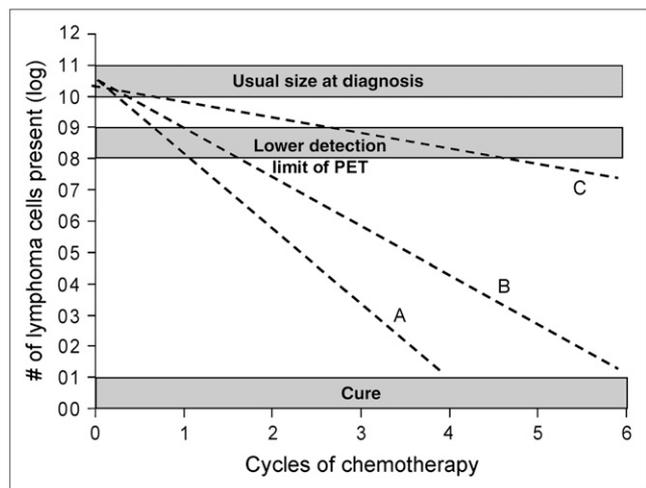


FIGURE 4. Kinetics of tumor cell killing and relationship to PET. Line B represents minimum rate of tumor cell killing that would lead to cure. Line A represents even more brisk tumor response that would produce cure after only 4 cycles of chemotherapy. Both of these lines would be associated with negative PET scan results after 2 cycles of chemotherapy. In contrast, line C represents rate of tumor cell killing that would be associated with negative PET scan results after 4–6 cycles of chemotherapy but would not produce cure. Importantly, PET scan results for line C would be positive after 2 or 3 cycles.

uptake that may occur early after treatment, that is, “stunning” of tumor uptake (2).

Most of the outcome data for PET after treatment are from studies involving chemotherapy; relatively few data are thus far available for patients treated with radiation, radioimmunotherapy, or other biologic therapies. Longer and more variable intervals (spanning weeks to months) have been advised after radiation therapy (33), because tumor response is more gradual and because inflammation can confound the PET result. The optimal timing is not yet known and may depend on the radiation dose (33). The time course of the metabolic response to radioimmunotherapy has begun to be defined for lymphoma (34).

Histologic Evaluation

The clinical utility of ^{18}F -FDG PET depends on the pathologic subtype but not necessarily on the grade of tumor (12). For example, in 1 series, ^{18}F -FDG PET detected 98% of follicular (low-grade) lymphomas but only 67% of marginal-zone lymphomas (which are also low grade) (12). Most of the PET data are for B-cell lymphomas, as T-cell lymphomas are comparatively rare.

Classical Hodgkin's lymphoma deserves special consideration in this regard. In NHL, as in most solid-tumor malignancies, the bulk of the tumor is composed of malignant cells. Curiously, in Hodgkin's lymphoma, typically less than 1% of the tumor mass comprises malignant cells; the remainder is a benign inflammatory infiltrate. Thus, the PET signal almost certainly originates not only from the malignant cells but also from the infiltrating lymphocytes that comprise the bulk of the tumor. This PET signal that originates from infiltrating lymphocytes is expected to affect overall ^{18}F -FDG uptake before as well as after treatment. The variable positive predictive value of PET for Hodgkin's lymphoma (Table 2), as opposed to NHL, may simply be attributable to the relatively small number of high-risk patients but may also reflect this difference in tumor histology.

MANAGING POSITIVE POSTTHERAPY PET RESULTS

Whereas there are defined approaches to managing relapsing or refractory lymphoma, how to manage positive PET results in an otherwise “responding” patient is not established and is the basis for ongoing and emerging trials. Certainly, positive PET results after the completion of therapy raise concern, and it may be tempting to extend or escalate therapy in patients with such results. However, it is not yet known which management strategies are most likely to translate into a clinical benefit. For the purposes of illustration, we consider several scenarios involving positive posttreatment PET results outside a clinical trial.

Extending Course of Chemotherapy

Viable lymphoma that persists despite 6 cycles of CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone) or ABVD (doxorubicin-bleomycin-vinblastine-dacarbazine)

treatment is very likely to be inherently resistant to that regimen. This conclusion is based on the kinetics of tumor killing (30). Therefore, it is doubtful that additional cycles of the same chemotherapy will benefit a patient, even if there has been a seemingly brisk response on the basis of CT criteria.

Adding Radiation

Because of its cumulative late toxicities and questionable impact on overall survival, the role of consolidative radiation for Hodgkin's lymphoma and NHL is controversial. This is particularly the case for bulky or limited-stage disease. There is promise for PET/CT in helping to guide not only radiation planning but also the decision to use radiation.

Let us assume that, after a full course of chemotherapy, residual ^{18}F -FDG uptake in a mediastinal mass is known to represent viable tumor rather than inflammation. It is possible that radiation therapy may eradicate disease that has persisted despite a full course of chemotherapy. On the other hand, such disease may very well be radioresistant as well as chemoresistant; thus, consolidative radiation would increase the risk of therapeutic toxicities without significantly reducing the tumor burden. These toxicities, in turn, could complicate future and potentially curative treatments, such as blood or marrow transplantation (BMT). For example, pulmonary function in a patient with Hodgkin's lymphoma may deteriorate because of the combined insult of bleomycin and radiation.

Chemoresistance and radioresistance coexist commonly in patients with relapsing lymphoma. For example, salvage radiation is less likely to be beneficial for Hodgkin's lymphoma that relapses early (less than 1 y) after chemotherapy (35), and it is not uncommon for disease to recur in a previously irradiated site. It follows that there may be even less benefit to the use of radiation for disease that remains ^{18}F -FDG avid after a full course of chemotherapy. Efforts are needed to better guide patient selection in this regard. Outside a clinical trial, one should not assume that radiation is the natural next step for eradicating residual lymphoma.

Intensifying Treatment with BMT

High-dose therapy with autologous BMT is superior to nonmyeloablative therapy for patients with relapsing aggressive NHL, but only provided that the disease is chemosensitive (i.e., first responds to a trial of salvage chemotherapy) (36). The benefit of early transplantation (in first remission) is a matter of debate but is most apparent in high-risk patients (37). Because of the morbidity, the 5%–8% mortality rate, and the expense of autologous BMT, better ways of selecting patients for this intensive approach are needed. Traditionally, such patients have been stratified on the basis of validated prognostic indices (38); however, these are population-based, rather than patient-specific, parameters. Given the prognostic power of PET, it is possible that PET/CT may help to optimize patient selection for BMT. For example, early BMT could be avoided in patients who were identified as high-risk patients by standard prognostic

indices but whose PET results became negative after 2 or 3 cycles of chemotherapy.

In the nonprotocol setting, we would not advocate BMT solely on the basis of a residually positive PET scan result after first-line therapy. This is because the positive predictive value of PET is not 100%. Because of the clinical consequences, we would first advocate either biopsy confirmation of disease persistence or follow-up radiographic assessment to confirm disease progression.

It has been appreciated that PET has significant prognostic value when performed before transplantation (39,40). Metabolic imaging before transplantation has thus expanded the concept of chemosensitive or chemoresistant relapse (39). Because of relatively poor outcomes, skepticism has been generated about the appropriateness of BMT for patients who have persistently positive PET results after salvage nonmyeloablative chemotherapy. However, although it is tempting to regard a PET result as positive or negative for the purposes of treatment decisions, there clearly is a continuum. It is possible that lymphoma with “mild” ^{18}F -FDG uptake may be less resistant (and hence more amenable to cure) than lymphoma with intense uptake. The effectiveness of BMT, then, may rest not only on whether the PET result is positive but by how much. Because such a scenario is unlikely to be an all-or-nothing situation, we would not deny patients BMT solely on this basis. Indeed, some of these patients may stand to benefit most from treatment intensification.

MANAGING NEGATIVE PET RESULTS

What about de-escalation of therapy on the basis of negative PET results? It should be emphasized that, in studies to date, patients with negative midtreatment PET results and a favorable outcome still completed a full course of therapy. Some may find it tempting to shorten the chemotherapy course or omit consolidative radiation therapy if an interim PET result is regarded as negative. Data are not yet available to support this approach, although trials are ongoing or planned.

It is also critical to keep in mind that a negative PET result does not necessarily indicate total eradication of disease (Fig. 5). Rather, as discussed previously, it simply implies a certain amount of cell killing. Thus, patients with true-negative midtreatment or posttreatment PET results represent a heterogeneous group in terms of relapse risk.

INDIVIDUALIZED THERAPY BASED ON PET OR PET/CT

We propose a conservative algorithm for integrating PET/CT into the management of aggressive lymphomas on the basis of available published data. The addition of PET is certainly helpful in staging and improves diagnostic accuracy but should not unduly delay prompt initiation of treatment if such is indicated. In our experience, it is generally very helpful to obtain a baseline PET study for future comparison. At present, for early therapy monitoring and risk stratifica-

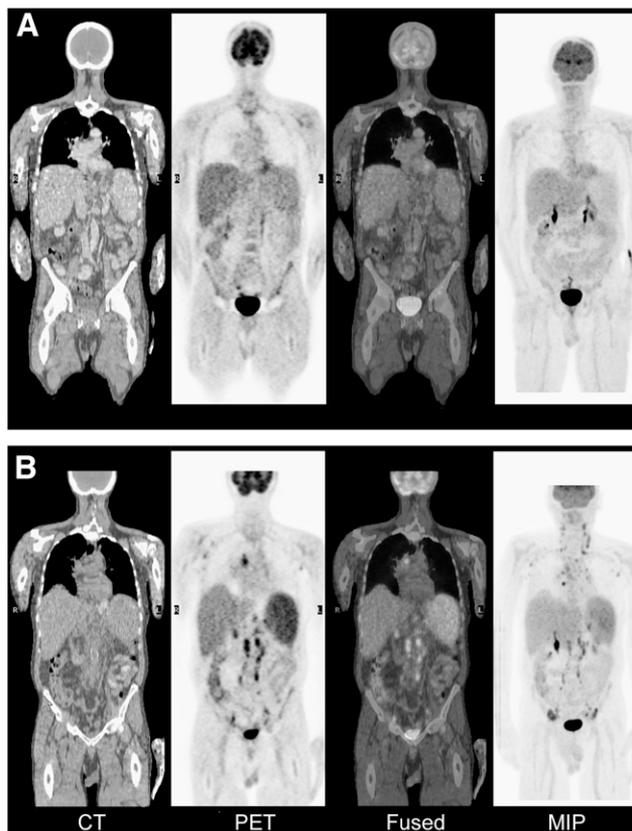


FIGURE 5. PET/CT for monitoring response and remission status. After 4 cycles of chemotherapy for peripheral T-cell lymphoma (baseline imaging not shown), PET/CT (A) was negative for active disease, and patient completed 2 more cycles. Two months after therapy completion, worrisome symptoms developed, and PET/CT (B) showed multiple ^{18}F -FDG-avid lymph nodes above and below diaphragm. CT at that time was not definitively abnormal but at 2 mo later showed definitive tumor progression. This case indicates that negative PET after treatment does not mean absence of active tumor and also indicates how PET/CT can be more sensitive than CT for detecting early recurrence. MIP = maximum-intensity projection.

tion, midtreatment PET/CT is best obtained in the context of a clinical trial, because of the great uncertainties about how to manage the results. It is, however, clear that a true-positive midtreatment PET result is associated with a significantly increased risk of treatment failure.

PET/CT can be more routinely considered after therapy completion to document the depth of remission. Beforehand, however, one should consider whether and how the information will influence patient management. Outside a clinical trial, if a PET result after therapy is positive but there is otherwise no evidence of persistent or progressive disease, other confirmation of disease persistence should be sought before treatment is modified. One option is to obtain a biopsy of the suspected lesion. However, this option may be risky, impractical, or impossible, depending on the site. An attractive, noninvasive alternative is to wait and reassess soon afterward with repeat imaging (e.g., repeating PET or PET/CT in 1 or 2 mo).

Uptake on ^{18}F -FDG PET commonly precedes the development of morphologically or clinically evident disease progression (Fig. 5). At present, however, the role of PET/CT rather than CT for routine surveillance is still in evolution. One must weigh the added expense and radiation exposure of sequential PET/CT scans and also consider the particular clinical situation. The clinical impact of detecting relapse early depends on the types of treatment available (palliative vs. curative) and the biology of the lymphoma (indolent vs. aggressive). For example, early detection is less important for patients with indolent NHL treated with palliative rather than curative intent. On the other hand, relapse of a highly aggressive lymphoma is best detected early, so as to permit the institution of therapy before clinical deterioration occurs. Potentially curative therapies, such as BMT, may also be available, as in patients with diffuse large B-cell lymphoma or Hodgkin's lymphoma. Because radiographic surveillance is advised for aggressive lymphomas, PET/CT may have an expanding role for patients with such lymphomas.

Because the management implications are potentially great, the importance of the oncologist clarifying a positive PET finding with the radiologist cannot be overemphasized.

CONCLUSION

The integration of PET and PET/CT adds a new dimension to response and risk assessment in lymphoma. There is potential not only to improve the outcomes of suboptimally responding patients through earlier intervention but also to spare low-risk patients from overly aggressive treatments. Thus, more precise tailoring of the treatment plan to the individual patient on the basis of the PET/CT result should be feasible.

Many of the diagnostic and management questions considered here are relevant to other tumor types. For instance, how positive is positive after treatment? What constitutes an adequate metabolic response? What is the appropriate threshold for changing management on the basis of a mid-treatment or posttreatment PET result? Given the many potential causes of a false-positive or false-negative PET result and until more clinical data emerge, a conservative strategy seems best in the nonprotocol setting. The prognostic value of PET for lymphoma has been established, and the next step is to define how to use this information to optimize patient outcomes. Ideally, through the use of PET/CT, the choice of therapy, its intensity, and its duration will become better suited to the biology of the individual patient.

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