The Impact of Fluorodeoxyglucose–Positron Emission Tomography in Primary Staging and Patient Management in Lymphoma Patients

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KEYWORDS

• PET/CT • FDG • Lymphoma • Staging

Positron emission tomography (PET) imaging became a clinical force in the mid-to- late 1990s when the US Health Care Administration approved whole-body PET imaging for several oncological indications. Following the initial approval for fluorodeoxyglucose (FDG)-PET characterization of solitary lung nodules, several other indications were approved, among them diagnosing, staging, and restaging of lymphoma. FDG-PET has taken the place of gallium-67 (Ga-67) scintigraphy as the modality of choice for functional and metabolic imaging of patients who have lymphoma.

With the advance of combined PET/CT devices,[1] anatomic masses can be dissected simultaneously based on size criteria and molecular characteristics such as their glucose metabolism.[2] This is important, because clinical practice and clinical trials still rely on anatomic response criteria,[3] and the value of molecular and anatomic tumor characterizations for response predictions can be compared directly.[4] The ability to accurately characterize masses and PET's/CT's high sensitivity and specificity for staging, restaging, and treatment monitoring have led to wide-spread acceptance of PET/CT imaging in the imaging of lymphoma.[5–7]

The important role of FDG-PET imaging in lymphoma is emphasized by the recent report of the International Harmonization Project.[8,9] The harmonization project recommendations are among the first to formally acknowledge the importance of glucose metabolic imaging for managing patients who have cancer.

Taking into account variability among readers and equipment, the working group arrived at the following recommendations:

1. FDG-PET is recommended strongly before treatment in patients with routinely FDG avid lymphoma such as diffuse large B cell lymphoma (DLBCL) or Hodgkin lymphoma (HL).
2. Treatment effects should be assessed 6 to 8 weeks after completion of chemotherapy.
3. Quantification of FDG uptake with standardized uptake values (SUV) and measurement of changes are not necessary, because visual

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assessments of treatment effects after completion of therapy are sufficient.[9]

IMAGING WITH FLUORODEOXYGLUCOSE-6-PHOSPHATE

Increased glucose metabolic activity as a hallmark of malignant degeneration initially was described in 1924 by Warburg.[10] This increase in glycolytic activity takes place even in the presence of oxygen. The increased glycolytic activity of tumors has been exploited for imaging cancer with PET and the glucose analog FDG.[11,12]

Competing with serum glucose FDG targets membrane-bound glucose transporters (Glut-1 and Glut-3) that shuttle FDG into tumor cells and hexokinases (HK-1 and HK-2), which phosphorylate FDG to FDG-6-phosphate. Both of these enzymes are overexpressed in many cancers.[13] Unlike glucose-6-phosphate, FDG-6-phosphate is no longer a substrate for the subsequent steps in the glycolytic pathway. Furthermore, glucose-6-phosphatase that would reverse the actions of hexokinase is available only in very limited amounts in tumor cells. Thus, FDG-6-phosphate essentially is trapped in tumor cells in proportion to their glycolytic activity (**Fig. 1**).

In vivo detection of fluorine-18 (F-18) positron emission can be achieved by the PET scanner that was invented in the early 1970s.[14] Positrons, however, are not detected directly as they travel a few millimeters from the site of decay before undergoing an annihilation reaction with electrons in tissue.[15] This annihilation reaction results in the simultaneous emission of two photons with 511 keV (the mass energy of an electron/positron) that leave the annihilation site at and angle of approximately 180° and are detected by the PET scanner (**Fig. 2**).

STANDARDIZED UPTAKE VALUES

PET images can be analyzed visually, semiquantitatively by means of SUV,[16] or quantitatively using

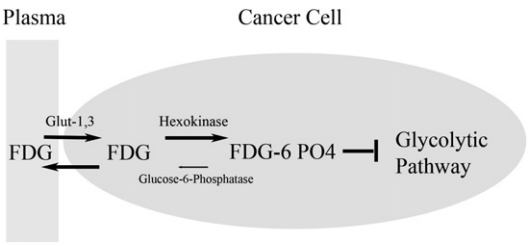

Fig. 1. Fluorodeoxyglucose (FDG) uptake by means of glucose transporters Glut 1 and 3, with subsequent phosphorylation and trapping of the phosphorylated FDG (FDG-PO4) in a cancer cell.

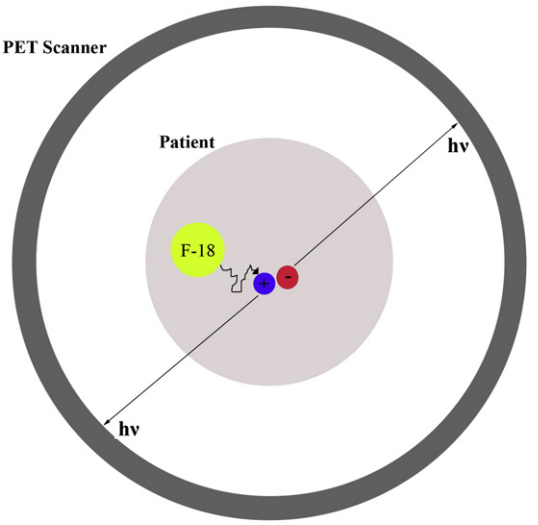

Fig. 2. Detection of photons (hν) originating from the annihilation reaction of a positron (resulting from the decay of the F-18 isotope) and a tissue electron.

appropriate tracer kinetic models.[17] Because of their simplicity, PET scans most frequently are analyzed visually or by means of SUV that is defined as:

$$\frac{\text{decay-corrected activity [kBq]/tissue volume[mL]}}{\text{injected-FDG activity [kBq]/body weight [g]}}$$

The reproducibility of SUVs and that of more sophisticated model-based quantitative approaches that for instance measure tumor glucose use in units of μmol/g/min was established by measuring tumor FDG uptake twice within 1 to 2 weeks in patients who had lung cancer.[17] This study demonstrated that simple SUV measurements are reproducible and suffice for estimating tumor glucose metabolic activity. The more computationally demanding modeling approach usually is reserved for research protocols.[18] Importantly, in lymphoma, visual assessments of treatment responses are sufficient in clinical practice.[8,9]

The following discussion will focus on the role of FDG PET and PET/CT for staging of lymphoma. In particular, the authors will discuss whether FDG PET adds to the staging information provided by CT and other conventional imaging modalities. Finally, they will examine whether and how PET/CT imaging findings translate into changes in patient management.

FLUORODEOXYGLUCOSE–POSITRON EMISSION TOMOGRAPHY/CT COST AND AVAILABILITY

More than 1800 PET/CT and PET scanners are distributed throughout the United States.[19] With the emergence of commercial radio-pharmacies that produce FDG in small self-shielded

cyclotrons, more than 95% of all cancer patients now have access to PET/CT imaging. Thus, there are essentially no limitations to the use of PET and the old argument, that PET imaging is only available in selected centers, can be put to rest. Another outdated argument is that whole-body FDG PET imaging is expensive while CT imaging is considered inexpensive. Current technical and professional reimbursement rates for both whole-body contrast CT and PET/CT average around $1000. Moreover, combined FDG PET/CT does not increase health care costs. Providing the combined anatomic (CT) and glucose metabolic (PET) information is reimbursed at the same level as PET or CT alone.

TECHNICAL CONSIDERATIONS

Most PET examinations in lymphoma and other cancers are performed as part of PET/CT studies that can be performed in less than 10 minutes in some patients.[20,21] PET/CT also increases patient comfort by reducing the need for multiple visits in clinics. PET image interpretation is facilitated by complementary anatomic information from CT, resulting in fewer equivocal findings, increased reader confidence[22,23], and more accurate assessments of the extent of disease.[24,25] PET/CT interpretations yield a higher diagnostic accuracy than side-by-side PET and CT interpretations in some[23,26] but not in other cancers (**Fig. 3**).[27]

Before treatment, most non-HL (NHL) and HL can be staged accurately with both CT and PET. Arguments for the preferential use of CT include its high sensitivity (because of its superior spatial resolution) and accuracy, its wide availability, and its alleged relatively low cost. Disadvantages include its limited specificity, its inability to determine bone marrow involvement, and the high radiation dose to patients, which is estimated to average as much as 25 mSv.[28]

A recent study suggested that separate CT studies (in addition to PET/CT) are unnecessary in patients who have lymphoma.[29] The addition of PET/CT to CT changed the management decisions in 25% of NHL and 33% of HL patients, mostly in early disease stages.

Initial studies using PET/CT imaging demonstrated its diagnostic advantage over PET and CT alone.[24,30] This diagnostic advantage was achieved by using low-dose noncontrast-enhanced CT rather than fully diagnostic contrast CT studies. It remains unclear from the available literature whether the CT portion of PET/CT should be diagnostic (ie, performed after the administration of intravenous contrast) or whether a low-dose CT would suffice for this indication as suggested in one study. In this report of 47 patients, contrast-enhanced PET/CT resulted in a smaller number of indeterminate nodes and detected a larger number of extranodal sites but did not have a significant impact on patient management. PET and PET/CT arrived at a different disease stage in only one of the 47 patients.

Another study in 64 patients compared the diagnostic performance of unenhanced PET/CT with

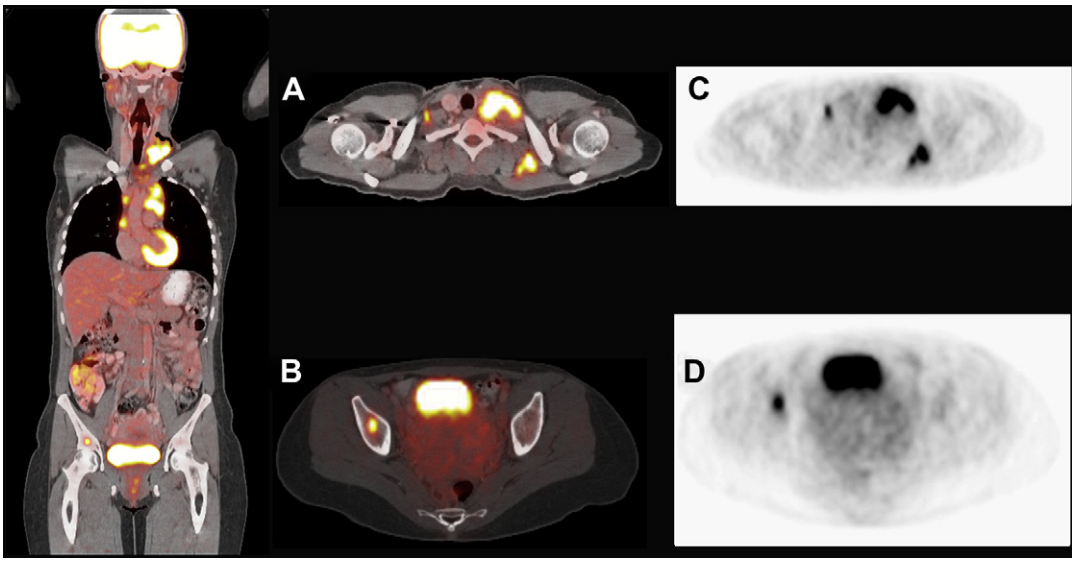

Fig. 3. 46-year-old woman with a history of nodular sclerosing HD. Selected fused positron emission tomography and axial slices demonstrate supraclavicular adenopathy (*A, C*) and bone involvement of the right acetabulum (*C, D*). Bone involvement would not have been identified on CT alone.

that of contrast-enhanced CT for lymphoma staging.[31] Nonenhanced PET/CT alone was superior to contrast CT, especially for staging of extranodal involvement. Sensitivity of nonenhanced PET/CT and enhanced CT was 88% and 50%, while specificities were 100% and 90%. Unfortunately, no direct comparison between contrast-enhanced and nonenhanced PET/CT was performed.

The ability of enhanced and nonenhanced PET/CT for staging pelvic and retroperitoneal nodes was evaluated by Morimoto and colleagues.[32] Standard clinical assessment and clinical follow up served as reference standards, and thus no true gold standard was available. The nodal stage was correct in 79% of the patients with contrast CT and in 71% on noncontrasted PET/CT ($P<.05$). Specifically, noncontrast CT was less accurate for assessing external and internal iliac node involvement.

More recently, Pfannenberg and colleagues[33] compared contrast-enhanced to nonenhanced PET/CT in a large group of cancer patients that also included some who had lymphoma. The CT protocol included standard multiphase acquisitions: an arterial phase thorax and liver scan, a portal–venous abdomen and pelvis scan, and if necessary, a postcontrast liver scan. The authors reported a considerable impact of intravenous contrast CT, specifically in patients who had metabolically faint lesions; in addition, and as expected, lesion localization and staging were improved. Finally, patient management was affected in 21 of 52 patients (42.7%). These findings suggest that contrast-enhanced PET/CT might be the preferred protocol in patients who have low-grade lymphoma in whom lesions frequently exhibit low or faint FDG uptake.

The number of lymphoma patients in whom potential benefits of intravenous contrast administration have been evaluated systematically is still too low to permit firm conclusions. Several arguments, however, can be made for the use of oral and intravenous contrast with PET/CT. First, contrast enhancement is the current standard of care in CT imaging. Moreover, most lymphoma patients who receive a non-contrast-enhanced PET/CT will be referred for a separate additional contrast CT study, which adds to the radiation burden, the time spent in imaging clinics, and the complexity of image interpretation. For these reasons, the authors suggest performing PET/CT after oral and during intravenous contrast enhancement unless there are medical contraindications (**Fig. 4**).

Intravenous and oral contrast material (and metallic material) is dense, resulting in overcorrection for photon attenuation[34–36] in tissues, which in turn results in artificially increased FDG uptake, referred to as pseudo-FDG uptake. Clinically, however, this does not represent a significant problem. First, the origins of contrast-induced artifacts frequently are identified by blending PET and CT images. Secondly, in cases of ambiguity, nonattenuation-corrected images, which in case of artifact do not demonstrate increased uptake, are readily available for inspection.

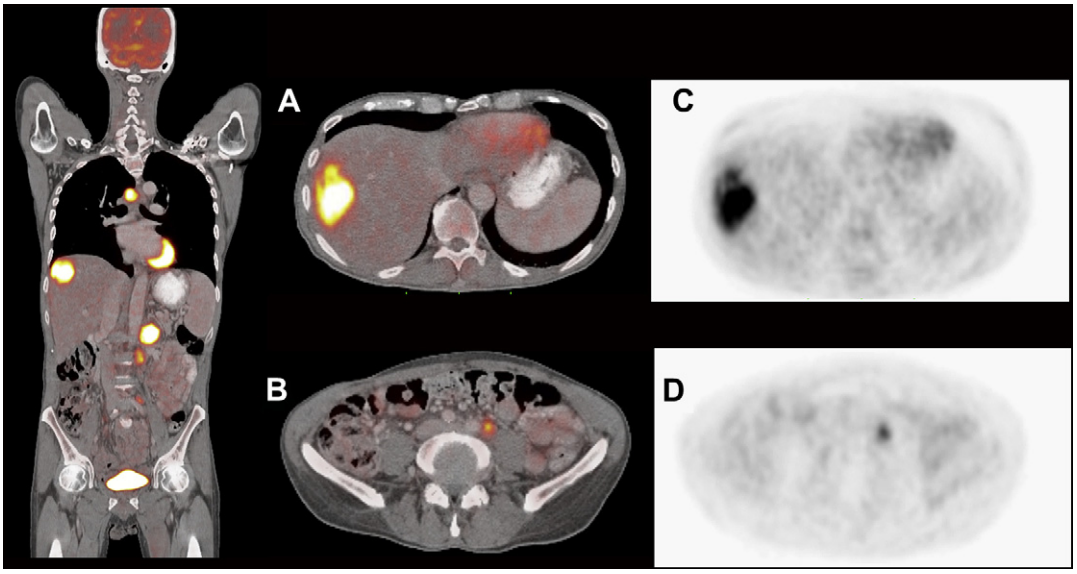

Fig. 4. IV and PO contrast-enhanced positron emission tomography (PET)/CT of a 55-year-old man with a history of anaplastic non-Hodgkin lymphoma. Selected fused PET and axial slices demonstrate liver involvement *(A, C)* and retroperitoneal adenopathy difficult to distinguish from ureteral activity without intravenous contrast *(C, D)*.

ARTIFACTS, PITFALLS, AND POTENTIALLY FALSE-POSITIVE STUDIES

Nonmalignant conditions such as inflammation, infection, and granulomatous eg, sarcoidosis[37,38] and physiologic FDG uptake such as in brown adipose tissue,[39] activated muscle (**Fig. 5**), or hyperplasia of the thymus[40] can cause focally increased FDG uptake, and potentially lead to false-positive studies. Similarly, abnormal FDG uptake has been associated with hyperplasia in the bone marrow and spleen after chemotherapy or in patients receiving granulocyte colony-stimulating factor after chemotherapy.[41] Conversely false-negative PET scans usually result from lesions below the resolution of the scanner, generally 5 to 10 mm.

GLUCOSE METABOLIC ACTIVITY VARIES AMONG DIFFERENT TYPES OF NON-HODGKIN LYMPHOMA

Lymphomas differ with regard to their glucose metabolic activity. Systematic studies have shown that indolent lymphomas exhibit lower glucose metabolic activity and hence FDG uptake than the more aggressive ones.[42] For instance, diffuse large B-cell, and high-grade follicular lymphoma had, on average, threefold higher FDG SUVs than indolent lymphomas such as low grade follicular, lymphocytic–plasmocytic, mantle cell, marginal zone, or small cell lymphoma.[43]

These differences in glucose metabolic activity are explained among other factors by differing proliferative activities among lymphoma types and likely account for their variable detection rates as reported in the literature.[43,44]

The variability in glycolytic activity and FDG uptake has implications for both staging of disease and treatment monitoring. For instance, when baseline FDG uptake is low, treatment-induced changes in FDG uptake are difficult to quantify. Nevertheless, there might be a role of FDG PET or PET/CT for staging and monitoring even in the few low-grade lymphomas with very low FDG uptake, since their transformation into high-grade lymphomas is associated with marked increases in glucose metabolic activity, which are detectable with PET.[45]

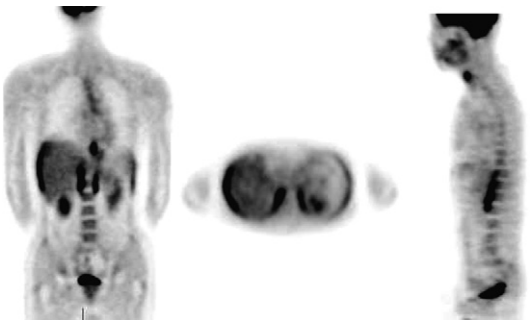

Fig. 5. Patient with chronic hiccups. Intense fluorodeoxyglucose uptake throughout the muscle tissue of the diaphragm can be seen.

The staging accuracy of FDG PET is determined by the degree of FDG uptake in individual lesions. Because low-grade, indolent lymphomas grow more slowly than high-grade lymphomas, their energy requirements are lower, and consequently, their FDG uptake also would be expected to be lower. Nevertheless, not only high-grade, but also most low-grade lymphomas can be staged accurately with FDG PET (**Fig. 6**).

Limitations, however, do exist. For instance, Jerusalem and colleagues[46] demonstrated that in contrast to low-grade follicular lymphoma, small lymphocytic lymphomas were staged more successfully with CT than with FDG PET. No semiquantitative analysis by means of SUV was performed in their study. Lower detection rates (sensitivity of 67%) of FDG PET in marginal zone lymphoma (MALT) and peripheral T cell lymphoma (sensitivity of 40%) have been reported by others.[43] No semiquantitative analysis, however, was available in this report.

T cell lymphomas are frequently primarily extranodal or involve extranodal sites. Limited experience suggests that FDG PET may be useful in primary extranodal T cell lymphomas such as enteropathy-associated T cell lymphoma (EATCL) and cutaneous T cell lymphomas such as mycosis fungoides.[47,48] Newer studies[49] suggest a higher rate of FDG-positive T cell lymphoma (**Table 1**), and standardized uptake values in T cell lymphoma show a wide range. Some T cell lymphomas are weakly FDG PET avid.

In another retrospective study,[50] the follicular, nontransformed type had a significantly higher SUV (7.7+-4.6) than marginal zone tumors (3.8, +- 1.3), or small lymphocytic lymphoma/chronic lymphocytic lymphoma type (2.5+- 0.7). Perry and colleagues[51] evaluated FDG uptake in 33 patients with extra-nodal MALT lymphoma. While overall disease detection was low at around 55% detectability was site and grade dependent. For instance, gastric MALT was detected in less than 40% of the patients while lung involvement was correctly identified in 5/5 patients. FDG PET correctly detected disease in all seven patients who had stage 3 or 4 disease, while sensitivity dropped to 42% in patients who had stage 1 or 2 MALT. Similar observations of site and grade dependency were made by others.[52]

The notion that follicular lymphoma of any grade can be staged reliably with FDG PET was

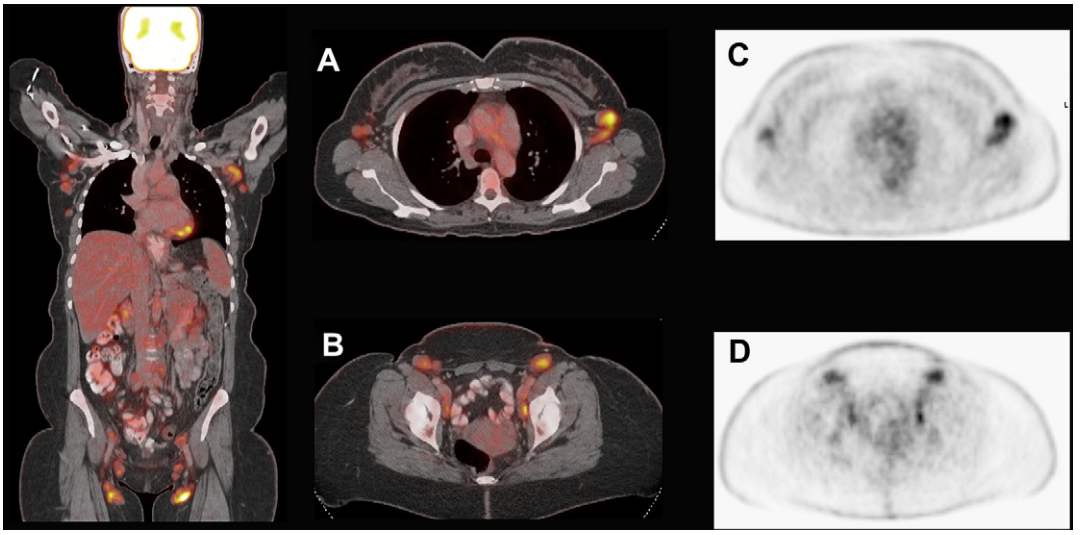

Fig. 6. 48-year-old woman with a history of cutaneous T cell lymphoma. Despite this being a low-grade lymphoma, selected fused and PET and axial slices demonstrate significant FDG uptake in axillary (*A, C*) and inguinal (*B, C*) adenopathy. Increased FDG uptake in the skin, best seen on the PET images (*C, D*), reflects cutaneous lymphomatous involvement.

confirmed by Wohrer and colleagues[53] in a study of 64 patients with grade 1 through 3 disease. There was only a trend toward higher maximum SUV (SUVmax) in aggressive versus indolent lymphoma (median SUVmax: 11.4 versus 5.7; $P = .085$).

In a more recent study, the SUVmax varied substantially among different lymphoma types and ranged from 3.2 in diffuse small-cleaved lymphoma to 43.0 in recurrent diffuse large B cell lymphoma.[42] Aggressive lymphomas (n = 63) had on average a three times higher SUVmax than indolent lymphoma (n = 28; $P<.01$). Using an SUV of 10 as a cutoff, FDG PET separated aggressive from indolent lymphoma with a sensitivity of 71% and a specificity of 81%.

Another study in low-grade follicular lymphoma[54] reported SUVmax that ranged from 5.2 to 8.1. Grades 1 and 2 follicular lymphomas appeared to have a comparable SUVmax, again suggesting that low-grade follicular lymphoma can be imaged with FDG PET.

Table 1
Fluorodeoxyglucose uptake of selected lymphoma

Diffuse large B-cell lymphoma	Moderate to high
Follicular lymphoma	Low to moderate
Mantle cell lymphoma	Low to high
T cell lymphoma	Low to high[a]
Marginal zone lymphoma (including MALT lymphoma)	None to high[b]
Small lymphocytic lymphoma of chronic lymphocytic lymphoma type	Low to moderate
Hodgkin lymphoma (classic form)	High
Hodgkin lymphoma (nodular lymphocyte predominant)	Moderate

Please note that there is a significant range for the reported standardized uptake values (SUV)max in patients with similar lymphoma.

[a] Despite high positive rates of peripheral T cell lymphoma, fluorodeoxyglucose (FDG)–positron emission tomography results in a change of stage in a small number of patients (many patients are stage 4 by conventional modalities). Includes: peripheral T-cell lymphoma, NOS, mycosis fungoides, angioimmunoblastic T cell lymphoma, adult T-cell/human T-lymphotropic virus-1 associated lymphoma, NK/T-cell nasal-type lymphoma, anaplastic large-cell lymphoma, and others.

[b] Approximately 35% of marginal zone lymphomas have no FDG uptake. One publication[52] showed SUV as low as 1.4 but also high as 26.

FLUORODEOXYGLUCOSE UPTAKE IN HODGKIN LYMPHOMA

Since the cytologic and immunochemical atypical cells (Reed-Sternberg cells and variants) may represent 1% to 3% of the tumor bulk, PET activity in classical HL almost exclusively reflects the reactive microenvironment (lymphoid hyperplasia) within which the malignant cells are found, rather than the neoplastic population itself. This is in contrast to NHLs, where, with few exceptions, most of the tumor bulk consists of neoplastic cells.

Few studies have examined differences among glucose metabolism of the different histopathologic subtypes of HL. These include classical HL (nodular sclerosing, mixed cellularity, lymphocyte rich, and lymphocyte depleted) as well as the nonclassical nodular lymphocyte-predominant HL, an entity that behaves and is being treated more like a low-grade NHL.

Döbert and colleagues[55] reported SUVmax values of 5.2 for the nodular sclerosing, 3 for the mixed cellularity, and 2.6 for the nodular lymphocyte-predominant subgroup (a nonclassical HL). In this group of 44 patients who had HL, tumor FDG uptake did not seem to be affected significantly by the histopathological subtype. The number of patients, however, was too small for a reliable statistical analysis. A more recent prospective study by Hutchings and colleagues[56] studied FDG uptake in 60 patients who had newly diagnosed HL. Contrary to Dobert and colleagues, SUVmax of the different subtypes differed significantly and ranged from 8.3 in nodular lymphocyte-predominant HL up to 14.6 in the mixed cellularity subtype.

Differences in SUVs among studies likely are explained by differences in image acquisition protocols, region of interest (ROI) approaches, and differences in imaging equipment. This emphasizes the need for standardization of image acquisition and interpretation approaches across institutions.

THE ROLE OF POSITRON EMISSION TOMOGRAPHY AND POSITRON EMISSION TOMOGRAPHY/CT IMAGING IN STAGING OF LYMPHOMA

Lymphoma is a tissue biopsy-based diagnosis. Once established, the assumption that most (if not all) enlarged lymph nodes and most (if not all) extranodal lesions are lymphoma involved is reasonable. Therefore, CT-based initial staging has remained the mainstay of the noninvasive diagnostic workup. On the other hand, because all lymphoma patients who have potentially curable disease undergo chemotherapy or chemo/radiation treatment, and FDG PET is far superior to CT for treatment monitoring and response assessment, a baseline PET/CT scan represents a more rational initial staging approach.

The Ann Arbor Staging[57] accounts for number of tumor sites (nodal and extra-nodal), location, and the presence or absence of systemic (“B”) symptoms. The disease stage has considerable impact on treatment. For example stage I follicular lymphoma is treated with local radiation only, and systemic therapy is reserved for higher stages of disease[58] The majority of patients with aggressive lymphomas have advanced stage disease (ie, stage 4) at presentation. There appear to be limited therapeutic consequences from distinguishing stage 3 from stage 4 disease in NHL, because treatment options are nearly identical. In HL the stage also dictates the appropriate treatment.[59]

Several studies have suggested a superior staging accuracy of PET when compared with CT[60] as also listed in **Table 2**.[30,61–65] The consequence is a significant upward stage migration of patients who have HL and NHL.[66] This stage migration effect has the potential to improve reported patient outcomes in both the lower stage and the higher stage patient populations, independent of the treatment program.

In addition, given that lymphoma is treatable and curable, and several lines of treatment are available, the imaging modality that allows not only for staging but also for treatment monitoring should be selected. Other arguments for using FDG-PET/CT as the primary staging modality include: its ability to assess bone marrow involvement, andits relatively low radiation dose when compared with diagnostic CT or with PET and CT interpreted side by side. As discussed previously, limitations include its inability to stage some of the less FDG-avid lymphomas[42,43] and its limited spatial resolution.

Functional imaging in lymphoma was provided for a long time by whole-body Ga-67 imaging. An early study in aggressive NHL and HL[67] reported significantly higher site and patient sensitivity for FDG PET than Ga-67 scintigraphy (100% versus 71.5% and 100% versus 80.3%, respectively). In a more recent and apparently prospective study, Tsukamoto and colleagues[64] compared in 191 of 222 lymphoma patients the staging accuracy of FDG PET to that of Ga-67 imaging (see **Table 2**). FDG PET was superior to Ga imaging for follicular lymphoma, for mantle cell lymphoma, and for the nasal type of natural killer/T cell lymphoma. Although this study had limitations (ie, lack of true gold standard and reference standard of limited value) it still strongly underscores the usefulness

Table 2
Staging accuracy of PET versus CT and gallium

Author	Year	Type	Indication	N	PET			CT[a] or Gallium[b]			p value
					Sens	Spec	Acc	Sens	Spec	Acc	
Wirth[63]	2002	NHL/HD	ST/RST	50	82	—	—	69[b]	—	—	0.01
Kostakoglu[61]	2002	NHL/HD	ST/RST	51	100	—	—	81[b]	—	—	Not reported
Freudenberg[30]	2004	NHL/HD	RST	27	96 (PET/CT)	99	98	61[a]	89	84	0.005 (Sens) 0.003 (Spec)
La Fougre[62]	2006	NHL/HD	ST/RST	50	98	99	—	87[a]	80	—	Not reported
Tsukamoto[64]	2007	NHL/HD	ST/RST	191	90.5	—	—	56.7[b]	—	—	Not reported
Nogami[65]	2007	NHL	RST	50	86.1	99.4	91	59.4[a]	96.1	91	<.001

Abbreviations: Acc, Accuracy; HD, Hodgkin disease; N, number of patients; NHL, non-Hodgkin lymphoma; PET, positron emission tomography; RST, restaging; Sens, sensitivity; Spec, specificity; ST, staging.
[a] Versus CT
[b] Versus Gallium

of PET imaging for staging of a range of lymphoma types and its superiority over Ga imaging.

EVALUATION OF BONE MARROW INVOLVEMENT

One important aspect of staging is the evaluation of bone marrow involvement.[68] In a prospective study the accuracy of PET/CT, bone marrow biopsy and MRI for detecting marrow involvement was compared in 47 patients with aggressive, most frequently diffuse large B-cell lymphoma. Both MRI and PET/CT identified 9 patients with bone marrow involvement while bone marrow aspiration identified only two patients. It seems likely that the noninvasively identified lesions truly represented areas of marrow involvement since all disappeared or had markedly reduced FDG uptake halfway through or at the end of treatment. No image-guided biopsies were performed to confirm this finding, however.

Using stringent inclusion criteria for a meta-analysis, Pakos and colleagues[69] identified 13 appropriate studies that enrolled a total of 587 patients. The sensitivity rates of 18F-FDG PET for identifying lymphomatous bone marrow involvement ranged from 0% to 100% across the studies with specificities ranging from 72% to 100%. When all patients were lumped, the sensitivity and specificity of FDG PET for identifying bone marrow involvement were 51% and 91%. These results clearly indicate that PET alone is not sufficient to replace biopsy for bone marrow staging. FDG PET, however, could provide valuable information in patients with heterogeneous bone marrow involvement, in whom biopsy sampling errors can occur. For instance, in six patients, all of whom had negative bone marrow biopsies, FDG PET revealed focal bone marrow infiltrates.[70]

IMPACT OF FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY ON DISEASE MANAGEMENT

Patient prognosis depends upon histopathology and clinical parameters that are used to calculate disease-specific prognostic indices (international prognostic index, Follicular Lymphoma International Prognostic Index[71]). Because stage usually depends upon the location and number of disease sites, it is not a true measure of tumor burden. Staging is an important prognostic determinant in NHL, and it affects the overall therapeutic strategy. It is performed to identify the small number of patients with early stage disease who can be treated with local therapy or combined modality treatment; it is also useful to stratify within histologic subtypes to determine prognosis and identify the best treatment approach.

Table 3
Impact of fluorodeoxyglucose –positron emission tomography on patient management

Author/#	Year	Type	Indication	N	R/P	Δ Stage (%)	Δ Management (%)
Montravers[72]	2002	Pediatric HD/NHL	ST/RST	12	R	50	23
Depas[73]	2004	Pediatric HD/NHL	ST	19	R	10.5	10.5
Hermann[74]	2005	Pediatric HD/NHL	ST	25	R	24	NA
Shah[75]	2000	HD/NHL	ST	29	R	—	31
Schöder[76]	2002	HD/NHL	ST/RST Monitoring	52	P	44	42
Sasaki[77]	2002	NHL	ST	42	R	NA	17
Talbot[78]	2002	HD/NHL	ST/RST	43	P	43	39
Naumann[79]	2004	HD	ST	88	P	20	18[a]
Raannani[29]	2005	HD/NHL	ST	103	R	36	45
Hutchings[56]	2006	HD	Radiation Planning	30	P	—	33 8
Rigacci[80]	2007	HD	ST	186	P	16	NA
Hernandez[81]	2006	HD/NHL	ST	47	P	23	15

Abbreviations: HD, Hodgkin disease; N, number of patients; NHL, non-Hodgkin lymphoma; RST, restaging; ST, staging.
[a] Potential management change; R/P, Retrospective/Prospective.

The impact of FDG PET imaging on patient management has been investigated by several groups (**Table 3**).[29,56,72–81] In a simple questionnaire study[76] comparable in design to the current National Outpatient PET Registry (NOPR) study,[82] referring physicians were asked among others to indicate: patient stage and intended management before PET, and changes in stage and management following PET. The response rate was only around 50% in this study. The completed questionnaires, however, revealed a substantial impact of FDG PET on stage and patient management that was affected in 39% of patients who had HL and 44% of those who had NHL.

The impact of FDG PET staging on patient management ranged from 8 to 45% in other prospective and retrospective studies (see **Table 3**). It tended to be lower in three studies that were conducted in pediatric patients (ranging from 10%–23%)[72–74] when compared with the adults in which FDG-PET affected treatment decisions in 8%–45% of the patients.[29,56,75–81]

A recent prospective multicentric study by Rigacci and colleagues[80] investigated the contribution of PET scanning to the staging of HL by CT and attempted to determine whether it has any impact on the therapeutic approach. Out of 186 patients, six consecutive patients who had HL from six Italian centers, PET stage in comparison with CT stage was higher in 27 patients (14%) and lower in 3 patients (1%). PET scanning upstaged 10 patients (8%) from localized to advanced disease and resulted in a change of treatment plan. FDG PET was shown to be a relevant, noninvasive method that supplements conventional procedures and therefore should be used routinely to stage HL, particularly in early stage patients, where a change in stage may modify disease management.

The impact of FDG PET staging on patient management ranged from 8% to 45% in other prospective and retrospective studies (see **Table 3**). It tended to be lower in three studies that were conducted in pediatric patients[72–74] (ranging from 10% to 23%) when compared with the adults in whom FDG-PET affected treatment decisions in 8% to 45% of the patients.

TREATMENT RESPONSE ASSESSMENT

Many studies have reported the prognostic significance of changes in glucose metabolic activity in response to treatment.[83–88] The value of PET for monitoring of treatment is reflected in the recently published guidelines of the International Harmonization Project.[9,89] Please refer to the articles by Schoeder and Cheson in this issue, which discuss this topic in detail.

SUMMARY

Fully diagnostic PET/CT scans acquired during oral and intravenous contrast can be provided to patients and referring physicians in a single imaging session. Although FDG uptake varies, most low-grade lymphomas exhibit sufficient FDG avidity to also be staged reliably with FDG PET/CT.

PET/CT imaging is more accurate for lymphoma staging than PET or CT alone and has substantial impact on patient management. This accurate whole-body glucose metabolic survey should serve as the baseline for subsequent treatment response evaluations. PET/CT has evolved to become the modality of choice for staging of nodal and extranodal lymphoma, for assessing therapeutic response, and for establishing patient prognosis.

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