^{18}F-FDG Avidity in Lymphoma Readdressed: A Study of 766 Patients

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PET/CT with ^{18}F-FDG is an important noninvasive diagnostic tool for management of patients with lymphoma, and its use may surpass current guideline recommendations. The aim of the present study is to enlarge the growing body of evidence concerning ^{18}F-FDG avidity of lymphoma to provide a basis for future guidelines. **Methods:** The reports from ^{18}F-FDG PET/CT studies performed in a single center for staging of 1,093 patients with newly diagnosed Hodgkin disease and non-Hodgkin lymphoma between 2001 and 2008 were reviewed for the presence of ^{18}F-FDG avidity. Of these patients, 766 patients with a histopathologic diagnosis verified according to the World Health Organization classification were included in the final analysis. ^{18}F-FDG avidity was defined as the presence of at least 1 focus of ^{18}F-FDG uptake reported as a disease site. Nonavidity was defined as disease proven by clinical examination, conventional imaging modalities, and histopathology with no ^{18}F-FDG uptake in any of the involved sites. **Results:** At least one ^{18}F-FDG–avid lymphoma site was reported for 718 patient studies (94%). Forty-eight patients (6%) had lymphoma not avid for ^{18}F-FDG. ^{18}F-FDG avidity was found in all patients (100%) with Hodgkin disease (n = 233), Burkitt lymphoma (n = 18), mantle cell lymphoma (n = 14), nodal marginal zone lymphoma (n = 8), and lymphoblastic lymphoma (n = 6). An ^{18}F-FDG avidity of 97% was found in patients with diffuse large B-cell lymphoma (216/222), 95% for follicular lymphoma (133/140), 85% for T-cell lymphoma (34/40), 83% for small lymphocytic lymphoma (24/29), and 55% for extranodal marginal zone lymphoma (29/53). **Conclusion:** The present study indicated that with the exception of extranodal marginal zone lymphoma and small lymphocytic lymphoma, most lymphoma subtypes have high ^{18}F-FDG avidity. The cumulating evidence consistently showing high ^{18}F-FDG avidity in the potentially curable Burkitt, natural killer/T-cell, and anaplastic large T-cell lymphoma subtypes justifies further investigations of the utility of ^{18}F-FDG PET in these diseases at presentation.

Key Words: lymphoma; ^{18}F-FDG; PET/CT; avidity; WHO

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Lymphoma is a heterogeneous group of diseases representing the fifth most common malignancy in the United States, with an estimated 74,340 new cases predicted for 2008 (*1*). Subtypes of lymphoma differ in molecular characteristics and biologic behavior. Based on clinical characteristics, this entity is divided into aggressive and indolent types (*2,3*). The currently accepted histopathologic classification system of the World Health Organization integrates morphologic, immunohistochemical, and genetic features (*4*). The most important factors influencing therapeutic decisions and prognosis are histologic subtype and extent of disease. Accurate assessment of lymphoma patients at initial presentation is therefore mandatory (*2,3*).

Previous studies assessing ^{18}F-FDG avidity in different histologic subtypes of lymphoma have included relatively small and heterogeneous populations of patients referred for staging, evaluated after treatment, or evaluated for restaging after recurrence (*5,6*). Although most lymphoma subtypes have been shown to be highly avid for ^{18}F-FDG, a lower ^{18}F-FDG avidity has been reported for lymphoma subtypes such as small lymphocytic lymphoma (*7*), peripheral T-cell lymphoma (*5*), anaplastic large T-cell lymphoma (*8*), and extranodal marginal zone lymphomas, including the mucosa-associated lymphoid tissue (MALT) marginal zone lymphoma (*9,10*) and splenic marginal zone lymphoma (*6*).

Current guidelines recommend the use of ^{18}F-FDG imaging for staging and pretreatment evaluation of lymphoma subtypes with known high ^{18}F-FDG avidity and proven clinical relevance to patient management. These recommendations are based on literature reports that include, as a rule, information on mainly common lymphoma subtypes and only a paucity of data on the less frequent entities. The International Harmonization Project (*11*) and the National Comprehensive Cancer Network (*12*) recommend ^{18}F-FDG imaging before treatment for the routinely tracer-avid, potentially curable lymphomas: diffuse large B-cell lymphoma and Hodgkin disease. The International

Harmonization Project also states that for other subtypes considered as having variable tracer avidity, ^{18}F-FDG imaging is recommended only if patients are included in clinical trials with response rate representing a major endpoint (*11*).

Hybrid PET/CT with ^{18}F-FDG has largely replaced separately acquired PET and CT examinations for many oncologic indications (*13*). The use of ^{18}F-FDG PET/CT for assessment of lymphoma has particularly increased and may surpass the guideline recommendations (*14*). The National Comprehensive Cancer Network report states that ^{18}F-FDG PET/CT for assessment of lymphoma may account for more than 50% of studies performed at a referral institution (*12*).

The aim of the present study was to enlarge the growing body of evidence concerning ^{18}F-FDG avidity in different types of lymphoma by reviewing the reports of ^{18}F-FDG PET/CT studies of 766 lymphoma patients referred to our institution for staging.

MATERIALS AND METHODS

Patient Population

The ^{18}F-FDG PET/CT reports of 1,093 patients with newly diagnosed lymphoma examined between September 2001 and March 2008 at the Rambam Health Care Campus were considered for review. Three hundred twenty-seven patients were excluded from further analysis for the following reasons: the histopathologic report was unavailable (n = 213), the histopathologic report did not describe and classify the findings according to the World Health Organization lymphoma classification (n = 52), the single site of disease had been excised before the PET/CT study was performed (n = 45), or a composite lymphoma had been present (n = 17).

Seven hundred sixty-six patients were analyzed, 411 of whom were male and 355 female, with an age range of 3–93 y and a mean age of 53 y. Thirty-seven patients were children aged 18 y or younger. The study was approved by the Institutional Review Board.

^{18}F-FDG PET/CT and Evaluation

Patients were instructed to fast, except for carbohydrate-free oral hydration, for at least 4 h before the injection of 370–555 MBq (10–15 mCi) of ^{18}F-FDG. After injection, the patients were kept lying comfortably over the uptake phase and instructed to void immediately before imaging. The whole-body PET/CT acquisition started 60–90 min after ^{18}F-FDG injection using a hybrid system (Discovery LS; GE Healthcare). The CT acquisition was performed at 80 mAs and 140 kV. The ^{18}F-FDG PET acquisition was performed using a 4-mm slice thickness. PET images were reconstructed iteratively using ordered-subset expectation maximization software. CT data were used for low-noise attenuation correction of PET data and for fusion with attenuation-corrected PET images.

The original evaluation of scans was performed by a team of at least 2 nuclear medicine physicians aware of the patient's clinical history. A site of increased ^{18}F-FDG uptake was defined as benign when related to physiologic biodistribution of ^{18}F-FDG or to a known nonmalignant process. Any area of focal ^{18}F-FDG activity of intensity higher than that of surrounding tissues and unrelated to normal physiologic or benign ^{18}F-FDG uptake was defined as malignant. Reports from the original reading were prospectively summarized.

A lymphoma avid for ^{18}F-FDG was defined as the presence of at least 1 focus of ^{18}F-FDG uptake reported as a disease site. A lymphoma not avid for ^{18}F-FDG was defined as disease proven by clinical examination, conventional imaging modalities, and histopathology but with no evidence of ^{18}F-FDG uptake in any of the involved sites. The patient-based percentage of ^{18}F-FDG avidity was calculated as the ratio of patients with ^{18}F-FDG–avid lymphoma, divided by all lymphoma patients, multiplied by 100.

^{18}F-FDG avidity was assessed in relation to the histopathologic subtype according to the World Health Organization classification. In patients with non-Hodgkin lymphoma (NHL), ^{18}F-FDG avidity was also assessed in relation to clinical classification as aggressive lymphoma subtypes (diffuse large B-cell lymphoma, Burkitt lymphoma, mantle cell lymphoma, lymphoblastic lymphoma, anaplastic large T-cell lymphoma, extranodal natural killer/T-cell lymphoma, angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma, enteropathy-type T-cell lymphoma) and indolent lymphoma subtypes (follicular lymphoma [all grades], extranodal marginal zone lymphoma [MALT and splenic], nodal marginal zone lymphoma, small lymphocytic lymphoma, plasmacytoma, primary cutaneous anaplastic large T-cell lymphoma, and lymphomatoid papulosis).

RESULTS

At least one ^{18}F-FDG–avid lymphoma site was detected in 718 patients (94%), including all 233 patients with Hodgkin disease (175 nodular sclerosis, 32 mixed cellularity, 4 lymphocyte-rich, 1 lymphocyte-depleted, 1 nodular lymphocyte-predominant, and 20 with unspecified classic Hodgkin disease) and all patients with Burkitt lymphoma (n = 18), mantle cell lymphoma (n = 14), anaplastic large T-cell lymphoma (n = 14), nodal marginal zone lymphoma (n = 8), lymphoblastic lymphoma (n = 6), angioimmunoblastic T-cell lymphoma (n = 4), plasmacytoma (n = 3), and natural killer/T-cell lymphoma (n = 2). An ^{18}F-FDG avidity of 97% was found in patients with diffuse large B-cell lymphoma (216/222), 95% for patients with follicular lymphoma (133/140: 24/24 grade I, 47/48 grade II, 33/37 grade III, and 29/31 grade not specified), and 90% for patients with peripheral T-cell lymphoma (9/10) (Table 1).

^{18}F-FDG avidity below 90% was found in small lymphocytic lymphoma (83%; 24/29), enteropathy type T-cell lymphoma (67%; 2/3), extranodal marginal zone lymphoma (55%; 29/53), lymphomatoid papulosis (50%; 1/2), and primary cutaneous anaplastic large T-cell lymphoma (40%; 2/5) (Table 1).

According to the clinical classification for NHL, 97% (285/293) of the aggressive NHL cases and 83% (200/240) of the indolent NHL cases were ^{18}F-FDG–avid (Table 2).

There were 48 lymphoma patients with disease that was not ^{18}F-FDG–avid, accounting for 6% of the total study population. All were over the age of 18 y. Six of the 222 patients (3%) with diffuse large B-cell lymphoma had disease that was not ^{18}F-FDG–avid, including 2 patients with cutaneous lymphoma, 1 patient with a single site in the

TABLE 1. ^{18}F-FDG Avidity of Lymphoma According to World Health Organization Histopathologic Classification

Histology	*n*	^{18}F-FDG–avid	Negative	% ^{18}F-FDG avidity
Hodgkin disease	233	233	0	100
Burkitt lymphoma	18	18	0	100
Mantle cell lymphoma	14	14	0	100
Anaplastic large T-cell lymphoma	14	14	0	100
Marginal zone lymphoma, nodal	8	8	0	100
Lymphoblastic lymphoma	6	6	0	100
Angioimmunoblastic T-cell lymphoma	4	4	0	100
Plasmacytoma	3	3	0	100
Natural killer/T-cell lymphoma	2	2	0	100
Diffuse large B-cell lymphoma	222	216	6	97
Follicular lymphoma	140	133	7	95
Peripheral T-cell lymphoma	10	9	1	90
Small lymphocytic lymphoma	29	24	5	83
Enteropathy-type T-cell lymphoma	3	2	1	67
Marginal zone lymphoma, splenic	3	2	1	67
MALT marginal zone lymphoma	50	27	23	54
Lymphomatoid papulosis	2	1	1	50
Primary cutaneous anaplastic large T-cell lymphoma	5	2	3	40
All	766	718	48	94

colon, 1 patient with disease confined to the bone marrow, 1 whose diagnosis was made from a pleural effusion, and 1 with disease involving the maxillary sinus. One of the 3 patients with enteropathy-type T-cell lymphoma showed no ^{18}F-FDG uptake in the known site of disease in the small bowel. One of the 10 patients (10%) with peripheral T-cell lymphoma had disease that was not ^{18}F-FDG–avid and involved the buccal mucosa. Seven of the 140 patients (5%) with follicular lymphoma had disease that was not ^{18}F-FDG–avid, including 2 with disease confined to the bone marrow and 5 who had only skin lesions. Twenty-three of the 50 patients (46%) with MALT marginal zone lymphoma had nonavid disease, including 17 patients with involvement of the gastrointestinal tract (16 stomach, 1 colon), 3 with involvement of the skin, 1 with bone marrow and spleen involvement, 1 with involvement of the tracheal mucosa, and 1 with disease in the orbit. One of the 3 patients with splenic marginal zone lymphoma had nonavid disease. One of 2 patients with lymphomatoid papulosis of the skin had nonavid disease, as well as 3 of the 5 patients (60%) with primary cutaneous anaplastic large T-cell lymphoma involving the skin. Five of 29 cases (17%) of small lymphocytic lymphoma were not ^{18}F-FDG–avid. All included nodal disease, with additional bone marrow involvement found in 4 of the 5 (Tables 1 and 3).

TABLE 2. ^{18}F-FDG Avidity of NHL According to Clinical Classification

Clinical subtype	*n*	^{18}F-FDG–avid	Negative	% ^{18}F-FDG avidity
Aggressive*	293	285	8	97
Indolent†	240	200	40	83

*Diffuse large B-cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma, mantle cell lymphoma, anaplastic large T-cell lymphoma, extranodal natural killer/T-cell lymphoma, angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma, and enteropathy-type T-cell lymphoma.

†Follicular lymphoma (all grades), marginal zone lymphoma (nodal and extranodal), small lymphocytic lymphoma, plasmacytoma, primary cutaneous anaplastic large cell lymphoma, and lymphomatoid papulosis.

DISCUSSION

In the present study of 766 patients referred for staging of lymphoma,^{18}F-FDG–avid disease was found in 94%—equal to (*5*) or similar to (92% (*6*)) the percentages reported in previous studies that included smaller and more heterogeneous populations (Table 3). A metaanalysis performed by Isasi et al. (*15*) including 20 studies with a cumulated number of 854 patients reported a median sensitivity of 90%.

The present results demonstrated that although NHL had an overall ^{18}F-FDG avidity of 91%, the avidity was lower in indolent disease (83%) than in aggressive disease (97%). ^{18}F-FDG avidity correlates better with the histopathologic subtype of NHL than with clinical characteristics, as previously noted (*5,6*). Indolent NHL subtypes such as plasmacytoma, nodular marginal zone lymphoma, and—regardless of grade—follicular lymphoma showed high ^{18}F-FDG avidity, whereas the aggressive NHL-enteropathy type of T-cell lymphoma had low ^{18}F-FDG avidity.

MALT marginal zone lymphoma demonstrated an ^{18}F-FDG avidity of 54%, an incidence that is at the lower limit of the previously reported wide range of 55%−82% (*10,16–19*). These different results may be due both to the small number of studied patients that were included in most of the previous reports and to a possible difference in the location of disease in the various series. There is a known variability in ^{18}F-FDG avidity between MALT marginal

TABLE 3. ^{18}F-FDG Avidity of Various Subtypes of Lymphoma in Present Study as Compared with Previous Literature Data

Histology	Weiler-Sagie (*n* = 766)	Tsukamoto (*6*) (*n* = 255)	Elstrom (*5*) (*n* = 172)	Other publications
Hodgkin disease	100% (*n* = 233)	97% (*n* = 23)	98% (*n* = 47)	Rigacci (*24*) 100% (*n* = 186)
Burkitt lymphoma	100% (*n* = 18)	100% (*n* = 5)	100% (*n* = 1)	
Mantle cell lymphoma	100% (*n* = 14)	100% (*n* = 9)	100% (*n* = 7)	Gill (*25*) 100% (*n* = 9)
Anaplastic large T-cell lymphoma	100% (*n* = 14)	100% (*n* = 5)	100% (*n* = 2)	
Marginal zone lymphoma, nodal	100% (*n* = 8)			Hoffmann (*18*) 83% (*n* = 6)
Lymphoblastic lymphoma	100% (*n* = 6)			
Angioimmunoblastic T-cell lymphoma	100% (*n* = 4)	100% (*n* = 5)		Kako (*8*) 100% (*n* = 4)
Natural killer/T-cell lymphoma	100% (*n* = 2)	100% (*n* = 7)	100% (*n* = 1)	Karantanis (*26*) 100% (*n* = 10), Kako (*8*) 100% (*n* = 8)
Diffuse large B-cell lymphoma	97% (*n* = 222)	97% (*n* = 81)	100% (*n* = 51)	Lin (*27*) 100% (*n* = 92)
Follicular lymphoma	95% (*n* = 140)	91% (*n* = 44)	98% (*n* = 42)	Karam (*9*) 100% (*n* = 17)
Peripheral T-cell lymphoma	90% (*n* = 10)	98% (*n* = 9)	40% (*n* = 5)	Bishu (*20*) 86% (*n* = 24), Kako (*8*) 91% (*n* = 11)
Small lymphocytic lymphoma	83% (*n* = 29)	50% (*n* = 4)	100% (*n* = 1)	Karam (*9*) 47% (*n* = 15)
Enteropathy-type T-cell lymphoma	67% (*n* = 3)			Hoffmann (*23*) 100% (*n* = 4), Hadithi (*22*) 100% (*n* = 8)
Marginal zone lymphoma, unspecified			67% (*n* = 12)	
Marginal zone lymphoma, splenic	67% (*n* = 3)	53% (*n* = 10)		
MALT marginal zone lymphoma	54% (*n* = 50)	82% (*n* = 52)		Perry (*10*) 55% (*n* = 33), Radan (*19*) 71% (*n* = 24), Alinari (*16*) 81% (*n* = 26), Beal (*17*) 81% (*n* = 42)
Lymphomatoid papulosis	50% (*n* = 2)			
Primary cutaneous anaplastic large T-cell lymphoma	40% (*n* = 5)			Kako (*8*) 60% (*n* = 5)
Mycosis fungoides			100% (*n* = 1)	
Subcutaneous paniculitis-like T-cell lymphoma		71% (*n* = 1)		
Cutaneous B-cell lymphoma			0% (*n* = 2)	

zone lymphoma of the gastrointestinal tract (mainly the stomach) and MALT marginal zone lymphoma involving other organs such as the orbit, skin, or lungs (*10*).

Small lymphocytic lymphoma exhibited a relatively low ^{18}F-FDG avidity, 83%, in a group that, to the best of our knowledge, includes the largest number of newly diagnosed patients reported to date, 29. Previous studies including smaller patient series have reported a significantly lower ^{18}F-FDG avidity, around 50% (Table 3) (*6,9*). Furthermore, of the total of 766 patients, small lymphocytic lymphoma was the only lymphoma subtype with nonavid nodal sites of disease.

The relatively low ^{18}F-FDG avidity (67%) found in a small group of 3 patients with splenic marginal zone lymphoma is consistent with that of previous literature reports (Table 3) (*6*).

It is notable that one third of the cases that were not ^{18}F-FDG–avid occurred in patients with disease confined to the skin, regardless of histologic subtype. Highly variable ^{18}F-FDG avidity has previously been reported in small subsets of 1–24 patients with cutaneous lymphoma of B- and T-cell origin (Table 3) (*5,6,8,20,21*).

In addition to Hodgkin disease, which was ^{18}F-FDG–avid in all 233 patients who had the disease, the commonly encountered aggressive diffuse large B-cell lymphoma-NHL subtype was also associated with a high ^{18}F-FDG avidity rate of 97%. Less common aggressive NHL subtypes such as mantle cell lymphoma, Burkitt lymphoma, lymphoblastic lymphoma, anaplastic large T-cell lymphoma, angioimmunoblastic T-cell lymphoma, and natural killer/T-cell lymphoma had an ^{18}F-FDG avidity of 100%. Only 1 of 10 cases of peripheral T-cell lymphoma in the present series was not ^{18}F-FDG–avid, in contrast to the results of Elstrom et al. (*5*), who reported a low ^{18}F-FDG avidity of 40% in a small sample of 5 patients. The only aggressive lymphoma with a relatively low ^{18}F-FDG avidity, 67%, was enteropathy-type T-cell lymphoma, contrary to previously reported higher uptake rates (*22,23*).

Although this study contributes to the growing body of evidence concerning the overall ^{18}F-FDG avidity of lymphomas and defines the distinct histopathologic subtypes exhibiting a higher rate of nonavid cases, the study is subject to several relative limitations. The degree of ^{18}F-FDG avidity was not assessed quantitatively; however, according to the International Harmonization Project, visual assessment of the presence and intensity of ^{18}F-FDG uptake is considered sufficient and is recommended in the clinical setting. Despite the significant increase in the number of patients analyzed in all subtypes of lymphoma, compared with previous studies, many histologic subgroups still consist of few patients.

Further projects will pursue additional issues raised by the current results. These include a site- and location-based analysis of ^{18}F-FDG avidity in various histologic subtypes of lymphoma to correlate the inherent metabolic characteristics related to histology with lesion size and pattern of distribution. Specifically, the present results suggest that lymphoma involving the skin and possibly disease in the mucosa or pleural fluid may be either less ^{18}F-FDG–avid or more difficult to detect, and these preliminary findings warrant an in-depth analysis of larger patient groups.

CONCLUSION

In this large group of 766 patients with newly diagnosed lymphoma evaluated in a single institution, most of the lymphoma subtypes were ^{18}F-FDG–avid. MALT marginal zone lymphoma and small lymphocytic lymphoma showed lower ^{18}F-FDG avidity and therefore a lower detectability rate, and additional diagnostic modalities apart from ^{18}F-FDG imaging may provide important clinical information on these specific histologic subtypes. The cumulating evidence consistently showing high ^{18}F-FDG avidity in the potentially curable Burkitt lymphoma, natural killer/T-cell lymphoma, and anaplastic large T-cell lymphoma subtypes justifies further investigations of the utility of ^{18}F-FDG PET in these diseases at presentation.

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