STUDY

Staging Accuracy in Mycosis Fungoides and Sézary Syndrome Using Integrated Positron Emission Tomography and Computed Tomography

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Objectives: To evaluate the usefulness of integrated positron emission tomography and computed tomography (PET/CT) in staging mycosis fungoides (MF) and Sézary syndrome and to correlate PET/CT data with histopathologic diagnosis of lymph nodes (LNs).

Design: A single-center, prospective cohort analysis.

Setting: Academic referral center for cutaneous lymphoma.

Patients: Thirteen patients with MF and SS at risk for secondary LN involvement.

Interventions: Patients were clinically evaluated based on general physical examination, total body skin examination, and laboratory screening. They underwent integrated PET/CT followed by excisional biopsy of LNs.

Main Outcome Measures: We used PET/CT to assess LN size and metabolic activity. Enlarged LNs were defined as axillary or inguinal LNs with a short axis 1.5 cm or larger; or cervical LN, with a short axis 1.0 cm or larger. We classified LN pathologic results according to National Cancer Institute (LN1-4) and World Health Organization (WHO 1-3) criteria. We quantified PET activity using standardized uptake value (SUV) and correlated with LN grade.

Results: Based on CT size criteria alone, only 5 patients had enlarged LNs, whereas PET revealed hypermetabolic LNs in all 13 patients. Six patients had LN1-3, and 7 had effacement of LN architecture by lymphoma cells (LN4). Of the 7 patients with LN4 nodes, 4 had SS, and 3 had tumorous MF. Two patients with LN4 nodes had inguinal LNs smaller than 1.5 cm and would have been assigned an N0 classification without the use of integrated PET/CT. Correlation of SUV with LN grade revealed that LN1-3 nodes were associated with a mean SUV of 2.7 (median SUV, 2.2; range, 2.0-4.7) and LN4 nodes were associated with a mean SUV of 5.4 (median SUV, 3.9; range, 2.1-11.8). Patients with large cell transformation had the highest SUVs.

Conclusions: For staging MF and SS, PET/CT was more sensitive in detecting LN involved by lymphoma compared with CT data alone and thus may provide more accurate staging and prognostic information. The intensity of PET activity correlated with histologic LN grade.

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MYCOSIS FUNGOIDES (MF) is a non-Hodgkin lymphoma of T-cell origin that primarily involves the skin. Although the disease is relatively rare, with an annual incidence of 0.36 per 100 000,[1] it is the most common cutaneous lymphoma. Mycosis fungoides has distinctive histologic and clinical features. Its presentation in the skin is polymorphous, manifesting as patches, plaques, tumors, or erythroderma.[2] In the advanced stage, lymph nodes (LNs) or viscera become involved with lymphoma. Sézary syndrome (SS) is a constellation of erythroderma, lymphadenopathy, and circulating peripheral blood Sézary cells and is considered to be the leukemic variant of MF.[3]

The staging of patients with MF is based primarily on extent of skin disease, type of skin lesion, and involvement of extracutaneous sites, such as LNs, viscera, and peripheral blood.[4] Accurate staging is important clinically for prognostic purposes and to help determine appropriate treatment options. Previous studies have demonstrated that patients with limited patch or plaque disease do not have an altered life expectancy compared with a matched control population,[5] whereas

Table 1. Clinical Staging System for Mycosis Fungoides and Sézary Syndrome

	TNM Classification		
	T	N	M
Stage			
IA	T1, limited patch or plaque; <10% BSA	N0, nodes uninvolved	M0, no visceral involvement
IB	T2, generalized patch or plaque; ≥10% BSA	N0	M0
IIA	T1-2	N1, nodes enlarged, histologically uninvolved	M0
IIB	T3, tumors	N0-1	M0
IIIA	T4, erythroderma	N0	M0
IIIB	T4	N1	M0
IVA	T1-4	N3, nodes enlarged, histologically involved	M0
IVB	T1-4	N0-3	M1, visceral involvement
B Classification*			
B0	No circulating Sézary cells		
B1	PBSC >20%, <1000/mm^3 by morphologic traits		
B2	Sézary syndrome defined as ≥1 of the following: PBSC ≥1000/mm^3, CD4/CD8 ratio ≥10, CD4+CD7– cells ≥40% or CD4+CD26 – cells ≥30% of lymphocytes		

Abbreviations: B, blood; BSA, body surface area; PBSC, peripheral blood Sézary cell; TNM, tumor node metastasis.
*Redefined B criteria.[3]

those with extracutaneous involvement have a median survival of only 13 months.[6] The traditional approach to staging involves skin and general physical examinations, including palpation of superficial LNs. In patients with large cell transformation (defined as >25% large cells on biopsy findings), tumors, erythroderma, enlarged LNs on physical examination, or suspicious laboratory parameters, such as elevated lactate dehydrogenase levels or presence of Sézary cells, a contrast computed tomographic (CT) scan of the chest, abdomen, and pelvis is also performed.[7,8] If any LNs are significantly enlarged on CT, patients are referred for further LN evaluation; depending on the institution, LN evaluation may include fine-needle aspiration (FNA), core biopsy, or excisional biopsy.

The disadvantage of staging based on a CT scan is that this test provides anatomic information only. Lymph nodes in patients with MF and SS can be enlarged from nonspecific inflammatory changes, such as dermatopathic lymphadenopathy, rather than malignant infiltration.[9] Conversely, LNs involved with lymphoma may not be enlarged sufficiently to meet the CT size criteria for a pathologic node, resulting in false-negative test results. The upper normal limit for the size of an LN has been debated, and the criteria vary with the location of the nodes. Cheson et al[10] suggest that an LN larger than 1.0 cm in the long axis should be considered suspicious for involvement with lymphoma. However, because MF and SS are frequently associated with dermatopathic lymphadenopathy, this criterion may not be appropriate for this disease. Other published studies from the radiology field define enlarged LNs in MF and SS as axillary or inguinal nodes larger than 1.5 cm in the short axis and mediastinal, hilar, or abdominopelvic nodes larger than 1.0 cm in the short axis.[7,8]

Recently, positron emission tomography (PET) using an 18-fluorine–labeled glucose analogue, fluorodeoxyglucose, has been used in the staging and assessment of tumor response in nodal-based lymphomas and solid tumors.[11] Studies comparing PET with CT have shown that PET has increased sensitivity as well as specificity in evaluating these diseases.[12-14] Also, by identifying additional malignant foci that were not found by CT alone, PET can lead to significant changes in patient treatment.[15-19] Integrated PET/CT scans are now available that provide concurrent anatomic information from CT along with functional information provided by PET.

Although many studies have been published that analyze the contribution of PET or PET/CT to staging nodal lymphomas, less is known about the potential role of PET or PET/CT in diagnosing primary cutaneous lymphomas that may have secondary nodal involvement. There have been case reports on the usefulness of PET to assess tumor burden and treatment response in subcutaneous panniculitic T-cell lymphoma and cutaneous follicle center B-cell lymphoma.[20] However, to our knowledge, the usefulness of integrated PET/CT in evaluating MF and SS has not been investigated. Thus, in this study we assessed the role of integrated PET/CT in the staging of 13 patients with MF and SS. We also compared and attempted to correlate the results of PET with the histopathologic degree of LN involvement.

METHODS

STAGING

Patients were assigned stages based on findings from general physical examination, total-body skin examination, laboratory screening, and appropriate imaging studies. During physical examination, palpation of superficial LNs in the cervical, supraclavicular, axillary, epitrochlear, and inguinal LN chains was performed. Skin examination included assessment of percentage of body surface area involved and categorization of skin lesions into patches, plaques, tumors, or erythroderma (**Table 1**). Laboratory testing included complete blood cell count with manual differential cell count, basic metabolic panel, hepatic function tests,

lactate dehydrogenase level, and peripheral blood screen for Sézary cells by morphologic traits. If there was a clinical suspicion for increased Sézary cells, a Sézary panel with flow cytometry was also performed. Sézary syndrome (B2) was defined as an absolute Sézary cell count of 1000/mm^3 or greater, a CD4/CD8 (helper/suppressor) ratio of 10 or greater, CD4+CD26– population of 30% or more, or CD4+CD7– population of 40% or more.[3] Patients were assigned TNM categories described by the National Cancer Institute workshop[4]; SS was defined according to the redefined B classification described by Vonderheid and Bernengo[3] and Vonderheid et al,[21] summarized in Table 1. The redefined B classification proposes that B2 be considered stage IVA; however, this proposal has not been formally accepted. Herein, stage IVA is defined as positive lymph node involvement.

PATIENTS

Appropriate institutional review board approval for this project was obtained. Patients were seen in the Multidisciplinary Cutaneous Lymphoma Clinic at Stanford University Medical Center, Stanford, Calif. An integrated PET/CT scanner has been available at our institution since January 2003. Patients with the diagnosis of MF and SS were referred for PET/CT if they were considered at risk for secondary LN involvement (those with large cell transformation, tumors, erythroderma, or enlarged LNs on physical examination). Patients were included in the analysis if (1) they had undergone PET/CT scans performed at our institution, (2) their scan showed suspicious metabolic activity in at least 1 LN region or enlarged LNs according to CT size criteria, and (3) they had subsequent LN biopsy specimens taken either at Stanford University Medical Center or at an outside institution. Patients who had undergone PET/CT scans but were excluded from analysis were those who (1) had diagnoses other than MF and SS, (2) had clinically insignificant LN metabolic activity and LN size within the reference range, (3) refused to undergo a biopsy of their LNs, or (4) had already been diagnosed with LN or visceral involvement by MF.

PET/CT DATA ACQUISITION

Images were obtained using a PET/CT scanner (Discovery LS; GE Medical Systems, Waukesha, Wis). All patients fasted for a minimum of 8 hours before the intravenous injection of our institution's standard adult dose of 555 MBq (15 mCi) of 18F-fluorodeoxyglucose. Approximately 60 minutes after radiopharmaceutical administration, a CT scan was acquired from the top of the head through the inguinal region. The parameters of the multidetector helical CT were 140 kVp, 80 mA, 0.8 second per CT rotation, pitch of 6, and a table speed of 22.5 mm/s. Following the completion of the CT images, a PET emission scan was acquired in 6 to 8 positions at 5 minutes per position. The CT images were used for attenuation correction and for localization of suspicious PET findings. The PET emission images were reconstructed using an iterative algorithm (ordered-subset expectation maximum). The images were analyzed by an experienced nuclear medicine physician and a radiologist using eNTEGRA software (ELGEMS, Haifa, Israel) both separately and together. All standardized uptake values (SUVs) reported in this study were corrected for body weight and represented the maximum value for a given lesion.

LN BIOPSY AND PATHOLOGIC RESULTS

Patients were referred to a general surgeon for an LN biopsy. Surgeons reviewed the radiologic data from PET/CT scans and performed biopsies on the LN region with the highest SUV. The LN biopsy samples were from the axillary, inguinal, or cervical regions.

Table 2. NCI and WHO Lymph Node (LN) Histopathologic Classification Systems

NCI Stage	WHO Stage	Histologic Features
LN1	1	Dermatopathic lymphadenopathy; scattered cerebriform lymphocytes
LN2	1	Dermatopathic lymphadenopathy; small clusters of atypical, cerebriform lymphocytes
LN3	2	Dermatopathic lymphadenopathy; large clusters of atypical, cerebriform lymphocytes
LN4	3	Frank neoplasia; complete replacement of architecture with diffuse infiltrates of atypical, cerebriform lymphocytes

Abbreviations: NCI, National Cancer Institute; WHO, World Health Organization.

The LN biopsy specimens were routinely processed, embedded in paraffin, and stained with hematoxylin-eosin. Samples were classified according to the National Cancer Institute criteria (LN1-4)[9,22] and according to the World Health Organization criteria (WHO 1-3).[23] Comparison of these 2 classification schemes is summarized in **Table 2**. Slides of LN biopsy specimens from our institution and from outside institutions were directly reviewed by 2 pathologists (S.K. and R.W.) at Stanford with expertise in LN pathologic examination.

POLYMERASE CHAIN REACTION ANALYSIS

We applied polymerase chain reaction (PCR) analysis to assess clonal T-cell receptor (*TCR*) gene rearrangement to 3 LN2 samples and 1 LN3 sample. A standardized PCR technique as recently described[24] was used on the sample from patient 5. The remaining samples were analyzed as previously described.[25]

RESULTS

PATIENTS AND PET/CT DATA

We included 13 patients in the analysis. The mean age of the patients was 66 years (range, 32-89 years); 4 were women, and 9 were men. One patient had generalized patches and plaques (T2) with evidence of large cell transformation on previous skin biopsies. Four patients had tumor disease (T3), 1 had erythroderma without circulating Sézary cells (T4), and 7 had SS (T4, B2).

All 13 patients underwent PET/CT scans. Results are summarized in **Table 3**. The size of LNs, measured in centimeters in the short axis, was determined from the CT component (noncontrast) of the PET/CT scan. We defined enlarged LN size as axillary or inguinal nodes 1.5 cm or larger in the short axis or cervical nodes 1.0 cm or larger in the short axis. Based on CT size criteria alone, only 5 patients (patients 7, 8, 10, 12, and 13) had enlarged LNs. In comparison, PET scans showed that all 13 patients had hypermetabolic activity in at least 1 LN region. The SUVs ranged from 2.0 to 11.8.

For comparison, data from the physical examinations of LNs in our patients are also presented in Table 3. The largest diameter found on examination was recorded. Four patients did not have clinically significant lymphadenopathy, 4 patients had LNs estimated as 1 cm, and 5 patients had LNs estimated as 2 cm or larger.

Table 3. Summary of PET/CT and Lymph Node (LN) Pathologic Results

Patient	T Class	Physical Examination of LN, Largest Diameter, cm	LN Size on CT Scan, Short Axis, cm	Maximum SUV	Biopsy Site	NCI Grade	WHO Grade	*TCR* Clone*	Final Stage
1	T3	1	1.2	2.0	Axillary	LN1	1	. . .	IIB
2	T4	2	1.3	2.1	Axillary	LN1	1	ND	IIIB
3	T2	2	1.0	2.2	Inguinal	LN2	1	Positive	IIA
4	T4†	<1	1.2	4.7	Axillary	LN2	1	Positive	IIIB
5	T4†	2	1.2	3.0	Inguinal	LN2	1	Positive	IIIB
6	T4†	1	1.1	2.0	Inguinal	LN3	2	Positive	IIIB
7	T3	1	1.4	3.7	Cervical	LN4	3	ND	IVA
8	T4†	<1	1.5	3.2	Inguinal	LN4	3	ND	IVA
9	T3	<1	1.3	3.9	Inguinal	LN4+LCT	3	ND	IVA
10	T4†	3	3.2	11.8	Inguinal	LN4+LCT	3	ND	IVA
11	T4†	<1	1.3	6.6	Inguinal	LN4+LCT	3	ND	IVA
12	T4†	1	2.1	6.3	Inguinal	LN4+LCT	3	ND	IVA
13	T3	2	2.1	2.1	Axillary	LN4+LCT	3	ND	IVA

Abbreviations: CT, computed tomography; LCT, large cell transformation; NCI, National Cancer Institute; ND, not done; PET, positron emission tomography; SUV, standardized uptake value; T, tumor; *TCR*, T-cell receptor; WHO, World Health Organization.

*The polymerase chain reaction analysis for *TCR* clonality.

†Denotes Sézary syndrome (T4, B2).

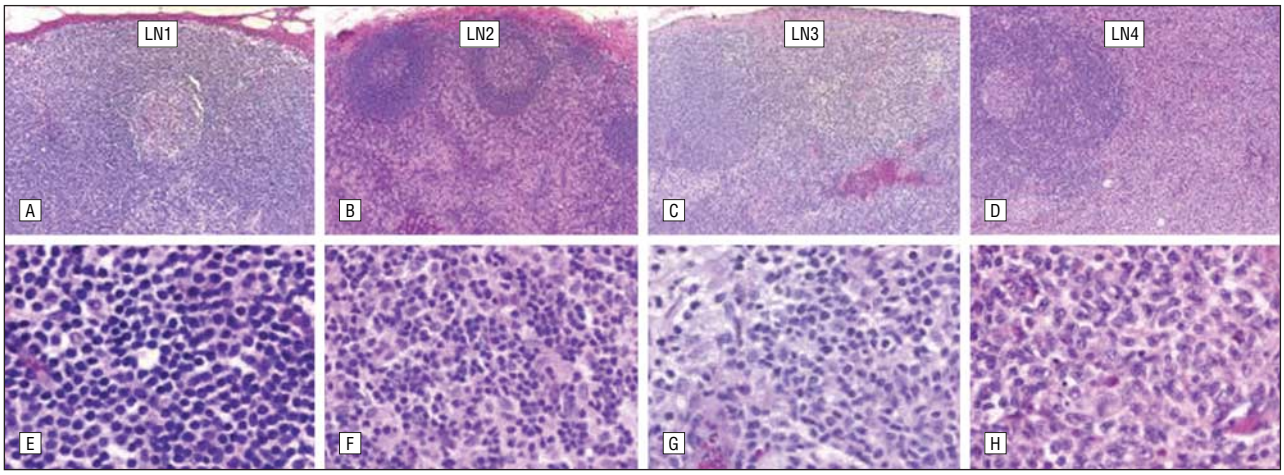

Figure 1. Low-power (A-D) (original magnification ×100) and high-power (E-H) (original magnification ×600) views of hematoxylin-eosin–stained pathologic findings from lymph nodes (LNs) classified according to National Cancer Institute (LN1-4) samples. LN1 (A and E): healthy LN with isolated hyperconvoluted, hyperchromatic lymphocytes. LN2 (B and F): dermatopathic lymphadenopathy with expansion of subcapsular sinus. High-power magnification reveals many atypical lymphocytes aggregating into small clusters of 3 to 6 cells. LN3 (C and G): dermatopathic lymphadenopathy with expansion of subcapsular sinus. Nodal architecture is preserved. Atypical lymphocytes aggregate into larger clusters. LN4 (D and H): effacement of LN architecture adjacent to a preserved germinal center. High-power magnification reveals large cell transformation.

PATHOLOGIC RESULTS AND PCR DATA

All patients underwent excisional LN biopsy based on the region with the most metabolically active node or nodes. The most common site for biopsy was the inguinal region (8 patients). Four patients underwent axillary LN biopsies, and 1 patient underwent a cervical LN biopsy. The extent of LN involvement was classified according to NCI and WHO criteria. Representative examples of LN1-4 pathologic results from patients in our study are shown in **Figure 1**, and results are summarized in Table 3. Two LN biopsy samples were classified as LN1, WHO 1; 3 samples were LN2, WHO 1; 1 was LN3, WHO 2; and 7 were LN4, WHO 3. Of the 7 patients with LN4 nodes, 5 also exhibited large cell transformation. Four patients with LN4 nodes had SS, and 3 had MF tumors. Based on the finding of LN4-grade nodes, these 7 patients were assigned a final stage of IVA.

Analysis for clonal *TCR* gene rearrangement by PCR was performed on the 4 LNs with intermediate grade (LN2-3). All 3 LN2 samples and 1 LN3 sample had evidence of *TCR* clonality (Table 3).

CORRELATION OF PET/CT AND PATHOLOGIC DATA

Two patients had LNs smaller than that defined by the CT size criteria and would have been assigned an incorrect stage without the use of integrated PET/CT. Patient 9 was a 32-year-old man with a history of stage IA MF whose disease progressed to tumor lesions. He did not have significant lymphadenopathy on clinical examina-

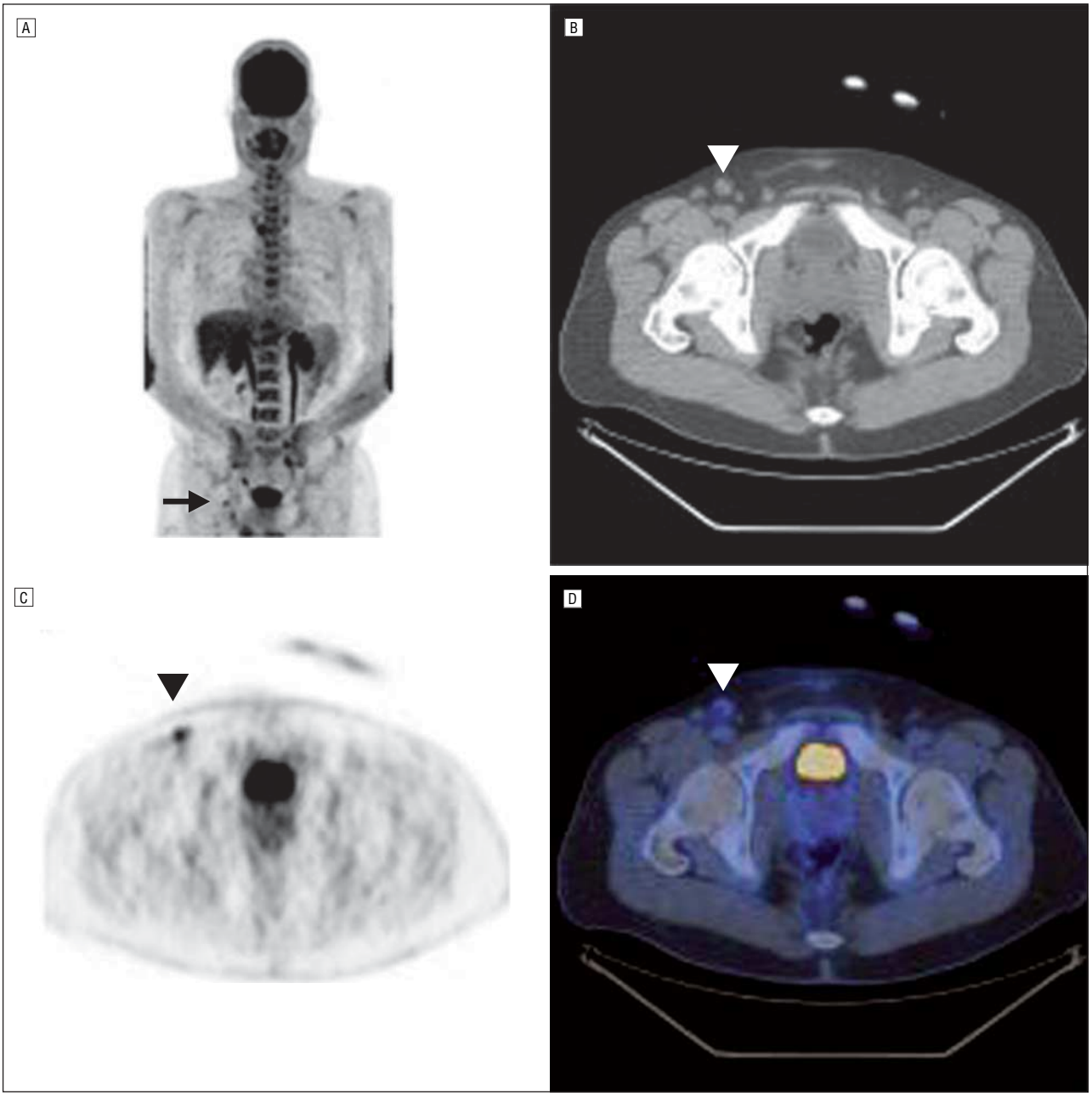

Figure 2. Positron emission tomographic and computed tomographic (PET/CT) images from patient 9, a 32-year-old man with a history of stage IA mycosis fungoides whose disease progressed to tumor lesions, identified a single hypermetabolic right inguinal lymph node (A) (arrow) that was 1.3 cm on the CT scan (B) (arrowhead) but was hypermetabolic on the PET scan with a standardized uptake value of 3.9 (C) (arrowhead). A fusion PET/CT image localizes the hypermetabolic activity within the lymph node (D) (arrowhead).

tion (Table 3); PET/CT identified a single hypermetabolic LN in the right inguinal region (**Figure 2**A). The LN size was measured as 1.3 cm in the short axis on CT (Figure 2B), less than the CT cutoff criteria of 1.5 cm. However, the SUV was 3.9 (Figure 2C). Subsequent biopsy findings classified this node as LN4 with large cell transformation, resulting in a final assignment of stage IVA for the patient. Patient 11 was an 81-year-old woman with Sézary syndrome. Clinical examination did not reveal significant lymphadenopathy (Table 3). Her PET/CT scans (data not shown) revealed multiple hypermetabolic LNs in bilateral axillary and inguinal regions with the largest node measuring 1.3 cm in the short axis. Biopsy findings revealed LN4, resulting in a final assignment of stage IVA. The remaining 5 patients with LN4 had enlarged LNs as defined by CT size criteria as well as increased metabolic activity on PET.

We quantified the intensity of PET activity using the SUV and correlated this with LN grade. LN1-3 nodes had a mean SUV of 2.7 (median, 2.2; range, 2.0-4.7); LN4 nodes with or without large cell transformation had a mean SUV of 5.4 (median, 3.9; range, 2.1-11.8). Comparison of SUVs from LN1-3 vs those of LN4 nodes is depicted graphically in **Figure 3**. The highest SUVs were associated with LN4 nodes with large cell transformation. LN1-4 nodes without large cell transformation were

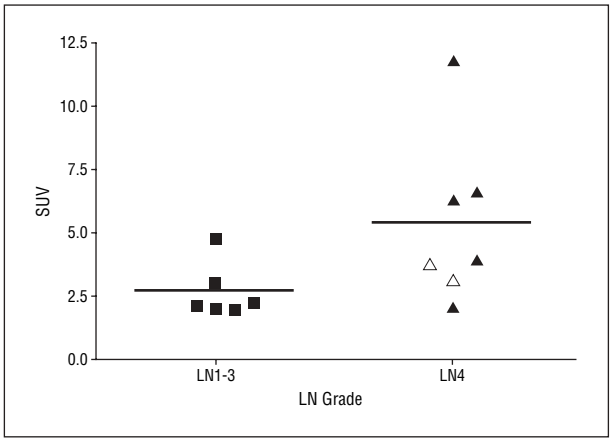

Figure 3. Graphic comparison of standardized uptake values (SUVs) from lymph nodes (LNs) classified as LN1-3 nodes in the left column (squares) vs LN4 nodes in the right column (triangles). The SUVs from LN4 nodes without large cell transformation are represented by open triangles; SUVs from LN4 nodes with large cell transformation are represented by solid triangles. The SUVs ranged from 2.0 to 11.8. The horizontal bar in each column represents the mean SUV in that group.

associated with a mean SUV of 2.9 (median, 2.6; range, 2.0-4.7), and LN4 nodes with large cell transformation were associated with a mean SUV of 6.1 (median, 6.3; range, 2.1-11.8).

COMMENT

Accurate staging of MF and SS is important for providing the patient with appropriate prognostic information and for guiding the clinician in selection of treatment options. Although physical examination with palpation of superficial LNs is routinely performed, it often incorrectly estimates the sizes of LNs.[26] Physical examination of the LNs of patients in our study also did not correlate well with PET/CT data or MF involvement of the nodes. To further define LN size and presence or absence of visceral disease, contrast CT has traditionally been used as part of the staging evaluation. Its main disadvantage is that it provides LN size data but no information regarding the cause of LN enlargement. Integrated PET/CT provides the powerful combination of anatomic data from CT and physiologic data from PET. Compared with PET alone, PET/CT provides definitive localization of hypermetabolic activity within specific anatomic structures, such as an LN.[27] Compared with CT alone, PET/CT has improved sensitivity and specificity. One study of patients with Hodgkin disease and non-Hodgkin lymphomas showed that the sensitivity and specificity of PET/CT were 90% and 97%, respectively, compared with 77% and 89% for contrast CT.[13] Although PET and PET/CT have been applied to the staging of solid tumors as well as Hodgkin disease and non-Hodgkin lymphomas, the role of PET/CT in staging MF and SS has not previously been investigated.

In this study, we applied PET/CT in the staging of 13 patients with MF and SS who were at risk for secondary LN involvement. We found that the PET component of the PET/CT was highly sensitive because it detected more diseased LNs compared with the CT component alone (5 patients with enlarged LNs on CT vs 13 patients with hypermetabolic LNs on PET). In particular, 2 patients with no significant palpable lymphadenopathy whose nodes did not meet CT size criteria were subsequently found to have LN involvement with large cell transformation. One patient was a 32-year-old man with a history of stage IA MF whose disease progressed to tumor lesions (Figure 2). After PET/CT and LN biopsy were performed, he received combination chemotherapy with cyclophosphamide, vincristine, doxorubicin, and prednisone. Without integrated PET/CT, this patient would have been assigned a stage IIB classification and thus been put at risk of being suboptimally treated. In addition, PET/CT potentially increases the specificity of detecting LN involvement in MF and SS. The higher SUVs in our series tended to correlate with pathologic findings of LN4 nodes, and even higher SUVs were associated with large cell–transformed LNs, suggesting that a node with a higher SUV would have an increased likelihood of involvement with MF and with large cell transformation.

There has been debate about the ability of PET to detect low-grade lymphomas, but several studies have found that PET can detect activity in both follicular and marginal zone lymphomas[28-30] and that the intensity of PET activity may show correlation with malignancy grade.[31,32] Rodriguez et al[31] demonstrated that low-grade non-Hodgkin lymphomas were associated with a mean SUV±SD of 6.37±5.3, whereas high-grade lymphomas were associated with a mean SUV±SD of 11.8±4.7. In our analysis, we found that PET/CT could be useful in evaluating MF and SS, which is often classified as a low-grade non-Hodgkin lymphoma. Furthermore, when we attempted to correlate the SUV from PET/CT with histologic LN grade, we found that LN1-3 nodes were associated with a mean SUV of 2.7 and LN4 nodes were associated with a mean SUV of 5.4. Also, the mean SUV of all nodes without large cell transformation was 2.9, whereas the mean SUV of those with large cell transformation was 6.1. Although there is some overlap between the 2 groups, most LN4 nodes were associated with an absolute SUV greater than 3, whereas most LN1-3 nodes were associated with an SUV of 3 or less. Other studies suggest that malignant involvement can be suspected at an SUV cutoff of around 2.5 to 3.0, although there still may be considerable overlap between SUVs of benign tissue and those of malignant tissue.[33] Comparisons with other published studies are limited because these data are derived from solid tumors and nodal-based lymphomas and no previous large studies have been published on SUVs for cutaneous lymphomas. Ongoing analysis of additional MF and SS patients may provide further information about whether an SUV cutoff can be defined in this disease that reliably predicts LN involvement and/or large cell transformation.

The variability of the SUV in malignant tissue relates to the fact that the value is affected by various factors including tumor type, proliferation rate, blood supply, and heterogeneity.[33] Moreover, nonspecific uptake of fluorodeoxyglucose occurs in inflammation and infection.[34] Consequently, the SUVs must always be placed into the overall clinical context and correlated with histologic data when possible. Rather than focusing solely on absolute

SUVs, examining the relative SUVs within each patient may provide useful information. By comparing SUVs in axillary vs those in inguinal regions, for instance, the surgeon can select the region with the most metabolically active LN for biopsy. Also, SUVs can be monitored over time to evaluate treatment response, and any sudden increase in SUV may be considered suspicious for recurrence of disease.[35]

Although PET/CT helps guide the surgeon in selecting the LN region on which to perform a biopsy, sampling errors can still occur at the time of biopsy. Although PET/CT may identify 1 or more hypermetabolic nodes in a single LN chain, intraoperatively it may not be obvious which node had the highest SUV. The surgeon must then rely on his or her best judgment in selecting the node or nodes to remove. Also, nodes can be enclosed within fibrofatty tissue, which can make it difficult to determine whether or how many nodes have been removed. In the future, use of an intraoperative PET probe, which has recently become available at our institution, may help identify hypermetabolic LNs at the time of surgery and decrease the probability of sampling error. Another approach that may improve sampling accuracy is FNA of diseased LNs. The target node or nodes identified by PET/CT can be localized by palpation or by CT guidance and sampled via percutaneous needle aspiration. This technique is less invasive than excisional LN biopsy. The aspirate can then be analyzed by a combination of cytologic criteria, flow cytometry, and PCR. Previous reports[36] have demonstrated that FNA with molecular analysis is useful for evaluating diseased LNs in MF and SS. Thus, combining PET/CT for staging with the use of an intraoperative PET probe or FNA may improve sensitivity in detecting LN involvement in MF and SS and may improve specificity by decreasing the chances of false-negative biopsies.

Several studies[37-39] have demonstrated that the presence of clonal *TCR* gene rearrangement in LNs is associated with a worse prognosis of MF. Clonality is also a proposed component of the revised staging system for MF and SS (Y.H.K., personal communication [ongoing] with the International Society for Cutaneous Lymphoma, 2006). In our study, PCR analysis was applied to nodes with intermediate LN grade, which included 3 LN2 samples and 1 LN3 sample. We did not apply PCR analysis to LN1 or LN4 samples because of a lower likelihood for eliciting additional useful prognostic information. All LN2-3 nodes were found to have *TCR* clonality. Of 4 patients, 3 had SS; it is possible that the finding of *TCR* clonality in these patients may be a result of the abundance of circulating Sézary cells rather than a reflection of the LN pathologic findings. Many clinicians believe that patients who have clone-positive nodes should be considered to have LN involvement with MF and thus should be assigned a stage IV classification; however, consensus on the exact role of clonal *TCR* gene rearrangement in staging MF AND SS has not yet been reached. Long-term follow-up of patients in our study will reveal whether they indeed have a worse prognosis compared with other patients without *TCR* clonality.

Although our patients all had active MF and SS, their PET/CT scans did not always highlight increased metabolic activity within their skin lesions. Patients with erythroderma rarely had evidence of hypermetabolic activity in the skin, which is not surprising given the often subtle histologic skin changes from patients with erythrodermic MF.[40] However, we have seen that in patients with tumor stage MF (T3), the PET/CT occasionally highlighted skin tumors very well (data not shown). Other studies have shown that hypermetabolic activity can be detected in the skin in cases of subcutaneous panniculitic T-cell lymphoma and cutaneous B-cell lymphoma.[20] Nevertheless, PET/CT can never replace a thorough skin examination.

Disadvantages of PET/CT include its limited availability in some regions and the high cost of the scanner itself. However, at our medical center we have found that a single PET/CT scan costs less than a contrast CT scan of the chest, abdomen, and pelvis and certainly less than ordering separate CT and PET scans. Another disadvantage is that the increased sensitivity of PET/CT may result in additional LN biopsies. In our series, 8 patients did not have enlarged LN according to CT size criteria but had at least mildly increased hypermetabolic activity on PET and thus were referred for LN biopsy. Of these 8, 6 had LN1-3 nodes and 2 had LN4 nodes with large cell transformation. Whether the cost of these additional biopsies is balanced by the identification of 2 patients with aggressive LN disease is not known. Active collection of additional patient data may provide a threshold SUV level for large cell transformation or LN4 disease, which may allow us to decrease the number of biopsies performed on LNs with lower, less suspicious SUVs. Thus, the clinical benefits derived from PET/CT may clearly outweigh the costs, but a focused cost-effective analysis has yet to be performed.

Our pilot study results in a small patient cohort support the use of PET/CT in staging MF and SS. Overall, PET/CT was useful because it detected more LNs involved with lymphoma than CT alone and thus provided more accurate staging and prognostic information. The intensity of PET activity may correlate with histologic degree or grade of LN involvement. The use of an intraoperative PET probe and/or FNA may help increase the accuracy of surgical sampling. With a larger patient cohort and improved LN sampling technique, we hope to further define whether PET/CT can be used to significantly differentiate between LN1-3 (±T-cell clonality) and LN4 and large cell *N* transformed LNs. Also, we would like to correlate PET/CT results with patients' long-term clinical outcome. Additional studies need to be performed to address the usefulness of PET/CT in evaluating other cutaneous lymphomas and to address the issue of its cost-effectiveness. Regardless, because of its advantages over either PET or CT alone, PET/CT is an ideal single modality imaging technique for staging MF and SS.

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Author Contributions: Dr Kim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tsai, Hoppe, and Kim. *Acquisition of data*: Tsai, Taur, Espinosa, Quon, Johnson, Warnke, Kohler, Hoppe, and Kim. *Analysis and interpretation of data*: Tsai, Kohler, Hoppe, and Kim. *Drafting of the manuscript*: Tsai and Kim. *Critical revision of the manuscript for important intellectual content*: Tsai, Quon, Johnson, Dick, Chow, Advani, Warnke, Kohler, Hoppe, and Kim. *Obtained funding*: Kim. *Study supervision*: Kim.

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