RESEARCH ARTICLE

Comparison of CT, PET, and PET/CT for Staging of Patients with Indolent Non-Hodgkin's Lymphoma

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Abstract

Purpose: The aim was to investigate the potential impact of positron emission tomography (PET)/computed tomography (CT) as compared to PET and CT on the staging of patients with indolent lymphoma.
Procedures: PET/CTs from 45 patients with indolent lymphoma undergoing staging or restaging were studied. Clinical follow-up, additional imaging, and histology served as the gold standard.
Results: PET/CT correctly diagnosed 92 nodal regions as positive for lymphomatous involvement and 458 as disease free vs 68 and 449 for PET and 64 and 459 for CT, respectively. The respective sensitivities, specificities, and accuracies were 99%, 100%, and 99.8% for PET/CT, 68%, 97.5%, and 92.2% for PET, and 70%, 100%, and 94.7% for CT. PET/CT performed significantly better than PET ($p<0.001$ for sensitivity, specificity, and accuracy) and CT ($p<0.001$ for sensitivity and accuracy). PET/CT also correctly identified significantly more extra-nodal lesions (22) than CT (14) and PET (nine).
Conclusions: PET/CT provides significantly more accurate information compared to PET and CT for the staging and re-staging of patients with indolent lymphoma.

Key words: PET, PET/CT, Indolent lymphoma

Introduction

Metabolic imaging with fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become the clinical standard for staging and evaluation of treatment response in patients with non-Hodgkin lymphoma (NHL) [1–5]. More recently, PET/computed tomography (CT) has been shown to stage lymphoma with a higher accuracy than PET alone [6–9]. These studies have focused on Hodgkin's disease or aggressive NHL.

Staging of disease has important treatment implications for indolent NHL (indolent lymphoma). For example, up to one third of patients with follicular lymphoma can present with stage I and II disease, and 70% to 90% of mucosa-associated lymphoid tissue (MALT) lymphomas may present with localized (stage IE–IIE) disease [10]. In these cases, patients can be treated with radiation only [11], whereas higher stages usually require systemic therapy.

However, very few studies have evaluated the role of FDG PET in patients with indolent lymphoma. Most of these studies concluded that PET appears useful for the staging of the follicular subtype but only has a limited usefulness in the other subtypes of indolent lymphoma [12–15]. Except for a small study in patients with MALT lymphoma by Perry et al. [16], no study has evaluated the role of PET/CT in the staging of indolent lymphoma.

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FDG uptake in indolent lymphoma appears to be lower than in aggressive lymphomas [17]. Data on the correlation between proliferative activity and glycolysis in malignant tissue, as measured by FDG uptake, are controversial [18, 19]. To date, the correlation between FDG uptake and proliferative activity specifically in indolent lymphoma has not been studied in detail.

To our knowledge, to date, no study has investigated the value of PET/CT over PET and CT for staging of indolent lymphoma. The aim of the present study was to investigate the potential impact of PET/CT as compared to PET and CT on the staging of patients with indolent lymphoma. For a better understanding of FDG uptake in indolent lymphoma, we also investigated the correlation between FDG uptake and proliferative activity as measured by Ki-67 staining.

Patients and Methods

Patients

From March 2004 to September 2006, 301 patients with indolent lymphoma were referred to our institution for PET/CT imaging. In 45 of these patients (26 male, 19 female, mean age of 56 ± 13 years) referred for staging ($n=20$) or restaging ($n=25$), a reliable reference standard was available. The reference standard was established by clinical follow-up including additional imaging in all patients and additional biopsy in 26 patients.

The histological tumor type was follicular lymphoma in 47% ($n=21$) of patients, nodal and extranodal marginal zone lymphoma in 26% ($n=12$), small lymphocytic lymphoma in 9% ($n=4$), mantle cell lymphoma in 9% ($n=4$) as well as lymphoplasmocytic lymphoma ($n=1$), cutaneous T-cell lymphoma ($n=2$), and T-cell/NK lymphoproliferative disorder ($n=1$) in altogether 9% (see Table 1).

Image Acquisition

PET/CT was performed using the Reveal RT scanner (Siemens Medical Systems). This system combines a dual-slice-detector CT scanner (Somatom Emotion) with an ECAT ACCEL PET scanner. The characteristics of the device have been described in detail previously [20].

Table 1. Patient characteristics

Number of patients	45
Gender	
Female	19
Male	26
Age (years)	
Mean	56
Range	21–78
Histology	
Follicular	21 (47%)
Marginal Zone (including MALT)	12 (26%)
Small lymphocytic lymphoma	4 (9%)
Mantle cell lymphoma	4 (9%)
Others (lymphoplasmocytic, cutaneous T-cell, T-cell/ NK)	4 (9%)
Scan Indication	
Initial staging	20
Restaging	25

While resting on a reclining chair, the patients received a 7.77 MBq (0.21 mCi) per kg bodyweight of ^{18}F-FDG intravenously (up to a maximum of 740 MBq [20 mCi]) and were asked to drink 900 mL of barium sulfate. The imaging sequence began 45 min after tracer injection. All patients were positioned on the imaging table with their arms up. After determining the imaging field (base of skull to mid thighs) with an initial scout scan, CT acquisition with intravenous contrast material was performed using the following parameters: 130 kVp, 120 mAs, 1-s tube rotation, 4-mm slice collimation, and bed speed of 8 mm/s (i.e., pitch of 2).

The CT scan was followed by the PET emission scan, using a weight-based protocol as recently described [20, 21]. Scanning encompassed six to eight bed positions (depending on patient height) from the mid-thigh to the base of the skull. PET images were acquired in 3D mode. Patients were instructed to breathe shallowly during the PET and CT portions of the study to minimize misregistration between PET and CT images [22].

Image Reconstruction

CT images were reconstructed using conventional filtered back-projection, at 3.4-mm axial intervals to match the slice separation of the PET data. PET images were reconstructed by using iterative algorithms (ordered-subsets expectation maximization, two iterations and eight subsets) to a final image resolution of 8.8 mm at full width at half maximum. Attenuation was corrected by mapping the CT Hounsfield units to the linear attenuation coefficients as previously described [23].

Image Analysis

PET, CT, and PET/CT acquired in this retrospectively enrolled population were interpreted prospectively as follows: CT and PET images were interpreted independently by one radiologist and one nuclear medicine specialist, respectively, who were blinded to any additional clinical and other imaging findings. PET/CT studies were read in consensus.

A lesion was classified as positive on PET if there was focally increased FDG uptake above background that was not explained by physiological activity. A lesion on CT was classified by lymph node size criteria (diameter >10 mm) or extra-nodal structural anatomical abnormality.

Unlike aggressive disease, indolent lymphomas do not exhibit uniformly increased FDG uptake [12–15]. Therefore, our image interpretation criteria were biased toward CT as follows: on PET/CT, a lymph node was classified as abnormal if there was increased FDG uptake and/or abnormal size regardless of FDG uptake. Extra-nodal lesions were interpreted as abnormal if they exhibited focally increased FDG uptake and/or pathological anatomical features on CT (regardless of the FDG uptake).

Staging and Analysis of Nodal Regions

Based on the lymph node regions originally defined by Kaplan and Rosenberg[24], we analyzed 13 lymph node regions per patients. Therefore, a total of 585 lymph node regions were analyzed. The patient stage was determined based on the Ann Arbor classification [25] from the number of positive nodal and extra-nodal regions by PET, CT, and PET/CT.

Quantitative Analysis of FDG Uptake

For the calculation of SUV, circular regions of interest (15-mm diameter) were placed on consecutive axial images of lesions visually identified to have abnormally increased FDG uptake. In the absence of visual FDG uptake, the biopsy site was used for the determination of SUV. The SUV was calculated as:

$$\mathrm{SUV} = \frac{\mathrm{decay-corrected\ activity(kBq)\ /tissue\ volume(ml)}}{\mathrm{injected-FDG\ activity(kBq)\ /body\ weight(g)}}$$

To minimize partial volume effects and assure reproducibility of measurements, the maximum SUV ($\mathrm{SUV_{max}}$) was used.

Immunohistochemical Staining with Ki-67

Ki-67 staining results from biopsies obtained for diagnostic purposes were available in 29 patients who had not undergone treatment between the biopsy and the PET/CT. Biopsies were performed within 4.38±4.79 weeks (0–16.43) of the PET/CT. The Ki-67 labeling index reflects cell proliferative activity and is defined as the percentage of nuclei stained per total number of nuclei in the sample. The immunohistochemistry and determination of the Ki-67 labeling index were performed according to standard protocol and routine at our institution [26, 27].

Proliferative activity by Ki-67 staining was then correlated with the $\mathrm{SUV_{max}}$ of the biopsied site.

SUV_{max} and Histology

$\mathrm{SUV_{max}}$ was also correlated with histology to determine whether the type of indolent lymphoma determines FDG uptake.

Standard of Reference

All patients had lymph node biopsy for histological diagnosis of disease. For ethical reasons, systematic biopsy of all sites for staging was not performed. Clinical evaluation and follow-up for 71±32 weeks (range, 16 to 131 weeks) for all patients, biopsy (n=26), and additional imaging consisting of CT, MRI or PET/CT (n=35) performed 4.55± 4.25 weeks after the initial scan (range, 0 to 17 weeks) served as the reference standard. Concordant positive findings of clinical evaluation, CT, PET, and PET/CT were regarded as true sites of disease. Concordant negative findings of clinical evaluation, CT, PET, and PET/CT were regarded as true absence of diseases. In cases of discordance between PET, CT, and PET/CT, response to treatment and follow-up data were used to assess the overall accuracy of the patient's disease status. Lesions were considered true positive if abnormalities either persisted on a follow-up PET or CT scan with no interval treatment or resolved on a follow-up scan in patients that had received interval treatment. Conversely, lesions that resolved on follow-up scanning without interval treatment were considered false positive.

Statistics

Using the standard of reference, sensitivity, specificity, and accuracy were calculated [28]. In addition, comparison between groups was performed using the unpaired t test and McNemar test. Correlations were sought using the Pearson correlation. A $p<0.05$ was considered significant.

Results

Thirty-three of 45 patients had evidence of active disease with a total of 117 of 585 nodal regions involved according to the reference standard. In addition, a total of 36 extranodal lesions were identified by the reference standard.

Staging Performance

Compared to the reference standard, the correct stage was determined by PET in 62% of patients (n=28), by CT in 58% (n=26), and by PET/CT in 76% (n=34). PET incorrectly assigned a higher stage in 7% of patients (n=3), CT in 7% (n=3), and PET/CT in 9% (n=4). PET incorrectly assigned a lower stage in 31% (n=14), CT in 36% (n=16), and PET/CT in 16% (n=7). There was no significant difference between the number of patients correctly staged by PET and PET/CT (p=0.24), and PET/CT only demonstrated a trend toward better performance than CT (p=0.079).

In detail, PET/CT correctly resulted in a higher stage than CT in 18% (n=8) of the patients and in a higher stage than PET in 20% (n=9) of patients. PET/CT correctly down-staged 4% (n=2) of patients compared to PET. Due to the selected image interpretation criteria, down-staging of CT by PET/CT was not possible.

Positive Nodal and Extra-nodal Regions

From a total of 585 nodal regions, PET/CT correctly diagnosed 92 nodal regions as positive for lymphomatous involvement and 458 as disease free vs 68 and 449 for PET and 64 and 459 for CT, respectively. The number of false-positive and false-negative nodal regions were eight and 27 for PET/CT, 18 and 50 for PET, and eight and 54 for CT, respectively. The respective sensitivities, specificities, and accuracies were 99%, 100%, and 99.8% for PET/CT, 68%, 97.5%, and 92.2% for PET, and 70%, 100%, and 94.7% for CT. PET/CT performed significantly better than PET (p< 0.001 for sensitivity, specificity, and accuracy) and CT (p< 0.001 for sensitivity and accuracy). Differences between PET and CT were not significant for sensitivity, significant for specificity (p<0.001), and tended to be significant for accuracy (p=0.089; see Table 2).

PET/CT was also significantly better in detecting extra-nodal lesions than CT (p<0.016) and PET (p= 0.06). Of the 36 extranodal lesions by gold standard (tissues /organs involved were the parotid gland, lung, stomach, liver, adrenal gland, kidney, spleen, skin, conjunctiva, meninges, the bone marrow, as well as muscle and soft tissue), PET/CT detected 25 extra-nodal lesions, CT 16, and PET nine (see Figs. 1 and 2). Of eight bone marrow sites, three were identified by PET, four by PET/CT, and none by CT alone. Of eight sites of lung involvement, PET only noted three, whereas CT and PET/CT correctly diagnosed all eight. From nine sites of soft tissue involvement, PET noted one, CT four,

Table 2. Performance for detection of nodal disease

	Sensitivity	Specificity	Accuracy
PET	68	97.5	92.2
CT	70	100	94.7
PET/CT	99	100	99.8
	$p<0.001$ vs PET, CT	$p<0.001$ vs PET	$p<0.001$ vs PET, CT

and PET/CT eight. Of 12 sites with organ involvement, PET correctly noted two, CT four, and PET/CT five.

The above includes six patients with extranodal marginal zone lymphoma. One of these six patients did not have active disease. Of the five remaining patients, organ involvement included the meninges, the parotid gland, conjunctiva, lung, liver, stomach, spleen, kidney, and the skin.

SUV_max vs Proliferative Activity and Histology

SUV_{max} ranged from 0.4 to 15.4 (mean±SD, 3.7±4.1) in follicular and from 0.8 to 9.8 (2.2±2.1) in non-follicular indolent lymphomas. The highest SUV_{max} as well as the lowest SUV_{max} occurred in follicular grade-1 lymphomas.

There was also a wide range of Ki-67 staining with the lowest proliferative activity observed in MALT lymphoma and the highest in mantle cell lymphoma. The correlation of SUV_{max} and Ki-67 index was not statistically significant.

No significant difference was found between the SUV_{max} of the various types of indolent lymphoma.
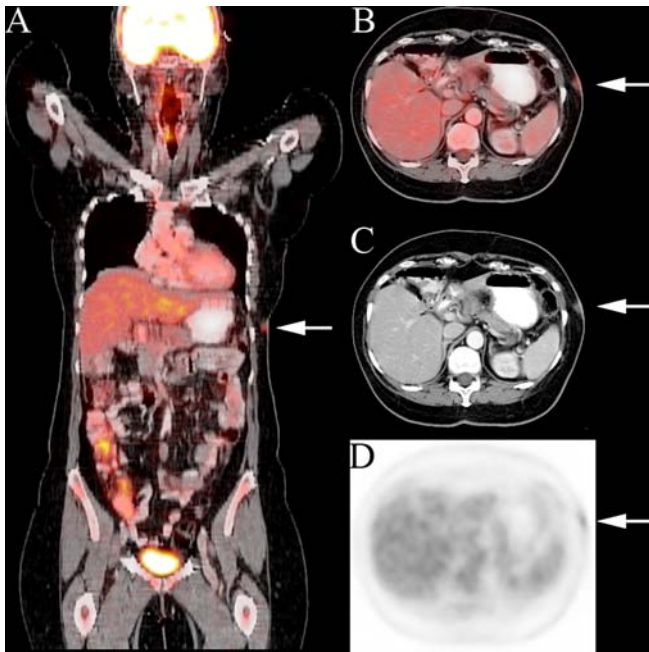

Fig. 1. A 59-year-old woman with a history of cutaneous T-cell lymphoma. Fused coronal (**a**) and axial PET/CT (**b**) slices demonstrate left flank skin involvement (*arrow*) missed on CT (**c**) and PET (**d**) interpretation.
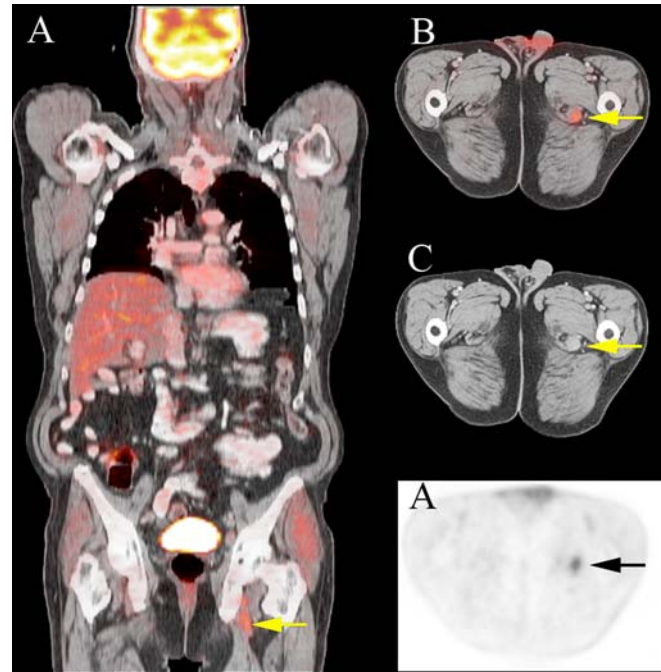

Fig. 2. A 62-year-old man with history of mantle cell lymphoma. Fused coronal (**a**) and axial PET/CT (**b**) slices demonstrate disease related FDG uptake in left obturator adenopathy (*arrow*) missed on CT (**c**) and PET (**d**) interpretation.

Discussion

For the group of patients studied, PET/CT was able to add clinically important information not available from CT or PET alone. On a regional-based analysis of patients with indolent lymphoma, PET/CT performed significantly better than PET and CT in correctly classifying lymph node groups as positive or negative for lymphomatous involvement. PET/CT was also able to detect more extra-nodal sites of disease than either CT or PET. There was no significant difference between the number of patients correctly staged by PET and PET/CT, and PET/CT only demonstrated a trend toward better performance than CT ($p=0.079$).

Few papers have looked at the value of FDG-PET over conventional imaging specifically for the staging of indolent lymphoma. Jerusalem et al. [13] reported that, in 42 patients with indolent lymphoma, PET was able to identify more lymph node areas infiltrated by indolent lymphoma compared to conventional staging procedures. Contrary to the findings of Jerusalem et al., we found no significant difference between the sensitivity of PET or CT for the detection of nodal groups with disease. However, PET/CT was significantly better in detecting nodal disease than either modality. Similarly, PET/CT detected more extra-nodal disease sites than PET or CT. For the overall staging of disease, Jerusalem et al. reported that PET plus a bone marrow biopsy compared to conventional staging procedures (also including a bone marrow biopsy) observed the same stage in 37 patients, a higher stage by PET in two patients,

and a higher stage by conventional procedures in three patients. In our study, PET/CT staged more patients correctly than either PET or CT, although the differences for overall staging only demonstrated a statistical trend to significance. Najjar et al. [29] reported a similar observation finding the combined information of separately acquired CT and PET more sensitive for staging indolent lymphoma than either modality alone. Disease occurring in normal appearing lymph nodes or extra-nodal sites can be picked up by PET. Conversely, CT can detect disease missed by PET either because of size or because of the absence of FDG uptake frequently encountered in the setting of indolent lymphoma. The additional value of fused imaging with PET/CT over side by side reading of CT and PET has been reported for multiple malignancies in general [30] as well as specifically for lymphoma [6, 7].

Data on the correlation between proliferative activity determined by Ki-67 staining and glucose metabolism in lymphomas, as measured by FDG uptake, are controversial. Okada et al. [18] report a positive correlation between proliferation and FDG uptake in a small series of patients with malignant lymphomas. We observed no statistically significant correlation between SUV_{max} and percentage of cells that stained positive with Ki-67. We therefore feel that, in indolent lymphoma, SUV_{max} cannot substitute for the prognostic value provided by Ki-67 reported in indolent lymphoma [31].

Comparing the SUV_{max} of the different subgroups of indolent lymphoma in our study, we found no significant differences in SUV_{max}. Although Karam et al. [12] did note a significantly higher SUV in follicular lymphoma than other indolent lymphoma, our findings are more in line with Schoeder et al. [17], noting no significant difference in FDG uptake within the histological subtypes of indolent lymphoma. Thus, it is likely that histological classification based on SUV measurements cannot be a substitute for the histological diagnosis based on actual tissue. However, as Bodet-Milin et al. reported [32], PET/CT might be of value in the assessment of patients with indolent lymphoma suspected to have undergone histological transformation of their indolent lymphomas, since this usually results in a significant increase of FDG uptake at the sites of transformation.

Limitations

Since biopsy of every suspicious lesion would not be ethical, a surrogate gold standard had to be found. Concordant positive findings of clinical evaluation, CT, PET, and PET/CT were regarded as true sites of disease. Concordant negative findings of clinical evaluation, CT, PET, and PET/CT were regarded as true absence of disease. In cases of discordance between PET, CT, and PET/CT, response to treatment and follow-up data were used to assess the overall accuracy of the patient's disease status. Lesions were considered true positive if abnormalities either persisted on a follow-up PET or CT scan with no interval treatment or resolved on a follow-up scan in patients that had

received interval treatment. Conversely, lesions that resolved on follow-up scanning without interval treatment were considered false positive. Since initial treatment response to indolent lymphoma is excellent [33–35], lesions that would have persisted despite interval treatment would also have been considered false positive. However, we did not encounter any patient in which this would have been the case.

The patient population studied was heterogeneous, and larger studies evaluating the individual subtypes of indolent lymphomas might be warranted to confirm our results.

The relatively low number of patients with a reliable reference standard (45 out of 301) likely results from the clinical course low grade lymphomas frequently take, i.e., long periods of clinically inactive disease only leading to a clinical evaluation by the treating physician if symptoms occur.

Conclusion

PET/CT provides important additional information over PET and CT for the staging and re-staging of patients with indolent lymphoma. Thus, the application of PET/CT rather than CT or PET is likely to be of benefit in the management of patients with indolent lymphoma. Given the frequent absence of significant FDG uptake in indolent lymphomas, in the untreated patient, enlarged nodes detected on CT should be regarded as pathological even in the absence of FDG uptake. On subsequent post-treatment scans, node size should be used to evaluate for treatment response rather than FDG uptake.

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