

# Combined PET and low-dose, noncontrast CT scanning obviates the need for additional diagnostic contrast-enhanced CT scans in patients undergoing staging or restaging for lymphoma

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**Background:** Positron emission tomography (PET) is more accurate than computed tomography (CT) in staging and restaging of lymphoma, but both are considered necessary. Increasingly, PET is carried out with a low-dose CT scan. Many patients undergo both PET/CT and standard diagnostic CT. The clinical utility of performing both studies in patients with lymphoma was evaluated.

**Patients and methods:** Patients with lymphoma who underwent concurrent PET/CT and diagnostic CT (a scan pair) were identified, and findings detected in either scan but not both were documented. Discrepancies were considered significant if they were related to either lymphoma or another disease process which potentially required intervention.

**Results:** Eighty-seven scan pairs were identified. PET/CT detected additional lesions over diagnostic CT in 30 patients, of which 11 demonstrated increased clinical stage. Lymphoma therapy changed based on PET/CT in two patients, and one occult rectal cancer was detected. In contrast, diagnostic CT detected five relevant findings, including two incidental findings (venous thrombosis) and three patients with splenic lesions, none of which could be confirmed as lymphoma. No patient had change of stage or lymphoma therapy based on diagnostic CT.

**Conclusion:** In our series, diagnostic CT did not add value to staging or restaging of lymphoma when carried out concurrently with PET/CT.

**Key words:** lymphoma, PET/CT, staging

## introduction

Positron emission tomography using 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG-PET) is increasingly used in the staging and restaging after therapy of patients with lymphoma. Several studies published in the past decade have demonstrated that FDG-PET can improve accuracy of staging over standard computed tomography (CT) imaging [1]. However, FDG-PET alone has not been considered sufficient to replace altogether the standard diagnostic contrast-enhanced CT; the two imaging modalities are complementary.

In addition to initial staging, FDG-PET contributes valuable information in the restaging evaluation after therapy of patients with lymphoma. Commonly, a residual anatomic abnormality may be present on CT after treatment, particularly of Hodgkin's lymphoma (HL) and some types of aggressive non-Hodgkin's lymphoma (NHL). FDG-PET can often help

distinguish residual viable lymphoma from nonviable scar tissue [2, 3]. Furthermore, FDG-PET can identify areas of residual disease not detected by follow-up CT. Recently, the International Working Group lymphoma response criteria were modified to include FDG-PET findings in response assessment of patients with HL and NHL [4], on the basis of data showing significantly improved prediction of clinical outcome when results of FDG-PET scanning are incorporated.

Increasingly, FDG-PET is now being carried out in conjunction with a low radiation dose, noncontrast CT scan for attenuation correction and anatomic localization of lesions (PET/CT). Combined PET/CT involves use of a combined full-ring detector PET scanner with a multidetector helical CT, allowing the PET scan to be acquired immediately after the CT scan. The images are then fused to give precise localization of FDG-avid lesions. Standard diagnostic, contrast-enhanced CT (diagnostic CT) provides higher resolution images as well as improved evaluation of solid organs through contrast enhancement than does the low-dose CT carried out in the combined study. Because of concern that relevant findings will be missed on PET/CT, currently many patients undergo both

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PET/CT and diagnostic CT in the initial staging of lymphoma as well as in treatment response evaluation.

While accurate assessment of disease extent both before after therapy play a critical role in care of patients with lymphoma, the drawbacks of such extensive imaging must also be considered. Recently, increased attention has been brought to the potential negative effects of the radiation associated with imaging studies, particularly CT scans. The possibility of long-term health effects related to radiation exposure, particularly in younger patients, is of concern [5]. While this risk appears to be low when weighed against appropriate treatment of existing lymphoma, this balance is predicated on the assumption that extensive imaging actually leads to improved outcome for patients. Furthermore, these imaging studies are expensive, a significant factor in this era of mounting health care costs.

We hypothesized that the additional functional, metabolic information provided by FDG–PET compensates in most cases for the low resolution and lack of contrast of the low-dose CT scan and that the addition of diagnostic, contrast-enhanced CT rarely provides additional clinically useful information in patients with HL or NHL undergoing initial staging or response assessment after therapy.

## patients and methods

We retrospectively identified patients based on a Nuclear Medicine database containing all patients who had undergone PET scan at the University of Michigan. We then identified from this database all patients with a diagnosis of HL or NHL who had undergone PET scan since the institution of combined PET/CT scanning at the University of Michigan. We selected for our analysis patients who had also undergone diagnostic, contrast-enhanced CT within 6 weeks of the PET/CT, with no intervening antilymphoma therapy.

The CT images were obtained following the administration of both oral and i.v. contrast. The studies were carried out utilizing standard diagnostic technique for the chest, abdomen and pelvis and utilized 5-mm collimation. The PET/CT studies were obtained 60 min following the i.v. administration of ~300 MBq 8 mCi of 2-fluoro-2-deoxy-D-glucose (FDG). Sequential noncontrast-enhanced CT and PET imaging were carried out from the base of skull to the proximal femora. Helical CT for PET coregistration was carried out with 5-mm collimation followed immediately by PET at multiple overlapping bed positions (5 min per bed position). The PET/CT images were obtained utilizing oral contrast and were acquired during free breathing.

All combined PET/CT scans were reviewed by the investigators (RLE and RKJB), and a prospectively designed case report form was used as a tool to record all abnormal findings. Subsequently, the CT scan portion of the combined study was reviewed alone in order to identify any abnormalities which were not FDG avid. The results of this review were then compared with the diagnostic CT scan report and discrepancies identified. Discrepancies were classified as potentially clinically important if they represented either areas of suspected lymphoma involvement or findings requiring further work-up or intervention. Thus, for example, small pulmonary nodules (<6 mm) as well as lesions considered to represent cysts in solid organs were considered not clinically important, whereas solid organ lesions suspicious for lymphoma or requiring further evaluation were considered clinically important. In order to confirm that discrepancies identified represented true differences, both the PET/CT and the diagnostic CT of scan pairs in which discrepancies were identified were then rereviewed.

The nature of the lesions was further investigated by reviewing the patients' medical history, determining whether biopsy had been carried out or whether clinical follow-up had clarified the nature of these lesions.

Clinically important lesions were classified as either incidental (a nonlymphoma clinically important finding, such as thrombosis) or representing lymphoma. Data were collected on whether discrepant findings on either scan had led to a change in lymphoma stage or treatment and whether incidental findings had prompted any intervention.

This study was approved by the Institutional Review Board of the University of Michigan.

## results

Eighty-seven scan pairs were identified in 73 patients. Characteristics of the patients and scans are shown in Table 1. Sixty-one studies were carried out at staging, before treatment, and 26 were carried out for assessment of response at the end of therapy. Thirty-eight scan pairs (44%) were identified in patients with diffuse large B-cell lymphoma (DLBCL), 37 (43%) with HL, two (2%) with grade 3 follicular lymphoma (FL), four (5%) with grade 1 or 2 FL, three (3%) with mantle cell lymphoma, two with marginal zone lymphoma and one with anaplastic large T-cell lymphoma. The median time between the PET/CT and diagnostic CT scans in a pair was 10 days (range 0–40).

In 52 of 87 scan pairs, no clinically significant differences were identified between the PET/CT and diagnostic CT (Table 2). In 30 cases, the PET/CT identified at least one potentially clinically significant finding, most of which were considered to represent sites of lymphoma. In one case, a rectal lesion identified on PET/CT but not visualized on diagnostic CT was subsequently found to represent a rectal cancer. In 11 cases (six DLBCL and five HL), PET/CT findings led to a change in stage. In seven patients (4 DLBCL and 3 HL), bone lesions were identified on PET/CT which were not visible by diagnostic CT and were confirmed on biopsy in four cases to represent lymphoma. In two patients, antilymphoma therapy was altered based on PET/CT findings, and one patient was treated for rectal cancer.

In five scan pairs (three DLBCL, two HL and one grade 3 FL), the diagnostic CT identified at least one potentially clinically important lesion (Table 3). In three of these cases, abnormalities were identified in the spleen that were interpreted as possibly consistent with involvement by lymphoma. In none of the patients did this finding change stage

**Table 1.** Eighty-seven scan pairs were identified in 73 patients

Histology	
Diffuse large B-cell lymphoma	38
Hodgkin's lymphoma	37
Follicular lymphoma grade 3	2
Follicular lymphoma grades 1–2	4
Mantle cell lymphoma	3
Marginal zone lymphoma	2
Anaplastic large-cell lymphoma	1
Time of scans	
Pretreatment	61
After treatment	26

**Table 2.** FDG–PET/CT versus diagnostic CT comparison

Clinically significant findings	
No change	52
Change with PET	30
Change with CT	5
Change in stage	
PET	11
CT	0
Change in management	
PET	3
CT	1

FDG–PET, positron emission tomography using <sup>18</sup>fluoro-2-deoxyglucose; CT, computed tomography.

**Table 3.** Potentially significant findings on diagnostic computed tomography

Patient	Finding	Outcome
Patient 1	Hypodensities in spleen	Indeterminate; patient achieved partial response overall with no change in spleen abnormalities
Patient 2	Hypodensities in spleen	Not lymphoma; patient treated to complete remission with no change in lesions
Patient 3	Hypodensity in spleen	Indeterminate; infarct versus lymphoma. Progression in multiple sites on follow-up without change of spleen lesion
Patient 4	Chronic deep vein thrombosis	Treated with warfarin for 3 months
Patient 5	Possible deep vein thrombosis	No intervention

or treatment plan. On follow-up, one of these findings was definitively identified as not representing lymphoma (no change was observed in the spleen lesion while all other lymphoma-related abnormalities resolved, with no progression on follow-up), while two remained unresolved. Of the two unresolved findings, both remained unchanged on follow-up in patients who did not achieve a complete response: one who experienced a partial response with subsequent progression and one who progressed on therapy.

In two patients, staging diagnostic CT identified vascular abnormalities suggestive of deep vein thrombosis. One of these findings was questionable and was not treated. Subsequent imaging showed no further evidence of clot. The other patient underwent anticoagulation for 3 months with no sequelae.

Twenty-six scan pairs were carried out after therapy for response evaluation and in no case was a discordant anatomic abnormality identified. In 14 cases, residual anatomic abnormalities were visualized on both scans. Twelve of these were not FDG avid, of which one patient experienced

progression within 1 year. Two showed persistent FDG avidity, and both patients experienced progression of their lymphoma.

## discussion

These data demonstrate that, in our series, contrast-enhanced diagnostic CT scan provided no additional information over PET/CT regarding lymphoma staging or restaging after therapy. In two patients, incidental findings of potential clinical importance unrelated to lymphoma were identified, and in one of these patients, the diagnostic CT led to an intervention. Indeterminate findings of possible splenic involvement by lymphoma observed only on diagnostic CT were not confirmed. Consistent with previous studies, PET/CT added information beyond that provided by diagnostic CT alone in both staging and restaging. No difference between HL and NHL regarding the additional utility of either the combined PET/CT or diagnostic CT was evident in our series.

Several previous reports address issues relevant to the current study. Schaefer et al. [6] reported a comparison of sensitivity and specificity of PET/CT versus diagnostic CT in 60 patients with lymphoma, finding improved sensitivity and specificity with PET/CT both at staging and restaging. Two patients had findings on diagnostic CT which were not noted on PET/CT, but in at least one instance, this was due to the lack of dedicated review of the PET-associated CT. Rodriguez-Vigil et al. [7] compared PET scans carried out in conjunction with low-dose-unenanced CT scans to PET scans carried out in conjunction with standard-dose i.v. contrast-enhanced CT in 47 patients with lymphoma. In two cases, additional lymphoma lesions were identified with the higher dose-enhanced CT, but in both cases an indeterminate finding was observed on the low-dose PET/CT. Of note, a venous thrombosis was detected in one patient only on contrast-enhanced CT. Raanani et al. reviewed 103 patients who underwent both PET/CT and diagnostic CT. They identified additional findings on diagnostic CT in 12% of patients leading to stage change. However, the time interval between scans was significantly longer than that in our study, in some cases >2 months, raising the possibility of true disease progression. Furthermore, dedicated review of the CT portion of the PET/CT was not carried out, limiting the interpretability of these additional findings [8]. Finally, a recent report by Gollub et al. [9] specifically addressed the limitations of the low-dose-unenanced CT standardly carried out with PET scans in a group of patients with heterogeneous cancers, including lymphoma. When compared with standard diagnostic CT, most discordant findings could be attributed to factors other than technical limitations of the combined PET/CT study. Potentially significant findings were missed on PET/CT in seven of 37 lymphoma patients. However, in only two did the findings prompt further evaluation and neither led to a change in planned therapy.

In the current study, we report comparison of PET/CT and diagnostic CT in a large series of patients with lymphoma seen at the University of Michigan Cancer Center. The goal of our study was to determine whether, in a patient undergoing PET/CT for staging or restaging of lymphoma, there is utility in obtaining an additional diagnostic CT scan. In addressing

this question, we were interested in determining the value of the technology, not the interpretation, since at many institutions, ours included, the CT portion of a PET/CT is not read independently, but is used solely for attenuation correction and lesion localization. Therefore, in our study, each PET/CT was reviewed by the investigators, paying particular attention to separate interpretation of the CT portion of the study in order to derive all the information present. Several examples of clinically relevant findings were identified on this dedicated review of the low-dose CT which were not detected on the routine PET/CT reading, including two large pleural effusions, hydronephrosis and bone fractures.

In comparing the low-dose CT scan carried out in conjunction with PET to standard diagnostic CT scans, potential causes for missed findings on the low-dose CT include the lack of i.v. contrast, lower resolution and artifact of nonbreath holding technique leading to poor evaluation of lung abnormalities. In our series, all discrepant diagnostic CT findings of potential importance could be attributed to lack of i.v. contrast. This observation is important for the following reasons. First, the trend toward increasing resolution in standard diagnostic CT scans with its attendant increased radiation exposure for patients appears to be unnecessary in the setting of a patient undergoing PET/CT. The use of only low-dose CT could save significant radiation exposure for this group of patients who in many cases undergo serial radiologic studies with associated radiation exposure. Recent articles highlighting the potential health consequences of diagnostic radiation underline the relevance of limiting this exposure [5]. Second, although there has been concern regarding the potential interference of i.v. contrast in attenuation correction and interpretation of PET scans, there is increasing evidence that, using modified attenuation correction and/or injection protocols, i.v. contrast need not interfere significantly with PET interpretation [10, 11].

The discovery of incidental findings on diagnostic CT is rare, but in our study one patient did undergo additional unplanned intervention on the basis of the incidental identification of a venous thrombosis on diagnostic CT. Other studies have also reported rare clinically important incidental findings which were missed on PET/CT [9]. Whether to continue to subject all patients to additional radiologic studies in light of these findings is debatable. The potential for addition of i.v. contrast to PET/CT studies would likely render this issue moot.

In conclusion, our data suggest that, in patients undergoing PET/CT for staging or restaging after therapy of lymphoma, diagnostic CT does not add useful information regarding extent of lymphoma if the low-dose CT scan is interpreted individually. Our data combined with previous reports indicate that the use of diagnostic contrast-enhanced CT scans may be limited to those patients with inconclusive findings on PET/CT, allowing significant savings in terms of cost and patient radiation exposure.

## funding

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