

Title	Is contrast material needed after treatment of malignant lymphoma in positron emission tomography/computed tomography?
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Is Contrast Material Needed after Treatment of
Malignant Lymphoma in Positron Emission
Tomography/Computed Tomography?

Abstract

Purpose

Positron emission tomography (PET)/computed tomography (CT) with ^{18}F -fluorodeoxyglucose (FDG) is widely used for post-therapeutic surveillance of malignant lymphoma. Debate still exists as to whether intravenous contrast media during the CT stage of a PET/CT scan should be used. The purpose of this study was to investigate the clinical value of contrast agent in PET/CT in patients with lymphoma following treatment.

Patients and methods

122 consecutive patients with malignant lymphoma underwent 146 PET/CT scans to monitor therapeutic response ($n = 57$) or surveillance during follow-up ($n = 89$). All patients had a conventional PET/CT scan with low-dose CT without contrast (ldCT), and then a full-dose CT scan with contrast (ceCT). Two datasets were interpreted separately and prevalence of discrepant results between the two methods was evaluated. In addition, differences of diagnostic performance were investigated for restaging.

Results

Both PET+ldCT and PET+ceCT were positive in 22 cases and negative in 35 cases

when monitoring response to therapy. There were no cases in which these techniques demonstrated inconsistent findings. For restaging, the patient-based sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of PET+IdCT were 70%, 91%, 76%, 87%, and 84%, respectively, and those of PET+ceCT were 74%, 92%, 81%, 89%, and 87%, respectively. Discrepant results between the two methods occurred in only 2 of 89 cases (2%).

Conclusion

PET/ceCT yielded more accurate findings than PET/IdCT in a limited number of cases.

PET/IdCT may, therefore, be sufficient for routine PET/CT scanning for post-therapeutic assessment or restaging of lymphoma patients.

Key words: Malignant lymphoma, PET/CT, Restaging, Contrast material.

Introduction

In the management of malignant lymphoma, diagnostic imaging is indispensable for creating an appropriate therapeutic strategy. Due to availability and low cost, computed tomography (CT) is the most commonly used imaging modality for evaluation of post-therapeutic condition, as well as initial staging before treatment. Iodine-based intravenous contrast material is often used during these scans to make interpretations more accurate and with confidence. However, it is difficult to evaluate the viability of lesions only by morphological information.

Positron emission tomography (PET) using ^{18}F -fluorodeoxyglucose (FDG) is a functional imaging tool, which detects viable lesions throughout the whole body. PET is thought to be useful for not only staging or restaging, but also for predicting prognosis of patients, especially after treatment [1,2]. PET can reflect biological status of the lesions earlier than morphological changes occur, which is useful in making decisions for therapeutic strategies. Although morphological changes have been traditionally used as an indicator of post-therapeutic status, it is currently recommended that PET findings, together with morphological findings, should be considered after chemotherapy and/or radiation therapy [3,4]. In order to overcome the lack of morphological information by PET, an inline PET-CT system has been developed, and metabolic information as well

as morphological status can be easily obtained at a single examination. This scanning method yields more findings that are accurate with higher confidence, as compared with CT alone or PET alone [5-7]. In addition, there has already been an article demonstrating that conventional contrast-enhanced CT might not be necessary when image fusion between PET and low-dose CT images is available using an inline PET/CT system [8].

A CT device, as a part of a combined PET/CT scanner, is a multidetector-row CT, which can be used as a standalone CT scanner in clinical situations. To reduce radiation exposure and cost, low-dose CT is usually adopted without intravenous contrast in conventional PET/CT scanning, which may cause limitations in image interpretation [9]. If full-dose CT scanning is performed with intravenous (IV) contrast, fused images between CT and PET may obtain more diagnostically valuable information to provide higher diagnostic accuracy. However, in monitoring or restaging after treatment in patients with lymphoma, systemic chemotherapy is under consideration for further therapeutic management. Therefore, unlike post-operative evaluation of colorectal cancer, it is not always necessary to detect each and every involved lesion, and patient-based evaluation is sufficient. However, whether low-dose unenhanced CT is sufficient after treatment or full-dose enhanced CT would be helpful to make

therapeutic decisions is still debatable.

The purpose of the current study was to compare the diagnostic performance between conventional PET/CT with low dose CT without contrast material (PET/ldCT) and PET/CT with full-dose CT and contrast enhancement (PET/ceCT).

Patients and methods

Patients

Between October 2007 and September 2008, 122 consecutive patients (69 males and 53 females; mean age, 61 years; range, 18-89 years) with histologically proven malignant lymphoma underwent 146 PET/CT scans for monitoring therapy response (n = 57) or surveillance after treatment (n = 89). The patients' characteristics are summarized in Table 1. Patients gave written informed consent, as required in our institutional review board.

PET/CT scanning

PET/CT scanning was performed using a combined PET/CT scanner (Discovery ST Elite-Performance, GE Healthcare). This system integrates a PET scanner with a multidetector-row CT (16 detectors), and permits the acquisition of coregistered CT and

PET images in a single examination. Patients fasted for at least 4 hours before

ref #2-2

administration of FDG. We checked patients' plasma glucose level just before injection of FDG, and there were no patients whose plasma glucose exceeded 150 mg/dl. The data acquisition started approximately 50 min after the injection of a standard dose of 200 - 250 MBq of ^{18}F -FDG. Initially, starting at the level of the thigh, the low-dose CT scans were acquired with the following parameters: 40 to 60 mA, 120 kV, 0.6-sec tube rotation, 3.75-mm section thickness. The CT scans were acquired during breath hold with the normal expiration position, and scanning included the area from the upper thigh to the skull base. Immediately after CT, a PET emission scan was acquired, with an acquisition time of 2 min per bed position. The total acquisition time was approximately 20 min. The CT data were used for attenuation correction, and images were reconstructed by using the 3-dimensional iterative reconstruction algorithm called VUE Point Plus.

Another CT scan with intravenous contrast material (Iopamiron Inj. Syringe, Bayer HealthCare), containing 300 or 370 mg/ml of iodine, was then performed, while the patient remained in the same position on the PET/CT table. We used the following parameters for CT scanning for diagnostic purpose: dose-modulated tube current up to 350 mA; tube voltage 120 kV; pitch 1.35; 27.0 mm/rotation speed; contrast volume, 100

ref #2-3

mL; injection rate 2.0 mL/sec; 100-sec delay. During full-dose CT with contrast, the patients remained in an unchanged supine position on the PET/CT, and scanning was performed during breath hold with the normal expiration position, similar to previous low-dose CT scanning. For image fusion, 3.75-mm slices were reconstructed. The low-dose CT without contrast, full-dose CT with contrast, and PET images were transferred to a commercially available workstation (Xeleris, GE Healthcare) in order to access all data. Oral CT contrast agent was not used in this investigation.

Image evaluation

At least two board-certified radiologists and nuclear medicine physicians (YN and MN) interpreted the images. These physicians had 13 and 6 years experience, respectively, with PET, and 17 and 9 years experience, respectively, with CT. At first, using all clinical information available at the time of PET scan, the dataset of PET and low-dose CT images were reviewed and findings were obtained by consensus. Then, a dataset of PET and full-dose enhanced CT images were also interpreted. The diagnostic

ref #1-1

criteria was as follows: when PET showed focal moderate to intense uptake, compared to surrounding tissue, we regarded it as positive unless normal physiological uptake or accumulation in benign condition was indicated by corresponding CT; when PET

showed mild to moderate uptake with corresponding morphological abnormalities on CT, we also considered it positive; and when PET showed equivocal uptake without morphological abnormality or PET showed no uptake with or without morphological abnormality on CT, we regarded it as negative. Quantitative analysis was not conducted in this investigation.

For monitoring after therapy, abnormal uptake indicating residual viable lesions was evaluated on patient-basis, and the difference of results was also assessed on region-basis. For restaging or follow-up, the sensitivity, specificity, and diagnostic accuracy were investigated on a patient-basis, based on clinical follow-up for at least 6 months, excluding three patients who died of lymphoma within 100 days after scanning, and the difference of diagnostic accuracy was evaluated. In addition, the difference of results between the two methods was also assessed on a region-basis.

ref #2-1

ref #2-1

All the patients were analyzed and there were no patients who were excluded from the analysis. For 13 patients who had repeated scans for restaging or follow-up purpose, only the initial results were used for calculating diagnostic performance.

Statistical analysis

McNemar test was used for evaluating difference of diagnostic performance, and

$p < 0.05$ was considered statistically significant.

Results

For monitoring of response after treatment

For monitoring after treatment, 48 patients had 57 PET/CT scans. Of these 57 scans, patient-based results were positive in 22 cases, and negative in 35 cases in both PET/IdCT and PET/ceCT. Table 2 demonstrates the number of patients for whom each interpretation method described lesions, which are classified by involved areas. There was no diagnostic discrepancy between the interpretation of PET/IdCT and PET/ceCT on a region basis, and positive findings in PET/ceCT were all interpreted as positive in PET/IdCT.

For surveillance during follow-up

For restaging or follow-up, 76 patients, including two patients who had had a PET/CT scan for monitoring after treatment before, received a PET/CT scan. Since 13 of 76 patients had the PET/CT examination twice for this purpose, a total of 89 PET/CT scans were performed. Based on the final diagnoses, 23 patients were considered positive for relapse and 53 patients had no recurrence, with a prevalence rate of 30.3%. The number

of patients for whom each method described suspicious relapsed lesions is demonstrated in Table 3. Patient-based sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of PET+IdCT were 70%, 91%, 76%, 87%, and 84%, respectively, and those of PET+ceCT were 74%, 92%, 81%, 89%, and 87%, respectively. No statistically significant difference was found between the two scanning techniques, although discrepant results between the two methods occurred in 2 of 89 cases (2%). A recurrent tumor in the pons was accurately diagnosed only by PET/ceCT in one case (Fig. 1), and intravenous thrombus was accurately diagnosed as negative involvement only by PET/ceCT in the other case (Fig. 2). In both interpretation methods, positive findings in four patients turned out to be false. Focal uptake in the left palatine tonsil, bilateral submandibular glands, mediastinal, and supraclavicular nodes were interpreted as positive for relapse, but they were unchanged or disappeared without any treatment on follow-up PET/CT. In addition, extranodal focal uptake in the right thigh was regarded as relapse in one patient, but decreased in size one month later due to antibiotic treatment, indicating inflammatory change.

Discussion

In PET/CT examinations, our data shows that full-dose enhanced CT could be useful

for accurate diagnosis in a small number of specific cases, while low-dose unenhanced CT may be enough in most cases after treatment of malignant lymphoma.

As a combined PET/CT scanner has been installed in many institutes, an increasing number of reports describing the clinical usefulness of iodine-based contrast material for PET/CT scanning have occurred. For example, Soyka et al. demonstrated the superior diagnostic accuracy and therapeutic impact of PET/CT with contrast material and concluded that PET/ceCT may be considered as the first-line diagnostic tool for restaging in patients with colorectal cancer [10]. For patients who were suspected of having recurrent ovarian cancer or uterine cervical cancer, PET/CT with contrast material yielded the most accurate diagnostic performance [11,12].

As for malignant lymphoma, it is still debatable whether or not IV contrast should be used in evaluating disease status. In initial staging, Rodriguez-Vigil et al. compared the diagnostic performance of PET/IdCT and PET/ceCT, and found one case in which a splenic hilar lesion was correctly diagnosed only via PET/ceCT, resulting in more accurate staging. However, there was no statistically significant difference between the two methods [13]. In contrast, Morimoto et al. demonstrated that more diagnoses that are accurate were acquired by PET/ceCT for evaluating pelvic lesions in initial staging of lymphoma [14]. In addition, Vera et al. proposed that contrast enhanced PET/CT

without low-dose CT is recommended as a one-stop imaging test for monitoring or restaging. CT with contrast material can be applicable for attenuation correction with minimal influence for quantitative values of lesions, and excess radiation exposure can be avoided by omitting low-dose CT [15]. In our series, two cases were accurately diagnosed only by PET/ceCT, but both PET/ldCT and PET/ceCT brought consistent results in the majority of cases. These findings were similar to our previous investigation [16]. When information obtained via PET is available, there are no significant differences in diagnostic performance, whether fused images between PET and CT are read, PET and CT are interpreted side-by-side, or only PET images are read. In short, PET/ceCT is useful and yields the highest diagnostic accuracy, but PET/ldCT may be sufficient in most cases. Therefore, the use of intravenous contrast should be carefully considered for certain inconclusive cases to reduce medical cost. This strategy might also be useful to reduce adverse effects caused by iodine-based contrast material and to save medical cost without degrading diagnostic performance.

In this population, there was one false negative case using PET/ldCT interpretation in patients who had a PET/CT scan for restaging. In the false negative case, positive involvement of the central nervous system (CNS) could only be diagnosed by PET/ceCT as one FDG-avid lesion was enhanced in the pons, which was confirmed by

MRI. It is well known that FDG accumulates in the brain, making it difficult to evaluate intracranial lesions. Therefore, if patients are suspected of having CNS involvement, the use of contrast material should be considered even in PET/CT studies.

ref #2-5

One false positive case occurred due to intravenous thrombus. It is known that FDG also accumulates in thrombus probably due to the infiltration of inflammatory cells, which can cause a false positive result in FDG-PET imaging [17,18]. This is a rarity, and accurate diagnosis was not obtained due to limited morphological information. In such a case, contrast material is helpful, but prior anticipation of accumulation in the thrombus may prove difficult, therefore the use of IV contrast should be considered when the possibility of uptake in the thrombus is suspected.

There are certain limitations in this study. Strictly speaking, we did not compare the difference between PET/CT with contrast and PET/CT without contrast in this investigation, but compared between PET plus low-dose CT without contrast and PET plus full-dose CT with contrast. It would have been more appropriate to compare PET plus full-dose CT without contrast and PET plus full-dose CT with contrast in order to investigate the clinical value of IV contrast. However, the diagnostic performance of PET plus full-dose CT without contrast should be better than PET plus low-dose CT without contrast. As the diagnostic performance of PET plus low-dose CT without

contrast and PET plus full-dose CT with contrast was comparable, PET plus full-dose CT without contrast should have the same diagnostic ability. Furthermore, final diagnoses were obtained by clinical follow-up including imaging tests.

Histopathological examination was not conducted due to an ethical issue; therefore

sensitivity of the scanning methods may have been overestimated. Finally, no

significant difference of sensitivity was observed between PET/IdCT and PET/ceCT, but

it might be because the number of extra-nodal lesions was small in our population, i.e.

five for monitoring therapy and eight for restaging or follow-up. As extra-nodal sites

ref #2-4

involved by lymphoma, stomach, bowel, liver, lung, and bone are representative organs.

ref #1-1

It is reported that PET/ceCT was more accurate and helpful for evaluating hepatic

lesions, compared to PET/IdCT, although it was a study for liver metastasis from

colorectal cancer [19]. According to our previous data, even extra-nodal lesions were

accurately diagnosed by PET, not by CT with contrast [16], but further investigations

with more cases of extra-nodal lesions is required to conclude that PET/Id CT would be

sufficient for cases with extra-nodal lesions.

Conclusions

PET/ceCT is useful in particular clinical situations, yielding higher diagnostic accuracy,

but cases where accurate diagnosis was obtained only via PET/ceCT were limited. For the purpose of monitoring therapy, the diagnostic performance was comparable between the two methods. IV contrast is not always necessary for post-therapeutic surveillance of malignant lymphoma when PET/CT is available, and should be considered only for use in certain undeterminable cases.

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Table 1. Patients' characteristics.

Male : Female	69 : 53
Age (y)	
Range	18 - 89
Mean	61
Purpose of scanning	
Monitoring therapeutic response	57
Restaging or follow-up	89
Histopathology	
Diffuse large B-cell lymphoma	63
Follicular lymphoma	17
Hodgkin lymphoma	8
Peripheral T-cell lymphoma	6
MALT lymphoma*	5
Extranodal NK/T-cell lymphoma, nasal type	4
Nodal marginal zone B-cell lymphoma	2
Mediastinal (thymic) large B-cell lymphoma	2
Angioimmunoblastic T-cell lymphoma	2

Precursor T-lymphoblastic leukemia	2
Anaplastic large cell lymphoma	2
Burkitt's lymphoma	1
Intravascular large B-cell lymphoma	1
Unknown	7
Prior treatment	
Chemotherapy	94
Chemoradiation therapy	21
Radiation therapy	4
Surgery and chemotherapy	2
Surgery only	1

*: Extranodal marginal zone B-cell lymphoma

Table 2. The number of patients for whom each method described the following involved areas.

Area	Cervical	SC	Axilla	Med	Paraaortic	Iliac	Inguinal	Mesenteric	Abd	Ex-nodal
PET+IdCT	9	3	3	5	5	4	3	9	4	5
PET+ceCT	9	3	3	5	5	4	3	9	4	5

Note. SC, Supraclavicular; Med, Mediastinal; Abd, Abdominal; Ex-nodal, Extra-nodal.

"Abd" included all abdominal nodal lesions except paraaortic, iliac or mesenteric nodes, e.g. hepatic hilar node.

Table 3. The Number of Patients for Whom Each Method Described the Following Involved Areas.

Area	Cervical	SC	Axilla	Med	Paraaortic	Iliac	Inguinal	Mesenteric	Abd	Ex-nodal
PET+IdCT	10 (2)	8 (1)	2 (0)	7 (1)	5 (0)	8 (1)	4 (0)	6 (0)	2 (0)	7 (1)
PET+ceCT	10 (2)	8 (1)	2 (0)	7 (1)	5 (0)	7 (0)	4 (0)	6 (0)	2 (0)	8 (1)

Note. SC, Supraclavicular; Med, Mediastinal; Abd, Abdominal; Ex-nodal, Extra-nodal.

"Abd" included all abdominal nodal lesions except paraaortic, iliac or mesenteric nodes, e.g. hepatic hilar node.

The number in parentheses demonstrates the number of false positive results

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Figure legends

Fig. 1.

An 81-year-old male with central nervous system involvement of recurrent malignant lymphoma. Axial slices of ldCT (A), fused image of ldCT with PET (B), PET (C), ceCT (D) and fused image of ceCT with PET (E) are demonstrated. A moderate uptake is observed in the posterior part of the pons (C: arrow), which was missed following interpretation of PET/ldCT scans. The accumulation corresponds to the enhanced mass on CT with contrast (D: arrowhead), and relapse of lymphoma was diagnosed via interpreting PET/ceCT.

Fig. 2.

A 44-year-old male who had been treated for anaplastic large cell lymphoma underwent a PET/CT scan for restaging. A coronal slice of ceCT (A), an axial slice of PET (B), ldCT (C), a fused image of ldCT with PET (D), ceCT (E), and a fused image of ceCT with PET (F) are demonstrated. A focal intense uptake was seen around the right iliac region (B: arrowhead), which was read as positive for relapse in interpreting PET/ldCT. Intravenous thrombus was demonstrated corresponding to the uptake by ceCT (A:

arrow), and the patient was treated with anticoagulant drugs.



