# Evaluation of lung lesions using FDG γ-camera PET equipped with a one-inch crystal

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**Abstract.** The aim of this study was to evaluate the clinical value of 18-fluorodeoxyglucose (FDG) imaging with γ-camera positron emission tomography (GCPET) equipped with a one-inch crystal for diagnosing lung lesions and determining the stage of non-small cell lung cancer (NSCLC) in regions with a high prevalence of inflammatory disease and tuberculosis. FDG-GCPET was used to examine 103 patients with suspected malignant lesions in the lung. The results of FDG-GCPET and conventional workup (CWU) including computed tomography (CT), ultrasonography and radionuclide bone scintigraphy were compared. The final diagnosis was based on the results of a histological analysis or follow-up of at least six months. The results showed 82 patients with malignant and 21 patients with benign lesions. If a lesion to background ratio ≥2.0 was used as the threshold, then the diagnostic sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of FDG-GCPET for NSCLC were 93.9, 57.1, 86.4, 89.5 and 70.6%, respectively. In 36 patients who underwent open-chest surgery, the diagnostic positive values of FDG-GCPET and CT for lymph-node involvement were 85% (17/20) and 65% (13/20), respectively. The diagnostic sensitivity, specificity, accuracy, PPV and NPV of FDG imaging were 85, 81.3, 83.3, 85 and 81.3%, respectively compared to the CT values of 65, 75, 69.4, 76.5 and 63.2%, respectively (NS). For the evaluation of distant metastases, 31 true-positive patients were identified during the follow-up. FDG imaging correctly identified 28 patients compared to 25 by CWU. In conclusion, FDG imaging with GCPET equipped with a one-inch crystal revealed a high lesion detection capability but a low level of clinical effectiveness for differentiating between malignant and benign lesions in the lung in regions with a high prevalence of inflammatory disease and tuberculosis. For N and M staging of NSCLC, this method may provide additional data that are not available from the CWU.

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## Introduction

[18F]-fluorodeoxyglucose (FDG) imaging has been widely used to evaluate patients suspected of having non-small cell lung cancer (NSCLC) including diagnosis of the primary lesion and assessment of the extent of locoregional and metastatic spread (1). Although FDG imaging using dedicated positron emission tomography (dPET) has shown a high diagnostic accuracy, it is an expensive modality. Consequently, its application has not been widespread even in developed countries. γ-camera PET (GCPET) is a less expensive alternative for clinical positron imaging with 18F-FDG. Although its counting-rate and sensitivity are slightly lower than the dPET scanner, previous studies performed with 18F-FDG and GCPET equipped with 5/8- or 6/8-inch NaI(Tl) crystals have shown a close correlation with dPET results for the detection and staging of lung cancer and other malignant tumors (2-6). There are more GCPET than dPET imaging systems in China although the latter may increase in the future. GCPET equipped with a one-inch crystal has a higher counting-rate and an increased sensitivity in the detection of lesions than with thinner crystals (7). However, few reports have described the use of FDG imaging with GCPET equipped with a one-inch crystal for the evaluation of lung lesions (8,9). Since FDG is not a cancer-specific agent, in regions of granulomatous disease or in a tuberculosis-endemic country, 18F-FDG PET may show high false-positive rates and thus a low specificity (10,11). The aim of this study was to evaluate the clinical value of FDG imaging with GCPET equipped with a one-inch crystal for the diagnosis of lung lesions and staging of lymph

node and distant metastases in NSCLC patients in regions with a high prevalence of inflammatory disease and tuberculosis.

## Materials and methods

*Patients*. All patients referred for a GCPET evaluation of lung lesions between November 2002 and December 2006 were analyzed retrospectively. Patients with small cell lung cancer were excluded from this study. This study included 103 patients whose diagnoses of lung lesions were unequivocal. A clinical diagnosis of primary lesions was confirmed either histologically or by follow-up. CT scans that showed smaller lesions or no change in the appearance of the lesions during a period longer than six months indicated that the lesion was benign. Patients who were pregnant or lactating were excluded from the study. Patients whose blood glucose reading was >11 mmol/l on the day of the study were deemed unsuitable and another appointment was scheduled.

The conventional workup (CWU), including a chest CT scan, radionuclide bone scintigraphy and ultrasonography of the abdomen and pelvis, was performed using standard procedures to detect the locoregional lymph node and distal metastases. The results of these examinations were compared with those of the FDG-GCPET scans.

Table I. Clinical characteristics.

| Characteristic | No. |
|---|---|
| Male/female[a] | 77/26 |
| Age (years) | 61±11 (34-83) |
| Tumor size (cm) | 3.8 (1-10) |
| Tumor size <1.5 cm[a] | 8 |
| Histological results[a] | 98 |
| Squamous cell carcinoma | 38 |
| Adenocarcinoma | 32 |
| Large-cell carcinoma | 6 |
| Bronchoalveolar carcinoma | 3 |
| Other types of carcinoma | 3 |
| Non-specific inflammation | 7 |
| Inflammatory pseudotumor | 2 |
| Tuberculoma | 4 |
| Hamartoma | 1 |
| Thymoma | 1 |
| Vasculoendothelioma | 1 |

[a]No. of evaluated patients, n=103.

*Patient preparation and the FDG-GCPET procedure*. Patients who underwent FDG imaging fasted overnight. Their glucose level was recorded before the examination. Patients rested in a quiet room for 40-60 min prior to an intravenous injection of 148-259 MBq (4-7 mCi) FDG.

All images were acquired on a GCPET scanner (E.Cam$^{deut}$, Siemens, Knoxville, TN, USA) equipped with a one-inch (25.4 mm) NaI(Tl) crystal that was placed into coincidence mode for acquisition. The axial field of view was 38 cm and the slice thickness was ~4.8 mm. The emission scan was started 60 min after the intravenous injection of FDG. Patients were scanned in two bed positions: over the pelvis/abdomen and then over the chest/neck. The acquisition matrix was 128x128, and the total acquisition time of the two bed positions was 45 min when using a circular orbit with 64 views for one bed position at 20 sec per view. The images were reconstructed with the ordered subset expectation maximization (OSEM) algorithm (two iterations with six ordered subsets). The random correction technique was used and no attenuation correction was performed in this study.

*Image interpretation*. Primary tumors, metastatic lymph nodes and metastatic distant lesions observed in the FDG images were analyzed visually. The lesion to background count (L/B ratio) was calculated for the primary tumors and metastatic lymph nodes, but not the distant metastatic lesions. Two independent nuclear medicine physicians blinded to the patient data or results of other imaging modalities interpreted the images independently. In cases of disagreement, the final decision was reached by consensus. A focal increased uptake of FDG in the surrounding normal tissue was interpreted as positive. The L/B ratio was then calculated.

The results of the FDG imaging and CT with respect to the locoregional metastatic lymph nodes were compared with each other and then with the final diagnosis based on the histopathological findings. The results of the FDG imaging and CWU with respect to the distant metastases were compared for each lesion identified in the FDG imaging field and then with the final diagnosis based on the follow-up.

*Final lymph node staging and confirmation of distant metastasis*. The final lymph node staging was based on a histological analysis. Thoracotomy (n=36) was usually performed within two weeks of FDG imaging and CT examination in resectable patients. The lymph nodes were removed and metastasis of the lymph nodes was confirmed by a pathological examination according to standard protocol. Briefly, the lymph nodes were fixed in formalin and embedded in paraffin. Then, 4 $\mu$m sections were cut and stained with hematoxylin and eosin. The classification of lymph node metastases was based on the ATS-LCSG map (12). The final diagnosis of distant metastasis that was detected by the FDG imaging and/or CWU was confirmed by a six-month follow-up. A hypermetabolic FDG lesion was considered to be true-positive for malignant involvement if it was resolved after therapy or was shown to have progressed by follow-up FDG imaging or other imaging. An FDG-negative CWU lesion was considered to be true-negative if it showed stability in size by conventional imaging follow-up for at least six months, or remained negative with repeated FDG imaging.

*Statistical analysis*. The L/B values are shown as mean ± SD. Statistical analysis for comparison of the L/B values between malignant and benign lesions was performed using Student's t-test.

The results of the FDG imaging for the diagnosis of primary tumors and the results of the FDG imaging and CT for evaluation of the locoregional lymph node metastasis were

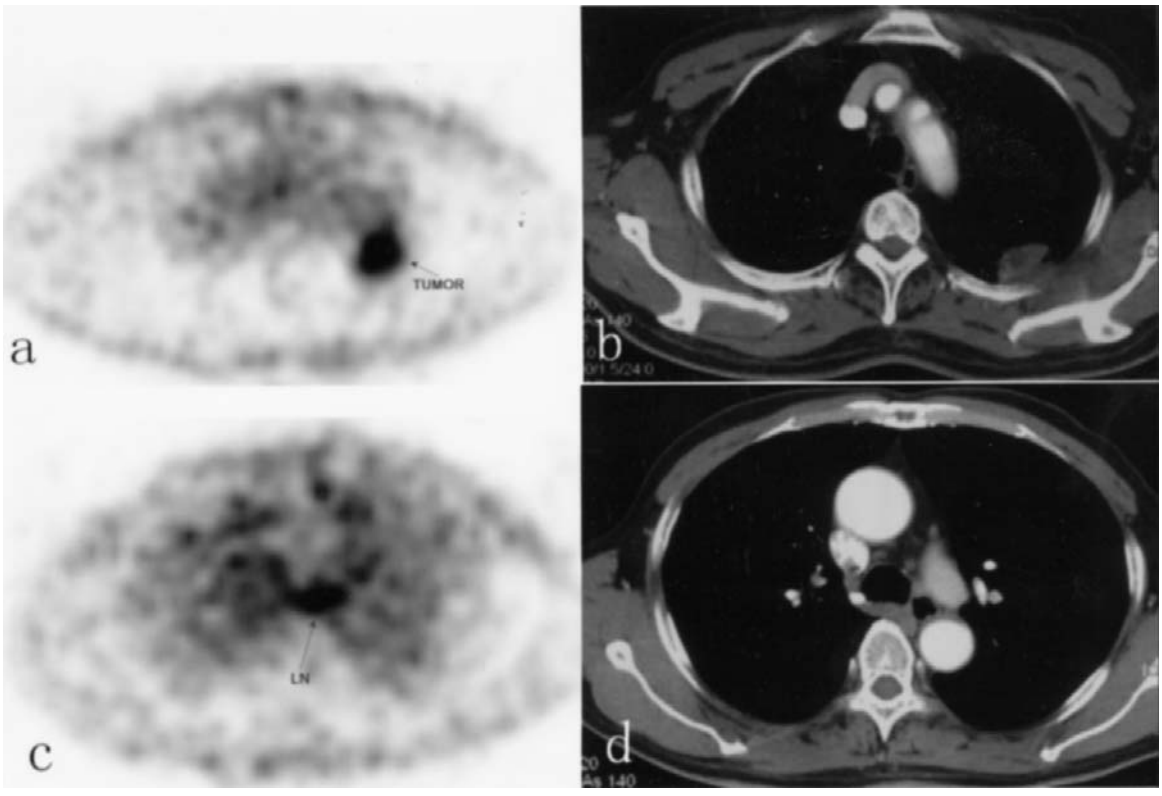


Figure 1. Images of squamous cell carcinoma in the left upper lobe of GCPET (a) and CT (b) in a 45-year-old man. The superior mediastinal lymph node metastasis is seen in GCPET (c, arrow) and confirmed histologically, which is uncertain in the CT (d).

classified into true-positive, true-negative, false-positive or false-negative with respect to the final diagnosis. From these data, sensitivity, specificity, accuracy, PPV and NPV were calculated. Differences in the data obtained by FDG imaging and the CT were statistically analyzed using McNemar's test. A value of $p<0.05$ was considered to be statistically significant.

## Results

Histological diagnoses of 98 out of the 103 (95.1%) patients were obtained by bronchoscopy in 21 patients, CT-guided biopsy in 33 patients and open-chest surgery in 44 patients. The other 5 patients were diagnosed during follow-up. There were 82 patients with NSCLC (all histologically confirmed) and 21 patients with benign lesions (16 based on the histological diagnosis and 5 during follow-up). The lesion size was determined from a pathological evaluation after surgery (44 patients) or from the CT scans (59 patients). The clinical characteristics of the patients and histological results are shown in Table I.

*Evaluation of lung lesions*. The L/B ratio of malignant (n=82) and benign lesions (n=21) was 4.40±1.96 (range, 1.0-11.63) and 2.57±1.65 (range, 1.12-7.01), respectively (t=3.93, $p<0.01$). When an L/B ratio ≥2.0 was used as the threshold, 86 positive patients were identified by FDG imaging including 77 patients with malignant lesions (Fig. 1) and nine patients with benign lesions (Fig. 2). Seventeen negative patients were identified by FDG imaging including 12 patients

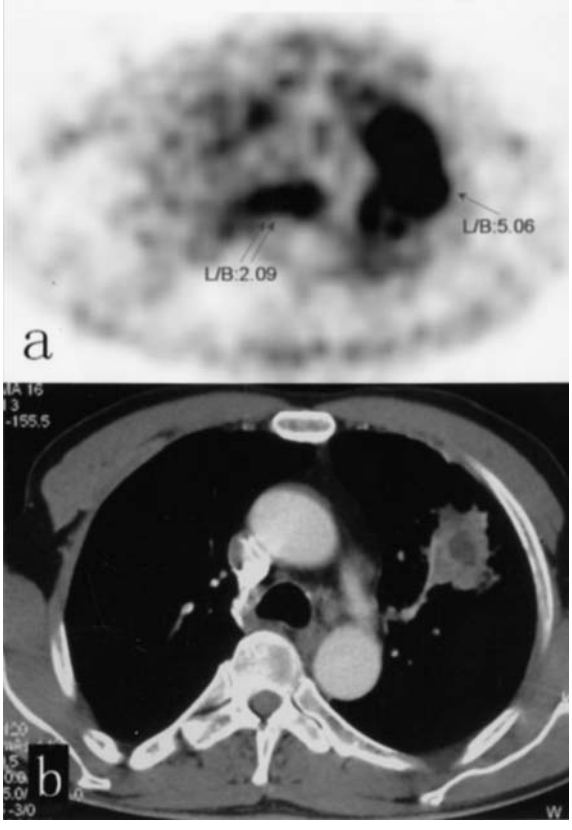


Figure 2. False-positive GCPET in a 56-year-old man with a pulmonary abscess. GCPET (a) shows a high accumulation of FDG in the left upper lobe (arrow, L/B:5.06). The CT (b) shows a large mass in the left upper lobe.

Table II. Diagnostic rates for the detection of malignant lung lesions and regional lymph nodes.

| Cancer type | Prevalence | Sensitivity (%) | Specificity (%) | Accuracy (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| Primary lung lesion (n=103)[a] | 82 | 93.9 | 57.1 | 86.4 | 89.5 | 70.6 |
| Regional lymph nodes (n=36)[a,b] | 20 | | | | | |
| CT | | 65 | 75 | 69.4 | 76.5 | 63.2 |
| GCPET | | 85 | 81.3 | 83.3 | 85 | 81.3 |

[a]No. of evaluated patients. [b]No statistically differences were found between CT and GCPET (McNemar test).

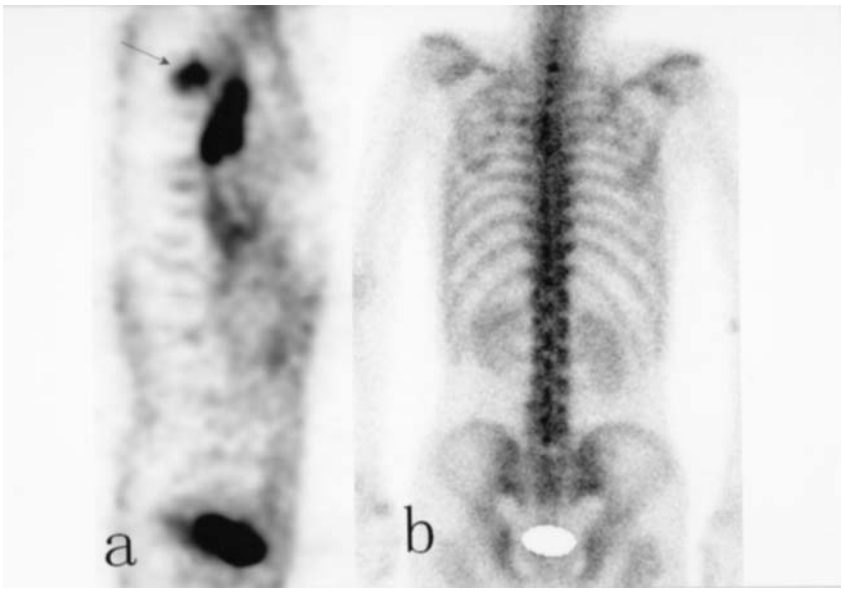


Figure 3. Thoracic vertebra metastasis (arrow) and mediastinal lymph-node metastases were detected in GCPET (a) in a patient with adenocarcinoma of the left lung, but the thoracic vertebra was not abnormal in radionuclide bone scintigraphy (b).

with benign lesions and five patients with malignant lesions. The diagnostic rate is shown in Table II. The average lesion size of the false-negative patients with NSCLC was 2.1 cm (ranges, 1.2-3 cm), with only one lesion <1.5 cm. The histological tumor types were adenocarcinoma (n=2), bronchoalveolar carcinoma (n=1), large cell carcinoma (n=1) and carcinoid (n=1). Nine false-positive patients were identified including patients with tuberculoma (n=4), pulmonary abscess (n=3) and inflammatory pseudotumor (n=2).

*Evaluation of lymph node involvement*. The lymph node staging determined by CT and FDG imaging was compared only in the group of patients that underwent open-chest surgery. Thirty-six patients with NSCLC underwent lobectomy and ipsilateral lymphadenectomy. Regional lymph node metastasis was identified by a histological examination in 20 patients (N1=10, N2=10). If an L/B ratio ≥1.5 was used as the threshold of lymph node involvement, the diagnostic positive rate of FDG imaging and CT were 85% (17/20) and 65% (13/20), respectively. The diagnostic effects of GCPET and CT are shown in Table II. No statistically significant differences in sensitivity and specificity were observed between GCPET and CT ($p<0.05$). FDG imaging and CT results did not correlate in 13 patients (Fig. 1). Of these 13 patients, FDG imaging was correct in eight patients, whereas the CT was correct in three patients. The two methods gave incorrect diagnoses in two patients. N3 lymph nodes were not obtained from this group of patients.

*Evaluation of distant metastasis*. Of the NSCLC patients, 37 were diagnosed with distant metastases based on FDG imaging and/or CWU. Based on the follow-up, 31 patients were true-positive. FDG imaging gave correct diagnoses in 28 patients compared to 25 after CWU. FDG imaging and CWU findings were coincidental in 22 patients with 21 identified as true-positives and one patient identified as a false-positive. In eight patients with positive FDG imaging results but negative CWU results, six patients were true-positive (Fig. 3) and two were false-positive. In six patients with positive CWU and negative FDG imaging results, three patients were true-positives and three were false-positives.

## Discussion

dPET has been shown to be a very effective modality for clinical positron imaging with FDG. However, the high cost

involved in the implementation and operation of a PET scanner has hindered its widespread use (2). GCPET is a less expensive alternative for clinical positron imaging with FDG. In our study, we used GCPET equipped with a one-inch crystal for FDG imaging in patients with lung lesions. We found that the sensitivity, specificity and accuracy for the diagnosis of NSCLC were 93.9, 57.1 and 86.4%, respectively. In addition, using this method we detected 5/6 NSCLC lesions that were <1.5 cm. The false-negatives obtained in this study were mainly related to histological types such as bronchoalveolar carcinoma, carcinoid and adenocarcinoma. The high level of sensitivity demonstrated its efficacy in detecting lung lesions which is in agreement with previous reports (3,13). The main disadvantage of GCPET is that it is slightly less sensitive than dPET for the detection of smaller lesions (4), even though the overall correlation of the two procedures is good in terms of clinical effectiveness and disease staging (5). This disadvantage may be overcome by thickening the crystal. Even-Sapir *et al* (9) showed that the number of accepted coincidence events of a one-inch NaI(Tl) crystal was 4-5 times higher than when using a 5/8-inch crystal (5.12±1.46 vs. 1.27±0.36 million). Furthermore, of the 59 lesions detected by GCPET equipped with a one-inch crystal, only 54 were detected by GCPET equipped with a 5/8-inch crystal.

FDG is not a cancer-specific agent. For example, activated inflammatory cells that have markedly increased glycolysis have been shown to have a high FDG uptake (14). In our study, the specificity of FDG imaging was low (57.1%) and 9/21 patients with benign lesions were incorrectly diagnosed with malignant lesions. These false-positive cases were due to inflammatory processes (tuberculosis and non-specific inflammatory diseases), which are a common cause of high false-positives in FDG imaging and independent of the equipment being used (10,11). In our study, among the 16 histologically confirmed patients with benign lesions, 13 (81%) were inflammatory lesions. This feature of FDG imaging reduces its clinical value for differentiating benign from malignant lesions in regions with a high prevalence of tuberculosis and inflammatory disease.

Establishing the N and M stages of NSCLC determines the course of treatment to be pursued in individual patients and is the primary prognostic factor. The use of CT, a routine non-invasive method for lymph node staging, is limited since the primary criterion for the detection of malignant lymph nodes is based on size (16). It has been shown that metastatic lymph nodes can be detected accurately by FDG-dPET (17). Furthermore, FDG-dPET was found to be more accurate than CT (17). The detection of lymph node metastases <1.5 cm is very difficult by GCPET. However, in this study, we found that the sensitivity of FDG-GCPET imaging when staging N0-N2 lymph nodes was relatively high (85%) compared to CT (65%). These results indicated that GCPET equipped with a one-inch crystal may play an important role in staging lymph nodes in NSCLC as previously reported (3,6). In our study, the specificity and accuracy of FDG imaging were 81.3 and 83.3%, respectively, compared with 75 and 69.4%, respectively for CT. The high level of specificity may be due to patient selection, since all the patients involved in the N-stages study underwent surgery. In addition, some false-positive patients were excluded from the study before surgery. The data obtained here suggest that a combination of FDG imaging and CT is necessary to improve the accuracy of lymph node staging. CT provides the localization information and improves specificity, especially in a tuberculosis-endemic region (10).

Although CWU such as contrast CT, radionuclide bone scintigraphy and ultrasonography is thought to be the simplest and most cost-effective means of confirming the presence of distant metastases in lung cancer, some studies suggest that FDG-dPET is the most accurate non-invasive technique currently available (18). Our study showed that FDG imaging using GCPET may also be sensitive in detecting distant metastases. FDG-GCPET detected 28/31 patients with distant metastases compared with the detection of 25/31 patients by CWU. Of the 31 patients, distant metastases were detected by FDG-GCPET and CWU in 21 patients, by FDG imaging alone in six patients and by CWU alone in three patients. These results suggested that GCPET was more sensitive in some patients, whereas CWU was more sensitive in others. In our study, we only compared lesions that were detectable in the GCPET fields between the neck and pelvis, i.e. the head and lower limbs were excluded. MRI is reportedly superior to FDG-PET for the detection of brain metastatic tumors (19). Thus, our data suggest that GCPET in combination with CWU is required for the detection of distant metastases. Considering the relatively lower cost of GCPET compared to dPET, our study suggests that FDG-GCPET is a suitable method for detecting distant metastases in patients with NSCLC. Furthermore, FDG-GCPET may play a complementary role in the identification and delineation of metastasis.

In conclusion, FDG imaging with GCPET equipped with a one-inch crystal showed a high lesion detection capability but low clinical effectiveness for differentiating the diagnosis of lung malignant and benign lesions in regions with a high prevalence of granulomatous disease and tuberculosis. For the N and M staging of NSCLC, GCPET may provide additional information that cannot be obtained by CWU. The low cost of FDG-GCPET means that FDG imaging is a suitable modality for the evaluation of malignant lesions, particularly in regions where dPET is unavailable or too expensive for the patient.

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