High Performance of ^{18}F -Fluorodeoxyglucose Positron Emission Tomography and Contrast-Enhanced CT in a Rapid Outpatient Diagnostic Program for Patients with Suspected Lung Cancer

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Key Words

Diagnostic service · Lung cancer · Lung cancer diagnosis · Lung cancer imaging · PET imaging in lung cancer · PET/CT fusion imaging · Pulmonary neoplasm · Rapid outpatient diagnostic program

Abstract

Background: The diagnostic evaluation of patients presenting with possible lung cancer is often complex and time consuming. A rapid outpatient diagnostic program (RODP) including ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) and contrast-enhanced computed tomography (CT) as a routine diagnostic tool may improve timeliness, however the diagnostic performance of such a combined approach of RODP remains unclear. **Objectives:** We evaluated timeliness of care and diagnostic performance of FDG-PET and contrast-enhanced CT (FDG-PET/CT) in an RODP for all patients referred with a chest X-ray suspicious of lung cancer. **Methods:** Charts of patients referred to the 2-day RODP of our tertiary care university clinic after an abnormal chest X-ray between 1999 and 2009 were reviewed. Between 1999 and 2005 co-registered FDG-PET and CT imaging took place; from September 2005 onwards, a hybrid system was used. We analyzed timeliness of care and diagnostic performance of FDG-PET/CT to differentiate malignant from benign lesions. **Results:** In 386 patients available for analysis, 260 were diag-

nosed with lung cancer and 23 had another type of malignancy; in 78 patients benign disease was confirmed, and in another 45 the diagnosis was not pathologically confirmed but a median 24.5-month follow-up confirmed a benign outcome. Sensitivity, specificity, negative and positive predictive values and accuracy of FDG-PET/CT to differentiate lung cancer from benign disease were 97.7, 60.2, 92.5, 84.0 and 85.8%, respectively. Lung cancer patients had a median referral, diagnostic and therapeutic delay of 7, 2 and 19 days, respectively. **Conclusions:** FDG-PET/CT in an RODP setting for suspected lung cancer has high performance in detecting cancer and facilitates timely care.

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Introduction

Lung cancer is the leading cause of cancer-related death in both men and women. The 5-year survival rate in the western world of the various types of lung cancer combined is approximately 16% and has not significantly improved in the last decade [1] despite constant new diagnostic and therapeutic developments. Obtaining a correct lung cancer diagnosis and stage is complex and may require multiple modalities such as ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET), computed tomography (CT), bronchoscopy, endoscopic ul-

trasound, CT-guided biopsy, and sometimes many more. In clinical practice, this has a tendency to negatively influence timeliness of lung cancer care. Many interventions have been reported to improve diagnostic delay, such as implementation of urgent referral guidelines [2], multidisciplinary meetings [3–5], nurse-led care [6] or two-stop pathways [7, 8]. The latter seems to have the most success in improving timeliness of care [9]. From a patient's point of view, shortening diagnostic delay can reduce emotional distress in suspected cancer [10–13]. Moreover, although many patients suspected of cancer eventually have a benign outcome, they do share the distress of diagnostic evaluation.

In an effort to improve the rapidity of the diagnostic process, a 2-day rapid outpatient diagnostic program (RODP) for patients with a radiological suspicion of lung cancer was implemented in the Radboud University Nijmegen Medical Center in 1999. As a first diagnostic step in all patients, we implemented in this RODP both FDG-PET and contrast-enhanced CT (FDG-PET/CT), a novel combination at that time that proved to be a superior imaging technique in lung cancer staging [14–17] compared to either FDG-PET with low-dose CT or CT alone. In a modest sample size, Aukema et al. [18] have already demonstrated that FDG-PET/CT within an RODP was feasible with a good negative predictive value (NPV) of 92% and a positive predictive value (PPV) of 77%. To our knowledge, the effect of an RODP including FDG-PET/CT on timeliness of care has not been described yet. The aim of this study was to assess the diagnostic performance of FDG-PET/CT as a first-line diagnostic tool and the effect on timeliness of care on patients referred to our RODP based on an abnormal chest X-ray.

Patients and Methods

Patients

A retrospective chart review was conducted in all 570 consecutive patients referred to the RODP between August 1999 and April 2009 after regional ethics committee approval. We selected all cases where referral was based on a chest X-ray to prevent bias of referring highly suspected patients and to facilitate comparison with the usual referral pattern. On referral, outpatients with a radiological suspicion of lung cancer (e.g. a nodule, mass, hilar enlargement or widened mediastinum) without clinical need for hospitalization or evident stage IV disease were selected by a respiratory physician to enter the RODP. Patients then underwent a full diagnostic workup (table 1) in 2 days comprising blood analysis, FDG-PET scanning, diagnostic CT scanning, electrocardiography, pulmonary physician consultation, pulmonary function testing on the 1st day, followed by bronchoscopy and disclosure of the cytology results on the 2nd day. In case of benign results on

Table 1. RODP schedule

Day 1 (Wednesday)
Laboratory investigation, electrocardiogram
¹⁸ F-DG injection
¹⁸ F-DG-PET/CT
Multidisciplinary evaluation of PET/CT
Pulmonary function testing
Chest physician visit, physical examination, report of PET/CT results (first 2 patients)
Day 2 (Thursday)
Physician visit, physical examination, report of PET/CT results (second 2 patients)
Bronchoscopy
Report of cytology results

FDG-PET/CT, bronchoscopy was cancelled. If further diagnostic or staging procedures were necessary, they were performed in a regular setting outside the RODP.

FDG-PET/CT

All patients underwent a whole-body FDG-PET. Prior to FDG injection, patients fasted for at least 6 h. Intake of sugar-free liquids was permitted. Patients were hydrated with 500 ml of water immediately prior to the procedure and 60 min after intravenous injection of approximately 250 MBq FDG (Covidien, Petten, The Netherlands) and 10 mg furosemide. Images were acquired from the area between the proximal femora to the base of the skull. Until September 2005, PET scans were acquired on an ECAT-EXACT full-ring PET scanner (Siemens/CTI, Knoxville, Tenn., USA) using 3-dimensional (3D) emission for 10 min per bed position and employing attenuation correction based on 2D ⁶⁸Ge transmission images for 2 min per bed position. PET scans were reconstructed using an iterative 2D ordered subset expectation maximization algorithm using two iterations, eight subsets and a 3D gaussian filter of 5 mm. From September 2005 onwards, PET scans were acquired with a hybrid PET/CT scanner (Biograph Duo, Siemens Medical Solutions Inc., Malvern, Pa., USA) containing a 2-slice CT scanner. A low-dose CT scan for localization and attenuation correction purposes was acquired in the caudocranial direction. Scanning parameters included 40 mAs (50 mAs for patient weight >100 kg and 60 mAs for >120 kg), 130 kV, 5-mm slice collimation, 0.8-second rotation time and pitch of 1.5, reconstructed to 3-mm slices for smooth coronal representation. Low-dose CT scans were acquired during timed unforced expiration breath hold. For PET, a 3D whole-body emission scan was acquired during free breathing. The acquisition time per bed position was 4 min for emission only.

A full-dose CT scan with contrast enhancement of the thorax and liver was acquired for diagnostic purposes in all patients. Using a dual-slice spiral CT scanner, thoracic images were acquired in a craniocaudal direction after a delay of 40 s after intravenous contrast injection of 100 ml Optiray 300 (Covidien, Hazelwood, Mo., USA) using care dose referenced at 80 mAs with the following parameters, 110 kV, volume CT dose index 5.36 mGy, rotation time 0.8, slice 3.0 mm with a pitch of 1.5 mm during a single breath hold. Scanning parameters for liver imaging were care dose referenced at 80 mAs, 130 kV, volume CT dose index 8.64 mGy, rotation time

Fig. 1. Flow chart of the study patients. HRCT = High-resolution CT.

Table 2. Cytological or histological diagnosis of all 386 evaluable patients

Pathological diagnosis	n (%)
Lung cancer (all subtypes)	236 (61.1)
NSCLC	212 (54.9)
Adenocarcinoma	96 (24.9)
Bronchoalveolar carcinoma	2 (0.5)
Squamous cell carcinoma	86 (22.3)
Large-cell carcinoma (not otherwise specified)	12 (3.1)
Large-cell neuroendocrine carcinoma	4 (1.0)
Undifferentiated NSCLC	4 (1.0)
Mixed NSCLC subtypes	8 (2.1)
SCLC	22 (5.7)
Mixed NSCLC/SCLC	2 (0.5)
Pulmonary metastasis of other cancer	23 (6.0)
Mesothelioma	4 (1.0)
Benign disease	
Pathologically confirmed as benign	78 (20.0)
No diagnosis, benign at follow-up	45 (11.7)

0.8, slice 3.0 mm with a pitch of 1.5 mm during breath hold. A delay of 12 s was set to automatically shift to the abdominal imaging.

All FDG-PET/CT images were reviewed prior to bronchoscopy in a joint-reading meeting in the presence of a nuclear medicine physician, a radiologist and a pulmonary physician. If FDG uptake was present, reports were reviewed to determine whether extrathoracic metastases or synchronous extrathoracic tumors were detectable in the above-defined areas scanned by diagnostic CT. If FDG uptake was absent, CT findings were reviewed and defined as non-malignant in case of sclerotic bone lesions, nodules with a benign calcification pattern, pleural plaques, infiltrates or mediastinal bulging by goiter, mediastinal fat or cardiomegaly.

Statistical Analysis

Descriptive statistics were used to summarize the demographic data collected. For normally distributed continuous variables means $\pm$ SD and for normally distributed variables medians and interquartile ranges (IQR) were reported. PPV and NPV were calculated. Different delays were defined as follows: the referral delay as the time between the referral (written or by phone) and the first ROPD day, the diagnostic delay as the time between the first ROPD day and the date of final (accurate) diagnosis, and the therapeutic delay as the time between the diagnosis and the start of treatment. All time intervals were calculated in calendar days (including weekends and holidays) if both defining dates had been recorded. All data were analyzed using the Statistical Package for Social Sciences (version 16.0; SPSS, Chicago, Ill., USA).

Results

Demographic Data and Clinical Characteristics

A flowchart of the ROPD patients included in the analysis is shown in figure 1. Of those evaluated in the ROPD between August 1999 and April 2009, we found 565 patients with available charts, of which 386 patients were suitable for analysis and 184 were excluded. Referral based on abnormal radiological investigation other than a chest X-ray was the most frequent reason for exclusion. Most patients were male ($n = 258$, 66.8%) and mean age was 64.3 years (SD 11.0). Referral was initiated by a general practitioner in 194 patients (50.3%), and in the remainder (192 patients) by a specialist consultant. The majority of patients ($n = 367$, 94.0%) had an Eastern Cooperative Oncology Group performance status of 0 or 1, and 37 patients (9.6%) suffered from diabetes mellitus. Cytological or histological results are described in table 2. Pathological diagnosis was obtained by ROPD bronchoscopy in 196 cases (50.8%). Other diagnostic procedures were CT-guided needle biopsy (23, 6.0%), thoracotomy or thoracoscopy (73, 18.9%), mediastinoscopy (24, 6.2%), endoscopic ultrasound (10, 2.6%) or a second bronchoscopy (5, 1.3%). In 236 patients (61.1%), a final diagnosis of lung cancer was made all subtypes considered [non-small-cell lung cancer

Table 3. Clinical and pathological disease stage (patients with no pathological confirmation before surgery were staged based on imaging and added to the clinical stage category)

NSCLC and SCLC stage		n (%)
Clinical stage (n = 236)	Ia	26 (11.0)
	Ib	31 (13.1)
	IIa	2 (0.8)
	IIb	7 (3.0)
	IIIa	46 (19.5)
	IIIb	42 (17.8)
	IV	80 (33.9)
	Double tumor	2 (0.8)
Pathological stage (n = 83)	Ia	24 (28.9)
	Ib	24 (28.9)
	IIa	1 (1.2)
	IIb	14 (16.9)
	IIIa	8 (9.6)
	IIIb	5 (6.0)
	IV	3 (3.6)
	Double tumor	3 (3.6)
pNx (incomplete pN stage)		1 (1.2)

(NSCLC) and small-cell lung cancer (SCLC) or both]. Twenty-seven patients (7.0%) were diagnosed with malignant pleural mesothelioma or pulmonary metastases of a nonpulmonary tumor. In 78 patients (20.2%), a benign diagnosis was confirmed (predominantly infectious, postinfectious or granulomatous abnormalities). In 45 patients (11.7%), no definite pathological diagnosis could be established, but according to the medical charts no malignancy was reported during a median follow-up of 24.5 months (IQR 17.0–48.5) in any of them. Table 3 describes the clinical and pathological disease stages (according to the TNM6 [19]) and shows that 122 lung cancer patients (51.7%) had clinically advanced (stage IIIb or IV) disease.

Diagnostic Performance of FDG-PET/CT as a First-Line Diagnostic Tool

Performance of FDG-PET/CT was assessed in a cross table for all patients (table 4). For diagnosis of malignancy, sensitivity was 97.7% (95% confidence interval 94.9–99.1%), specificity 60.2% (50.9–68.8%), NPV 92.5% (83.8–96.9%) and PPV 84.0% (79.3–87.8%). Accuracy, defined as the proportion of true results, was 85.8% (81.4–90.0%). Performances of hybrid FDG-PET/CT and separate FDG-PET and CT (before and after September 2005, respectively) were not statistically different.

In 19 cases (4.9%), suspected lesions showed radiologically benign anomalies on CT scan and negative

Table 4. FDG-PET/CT results and final diagnoses of malignancy in the 386 study patients

	Malignant	Benign	Total
PET/CT positive	257	49	306
PET/CT negative	6	74	80
Total	263	123	386

Table 5. CT characteristics in patients with CT-confirmed benign definite findings, n (%)

Total group	386
Definite benign CT findings	32 (8.3)
CT without abnormalities	13 (3.4)
Clearly benign lesion on CT alone	19 (4.9)
Sclerotic bone lesion	7
Calcified nodule	3
Pleural plaque	3
Postinfectious infiltrate	3
Mediastinal mass (goiter, fat or cardiomegaly)	3

FDG-PET (specified in table 5). In another 13 cases (3.1%), abnormalities were absent on FDG-PET or CT. In contrast, FDG-PET revealed metastatic disease in 26 (6.7%) patients (10.8% in the lung cancer patient sample) and a synchronous tumor of other cancer type in 9 patients (2.3% of the total patient group) outside the volume scanned by diagnostic CT. Finally, there were 6 false-negative cases, all with different histology: adenocarcinoma (7 mm), bronchoalveolar carcinoma (5 mm), squamous cell carcinoma (29 mm), malignant pleural mesothelioma (pleural fluid only), pulmonary metastases of ovarian cancer (multiple nodules, largest 12 mm) and adenoid cystic carcinoma (multiple nodules ranging from 15 to 23 mm).

Delays

For the total patient group, the median referral delay was 7 days (IQR 5–10) and the median diagnostic delay was 1 day (IQR 1–15). For patients ultimately diagnosed with lung cancer (NSCLC and SCLC), the median referral delay was also 7 days (IQR 5–9), the median diagnostic delay 2 days (IQR 1–17), and the median therapeutic delay 19 days (IQR 7–28). The median interval between RODP and all therapies spanned 25 days (IQR 18–39); specifically 23 days (IQR 18–32) for surgery, 27 days (IQR 14–41) for chemotherapy and 28 days (IQR 20–50) for radiotherapy.

Discussion

This is so far the largest study evaluating FDG-PET/CT as a frontline diagnostic tool in an RODP setting for suspected lung cancer. We demonstrate that an RODP integrating FDG-PET/CT provides not only excellent diagnostic performance in detecting lung cancer in patients referred with an abnormal chest X-ray but also minimizes diagnostic delay.

RODPs have shown to successfully reduce the diagnostic delay in two other studies that evaluated a two-stop service in suspected lung cancer with delays in presentation to surgery of 5 weeks [7] and to the start of any treatment of 3 weeks [8]. These studies were, however, performed in an era when FDG-PET was not yet (in contrast with today) a standard imaging tool in the diagnostic workup of lung cancer with superior imaging capabilities [14–17]. One would expect the combination of an RODP with FDG-PET/CT to improve the overall diagnostic workup quality in patients with suspected lung cancer. Our results confirm these expectations: with the demonstrated schedule of our RODP, the median time to establish a diagnosis was only 1 day, and treatment was initiated after a median of 25 days. Both these diagnostic and therapeutic delays were shorter than the median 7–37 days for diagnostic [2, 5, 20–28] and 31–104 days for therapeutic delays [4, 23, 29, 30] reported by others without an RODP.

Besides timeliness, our RODP including FDG-PET/CT had an excellent diagnostic performance with high sensitivity in diagnosing malignancy (97.7%). We herewith confirm the earlier results described by Aukema et al. [18] showing good performance of RODP using FDG-PET/CT in diagnosing pulmonary malignancy. In 114 patients referred with an abnormal chest X-ray, they demonstrated similar sensitivity, specificity and accuracy for diagnosing malignancy (97, 56 and 90%, respectively) despite a higher pretest probability of lung cancer (75 vs. 61% in the present study). This difference might be explained by a different referral pattern to their center with a specialized reference oncology status. Specificity was relatively lower in both their and our study (56 and 60%, respectively) and can be explained by the inclusion of patients on the basis of an abnormal chest X-ray. Studies evaluating the accuracy of FDG-PET/CT usually include patients with solitary pulmonary nodules on a CT scan, inherently lowering the probability of infectious or inflammatory disease compared to our selection of patients. FDG-PET/CT then demonstrates equal median sensitivity (97.0%, range 83–100%) but higher specificity (77.8%) [31].

The downside of incorporating both FDG-PET and a diagnostic CT in an RODP setting as a first-line diagnostic tool for all patients referred with an abnormal chest X-ray is that retrospectively in some cases additional imaging with FDG-PET to exclude malignancy might not have been required: In 32 patients (8.3%), malignancy might have been excluded on CT alone as the lesions showed typical benign characteristics. This number is in line with the study by Aukema et al. [18] reporting that around 10% abnormalities could have been judged as benign based on CT alone (asbestos-related benign pleural thickening and residual abnormality after inflammation). However, whether there is actually 'diagnostic overuse' in these cases cannot be judged retrospectively, as in both their and our study FDG-PET and CT images were jointly read. In contrast, in 35 patients (9.1%) FDG-PET/CT had significantly added value as it detected metastases or synchronous tumors outside the chest that would not have been detected by CT alone. This result is in line with prior prospective studies detecting distant metastases in 6–18% of potentially curable lung cancer patients [15, 16, 32–34]. Furthermore, FDG-PET/CT correctly suggested non-lung cancers in 9 RODP patients (2.3%), in line with other studies detecting unexpected synchronous tumors in 1.1–3.3% of cases [35, 36]. Whether detecting unexpected metastatic disease and synchronous tumors by FDG-PET/CT in the RODP counterbalances performing FDG-PET in case of radiologically benign lesions cannot be answered by our study; this should involve comparisons of other factors such as cost-effectiveness [37] and the prevention of futile thoracotomies [15, 35, 38]. Furthermore, there might be a benefit of an RODP in quickly ruling out the possibility of cancer and reducing distress levels [13] that were raised by the chest X-ray. To address these issues, we have performed the multicenter PENELOPE study (Pulmonary Evaluation of Neoplastic Lesions in Outpatients and Psychological Effects) evaluating distress and quality of life in patients with suspected lung cancer during and after their RODP compared to regular stepwise outpatient evaluation. We expect to publish results in 2013.

Conclusion

Our findings add to the limited knowledge available on rapid outpatient programs despite growing interest in the performance of these programs and possible effects on patient distress. Our study shows that in patients referred with an abnormal chest X-ray, an RODP integrating FDG-PET/CT provides excellent diagnostic performance in detecting lung cancer with minimized diagnostic delay.

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