Original article

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# Patients with known or suspected lung cancer: evaluation of clinical management changes due to $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) study

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*Aim* To determine prospectively from the referring physician's point of view the impact of $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) results on the management decisions in patients with known or suspected lung cancer.

*Methods* Seventy-five consecutive patients (58 men, 17 women; age range, 33–82 years; mean age, 64 years) with a diagnosis of a pulmonary lesion, obtained by means of morphological imaging studies and/or cytological sampling, were included in the study. The patient population consisted of three groups: (A) patients ($n=18$) with a solitary lung nodule; (B) patients ($n=37$) with untreated lung cancer; and (C) patients ($n=20$) with treated lung cancer. All were referred for whole-body $^{18}$F-FDG PET within 15 days (mean, 11 days) of lung lesion detection. To determine whether and how PET findings could modify the treatment strategy, a questionnaire was sent to the referring physician before and after the PET results. With regard to the treatment strategy, four major options were recognized: (1) further diagnostic investigations; (2) medical therapy; (3) surgical treatment; (4) wait-and-see. For data analysis, intermodality changes, defined as changes between treatment strategies related to PET findings, were considered.

*Results* Before the PET study, the planned management for the overall patient population was as follows: further diagnostic investigations in 44 cases (58%), medical therapy in 17 (23%), surgical treatment in nine (12%) and wait-and-see in five (7%). After the PET study, further diagnostic tools were indicated in 27 cases (36%), medical therapy in 17 (23%), surgical treatment in 28 (37%) and wait-and-see in three (4%). Relative to the initially planned strategy, changes in patient management after PET imaging occurred in 34 (45%) cases. Overall, the most relevant variation after PET concerned the surgical treatment strategy. The highest percentage (67%) of changes in management after PET was found in patients with a solitary pulmonary nodule; the percentages of changes of the three patient groups were significantly different (chi-squared test; $P=0.021$).

*Conclusions* In patients with known or suspected lung cancer, $^{18}$F-FDG PET results determined significant variations in major clinical management decisions. *Nucl Med Commun* 26:831–837 © 2005 Lippincott Williams & Wilkins.

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## Introduction

Lung lesions are a common finding in clinical practice [1,2]. In patients with pulmonary lesions, accurate pretreatment evaluation is a key requisite for choosing the appropriate therapeutic pathway [1,2]. The current primary diagnostic tools for these patients are conventional X-ray examination and computed tomography (CT), which can, however, show a range of possible imaging patterns characterized by indefinite or aspecific findings [3–5]. Therefore, although conventional imaging modalities are sensitive to morphological changes, lesion characterization can be difficult in certain settings. Many lesions that are indeterminate after conventional radiography, CT or magnetic resonance imaging (MRI) evaluation may require histological sampling with a transthoracic needle aspirate or by other invasive procedures, such as bronchoscopy or thoracotomy, for definite diagnosis [5–8]. The limitations of morphological imaging modalities, therefore, often make the management of patients with lung lesions somewhat problematic [9–11].

Positron emission tomography (PET) is a non-invasive imaging technique for studying the biochemical and

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metabolic changes in cancer tissue, with tomographic images having a spatial resolution in the range 4–6 mm [12]. PET with the use of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) has been shown to be effective in the identification of malignant tissue in several primary and metastatic tumour types [13,14]. As the PET technique can yield metabolic information, it is helpful for detecting and differentiating lesions when morphological imaging findings are equivocal or inconclusive. However, discrepancies between the functional information provided by $^{18}$F-FDG PET and the morphological information obtained by conventional imaging techniques have suggested that changes in the size or texture of tissues and organs cannot be used as the sole expressions of malignancy [15–18]. The possibilities given by PET imaging in modifying clinical work-up have been evaluated in previous series of cancer patients [19–21].

The present study was designed to determine the influence of $^{18}$F-FDG PET results on the management decisions in patients with known or suspected lung cancer from the referring physician's point of view.

## Materials and methods

### Patient population

Included in this prospective study were eighty-two consecutive patients with lung lesions, managed by the thoracic surgery departments of three university hospitals, who were referred for whole-body PET scanning at our institution between January 2000 and October 2003. Exclusion criteria included the presence of a blood glucose level of more than $140\,mg \cdot dl^{-1}$, a history of diabetes and intolerance to PET examination due to claustrophobia. Before being enrolled in the study, all subjects gave their informed consent to participate in the study. Seven patients were excluded from further analysis because of incomplete data. Thus, seventy-five patients (58 males, 17 females; age range, 33–82 years; mean age, 64 years) remained in the study. All patients had a previous diagnosis of a pulmonary lesion that was obtained, by means of morphological imaging examinations and/or cytological sampling, 9–15 days prior to PET scanning (mean, 11 days). Sixty-seven of the 75 patients included in the study underwent contrast-enhanced CT examination before PET scanning; the remaining eight underwent MRI examination because of their intolerance to the administration of iodinated contrast medium. The patient population was divided into three different groups.

(A) Patients ($n = 18$) with a solitary pulmonary nodule of indeterminate nature, ranging in maximum diameter from 1.5 to 2.7 cm (mean, 1.9 cm), depicted on radiological examination.
(B) Patients ($n = 37$; TNM staging system: 25 with stage IIa and 12 with stage IIb disease) with untreated lung cancer. Of these, 28 had a definite diagnosis set upon cytology: non-small-cell lung cancer ($n = 22$; adenocarcinoma, $n = 14$; squamous cell carcinoma, $n = 8$) and small-cell lung cancer ($n = 6$). The remaining nine patients in this group had a radiological diagnosis of lung cancer without cytological confirmation.
(C) Patients ($n = 20$; TNM staging system: eight with stage IV, seven with stage IIIb and five with stage IIIa disease) with treated lung cancer: non-small-cell lung cancer ($n = 16$; squamous cell carcinoma, $n = 7$; adenocarcinoma, $n = 9$) and small-cell lung cancer ($n = 4$). These patients had previously been treated with radiation therapy ($n = 14$) or chemotherapy ($n = 6$), and underwent PET study to monitor the response to therapy. The time between completion of treatment and PET study was at least 3 weeks (21–39 days; mean, 31 days).

### Computed tomography protocol

CT examinations were performed on a Hi-Speed Advantage scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA) or a Tomoscan-AV scanner (Philips Medical Systems, Best, The Netherlands). The scanners were used in a spiral mode with 2 s scanning times and suspended respiration. The thorax was examined during peak arterial enhancement after the start of an injection of 160 ml of 60% iodinated contrast material (injection rate, $3\,ml \cdot s^{-1}$). The thorax was scanned with 5 mm collimation; spiral CT was performed with a table speed of $5\,mm \cdot s^{-1}$ and a reconstruction thickness of 5 mm.

### Magnetic resonance imaging protocol

MRI studies were performed with a 1.5-T system (GEMS, Horizon Hi-Speed, Milwaukee, Wisconsin, USA). A body coil with a transverse field of view of 50 cm was used to image the thorax. Sagittal T2- and transverse T1- and T2-weighted images were obtained. For T2-weighted turbo spin-echo imaging, repetition times in ms/echo times in ms were 4500–4700/120; for T1-weighted spin-echo imaging, they were 500–600/12–15. The matrix size was $512 \times$ (180–240) pixels. The section thickness was 5–7 mm for transverse and 6 mm for sagittal planes. No gadolinium-based contrast material was administered.

### $^{18}$F-Fluorodeoxyglucose positron emission tomography protocol

The synthesis of $^{18}$F-FDG was carried out with a compact automated module connected to the cyclotron (CTI/Siemens RDS 112 cyclotron, Siemens/CPS, Knoxville, Tennessee, USA); $^{18}$F-FDG was used within 1 h of preparation. Quality control procedures were carried out, and only $^{18}$F-FDG with a radiochemical purity greater than 95% was employed. The $^{18}$F-FDG PET study was performed with a multiring whole-body

positron emission tomograph (GE Advance, General Electric Medical Systems) with a transverse field of view of 55.5 cm, covering an axial field of view of 14.5 cm. This tomograph allows data collection simultaneously from 35 equally spaced transaxial slices, 4.25 mm thick. All subjects were studied in the fasting condition (6 h), and only patients with blood glucose levels of less than 140 $mg \cdot dl^{-1}$ were injected with $^{18}$F-FDG. In addition, all patients were orally hydrated during the $^{18}$F-FDG uptake period and were asked to empty their bladder before positioning on the tomograph bed. Emission imaging started 45 min after an intravenous bolus injection of $^{18}$F-FDG (5.2 $MBq \cdot kg^{-1}$), with the subject lying supine with the arms over the head. Six bed positions, 5 min each, from the pelvis to the base of the head were acquired. The emission scan was followed by a 3-min transmission scan per bed with a $^{68}$Ge/$^{68}$Ga source external to the patient, corresponding to the same range as evaluated by the emission study. Acquisition data were reconstructed using iterative reconstruction and segmented attenuation correction in all studies.

### Image analysis

CT and magnetic resonance images were interpreted by consensus reading by two experienced investigators who did not know the results of the $^{18}$F-FDG PET studies: cross-sectional images on CT or MRI were analysed for the presence or absence of lung parenchymal lesions, lymph nodes in the mediastinum and distant metastases. $^{18}$F-FDG PET studies were not read blind, but were always evaluated within the context of a clinical readout session. Thus, PET images reconstructed in transaxial, coronal and sagittal views, and corrected for attenuation, were visually interpreted by consensus of three experienced nuclear medicine physicians. They had a knowledge of the clinical data and previous imaging findings obtained at conventional X-ray examination and by cross-sectional modalities, such as CT or MRI. An area of increased $^{18}$F-FDG uptake was defined as benign when related to the physiological biodistribution of $^{18}$F-FDG or to a known non-malignant inflammatory process. Any area of focal $^{18}$F-FDG activity with an intensity higher than that of surrounding tissues, and not related to normal physiological or benign tracer uptake, was defined as malignant. Any other area of increased $^{18}$F-FDG uptake that could not be clearly characterized was defined as an equivocal site on PET. The following criteria were adopted to differentiate between benign and malignant lymph nodes located in the hilar or mediastinal region. Lesions that showed intense $^{18}$F-FDG uptake and a nodular shape were defined as malignant, whereas lesions with $^{18}$F-FDG uptake comparable with mediastinal blood activity and lesions with a less circumscribed shape were considered as benign.

### Data collection

To evaluate the impact of PET data on management, for each patient included in the study, an anonymous case report containing all available clinical, imaging (conventional X-rays, CT or MRI) and cytological data was prepared by the coordinator of the study. The case report was submitted to the patient's referring physician, together with a detailed questionnaire (pre-PET questionnaire) which reported the possible work-up options. When the referring physician had returned the pre-PET questionnaire, the complete case report with the PET results was sent to him/her; the corresponding questionnaire (post-PET questionnaire) was attached and the referring physician was asked to complete it accurately. All physicians returned either pre- or post-PET questionnaires. With regard to the clinical management of the patients included in the study, four major strategies were recognized: (1) further invasive diagnostic investigations (tissue sampling procedures such as percutaneous fine needle biopsy or mediastinoscopy with biopsy); (2) medical therapy (various chemotherapeutic treatment protocols); (3) surgical treatment (pulmonary lobectomy or segmentectomy); (4) wait-and-see (mean time, 3 months).

### Data analysis

With regard to data analysis, the management variations considered in the study were the intermodality changes, defined as changes between treatment modalities (e.g. from surgery to medical therapy) which were related to PET imaging results. Intramodality changes, defined as changes within one treatment modality (e.g. from one surgical treatment to another), were not considered for data analysis. To compare the percentages of intermodality changes in the three groups of patients, the chi-squared statistical test was used; $P$ values of less than 0.05 were considered to be statistically significant.

## Results

### Changes in patient management: overall results

Before the PET investigation, the planned management for the overall patient population considered in this study was as follows: further diagnostic investigations in 44 cases (58%), medical therapy in 17 (23%), surgical treatment in nine (12%) and wait-and-see in five (7%). After the PET study, further diagnostic tools were indicated in 27 cases (36%), medical therapy in 17 (23%), surgical treatment in 28 (37%) and wait-and-see in three (4%). In particular, the need for further diagnostic examinations was confirmed after PET imaging in 21 of the 44 cases; of the remaining cases, six, 15 and two were shifted to medical therapy, surgical treatment and wait-and-see, respectively. Of the 17 patients in whom medical therapy was initially suggested, 11 were confirmed by PET, four were shifted to further diagnostic investigations and two were considered as candidates for surgery. Surgical treatment was confirmed in eight of the nine patients after PET; in the remaining case, the change was to further diagnostic investigations. The wait-and-see approach was confirmed after PET in only one of

the five cases; it changed to surgical treatment in three cases and to further diagnostic tools in the remaining case. In total, relative to the initially planned management, intermodality changes were indicated after PET scanning in 34 of the 75 (45%) patients. The overall changes in the initial treatment pathway are summarized in a contingency table which shows that, in our series, the most relevant changes in patient management concerned the surgical treatment strategy (Table 1). Indeed, surgery was indicated in nine (12%) and 28 (37%) of the 75 patients before and after the PET imaging results, respectively.

### Changes in patient management: group results

In group (A), which comprised 18 patients with a solitary lung nodule, the planned management before the PET study was as follows: further diagnostic investigations in 12 cases, medical therapy in none, surgery in one and wait-and-see in five. After PET scanning, changes in management were indicated in 12 of the 18 (67%) patients. In particular, in those patients for whom further diagnostic investigations were initially suggested, PET results did not change the management in five cases, but shifted the management to medical therapy in four, surgery in one and wait-and-see in two. The only patient in this group who was considered a candidate for surgical treatment needed further diagnostic investigations according to the PET results. The wait-and-see approach was confirmed in only one of five cases, with a shift to further diagnostic investigations in one case and surgical treatment in the remaining three. (Fig. 1)

**Table 1 Contingency table of overall changes in management after positron emission tomography (PET) results**

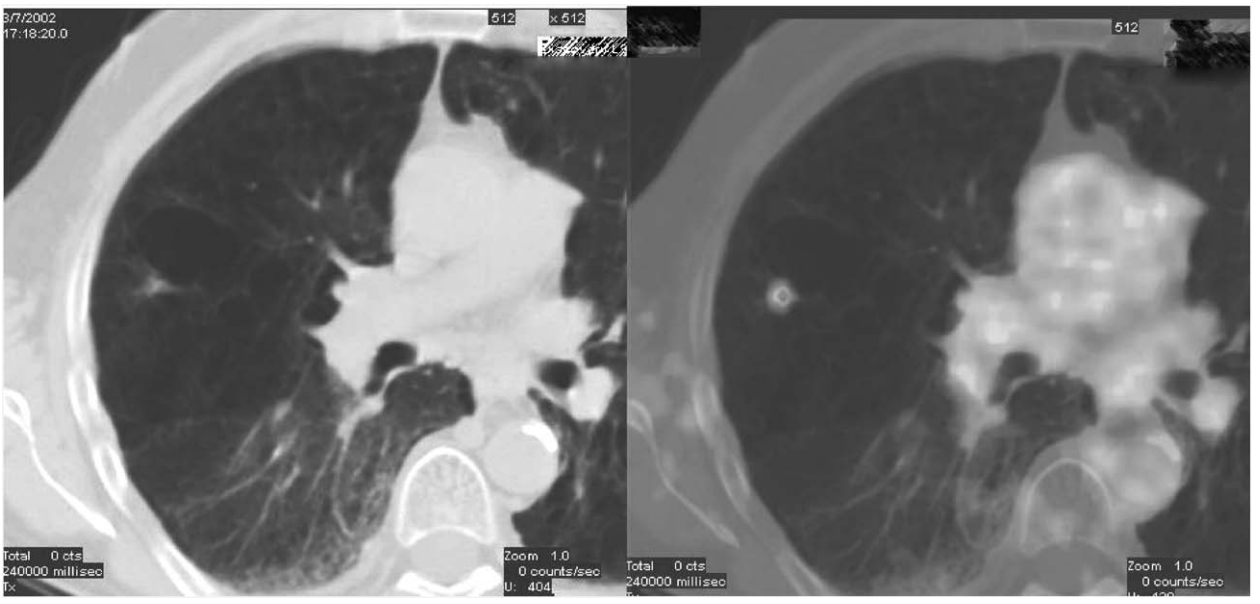
| | POST-PET | | | | |
|---|---|---|---|---|---|
| Pre-PET | FDI | MT | ST | WS | Total |
| FDI | 21 | 6 | 15 | 2 | 44 |
| MT | 4 | 11 | 2 | 0 | 17 |
| ST | 1 | 0 | 8 | 0 | 9 |
| WS | 1 | 0 | 3 | 1 | 5 |
| Total | 27 | 17 | 28 | 3 | 75 |

FDI, further diagnostic investigations; MT, medical therapy; ST, surgical treatment; WS, wait-and-see.

In group (B), which consisted of 37 patients with untreated lung cancer, the planned management before the PET study was as follows: further diagnostic investigations in 26 cases, medical therapy in seven, surgery in four and wait-and-see in none. After PET imaging, changes in management were indicated in 11 of the 37 (30%) patients. In particular, of the 26 patients for whom further diagnostic investigations were requested, 16 were confirmed after PET, eight were shifted to surgery and two to medical therapy (Fig. 2). Of the seven patients initially assigned to medical therapy, six were confirmed and one was shifted to further diagnostic tools after the PET results. All four cases initially considered for surgical treatment in this group were confirmed after PET imaging.

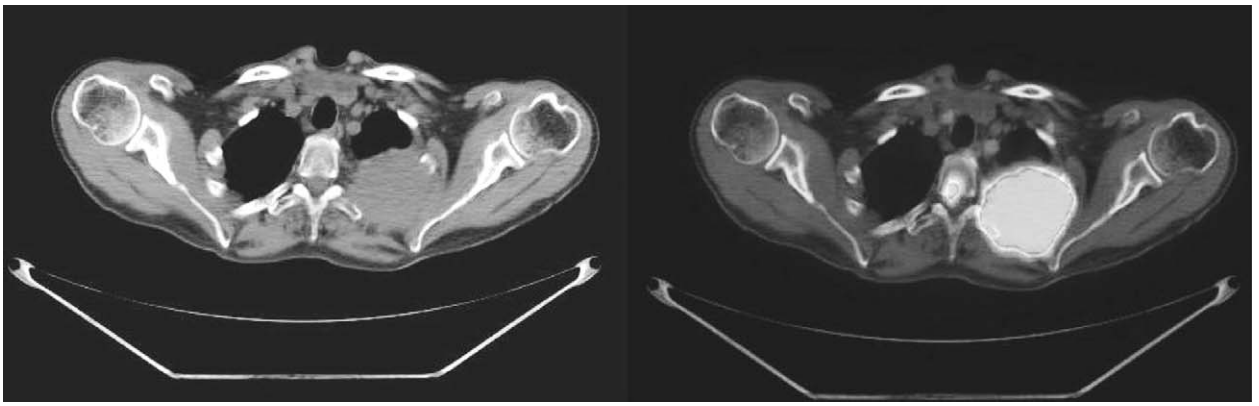
In group (C), which included 20 patients with treated lung cancer, the planned management before the PET study was as follows: further diagnostic investigations in

**Fig. 1**




A 41-year-old male patient, sent for the evaluation of a small (<1 cm) solitary lung nodule (group (A)). $^{18}$F-Fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) showed an increased uptake; the patient was therefore a candidate for surgery.

**Fig. 2**



A 55-year-old female patient, sent for pretreatment staging of a large lung carcinoma (group (B)). $^{18}$F-Fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) showed a small uptake in a vertebra, not previously diagnosed. The patient was therefore sent for chemotherapy.

**Table 2 Contingency table of patients with or without changes in management**

| | Group (A) | Group (B) | Group (C) | Total |
|---|---|---|---|---|
| No change | 6 | 26 | 9 | 41 |
| Change | 12 | 11 | 11 | 34 |
| Total | 18 | 37 | 20 | 75 |

Note: A=group of patients with indeterminate solitary pulmonary nodule; B=group of patients with untreated lung cancer; C=group of patients with treated lung cancer. Numbers are numbers of cases.

six cases, medical therapy in 10, surgical treatment in four and wait-and-see in none. After PET imaging, variations in management were indicated in 11 of the 20 (55%) patients. Of the six patients initially considered for further diagnostic investigations, all were shifted to surgery after PET. Five of the 10 patients initially considered for medical therapy were confirmed; of the others, two were shifted to surgery and the remaining three to further diagnostic investigations. All four patients considered as candidates for surgical treatment were confirmed after the PET study. In Table 2, the distribution of patients in the three different groups who did or did not undergo changes in management after the PET results is shown. The percentages of changes in the three groups were found to be significantly different (chi-squared test; $P = 0.021$).

## Discussion

In recent years, many studies performed on cancer patients have concluded that morphological imaging may inaccurately assess the disease when used alone, but the efficacy can be improved significantly when used in conjunction with $^{18}$F-FDG PET [12–15]. In addition, in lung cancer, several previous studies have shown that, mainly due to its high sensitivity for tumour tissue, $^{18}$F-FDG PET is a reliable imaging technique for staging the disease, thus allowing patients to be treated appropriately [16–24]. In a prospective study by Chin *et al.* [21], it has been suggested that, in selected cases, whole-body $^{18}$F-FDG PET may be able to replace the combination of conventional imaging modalities for the diagnosis and staging of lung cancer in a cost-effective manner. In a recent meta-analysis by Gould *et al.* [25], it was stated that $^{18}$F-FDG PET may allow the reliable identification of patients with pulmonary nodules and mass lesions. Promising results have also been reported by Kalff *et al.* [26] and by van Tinteren *et al.* [27] in the preoperative assessment of lung cancer with PET. However, the role of PET in the management of cancer patients has not yet been clarified definitively from the referring physician's perspective.

In the present study, in patients with known or suspected lung cancer, we evaluated whether and how PET findings could modify the treatment strategy from the referring physician's point of view. For this purpose, we sent out detailed questionnaires to the referring physicians regarding the clinical management variations that occurred after the PET results became known. In this way, the ability of PET imaging to determine clinical pathway modifications was assessed quantitatively. Our experience showed that PET data may affect management in almost one-half of cases. When considering the overall patient population of our study, the most meaningful result was that, of the 34 patients in whom variations occurred, the majority would have been shifted to possible surgical treatment after PET. This is important as a therapeutic option with curative intent administered as soon as possible, without awaiting evolution to malignancy in the case of indeterminate nodules, will certainly lead to the best achievable clinical outcome.

In our series, the difference in the percentages of changes after the PET study between the three patient groups

reached statistical significance, and a clear trend, which paralleled the known capability of PET in assessing solitary nodules, was found. Indeed, the highest percentage of management variations occurred in group (A), which included patients with a solitary lung nodule of indeterminate nature. This is not surprising, as some previous investigations have reported that, owing to the high proliferation potential of lung cancer, which is directly translated into elevated $^{18}$F-FDG uptake, PET imaging is highly accurate in differentiating malignant from benign solitary nodules, thus allowing these patients to be managed appropriately [25–27]. Currently, in these cases, further diagnostic investigation or a wait-and-see strategy is applied, as shown also by our data before PET imaging. However, in patients with a solitary malignant nodule, owing to the early stage of disease, surgery may be of value with curative intent. The identification of solitary nodules is therefore of crucial importance: in our series, of the 18 patients with an indeterminate solitary lung nodule, four were considered eligible for surgery after PET, compared with one before PET.

About one-half of patients in our series, all included in group (B), had untreated lung cancer diagnosed on the basis of cytological or radiological findings, and were mainly assigned to PET scanning for disease staging. The lowest percentage of management changes was found in this group. It is interesting to note, however, that most of the variations due to the PET results affected the surgical treatment option. Indeed, eight patients previously excluded from surgery were judged to be candidates for pulmonary lobectomy or segmentectomy after the PET study.

In group (C), which comprised patients with lung cancer treated by chemotherapy or radiation therapy who were referred to PET scanning for monitoring of the response to therapy, management changes were indicated in about one-half of cases. Such patients usually have poor therapeutic possibilities; nevertheless, eight patients in this group, in whom surgical resection had previously been ruled out, were reconsidered for surgery on the basis of the PET results. This is in line with the findings of Pandit *et al.* [23], who concluded in their retrospective review that $^{18}$F-FDG PET may help to decide the most appropriate treatment in patients with treated lung cancer. In contrast, in a recent study on a mixed population of treated and untreated lung cancer patients, Kamel *et al.* [24] found that $^{18}$F-FDG PET altered the overall management in only 12 of 42 (29%) cases. The discrepancy between their results and ours may be explained mainly by the different patient inclusion criteria. In our series, most of the patients with lung cancer had untreated limited disease, whereas, in the series of Kamel *et al.* [24], patients with untreated advanced disease and treated disease predominated. In addition, it should be noted that our study population comprised patients with lung cancer of various histological types. Conversely, Kamel *et al.* [24] considered only patients with small cell lung cancer, which is the most aggressive form, accounting for about 20% of all lung cancers, with an average 2-year survival of less than 10%. It is well known that, at the time of diagnosis, most patients with small cell lung cancer present with advanced disease. In such a patient population, it is reasonable to expect that PET may have limited influence on clinical management, particularly on surgical treatment options.

In summary, our overall results indicate that PET may have a considerable influence on the management of patients with known or suspected lung cancer, mainly because of its ability to help identify those cases that are potential candidates for surgical treatment. The results of the present study also pose the problem of the cost-effectiveness of using PET imaging in the management of these patients. In a previous study, Gambhir *et al.* [18] showed quantitatively the cost-effectiveness of a PET-based strategy in the management of patients with lung cancer or solitary pulmonary nodules. They concluded that a CT + PET strategy, allowing appropriate management, is more economical and shows a marginal increase in patient life expectancy when compared with the conventional strategy of CT alone.

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