Impact of ^{18}F-FDG PET scan on the prevalence of benign thoracic lesions at surgical resection*

Impacto do estudo com ^{18}F-FDG PET sobre a prevalência de achados de lesões torácicas benignas em ressecções cirúrgicas

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Abstract **Objective:** The main utility of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) lies in the staging of lung cancer. However, it can also be used to differentiate indeterminate pulmonary lesions, but its impact on the resection of benign lesions at surgery is unknown. The aim of this study was to compare the prevalence of benign lesions at thoracotomy carried out for suspected lung cancer, before and after the introduction of PET scanning in a large thoracic surgical centre. **Materials and Methods:** We reviewed our prospectively recorded surgical database for all consecutive patients undergoing thoracotomy for suspected or proven lung cancer and compared the prevalence of benign lesions in 2 consecutive 2-year groups, before (group I) and after (group II) the introduction of FDG-PET scan respectively. **Results:** Surgical resection was performed on 1233 patients during the study period. The prevalence of benign lesions at surgery in groups I and II was similar (44/626 and 41/607, both 7%), and also in group II between those who underwent FDG-PET scan and the remainder (21/301 and 20/306 respectively, both 7%). In group II, of the 21 patients with benign lesions, who underwent FDG-PET, 19 had a false positive scan (mean standardised uptake value 5.3 [range 2.6–12.7]). Of these, 13 and 4 patients respectively had non-diagnostic bronchoscopy and percutaneous transthoracic lung biopsy pre thoracotomy. There was no difference in the proportion of different benign lesions resected between group I and those with FDG-PET in group II. **Conclusion:** The introduction of FDG-PET scanning has not altered the proportion of patients undergoing thoracotomy for ultimately benign lesions, mainly due to the avidity for the isotope of some non-malignant lesions. Such false positive results need to be considered when patients with unconfirmed lung cancer are contemplated for surgical resection.
Key words: Positron emission tomography; Computed tomography; Lung – benign or congenital lesions; Lung cancer – diagnosis and staging; Lung cancer – surgery.

Resumo **Objetivo:** A principal utilidade da tomografia por emissão de pósitrons com 18-fluordeoxiglicose (FDG-PET) está no estadiamento do câncer de pulmão. Porém, ela também pode ser utilizada para diferenciar lesões pulmonares indeterminadas, mas seu impacto na ressecção cirúrgica de lesões benignas é desconhecido. O objetivo deste estudo foi comparar a prevalência de lesões benignas em toracotomias feitas por suspeição de câncer de pulmão, antes e após a introdução do FDG-PET, em um centro de referência de cirurgia torácica. **Materiais e Métodos:** Os autores analisaram, prospectivamente, uma base de dados cirúrgicos de todos os pacientes consecutivos submetidos a toracotomia por câncer de pulmão suspeito ou comprovado e compararam a prevalência de lesões benignas em dois grupos ao longo de dois anos consecutivos, respectivamente antes (grupo I) e depois (grupo II) da introdução da FDG-PET. **Resultados:** Ressecção cirúrgica foi feita em 1.233 pacientes durante o período do estudo. A prevalência de lesões benignas na cirurgia nos grupos I e II foi similar (44/626 e 41/607, ambas correspondendo a 7%), e também no grupo II, entre aqueles submetidos a FDG-PET e os restantes (21/301 e 20/306 respectivamente, ambos correspondendo a 7%). No grupo II, dos 21 pacientes com lesões benignas submetidos a FDG-PET, 19 tiveram um estudo falso-positivo (valor médio padrão de captação 5.3 [faixa 2.6–12.7]). Desses, respectivamente 13 e 4 pacientes tiveram broncoscopia não diagnóstica e biópsia transtorácica percutânea de pulmão antes da toracotomia. Não houve diferença na proporção de lesões benignas diferentes ressecadas entre o grupo I e aqueles submetidos a FDG-PET no grupo II. **Conclusão:** A introdução da FDG-PET não alterou a proporção de pacientes submetidos a toracotomia por lesões benignas, principalmente devido à avidez pelo isótopo de algumas lesões não malignas. Tais resultados falsos-positivos devem ser considerados nos casos em que se contempla a possibilidade de ressecção cirúrgica em pacientes com câncer de pulmão não confirmado.
Unitermos: Tomografia por emissão de pósitrons; Tomografia computadorizada; Pulmão – lesões benignas ou congênitas; Câncer de pulmão – diagnóstico e estadiamento; Câncer de pulmão – cirurgia.

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INTRODUCTION

Despite advances in imaging and interventional techniques, indeterminate pulmonary lesions are common and represent a diagnostic challenge in the evaluation of patients with suspected lung cancer. Although the majority will represent early malignancy, where resection is usually curative, separating these out from the remainder can be problematic. Accurate diagnosis is therefore imperative to avoid unnecessary surgery. Recently, 18-fluorodeoxyglucose positron emission tomography (FDG-PET), which measures tissue metabolic activity, has become available as an imaging modality to aid in the detection of malignancy in a number of organ systems. Its main use in pulmonary malignancy is to stage non-small cell lung cancer (NSCLC) and thereby prevent futile thoracotomies[1,2], but although it is superior to computed tomography (CT) scanning in the diagnosis of indeterminate pulmonary lesions[3], its role in their management is less clear and remains to be explored. Indeed, there have been no studies looking at its impact on thoracotomy rates for patients who ultimately have benign disease.

To investigate this further, we compared the prevalence of benign lesions at thoracotomy carried out for suspected lung cancer in two 2-year groups, before and after the introduction of PET scanning respectively, in a large thoracic surgical centre serving a catchment population of 2.5 million.

MATERIALS AND METHODS

We reviewed our prospectively recorded database for all patients who underwent surgical resection for proven or suspected NSCLC over a four year period (1233 cases). During this time patients were referred from other hospitals to our tertiary centre, and with the exception of the FDG-PET scan, all pre surgical imaging, invasive tests and multidisciplinary team decisions to treatment were performed at the referring hospitals. We compared the prevalence of benign lesions at surgery for 2 consecutive 2-year groups of patients: those who underwent surgery April 2003 to March 2005 (before the FDG-PET scan was available [group I, 626 patients]) with those undergoing surgery April 2005 to March 2007 (after the availability of the FDG-PET scan [group II, 607 patients of which 301 (50%) underwent FDG-PET scan]). For patients with an ultimately benign pathological diagnosis, data on demographics, imaging (CT and FDG-PET), lung pathology, methods of resection and perioperative mortality were reviewed. Information on the lesion size, location, margins, attenuation, presence of calcification and lymphadenopathy were recorded from the CT scan. The PET scan was performed using a dedicated PET scanner and interpreted by two experienced nuclear medicine radiologists. PET images were obtained 1 hour after intravenous injection of the 336 MBq FDG (227–400 MBq) in patients with blood glucose values < 11.1 mmol/L. The avidity of a lesion for FDG was measured using the maximum standardised uptake value (SUV), where a score > 2.5 was considered indicative of malignancy[4]. The study was approved by the local audit and research committee. Descriptive statistics in the form of percentages and mean ± standard deviation (SD) have been used to express the results. Chi-square and student's t test were used to compare data between the two groups. A p value of < 0.05 was considered significant.

RESULTS

Similar numbers of patients underwent resection in each of the 2-year groups, and with the exception of asbestos exposure, there was no difference in their clinical and pathological characteristics (Table 1). The number of patients with a definitive histological diagnosis of malignancy pre-resection was similar between groups I and II (278/626 [44%] vs 237/607 [39%] respectively; $\chi^2 = 3.43$, p = 0.07). Similarly, the resection rate for ultimately benign lesions was unchanged between groups I and II (44 vs 41 respectively, both 7%), and also in group II when subdivided into those who underwent FDG-PET and the remainder (21/301 vs 20/306, both 7%).

The 21 patients with resected benign lesions following FDG-PET were analysed in more detail: 19 of these had a (false) positive scan and the two with negative scans proceeded to thoracotomy due to preoperative inaccurate positive cytology in one and an increase in the size of the lesion on interval CT scan in the other. Excluding these two patients, there was no difference in the prevalence of benign lesions in group I and group II who underwent FDG-PET scan (44/626 [7%] vs 19/301 [6.3%] respectively; $\chi^2 = 0.17$, p = 0.68).

Table 2 shows the clinical and CT scan characteristics of the 19 patients with PET positive benign lesions: nearly all had a smoking history. On the CT scan, the average size of the lesion was 2.7 cm (1.1-5.0 cm); two thirds were ≤ 3 cm. All were non-calcified, and the majority had a solid consistency and spiculated or irregular mar-

Table 1 Clinical and pathological characteristics of 1233 patients who underwent surgery from 2003–2007.

Characteristics value	Group I (pre PET)	Group II (post PET)	P
Number of patients	626	607	
Age*	66 ± 9	66 ± 11	0.26
Sex: male/female	365/261	336/271	0.3
Smoking history	574 (92%)	548 (91%)	0.39
Asbestos exposure	114 (18%)	76 (13%)	0.006
COPD	148 (24%)	141 (23%)	0.86
Pathological proof of malignancy pre surgery	278 (44%)	237 (39%)	0.07
Malignant lesions at resection			
Primary	509 (81%)	490 (81%)	0.79
Secondary	73 (12%)	76 (12%)	0.64
Benign lesions at resection	44 (7%)	41 (7%)	0.97
Number of patients with PET scan		301 (50%)	
Pathological proof of malignancy pre surgery		113 (38%)	0.07
Malignant lesions at resection			
Primary		257 (85%)	0.14
Secondary		23 (8%)	0.07
Benign lesions at resection		21 (7%)	0.96

* Mean ± SD. Percentages are given in parenthesis. COPD, chronic obstructive pulmonary disease; PET, positron emission tomography.

Table 2 Clinical and CT scan characteristics of 19 patients with PET positive benign lesions.

Characteristics	Values
Age*	60 ± 8
Sex: male/female	11/8
Smoking history	18 (95%)
Asbestos exposure	6 (32%)
COPD	11 (58%)
FEV1†	79% (46–125)
FVC†	97% (77–124)
CT features	
Size*	2.7 ± 1 cm
Location	
Right upper/lower lobe/hilum	7/3/2
Left upper lobe/hilum	6/1
Attenuation	
Solid	14 (74%)
Ground glass	—
Cavitation	5 (26%)
Margins	
Smooth	6 (32%)
Spiculated	5 (26%)
Ill defined	8 (42%)
Lymphadenopathy	
Yes	1 (5%)
No	18 (95%)
Calcification	
Yes	—
No	19 (100%)
Increase in size	
Yes	3 (16%)
No	7 (37%)
No interval CT scans	9 (47%)

* Mean (SD), † Mean (range). Percentages are given in parenthesis. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

gins. Before surgery, 13 and 4 patients had non-diagnostic bronchoscopy and percutaneous transthoracic lung biopsy (PTLB) respectively. At thoracotomy, diagnosis was achieved by lobectomy in 9; wedge resection in 8 and 2 had frozen section biopsy alone. There were no perioperative deaths and the mean duration of hospital stay was 5 (2–11) days. There was a wide range of benign conditions resected (Table 3) with varying SUV values on FDG-PET scan. Furthermore the introduction of FDG-PET scanning did not alter proportion of different benign lesions resected (Table 4).

Table 3 Histopathology of resected benign lesions in 19 patients along with the PET-SUV values.

Diagnosis	SUV
Fibrosis	7.9
Fibrosis	3.9
Fibrosis	4.5
Fibrosis	4.5
Chronic inflammation and fibrosis	4.6
Tuberculosis	5.7
Tuberculosis	5.2
Tuberculosis	3.1
Aspergilloma	12.7
Aspergilloma	4.8
Rheumatoid nodule	3.7
Rheumatoid nodule	3.0
Organisisng pneumonia	4.2
Organising pneumonia	6.8
Infarct	2.6
Necrosis	3.5
Granuloma	11.5
Hamartoma	3.0
Bronchiolitis with interstitial lung disease	5.0

DISCUSSION

In patients with clinical features suggestive of pulmonary malignancy, management techniques are aimed at obtaining a histological diagnosis and then staging the disease in order to decide the best treatment strategy. However, in those patients with isolated pulmonary lesions where definitive histology can only be obtained at thoracotomy, imaging techniques are crucial in informing the clinician as to the likelihood of malignancy. The aim is to identify patients with early stage cancer that would benefit from curative resection, whilst avoiding unnecessary surgery in those with benign disease. The development of the CT scan provided information regarding the morphology of the lesion, its attenuation, extent, growth rate, identified regional and distant spread[5], and also led to a decline in the prevalence of benign lesions at surgical resection from 64% to 9% in a recent series of > 1500 patients[6]. However, although CT scanning can suggest cancer based on the morphology of a lesion, it cannot demonstrate increased metabolic activity, which is a hall mark of malignant disease. In this respect, a metabolic imaging technique such as the FDG-PET scan should be superior to CT in differentiating benign from malignant lesions[5]. Although FDG-PET has a major role in lung cancer in defining metastatic or local spread and thereby reducing futile thoracotomies, no studies have evaluated its impact on the prevalence of unexpected benign disease at resection for apparently malignant lone pulmonary lesions. We therefore looked at the prevalence of benign lesions in patients with isolated suspected malignant pulmonary lesions undergoing resection for a period of 2 years following the introduction of the FDG-PET scan and compared it with that in the preceding 2 years.

Our results show that FDG-PET scan did not reduce the resection rate for benign lesions. No previous studies have specifically addressed the issue of FDG-PET scans on the incidence of unexpected benign lesions at thoracotomy, but rather they have been targeted at preventing futile thoracotomies by identifying patients with otherwise unknown disseminated disease[7,8]. Of these, the PET in lung cancer staging (PLUS) study showed that PET scan reduced the number of futile thoracotomies, by identifying patients with locally advanced disease, post operative recurrence and death[7]. Of the 9 cases where benign lesions were discovered at thoracotomy, although 2 of these underwent FDG-PET scan, it is not clear whether these were falsely positive or merely reassured the clinician that there was no disseminated disease. Our study is therefore the largest in the literature, which specifically ad-

Table 4 Prevalence of common benign lesions resected pre and post PET scan.

Benign lesions	Prevalence		P value
	Pre PET (44/626)	Post PET (19/301)	
Tuberculosis	9	3	0.76
Hamartoma	8	1	0.29
Organising pneumonia	6	2	0.96
Aspergilloma	3	2	0.60
Fibrosis	2	5	0.49
Rheumatoid nodule	1	2	0.25
Others	15	4	0.46

dresses the impact of FDG-PET scan on unexpected benign lesions at thoracotomy.

In nearly all our cases, the clinician was misled by the high avidity for FDG by some benign lesions (false positive scans). False positive FDG-PET findings have been reported in 8–10% of indeterminate pulmonary lesions[9] and are seen in infectious and inflammatory conditions such as tuberculosis, histoplasmosis, aspergillosis, sarcoidosis, lipoid pneumonia, rheumatoid lung disease and suture/stapler granulomas[3,10,11]. The PET scan relies on an increased number of glucose transporter (GLUT) proteins and increased glycolytic activity of malignant cells to actively accumulate the radiotracer FDG, a glucose analogue labelled with positron-emitting radioisotopes[12]. However FDG uptake is not cancer specific since inflammatory cells (neutrophils, lymphocytes, macrophages and fibroblasts) also accumulate FDG and cause false positive results[13]. In activated inflammatory cells, glucose metabolism can multiply by 20–30 times, thereby increasing the uptake of FDG[14]. Specifically, GLUT proteins proliferate resulting in an increased cellular accumulation of FDG[15]. Indeed this property has led to the application of FDG-PET scans in the diagnosis and to monitor treatment response in some infectious and inflammatory conditions[16]. Although an SUV of > 2.5 is used to distinguish malignant from benign lesions, there is significant overlap in uptake values between the two conditions. Benign lesions accumulate FDG relatively early, whereas malignant cells retain FDG for longer periods: dual time point (early and delayed) imaging with an FDG retention index of > 10% has been reported to improve the accuracy of cancer diagnosis[17,18]. However, the routine use of dual time point FDG imaging is time consuming and resource intensive, and in populations with a high incidence of malignancy it adds little to the overall yield and is therefore not justified in clinical practice. Only single time point (early) images were acquired in our study.

In our study, the clinical and CT scan features of the resected benign lesions indicated a high suspicion for malignancy, and the patients came from a population with a high risk for the disease[12,19]. Attempts to obtain a positive histological diagnosis pre-thoracotomy, for example by PTLB, were only considered by the referring hospitals in 20% of cases. However, a negative or non-specific biopsy does not reliably rule out malignancy in patients with high suspicion for lung cancer, and a positive result in patients with resectable lesions is an indication for thoracotomy anyway. There is no convincing evidence that PTLB reduces unnecessary thoracotomies in patients who ultimately have benign disease at resection, and the consensus view is that patients with operable pulmonary lesions suspicious for lung cancer should be referred for surgery as PTLB is unlikely to alter patient management[20,21].

The limitations of our study are that we do not have information on those patients who had a negative FDG-PET scan and therefore were not referred to our centre for consideration of surgical resection, and that a proportion of patients (50%) did not benefit from this investigation after it became available. However, our aim was to specifically look at the trend of benign lesions resected since the introduction of this scanning technique in our practice, and some patients remained without scans because of the limited availability and long waiting times when the technique was first introduced. Furthermore the prevalence of benign lesions in patients who did not have an FDG-PET scan during the same period (20/306, 6.5%) was similar, reassuring us that the scanned group were representative. This study shows that the FDG-PET scan should be interpreted with caution in patients presenting with isolated pulmonary lesions, and may not add to the diagnostic process even in those with a high risk of lung cancer.

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