Original Article

The impact of ^{18}F-FDG PET/CT in staging of non-small cell lung cancer patients: the key to improve patient treatment strategy

Impacto do ^{18}F-FDG PET/CT no estadiamento de pacientes com câncer de pulmão: chave para melhorar o tratamento

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ABSTRACT

Lung cancer leads the cause of cancer-related deaths in men and women around the world. The most common is non-small cell lung cancer (NSCLC). Fast and accurate staging is essential for choosing treatment for NSCLC. The positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) can provide molecular and metabolic information, which acquired simultaneously with computed tomography (CT), has proved to be a very useful tool in the cancer diagnosis and staging. Identifying the stage of lung cancer is important to avoid unnecessary surgeries, reducing morbidity and treatment costs. This study aims to examine the impact of ^{18}F-FDG PET/CT in the initial evaluation of patients with NSCLC in the Brazilian reality. Twenty-six patients with histopathologic diagnosis of NSCLC were included. They underwent staging in two separated moments: first with morphological images (x-ray and computed tomography scan) and after with ^{18}F-FDG PET/CT. The performance of ^{18}F-FDG PET/CT changed lymph node staging in around 30% of the patients initially classified as potentially operable, with high sensitivity and negative predictive values. Regarding the stage of metastasis, ^{18}F-FDG PET/CT increased by 11.5% the detection of metastasis not previously detected. About the clinical staging, using the ^{18}F-FDG PET/CT significantly reduced the number of patients classified as potentially operable in the early stages, avoiding the use of unnecessary thoracotomies in 19.2% of patients. The metabolic information obtained by ^{18}F-FDG PET/CT demonstrated better accuracy when comparated to anatomic methods in the detection of lymph node and distant metastases. Thus, having important impact on therapeutic strategy and treatment cost related.

Keywords: Lung neoplasms/diagnosis; Neoplasm staging; Carcinoma, Non-small-cell lung; Positron-emission tomography.

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RESUMO

O câncer de pulmão lidera a causa de mortes relacionadas ao câncer em homens e mulheres em todo o mundo. O mais comum é o câncer do pulmão de células não pequenas (NSCLC), sendo essencial o seu estadiamento preciso para a escolha do tratamento. A tomografia por emissão de pósitrons (PET) com ^{18}F-fluorodeoxiglicose (^{18}F-FDG) pode fornecer informações molecular e metabólica que, quando adquiridas simultaneamente com tomografia computadorizada (TC), constituem-se instrumento muito útil no diagnóstico e no estadiamento do câncer. O estadiamento do câncer de pulmão é importante para evitar cirurgias desnecessárias, e reduzir a morbidade e os custos do tratamento. Este estudo objetivou analisar o impacto da ^{18}F-FDG PET/TC na avaliação de pacientes com NSCLC na realidade brasileira. Foram incluídos 26 pacientes com diagnóstico histopatológico de NSCLC que foram submetidos a estadiamento em dois momentos com: 1. Imagens morfológicas (raios-x e TC); 2. ^{18}F-FDG PET/CT. A ^{18}F-FDG PET/CT mudou 30% o estadiamento linfonodal classificado como operável com alta sensibilidade e valor preditivo negativo. Em relação ao estádio de metástase, a ^{18}F-FDG PET/CT aumentou em 11,5% a detecção de metástases não detectadas. A ^{18}F-FDG PET/CT reduziu significativamente o número de pacientes classificados como operáveis, evitando a realização de toracotomia desnecessária em 19,2% dos casos. A informação metabólica obtida pela ^{18}F-FDG PET/CT demonstrou melhor precisão quando comparada com métodos anatômicos na detecção de linfonodos e metástases à distância. Assim, demonstra impacto importante na estratégia e nos custos relacionados com o tratamento.

Palavras-chave: Neoplasias pulmonares/diagnóstico; Estadiamento de neoplasias; Carcinoma pulmonar de células não pequenas; Tomografia por emissão de pósitrons.

Introduction

Lung cancer (LC) leads the cause of cancer-related deaths in men and women around the world.[1] The non-small cell lung carcinoma (NSCLC) is the most common lung cancer and represents approximately 85% of cases.[2] This histological type displays rapid growth, extensive locoregional invasion and large capacity of metastasize (bone and brain). The majority of patients have advanced disease at diagnosis due to the late onset of symptoms (less than 25% are diagnosed in early stage).[3] Staging-related strategy for NSCLC treatment is crucial and its impact has great deal to patient outcome.

As treatment strategies for NSCLC patientes is determined predominantly by the initial stage. Stages I and II are candidates for curative surgery, followed by adjuvant chemotherapy for stage II. Stage IIIA patients usually receive chemo/radiation therapy before surgical ressection. While stages IIIA e IV patients are considered incurable and palliative treatment (chemotherapy, radiotherapy or combined approaches) is the option.

Thus, the accuracy of the diagnostic work-up is crucial for adequate therapeutic planning, avoiding unecessary therapies for advanced cases or changing for more aggressive therapeutic choices in downstaging cases of NSCLC patients.[4-7] The standard diagnostic work flow is based on imaging with CT. Despite all advances in CT technology, the morphological information provided has limitations in distinguishing between tumor and adjacent structures, limited sensitivity to detect microscopic disease and is often unable to discriminate if the lymph nodes are enlarged by malignant or benign pathology.[8]

The ability to measure the uptake of ^{18}F-fluorodeoxyglucose (^{18}F-FDG), an analog of glucose[9] and a proliferative cell marker,[10] and to evaluate the metabolic activity of the tumors[11] arose in the last two decades with positron emission tomography (PET). The staging of NSCLC was one of the first indications that led to the approval of the use of PET worldwide, which has been replaced by PET plus CT (PET/

CT) integrated providing both anatomic and metabolic information.[12] The PET/CT system provides the necessary anatomical detail for assessing tumor and distinguish between benign and malignant lesions with acuracy of 82%.[13] Therefore, the study of ^{18}F-FDG PET/CT, widely used in the evaluation of NSCLC, has an important role in staging and proven to be cost-effective.[5-7]

Since its introduction in Brazil, the ^{18}F-FDG PET/CT has been used to evaluate NSCLC patients, however not reimbursted by the National Health Insurance System (SUS) restricting access to the majority of the Brazilian population. Recently, the Brazilian government has approved the use of this technology for staging NSCLC in the National Health Insurance System (SUS),[14] which opens the possibility to improve NSCLC treatment for those covered by SUS. Thus, this study aims to analyze the impact of this technology (^{18}F-FDG PET/CT) in the initial evaluation of patients with NSCLC refered from a public thoracic surgery clinic.

Methods

Forty lung cancer patients were evaluated with ^{18}F-FDG PET/CT scan at our molecular imaging service from a single public thoracic surgic hospital. There were twenty-one men and nineteen women, 35-85 years, mean age was 64 year-old. The project was approved by the local Ethical Comitee and the exclusion criteria were: not diagnosed as NSCLC, had undergone previous lobectomy, and received previous chemo and/or radiation therapy.

^{18}F-FDG PET/CT were performed according to our research protocol for oncological patients using a Discovery 690 PET/CT scanner (GE, Miwaukee, WI, USA). Briefly, patients fasted for at least 6 h before the intravenous administration of 3.7 MBq/kg body weight of ^{18}F-FDG. Blood glucose level was checked before tracer administration and patients with glucose level above 190 mg/dL were excluded from the study.

CT scan were performed from the top of the head to mid thigh approximately 60 minutes after intravenous injection of ^{18}F-FDG using low-dose protocol for attenuation map without diagnostic purpose without oral or intravenous contrast media. Then, PET images were acquired for the same region. All images were reconstructed using OSEM-like reconstruction algorithm.

The ^{18}F-FDG PET/CT images was evaluated independently by two board certified nuclear physicians. The interpretation was defined into two categories: (1) PET-negative: defined as the absence of any area of pathological concentration of tracer and (2) PET positive: when observed the presence of abnormal radiotracer uptake, not attributed to the ^{18}F-FDG physiological biodistribution. In case of discrepancy, the interpretation was made by consensus between the investigators. In patients with PET-positive, the radiotracer concentration were analyzed semi-quantitatively by the maximum standardized uptake value (SUV_{max}) method in the transaxial plane corrected by the lean body mass.

All patients were also classified as lymph node-positive (LN+), which means the presence of an anomalous concentration of radiotracer in the hilar, mediastinal and/or distance, which indicates high metastatic potential, regardless of size lymph nodes, and identify probable sites of distant metastases, known as metastasis-positive (METS+).

Patients with NSCLC were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) TNM system[15] and clinical stage classification in two moments: 1- prior to study with ^{18}F-FDG PET/CT, according to information obtained by morphological image methods (CT and chest x-ray), and 2- after the metabolic study. The comparative analyses of the clinical stage and TNM descriptors were performed to verify whether there were any change in the initial staging of these patients before therapeutic approach.

In cases where the ^{18}F-FDG PET/CT suggested metastatic involvement of lymph nodes, histopathological confirmation by biopsy or surgery was performed in all cases without distant metastases to analyze concordance of metabolic findings with the actual lymph node involvement.

Results

Four patients were excluded from the initial sample, because of previous lobectomy for lung cancer (n = 2) and died before the data analysis (n = 2). After clinical retrospective analysis, twenty-six patients were classified as NSCLC, one with SCLC or high degree PNET, one patient with pulmonary hemangiopericytoma or extrapleural solitary fibrous tumor and the remaining eight patients did not undergo pathological study of tumor lesions by the end of period of data collection. Table 1 describes NSCLC patient's profile used for the present study (n = 26).

The lymph node staging, before molecular studies with ^{18}F-FDG PET/CT (Table 2), showed no lymph node involvement, classified as N0, in 12/26 (46.2%) patients with NSCLC. The remaining patients had positive lymph nodes as N1 in 2/14 (7.7%), N2 in 9/14 (34.6%) and N3 in 3/14 (11.5%). However, after the study with ^{18}F-FDG PET/CT, only six out of twenty-six NSCLC patients (23.1%) were lymph node negative (LN-).

A biopsy of mediastinal LN- was performed in five patients, confirming the absence of metastases in four (80%) cases and lymph node metastasis in only one (20%). The only case that was not biopsied had METS+.The ^{18}F-FDG PET/CT revealed abnormal lymph nodes (LN+) in 20/26 (76.9%) of NSCLC patients, the majority being classified as advanced stage N3, 11/20 (55%). The remaining were classified as N2, 6/20 (30%) and N1, 3/20 (15%) (Table 2).

When lymph node criteria for TNM staging was analyzed for patients before and after the ^{18}F-FDG PET/CT study, lymph node staging (N) remained unchanged in 13/26 (50%) cases, upstaging was presented in 11/26 (42.3%) cases and downstaging in only 2/26 (7.7). Among 13 patients with no change in lymph node staging, pathological confirmation by biopsy of lymph nodes occurred in eight patients (61.5%).

The M criteria for TNM staging by morphological methods performed before the study with ^{18}F-FDG PET/CT detected metastatic sites in 8/26 (30.8%) patients, 25% (2/8) thereof a distant site (M1b). The metabolic method of staging detected metastasis in 11/26 (42.3%) patients, 81.8% (9/11) of these in distant sites (liver, bone, brain, and adrenal), classified as M1b (Table 3).

Table 1. Non-Small Cell Lung Cancer patient's profile.

Patient	Gender	Age (years)	Histopathology Subtype	SUVmax
#1	F	61	SCC	16.9
#2	M	87	ADC	6.8
#3	M	77	ADC	6.5
#4	F	56	ADC	14.3
#5	M	73	SCC	11.4
#6	M	55	SCC	13.5
#7	F	50	ADC	13.9
#8	M	80	SCC	7.5
#9	M	78	METS	15.3
#10	F	62	ADC	9.8
#11	M	80	ADC	7.4
#12	F	63	ADC	10.8
#13	M	66	METS	11.5
#14	M	47	ADC	17.0
#15	F	55	ADC	38.2
#16	F	59	ADC	5.3
#17	F	62	SCC	22.6
#18	M	65	SCC	10.1
#19	M	79	SCC	26.9
#20	F	52	ADC	5.5
#21	M	61	ADC	4.9
#22	M	65	ADC	30.0
#23	M	61	SCC	20.9
#24	M	69	ADC	9.1
#25	M	66	ADC	15.1
#26	F	63	ADC	15.2
Mean		65.1		14.1
SD		10.3		8.1

Table 2. Lymph node staging in patients with NSCLC before and after performing the study with ^{18}F-FDG PET/CT.

TNM	Pre-PET/CT		Post-PET/CT	
	N	%	N	%
N0	12	46.2	6	23.1
N1	2	7.7	3	11.5
N2	9	34.6	6	23.1
N3	3	11.5	11	42.3
Total	26	100.0	26	100.0

After the study ^{18}F-FDG PET/CT, new metastastic sites were observed - not previously identified by other methods - upstaging in 7/26 (26.9%), downstaging in only 2/26 (7.7%) and no changes in classification in 17/26 (65.4%). The upstaging was considered in both patients: the ones who changed their rating of M0 to M1b (5/7) and the patients classified as M1a to M1b (2/7) (Table 4).

In addition to the isolated criteria of TNM, comparative analysis between the clinical stages of patients with NSCLC before and after the study of ^{18}F-FDG PET/CT was performed. After the study with ^{18}F-FDG PET/CT and anatomic-pathologic confirmation of lymph nodes, there was an upstaging in the clinical stage in 8/26 (30.8%) cases, downstaging on 6/26 (23.1%) and unaltered clinical stage in 12/26 (46.1%).

Table 3. Metastases staging in patients with NSCLC before and after performing the study with ^{18}F-FDG PET/CT.

TNM	Pre-PET/CT		Post-PET/CT	
	N	%	N	%
M0	18	69.2	15	57.7
M1a	6	23.1	2	7.7
M1b	2	7.7	9	34.6
Total	26	100.0	26	100.0

Table 4. Clinical stages of patients with NSCLC before and after performing the study with ^{18}F-FDG PET/CT.

Clinical Staging	Pre-PET/CT		Post-PET/CT	
	N	%	N	%
IA	0	0.0	0	0.0
IB	6	23.1	4	15.4
IIA	1	3.8	1	3.8
IIB	3	11.5	1	3.8
IIIA	6	23.1	5	19.3
IIIB	2	7.7	4	15.4
IV	8	30.8	11	42.3
Total	26	100.0	26	100.0

The staging performed by PET/CT increased the percentage of patients classified as advanced clinical stage (IIIB and IV) from 10/26 (38.5%) to 15/26 (57.7%) and reduced the percentage of patients classified as early stages of the disease (IA, IB, IIA and IIB) from 10/26 (38.5%) to 6/26 (23.1%). The upstaging occurred in 5/8 (62.5%) because new metastatic sites were detected, reclassified from M0 to M1b. The reduction of the clinical stage, downstaging, occurred due to changes in one of three classification parameters T, N and M, proportionally (33.3% each) (Table 5).

Table 5. Advantages of ^{18}F-FDG PET/CT in NSCLC patients.

Clinical Staging	Post-PET/CT	
	N	%
Upstaging	8	30.8
Downstaging	6	23.1
Unchanged	12	46.1
Total	26	100.0

Discussion

The present study showed that after the diagnosis of NSCLC and before the metabolic study, it was estimated that 53.9% of cases had localized disease (N0 and N1) amenable to resection, 34.6% had mediastinal lymph nodes affected and 30.8% distant metastasis. However, significant profile changes were observed after ^{18}F-FDG PET/CT scans: that was a significant reduction in patients

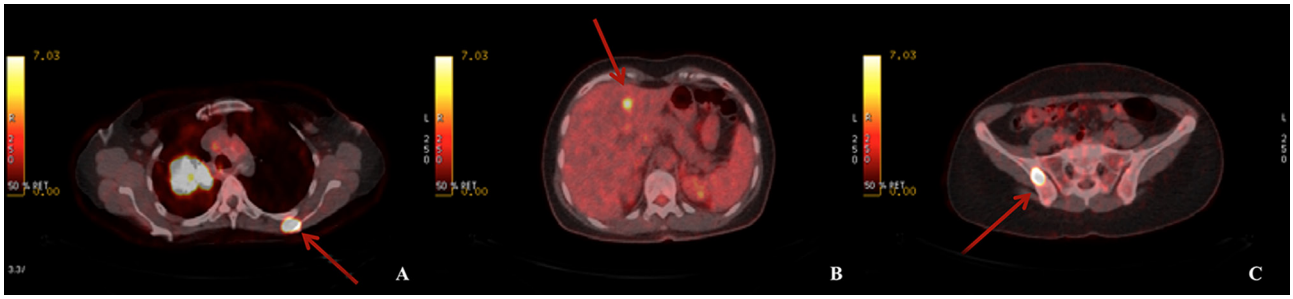

Figure 1. Typical case of NSCLC upstaging using [18]F-FDG PET/CT. Note: A) Primary lesion in the right lung and metastatic lesion in the scapula, B) metastatic lesion in the liver and C) metastatic lesion in the right ilium (sacroiliac joint).

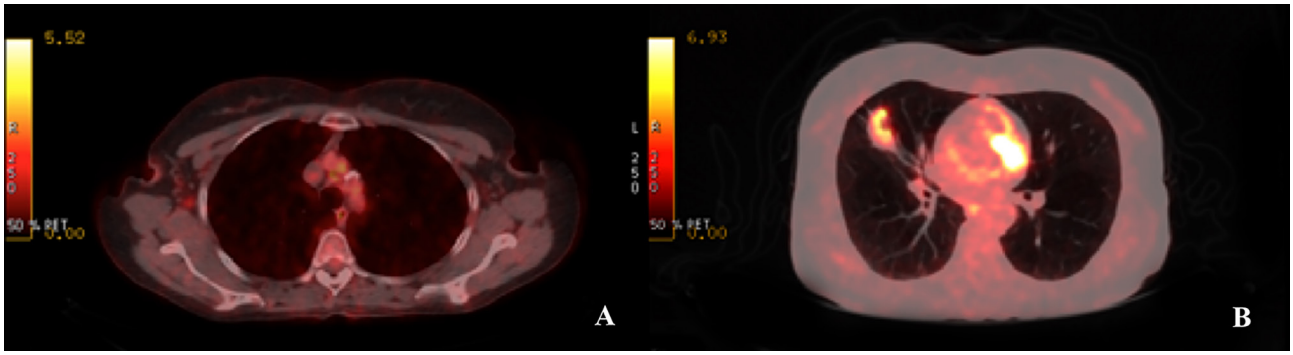

Figure 2. Typical case of NSCLC downstaging using [18]F-FDG PET/CT. Note: A) Enlarged lymph node in the mediastinum PET negative confirmed by histopatology and B) primary lesion in the righ lung.

with early-stage to 34.6% (23.1% change), involvement of mediastinal lymph nodes increased to 23.1% and detection of metastasis to 42.3%. These results came to corroborate the implementation of 18F-FDG PET/CT as an important diagnostic tool for initial staging in NSCLC patient in the Brazilian reality.

Previous studies[16-18] estimates that at the moment of the diagnosis of NSCLC only 20% patients have localized disease, 25% of patients have tumor extension to mediastinal lymph nodes, and most, 55% already have distant metastasis. With these data significant treatment strategies would be changed and a positive cost-effectiveness with [18]F-FDG PET/CT in staging work-out of NSCLC is undeniable.[5-7]

The study with [18]F-FDG PET/CT followed by anatomic-pathologic confirmation of lymph node involvement showed a reduction of approximately 30% of patients initially classified as potentially operable (stage N0, N1 and N2), with a proportional increase in cases of non-surgical candidates (stage N3), which promoted the appropriateness of therapeutic management, avoiding unnecessary surgeries as well as other studies have shown.[19] The pathologic evaluation of lymph nodes is required for metastatic involvement confirmation, because the noninvasive methods low specificity.[20]

Lymph node biopsy was performed in 15/26 patients (57.7%), and it was not performed in 11/26 patients (42.3%) because they already had distant metastasis. The negative predictive value of the metabolic method in lymph node staging was 80%, consistent with literature values.[19,20] This is the best performance indicator of [18]F-FDG PET/CT, being capable to identifiy not compromised nodes with good accuracy avoiding unnecessary invasive procedures.[19,20] In this sample, the only false-negative case can be explained by the long interval between the examination and biopsy (performed only three months later), which might have allowed the lymphatic spread of malignant cells in this period.

The findings of [18]F-FDG PET/CT led to usptaging in clinical stage on 8/26 (30.8%) of patients with NSCLC and downstaging in 6/26 cases (23.1%), consistent with the literature[21] which causes significant changes in the management of these patients. Relying on reducing the number of patients classified as potentially operable early stages, PET/CT avoided performing unnecessary thoracotomy in 19.2%, just like others studies suggested, a reduction of 50%.[22]

PET/CT is an accurate and noninvasive method in the staging of NSCLC, but some errors may exist. Several benign lesions that have increased glucose metabolism can accumulate [18]F-FDG and can be misinterpreted as malignant, such as infection, inflammation, and infarct.[16,20-22] In addition, iatrogenic causes of focal or diffuse [18]F-FDG uptake include, granulation tissue, healing wounds, chest tubes and gastrotomy tubes, percutaneous needle biopsy, and mediastinoscopy.[23]

Despite the extensive use of chest CT in staging lung cancer, this technology has not been proven accurate enough to alter the NSCLC patients outcomes. The introduction of [18]F-FDG PET/CT has come to change how we evaluate these tumors. The metabolic and biochemical information obtained demonstrate better accuracy than anatomic methods to locate metastasis. This study confirms that the addition of PET/CT in the preoperative evaluation of NSCLC improved the accuracy of clinical staging.

In conclusion, the highlighted information with molecular imaging studies by [18]F-FDG PET/CT, confirmed by pathological studies, altered the management of patients with NSCLC. By changing the cancer stage, it has a direct impact on therapy strategy. In addition, by adding an

[18]F-FDG PET/CT examination to the staging regimen for patients with NSCLC, it improves sensitivity in pre-operative staging, avoiding unecessary thoracotomies, showing a potential cost-effective technique in patients with NSCLC. The current findings came to corroborate the inclusion of this technology in the Brazilian National Health Insurance system for patients with NSCLC.

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