2-[^{18}F]-fluoro-2-deoxy-D-glucose positron-emission tomography is cost-effective in the initial staging of non-small cell lung cancer patients in Brazil*

A tomografia por emissão de pósitrons com 2-[^{18}F]-fluoro-2-desoxi-D-glicose é custo-efetiva em pacientes com câncer de pulmão não pequenas células no Brasil

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Abstract **Objective:** To evaluate the accuracy and cost-effectiveness of metabolic staging (MS) with FDG-PET as compared with the conventional staging (CS) strategy in the preoperative staging of non-small cell lung cancer (NSCLC). **Materials and Methods:** A total of 95 patients with initial diagnosis of NSCLC were staged before undergoing treatment. The MS and CS results were compared with regard to treatment definition and incidence of futile thoracotomies with both strategies. **Results:** Metabolic staging with FDG-PET upstaged 48.4% and downstaged 5.3% of the patients, and would lead to change in the treatment of 41% of cases. Thoracotomy was considered as futile in 47% of the patients with CS, and in 19% of the patients with MS. The cost of futile thoracotomies in eight patients with MS was R$ 79,720, while in 31 patients with CS it would be R$ 308,915. Just such saving in costs would be more than enough to cover the costs of all FDG-PETs (R$ 126,350) or FDG-PET/CTs (R$ 193,515) for the 95 patients. **Conclusion:** The metabolic staging with FDG-PET is more accurate than CS in patients with NSCLC. Both FDG-PET and FDG-PET/CT are cost-effective methods and their utilization is economically justifiable in the Brazilian public health system.
Keywords: Non-small cell lung cancer; FDG-PET; Staging; Cost-effectiveness.

Resumo **Objetivo:** Comparar a acurácia e a custo-efetividade do estadiamento metabólico (EM) com o FDG-PET em relação ao estadiamento convencional (EC) no estadiamento inicial de pacientes com câncer de pulmão não pequenas células (CPNPC). **Materiais e Métodos:** Noventa e cinco pacientes com diagnóstico inicial de CPNPC foram estadiados antes do início do tratamento. Os resultados do EC e EM foram comparados quanto a definição do tratamento e incidência de toracotomia fútil em cada estratégia. **Resultados:** O EM com FDG-PET classificou 48,4% dos pacientes como estádio mais avançado e 5,3% como menos avançado. O resultado do EM modificaria o tratamento em 41% dos pacientes. A toracotomia foi considerada fútil em 47% dos pacientes com EC e em 19% dos casos com EM. O custo das toracotomias fúteis em oito pacientes no EM foi de R$ 79.720, enquanto em 31 pacientes no EC seria de R$ 308.915. Apenas esta economia seria mais que suficiente para cobrir os custos de todos os exames de FDG-PET nos 95 pacientes (R$ 126.350) ou de FDG-PET/CT (R$ 193.515). **Conclusão:** O EM com FDG-PET tem maior acurácia que o EC em pacientes com CPNPC. A FDG-PET e FDG-PET/CT são custo-efetivas e sua utilização se justifica economicamente na saúde pública no Brasil.
Unitermos: Câncer de pulmão não pequenas células; FDG-PET; Estadiamento; Custo-efetividade.

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INTRODUCTION

Non-small cell lung cancer (NSCLC) corresponds to approximately 85% of all lung neoplasms, and is the main cause of deaths from lung cancer in Brazil nowadays. According to Instituto Nacional de Câncer (INCA) (National Cancer Institute),

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the estimated mortality due to NSCLC in Brazil reached 14,715 patients in the year of 2000[1], with 27,270 new cases in 2008[2].

The initial staging of NSCLC determines the best treatment approach and is essential to define the patient's prognosis[3,4]. Thus, an incorrect staging of NSCLC may lead to inappropriate treatment (futile surgeries in patients with advanced disease, as well as contraindication for curative surgery in patients with an otherwise curable disease)[5,6].

The TNM classification of malignant tumors, developed by the American Joint Committee on Cancer, is the most commonly utilized staging system, and is based on tumor size, regional lymph nodes involvement and presence of metastasis. The definition of the nodal stage (N) is particularly important in the decision making regarding neoadjuvant therapy to be adopted before surgical resection, potentially increasing the long-term survival of patients with stage IIIA NSCLC[7–9]. Several diagnostic tools have been investigated for the early detection and staging of NSCLC, including chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), bronchoscopy, videothoracoscopy, transesophageal ultrasonography (EUS) or transbronchial ultrasonography (EBUS) and mediastinoscopy.

Positron emission tomography (PET) with [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) has consistently played an important role in the noninvasive preoperative staging of patients with NSCLC[10–12]. As compared with CT, FDG-PET is more accurate in N and M staging and, therefore, has a considerable clinical impact in the identification of unresectable disease[13–15]. However, the additional costs arising from the introduction of this new technology must be determined. Thus, the present study is aimed at assessing the impact of metabolic staging (MS) with FDG-PET in the initial staging of patients with NSCLC in Brazil and determine the cost-effectiveness of such a strategy as compared with the conventional staging (CS).

MATERIALS AND METHODS

Patients

The present prospective study, approved by the Committee for Ethics in Research of Universidade de São Paulo/Hospital das Clínicas, included 95 consecutive patients with recent NSCLC diagnosis confirmed by biopsy. The patients were referred by the Service of Pneumology of Instituto do Coração (InCor) – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP). A term of free and informed consent was obtained from all eligible patients in the period between August 2005 and December 2007. Pregnancy and presence of other concomitant tumor were the exclusion criteria.

All the 95 patients were submitted to CS and MS, while MRI and scintigraphy were only performed in cases of clinical relevance.

Conventional staging

All the patients underwent CS, including physical examination, laboratory tests (LDH, alkaline phosphatase, liver enzymes, bilirubin, renal function, calcium) and CT (chest, abdomen and pelvis). At CT, slice thickness was 1 mm thickness, with administration of both oral and intravenous contrast.

Cranial MRI and bone scintigraphy were performed only in the presence of neurological symptoms and bone pain, respectively. EUS with biopsy was performed in the suspicion of mediastinal lymph nodes involvement.

The conventional clinical stage for each patient was attributed in accordance with "The revised TNM staging for lung cancer"[16].

FDG-PET

Tomographic images were acquired from the skull to the roots of the thighs in a dedicated PET apparatus (GE Advance; GE Healthcare, Waukesha, WI, USA), 60 to 90 minutes following intravenous injection of 296–444 MBq (8–12 mCi) of FDG. The images were reconstructed in the axial, sagittal and coronal planes. Attenuation correction was performed with ^{68}Ge sources.

The images were interpreted by two experienced nuclear physicians, both bearing nuclear medicine specialist title. The FDG-PET images were analyzed together with the CT images. Areas of non-physiological concentration with FDG concentration greater than the background concentration were classified as positive for disease. The metabolic stage for each patient was attributed according to the TNM staging system.

The time elapsed between the performance of CT and PET was not longer than two weeks.

Treatment and follow-up

The final TNM staging was obtained at a consensus meeting by a group of oncologists and imaging diagnosis specialists on the basis of all available data (clinical data, initial CT and PET-FDG, bronchoscopy, mediastinoscopy and EUS, as applicable). EUS was considered the reference standard in the preoperative evaluation of mediastinal lymph nodes.

For treatment planning purposes, the patients were divided into groups as follows: (i) stage I: curative surgery; (ii) stages II and IIIA (resectable disease): curative surgery with adjuvant chemotherapy; (iii) stage IIIB: combined chemotherapy-radiotherapy; (iv) stage IV: palliative chemotherapy. Treatment changes after MS were determined in cases of changes in the original treatment plan with basis on FDG-PET results. Positive findings only at FDG-PET study were confirmed by biopsy or TEUS at the discretion of the assisting physician.

All the patients were followed-up according to the local conventional standard, being evaluated at every three months or at shorter intervals, for at least one year.

Reference standard and data analysis

Considering that the histological analysis of all possible sites of involvement by NSCLC is not feasible for obvious ethical and practical reasons, the definition of the diagnostic methods accuracy was based on combined results from conventional methods and FDG-PET to define a reference standard. Intermethod agreement on positive findings at CT and PET (or at bone scintigraphy and MRI, if applicable) has led to interpretation of such findings as true-positive. Agreement between negative clinical and imaging findings has led to interpretation of such findings as true-negative. In cases of disagreeing nodal stages (N) at MS and CS, the criteria utilized to define the result was the anatomopathological evaluation by means of EUS at

stages IIIA or IIIB, or by lymph nodes sampling at thoracotomy, or development of local recurrence, distant metastasis or death up to one year after thoracotomy (stage IV of the disease). The data were prospectively collected.

In the clinical stage analysis, CS and MS results were compared in cases where FDG-PET indicated a change in the surgical approach as the patient stage changed from I-IIIA to IIIB-IV, and vice-versa; and in radiotherapy, as the stage changed from IIIB to IV and vice-versa.

Regarding patients considered eligible for surgery at CS and MS, thoracotomy was considered as futile in cases where anatomopathological evaluation of the surgical specimens confirmed disease at stage IIIB or IV, or in the case of recurrence or death due to any cause up to one year after surgery.

The diagnostic accuracy was analyzed by summing up the number of patients with true-positive and true-negative results, and dividing the result by the total number of patients. The intermethod agreement was evaluated by means of the McNemar χ^2 test. The software SPSS 10.0 for Windows (SPSS Inc.; Chicago, IL, USA) was utilized for statistical analysis.

Cost-effectiveness analysis

All the health care resources required for patients' assessment and treatment were prospectively evaluated and quantified. Drugs, procedures (including investigations, chemotherapy, radiotherapy, surgical procedures, days of hospitalization, outpatient and hospital assistance) or any other resources utilized for local care were calculated by micro-costing methodology. The HC-FMUSP is a public hospital, and all material purchase is performed by means of electronic tendering in statewide bids. The costs of resources were updated for 2010. Medical fees were not included.

The clinical stage of the patient defines which treatment he/she should undergo. The mean cost of each staging of the disease was calculated for each group. The economic impact of CS (strategy I), CS + FDG-PET (strategy II), and PET/CT (strategy III) was calculated.

The calculations of costs for staging and first-line treatment strategies were based on the actual costs of strategy II (CS + FDG-PET) and estimated for strategies I and III.

RESULTS

The patients' clinical characteristics are described on Table 1.

Accuracy and impact on changes in CS and in therapy

Table 2 shows the comparison of CS and MS with FDG-PET. There was agreement between CS and MS in 44/95 (46.3%) of the patients. Intermethod agreement was not observed in 51/95 patients (53.7%): 46/95 (48.4%) patients had their staging changed to more advanced stages with the information provided by FDG-PET (Figure 1), while 5/95 (5.3%) patients had their staging modified to earlier stages (Figure 2).

Considering all the cases in the present study, the inclusion of FDG-PET in CS would change the treatment in 39/95 patients (41.0%) as regards the surgical therapeutic approach (I-IIIA ↔ IIIB-IV), and in 7/95 patients (7.4%) (stage IIIB ↔ IV) as regards radiotherapy.

As regards the reference standard, PET has correctly staged 86/95 patients (90.5%) as compared with 53/95 cases (55.8%) with CS. Results of PET were considered as false-positive in 8 patients, and CT, in four cases; while PET results were considered as false-negative in one patient, and CT in 38 patients. Statistically significant difference was observed between CT and PET results (MacNemar test χ^2: $p < 0.001$).

As regards the final treatment, information from PET would determine change in treatment for 39 patients; in 9 cases the treatment was that suggested by CS, while in 30 patients the results were defined by PET, avoiding surgery in 21 patients, suggesting surgery for two patients and radiotherapy for six patients, and avoiding it for one patient. Finally, considering the final treatment result, MS has correctly defined the treatment in 86/95 (90.5%) of the patients, and CS in 65/95 (68.4%).

Futile thoracotomy

The staging data determined the indication for curative surgical treatment with thoracotomy in 33 patients submitted to MS and in 66 patients submitted to CS.

Among the 66 patients with indication for surgical treatment by CS, the procedure was considered futile in 31 patients (47%): 11 patients with confirmed stage IV, 9 were reclassified as inoperable NSCLC based on anatomopathological findings by EUS, and

Table 1 Clinical characteristics of the 95 NSCLC patients.

Characteristics	95 Patients
Sex	
Female	26 (27.4%)
Male	69 (72.6%)
Age (mean ± SD)	64.6 (± 8.8)
Conventional clinical staging	
I	24 (25.3%)
II	17 (17.9%)
IIIA	25 (26.3%)
IIIB	12 (12.6%)
IV	17 (17.9%)

SD, standard deviation.

Table 2 Comparison of CS and MS with FDG-PET in the 95 NSCLC patients. In bold, the number of patients who had their treatments changed with basis on FDG-PET findings.

	MS							
CS	IA	IB	IIA	IIB	IIIA	IIIB	IV	Total
IA	3	—	—	—	—	**1**	—	4
IB	—	5	—	1	6	**6**	**2**	20
IIA	—	—	2	—	1	**1**	—	4
IIB	—	—	—	4	4	**2**	**3**	13
IIIA	—	—	—	—	12	**6**	**7**	25
IIIB	—	—	—	**1**	**1**	4	**6**	12
IV	—	—	—	—	**2**	**1**	14	17
Total	3	5	2	6	26	21	32	95

CS, conventional staging; MS, metabolic staging.

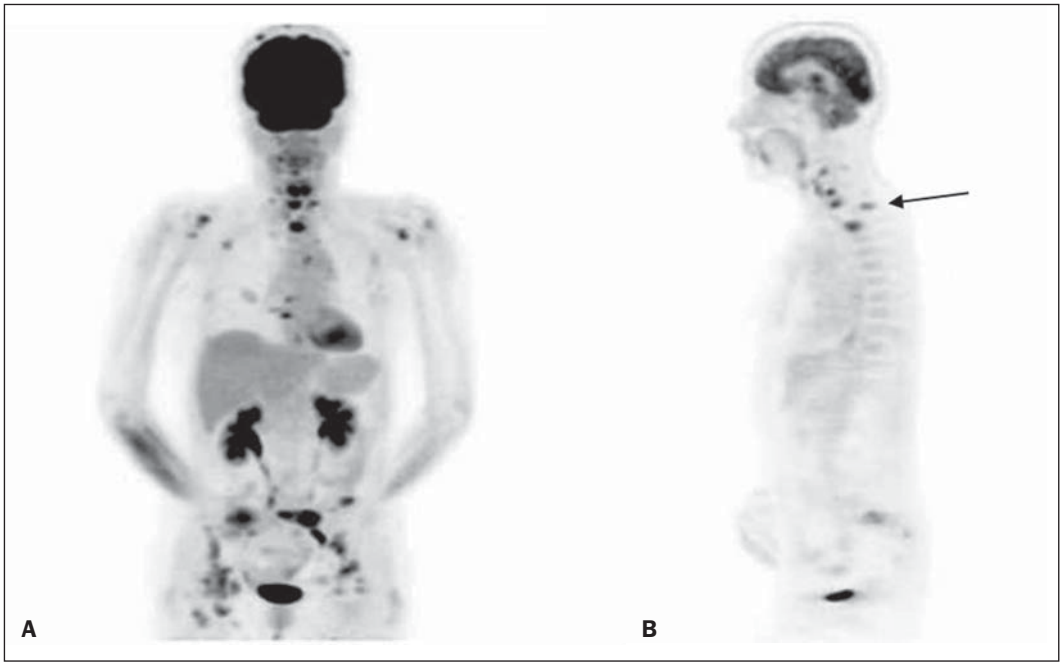

Figure 1. Female patient, smoker, at initial NSCLC staging. At CS, patient presented operable disease. However, FDG-PET scan demonstrated increased FDG uptake bilaterally in cervical lymph nodes and in the mediastinum, besides bone metastasis (**A:** 3D reformation), notably in the cervical and thoracic spine (**B:** sagittal view).

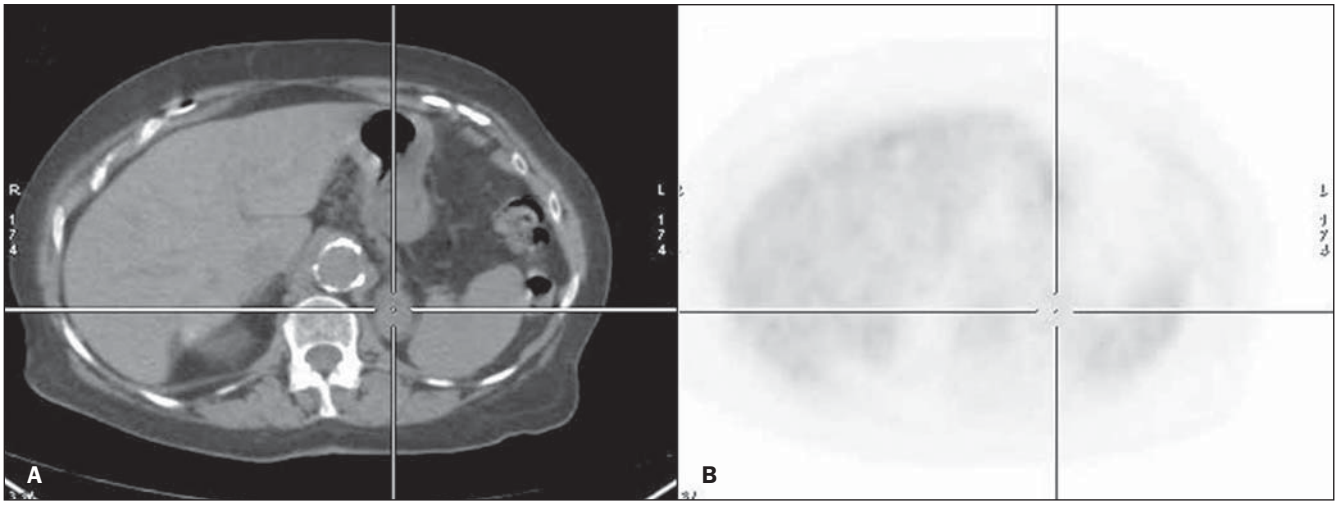

Figure 2. Male patient, smoker, at initial NSCLC staging. At CS, patient presented inoperable disease. Probable left adrenal metastasis at CT (**A:** axial section), however without increase in metabolism (**B:** axial section). Follow-up studies did not demonstrated any change in the the left adrenal gland.

15 died less than one year after thoracotomy.

Considering MS, 8/42 patients (19%) would be submitted to futile thoracotomy: one inoperable case based on EUS, one patient with stage IV, who died, besides six other patients (four patients stage 3A and two stage 2B) who also died less than one year after thoracotomy.

Local costs analysis

The mean costs of the procedures were the following: biopsy, R$ 624; CT, R$ 1,200; MRI, R$ 400; laboratory and biochemistry, R$ 398; EUS, R$ 1,287; FDG-PET, R$ 1,330; PET/CT, R$ 2,037.The costs of the three different strategies are presented on Table 3.

The mean costs of each treatment modality were the following: surgery and hospital procedures, R$ 9,965; adjuvant chemotherapy, R$ 8,422; radiotherapy, R$ 8,000. The costs of staging and first-line treatment are presented on Table 4.

The initial staging of the 95 patients with CT had a total cost of R$ 114,000, while that cost with FDG-PET was R$ 126,350. The calculated cost for PET/CT would be R$ 193,515 for the same patients. The MS by means of FDG-PET would change the disease stage in a considerable number of patients, determining changes in treatment strategies in 39/95 patients (41.0%).

The number of supplementary studies, such as cranial MRI and bone scintigraphy would remain the same with both strategies. However, in CS, EUS would be performed in 26 patients with stages IB to IIIA

Table 3 Summary of the costs with CS strategy, MS with FDG-PET and simulation of the cost with PET/CT in the 95 NSCLC patients.

Procedure	Cost	*n*	Total	*n*	Total	*n*	Total
Biopsy	R$ 624	95	R$ 59,280	95	R$ 59,280	95	R$ 59,280
Laboratory tests	R$ 398	95	R$ 37,810	95	R$ 37,810	95	R$ 37,810
CT	R$ 1,200	95	R$ 114,000	95	R$ 114,000	—	—
PET	R$ 1,330	—	—	95	R$ 126,350	—	—
PET/CT	R$ 2,037	—	—	—	—	95	R$ 193,515
Cranial MRI	R$ 400	28	R$ 11,200	28	R$ 11,200	28	R$ 11,200
Bone scintigraphy	R$ 138	43	R$ 5,934	43	R$ 5,934	43	R$ 5,934
EUS in stage IB and IIIA with suspected N2	R$ 1,287	26	R$ 33,462	27	R$ 34,749	27	R$ 34,749
		Total	R$ 261,686		R$ 389,323		R$ 342,488
		Mean	R$ 2,755		R$4,098		R$ 3,605

CT, computed tomography; FDG, fluoro-deoxy-glucose; PET, positron emission tomography; MRI, magnetic resonance imaging; EUS, transesophageal ultrasonography.

Table 4 Summary of the treatment costs based on CS and MS with FDG-PET and CT.

			Staging with CT		Staging with CT and FDG-PET	
Stage	Treatment	Cost	*n*	Cost	*n*	Cost
I	Surgery and hospital procedures	R$ 9,965	24	R$ 239,160	8	R$ 79,720
IIA a IIIA	Surgery and chemotherapy	R$ 18,387	42	R$ 772,254	34	R$ 625,158
IIIB	Chemotherapy and radiotherapy	R$ 16,422	12	R$ 197,064	21	R$ 344,862
IV	Chemotherapy	R$ 8,422	17	R$ 143,174	32	R$ 269,504
		Total	95	R$ 1,351,652	95	R$ 1,319,244
		Mean		R$ 14,228		R$ 13,887

with N2 disease; and in MS with strategy II or III the EUS would be performed in 27 patients.

The cost of futile thoracotomy in 31 conventionally staged patients reached R$ 308,915, while in eight patients with MS, the cost reached R$ 79,720, representing total savings of R$ 229,195.

The mean cost of staging and first-line treatment with strategy I by CS would be R$ 16,983 per patient; with strategy II (CT + PET) it would be R$ 17,985; and with strategy III (PET/CT) the mean cost would be R$ 17,492 per patient.

DISCUSSION

Patients with NSCL at clinical stages IA, IB, IIA, IIB of the disease might benefit from curative surgical resection. Patients with stages IIIB and IV are inoperable, while patients with stage IIIA rarely meet the criteria for surgery. The current role of neoadjuvant chemotherapy for selected patients with stage IIIA remains controversial[16].

The present study results confirm the benefits of MS as compared with CS, leading to a more accurate definition of the disease stage and, therefore, an increasingly more refined treatment strategy for the patient. The data from FDG-PET resulted in the modification of the stage in approximately half the cases (51/95; 53.7%) and changes in treatment in approximately one-third (30/95; 31.6%) of the cases, particularly avoiding unnecessary treatment in one-third of the patients (21 cases had contraindications for surgery, and 6 cases for radiotherapy) while suggesting more aggressive treatment for only three patients (surgical treatment for two patients and radiotherapy for one patient).

Several other studies have demonstrated the significant clinical impact of FDG-PET on the initial staging of NSCLC patients, ranging from 22% to 67%[5,17–19]. As CS and CS + MS strategies are compared, it is also important to consider the costs of exams and subsequent procedures performed for the investigation of the results of such new method. In the present study, the investigation strategy including FDG-PET increased the number of subsequent procedures in only one of the 95 patients.

Randomized studies[5,20,21] suggest that FDG-PET and FDG-PET/CT improve the accuracy in the mediastinal staging of NSCLC, as compared with CT, confirming the results reported by previous non-randomized studies[22–28]. Typically, hybrid PET/CT devices present a better performance than PET alone, optimizing the interpretation of both modalities as it allows for the anatomical identification of areas with increased metabolism[29–33].

Three important randomized studies reported the impact of adding FDG-PET to conventional staging for NSCLC[5,21,22]. Their results were different. Viney et al.[20] have faced as primary result the performance of thoracotomy, which was performed in 98% of their patients of the CS group and in 96% of the group MS with FDG-PET besides CS ($p = 0.44$), and demonstrated that the addition of PET did not significantly reduce the number of thoracotomies. The main result of the study developed by van Tinteren et al.[5] was futile thoracotomy. The rate of futile thoracotomies was 41% in the CS group and 21% in the group of MS with PET in association with CS ($p < 0.003$). In 2009, Fischer et al.[21] randomized the investigation by means of CS and MS followed by the in-

vestigation of any abnormality. The rate of futile thoracotomies was 52% in the CS group and 35% in the group with CS associated with MS. The present study results are in agreement with those of the latter two studies, demonstrating the benefits of MS, with a significantly lower rate of futile thoracotomies in comparison with the rate obtained by CS (19% versus 47%).

There are scarce studies approaching the utilization of FDG-PET in Brazilian patients[34,35], and studies approaching analysis of its cost-effectiveness are even rarer[36]. The rational utilization of financial resources is extremely relevant for the public health system, moreover in developing countries such as Brazil. Additionally, one should take into consideration that results of cost-effectiveness studies in certain countries may not necessarily apply to others. In the case of the present study, the results corroborate those of studies developed in other countries and demonstrate the cost-effectiveness of MS with FDG-PET in cases of NSCLC. The costs of futile thoracotomies in eight patients with MS reached R$ 79.720, while those costs in 31 patients with CS reached R$ 308.915. Just such saving in costs (R$ 229.195) would be more than enough to cover the costs of all FDG-PETs (R$ 126,350) or even FDG-PET/CTs (R$ 193,515) for all of the 95 patients.

One should take into consideration that the present study results may be questioned with respect to the utilization of PET apparatuses instead of PET/CT apparatuses for staging of NSCLC. However, it is interesting to notice that the data regarding accuracy data in the present study are quite similar to reported data for PET/CT. This can be explained by the careful correlation of the PET and CT images during the reading of the FDG-PET studies. The main disadvantage in the present study is the absence of histological confirmation of all the lesions. Until recently, mediastinoscopy was considered as being the gold standard for N staging[16]. However, new and less invasive technologies are emerging, such as the case of EUS and EBUS. Thus, due to superimposition of anatomical areas, mediastinoscopy was not mandatory in the present study. Additionally, a randomized and controlled study would have been more elegant, however, ethical considerations impaired such option.

CONCLUSION

The present study demonstrates that MS with FDG-PET is more accurate than CS with CT. Additionally, FDG-PET is a cost-effective imaging method in initial staging of NSCLC, allowing a better selection of patients for the most appropriate treatment in approximately one-half of the cases and reducing the number of futile thoracotomies from 47% to 19%.

The introduction of MS with FDG-PET or FDG-PET/CT is a very cost-effective option, with acceptable cost for NSCLC staging, and therefore, its utilization is economically justifiable in the Brazilian public health system.

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