ORIGINAL ARTICLE

Preoperative Staging of Lung Cancer with Combined PET–CT

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ABSTRACT

BACKGROUND

Fast and accurate staging is essential for choosing treatment for non–small-cell lung cancer (NSCLC). The purpose of this randomized study was to evaluate the clinical effect of combined positron-emission tomography and computed tomography (PET–CT) on preoperative staging of NSCLC.

METHODS

We randomly assigned patients who were referred for preoperative staging of NSCLC to either conventional staging plus PET–CT or conventional staging alone. Patients were followed until death or for at least 12 months. The primary end point was the number of futile thoracotomies, defined as any one of the following: a thoracotomy with the finding of pathologically confirmed mediastinal lymph-node involvement (stage IIIA [N2]), stage IIIB or stage IV disease, or a benign lung lesion; an exploratory thoracotomy; or a thoracotomy in a patient who had recurrent disease or death from any cause within 1 year after randomization.

RESULTS

From January 2002 through February 2007, we randomly assigned 98 patients to the PET–CT group and 91 to the conventional-staging group. Mediastinoscopy was performed in 94% of the patients. After PET–CT, 38 patients were classified as having inoperable NSCLC, and after conventional staging, 18 patients were classified thus. Sixty patients in the PET–CT group and 73 in the conventional-staging group underwent thoracotomy ($P=0.004$). Among these thoracotomies, 21 in the PET–CT group and 38 in the conventional-staging group were futile ($P=0.05$). The number of justified thoracotomies and survival were similar in the two groups.

CONCLUSIONS

The use of PET–CT for preoperative staging of NSCLC reduced both the total number of thoracotomies and the number of futile thoracotomies but did not affect overall mortality. (ClinicalTrials.gov number, NCT00867412.)

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Staging of non–small-cell lung cancer (NSCLC) was one of the first approved indications for the use of positron-emission tomography (PET).[1,2] Since 2001, combined PET and computed tomography (PET–CT) has rapidly replaced stand-alone PET.[3,4] The diagnostic capability of PET–CT in the preoperative staging of NSCLC is superior to that of CT alone and PET alone.[5] The advantage is based mainly on a more accurate assignment of tumor stage (T stage) and to a lesser extent on defining the lymph-node stage (N stage).[5-7] Whether the improved diagnostic accuracy improves management of the disease is unknown.

Two randomized trials have assessed the clinical effect of stand-alone PET. In a trial by van Tinteren et al.,[8] the addition of stand-alone PET to conventional staging of NSCLC reduced the number of futile thoracotomies by 50%. A second randomized trial, however, did not show that adding PET reduced the number of thoracotomies.[9]

Identifying the stage of lung cancer helps determine the appropriate treatment and is essential for prognosis.[10,11] Incorrect staging of NSCLC can result in resections of benign nodules and early local or distant relapse after surgery with curative intent.[8,12] We report on a randomized trial to assess the clinical influence of preoperative staging with PET–CT.

Methods

Patients

We recruited patients from three departments of pulmonology in the area of Copenhagen. Patients were eligible if they were 18 to 80 years of age, had newly diagnosed or highly suspected NSCLC, and were considered to have operable disease after conventional-staging procedures[13] (i.e., medical history, physical examination, blood test, contrast-enhanced CT scan of the chest and upper abdomen, and bronchoscopy). Exclusion criteria were type 1 diabetes, another malignant condition, confirmed distant metastases, known claustrophobia, and an estimated forced expiratory volume in 1 second of less than 30% after surgery. After conventional staging, eligible patients were randomly assigned in a 1:1 ratio to PET–CT and conventional staging, followed by further invasive diagnostic procedures such as mediastinoscopy and endoscopic or endobronchial ultrasonography (the PET–CT group), or to conventional staging and invasive diagnostic procedures alone (the conventional-staging group). In both groups, mediastinoscopy was mandatory. Randomization was performed centrally with the use of a permuted-block design, stratified according to sex and recruiting center.

Study Design

The study was initiated by the investigators, and the authors planned the study, gathered and analyzed data, wrote the manuscript, and made the decision to publish the findings. No financial support was received from companies that make PET–CT scanners. The study was approved by the ethics committee of each participating hospital and was conducted according to the Declarations of Helsinki and Tokyo. Written informed consent was obtained from all patients. Data were collected in a central database, managed by the Clinical Research Unit at the Department of Oncology, Rigshospitalet, Copenhagen.

PET–CT Imaging

All PET–CT scans were obtained in the Department of Clinical Physiology, Nuclear Medicine, and PET, Rigshospitalet. After a 6-hour fast, 400 MBq of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) was given intravenously, and after a 1-hour rest, the patient was scanned from the head to the upper thigh with the use of an integrated PET–CT system (GE Discovery LS, GE Healthcare). A diagnostic CT scan, obtained with the use of a standard protocol (80 to 100 mA, 120 kV, a tube-rotation time of 0.5 second per rotation, a pitch of 6, and a slice thickness of 5 mm, with 70 ml of intravenous contrast medium containing 300 mg of iodine per milliliter [Ultravist, Bayer Schering], administered at a rate of 2.5 ml per second), preceded the PET scan (a 5-minute emission scan per table position and 25 minutes total). The PET scan was reconstructed by filtered back-projection and ordered-subset expectation-maximization (OS-EM), with data from the CT scan used for attenuation correction.

An experienced radiologist and a nuclear medicine specialist evaluated the PET–CT images side by side, and a consensus was reached on the findings. A lesion with increased uptake of ^{18}F-FDG in three planes as compared with background on a PET scan was classified as malignant. If the image could not be interpreted with confidence, the standardized uptake value (SUV), defined as

the activity per milliliter within the region of interest divided by the injected dose in megabecquerels per gram of body weight, was calculated, and lesions with an SUV above 2.5 were deemed malignant. The tumor–node–metastasis (TNM) stage was assigned according to the revised classification of Mountain.[14]

TREATMENT AND FOLLOW-UP

Before a decision to operate was made, a consensus on the TNM stage was reached by a pulmonologist and a thoracic surgeon on the basis of all available information (clinical data, initial CT scanning, PET–CT imaging, bronchoscopy, mediastinoscopy, and if available, endoscopic ultrasonography with fine-needle aspiration or endobronchial ultrasonography). Mediastinoscopy and endoscopic or endobronchial ultrasonography served as the standard for preoperative assessment of mediastinal lymph nodes. All patients with stage I to stage IIB NSCLC were offered surgery. Patients with involvement of mediastinal

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	PET–CT (N=98)	Conventional Staging (N=91)	P Value
Patients			
Age (yr)			0.22
Mean	63	64	
Range	42–80	38–80	
Male sex (no. of patients)	53	49	0.97
Female sex (no. of patients)	45	42	
ECOG performance status (no. of patients)†			0.89
0–1	93	86	
2	1	1	
Not available	4	4	
Lactate dehydrogenase (U/liter)			0.91
Mean	290	288	
Range	107–618	119–688	
Tumor			
Size on CT (mm)			0.35
Mean	46.5	43.6	
Range	10.0–110.0	15.0–130.0	
Localization in lung on CT (no. of foci)			0.72
Central	15	12	
Intermediate	13	10	
Peripheral	22	20	
Not available	42	49	
Prerandomization assessments			
TNM stage based on CT of thorax and abdomen (no. of patients)			0.77
IA	13	9	
IB	17	13	
IIA	0	0	
IIB	5	7	
IIIA	26	28	
IIIB	32	32	
IV‡	5	2	

Table 1. (Continued.)

Characteristic	PET–CT (N=98)	Conventional Staging (N=91)	P Value
Ultrasonography of abdomen (no. of patients)	7	6	
Cytology on pleural effusion (no. of patients)	1	2	0.61
MRI of the brain (no. of patients)	1	0	
Mediastinoscopy (no. of patients)			
Total	89	88	
Positive yield§	9	12	0.35
Endoscopic ultrasonography (no. of patients)			
Total	42	30	0.18
Fine-needle aspiration	36	24	
Positive yield§	16	7	0.32
Histologic features at operation (no. of patients)			0.28
Squamous-cell carcinoma	22	22	
Adenocarcinoma	30	29	
Large-cell carcinoma	4	12	
Bronchoalveolar carcinoma	0	1	
NSCLC with no further specification	5	4	
Other¶	2	2	
Benign lung lesion	0	3	

* ECOG denotes Eastern Cooperative Oncology Group, MRI magnetic resonance imaging, NSCLC non–small-cell lung cancer, PET–CT combination positron-emission tomography and computed tomography, and TNM tumor–node–metastasis.
† In this study, ECOG performance scores ranged from 0 to 2, with higher scores indicating greater impairment.
‡ In the PET–CT group, three patients had solitary metastasis in the ipsilateral lung but the other lobe, and two patients had unilateral adrenal metastasis. In the conventional-staging group, two patients had solitary metastasis in the ipsilateral lung but the other lobe.
§ A positive yield was defined as stage N2 to N3 disease.
¶ In the PET–CT group, one patient had pleomorphic carcinoma, and one had carcinoid tumors. In the conventional-staging group, one patient had adenosquamous carcinoma, and one had carcinoid tumors.

lymph nodes or distant metastases (stage IIIA [N2] to stage IV) were considered to have inoperable disease and were offered chemotherapy with or without radiotherapy. Positive findings on PET–CT were further evaluated by biopsy or other imaging techniques (ultrasonography, radiography, or magnetic resonance imaging) at the discretion of the referring clinician. Follow-up data were retrieved from medical records and the local registry of patients.

STATISTICAL ANALYSIS

The primary end point of the study was the frequency of futile thoracotomies. The criteria for classifying a thoracotomy as futile included any one of the following findings or results: a benign lung lesion, pathologically proven mediastinal lymph-node involvement (stage IIIA [N2]), stage IIIB or IV disease, inoperable T3 or T4 disease, or recurrent disease or death from any cause within 1 year after randomization.[8]

To observe a difference of 15% in the number of futile thoracotomies between the PET–CT group and the conventional-staging group, with two-sided type I and type II error rates of 5% and 10%, respectively, an estimated 215 consecutive, unselected patients would have to be randomly assigned to each group. An interim analysis was planned after the inclusion of 220 patients. However, the study was closed after the inclusion of only 189 patients because of slow accrual. Until then, no data were analyzed.

The total number of thoracotomies and the number of futile thoracotomies in each group were compared by means of a chi-square test with a two-sided significance level of 0.05. When

the expected number in any cell was less than five, a Fisher's exact test for two-by-two tables and a Fisher–Freeman–Halton test for two-by-k tables for binary comparison were used. Clinical characteristics of patients at randomization were compared with the use of an independent t-test for continuous variables and a chi-square test or Fisher's exact test for categorical variables. All reported P values are two-sided and have not been adjusted for multiple comparisons. Confidence intervals for sensitivity and specificity were calculated with the use of the Wilson score method. Survival data were analyzed with the use of a log-rank test. Statistical analysis was performed with the use of SPSS software, version 16, and StatXact software, version 8.

RESULTS

BASELINE CHARACTERISTICS

From January 2002 through February 2007, a total of 189 patients were enrolled and randomly assigned to either the PET–CT group (98 patients) or the conventional-staging group (91 patients). Eleven patients in the PET–CT group did not undergo PET–CT because of an unacceptably long waiting time for a scan or technical problems with the PET–CT equipment. One patient underwent PET–CT but declined all further staging procedures and surgery. Mediastinoscopy was performed in 89 patients in the PET–CT group (91%) and 88 in the conventional-staging group (97%) (P=0.33). Endoscopic ultrasonography was performed in 42 patients in the PET–CT group (43%) and 30 in the conventional-staging group (33%) (P=0.18). Table 1 shows the clinical characteristics of the patients in the two groups.

Table 2. Operability.*

Characteristic	PET–CT (N=98)	Conventional Staging (N=91)	Total (N=189)
	number (percent)		
Operable			
Yes†	60 (61)	73 (80)	133 (70)
No	38 (39)	18 (20)	56 (30)
Reason for nonoperability			
Stage IV	11 (29)	0	11 (20)
Stage IIIB	12 (31)	6 (33)	18 (32)
Stage IIIA (N2)	14 (37)	12 (67)	26 (46)
Other‡	1 (3)	0	1 (2)
Total	38 (100)	18 (100)	56 (100)
Reason for staging up			
PET–CT	13 (34)	0	13 (23)
Endoscopic ultrasonography	7 (19)	7 (39)	14 (25)
CT plus mediastinoscopy	16 (42)	11 (61)	27 (48)
Other§	2 (5)	0	2 (4)

* PET–CT denotes combination positron-emission tomography and computed tomography.
† P=0.004 for the comparison between the two groups.
‡ One patient had stage IA non–small-cell lung cancer (NSCLC) at consensus on tumor–node–metastasis staging but declined to undergo surgery.
§ One patient had stage IA NSCLC but declined surgery, and one patient had stage IV NSCLC according to CT and PET–CT scans and declined further staging.

NUMBER OF THORACOTOMIES

After staging, 60 patients in the PET–CT group (61%) and 73 in the conventional-staging group (80%) were considered to have operable disease and underwent thoracotomy (P=0.004) (Table 2). After the exclusion of the 14 patients in the PET–CT group who did not undergo PET–CT and the 1 patient who underwent PET–CT but declined all further procedures, 52 of 83 patients in the PET–CT group (63%) underwent surgery, as did 73 of 91 in the conventional-staging group (80%) (P=0.01).

In the PET–CT group, 38 patients were not offered surgery after final staging (Table 2). Of these 38 patients, 1 declined to undergo surgery, 1 had unconfirmed stage IV disease, and 13 (34%) were categorized as having inoperable NSCLC on the basis of PET–CT only. PET–CT scans showed previously unrecognized distant metastases in 9 of the 13 patients and unknown mediastinal metastases in 4 patients. The unknown mediastinal metastases were confirmed by endoscopic ultrasonography (three patients) or endobronchial ultrasonography (one patient). Seven patients in the PET–CT group had NSCLC that was categorized as inoperable on the basis of endoscopic ultrasonography with fine-needle aspiration alone — according to TNM staging, two patients had N2 disease, three had N3 disease, and two had inoperable T4 disease. Sixteen patients had NSCLC that was categorized as inoperable on the basis of mediastinoscopy; in 10 of these patients, NSCLC was also categorized as inoperable on the basis of the PET–CT scan. Three of the 16 patients did not undergo PET–CT.

In the conventional-staging group, 18 patients were not offered surgery after final staging. No patient was found to have stage IV disease, but

6 patients had stage IIIB disease and 12 had stage IIIA (N2) disease. Endoscopic ultrasonographic images showed unknown mediastinal metastases in 7 of these 18 patients. The remaining 11 patients with inoperable NSCLC were categorized as such on the basis of mediastinoscopy.

FUTILE THORACOTOMIES

Of the 60 patients in the PET–CT group who underwent thoracotomy, the procedure was futile in 21 patients (35%). In the conventional-staging group, 38 of 73 patients (52%) underwent a futile thoracotomy (P=0.05) (Table 3). After the exclusion of the 14 patients in the PET–CT group who did not undergo PET–CT and the 1 patient who underwent PET–CT but declined further procedures, 13 of 52 patients in the PET–CT group (25%) underwent a futile thoracotomy, as compared with 38 of 73 patients in the conventional-staging group (52%) (P=0.002). Altogether, a total of 21 of 98 patients in the PET–CT group (21%) and 38 of 91 in the conventional-staging group (42%) underwent a futile thoracotomy. In other words, for every five PET–CT scans, one futile thoracotomy was avoided.

A total of 39 patients in the PET–CT group (40%) and 35 in the conventional-staging group (38%) underwent surgery that was considered justifiable (nonfutile). Futile thoracotomies were performed in both groups, regardless of the clinical stage at presentation (Table 4).

DIAGNOSTIC ACCURACY

The diagnostic accuracy and sensitivity of the staging regimen in the two groups in terms of predicting operability can be calculated, assuming that none of the patients who were categorized as having inoperable disease after staging should have undergone surgery (specificity, 100%). For the PET–CT group, the diagnostic accuracy and sensitivity were 79% (95% confidence interval [CI], 69 to 86) and 64% (95% CI, 52 to 75), respectively. For the conventional-staging group, the accuracy and sensitivity were 60% (95% CI, 50 to 70) and 32% (95% CI, 21 to 45), respectively.

FOLLOW-UP

All patients were followed until death or for at least 12 months after inclusion in the trial. The mean follow-up time in both groups was 27 months. Chemotherapy, radiotherapy, or both were given in 61% of the patients in the PET–CT group and in 57% in the conventional-staging group (P=0.05). There were no significant differences in survival between the two groups; median survival was 31 months in the PET–CT group and 49 months in the conventional-staging group (P=0.29). At follow-up, 56% of all patients had died (61% in the PET–CT group and 51% in the conventional-staging group, P=0.15). In most patients, death was caused by lung cancer; however, in six patients, death was caused by other factors. In the conventional-staging group, one patient with no known brain metastasis died from status epilepticus, and in the PET–CT group, five patients died from causes not directly related to lung cancer (stroke, esophageal cancer, exacerbation of chronic obstructive pulmonary disease, and acute myocardial infarction each caused one death, and one patient died of an unknown cause 4.5 years after successful surgery). One death in each group was attributable to complications after primary surgery.

Of the 21 patients in the PET–CT group who underwent a futile thoracotomy, 4 had a relapse or died from lung cancer within 1 year after inclusion in the trial (Table 3). Of the 38 patients in the conventional-staging group who underwent a futile thoracotomy, 13 had a relapse and 4 died of lung cancer within 1 year after inclusion.

Table 3. Distribution of Futile Thoracotomies.*

Characteristic	PET–CT	Conventional Staging	Total
		number (percent)	
Futile thoracotomy			
No	39 (65)	35 (48)	74 (56)
Yes†	21 (35)	38 (52)	59 (44)
Total	60 (100)	73 (100)	133 (100)
Reason that thoracotomy was considered futile			
Exploratory thoracotomy	5 (24)	4 (11)	9 (15)
Benign lung lesion	0	3 (8)	3 (5)
Stage IV disease	3 (14)	0	3 (5)
Stage IIIB disease	4 (19)	8 (21)	12 (20)
Stage IIIA (N2) disease	5 (24)	6 (16)	11 (19)
Recurrence within 12 mo	3 (14)	13 (34)	16 (27)
Death within 12 mo	1 (5)	4 (11)	5 (8)
Total	21 (100)	38 (100)	59 (100)

* PET–CT denotes combination positron-emission tomography and computed tomography. Percentages may not total 100 because of rounding.
† P=0.05 for the comparison between the two groups.

Table 4. Futile Thoracotomies According to Clinical Stage at Presentation.*

TNM Stage	PET–CT†		Conventional Staging‡	
	No Futile Thoracotomy	Futile Thoracotomy	No Futile Thoracotomy	Futile Thoracotomy
	number (percent)			
IA–IIB	20 (51)	10 (48)	13 (37)	14 (37)
IIIA	8 (21)	5 (24)	11 (31)	9 (24)
IIIB–IV	11 (28)	6 (29)	11 (31)	15 (39)
Total	39 (100)	21 (100)	35 (100)	38 (100)

* PET–CT denotes combination positron-emission tomography and computed tomography, and TNM tumor–node–metastasis. Percentages may not total 100 because of rounding.
† P=0.95 for the comparison between the performance of and the nonperformance of thoracotomy.
‡ P=0.70 for the comparison between the performance of and the nonperformance of thoracotomy.

During the follow-up period, 21 of 60 patients in the PET–CT group who underwent surgery and 26 of 73 in the conventional-staging group had a relapse (P=0.94). In the PET–CT group, 62% of patients had a local or regional relapse and 38% a distant relapse. In the conventional-staging group, 35% had a local or regional relapse, whereas 58% had a relapse at distant sites (P=0.007); localization of the relapse was imprecise for the remaining 7%.

DISCUSSION

This randomized trial of combined PET–CT for the staging of lung cancer was closed prematurely because of slow accrual, but the findings confirm that PET–CT improves the preoperative staging of NSCLC, as Lardinois and colleagues also found.[5] Furthermore, PET–CT has a potential clinical effect in that it reduces the number of futile thoracotomies and the total number of thoracotomies.

Our findings are similar to the results of the 2002 trial by van Tinteren et al. involving 188 patients with NSCLC,[8] which showed that staging with stand-alone PET resulted in a relative reduction in the risk of futile thoracotomy of 51% and an absolute risk reduction of 20 percentage points. Despite a different distribution of clinical stage in the two studies (70% of the patients in the trial by van Tinteren et al. were classified as having TNM stage I to stage II disease at presentation, whereas only 34% of our patients presented with localized disease), the results were similar.

The definition of futile thoracotomy is controversial. Thoracotomy was considered futile if disease recurred or the patient died within 12 months after surgery (Table 3), which was the case in 20% of the patients in the PET–CT group and 45% in the conventional-staging group. Excluding these patients, the percentage of futile thoracotomies was virtually the same in the two groups (28% and 29% of all thoracotomies, respectively; P=1.00). However, if our definition of futile thoracotomy is accepted as a valid end point, the significantly higher number of early deaths and relapses in the conventional-staging group than in the PET–CT group was not due to chance or more successful surgery in the PET–CT group but instead reflects a better selection of patients for surgery in the PET–CT group.

An Australian multicenter study of 184 patients, 92% of whom had stage I NSCLC, showed no significant difference in the total number of thoracotomies between the group that underwent staging with stand-alone PET and the group that underwent staging without stand-alone PET.[9] This study, however, did not use confirmatory invasive procedures (only 10 patients underwent mediastinoscopy).[15]

One of the strengths of the present study is the use of mediastinoscopy in most patients (94%), which revealed positive lymph nodes in 11% of the patients. Five of 21 patients in the PET–CT group (24%) and 6 of 38 patients in the conventional-staging group (16%) underwent thoracotomy that was futile because of incidental N2 disease (i.e., N2 disease detectable only by pathological examination of the surgical specimen). However, the effect of incidental N2 disease on the prognosis can be disputed, and it could be argued that these thoracotomies were not futile.[16] Classifying the thoracotomies as justified in these 11 patients results in a frequency of futile thoracotomies of 27% (16 of 60) in the PET–CT group and 44% (32 of 73) in the conventional-staging group, which is still a significant difference (P=0.04).

In conclusion, we found that adding a PET–CT examination to the diagnostic regimen for patients with NSCLC improves sensitivity in preoperative staging. The addition of a PET–CT examination reduces the frequency of futile thoracotomies and the total number of thoracotomies, with no effect (negative or positive) on overall survival.

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CLINICAL TRIAL REGISTRATION

The *Journal* requires investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors (ICMJE) will consider most clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). Current information on requirements and appropriate registries is available at www.icmje.org/faq.pdf.