Impact of FDG-PET-Induced Treatment Choices on Long-Term Outcome in Non-Small Cell Lung Cancer

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Key Words

FDG-PET scan • Long-term survival • Non-small cell lung cancer • Prognosis • TNM staging

Abstract

Background: The TNM staging reflects the anatomic extent of lung cancer and estimates the survival expectation. Addition of FDG-PET to conventional staging (CS) improves accuracy, but few data have described the impact of this on long-term survival in relation to treatment. **Objectives:** To study the influence of FDG-PET on long-term outcome. **Methods:** Long-term outcome data of patients were retrieved out of previously published PET studies of the Leuven Lung Cancer Group. All patients had a potential for radical treatment, and at least 5-year follow-up data. Patients were dichotomized in early (I–IIIA) versus late (IIIB–IV) stages. **Results:** A first analysis – comparison of the 2 staging algorithms, CS alone versus CS+PET – confirmed the better staging capabilities of the latter. A second analysis, focusing on discordant findings and interaction of both staging algorithms, demonstrated that patients with early stage on PET did well, while those with late stage on PET did poorly, irre-

spective of findings on CS. The third analysis focused on the relation between treatment choices at the multidisciplinary board and outcome, which is especially relevant in patients with discordant finding on CS and CS+PET. From all radically treated patients, only those with early stage on CS+PET had a good outcome, but not those with early stage on CS and an unexplained late stage finding on PET. **Conclusion:** This long-term follow-up analysis confirms that addition of PET to CS results in better stage designation and prognosis. Additionally, discordant findings between CS and CS+PET should be considered relevant, with need for cytological/histological examination.

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Introduction

Lung cancer, with 80–85% being non-small cell lung cancer (NSCLC), is the leading cause of cancer-related death in the Western world. The prognosis of NSCLC is strongly related to the extent of disease at diagnosis, which is defined by the TNM stage [1]. Stage also is a major determinant of the choice of treatment.

Conventional staging (CS) is based on different diagnostic tests including imaging techniques such as spiral computer tomography (CT), ultrasound (US), magnetic resonance imaging (MRI) and bone scintigraphy, as well as more invasive procedures such as bronchoscopy or mediastinoscopy. The current staging procedure is, however, far from perfect, as quite some patients without detection of metastatic disease at the time of diagnosis will nonetheless relapse with systemic disease [2]. It can be assumed that these metastases were already present at the time of initial staging but remained undetected with CS.

Metabolic imaging with positron emission tomography and ^{18}F -fluoro-deoxy-glucose (FDG-PET) is able to characterise tissues and to detect potential tumour involvement before anatomical changes occur. The benefits of using FDG-PET in NSCLC staging have been shown in a vast number of series, including randomised data [3, 4]. PET complements CS because of the more accurate assessment of locoregional lymph node spread, detection of metastatic lesions not detected on CS and appropriate differentiation between the malignant or benign character of lesions that remain equivocal on CS [5–8]. Different studies have also shown the impact of PET on stage designation and intent of treatment [9–17].

Few data are, however, available on the predictive value of PET stage – when used as an adjunct to CS – on long-term outcome. We therefore retrieved and analysed follow-up data of at least 5 years of patients included in previous PET protocols in our group. First, we looked for the accuracy of staging based on CS alone versus PET+CS due to more precise stage designation and subsequent effect on treatment decision. A second analysis focused on discordant findings between both staging algorithms and their interaction. Finally, the impact of FDG-PET-induced treatment choices at the multidisciplinary board on outcome was studied, which is especially relevant in patients with discordant finding on CS and CS+PET.

Methods

Patients

After approval by the Institutional Review Board, patients of the databases of different previous prospective FDG-PET studies of the Leuven Lung Cancer Group [18–20] were analysed for long-term overall survival. Patients in these studies had their PET scan performed in the interval from January 1995 until February 1998. The scope of this analysis were the NSCLC patients with a potential for radical treatment who were discussed at the weekly multidisciplinary lung cancer round in the same time interval.

CS and Treatment

CS in our group in the considered time interval consisted of a thorough clinical history and physical examination, blood tests including a complete blood count, serum calcium, and liver function tests. All patients had a contrast-enhanced CT scan of the thorax and an upper abdominal CT or ultrasound. Brain CT was performed in case of neurological symptoms and in all patients with non-squamous histology. Bone scintigraphy was carried out in patients with bone pain, raised alkaline phosphatase or serum calcium, completed by bone radiographs, bone CT or bone MRI in case of equivocal findings. Mediastinoscopy was performed in all patients, except those with peripheral T1–T2 squamous cell carcinoma and no enlarged lymph nodes on CT scan. For this manuscript, a clinical stage was assigned to all patients based on the CS findings, and according to the 1997 TNM system [1].

In the time frame the study was done, the treatment strategy for stage I and II was surgical resection or radical radiotherapy in case of medical inoperability. For stage IIIA, cisplatin-based induction chemotherapy was given, followed in responders by either attempted complete resection (completed by postoperative radiotherapy in case of persistent N2 in the resection specimen) or radical radiotherapy in case of medical inoperability. In non-responders, chemotherapy was followed by palliative radiotherapy. Treatment for stage I–IIIA was considered radical, except for patients with stage IIIA non-responding to chemotherapy. Stage IIIB and IV were considered advanced stages and in general received non-radical treatment consisting of either palliative radiotherapy, chemotherapy or best supportive care.

Whole-Body PET Scan

The method of PET scanning was detailed in the previous reports [18–20]. In brief, patients fasted for at least 6 h. Whole-body images were acquired on a CTI-Siemens 931/08/12 PET camera, 60–90 min after injection of 6.5 MBq/kg FDG, starting from the pelvis up to the head (10 bed positions, 4-min emission scan per bed position). Coronal, sagittal and transaxial images were iteratively reconstructed (32 iterations) [21]. All whole-body PET images were reanalysed by 2 nuclear medicine physicians (S.S., I.D.) without knowledge of the CS. Images were interpreted visually on a computer display. Any focal uptake, incompatible with normal anatomy and not localised in the primary tumour or locoregional lymph nodes, was considered as metastatic disease. In case of discordance between the 2 readers at first review, a final decision was made based on consensus.

Follow-Up

Follow-up data were gathered from own clinical follow-up and contact with referring physicians or with general practitioners. Duration of survival was defined as the time between the date of PET and the date of death or last follow-up visit.

Study Design and Statistical Analysis

To perform the survival analyses, patients were dichotomized into 2 groups regarding stage, creating an 'early stage' group (patients staged I–IIIA) and a 'late stage' group (IIIB–IV). This dichotomization was chosen because, in our clinical experience [22], it best reflects groups of patients with better versus worse prognostic outcome. The findings based on CS alone versus CS+PET resulted in 4 distinct groups: patients with early stage on CS and early stage on CS+PET (early stage CS/early stage CS+PET),

Table 1. Characteristics of the 139 patients

Age	
Median, years ¹	65 (34–83)
Gender	
Female	14 (10.1%)
Male	125 (89.9%)
Histology	
Squamous cell carcinoma	86 (61.9%)
Non-squamous cell carcinoma	53 (38.1%)
Treatment	
Surgery complete resection	96 (69.1%)
Radical radiotherapy	7 (5.0%)
Chemotherapy + surgery	6 (4.3%)
Chemotherapy + radical radiotherapy	1 (0.7%)
Total with radical treatment	110 (79.1%)
Surgery incomplete resection	1 (0.7%)
Non-radical radiotherapy	9 (6.5%)
Chemotherapy + non-radical radiotherapy	13 (9.3%)
Chemotherapy	3 (2.2%)
Best supportive care	3 (2.2%)
Total with non-radical treatment	29 (20.9%)
Follow-up	
Total group: median, months ²	34.7 (27.5)
Surviving patients: median, months ²	89.3 (34.7)
Stage designation	
CS early/CS+PET early	103 (74.1%)
CS early/CS+PET late	14 (10.0%)
CS late/CS+PET early	13 (9.4%)
CS late/CS+PET late	9 (6.5%)

¹ Figures in parentheses are ranges.

² Figures in parentheses are SD.

Table 2. Patients with metastatic stage on CS, changed to lower stage by PET, and ensuing outcome

CS stage	Site of M1 on CS	CS+PET stage	Investigation or follow-up
IV	other lung (CT)	IA	survival
cT1N0M1		cT1N0M0	76.6 months
IV	other lung (CT)	IB	survival
cT2N0M1		cT2N0M0	91.9 months
IV	other lung (CT)	IB	survival
cT2N0M1		cT2N0M0	87.0 months
IV	other lung (CT)	IB	survival
cT2N0M1		cT2N0M0	83.0 months
IV	adrenal gland (CT)	IB	survival
cT2N0M1		cT2N0M0	46.5 months
IV	other lung (CT)	IB	survival
cT2N0M1		cT2N0M0	42.3 months
IV	adrenal gland (CT)	IIB	survival
cT3N0M1		cT3N0M0	90.9 months
IV	adrenal gland (CT)	IIIA	survival
cT2N1M1		cT2N2M0	48.6 months
IV	other lobe (CT)	IIIA	survival
cT3N2M1		cT3N2M0	25.2 months
IV	other lung (CT)	IB	wedge excision: benign
cT2N0M1		cT2N0M0	
IV	other lung (CT)	IIA	wedge excision: benign
cT2N0M1		cT2N0M0	
IV	other lobe (CT)	IIIB	survival
cT4N2M1		cT4N2M0	10.8 months
IV	liver (CT/MRI)	IIIB	survival
cT3N1M1		cT2N3M0	9 months

and likewise early stage CS/late stage CS+PET, late stage CS/early stage CS+PET, and late stage CS/late stage CS+PET.

Continuous variables are reported with their median value and range. Survival analyses were performed with the Kaplan-Meier method and log rank test. Reported p values are two-sided.

Results

A total of 139 patients were available for analysis. Patient and tumour characteristics, as well as information on treatment and follow-up, are shown in table 1. Treatment was with radical intent in 79.1% of the patients and consisted of surgery or radical radiotherapy in the majority of cases. Only 7 patients received radical combined modality treatment. Among the non-radically-treated patients, most received induction chemotherapy (only disease stabilization after chemotherapy) followed by

non-radical radiotherapy or non-radical radiotherapy alone. One patient had an incomplete resection. Some patients, initially considered for radical treatment and presented at the multidisciplinary round had confirmed metastatic disease and treatment was adapted to palliative approach. Median follow-up time was 89.3 months (SD 27.5) for the surviving patients and 34.7 months (SD 35.5) for the total group of patients. At the moment the survival analysis was performed, 45 patients were still alive (32.4%).

Stage Designation

Based on CS, 20 patients were staged IA (14.4%), 48 patients IB (34.5%), 17 patients IIB (12.2%), 32 patients IIIA (23.0%), 8 patients stage IIIB (5.8%) and 14 patients stage IV on CS (10.1%; table 1).

In our analysis, addition of PET scan to CS proved to give additional information in 40 of the 139 patients (29%).

Table 3. Patients with non-metastatic disease on conventional staging, but suggested stage IV disease on PET

CS stage	Site of M1 on PET	Investigation or follow-up	TTP and progression site/investigation	Intent of treatment	Survival months
IA cT1N0M0	lung (other lobe)	follow-up positive	14 months lung and bone	radical	15.2
IB cT2N0M0	other lung	follow-up positive	15 months lung	radical	15.1
IIIB cT4N0M0	other lung	follow-up positive	21 months lung	radical	28.4
IB cT2N0M0	liver	follow-up positive	17 months liver, lung, bone	radical	21.5
IB cT2N0M0	liver	follow-up positive	4 months liver	radical	7.2
IIIA cT2N2M0	other lung	follow-up positive	11 months lung, bone, adrenal	radical	28
IIIA cT2N2M0	adrenal gland	follow-up positive	9 months lung, adrenal	non-radical	11.1
IIIB cT2N3M0	bone	follow-up positive	4 months bone	non-radical	8.4
IIIA cT2N2M0	bone	follow-up positive	3 months bone	non-radical	6.4
IIIA cT2N2M0	bone	follow-up positive	3 months bone and pleura	non-radical	7.7
IIIA cT1N2M0	bone	follow-up positive	3 months bone	non-radical	3.6
IA cT1N0M0	pleura	follow-up positive	25 months pleura	non-radical	28
IIIB cT2N1M0	other lung	investigation positive	wedge resection, other lung malignant	radical	40.6
IIIA cT3N2M0	pleura	investigation positive	pleura malignant at surgery	non-radical	8.8
IB cT2N0M0	other lung	investigation negative	pneumoconiosis at biopsy	radical	20
IA cT1N0M0	pleura	investigation negative	pleura benign at pleuroscopy	radical	16.9

TTP = Time to progression.

In the group of 14 patients with stage IV disease based on CS, adding PET scan permitted assignment to a lower stage in 13 of them (1 patient had FDG uptake in an enlarged adrenal gland, nonetheless proven to be adrenal adenoma at resection). The 13 patients with false-positive stage IV findings on CT scan are listed in table 2. In all but 2 patients, the non-metastatic status suggested by PET was confirmed. Nine patients had a follow-up and survival time compatible with non-metastatic NSCLC (table 2; upper part), while pulmonary wedge resection confirmed the benign lesion of the CT abnormality in 2 others (middle part). Two patients had a bad outcome despite the fact that staging with CS+PET suggested non-

metastatic disease (lower part). In these 2 cases, down-staging based on CS+PET staging resulted however in advanced stage IIIB disease, which may have played a role in bad survival, but certainty about the extrathoracic lesion lacked in these cases.

The reverse, change to metastatic disease, was seen in 16 patients (table 3). In 12 patients (table 3; upper part), follow-up confirmed the metastatic status detected on PET. Advice of the multidisciplinary round was to classify 6 of these patients as early stage, and to offer the patient the advantage of doubt by radical treatment. The staging of 6 others was adapted to advanced disease, who were all non-radically treated. Each of the 12 patients had

Fig. 1. Survival according to CS alone (a) versus CS+PET (b).

a bad outcome and died from their cancer. It should be noted that 3 of them survived for about 28 months, a rather long survival time for metastatic disease. One of these patients had an indolent tumour progression, and both others responded very well to systemic treatment.

Two patients had abnormal FDG uptake suggestive for stage IV, confirmed by further investigation (table 3; middle part): one patient had pleural metastasis found at surgical thoracoscopy and subsequently had non-radical treatment, the other underwent a wedge resection of the contralateral malignant lung nodule and had radical surgery for the primary tumour.

Fig. 2. Survival based on categories of staging.

In 2 patients (table 3; lower part), the abnormal FDG uptake on PET suggestive of stage IV disease was not confirmed by invasive tests (pneumoconiosis nodule in other lung and negative pleuroscopy). Both patients had bad outcome despite radical treatment of the primary tumour.

Additionally, PET scan suggested a second primary tumour in 10 patients. This was pathologically verified in 3, while in 7 others further examinations could not confirm the suggested second primary tumour. These findings obviously did not influence TNM classification of the NSCLC.

Outcome

In the total group of 139 patients, the median survival time was 35.6 months, with a 5-year survival rate of 39.8%.

In the first analysis, outcome in patients with early and late stage based on CS only was compared and the same was done based on staging with CS+PET. When using CS only, 117 patients were classified as early stage and 22 patients as advanced stage. Median and 5-year survival rates for early versus late stage were 39.8 versus 33.3 months and 40.2 versus 37.4%, respectively ($p = 0.3782$; fig. 1a). With CS+PET, 116 patients were in the early stage group and 23 in the late stage group. Median and 5-year survival rates were 57.2 versus 14 months and 47.5 versus 0%, respectively ($p < 0.0001$; fig. 1b).

The second analysis shows the cross-relationship between CS versus CS+PET and early versus late stages,

Fig. 3. Survival prediction by CS (a) versus CS+PET (b), stratified by therapy intention.

thereby creating 4 patient groups (fig. 2). In the first group with early stage on both CS and PET ($n = 103$), the median and 5-year survival were 50.5 months and 45.8%, respectively. In the second group ($n = 13$) with late CS and early PET, the median and 5-year survival data were 83.0 months and 63.3%, respectively. In the third group, with early stage at CS but late stage on PET ($n = 14$), outcome was poor with a median survival time of 15.2 months and no patient surviving 5 years. Finally, the fourth group with late stage findings on CS and PET ($n = 9$) had the worst outcome with a median survival time of 11.3 months and no 5-year survivors.

The third analysis depicted the interaction with treatment (fig. 3). As the results of PET regarding M-stage were not blinded to the treating physicians, this information was used at the weekly multidisciplinary round for final stage designation and optimal treatment selection. In the model with CS alone, the patients did well irrespective of their early or late stage designation, if a radical treatment strategy was chosen based on the data of CS+PET, and the reverse was true for patients with advanced stage on CS+PET (fig. 3a). Thus, the only group with a significantly better long-term prognosis ($p < 0.0001$) were the patients with early stage on CS+PET who received a radical treatment (fig. 3b).

Discussion

PET has an important place in the staging of patients with NSCLC. Due to more accurate stage designation when PET is added to CS alone, the treatment may change from radical to palliative in some, or from palliative to radical in others. This finding, reported in different other series [11, 14, 23], was also in place in our analysis. PET in addition to CS resulted in a significantly better prognostic discrimination between early (I-IIIA) and late (IIIB-IV) stage NSCLC (fig. 1).

Far less data are available, however, on how addition of FDG-PET to CS and its impact on treatment choices influences outcome, and certainly long-term (that is, at least 5-year) outcome. Indeed, a considerable percentage of patients with early stage according to CS, and radically treated, will face metastatic relapse. Our data suggest that additional findings provided by PET (that is, not suspected on CS) should always be considered carefully. In the case of multiple lesions beyond the primary tumour (for example, PET scan showing multifocal bone lesions), the malignant character of these lesions is obvious most of the time. Solitary lesions, on the other hand, are a diagnostic challenge and maximal effort is needed to prove their true pathology, in order to avoid futile radical treatments in true positive findings, and to not withhold a possible radical treatment in case of non-metastatic NSCLC (inflammatory lesions/second primary tumour) [24]. In our correlation analysis, patients with early stage on PET did well, irrespective of the stage designation after CS, and vice versa (fig. 2), suggesting that if histological proof of malignancy cannot be obtained (for example, contralateral nodule that cannot be reached by wedge excision), the correct staging and long-term prognosis often is the one suggested by PET scan.

These findings were of course influenced by the treatment administered, but remained valid even when stratified for the treatment administered. Patients in whom we made a choice for radical treatment based on the weekly multidisciplinary review did better, irrespective of their CS stage designation (fig. 3a). But radically treated patients with an advanced stage based on CS+PET had a poor outcome, comparable with all others with non-radical treatment (fig. 3b).

Our study has some important limitations because of its retrospective nature. First, in the evaluation of the additional value of PET on outcome, we could correlate with a well-defined CS, but we could not take other prognostic factors such as performance status or smoking history into account. The influence of performance status is most likely limited, however, as nearly all patients presented at the weekly multidisciplinary round have a performance status of 0–1. Second, the interpretation of all staging

data in regard to treatment is unlikely to be as rigorous as in a prospectively defined protocol. Nonetheless, as all patients were consecutive ones considered for radical treatment, and as treatment decisions at the weekly multidisciplinary round were according to local well-defined guidelines, we think this potential bias is not of major importance. Third, the overall number of patients is limited, resulting in some small groups when results were stratified by treatment. But on the other hand, the nearly complete long-term follow-up in our study is quite unique in a study of this kind.

With the limitations of a retrospective nature in mind, our long-term follow-up findings nonetheless suggest that addition of PET to CS not only results in better stage designation, but also in better prediction of long-term outcome. More data coming from PET databases in relation to long-term follow-up are needed to confirm this finding.

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