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The prognostic value of positron emission tomography in non-small cell lung cancer: Analysis of 266 cases☆

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Summary Positron emission tomography (PET) is more accurate than computed tomography (CT) in the staging of non-small cell lung cancer (NSCLC). We analyzed the prognostic value of PET for survival in NSCLC patients.
Methods: Consecutive patients with proven NSCLC with PET for staging were selected. Staging by laboratory tests, bronchoscopy, chest X-ray, and CT was performed in all patients, leading to a clinical stage (c-TNM) prior to PET. A separate classification (pet-TNM) was obtained from PET images by observers blinded to clinical data. We performed univariate survival analysis with ECOG performance score, sex, weight loss, comorbidity, histology, c-TNM, and pet-TNM as variables. Cox regression analysis was performed with significant variables from the univariate analyses.
Results: Two hundred and sixty-six patients were included, 205 men and 61 women. c-TNM and pet-TNM were identical in 150 (56%) patients, 69 were upstaged, and 47 were downstaged by PET. At time of analysis, 198 (74%) patients had died. Univariate analysis showed significant survival differences for ECOG performance score (0 versus 1/2), weight loss (<10% versus ≥10%), pulmonary comorbidity, c-TNM, and pet-TNM (stage IA versus IB, IIA, IIB, IIIA, IIIB, IV). Cox regression analysis identified pet-TNM as the most significant ($p < 0.001$) prognostic factor, followed by ECOG performance score ($p = 0.018$).
Conclusion: Tumor stage as determined by PET is the most significant prognostic factor for survival in patients with NSCLC.

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1. Introduction

Lung cancer staging is important for determining optimal treatment and prognosis. In practice, a presumptive diagnosis is made on the basis of presentation, risk factors, and physical examination. Subsequently, lung cancer staging is performed with chest radiography, bronchoscopy, computed tomography (CT), and tests to exclude distant metastases [1]. After that, therapy is started and a prognosis can be calculated. Survival curves of non-small cell lung cancer (NSCLC) by Mountain and Dresler were constructed using data from the 10 years prior to publication, i.e. data obtained with radiography, bronchoscopy, and CT [2].

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) as a tracer is a functional imaging technique, which appears to be valuable for staging of NSCLC [3]. PET proved to be more accurate than CT in distinguishing malignant from benign pulmonary nodules, and it is the most accurate non-invasive procedure for the detection of NSCLC metastases to mediastinal lymph nodes and distant sites [4,5].

Whether PET has independent prognostic value has not been evaluated but survival prediction with PET has been subject of several studies, all with a limited number of patients [6—13]. In the largest of these studies, 162 patients were included, and FDG uptake within the primary tumor was strongly associated with survival [13].

We analyzed the prognostic significance of NSCLC staging by PET for survival and determined its relation with known prognostic factors such as clinical stage, weight loss, and performance status.

2. Methods

2.1. Patients

We selected consecutive patients who underwent PET for the staging of lung cancer. The study was approved by the Medical Ethics Committee of the Groningen University Hospital. Only patients with pathologically proven NSCLC were eligible. Patients with small-cell lung cancer as well as patients with bronchiolo-alveolar cell carcinoma were excluded. All patients were evaluated at the thoracic oncology unit by history, physical examination, complete blood cell count, renal and liver function tests, chest radiography, bronchoscopy, and CT of the chest and upper abdomen prior to PET. Bone scans, upper abdominal ultrasound, and CT or magnetic resonance imaging (MRI) of the brain were performed only in case of symptoms or signs suggestive of specific metastases.

Before PET was performed, a clinical stage (c-TNM) was determined in each patient using all clinical data available. Patients with clinical stages I—IIIB were referred for PET to determine a pet-TNM stage. Patients with clinical stage IV were not referred for PET.

All tumor stages, both clinical and PET stages, were described according to the revised international staging system for NSCLC adopted by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer [14].

2.2. Positron emission tomography

Patients had to fast for 6 h before PET scanning, but they were allowed to drink water and take their usual medications. FDG was synthesized according to Hamacher et al. by an automated computer controlled synthesis module [15,16]. Whole body PET was performed with an ECAT 951/31 or an ECAT HR + scanner (Siemens/CTI, Knoxville, TN, USA). Fields of view were 10.8 and 15.0 cm, respectively, with resolutions of 6 and 5 mm full width at half maximum. Scanning was started 90 min after intravenous injection of 370 MBq of FDG. PET images were reconstructed into coronal, sagittal, and transverse sections, and into an upright rotating projection. Standard ECAT/CAPP software (Siemens/CTI) was used for PET analysis.

PET scans were interpreted by an experienced nuclear physician and a research physician experienced in the analysis of PET images. PET image interpretation was performed blinded to all clinical data, including clinical stage (c-TNM). For each patient, a PET stage (pet-TNM) was determined. FDG uptake was qualitatively assessed, and a hotspot was defined as a focal increase in FDG uptake compared to the background, not explained by physiological tracer uptake. PET images were used to localize pulmonary, mediastinal, and distant hotspots, and to choose the easiest location for histological verification.

2.3. Follow-up

After PET, patients were treated at the pulmonary oncology department. Surgery was performed for stages I—IIIA, chemoradiotherapy for stage IIIB, and chemotherapy for stage IV.

All patients were followed for at least 1 year after the date of PET, unless they died earlier. Dates and causes of death were recorded. Duration of survival was defined as the time between the date of PET and the date of death or last follow-up visit.

2.4. Statistical analysis

Statistical analysis was performed with SPSS 11.5 (SPSS Inc., Chicago, IL). Continuous variables are reported as medians with ranges. Dichotomous variables are reported as percentage with 95% confidence interval (95% CI). The McNemar test was used to compare c-TNM and pet-TNM. Univariate survival analyses were performed with the Kaplan—Meier method and log rank test. Significant variables in the univariate analyses were used for multivariate analysis. Correction for interaction variables was performed. Multivariate analysis was performed with the Cox proportional hazards model, with forward stepwise covariate entry, and significance levels of 0.05 for entry and 0.10 for removal. Reported p values are two-sided, and $p < 0.05$ is considered indicating significance.

3. Results

3.1. Patients

Between October 1996 and December 2001, PET was performed in 399 subsequent patients with suspected

Table 1 General characteristics of the 266 patients

Characteristics	Patients	
	No.	%
Median age: 63 years (range, 29—88)		
Sex		
Male	205	77
Female	61	23
ECOG performance score		
0	112	42
1	135	51
2	19	7
Weight loss		
<10% of normal weight	237	89
≥10% of normal weight	29	11
Pulmonary comorbidity		
None	177	67
Chronic obstructive pulmonary disease	77	29
Asthma	12	5
Vascular comorbidity		
None	179	67
Peripheral	24	9
Cardiac	20	8
Cerebral	6	2
Combination	37	14

lung cancer. We excluded 95 patients who did not have pathologically proven NSCLC, and 38 patients who underwent PET for treatment evaluation instead of staging, resulting in 266 patients who were eligible for analysis. Patient characteristics are outlined in Table 1. Histological subgroups of NSCLC are outlined in Table 2.

c-TNM and pet-TNM were determined in all 266 patients. In 150 (56%) patients, c-TNM and pet-TNM were identical, while 69 (26%) patients were upstaged and 47 (18%) patients were downstaged by PET. In two (0.8%) patients, PET was negative; these patients were diagnosed with squamous cell carcinoma and large cell carcinoma. A statistically significant difference was observed between c-TNM and pet-TNM ($p = 0.031$).

Table 2 Pathological diagnoses of the 266 patients

Characteristics	Patients	
	No.	%
Squamous cell carcinoma	98	37
Adenocarcinoma	80	30
Large cell carcinoma	80	30
Large cell neuro-endocrine carcinoma	4	2
Adenosquamous carcinoma	2	1
Pleomorphic carcinoma	2	1

3.2. Treatment

First-line treatment consisted of surgery in 72 (27%) patients, chemotherapy in 78 (29%) patients, radiotherapy in 29 (11%) patients, a combination in 65 (24%) patients, and no treatment in 22 (8%) patients. Tumor progression occurred in 141 patients after a median progression free interval of 8 months (range, 1—50 months). Of these 141 patients, 101 received second-line treatment, surgery being in 10 patients, chemotherapy in 46 patients, radiotherapy in 41 patients, and a combination in 4 patients.

3.3. Survival and prognostic factors

At time of analysis, 198 (74%) of the 266 patients had died. Cause of death was lung cancer in 179 patients, rectal carcinoma in 1 patient, and intercurrent non-malignant diseases in 18 patients. Sixty-eight patients were still alive, 10 with and 58 without lung cancer.

The prognostic value for survival of c-TNM and pet-TNM were analyzed. For this analysis, eight variables traditionally regarded as being related to NSCLC survival were selected to join c-TNM and pet-TNM in multivariate survival analysis, in order to correct for possible confounding. These additional variables included age, sex, ECOG performance score, weight loss prior to staging, (cardio)vascular comorbidity, pulmonary comorbidity, and histology (squamous versus non-squamous as well as adeno versus non-adeno). Age was the only continuous variable; all others were dichotomous categorical variables.

As first step, separate univariate survival analyses were performed for each of the categorical variables (Table 3). Of all these variables, ECOG performance score (0 versus 1/2), weight loss (<10% versus ≥10%), pulmonary comorbidity (absent versus present), c-TNM (IA versus IB, IIA, IIB, IIIA, IIIB, IV), and pet-TNM (IA versus IB, IIA,

Table 3 Univariate survival analyses (Kaplan—Meier method)

Variable	Log rank test significance
Sex (male vs. female)	0.3118
ECOG performance score (0 vs. 1—2)	0.0001
Weight loss (<10% vs. ≥10%)	0.0003
Vascular comorbidity (absent vs. present)	0.3554
Pulmonary comorbidity (absent vs. present)	0.0328
Histology (squamous vs. non-squamous)	0.8395
Histology (adeno vs. non-adeno)	0.2800
c-TNM (IA vs. IB, IIA, IIB, IIIA, IIIB, IV)	<0.0001
pet-TNM (IA vs. IB, IIA, IIB, IIIA, IIIB, IV)	<0.0001

Table 4 Cox proportional hazards model of prognostic factors

Covariate	Significance	Relative risk[a]	95% CI[a]
Age	0.216		
Pulmonary comorbidity (absent vs. present)	0.130		
Weight loss (<10% vs. ≥10%)	0.115		
ECOG performance score (0 vs. 1—2)	0.018	1.43	1.06—1.92
c-TNM	0.054[†]		
pet-TNM	<0.001[‡]		
Stage IB vs. stage IA	0.049	3.36	1.00—11.27
Stage IIA vs. stage IA	0.012	6.25	1.49—26.18
Stage IIB vs. stage IA	0.007	5.55	1.58—19.50
Stage IIIA vs. stage IA	0.001	8.19	2.49—26.94
Stage IIIB vs. stage IA	<0.001	12.71	3.90—41.44
Stage IV vs. stage IA	<0.001	20.23	6.32—64.63

[a] Relative risks and 95% confidence intervals are reported for significant covariates only.
[†] Overall significance for c-TNM. Differences between c-TNM stages were likewise not significant.
[‡] Overall significance for pet-TNM. Survival of patients in each single pet-TNM stage was significantly different from survival of patients in pet-TNM stage IA.

IIB, IIIA, IIIB, IV) were significant at univariate survival analysis.

These five significant variables were subsequently entered into a Cox proportional hazards model, with the addition of the continuous variable age. Before entering, the categorical variables were checked for proportionality by entering them one by one as strata into the model, all other variables being covariates. Hazard plots showed that all categorical variables were proportionally related to baseline. After this, all categorical variables as well as the age variable were entered as covariates into the Cox proportional hazards model. Interaction variables ECOG performance score × weight loss, ECOG performance score × pulmonary comorbidity, and c-TNM × pet-TNM did not influence outcomes.

In the Cox proportional hazards model (Table 4), pet-TNM was the most significant prognostic factor for survival ($p < 0.001$, higher PET stages predicting worse survival), followed by ECOG performance score ($p = 0.018$). Survival of patients in each single pet-TNM stage was significantly different from survival of patients in pet-TNM stage IA, with an increasing hazard ratio for death for patients in subsequently higher stages.

Age, weight loss, and pulmonary comorbidity did not reach significance, while c-TNM ($p = 0.051$) approached significance.

4. Discussion

Our report is the largest study on the prognostic value of PET in NSCLC. We found tumor extension in the lung, mediastinal lymph nodes, and at distant sites as determined by PET to be the most significant prognostic factor for survival, although clinical staging did approach significance. PET, like any other staging modality, may produce false-negative results. However, the false-negative rate in the present study was extremely low, i.e. 2 out of 266 patients. CT, on the other hand, did not produce false-negative results. The significance of PET in our study confirms the results of eight earlier, but smaller, studies [6—13]. In these studies, PET proved to be an important prognostic factor, but the procedures and tests by which these results were obtained differed markedly. In two of the eight studies, the Cox proportional hazards model was used to show that staging with PET had a much stronger prognostic value for NSCLC than clinical staging without PET [10,13]. In one-third study, the prognostic value of PET was simply determined on the basis of positive or negative PET images after treatment [9]. In six studies, an arbitrary cut-off of the standardized uptake value (SUV) was used to dichotomize patients into a high and a low SUV group. SUV cut-off values were mostly determined post hoc by calculating median SUV of the study population or the SUV cut-off value with the highest discrimination in survival. This resulted in cut-off values of 5, 7, 10, or 20 [6—8,11—13].

In the present study, PET images were analyzed qualitatively, i.e. without the use of a SUV, and we were able to show that qualitative PET assessment had prognostic impact. Qualitative assessment of PET results in fast and useful information, and is the most commonly applied form of PET analysis in daily practice. The calculation of a SUV is useful for research purposes, but calculation increases the amount of time needed for analysis. Furthermore, the interpretation of a SUV in daily practice is complicated by the fact that most studies determined a SUV cut-off values by calculating the median SUV of the study population post hoc, i.e. after the study had been closed. Clinicians and researchers simply do not know the best cut-off SUV yet, waiting for a prospective study validating a previously determined generally accepted 'standard' SUV cut-off value. The next problem may be which SUV to use; it may be the maximum or mean SUV of the primary tumor, lymph nodes, or even of distant metastases. Thus, SUV is surrounded by too many questions to simply indicate its usefulness. This clinical dilemma is illustrated by two studies by Vesselle et al. In one study, the relation between SUV and tumor proliferation rate is demonstrated, but in another study, they found an association between tumor stage and SUV which disappeared after correction of tumor uptake for lesion size [17,18]. These uncertainties about SUV, and the fact that SUV's were calculated in only about half of the participants

in our study, did support us not to use SUV's. Even without calculating SUV's, we were able to demonstrate that tumor extension by lymphatic and hematogenous spread as qualitatively imaged by elevated FDG activity on PET may best determine prognosis.

Patients in the study were required to have NSCLC. However, bronchiolo-alveolar carcinoma (BAC) was excluded. The performance of PET in the detection of BAC, especially pure forms of BAC, seems to be suboptimal. The strategy to exclude BAC from the study resulted in the exclusion of only two patients [19].

Patients were selected for PET on the basis of history, physical and laboratory examinations, chest X-ray, bronchoscopy, and CT. Patients with presumed resectable disease were selected for PET, to exclude distant metastasis and to be informed on their mediastinal status. This strategy excluded obvious stage IV patients with worse performance status. The current staging strategy was developed because PET resources were limited, especially in the beginning of the study period, and because traditional staging without PET was the gold standard for NSCLC. It was not until recently that PET has found its place in the *standard* work-up algorithm of NSCLC in our hospital. With the present results and the outcomes of two meta-analyses in mind, PET can best be performed after clinical staging with chest radiography, bronchoscopy, and CT of the chest and upper abdomen [3,20]. Local tumor growth can reliably be assessed by CT, which can serve as a selection of NSCLC patients for PET, although it has to be emphasized that in our study, PET staging was performed independently from (i.e. blinded to) clinical stage.

5. Conclusions

In this study on prognostic factors for survival of 266 NSCLC patients, tumor stage as determined by qualitative analysis of FDG uptake as measured by PET proved to be the most significant prognostic factor for survival. This was followed by ECOG performance score. Weight loss, clinical tumor stage, age, sex, cardiovascular comorbidity, pulmonary comorbidity, and tumor histology did not reach significance.

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