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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, 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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KEYWORDS
Positron emission tomography; Carcinoma; Non-small cell lung; Prognosis; Cancer staging; Computed tomography; 18F-fluorodeoxyglucose
was strongly associated with survival [13].

were included, and FDG uptake within the primary tumor patients [6—13]. In the largest of these studies, 162 patients been evaluated but survival prediction with PET has been
detection of NSCLC metastases to mediastinal lymph nodes
and it is the most accurate non-invasive procedure for the
distinguishing malignant from benign pulmonary nodules,
NSCL [3]. PET proved to be more accurate than CT in
performance status.
prognostic factors such as clinical stage, weight loss, and
determined in each patient using all clinical data available.

gible. 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 his-
torical verification.

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 Hospi-
tal. Only patients with pathologically proven NSCLC were eli-
gible. 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 his-
tory, 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 mag-
netic 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—IIA 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 sys-
tem 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 med-
ications. 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 res-
olutions 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 projec-
tion. 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 anal-
ysis 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—IIA,
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 multi-
ariate 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

1. Introduction

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

Positron emission tomography (PET) with 18F-fluo-
rodeoxyglucose (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.
Prognostic value of positron emission tomography in non-small cell lung cancer

Table 1: General characteristics of the 266 patients

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

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.  

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 vs. 1/2), weight loss (<10% vs. ≥10%), pulmonary comorbidity (absent vs. present), c-TNM (IA vs. IB, IIA, IIB, IIIA, IIIB, IV), and pet-TNM (IA vs. IB, IIA, IIIB, IV) were significant in univariate analyses (Table 3).

Table 3: Univariate survival analyses (Kaplan–Meier method)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Log rank test significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male vs. female)</td>
<td>0.3118</td>
</tr>
<tr>
<td>ECOG performance score (0 vs. 1–2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight loss (&lt;10% vs. ≥10%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Vascular comorbidity (absent vs. present)</td>
<td>0.3554</td>
</tr>
<tr>
<td>Pulmonary comorbidity (absent vs. present)</td>
<td>0.0028</td>
</tr>
<tr>
<td>Histology (squamous vs. non-squamous)</td>
<td>0.8395</td>
</tr>
<tr>
<td>Histology (adeno vs. non-adeno)</td>
<td>0.2800</td>
</tr>
<tr>
<td>c-TNM (IA vs. IB, IIA, IIB, IIIA, IIIB, IV)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pet-TNM (IA vs. IB, IIA, IIB, IIIA, IIIB, IV)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 2: Pathological diagnoses of the 266 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>98 37</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>80 30</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>80 30</td>
</tr>
<tr>
<td>Large cell neuro-endocrine carcinoma</td>
<td>4 2</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>2 1</td>
</tr>
<tr>
<td>Pleomorphic carcinoma</td>
<td>2 1</td>
</tr>
</tbody>
</table>
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 [17,16]. These uncertainties about SUV, and the fact that SUV's were calculated in only about half of the participants

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Cox proportional hazards model of prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariate</td>
<td>Significance</td>
</tr>
<tr>
<td>Age</td>
<td>0.216</td>
</tr>
<tr>
<td>Pulmonary comorbidity (absent vs. present)</td>
<td>0.130</td>
</tr>
<tr>
<td>Weight loss (&lt;10% vs. ≥10%)</td>
<td>0.115</td>
</tr>
<tr>
<td>ECOG performance score (0 vs. 1—2)</td>
<td>0.018</td>
</tr>
<tr>
<td>c-TNM</td>
<td>0.054</td>
</tr>
<tr>
<td>pet-TNM</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage IB vs. stage IA</td>
<td>0.049</td>
</tr>
<tr>
<td>Stage IIA vs. stage IA</td>
<td>0.012</td>
</tr>
<tr>
<td>Stage IIB vs. stage IA</td>
<td>0.007</td>
</tr>
<tr>
<td>Stage IIA vs. stage IA</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage III vs. stage IA</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage IV vs. stage IA</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a Relative risks and 95% confidence intervals are reported for significant covariates only.

1 Overall significance for c-TNM. Differences between c-TNM stages were likewise not significant.

2 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.
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.

Acknowledgments

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References