Journal of BUON **17:** 724-728, 2012

ORIGINAL ARTICLE

Prognostic value of fluorine-18 fluorodeoxyglucose positron emission tomography in patients with advanced non-small cell lung cancer: Single center experience

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Summary

Purpose: *The purpose of this retrospective single-center study was to evaluate the prognostic implication on overall survival (OS) of the F-18 FDG PET scan in locally advanced or metastatic non small cell lung cancer (NSCLC) patients.*

Methods: *We retrospectively reviewed 120 locally advanced or metastatic NSCLC patients (December 2004-November 2011) treated/followed at the Dicle University, School of Medicine, Department of Medical Oncology.*

SUVmax and other potential prognostic variables (n=18) were chosen for analysis. Univariate and multivariate analyses were conducted to identify prognostic factors for OS.

Results: *Among 18 variables of univariate analysis, 6 were identified to bear prognostic significance: sex (p=0.01), performance status (PS) (p =0.03), stage (p=0.04), bone metastases (p=0.002), serum albumin (p=0.01) and blood glucose level (p=0.03). Multivariate analysis showed that PS, bone metastases and serum albumin level were independent prognostic factors for OS (p=0.01, p=0.004, p=0.003, respectively).*

Conclusion: *PS, serum albumin levels and bone metastases were independent prognostic factors, while FDG uptake of the primary lesion was not associated with prognosis of OS in locally advanced or metastatic NSCLC patients.*

Key words: advanced non-small cell lung cancer, F-18 FDG PET, prognostic factors

Introduction

Lung cancer is the most common among cancer-related deaths in both men and women worldwide [1] and NSCLC constitutes 80-85% of all lung cancer cases. At the time of diagnosis, two-thirds of patients with lung cancer are diagnosed with advanced disease. The median OS for advanced disease is 5.8-12.6 months and the 5-year OS rate is less than 10% [2,3].

The Elderly Lung Cancer Vinorelbine Italian Study Group (ELVIS) showed that systemic chemotherapy resulted in significant survival benefits when compared with best supportive care [4]. Platinum-based doublets are considered the standard therapy for patients with advanced NSCLC [5,6].

Although a number of studies in patients with early-stage NSCLC have shown that the metabolic activity as depicted on FDG PET is correlated with survival [7-14], there are only few studies about this activity as shown on FDG PET in relation to survival in advanced NSCLC patients (7,15,16). It remains ambiguous whether FDG PET in patients with advanced stage (III-IV) NSCLC will ensure prognostic knowledge for survival.

The aim of this study was to investigate the prognostic significance of some characteristics of patients with advanced NSCLC. We also investigated specifically the prognostic implication of F-18 FDG PET in OS in patients receiving first-line platinum-based doublets.

Methods

Patient population

We retrospectively reviewed 120 NSCLC patients who had undergone an FDG-PET scan and were treated from September 2004 to November 2011 at the Dicle University, School of Medicine, Department of Medical Oncology.

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Received 28-02-2012; Accepted 17-03-2012

All of them had locally advanced or metastatic disease or recurrence after curative surgery for NSCLC. Patients who had received neoadjuvant or adjuvant treatment were excluded from study.

Treatment

Patients with stage IV disease were treated with first-line cisplatin-based chemotherapy. Patients with stage III were treated with radiotherapy up to a maximum of 50 Gy and 3 or 4 courses of cisplatin plus docetaxel chemotherapy.

FDG-PET imaging

Whole-body FDG-PET was performed prior to the start of chemotherapy (Biograph 6 PET/CT scanner; CTI/Siemens, Knoxville, TN).

After a 4-h fasting, patients were administered i.v. 370-555 MBq 18F-FDG. Then, 1 h post-injection, CT and PET scans were performed. Blood glucose levels were required to be less than 150 mg/dl prior to FDG injection.

SUV was defined as: SUV = (activity / unit volume) / (injected dose / body weight). The maximum standardized uptake value (SUVmax) was defined as the SUV of a one pixel region of interest corresponding to the maximum value within the entire primary tumor.

Factors analyzed

Eighteen potential prognostic variables were chosen on the basis of previously published clinical trials.

The variables were divided into the following categories: age (<65 or ≥ 65 years), gender (male or female), ECOG PS (0-1, 2-3), histology (squamous cell carcinoma or nonsquamous cell carcinoma), stage (III or IV), weight loss ≥ 5% within the previous 3 months (present or absent), diabetes mellitus (present or absent), smoking history (present or absent), site of metastases (presence vs. absence of liver, bone or brain), SUV max values (<12.9 or ≥ 12.9), and laboratory parameters (hemoglobin, white blood cells (WBC), serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), albumin and blood sugar) (<median or ≥ median) at the time of first-line chemotherapy administration.

In previous studies SUVmax values ranged between 5 and 20 with log-rank probability values to determine a prognostic cut-off point for SUVmax. Because no statistically significant value was found, SUVmax was dichotomized at its median of 12.9 in the present study.

Statistical analysis

All of the analyses were performed using the SPSS statistical software program package (SPSS, version 11.5 for windows). OS was calculated from the start of the first cycle of chemotherapy to the date of death from any cause or the date of the last follow-up and estimated using the Kaplan-Meier method. The Cox proportional hazards regression model was used to determine statistically significant variables related to OS. Differences were assumed to be significant when P value was less than 0.05.

Results

Patient characteristics

The median patient age was 57 years (range 28-76) with 103 (85.8%) males and 17 (14.2%) females. The number of patients with a PS score 0-1 was 85 (70.8%). Seventy-one patients (59.2%) had metastatic NSCLC and 49 (40.8%) had locally advanced NSCLC. Squamous cell carcinoma was the most common histologic type (40.0%). The median OS was 10.0 months (range 1-53). The patient baseline characteristics are listed in Table 1.

Prognostic factors analysis

The results of univariate analysis are summarized

Table 1. Patient and disease characteristics

Characteristics	*N (%)*
Sex	
Male	103 (85.8)
Female	17 (14.2)
Age, years, median (range)	57 (28-76)
Age (years)	
<65	85 (70.8)
≥65	35 (29.2)
ECOG performance status	
0-1	85 (70.8)
2-3	30 (25.0)
Unknown	5 (4.2)
Smoking history	
Current or former	98 (81.7)
Never	22 (18.3)
Weight loss	
Yes	19 (15.8)
No	96 (80.0)
Unknown	5 (4.2)
Diabetes mellitus	
Yes	110 (91.7)
No	10 (8.3)
Stage	
III	49 (40.8)
IV	71 (59.2)
Histology	
Squamous cell carcinoma	48 (40.0)
Nonsquamous cell carcinoma	41 (34.2)
Unknown	31 (25.8)
Metastatic sites	
Liver	15 (12.5)
Brain	16 (13,3)
Bone	36 (30.0)
SUVmax (mean ± SD)	13.9 ± 7.8
OS, mos median (range)	10 (1-53)
Laboratory parameters, median	
Hemoglobin, g/l	13.0
WBC, mm^3	10000
ALT, U/l	23
Albumin, g/dl	3.2
Alkaline phosphatase, U/l	108
LDH, U/l	233
Blood sugar, mg/dl	115

mos: months, OS: overall survival, SD: standard deviation, WBC: white blood cells, ALT: alanine aminotransferase, LDH: lactate dehydrogenase

Table 2. Univariate analysis of survival time by categorical variable

Variables	*Log-rank test value*	*Degrees of freedom*	*p-value*
Sex	6.2	1	0.01
Age	0.2	1	0.86
Stage	6.0	1	0.04
Smoking history	1.5	1	0.22
Performance status	4.7	1	0.03
Histology	0.1	1	0.90
Weight loss	0.8	1	0.36
Diabetes mellitus	0.2	1	0.62
SUVmax, median	0.07	1	0.79
Metastatic sites			
Liver	0.002	1	0.96
Bone	9.6	1	0.002
Brain	0.5	1	0.45
Laboratory parameters, median			
Hemoglobin	0.07	1	0.78
WBC	1.8	1	0.17
ALT	0.9	1	0.33
Albumin	6.0	1	0.01
Alkaline phosphatase	0.5	1	0.46
LDH	0.9	1	0.33
Blood sugar	4.5	1	0.03

For abbreviations see footnote of Table 1

Table 3. Multivariate analysis of prognostic factors

Parameters	*OR*	*95% CI*	*p-value*
Albumin	0.15	0.04-0.52	0.003
Performance status	3.83	1.33-11.0	0.01
Bone metastases	5.75	1.72-19.2	0.004

95% CI: 95% confidence interval, OR: odds ratio

in Table 2. Among the 18 variables of univariate analysis, 6 were identified to have prognostic significance: sex (p=0.01), PS (p =0.03), stage (p=0.04), bone metastases (p=0.002), serum albumin (p=0.01) and blood sugar level (p=0.03).

Multivariate analysis included the 6 significant factors of univariate analysis. The results of multivariate analysis are displayed in Table 3 and show that PS, bone metastases and serum albumin level were independent prognostic factors for OS (p=0.01, p=0.004, p=0.003 respectively) (Figures 1-3).

Discussion

Systemic chemotherapy for patients with advanced NSCLC has limited impact on OS, not merely due to low response rates, but also because of severe adverse effects. Patients eligible for chemotherapy should be selected carefully. Very different prognostic factors for survival have been identified in patients with advanced NSCLC [11,17-19].

The importance of FDG PET for survival in advanced NSCLC still remains a subject controversy [9,12, 5-16], although a number of studies showed that the degree of SUVmax was strongly of associated with increased OS [7,9,15]. Contrary to this, Vesselle et al.

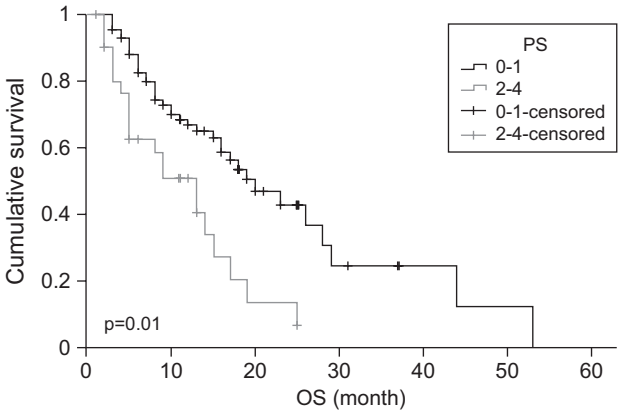

Figure 1. Overall survival according to performance status.

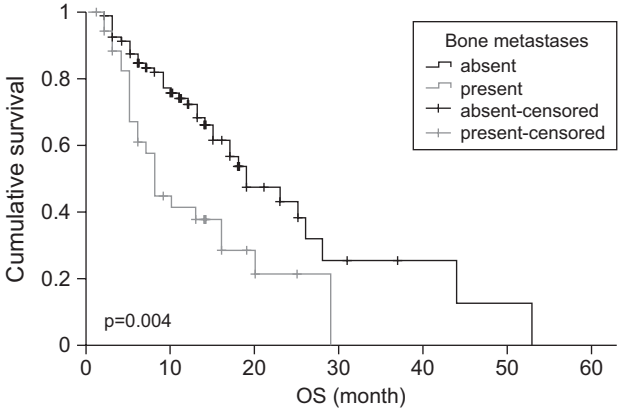

Figure 2. Overall survival according to bone metastases.

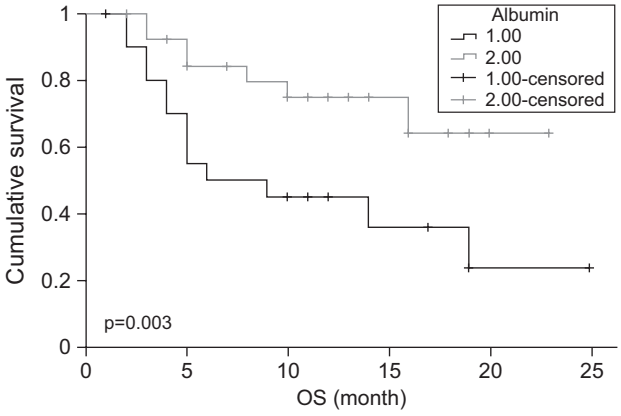

Figure 3. Overall survival according to serum albumin level.

[12] and Hoang et al. [16] did not observe a prognostic value of SUVmax. Similarly, in our multivariate analysis we also found that SUVmax was not associated with survival. This result might be due to methodological bias since SUVmax value could vary greatly depending on the PET system, acquisition and processing protocol.

Poor PS is usually accepted as a negative prognostic factor for all cancer patients [20-22]. The importance of PS was also confirmed in advanced NSCLC patients [23]. In our study it was shown that poor PS was an independent prognostic factor for survival.

An association between decreased serum albumin levels and decreased survival has been demonstrated in patients with advanced NSCLC [24-26]. Similarly, serum albumin level was found to be an independent prognostic factor of survival in the present study. The decreased serum albumin level may play a role in the pathogenesis of cancer cachexia and also may represent the patient's nutritional status. The consequences of malnutrition may include increased risk of complications and decreased response and tolerance to chemotherapy.

A number of authors [24,27] had shown that bone metastases had no significant effect on survival, while Espinosa et al. [26] and James al. [28] reported a prognostic value of the prevalence of bone metastases in patients with advanced NSCLC. Surprisingly, the third independent prognostic factor for survival in our study was bone metastases, because they were not life-threatening. This finding may also be related to the decreased PS (due to pain).

In conclusion, PS, serum albumin levels and bone metastases were identified as important prognostic factors for OS, while FDG uptake of the primary lesion showed no prognostic significance for OS in advanced NSCLC patients. These findings may facilitate pretreatment prediction of survival and can be used for selecting patients for more correct choice of treatment. Prospective clinical trials with larger number of patients might shed more light in this interesting field.

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