ORIGINAL ARTICLE

Is post-treatment standardized uptake value a prognostic factor in unresectable non-small cell lung carcinoma?

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ABSTRACT

Aim Concurrent chemoradiotherapy (CRT) is the standard of care for locally advanced, unresectable non-small cell lung carcinoma (NSCLC). The aim of this study was to assess the prognostic value of maximum standardized uptake values (SUV_{max}) in patients with unresectable stage III NSCLC treated with concurrent CRT.

Method ^{18}F-FDG PET-CT scans were obtained before and after treatment in patients with unresectable stage III NSCLC treated with concurrent CRT. To determine the prognostic value of SUV_{max} of the primary tumor (PT), univariate and multivariate Cox regression model were carried out.

Results Between January 2008 and December 2013, this study included 43 patients (median age 56 years, 95% male). Univariate analysis showed that having a high post-treatment PT-SUV_{max} was associated with a higher risk of death and having a high post-treatment PT-SUV_{max} with a higher risk of disease recurrence. Multivariate analysis showed that having a low post-treatment PT-SUV_{max} (cut off 3.9) was associated with longer overall and progression free survival (HR 8.55, 95% CI; 2.56-28.55, p=0.000 and HR 2.854, 95% CI; 1.43-5.67, p=0.003, respectively).

Conclusion Post-treatment PT-SUV_{max} may be an independent prognostic factor in patients with unresectable stage III NSCLC treated with concurrent chemoradiotherapy.

Key words: lung cancer, prognosis, positron emission tomography

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INTRODUCTION

About one third of patients with non-small cell lung cancer (NSCLC) present locally advanced disease at the time of the diagnosis (1). The standard of care in patients with unresectable, stage III, NSCLC and good performance status is concurrent chemoradiotherapy (CRT) (2). Despite curative treatment with concurrent chemoradiotherapy (CRT), only a low rate of patients become long-term survivors and 15-40% develop recurrence (3,4). Several prognostic factors have been studied, but the two most prominent are performance status and the distinction between stage IIIA and IIIB in stage III NSCLC. Other prognostic factors have been suggested such as age, weight loss, response to treatment and some characteristics describing the locoregional extension of the tumour (4).

Positron emission tomography (PET) is an imaging method based on the metabolic activity of viable tumor cells. The PET-CT (computer tomography) is superior over conventional staging methods in the initial staging of NSCLC (5). A decrease in fludeoxyglucose (FDG) uptake in the primary tumor and/or lymph nodes is expected in patients who responded well to treatment (6, 7). Standardized uptake value (SUV) is a semi-quantitative index of radiolabeled glucose uptake in tumor tissue and has been demonstrated to be correlated with some prognostic factors, including tumor differentiation and aggressiveness (8-10). Prior studies reported that pretreatment maximum SUV (SUV_{max}) of primary tumor predicted treatment response, poor prognosis and especially recurrence and survival (11-19). Nearly most of them included patients with different stages of NSCLC and treated by different therapy modalities. Data evaluating the predictive value SUV_{max} in prognosis, treatment response, clinical outcome and survival in unresectable stage III NSCLC treated with CRT are still limited (4, 19-23).

The aim of this prospective cohort study was to investigate the prognostic value of PET-CT obtained after concurrent CRT in patients with stage III, unresectable NSCLC.

PATIENTS AND METHODS

Patients and study design

Patients treated with CRT for unresectable stage III NSCLC (according to the 6th edition of the TNM staging system) (24) in Suat Seren Chest Disease and Surgery Training and Research Hospital between January 2008 and December 2013 enrolled in the study.

Patients who met the following criteria were included in the study: the FDG uptake by PET-CT before and after concurrent CRT, unresectable stage III disease defined by multidisiplinary team, and those with histological diagnosis.

Methods

All patients received cisplatin 50 mg/m^2 intravenously (IV) on days 1, 8, 29, and 36 with etoposid 50 mg/m^2 IV on days 1-5 and 29-33. Radiotherapy (RT) was delivered using conventional fractionation (1.8-2.0 Gy per day, 5 days per week) with a total dose of 60-66 Gy using 6-10 MV photon beams. All patients received 3D conformal radiotherapy. The gross tumor volume (GTV) consisted of the primary tumor and the regional lymph nodes considered positive (SUV_{max} >2.5) on PET scan even if not involved by CT scan. Any intrathoracic lymph nodes with a diameter greater than 10 mm in the short axis were included in GTV regardless of the PET scan. Adjuvant chemotherapy was not allowed.

Initial (pre-treatment) ^{18}F-FDG PET/CT scans were obtained within 30 days before the treatment. Post-treatment ^{18}F-FDG PET/CT scans were performed at 90 days after CRT. Post-treatment PET-CT were not performed in patients with clear evidence of progression with systemic disease or who died before undergoing post-treatment PET/CT scan or who had reimbursment problem for post-treatment PET-CT scans.

All patients involved in the study underwent whole-body ^{18}F-FDG PET-CT scaning (Biograph 16 HR, by Siemens Medical Solutions, Illinois, United States). The PET component was a high resolution scanner with a spatial resolution of 4.7mm and had no interval, thus allowing 3-dimensional-only acquisitions. The CT portion of the scanner was the Somatom Sensation 16-slices. All patients were advised to fast for at least six hours before PET-CT scan. All patient's were required a blood sugar level of less than 180 mg/dL before ^{18}F-FDG (0.10 mCi/kg) intavenous injection. After injection, the patients rested for a period of about 60±10 minutes in a comfortable room and chair. The patients were positioned

supine, with both arms positioned over the head. Next tomography images were acquired in order to attenuate correction and anatomic localization, PET images were acquired in axial planes from the proximal femur until the vertex, 5-7 bed positions in a 2-minutes per bed postion. Processed images were displayed in coronal, transverse, and sagittal planes.

The PET-CT scans were interpreted semiquantitatively by two nuclear medicine physicians with experience in lung cancer and reported the SUV_{max} values in the primary tumor and in each regional lymph nodes. The final PET interpretation was based on a consensus of the two observers. The SUV for the region of interest (ROI) was decided using SUV_{max} which indicates the highest single voxel SUV within ROI. The lesions with SUV_{max}>2.5 were considered as pathological.

Patients also underwent response evaluation with CT of chest through the upper abdomen in 4 weeks of completing treatment and follow-up continued every 3 months for the first 2 years, every 6 months for third year, and yearly thereafter, with repeated CT of chest through the adrenals on each visit.

Statistical analysis

Overall and progresion free survival (OS and PFS, respectively) were estimated by the Kaplan–Meier method. Univariate and multivariate Cox regression (Backward Stepwise) model were carried out to determine prognostic factors for OS and PFS. Multivariate analysis was performed to the variables that were 2> WALD values with the univariate analysis. Results of this model were presented as Hazard Ratio (HR) and 95% confidence intervals (95% CIs) for OR and PFS. The $p \leq 0.05$ was considered statistically significant. To analyze the impact of SUV on the study end points, the median values were used to divide patients into groups of equal numbers. The variables associated with PET scaning were defined as follows; ΔPT SUV_{max}; Pre-treatment Primary Tumor SUV_{max} - Post-treatment Primary Tumor SUV_{max}, ΔPT % SUV_{max}; Pre-treatment Primary Tumor SUV_{max} - Post-treatment Primary Tumor SUV_{max} / Pre-treatment Primary Tumor SUV_{max} X 100, Post-PT SUV_{max}; Post-treatment Primary Tumor $SUV_{max.}$

RESULTS

Between January 2008 and December 2013, 67 patients were treated with CRT for unresectable stage III NSCLC, of whom 43 met all inclusion criteria for this analysis (Figure 1).

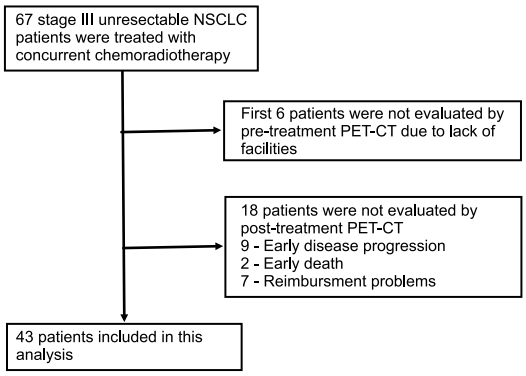

Figure 1. Patient selection

The median age of patients was 56 years (40-71) with 41 (95.3%) males. Squamous cell carcinoma (79.1%) was the most common histologic type. All patients were designated as stage III (including 28 patients who were in stage IIIb, (65.1 %), and all patients had good performance status. The median follow-up time was 20.4 months (8.3–84.0). The median OS and 4-year OS were 25.1 (95%, CI: 20.0-30.1) months and 21.7%, respectively. The median PFS and 3-year PFS were 12.5 (95%, CI: 9.0-15.9) months and 17.5%, respectively (Table 1).

Table 1. Patient characteristics

	No (%) of patients
Age median (range) (years)	56 (40-71)
Gender	
Males	41 (95.3)
Females	2 (4.7)
TNM stage	
T3N1	1 (2.3)
T3N2	2 (4.7)
T3N3	1 (2.3)
T4N0	8 (18.6)
T4N2	21 (48.8)
T4N3	4 (9.3)
T2N3	1 (2.3)
T2N2	3 (7.0)
T1N2	1 (2.3)
T1N3	1 (2.3)
Disease stage	
IIIa	15 (34.9)
IIIb	28 (65.1)
Histology	
Squamous Cell	34 (79.1)
Non-squamous Cell	9 (20.9)
Performance status	
ECOG 0	32 (74.4)
ECOG 1	11 (25.6)

ECOG, Eastern Cooperative Oncology Group

Among the 6 variables of univariate analysis, one was significantly associated with overall survival: post-PT SUV_{max} (hazard ratio [HR], 3.227; p=0.002) (Table 2). Multivariate analysis for OS included the 4 variables (Wald>2) of univariate analysis (Table 2). The results displayed that post-PT SUV_{max} was an independent prognostic factor (HR, 8.558, 95% CI; 2,565-28,552, p=0.000) for overall survival. ΔPT % SUV_{max} showed a trend for overall survival (p=0.051).

Table 2. Univariate analyses of pre and post-treatment variables for overall survival after concurrent chemoradiotherapy

Variable	Wald test	p	HR	95.0% CI for HR	
				Lower	Upper
Stage IIIa vs Stage IIIb	2.070*	0.150	0.585	0.282	1.214
Squamous vs Non-squamous	0.672	0.412	0.669	0.256	1.749
ECOG 0 vs 1	3.537*	0.060	2.098	0.969	4.541
Δ PT %SUVmax ≤ vs >72.6	2.742*	0.098	1.859	0.892	3.873
ΔPT SUVmax ≤ vs >12.1	1.282	0.258	1.520	0.736	3.138
Post-PT SUVmax ≤3 vs >3.9	9.245*	0.002†	3.227	1.517	6.889

*Wald test >2, †p<0.05; HR, hazard ratio; Sig, significance; ECOG, Eastern Cooperative Oncology Group; PT; primary tumor; $SUV_{max,}$ maximum standard uptake value

One variable was significantly associated with PFS in univariate analysis; post-PT SUV_{max} (HR; 2.721; p=0.004) (Table 3). Multivariate analysis for PFS included the 4 variables (Wald>2) of univariate analysis (Table 3). The results displayed that post-PT SUV_{max} was an independent prognostic factor (HR, 2.854, 95% CI; 1,437-5,670, p=0.003) for PFS.

Table 3. Univariate analyses of pre and post-treatment variables for progression free survival after concurrent chemoradiotherapy

Variable	Wald tes t	p	HR	95.0% CI for HR	
				Lower	Upper
Stage IIIa vs Stage IIIb	2.278*	0.131	0.591	0.299	1.170
Squamous vs Non-squamous	0.729	0.393	0.681	0.282	1.645
ECOG 0 vs 1	2.437*	0.118	1.787	0.862	3.705
Δ PT %SUVmax ≤ vs >72.6	2.912*	0.088	1.813	0.915	3.592
ΔPT SUVmax ≤ vs >12.1	0.061	0.804	1.088	0.557	2.127
Post-PT SUVmax ≤ vs >3.9	8.237*	0.004†	2.721	1.374	5.392

*Wald>2, †p<0.05; PT, primary tumor; HR, hazard ratio; Sig, significance; ECOG, Eastern Cooperative Oncology Group; PT; primary tumor; $SUV_{max,}$ maximum standard uptake value

DISCUSSION

This study showed that post-treatment primary tumor SUV_{max} can be an independent prognostic factor for PFS and OS. Cut off level of post-treatment primary tumor SUV_{max} was determined as 3.9. We found no further significant prognostic factors associated with survival in the current study.

An assessment of tumor response to therapy using PET-CT has been proposed and supported in various malignancies (25-28). Higher FDG uptake has been suggested by clinicians to be a useful prognostic indicator as a noninvasive method in a routine clinical setting (29-32). Eschmann et al. reported FDG uptake as an independent prognostic factor in patients with stage III NSCLC (33). Also, it has been used to predict response to chemotherapy and clinical outcome in stage III NSCLC treated with conventional radiotherapy (34, 35). As contrary, Ikushima et al. reported that FDG uptake has no prognostic significance for predicting survival and Vesselle et al pointed that the predictive value of FDG uptake disappears after considering tumor size (36, 37). Also Machtay et al. exuded that neither pretreatment SUV_{max} nor SUV_{peak} could predict long term prognosis (22). Similar to these studies we found no further prognostic significance of pre-treatment SUV_{max} after multivariate analysis.

In previous studies, FDG PET/CT after definitive chemoradiation therapy was shown to predict survival in patients with NSCLC (20, 37). Mc Manus et al. demonstrated that in patients with NSCLC who were treated with concurrent chemoradiotherapy, post-treatment PET scan was a better predictor than CT (20).

Xiang et al. reported that post treatment SUV predicted local recurrence free survival, PFS and OS (23). Lopez Guerra et al. showed that the post RT SUV_{max} in both the primary tumor and the lymph node was a predictor of survival, -specifically the higher residuel SUV_{max} after RT, the poorer for OS and PFS (21). Similar to these studies, Machtay reported that post treatment tumor SUV_{max} is associated with worse survival in stage III NSCLC (22). Consistent with these studies, we found post-treatment primary tumor SUV_{max} was an independent prognostic factors for PFS and OS. Predicting survival and identifying patients who have high risk for progression seems to be important for deciding further management strategies such as new targeting therapies, consolidation or maintenance treatments. Similar to Xiang et al. (23) there was no correlation between ΔSUV and survival in our study, although previous studies have shown such an association among patients with stage III/IV NSCLC treated with chemotherapy. And, patients demonstrating

an absence of metabolic response on post-treatment PET had a shorter time to disease progression and decreased overall survival (38, 40).

The cut-off values used for survival have varied across all previous studies. The best cut-off value that could be used universally remains unknown. Lopez Guerra et al. reported the median post-treatment PT SUV_{max} was 3.7 and patients with SUV_{max} less than the median had a 2 year survival rate 50% when compared with 20% for patients greater than the median (21). Machtay et al. studied various cut off ranges but they could not identify a clinically sufficent cut off value (22). Ryu et al. reported FDG uptake by residual tumor masses 2 weeks after induction chemoradiotherapy predicted pathologic response with 88% sensitivity when an SUV cutoff of 3.0 was used (40). In Xiang et al.'s findings, cut off value 3.6 predicts local relaps free survival (23). In consistence with this study, cutt of value of 3.9 was found in our study population. Variability of these values may be because of the different prevalence of NSCLC subtype and whether or not carcinoids have been studied as well.

The optimal timing of post-treatment PET scan has also been questioned by previos studies, especially in light of potential alteration of the SUV_{max} reading due to the inflammatory response associated with chemoradiotherapy in various malignancies (40, 41). Lopez Guerra et al. suggested that scans done sooner than 2.5 mo after RT may not reflect much of the effect of the RT (21). In our study, all post-treatment PET scans were invariably performed at 90 days after the treatment.

These results are limited by the modest sample size. Also, post-treatment biopsies were not performed. So, we could not exactly confirm whether high post-treatment SUV_{max} represented tumor versus radiation induced inflamation.

İn conclusion, post-treatment primary tumor SUV_{max} may be an independent prognostic factor for unresectable stage III NSCLC. High values than cut off point 3.9 predicts a worse prognosis in this patient group. This study can provide a basis for further trials for evaluating PET scanning as a prognostic indicator in this group of patients.

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Competing interest: none to declare.

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