RESEARCH ARTICLE

Differences in the Prognostic Significance of the SUVmax between Patients with Resected Pulmonary Adenocarcinoma and Squamous Cell Carcinoma

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Abstract

Background: The purpose of this study was to determine the prognostic significance of the maximum standardized uptake value (SUVmax) on F-18-fluorodeoxyglucose (FDG)-positron emission tomography (PET) in patients undergoing surgical treatment for non-small cell lung cancer. Materials and Methods: Seventy-eight consecutive patients (58 with adenocarcinomas, 20 with squamous cell carcinomas) treated with potentially curative surgery were retrospectively reviewed. Results: The SUVmax was significantly higher in the patients with recurrent than with non-recurrent adenocarcinoma (p<0.01). However, among the patients with squamous cell carcinoma, there were no differences with or without recurrence (p=0.69). Multivariate analysis indicated that the SUVmax of adenocarcinoma lesions was a significant predictor of disease-free survival (p=0.04). In addition, an SUVmax of 6.19, the cut-off point based on ROC curve analysis of the patients with pathological IB or more advanced stage adenocarcinomas, was found to be a significant predictor of disease-free survival (p<0.01). Conclusions: SUVmax is a useful predictor of disease-free survival in patients with resected adenocarcinoma, but not squamous cell carcinoma. Patients with adenocarcinoma exhibiting an SUVmax above 6.19 are candidates for more intensive adjuvant therapy.

Keywords: Non-small cell lung cancer - histologic type - PET - maximum standardized uptake value - prognosis

Asian Pac J Cancer Prev, **15 (23)**, 10171-10174

Introduction

Recently, [18F] fluorodeoxyglucose (FDG)-positron emission tomography (PET) has become a valuable tool for evaluating the clinical stage (de Geus-Oei et al., 2007; Al-Jahdali et al., 2012; Liu et al., 2012; Mutlu, et al., 2013), response to therapy (Mac Manus et al., 2003; Hoekstra et al., 2005; Al-Jahdali, et al., 2012; Ding et al., 2012), metastatic potential (Kaya et al., 2008; Zhu et al., 2013) and diagnosis of recurrence (Hicks et al., 2001) in patients with non-small cell lung cancer (NSCLC). Previous studies have shown a correlation between the survival rate and the FDG-PET activity evaluated according to the maximum standardized uptake value (SUVmax) in patients with resected NSCLC (Vansteekiste et al., 1999; Patz et al., 2000; Higashi et al., 2002; Sasaki et al., 2005; Al-Sarraf et al., 2008; Higuchi et al., 2014; Hasbek et al., 2014). However, the prognostic significance of the SUVmax based on the histologic type has not yet been fully elucidated. Therefore, we performed a retrospective analysis of NSCLC patients who underwent complete surgical resection at our institution, focusing on the correlation between the prognosis and histologic type.

Materials and Methods

Patients

We retrospectively reviewed the medical records of consecutive NSCLC patients treated with potentially curative surgery at our institution between January 2007 and December 2011. The postoperative follow-up period was at least 24 months, except for the patients who developed recurrence within 24 months. Because most cases of recurrence of NSCLC have been reported to occur within the first 24 months postoperatively in previous reports (Martini et al., 1995; Walsh et al., 1995; Alberts, 2007; Sugimura et al., 2007), the current patients were divided into two groups: those with/without recurrence at postoperative 24 months. The clinicopathological factors, including the SUVmax, of the two groups were subsequently compared.

FDG-PET

Thoracic PET was performed using a dedicated PET camera (Headtome IV; Shimazu, Kyoto, Japan) with four rings that provided seven tomographic slices (Higashi, et al., 2002). The intrinsic resolution was 5 mm in full width

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at half maximum at the center. Each subject underwent transmission scanning for attenuation correction for 10 minutes after at least four hours of fasting. Immediately after obtaining the transmission scan, 18F-FDG was administered intravenously, and a static scan (14-24 tomographic slices at 6.5 mm intervals) was obtained 40 minutes later for 10-20 minutes using a 128 x 128 matrix. The average injection dose of 18F-FDG was 185 MBq.

Statistical analysis

The data for the two groups were compared using the t-test or Mann-Whitey U test. Survival curves were generated according to the Kaplan-Meier method and compared using the log rank test. The multivariate analysis was carried out using the Cox proportional hazards model. $p<0.05$ was regarded as statistically significant.

Results

Between January 2007 and December 2011, 82 patients underwent complete pulmonary resection. Of these subjects, 58 had adenocarcinoma, 20 had squamous cell carcinoma and the remaining four had other histologic types. Due to the small number of patients with other histologic types, only those with adenocarcinoma or squamous cell carcinoma were enrolled in the analysis.

Twenty-one patients developed recurrence within 24 months, and 57 patients exhibited no episodes of recurrence. The number of patients who developed recurrence according to the histological types was 15 for adenocarcinoma and six for squamous cell carcinoma.

The correlation between recurrence and the SUVmax is shown in Table 1.Among all the patients, the SUVmax was significantly higher in the recurrent cases than in the non-recurrent cases ($p=0.01$). According to the histologic type, however, the SUVmax was also significantly higher in the recurrent adenocarcinoma cases than in the non-recurrent cases ($p<0.01$), but this parameter did not differ between the recurrent and non-recurrent cases among the patients with squamous cell carcinoma ($p=0.69$), thus suggesting that the SUVmax is not a useful prognostic indicator in squamous cell carcinoma patients.

Since the SUVmax in the patients with resected adenocarcinoma influenced their prognosis, we conducted further analyses in the adenocarcinoma subjects only. Several clinicopathological factors of the recurrent and non-recurrent patients with resected adenocarcinoma are also shown in Table 1. There were significant differences between the recurrent and non-recurrent cases in age, tumor size, SUVmax, pN and pStage. A multivariate survival analysis was also performed in which the factors that were found to affect the incidence of recurrence in the previous analysis (age, tumor size, SUVmax and pStage) were selected as covariants. However, the pN factor was excluded from the covariants due to an extremely strong correlation with the pStage. Furthermore, the CEA level was added to the covariants, as previous reports have suggested that this parameter is a useful predictor of the prognosis. In this multivariate analysis, age ($p<0.01$), pStage ($p=0.02$) and SUVmax ($p=0.04$) were found to be significantly correlated with the disease-free survival (Table 2a).

Identifying patients at high risk of developing recurrence would help to select candidates for more intensive adjuvant therapy, especially in patients with resected pStage IB adenocarcinoma or more advanced diseases. In this study, the cut-off point for the SUVmax in such patients was calculated to be 6.19 according to the ROC curve analysis. The characteristics of such patients according to SUVmax are shown in Table 3. The rate of recurrence was significantly higher among the patients with an SUVmax above 6.19 ($p=0.04$) than among those with lower SUVmax. Furthermore, according to a multivariate survival analysis using the same covariants as the previous analysis, age ($p<0.01$), pStage ($p=0.04$) and SUVmax (based on the cut-off value of 6.19; $p<0.01$)

Table 1. Correlation between Recurrence and the SUVmax as Well as other Clinicopathological Factors

	Recurrence	Non-recurrence	P value
Total (cases)	21	57	
SUVmax	9.52±5.31	5.84±5.74	0.01
Squamous cell carcinoma (cases)	6	14	
SUVmax	13.26±7.85	12.00±5.77	0.69
Adenocarcinoma (cases)	15	43	
SUVmax	8.02±3.14	3.83±4.1	< 0.01
Gender Male /Female)	8/7	20/23	0.65
Age (y.o.)	74.9±6.2	65.5±8.0	< 0.01
Smoking index	508.0±883.6	427.4±680.5	0.72
CEA (ng/ml)	6.5±3.8	4.8±5.8	0.29
Tumor size (mm)	52.3±54.6	24.5±9.9	< 0.01
pN (N0/N1/N2)	8/2/5	38/3/2	< 0.01
pStage(IA/IB/IIA/IIB/IIIA)	2/4/2/1/6	29/8/4/0/2	< 0.01

Table 2. Results of Multivariate Analysis for Adenocarcinoma Patients

(a) all cases	P value	Hazard ratio	95% CI
Age	<0.01	1.1903	1.0769 - 1.3156
CEA	0.27	0.9888	0.9690 - 1.0089
Tumor size	0.38	1.0060	0.9926 - 1.0197
pStage	0.02	1.6999	1.1048 - 2.6153
SUVmax	0.04	1.2567	1.0151 - 1.5557
(b) pStage IB or more advanced cases	P value	Hazard ratio	95% CI
Age	<0.01	1.251	1.0616 - 1.4742
CEA	0.22	0.9859	0.9639 - 1.0084
Tumor size	0.32	1.0063	0.9939 - 1.0188
pStage	0.04	1.7831	1.0023 - 3.1723
SUV cut-off 6.19	<0.01	11.6980	1.9274 - 71.0004

Table 3. Characteristics of the Adenocarcinoma Patients with pStage IB or More Advanced Disease According to the SUVmax

	SUV<6.19 (n=14)	SUV≥6.19 (n=13)	P value
Gender (Male/Female)	9/5	6/7	0.35
Age (y.o.)	69.2±8.6	68.1±12.2	0.77
Smoking index	597.1±760.8	593.1±938.1	0.99
CEA (ng/ml)	4.5±2.8	9.3±8.5	0.05
Tumor size (mm)	34.0±11.3	57.3±57.3	0.14
SUVmax	3.38±1.76	10.88±4.38	< 0.01
pN (N0/N1/N2)	10/1/3	5/4/4	0.16
pStage (IB/IIA/IIB/IIIA)	9/2/0/3	3/4/1/5	0.06
Recurrence rate	28.6%	69.2%	0.04

were significantly correlated with the disease-free survival (Table 2b). Finally, the disease-free survival curves revealed a significantly high risk for recurrence among the patients with an SUVmax above 6.19 (Figure 1).

Discussion

Recently, FDG-PET has become a valuable tool for evaluating patients with NSCLC, and many studies have indicated the utility of FDG-PET for evaluating the clinical stage (de Geus-Oei et al., 2007; Al-Jahdali et al., 2012), chemotherapy effect and recurrence (Hoekstra et al., 2005; Al-Jahdali et al., 2012), and also for predicting the prognosis in patients with resected NSCLC (Al-Sarraf et al., 2008; Higuchi et al., 2014). However, in this study, we demonstrated differences in the prognostic significance of the SUVmax according to the histologic type of NSCLC. The SUVmax was high in both the non-recurrent and recurrent patients with squamous cell carcinoma, which indicated the absence of a correlation between the SUVmax and recurrence in the patients with squamous cell carcinoma, whereas a significant correlation was noted between the SUVmax and recurrence in the adenocarcinoma patients. Therefore, we consider that the prognostic significance of the SUVmax is deeply affected by the histologic type and that such analyses should be performed separately. Large differences in the cut-off value for the SUVmax have been demonstrated in previous reports, ranging from 5 to 20. One reason for these differences may due to differences in the histologic types of the cases assessed in each study.

The present findings suggested that an SUVmax of more than 6.19 in adenocarcinoma patients with pStage IB or more advanced disease is predictive of a higher likelihood of recurrence. More intensive therapy, including adjuvant chemotherapy, should therefore be considered in patients belonging to this group.

Although the SUVmax has been reported to be a predictor of recurrence and prognosis in other reports, the cut-off values of the SUVmax were inconsistent in those reports. Unfortunately, the SUVmax functions as a semi-quantitative tool for measuring the level of 18FDG uptake in tumor cells and is affected by the metabolic status of the patient. At present, different PET scanners show different SUVmax and it is difficult to standardize the optimal cut-off point. However, some studies have recently sought to standardize the SUVmax (Shiono, et al., 2011), and further research on this issue should be conducted in large-scale prospective studies in the future.

In conclusion, the SUVmax is a useful predictor of the disease-free survival in patients with resected adenocarcinoma, although it is not a useful predictor in patients with resected squamous cell carcinoma. Based on the results of this study, patients with resected adenocarcinoma demonstrating an SUVmax of more than 6.19 are thought to be candidates for more intensive adjuvant therapy.

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