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Original Article

수술로 제거된 비소세포폐암의 예후 예측에 있어 FDG-PET 최대 표준화 섭취계수의 유용성

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Prognostic Usefulness of Maximum Standardized Uptake Value on FDG-PET in Surgically Resected Non-small-cell Lung Cancer

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Purpose: FDG uptake on positron emission tomography (PET) has been considered a prognostic indicator in non-small cell lung cancer (NSCLC). The aim of this study was to assess the clinical significance of maximum value of SUV (maxSUV) in recurrence prediction in patients with surgically resected NSCLC. **Materials & methods:** NSCLC patients (n=42, F:M=14:28, age 62.3±12.3 y) who underwent curative resection after FDG-PET were enrolled. Twenty-nine patients had pathologic stage I, and 13 had pathologic stage II. Thirty-one patients were additionally treated with adjuvant oral chemotherapy. MaxSUVs of primary tumors were analyzed for correlation with tumor recurrence and compared with pathologic or clinical prognostic indicators. The median follow-up duration was 16 mo (range, 3-26 mo). **Results:** Ten (23.8%) of the 42 patients experienced recurrence during a median follow-up of 7.5 mo (range, 3-13 mo). Univariate analysis revealed that disease-free survival (DFS) was significantly correlated with maxSUV (<7 vs. ≥7, p=0.006), tumor size (<3 cm vs. ≥3 cm, p=0.024), and tumor cell differentiation (well/moderate vs. poor, p=0.044). However, multivariate Cox proportional analysis identified maxSUV as the single determinant for DFS (p=0.014). Patients with a maxSUV of ≥7 (n=10) had a significantly lower 1-year DFS rate (50.0%) than those with a maxSUV of <7 (n=32, 87.5%). **Conclusion:** MaxSUV is a significant independent predictor for recurrence in surgically resected NSCLC. FDG uptake can be added to other well-known factors in prognosis prediction of NSCLC. (Nucl Med Mol Imaging 2006;40(4):205-210)

Key Words: FDG uptake, non-small-cell lung cancer, positron emission tomography, F-18 fluorodeoxyglucose, prognosis

Introduction

Prognosis of non-small cell lung cancer (NSCLC) is primarily determined by tumor-node-metastasis (TNM) staging system.[1] However, the staging system is not satisfactory enough to explain the chance of recurrence after curative surgery.[2,3] Approximately, 25-50% of patients suffer relapse after curative resection of NSCLC.[2,4,5]

NSCLC features the characteristics of derangements of glucose metabolism.[6] Altered glucose metabolism of NSCLC can be assessed *in vivo* by positron emission tomography (PET) using 2-deoxy-2-F18-fluoro-D-glucose (FDG)[7] and FDG uptake has been identified as an independent prognostic indicator for survival in NSCLC.[2,8-10] The standardized uptake value (SUV) has been widely advocated as a representative of FDG uptake.

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However, the prognostic significance of maximum value of SUV (maxSUV) has not been fully evaluated. In this regard, we assessed the role of the semi-quantitative measure of FDG uptake on PET in prediction of recurrence in patients with surgically resected NSCLC.

Materials and Methods

1. Patients

Forty-two patients (F:M=14:28, age 62.3±12.3 y, stage I or II) who underwent cure-intent lung resection after FDG-PET due to confirmed NSCLC between July 2003 and September 2004 were enrolled in this study. Primary masses were resected through lobectomy or pneumonectomy, and mediastinal lymph node dissections including N1 and N2 stages were performed. Exclusion criteria consisted of pathologic stage III or IV, recurrent NSCLC, intravenous neo-adjuvant/adjuvant chemotherapy, or post-operative radiation therapy. Patients who had been treated with adjuvant oral chemotherapeutic agents were included. All patients underwent FDG-PET study within 4 weeks before surgery.

2. FDG-PET

All patients were fasted for at least 6 hours before FDG-PET whole-body scanning (Allegro, Philips Medical Systems, Cleveland, OH). F-18 FDG was intravenously injected at 5.18 MBq/kg (0.14 mCi/kg). Whole-body scanning was performed at 50 minutes after FDG injection from skull base to upper thigh. The 3D row-action maximum-likelihood algorithm was adopted for image reconstruction, and the resolution of the reconstructed trans-axial images was 4.8mm. Region of interests (ROIs) were drawn over main masses on trans-axial images. Standardized uptake values (SUVs) were calculated as: SUV = radioactivity in ROI (Bq/ml)×lean body mass (kg) / injected radioactivity (Bq). Lean body masses were calculated using a formula, which can be found at www.intmed.mcw.edu/clincalc/body.html.[11] Maximum SUV (maxSUV) was considered representative of FDG uptake. The mean serum glucose level, measured before FDG injection, of the 42 patients was 94.8±12.5 mg/dl.

Table 1. Patient Characteristics (n=42).

Characteristics	No. of patients	%
Sex		
Female	14	33.3
Male	28	66.7
Tumor-cell type		
Squamous cell ca*	14	33.3
Adenocarcinoma	25	59.5
Adenosquamous cell ca*	3	7.1
Differentiation		
Well	12	28.6
Moderate	24	57.1
Poor	6	14.3
LN† metastasis		
Yes	13	31.0
No	29	69.0

*ca: carcinoma
†LN: lymph node

3. Statistical Analysis

Statistical analysis was performed using SPSS software (version 12.0). Recurrence of disease was confirmed by histology or by a combination of at least two imaging modalities and a clinical correlation. For disease-free survival (DFS) analysis, maxSUVs of primary masses were stratified into two groups to identify the best discriminatory cutoff value for DFS prediction, and analysis was conducted using the Kaplan-Meyer log-rank test. Groups were dichotomized as follows; around median values of 4 to 8 for maxSUV and at 3 cm for tumor size. Other prognostic factors, such as, pathologic stage, tumor-cell type, tumor-cell differentiation, lymph node metastasis, oral chemotherapy and gender were also assessed for prediction of DFS. In addition, maxSUV and tumor size were separately entered as continuous values in a Cox proportional hazard model to assess their associations with DFS. Interactions between variables found to affect DFS were evaluated by multivariate analysis using the Cox proportional hazard model. P values of less than 0.05 were considered significant.

Results

4. Patient characteristics

The characteristics of the 42 patients are summarized in Table 1. Thirteen patients had pathologic stage IA, 16 stage IB, 5 stage IIA and 8 stage IIB NSCLC. Eleven

Table 2. Post-surgical Adjuvant Oral Chemotherapy versus Stage of 42 Patients

Stage	No of Patients with oral chemotherapy	%
IA	7/13	54
IB	12/16	75
IIA	4/5	80
IIB	8/8	100

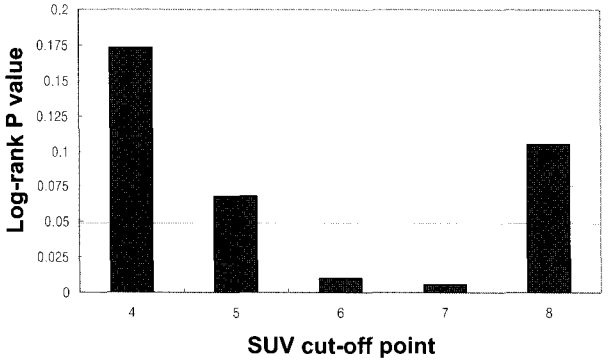

Fig. 1. Relationship between various maxSUV cut-off values and their discriminative significance for disease-free survival, as assessed by the Log-rank test.

patients were treated by surgery only and 31 patients by adjuvant oral chemotherapy with Uracil-Tegafur after surgery (Table 2). Median follow-up time was 16 months (range = 3-26 months, mean±s.d. = 15.6±5.7 months).

5. Univariate analysis for disease-free survival

Ten (23.8%) of the 42 patients suffered recurrence during follow-up at a median 7.5 months (range = 3-13 months, mean±s.d. = 8.1±4.0 months). Thirty-two patients (76.2%) without recurrence had a median follow-up time of 17 months (range = 13-26 months, mean±s.d. = 18.0 ±3.8 months). Univariate analysis revealed that maxSUV was significantly correlated with DFS by the log-rank test (Table 3). Analysis based on dichotomizing maxSUV identified a cut-off value of 7 as the best discriminatory value for DFS (Fig. 1). Tumor size (<3 cm vs. ≥3 cm) were significantly correlated with DFS with a p value of 0.024 (Table 3). In addition, DFS was significantly correlated with tumor cell differentiation (well and moderate vs. poor; p=0.044), but DFS was not found to relate with pathologic stage (stage I vs. stage II), lymph node metastasis, oral adjuvant chemotherapy, tumor-cell

Table 3. Univariate Analysis of Disease-free Survival

Variables	Log-rank P
MaxSUV (<7 vs. ≥7)	0.006
Tumor size (<3cm vs. ≥3cm)	0.024
Sex (male vs. female)	0.682
Stage (I vs. II)	0.956
Lymph node metastasis (yes vs. no)	0.956
Tumor-cell type (sqc vs. non-sqc)*	0.800
Differentiation (well and mod† vs. poor)	0.044
Oral chemotherapy (yes vs. no)	0.803

*sqc: squamous cell carcinoma, non-sqc: non squamous cell carcinoma.
†mod: moderate

type (squamous vs. non-squamous cell carcinoma) or gender (Table 3). For the analysis of continuous variables, tumor size was not significantly related with DFS (p=0.097). MaxSUV was found as the only continuous variable associated significantly with DFS (p=0.026). A one-unit increase in maxSUV corresponded to an increase in the hazard ratio of recurrence by a factor 1.313 (with a 95% confidence interval: 1.034-1.668).

6. Multivariate analysis with respect to disease-free survival

Combinatorial effects and interactions between variables were examined in Cox proportional hazard models. The three variables subjected to this analysis were maxSUV, tumor size and differentiation. We found that only maxSUV remained an independent predictor of DFS (p=0.014), and that patients with a maxSUV of ≥7 were 4.757 times more likely to experience recurrence than those with a maxSUV of <7 (Table 4). Patients with a maxSUV of ≥7 (n=10) had a significantly lower 1-year DFS rate (50.0%) than those with a maxSUV of <7 (n=32, 87.5%) (Fig. 2).

7. Correlations of maxSUV with tumor cell type and differentiation

MaxSUVs of squamous cell carcinoma (5.9±2.0) were significantly higher than those of adenocarcinomas (3.4± 2.6, p<0.01). Adenosquamous cell carcinoma had comparative values of maxSUV (6.5±3.6) to squamous cell carcinoma, but small number of adenosquamous cell carcinoma (n=3) prohibited proper statistical test (Fig. 3). Differentiation of tumor cell was correlated with maxSUV

Table 4. Results of Multivariate Analysis of Disease-free Survival (Cox Proportional Hazard Model)

Variable	P value	Relative risk	95% CI*
MaxSUV (<7 vs. ≥7)	0.014	4.757	1.365-16.582
Tumor size (<3cm vs. ≥3cm)	0.299		
Differentiation (well/moderate vs. poor)	0.301		

*95% confidence interval for relative risk.

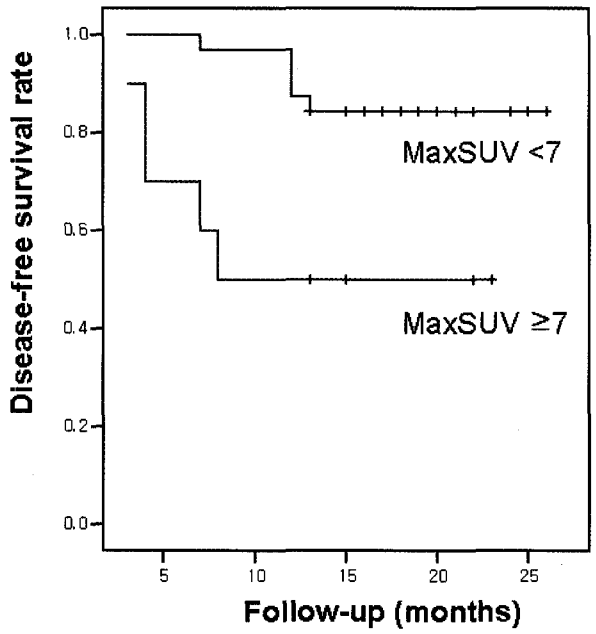

Fig. 2. Disease-free survival rate curves with maxSUV cut-off at 7. The patients with maxSUV ≥7 (n=10) had lower 1 year disease-free survival rate (50.0%) than those with maxSUV <7 (n=32, 87.5%).

(Spearman's rho = 0.639, p<0.001). The poorer differentiation of tumor was related to the higher values of maxSUV.

Discussion

This study revealed that maxSUV is the most important prognostic marker for recurrence of NSCLC among various prognostic factors. Moreover, maxSUV was also a continuous variable which showed significant correlation with DFS and identified as the only independent predictor of recurrence after analyzing for combinatorial effects and interactions with other prognostic factors. Although tumor size and cell differentiation were identified as significant prognostic indicators by univariate analysis, but their significance was lost during multivariate analysis.

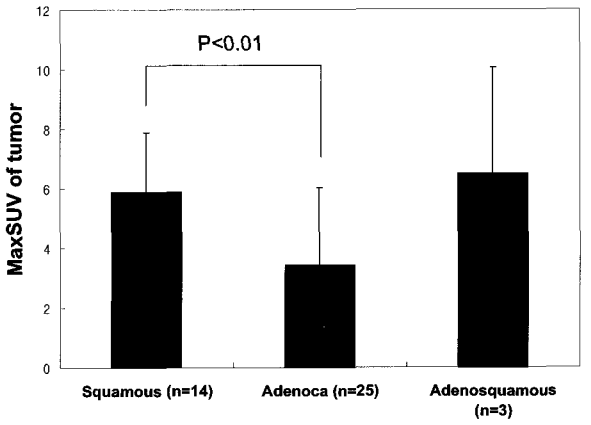

Fig. 3. MaxSUV and tumor cell types. Squamous cell carcinoma had higher values of maxSUV than adenocarcinoma (p<0.01). MaxSUVs of adenosquamous cell carcinoma was similar to those of squamous cell carcinoma but statistical comparison was not performed due to small number of cases. Data are presented with mean±standard deviation.

As a representative of FDG uptake, maxSUV had some advantages. First, partial volume effect of low resolution PET system can be reduced by adopting maximum value of SUV as a surrogate for FDG uptake. Second, the identification of maxSUV is an inherently operator-independent procedure. Thus, consistent values of maxSUV can be obtained in a given mass. Third, highest value of SUV in a pixel may indicate the highest malignant clone of the tumor. In this regard, maxSUV may be suitable for prognosis evaluation.

The prognostic significance of FDG uptake has been demonstrated in various stages of NSCLC, not only in patients with surgically curable NSCLC[2,3,8] but also in those with non-curable NSCLC.[12,13] In the present study, FDG uptake was found to be an independent prognostic marker for recurrence in NSCLC patients with stage I and II. However, TNM staging and effect of oral chemotherapy were not found to relate with prognosis. These findings can be explained in that the follow up duration was not long

enough to evaluate the mortality, and 12 of 13 patients with stage II were additionally treated with post-surgical oral chemotherapy compared with only 19 of 29 patients of stage I (Table 2).

FDG uptake of lung cancer has already been reported to correlate with level of glucose metabolism represented by Glut-1 expression.[14,15] FDG accumulation in the tumor may be also affected by multiple other biological factors including hexokinase and glucose-6-phosphatase activities in cancer cells,[16-18] tumor blood flow, intratumoral microvessel densities,[19] and number of viable tumor cells.[20] The more aggressive the tumor behavior, the more aggressive the biological factors represented by FDG uptake. Therefore, the greater FDG uptake in the tumor may appear the more aggressive disease and the higher risk for recurrence in NSCLC.

However, this study had certain limitations. The direct correlation of FDG uptake with the above-mentioned biological factors of the tumor were not assessed and the small number of study cases did not allow a detail analysis for subgroup in interaction between each stage and effect of oral chemotherapy. More cases, and longer follow-up durations would undoubtedly further elucidate the clinical usefulness of FDG uptake in terms of the accurate staging and effect of oral chemotherapy on surgically resected NSCLC.

요 약

목적: PET에서 측정되는 FDG 섭취가 비소세포폐암의 예후예측인자로 인정받고 있으나 최대 표준화섭취계수(maximum standardized uptake value, 이하 maxSUV)의 예후예측 성능에 대해서는 충분한 연구가 이루어지지 않았다. 저자들은 수술로 제거된 비소세포폐암 환자에서 maxSUV의 재발예측 성능을 알아 보았다. **대상 및 방법:** FDG-PET을 실시한 후 4주 이내에 근치적인 수술을 시행받은 42명의 환자(여:남=14:28, 평균나이 62.3±12.3세)를 대상으로 하였으며 수술 후 병리학적인 stage는 29명은 stage I, 13명은 stage II이었다. 21명의 환자들은 수술 후 경구용 항암제 치료를 받았다. 추적관찰 기간(중앙값 16개월, 범위 3-26개월) 동안 재발여부와 maxSUV와의 연관성을 분석하였다. **결과:** 10명(23.8%, 10/42)의 환자에서 재발이 확인되었다(추적관찰 기간: 중앙값 7.5개월, 범위 3-13개월). 단변량분석에서 maxSUV (<7 vs. ≥7, p=0.006), 종양의 크기(<3 cm vs. ≥3 cm, p=0.024), 그리고 종양의 분화도(well/moderate vs. poor, p=0.044)가 비재발-생존기간과 유의한 상관이 있었다. Cox 위험도 모델을 이용한 다변량분석에서는 maxSUV만이 유일한 재발 예측인자이었다.(p=0.014) MaxSUV가 7이상인 환자들(n=10)은 1년 비재발 생존률이 50.0%인 반면에 maxSUV가 7미만인 환자들(n=32)은 1년 비재발 생존률이 87.5%이었다. **결론:** MaxSUV는 수술로 제거된 비소세포폐암의 재발을 예측하는 독립적인 인자이었다. FDG 섭취 정도는 기존에 알려져 있는 인자들과 함께 비소세포폐암의 예후에 대한 유용한 정보를 제공할 것으로 기대된다.

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