ORIGINAL PAPER

Nagoya J. Med. Sci. **77**. 475 ~ 480, 2015

Which variables should be considered in patients with stage II and III non-small cell lung cancer after neoadjuvant therapy?

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ABSTRACT

This study was designed to elucidate the predictive usefulness of the response evaluation criteria in solid tumors (RECIST), a volume response (VR; a > 50% reduction in the tumor volume) and the post-neoadjuvant therapy maximum standardized uptake value (post-SUVmax) in patients with non-small cell lung cancer (NSCLC) after neoadjuvant therapy. Between December 2006 and June 2012, 33 patients with clinical stage II and III NSCLC who underwent pulmonary resection following neoadjuvant therapy were enrolled. The relationships between the variables and a pathological complete response (pCR), the disease-free survival (DFS) and the overall survival (OS) were analyzed. As neoadjuvant therapy, 24 patients received chemoradiotherapy, five patients received chemotherapy and four patients were given radiation therapy. Based on the RECIST, 12 tumors were classified as having a partial response and 21 tumors were classified as stable disease. Twenty-one tumors showed a VR and 12 did not. Twenty-five tumors had a post-SUVmax ≤7.5 and eight had a post-SUVmax >7.5. Eight tumors had a pCR. In the multivariate Cox regression analysis, both a non-VR and a post-SUVmax >7.5 were significant variables predicting the DFS (p = 0.0422 and 0.0127, respectively), but either was not for OS. The post-SUVmax was also a significant variable for the pCR rate (p = 0.0067). The post-treatment SUVmax can be a valid alternative variable that can be used to predict the effect of neoadjuvant therapy and the survival of patients with stage II and III NSCLC.

Key Words: lung cancer, neoadjuvant therapy, tumor volume, SUVmax, PET

INTRODUCTION

Neoadjuvant therapy followed by surgical resection has been attempted to improve the survival of patients with locally-advanced non-small cell lung cancer (NSCLC).[1-4] Proven strategies to select patients who would obtain a survival benefit from surgery after neoadjuvant therapy have not been established, except for the response evaluation criteria in solid tumors (RECIST) and re-staging. Besides the RECIST, several studies have assessed the prognostic significance of a reduction in the maximum standardized uptake value (SUVmax) on ^{18}F-fluorodeoxyglucose positron emission tomography (PET) in monitoring the response to treatment.[5-8] However, there has

Received: April 28, 2015; accepted: July 21, 2015

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been no uniform agreement regarding metabolic-based assessments. In addition, we hypothesized that a reduction in the tumor volume would show a stronger correlation with the outcomes than the diameter-based RECIST criteria.

Therefore, this study was designed to evaluate the predictive significance of the variables obtained by diagnostic imaging in patients who underwent surgical resection after neoadjuvant therapy for NSCLC, and included the variables of the RECIST, the volume-based assessment and the SUVmax-based assessment.

MATERIALS AND METHODS

This study was conducted with the approval of the Institutional Review Board of Nagoya University Hospital. Between December 2006 and June 2012, 41 consecutive patients were diagnosed with clinical stage II and III NSCLC and underwent pulmonary resection following neoadjuvant therapy. We retrospectively reviewed the medical records of these patients. Five patients with R2 resection, two patients who did not undergo a post-neoadjuvant treatment PET scan and one patient who died within the first 30 days after the operation were excluded from the analysis. Consequently, 33 patients constituted the study population.

All patients had histological or cytological confirmation of NSCLC before they received neoadjuvant therapy. As neoadjuvant therapy, 24 patients received one or two cycles of platinum-based chemotherapy combined with 40–64 Gy of concurrent radiotherapy. Five patients received one to six cycles of platinum-based chemotherapy and four patients were given radiation of 40–60 Gy. PET scans were performed with a PET-CT scanner (Biography 16; Siemens Medical Solutions, Erlangen, Germany). The FDG dose was 3.7 MBq/kg (body weight <60 kg) or 4.07 MBq/kg (body weight ≥60 kg). The maximum value in a region of interest around the pulmonary lesion (not the lymph nodes) was defined as the SUVmax. Post-SUVmax was defined as the post-neoadjuvant treatment SUVmax. A partial response (PR) and stable disease (SD) were defined according to the RECIST.[9] Volume response (VR) was defined as a more than 50% reduction of the tumor volume (tumor volume = a × b × c × 0.52, using the three orthogonal crystal axes a, b and c from the data obtained by CT scans).

The DFS was defined as the time from the pretreatment histological diagnosis to relapse or death due to any cause. The OS was defined as the time from pretreatment histological diagnosis to death due to any cause. The seventh edition of the tumor-node-metastasis classification was applied in this cohort,[10] and the pathological diagnosis of the tumor was made based on the World Health Organization classification.[11] A pCR was defined as no evidence of residual vital tumor cells around the primary pulmonary lesion. The correlations between the variables and the pCR of the primary tumor, the DFS and the OS were analyzed.

The chi-square test was used for comparisons of proportions. A logistic regression analysis was performed to evaluate the diagnostic accuracy of the data for the imaging tests used to assess whether there was a pCR. The Kaplan–Meier method was used to estimate the DFS and OS, and the log-rank test was used to compare the survival curves. We performed the multivariate Cox regression analyses to estimate hazard ratios (HRs) and 95% confidence interval (CI) for DFS and OS. As the variables, we select VR (and non-VR), post-SUVmax as well as the variables which were considered to be important based on the current evidence.[1-8] Consequently, the following variables were included: neoadjuvant therapy, VR (and non-VR), post-SUVmax and clinical stage after neoadjuvant therapy. Statistical significance was defined as a value of $p < 0.05$. All analyses were conducted using the JMP software program (version 8.0.1, SAS institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the clinicopathological characteristics of the patients. Based on the RECIST, 12 tumors were classified to have a PR and 21 tumors were classified as SD. In the volume-based assessment, 21 tumors showed a VR, and 12 tumors did not. In the SUVmax-based assessment, 25 tumors [20 (83%) tumors with chemoradiotherapy, 2 (40%) tumors with chemotherapy and 3 (75%) tumors with radiotherapy] had a post-SUVmax ≤7.5 and eight tumors had a post-SUVmax >7.5. Twenty-four patients underwent concomitant resection of neighboring structures. A pCR around the primary pulmonary lesion was observed in eight patients (24%).

Table 1 The characteristics of patients who underwent pulmonary resection after neoadjuvant therapy

Total number		33
Age, years	(mean ± SD)	61.3 ± 8.6
Sex	Female	3
	Male	30
Histology	Squamous cell carcinoma	16
	Adenocarcinoma	14
	Others	3
Neoadjuvant therapy	Chemoradiotherapy	24
	Chemotherapy	5
	Radiotherapy	4
Clinical stage	II/ III	17/ 16
Clinical stage after neoadjuvant therapy	I, II/ III	23/ 10
RECIST	PR/ SD	12 (36%)/ 21 (64%)
Tumor volume	VR (50% reduction)/ non-VR	21 (64%)/ 12 (36%)
Pre-treatment SUVmax	≤7.5/ >7.5	3 (14%)/ 19 (86%)
Post-treatment SUVmax	≤7.5/ >7.5	25 (76%)/ 8 (24%)
Pathological response	pCR/ non-pCR	8 (24%)/ 25 (76%)
Pathological stage	0/ I/ II/ III	7/ 5/ 14/ 7

RECIST: response evaluation criteria in solid tumors; SUVmax: maximum standardized uptake value; pCR: pathological complete response

With a median follow-up period of 42 months, the estimated three-year DFS and OS were 70% and 78%, respectively. Figure 1 shows the DFS and OS curves based on the RECIST, VR and post-SUVmax. Not the RECIST, but the VR and a post-SUVmax were significant variables predicting the DFS. In the multivariate Cox regression analysis, only the non-VR and post-SUVmax >7.5 were significant variables predicting the DFS (HR 3.9, 95% CI 1.0–15.8, p = 0.0422 and HR 6.1, 95% CI 1.5–25.5, p = 0.0127, respectively), but either was not for OS. The post-SUVmax as a continuous valuable had a significant correlation with a pCR (p = 0.0067), while the RECIST and non-VR did not. The post-SUVmax of the eight nodules with a pCR ranged from 1.9 to 4.2.

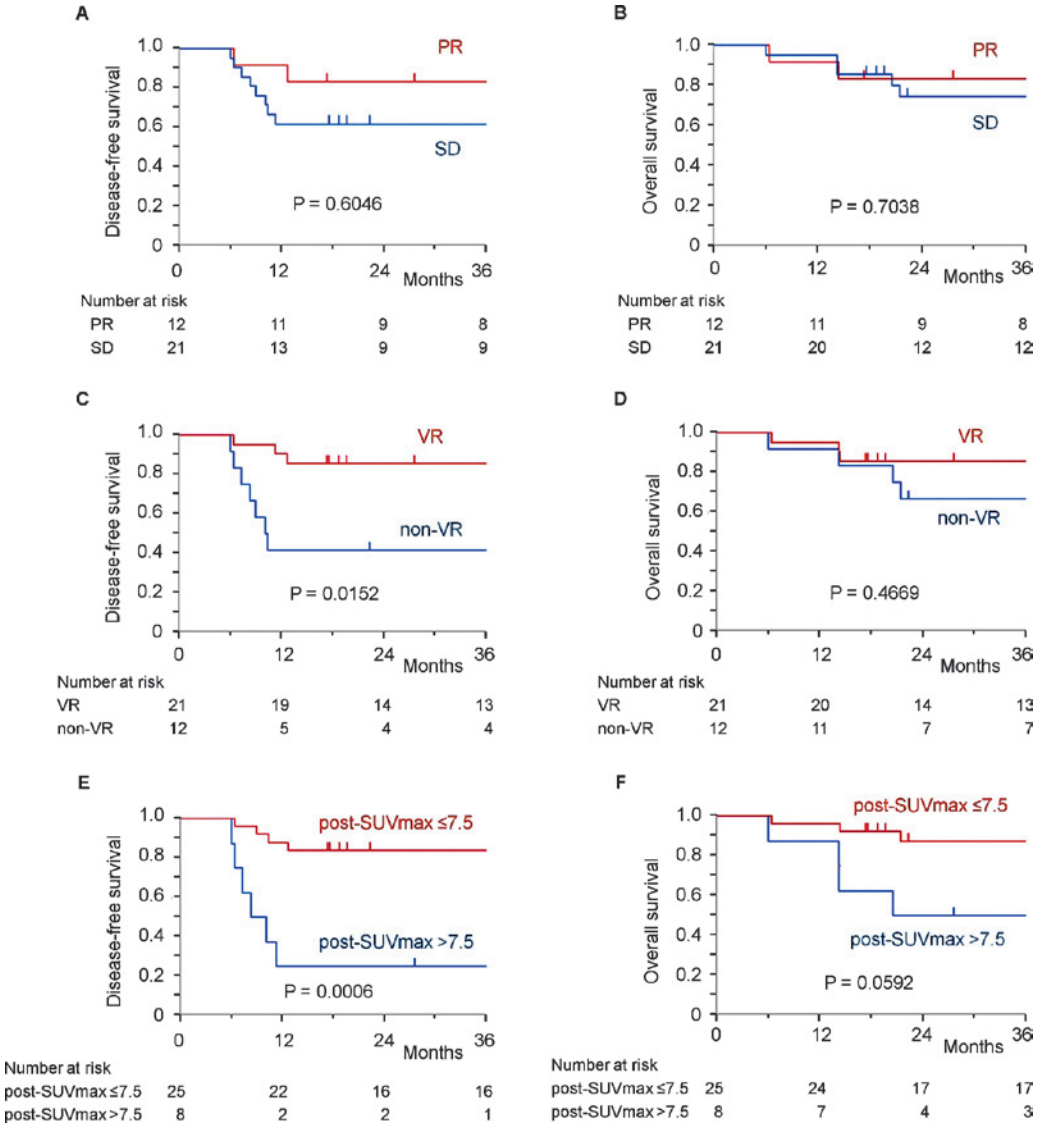

Fig. 1 The disease-free survival and overall survival curves categorized based on the RECIST (A, B), the tumor volume response (VR: a more than 50% reduction in the tumor volume) (C, D) and the metabolic response (with the cut-off value of the post-SUVmax set at 7.5) (E, F)

DISCUSSION

In this study, the results indicated that a post-SUVmax >7.5 and a non-VR following neoadjuvant therapy can be valid variables to predict the DFS. Further investigation will be necessary to confirm its significance for the OS. These results should be considered, especially in patients considered to be at high risk for invasive surgery.

The pathological response after neoadjuvant therapy in resectable NSCLC was reported to have the potential to be a surrogate endpoint for predicting the survival.[12] Our results indicate

that the post-SUVmax has a significant correlation with the pCR, while volume-based assessment does not.

There were a number of possible limitations associated with our retrospective study which should be recognized. First, the small number of patients and the short follow-up period should be noted. Moreover, the number and outcomes of patients who were rejected for surgery were not clear. Second, there were a wide variety of neoadjuvant treatments administered. Patients with neoadjuvant therapy performed outside our institution were also included for consideration. Third, we used a SUVmax of 7.5, which was an integral multiplication of the value of 2.5 widely used to discriminate between benign and malignant diseases. One study proposed the use of cut-off values for the post-treatment peak standardized uptake value of 7.0 for the clinical decision-making after chemoradiotherapy.[13] However, the exact significance of the cut-off value for the post-SUVmax remains vague due to the shortage of evidence.

In conclusion, the post-treatment SUVmax can be a valid alternative variable that can be used to predict the effect of neoadjuvant therapy and the survival of patients with stage II and III NSCLC.

ACKNOWLEDGEMENTS

This study was supported in part by a grant from the Takeda Science Foundation.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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