Prognostic factors and the significance of treatment after recurrence in completely resected stage I non-small cell lung cancer

Running head: Postrecurrence survival in stage I NSCLC

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All authors declare that they have no conflicts of interest associated with this study.

Abstract

Introduction: The objective of this study was to identify the clinicopathological factors influencing postrecurrence survival (PRS), and the effect of postrecurrence therapy (PRT) on patients with completely resected stage I non-small cell lung cancer (NSCLC).

Methods: We reviewed the data of 919 patients in whom complete resection of stage I NSCLC had been performed.

Results: Of the 919 patients, 170 had recurrent disease (18.5%). Initial PRT was performed in 118 (69.4%) patients (surgery 8, chemotherapy 79, radiotherapy 10, chemoradiotherapy 21). On multivariate analyses, PRT (HR0.542; 95%CI0.344-0.853; p=0.008), female gender (HR0.487; 95%CI0.297-0.801; p=0.005) and differentiation (HR1.810; 95%CI1.194-2.743; p=0.005) demonstrated a statistically significant association with favorable PRS. Bone metastasis (HR3.288; 95%CI1.783-6.062; p<0.001), liver metastasis (HR4.518; 95%CI1.793-11.379; p=0.001), chemotherapy (HR0.478; 95%CI0.236-0.975; p=0.040), epidermal growth factor receptor-tyrosine kinase inhibitors treatment (EGFR-TKIs; HR0.460; 95%CI0.245-0.862; p=0.015), and non-adenocarcinoma (HR2.136; 95%CI1.273-3.585; p=0.004) were independently and significantly associated with PRS in the 118 patients who underwent any PRT.

Subgroup analysis with a combination of these 5 PRS factors in the patients who underwent any PRT revealed median PRS times of 42.4 months for 20 patients lacking all 5 risk factors and 18.8 months for 98 patients with at least one of these risk factors, respectively (p=0.001).

Conclusion: PRT, gender and differentiation were independently associated with PRS. In the patients who underwent any PRT, PRS was related to EGFR-TKIs, chemotherapy, histology, and initial recurrence sites. One challenge for the future will be to create systematic treatment strategies for recurrent NSCLC according to the risk factor status of individual patients.

Introduction

Surgical resection with a curative intent is considered the standard of care for early stage non-small cell lung cancer (NSCLC), but more than 20% of patients had recurrence, even in pathological stage I cases.[1-6] Recurrence after complete resection for stages I-III of NSCLC ranges from 30% to 75%, and has been reported to depend on pathological staging and follow-up period.[1,6-8] The majority of recurrences occur within the first 2 years,[1,6] although there are several studies showing late recurrences 5 years or more after resection.[9-11] Long-term continuous follow-up is required to establish accurate recurrence rates and patterns.

Although several studies focusing on postrecurrence survival (PRS) of patients in stages I or stage I-III NSCLC have been reported,[2-4,8,12-14] no standard treatment strategy for recurrent disease based on prospective studies has been established. However, a standard treatment strategy is necessary because much longer follow-up periods and robust protocols are required to evaluate PRS objectively. It is difficult to generalize about multifactorial patient backgrounds, which depend on disease, treatment, and performance status (PS) at recurrence. The prognostic factors predicting PRS or the appropriate treatment are still controversial.

In recent years, encouraging new treatments (including epidermal growth factor

receptor-tyrosine kinase inhibitors [EGFR-TKIs], anaplastic lymphoma kinase inhibitors, pemetrexed, and bevacizumab) have afforded benefits to certain patients with advanced or recurrent NSCLC.[15-21] Advances in postrecurrence therapy (PRT) may provide improvement in overall survival (OS) among the patients who undergo surgery. The objective of the present study was to identify the clinicopathological factors influencing PRS, and their effect of PRT on stage I NSCLC.

Materials and Methods

From January 1990 through December 2007, 1214 patients underwent complete resection for pathological stage I NSCLC at our hospital. Complete resection was defined as demonstrating cancer-free surgical margins, both grossly and histologically. All patients underwent radical anatomical lobar resection and systematic mediastinal lymph node dissection. The following exclusion criteria were applied: preoperative chemotherapy, radiation therapy, or both (n = 38); low-grade malignant tumors, including carcinoids, mucoepidermoid carcinomas, or adenoid cystic carcinomas (n = 20); death within 30 days of operation (n = 9). Of the remaining 1147 patients, complete follow-up was available for 919 patients, who composed the subjects of this study.

Preoperative evaluation included physical examination, chest radiography, computed tomography (CT) of the chest and abdomen, bone scintigraphy, blood examination, and since the early 2000s, positron-emission tomography (PET) scan (recently integrated PET-CT scan). Histologic subtypes of lung cancer were determined according to the World Health Organization classification,[22] and disease stage was determined in accordance with the 7th Edition of the TNM Classification for Lung and Pleural Tumors.[23]

The follow-up schedule consisted of a clinic visit every 3 months in the first 1 year after resection, every 6 months from the 2nd to the 5th year, and annually thereafter, on an outpatient basis, and aimed at continuing follow-up for 10 years after resection. Follow-up procedures included physical examination, chest radiography, and blood examination (including serum tumor markers). CT of the chest and abdomen was performed every 6 months in the first 2 years, and annually from the 3rd to the 5th year. Whenever any symptoms or signs of recurrence were detected, magnetic resonance imaging (MRI) of the brain, and bone scintigraphy were performed.

Recurrences were diagnosed by physical examination and diagnostic imaging. Histological or cytological confirmation of the recurrence was made when clinically feasible. Local recurrence was defined as disease recurrence at the surgical margin,

ipsilateral hemithorax or mediastinum. Radiographic lymph node recurrence was defined as enlarged lymph nodes measuring > 1 cm on the short axis by CT and/or hypermetabolic lymph nodes on PET-CT scans. Pathological confirmation of recurrence was made by endobronchial ultrasound-guided transbronchial needle aspiration of enlarged lymph nodes during follow-up. Distant metastasis was defined as disease recurrence in the contralateral lung or outside the hemithorax and mediastinum. A second primary tumor was recorded when a patient presented with a new histological type, and with clinical features consistent with a new primary tumor. Data collected from our department database of patients, telephone interviews and correspondence from outside sources during the follow-up periods were included.

Clinical characteristics were retrieved from available clinical records. The following clinicopathological factors were assessed in the PRS analysis: age, gender, smoking status, T status (T1 vs. T2), tumor size (0-30 mm vs. > 30 mm), tumor differentiation (well/moderate vs. poor), pathological vascular invasion, pleural invasion, histology (adenocarcinoma vs. others), and extent of resection (single lobe lobectomy vs. more extensive resection, namely bilobectomy/pneumonectomy).

Length of the recurrence-free period was calculated in months from date of resection to date of initial recurrence or last follow-up showing no recurrence. To calculate the

recurrence-free proportion (RFP), patients who died without recognized recurrence or who were known to have no recurrence at the date of last contact were censored. Length of PRS was measured from date of initial recurrence to date of death from any cause or date on which the patient was last known to be alive. PRS and RFP curves were plotted using the Kaplan-Meier method, and differences in variables were determined using the log-rank test or the Breslow tests. Categorical comparison was performed using the χ^2 test for discrete data and Student's t-test for continuous data. Multivariate analyses were performed using the Cox proportional hazards regression model. A backward stepwise selection procedure was implemented. All tests were two-sided, and p-values of less than 0.05 were considered to indicate a statistically significant difference. Statview 5.0 software (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived, by the Institutional Review Board at Tokyo Medical University (No. 2133).

Results

Median follow-up time for survivors was 62.0 months (range: 1.4-247.6 months). The RFP was 82.2% at 5 years after operation. Of the 919 patients, 170

(18.5%) had recurrent disease, with a median age of 66 at the time of initial recurrence. Median PRS time for these patients was 17.6 months (range: 0.4-103.0 months). The 1- and 2-year PRS proportions were 73.5% and 51.4%, respectively (Figure 1).

Table 1 shows 5-year RFPs and univariate/multivariate analyses of recurrence according to clinicopathological characteristics of stage I NSCLC patients. Univariate analysis identified 5 significant risk factors: male gender, pathologically vascular invasion, pleural invasion, poorly-differentiated carcinoma, and non-adenocarcinoma. Multivariate analysis demonstrated that pathological vascular invasion (hazard ratio [HR] 2.306; 95% confidence interval [CI] 1.621-3.280; $p < 0.001$), pleural invasion (HR 1.489; 95% CI 1.048-2.115; $p = 0.026$), and poorly-differentiated carcinoma (HR 1.842; 95% CI 1.328-2.555; $p < 0.001$) were statistically significant predictors of recurrence.

Initial recurrence sites and PRT are shown in Table 2. Type of recurrence included only local in 43 patients (25.3%), distant in 113 (66.5%), and both in 14 (8.2%). Most commonly involved organs were the lung, the site of recurrence in 66 patients (ipsilateral 23, contralateral/bilateral 43), followed by regional lymph nodes in 37, brain in 30, bone in 21, and liver in 16. Initial PRT was performed in 118 (69.4%) patients, and included surgery for 8, chemotherapy for 79, radiotherapy for 10, and chemoradiotherapy for 21. Surgical resections in the 8 patients were in 3 with solitary

pulmonary metastasis, 3 with solitary brain metastasis, 1 with adrenal gland metastasis, and 1 with chest wall and axillary lymph node involvement. Forty-one (24.1%) patients had no treatment for recurrence. 118 patients who underwent any PRT, 66 (55.9%) underwent second-line or subsequent therapy, including chemotherapy for 58, and EGFR-TKIs for 27 (gefitinib 22, erlotinib 3, both 2). Among the latter 27 patients, EGFR mutations were detected in 12, 4 had wild-type *EGFR*.

Table 3 shows univariate/multivariate analyses of PRS. Univariate analysis identified 6 significant risk factors for PRS: male gender, smoker, poorly-differentiated carcinoma, non-adenocarcinoma, no PRT, and shorter recurrence-free interval ($\leq$ 24 months; median recurrence-free period was 24 months). Multivariate analysis demonstrated that PRT (HR 0.542; 95% CI 0.344-0.853; p = 0.008), female gender (HR 0.487; 95% CI 0.297-0.801; p = 0.005) and differentiation (HR 1.810; 95% CI 1.194-2.743; p = 0.005) had a statistically significant association with favorable PRS.

The results of multivariate analysis of PRS determined that PRT had strong impact on PRS. Therefore, we further examined PRS in the 118 patients who underwent any PRT (Table 4). Univariate analysis identified 9 significant risk factors for PRS: male gender, smoker, poorly-differentiated carcinoma, bone metastasis, liver metastasis, no chemotherapy or EGFR-TKI, no second-line therapy, and multiple organ metastases.

Multivariate analysis demonstrated that bone metastasis (HR 3.288; 95% CI 1.783-6.062; $p < 0.001$), liver metastasis (HR 4.518; 95% CI 1.793-11.379; $p = 0.001$), chemotherapy (HR 0.478; 95% CI 0.236-0.975; $p = 0.040$), EGFR-TKI therapy (HR 0.460; 95% CI 0.245-0.862; $p = 0.015$), and non-adenocarcinoma (HR 2.136; 95% CI 1.273-3.585; $p = 0.004$) had a statistically significant association with PRS.

Subgroup analysis with a combination of these 5 PRS factors (no EGFR-TKI and chemotherapy, presence of liver or bone metastasis, non-adenocarcinoma) in patients with recurrence who underwent any PRT revealed median PRS times of 42.4 months for 20 patients lacking all 5 unfavorable factors and 18.8 months for 98 patients with one of these risk factors, respectively (Figure 2). The difference in PRS was statistically significant between the two groups ($p = 0.001$).

Discussion

We set out to identify clinicopathological factors influencing PRS of stage I NSCLC patients. Although curative surgical resection is the most effective therapy for stage I NSCLC patients, a considerable number of patients will develop recurrence. In the current study, overall incidence of recurrence was 18.5%, and median PRS time was 17.6 months. Initial location of recurrence was at a distant site in 74.7%, and the

proportions of recurrences within 2 or 3 years after surgery were 48.2% and 66.5%, respectively (unpublished data). Previous studies have reported that the incidence of recurrence in stage I NSCLC patients was 14-36%, with the 1-year survival rate ranging from 30% to 68% (details in Table 5).[1-6,8,24]

We examined risk factors for recurrence in stage I NSCLC, and identified 3: pathological vascular invasion, pleural invasion, and poorly-differentiated carcinoma. These standard pathological factors have also been reported to be good predictors of OS for patients with stage I NSCLC.[25-36] In our study, univariate analysis for PRS identified 6 significant risk factors (male gender, smoking, poorly-differentiated carcinoma, non-adenocarcinoma, no PRT, and shorter recurrence-free interval; $\leq$ 24 months), while multivariate analysis revealed that gender, PRT, and differentiation were independent prognostic factors. Only differentiation was a significant predictor of recurrence and poor PRS, and pathological vascular invasion and pleural invasion had no significant impact on PRS. PRS may be associated with recurrent disease characteristics, including the recurrence site, PRT, recurrence-free interval, or PS at time of recurrence, rather than with the biologically aggressive characteristics of lung cancer.

Previous studies have demonstrated the survival benefit of PRT in stage I NSCLC patients. Nakagawa et al. and Hung et al. demonstrated that patients with stage I

NSCLC treated either surgically or non-surgically had a significantly better PRS than those with supportive care alone.[2-4] In our study, PRT provided a more favorable PRS than that of no treatment, similarly to previous reports. However, the results of PRS in the patients who underwent any PRT showed that surgical resection was not related to a favorable outcome. This may have been because the number of patients who received surgery for recurrent disease was too small to provide any supportive data in terms of survival benefit. However, in cases of surgical resection for recurrent lung metastasis, objective evidence supporting the role of surgery is limited because it may be difficult to distinguish second primary tumors from recurrent pulmonary metastasis. Advances in genomic analysis, molecular biological tools, or diagnostic imaging may enable more accurate diagnosis of a solitary pulmonary lesion.

Among the cohort of 118 patients with any PRT, we identified 5 independent favorable prognostic factors of PRS by multivariate analysis: the absence of bone or liver metastasis, chemotherapy, EGFR-TKI therapy, and non-adenocarcinoma. Moreover, the result of the study showed an important aspect of a prognostic-factor based risk stratification. Median PRS times of 42.4 months for the patients lacking all 5 factors and 18.8 months for the patients with one of these risk factors ($p = 0.001$).

Some authors have found that the site of initial recurrence was a prognostic factor

for PRS, which agrees with the current study. Yoshino et al. demonstrated that bone metastasis was a marginally prognostic factor for PRS in stage I-III patients at the first resection.[8] Assessment of bone metastatic type, osteoblastic or osteolytic, may be important as a part of postrecurrence therapeutic strategy because it has been noted that osteoblastic tumors would have lead to both a better prognosis and activating *EGFR* mutation presence.[37]

Major advances in NSCLC management have resulted from the understanding of molecular biology, development of molecule-targeting agents, and identification of biomarkers for targeted treatment. Since 2002, gefitinib has been used in Japan for the treatment of inoperable or recurrent NSCLC, and we started to administer it around the same period. It is now felt that EGFR-TKIs can improve the survival of some previously treated and untreated advanced NSCLC patients, with the overall benefit being driven primarily by the subgroup with *EGFR* mutations.[15-17,38,39] EGFR-TKIs have also improved endurance and health-related quality of life compared with platinum-based doublet chemotherapy.[15-17] EGFR-TKIs are therefore good candidates for first-line PRT in resected adenocarcinoma patients with distant metastases, but only in those with *EGFR* mutations.

There are several limitations in the present study. This study is retrospective, and

bias may exist. First, patient selection bias regarding PRT was unavoidable. Curative intent therapy or systematic treatment is difficult to perform in patients with poor PS. In the current study, PS or comorbidities at the time of recurrence was not accurately evaluated. Second, distinguishing second primary tumors from recurrent pulmonary metastasis was difficult. Even if a pathologic specimen was obtained, definitive diagnosis could be difficult under the current morphology-based diagnostic criteria. Third, complete follow-up was not available for all eligible patients.

There are presently no clinical guidelines for PRT regarding resected NSCLC based on large-scale prospective studies. Molecularly-targeted therapy, chemotherapeutic regimens, and surgical strategies have evolved substantially over the decades. A challenge for the future will be to create systematic treatment strategies for recurrent NSCLC, according to the individual patient's recurrent disease characteristics, including the initial recurrence site, age, gender, PS, or recurrence-free interval, and original tumor characteristics.

Conclusion

This study showed that male gender, the absence of PRT, and poorly-differentiated carcinoma were independent unfavorable prognostic factors of PRS in resected stage I

NSCLC patients. Moreover, in patients who underwent any PRT, receiving EGFR-TKIs and chemotherapy, absence of liver or bone metastasis, and non-adenocarcinoma had a statistically significant association with favorable PRS. Further clinical studies may give more accurate information about the benefits of PRT for survival, and lead to the improvement of clinical assessment and therapeutic strategies in recurrent NSCLC.

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Author contributions

Dr Shimada: contributed to the design and coordination of the study, prepared the manuscript, and read and approved the final manuscript.

Dr Ikeda: contributed to the design and coordination of the study, revised the article for important intellectual content, and read and approved the final manuscript.

Dr Saji: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Yoshida: contributed to preparing the manuscript, and read and approved the final manuscript.

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Dr Usuda: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Kajiwara: contributed to preparing the manuscript, and read and approved the final manuscript.

Dr Ohira: contributed to preparing the manuscript, and read and approved the final manuscript.

Figure legends

Figure 1

Postrecurrence survival curve of patients with recurrence

Figure 2

Postrecurrence survival curves of the patients lacking all 5 unfavorable factors (not receiving EGFR-TKI therapy and chemotherapy, liver or bone metastasis positive, non-adenocarcinoma) (A), and the patients with one of the risk factors (B)

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