Prognostic Factors in Non-small Cell Lung Cancer Patients with Postoperative Recurrence Following Third-Generation Chemotherapy

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Abstract. *Aim: To analyse the prognostic factors for patients with non-small cell lung cancer (NSCLC) who underwent cytotoxic chemotherapy with third generation agents or epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) for recurrence. Patients and Methods: Between 1997 and 2005, 479 patients underwent a complete resection for NSCLC. Of these, 112 patients underwent chemotherapy for postoperative recurrence. Results: Median postrecurrence survival time for these 112 patients was 25.6 months. Univariate analysis showed female gender, age younger than 65 years, ECOG performance status of 0-1, never-smoker status, and adenocarcinoma prolonged survival, whereas metastasis to the liver or adrenal gland shortened survival. Multivariate analysis revealed age, performance status, cell type and metastasis to the adrenal gland to be independent prognostic factors. Conclusion: Age, performance status, cell type, and metastasis to the adrenal were independent prognostic factors in NSCLC patients treated with third-generation agents or EGFR-TKI for recurrence.*

Non-small cell lung cancer (NSCLC) is currently the leading cause of cancer-related deaths worldwide (1). Surgery is the only potentially curative treatment, but it is only indicated for about 40% of all NSCLC patients. Adjuvant therapy has been known to prolong survival in stage IB-III patients (2,3). However despite these treatments, 25-80% of patients with NSCLC are reported to relapse and die from lung cancer within 5 years (4). Recurrence in distant organs is the most common pattern of postoperative recurrence suggesting that the disease has already become systemic by the time of surgery. Systemic chemotherapy has thus become the standard of care for NSCLC patients with postoperative recurrence.

In the last decade, several third-generation cytotoxic chemotherapeutic agents have been used in the treatment of advanced and recurrent NSCLC, including vinorelbine, gemcitabine, paclitaxel, docetaxel and irinotecan. Platinum-based doublet chemotherapy with one of these agents has been demonstrated to provide both a better response and prognosis than either first- or second-generation agents, such as mitomycin, vindesin, and ifosfamide. The results have already been confirmed in meta-analyses (5, 6). This has therefore become the standard of care as the first-line therapy for most advanced NSCLC patients. Furthermore, molecular targeted agents have also been developed and recognized as promising agents for many malignancies. Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib have been used against NSCLC and they have shown extremely good responses in some populations of NSCLC patients (7-11).

The present study focused on NSCLC patients with postoperative recurrence that underwent chemotherapy with either these third-generation chemotherapeutic agents or EGFR-TKI. Data was then retrospectively analyzed for postrecurrence survival time and any prognostic factors were identified.

Patients and Methods

A total of 479 NSCLC patients underwent a complete resection of the tumor (R0 resection) at the National Kyushu Cancer Center, Japan, between March 1997 and August 2005. All surgical specimens underwent pathological examinations and the pathological stage of each tumor was classified according to the TNM classification of the Union Internationale Contre Cancer (12). As of 2007 January, postoperative recurrence had been found in 121 patients. Nine patients did not undergo any chemotherapy and they were excluded from the present study due to a poor Eastern Cooperative Oncology Group (ECOG) performance status. Data were collected from 112 patients with postoperative recurrence, who underwent chemotherapy

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with either third-generation chemotherapeutic agents or EGFR-TKI. The most frequently used agents as a first-line chemotherapy for recurrent disease were gemcitabine (n=40) followed by vinorelbine (n=33), gefitinib (n=15), paclitaxel (n=14), docetaxel (n=5), and irinotecan (n=5). Cytotoxic chemotherapy included platinum-based chemotherapy for 78 patients. The mutation status of *EGFR* gene of the tumor was not evaluated for patients treated with EGFR-TKI.

The patients presented for follow-up visits every 2 months for the first 2 years after surgery, and then every 3-4 months thereafter. Each follow-up included a physical examination, a complete blood count, blood biochemistry and chest radiography. When a recurrence of lung cancer was suspected further evaluations such as computed tomography (CT), magnetic resonance imaging (MRI) and radionuclide bone scans, were added. A pathological examination was performed for confirmation purposes if clinically feasible. Radiographic evidence (radiography, CT, MRI or radionuclide scan) were accepted for cases in which such an examination was not feasible. Differentiation between second primary lung cancer and intra-pulmonary metastases was in general, performed according to the definitions proposed by Martini and Melamed (13). The final decisions on the diagnosis, treatment plan, and assessment of chemotherapeutic effect were made in clinical conferences. In general, patients with an ECOG performance status of 0 to 2 were considered to be candidates for systemic therapy with third-generation chemotherapeutic agents or EGFR-TKI for postoperative recurrence. A lesion that recurred only in the regional lymph nodes or surgical margin was considered to be a local recurrence and radiotherapy was added to chemotherapy. Radiotherapy was also administered for brain and bone metastases causing symptoms. A recurrent lesion in the ipsilateral lung or adrenal gland was considered as an indication for surgery. All treatments were carried out after informed consent was obtained from the patient.

The follow-up data for tumor recurrence and overall survival were obtained at regular intervals. Postrecurrence survival was based on the number of days from detection of the first recurrent site until death. The data for the patients who were still alive at the time of the last follow-up visit were censored.

The probabilities of postrecurrence survival rates were estimated using the Kaplan-Meier method. The log-rank test was used for univariate analysis of survival differences. Joint effects were assessed in the multivariable Cox analysis. Values of $p<0.05$ were considered to be statistically significant.

Results

The clinico-pathological characteristics of the 112 patients with NSCLC who underwent chemotherapy with either third-generation agents or EGFR-TKI are shown in Table I. Postoperative recurrence occurred in 34 females (30.4%) and 78 males (69.6%). The mean age of the patients was 64.0 years (range, 35-83 years) and 107 patients (95.5%) had an ECOG performance status of 0 or 1 at the diagnosis of the initial recurrence; the remaining 5 patients (4.5%) had an ECOG performance status of 2. A total of 71 patients (63.4%) were current or ex-smokers at the time of surgery. The most common cell type was adenocarcinoma (68.8%), followed by squamous cell carcinoma (22.3%). The pathological diagnosis was stage I in 40 patients (35.7%), stage II in 18 patients

Table I. *Clinico-pathological characteristics and a univariate analysis for postrecurrence survival (PRS) in patients with non-small cell lung cancer who underwent chemotherapy with either third-generation agents or EGFR-TKI.*

Factors	n	2-year PRS (%)	MST (months)	*P-value*
Gender				
Female	34	77.3	42.7	0.0061
Male	78	41.0	18.7	
Age				
≤64 years	59	64.0	32.4	0.0071
>64 years	53	39.1	15.5	
ECOG performance status				
0-1	107	55.0	26.2	<0.0001
2	5	0	7.8	
Smoking				
Never-smoker	41	71.5	44.8	0.0023
Smoker	71	41.4	17.1	
Cell type				
Adenocarcinoma	77	63.9	32.4	0.0002
Other	35	29.4	14.1	
Pathological stage[a]				
I	40	56.6	26.2	0.8076
II-IV	72	50.2	24.9	
Induction therapy				
Yes[b]	19	54.7	25.6	0.8387
No	93	51.7	24.9	
Adjuvant therapy				
Yes[c]	29	35.0	17.1	0.6441
No	83	56.4	26.2	
Disease free interval				
>1 year	55	57.8	26.2	0.2093
≤1 year	57	46.4	19.6	
Pattern of recurrence				
Local	35	54.0	24.9	0.3780
Distant	77	51.0	25.6	
Lung metastasis				
Yes	38	44.3	19.7	0.1327
No	74	56.1	27.9	
Bone metastasis				
Yes	20	57.7	27.9	0.9853
No	92	50.9	24.9	
Brain metastasis				
Yes	19	35.5	19.6	0.4447
No	93	55.1	26.2	
Liver metastasis				
Yes	7	17.9	10.4	0.0140
No	109	53.3	25.6	
Adrenal gland metastasis				
Yes	6	0	10.4	0.0002
No	106	55.8	27.3	
Recurrent metastases in other organs				
Single	76	56.8	27.3	0.1024
Multiple	36	41.6	19.6	

MST, Median survival time from detection of initial recurrence; ECOG, Eastern Clinical Oncology Group. [a]Pathological stage was determined at the time of operation for the primary tumor; [b]chemotherapy in 6 patients and chemo-radiotherapy in 13 patients; [c]chemotherapy in 19 patients, chemo-radiotherapy in 8 patients and radiation in 2 patients.

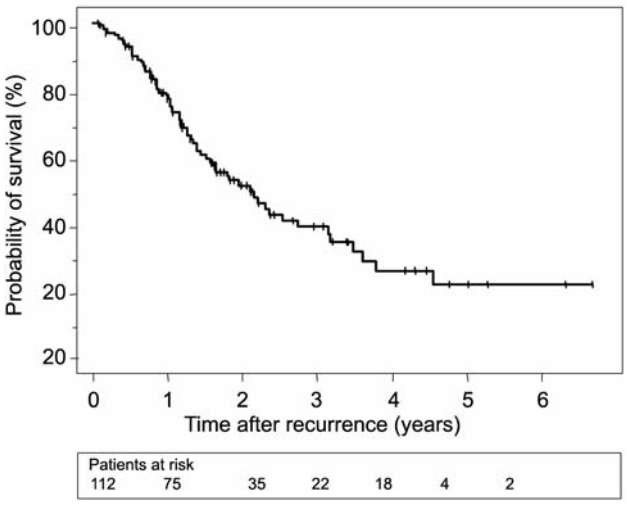

Figure 1. *Postrecurrent survival curve in 112 patients with non-small cell lung cancer who underwent chemotherapy with either third generation agents or EGFR-TKI.*

Table II. *Multivariable Cox analysis of factors associated with the postrecurrent survival in patients with non-small cell lung cancer who underwent chemotherapy with either third generation agents or EGFR-TKI.*

Factors	HR	95%CI	*P*
Gender			
Female	0.869	(0.389-1.943)	0.7322
Smoking			
Non-smoker	0.434	(0.188-1.001)	0.0503
Cell type			
Adenocarcinoma	0.509	(0.276-0.942)	0.0314
Age			
≤64 years	0.437	(0.237-0.805)	0.0079
ECOG performance status			
0-1	0.108	(0.034-0.344)	0.0002
Liver metastasis			
Yes	1.981	(0.648-6.052)	0.2302
Adrenal gland metastasis			
Yes	11.11	(3.922-31.25)	<0.0001

HR, hazard ratio; 95%CI, 95% confidence interval; ECOG, Eastern Clinical Oncology Group.

(16.1%) and stage III in 53 patients (47.3%). One patient with stage IV disease (0.9%) displayed pulmonary metastasis in a different lobe ipsilateral to the main tumor, which had been resected by a pneumonectomy. The mean disease-free interval from surgery was 20.7 months (range, 1.1-71.5 months). Metastasis was confined to a single organ in 76 patients (67.9%) and was present in ≥2 organs in 36 patients (32.1%).

The median follow-up time from detection of the first recurrence was 15.5 months (range, 1-79 months) and 57 patients (50.4%) were alive at the last follow-up. The Kaplan-Meier curve for postrecurrence survival is shown in Figure 1. The median postrecurrence survival time of these patients was 25.6 months and the postrecurrence survival rate at 2 years was 52.1%.

The factors influencing postrecurrence survival were analyzed in the 112 NSCLC patients. Univariate analysis of the relationship between postrecurrence survival and clinical parameters showed that female gender (p=0.0061), age ≤64 years (p=0.0071), ECOG performance status 0-1 (p<0.0001), never-smoker (p=0.0023), and adenocarcinoma (p=0.0002) significantly prolonged postrecurrence survival. Metastases to the liver (p=0.0140) and adrenal glands (p=0.0002) significantly shortened the postrecurrence survival (Table I).

Multivariate analysis was performed using these prognostic factors with values of p<0.1 in the univariate analysis. Age (p=0.0079), ECOG performance status (p=0.0002), cell type (p=0.0314), and metastasis to the adrenal gland (p<0.0001) were identified as independent factors in terms of postrecurrence survival (Table II).

In addition, the prognostic impact of selected therapy for postoperative recurrence was analyzed in these patients. Radiotherapy (39.3%) and surgery (14.3%) were applied in addition to systemic chemotherapy in patients with local recurrence, brain or bone metastases, and single site recurrence in ipsilateral lung. In the present study, no single metastasis to the adrenal gland was found. In addition, no significant difference was observed in the postrecurrence survival time related to the additional radiotherapy and surgery.

No significant difference in the postrecurrence survival was demonstrated in relation to the chemotherapy agents initially selected to treat recurrence. There was no significant difference in the postrecurrence survival between the patients initially treated with platinum and non-platinum chemotherapy. The median postrecurrence survival time and rate at 2 years in the patients treated with platinum were 24.1 months and 48.0%, respectively. In contrast, patients treated with non-platinum had a median postrecurrence survival time and rate at 2 years of 44.1 months and 53.1%, respectively (p=0.4050). There was no significant difference in postrecurrence survival between patients initially treated with cytotoxic agents and EGFR-TKI. The median postrecurrence survival time and rate at 2 years in patients treated with cytotoxic agents were 24.0 months and 49.2%, respectively, whereas value for patients treated with EGFR-TKI were 38.8 months and 84.6%, respectively (p=0.1265).

Forty-four patients (39.3%) displayed either a complete or partial response to the initial therapy for postoperative recurrence, and postrecurrence survival time was significantly longer for these patients than for the 68 patients (60.7%) with stable or progressive disease. The median postrecurrence survival time and rate at 2 years in patients

with a complete or partial response to initial therapy were 37.6 months and 71.0%, respectively, in comparison to 18.1 months and 38.8%, respectively, in patients with stable or progressive disease (p=0.0043).

Discussion

Systemic chemotherapy is commonly indicated for patients with postoperative recurrence. New third generation cytotoxic chemotherapeutic agents have been established for advanced NSCLC this decade, including vinorelbine, gemcitabine, paclitaxel, docetaxel, and irinotecan. Meta-analyses of independent studies showed that these agents were preferable to the first- or second-generation agents in combination with cisplatin (5, 6). Thus the administration of third generation agents with cisplatin has been used as a standard treatment for patients with advanced NSCLC and it has also been indicated for patients with postoperative recurrence. Molecular targeting agents are also promising for many malignancies. EGFR-TKIs, such as gefitinib and erlotinib, have been indicated for advanced and recurrent NSCLC (7-11). However, the use of these third-generation agents and EGFR-TKI postrecurrence survival has not yet been studied in detail.

Several studies have investigated the prognostic factors in patients with postoperative recurrence after complete resection of primary NSCLC (14-18). Sugimura *et al*. (18) demonstrated that the addition of any treatment for patients with postoperative recurrence significantly prolongs survival, and preoperative chemotherapy, postoperative radiotherapy, poor ECOG performance status, short disease-free interval from the initial resection of recurrent tumor, symptoms at recurrence, and certain locations of recurrence were poor prognostic factors. However, comparing the findings of that study to the present study was difficult because the present study analyzed only patients who underwent chemotherapy for postoperative recurrence and excluded patients who only received supportive care. A selection bias was considered likely between patients with and without any treatment in this retrospective setting. Patients with a poor ECOG performance status, particularly ≥3, are generally considered to be candidates for supportive care. In fact, 9 out of the 121 patients in the present study had a poor ECOG performance status and thus received no chemotherapy. Their median survival time for these 9 patients was 6.3 months (data not shown), in comparison to 25.6 months for the 112 patients examined in the present study. The present study intended to demonstrate the postrecurrence prognostic factors for patients treated with third-generation chemotherapeutic agents and EGFR-TKI for postoperative recurrence after a complete resection.

Unlike other studies, tumor stage, induction or adjuvant therapy, disease-free interval, and surgery for recurrence were not associated with the postrecurrence survival in the present study. Conversely, a younger age, a good ECOG performance status, and an adenocarcinoma cell type were all found to contribute to a good prognosis and adrenal gland metastasis was revealed to contribute to a poor prognosis. Age and ECOG performance status are well-known predictive factors for cytotoxic chemotherapeutic agents, as well as the prognostic factors for patients with advanced NSCLC (19). The selection of these as prognostic factors for patients with recurrent NSCLC is thus understandable in the present study. On the other hand, the reason for the good prognosis for adenocarcinoma cell type cases remains unclear. An adenocarcinoma cell type has not been demonstrated to be a good prognostic factor by subset analyses in any major studies of cytotoxic chemotherapeutic agents. However, gefitinib has been widely shown to be effective for adenocarcinoma cell type (7, 9). Although the cell type of all 15 patients who were treated with gefitinib as first-line chemotherapy was adenocarcinoma in the present study, this failed to demonstrate a significant survival benefit. However, 38 (49.4%) out of 77 adenocarcinoma patients were treated with gefitinib in their clinical courses and they have shown a favorable prognosis. The median postrecurrence survival time and rate at 2 years in these 38 patients were 53.7 months and 73.7%, respectively (data not shown). These results suggest that gefitinib as either a second-line or even later stage treatment might have influenced the favorable prognosis of adenocarcinoma patients. It is necessary to conduct a prospective study to determine whether gefitinib at any stage of treatment influences the survival in patients with NSCLC.

Recent studies have demonstrated that the mutation status of the *EGFR* gene of the tumor predicts the effect of gefitinib sensitivity in patients with advanced NSCLC (9-11, 20). Although this was not routinely evaluated in the present study, selecting patients for gefitinib according to *EGFR* status might lead to a better prognosis in patients with postoperative recurrence.

Tanvetyanon *et al*. (21) reported that patients who underwent an adrenalectomy for single adrenal metastasis have a good prognosis. The median survival time in patients with adrenalectomy for recurrence was 31 months and the 5-year survival rate was 25%. In the current series, all 6 patients with adrenal metastasis displayed multiple metastases to other organs and no adrenalectomies were performed. This suggests that single adrenal metastasis may have a good prognosis after surgery, whereas adrenal metastasis with other metastatic sites has a poor prognosis.

The response rate to first- or second-generation agents such as mitomycin, vindesin, and ifosfamide for advanced NSCLC is 10-20%. The response rate of initial therapy in the present study for postoperative recurrence was 39.3% with third-generation agents and EGFR-TKI and responders demonstrated a favorable prognosis. This suggests that the

development of therapeutic agents for NSCLC has played an important role in improving the prognosis of patients with postoperative recurrence.

In conclusion, age, the ECOG performance status, cell type and metastasis to the adrenal gland were all shown to be independent prognostic factors in NSCLC patients who underwent chemotherapy with third-generation agents and EGFR-TKI for postoperative recurrence. The responders to first-line therapy for postoperative recurrence also demonstrated a good prognosis. Further studies which focus on clinical factors predicting the effects of third-generation chemotherapeutic agents and EGFR-TKI are therefore needed.

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