

# Post-recurrence survival of patients with non-small-cell lung cancer after curative resection with or without induction/adjuvant chemotherapy

Shinsuke Saisho\*, Koichiro Yasuda, Ai Maeda, Takuro Yukawa, Riki Okita, Yuji Hiram, Katsuhiko Shimizu and Masao Nakata

Department of General Thoracic Surgery, Kawasaki Medical School Hospital, Kurashiki Okayama, Japan

\* Corresponding author. Department of General Thoracic Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki Okayama 701-0192, Japan. Tel: +81-86-4621111; e-mail: s.saisho@med.kawasaki-m.ac.jp (S. Saisho).

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## Abstract

**OBJECTIVES:** Recently, the prognosis of patients with non-small-cell lung cancer (NSCLC) has improved, thanks to the standardization of adjuvant chemotherapy and the introduction of molecular-targeted drugs, notably epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and other new anti-cancer agents. However, the survival characteristics and prognosis of patients with recurrent NSCLC after curative resection are not well understood.

**METHODS:** Of the 430 consecutive patients with NSCLC who underwent complete surgical resection at our institution between January 2004 and July 2011, we included 76 patients with recurrence whose post-recurrence treatment and outcome could be confirmed. We then retrospectively evaluated the effect of prognostic factors on post-recurrence survival.

**RESULTS:** There were 50 men and 26 women, and the median age at recurrence was 74.5 years. The median time from surgical resection to recurrence was 12.7 months. Thirty-eight of the 76 (50%) patients underwent multimodality treatment with surgery and pre-operative and/or postoperative chemotherapy as their initial treatment. For recurrence, systemic chemotherapy was administered to 64 (84%) patients, and the disease control rate for first-line chemotherapy was 55%. The 1- and 2-year post-recurrence survival rates were 68.3 and 45.8%, respectively, and the median post-recurrence survival time was 17.7 months. Six independent prognostic factors were identified: wild-type EGFR, no adjuvant chemotherapy for the primary lung cancer, age  $\geq 80$  years at recurrence, a poor Eastern Cooperative Oncology Group performance status at recurrence, symptomatic at recurrence and no systemic chemotherapy for recurrence, which significantly decreased the post-recurrence survival.

**CONCLUSIONS:** The prognosis of patients with NSCLC recurrence after surgery is currently improving. Our results suggested two new prognostic factors, adjuvant chemotherapy and EGFR mutations, neither of which have been previously reported. Treatment strategies for postoperative recurrence should be established based on a more detailed subdivision of factors, such as histology and molecular markers, in the future.

**Keywords:** Non-small-cell lung cancer • Post-recurrence survival • Adjuvant chemotherapy

## INTRODUCTION

The 5-year survival rates after curative resection for non-small-cell lung cancer (NSCLC) have improved remarkably from 52.6% for patients who underwent resection in 1994 [1] to 61.4% in 1999 [2] and 69.6% in 2004 [3]. This improvement is believed to be a consequence of the increase in the detection of small-sized lung cancers, thanks to improvements in diagnostic imaging, such as computed tomography (CT) and  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET), as well as other factors, such as the standardization of adjuvant chemotherapy. Several randomized controlled trials (RCTs) were reported in the first half of the 2000s, demonstrating the efficacy of adjuvant chemotherapy followed by complete surgical resection; now, this regimen

has been accepted as the standard treatment for pathological Stages II and IIIA NSCLC [4–6]. Preoperative induction chemo- or chemoradiotherapy for superior sulcus tumours [7, 8] and resectable clinical Stage IIIA NSCLC with mediastinal lymph node metastasis [9–12] are also being proactively tested. Thus, attempts are now underway to improve the prognosis of Stage II or more advanced NSCLC with a high risk of recurrence using multimodality treatment, including surgery.

Although the rate of recurrence after the total resection of NSCLC varies according to the pathological stage, it is relatively high at 30–75%, and the prognosis remains poor [13, 14]. Most studies of the treatment for recurrent NSCLC after curative resection and its prognostic factors have investigated patients from before 2000, prior to the establishment of adjuvant

**Table 1:** Patient characteristics

Clinicopathological background	
Age at recurrence (years)	
Median	74.5
Range	48–87
Sex	
Male	50
Female	26
Performance status at recurrence	
0	23
1	33
2	13
3	6
4	1
Smoking status	
Non-smoker	23
Light smoker	10
Heavy smoker	40
Unknown	3
Smoking index (pack-years)	
Median	31
Range	6.7–90
Histology	
Adenocarcinoma	53
Squamous cell carcinoma	15
Large cell carcinoma	3
Adenosquamous carcinoma	3
Pleomorphic carcinoma	2
Pathological stage	
IA/IB	14/14
IIA/IIB	6/11
IIIA/IIIB	30/1
Epidermal growth factor receptor mutation status	
Mutation	28
Wild-type	39
Unknown	9
Initial treatment	
Surgical approach	
Thoracotomy	43
Video-assisted thoracoscopic surgery	33
Surgical procedures	
Pneumonectomy	0
Lobectomy	60
Segmentectomy	6
Wedge resection	10
Lymph nodes dissection	
Systematic lymph node dissection	56
Mediastinal lymph node sampling	11
Hilar lymph node sampling	10
Induction chemotherapy	
No	71
Yes	5
Adjuvant chemotherapy	
No	41
Yes	35
Platinum-based	19
Uracil-tegafur	16
p-Stage IA	
Yes (%)	4 (28)
p-Stage IB	
Yes (%)	10 (71)
p-Stage II	
Yes (%)	8 (47)
p-Stage III	
Yes (%)	13 (42)
Recurrent disease	
Symptoms at recurrence	
Yes	25
No	51
Disease-free survival (months)	
Median	12.8
Range	0.9–66.1

Recurrent site	
Local (intrathoracic)	42
Distant (extrathoracic)	16
Both	18
No. of recurrent foci	
Single	29
Multiple	47
Therapy for recurrence	
Systemic chemotherapy	64
Palliative care	12
No. of chemotherapeutic regimen	
Median	2
Range	1–7
First-line therapeutic response	
Complete response	4
Partial response	23
Stable disease	8
Progressive disease	21
Not evaluable	8 <sup>a</sup>
EGFR-TKIs for recurrence	
Yes	36
No	40

TKIs: tyrosine kinase inhibitors.

<sup>a</sup>n = 6, non-measurable recurrent lesion on the RECIST guideline; n = 2, early discontinuation of chemotherapy due to adverse events.

chemotherapy as a standard treatment. Thus, few studies have addressed the effect of preoperative induction therapy and adjuvant chemotherapy on the treatment and prognosis after recurrence [15–19].

The objective of this study was to elucidate the effect of preoperative and postoperative chemotherapy, particularly platinum-based chemotherapy (which is the standard regimen for Stage II and IIIA NSCLC), on the post-recurrence prognosis.

## MATERIALS AND METHODS

### Patients and methods

Of 430 NSCLC patients who underwent curative surgical resection at Kawasaki Medical School Hospital, Kurashiki, Japan, between January 2004 and July 2011, postoperative recurrences had occurred in 109 patients (25%) as of February 2012. Of these 109 patients, complete information on the post-recurrence treatment and prognosis was available for 76 patients (70%), and they were included in this analysis. We retrospectively evaluated the effect of clinical factors, oncological factors, initial treatment (surgical procedures and whether preoperative or postoperative chemotherapy was used and if so, what regimen), treatment for recurrence (regimen and therapeutic efficacy) and other factors of post-recurrence prognosis.

Data including age, sex, smoking status, histopathological diagnosis (histology and pathological stage), surgical procedures, whether preoperative or postoperative chemotherapy was used, and if so, what regimen, epidermal growth factor receptor (EGFR) mutations, Eastern Cooperative Oncology Group performance status (ECOG-PS), symptoms at the time of recurrence, site of recurrence, post-recurrence treatment and response, and survival were gathered from the patients' medical records. Histology was categorized according to the World Health Organization Classification of Tumours, 3rd edition [20], and the TNM classification was assigned according to the International Union Against Cancer staging system [21]. The response to chemotherapy was

evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (version 1.1) [22].

All patients had been preoperatively staged using contrast-enhanced CT, FDG-PET and magnetic resonance imaging (MRI) of brain. Routine mediastinoscopy or endobronchial ultrasound with transbronchial needle aspiration to detect occult mediastinal lymph node metastases was not performed.

As a general rule in surgical procedures, we performed a standard surgical procedure, that is, lobectomy with systematic or selective mediastinal lymph node dissection. However, in high-risk patients who were unable to tolerate a lobectomy as assessed by cardiopulmonary function, sublobar resection was selected. Induction therapy was indicated for clinical Stage IIIA patients with resectable mediastinal lymph node metastasis. Adjuvant platinum-based doublet chemotherapy was indicated for pathological Stage II and IIIA patients. On the other hand, adjuvant therapy with oral uracil-tegafur was indicated for pathological Stage IB patients.

In general, a follow-up examination was done every 3 months for the first 2 years, and thereafter every 6–12 months. The follow-up procedures included a physical examination, the serum level of carcinoembryonic antigen and chest radiography. Screening examinations by CT or FDG-PET were done every 6 or 12 months for 5 years.

Recurrent NSCLC was diagnosed based on a physical examination and diagnostic imaging such as CT, MRI and FDG-PET. Histopathological confirmation of the diagnosis was made only when clinically required; as a result, recurrence was histologically confirmed in only 10 of 76 patients.

Written informed consent was obtained from each patient, and the study was approved by the institutional review board of Kawasaki Medical School (IRB no. 1181).

## Statistical analysis

The Kaplan–Meier method was used to analyse survival. The  $\chi^2$  test was used to compare clinicopathological factors between groups. For univariate analyses of the clinicopathological factors, differences were evaluated using the log-rank test, and a multivariate analysis of independent prognostic factors was conducted using Cox's proportional hazards regression model. Differences were considered significant when the *P*-value was <0.05.

## RESULTS

### Patient backgrounds

The patient characteristics are given in Table 1. There were 50 men and 26 women. The median age at the time of recurrence was 74.5 (range, 48–87 years). The median disease-free interval from the initial surgery until recurrence was 12.7 months (range 27 days–66.1 months). Regarding the pathological findings, the most common histology was adenocarcinoma in 53 (70%) patients, and the most common pathological Stage was IIIA in 30 cases (39%). Sixty-seven (88%) patients had been screened for EGFR mutation, and EGFR mutations and wild-type EGFR were found in 28 and 39 patients, respectively.

### Initial treatment for NSCLC

The initial treatment was surgery alone in 38 patients; multimodality treatment including surgery and preoperative and/or postoperative chemotherapy was performed in the other 38 (50%) patients. Of these, 5 (7%) patients underwent induction chemotherapy or chemoradiotherapy followed by surgery, and 35 (41%) underwent adjuvant chemotherapy, with 2 patients undergoing both preoperative and postoperative chemotherapy. The induction chemotherapy consisted of platinum-based doublet chemotherapy in all 5 patients, with 2 also undergoing concurrent radiotherapy. The adjuvant chemotherapy consisted of platinum-based doublet chemotherapy in 19 patients and oral uracil-tegafur in 16. Twenty-two (29%) patients had been treated with platinum-based doublet chemotherapy either preoperatively or postoperatively.

### Recurrence and post-recurrence therapy

Symptoms were evident in 25 (33%) patients at the time of recurrence. The initial recurrence was intrathoracic in 42 patients, extrathoracic in 16 and a combination of intrathoracic and extrathoracic in 18. Forty-seven (62%) patients developed recurrences in multiple organs.

Treatment for recurrence included systemic chemotherapy in 64 (84%) patients and local therapy only in 2 (stereotactic radiosurgery for brain metastases in 2 patients who had only brain recurrences). The remaining 10 patients received only palliative care because of a poor ECOG-PS, an advanced age and so on. Of the 64 patients who underwent chemotherapy, the response to first-line chemotherapy was a complete response (CR) in 4 patients, a partial response (PR) in 23, stable disease (SD) in 8, progressive disease (PD) in 21 and not evaluable (NE) in 8, with a disease control rate for first-line chemotherapy of 55%. EGFR tyrosine kinase inhibitors (TKIs; gefitinib and erlotinib) were used in 36 (47%) patients; none of the patients were treated with a vascular endothelial growth factor inhibitor (bevacizumab).

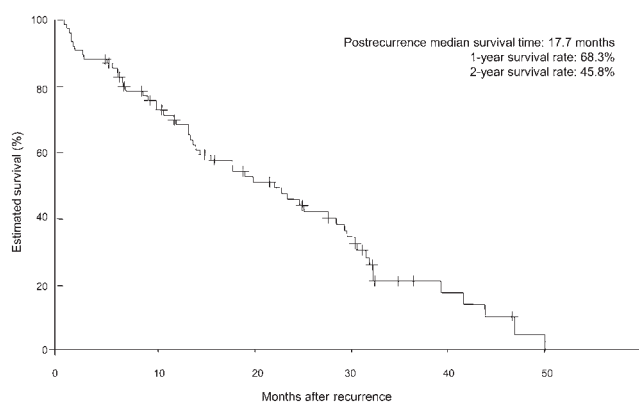
### Post-recurrence survival

The post-recurrence follow-up period ranged from 10 days to 50.1 months (median, 15.0 months), and the 1- and 2-year post-recurrence survival rates were 68.3 and 45.8%, respectively; the median survival time (MST) after recurrence was 17.7 months (Fig. 1). Post-recurrence survival was analysed with respect to clinical factors (age at recurrence, sex, ECOG-PS at recurrence and smoking status), pathological factors (histology, pathological stage and EGFR mutation status), initial treatment (surgical procedure, whether induction chemo/chemoradiotherapy or adjuvant chemotherapy was used and their regimens) and factors related to recurrence (symptoms at recurrence, postoperative recurrence-free period, site and type of recurrence, use of systemic chemotherapy or EGFR-TKIs, response to first-line chemotherapy). Univariate analyses showed that the patient outcome was significantly poorer for patients with an age of  $\geq 80$  years at surgery, non-adenocarcinoma, wild-type EGFR, no adjuvant chemotherapy, no preoperative or postoperative chemotherapy, an age of  $\geq 80$  years at recurrence, a poor ECOG-PS at recurrence (PS 2–4), a postoperative recurrence-free period <12 months

**Table 2:** Predictors of post-recurrence survival; baseline and primary lung cancer characteristics

	Post-recurrence survival			P-value <sup>a</sup>	
	Patients (%)	MST (months)	2 year (%)	Univariate	Multivariate
Sex					
Male	50 (66)	11.7	37.2	0.2110	
Female	26 (34)	21.6	60.5		
Age at surgery (years)				0.0128	0.460
≤79	66 (87)	17.7	49.5		
≥80	10 (13)	9.2	18.0		
Smoking status				0.4185	
Smoker	50 (66)	11.7	40.2		
Non-smoker	23 (30)	21.6	57.5		
Histology				0.0060	0.159
Adenocarcinoma	53 (70)	19.8	52.9		
Non-adenocarcinoma	23 (30)	8.4	26.5		
Epidermal growth factor receptor mutation status				0.0378	0.012
Mutation	28 (37)	22.8	64.4		
Wild-type	39 (51)	10.5	29.8		
Pathological stage				0.9820	
IA-IB	28 (37)	13.9	43.2		
IIA-IIIB	48 (63)	15.5	47.3		
Initial surgery				0.1290	
Lobectomy	60 (79)	17.7	51.3		
Limited resection	16 (21)	9.8	15.5		
Induction chemotherapy				0.6514	
Yes	5 (7)	17.7	20.0		
No	71 (93)	15.5	48.2		
Adjuvant chemotherapy				0.0021	0.001
Yes	35 (46)	21.6	64.8		
No	41 (54)	9.8	29.0		
Chemotherapeutic regimen				0.0082 <sup>b</sup>	0.291 <sup>b</sup>
Platinum-based	22 (29)	19.0	49.9		
Uracil-tegafur	16 (21)	21.6	72.2		
No	38 (50)	9.2	32.3		
Platinum-based chemotherapy				0.3921	
Yes	22 (29)	13.2	47.0		
No	54 (71)	19.0	49.9		

MST: median survival time

<sup>a</sup>Log-rank test for comparison of post-recurrence survival among groups.<sup>b</sup>P-value for Platinum-regimen and uracil-tegafur vs no perioperative chemotherapy.**Figure 1:** Survival curve illustrating the post-recurrence survival of 76 patients.

and no systemic chemotherapy for recurrence. Multivariate analysis of these factors identified six factors as independent prognostic factors: wild-type EGFR, no adjuvant chemotherapy, an age ≥80 years at recurrence, ECOG-PS 2–4, symptomatic and no

chemotherapy for recurrence (Tables 2 and 3, Figs 2 and 3). A multivariate analysis of the 64 patients who underwent systemic chemotherapy showed that the response to first-line chemotherapy for recurrence ( $P < 0.001$ ) and the postoperative recurrence-free period ( $P = 0.026$ ) were independent prognostic factors (Table 4).

## DISCUSSION

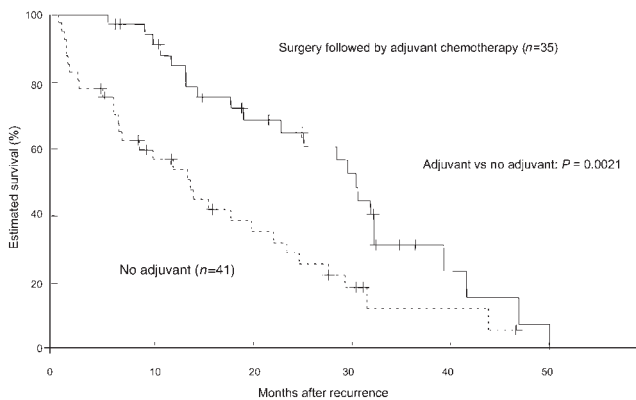
In recent years, not only have numerous RCTs established evidence for chemotherapy, but new anti-cancer agents and molecular-targeted drugs have also been introduced, and personalized treatment strategies are now being recommended based on histology and molecular markers [23]. This standardization and personalization of treatment for NSCLC is improving the prognosis of patients with NSCLC. On the other hand, few studies have evaluated treatments for recurrent NSCLC after curative resection. In clinical practice, chemotherapy for recurrence is routinely administered based on the recommended regimen for unresectable advanced NSCLC. However, patients

**Table 3:** Predictors of post-recurrence survival: recurrent disease characteristics

	Post-recurrence survival			P-value <sup>a</sup>	
	Patients (%)	MST (months)	2 year (%)	Univariate	Multivariate
Age at recurrence (years)					
≤79	62 (82)	17.7	49.6	0.0182	0.001
≥80	14 (18)	9.2	20.4		
Performance status at recurrence					
0–1	56 (74)	18.8	58.1	< 0.0001	0.012
2–4	20 (26)	6.3	15.0		
Symptoms					
Yes	25 (33)	6.5	25.1	0.0032	0.003
No	51 (67)	21.5	55.4		
Disease-free interval (months)					
<12	33 (43)	13.3	26.4	0.0084	0.621
≥12	43 (57)	19.8	65.7		
Intra- or extrathoracic recurrence					
Intrathoracic only	42 (55)	15.5	42.8	0.1024	
Extrathoracic only	16 (21)	9.0	23.8		
Both	18 (24)	19.8	56.1		
Initial recurrence					
Single site	29 (38)	18.8	48.0	0.167	
Multiple	47 (62)	13.6	44.7		
Systemic chemotherapy					
Yes	64 (84)	17.7	50.2	<0.0001	0.003
No	12 (16)	1.2	12.5		
EGFR-TKIs (gefitinib and erlotinib)					
Yes	36 (47)	15.5	42.9	0.4205	
No	40 (53)	14.4	48.2		

EGFR-TKI: epidermal growth factor receptor tyrosine kinase inhibitors; MST: median survival time.

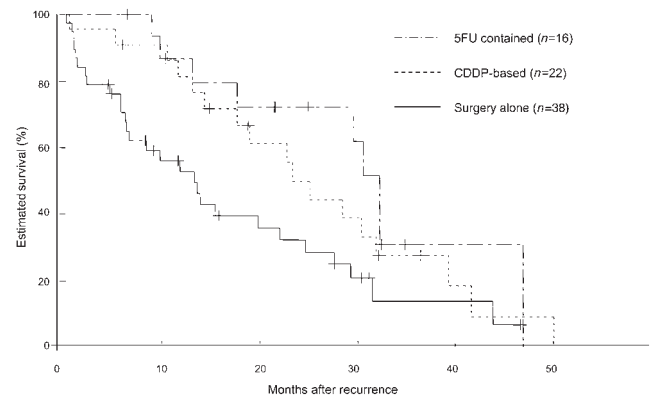
<sup>a</sup>Log-rank test for the comparison of post-recurrence survival among groups.



**Figure 2:** Survival curves illustrating the post-recurrence survival of 35 patients who initially underwent surgery followed by adjuvant chemotherapy and 41 patients who underwent surgery alone. The curves differed significantly for the patients treated with surgery followed by adjuvant chemotherapy vs the patients treated with surgery alone ( $P = 0.0021$ ).

with postoperative recurrent disease can be anticipated to have a poor ECOG-PS and organ function as a result of pulmonary resection or old age. Furthermore, recurrence after pre/postoperative chemotherapy can theoretically be regarded as the proliferation of tumour cells resistant to anti-cancer agents. Therefore, the treatment and prognosis of postoperative recurrence must differ in some aspects from those used for clinical Stage IV NSCLC.

Previous studies of recurrent NSCLC have described a post-recurrence survival rate of 15–20% at 2 years and a post-



**Figure 3:** Survival curves illustrating the post-recurrence survival of 22 patients who received platinum-based induction or adjuvant chemotherapy, 16 who received adjuvant chemotherapy with uracil-tegafur and 38 who did not receive pre- or postoperative chemotherapy. The curves differed significantly for patients who received adjuvant chemotherapy with uracil-tegafur vs those who received no perioperative chemotherapy ( $P = 0.0089$ ). However, the curves did not differ significantly for patients who received pre- or postoperative platinum-based chemotherapy vs patients who received no perioperative chemotherapy ( $P = 0.1031$ ) or for patients who received adjuvant chemotherapy with uracil-tegafur compared with those who received pre- or postoperative platinum-based chemotherapy ( $P = 0.4231$ ).

recurrence MST of 8–13 months [17–19]. In this study, we only investigated patients who had undergone surgery after the mid-2000s, once adjuvant chemotherapy had become established as a standard therapy and found a 2-year post-recurrence



**Table 4:** Predictors of post-recurrence survival for 64 patients who received systemic chemotherapy

	Univariate P-value <sup>a</sup>	Multivariate
Sex		
Male vs female	0.6402	
Age at surgery (years)		
≤79 vs ≥80	0.1273	
Age at recurrence (years)		
≤79 vs ≥80	0.0783	
Performance status at recurrence		
0–1 vs 2–4	0.0010	0.494
Smoking status		
Smoker vs non-smoker	0.7829	
Histology		
Ad vs non-ad	0.2304	
EGFR mutation status		
EGFR mutation vs wild-type	0.1481	
Pathological stage		
IA–IB vs IIA–IIIB	0.4776	
Initial surgery		
Lobectomy vs limited resection	0.4904	
Induction chemotherapy		
Yes vs no	0.8522	
Adjuvant chemotherapy		
Yes vs no	0.0507	0.207
Perioperative chemotherapy		
Yes vs no	0.2780	
Platinum-based chemotherapy		
Yes vs no	0.6443	
Symptoms at recurrence		
Yes vs no	0.0867	
Disease-free interval (months)		
<12 vs ≥12	0.0351	0.026
Recurrent site		
Intra vs extra	0.4756	
Initial recurrence		
Single vs multiple	0.1266	
EGFR-TKIs (gefitinib and erlotinib)		
Yes vs no	0.1566	
Response of initial chemotherapy		
CR/PR/SD vs PD	<0.0001	<0.001

Ad: adenocarcinoma; EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitors; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable.

<sup>a</sup>Log-rank test for the comparison of post-recurrence survival among groups.

survival rate of 45.8% and a post-recurrence MST of 17.7 months, an improvement in outcome compared with previous reports. This improvement likely reflects the effects of new anti-cancer agents, including EGFR-TKIs. This change in lung cancer chemotherapy can also be expected to have exerted an effect on prognostic factors for recurrent NSCLC. Factors previously reported as affecting the prognosis for recurrent NSCLC include ECOG-PS, whether symptoms are present at the time of recurrence, the postoperative recurrence-free period and pre- or postoperative chemotherapy. Among these, adjuvant chemotherapy has been regarded as a predictor of a poor prognosis for patients with recurrent NSCLC, although this topic has only been addressed by a few studies [15–19]. In our study, 38 (50%) patients received pre- and/or postoperative chemotherapy, with 22 undergoing platinum-based doublet chemotherapy pre- or

postoperatively and 16 undergoing adjuvant chemotherapy with oral uracil-tegafur. Among these patients, those who underwent adjuvant chemotherapy had a significantly better outcome than those who did not. This finding differs from that of previous studies. Two possible reasons for this discrepancy can be considered: first, the therapeutic efficacy of EGFR-TKIs and other new anti-cancer agents, and secondly, the use of adjuvant chemotherapy with oral fluorouracil. In Japan, oral uracil-tegafur (referred to as UFT) is routinely used for adjuvant chemotherapy for completely resected pathological Stage IB NSCLC [24, 25]. In our study, oral uracil-tegafur was administered to 16 of the 76 (21%) patients, and the outcomes of these 16 patients were comparatively good (Fig. 3).

Because of the retrospective nature of this analysis, our study has some limitations. First, 33 patients (30% of the recurrent patients) had to be excluded because their post-recurrence course of treatment or outcome could not be analysed. The exclusion of 30% of the patients may have affected our results. Secondly, this study analysed only a small number of patients, and this number was lower than those included in previous studies. So, the conclusions drawn by this study limited the significance of the results obtained. Thirdly, screening for EGFR mutations was not performed in 9 of the 76 (12%) patients. Finally, the response to first-line chemotherapy was not evaluable in 8 of the 64 patients (13%) who underwent systemic chemotherapy for recurrence. These patients discontinued chemotherapy at an early stage because of chemotherapy-induced adverse events or an aggravated general condition caused by disease progression. To resolve these problems, analyse the prognosis of patients with recurrent NSCLC, and establish treatment strategies, multicenter, large-scale, prospective studies are required.

In this study, we investigated the post-recurrence outcome and prognostic factors for patients who had undergone surgery for NSCLC. The prognostic factors included EGFR mutation, adjuvant chemotherapy, ECOG-PS, age, symptoms at the time of recurrence and the use of systemic chemotherapy for recurrence. Although the post-recurrence outcome was better than in previous studies, the outcome for recurrent NSCLC remains poor. The use of adjuvant chemotherapy for initial treatment in accordance with the treatment guidelines is important. Further investigation and standardization of post-recurrence treatment are required.

**Conflict of interest:** All authors declare that they have no competing interests.

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