Yonago Acta Medica 2017;60:213–219 doi: 10.24563/yam.2017.12.001 *Original Article*

Prognostic Factors for Post Recurrence Survival in Resected Pathological Stage I Non-small Cell Lung Cancer

Yasuaki Kubouchi, Yoshiteru Kidokoro, Takashi Ohno, Yohei Yurugi, Makoto Wakahara, Tomohiro Haruki and Hiroshige Nakamura

Division of General Thoracic Surgery, Department of Surgery, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8504, Japan

ABSTRACT

Background Recurrence of lung cancer after surgical resection is a major obstacle in the cure and long-term survival of patients and has become the most common cause of death. However, prognostic factors and efficacy of therapy after recurrence remain controversial. We evaluated the prognostic factors of post recurrence survival (PRS) in patients of resected stage I non-small cell lung cancer (NSCLC).

Methods Of the 551 patients who underwent surgery for stage I NSCLC between 2005 and 2013, we reviewed 89 (16.2%) patients who had recurrence. We examined PRS using the Kaplan–Meier method and multivariate Cox regression analyses.

Results The median follow-up period after recurrence was 21.0 months. The median recurrence free interval (RFI) was 16.8 months. The 1-year PRS and 3-year PRS were 65.6% and 44.7%, respectively. Multivariate analysis revealed that size of primary lesion > 25 mm (P = 0.048), RFI ≤ 17 months (P = 0.048) and no treatment for recurrence (P < 0.001) were independent poor-prognosis factors of PRS. We further examined PRS in 66 patients who underwent any post recurrence therapy. For the patients who underwent treatment after recurrence, bone metastasis (P = 0.025) and treatment without epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (P = 0.049) were independent poor prognostic factors.

Conclusion PRS may be associated with characteristics of a recurrent lesion, including the biology of the recurrent tumor, RFI, recurrent site, the treatment for recurrence, rather than characteristics of primary lesion. Although further validation is needed, this information is important for the design of clinical trials for post-recurrence therapy.

Key words epidermal growth factor receptor tyrosine kinase inhibitors; non-small cell lung cancer; post recurrence survival; prognostic factor

Lung cancer is the leading cause of cancer deaths in Japan and around the world. Although surgical resection is the most appropriate choice of treatment for early stage non-small cell lung cancer (NSCLC),[1] the recurrence rate of stage I NSCLC has been reported to be 18.5%–28%.[2–5] According to the Japanese Lung Cancer Registry Study, tumor recurrence remains a major cause of post-operative death.[6] Despite the administration of multimodality therapy, including chemotherapy, radiation therapy, or a combination of other therapeutic modalities, most lung cancer patients with postoperative recurrence have little possibility of cure.[2, 7, 8] Although several studies have described prognostic factors for the post-recurrence survival (PRS) of patients with stage I or I–III NSCLC and for the PRS of lung adenocarcinoma patients,[2–5, 7–14] the predictive prognostic factors for PRS of NSCLC remain controversial. The aim of this study was to evaluate the prognostic factors of PRS in patients with completely resected stage I NSCLC.

MATERIALS AND METHODS

Of 551 patients who underwent complete resection for pathological stage I NSCLC between January 2005 and December 2013 at Tottori University Hospital (Yonago, Japan), we retrospectively analyzed the cases of the 89 (16.2%) patients who developed postoperative recurrence. The following exclusion criteria were applied: induction chemotherapy or radiation therapy or both; low-grade pulmonary malignant tumor including carcinoid tumor; positive pleural lavage cytology; and death within 30 days of the patient's resection. Complete resection was defined as the demonstration of cancer free surgical margins including pleural lavage cytology, both grossly and histologically.

Patients were followed up every 3 months in the

Corresponding author: Yasuaki Kubouchi, MD
kuboyasu1118@med.tottori-u.ac.jp
Received 2017 September 1
Accepted 2017 October 4
Abbreviations: CEA, carcinoembryonic antigen; CT, computed tomography; EGFR, epidermal growth factor receptor; H&E, haematoxylin and eosin; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PET, positron emission tomography; PRS, post recurrence survival; PS, performance status; RFI, recurrence free interval; TKIs, tyrosine kinase inhibitors

first 2 years after resection, then every 3–6 months thereafter. The follow-up procedures included physical examination, chest X-ray, hematological examination and serum tumor markers. Chest and abdomen computed tomography (CT) scans were performed every year. Whenever recurrent disease was suspected, magnetic resonance imaging (MRI) of the brain and positron emission tomography (PET) of the whole body were performed. After the initial diagnosis of recurrence, further examination including contrast-enhanced CT, brain MRI and PET were performed to check for other metastatic sites.

Tumor stage was determined based on the seventh TNM classification of lung cancer. The pathological diagnosis was performed using hematoxylin and eosin (H&E) stained sections according to the World Health Organizing classification for lung cancer. The date of recurrence was defined as the date when the physician recognized the recurrent disease, regardless of histological or cytological confirmations. Elevation of the serum tumor markers alone did not define recurrence. Locoregional recurrence was defined as the recurrence in surgical margin, ipsilateral hemithorax, or mediastinal lymph nodes, and distant metastasis was defined as the recurrence in the contralateral hemithorax or extrathoracic organs. When there were simultaneous locoregional and distant recurrence, it was defined as distant metastasis. When a patient presented with a new histological type, or with clinical features consistent with a new primary lung cancer, it was defined as a second primary tumor.

RFI was defined as the time in months from the date of resection for primary lung cancer to the date of the initial recurrence. The length of PRS was defined as the time in months from the date of the initial relapse to the date of death from any cause or the date of which the patient was last known to be alive.

The Kaplan-Meier method was used for calculation of the PRS, and differences in survival were determined by log-rank test. The cut-off values of each continuous variable, such as age, tumor size, RFI and CEA were defined using ROC curve. AUC sensitivity and specificity were calculated by dividing patients into two groups: surviving or dead. Univariate and multivariate analyses were performed by the Cox proportional hazards model using SPSS version 23 (IBM SPSS Statistics; IBM Corporation, Armonk, NY). Only variables with P-value < 0.05 after the univariate analysis were entered into the multivariate analysis. Statistical significance was defined as P-value < 0.05.

RESULTS

Patient characteristics

The median follow-up time after recurrence was 21.0 months (range 1.0–87.0 months). The characteristics of these 89 patients with resected p-stage I NSCLC are summarized in Table 1. The mean age of the 89 patients at recurrence was 74.4 ± 9.3 years (range 34–92 years). Sixty-nine patients (77.5%) were male; 20 (22.5%) were female. Seventy patients (78.7%) were former or current smokers. The mean size was 24.5 ± 10.3 mm (range 12–50 mm). Fifty-five patients (61.8%) underwent lobectomy and the remaining 34 patients (38.2%) underwent sublobar resection including segmentectomy (n = 7) and wedge resection (n = 27). The most common pathological type of the resected specimens was adenocarcinoma in 51 patients (57.3%) and squamous cell carcinoma in 32 patients (36.0%). The number of patients who were diagnosed with presence of vascular invasion was 58 (65.2%); lymphatic invasion was 76 (85.4%), and pleural invasion was 25 (28.1%).

Analysis of recurrence pattern and post recurrence therapy

The patterns of recurrence and the frequency of initial recurrent site are listed in Table 2. The median RFI was 16.8 months (range 1.0–116.0 months). Of 89 patients, 25 (28.1%) had symptoms at the time of the initial recurrence. The mean serum carcinoembryonic antigen (CEA) at recurrence was 7.1 ± 7.5 ng/mL (range 0.8–39.5 ng/mL) (normal range is 0–5.0 ng/mL).

The pattern of recurrence was locoregional in 22 (24.7%) and distant in the other 67 (75.3%). Forty-nine (55.0%) patients had a single organ metastasis; the other 40 (45.0%) had multiple organ metastases. The most common organs of recurrence were the contralateral lung in 42 (48.8%), followed by the ipsilateral thorax in 22 (24.7%), bone in 18 (20.2%), brain in 12 (13.5%), liver in nine (10.1%), pleural effusion/dissemination in five (5.6%), and adrenal gland in five (5.6%).

Twenty-three patients did not receive post recurrent therapy. They did not receive the treatment because 18 of 23 patients were over 80 years old, 3 were performance status (PS) > 2 and 2 were rejected treatment. Surgical therapy was performed in 7 patients for the recurrence. Of these seven patients, 2 underwent surgery alone, 4 underwent surgery with chemotherapy, and 1 underwent surgery with radiation therapy. Of 55 patients who received chemotherapy, 21 received EGFR-TKIs therapy. Among 21 patients treated with EGFR-TKIs, EGFR mutation was positive in 14 and not examined in 7. EGFR mutation was negative in 24 of 34 patients who received chemotherapy other than EGFR-TKIs and not tested in

Table 1. Characteristics of 89 patients with resected stage I NSCLC

Variable		Data
Age at recurrence, yrs (mean ± SD)		74.4 ± 9.3
Sex, *n* (%)	Male	69 (77.5)
	Female	20 (22.5)
Smoking history, *n* (%)	Absent	19 (21.3)
	Present	70 (78.7)
Tumor size, mm (mean ± SD)		24.5 ± 10.3
Resection type, *n* (%)	Wedge resection	27 (30.3)
	Segmentectomy	7 (7.9)
	Lobectomy	55 (61.8)
Adjuvant therapy, *n* (%)	Absent	49 (55.1)
	Present	40 (44.9)
p-Stage, *n* (%)	IA	43 (48.3)
	IB	46 (51.7)
Histological type, *n* (%)	Adenocarcinoma	51 (57.3)
	Squamous cell carcinoma	32 (36.0)
	Others:	6 (6.7)
	Adenosquamous	3
	LCNEC	3
Vascular invasion, *n* (%)	Absent	31 (34.8)
	Present	58 (65.2)
Lymphatic invasion, *n* (%)	Absent	13 (14.6)
	Present	76 (85.4)
Pleural invasion, *n* (%)	Absent	64 (71.9)
	Present	25 (28.1)
EGFR mutation, *n* (%)	Absent	36 (40.4)
	Present	15 (16.9)
	Not available	38 (42.7)

EGFR, epidermal growth factor receptor; LCNEC, large cell neuroendocrine carcinoma; NSCLC, non-small cell lung cancer; yrs, years.

the remaining 10.

Analysis of PRS and prognostic factors

The median PRS interval was 29.0 months, and the 1-year PRS and 3-year PRS rates were 65.6% and 44.7%, respectively. The cut-off values of age, tumor size, RFI and CEA was 75 years old (AUC 0.510, 48.5% sensitivity, 46.7% specificity), 25 mm (AUC 0.656, 51.5% sensitivity, 60.0% specificity), 17 months (AUC 0.318, 39.4% sensitivity, 30.0% specificity) and 5.0 ng/mL (AUC 0.494, 36.4% sensitivity, 73.3% specificity), respectively. The univariate analysis indicated that male sex (P = 0.035), smoking history (P = 0.034), larger tumor size (> 25 mm) (P = 0.008), stage IB (P = 0.044), RFI within 17 months (P = 0.011), presence of symptoms (P = 0.001), bone metastasis (P = 0.001), liver metastasis (P = 0.009) and not having received any treatment (P < 0.001) were significant poor prognosis factors of PRS (Table 3). Regarding histological types, squamous cell carcinoma had a significantly poor prognostic factor compared to adenocarcinoma [hazard ratio (HR): 2.347, 95% confidence interval (CI): 1.192–4.201, P = 0.003], and tended to have poor prognosis compared to other histological types (LCNEC and adenosquamous cell carcinoma) (HR: 6.998, 95% CI: 1.212–55.621, P = 0.071).

The multivariate analysis revealed that larger tumor size (> 25 mm) (HR: 2.271, 95% CI: 1.00–5.16, P = 0.048), RFI within 17 months (HR: 1.887, 95% CI: 0.99–3.60, P = 0.048) and no treatment for recurrence (HR: 4.955, 95% CI: 2.44–10.05, P < 0.001) were the independent poor-prognosis factors of PRS (Table 3).

Since post recurrence therapy had a strong impact on PRS (Fig. 1A), we further examined the PRS in the 66 patients who underwent any type of post recurrence therapy. Univariate analysis revealed that RFI within 17 months (P = 0.017), bone metastasis (P = 0.007), liver metastasis (P = 0.018) and treatment without EGFR-TKIs (P = 0.040) were significant poor-prognosis factors of PRS. Multivariate analysis demonstrated that bone metastasis (HR: 3.484, 95% CI: 1.173–10.350, P = 0.025) and no EGFR-TKIs therapy (HR: 2.100, 95% CI: 0.928–4.754, P = 0.049) were significantly associated with PRS (Table 4).

The PRS curves stratified according to bone metastasis and EGFR-TKIs are shown in Figs. 1B and C, respectively. The patients with bone metastasis showed significantly poor survival (P = 0.004), whereas the patients who underwent treatment with EGFR-TKIs showed significantly good survival (P = 0.039). The median PRS of the patients with and without bone metastasis were 15.0 months and 44.0 months, respectively. The median PRS values of the patients with EGFR-TKIs treatment and those without such treatment were 49.0 months and 29.0 months, respectively. Among 45 patients without EGFR-TKIs treatment, EGFR mutation was negative in 27 and not examined in 18.

DISCUSSION

We analyzed the predictive factors for PRS after complete resection in patients with p-stage I NSCLC. Tumor size, RFI and treatment for recurrence were significant prognostic factors of PRS in the multivariate analysis. For the patients who underwent treatment for recurrence, bone metastasis and treatment without EGFR-TKIs were significant poor-prognosis factors of PRS in the multivariate analysis. Although several studies have

demonstrated the PRS rate and predictive factors of PRS in resected p-stage I NSCLC patients,[2–5] the predictive prognostic factors of PRS remain controversial.

Although pathologic vascular invasion and pleural invasion are known to be prognostic factors for the patients with stage I NSCLC,[15–20] these pathological factors had no significant impact on PRS in the present study. PRS may be associated with characteristics of recurrent lesion, including the biology of the recurrent tumor, RFI, recurrent site, the treatment for recurrence, rather than with the biological characteristics of primary lung cancer.

RFI has been reported to be a predictive factor of PRS in resected NSCLC.[3, 5, 7, 8] In particular, Shimada et al. and Song et al. reported that a shorter RFI was a poor prognosis factor of PRS in p-Stage I NSCLC, and they noted that most of the recurrences occurred within 24 months of the operation.[3, 5] In the present study, the proportions of recurrences within 2 and 3 years after surgery were 65.2% and 74.2%, respectively, and the median RFI was 16.8 months. We observed that an RFI ≤ 17 months was a predictor for PRS in resected stage I NSCLC. Song et al. described that the RFI is a direct measure of a patient's tumor biology.[5] In cases of short RFIs, there might be systemic micrometastases that could not be detected before surgery.

Several studies have demonstrated that an initial recurrent site was a prognostic factor for PRS, which agrees with our present finding. Shimada et al. showed that bone metastasis was a poor prognostic factor for PRS in patients with stage I NSCLC,[3] and Yoshino et al. also demonstrated that bone metastasis was a marginal poor-prognostic factor for PRS in patients with stage I-III NSCLC.[21] In our present analysis, bone metastasis was a significant poor prognostic factor for patients who had undergone any post recurrence treatment. It is relatively easy to detect local recurrence and pulmonary metastasis by using CT at an early stage, but it is often difficult to find the bone and liver metastases. To find them, bone scintigraphy, PET and abdominal ultrasound are also necessary, but these imaging examinations are not routinely performed for surveillance. When bone or liver metastases are detected, either of these has already caused multiple organ metastases, which is considered to be the cause of poor PS. Of the 11 patients with bone metastasis, ten had multisite metastasis and six had a PS > 2. Failure to undergo systemic chemotherapy due to a poor PS is likely to be a factor in poor prognoses.

The survival benefit of systemic chemotherapy for postoperative recurrence remains controversial. Yano et al. showed that systemic chemotherapy had no significant effect on prognosis after local recurrence, whereas radiation therapy improved the survival after local recurrence.[22] On the other hand, several studies demonstrated that patients with stage I NSCLC who received post recurrence therapy had a significantly better PRS than those who didn't receive post recurrence therapy.[2, 3, 5] Our present findings also showed that post recurrence therapy was a significant prognostic factor after recurrence. In our study, post recurrence therapy with surgery did not contribute to the PRS. The reason may be that the number of patients who received post recurrence surgery therapy was too small to provide any supportive data in terms of PRS benefit. To examine the survival benefit of post recurrence therapy with chemotherapy and surgery, multicenter large-scale analyses are needed.

Several studies reported a relationship between the use of EGFR-TKIs therapy and PRS in patients with recurrent NSCLC.[3, 11, 13] Takanaka et al. and Kudo et al. noted that post recurrence therapy with EGFR-TKIs prolonged the PRS in resected stage I–IV NSCLC patients.[11, 13] Similarly, Shimada et al. reported that EGFR-TKIs therapy improved the PRS in resected stage I NSCLC patients.[3] In this study, there were 14 patients

Table 2. Initial site and pattern of recurrence in 89 patients

Variables	Data
Recurrence symptoms, *n* (%)	
Present	25 (28.1)
Absent	64 (71.9)
CEA at recurrence, ng/mL (mean ± SD)	7.1 ± 7.5
The median RFI, months (range)	16.8 (1–116)
Initial recurrence site	
Ipsilateral thorax	22
Lung	42
Bone	18
Brain	12
Liver	9
Adrenal gland	5
Pleural effusion/dissemination	5
Skin	2
Renal	2
Colon	2
Muscle	1
Post-recurrence therapy, *n* (%)	
None	23 (25.8)
Surgery alone	2 (2.2)
Surgery+chemotherapy	4 (4.4)
Surgery+radiation therapy	1 (1.1)
Chemotherapy alone	47 (52.8)
Chemo-radiation therapy	8 (9.0)
Radiation therapy alone	4 (4.5)

CEA, carcinoembryonic antigen; RFI, recurrence free interval.

Table 3. Univariate and multivariate analyses for post recurrence survival in 89 patients with resected p-stage I NSCLC

Variables	Univariate	Multivariate	
	P-value	HR (95% CI)	*P*-value
Sex (female vs. male)	0.035	0.983 (0.156–6.174)	0.983
Age at recurrence (≤ 75 vs. > 75 yrs)	0.160	–	–
Smoking history (yes vs. no)	0.034	2.314 (0.30–17.86)	0.421
Tumor size (> 25 mm vs. ≤ 25 mm)	0.008	2.271 (1.00–5.16)	0.048
Resection type (lobectomy vs. sublobar)	0.247	–	–
Adjuvant (present vs. absent)	0.911	–	–
p-Stage (IA vs. IB)	0.044	0.912 (0.38–2.17)	0.835
Histological type		–	–
Adenocarcinoma	0.001	0.647 (0.32–1.297)	0.220
Squamous cell carcinoma		–	–
Others	0.055	0.150 (0.02–1.16)	0.069
Vascular invasion (present vs. absent)	0.543	–	–
Lymphatic invasion (present vs. absent)	0.656	–	–
Pleural invasion (present vs. absent)	0.795	–	–
RFI (≤ 17 M vs. > 17 M)	0.011	1.887 (0.99–3.60)	0.048
Recurrence pattern (distant vs. locoregional)	0.212	–	–
CEA at recurrence (> 5 vs. ≤ 5)	0.564	–	–
Symptom at recurrence (present vs. absent)	0.001	1.026 (0.49–2.15)	0.945
Pulmonary metastasis (present vs. absent)	0.168	–	–
Brain metastasis (present vs. absent)	0.618	–	–
Bone metastasis (present vs. absent)	0.001	2.085 (0.86–5.04)	0.103
Liver metastasis (present vs. absent)	0.009	1.256 (0.49–3.24)	0.637
Post-recurrence therapy (absent vs. present)	< 0.001	4.955 (2.44–10.05)	< 0.001

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; M, months; NSCLC, non-small cell lung cancer; RFI, recurrence free interval; yrs, years.

Table 4. Univariate and multivariate analyses for post-recurrence survival in 66 patients who underwent post-recurrence therapy

Variables	Univariate	Multivariate	
	P-value	HR (95% CI)	*P*-value
Recurrence pattern (distant vs. locoregional)	0.206	–	–
CEA at recurrence (> 5 vs. ≤ 5)	0.534	–	–
RFI (≤ 17 M vs. > 17 M)	0.017	1.614 (0.745–3.496)	0.225
Pulmonary metastasis (present vs. absent)	0.860	–	–
Brain metastasis (present vs. absent)	0.870	–	–
Bone metastasis (present vs. absent)	0.007	3.484 (1.173–10.350)	0.025
Liver metastasis (present vs. absent)	0.018	1.271 (0.386–4.182)	0.693
Treatment after recurrence with chemotherapy (absent vs. present)	0.241	–	–
Treatment after recurrence with surgery (absent vs. present)	0.293	–	–
Treatment after recurrence with EGFR-TKIs (absent vs. present)	0.040	2.100 (0.928–4.754)	0.049

CEA, carcinoembryonic antigen; CI, confidence interval; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; HR, hazard ratio; M, months; RFI, recurrence free interval.

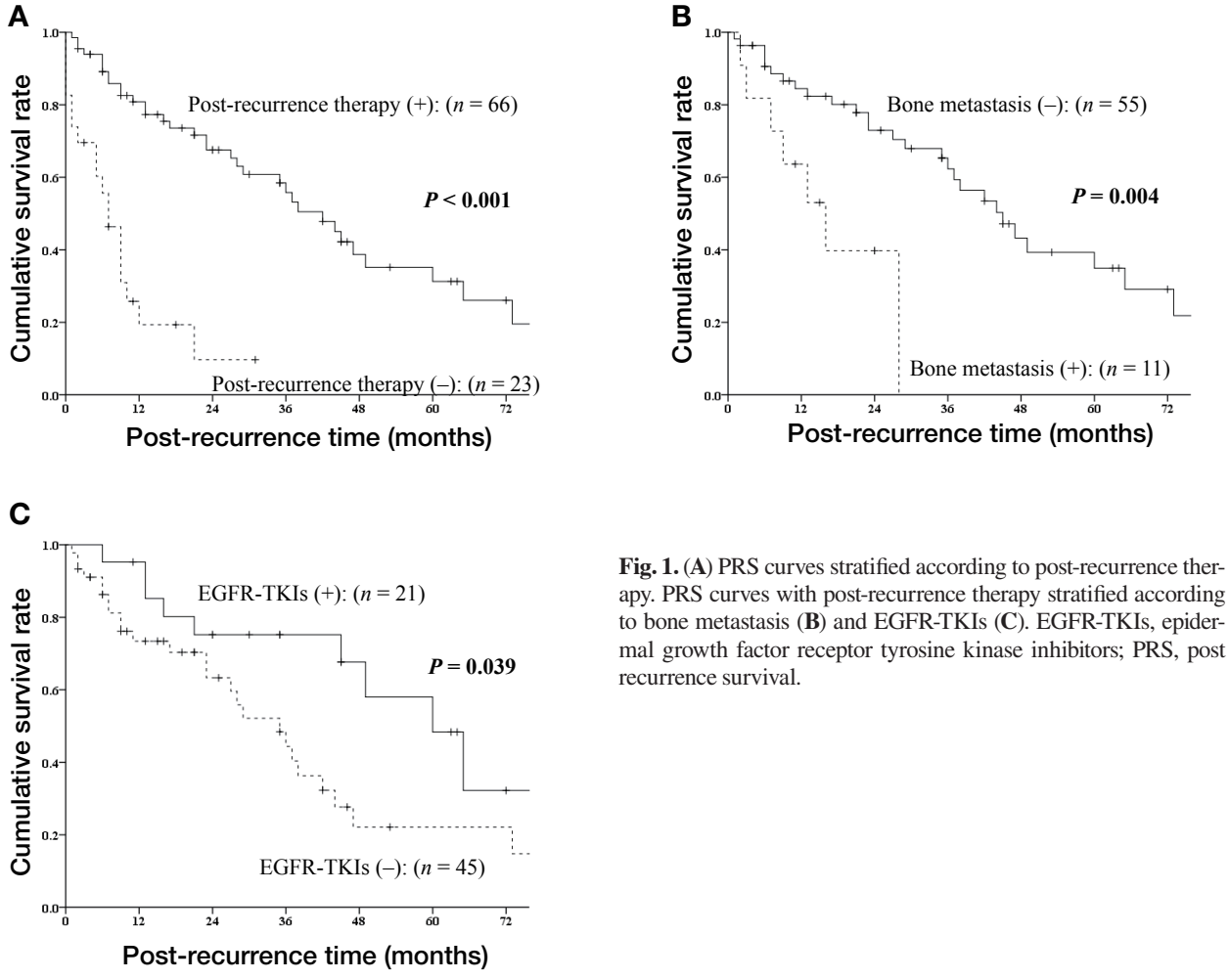

Fig. 1. (**A**) PRS curves stratified according to post-recurrence therapy. PRS curves with post-recurrence therapy stratified according to bone metastasis (**B**) and EGFR-TKIs (**C**). EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; PRS, post recurrence survival.

who were EGFR mutation positive in the treatment intervention group, and all patients received EGFR-TKIs therapy as first-line treatment. Seven patients received EGFR-TKIs therapy although their EGFR mutation status was unknown. Our study also showed that EGFR-TKIs therapy provided a better survival benefit than post recurrence therapy without EGFR-TKIs. The median PRS of our patients who received EGFR-TKIs therapy was 49.0 months, whereas that of the patients without EGFR-TKIs therapy was 29.0 months. Survival was considered to be prolonged by administering EGFR-TKIs to the patients with EGFR mutation. Therefore, especially in adenocarcinoma, it is important to confirm the EGFR mutation status after recurrence and not to miss the patients who can receive EGFR-TKIs treatment.

There are several limitations associated with our study. First, patient selection bias and lead-time bias might be obligatory due to the retrospective single-institute nature of the study. Second, distinguishing between second primary lung cancer and recurrent pulmonary metastasis was difficult. Only 43.0% of our patients underwent a pathological evaluation of pulmonary metastasis. Even though pathological specimens were obtained, a definitive diagnosis could be difficult under the current morphological and immunohistochemical analyses. Third, there was a selection bias for the treatment. Curative intent therapy is difficult to perform in patients with a poor PS and/or extensive disease. Fourth, we could not examine the EGFR mutation status in all recurrent cases. Lastly, a lack of uniformity in screening for cancer recurrence might have influenced the detection of recurrent disease and RFI.

In conclusion, our analyses showed that tumor size, RFI, and post recurrence therapy were prognostic factors for PRS. In the patients who underwent treatment after recurrence, bone metastasis and treatment with EGFR-TKIs were independent prognostic factors for PRS. Although further validation of our findings is necessary, this information is important for the design of future clinical trials for therapy after recurrence among NSCLC patients.

Acknowledgments: This article has been edited by native English-speaking experts of KN INTERNATIONAL INC.

Ethical Statement: A signed informed consent form was obtained from each participant. The study was approved by the ethics review committee of Tottori University Hospital (No.1608A084).

The authors declare no conflicts of interest.

REFERENCES

1 Scott WJ, Howington J, Feigenberg S, Movsas B, Pisters K. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132:234S-42S. PMID: 17873171.

2 Nakagawa T, Okumura N, Ohata K, Igai H, Matsuoka T, Kameyama K. Postrecurrence survival in patients with stage I non-small cell lung cancer. Eur J Cardiothorac Surg. 2008;34:499-504. PMID: 18579404.

3 Shimada Y, Saji H, Yoshida K, Kakihana M, Honda H, Nomura M, et al. Prognostic factors and the significance of treatment after recurrence in completely resected stage I non-small cell lung cancer. Chest. 2013;143:1626-34. PMID: 23348916.

4 Hung JJ, Jeng WJ, Chou TY, Hsu WH, Wu KJ, Huang BS, et al. Prognostic value of the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification on death and recurrence in completely resected stage I lung adenocarcinoma. Ann Surg. 2013;258:1079-86. PMID: 23532112.

5 Song IH, Yeom SW, Heo S, Choi WS, Yang HC, Jheon S, et al. Prognostic factors for post-recurrence survival in patients with completely resected stage I non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45:262-7. PMID: 23811122.

6 Sawabata N, Miyaoka E, Asamura H, Nakanishi Y, Eguchi K, Mori M, et al. Japanese Joint Committee for Lung Cancer Registration. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. J Thorac Oncol. 2011;6:1229-35. PMID: 21610521.

7 Sugimura H, Nichols FC, Yang P, Allen MS, Cassivi SD, Deschamps C, et al. Survival after recurrent nonsmall-cell lung cancer after complete pulmonary resection. Ann Thorac Surg. 2007;83:409-17. PMID: 17257962.

8 Williams BA, Sugimura H, Endo C, Nichols FC, Cassivi SD, Allen MS, et al. Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. Ann Thorac Surg. 2006;81:1021-7. PMID: 16488713.

9 Sonobe M, Yamada T, Sato M, Menju T, Aoyama A, Sato T, et al. Identification of subsets of patients with favorable prognosis after recurrence in completely resected non-small cell lung cancer. Ann Surg Oncol. 2014;21:2546-54. PMID: 24633668.

10 Takenaka T, Inamasu E, Yoshida T, Toyokawa G, Nosaki K, Hirai F, et al. Post-recurrence survival of elderly patients 75 years of age or older with surgically resected non-small cell lung cancer. Surg Today. 2016;46:430-46. PMID: 26070907.

11 Takenaka T, Takenoyama M, Yamaguchi M, Toyozawa R, Inamasu E, Kojo M, et al. Impact of the epidermal growth factor receptor mutation status on the post-recurrence survival of patients with surgically resected non-small-cell lung cancer. Eur J Cardiothorac Surg. 2015;47:550-5. PMID: 24894095.

12 Ujiie H, Kadota K, Chaft JE, Buitrago D, Sima CS, Lee MC, et al. Solid predominant histologic subtype in resected stage I lung adenocarcinoma Is an independent predictor of early, extrathoracic, multisite rrecurrence and of poor postrecurrence survival. J Clin Oncol. 2015;33:2877-84. PMID: 26261257.

13 Kudo Y, Shimada Y, Saji H, Kato Y, Yoshida K, Matsubayashi J, et al. Prognostic factors for survival after recurrence in patients with completely resected lung adenocarcinoma: important roles of epidermal growth factor receptor mutation status and the current staging system. Clin Lung Cancer. 2015;16:e213-21. PMID: 25986624.

14 Hung JJ, Yeh YC, Jeng WJ, Chien HC, Wu YC, Chou TY, et al. Prognostic factors of survival after recurrence in patients with resected lung adenocarcinoma. J Thorac Oncol. 2015;10:1328-36. PMID: 26291011.

15 Ichinose Y, Yano T, Asoh H, Yokoyama H, Yoshino I, Katsuda Y. Prognostic factors obtained by a pathologic examination in completely resected non-small-cell lung cancer. An analysis in each pathologic stage. J Thorac Cardiovasc Surg. 1995;110:601-5. PMID: 7564425.

16 Kobayashi N, Toyooka S, Soh J, Ichimura K, Yanai H, Suehisa H, et al. Risk factors for recurrence and unfavorable prognosis in patients with stage I non-small cell lung cancer and a tumor diameter of 20 mm or less. J Thorac Oncol. 2007;2:808-12. PMID: 17805057.

17 Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Poor prognostic factors in patients with stage IB non-small cell lung cancer according to the seventh edition TNM classification. Chest. 2011;139:855-61. PMID: 20724736.

18 Shimada Y, Ishii G, Hishida T, Yoshida J, Nishimura M, Nagai K. Extratumoral vascular invasion is a significant prognostic indicator and a predicting factor of distant metastasis in non-small cell lung cancer. J Thorac Oncol. 2010;5:970-5. PMID: 20512073.

19 Shimizu K, Yoshida J, Nagai K, Nishimura M, Ishii G, Morishita Y, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. J Thorac Cardiovasc Surg. 2005;130:160-5. PMID: 15999057.

20 Tsuchiya T, Akamine S, Muraoka M, Kamohara R, Tsuji K, Urabe S, et al. Stage IA non-small cell lung cancer: vessel invasion is a poor prognostic factor and a new target of adjuvant chemotherapy. Lung Cancer. 2007;56:341-8. PMID: 17350137.

21 Yoshino I, Yohena T, Kitajima M, Ushijima C, Nishioka K, Ichinose Y, et al. Survival of non-small cell lung cancer patients with postoperative recurrence at distant organs. Ann Thorac Cardiovasc Surg. 2001;7:204-9. PMID: 11578260.

22 Yano T, Hara N, Ichinose Y, Asoh H, Yokoyama H, Ohta M, et al. Local recurrence after complete resection for non-small-cell carcinoma of the lung. Significance of local control by radiation treatment. J Thorac Cardiovasc Surg. 1994;107:8-12. PMID: 8283923.