research article

Clinical impact of post-progression survival in patients with locally advanced non-small cell lung cancer after chemoradiotherapy

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Background. The efficacy of first-line chemoradiotherapy for overall survival (OS) might be confounded by the subsequent treatments in patients with locally advanced non-small cell lung cancer (NSCLC). In this study, we assessed the associations of progression-free survival (PFS) and post-progression survival (PPS) with OS after chemoradiotherapy for locally advanced NSCLC using patient-level data.

Patients and methods. Between January 2011 and December 2018, 45 patients with locally advanced NSCLC who had received first-line chemoradiotherapy and in whom recurrence occurred were analysed. The associations of PFS and PPS with OS were analysed at the individual level.

Results. Linear regression and Spearman rank correlation analyses revealed that PPS was strongly correlated with OS ($r = 0.72$, $p < 0.05$, $R^2 = 0.54$), whereas PFS was moderately correlated with OS ($r = 0.58$, $p < 0.05$, $R^2 = 0.34$). The Glasgow prognostic score and liver metastases at recurrence were significantly associated with PPS ($p < 0.001$).

Conclusions. The current analysis of individual-level data of patients treated with first-line chemoradiotherapy implied that PPS had a higher impact on OS than PFS in patients with locally advanced NSCLC. Additionally, current perceptions indicate that treatment beyond progression after first-line chemoradiotherapy might strongly affect OS.

Key words: chemoradiotherapy; Glasgow prognostic score; locally advanced non-small cell lung cancer; overall survival; post-progression survival; progression-free survival

Introduction

Lung cancer is the deadliest carcinoma globally, with non-small cell lung cancer (NSCLC) accounting for approximately 80–85% of all lung cancers.[1] Overall survival (OS) is considered the most reliable and appropriate endpoint in oncology clini-

cal trials, especially when it can be adequately assessed.[2] The OS is accurate and easy to measure due to the easiness of recording the date of death. Additionally, alternative measures, such as tumor shrinkage and progression-free survival (PFS), are considered helpful endpoints in cancer clinical trials because they can be measured earlier and seam-

lessly and occur more continually than the major endpoint of interest (the 'true endpoint').

With the pattern of anticancer therapy in NSCLC shifting to single agents and their combinations, the impact of first-line treatment on OS may be greatly influenced by subsequent therapies.[3] In fact, some clinical trial results for NSCLC have reported that prolongation of PFS by first-line chemotherapy does not necessarily affect the prolongation of OS.[4] Similar to breast, ovarian, and colorectal cancers [5-7], the number of drugs available for previously treated patients with advanced NSCLC after first-line chemotherapy is increasing. At the clinical trial level, post-progression survival (PPS) has shown a high correlation with OS following first-, second-, and third-line treatment for metastatic NSCLC.[8-10] In particular, from 2002 to 2012, PPS was reported to be highly correlated with OS, which coincided with the initiation of the use of molecular targeted drugs, such as gefitinib and erlotinib, for metastatic NSCLC.[8,9] A method of assessing PPS, calculating OS as PFS + PPS, was first reported in 2009 by Broglio et al.[2] Many different prognostic factors for PFS and OS have been reported. Among them, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) has been reported to be a powerful prognostic factor.[11,12] In addition, Glasgow prognostic score (GPS) is a systemic inflammatory response-based scoring method that comprises albumin concentrations and serum C-reactive protein (CRP)[13] and is an independent prognostic index for NSCLC.[14-20] However, the prognostic factors for PPS remain unclear.

The effects of treatments administered after disease progression on survival at the individual level are of great interest. We have previously demonstrated that PPS beyond first- and second-line therapy for NSCLC is strongly associated with OS at the individual level.[21] However, the associations of PFS and PPS at the individual level with OS after first-line chemoradiotherapy in patients with locally advanced NSCLC have not been reported to date. Our hypothesis is that the OS of patients with recurrence after chemoradiotherapy may also be strongly related to PPS. Thus, evaluating whether PFS or PPS could have a higher impact on OS beyond first-line chemoradiotherapy in patients with locally advanced NSCLC based on individual-level data may be of practical significance.

Approximately 30% of NSCLC patients have locally advanced lesions that cannot be resected at diagnosis[22], and a previous report demonstrated that adding chemotherapy to radiotherapy increased survival benefits.[23] A meta-analysis reported that concurrent chemoradiation is the most effective treatment for this patient population[24], and, accordingly, chemoradiotherapy is currently recommended as the standard first-line therapy for locally advanced NSCLC.

Stage III NSCLCs are heterogeneous tumours characterized by different levels of nodal involvement. In phase III trials, the median OS of stage III NSCLC patients improved from 12 to 23.3 months.[24,25] Recently, a global phase III trial of durvalumab versus placebo, which was conducted to evaluate the effect of maintenance therapy in patients with stage III NSCLC who had received concurrent platinum-based chemoradiotherapy[26,27], showed that PFS (16.8 months) in the durvalumab group was statistically significantly better than that in the placebo group (5.6 months). However, although some patients attain primary clinical response or stable disease with first-line treatment, most undergo disease progression and death. In this study, we evaluated concurrent chemoradiotherapy because it is the standard first-line treatment for locally advanced NSCLC. For patients with locally advanced NSCLC, longer OS implies that they can benefit from multiple therapeutic options after concurrent chemoradiotherapy relapse.

Although numerous studies have been conducted on pre-treated individuals with locally advanced NSCLC, none of the studies related to PPS at an individual level are currently available. Thus, we assessed the correlations of PFS and PPS with OS at the individual level in locally advanced NSCLC cases after first-line concurrent chemoradiotherapy. Moreover, we analysed the prognostic values of various patient characteristics for PPS.

Patients and methods

Patients

A total of 45 consecutive patients with locally advanced NSCLC who had been treated with first-line concurrent chemoradiotherapy at the Gunma Prefectural Cancer Center between January 2011 and December 2018, and in whom recurrence of the chemoradiotherapy had occurred, were enrolled and retrospectively analysed. Flow chart showing patient selection was shown in Figure 1. The inclusion criteria were as follows: (1) histopathologically or cytologically verified NSCLC; (2) first-line concurrent chemoradiotherapy; (3) treatment with curative intent thoracic radiation > 50 Gy concurrent with platinum-based chemotherapy; and (4) recurrent disease after chemoradiotherapy. The criteria
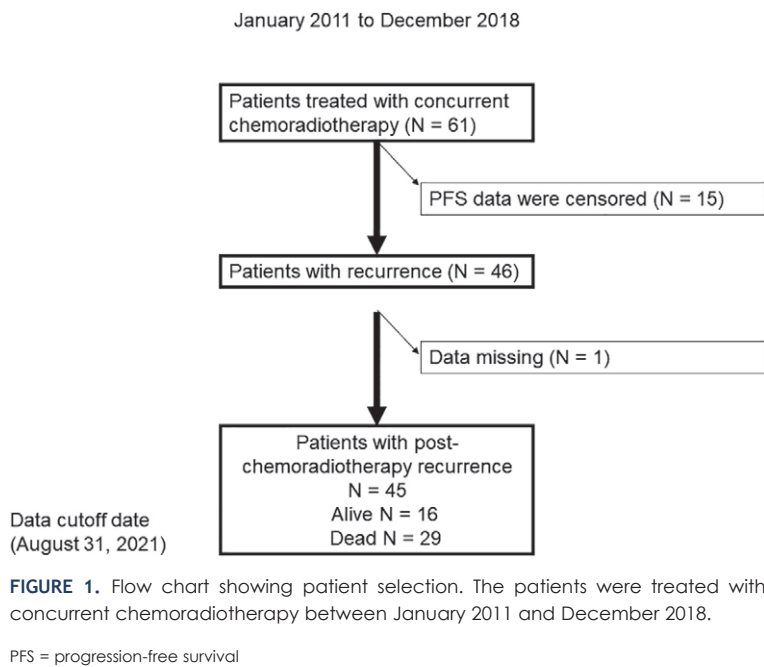
January 2011 to December 2018

FIGURE 1. Flow chart showing patient selection. The patients were treated with concurrent chemoradiotherapy between January 2011 and December 2018.

PFS = progression-free survival

for oligo-recurrence were defined as follows: (1) one or more local/distant recurrences, usually in one or more organs or lymph nodes; (2) disease control at the primary cancer site; (3) one or more distant and local recurrences that can be controlled by local treatment; and (4) no distant or local recurrences other than those controlled in (3).[28] The study protocol was approved by the Ethics Committee of the Gunma Prefectural Cancer Center. The protocol was performed in accordance with the 1964 Declaration of Helsinki (revised in 2008). Because of the retrospective nature of the study, the requirement for informed consent from patients was waived, but the opportunity to opt out was guaranteed.

Treatment methods

Radiotherapy comprised 6M or 10M X-rays at 2 Gy each, usually five times a week, Monday through Friday. The treatment plan for all patients was based on a three-dimensional treatment planning system; tumour size was determined according to the presence or absence of lymph node metastasis by computed tomography (CT). The clinical target volume was defined and outlined as the tumour volume and lymph node area, *i.e.*, 5–10 mm around the ipsilateral sternum and mediastinum. The planned target volume (PTV) 1 was the clinical target volume plus a 5–10 mm margin, and PTV 2 was the gross tumour volume plus a 5–10 mm margin. PTV 2 did not include the prophylactic

lymph node area. Additional margins were added as needed. Beam shaping was performed using a multileaf collimator. The prescribed standard treatment included 40 Gy for PTV 2 and 40 Gy for PTV 1, and other objectives included limiting the relative volume of the normal lung (V20) irradiated at doses greater than 20 Gy to no more than 35% and limiting the maximum spinal cord dose to no more than 44 Gy. At this point, the doses were prescribed to the isocenter. Patients treated with carboplatin plus paclitaxel were administered with paclitaxel and carboplatin weekly for 6 weeks. Carboplatin was administered at a fixed dose of the area under the plasma concentration time curve, 2 mg/ml/min on day 1, and paclitaxel was intravenously administered at a starting dose of 40 mg/m^2/day on day 1. Thoracic radiotherapy was started on day 1 at a dose of 2.0 Gy daily, five times per week. A total dose of 60 Gy was administered in 30 fractions over a 6-week period. Patients treated with cisplatin plus vinorelbine were administered with cisplatin and vinorelbine every four weeks for a maximum of four cycles. Vinorelbine (20 mg/m^2), on days 1 and 8 and cisplatin (80 mg/m^2) on day one was administered intravenously. Low-dose carboplatin (30 mg/m^2 in a 30-min infusion) was administered 1 h before radiotherapy daily for the first 20 fractions. Planned radiotherapy of 60 Gy was administered as 30 fractions from 6 to 9 weeks. The basic policy was that low-dose carboplatin should be applied to elderly patients. The platinum-based chemotherapeutic regimen was selected by the treating physician.

Evaluation of efficacy

Albumin and serum CRP levels were measured at recurrence after chemoradiotherapy. GPS values were defined as follows: a GPS of 0 (albumin ≥ 3.5 mg/dl and CRP < 1.0 mg/dl), a GPS of 1 (albumin < 3.5 mg/dl or CRP ≥ 1.0 mg/dl), or a GPS of 2 (albumin < 3.5 mg/dl and CRP ≥ 1.0 mg/dl). Tumor response was quantified as the best overall response and maximum tumor shrinkage. Radiographic tumour responses were evaluated using the RECIST version 1.1 as follows: complete response (CR), disappearance of all target lesions; partial response (PR), decrease in the sum of the target lesion diameters by at least 30% compared to baseline diameters; progressive disease (PD), increase of at least 20% in the sum of the target lesion diameters compared to the smallest sum during the study; and stable disease (SD), insufficient shrinkage or expansion to qualify as PR or PD.[29] PFS was calculated from the initiation of chemoradiotherapy until PD or death

from any cause, and OS was recorded from the first day of chemoradiotherapy until death or was censored on the date of the last follow-up. PPS was recorded as the time from disease progression following the first-line treatment to the date until death or was censored on the date of the last follow-up.

Statistical analyses

Spearman's rank correlation and linear regression analyses were performed to determine whether PFS or PPS were correlated with OS. The Kaplan-Meier method was applied to assess survival, and differences were analyzed using the log-rank test. Differences were considered statistically significant at a *p*-value < 0.05, and the two-tailed significance level was set at 0.05. A proportional hazards model with stepwise regression was used to examine prognostic factors for PPS, and hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed. All statistical analyses were performed using JMP version 11.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Patients' background, treatment response, and efficacy

The characteristics of the study participants are summarized in Table 1. Of the 45 patients (median age, 71 years; range, 42–82 years) enrolled in the current study, during a median follow-up of 31.5 months (range, 2.6–77.9 months), 29 patients died. CR, PR, SD, and PD were observed in 0, 26, 15, and 4 patients, respectively. The response rate was 57.8% (95% CI: 43.3–72.2), and the disease control rate was 91.1% (95% CI: 82.7–99.4). The median PFS and OS were 10.8 months and 31.6 months, respectively (Figure 2 and Figure 3A, B).

The treatments used after the progression following chemoradiotherapy are shown in Table 2. After chemoradiotherapy, 10 patients did not receive any further treatment, and the median number of subsequent treatments was one (range, 0–4 regimens).

Relevance of progression-free survival and post-progression survival to overall survival

The associations between PFS and OS and between PPS and OS are shown in Figure 4A, B. Spearman's rank correlation coefficient and linear regression analyses showed that PPS was highly correlated

TABLE 1. Baseline patient characteristics

Characteristic	N = 45
Gender	
Male/female	33/12
Median age at chemoradiotherapy (years)	71 (41–80)
Median age at progressive disease (years)	71 (42–82)
Performance Status at progressive disease	
0/1/2/3/4	15/22/4/4/0
Smoking history	
Yes/No	36/9
Histology	
Adenocarcinoma/squamous cell carcinoma/others	23/16/6
Clinical stage at diagnosis	
IIIA/IIIB/IIIC	28/14/3
Driver mutation/translocation	
EGFR/ALK/ROS-1/BRAF/others/negative or unknown	6/2/1/0/0/36
PD-L1 TPS	
< 1% / 1–49% / ≧ 50%/unknown	6/5/8/26
Progression-free survival (months)	.
< 6 / ≧ 6	13/32
Overall response to chemoradiotherapy	
CR/PR/SD/PD/NE	0/26/15/4/0
Glasgow prognostic score (GPS)	
0–1/2	32/13
Administration of tyrosine kinase inhibitors	
Yes/No	11/34
Administration of immune checkpoint inhibitors	
Yes/No	12/33
Administration of durvalmab	
Yes/No	2/43
Recurrent pattern	
Local recurrence/distant metastasis	17/28
Intracranial metastases at recurrence	
Yes/No	7/38
Liver metastases at recurrence	
Yes/No	3/42
Bone metastases at recurrence	
Yes/No	15/30
Oligorecurrrence	
Yes/No	11/34
Radiotherapy after recurrence (any site)	
Yes/No	19/26
Number of drug therapies after chemoradiotherapy	
0/1/2/3/4	14/18/9/2/2
Median (range)	1
Median (range) radiation dosage (Gy)	60 (58–70)
Chemotherapy regimen	
CDDP + VNR	1
CDDP + S-1	0
CBDCA + PTX	30
Low dose CBDCA	14

ALK = anaplastic lymphoma kinase; *BRAF* = v-raf murine sarcoma viral oncogene homolog B1; CBDCA = carboplatin; CDDP = cisplatin; CR = complete response; EGFR = epidermal growth factor receptor; NE = not evaluated; PD = progressive disease; PD-L1 = programmed cell death 1 ligand 1; PS = performance status; PR = partial response; PTX = paclitaxel; *ROS -1* = c-ros oncogene 1; S-1 = an oral fluoropyrimidine derivative; SD = stable disease; TPS = tumor proportion score; VNR = vinorelbine

TABLE 2. The treatments after post-chemoradiotherapy recurrence

	first-line	second-line	third-line	≧ fourth-line	Total
Platinum combination	11	3	2	0	16
Platinum combination + ICIs	0	0	0	0	0
Docetaxel	0	4	2	0	6
Docetaxel+ ramcirumab	0	0	0	0	0
Pemetrexed	0	0	2	0	2
S1	1	0	0	3	4
Others (single agents)	0	1	0	0	1
EGFR-TKIs	6	1	0	0	7
ALK-TKIs	3	1	0	0	4
ICI monotherapy	1	5	2	1	9
Ipilimumab+nivolumab	1	0	0	0	1
Investigational agents	0	0	0	0	0
Radiotherapy alone	12	1	0	0	13
Best supportive care	10	-	-	-	10

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; ICI = immune checkpoint inhibitor; S-1 = an oral fluoropyrimidine derivative; TKI = tyrosine kinase inhibitor
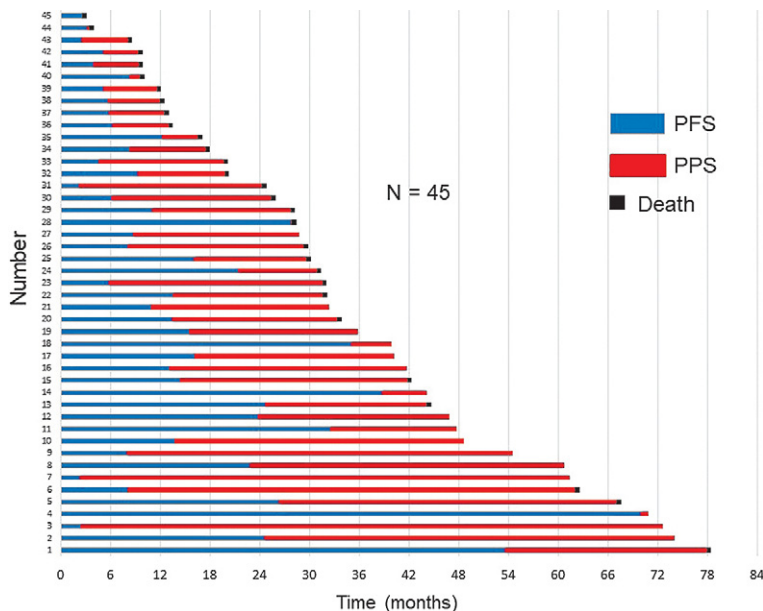

FIGURE 2. PROGRESSION-FREE survival (PFS) and post-progression survival (PPS) in the overall population.

factors influencing PPS. In the univariate analysis (Table 3), histology, driver mutation/translocation, GPS at recurrence (0–1 vs. 2), and liver metastases at recurrence were significantly correlated with PPS ($p < 0.05$). On multivariate analysis, only GPS (0–1 vs. 2) and liver metastases at recurrence were significantly correlated with PPS ($p < 0.05$) (Table 3).

Next, log-rank tests demonstrated that PPS has a different prognosis for patients according to GPS at relapse (0–1 vs. 2) ($p < 0.0001$) and liver metastases at recurrence (log-rank test, $p = 0.0009$). Patients with GPS 0–1 had a median PPS of 25.7 months compared to 6.7 months for patients with GPS 2 (log-rank tests, $p < 0.0001$). Moreover, the PPS for patients with liver metastases and without liver metastases were 4.2 and 21.3 months, respectively (log-rank test, $p = 0.0009$) (Figure 5). These results were consistent when adjusted for multivariate Cox proportional hazards analysis (Table 3).

Discussion

Here, we assessed the association between OS and PFS and between OS and PPS after first-line chemoradiotherapy at the individual level and elucidated that PPS was highly correlated with OS, whereas PFS was weakly correlated with OS. Furthermore, GPS and liver metastases at recurrence were found to be independent prognostic clinical factors for PPS.

with OS ($r = 0.72$, $p < 0.05$, $R^2 = 0.54$), whereas PFS was weakly associated with OS ($r = 0.58$, $p < 0.05$, $R^2 = 0.34$).

Evaluation of factors influencing post-progression survival

Since PPS was more strongly associated with OS than did PPS, the next step was to examine the

TABLE 3. Univariate Cox regression analysis of patient characteristics for post-progression survival

| | Median PPS | Post-progression survival | | | | | |
| | | Univariate analysis | | | Multivariate analysis | | |
Factors	(months)	HR	95% CI	*p* value	HR	95% CI	*p* value
Gender							
Male/female	18.1/25.7	1.49	0.63–4.07	0.37			
Age at recurrence (years)							
< 75 / ≧ 75	20.0/19.5	0.78	0.36–1.77	0.54			
PS at recurrence							
0–1 / ≧ 2	21.3/2.8	0.42	0.18–1.09	0.07			
Smoking history							
Yes/No	16.7/25.7	1.87	0.71–6.39	0.21			
Histology							
Adenocarcinoma/non-adenocarcinoma	25.7/10.5	0.37	0.17–0.79	**0.0099**	1.06	0.36–3.04	0.90
Driver mutation/translocation							
Yes/No	27.3/15.1	0.32	0.07–0.95	**0.038**	0.61	0.13–2.23	0.47
Best overall response of chemoradiotherapy							
PR/non-PR	15.1/22.1	1.82	0.86–4.11	0.11			
Progression-free survival							
< 6 months / ≧ 6 months	6.4 / 24.4	1.97	0.89–4.19	0.09			
Glasgow prognostic score (GPS) at recurrence							
0–1/2	25.7/6.7	0.23	0.11–0.52	**0.0006**	0.2	0.06–0.55	**0.0019**
Recurrence pattern							
Local recurrence/distant metastasis	40.7/16.7	0.45	0.18–1.03	0.05			
Intracranial metastases at recurrence							
Yes/No	6.7/21.3	1.75	0.64–4.09	0.25			
Liver metastases at recurrence							
Yes/No	4.2/21.3	6.82	1.50–22.8	**0.016**	12.7	2.40–56.8	**0.0048**
Bone metastases at recurrence							
Yes/No	18.1/20.0	1.40	0.60–3.06	0.41			
Oligorecurrence at recurrence							
Yes/No	22.1/19.2	0.77	0.30–1.75	0.55			

Values in bold are statistically significant (*p* < 0.05). CI = confidence interval; HR = hazard ratio; PS = performance status; PR = partial response

The usefulness of alternative endpoints has been demonstrated by several meta-analyses[30,31], and biostatisticians have previously reported a variety of alternative endpoints.[32,33] In extensive-disease small cell lung cancer, response to treatment and PFS have been proposed as valid alternative endpoints to OS[34], but their potency is disputable in advanced NSCLC.[35] Broglio *et al.* reported on the concept of PPS (defined as PPS = OS - PFS), which they examined in a presumptive clinical study based on the hypothesis that therapy affects PFS but not PPS.[2] Furthermore, PPS has been demonstrated to be highly correlated with OS after first-line treatment for metastatic NSCLC at the clinical trial level.[8,9] These results correspond to those reported here, but unlike our present report, other prior analyses have reported the opposite, that PFS is a valid surrogate for OS in metastatic NSCLC.[36,37]

In this population of patients treated with chemoradiotherapy, PPS had a strong effect on OS, but PFS did not have a sufficient effect on OS. Moreover, we demonstrated that PFS was shorter than PPS; thus, PPS was more strongly correlated
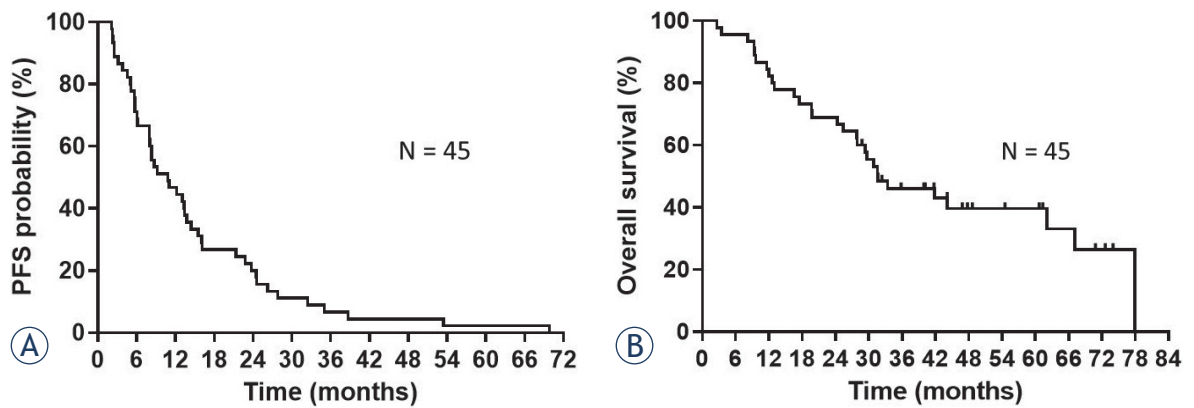
FIGURE 3. Kaplan-Meier survival plots showing the **(A)** progression-free survival (PFS) and **(B)** overall survival (OS) of all patients. Median progression-free survival: 10.8 months; median overall survival: 31.6 months; median follow-up: 31.5 months.

with OS than PFS, with a linear PPS-OS correlation (Figure 4A, B), which is evidenced by the large R^2 value. This finding suggests that the treatment used was too weak for PFS to affect OS positively. Hence, in clinical trial settings in which patients are predicted to have a brief PFS after first-line chemoradiotherapy, it is important to control the factors that reflect the PPS.

Based on trial-level data for the first-line treatment of advanced NSCLC, a favourable PS and administration of first-line monotherapy and molecular targeted therapy are associated with a longer PPS.[8] In addition, individual-level data of patients with postoperative recurrence of NSCLC show that PPS is influenced by PS at recurrence and the use of tyrosine kinase inhibitors (TKIs).[38] Several reports have also demonstrated that PPS is highly associ-

ated with OS after first-line chemotherapy and that factors affecting PPS include PS and response to chemotherapy.[39-41] However, the factors influencing PPS based on individual-level data after first-line chemoradiotherapy for patients with locally advanced NSCLC are not well understood; thus, we have further attempted to explore the clinical factors influencing PPS.

We found that the GPS (0–1/2) and liver metastases at recurrence (presence/absence) were highly associated with PPS, and we confirmed these associations using log-rank tests. The patient cohort with a GPS of 0–1 had a significantly longer PPS than that with a GPS of 2. In addition to disease stage and conventional prognostic factors, GPS has been demonstrated to be useful in determining the prognosis of lung cancer.[14-19] The GPS is composed
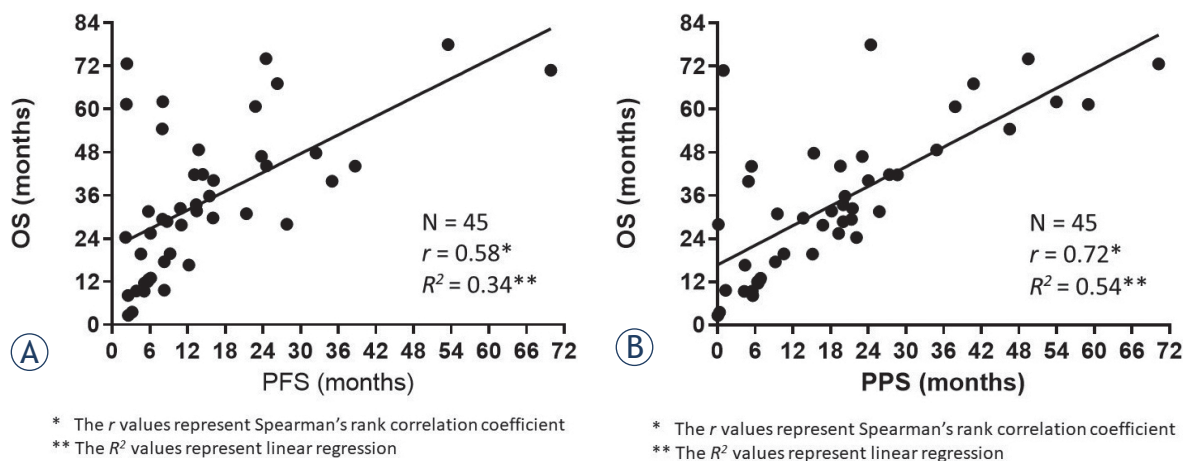
* The *r* values represent Spearman's rank correlation coefficient
** The R^2 values represent linear regression

FIGURE 4. Correlations between **(A)** overall survival (OS) and progression-free survival (PFS) and **(B)** between overall survival and post-progression survival (PPS).

*The *r* values represent Spearman's rank correlation coefficient. **The R^2 values represent the linear regression.
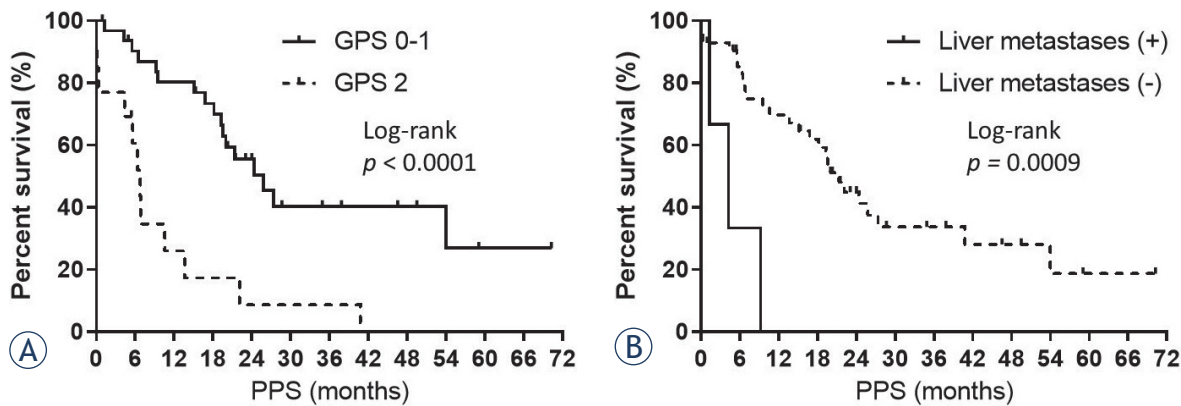
FIGURE 5. **(A)** Kaplan-Meier plots showing post-progression survival (PPS) according to Glasgow prognostic score (GPS) at relapse, GPS 0–1, median = 25.7 months; GPS 2, median = 6.7 months. **(B)** Kaplan-Meier plots showing PPS according to liver metastases at recurrence, Without liver metastases, median = 21.3 months; With liver metastases, median = 4.2 months

of albumin and serum CRP levels, and these clinical parameters are monitored in clinical practice. In the present study, multivariate analysis demonstrated that GPS, but not PS, correlated independently with PPS. PS is a subjective scoring system that evaluates the overall general condition of cancer patients. In the present study, univariate analysis showed a trend towards better PPS for progressive disease in patients with PS 0–1 than in those with PS 2 or higher, but there was no significant difference. PS has been demonstrated to be a potent prognostic factor[11,12], but even for patients treated with chemoradiotherapy in the present cohort, PS at recurrence did not have a significant impact on the disease course. In contrast, GPS is an objective and reproducible parameter, which is useful for a more accurate classification of patients by the three-index rating system. Consequently, GPS may be suitable for clinical pre-treatment evaluations. Furthermore, in the current study, the presence of liver metastasis at the time of recurrence was an independent prognostic factor for PPS. Previous studies reported that NSCLC patients with liver metastases have a poor prognosis.[42-44] However, the number of cases with liver metastasis in the present study was small, and our findings need to be confirmed using a larger sample. Moreover, the presence of driver gene mutation/translocation was statistically significant for PPS in the univariate analysis but not in the multivariate analysis. The reason for this outcome is unclear but may be due to the small size of the patient population. In order to resolve the reason for this, we believe that it is necessary to conduct a study with a larger sample size.

Notably, the number of chemotherapeutic regimens for disease progression after first-line chemoradiotherapy is increasing primarily due to the development of more anticancer agents, such as docetaxel, pemetrexed, oral fluoropyrimidine derivative S-1, TKIs, and immune checkpoint inhibitors (ICIs), available for further-line treatment of metastatic NSCLC. As shown in Table 2, various anticancer agents were administered to the patient population in the current analysis. Durvalumab was used in two patients as maintenance therapy after chemoradiotherapy. Maintenance therapy with durvalumab has been reported to improve the prognosis after concurrent chemoradiotherapy[26,27] and is currently the standard of care; it has been used in clinical practice in Japan since 2018. The patients included in the current study were from an earlier era when durvalumab was not the standard care. Our findings may lead to high expectations for PPS after durvalumab use in clinical practice, and it was meaningful to include many cases before the use of durvalumab in the present study. Cytotoxic anticancer drugs have been reported to be highly effective after ICI use. For example, docetaxel plus ramucirumab demonstrated a higher response rate when administered after ICI failure compared to treatment regimens without prior ICI use.[27] The aforementioned treatment sequence may vary according to the clinical practice guidelines for durvalumab. In the future, it will be important to conduct a similar study on patients who have received durvalumab to determine if our findings will be replicated.

This study has several limitations. The number of patients included in the analysis was relatively small. However, since the number of patients with locally advanced NSCLC treated with first-line concurrent chemoradiotherapy is limited at any

facility, the problem of this limitation is difficult to resolve as the aim of this analysis was to evaluate cases with a similar treatment background. Notwithstanding, our facility treats a relatively large number of patients with locally advanced NSCLC, and we have a fairly consistent treatment strategy and follow the standard care guidelines. Despite the possibility of bias due to the single-center nature of the study, understanding the nature of this bias can allow us to make a clinical sense of the results. Second, the point of disease progression might have varied because each physician decided when to record the response and disease progression. However, this variability is considered a limitation of all retrospective studies and is difficult to resolve and should be taken into account when interpreting the results.

Conclusions

In conclusion, our analysis of individual-level data for first-line chemoradiotherapy demonstrated that PPS was highly correlated with OS in patients with locally advanced NSCLC. Furthermore, GPS and liver metastases at recurrence were found to be independent prognostic factors for PPS. Thus, we conclude that the treatment course for disease progression after first-line chemoradiotherapy has a significant impact on OS, and the clinical significance of these findings should be verified in a larger patient cohort for generalizability to other patient populations.

Acknowledgments

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