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

Hisao Imai1,2, Daijiro Kobayashi3, Kyoichi Kaira2, Sayaka Kawashima4, Ken Masubuchi1, Masumi Murata3, Takeshi Ebara3,5, Yoshizumi Kitamoto3, Koichi Minato1

1 Division of Respiratory Medicine, Gunma Prefectural Cancer Center, Ota, Gunma, Japan
2 Department of Respiratory Medicine, Comprehensive Cancer Center, International Medical Center, Saitama Medical University, Hidaka, Saitama, Japan
3 Division of Radiation Oncology, Gunma Prefectural Cancer Center, Ota, Gunma, Japan
4 Division of Pharmacy, Gunma Prefectural Cancer Center, Ota, Gunma, Japan
5 Department of Radiation Oncology, Kyorin University, School of Medicine, Mitaka, Tokyo, Japan

Received 2 November 2021
Accepted 13 January 2022
Correspondence to: Hisao Imai, M.D., Ph.D., Division of Respiratory Medicine, Gunma Prefectural Cancer Center 617-1, Takahayashinishi, Ota, Gunma 373-8550, Japan. E-mail: m06701014@gunma-u.ac.jp

Hisao Imao and Daijiro Kobayashi contributed equally and share the first authorship.
Disclosure: No potential conflicts of interest were disclosed.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 clinical 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. 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. Similar to breast, ovarian, and colorectal cancers, 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. 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. A method of assessing PPS, calculating OS as PFS + PPS, was first reported in 2009 by Broglio et al. 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. In addition, Glasgow prognostic score (GPS) is a systemic inflammatory response-based scoring method that comprises albumin concentrations and serum C-reactive protein (CRP) and is an independent prognostic index for NSCLC. 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. 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, and a previous report demonstrated that adding chemotherapy to radiotherapy increased survival benefits. A meta-analysis reported that concurrent chemoradiation is the most effective treatment for this patient population, 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. 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, 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...
Radiation Oncol 2022; 56(2): 228-237.

Imai H et al. / Survival in NSCLC patients after chemoradiotherapy

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). 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/m²/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/m²), on days 1 and 8 and cisplatin (80 mg/m²) on day one was administered intravenously. Low-dose carboplatin (30 mg/m² 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 chemotherapy 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. 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 follow-up after 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 |
| 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 | 0/2/6/15/4/0 |
| 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 durvalumab Yes/No | 2/43 |
| Recurrent pattern | Local recurrence/distant metastasis | 17/28 |
| Intraocular metastases at recurrence Yes/No | 7/38 |
| Liver metastases at recurrence Yes/No | 3/42 |
| Bone metastases at recurrence Yes/No | 15/30 |
| Oligorecurrence 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**
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 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.
The usefulness of alternative endpoints has been demonstrated by several meta-analyses and biostatisticians have previously reported a variety of alternative endpoints. In extensive-disease small cell lung cancer, response to treatment and PFS have been proposed as valid alternative endpoints to OS, but their potency is disputable in advanced NSCLC. 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. Furthermore, PPS has been demonstrated to be highly correlated with OS after first-line treatment for metastatic NSCLC at the clinical trial level. 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.

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

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

| Factors                                    | Median PPS (months) | Post-progression survival | Univariate analysis | Multivariate analysis |
|--------------------------------------------|---------------------|---------------------------|---------------------|----------------------|
| 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**           |
| Driver mutation/translocation               |                     |                           |                     |                      |
| Yes/No                                     | 27.3/15.1           | 0.32                      | 0.07–0.95           | **0.038**            |
| Best overall response of chemoradiotherapy |                     |                           |                     |                      |
| PR/non-PR                                  | 15.1/22.1           | 1.82                      | 0.86–4.11           | 0.11                 |
| Progress-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**           |
| 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**            |
| 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.
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. 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). Several reports have also demonstrated that PPS is highly associated with OS after first-line chemotherapy and that factors affecting PPS include PS and response to chemotherapy. 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. The GPS is composed

*The $r$ values represent Spearman’s rank correlation coefficient. **The $R^2$ values represent linear regression.
Imai H et al. / Survival in NSCLC patients after chemoradiotherapy

Survival in NSCLC patients after 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 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. 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

The authors appreciate Ms. Hiromi Sakamoto, Ms. Tomoko Nakajima, and Ms. Eri Kogure for their assistance in preparing this research. We appreciate Editage (www.editage.jp) for English language editing.

References

1. Siegel RL, Miller KD, Fuchs HE. Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021; 71: 7-33. doi: 10.3322/caac.21654
2. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 2009; 101: 1642-9. doi: 10.1093/jnci/djp369
3. Soria JC, Massard C, Le Chevalier T. Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy? Ann Oncol 2010; 21: 2324-32. doi: 10.1093/annonc/mdq204
4. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbonouva V, Hirsh V, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. J Clin Oncol 2009; 27: 1227-34. doi: 10.1002/10.1020/ICO.2007.14.5466
5. Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. J Clin Oncol 2010; 28: 1958-62. doi: 10.1002/10.1020/ICO.2009.25.5414
6. Sundar S, Wu J, Hillaby K, Yap J, Lilford R. A systematic review evaluating the relationship between progression free survival and post progression survival in advanced ovarian cancer. Gynecol Oncol 2012; 125: 493-9. doi: 10.1016/j. ygyno.2011.12.420
7. Petrelli F, Barni S. Correlation of progression-free and post-progression survival with overall survival in advanced colorectal cancer. Ann Oncol 2013; 24: 186-92. doi: 10.1093/annonc/mds289
8. Hotta K, Kiura K, Fujitaya V, Takigawa N, Hisamato A, Ichihara E, et al. Role of survival post-progression in phase III trials of systemic chemotherapy in advanced non-small-cell lung cancer: a systematic review. PLoS One 2011; 6; e26646. doi: 10.1371/journal.pone.0026646
9. Hayashi H, Okamoto I, Morita S, Taguri M, Nakagawa K. Postprogression survival for first-line chemoradiotherapy of patients with advanced non-small-cell lung cancer. Ann Oncol 2013; 23: 1537-41. doi: 10.1093/annonc/mds487
10. Hayashi H, Okamoto I, Taguri M, Morita S, Nakagawa K. Postprogression survival in patients with advanced non-small-cell lung cancer who receive second-line or third-line chemotherapy. Clin Lung Cancer 2013; 14: 261-6. doi: 10.1016/j.cllc.2012.09.006
11. Capewell S, Sudlow MF. Performance and prognosis in patients with lung cancer. The Edinburgh Lung Cancer Group. Thorax 1990; 45: 951-6. doi: 10.1136/thx.45.12.951
12. Kawaguchi T, Takada M, Kubo A, Matsumura A, Fuji S, Tamura A, et al. Performance status and smoking status are independent favorable prognostic factors for survival in non-small cell lung cancer: a comprehensive analysis of 26,957 patients with NSCLC. J Thorac Oncol 2010; 5: 620-30. doi: 10.1097/JTO.0b013e3181d2dcd9
13. McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc 2008; 67: 257-62. doi: 10.1017/S0029665108007131
14. Forrest LM, McMillan DC, Mcardle CS, Angerson WI, Dunlop DJ. Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer. Br J Cancer 2004; 90: 1704-6. doi: 10.1038/sj.bjc.6601789
15. Gioulbasanis I, Pallis A, Vlahostergios PJ, Xyrafas A, Giannousi Z, Perdikouri IE, et al. The Glasgow Prognostic Score (GPS) predicts toxicity and efficacy in platinum-based treated patients with metastatic lung cancer. Lung Cancer 2012; 77: 383-8. doi: 10.1016/j.lungcan.2012.05.008
16. Leung EY, Scott HR, Mcmillan DC. Clinical utility of the pretreatment Glasgow prognostic score in patients with advanced inoperable non-small cell lung cancer. J Thorac Oncol 2012; 7: 655-62. doi: 10.1097/JTO.0b013e318244f1e1
17. Umihanic S, Umihanic S, Jamakosmanovic S, Brisk S, Osmic M, Dedic S, et al. Glasgow prognostic score in patients receiving chemotherapy for non-small-cell lung cancer in stages IIIb and IV. Med Arch 2014; 68: 83-5. doi: 10.5455/medarh.2014.68.83-5
18. Jiang AG, Chen H, Lu HY. Comparison of Glasgow prognostic score and prognostic index in patients with advanced non-small cell lung cancer. J Cancer Res Clin Oncol 2015; 141: 563-8. doi: 10.1007/s00432-014-1339-4
19. Simmons CP, Koiris F, Fallon MT, Fearon KC, Bowden J, Solheim TS, et al. Prognosis in advanced lung cancer—a prospective study examining key clinicopathological factors. Lung Cancer 2015; 88: 304-9. doi: 10.1016/j.lungcan.2015.03.020
20. Imai H, Kaira K, Minato K. Clinical significance of post-progression survival in lung cancer. Thorac Cancer 2017; 8:379-86. doi: 10.1111/1759-7714.12463
22. Govindan R, Bogart J, Vokes EE. Locally advanced non-small cell lung cancer: the past, present, and future. J Thorac Oncol 2008; 3: 917-28. doi: 10.1097/JTO.0b013e31810270b

23. Sause W, Kolesar P, Taylor SJ, Johnson D, Livingston R, Komaki R, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 2000; 117: 358-64. doi: 10.1378/chest.117.2.358

24. Auperin A, Le Peuchou C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010; 28: 2181-90. doi: 10.1200/JCO.2009.26.2543

25. Vokes EE, Herrndon JE, 2nd, Kelley MJ, Cicchetti MG, Ramnath N, Neill H, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007; 25: 1698-704. doi: 10.1200/JCO.2006.07.3569

26. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017; 377: 1919-29. doi: 10.1056/NEJMoa1709937

27. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018; 379: 2342-50. doi: 10.1056/NEJMoa1809697

28. Nishi Y, Hayakawa K. Oligometastases and oligo-recurrence: the new era of cancer therapy. Jpn J Clin Oncol 2010; 40: 107-11. doi: 10.1093/jjco/hyp167

29. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47. doi: 10.1016/j.ejca.2008.10.026

30. Johnson KR, Ringland C, Stokes BJ, Anthony DM, Freemantle N, IRS A, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 2006; 7: 741-6. doi: 10.1016/S1470-2045(06)70800-2

31. Hotta K, Fujiwara Y, Matsuo K, Kiura K, Takigawa N, Tabata M, et al. Time to progression as a surrogate marker for overall survival in patients with advanced non-small cell lung cancer. J Thorac Oncol 2009; 4: 311-7. doi: 10.1097/JTO.0b013e31819f9bd2

32. Weir CJ, Walley RJ. Statistical evaluation of biomarkers as surrogate endpoints a literature review. Stat Med 2006; 25: 183-203. doi: 10.1002/sim.2319

33. Fleischer F, Gaschler-Markefski B, Bluhmki E. A statistical model for the dependence between progression-free survival and overall survival. Stat Med 2009; 28: 2669-86. doi: 10.1002/sim.3637

34. Foster NR, Qii Y, Shi Q, Krook JE, Kugler JW, Jett JR, et al. Tumor response and progression-free survival as potential surrogate endpoints for overall survival in extensive stage small-cell lung cancer: findings on the basis of North Central Cancer Treatment Group trials. Cancer 2011; 117: 1262-71. doi: 10.1002/cncr.25526

35. Berghmans T, Pasieau F, Paesmans M, Bondueille V, Cadranel J, Co Toth I, et al. Surrogate markers predicting overall survival for lung cancer: ELCWP recommendations. Eur Respir J 2012; 39: 9-28. doi: 10.1183/09031936.00193110

36. Tsujino K, Kawaguchi T, Kubo A, Aono N, Nakao K, Koh Y, et al. Response rate is associated with prolonged survival in patients with advanced non-small cell lung cancer treated with gefitinib or erlotinib. J Thorac Oncol 2009; 4: 994-1001. doi: 10.1097/JTO.0b013e3181a94a21

37. Li X, Liu S, Gu H, Wang D. Surrogate end points for survival in the target treatment of advanced non-small cell lung cancer with gefitinib or erlotinib. J Cancer Res Clin Oncol 2012; 138: 1963-9. doi: 10.1007/s00432-012-1278-z

38. Imai H, Onozato R, Kaira K, Kawashima S, Masubuchi K, Nagashima T, et al. Course of postoperative relapse in non-small cell lung cancer is strongly associated with post-progression survival. Thorac Cancer 2021; 12: 2740-8. doi: 10.1111/1759-7714.14119

39. Imai H, Takahashi T, Mori K, Ono A, Akamatsu H, Shukuya T, et al. Individual-level data on the relationships of progression-free survival, post-progression survival, and tumor response with overall survival in patients with advanced non-squamous non-small cell lung cancer. Neoplasmo 2014; 61: 233-40. doi: 10.4149/neop_2014_030