


Early recurrence factors in patients with stage III non-small cell lung cancer treated with concurrent chemoradiotherapy

Yutaka Takahara  | Takuya Tanaka | Yoko Ishige | Ikuyo Shionoya |
Kouichi Yamamura | Takashi Sakuma | Kazuaki Nishiki | Keisuke Nakase |
Masafumi Nojiri | Ryo Kato | Shohei Shinomiya | Taku Oikawa | Shiro Mizuno

Department of Respiratory Medicine, Kanazawa Medical University, Kahoku-gun, Japan

Correspondence

Yutaka Takahara, Department of Respiratory Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920-0293, Japan.
Email: takahara@kanazawa-med.ac.jp

Abstract

Background: The clinical characteristics and risk factors for cancer recurrence have not been well evaluated regarding early recurrence in patients with unresectable locally advanced non-small cell lung cancer (LA-NSCLC) who receive concurrent chemoradiotherapy (CRT).

The aim of this study was to determine the clinical characteristics and risk factors of patients with stage III unresectable LA-NSCLC treated with CRT who developed early recurrence.

Methods: We retrospectively reviewed the clinical records of 46 patients diagnosed with stage III unresectable LA-NSCLC treated with CRT at our center between July 2012 and July 2021. A tumor proportion score (TPS) < 50% was defined as “low expression” and a TPS > 50% was defined as “high expression.”

Results: A total of 17 (37.0%) patients had a confirmed recurrence within 1 year of treatment. More patients had a lower body mass index in the early recurrence group than in the later recurrence group ($p = 0.038$). A higher number of patients in the late recurrence group underwent surgery after CRT ($p = 0.036$). Patients with a higher TPS were more likely to experience late recurrence than early recurrence ($p = 0.001$), whereas more patients with stage N3 disease were in the early recurrence group ($p = 0.011$). Multivariate analysis identified lower TPS expression as an independent risk factor for early recurrence after CRT. Overall survival was prolonged in the late recurrence group ($p < 0.001$).

Conclusions: A lower TPS may be a predictor of early recurrence after CRT in patients with LA-NSCLC. These patients should be closely monitored for post-treatment recurrence.

KEYWORDS

body mass index, chemoradiotherapy, neoplasm recurrence, non-small cell lung carcinoma, tumor proportion score

INTRODUCTION

The five-year survival rate for stage III non-small cell lung cancer (NSCLC) patients treated with concurrent chemoradiotherapy (CRT) is approximately 20%. A certain percentage of this patient group can be cured, although recurrence commonly occurs.^{1,2} Maintenance therapy with durvalumab, an antiprogrammed death-ligand 1 (anti-PDL1)

antibody, produced long-term responses in some patients with stage III NSCLC that did not progress after CRT in recent reports.^{3,4} However, approximately 40% of patients taking durvalumab experienced disease progression within 1 year in one study.⁵

Various risk factors for early recurrence in patients with NSCLC after surgical treatment have been reported such as nonsquamous carcinoma,⁶ pathological N2 lung cancer,⁶

tumor size,⁷ preoperative nutritional status,⁸ and serum carcinoembryonic antigen (CEA) level.⁹ However, to our knowledge, no study has focused on unresectable LA-NSCLC treated with CRT, or examined the clinical characteristics of patients who developed early recurrence, or examined the factors contributing to early recurrence. In this study, we aimed to identify the clinical characteristics and risk factors for early recurrence in patients with unresectable LA-NSCLC who experienced disease progression within 1 year after CRT.

METHODS

We retrospectively reviewed patients diagnosed with unresectable LA-NSCLC who underwent chemoradiotherapy. Patients were enrolled at least 1 year after treatment. Data were collected on age, sex, smoking history, performance status (PS), body mass index (BMI), histological lung cancer type, tumor stage, tumor proportion score (TPS), the neutrophil-to-lymphocyte ratio (NLR), and treatment details. Responses were evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Patients were excluded from the study if they had a history of tumors in other organs, or if they could not be followed up within 1 year after treatment or if CRT was interrupted (e.g., because of the development of pneumonia). This study was approved by the Review Committee of Kanazawa Medical University Hospital (Kahoku, Japan; approval number: I757) and was conducted in accordance with the principles of the Declaration of Helsinki. The need for patient consent was waived owing to the retrospective nature of the study.

CRT

All patients had a histopathological diagnosis of NSCLC and were determined to have inoperable and locally advanced disease after a joint conference with a respiratory surgeon. The indications for CRT were carefully evaluated at a joint conference, which included radiologists employed at our institution. All patients received at least one cycle of platinum-based chemotherapy and concurrent chest radiotherapy.

Treatment after CRT

After confirming treatment response, using post-CRT computed tomography, surgery was performed if medically appropriate and if tumor resection was feasible. For patients with tumors that were not surgically resectable, maintenance therapy with durvalumab (10 mg/kg) was administered.

Immunohistochemical staining

Immunohistochemistry (IHC) was conducted using a PDL1 kit (PDL1 IHC 22C3 pharmDX; Dako), based on the

manufacturer's instructions.¹⁰ The TPS was used to classify the expression status as "low" (i.e., <50%) or "high" (i.e., >50%).

Group classification

Early recurrence was defined as confirmed disease progression within 1 year after the initiation of cancer treatment. Patients who showed disease progression within the first year of treatment were classified into the early recurrence group, and patients who did not relapse during the observation period or who relapsed after the first year of treatment were classified into the late recurrence group. Clinical information in the two groups was compared, using standard statistical tests, as described later.

Statistical analysis

All analyses were performed using SPSS statistical software (version 26.0; SPSS Inc.). Statistical significance was set at a two-sided p -value of <0.05. All categorical variables were analyzed using chi-square tests, except for variables with predictive frequencies of <5. Variables with predictive frequencies of <5 were analyzed using Fisher's exact test. Unpaired t -tests were used to compare the means of the continuous variables between the two groups.

Univariate and multivariate analyses were performed using logistic regression. Survival curves were generated using the Kaplan–Meier method. The analysis covered the period from the start of lung cancer treatment until death or until discontinuation from follow-up. Survival analysis was conducted in early August 2022. Log-rank tests were used to evaluate differences in survival, based on early or late recurrence. A risk rate of <5% was statistically significant.

RESULTS

Patient background

We retrospectively reviewed patients with unresectable LA-NSCLC who were diagnosed between July 2012 and July 2022 and underwent chemoradiotherapy. Among the 57 patients initially considered for enrollment, 46 patients were included in the final analysis, after applying the aforementioned exclusion criteria (Figure 1). A total of 17 (37.0%) patients were categorized into the early recurrence group and 29 (63.0%) patients were categorized into the late recurrence group. Patient characteristics are shown in Table 1.

Patients with a higher TPS expression were statistically significantly more likely to experience late recurrence ($p = 0.001$). Patients in the early recurrence group had a statistically significantly greater occurrence of distant metastasis at the time of recurrence ($p = 0.001$). More patients in the early recurrence group than in the late recurrence group had stage N3 disease ($p = 0.011$).

FIGURE 1 Study flowchart. Fifty-seven patients with locally advanced non-small cell lung carcinoma (LA-NSCLC) were initially included in this study. Among them, seven patients with a history of cancer in other organs and one patient who was transferred to another hospital within 1 year after concurrent chemoradiotherapy (CRT), which made follow-up impossible, were excluded. In addition, three patients whose CRT was interrupted by the onset of pneumonia or other problems were excluded. 46 patients were ultimately included in this study. COPD, chronic obstructive pulmonary disease

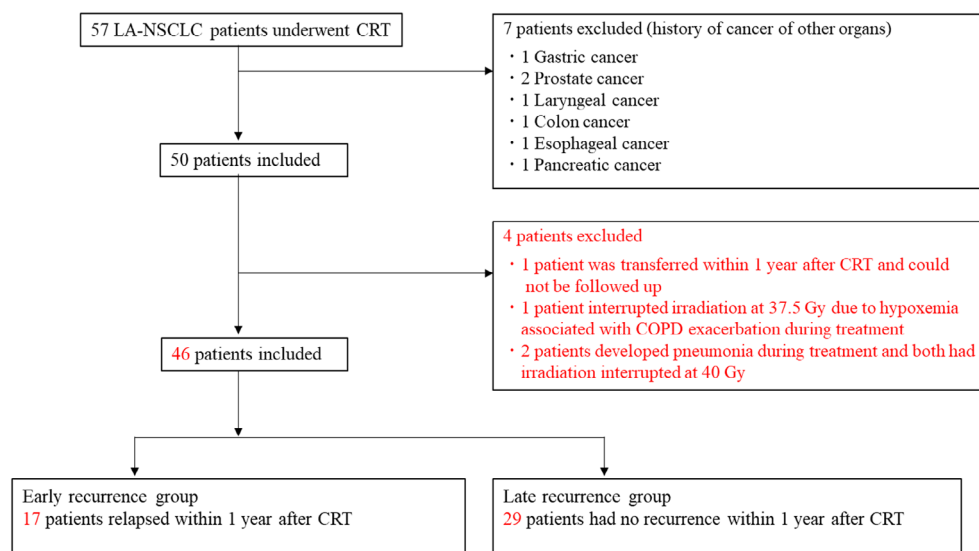


TABLE 1 Patient characteristics

Variables	Early recurrence	Late recurrence	p-value
Total no.	17 (37.0%)	29 (63.0%)	
Age, y, mean (range)	70.0 (57–83)	66.4 (44–83)	0.132
Sex (male/female)	16/1	25/4	0.637
Smoking history (never/prior • current)	0/17	4/25	0.281
ECOG PS (0–1/2–4)	16/1	29/0	0.370
Duration to recurrence (month)	6.2 (2.1–12.0)	28.48 (12.7–64.3)	
BMI, no. (range)	21.4 (16.9–26.9)	23.4 (18.3–30.2)	0.038 ^b
CRT chemotherapy regimen (platinum-doublet/low-dose CBDCA)	16/1	28/1	1.000
Radiation dose (Gy)	60.6 (56–64)	56.8 (30–64)	0.038 ^b
Response to chemoradiotherapy (PR/SD)	14/3	25/4	1.000
Durvalumab maintenance therapy (yes/no)	5/12	12/17	0.417
Surgical resection (yes/no)	0/17	7/22	0.036 ^a
Tumor type (adenocarcinoma/nonadenocarcinoma)	9/8	15/14	0.936
Tumor size (mm)	45.1 (19.0–82.0)	46.2 (12.0–75.0)	0.402
Direct invasion (yes/no)	10/7	12/17	0.253
N stage (N3/N0–N2)	9/8	5/24	0.011 [*]
Driver mutation (wild-type/positive/unknown)	9/2/6	13/4/12	0.747
PDL1 expression (22C3) (low/high/unttested)	2/1/14	7/14/8	0.001 ^a
Recurrence status (local recurrence/distant metastasis)	6/11	21/8	0.001 [*]
Albumin	3.5 (2.7–4.5)	3.6 (2.9–4.3)	0.389
NLR	3.93 (1.21–15.98)	3.38 (1.20–9.50)	0.561
CEA (ng/ml)	9.5 (1.9–32.2)	37.3 (1.1–874.4)	0.362
CYFRA 21–1 (ng/ml)	6.9 (1.9–23.5)	5.3 (1.0–26.1)	0.416
SCC-Ag (ng/ml)	2.4 (0.5–17.5)	1.5 (0.5–3.8)	0.352

Abbreviations: Adeno, adenocarcinoma; BMI, body mass index; CBDCA, carboplatin; CEA, carcinoembryonic antigen; CYFRA 21–1, cytokeratin subunit 19; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; PD, progressive disease; PDL1, programmed death ligand 1; PR, partial response; PS, performance status; SCC-Ag, serum squamous cell carcinoma antigen; withdrawal period, time from discontinuation of initial ICI therapy to a rechallenge with ICIs.

^{*} $p < 0.05$.

^aBased on Fisher's exact test.

^bBased on the unpaired *t*-test.

TABLE 2 Univariable and multivariable analysis of risk factors for early recurrence in LA-NSCLC after CRT

Characteristics	Univariable analysis		Multivariable analysis	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Age (≥ 75 vs. < 75 years)	1.080 (0.292–3.989)	0.908		
Sex (female vs. male)	2.560 (0.262–25.013)	0.419		
Tumor type (adenocarcinoma vs. nonadenocarcinoma)	0.952 (0.287–3.159)	0.936		
BMI (< 20 vs. ≥ 20 kg/m ²)	0.293 (0.069–1.251)	0.097	0.296 (0.032–2.702)	0.280
CRT chemotherapy regimen (platinum-doublet vs. low-dose CBDCA)	1.750 (0.102–29.924)	0.699		
Response to chemoradiotherapy (PR vs. SD)	1.339 (0.261–6.861)	0.726		
Driver mutations (wild-type vs. positive)	1.625 (0.444–5.946)	0.463		
TPS ($< 50\%$ vs. $\geq 50\%$)	0.163 (0.027–0.983)	0.048	0.059 (0.005–0.699)	0.025
Albumin (< 4 vs. ≥ 4)	1.485 (0.328–6.717)	0.608		
NLR (< 5 vs. ≥ 5)	0.375 (0.073–1.930)	0.241		
CEA (≥ 5 vs. < 5)	4.000 (1.049–15.253)	0.042	4.775 (0.779–29.286)	0.058
CYFRA 21–1 (≥ 3.5 vs. < 3.5)	1.231 (0.095–15.872)	0.874		
SCC-Ag (≥ 0.5 vs. < 0.5)	0.9727 (0.201–4.700)	0.972		
N stage (N3 or N0–N2)	5.400 (1.393–20.929)	0.015	6.837 (0.936–49.913)	0.091
Direct invasion (yes or no)	0.494 (0.472–6.084)	0.419		
Durvalumab therapy (yes or no)	1.867 (0.532–6.551)	0.256		

Abbreviations: BMI, body mass index; CBDCA, carboplatin; CEA, carcinoembryonic antigen; CI, confidence interval; CRT, concurrent chemotherapy; CYFRA 21–1, cytokeratin subunit 19; NLR, neutrophil-to-lymphocyte ratio NSCLC, non-small cell lung cancer; OR, odds ratio; SCC-Ag, serum squamous cell carcinoma antigen; SD, standard deviation; TPS, tumor proportion score.

No statistically significant differences existed in age, sex, smoking history, PS, primary tumor size, direct tumor invasion of major organs, durvalumab maintenance treatment, albumin levels, the NLR, CEA levels, serum squamous cell carcinoma antigen level, and fragments of cytokeratin subunit 19 between the two groups.

Histological type

Among the early recurrence group, the histological types of cancer were adenocarcinoma ($n = 9$), squamous cell carcinoma ($n = 7$), and large cell neuroendocrine carcinoma ($n = 1$). However, in the late recurrence group, the histological types of cancer were adenocarcinoma ($n = 15$), squamous cell carcinoma ($n = 12$), large cell neuroendocrine carcinoma ($n = 1$), and not otherwise specified (NOS; $n = 1$). No statistically significant difference in lung cancer histology existed between the two groups.

Genetic abnormalities

Genetic abnormalities in the early recurrence group included one case of epidermal growth factor receptor (*EGFR*) mutation (exon 18, G719X) and one case of anaplastic lymphoma kinase (*ALK*) rearrangement. In the late recurrence group, three cases of *EGFR* mutation (a compound mutation of exon 18 G719X and exon 20 S768I; exon 21, L858R; and a compound mutation of

EGFR exon 20 T790M and exon 21 L858R) and one case of *ALK* rearrangement were detected. No statistically significant differences existed in genetic abnormalities between the two groups.

Systemic chemotherapy

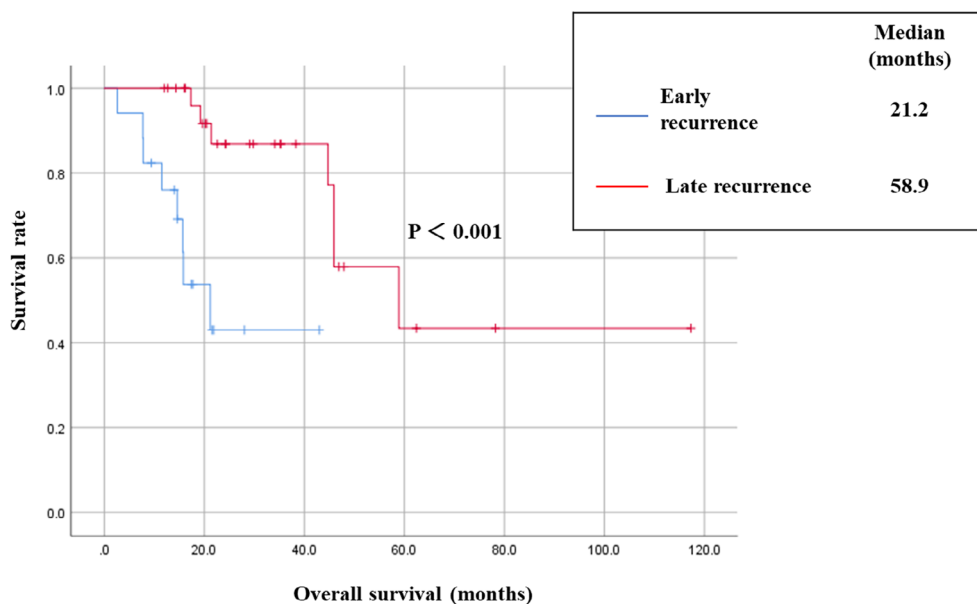
In the early recurrence group, 16 patients were treated with carboplatin (CBDCA) + paclitaxel (PTX; nab-PTX) and one patient was treated with low-dose CBDCA for systemic chemotherapy. In the late recurrence group, 27 patients were treated with CBDCA + PTX (i.e., nab-PTX), one patient was treated with cisplatin + tegafur/gimeracil/oteracil (TS-1), and one patient was treated with low-dose CBDCA. No statistically significant differences existed in systemic chemotherapy between the two groups.

Radiotherapy

Most patients received 60 Gy of radiation therapy. We noted that patients who underwent surgery after CRT had undergone surgery after 50 Gy of irradiation. In the late recurrence group, one patient underwent tumor resection after 30 Gy of irradiation. The radiation dose was higher in the early recurrence group than in the late recurrence group ($p = 0.038$).

No patient experienced disease progression after CRT. No statistically difference existed in treatment response

FIGURE 2 Overall survival for patients in the early recurrence and late recurrence groups. The median survival for patients in the late recurrence group was 58.9 months, as compared to 21.2 months for patients in the early recurrence group. There was a statistically significant difference between the two groups ($p < 0.001$, log-rank test)



between the two groups. We note that no patient in the early recurrence group underwent surgery after CRT, which represented a statistically significant difference between the two groups ($p = 0.036$).

Univariate and multivariate analysis

The dependent variable on regression analysis was the presence (vs. absence) of early recurrence. The independent variables were BMI levels, TPS expression, CEA levels, and N3 stage. Binomial logistic regression analysis was conducted.

In the univariate model, N3 stage cancer ($p = 0.015$; odds ratio [OR], 5.400; 95% confidence interval [CI]: 1.393–20.929), lower TPS ($p = 0.048$; OR, 0.163; 95% CI: 0.027–0.983), and high CEA level ($p = 0.042$, OR, 4.000; 95% CI: 1.049–15.253) were statistically significant risk factors for early recurrence. However, multivariate analysis showed a high incidence of only lower TPS expression ($p = 0.025$; OR, 0.059; 95% CI: 0.005–0.699). Lower TPS expression was identified as an independent risk factor for early recurrence in LA-NSCLC after CRT (Table 2).

The survival curves for the early and late recurrence groups are shown in Figure 2. Statistically significantly prolonged survival occurred in the late recurrence group ($p < 0.001$).

DISCUSSION

To our knowledge, no previous report has evaluated patients with unresectable LA-NSCLC treated with CRT who developed early recurrence within 1 year to examine their clinical characteristics as well as factors predicting early recurrence. Identification of risk factors for early recurrence will lead to appropriate plans for follow-up examinations after CRT,

and prompt retreatment of patients with lung cancer through the early detection of recurrence, thereby improving prognoses in these patients.

In this study, lower TPS expression was an independent risk factor for early recurrence after CRT in patients with LA-NSCLC. In addition, patients with higher TPS expression were statistically significantly more likely to experience a late recurrence.

The relationship between PDL1 expression and prognosis in patients with NSCLC has been studied and reviewed in many previous reports.¹¹ Most reports suggest that PDL1 expression is associated with a poor prognosis, although other reports have suggested that PDL1 expression is associated with a good prognosis. No clear answers have been obtained to date. In addition, in five studies^{12–15} that evaluated the association between TPS expression and prognosis in a group of LA-NSCLC patients who did not receive durvalumab after CRT, noted that a higher TPS expression was associated with poor prognosis.

Contrary to the results of these studies, the results of the present study suggested that high TPS expression is a favorable prognostic factor in patients with LA-NSCLC who are treated with CRT. However, recent reports have shown that high TPS expression was associated with a favorable prognosis in patients with LA-NSCLC who were treated with durvalumab after CRT.^{16–18} The present study also included patients who received durvalumab as maintenance therapy, which suggested that durvalumab maintenance therapy after CRT may have had a favorable prognostic impact in patients with high TPS expression.^{19,20}

The results of this study suggested that high TPS expression may be associated with a lower risk of early recurrence and therefore suggests a better prognosis for patients with LA-NSCLC who are treated with durvalumab after CRT. However, in this study, PDL1 was not measured in a large proportion of patients in the early recurrence group (14/17,

82.4%). The role of PDL1 as a predictive biomarker before undergoing CRT remains unclear. Further analyses based on case studies are therefore necessary.

In this study, a statistically significantly higher number of patients had a high BMI in the late recurrence group. In previous studies, high BMI has been reported as a factor influencing a favorable prognosis in patients with NSCLC who have undergone surgical resection.²¹⁻²⁴ The reason for the better prognosis evidenced in the late recurrence group may be related to the fact that more patients in the late recurrence group than in the early recurrence group had a higher BMI and had undergone surgery.

In addition, a strong association between a low BMI at the time of lung cancer diagnosis and death has been reported in previous work.²⁵ No previous studies have examined the association between early recurrence after CRT and BMI in patients with LA-NSCLC. However, a possibility is that low BMI may have exerted a negative effect on cancer control.^{21,26-28}

Cancer patients with a high BMI who receive immune checkpoint inhibitors have improved overall survival outcomes, compared to patients with a normal BMI.²⁸ Therefore, durvalumab may have had a reduced effect in the early recurrence group because of low BMIs. However, BMI was not identified as a significant risk factor, based on multivariate analysis in this study. Further study of most patients is needed to determine the impact of BMI among patients with CRT-treated LA-NSCLC.

In this study, the number of patients who underwent surgery after CRT was statistically significantly greater in the late recurrence group than in the early recurrence group. This factor may have resulted in a significantly higher radiation dose in the early recurrence group. Patients with stage IIIA NSCLC can be divided into various populations with regard to prognosis, and a multidisciplinary treatment team, which includes respiratory surgeons, is recommended to determine a treatment strategy.²⁹ Whether surgery after CRT improves prognoses in patients with LA-NSCLC remains unclear. However, the benefit of preoperative chemoradiotherapy has been demonstrated in patients with stage IIIA NSCLC with ipsilateral mediastinal lymph node metastases (N2) who are eligible for lobectomy.³⁰

The results of this study also suggest that radical resection should be considered in patients with LA-NSCLC (N2) after undergoing CRT, with the aim of improving long-term prognosis. In addition, examining the association between early recurrence and surgery after CRT was considered necessary in the current study. However, surgery could not be included as a covariate in the multivariate analyses because patients who underwent surgery after CRT were not included in the early recurrence group. Therefore, whether surgery after CRT may have reduced the risk of early recurrence in the present study is unclear. This question should be examined in future research.

In the univariate model of this study, a high CEA level was a statistically significant risk factor for early recurrence. However, no significant results were found in the

multivariate analysis. High CEA levels have been associated with poor prognosis in patients with NSCLC.^{31,32} Elevated CEA levels may be associated with early recurrence, and poor prognosis may be associated with early recurrence in LA-NSCLC patients undergoing CRT. However, the patients with NSCLC included in this study were a heterogeneous group of patients with different histologic types such as adenocarcinoma and squamous cell carcinoma. The association between CEA values and early recurrence should ideally be evaluated in a larger group of patients with subgroup analysis based on histological type.

This study had some limitations. First, it was a retrospective study conducted at a single institution. The potential for bias with regard to patient selection and information collection is therefore significant. Furthermore, more patients with distant metastatic recurrence were in the early recurrence group, which suggested that the presence of subclinical distant metastasis before treatment may be a factor in early recurrence.

Second, the study included four patients who completed treatment in 2021. These patients were observed for more than 1 year; however, this period may be insufficient to assess survival. Studies with a longer term are needed to further evaluate the association between early recurrence after CRT and survival.

Third, a very small sample size of 46 patients was reviewed in our study. Patients with unresectable stage III NSCLC constitute a heterogeneous group of patients with varying disease status and prognosis.³³⁻³⁵ Additional studies involving a larger number of cases are needed to determine whether the results of this study can be generalized.

In this study, bias was detected between the two groups. All patients who underwent surgery after CRT were included in the late recurrence group, and the number of patients presenting with stage N3 disease was statistically significantly higher in the early recurrence group.

However, the late recurrence group also included five patients with stage N3 disease. Survival was statistically significantly prolonged in the late recurrence group than in the early recurrence group. Therefore, although our results are preliminary and require additional studies, the findings of this study are critically important to report because the findings suggest that CRT should be considered, even for patients with N3 stage LA-NSCLC, because of the potential of this treatment for long-term disease control.

In conclusion, based on the results of our study, lower TPS expression may be a predictor of early relapse after CRT in patients with LA-NSCLC. These patients should be carefully monitored for relapse after treatment. In addition, even patients with LA-NSCLC who are expected to progress such as patients with N3 stage disease should be considered for CRT because of the potential efficacy of this treatment in regard to long-term disease control.

ACKNOWLEDGMENTS

This research received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors have no actual or potential conflicts of interest to declare.

ORCID

Yutaka Takahara  <https://orcid.org/0000-0001-6863-0074>

REFERENCES

- Bradley JD, Hu C, Komaki RU, et al. Long-term results of RTOG 0617: a randomized phase 3 comparison of standard dose versus high dose conformal chemoradiation therapy +/- cetuximab for stage III NSCLC. *J Clin Oncol*. 2020;38:706–14.
- Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. *World J Clin Oncol*. 2017;8:1–20.
- 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.
- 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.
- Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC—an update from the PACIFIC trial. *J Thorac Oncol*. 2021;16:860–7.
- Tsukioka T, Izumi N, Komatsu H, et al. Tumor size and N2 lymph node metastasis are significant risk factors for early recurrence in completely resected centrally located primary lung cancer patients. *Anticancer Res*. 2021;41:2165–9.
- Zhang Y, Sun Y, Xiang J, Zhang Y, Hu H, Chen H. A clinicopathologic prediction model for postoperative recurrence in stage Ia non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2014;148:1193–9.
- Kawai H, Ota H. Low perioperative serum prealbumin predicts early recurrence after curative pulmonary resection for non-small-cell lung cancer. *World J Surg*. 2012;36:2853–7.
- Kuo SW, Chen JS, Huang PM, Hsu HH, Lai HS, Lee JM. Prognostic significance of histologic differentiation, carcinoembryonic antigen value, and lymphovascular invasion in stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2014;148:1200.e3–7.e3.
- Roach C, Zhang N, Corigliano E, Jansson M, Toland G, Ponto G, et al. Development of a companion diagnostic PD-L1 immunohistochemistry assay for pembrolizumab therapy in non-small-cell lung cancer. *Appl Immunohistochem Mol Morphol*. 2016;24:392–7.
- Takada K, Toyokawa G, Shoji F, Okamoto T, Maehara Y. The significance of the PD-L1 expression in non-small-cell lung cancer: trenchant double swords as predictive and prognostic markers. *Clin Lung Cancer*. 2018;19:120–9.
- Tokito T, Azuma K, Kawahara A, Ishii H, Yamada K, Matsuo N, et al. Predictive relevance of PD-L1 expression combined with CD8+ TIL density in stage III non-small cell lung cancer patients receiving concurrent chemoradiotherapy. *Eur J Cancer*. 2016;55:7–14.
- Gennen K, Käsmann L, Taugner J, Eze C, Karin M, Roengvoraphoj O, et al. Prognostic value of PD-L1 expression on tumor cells combined with CD8+ TIL density in patients with locally advanced non-small cell lung cancer treated with concurrent chemoradiotherapy. *Radiat Oncol*. 2020;15:5.
- Sui X, Jiang L, Teng H, Mi L, Li B, Shi A, et al. Prediction of clinical outcome in locally advanced non-small cell lung cancer patients treated with chemoradiotherapy by plasma markers. *Front Oncol*. 2021;17:625911.
- Wang Y, Kim TH, Fouladdel S, Zhang Z, Soni P, Qin A, et al. PD-L1 expression in circulating tumor cells increases during radio(chemo) therapy and indicates poor prognosis in non-small cell lung cancer. *Sci Rep*. 2019;9:566.
- Shirasawa M, Yoshida T, Imabayashi T, Okuma K, Matsumoto Y, Masuda K, et al. Baseline PD-L1 expression and tumour-infiltrated lymphocyte status predict the efficacy of durvalumab consolidation therapy after chemoradiotherapy in unresectable locally advanced patients with non-small-cell lung cancer. *Eur J Cancer*. 2022;162:1–10.
- Jazieh K, Khorrami M, Saad A, Gad M, Gupta A, Patil P, et al. Novel imaging biomarkers predict outcomes in stage III unresectable non-small cell lung cancer treated with chemoradiation and durvalumab. *J Immunother Cancer*. 2022;10:e003778.
- Desilets A, Blanc-Durand F, Lau S, Hakozaki T, Kitadai R, Malo J, et al. Durvalumab therapy following chemoradiation compared with a historical cohort treated with chemoradiation alone in patients with stage III non-small cell lung cancer: a real-world multicentre study. *Eur J Cancer*. 2021;142:83–91.
- Schmidt LH, Kummel A, Görlich D, Mohr M, Bröckling S, Mikesch JH, et al. PD-1 and PD-L1 expression in NSCLC indicate a favorable prognosis in defined subgroups. *PLoS One*. 2015;10:e0136023.
- Fujimoto D, Uehara K, Sato Y, Sakanoue I, Ito M, Teraoka S, et al. Alteration of PD-L1 expression and its prognostic impact after concurrent chemoradiation therapy in non-small cell lung cancer patients. *Sci Rep*. 2017;7:11373.
- Takada K, Shimokawa M, Akamine T, et al. Association of low body mass index with poor clinical outcomes after resection of non-small cell lung cancer. *Anticancer Res*. 2019;39:1987–96.
- Benker M, Citak N, Neuer T, Opitz I, Inci I. Impact of preoperative comorbidities on postoperative complication rate and outcome in surgically resected non-small cell lung cancer patients. *Gen Thorac Cardiovasc Surg*. 2022;70:248–56.
- Sepesi B, Gold KA, Correa AM, Heymach JV, Vaporciyan AA, Roszik J, et al. The influence of body mass index on overall survival following surgical resection of non-small cell lung cancer. *J Thorac Oncol*. 2017;12:1280–7.
- Fukumoto K, Mori S, Shintani Y, Okami J, Ito H, Ohtsuka T, et al. Impact of the preoperative body mass index on the postoperative outcomes in patients with completely resected non-small cell lung cancer: a retrospective analysis of 16,503 cases in a Japanese lung cancer registry study. *Lung Cancer*. 2020;149:120–9.
- Shepshelovich D, Xu W, Lu L, Fares A, Yang P, Christiani D, et al. Body mass index (BMI), BMI change, and overall survival in patients with SCLC and NSCLC: a pooled analysis of the international lung cancer consortium. *J Thorac Oncol*. 2019;14:1594–607.
- Lee JH, Yoon YC, Kim HS, Cha MJ, Kim JH, Kim K, et al. Obesity is associated with improved postoperative overall survival, independent of skeletal muscle mass in lung adenocarcinoma. *J Cachexia Sarcopenia Muscle*. 2022;13:1076–86.
- Minami S, Ihara S, Nishimatsu K, Komuta K. Low body mass index is an independent prognostic factor in patients with non-small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitor. *World J Oncol*. 2019;10:187–98.
- Nie RC, Chen GM, Wang Y, Yuan SQ, Zhou J, Duan JL, et al. Association between body mass index and survival outcomes in patients treated with immune checkpoint inhibitors: meta-analyses of individual patient data. *J Immunother*. 2021;44:371–5.
- Muralidaran A, Detterbeck FC, Boffa DJ, Wang Z, Kim AW. Long-term survival after lung resection for non-small cell lung cancer with circulatory bypass: a systematic review. *J Thorac Cardiovasc Surg*. 2011;142:1137–42.
- Albain KS, Swann RS, Rusch VW, Turrisi AT III, Shepherd FA, Smith C, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374:379–86.
- Ardizzoni A, Cafferata MA, Tiseo M, Filiberti R, Marroni P, Grossi F, et al. Decline in serum carcinoembryonic antigen and cytokeratin 19 fragment during chemotherapy predicts objective response and survival in patients with advanced non-small cell lung cancer. *Cancer*. 2006;107:2842–9.
- Arrieta O, Villarreal-Garza C, Martínez-Barrera L, Morales M, Dorantes-Gallareta Y, Peña-Curiel O, et al. Usefulness of serum carcinoembryonic antigen (CEA) in evaluating response to chemotherapy in patients with advanced non-small cell lung cancer: a prospective cohort study. *BMC Cancer*. 2013;13:254.
- Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for

- diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28(suppl 4): iv1–iv21.
34. Choi HS, Jeong BK, Jeong H, Lee YH, Ha IB, Song JH, et al. Application of the new 8th TNM staging system for non-small cell lung cancer: treated with curative concurrent chemoradiotherapy. *Radiat Oncol.* 2017;12:122.
 35. Ettinger DS, Aisner DL, Wood DE, et al. NCCN guidelines insights: non-small cell lung cancer, version 5.2018. *J Natl Compr Cancer Network.* 2018;16:807–21.

How to cite this article: Takahara Y, Tanaka T, Ishige Y, Shionoya I, Yamamura K, Sakuma T, et al. Early recurrence factors in patients with stage III non-small cell lung cancer treated with concurrent chemoradiotherapy. *Thorac Cancer.* 2022;13(24): 3451–8. <https://doi.org/10.1111/1759-7714.14704>