Original Article

Factors predicting early recurrence in patients with unresectable stage III non-small cell lung cancer on durvalumab consolidation after chemoradiotherapy

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Background: Durvalumab consolidation after concurrent chemoradiotherapy (CCRT) is the present standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC). However, some patients experience early recurrence. This study sought risk factors for early recurrence during durvalumab consolidation.

Methods: This retrospective multicenter study was conducted between September 2017 and September 2022. We categorized patients into early and non-early recurrence groups. Early recurrence was defined as recurrence within 6 months after the first dose of durvalumab.

Results: Of the 222 patients, 40 (18.0%) experienced early recurrence and 182 (82.0%) experienced non-early recurrence. The former group was younger than the latter group (P=0.02). Patients exhibiting lower-level programmed cell death-ligand 1 (PD-L1) expression were more likely to experience early recurrence (P=0.02). Stage IIIC patients tended to experience more early recurrence than stage IIIA/IIIB patients (P=0.055). Multivariate analyses revealed that older age [odds ratio (OR), 0.945; 95% confidence interval (CI): 0.902–0.991; P=0.02] and PD-L1 level ≥50% (OR, 0.303; 95% CI: 0.125–0.736; P=0.008) protected against early recurrence in NSCLC patients on durvalumab consolidation. Median overall survival was significantly longer in the non-early recurrence group than in the early recurrence group (non-evaluable *vs.* 11.0 months, respectively; P<0.001).

Conclusions: Younger age and lower PD-L1 expression predicted early recurrence during durvalumab consolidation after CCRT. Careful follow-up of such patients is essential.

Keywords: Chemoradiotherapy; durvalumab; early recurrence; non-small cell lung cancer (NSCLC)

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Introduction

Approximately 30–35% of patients with non-small cell lung cancer (NSCLC) present with locally advanced disease at the time of diagnosis (1). Treatment strategies for such patients have evolved over the decades, from radiation alone, through sequential chemoradiotherapy, to concurrent chemoradiotherapy (CCRT) (2-4). Although CCRT improves locoregional control compared to the sequential strategy, 5-year overall survival (OS) remains low, at 10–15% (3). Therefore, consolidation chemotherapy, targeted therapy, and immunotherapy have become increasingly accepted for patients with locally advanced NSCLC (5).

The recent landmark PACIFIC trial highlighted the efficacy of consolidation durvalumab, an anti-programmed death-ligand 1 (anti-PD-L1) antibody, which is now the standard of care for patients with unresectable stage III NSCLC who experience no disease progression after definitive CCRT (6). Durvalumab consolidation significantly prolonged progression-free survival (PFS) compared to placebo (16.9 *vs.* 5.6 months); however, almost one-third of patients discontinued durvalumab within 1 year because of disease progression (7). As early recurrence after initial treatment is associated with poor long-term survival (8), risk factors for recurrence after CCRT in patients with stage III NSCLC have been sought (9,10). However, such factors for those on durvalumab consolidation remain poorly defined. A previous study showed that a lower tumor proportional score predicted early recurrence after CCRT, but only one patient subgroup was on maintenance durvalumab; this compromised interpretation (11).

In this study, we sought risk factors for early recurrence during durvalumab consolidation of unresectable stage III NSCLC patients who had received CCRT. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1112/rc).

Highlight box

Key findings

- About 18% of patients experienced early recurrence during durvalumab consolidation after concurrent chemoradiotherapy (CCRT) in unresectable stage III non-small cell lung cancer (NSCLC).
- Younger age and lower programmed cell death-ligand 1 (PD-L1) expression predicted the early recurrence in patients on durvalumab consolidation.

What is known and what is new?

- Prognostic factors for early recurrence during durvalumab consolidation remain poorly identified.
- Age and PD-L1 expression status were related to the early recurrence during durvalumab consolidation.

What is the implication, and what should change now?

- Patients with younger age and lower PD-L1 expression require close monitoring for early recurrence during durvalumab consolidation after CCRT in unresectable stage III NSCLC.

Methods

Study design and population

This multicenter, retrospective observational study was conducted in 11 tertiary hospitals in South Korea from September 2017 to September 2022. Patients included in this study had unresectable stage III NSCLC and received at least one dose of consolidation durvalumab after completing CCRT without disease progression. Complete CCRT was defined as at least two cycles of platinum-based chemotherapy with concurrent radiotherapy. To avoid the potential confounding effects of treatment-related complications on long-term prognosis, patients who discontinued durvalumab within 6 months due to adverse events or other medical problems were excluded. Also, patients who are receiving durvalumab for less than 6 months were excluded as it was considered inappropriate to fully evaluate the long-term efficacy of treatment in such cases (*Figure 1*). This study is a secondary subgroup analysis of the data of a previous work (12).

Patients were divided into two groups by the time of recurrence. The early recurrence group contained patients who had recurred within 6 months of durvalumab consolidation commencement, and the non-early recurrence group included patients who had recurred

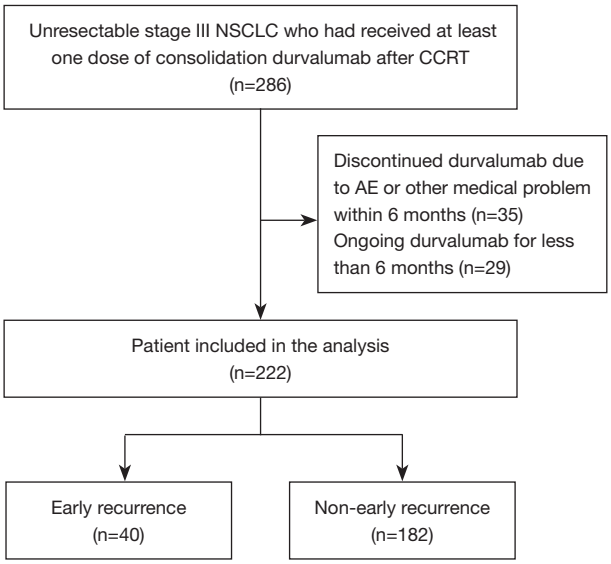

Figure 1 Flow chart of study patients. AE, adverse event; CCRT, concurrent chemoradiotherapy; NSCLC, non-small cell lung cancer.

after 6 months or who did not experience recurrence. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards (IRBs) of the participating institutions: Kyungpook National University Hospital IRB (KNUH 2022-11-019), Yeungnam University Hospital IRB (YUMC 2022-10-021), Kyungpook National University Chilgok Hospital IRB (KNUCH 2023-08-020), Keimyung University Dongsan Hospital IRB (2023-04-005), Daegu Catholic University Medical Center IRB (CR-23-113-L), Pusan National University Hospital IRB (2210-009-119), Pusan National University Yangsan Hospital IRB (05-2022-272), Kosin University Gospel Hospital IRB (KUGH 2022-10-012), Dong-a University Hospital IRB (DAUHIRB-22-243), Inje University Haeundae Paik Hospital IRB (HPIRB 2022-11-028), and Gyeongsang National University Changwon Hospital IRB (GNUCH 2023-07-015). The requirement for informed consent was waived because of the retrospective study design.

Data collection

Patient demographics and disease and treatment-related profiles were retrieved from electronic medical records. The baseline characteristics included patient age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking status, all comorbidities, histological cancer type, and clinical stage. Clinical stages were defined based on the 8th edition of the tumor-node-metastasis (TNM) clinical staging system of the American Joint Committee on Cancer and Union for International Cancer Control (1). PD-L1 expression levels were assessed using the Ventana PD-L1 (SP263) immunohistochemical assay; driver oncogenic mutations included epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements. For CCRT, detailed chemotherapy regimens, radiation doses, and best treatment responses were collected. Treatment responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (13).

Statistical analysis

Continuous variables are expressed as means ± standard deviation (SD) and Student's *t*-test was used for between-group comparisons. Categorical variables are expressed as numbers (percentages) and the Pearson chi-squared or Fisher exact test was employed for comparisons. Participants with missing data were excluded from the analysis. In survival analysis, OS was calculated from the date of durvalumab initiation to the date of death from any cause, or to the last follow-up. OS values were compared between groups using the Kaplan-Meier method and log-rank test. Univariate and multivariate logistic regression analyses were performed to identify factors associated with early recurrence; odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All statistical analyses employed SPSS v22.0 for Windows (SPSS Inc., Chicago, IL, USA) and R statistical software (R Core Team, Vienna, Austria). Significance was evaluated at a level of $P<0.05$.

Results

Patient, disease, and treatment characteristics

Of the 286 patients, 222 were included in the final analysis after excluding 64 who had discontinued durvalumab within 6 months because of adverse events (n=35) and those who were presently on durvalumab (n=29). Of the 222 patients, 40 (18.0%) were in the early recurrence group and 182 (82.0%) in the non-early recurrence group (*Figure 1*). Early recurrence patients were significantly younger than those of the non-early recurrence group (63.7±8.7 *vs.* 67±7.8 years; P=0.02) (*Table 1*). Most patients were male and ever-smokers. ECOG PS scores and proportions of patients with comorbidities were comparable between the two groups.

Table 1 Baseline characteristics of patients by early recurrence and non-early recurrence status

Variable	Total (n=222)	Early recurrence (n=40)	Non-early recurrence (n=182)	P
Age, years	66.4±8.0	63.7±8.7	67±7.8	0.02
Male	191 (86.0)	34 (85.0)	157 (86.3)	0.84
ECOG PS				
0–1	213 (95.9)	37 (92.5)	176 (96.7)	0.22
2–3	9 (4.1)	3 (7.5)	6 (3.3)	
Smoking status				
Never-smoker	37 (16.7)	7 (17.5)	30 (16.5)	0.88
Ex-smoker/current smoker	185 (83.3)	33 (82.5)	152 (83.5)	
Comorbidities				
COPD	88 (39.6)	13 (32.5)	75 (41.2)	0.31
IPF	5 (2.3)	1 (2.5)	4 (2.2)	> 0.99
Diagnosis				
First diagnosis	195 (87.8)	36 (90.0)	159 (87.4)	0.64
Recurrence	27 (12.2)	4 (10.0)	23 (12.6)	
Histology				
ADC	78 (35.1)	10 (25.0)	68 (37.4)	0.59
SQC	116 (52.3)	24 (60.0)	92 (50.5)	
NOS	24 (10.8)	5 (12.5)	19 (10.4)	
LCNEC	3 (1.4)	1 (2.5)	2 (1.1)	
Others	1 (0.5)	0 (0)	1 (0.5)	
Stage (TNM edition 8)				
IIIA	86 (38.7)	12 (30.0)	74 (40.7)	0.055
IIIB	106 (47.7)	18 (45.0)	88 (48.4)	
IIIC	30 (13.5)	10 (25.0)	20 (11.0)	
PD-L1 IHC status (SP263)				
<1%	10 (4.5)	3 (7.5)	7 (3.8)	0.02
1–49%	121 (54.5)	29 (72.5)	92 (50.5)	
≥50%	85 (38.3)	8 (20.0)	77 (42.3.)	
Unknown	6 (2.7)	0 (0)	6 (3.3)	
Driver of oncogenic variation				
EGFR				
Positive	24 (10.8)	5 (12.5)	19 (10.4)	0.15
Negative	182 (82.0)	35 (87.5)	147 (80.8)	
Unknown	16 (7.2)	0 (0)	16 (8.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total (n=222)	Early recurrence (n=40)	Non-early recurrence (n=182)	P
ALK				
Positive	10 (4.5)	2 (5.0)	8 (4.4)	0.49
Negative	197 (88.7)	37 (92.5)	160 (87.9)	
Unknown	15 (6.8)	1 (2.5)	14 (7.7)	
Chemotherapy regimen				
Paclitaxel/cisplatin	157 (70.7)	25 (62.5)	132 (72.5)	0.68
Paclitaxel/carboplatin	57 (25.7)	14 (35.0)	43 (23.6)	
Pemetrexed/cisplatin	1 (0.5)	0 (0)	1 (0.5)	
Pemetrexed/carboplatin	0 (0)	0 (0)	0 (0)	
Etoposide/cisplatin	2 (0.9)	0 (0)	2 (1.1)	
Etoposide/carboplatin	1 (0.5)	0 (0)	1 (0.5)	
Others	4 (1.8)	1 (2.5)	3 (1.6)	
Radiation dose, Gy	62.7±4.4	62.1±3.7	62.8±4.6	0.31
CCRT response				
PR	179 (80.6)	32 (80.0)	147 (80.8)	0.91
SD	43 (19.4)	8 (20.0)	35 (19.2)	

Data are means ± standard deviation or numbers (%). ADC, adenocarcinoma; ALK, anaplastic lymphoma kinase; CCRT, concurrent chemoradiotherapy; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; IPF, idiopathic pulmonary fibrosis; LCNEC, large cell neuroendocrine carcinoma; NOS, not otherwise specified; PD-L1, programmed cell death-ligand 1; PR, partial response; SD, stable disease; SQC, squamous cell carcinoma; TNM, tumor-node-metastasis.

Squamous cell carcinoma was the most common histological cancer type in both groups, followed by adenocarcinoma; no driver mutation was associated with early recurrence. The proportion of patients with stage IIIC cancer was somewhat higher in the early recurrence group than the non-early recurrence group, but this difference was not significant (P=0.055). Patients exhibiting low PD-L1 expression (<1%) were more likely to experience early recurrence (P=0.02). Chemotherapy regimens, radiation doses, and responses to CCRT were comparable between groups.

Risk factors for early recurrence and poor survival

Univariate and multivariate regression analyses were performed to identify factors associated with early recurrence (*Table 2*). According to univariate analysis, age and PD-L1 expression were associated with early recurrence. Multivariate analysis showed that older age (OR: 0.945, 95% CI: 0.902–0.991, P=0.02) and PD-L1 expression ≥50% (OR: 0.303, 95% CI: 0.125–0.736, P=0.008) were significantly associated with less early recurrence after durvalumab consolidation. Median OS was significantly longer in the non-early recurrence group than in the early recurrence group [non-evaluable (NE) *vs.* 11.0 months, respectively; P<0.001] (*Figure 2*).

Discussion

We sought risk factors for early recurrence (within 6 months of durvalumab consolidation), which are important because early detection and localized treatment may improve survival. To our knowledge, this is the largest study to have investigated risk factors for early recurrence in NSCLC patients who had undergone CCRT followed by durvalumab treatment.

Older age protected against early recurrence, which is consistent with a previous report. Younger age independently predicted early relapse during durvalumab

Table 2 Univariate and multivariate analyses of risk factors for early recurrence in NSCLC patients on durvalumab consolidation

Variable	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P value
Age	0.951 (0.912–0.992)	0.02	0.945 (0.902–0.991)	0.02*
Male sex	0.902 (0.344–2.369)	0.84	0.864 (0.248–3.016)	0.82
ECOG PS 0–1	0.420 (0.101–1.758)	0.24	0.326 (0.057–1.855)	0.21
Ever-smoking	0.930 (0.377–2.299)	0.88	1.013 (0.303–3.382)	0.98
First diagnosis	1.302 (0.424–3.997)	0.65	1.180 (0.334–4.163)	0.80
Non-squamous histology	0.681 (0.340–1.367)	0.28	0.588 (0.262–1.319)	0.20
Stage IIIA	0.640 (0.306–1.339)	0.24	0.714 (0.320–1.596)	0.41
Driver oncogenic variation	1.094 (0.438–2.734)	0.85	1.135 (0.388–3.317)	0.82
PD-L1 ≥50%	0.321 (0.140–0.737)	0.007	0.303 (0.125–0.736)	0.008*
Cisplatin-containing regimen	0.580 (0.282–1.193)	0.14	0.577 (0.258–1.289)	0.18
COPD	0.687 (0.333–1.418)	0.31	0.662 (0.297–1.476)	0.31
CCRT best PR	0.952 (0.404–2.246)	0.91	1.208 (0.433–3.369)	0.72

*, statistically significant. CCRT, concurrent chemoradiotherapy; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; OR, odds ratio; PD-L1, programmed cell death-ligand 1; PR, partial response.

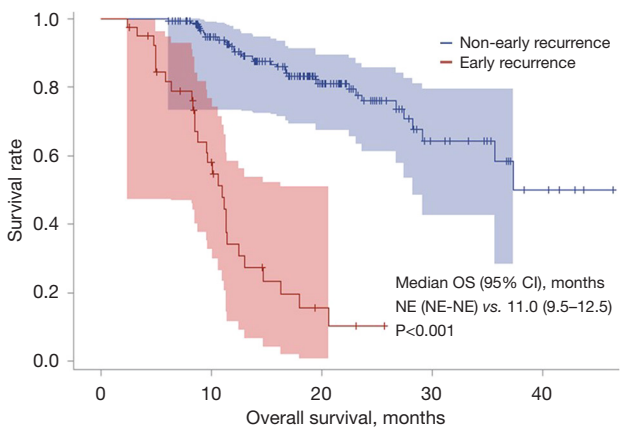

Figure 2 OS for patients in the non-early recurrence and early recurrence group. CI, confidence interval; NE, non-evaluable; OS, overall survival.

consolidation therapy (OR, 0.792) (14). The 5-year PFS outcomes of the PACIFIC trial did not differ significantly between those aged ≥65 and <65 years [hazard ratio (HR), 1.11; 95% CI: 0.92–1.34]. However, the OS of older patients was significantly poorer (HR, 1.30; 95% CI: 1.06–1.59) for those aged ≥65 years compared to <65 years (7). Immunosenescence in elderly patients remodels the lymphoid organs and changes immune function, such that the senescent microenvironment greatly favors tumor metastasis and invasion (15). Tumor proliferation has been found to be slower in older mice (16), and older patients with bronchial cancer exhibited slower tumor growth and fewer metastases, suggesting that aging-specific factors impeded tumor growth and spread (17). Retrospective studies such as the present study are not optimal for drawing meaningful conclusions in the present era of immuno-oncology. Prospective large-scale studies are required to define the association between aging and cancer progression.

In the present study, patients exhibiting lower PD-L1 expression were at greater risk of early recurrence. In the PACIFIC trial, durvalumab (compared to placebo) significantly increased PFS and OS among all PD-L1 subgroups, with the exception of OS in patients with PD-L1 expression <1%. In such patients, a favorable trend was apparent, but statistical significance was not reached (HR, 0.80; 95% CI: 0.53–1.20). Post-hoc analysis revealed that high PD-L1 expression afforded a greater survival benefit (7). A previous study investigated factors associated

with early recurrence, defined as confirmed disease progression within 1 year after initiation of cancer treatment, in patients with stage III NSCLC who had received CCRT; multivariate analysis showed that lower PD-L1 expression was an independent risk factor for early recurrence (11), which is consistent with our findings.

The OS of our early recurrence group was shorter than that of the non-early recurrence group, as also reported in previous studies (11,14). Together, these results suggest that sustained efficacy of CCRT and durvalumab increases the OS of patients with unresectable NSCLC. Therefore, in addition to the age and PD-L1 expression levels, further research is needed to identify novel predictive markers, which will help establish tailored treatment strategies for patients before initiating durvalumab following chemoradiotherapy.

Although stage IIIA patients included in the present study tended to exhibit a lower early recurrence rate than those in other studies, our multivariate analysis revealed no significant difference between stage IIIA and stage IIIB/IIIC. Takahara *et al.* (11) reported that an early recurrence group contained a greater proportion of stage N3 patients than a later recurrence group; although their multivariate analysis revealed a higher OR for stage N3 patients (6.84) than for stage N0–N2 patients, the difference was not significant (P=0.09).

Nam *et al.* (14) reported that stage IIIC patients exhibited a higher adjusted OR (23.85) than stage IIIA patients; however, the difference was again non-significant (P=0.13). Thus, it appears that CCRT followed by durvalumab is useful if PD-L1 expression is high, even in patients with unresectable stage IIIC NSCLC.

The ongoing phase III ADRIATIC study will assess the efficacy and safety of durvalumab with or without tremelimumab as consolidation therapy for patients with limited-stage small cell lung cancer (SCLC) who do not progress after CCRT (18). Biomarkers are required to assess the effectiveness of CCRT and consolidation agents used to treat SCLC, and more prospective studies are needed.

This study had certain limitations. First, although we evaluated multicenter data, our findings cannot be generalized because this study was retrospective. Patients with first diagnoses of unresectable stage III NSCLC who were deemed too old, had poor ECOG status, or had many comorbidities, may not have received CCRT and/or durvalumab. Also, the exclusion criteria may also limit the generalizability of the current study. Second, we studied only 40 patients exhibiting early recurrence. However, this is the largest study to date that sought to identify the risk of early recurrence among NSCLC patients who had received CCRT followed by durvalumab. Third, neither tumor activity nor tumor recurrence profiles were subjected to molecular analysis, and we did not sequence detailed genomes that might predict early recurrence to the retrospective nature of the study. Further studies with next-generation sequencing might identify important genetic variants associated with early recurrence.

Conclusions

Durvalumab consolidation is the standard treatment for patients with unresectable stage III NSCLC who do not experience disease progression following definitive CCRT. Younger age and lower PD-L1 expression predicted early recurrence during durvalumab consolidation, and such patients require meticulous follow-up.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1112/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1112/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1112/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review boards of the participating institutions: Kyungpook National University Hospital IRB (KNUH 2022-11-019), Yeungnam University Hospital IRB (YUMC 2022-10-021), Kyungpook National University Chilgok Hospital IRB (KNUCH 2023-08-020), Keimyung University Dongsan Hospital IRB (2023-04-005), Daegu Catholic University Medical Center IRB (CR-23-113-L), Pusan National University Hospital IRB (2210-009-119), Pusan National University Yangsan Hospital IRB (05-2022-272), Kosin University Gospel Hospital IRB (KUGH 2022-10-012), Dong-a University Hospital IRB (DAUHIRB-22-243), Inje University Haeundae Paik Hospital IRB (HPIRB 2022-11-028), and Gyeongsang National University Changwon Hospital IRB (GNUCH 2023-07-015). The requirement for informed consent was waived because of the retrospective study design.

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