



# A retrospective comparative cohort study: concurrent versus consolidative immunotherapy with chemoradiotherapy in EGFR- or ALK-negative unresectable stage III non-small cell lung cancer

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**Background:** The treatment of stage III non-small cell lung cancer (NSCLC) is very challenging because it is a heterogeneous group of diseases. This study was to investigate whether concurrent immunotherapy with chemoradiotherapy was associated with improved outcomes compared to consolidative immunotherapy following chemoradiotherapy in patients with unresectable stage III NSCLC, which may provide evidence-based medical evidence for the treatment of stage III NSCLC.

**Methods:** A total of 78 epidermal growth factor receptor or anaplastic lymphoma kinase (EGFR/ALK) negative patients from the clinical database of the Shanghai Pulmonary Hospital with locally advanced unresectable NSCLC and we evaluated them for baseline clinical factors, follow-up. Patients underwent concurrent immunotherapy with chemoradiotherapy or consolidative immunotherapy after chemoradiotherapy. Patients were classified based on initial site of progression (primary versus non-primary site). The study endpoints were progression-free survival (PFS) and time to death or distant metastasis (TDDM). Cox proportional hazards analysis was used to assess the factors affecting PFS and TDDM.

**Results:** The median follow-up time for both groups was 26 months, and there was no significant difference in baseline clinical characteristics ( $P>0.05$ ). The patients receiving concurrent immunotherapy ( $n=36$ ) had a longer PFS than those receiving consolidative immunotherapy ( $n=42$ ) (median 32.4 *vs.* 15.5 months;  $P<0.01$ ). The TDDM was also longer in patients with concurrent immunotherapy than those with consolidative immunotherapy (median 57.3 *vs.* 31.0 months;  $P=0.01$ ). Furthermore, in a subset of patients with initial site of progression at a non-primary-site, patients undergoing concurrent immunotherapy had longer PFS than those undergoing consolidative immunotherapy (median 22.7 *vs.* 11.9 months;  $P=0.03$ ).

**Conclusions:** Concurrent immunotherapy with chemoradiotherapy may be associated with improved disease progression outcomes as compared to consolidative immunotherapy following chemoradiotherapy.

**Keywords:** Non-small cell lung cancer (NSCLC); immunotherapy; chemoradiotherapy; epidermal growth factor receptor (EGFR); anaplastic lymphoma kinase (ALK)

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## Introduction

Non-small cell lung cancer (NSCLC) accounts for 80–85% of all cases of lung cancer (1), with stage III NSCLC accounting for approximately one-third all cases at diagnosis (2). Stage III NSCLC is highly heterogeneous, with a wide spectrum of disease distribution and an equally complex range of treatment options (3).

Standard treatment for unresectable stage III NSCLC that does not involve sensitizing epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) changes consists of radiotherapy concurrent with platinum-based doublet chemotherapy followed by immunotherapy (4,5). Despite the survival benefit granted by immunotherapy in this setting, only 1/3 of patients are alive and disease free at 5 years (6). In one study, the 5-year overall survival (OS) was improved by 9% when consolidative immunotherapy following chemoradiotherapy was applied as compared to chemoradiotherapy alone (7).

Previous studies have reported that patients receiving radiotherapy and/or chemotherapy show significant immunogenic patterns, which may improve the response

to immunotherapy (8,9). This inspired us to investigate a better clinical treatment protocol by exploring the sequential order of immunotherapy and radiochemotherapy. Therefore, comparisons of concurrent immunotherapy with chemoradiotherapy or consolidative immunotherapy following chemoradiotherapy warrants further investigation (6,7,10).

In our study, we conducted a single-institution retrospective study to investigate whether immunotherapy concurrent with chemoradiotherapy could be associated with disease control outcomes as compared to consolidative immunotherapy following chemoradiotherapy, which may provide evidence-based medical evidence for the treatment of stage III NSCLC. We present this article in accordance with the STROBE reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-575/rc>).

## Methods

### Patients

From January 1, 2020, to June 31, 2022, 238 patients with locally advanced NSCLC [stage III according to the American Joint Committee on Cancer (AJCC), eighth edition] without sensitizing EGFR/ALK alterations were screened in Shanghai Pulmonary Hospital (Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai, China). These patients had received immunotherapy [anti-programmed cell death protein 1 (PD-1) antibody] during and/or before definitive concurrent chemoradiotherapy.

### Inclusion and exclusion criteria

The following inclusion criteria were employed: (I) pathologically confirmed stage III NSCLC; (II) no sensitizing EGFR or ALK alterations; (III) presence of unresectable lesions; (IV) first-line therapy of immunotherapy and definitive concurrent chemoradiotherapy.

The exclusion criteria were as follows: (I) radical surgery; (II) immunotherapy not used for locally advanced unresectable disease; (III) no immunotherapy or thoracic definitive concurrent chemoradiotherapy; (IV) an incomplete medical record.

### Highlight box

#### Key findings

- Concurrent immunotherapy with chemoradiotherapy may be associated with delayed disease progression as compared to consolidative immunotherapy following chemoradiotherapy.

#### What is known and what is new?

- One treatment modality for unresectable stage III non-small cell cancer (NSCLC) in patients without sensitizing epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) changes is radiotherapy concurrent with platinum-based doublet chemotherapy, which may be followed by immunotherapy.
- Our findings indicated that for unresectable stage III NSCLC without sensitizing EGFR/ALK alterations, consolidative immunotherapy following chemoradiotherapy may be less effective than immunotherapy concurrent with chemoradiotherapy.

#### What is the implication, and what should change now?

- Based on the results of this study, we suggest that immunotherapy concurrent with chemoradiotherapy might improve outcomes as compared to sequential approach in patients with unresectable stage III NSCLC without EGFR/ALK mutations.

### Study design

According to the sequence of immunotherapy and chemoradiotherapy, the patients were divided into two groups: concurrent immunotherapy (n=36; defined as concurrent chemotherapy, radiotherapy, and immunotherapy followed by consolidative immunotherapy) and consolidative immunotherapy (n=42; defined as concurrent chemotherapy and radiotherapy followed by consolidative immunotherapy). In addition, the patients who experienced disease progression (n=52) were further classified into those with site of initial progression as the primary site (n=21) versus a non-primary site (n=31).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Ethics Committee of Shanghai Pulmonary Hospital (No. K23-215) and informed consent was taken from all the patients.

### Follow-up

The following tests were used as a clinical baseline assessment: brain magnetic computed tomography (CT) or resonance imaging (MRI), chest CT, abdominal ultrasound, and bone scan. Additional, tumor imaging with abdominal ultrasound and chest CT was performed every 2–3 months, brain MRI or CT was completed every 3 months, and bone scan was conducted every 4–6 months. Brain MRI or bone scan was immediately performed if the patient developed brain or bone symptoms, respectively.

Patients' follow-up data and medical records were collected. The following information was collected: age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS), symptoms, histological type, programmed death-ligand 1 (PD-L1) status, disease stage, radiotherapy dose, and initial progression site. The baseline data were classified according to the following criteria: age (<60 or ≥60 years), sex (male or female), smoking history (current/former or never), ECOG-PS (0 or 1), symptoms (yes or no), histology type (nonsquamous or squamous), PD-L1 status (positive or negative), disease stage (IIIA or IIIB–C), chemoradiotherapy dose (<60 or ≥60 Gy), and initial progression site (primary or non-primary).

### Evaluation method and treatment options

Intracranial lesions were assessed with brain MRI or CT, while extracranial lesions were assessed with bone scan, chest CT and abdominal ultrasound. Durvalumab

was administered at a dose of 10 mg/kg (every 2 weeks) or (1,500 mg every 4 weeks), and camrelizumab was administered at a dose of 200 mg every 3 weeks. In the consolidative immunotherapy group, the patients received chemoradiotherapy, which was followed by immunotherapy with durvalumab up to disease progression or 1 year according to the relevant guidelines (4,5). In the concurrent immunotherapy group, patients received 1 cycle of platinum-based chemotherapy and camrelizumab (200 mg) first. After 3–4 weeks, patients received camrelizumab (200 mg every 3–4 weeks) plus concurrent chemoradiotherapy for 2 cycles, which was followed by camrelizumab administration (200 mg every 3–4 weeks) up to disease progression or 1 year. Thoracic radiotherapy was performed 5 days a week in fractions of 2 Gy per fraction to a target dose of 50–70 Gy. Progression-free survival (PFS) was defined as the time interval between the initiation of treatment and disease progression. The time to death or distant metastasis (TDDM) was defined as the time interval between the initiation time of treatment and the time of distant metastasis.

PFS was the primary endpoint, while TDDM was a secondary endpoint. Additionally, PFS of the primary site was a secondary endpoint for patients with initial progression of the primary site, while PFS of the nonprimary site was the secondary endpoint for those with initial progression of a nonprimary site.

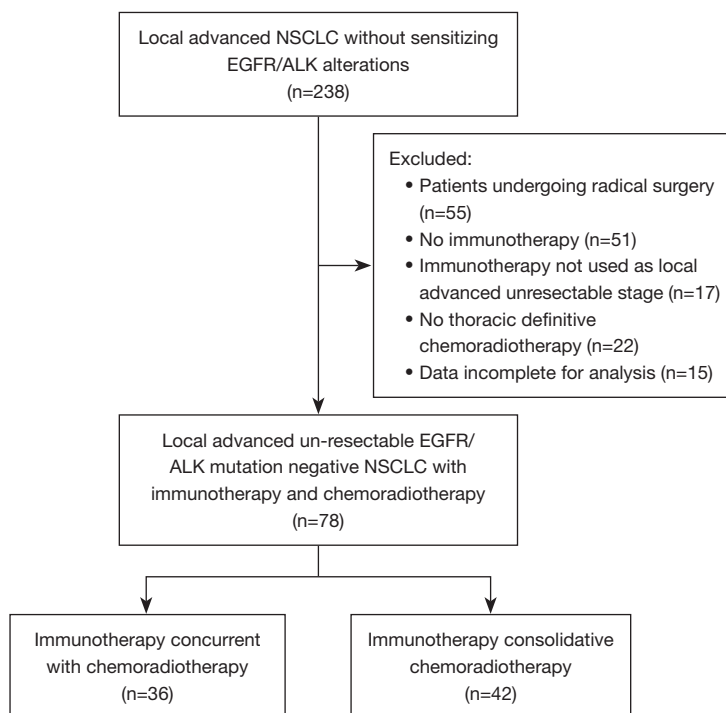
### Statistical analysis

The  $\chi^2$  test was used to analyze the categorical patient variables. PFS and TDDM were assessed with the Kaplan-Meier method and the log-rank test. Furthermore, multivariate analysis was conducted to assess the association of independent prognostic factors with PFS and TDDM, and survival analysis was conducted using Cox proportional hazards regression modeling. A two-sided P value less than 0.05 was regarded as a statistically significant difference. SPSS software version 23.0 (IBM Corp., Armonk, NY, USA) was used to analyze all statistical data, and Prism software (GraphPad Software, San Diego, CA, USA) was used to create the survival curves.

## Results

### Patient characteristics

From January 1, 2020, to June 31, 2022, a total of 238 patients with locally advanced (stage III, AJCC eighth edition) NSCLC without sensitizing EGFR/ALK alterations



**Figure 1** Patient selection flowchart. NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

were screened. Of these patients, 160 were excluded due to failure to meet the inclusion criteria (55 patients undergoing radical surgery, 51 patients not administered immunotherapy, 17 patients in whom immunotherapy was not used for treatment at the locally advanced unresectable stage, 22 patients without definitive thoracic concurrent chemoradiotherapy, and 15 patients with incomplete medical records). Finally, 78 patients who met the inclusion criteria were enrolled for analysis. The flowchart of patient screening is presented in *Figure 1*. Of these 78 patients, 36 (46.2%) received concurrent immunotherapy, whereas 42 (53.8%) received consolidative immunotherapy.

The median follow-up time among all patients was 26 months [95% confidence interval (CI): 22.3–29.9]. No difference was found in age, sex, smoking history, ECOG-PS, symptoms, histological type, PD-L1 status, disease stage, radiotherapy dose, or initial progression site between the concurrent and consolidative immunotherapy groups. The baseline characteristics of patients are listed in *Table 1*.

### PFS analysis

Patients who received concurrent immunotherapy had a

significantly longer PFS (32.4 months; 95% CI: 20.5–44.2) than did those who received consolidative immunotherapy (15.5 months; 95% CI: 8.9–22.0) ( $P < 0.01$ ; *Figure 2*). The hazard ratio (HR) of progression for the immunotherapy concurrent with chemoradiotherapy group compared with consolidative immunotherapy following chemoradiotherapy group was 0.40 (95% CI: 0.23–0.69).

After significant covariables of PFS were controlled for, including therapy strategy, age, sex, smoking history, ECOG-PS, symptoms, histological type, PD-L1 status, disease stage, and radiotherapy dose, the following characteristics were associated with improved PFS: immunotherapy sequencing (concurrent *vs.* consolidative: adjusted HR 0.334, 95% CI: 0.164–0.680;  $P = 0.003$ ), PD-L1 status (positive *vs.* negative: adjusted HR 0.240, 95% CI: 0.110–0.524;  $P < 0.001$ ), and radiotherapy dose ( $< 60$  *vs.*  $\geq 60$  Gy: adjusted HR 0.267, 95% CI: 0.118–0.604;  $P = 0.002$ ) (*Figure 3*).

### PFS analysis of progression

Of those patients who experienced progression ( $n = 52$ ), the primary site and nonprimary site was the initial progression point in 21 (40.4%) and 31 (59.6%) patients,

**Table 1** Patient characteristics

Characteristics	Total	Concurrent immunotherapy (n=36), n (%)	Consolidative immunotherapy (n=42), n (%)	P
Age, years				0.544
<60	31 (39.7)	13 (36.1)	18 (42.9)	
≥60	47 (60.3)	23 (63.9)	24 (57.1)	
Sex				0.246
Male	58 (74.4)	29 (80.6)	29 (69.0)	
Female	20 (25.6)	7 (19.4)	13 (31.0)	
Smoking history				0.349
Current/former	19 (24.4)	7 (19.4)	12 (28.6)	
Never	59 (75.6)	29 (80.6)	30 (71.4)	
ECOG-PS				0.116
0	38 (48.7)	21 (58.3)	17 (40.5)	
1	40 (51.3)	15 (41.7)	25 (59.5)	
Symptoms				0.875
Yes	21 (26.9)	10 (27.8)	11 (26.2)	
No	57 (73.1)	26 (72.2)	31 (73.8)	
Histology type				0.515
Nonsquamous	49 (62.8)	24 (66.7)	25 (59.5)	
Squamous	29 (37.2)	12 (33.3)	17 (40.5)	
PD-L1 status				0.807
Positive	40 (51.3)	19 (52.8)	21 (50.0)	
Negative	38 (48.7)	17 (47.2)	21 (50.0)	
Disease stage				0.362
IIIA	18 (23.1)	10 (27.8)	8 (19.0)	
IIIB/IIIC	60 (76.9)	26 (72.2)	34 (81.0)	
Radiotherapy dose, Gy				0.875
<60	21 (26.9)	10 (27.8)	11 (26.2)	
≥60	57 (73.1)	26 (72.2)	31 (73.8)	
Initial progression site				0.277
Primary site	22 (28.2)	8 (22.2)	14 (33.3)	
Others	56 (71.8)	28 (77.8)	28 (66.7)	

ECOG-PS, Eastern Cooperative Oncology Group-performance status; PD-L1, programmed death- ligand 1.

respectively. In the group of nonprimary site progression, patients who received concurrent immunotherapy had a significantly longer PFS (22.7 months; 95% CI: 7.5–33.0) than did those who received consolidative immunotherapy (11.9 months; 95% CI: 4.2–19.5) ( $P=0.03$ ; *Figure 4A*).

However, in the group with primary site progression, no significance difference between those receiving concurrent immunotherapy (8.5 months; 95% CI: 0–18.2) compared to consolidative immunotherapy (9.3 months; 95% CI: 2.4–15.3) ( $P=0.45$ ; *Figure 4B*).



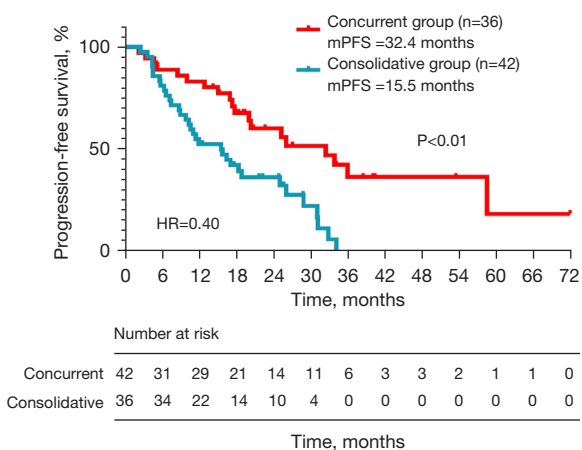
**TDDM and survival status analysis**

Notably, patients undergoing concurrent immunotherapy had a significantly longer TDDM (57.3 months; 95% CI: 40.3–74.2) than those undergoing consolidative immunotherapy (31.0 months; 95% CI: 18.5–43.5) (P=0.01; Figure 5).

After the significant covariables of TDDM were controlled for, including therapy strategy, age, sex, smoking history, ECOG-PS, symptoms, histological type, PD-L1 status, disease stage, and radiotherapy dose, the following

characteristics were associated with improved TDDM: immunotherapy sequencing (immunotherapy concurrent with chemoradiotherapy vs. consolidative immunotherapy following chemoradiotherapy: adjusted HR 0.154, 95% CI: 0.049–0.479; P=0.001), PD-L1 status (positive vs. negative: adjusted HR 0.186, 95% CI: 0.052–0.663; P=0.009), and radiotherapy dose (<60 vs. ≥60 Gy: adjusted HR 0.118, 95% CI: 0.031–0.444; P=0.002) (Figure S1).

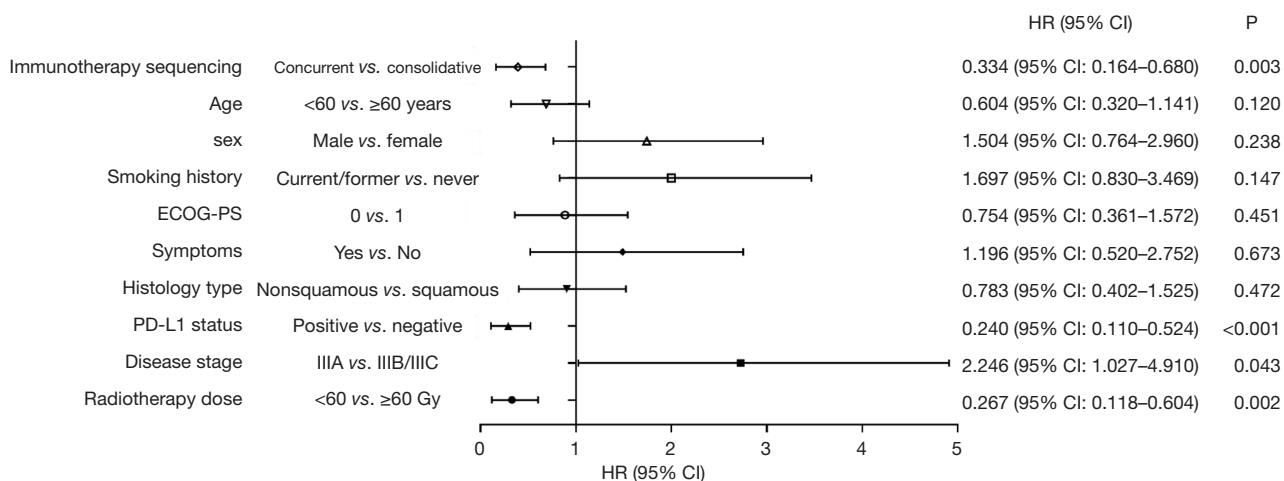
At the follow-up cutoff date of April 1, 2023, 73% (n=57) of patients were still alive (27 receiving consolidative immunotherapy following chemoradiotherapy; 30 receiving immunotherapy concurrent with chemoradiotherapy).



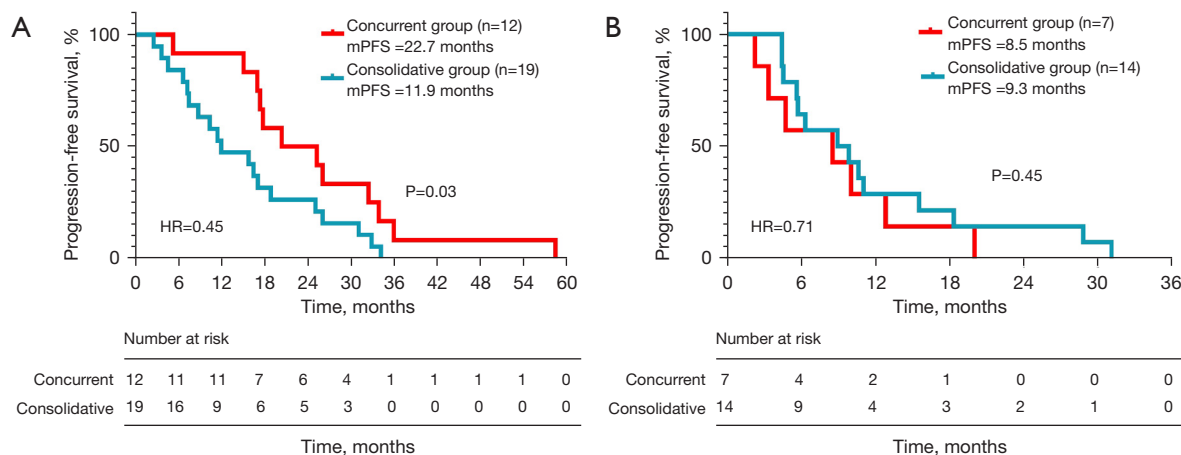
**Figure 2** Survival analysis of PFS in all patients. HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival.

**Discussion**

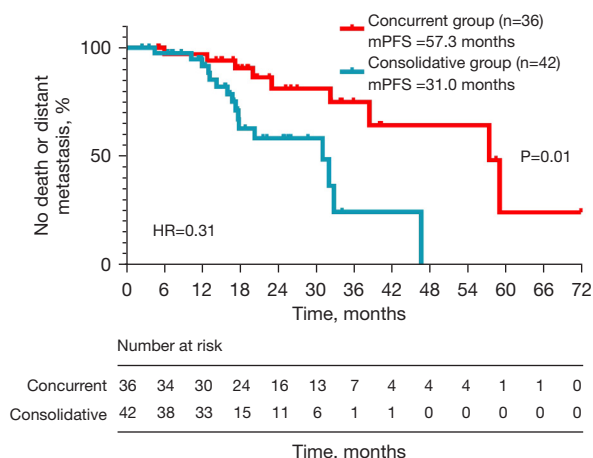
As patients with EGFR/ALK-negative stage III unresectable NSCLC have an improving but suboptimal prognosis, treatment modalities for this condition urgently need to be improved (11). We thus conducted a retrospective analysis to compare the efficacy of concurrent immunotherapy with chemoradiotherapy with that of consolidative immunotherapy following chemoradiotherapy. Our findings suggest that for this population, PFS of the concurrent immunotherapy group was significantly longer than that of the consolidative immunotherapy group, especially among those who had a non-primary initial site of recurrence. The PACIFIC trial is the most widely recognized radioimmunotherapy combination therapy for NSCLC (12). The PACIFIC trial found that the use of durvalumab at the



**Figure 3** In the multivariable model, therapy strategy, PD-L1 status and radiotherapy dose were independently correlated with progression-free survival among all patients. ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-L1, programmed death-ligand 1; HR, hazard ratio; CI, confidence interval.



**Figure 4** Survival analysis of PFS in all patients that experienced progression. (A) For patients in whom initial progression occurred at a nonprimary site, those who received immunotherapy concurrent with chemoradiotherapy had a significantly longer progression-free survival than did those who received consolidative immunotherapy following chemoradiotherapy. (B) For patients in whom initial progression occurred at the primary site, there was no significant difference between groups. HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival.



**Figure 5** Survival analysis of patients for whom TDDM was recorded. HR, hazard ratio; mPFS, median progression-free survival; TDDM, time to death or distant metastasis.

end of chemoradiotherapy provided robust and sustained OS compared to chemoradiotherapy alone (OS; 47.5 *vs.* 29.1 months; HR 0.72) and extensive PFS benefit (PFS: 16.9 *vs.* 5.9 months; HR 0.55), with 42.9% of patients remaining alive at 5 years (7). Similarly, in the GEMSTONE-301 trial, sugemalimab after chemoradiotherapy showed sustained improvement in PFS as compared to chemoradiotherapy along (PFS: 9.0 *vs.* 5.8 months; HR 0.64; P=0.002) (13). Moreover, the GEMSTONE-301 trial further demonstrated

that both sugemalimab after concurrent chemoradiotherapy and sequential chemoradiotherapy could provide a longer PFS than could placebo (14). Several studies have demonstrated that consolidative immunotherapy with chemoradiotherapy can effectively improve the survival prognosis of patients with EGFR/ALK-negative stage III unresectable NSCLC (15). Some studies have also analyzed the efficacy of chemoradiotherapy combined with immunotherapy compared to that of placebo treatment. For example, in the KEYNOTE-799 trial, patients with NSCLC received 1 cycle of induction pembrolizumab and chemotherapy, then pembrolizumab and chemoradiotherapy for 2 cycles, and finally 14 cycles of consolidative pembrolizumab (16). The median PFS was 30.6 months (95% CI: 16.6 to not reached) (17).

Unfortunately these observational studies did not elucidate the differences in efficacy between concurrent and consolidative immunotherapy. We speculate that possible reasons may be as follows. First, not all radiotherapy-induced microenvironments are beneficial for immune activation. Previous research has shown that M2 macrophages accumulate in hypoxic areas in the irradiated region, with the number of immunosuppressive T regulatory cells increasing after radiotherapy (18,19). Furthermore, radiotherapy could kill tumor cells and expose new antigens, which may also lead to the death of immune cells in the chemoradiotherapy area and reduce

blood volume exposure (20-22). In addition, maintaining lymph node integrity before immunotherapy may improve the efficacy of immunotherapy (23,24). Therefore, immunotherapy prior to or concurrent with definitive chemoradiotherapy may bring superior therapeutic benefits than may immunotherapy following definitive chemoradiotherapy. In our study, we performed subgroup analysis which indicated that in patients whose initial progression point was a nonprimary site, those receiving immunotherapy concurrent with chemoradiotherapy had a significantly longer PFS than did those receiving consolidative immunotherapy following definitive chemoradiotherapy.

In the GEMSTONE-301 trial, it was also suggested that radiotherapy with a dose <60 Gy may provide a more robust PFS benefit than that with a dose  $\geq 60$  Gy (HR 0.49 vs. 0.69). Furthermore, our findings indicated that lower doses of radiation may provide better therapeutic benefits than may higher doses, which is consistent with the general results of the GEMSTONE-301 trial. However, these results should be interpreted with caution since they were derived from subgroup analyses.

The significance of our paper lies in reporting novel findings that may reflect the current situation in treatment for unresectable stage III NSCLC. However, several limitations to our study exist. First, patients received different immunotherapy regimens. Second, a nonrandom, single-institution, retrospective design was employed that likely included confounding factors and unrecognized biases. Third, the impact of adverse events on toxicity and quality of life was not assessed.

Our study suggests a difference in efficacy between immunotherapy concurrent with chemoradiotherapy and consolidative immunotherapy following chemoradiotherapy. However, the reasons for the differences in efficacy resulting from the different treatment sequences of immunotherapy and chemoradiotherapy have not been studied yet. Therefore, this will be a focus of our upcoming research.

## Conclusions

Compared to consolidative immunotherapy following chemoradiotherapy, concurrent immunotherapy with chemoradiotherapy may be associated with prolonged PFS, especially in patients whose primary site does not exhibit initial progression. Continued enrollment on phase III randomized controlled trials like EA5181 and KEYLYNK-12 are necessary to prospectively confirm

the potential value of concurrent immunotherapy in addition to consolidative immunotherapy in the context of chemoradiotherapy.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://tclr.amegroups.com/article/view/10.21037/tclr-23-575/rc>

*Data Sharing Statement:* Available at <https://tclr.amegroups.com/article/view/10.21037/tclr-23-575/dss>

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://tclr.amegroups.com/article/view/10.21037/tclr-23-575/coif>). C.G. received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events for MSD, BMS, Amgen, Novartis, Astra Zeneca, Roche, Sanofi, Pfizer, Eli Lilly, Takeda, Boehringer. C.G. reports participation on a Data Safety Monitoring Board or Advisory Board for MSD, BMS, Amgen, Novartis, Astra Zeneca, Roche, Sanofi, Pfizer, Eli Lilly, Takeda, Boehringer, Karyopharm, GSK and received consulting fees for Menarini. H.S.P. has received institutional grants from RefleXion and Merck, and personal fees from AstraZeneca (consulting, advisory board), Bristol Myers Squibb (honoraria), Daiichi Sankyo (honoraria), G1 Therapeutics (honoraria), Galera (advisory board), and RefleXion (consulting). The other 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 Institutional Ethics Committee of Shanghai Pulmonary Hospital (No. K23-215) and informed consent was taken from all the patients.

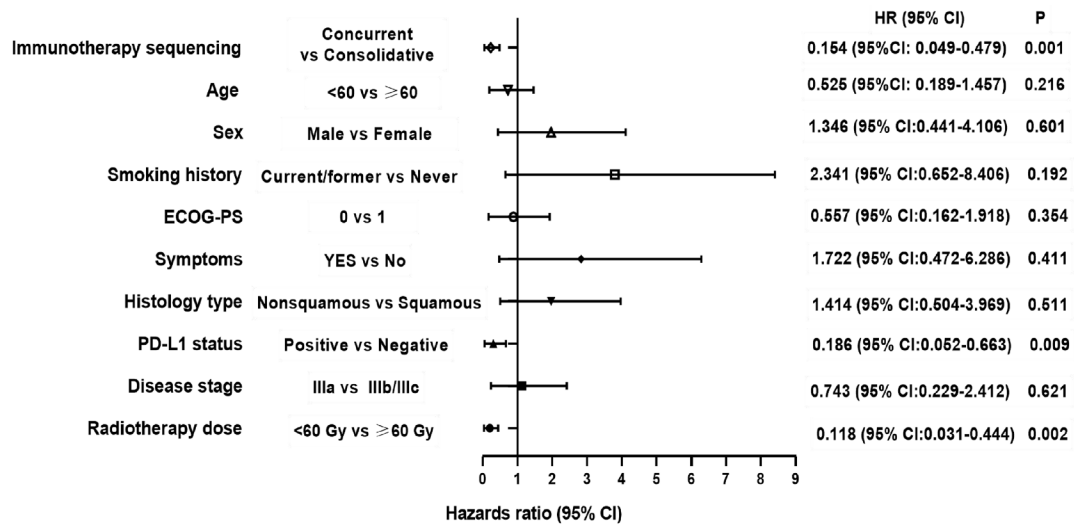
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## References

- Giaccone G, Zucali PA. Src as a potential therapeutic target in non-small-cell lung cancer. *Ann Oncol* 2008;19:1219-23.
- Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181-90.
- Evison M; . The current treatment landscape in the UK for stage III NSCLC. *Br J Cancer* 2020;123:3-9.
- Guidelines Working Committee of Chinese Society of Clinical Oncology. Guidelines of Chinese Society of Clinical Oncology (CSCO): Non-Small Cell Lung Cancer. Beijing: People's Medical Publishing House; 2023.
- Ettinger D WD, Aisner D, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 5.2022; 2022. Available online: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450>
- Cortiula F, Reymen B, Peters S, et al. Immunotherapy in unresectable stage III non-small-cell lung cancer: state of the art and novel therapeutic approaches. *Ann Oncol* 2022;33:893-908.
- Spigel DR, Faivre-Finn C, Gray JE, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol* 2022;40:1301-11.
- Yu WD, Sun G, Li J, et al. Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy. *Cancer Lett* 2019;452:66-70.
- Kroeze SG, Fritz C, Hoyer M, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review. *Cancer Treat Rev* 2017;53:25-37.
- Reck M, Lee KH, Frost N, et al. Two-year update from KEYNOTE-799: Pembrolizumab plus concurrent chemoradiation therapy (cCRT) for unresectable, locally advanced, stage III NSCLC. *J Clin Oncol* 2022;40:8508.
- Nakamura M, Kageyama SI, Niho S, et al. Impact of EGFR Mutation and ALK Translocation on Recurrence Pattern After Definitive Chemoradiotherapy for Inoperable Stage III Non-squamous Non-small-cell Lung Cancer. *Clin Lung Cancer* 2019;20:e256-64.
- Alaswad M. Locally advanced non-small cell lung cancer: current issues and recent trends. *Rep Pract Oncol Radiother* 2023;28:286-303.
- Zhou Q, Chen M, Jiang O, et al. Sugemalimab versus placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2022;23:209-19.
- Wu YL, Zhou Q, Chen M, et al. Sugemalimab vs Placebo after cCRT or sCRT in pts with Unresectable Stage III NSCLC: Final PFS Analysis of a Phase 3 Study. *WCLC* 2022; OA02.05.
- Käsmann L, Taugner J, Eze C, et al. Prospective evaluation of immunological, molecular-genetic, image-based and microbial analyses to characterize tumor response and control in patients with unresectable stage III NSCLC treated with concurrent chemoradiotherapy followed by consolidation therapy with durvalumab (PRECISION): protocol for a prospective longitudinal biomarker study. *Transl Lung Cancer Res* 2022;11:1503-9.
- Manapov F, Kenndoff S, Käsmann L. NICOLAS, DETERRED and KEYNOTE 799: focus on escalation of conventionally fractionated chemoradiotherapy by immune checkpoint inhibition in unresectable stage III non-small cell lung cancer. *Transl Lung Cancer Res* 2022;11:702-5.
- Jabbour SK, Lee KH, Frost N, et al. Pembrolizumab Plus Concurrent Chemoradiation Therapy in Patients With Unresectable, Locally Advanced, Stage III Non-Small Cell Lung Cancer: The Phase 2 KEYNOTE-799 Nonrandomized Trial. *JAMA Oncol* 2021. [Epub ahead of print]. doi: 10.1001/jamaoncol.2021.2301.
- Chiang CS, Fu SY, Wang SC, et al. Irradiation promotes an m2 macrophage phenotype in tumor hypoxia. *Front*

- Oncol 2012;2:89.
19. Schae D, Xie MW, Ratican JA, et al. Regulatory T cells in radiotherapeutic responses. *Front Oncol* 2012;2:90.
  20. Gunderson AJ, Young KH. Exploring optimal sequencing of radiation and immunotherapy combinations. *Adv Radiat Oncol* 2018;3:494-505.
  21. Kaur P, Asea A. Radiation-induced effects and the immune system in cancer. *Front Oncol* 2012;2:191.
  22. Baudoux N, Friedlaender A, Addeo A. Management of stage IIIA non-small cell lung cancer (NSCLC): role of the chemotherapy. *Curr Chall Thorac Surg* 2022;4:18.
  23. Rahim MK, Okholm TLH, Jones KB, et al. Dynamic CD8(+) T cell responses to cancer immunotherapy in human regional lymph nodes are disrupted in metastatic lymph nodes. *Cell* 2023;186:1127-1143.e18.
  24. Käsmann L, Nieto A, Taugner J, et al. PD-L1 expression on tumor cells as a potential predictive biomarker for patients with unresectable stage III non-small cell lung cancer treated with chemoradiotherapy followed by durvalumab. *Transl Cancer Res* 2023;12:705-8.

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**Figure S1** In the multivariable model, therapy strategy, programmed death-ligand status, and radiotherapy dose were independently correlated with TDDM among all patients. ECOG, Eastern Cooperative Oncology Group; PS, performance status; PD-L1, programmed death-ligand 1; HR, hazard ratio; CI, confidence interval; TDDM, time to death or distant metastasis.