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LETTER

Induction immunochemotherapy followed by definitive radiotherapy in patients with limited-stage small cell lung cancer: a multicenter study

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The standard treatment for limited-stage small cell lung cancer (LS-SCLC) is systemic chemotherapy with concurrent or sequential radiotherapy[1]. The recent ADRIATIC trial demonstrated that durvalumab, as a consolidation therapy, could significantly improve the overall survival (OS) (P = 0.01) and progression-free survival (PFS) (P = 0.02) in patients with LS-SCLC[2]. However, the results of the phase 3 NRG-LU005 trial showed that adding atezolizumab to chemoradiotherapy failed to improve survival in patients with LS-SCLC[3]. NRG-LU005 trial failure demonstrated that combining concurrent immunotherapy with radiotherapy for the treatment of LS-SCLC was not feasible. In addition to consolidation immunotherapy, induction immunochemotherapy followed by definitive chemoradiotherapy has emerged as a viable therapeutic modality that could help reprogram the immunosuppressive tumor microenvironment and amplify the effects of subsequent radiotherapy[4]. A retrospective real-world study to determine the efficacy and safety of induction immunochemotherapy followed by definitive radiotherapy in patients with LS-SCLC was conducted and patients with LS-SCLC were enrolled from four tertiary medical centers.

Patient characteristics

A total of 568 patients with LS-SCLC were enrolled from 4 tertiary medical centers between January 2020 and December 2024 (**Figure S1**). The patients were classified into immune-chemoradiotherapy (I-CRT) (n = 101) and chemoradiotherapy (CRT) groups (n = 467) according to the therapeutic strategy. In the I-CRT group 47 patients (46.5%) were <60 years of age and 63 (62.4%) had a history of smoking cigarettes. Most of the patients were male (80.2%) with an Eastern Cooperative Oncology Group (ECOG) score ≥1 (81.2%), diagnosed as T3–4 (54.5%), N2–3 (79.2%), and stage III (87.1%). Fifty-one patients (50.5%) underwent prophylactic cranial irradiation (PCI). In the CRT group 271 patients (58.0%) were ≥60 years and 266 patients (57.0%) had a history of smoking cigarettes. Most of the patients were male (72.8%) with an ECOG score ≥1 (83.3%), diagnosed as T1–2 (53.1%), N2–3 (82.0%), and stage III (85.7%). A total of 208 (44.5%) patients underwent PCI. Chi-square test analysis showed no statistically significant differences in the baseline characteristics between the two groups (**Table S1**).

After propensity score matching, a total of 382 patients were included in the matched cohort, which was comprised of 98 patients in the I-CRT group and 284 in the CRT group. Baseline and therapeutic characteristics were well-balanced between the two groups with all standardized mean differences (SMDs) <0.1. Inverse probability of treatment weighting (IPTW) was also applied to the original cohort as a complementary sensitivity analysis. All covariates remained well-balanced after weighting (SMDs <0.1; **Table S2**).

Efficacy

The results showed that patients in the I-CRT group had a better PFS (mPFS: 15.53 *vs.* 11.40 months; HR: 0.608, 95%

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CI: 0.468–0.790; $P < 0.001$) compared to patients in the CRT group (**Figure 1A**). The PFS rate was 58.1% in the I-CRT group and 44.2% in the CRT group at 12 months, and 41.1% and 21.3% at 24 months, respectively. Patients in the I-CRT group had a longer OS compared to patients in the CRT group (mOS: NR *vs.* 38.3 months; HR: 0.637, 95% CI: 0.442–0.917; $P = 0.029$; **Figure 1B**) based on the OS analysis. The OS rate was 92.6% and 92.1% at 12 months and 80.7% and 71.5% at 24 months in the I-CRT and CRT groups, respectively. I-CRT remained associated with a significantly lower risk of cancer-specific death (sub-distribution HR = 0.62, 95% CI 0.40–0.96, $P = 0.031$) based on the competing-risk analysis with non-cancer death as the competing event, which was consistent with the OS benefit observed in the primary Cox analysis. The cumulative incidence curves showed markedly lower cancer mortality in the I-CRT group, while non-cancer mortality was comparable between groups (**Figure S2**). Gray's test confirmed a statistically significant difference in cancer-specific mortality ($P = 0.031$). In addition, the interaction between treatment and ECOG performance status was not significant (HR for interaction = 0.811, 95% CI: 0.200–3.292, $P = 0.769$), indicating that the benefit of I-CRT was consistent in patients who had different levels of ECOG performance status.

A significant difference in the overall response rate (ORR) was detected, favoring the I-CRT group (80.6% *vs.* 69.4%). In contrast, the disease control rate (DCR) was comparable between the groups (94.9% *vs.* 95.1%; **Figure 1C, D**). Before definitive radiotherapy, the patients in the I-CRT group achieved a higher ORR than the patients in the CRT group (66.3% *vs.* 52.8%; **Figure S3**). The following subgroups exhibited significant OS benefits in the exploratory analyses of OS: age <60 years; T3–4 stage; N2–3 stage; concurrent chemoradiotherapy (CCRT); and twice-daily radiotherapy and etoposide + carboplatin (**Figure S4**). All subgroup analyses were exploratory and no adjustments were made for multiple comparisons.

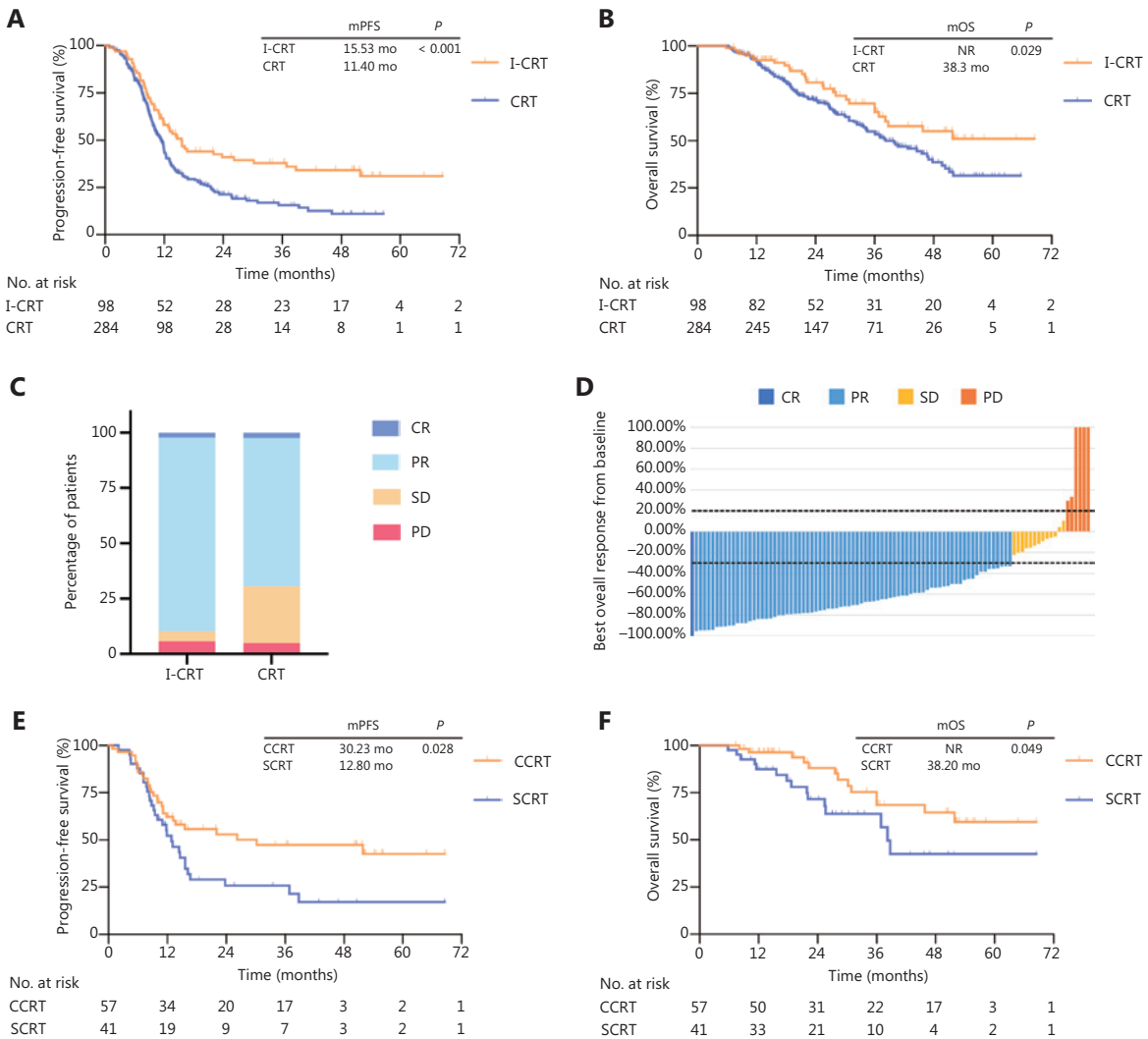

Figure 1 Continued

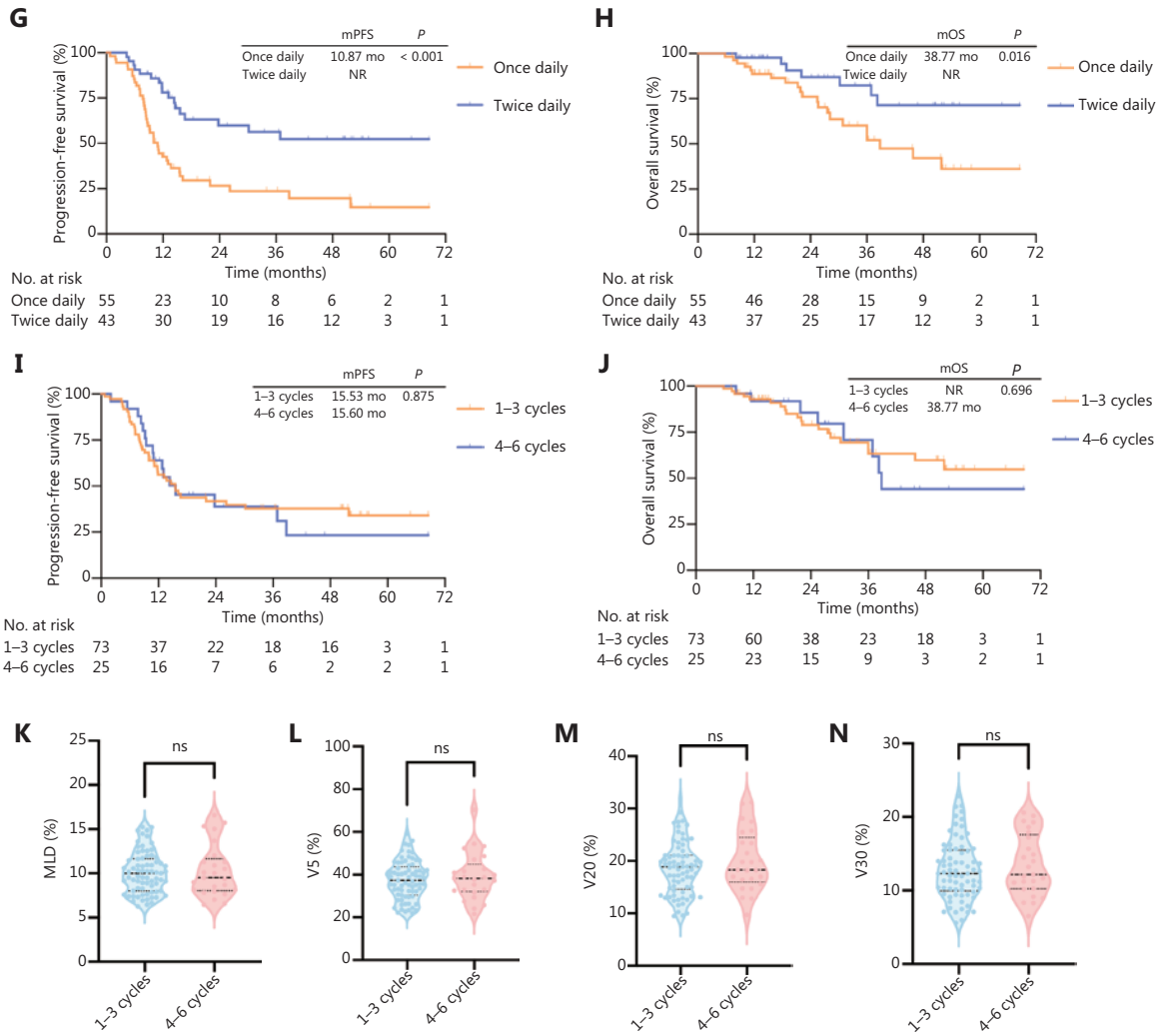

Figure 1 Efficacy of the induction immunochemotherapy followed by definitive radiotherapy and exploratory subgroup survival analysis. (A, B) PFS and OS of patients in the I-CRT and CRT groups. (C) Tumor response of patients in the I-CRT and CRT groups. (D) Waterfall plot of the best overall response from baseline in the I-CRT group. (E, F) PFS and OS of patients in the CCRT and SCRT groups. (G, H) PFS and OS of patients in the "once-daily" and "twice-daily" groups. (I, J) PFS and OS of patients in the "1–3 cycles" and "4–6 cycles" groups. (K–N) Dosimetric parameters of patients in the "1–3 cycles" and "4–6 cycles" groups, including MLD (K), V5 (L), V20 (M), and V30 (N). CCRT, concurrent chemoradiotherapy; MLD, mean lung dose; OS, overall survival; PFS, progression-free survival; SCRT, sequential chemoradiotherapy; V5, volume of lung parenchyma receiving ≥ 5 Gy; V20, volume of lung parenchyma receiving ≥ 20 Gy; V30, volume of lung parenchyma receiving ≥ 30 Gy.

Therefore, these findings should be interpreted with caution and viewed as hypothesis-generating. In addition, ECOG performance status (P = 0.012), treatment sequence (P = 0.019), and radiotherapy schedule (P < 0.001) were independent prognostic factors for PFS. ECOG performance status (P = 0.034) and radiotherapy schedule (P = 0.013) were independent prognostic factors for OS (**Table S3**).

Safety

The overall incidences of adverse events (AEs) were 96.9% and 98.6% in the I-CRT and CRT groups, respectively. Sixty-three patients (64.3%) in the I-CRT group had grade ≥3 AEs. The most common grade ≥3 AEs were neutropenia (58.2%), leucopenia (29.6%), pneumonia (10.2%), and thrombocytopenia (8.2%). A total of 168 patients (59.2%) in the CRT group had grade ≥3 AEs. The most common grade ≥3 AEs were neutropenia (50.7%), leucopenia (30.6%), thrombocytopenia (6.0%), and pneumonia (5.6%). Notably, patients in the I-CRT group had a higher incidence of pneumonia (48.0% *vs.* 39.4%) and grade ≥3 pneumonia (10.2% *vs.* 5.6%) than patients in the CRT group (**Table 1**). Although the inclusion of immunotherapy was associated with a higher rate of AEs, these AEs were largely hematologic. Notably, no grade 5 AEs were recorded, indicating that the overall safety profile remained manageable.

Table 1 Adverse events

	No. (%) of patients in the I-CRT group (n = 98)		No. (%) of patients in the CRT group (n = 284)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any adverse event of any cause	95 (96.9)	63 (64.3)	280 (98.6)	168 (59.2)
Nausea/vomiting	46 (46.9)	2 (2.0)	190 (66.9)	2 (0.7)
Leucopenia	86 (87.8)	29 (29.6)	259 (91.2)	87 (30.6)
Neutropenia	78 (79.6)	57 (58.2)	256 (90.1)	144 (50.7)
Thrombocytopenia	29 (29.6)	8 (8.2)	87 (30.6)	17 (6.0)
Rash	9 (9.2)	0	18 (6.3)	0
Elevated ALT/AST	30 (30.6)	0	102 (35.9)	1 (0.4)
Esophagitis	42 (42.9)	1 (1.0)	138 (48.6)	0
Pneumonia	47 (48.0)	10 (10.2)	112 (39.4)	16 (5.6)

The incidence of immune-related adverse events (irAEs) is presented in **Table S4**. Survival analysis showed that PFS (P = 0.659) and OS (P = 0.826) were comparable between patients who did and did not develop irAEs (**Figure S5A, B**).

Exploratory subgroup efficacy and safety analysis

Patients were classified into CCRT and sequential chemoradiotherapy (SCRT) groups based on the treatment sequence. Patients in the CCRT group had a better PFS (mPFS: 30.23 *vs.* 12.80 months, HR: 0.568, 95% CI: 0.343–0.966, P = 0.028) and OS (mOS: NR *vs.* 38.20 months, HR: 0.487, 95% CI: 0.225–0.973, P = 0.049) than patients in the SCRT group (**Figure 1E, F**). The incidences of AEs (100% *vs.* 92.7%) and grade ≥3 AEs (64.9% *vs.* 63.4%) were comparable between the two patient groups (**Figure S6A**). Patients were classified into "once daily" and "twice daily" groups according to the radiotherapy pattern. Patients in the "twice daily" group had a better PFS (mPFS: NR *vs.* 10.87 months, HR: 0.353, 95% CI: 0.211–0.592, P < 0.001) and a superior OS (mOS: NR *vs.* 38.77 months, HR: 0.367, 95% CI: 0.175–0.771, P = 0.016) compared to patients in the "once daily" group (**Figure 1G, H**). In addition, the incidences of AEs (97.7% *vs.* 96.4%) and grade ≥3 AEs (67.4% *vs.* 61.8%) were comparable between the two patient groups (**Figure S6B**). The treatment regimens are shown in **Table S5**. Patients were classified into "anti-PD-1" and "anti-PD-L1" groups according to the immunotherapy regimens. In addition, the distribution of immunotherapy agents is summarized in **Table S6**. No significant differences in PFS or OS were detected between patients stratified by immunotherapy regimens (**Figure S5C, D**).

Determination of the optimal induction cycles

Patients were classified into "1–3 cycles" and "4–6 cycles" to determine the best induction treatment cycles. These two groups exhibited no significant difference in PFS (mPFS: 15.53 *vs.* 15.60 months, HR: 0.955, 95% CI: 0.534–1.709, P = 0.875) and OS (mOS: NR *vs.* 38.77 months, HR = 0.850, 95% CI: 0.363–1.991, P = 0.696; **Figure 1I, J**). However, *post-hoc* power analysis revealed that this subgroup comparison was substantially underpowered. The study had 21.9% power to detect a clinically meaningful hazard ratio of 0.70 for PFS and 12.8% for OS based on 58 PFS and 28 OS events. Therefore, the lack of statistically significant survival differences should be interpreted with caution because survival differences may stem from insufficient statistical power rather than true equivalence. The incidence of AEs and grade ≥3 AEs were 95.9% and 63.5% in the "1–3 cycles" group, and 96.0% and 64.0% in the "4–6 cycles" group, respectively. Notably, a significant increase in the incidence of pneumonia (60.0% *vs.* 43.2%) and grade ≥3 pneumonia (20.0% *vs.* 6.8%) occurred in patients receiving 4–6 cycles of induction treatment (**Figure S6C**). The dosimetric parameters of patients receiving induction immunochemotherapy were then collected. There were no significant differences in the mean lung dose (P = 0.961), V5 (P = 0.746), V20 (P = 0.418), or V30 (P = 0.571) between the two patient groups (**Figure 1K–N**). These findings indicated that the increase in pneumonia incidence was attributable to the extended duration of immunotherapy rather than variations in radiotherapy dose distribution.

The contrasting outcomes of the ADRIATIC and NRG-LU005 trials underscore the pivotal impact of therapeutic sequence on the efficacy of combined radiotherapy and

immunotherapy[2,3]. The NRG-LU005 trial protocol specified target delineation based on pre-chemotherapy CT imaging, which did not account for potential tumor reduction after induction therapy. Therefore, the irradiated volumes may not have adapted to the tumor size after induction therapy, thereby encompassing more normal lung tissue and potentially explaining the higher incidence of pneumonia. AEs led to immunotherapy discontinuation in 25.6% of patients in the PACIFIC-2 trial, which may partly explain failure to demonstrate a survival benefit[5]. Integrating concurrent immunotherapy in the CheckMate 73L trial also caused increased toxicity[6]. In contrast to combining immunotherapy with chemoradiotherapy, induction immunochemotherapy prior to definitive radiotherapy can reduce the tumor volume, thereby facilitating a smaller and more precise radiation target volume. In addition, sequential administration of immunotherapy and radiotherapy is associated with lower toxicity and improved patient tolerance. Furthermore, induction therapy helps avoid the potential attenuation of immunotherapeutic efficacy by radiotherapy, allowing full utilization of the immune microenvironment that has not been compromised by radiation[7]. An interesting observation in our study was the lower incidence of nausea and vomiting in the I-CRT group compared to the CRT group, despite the addition of immunotherapy. This finding may be explained by several factors: more aggressive antiemetic prophylaxis; the relatively low emetogenic potential of immunotherapy; and potential underreporting of mild symptoms in the I-CRT group due to the retrospective study design.

Induction immunochemotherapy can extend the benefits of immunotherapy to a broader patient population by utilizing an intact immune system that is not diminished by CRT[7,8]. Induction immunochemotherapy serves to reprogram the immunosuppressive tumor microenvironment, thereby potentiating the efficacy of subsequent radiotherapy[4]. In addition, preclinical findings have indicated that immune activation potently enhances immune surveillance, which leads to more effective control of micro-metastatic disease[9]. Wu et al.[7] concluded that induction immunochemotherapy followed by definitive CRT is feasible for patients with unresectable locally advanced non-small cell lung cancer (NSCLC) with tolerable toxicities. In the current study the I-CRT group had a significantly improved PFS ($P < 0.001$) and OS ($P = 0.029$) with a higher ORR and comparable DCR compared to the CRT group. Notably, a phase II open-label trial (ChiCTR2000032275) showed that induction camrelizumab plus chemotherapy followed by chemoradiotherapy significantly improved survival outcomes compared to CCRT alone, demonstrating a higher 1-year PFS rate and prolonged median PFS ($P = 0.047$). This benefit was accompanied by a 100% 1-year OS rate and a significantly improved median OS ($P = 0.044$)[10]. Excessively prolonging induction immunotherapy cycles does not confer a further survival advantage and may even compromise efficacy by promoting disease progression and exacerbating AEs.[11]. In the current study no significant difference in prognosis was observed between patients receiving 1–3 *vs.* 4–6 cycles of induction immunochemotherapy. Moreover, treatment extension was associated with a higher incidence of all-grade and grade ≥3 pneumonia.

This study had several limitations. First, the retrospective design inherently carries the potential for selection bias and residual confounding, despite our use of propensity score matching (PSM) and IPTW to adjust for measured covariates. Large-scale, prospective studies are warranted to validate our findings. In addition, although the primary analyses were adequately powered, the subgroup comparison of different induction cycles (1–3 cycles *vs.* 4–6 cycles) was substantially underpowered. *Post-hoc* analysis revealed only 21.9% and 12.8% power to detect a clinically meaningful HR of 0.70 for PFS and OS, respectively. Therefore, this specific negative finding should be interpreted with caution because the finding may reflect a false negative rather than true equivalence.

Collectively, the results indicate that induction immunochemotherapy followed by definitive radiotherapy significantly improved the survival of patients with LS-SCLC. Concurrently, the incidence of AEs and grade ≥3 AEs was comparable to standard chemoradiotherapy. A subsequent analysis identified 1–3 cycles as the optimal number of cycles for induction immunochemotherapy. The findings herein support the use of induction immunochemotherapy followed by definitive radiotherapy as a therapeutic strategy. Further validation using larger prospective clinical trials is warranted.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Zhaoqin Huang, Yu Chen, and Xiangjiao Meng
Collected the data: Junxu Wen, Qian Wang, Shanshan Li, and Heng Zhao

Contributed data or analysis tools: Xinrui Yu, Yang Liu, and Xiaoyan Yin
Performed the analysis: Junxu Wen and Qian Wang
Wrote the paper: Junxu Wen and Qian Wang.

Data availability statement

The data generated in this study are available upon request from the corresponding authors.

References

1. Zhao H, Qi Y, Zhang L, Xing M, Yang F. Thoracic radiotherapy timing and prognostic factors in elderly patients with limited-stage small cell lung cancer. Precis Radiat Oncol. 2024; 8: 14-21.
2. Cheng Y, Spigel DR, Cho BC, Laktionov KK, Fang J, Chen Y, et al. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. N Engl J Med. 2024; 391: 1313-27.
3. Higgins K, Hu C, Ross HJ, Jabbour SK, Kozono DE, Owonikoko TK, et al. Concurrent chemoradiation ± atezolizumab (atezo) in limited-stage small cell lung cancer (LS-SCLC): results of NRG oncology/alliance LU005. Int J Radiat Oncol Biol Phys. 2024; 120: S2.
4. Ngwa W, Irabor OC, Schoenfeld JD, Hesser J, Demaria S, Formenti SC. Using immunotherapy to boost the abscopal effect. Nat Rev Cancer. 2018; 18: 313-22.
5. Bradley JD, Sugawara S, Lee KH, Ostoros G, Demirkazik A, Zemanova M, et al. Simultaneous durvalumab and platinum-based chemoradiotherapy in unresectable stage III non-small cell lung cancer: the phase III PACIFIC-2 study. J Clin Oncol. 2025; 43: 3610-21.
6. Peters S, Tan DSW, Gerber DE, Urbanic J, Ramalingam SS, Yu J, et al. 65O CheckMate 73L: Phase III study comparing nivolumab (N) + concurrent chemoradiotherapy (CCRT) followed by N ± ipilimumab (I) v CCRT followed by durvalumab (D) for previously untreated, locally advanced stage (stg) III NSCLC. Immunooncol Technol. 2024; 24: 100808.
7. Wu L, Yan Y, Xu Y. Induction immunochemotherapy followed by definitive chemoradiotherapy for unresectable locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2023; 117: e75.
8. Zhang Z, Liu X, Chen D, Yu J. Radiotherapy combined with immunotherapy: the dawn of cancer treatment. Signal Transduct Target Ther. 2022; 7: 258.
9. Liu J, Blake SJ, Yong MC, Harjunpää H, Ngiow SF, Takeda K, et al. Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. Cancer Discov. 2016; 6: 1382-99.
10. Liu D, Hu M, Yang L, Ni J, Xu Y. PT2.13.01 A phase II trial of induction camrelizumab plus chemotherapy followed by chemoradiotherapy and consolidation in limited-stage SCLC. J Thorac Oncol. 2025; 20: S615.
11. Guan S, Wang Y, Liu Q, Yan M, Ren K, Wang J, et al. Induction chemoimmunotherapy may achieve non-inferior outcomes to consolidation immunotherapy in patients with unresectable stage III NSCLC: a real-world multicenter retrospective study. Front Immunol. 2025; 16: 1591134.

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