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RESEARCH

Comparison of neoadjuvant chemoimmunotherapy with planned surgery and concurrent chemoradiation followed by immunotherapy for potentially resectable stage III non-small-cell lung cancer: a retrospective study

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Abstract

Objective Despite the promising potential of neoadjuvant chemoimmunotherapy for non-small cell lung cancer (NSCLC), there is limited consensus on the optimal treatment strategy for potentially resectable NSCLC. This study aimed to evaluate the efficacy and safety of neoadjuvant chemoimmunotherapy (neoCT/IO) with planned surgery versus definitive concurrent chemoradiation followed by immunotherapy (cCRT + IO) in potentially resectable stage III NSCLC.

Methods This retrospective study analyzed data from patients with potentially resectable stage III NSCLC who underwent neoCT/IO with planned surgery or cCRT + IO between March 2020 and June 2023. Propensity score matching (PSM) was used to balance heterogeneity between groups. Efficacy outcomes, safety profiles and patterns of disease recurrence were assessed.

Results A total of 308 eligible patients were included in this study, of whom 195 (63.3%) underwent neoCT/IO and 113 (36.7%) received cCRT + IO. The neoCT/IO group consisted of patients who underwent neoCT/IO + Surgery and neoCT/IO + Radiotherapy. After 1:1 PSM, each group consisted of 105 patients. The median progression-free survival (PFS) was 25.9 months in the cCRT + IO group and not reached (NR) in the neoCT/IO group (hazard ratio: 2.91, 95% confidence interval: 1.77–4.78; $p < 0.001$). Median overall survival (OS) was NR in either group, with 3-year OS rates of 87.5% in the neoCT/IO group and 75.0% in the cCRT + IO group ($p = 0.22$). The incidence of grade 3/4 treatment-related adverse events was similar in both groups, except for a higher incidence of grade 3/4 hematological toxicity in the cCRT + IO group.

Conclusions For patients with potentially resectable stage III NSCLC, neoCT/IO appears to be a safe approach and may offer better survival outcomes compared with cCRT + IO. Prospective randomized trials are needed to further validate these findings.

Keywords Potentially resectable NSCLC · Induction chemoimmunotherapy · Concurrent chemoradiation · Survival · Safety profile

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Introduction

Stage III non-small cell lung cancer (NSCLC) is a locally advanced disease that accounts for approximately 30% of NSCLC cases [1]. Notably, patients with stage III NSCLC exhibit significant heterogeneity and can be classified as resectable, potentially resectable or unresectable. Recent advancements in cancer immunotherapy have significantly improved the prognosis for locally advanced NSCLC. For patients with resectable stage III NSCLC, neoadjuvant chemoimmunotherapy has proved effective and feasible in reducing tumor size, increasing the R0 resection rate and improving survival. Recent results from the phase III clinical trial CheckMate 816 demonstrated that neoadjuvant nivolumab in combination with chemotherapy followed by surgery in patients with resectable stage IIIA NSCLC significantly improves event-free survival (EFS; 31.6 months vs. 15.7 months) and complete pathological response (pCR; 23.0% vs. 0.9%) compared with neoadjuvant chemotherapy alone [2]. Data from the phase II randomized controlled trials NADIM [3] and KEYNOTE-671 [4] further support the benefits of neoadjuvant immunotherapy combined with chemotherapy followed by surgery in patients with resectable stage III NSCLC. For patients with more advanced, unresectable stage III NSCLC, concurrent chemoradiotherapy (cCRT) followed by immune checkpoint inhibitor (ICI) consolidation is the standard treatment, as evidenced by findings from the PACIFIC and GEMSTONE-301 trials [5–7]. Recently, given the benefits of neoadjuvant immunotherapy in improving oncological resectability in resectable disease, many studies have demonstrated that neoadjuvant chemoimmunotherapy can be used for initially unresectable cases, leading to downstaging from unresectable to resectable disease. In a phase II trial conducted by Wu et al., surgical conversion after neoadjuvant chemoimmunotherapy was feasible in 25% of patients with unresectable disease, with all resected patients achieving R0 resection and 26% showing pCR. Moreover, the surgical conversion could translate into survival benefits as evidenced by a prolonged EFS in patients who underwent resection compared to those who received radiotherapy [8]. Similarly, another study by He et al. supported that surgical conversion following neoadjuvant chemoimmunotherapy is safe and associated with longer progression-free survival (PFS) in patients with initially unresectable stage IIIB NSCLC [9].

Despite advancements in novel therapeutics, the optimal treatment modality for patients with potentially resectable stage III NSCLC remains controversial. Generally, the most effective treatment regimen is multimodal, incorporating both systemic and local therapies to control distant and local disease. However, the ideal combination and sequencing of these treatments are still uncertain, requiring careful evaluation by an experienced multidisciplinary team (MDT) to select the most appropriate strategy [10, 11]. In the pre-immunotherapy era, previous studies reported comparable 5-year overall survival (OS) and PFS rates between patients who underwent surgery and those who received cCRT for potentially resectable stage IIIA-B NSCLC [12, 13]. Nevertheless, the impact of integrating immunotherapy into these two multimodal treatment strategies on long-term survival outcomes in this population has not been thoroughly investigated. Therefore, we conducted a retrospective, propensity score-matched study to directly compare the clinical efficacy and safety profiles of these treatment modalities, aiming to identify the best treatment options for patients with potentially resectable stage III NSCLC.

Materials and methods

Study design and patient selection

Patients with potentially resectable stage III NSCLC who received either neoadjuvant chemotherapy and immunotherapy (neoCT/IO) with planned surgery or cCRT followed by immunotherapy (cCRT + IO) between March 2020 and June 2023 at Shandong Cancer Hospital and Institute were recruited for this study (Fig. 1). Potentially resectable disease was evaluated by an MDT including thoracic surgeons, radiation oncologists and radiologists according to the National Comprehensive Cancer Network (NCCN) [14] and Chinese Society of Clinical Oncology (CSCO) guidelines for NSCLC, which was defined as the patients with stage III NSCLC who were deemed unsuitable for complete (R0) resection upon initial diagnosis and have the potential to reduce tumor size, decrease surgical risk, achieve conversion to surgical resectability or convert metastatic lymph nodes to achieve a downgraded N stage after neoadjuvant therapy. To determine the subsequent treatment modality, all patients were assessed by an MDT with further consideration of patients' operability status and surgical intention. Patients who reach the surgical resection criteria but experience intolerable comorbidities (e.g., vascular, renal, heart, diabetes) and exhibit poor lung functions were included in the cCRT + IO group. Similarly, those who were recommended but refused surgical resection and underwent chemoradiation instead were also included in the cCRT + IO cohort. The neoCT/IO cohort included patients who underwent neoadjuvant chemotherapy and immunotherapy followed by surgical resection (neoCT/IO + Surgery) or radiotherapy-based salvage treatment (neoCT/IO + Radiotherapy), while the

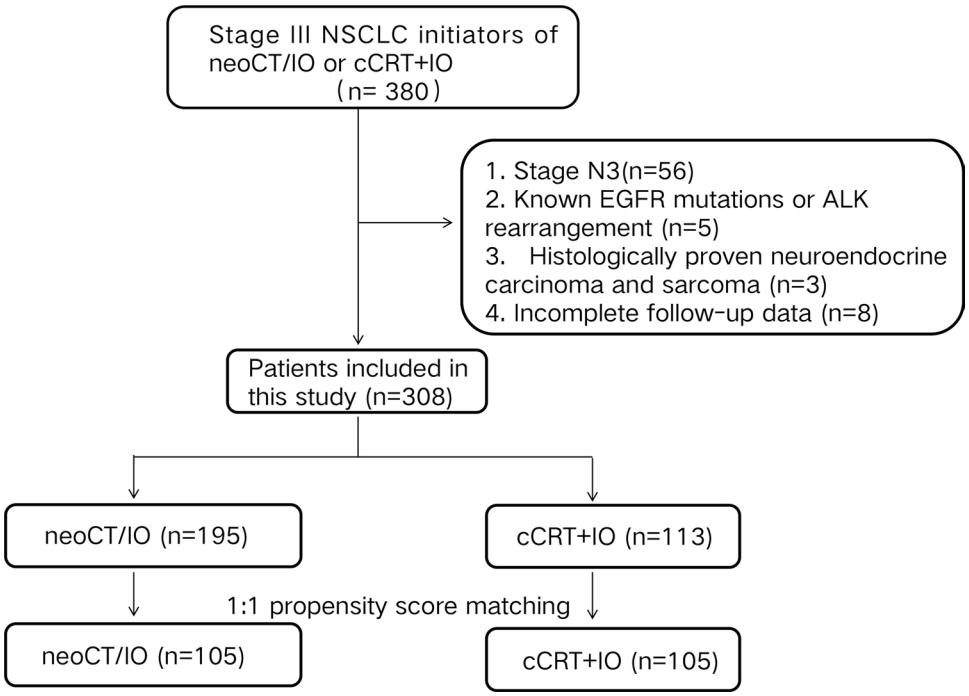


Fig. 1 Patient selection flowchart. Abbreviations: EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase

cCRT + IO cohort consisted of patients who received concurrent chemotherapy and radiation, followed by consolidation immunotherapy. The inclusion criteria were as follows: (1) histologically confirmed, potentially resectable NSCLC clinically staged as T1-4N1-2M0 (stage IIIA–IIIB) prior to treatment according to UICC/AJCC staging standards (8th edition); (2) age ≥ 18 years; and (3) treatment with neoCT/IO or cCRT + IO. The exclusion criteria were as follows: (1) N3 stage patients with unresectable disease; (2) stage III patients with resectable disease; (3) patients with mutant driver genes, such as epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements; (4) histologically proven neuroendocrine carcinoma or sarcoma; and (5) missing treatment or survival data.

For initial evaluation and staging, enhanced chest computed tomography (CT) scan, brain MRI, bone scanning and abdominal CT were routinely performed. Positron emission tomography–CT (PET/CT) was performed on patients with bulky mediastinal mass. Fiberoptic bronchoscopy or subcutaneous needle biopsy was conducted for histological and driver mutation examination. After induction immune-chemotherapy, candidates for subsequent operation should have confirmed lymph node downstaging assessed by enhanced chest CT scan or PET/CT and with (1) no bulky mediastinal mass; (2) no sign of direct tumor invasion to great vessels, diaphragm, heart, trachea and carina (to ensure complete resection of tumor); and (3) no progression and distant metastasis. The resectability was redeemed by an expert group of thoracic surgeons, oncologists and radiologists.

Study outcomes

Demographic characteristics and therapeutic data, including age, sex, smoking history, Karnofsky Performance Status (KPS), histological subtypes, clinical stage, T and N stages and disease progression, were extracted from the electronic medical record system. OS (time from pathological diagnosis to death or last follow-up) and PFS (time from pathological diagnosis to disease progression determined by imaging CT/PET-CT/biopsies or death from any cause) were analyzed. Patient follow-up was conducted every 3 months during the first 2 years post-surgery and every 6 months thereafter until either disease recurrence or the follow-up cutoff. Adverse events (AEs) were documented and graded according to the Common Terminology Criteria for Adverse Events (version 5.0).

Statistical analysis

The Chi-square test or Fisher's exact test was used to compare categorical variables between the groups, with results presented as frequencies and percentages. Survival probabilities were calculated using the Kaplan–Meier method and compared using the log-rank test. One-to-one propensity score matching (PSM) with a caliper of 0.05 was performed to minimize confounding further. Propensity scores were

calculated based on age, sex, histology, smoking history, KPS score and clinical T and N stages. Subgroup analyses for PFS and OS were performed to assess the consistency of treatment effects across patient subgroups. These analyses used an unstratified Cox proportional hazards model with treatment as a covariate. A *p*-value of less than 0.05 was considered statistically significant. Statistical analysis and graphing were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

A total of 308 eligible patients were included in this study. Of these patients, 195 (63.3%) underwent neoCT/IO and 113 (36.7%) underwent cCRT + IO. Prior to matching, no significant differences were observed between the two groups regarding age, sex, histological subtype, smoking history and N stage. However, the cCRT + IO group exhibited a higher prevalence of patients with KPS of 80, T4 stage and stage IIIB disease. After PSM, all baseline characteristics were well balanced, with no significant differences between the two groups. Each matched group comprised 105 patients. The baseline demographic and clinical characteristics of the patients are summarized in Table 1.

Treatment

Patients were classified into two groups based on their treatment modality: the cCRT + IO group and the neoCT/IO group. In the cCRT + IO group, all patients received cCRT with a median of four cycles of platinum-based doublet chemotherapy and a median radiotherapy dose of 60 Gy (range: 54–66). Following this, all patients underwent immunotherapy consolidation until disease progression or intolerable treatment-related adverse events.

In the neoCT/IO cohort, all patients received a median of two cycles of neoadjuvant chemoimmunotherapy, which included the ICIs atezolizumab, camrelizumab, nivolumab, sintilimab, tislelizumab and toripalimab. Following the completion of neoadjuvant chemoimmunotherapy, 152 of the

Table 1 Baseline demographic and clinical characteristics of the patients

Subgroup	Before PSM		*P*	After PSM		*P*
	neoCT/IO (*n* = 195)	(*n* = 113) cCRT + IO		neoCT/IO (*n* = 105)	cCRT + IO (*n* = 105)	
Age	62.58 ± 7.59	63.84 ± 7.73	0.166	61.86 ± 7.46	63.73 ± 7.78	0.076
Sex, n (%)			0.132			0.139
Male	175 (89.74)	107 (94.69)		93 (88.57)	99 (94.29)	
Female	20 (10.26)	6 (5.31)		12 (11.43)	6 (5.71)	
Histology, *n* (%)			0.293			0.084
Squamous	145 (74.36)	90 (79.65)		72 (68.57)	83 (79.05)	
Adenocarcinoma	50 (25.64)	23 (20.35)		33 (31.43)	22 (20.95)	
KPS score, *n* (%)			0.065			1.000
80	56 (28.72)	44 (38.94)		39 (34.29)	36 (34.29)	
90	139 (71.28)	69 (61.06)		69 (65.71)	56 (65.71)	
Smoking history,*n* (%)			0.969			0.886
Never	66 (33.85)	38 (33.63)		39 (37.14)	38 (36.19)	
Ever	129 (66.15)	75 (66.37)		66 (62.86)	67 (63.81)	
TNM stage, *n* (%)			0.017			1.000
IIIA	144 (73.85)	68 (60.71)		66 (62.86)	66 (62.86)	
IIIB	51 (26.15)	44 (39.29)		39 (37.14)	39 (37.14)	
T stage, *n* (%)			0.075			1.000
1	10 (5.13)	10 (8.85)		8 (7.62)	8 (7.62)	
2	68 (34.87)	25 (22.12)		25 (23.81)	25 (23.81)	
3	47 (24.10)	23 (20.35)		22 (20.95)	22 (20.95)	
4	70 (35.90)	55 (48.67)		50 (47.62)	50 (47.62)	
N stage, *n* (%)			0.312			0.614
0	28 (14.36)	9 (7.96)		20 (19.05)	9 (8.57)	
1	37 (18.97)	24 (21.24)		13 (12.38)	24 (22.86)	
2	130 (66.67)	80 (70.80)		72 (68.57)	72 (68.57)	

195 (77.9%) patients were considered suitable for surgery. Two patients refused surgery at their own discretion, and the other 150 patients ultimately underwent surgery, yielding a conversion rate of 77.9% and resection rate of 76.9%. In the CT/IO + Surgery cohort, 9 patients (6%) underwent pneumonectomy, 131 patients (87.3%) underwent lobectomy and 10 patients (6.7%) underwent sleeve lobectomy combined with routine mediastinal lymphadenectomy. The median interval to surgery was 36 days from the last dose of chemoimmunotherapy, and complete R0 resection was achieved in all 150 patients. Postoperative pathological assessments revealed that 89 patients (59.3%) attained major pathological response (MPR), including 61 patients (40.7%) who achieved pathological complete response (pCR). The other 45 patients who did not reach the surgical resection criteria or refused surgery were included in the neoCT/IO + Radiotherapy cohort and received a radiotherapy-based salvage treatment with a median radiotherapy dose of 60 Gy (range: 50–66).

Efficacy

As of the data cutoff date in August 2024, the median follow-up duration was 28.3 months (95% confidence interval [CI]: 26.3–30.3) for the neoCT/IO cohort and 29.8 months (95% CI: 28.4–31.2) for the cCRT + IO cohort.

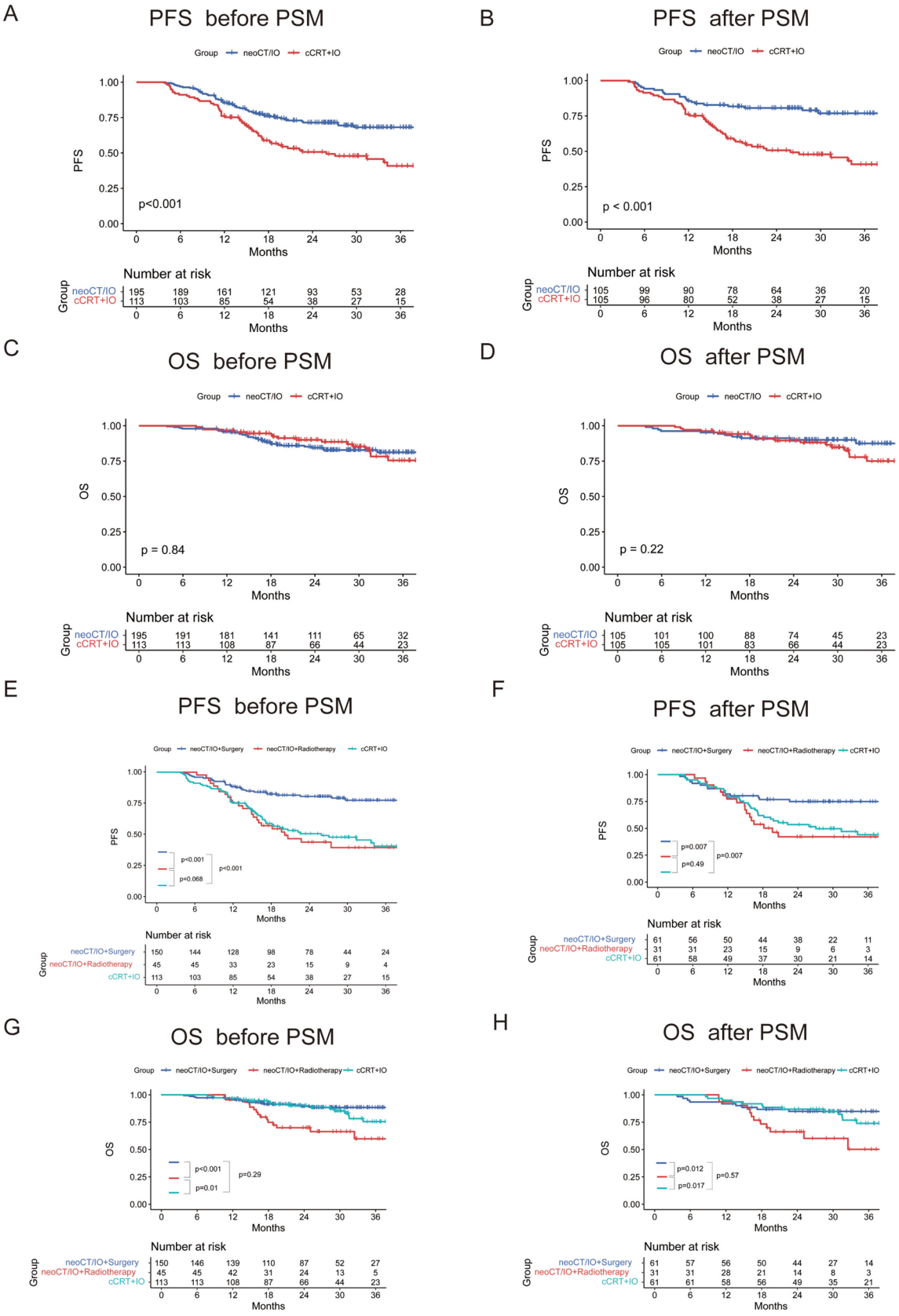
Before PSM, patients receiving cCRT + IO demonstrated a significantly shorter median PFS of 25.9 months (95% CI: 14.1–37.7) compared with those undergoing neoCT/IO (not reached [NR], 95% CI: NR-NR; hazard ratio [HR]; 2.05, 95% CI: 1.41–2.98, $p < 0.001$, Fig. 2A). At the 2-year mark, the PFS rate was 71.5% in the neoCT/IO group, while it was 50.7% in the cCRT + IO group. At 3 years, the PFS rates were 68.2% and 40.8% in the two groups, respectively. After 1:1 PSM, similar results were observed in the matched population, with a median PFS of 25.9 months in the cCRT + IO group and NR in the neoCT/IO group (HR 2.91, 95%CI: 1.77–4.78; $p < 0.001$, see Fig. 2B). The 2- and 3-year PFS rates in the neoCT/IO and cCRT + IO groups were 80.6% versus 50.7% and 76.9% versus 40.8%, respectively. Univariate and multivariate Cox regression analyses further validated that neoCT/IO was associated with improved PFS compared with cCRT + IO before and after PSM ($p < 0.001$) (Tables 2 and 3). The median OS was NR in either cohort, with a 3-year OS rate of 81.2% in the neoCT/IO group compared with 75.5% in the cCRT + IO group ($p = 0.84$, Fig. 2C). After PSM, OS was also not significantly different between the two groups (HR: 1.61, 95% CI: 0.75–3.43, $p = 0.22$, Fig. 2D). The 3-year OS rates were 87.5% in the neoCT/IO group and 75.0% in the cCRT + IO group. Furthermore, a same PSM method was utilized in the neoCT/IO + Surgery, neoCT/IO + Radiotherapy and cCRT + IO groups, which included 61, 31 and 61 patients, respectively, in a ratio of 2:1:2. The PFS and OS were compared among three groups. Notably, the neoCT/IO + Surgery group exhibited significantly prolonged PFS and OS than neoCT/IO + Radiotherapy groups before and after PSM. In comparison with cCRT + IO patients, the benefits of neoCT/IO + Surgery for PFS were pronounced. However, no significant difference in OS was observed between the two groups (Fig. 2E–H). To further identify the potential population that may benefit from neoCT/IO or cCRT + IO, we conducted a subgroup analysis of PFS and OS within a matched population (Fig. 3). In the subgroup of 107 patients aged < 65 years, PFS was significantly longer in the neoCT/IO group compared with the cCRT + IO group (median PFS: NR vs. 20.6 months, $p < 0.001$, Fig. 4A). There was a similar trend toward longer OS in the neoCT/IO group compared with the cCRT + IO group ($p = 0.021$, Fig. 4B). In the subgroup of 155 patients with squamous histology, PFS was also longer in the neoCT/IO group compared with the cCRT + IO group (median PFS: NR vs. 25.9 months, $p < 0.001$, Fig. 4C). However, no significant difference in OS was observed between the neoCT/IO and cCRT + IO groups ($p = 0.34$, Fig. 4D). Similar PFS and OS results were observed in the subgroup of patients with clinical stage IIIA disease (median PFS: NR vs 27.1 months, $p < 0.001$, Fig. 4E and F).

Patterns of disease recurrence

As of the cutoff date, progressive disease was identified in 29 patients (19.3%) in the neoCT/IO + Surgery group, 25 patients (55.6%) in the neoCT/IO + Radiotherapy group and 57 patients (50.4%) in the cCRT + IO group in the whole population. Regarding the pattern of relapse, six patients in the neoCT/IO + Surgery group, two patients in the neoCT/IO + Radiotherapy group and one patient in the cCRT + IO group exhibited unclear relapse patterns. After excluding these patients, no significant difference was observed in the sites of first recurrence between the three groups. However, the rate of local relapse rate in the neoCT/IO + Surgery group (21.7%) was lower than that in the neoCT/IO + Radiotherapy group (87.0%) and cCRT + IO group (62.5%), particularly at the primary tumor site (8.6% vs. 73.9% vs. 48.2%, Table 4).

Adverse events

Treatment-related AEs (TRAEs) occurred in 140 patients (93.3%) in the neoCT/IO + Surgery group, 40 patients (88.9%) in the neoCT/IO + Radiotherapy group and 113 patients (100.0%) in the cCRT + IO group, with no grade 5 TRAEs reported. Hematological toxicity was the most frequently observed TRAE in all groups. The incidence of grade 3/4 hematological toxicity was significantly higher in the cCRT + IO group compared with the neoCT/


A
PFS before PSM
Group neoCT/IO cCRT+IO
PFS
p<0.001
Months
Number at risk
neoCT/IO 195 189 161 121 93 53 28
cCRT+IO 113 103 85 54 38 27 15
B
PFS after PSM
p < 0.001
neoCT/IO 105 99 90 78 64 36 20
cCRT+IO 105 96 80 52 38 27 15
C
OS before PSM
OS
p = 0.84
neoCT/IO 195 191 181 141 111 65 32
cCRT+IO 113 113 108 87 66 44 23
D
OS after PSM
p = 0.22
neoCT/IO 105 101 100 88 74 45 23
cCRT+IO 105 105 101 83 66 44 23
E
PFS before PSM
Group neoCT/IO+Surgery neoCT/IO+Radiotherapy cCRT+IO
p<0.001
p=0.068
p<0.001
neoCT/IO+Surgery 150 144 128 98 78 44 24
neoCT/IO+Radiotherapy 45 45 33 23 15 9 4
cCRT+IO 113 103 85 54 38 27 15
F
PFS after PSM
p=0.007
p=0.49
p=0.007
neoCT/IO+Surgery 61 56 50 44 38 22 11
neoCT/IO+Radiotherapy 31 31 23 15 9 6 3
cCRT+IO 61 58 49 37 30 21 14
G
OS before PSM
p<0.001
p=0.01
p=0.29
neoCT/IO+Surgery 150 146 139 110 87 52 27
neoCT/IO+Radiotherapy 45 45 42 31 24 13 5
cCRT+IO 113 113 108 87 66 44 23
H
OS after PSM
p=0.012
p=0.017
p=0.57
neoCT/IO+Surgery 61 57 56 50 44 27 14
neoCT/IO+Radiotherapy 31 31 28 21 14 8 3
cCRT+IO 61 61 58 56 49 35 21

◂**Fig. 2** PFS and OS between the neoCT/IO and cCRT + IO groups before and after PSM(A-D). A. PFS before PSM. B. PFS after PSM. C. OS before PSM. D. OS after PSM. PFS and OS among neoCT/IO + Surgery, neoCT/IO + Radiotherapy and cCRT + IO groups before and after PSM (E–H). E. PFS before PSM. F. PFS after PSM. G. OS before PSM. H. OS after PSM. Abbreviations: PFS, progression-free survival; OS, overall survival; PSM, propensity score matching

IO + Radiotherapy and neoCT/IO + Surgery group, with rates of 38.9%, 20.0% and 10.7%, respectively (Table 5). The incidence of other grade 3/4 TRAEs did not differ significantly between the three groups.

Discussion

Despite the significant improvements in survival associated with immunotherapy in combination with surgery or CRT, the debate over the optimal treatment for stage III NSCLC persists due to its heterogeneity. In this retrospective study, we evaluated the efficacy and safety of neoadjuvant chemoimmunotherapy (neoCT/IO) with planned surgery compared with concurrent chemoradiotherapy followed by immunotherapy (cCRT + IO) in patients with potentially resectable stage III NSCLC. After adjusting for potential confounding factors, patients in the neoCT/IO group with planned surgery exhibited no statistically significant improvement in OS despite a significantly prolonged PFS compared with those who underwent cCRT + IO.

The results of this study are based on current and ongoing literature evaluating the use of immunotherapy for locally advanced NSCLC. In this study, the 3-year PFS and OS rates are 80.6% and 87.5% in patients who received neoadjuvant chemoimmunotherapy, superior to the outcomes from other neoadjuvant chemoimmunotherapy trials, such as CheckMate 816 (stage IB-IIIA, 3-year EFS 57% and 3-year OS

Table 2 Univariate and multivariate Cox regression analyses for PFS before PSM

Variables	Univariate			Multivariate		
	HR	95%CI	*P*	HR	95%CI	*P*
Age	1.02	1–1.04	0.119			
Group						
neoCT/IO	1.00 (Reference)			1.00 (Reference)		
cCRT + IO	2.05	1.41–2.98	< 0.001	2.05	1.41–2.98	< 0.001
Histology						
Squamous	1.00 (Reference)					
Adenocarcinoma	0.93	0.60–1.45	0.764			
Sex						
Male	1.00 (Reference)					
Female	0.86	0.43–1.69	0.656			
KPS						
80	1.00 (Reference)					
90	0.81	0.55–1.19	0.280			
Smoking						
Never	1.00 (Reference)					
Ever	1.15	0.77–1.71	0.489			
Clinical						
IIIA	1.00 (Reference)					
IIIB	0.90	0.60–1.37	0.628			
T stage						
1	1.00 (Reference)					
2	0.69	0.33–1.45	0.331			
3	0.57	0.26–1.24	0.154			
4	0.74	0.36–1.51	0.414			
N stage						
0	1.00 (Reference)					
1	1.40	0.70–2.78	0.341			
2	1.23	0.67–2.27	0.500			

HR; hazard ratio, CI; confidence interval

Table 3 Univariate and multivariate Cox regression analyses for PFS after PSM

Variables	Univariate			Multivariate		
	HR	95%CI	*P*	HR	95%CI	*P*
Age	1.02	0.99–1.05	0.145			
Group						
neoCT/IO	1.00 (Reference)			1.00 (Reference)		
cCRT + IO	2.91	1.77–4.78	< 0.001	2.91	1.77–4.78	< 0.001
Histology						
Squamous	1.00 (Reference)					
Adenocarcinoma	0.99	0.60–1.64	0.983			
Sex						
Male	1.00 (Reference)					
Female	0.98	0.45–2.14	0.969			
KPS						
80	1.00 (Reference)					
90	0.92	0.58–1.47	0.739			
Smoking						
Never	1.00 (Reference)					
Ever	1.14	0.71–1.82	0.592			
Clinical						
IIIA	1.00 (Reference)					
IIIB	1.11	0.70–1.77	0.653			
T stage						
1	1.00 (Reference)					
2	0.57	0.23–1.41	0.224			
3	0.72	0.30–1.76	0.473			
4	0.74	0.33–1.67	0.474			
N stage						
0	1.00 (Reference)					
1	1.59	0.70–3.60	0.267			
2	1.31	0.64–2.66	0.455			

HR; hazard ratio, CI; confidence interval

78%) [15], AEGEAN (stage II-IIIB, 3-year EFS 60.1% and 3-year OS 67.1%) [16] and KEYNOTE-671 (stage II-IIIB, 3-year EFS 54.3% and 3-year OS 71.3%) [4]. The pathological response rates (MPR 59.3% and pCR 40.7%) in CT/IO + Surgery group are also higher than those reported in previous clinical trials (MPR rate: range from 30.2 to 36.9%, pCR rate: range from 17.2 to 24%). These results may be attributed to the high proportion of patients with squamous cell carcinoma in our study (74.4%) relative to previous clinical trials (range from 43.1 to 48.6%). Squamous cell carcinoma is known to demonstrate a more favorable pathological response to neoadjuvant therapy, which is correlated with an increased rate of surgical conversion and improved survival outcomes [17–19]. In patients with stage III NSCLC who underwent cCRT + IO, the 3-year PFS and OS rates were 39.7% and 56.7%, respectively, according to the findings of the PACIFIC trial [6]. Another real-world, non-randomized study, the PACIFIC-R, further demonstrated a 3-year PFS rate of 42.2% and an OS rate of 63.2% in stage III NSCLC [20]. In our study, the 3-year PFS and OS rates (40.8% and 75.0%, respectively) in the cCRT + IO group were superior to those in the PACIFIC trials, likely owning to the exclusion of patients with more advanced N3 stage disease. Moreover, our study benefited from the incorporation of real-world data on the use of immunotherapy.

Thus far, only a few studies have directly compared the efficacy of these two multimodal treatment regimens in patients with stage III NSCLC. In the pre-immunotherapy era, the most recent randomized trial comparing surgery with cCRT was the ESPATUE trial. The trial found no significant OS or PFS benefits associated with surgical intervention after induction treatment, compared with cCRT, for resectable stage IIIA-B disease [12]. A meta-analysis that included six additional randomized trials further supported the findings of the ESPATUE trial [13]. However, none of these randomized trials evaluated the combination of immunotherapy with either surgery or cCRT. Our findings demonstrate superior PFS in the neoCT/IO group compared with

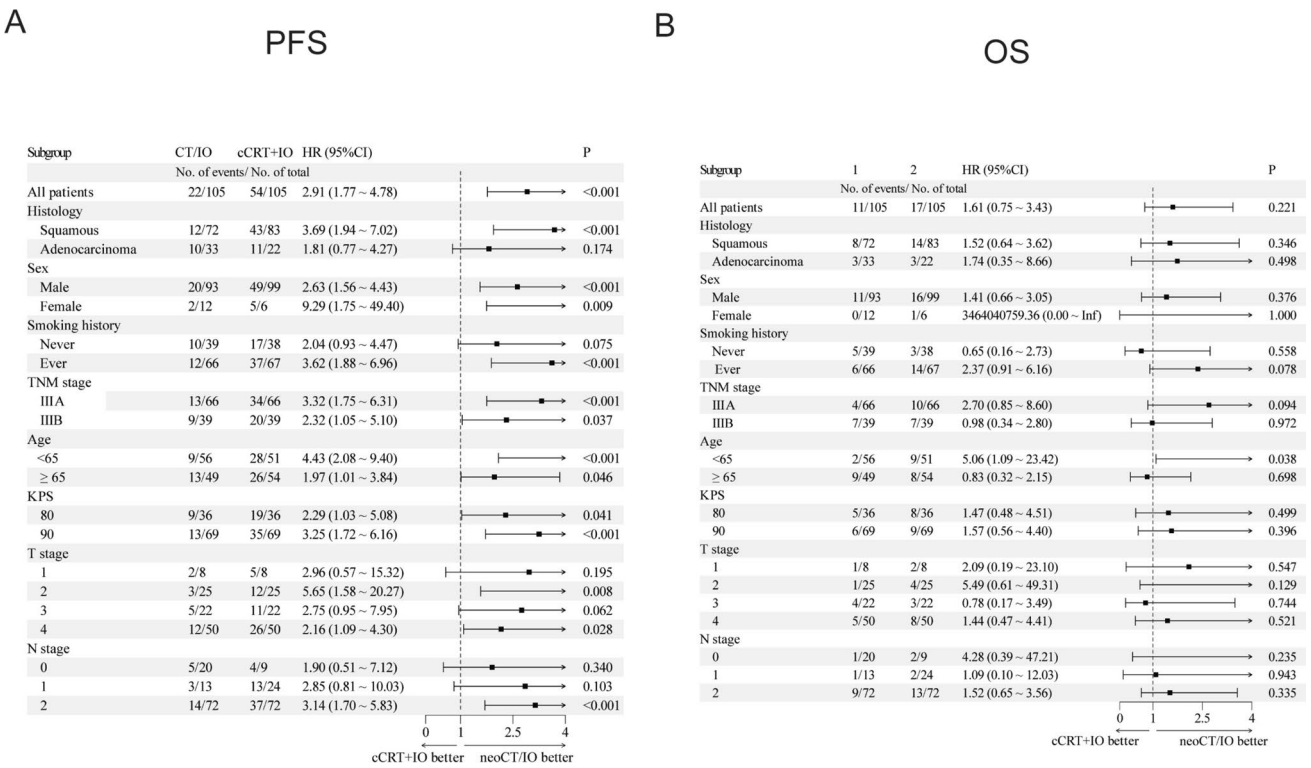


Fig. 3 Subgroup analyses of PFS (A) and OS (B) in matched populations receiving neoCT/IO and cCRT + IO treatment. Abbreviations: PFS, progression-free survival; OS, overall survival

the cCRT + IO group, particularly among patients under 65 years of age, those with squamous cell carcinoma and those classified as stage IIIA. Furthermore, the locoregional recurrence rate, especially at the primary tumor site, was lower in the neoCT/IO + Surgery group than in the neoCT/IO + Radiotherapy group and cCRT + IO group. Consistent with our findings, a phase III trial conducted by Kathy et al. involving patients with stage IIIA (N2) NSCLC demonstrated that those who underwent surgery following induction CRT exhibited significantly improved local control and PFS compared with those who received definitive CRT alone [21]. Even among early-stage patients treated with stereotactic body radiotherapy (SBRT), the incidence of locoregional recurrence was higher than in those who underwent surgical intervention [22]. Wang et al. further supported the notion that surgical resection may achieve better local control than radiotherapy when combined with immunotherapy [23]. Owing to the relatively shorter follow-up period, the OS outcome was NR in either group. However, we observed a trend toward longer OS in the neoCT/IO group compared with the cCRT + IO group. With extended follow-up, the neoCT/IO group may demonstrate superiority over radiotherapy in prolonging OS. Long-term follow-up and data from prospective randomized trials are required to validate these findings.

In addition to evaluating the efficacy of the two treatment groups, the impact of different treatment modalities on organ preservation and quality of life has become a topic of significant interest for both patients and clinicians. Organ preservation strategies allow patients with favorable clinical responses after neoadjuvant therapy to avoid the morbidities associated with complex radical surgery, thereby maintaining organ function and quality of life. These strategies have been widely applied in patients with laryngeal [24], bladder [25], esophageal [26] and rectal cancers [27, 28]. In the case of locally advanced NSCLC, neoadjuvant therapy is typically recommended to reduce tumor size, downstage the disease and increase the R0 resection rate. Unfortunately, in the era of chemotherapy, neoadjuvant chemotherapy with or without radiotherapy has not consistently achieved satisfactory treatment responses, and many patients still require extensive or complex surgeries, which are associated with high postoperative mortality and poor quality of life, particularly in those likely to undergo pneumonectomy [13, 21, 29, 30]. Recently, advancements in neoadjuvant immunotherapy, which offer favorable safety profiles and long-term survival outcomes, have opened the possibility of applying organ preservation strategies with modified surgery in resectable NSCLC [31]. However, owing to the retrospective nature of our study, we did not evaluate data regarding the loss of lung function resulting from either surgical intervention or

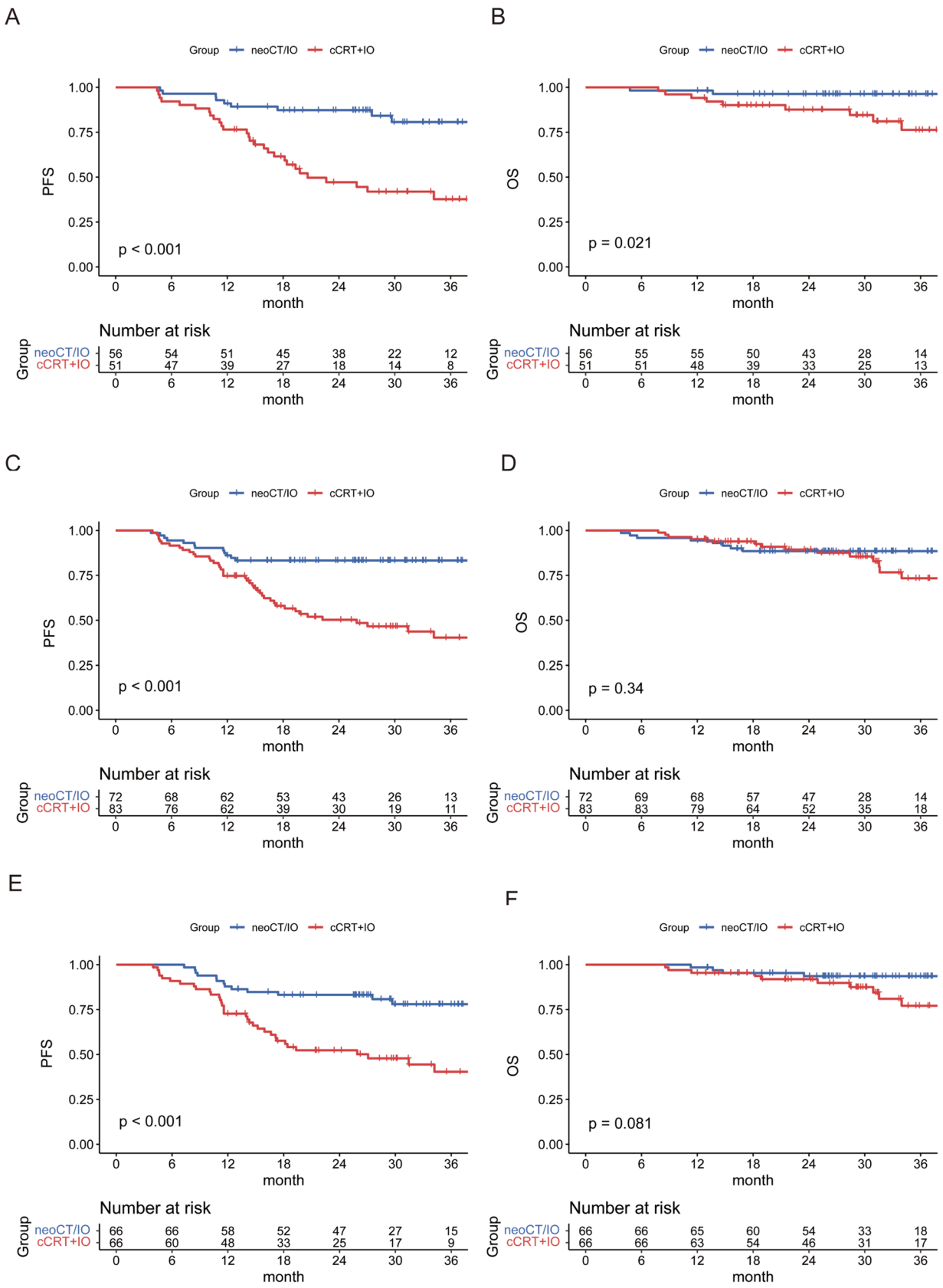


Fig. 4 PFS and OS after PSM in subgroup patients with < 65 years old (A and B), squamous histology (C and D) and clinical stage IIIA (E and F)

radiation therapy, and further prospective studies are warranted to address this limitation.

Although the distinct treatment modalities resulted in slightly different spectra of TRAEs among the three treatment groups in this study, the common TRAEs were relatively similar across three treatment groups. Notably, none of the patients experienced grade 5 TRAEs. No statistically significant difference was observed in the incidence of grade 3/4 TRAEs, except for hematological toxicity, which was higher but still within an acceptable range in patients receiving cCRT + IO. The most prevalent postoperative complication was anemia, occurring in 57.1% of patients. Pneumonitis remains a concern and is frequently reported as an AE associated with ICIs and radiotherapy [32, 33], especially in patients receiving a combination of both therapies [34]. In this study, pneumonitis was observed in 32.7% of patients in the cCRT + IO group, with an incidence of grade 3/4 pneumonitis at 2.6%. This finding is consistent with data from other studies investigating immunotherapy in combination with radiotherapy, including immunotherapy combined with concurrent radiotherapy (4%) [35], concurrent immunotherapy with cCRT (3.3%) [18], induction chemoimmunotherapy followed by CRT (5.0–5.7%) [36] and immunotherapy consolidation following cCRT (3.4%-6.5%) [37, 38]. Furthermore, the incidence of grade 3/4 pneumonia did not significantly differ between the neoCT/IO + Surgery, neoCT/IO + Radiotherapy and cCRT + IO groups, indicating a comparable safety profile for these three treatment modalities.

This study has some limitations, including its retrospective design, single-center nature and relatively small sample size. Additionally, PD-L1 expression data were sparse, and the variability in immunotherapy regimens encountered in real-world settings could not be adequately controlled. It is likely that patients in the cCRT + IO group received durvalumab and sugemalimab, whereas those in the neoCT/IO group may have been administered other novel immunotherapeutic agents, such as tislelizumab, atezolizumab or pembrolizumab, potentially influencing differences in survival outcomes. Furthermore, the patients' operability status which differs between neoCT/IO and cCRT + IO group was not corrected with the PSM as the patients selected for neoCT/IO + Surgery may have less comorbidities (e.g., vascular, renal, heart, diabetes) and better lung functions. Finally, owing to the relatively short follow-up period, the OS outcome remains immature, limiting further exploration of the exact role of different treatment modalities on prognosis.

Conclusion

This retrospective study of patients with potentially resectable stage IIIA-B NSCLC demonstrated that multimodal treatment regimens incorporating immunotherapy result in favorable survival outcomes. Furthermore, preliminary results from propensity score-matched analyses suggest that neoCT/IO appears to be safe and may prolong survival compared with cCRT + IO. Prospective randomized trials are warranted to further validate these findings.

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Author contributions YN was involved in conceptualization, data curation, formal analysis, interpretation, writing–original draft, agrees with manuscript results and conclusions, and critically edited and reviewed the article. XY took part in data curation, interpretation, agrees with manuscript results and conclusions, and critically edited and reviewed the article. QH was responsible for data curation, formal analysis, agreement with manuscript results and conclusions, and critically edited and reviewed the article. YQ, YF and MQ agree with manuscript results and conclusions, and critically edited and reviewed the article. HZ participated in conceptualization, project administration and writing—review and editing. HB performed conceptualization, funding acquisition, project administration and writing—review and editing. All authors read and approved the final manuscript.

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Data availability All data used in this study are archived and could be available on a reasonable request.

Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval The study was approved by all participating institutions. The study was conducted in accordance with the Declaration of Helsinki and International Good Clinical Practice Guidelines. The need for informed consent was waived by the Ethics Committee of Shandong Cancer Hospital and Institute, because of the retrospective nature of the study.

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