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Perioperative or neo/adjuvant chemoimmunotherapy versus chemotherapy for resectable non-small cell lung cancer: a systematic review and network meta-analysis

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Abstract

Introduction Lung cancer, particularly non-small cell lung cancer (NSCLC), is a leading cause of cancer-related deaths globally. Despite surgery being the main treatment for resectable NSCLC, many patients experience postoperative recurrence. Neoadjuvant chemotherapy may shrink tumors and improve surgical outcomes, while adjuvant chemotherapy targets residual disease post-surgery. Recent advancements in immunotherapy have introduced its use in the perioperative phase for resectable NSCLC. This study investigates the relative benefits and potential complications of neoadjuvant, adjuvant, and perioperative immunotherapy combined with chemotherapy compared to chemotherapy alone, focusing on event-free survival (EFS), overall survival (OS), and adverse events (AEs).

Methods This systematic review and network meta-analysis followed PRISMA guidelines and was registered with PROSPERO. The authors searched PUBMED, Embase, and Cochrane databases for randomized controlled trials (RCTs) involving patients with resectable NSCLC treated with neoadjuvant/adjuvant immunotherapy or chemotherapy. Statistical analyses were performed using a frequentist network meta-analysis method in R software.

Results From an initial 5902 articles, 13 RCTs involving 6704 patients were included after extensive filtering. PFS: Neoadjuvant and perioperative immunotherapy combined with chemotherapy showed significant benefits compared to chemotherapy alone. OS: Perioperative immunotherapy was notably more effective than adjuvant immunotherapy and standard chemotherapy. Chemotherapy generally had fewer severe adverse effects compared to neoadjuvant and perioperative immunotherapy. However, these immunotherapy combinations are generally well tolerated.

Conclusions The findings indicate that neoadjuvant and perioperative immunotherapy combined with chemotherapy can significantly improve overall survival in patients with resectable NSCLC compared to standard chemotherapy. However, additional adverse effects associated with long-term immunotherapy require careful management. The lack of significant benefits in specific subgroups suggests a need for further research. The study stresses the importance

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of optimizing treatment strategies and potentially reassessing immunotherapy's role in certain patient populations. Future clinical trials are anticipated to clarify these results further.

Keywords Chemoimmunotherapy, Chemotherapy, Immunotherapy, Resectable non-small cell lung cancer, Surgery

Introduction

Lung cancer is a major cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, accounting for approximately 85% of all lung cancer cases [2]. NSCLC is typically categorized into three major subtypes according to its histological features: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Surgery is still the main approach for treating resectable NSCLC, yet only approximately 25% of patients are diagnosed with resectable disease, and approximately 30% to 55% of patients experience recurrence postoperatively [3]. Neoadjuvant chemotherapy administered in the perioperative period can substantially decrease tumor size, enhance surgical success, and promote postoperative recovery. In contrast, adjuvant chemotherapy assists in removing the remaining microlesions after surgery, subsequently lowering the recurrence rate. For almost three decades, perioperative and neoadjuvant chemotherapy have been regarded as extending patients' postoperative disease-free survival (DFS) [4]; however, there are no significant differences in survival benefits among various chemotherapy regimens during different perioperative periods, although they are generally well tolerated [5]. A direct comparison between neoadjuvant and adjuvant chemotherapy revealed no significant statistical difference in the event-free survival (EFS), described as DFS, of neoadjuvant chemotherapy versus the failure-free survival (FFS) of adjuvant chemotherapy [6]. In recent years, immunotherapy has increasingly emerged as a significant trend in cancer treatment, and combined immunotherapy has progressed from late-stage treatments to the perioperative phase in lung cancer [2]. In patients with gene-negative resectable NSCLC, adjuvant immunotherapy [7] combined with chemotherapy has established a standard postoperative regimen for treatment. Neoadjuvant [8] and perioperative [9] immunotherapy combined with chemotherapy may provide improved EFS in resectable NSCLC, particularly those with pathological major pathologic response (MPR) and pathologic complete response (pCR). Nonetheless, neoadjuvant and perioperative immunotherapy combined with chemotherapy may render certain patients intolerant or lead to progression, disqualifying them from undergoing surgery.

Since the clinical trial populations for resectable NSCLC are consistent, we will integrate all populations from the studies included. The disease-free survival (DFS) in adjuvant treatments denotes the duration from randomization until disease recurrence or death from any cause. The event-free survival (EFS) associated with neoadjuvant and perioperative adjuvant treatments refers to the period from randomization to the first occurrence of any of the following events: disease progression preventing surgical intervention, local or distant recurrence, or death from any cause. Progression-free survival (PFS) refers to the duration from randomization to tumor progression or death from any cause.

Based on existing evidence, it is uncertain whether there are advantages and disadvantages among these three modes of neoadjuvant, adjuvant, and perioperative immunotherapy combined with chemotherapy, or if there are any differences in benefits, we aimed to compare these three modes of combined immunotherapy via network meta-analysis of randomized controlled trials to assess PFS, overall survival (OS), adverse events (AEs), and subgroup analyses.

Methods

Research design

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol for this study has been registered with PROSPERO (CRD42024564125).

Search strategy and inclusion criteria

We decided to include published randomized controlled trials with two or more arms from the PUBMED, Embase, and Cochrane databases from their inception until the last search update on June 25, 2024. These trials pertained to perioperative (including neoadjuvant/adjuvant) immunotherapy treatments, chemotherapy, or both for patients with resectable lung cancer, with language restriction to English. The complete search strategy is presented in Table S1. Included in this review were published articles reporting trial-level data related to perioperative chemotherapy or chemotherapy-immunotherapy, encompassing those with complete data from conference abstracts. Retrospective studies, editorials, reviews, gray literature, and any other publication types lacking trial-level evidence were excluded from this analysis. Clinical trial reports utilizing radiotherapy, including neoadjuvant chemoradiotherapy, molecularly targeted therapy, or monotherapy with immunotherapy, along with NSCLC

studies without Tumor, Node, Metastasis staging, were excluded. Studies involving only adult patients were included. All articles were screened based on the title and abstract by two independent reviewers (QZ and DJ), compiled by YL, and discussed in cases of disagreements for resolution. The outcomes included PFS (EFS/DFS), overall survival (OS), and adverse events (AEs) of grade 3 or greater.

Quality assessment

Bias assessment of the included studies was performed using RevMan 5.3. Bias risk was assessed by two independent reviewers (QZ and JD) using the modified Cochrane risk of bias tool, with disagreements settled by a third reviewer (YL). We assessed the risk of bias in the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions, which included factors like random sequence generation, allocation concealment, blinding of both researchers and participants, blinding in outcome assessment, incomplete outcome data, and selective reporting; every study was rated for risk of bias as either high, low, or unclear. Those studies exhibiting low risk of bias in three critical areas (random sequence generation, allocation concealment, and missing participant outcome data) were classified as having low overall risk of bias. All other studies were deemed to have a high overall risk of bias. This report complies with the recommendations of the PRISMA extension for systematic reviews and meta-analyses, which necessitates the reporting of systematic reviews related to network meta-analyses of healthcare interventions.

Statistical analysis

This research utilized a frequentist network meta-analysis method, analyzed via the netmeta package in R software [10]. This approach is grounded in graph theory and circuit theory, enabling simultaneous comparisons of the relative effects of multiple interventions. The first step involved constructing a network graph to visualize all direct comparisons. The primary analysis was performed using a random-effects model to encompass heterogeneity across studies. The summary effect estimates and their 95% confidence intervals for each pair of interventions were computed.

Cochran's Q statistic was used to evaluate overall heterogeneity, the I^2 statistic was calculated to quantify the level of heterogeneity, and a design-by-treatment interaction model was applied to evaluate network consistency [11]. If significant discrepancies were identified, net splitting methods were utilized to pinpoint the sources of inconsistency [12]. P scores were computed to rank the interventions, comprehensively considering effect estimates and precision [13]. We utilized a comparison-adjusted funnel plot to evaluate small-sample effects or publication bias [14]. Sensitivity analysis: The following sensitivity analyses were performed: (1) reanalysis using a fixed-effects model; (2) exclusion of studies classified as having a high risk of bias; and (3) include additional sensitivity analyses as applicable to specific studies. All analyses were performed in R version 4.4.0 using the netmeta package (version 1.3–0). Statistical significance was set at $\alpha = 0.05$, and all tests were two-tailed.

Results

A preliminary database search (PubMed 2324, Embase 1674, Cochrane Library 1904) retrieved a total of 5902 articles. Following the removal of duplicates, 5357 articles were left. We then reviewed their titles and abstracts, leading to the exclusion of 5805 articles, of which 545 were duplicated, 4661 were unrelated studies, 155 covered reviews, 23 were case reports, 74 were retrospective studies, and 347 were meta-analyses; after reading thoroughly, 97 documents were included for discussion, and following discussions among members, 46 articles were excluded, which included nine conference papers, 10 studies with inconsistent research populations, 9 duplicates, 2 single-group studies, 16 study protocols, and 7 entries lacking further information; 2 retrospective studies. Fifty-one studies were included in qualitative synthesis, 32 articles were not retrieved, and 6 articles were different reports from the same study. A total of 13 RCTs met the inclusion criteria following screening, while one [4] study did not provide hazard ratio [HR] or relevant subgroup metrics regarding PFS/OS for neoadjuvant versus adjuvant chemotherapy and were therefore excluded; Fig. S1 illustrates the literature screening flowchart. As KEYNOTE091 [15] did not require the use of combination chemotherapy regimens, it was only included in the chemotherapy subgroup. Ultimately, twelve [5, 7–9, 15–28] studies were evaluated, comprising a total of 18 publications.

Features of included studies

Ultimately, 12 qualifying studies were included, involving 6705 patients, comprising 4981 males and 1724 females, as detailed in which reports the basic characteristics of the principal studies. Among them, 3187 had squamous cell carcinoma, and 3363 had non-squamous cell carcinoma; 138 patients had stage IA disease; 2664 were diagnosed with stage IB to II, 2749 had stage IIIA, and 45 had stage IIIB. Among these, 2079 exhibited PD-L1 expression $< 1\%$, and $2466 \geq 1\%$, with 421 individuals not undergoing surgical resection after neoadjuvant treatment. Of these, 222 patients were allocated to neoadjuvant chemotherapy-immunotherapy, 1477 to perioperative chemotherapy-immunotherapy, 1097 to

Table 1 Characteristics of included studies

Trials	Year	Phase	Treatment	Age	Sample	Sex		Histological types		Smoking status			STAGE					PD-L1		Not resected
						Male	Female	Sq	N sq	Never	Current	Former	IB	IIA	IIB	IIIA	IIIB	< 1%	≥ 1%	
NADIM II	2023	II	PNC	65 (58–70)	57	21	36	21	36	5	22	30				44	13			4 (7)
			PC	63 (57–66)	29	13	16	14	15	0	8	21				24	5			9 (45)
CheckMate 77 T	2023	III	PNC	66 (37–83)	229	167	62	116	113	212	17							93 (40.6)	128 (55.9)	34 (14.8)
			NC	66 (35–86)	232	160	72	118	114	205	27							93 (40.1)	128 (55.2)	25 (10.8%)
Neotorch	2023	III	PTRC	62 (56–65)	202	181	21	157	45	144	30					136 (67.3)	65 (32.2)	51 (25.3)	133 (65.9)	36 (18.8)
			PC	61 (56–65)	202	189	13	157	45	179	23					136 (67.3)	64 (31.7)	54 (26.7)	132 (65.4)	54 (26.7)
AEGEAN	2022	III	PDC	65 (30–88)	366	252	114	169	196	271	95			II	104 (28.4)	173 (47.3%)	88 (24.0%)	122 (33.3)	244 (66.7)	71 (19.4)
			NC	65 (39–85)	374	278	96	191	179	279	95				110 (29.4)	165 (44.1%)	98 (26.2%)	125 (33.4)	249 (66.6)	72 (19.3)
CheckMate 816	2022	III	NNC	64 (41–82)	179	128	51	87	92	19		160		IB or II	65 (36.3)	113 (63.1)		78 (43.6)	89 (49.7)	28 (15.6)
			NC	65 (34–84)	179	127	52	95	84	20		158			62 (34.6)	115 (64.2)		77 (43.0)	89 (49.7)	37 (20.7)
TD-FORE-KNOW	2023	II	NCC	61 (54–65)	43	34	9	27	16	12		31				30 (69.8)	13 (30.2)	7 (16.3)	16 (37.2)	3
			NC	61 (54–65)	45	40	5	32	13	8		37				36 (80.0)	9 (20.0)	8 (17.8)	11 (24.4)	3
KEY-NOTE-671	2024	III	PPC	63 (26–83)	397	279	118	171	226	54	96	247			118 (29.7%)	217 (54.7%)	62 (15.6%)	138 (34.8%)	259 (65.2%)	5 (1.5%)
			NC	64 (35–81)	400	284	116	173	227	47	103	250			121 (30.3)	225 (56.3%)	54 (13.5%)	151 (37.8%)	249 (62.2%)	15 (4.7%)
CSLC0501	2018	III	NC	58 (26–75)	97	79	18	50	47	28	69		30 (31.3)	11 (11.5)	26 (27.1)	29 (30.2)				15 (15.5)
			AC	57 (31–76)	101	80	21	52	49	30	71		34 (33.7)	13 (12.9)	30 (29.7)	24 (23.8)				0
IMpower010	2023	III	AAC	62 (55–67)	507	337	170	179	328	114	76	317	65 (13%)	147 (29%)	90 (18%)	205 (40%)		210 (41%)	248	
			AC	62 (56–67)	498	335	164	167	331	108	86	304	58 (12%)	148 (30%)	84 (17%)	208 (42%)		234 (47%)	228	

Table 1 (continued)

Trials	Year	Phase	Treatment	Age	Sample	Sex		Histological types		Smoking status			STAGE					PD-L1		Not resected
						Male	Female	Sq	N sq	Never	Current	Former	IB	IIA	IIB	IIIA	IIIB	< 1%	≥ 1%	
IFCT 0002	2013	III	NC	60 (34.5–75.2)	267	215	52	115	152				127 (47.6%)	10 (3.7%)	79 (29.6%)					
			PC	61.7 (36.7–75.6)	261	212	49	116	145				120 (46.0%)	11 (4.2%)	71 (27.2%)					
RATION-ALE-315	2023	III	PTSC	62 (30–80)	226	205	21	179	45	34		192			93 (41.2)	132 (58.4)		89 (39.4)	130 (57.5)	36 (15.9%)
			NC	63 (36–78)	227	205	22	175	50	39		188			93 (41.0)	132 (58.1)		84 (37.0)	131 (57.7)	54 (23.8%)
KEY-NOTE-091	2022	III	APC	65 (59–70)	590	401	189	192	398	87	75	428	84 (14%)	II	177 (30%)	329 (56%)		233 (39%)	257 (61%)	
			AC	65 (59–70)	587	403	184	224	363	66	90	431	85 (14%)		162 (28%)	338 (58%)		232 (40%)	253 (60%)	

Abbreviations PC, perioperative chemotherapy; *PNC*, perioperative nivolumab chemotherapy; *PTRC*, perioperative toripalimab chemotherapy; *PDC*, perioperative durvalumab chemotherapy; *PPC*, perioperative pembrolizumab chemotherapy; *PTSC*, perioperative tislelizumab chemotherapy; *NC*, neoadjuvant chemotherapy; *NCC*, neoadjuvant camrelizumab chemotherapy; *NNC*, neoadjuvant nivolumab chemotherapy; *AC*, adjuvant chemotherapy; *AAC*, adjuvant atezolizumab chemotherapy; *APC*, adjuvant pembrolizumab chemotherapy; *EFS*, event-free survival; *DFS*, disease-free survival; *PFS*, progression-free survival; *OS*, overall survival

adjuvant chemotherapy-immunotherapy, 492 to perioperative chemotherapy, 2020 to neoadjuvant chemotherapy, and 1396 to adjuvant chemotherapy. Six studies compared perioperative immunotherapy combined with chemotherapy, while three compared perioperative chemotherapy; these included NADIM II, Neotorch, and KEYNOTE-067; the other three studies compared neoadjuvant chemotherapy, including CheckMate 77 T, AEGEAN, and RATIONALE-315. Two studies evaluated adjuvant immunotherapy against adjuvant chemotherapy, specifically IMpower010 and a subgroup from KEYNOTE-091; one study contrasted neoadjuvant chemotherapy with adjuvant chemotherapy, CSLC0501; one study compared perioperative chemotherapy with neoadjuvant chemotherapy, IFCT 0002. Table 1 summarizes the characteristics of these studies. All studies exhibiting low risk of bias in three critical areas (random sequence generation, allocation concealment, and missing participant outcome data) were classified as having low overall risk of bias (Figs. S2 and S3).

Network analysis

Combined analysis

Initially, we divided immunotherapy combined with chemotherapy into neoadjuvant immunotherapy (NIC), adjuvant immunotherapy (AIC), and perioperative immunotherapy (PIC), in comparison with the control group (C). The network diagram created via network meta-analysis (NMA) is illustrated in Fig. S4 and the NMA results are shown in Table 2. In terms of PFS (Table 2A, Fig. 1A), 10 studies reported HR values and confidence intervals for PFS (I^2 = 52.5%, 0.0%, and 78.6%). Both direct and indirect comparisons indicate that in every case, NIC: C (HR, 0.39; 95% CI, 0.26, 0.59), PIC: C (HR, 0.41; 95% CI, 0.34, 0.49), and AIC: C (HR, 0.63; 95% CI, 0.49, 0.82, I^2 = 0%), reveal that immunotherapy combined with chemotherapy provides significantly higher benefits compared to chemotherapy. In comparison to adjuvant immunotherapy, both neoadjuvant (HR, 0.61; 95% CI, 0.38, 1.00) and perioperative immunotherapy (HR, 0.64; 95% CI, 0.46, 0.88) demonstrate significant benefits, with statistical significance. Additionally, neoadjuvant therapy appears marginally superior to perioperative immunotherapy (HR, 0.96; 95% CI, 0.62, 1.50), but this does not reach statistical significance. In terms of OS (Table 2B, Fig. 1B), 6 studies reported the HR and confidence intervals for OS (I^2 = 0%, 0.0%; 84.7%). Perioperative immunotherapy is more effective than adjuvant immunotherapy (HR, 0.71; 95% CI, 0.53, 0.94) and chemotherapy (HR, 0.66; 95% CI, 0.53, 0.82), demonstrating statistically significant benefits that suggest survival advantages with perioperative treatment. Regarding adverse reactions of grade 3 or higher (Table 2C, Fig. 1C), 11 studies reported the number of adverse events (I^2 = 16.2%, 0.0%; 60.1%), suggesting that chemotherapy may have less adverse effects compared to neoadjuvant immunotherapy (HR, 0.95; 95% CI, 0.61, 1.49), though this difference is not statistically significant. In comparison, chemotherapy has significantly fewer adverse effects than perioperative immunotherapy (HR, 0.78; 95% CI, 0.65, 0.94) and adjuvant immunotherapy (HR, 0.59; 95% CI, 0.45, 0.77).

Table 2 Combined meta-analysis

random.V1	random.V2	random.V3	random.V4
A. Combined analysis of PFS league chart			
NIC			**0.39 (0.26, 0.59)**
0.96 (0.61, 1.51)	PIC		**0.40 (0.34, 0.49)**
0.61 (0.38, 1.00)	**0.64 (0.46, 0.88)**	AIC	**0.63 (0.49, 0.82)**
0.39 (0.26, 0.59)	**0.40 (0.34, 0.49)**	**0.63 (0.49, 0.82)**	C
B. Combined analysis of OS league chart			
NIC			0.57 (0.31, 1.07)
0.86 (0.45, 1.68)	PIC		**0.66 (0.53, 0.82)**
0.58 (0.29, 1.14)	**0.67 (0.48, 0.93)**	AIC	0.99 (0.77, 1.28)
0.57 (0.31, 1.07)	**0.66 (0.53, 0.82)**	0.99 (0.77, 1.28)	C
C. Combined analysis of AD league chart			
C	0.97 (0.63, 1.48)	**0.78 (0.66, 0.93)**	**0.48 (0.32, 0.71)**
0.97 (0.63, 1.48)	**NIC**		
0.78 (0.66, 0.93)	0.81 (0.51, 1.28)	**PIC**	
0.48 (0.32, 0.71)	**0.49 (0.28, 0.88)**	**0.61 (0.40, 0.94)**	**AIC**

A lower left HR/OR below 1 favors the column-defining treatment. The top right HR/OR is a direct comparison below 1 in favor of horizontal column treatment. Comparisons with differences of statistical significance ($P < 0.05$) are highlighted in bold format

Separate analysis of treatment regimen

A separate analysis of each drug is depicted in the network diagram created via network meta-analysis (NMA), as shown in Fig. S5, and the NMA results are displayed in Table 3. For PFS (Table 3A, Fig. 2A), 11 studies were included (Q test = 0%), indicating clear benefits with statistical significance for neoadjuvant (NCC, NNC) and perioperative immunochemotherapy (PTSC, PNC, PPC, PDC) compared to perioperative chemotherapy, adjuvant immunochemotherapy, and adjuvant chemotherapy. Regarding OS (Table 3B, Fig. 2B), 8 studies were included (Q test = 0%), indicating significant survival benefits for neoadjuvant immunotherapy (NNC) and perioperative treatments (PTRC, PTSC, PPC) compared to AAC and AC. In terms of grade 3 or higher adverse reactions

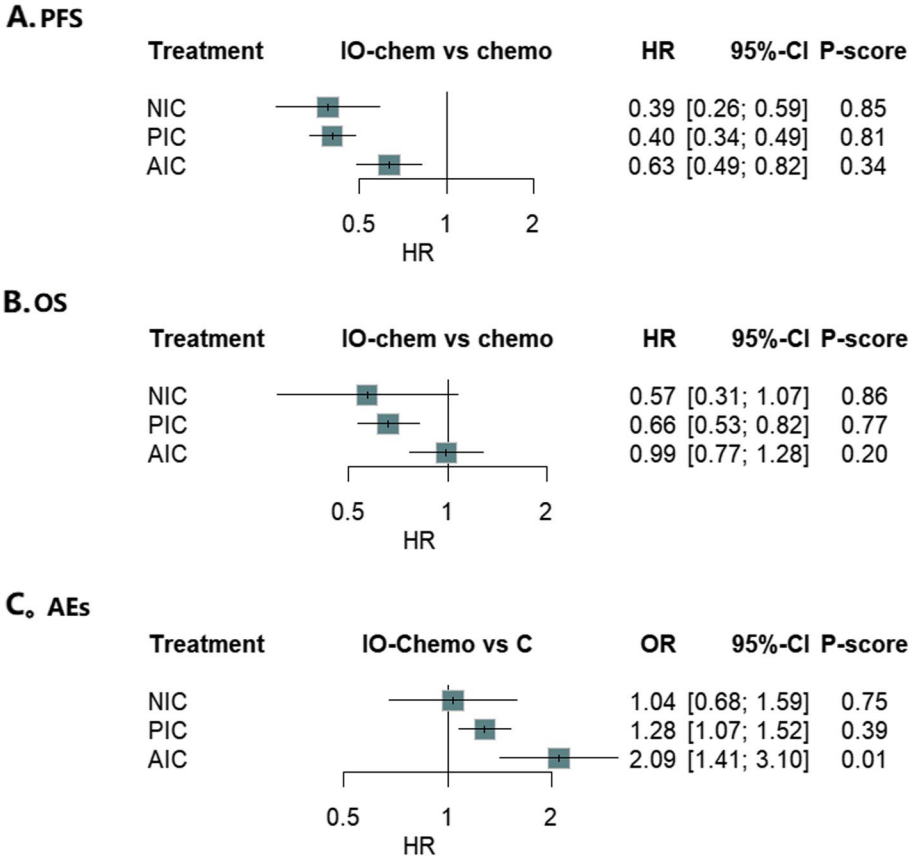

Fig. 1 Combined analysis of forest maps

(Table 3C, Fig. 3C), 10 studies were included ($I^2=0\%$), revealing significantly lower adverse reactions for PPC, PNC, AAC, and NCC compared to NC, with statistical significance. Compared to PPC, PNC, and NCC, PC was associated with significantly lower adverse effects and reached statistical significance. NNC, PDC, PTRC, and PTSC showed increased adverse effects relative to standard chemotherapy (PC, AC, NC), though this did not achieve statistical significance.

Subgroup analysis

Because most articles lacked OS subgroup analysis, we conducted benefit analysis solely for PFS while combining the control group of perioperative/neoadjuvant/adjuvant chemotherapy treatments. Histological subgroup analysis included eight studies (AAC, NNC, PDC, PNC, PPC, PTRC, and PTSC). In lung adenocarcinoma (Fig. 3, $I^2=56.6\%$ (0.0%; 89.6%)), there was a trend indicating benefits from perioperative/neoadjuvant/adjuvant immunochemotherapy in comparison to chemotherapy, although none was statistically significant. Within the squamous cell carcinoma subgroup (Fig. 3, $I^2=0\%$), PTRC (HR, 0.35; 95% CI, 0.23, 0.53), PNC (HR, 0.48; 95% CI, 0.33, 0.72), PTSC (HR, 0.56; 95% CI, 0.38, 0.83), and PPC (HR, 0.57; 95% CI, 0.42, 0.78) all showed benefits over chemotherapy, reaching statistical significance. In the PDL1 stratified subgroup (Fig. 4), the PDL1 < 1% group included 7 studies with AAC, NNC, PDC, PNC, PPC, PTRC, and PTSC (Q test = 0%), all demonstrating a tendency for benefits over chemotherapy, although no statistical significance was achieved. In the PDL1 1–49% subgroup ($I^2=0\%$), APC, PTRC, PTSC, and PPC demonstrated benefits compared to chemotherapy that were statistically significant. For the PDL1 ≥ 50% group, 7 studies were included: AAC, PTRC, PTSC, NNC, PDC, PNC, and PPC (Q test = 0%). PNC, NNC, PTRC, PPC, and AAC demonstrated statistical significance compared to chemotherapy.

Discussion

Advances in immunotherapy are reshaping the framework of perioperative treatment, and early consensus recommendations for neoadjuvant and adjuvant therapy for resectable NSCLC have been published [29], establishing immunochemotherapy as a foundational treatment approach during the perioperative period. The

Table 3 League table of separate analysis-treatment regimen

A. Separate analysis-treatment regimen of PFS

random.V1	random.V2	random.V3	random.V4	random.V5	random.V6	random.V7	random.V8	random.V9	random.V10	random.V11	random.V12
NCC							**0.21 (0.09, 0.52)**				
0.53 (0.20, 1.38)	**PTSC**						**0.40 (0.29, 0.56)**				
0.50 (0.19, 1.31)	0.95 (0.59, 1.52)	**PNC**					**0.42 (0.30, 0.58)**			**0.25 (0.13, 0.47)**	
0.47 (0.18, 1.22)	0.89 (0.55, 1.42)	0.93 (0.58, 1.49)	**NNC**				**0.45 (0.32, 0.63)**				
0.46 (0.18, 1.16)	0.87 (0.58, 1.29)	0.91 (0.61, 1.36)	0.98 (0.66, 1.46)	**PPC**			**0.46 (0.37, 0.57)**				
0.44 (0.13, 1.48)	0.84 (0.36, 1.99)	0.89 (0.43, 1.82)	0.95 (0.40, 2.25)	0.97 (0.43, 2.21)	**PTRC**					**0.28 (0.20, 0.40)**	
0.39 (0.15, 1.01)	0.75 (0.49, 1.14)	0.79 (0.52, 1.20)	0.84 (0.55, 1.28)	0.86 (0.62, 1.20)	0.89 (0.39, 2.04)	**PDC**	**0.53 (0.41, 0.69)**				
0.21 (0.09, 0.52)	**0.40 (0.29, 0.56)**	**0.42 (0.30, 0.58)**	**0.45 (0.32, 0.63)**	**0.46 (0.37, 0.57)**	0.47 (0.21, 1.04)	**0.53 (0.41, 0.69)**	**NC**				**0.48 (0.34, 0.69)**
0.17 (0.06, 0.45)	**0.32 (0.19, 0.54)**	**0.34 (0.20, 0.57)**	**0.36 (0.21, 0.61)**	**0.37 (0.23, 0.58)**	**0.38 (0.16, 0.92)**	**0.43 (0.27, 0.69)**	0.80 (0.54, 1.20)	**APC**			**0.60 (0.49, 0.73)**
0.15 (0.06, 0.41)	**0.29 (0.17, 0.48)**	**0.30 (0.18, 0.51)**	**0.32 (0.19, 0.55)**	**0.33 (0.21, 0.52)**	**0.34 (0.14, 0.83)**	**0.38 (0.24, 0.62)**	0.72 (0.48, 1.08)	0.90 (0.68, 1.18)	**AAC**		**0.67 (0.55, 0.82)**
0.12 (0.04, 0.39)	**0.24 (0.11, 0.52)**	**0.25 (0.13, 0.47)**	**0.27 (0.12, 0.59)**	**0.27 (0.13, 0.57)**	**0.28 (0.20, 0.40)**	**0.32 (0.15, 0.67)**	0.59 (0.29, 1.21)	0.74 (0.33, 1.68)	0.83 (0.37, 1.87)	**PC**	
0.10 (0.04, 0.27)	**0.19 (0.12, 0.31)**	**0.20 (0.12, 0.33)**	**0.22 (0.13, 0.35)**	**0.22 (0.15, 0.33)**	**0.23 (0.10, 0.54)**	**0.26 (0.17, 0.40)**	**0.48 (0.34, 0.69)**	**0.60 (0.49, 0.73)**	**0.67 (0.55, 0.82)**	0.81 (0.37, 1.79)	**AC**

B. Separate analysis-treatment regimen of OS

random.V1	random.V2	random.V3	random.V4	random.V5	random.V6	random.V7	random.V8	random.V9
PNC					**0.43 (0.19, 0.98)**			
0.75 (0.26, 2.17)	**NNC**					0.57 (0.31, 1.07)		
0.70 (0.27, 1.82)	0.93 (0.40, 2.15)	**PTRC**			0.62 (0.38, 1.01)			
0.69 (0.26, 1.84)	0.92 (0.42, 2.02)	0.99 (0.48, 2.05)	**PTSC**			**0.62 (0.39, 0.99)**		
0.58 (0.23, 1.45)	0.78 (0.39, 1.56)	0.84 (0.45, 1.56)	0.84 (0.48, 1.47)	**PPC**		**0.73 (0.55, 0.98)**		
0.43 (0.19, 0.98)	0.58 (0.29, 1.14)	0.62 (0.38, 1.01)	0.63 (0.37, 1.07)	0.74 (0.50, 1.09)	**PC**	0.99 (0.77, 1.28)		
0.43 (0.18, 1.01)	0.57 (0.31, 1.07)	0.61 (0.35, 1.06)	**0.62 (0.39, 0.99)**	0.73 (0.55, 0.98)	0.99 (0.77, 1.28)	**NC**		0.73 (0.51, 1.06)

Table 3 (continued)

0.32 (0.12, 0.84)	**0.42 (0.20, 0.92)**	**0.45 (0.22, 0.93)**	**0.46 (0.24, 0.88)**	**0.54 (0.32, 0.93)**	0.73 (0.44, 1.23)	0.74 (0.47, 1.16)	**AAC**	0.99 (0.77, 1.28)		
0.31 (0.12, 0.80)	**0.42 (0.20, 0.87)**	**0.45 (0.23, 0.87)**	**0.45 (0.25, 0.83)**	**0.54 (0.33, 0.86)**	0.73 (0.46, 1.14)	0.73 (0.51, 1.06)	0.99 (0.77, 1.28)	**AC**		
C. Separate analysis-treatment regimen of AD										
random.V1	**random.V2**	**random.V3**	**random.V4**	**random.V5**	**random.V6**	**random.V7**	**random.V8**	**random.V9**	**random.V10**	**random.V11**
AC			0.73 (0.41, 1.28)					**0.48 (0.34, 0.68)**		
0.91 (0.47, 1.77)	**PC**		0.80 (0.57, 1.14)		0.68 (0.46, 1.01)				0.48 (0.12, 1.89)	
0.81 (0.40, 1.65)	0.89 (0.52, 1.54)	**NNC**	0.89 (0.59, 1.36)							
0.73 (0.41, 1.28)	0.80 (0.57, 1.12)	0.89 (0.59, 1.36)	**NC**	0.98 (0.74, 1.31)		0.82 (0.56, 1.22)	**0.73 (0.55, 0.97)**		0.70 (0.47, 1.05)	0.36 (0.11, 1.15)
0.71 (0.38, 1.35)	0.78 (0.50, 1.22)	0.88 (0.53, 1.46)	0.98 (0.74, 1.31)	**PDC**						
0.62 (0.28, 1.34)	0.68 (0.46, 1.01)	0.76 (0.39, 1.48)	0.85 (0.50, 1.44)	0.87 (0.48, 1.58)	**PTRC**					
0.60 (0.30, 1.20)	0.66 (0.39, 1.10)	0.73 (0.41, 1.31)	0.82 (0.56, 1.22)	0.84 (0.51, 1.37)	0.97 (0.50, 1.86)	**PTSC**				
0.53 (0.28, 1.00)	**0.58 (0.37, 0.91)**	0.65 (0.39, 1.08)	**0.73 (0.55, 0.97)**	0.74 (0.50, 1.12)	0.86 (0.47, 1.56)	0.89 (0.55, 1.44)	**PPC**			
0.48 (0.34, 0.68)	0.52 (0.25, 1.11)	0.59 (0.27, 1.29)	0.66 (0.34, 1.29)	0.67 (0.32, 1.39)	0.77 (0.33, 1.81)	0.80 (0.37, 1.74)	0.90 (0.44, 1.87)	**AAC**		
0.50 (0.25, 1.00)	**0.55 (0.33, 0.91)**	0.62 (0.35, 1.09)	0.69 (0.47, 1.02)	0.70 (0.43, 1.14)	0.81 (0.43, 1.54)	0.84 (0.48, 1.46)	0.94 (0.58, 1.53)	1.05 (0.48, 2.28)	**PNC**	
0.26 (0.07, 0.96)	**0.29 (0.09, 0.97)**	0.32 (0.09, 1.11)	0.36 (0.11, 1.15)	0.37 (0.11, 1.22)	0.43 (0.12, 1.52)	0.44 (0.13, 1.50)	0.50 (0.15, 1.64)	0.55 (0.15, 2.10)	0.53 (0.16, 1.78)	**NCC**

A lower left HR/OR below 1 favors the column-defining treatment. The top right HR/OR is a direct comparison below 1 in favor of horizontal column treatment. Comparisons with differences of statistical significance ($P < 0.05$) are highlighted in bold format

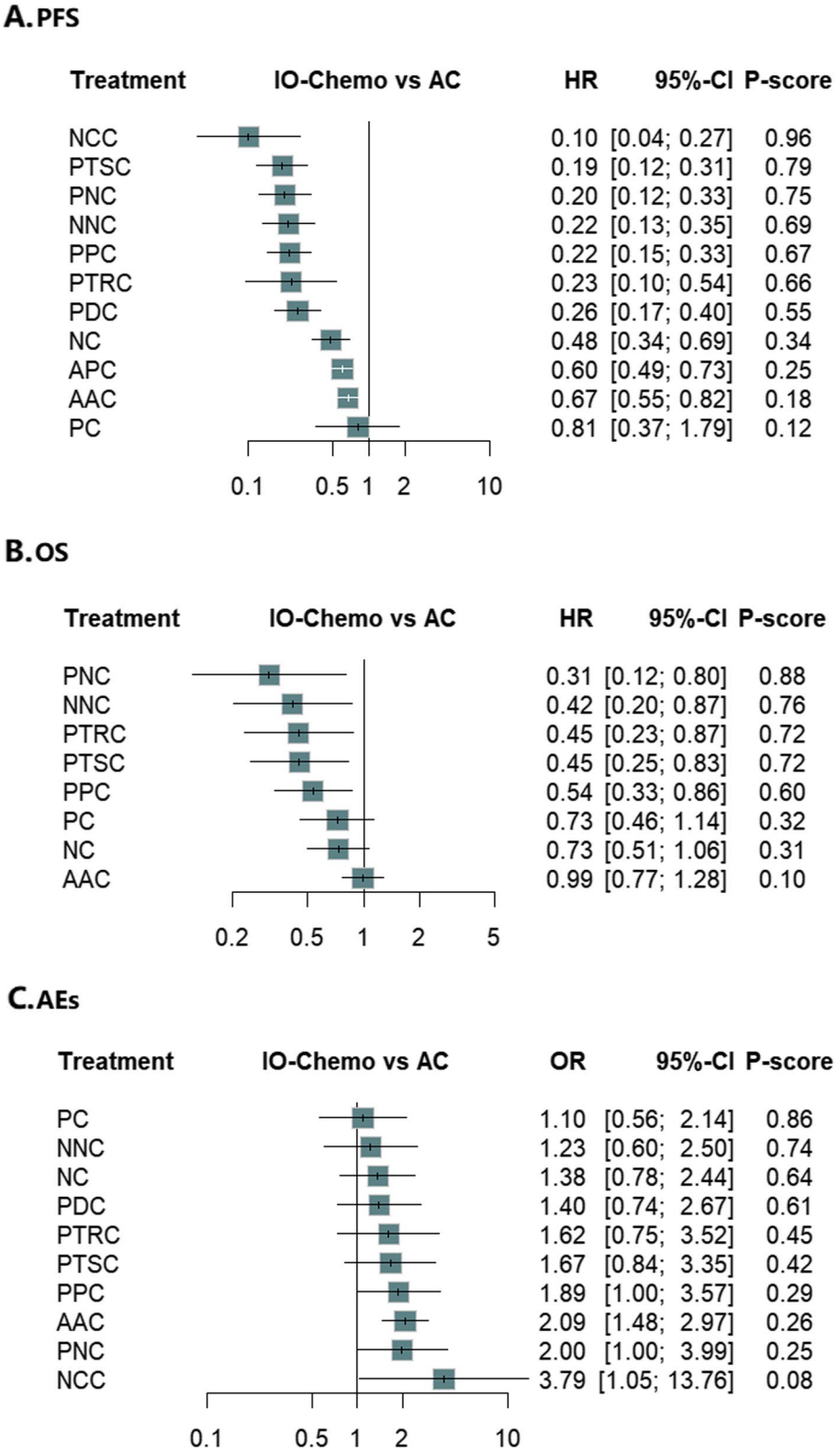

Fig. 2 Separate analysis of forest maps

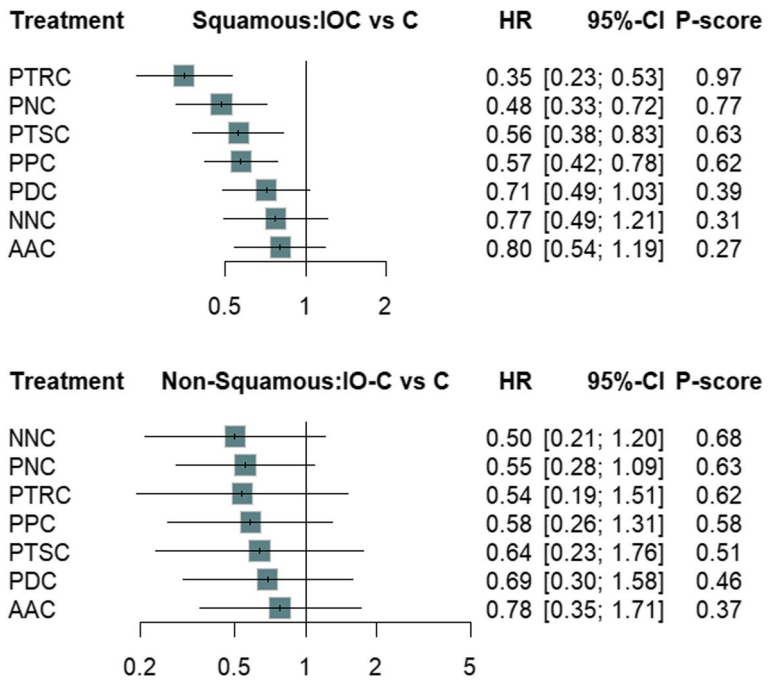

Fig. 3 Histological subgroup of forest maps

variety of choices available in perioperative immunotherapy highlights the importance of optimizing treatment strategies. Exploring the optimal timing of the introduction of immunochemotherapy during the perioperative phase is crucial [30]. Our research analyzed the advantages and disadvantages of perioperative, neoadjuvant, and adjuvant immunochemotherapy. Our findings indicate that immunotherapy combined with chemotherapy improves PFS regardless of the approach, whereas adjuvant immunotherapy does not improve OS. Neoadjuvant immunotherapy (NNC) and perioperative immunotherapy (PNC, PTRC, PTSC, and PPC) have demonstrated improved OS in resectable NSCLC compared to chemotherapy. Adjuvant immunotherapy (AAC) and perioperative immunotherapy (PPC, PNC) exhibit an increase in adverse reactions compared with standard chemotherapy; however, they are well tolerated [31]. Continuation of immunotherapy may result in additional adverse effects. Among subgroup analyses, all types of immunochemotherapy lacked statistically significant benefits for lung adenocarcinoma. In the PDL1 < 1% group, combined immunotherapy compared to chemotherapy did not yield statistically significant survival benefits. Additional investigations and population stratification are warranted [30].

Immunotherapy combined with chemotherapy may offer notable survival benefits to patients with advanced lung cancer. For patients with resectable NSCLC, neoadjuvant and perioperative immunochemotherapy [32–34] can decrease the preoperative tumor load, enhance antigen exposure, and improve therapeutic efficacy by increasing the mPR/pCR and R0 resection rates [35–37]. Recent meta-analyses [31, 38, 39] suggest that perioperative and neoadjuvant immunotherapies are safe and effective for early resectable NSCLC. The meta-analyses focused on pCR, MPR, resection rates, and complications. A meta-analysis indicated [40]. In resectable NSCLC, perioperative immunochemotherapy did not result in improvements in EFS or OS when compared to neoadjuvant immunotherapy alone, and the requirement for additional immunotherapy cycles may lead to a higher occurrence of treatment-related adverse events (AEs). A systematic review and meta-analysis [40] indicated that perioperative immunotherapy may be more efficient than adjuvant and neoadjuvant treatments compared to chemotherapy. NIC/PIC immunotherapy substantially improved DCR, MPR, and EFS, whereas AIC immunotherapy significantly enhanced DFS; NIC and AIC immunotherapy did not demonstrate significant differences in OS, with only PIC immunotherapy revealing benefits for OS; AD and PE immunotherapy were significantly linked to a higher incidence of adverse events (AEs) of grade > 3 in comparison to chemotherapy, which aligns perfectly with the combined analysis presented in this study; a retrospective study performed a head-to-head comparison of neoadjuvant immunotherapy versus adjuvant therapy [41]. The results indicate that for patients with resectable stage II-IIIB NSCLC, neoadjuvant

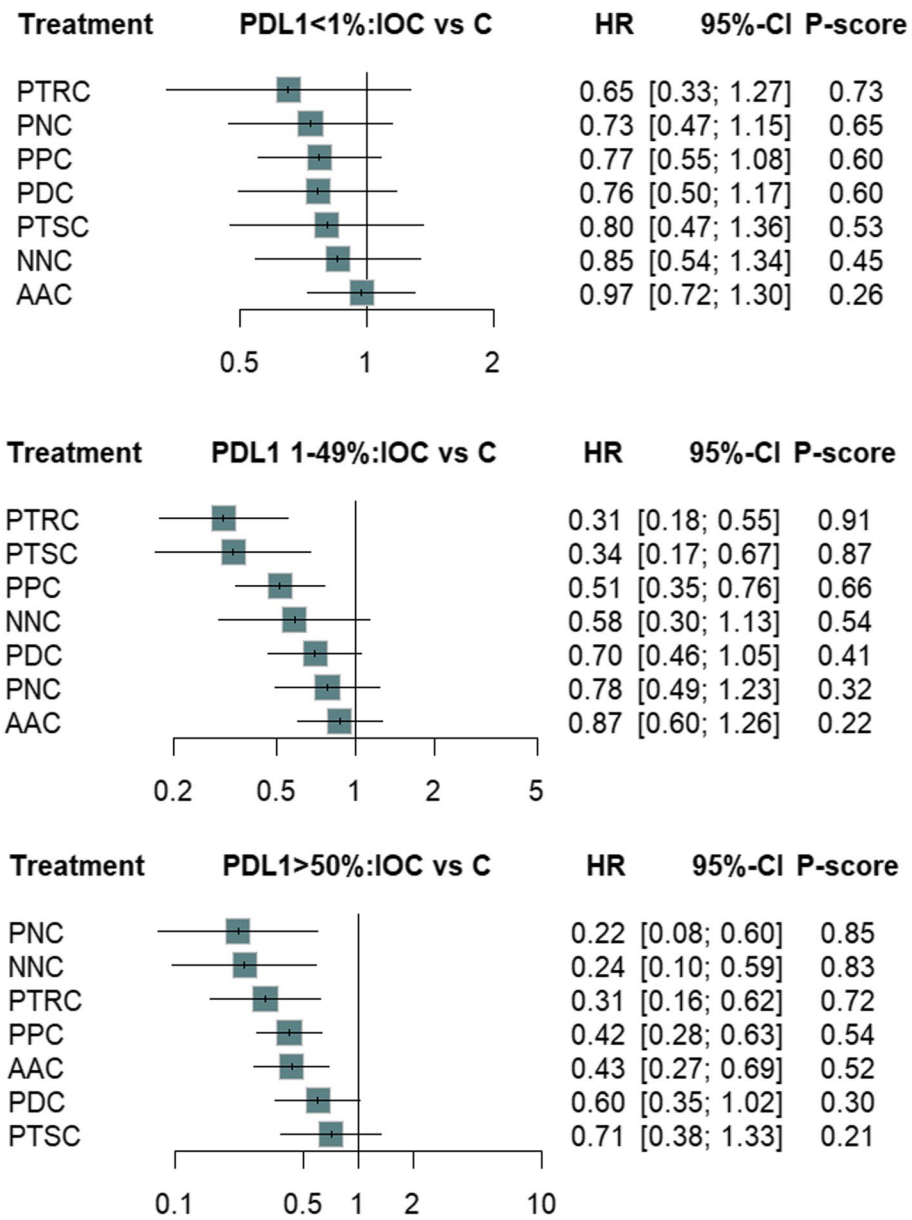

Fig. 4 PDL1 subgroup of forest maps. Results of the random-effects Hedges model are presented. Horizontal lines indicate the 95% CI of each study, diamonds are the pooled estimate with 95% CI (weight, 100%), and the vertical dotted line is the line of no effect

immunochemotherapy offers significant OS advantages over adjuvant immunotherapy. However, this is not the first meta-analysis comparing perioperative, neoadjuvant, and adjuvant immunochemotherapy. This is the first meta-analysis to conduct separate analyses of each drug, and the findings indicate that neoadjuvant and perioperative adjuvant immunochemotherapy can yield statistically significant survival advantages.

Theoretically, EFS is lower than DFS in the same study, suggesting that the benefits of surgery post-treatment for patients undergoing neoadjuvant or perioperative therapy may exceed the clinical data; patients who underwent neoadjuvant therapy but could not successfully undergo surgery clearly had worse survival outcomes [42, 43]. These patients cannot be directly compared with the PACIFIC [44] study findings. Following concurrent chemoradiotherapy with immunotherapy maintenance, the survival of this patient group lacks adequate exploration in large samples and might necessitate additional population selection. The benefit of adjuvant immunotherapy is that patients can achieve as much complete resection as

possible, and without prior induction treatment, there is less local inflammation and fibrosis, which may streamline the entire surgical procedure. Additionally, the trailing effects of immunotherapy could lead to better long-term outcomes for patients receiving immunochemotherapy during the entire perioperative treatment period [45].

Limitations

There are several limitations to this study. Firstly, while head-to-head comparisons of neoadjuvant, perioperative, and adjuvant therapies have been performed during the chemotherapy era, no such studies exist for immunochemotherapy. Second, in the included studies, some patients who received neoadjuvant or perioperative therapy might lose the chance for surgery, potentially leading to biases. All included studies focused on resectable NSCLC, maintaining homogeneity in the study population, allowing for comparability. Moreover, neoadjuvant therapy, being a stronger intervention, might yield better treatment effects intrinsically than adjuvant therapy, which is a weaker intervention. Patients who are ineligible for surgery represent a portion of the risk spectrum. Third, EFS and DFS primarily compare progression-free survival or mortality post-treatment in these studies, making the use of PFS as a substitute somewhat justified, although it may lead to biases. Fourth, while the populations in the included studies were similar, the variation in staging is considerable, with the TNM staging system transitioning from the 7th to the 8th edition, and some studies have even incorporated descriptions from the 9th edition (e.g., multiple descriptions of N2), potentially resulting in bias. Fifth, some treatments involved 4 cycles. Others completed 3 cycles of neoadjuvant therapy, which may affect surgical resection rates and long-term prognoses as well [46]. Finally, there is a lack of sufficient studies offering stratified OS data at present; we anticipate enhancements in future research.

Conclusion

This meta-analysis revealed that neoadjuvant and perioperative immunochemotherapy offers improved OS benefits compared to chemotherapy for the total population. Long-term immunotherapy maintenance in adjuvant and perioperative settings introduces additional adverse events, requiring a balance between benefits and improvements in survival. In both PDL1 < 1% patients and those with lung adenocarcinoma, no significant PFS benefits were observed for any type of immunotherapy compared to chemotherapy. The need for immunotherapy maintenance in this patient group may require reassessment. Preoperative immunotherapy provides significant advantages, necessitating further predictive assessments to ensure appropriate treatment continuation. We anticipate that future phase III clinical trials will further confirm the results involving adjuvant chemotherapy versus neoadjuvant and perioperative therapies.

Abbreviations

AAC	Adjuvant atezolizumab chemotherapy
AC	Adjuvant chemotherapy
AIC	Adjuvant chemoimmunotherapy
APC	Adjuvant pembrolizumab chemotherapy
DFS	Disease-free survival
EFS	Event-free survival
FFS	Failure-free survival
HR	Hazard ratio
MPR	Major pathologic response
NC	Neoadjuvant chemotherapy
NCC	Neoadjuvant camrelizumab chemotherapy
NIC	Neoadjuvant chemoimmunotherapy
NNC	Neoadjuvant nivolumab chemotherapy
NSCLC	Non-small cell lung cancer
OS	Overall survival
PC	Perioperative chemotherapy
pCR	Pathologic complete response
PDC	Perioperative durvalumab chemotherapy
PFS	Progression-free survival
PIC	Perioperative chemoimmunotherapy
PNC	Perioperative nivolumab chemotherapy
PPC	Perioperative pembrolizumab chemotherapy
PTRC	Perioperative toripalimab chemotherapy
PTSC	Perioperative tislelizumab chemotherapy

Supplementary Information

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Supplementary Material 1. Figure S1. PRISMA_2020_flow_diagram_new_SRs_v1.

Supplementary Material 2. Figure S2. Risk of bias graph.

Supplementary Material 3. Figure S3. Risk of bias summary.

Supplementary Material 4. Figure S4. Combined analysis of network diagram.

Supplementary Material 5. Figure S5. Separate Analysis of Network Diagram.

Supplementary Material 6. Table S1. Search terms and results for each electronic database.

Authors' contributions

YL and DL acted as principal investigators; they had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. DJ and QZ were responsible for the study concept and design, and supervised the study. All of the authors contributed to the acquisition, analysis, or interpretation of the data, and critical revision of the manuscript for important intellectual content. DJ and QZ drafted the manuscript. ZYM and YL conducted the statistical analysis. DJ, QZ, and YL provided administrative, technical, and material support. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

All relevant data are within the manuscript and its additional files.

Declarations

Competing interests
The authors declare no competing interests.

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