Neoadjuvant Immunotherapy and Non–Small Cell Lung Cancer

A Systematic Review and Meta-analysis of Randomized Controlled Trials

Shaofu Yu, MS,‡ Shasha Zhai, BS,† Qian Gong, MS,§ Chunhong Xiang, BS,* Jianping Gong, BS,* Lin Wu, MD,‡ and Xingxiang Pu, MD‡*

Objectives: To systematically evaluate the effectiveness and safety of neoadjuvant immunotherapy for patients with non–small cell lung cancer (NSCLC).

Methods: Randomized controlled trials of neoadjuvant immunotherapy in treating patients with NSCLC were comprehensively retrieved from electronic databases, eligible studies, previous systematic reviews and meta-analyses, guidelines, and conference abstracts. The meta-analysis was performed by the Stata/SE 12.0 software.

Results: Eleven randomized controlled trials were eventually included. The results of the meta-analysis showed that neoadjuvant immunochemotherapy significantly improved the objective response rate compared with neoadjuvant chemotherapy (CT; 62.46% vs 41.88%, $P = 0.003$), but the objective response rate of neoadjuvant double-immunotherapy was roughly comparable to that of neoadjuvant single-immunotherapy (15.74% vs 10.45%, $P = 0.387$). Major pathologic response (MPR) rate and pathologic complete response (pCR) rate of neoadjuvant immunochemotherapy and neoadjuvant double-immunotherapy were significantly superior to neoadjuvant CT alone and neoadjuvant single-immunotherapy, respectively. Compared with neoadjuvant CT alone, neoadjuvant immunochemotherapy increased the down-staging rate (40.16% vs 26.70%, $P = 0.060$), the surgical resection rate (83.69% vs 73.07%, $P = 0.231$), and R0 resection rate (86.19% vs 77.98%, $P = 0.502$), but there were no statistically significant differences. Neoadjuvant immunochemotherapy did not increase the postoperative complications rate than neoadjuvant CT alone (40.20% vs 41.30%, $P = 0.920$). In terms of safety, neoadjuvant immunochemotherapy and neoadjuvant double-immunotherapy did not increase the incidence of treatment-related adverse events (TRAEs) and the grade 3 or higher TRAEs.

Conclusions: In summary, neoadjuvant immunochemotherapy had better clinical efficacy than neoadjuvant CT for patients with NSCLC. MPR rate and pCR rate of neoadjuvant immunochemotherapy and neoadjuvant double-immunotherapy were significantly superior to neoadjuvant CT and neoadjuvant single-immunotherapy, respectively, for patients with NSCLC, showing that MPR rate and pCR rate were probably considered as alternative endpoints for survival benefit. TRAEs were comparable between the corresponding groups. The long-term survival outcome of neoadjuvant immunotherapy for patients with NSCLC needs to be further confirmed to better guide clinical practice.

Key Words: non–small cell lung cancer, NSCLC, neoadjuvant immunotherapy, randomized controlled trials, systematic review, meta-analysis

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From the *Department of Clinical Pharmacy, the Second People's Hospital of Huaihua; †Department of Trauma Surgery, the First Affiliated Hospital of Hunan University of Medicine, Huaihua; ‡The Second Department of Thoracic Medical Oncology, Hunan Cancer Hospital, Changsha; and §Department of Clinical Pharmacy, Hunan Cancer Hospital, Changsha, Hunan, China.

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Correspondence: Xingxiang Pu (puxingxiang@hnca.org.cn) and Lin Wu (wulin@hnca.org.cn), The Second Department of Thoracic Medical Oncology, Hunan Cancer Hospital, Tongzipo Road 283, Changsha, Hunan 410000, China.

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According to the latest global cancer data released by the International Agency for Research on Cancer in 2020, the global incidence and mortality of lung cancer ranked second and first, respectively, among all cancer types in the world, and the incidence and mortality rates of lung cancer in China both ranked first among all cancer types.[1] The main types of lung cancer are non–small cell lung cancer (NSCLC) and small cell lung cancer, of which NSCLC accounts for about 85%.[2]

Neoadjuvant therapy refers to the treatment performed before surgery, which aims to reduce tumor shrinkage and downstage, improve the R0 resection rate, reduce the risk of recurrence, and thus prolong disease-free survival and overall survival (OS).[3] Compared with surgery alone, neoadjuvant chemotherapy (CT) combined with surgery could improve the prognosis of patients with NSCLC, but the 5-year OS rate increased by only 5%, still <50%.[4]

For a large number of patients with NSCLC who are feasible for surgical resection, it has become an important research direction to find a neoadjuvant therapy with good tolerance that can further improve the survival period and survival rate.[5] The CheckMate 159 study[6] was the first to report the safety and feasibility of neoadjuvant immunotherapy in patients with resectable stage I to IIIA NSCLC. The results showed that neoadjuvant immunotherapy with nivolumab was well tolerated, the incidence of treatment-related adverse events (TRAEs) was only 23%, of which only one case had grade 3 adverse reactions (adverse events), and no surgery was delayed. In addition, the major pathologic response (MPR) rate was as high as 45%, the pathologic complete response (pCR) rate was 15%, and 80% of patients had no recurrence after surgery with a median follow-up time of 12 months.

The CheckMate 816 study[7] was a randomized controlled trial (RCT) of neoadjuvant nivolumab immunotherapy combined with CT versus neoadjuvant CT alone in patients with resectable stage IB to IIIA NSCLC. The results showed that compared with neoadjuvant CT alone, neoadjuvant immunochemotherapy significantly increased MPR rate (36.9% vs 8.9%, $P < 0.001$), pCR rate (24.0% vs 2.2%, $P < 0.001$), and median event-free survival (EFS; 31.6 vs 20.8 mo, $P = 0.005$), with no increase in TRAEs or the grade 3 or higher TRAEs. Based on the CheckMate 816 study, both the National Comprehensive Cancer Network guideline[8] and the Chinese Society of Clinical Oncology guideline[9] in 2022 recommended the combination of nivolumab and CT for the neoadjuvant treatment of NSCLC. On January 17, 2023, the National Medical Products Administration approved neoadjuvant nivolumab plus platinum-based CT for adult patients with resectable NSCLC (tumors ≥4 cm or positive lymph node), becoming currently the first and the only neoadjuvant immunotherapy approved for NSCLC in China.

Through a previous literature search, we found that the current systematic reviews and meta-analyses[10–17] of neoadjuvant immunotherapy in NSCLC were just based on single-arm studies, or single-arm and multiarm mixed studies, but not based on RCTs. In this study, a systematic review and meta-analysis were conducted based on the RCTs (Supplemental Materials, Table S1, Supplemental Digital Content 1, http://links.lww.com/AJCO/A493; "Preferred Reporting Items for Systematic Reviews and Meta-analyses" checklist) to evaluate the efficacy and safety of neoadjuvant immunotherapy for NSCLC, to provide more reliable clinical evidence for neoadjuvant immunotherapy of patients with NSCLC.

METHODS

Inclusion Criteria

Study Design

Randomized controlled trials.

Participants

Patients with resectable or potentially resectable stage I to IIIB NSCLC were clearly diagnosed by pathology and imaging examinations.

Interventions

The treatment group was treated with neoadjuvant immunotherapy combined with CT [immune checkpoint inhibitor (ICI)] + CT), immunotherapy combined with immunotherapy (ICI + ICI), or immunotherapy combined with radiotherapy (RT) (ICI + RT), with no limitation on immunotherapy drugs, CT drugs, or RT programs. The control group was treated with neoadjuvant CT, immunotherapy (ICI), or RT alone, and the specific scheme was the same as that of the treatment group.

Outcomes

Clinical complete response (cCR) rate, clinical partial response (cPR) rate, objective response rate (ORR), disease control rate (DCR), pCR rate, MPR rate, T-lymphocyte subsets, surgical resection rate, postoperative complications rate, thoracoscopy rate, thoracotomy rate, the incidence of TRAEs, and the grade 3 or higher TRAEs.

Exclusion Criteria

(1) Patients with NSCLC who have received antitumor treatment in the past, (2) retrospective studies, (3) case reports, reviews, or comments, (4) studies with missing or incomplete data that were not available by contacting the original author, and (5) if the study was published repeatedly, only the latest one will be included.

Search Strategy

Relevant RCTs of neoadjuvant immunotherapy in treating patients with NSCLC were comprehensively retrieved from electronic databases from inception to December 28, 2022, including PubMed, Embase, the Cochrane Library, Web of Science, and Chinese Biomedical Literature Database. We used search terms, such as "immunotherapy," "immune checkpoint inhibitor," "immune checkpoint blockade," neoadjuvant therapy," "neoadjuvant immunotherapy," "neoadjuvant immunochemotherapy," "induction therapy," "lung neoplasms," "lung cancer," "carcinoma of the lung," "non-small cell lung cancer," and "carcinoma, non-small-cell lung." In addition, references to all eligible studies, previous systematic reviews, and meta-analyses, as well as National Comprehensive Cancer Network, ASCO, ESMO, Chinese Society of Clinical Oncology guidelines, and conference abstracts, were reviewed to obtain other relevant studies. The specific literature search strategy was presented in Supplemental Materials, Frame S1 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A493).

Study Selection and Data Extraction

Literature screening and data extraction were completed by 2 researchers independently. In case of disagreement, they discussed with the third researcher to reach an agreement. The data were extracted according to the extraction table designed in advance, and the extracted contents included first author, publication year, clinical trial name, registration number, type of literature, study phase, tumor stage, study arms, interventions, cases, sex, pathologic type, smoking status, Eastern Cooperative Oncology Group, programmed cell death ligand 1 (PD-L1) expression level, and outcomes.

Assessment of Risk of Bias

Two authors researchers independently assessed the methodological quality of the included RCTs using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook/PDF/v5.2/chapter-08), and the risks of bias were classified as low, high, or unclear risk.

Statistical Analysis

Dichotomous data were presented as relative risk (RR) or risk difference (RD) with 95% CI, and continuous data were presented as weighted mean difference (WMD) with 95% CI. Heterogeneity among the studies was evaluated by χ^2 and I^2 tests. When high homogeneity among the studies was presented with $P > 0$ and $I^2 \leq 50\%$, the fixed-effect model was used to pool the data. Otherwise, the random-effect model was applied[18]. A statistically significant difference was defined as $P < 0.05$. The meta-analysis was conducted using the Stata/SE 12.0 software. Begg tests were applied to explore publication bias for each outcome which included 10 or more studies.

RESULTS

The Selection and Characteristics of Included Studies

A total of 1370 relevant literature were obtained through a comprehensive search. After literature screening, 11 RCTs[7,19–28] were finally included, containing 971 patients. The "Preferred Reporting Items for Systematic Reviews and Meta-analyses" flow diagram is shown in Figure 1. The baseline characteristics of the included studies are presented in Table 1 and Table 2.

Assessment of Methodological Quality

There were different degrees of bias in the methodological quality of the included studies. Eight studies[7,19–23,26,28] did not specify the method of random sequence generation, so they were judged as "unclear risk." One study[24] adopted "block randomization," and 2 studies[25,27] adopted "random number table method," so they were all judged as "low risk." All the studies were judged as "unclear risk" because none mentioned allocation concealment methods. Four studies[7,20,22,24] were judged as "high risk" with "open-label," and other studies[19,21,23,25–28] did not mention blinding and were judged as "unclear risk." In terms of selective outcome reporting, one or more outcomes concerned by 6 studies[19,23–26,28] were not fully reported, so they were determined as "high risk," and the remaining studies[7,20–22,27] were determined as "low risk." All studies did not mention incomplete outcome data and other sources of bias, and were, therefore, judged as "unclear risk." Methodology quality assessment results of included studies are presented in Table 3.

Meta-analysis Results

The summary of meta-analysis results is summarized in Table 4. The outcomes of the included studies are shown in Supplemental Materials, Table S2 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A493) The detailed forest plots are presented in Supplemental Materials, Figures S1 to S17 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A493).

Radiologic Response

Clinical Complete Response Rate

Five studies[7,19,25,27,28] compared the cCR rate of patients with NSCLC between neoadjuvant immunochemotherapy and CT, and the result showed that there was no statistically significant difference (RR = 1.69, 95% CI: 0.94~3.04, P = 0.079). One study[24] described the cCR rate of patients with NSCLC treated with neoadjuvant immunoradiotherapy versus immunotherapy, and no patients in both groups obtained cCR.

Clinical Partial Response Rate

Six studies[7,19,21,25,27,28] and 2 studies[20,26], respectively, compared the cPR rate of patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy. The results showed that the cPR rate of patients with NSCLC was significantly increased by neoadjuvant immunochemotherapy compared with CT alone (RR = 1.29, 95% CI: 1.06~1.57, P = 0.010), but there was no statistically significant difference between neoadjuvant double-immunotherapy and single-immunotherapy (RR = 0.94, 95% CI: 0.39~2.22, P = 0.881).

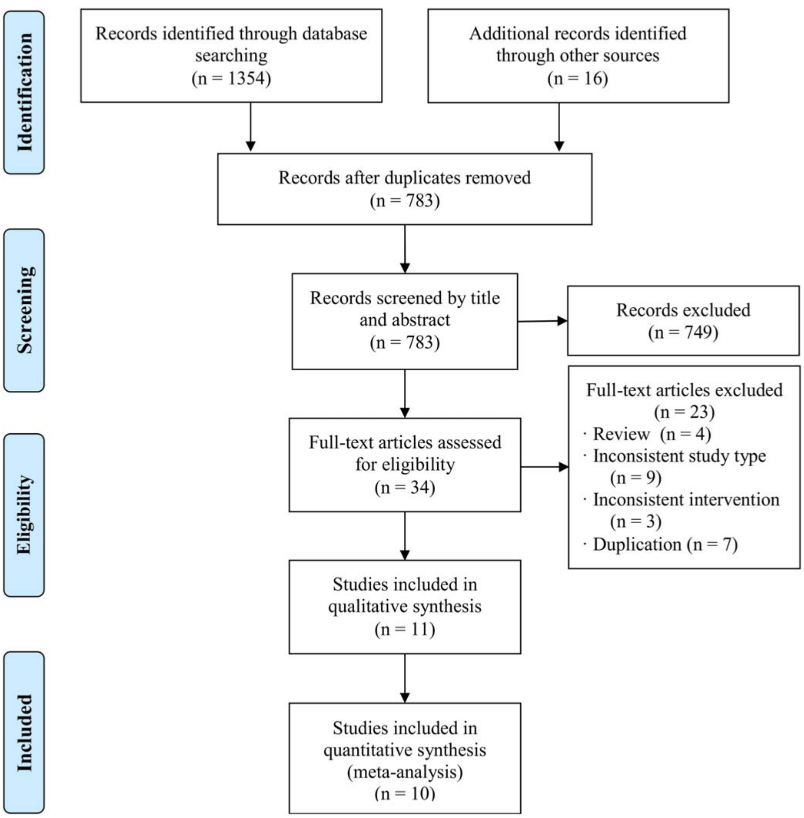

FIGURE 1. "Preferred Reporting Items for Systematic Reviews and Meta-analyses" flow diagram of the selection process of the studies included in the systematic review and meta-analysis. full color online

TABLE 1. Characteristics of Included Studies

References	Clinical trial	Registration number	Type of literature	Literature language	Study phase	Study arms	Interventions	Cases (each arm, n)	Outcomes
Bai[19]	—	—	Article	Chinese	—	Double arms	Arm 1: ICI + CT camrelizumab (PD-1 inhibitor) 200 mg/sintilimab (PD-1 inhibitor) 200 mg + paclitaxel (albumin-bound) 260 mg/m^2 + cisplatin 75 mg/m^2 q21d for 2 cycles Arm 2: CT. The CT methods were similar to those of arm 1	34/31	cCR rate, cPR rate, ORR, DCR, pCR rate, MPR rate, T-lymphocyte subsets, surgical resection rate, postoperative complications rate, thoracoscopy rate, thoracotomy rate, the incidence of TRAEs, grade 3 or higher TRAEs
Cascone[20]	NeoCOAST	NCT03794544	Conference abstract	English	II	Four arms	Arm 1: ICI + ICI durvalumab (PD-L1 inhibitor) 1500 mg q28d for 1 cycle + oleclumab (CD73 inhibitor) 3000 mg q14d for 2 cycles Arm 2: ICI + ICI durvalumab (PD-L1 inhibitor) 1500 mg q28d for 1 cycle + monalizumab (NKG2A inhibitor) 750 mg q14d for 2 cycles Arm 3: ICI + ICI durvalumab (PD-L1 inhibitor) 1500 mg q28d for 1 cycle + danvatirsen (STAT3 inhibitor) 200 mg d1, d3, d5 of week 0 (7 d danvatirsen lead-in period) for 1 cycle and 200 mg d1 q7d for 4 cycles Arm 4: ICI durvalumab (PD-L1 inhibitor) 1500 mg q28d for 1 cycle	21/20/16/27	cPR rate, ORR, DCR, pCR rate, MPR rate, the surgical resection rate, the incidence of TRAEs, the grade 3 or higher TRAEs
Feng[21]	—	—	Article	English	—	Double arms	Arm 1: ICI + CT pembrolizumab (PD-1 inhibitor)/toripalimab (PD-1 inhibitor) + gemcitabine/paclitaxel/paclitaxel (albumin-bound) + cisplatin/carboplatin q21d for 2 cycles Arm 2: CT. The CT methods were similar to those of arm 1	8/13	cPR rate, ORR, DCR, pCR rate, MPR rate, T-lymphocyte subsets, the surgical resection rate, R0 resection rate, the down-staging rate, the surgical delay rate, the incidence of TRAEs, the grade 3 or higher TRAEs
Forde[7]	CheckMate 816	NCT02998528	Article	English	III	Double arms	Arm 1: ICI + CT nivolumab (PD-1 inhibitor) 360 mg + pemetrexed + cisplatin/paclitaxel + carboplatin (NSQ) or gemcitabine + cisplatin /paclitaxel + carboplatin (SQ) or paclitaxel + carboplatin (both) q21d for 3 cycles Arm 2: CT pemetrexed + cisplatin (NSQ) or vinorelbine/docetaxel/gemcitabine + cisplatin (SQ) or paclitaxel + carboplatin (both) q21d for 3 cycles	179/179	cCR rate, cPR rate, ORR, DCR, pCR rate, MPR rate, surgical resection rate, R0 resection rate, down-staging rate, surgical delay rate, thoracoscopy rate, thoracotomy rate, the incidence of TRAEs, grade 3 or higher TRAEs
Mariano[22]	NADIM II	NCT03838159	Conference abstract	English	II	Double arms	Arm 1: ICI + CT nivolumab (PD-1 inhibitor) 360 mg + paclitaxel 200 mg/m^2 + carboplatin AUC5 q21d for 3 cycles Arm 2: CT. The CT methods were similar to those of arm 1	57/29	pCR rate, MPR rate, surgical resection rate, down-staging rate, the incidence of TRAEs, grade 3 or higher TRAEs

Schuler[23]	NEOpredict-Lung	NCT04205552	Conference abstract	English	II	Double arms	Arm 1: ICI + ICI nivolumab (PD-1 inhibitor) 240 mg + relatlimab (LAG-3 inhibitor) 80 mg q14d for 2 cycles Arm 2: ICI nivolumab (PD-1 inhibitor) 240 mg q14d for 2 cycles	30/30	ORR, pCR rate, MPR rate, the surgical resection rate, R0 resection rate, the incidence of TRAEs, the grade 3 or higher TRAEs
Altorki[24]	—	NCT02904954	Article	English	II	Double arms	Arm 1: ICI + RT durvalumab (PD-L1 inhibitor) 1120 mg q21d for 2 cycles + SBRT 8 Gy × 3 fractions* Arm 2: ICI. The ICI methods were similar to those of arm 1	30/30	cCR rate, cPR rate, ORR, DCR, pCR rate, MPR rate, R0 resection rate, surgical resection rate, surgical delay rate, thoracoscopy rate, thoracotomy rate, grade 3 or higher TRAEs
Bai[25]	—	ChiCTR2000037950	Article	Chinese	—	Double arms	Arm 1: ICI + CT camrelizumab (PD-1 inhibitor) 200 mg d1 + paclitaxel (albumin-bound) 260 mg/m^2 d1 + cisplatin 75 mg/m^2 d2-d3 q21d for 2 cycles Arm 2: CT. The CT methods were similar to those of arm 1	34/34	cCR rate, cPR rate, ORR, DCR, pCR rate, MPR rate, T-lymphocyte subsets, surgical resection rate, postoperative complications rate, thoracoscopy rate, thoracotomy rate, incidence of TRAEs
Cascone[26]	NEOSTAR	NCT03158129	Article	English	II	Double arms	Arm 1: ICI + ICI nivolumab (PD-1 inhibitor) 3 mg/kg d1, d15, d29 q14d for 3 cycles + ipilimumab (CTLA-4 inhibitor) 1 mg/kg d1 for 1 cycle Arm 2: ICI nivolumab (PD-1 inhibitor) 3 mg/kg d1, d15, d29 q14d for 3 cycles	21/23	cCR rate, cPR rate, ORR, DCR, pCR rate, MPR rate, T-lymphocyte subsets, surgical resection rate, R0 resection rate, surgical delay rate, the incidence of TRAEs, grade 3 or higher TRAEs
Liu[27]	—	—	Article	Chinese	—	Double arms	Arm 1: ICI + CT pembrolizumab (PD-1 inhibitor) 200 mg d1 + vinorelbine 25 mg/m^2 d1, d8 + cisplatin 20 mg/m^2 d1, d8 q21d for 2 cycles Arm 2: CT. The CT methods were similar to those of arm 1	48/50	cCR rate, cPR rate, ORR, DCR, T-lymphocyte subsets
Lei[28]	—	NCT04338620	Conference abstract	English	II	Double arms	Arm 1: ICI + CT camrelizumab (PD-1 inhibitor) 200 mg d1 + paclitaxel (albumin-bound) 130 mg/m^2 d1, d8 + cisplatin 75 mg/m^2 d1 q21d for 3 cycles Arm 2: CT. The CT methods were similar to those of arm 1	14/13	cCR rate, cPR rate, ORR, pCR rate, MPR rate, surgical resection rate, the incidence of TRAEs

*Three consecutive daily fractions of 8 Gy stereotactic body radiotherapy delivered to the primary tumor immediately before the first cycle of durvalumab.

cCR indicates clinical complete response; cPR, clinical partial response; CT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; ICI, immune checkpoint inhibitor; LAG-3, lymphocyte activation gene 3; MPR, major pathologic response; NKG2A, natural killer cell receptor; NSQ, nonsquamous; ORR, objective response rate; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SQ, squamous; STAT3, signal transducer and activator of transcription 3; TRAE, treatment-related adverse event.

TABLE 2. A Summary of Patient Baseline Characteristics in Included Studies

References	Tumor stage	Study arms	Cases (each arm, n)	AC (each arm, n)	SCC (each arm, n)	Sex; M:F (each arm, n)	Smoking status; never: current – former (each arm, n)	ECOG PS 0:1 (each arm, n)	PD-L1 TPS <1%: ≥1%: NM (each arm, n)
Bai[19]	IIIA	Double arms	34/31	15/12	16/17	20:14/18:13	16:18/12:19	—	14:20:0/21:10:0
Cascone[20]	I~IIIA	Four arms	21/20/16/27	14/11/8/18	7/6/4/9	12:9/14:6/10:6/14:13	1:20/1:19/1:15/6:21	12:9/12:8/10:6/19:7	6:5:10/2:6:12/5:2:9/3:6:18
Feng[21]	IIA~IIIB	Double arms	8/13	—	7/12	8:0/12:1	0:8/1:12	—	—
Forde[7]	IB~IIIA	Double arms	179/179	—	87/95	128:51/127:52	19:160/20:158	124:55/117:62	78:89:12/77:89:13
Mariano[22]	IIIA~IIIB	Double arms	57/29	25/11	21/14	36:21/16:13	5:52/0:29	31:26/16:13	—
Schuler[23]	IB~IIIA	Double arms	30/30	15/13	9/10	17:13/15:15	—	—	8:22:0/6:24:0
Altorki[24]	I~IIIA	Double arms	30/30	18/16	12/11	15:15/16:14	4:26/6:24	23:7/21:9	6:23:1/15:13:2
Bai[25]	IIIA~IIIB	Double arms	34/34	16/14	15/18	21:13/19:15	9:25/12/22	—	16:18:0/23:11:0
Cascone[26]	IA~IIIA	Double arms	21/23	13/13	7/10	13:8/15:8	3:18/5:18	10:11/16:7	—
Liu[27]	IIIB	Double arms	48/50	—	—	25:23/26:24	—	—	—
Lei[28]	IIIA~IIIIB	Double arms	14/13	—	—	—	—	—	—

AC indicates adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; NM: not mentioned; PD-L1, programmed cell death ligand 1; PS, performance status; SCC: squamous cell carcinoma; TPS, tumor proportion score.

TABLE 3. Methodology Quality Assessment of Included Studies

References	Random sequence generation	Allocation concealment	Blinding: Participants and personnel	Blinding: Outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Bai[19]	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	Unclear
Cascone[20]	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Feng[21]	Unclear	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Forde[7]	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Mariano[22]	Unclear	Unclear	High risk	High risk	Unclear	Low risk	Unclear
Schuler[23]	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	Unclear
Altorki[24]	Low risk	Unclear	High risk	High risk	Unclear	High risk	Unclear
Bai[25]	Low risk	Unclear	Unclear	Unclear	Unclear	High risk	Unclear
Cascone[26]	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	Unclear
Liu[27]	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Lei[28]	Unclear	Unclear	Unclear	Unclear	Unclear	High risk	Unclear

One study[24] found that compared with neoadjuvant immunotherapy alone, neoadjuvant immunoradiotherapy significantly improved the cPR rate of patients with NSCLC ($P = 0.001$).

Objective Response Rate

Six studies[7,19,21,25,27,28] and 3 studies[20,23,26], respectively, described ORR of patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy. The results presented that ORR of patients with NSCLC was significantly improved by neoadjuvant immunochemotherapy than CT alone (RR = 1.31, 95% CI: 1.09~1.56, $P = 0.003$), but there was no statistically significant difference between neoadjuvant double-immunotherapy and single-immunotherapy (RR = 1.35, 95% CI: 0.68~2.66, $P = 0.387$). One study[24] showed that neoadjuvant immunoradiotherapy significantly increased the cPR rate of patients with NSCLC compared with neoadjuvant immunotherapy alone ($P = 0.001$).

Disease Control Rate

Five studies[7,19,21,25,27] and 2 studies[20,26] described DCR of patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy, respectively. The results presented that there were no statistically significant differences between neoadjuvant immunochemotherapy versus CT (RR = 1.06, 95% CI: 0.94~1.20, $P = 0.351$) and neoadjuvant double-immunotherapy versus single-immunotherapy (RR = 0.99, 95% CI: 0.79~1.25, $P = 0.959$). One study[24] showed that there was no statistically significant difference in DCR of patients with NSCLC between neoadjuvant immunoradiotherapy and immunotherapy alone ($P = 0.085$).

Pathologic Response

Pathologic Complete Response Rate

Six studies[7,19,21,22,25,28] and 2 studies[20,26], respectively, compared the pCR rate of patients with NSCLC treated by neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy. The results showed that there were statistically significant differences between neoadjuvant immunochemotherapy versus CT (RR = 5.06, 95% CI: 2.86~8.97, $P = 0.000$) and neoadjuvant double-immunotherapy versus single-immunotherapy (RR = 2.84, 95% CI: 1.05~7.71, $P = 0.040$). One study[24] showed that compared with neoadjuvant immunotherapy alone, neoadjuvant immunoradiotherapy significantly increased the pCR rate of patients with NSCLC ($P = 0.002$).

Major Pathologic Response Rate

Six studies[7,19,21,22,25,28] and 2 studies[20,26] described the MPR rate of patients with NSCLC treated by neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy, respectively. The results found that MPR rates were both significantly increased in neoadjuvant immunochemotherapy versus CT (RR = 2.38, 95% CI: 1.71~3.33, $P = 0.000$) and neoadjuvant double-immunotherapy versus single-immunotherapy (RR = 1.93, 95% CI: 1.06~3.51, $P = 0.032$). One study[24] showed that there was a statistically significant difference in the MPR rate of patients with NSCLC treated with neoadjuvant immunoradiotherapy versus immunotherapy alone ($P < 0.001$).

Surgery-related Outcomes

The Down-staging Rate

Three studies[7,21,22] compared the down-staging rate of patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT, and the result found that there was no statistically significant difference (RR = 1.32, 95% CI: 0.99~1.77, $P = 0.060$).

The Surgical Resection Rate

Seven studies[7,19,21,22,25,27,28] and 3 studies[20,23,26] compared the surgical resection rate of patients with NSCLC treated by neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy, respectively. The results showed that there was no statistically significant difference between neoadjuvant immunochemotherapy versus CT (RR = 1.08, 95% CI: 0.95~1.22, $P = 0.231$) and neoadjuvant double-immunotherapy versus single-immunotherapy (RR = 0.99, 95% CI: 0.81~1.20, $P = 0.884$). One study[24] found that the surgical resection rate of patients with NSCLC treated with neoadjuvant immunoradiotherapy versus immunotherapy alone was equal.

R0 Resection Rate

Three studies[7,21,22] and 2 studies[23,25], respectively, compared the R0 resection rate of patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy. The results showed that there were no statistically significant differences between neoadjuvant immunochemotherapy versus CT (RR =

TABLE 4. Summary Table of Meta-analysis Results

Outcomes	No. trials	Test for heterogeneity		Effect model	Results of meta-analysis	
		P	I^2 (%)		Effect size (95% CI)	*P*
Radiologic response						
cCR rate						
ICI + CT vs CT	5[7,19,25,27,28]	0.532	0	Fixed-effect model	RR: 1.69 (0.94, 3.04)	0.079
cPR rate						
ICI + CT vs CT	6[7,19,21,25,27,28]	0.945	0	Fixed-effect model	RR: 1.29 (1.06, 1.57)	0.010
ICI + CT vs ICI	2[20,26]	0.817	0	Fixed-effect model	RR: 0.94 (0.39, 2.22)	0.881
ORR						
ICI + CT vs CT	6[7,19,21,25,27,28]	0.974	0	Fixed-effect model	RR: 1.31 (1.09, 1.56)	0.003
ICI + CT vs ICI	3[20,23,26]	0.766	0	Fixed-effect model	RR: 1.35 (0.68, 2.66)	0.387
DCR						
ICI + CT vs CT	5[7,19,21,25,27]	0.989	0	Fixed-effect model	RR: 1.06 (0.94, 1.20)	0.351
ICI + CT vs ICI	2[20,26]	0.997	0	Fixed-effect model	RR: 0.99 (0.79, 1.25)	0.959
Pathologic response						
pCR rate						
ICI + CT vs CT	6[7,19,21,22,25,28]	0.880	0	Fixed-effect model	RR: 5.06 (2.86, 8.97)	0.000
ICI + CT vs ICI	2[20,26]	0.946	0	Fixed-effect model	RR: 2.84 (1.05, 7.71)	0.040
MPR rate						
ICI + CT vs CT	6[7,19,21,22,25,28]	0.773	0	Fixed-effect model	RR: 2.38 (1.71, 3.33)	0.000
ICI + CT vs ICI	2[20,26]	0.976	0	Fixed-effect model	RR: 1.93 (1.06, 3.51)	0.032
Surgery-related outcomes						
Down-staging rate						
ICI + CT vs CT	3[7,21,22]	0.505	0	Fixed-effect model	RR: 1.32 (0.99, 1.77)	0.060
Surgical resection rate						
ICI + CT vs CT	7[7,19,21,22,25,27,28]	0.996	0	Fixed-effect model	RR: 1.08 (0.95, 1.22)	0.231
ICI + CT vs ICI	3[20,23,26]	0.997	0	Fixed-effect model	RR: 0.99 (0.81, 1.20)	0.884
R0 resection rate						
ICI + CT vs CT	3[7,21,22]	0.810	0	Fixed-effect model	RR: 1.06 (0.89, 1.26)	0.502
ICI + CT vs ICI	2[23,25]	0.954	0	Fixed-effect model	RR: 0.99 (0.74, 1.32)	0.942
Surgical delay rate						
ICI + CT vs CT	2[7,21]	0.858	0	Fixed-effect model	RD: −0.02 (−0.06, 0.03)	0.485
Thoracoscopy rate						
ICI + CT vs CT	3[7,19,25]	0.512	0	Fixed-effect model	RR: 1.48 (1.04, 2.10)	0.028
Thoracotomy rate						
ICI + CT vs CT	3[7,19,25]	0.541	0	Fixed-effect model	RR: 0.89 (0.74, 1.07)	0.202
Postoperative complications rate						
ICI + CT vs CT	3[7,19,25]	0.627	0	Fixed-effect model	RR: 0.99 (0.76, 1.28)	0.920
Immune function with T-lymphocyte subsets						
Positive rate of CD3+ cells						
ICI + CT vs CT	3[19,25,27]	0.057	65.0	Random-effect model	WMD: 7.01 (4.02, 10.01)	0.000
Positive rate of CD4+ cells						
ICI + CT vs CT	3[19,25,27]	0.000	98.6	Random-effect model	WMD: 13.35 (1.35, 25.34)	0.029
Positive rate of CD8+ cells						
ICI + CT vs CT	2[19,25]	0.033	78.1	Random-effect model	WMD: 6.13 (1.36, 10.90)	0.012
Ratio of CD4+/CD8+ cells						
ICI + CT vs CT	3[19,25,27]	0.285	20.4	Fixed-effect model	WMD: 0.36 (0.26, 0.45)	0.000
Safety						
The incidence of TRAEs						
ICI + CT vs CT	3[7,21,22]	0.966	0	Fixed-effect model	RR: 0.97 (0.84, 1.12)	0.675
ICI + CT vs ICI	1[20] (with four arms)	0.951	0	Fixed-effect model	RR: 1.34 (0.86, 2.09)	0.193
Grade 3 or higher TRAEs						
ICI + CT vs CT	3[7,21,22]	0.116	53.5	Random-effect model	RD: 0.01 (−0.06, 0.08)	0.815
ICI + CT vs ICI	2[20,26]	0.789	0	Fixed-effect model	RD: 0.02 (−0.05, 0.08)	0.602

cCR indicates clinical complete response; cPR, clinical partial response; CT, chemotherapy; DCR, disease control rate; ICI, immune checkpoint inhibitor; MPR, major pathologic response; ORR, objective response rate; pCR, pathologic complete response; RD, risk difference; RR, relative risk; TRAE, treatment-related adverse event; WMD, weighted mean difference.

1.06, 95% CI: 0.89~1.26, $P = 0.502$) and neoadjuvant double-immunotherapy versus single-immunotherapy (RR = 0.99, 95% CI: 0.74~1.32, $P = 0.942$). One study[24] showed that there was no statistically significant difference in the R0 resection rate of patients with NSCLC between neoadjuvant immunoradiotherapy and immunotherapy alone ($P = 0.298$).

The Surgical Delay Rate

Two studies[7,21] described the surgical delay rate of patients with NSCLC between neoadjuvant immunochemotherapy and CT, and the result found that there was no statistically significant difference (RD = −0.02, 95% CI: −0.06~0.03, $P = 0.485$). One study[24] showed that the surgical delay rate of patients with NSCLC treated with neoadjuvant immunoradiotherapy was the same as immunotherapy alone.

The Thoracoscopy Rate

Three studies[7,19,25] compared the thoracoscopy rate of patients with NSCLC between neoadjuvant immunochemotherapy and CT, and the result found that compared with neoadjuvant CT alone, patients with NSCLC treated by neoadjuvant immunochemotherapy preferred to apply thoracoscopy (RR = 1.48, 95% CI: 1.04~2.10, P = 0.028). One study[24] showed that there was no statistically significant difference in the thoracoscopy rate of patients with NSCLC treated with neoadjuvant immunoradiotherapy versus immunotherapy alone (P = 0.768).

The Thoracotomy Rate

Three studies[7,19,25] described the thoracotomy rate of patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT, and the result found that there was no statistically significant difference (RR = 0.89, 95% CI: 0.74~1.07, P = 0.202). One study[24] showed that there was no statistically significant difference in the thoracoscopy rate of patients with NSCLC between neoadjuvant immunoradiotherapy and immunotherapy alone (P = 0.768).

The Postoperative Complications Rate

Three studies[7,19,25] compared the postoperative complications rate of patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT, and the result found that there was no statistically significant difference (RR = 0.99, 95% CI: 0.76~1.28, P = 0.920). One study[24] showed that the postoperative complications rate of patients with NSCLC between neoadjuvant immunoradiotherapy and immunotherapy alone was equal.

Immune Function With T-lymphocyte Subsets

The Positive Rate of CD3+, CD4+, and CD8+ Cells

Three studies[19,25,27], 3 studies,[19,25,27] and 3 studies[19,25], respectively, described the change of the positive rate of CD3+, CD4+, and CD8+ cells in patients with NSCLC before and after treatment with neoadjuvant immunochemotherapy versus CT. The results showed that compared with neoadjuvant CT alone, neoadjuvant immunochemotherapy significantly improved the positive rate of CD3+ cells (WMD = 7.01, 95% CI: 4.02~10.01, P = 0.0008), CD4+ cells (WMD = 13.35, 95% CI: 1.35~25.34, P = 0.029), and CD8+ cells (WMD = 6.13, 95% CI: 1.36~10.90, P = 0.012).

The Ratio of CD4+/CD8+ Cells

Three studies[19,25,27] compared the change in the ratio of CD4+/CD8+ cells in patients with NSCLC before and after treatment with neoadjuvant immunochemotherapy versus CT. The result found that compared with neoadjuvant immunotherapy alone, neoadjuvant immunochemotherapy significantly increased the ratio of CD4+/CD8+ cells (WMD = 0.36, 95% CI: 0.26~0.45, P = 0.000).

Safety

The Incidence of Treatment-related Adverse Events

Three studies[7,21,22] and 1 study (with 4 arms),[20] respectively, compared the incidence of TRAEs in patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy in detail. The results found that there were no statistically significant differences between neoadjuvant immunochemotherapy versus CT (RR = 0.97, 95% CI: 0.84~1.12, P = 0.675) and neoadjuvant double-immunotherapy versus single-immunotherapy (RR = 1.34, 95% CI: 0.86~2.09, P = 0.193).

The Grade 3 or Higher Treatment-related Adverse Events

Three studies[7,21,22] and 2 studies[20,26], respectively, described the grade 3 or higher TRAEs of patients with NSCLC treated with neoadjuvant immunochemotherapy versus CT and neoadjuvant double-immunotherapy versus single-immunotherapy in detail. The results showed that there were no statistically significant differences between neoadjuvant immunochemotherapy versus CT (RD = 0.01, 95% CI: −0.06~0.08, P = 0.815) and neoadjuvant double-immunotherapy versus single-immunotherapy (RD = 0.02, 95% CI: −0.05~0.08, P = 0.602). One study[24] showed that there was no statistically significant difference in the grade 3 or higher TRAEs of patients with NSCLC between neoadjuvant immunoradiotherapy and immunotherapy alone (P = 0.739).

Publication Bias

Begg funnel plot was drawn based on the relevant studies[7,19–23,25–28] related to the outcome of "the surgical resection rate," and the result showed that there was no publication bias because of P = 0.15 (Fig. 2).

DISCUSSION

In recent years, the application of tumor immunotherapy has been advancing. Before surgery, patients with malignant tumors tend to have better performance status (PS), a more complete immune system, and a relatively large tumor volume. Moreover, the integrity of their blood vessels and lymphatic vessels ensures that the drugs can reach the lesions better, and the antigen load of antigen-presenting cells is relatively large, which makes the neoadjuvant immunotherapy cause a strong antitumor T-cell response. Therefore, the efficacy of neoadjuvant immunotherapy applied before surgery is theoretically better than that of adjuvant immunotherapy applied after surgery.[29–31] "Expert consensus on neoadjuvant immunotherapy for non–small cell lung cancer"[29] points out that patients with resectable stage IB to IIIA NSCLC can consider

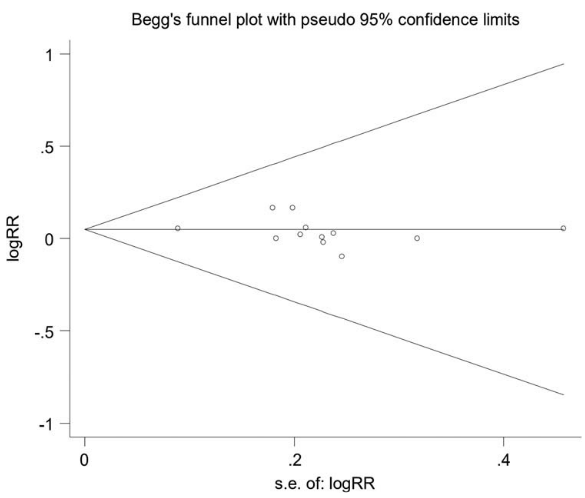

FIGURE 2. Begg funnel plot for the publication bias test.

TABLE 5. Ongoing RCTs* of Neoadjuvant Immunotherapy in Patients With NSCLC

Registration number	Clinical trial	Study phase	Start year	Tumor stage	Study arms	Interventions	Target enrolled (n)	Primary outcomes	Secondary outcomes
NCT04379635	RATIONALE 315	III	2020	II-IIIA	Double arms	Arm 1: tislelizumab (PD-1 inhibitor) + platinum-doublet CT Arm 2: platinum-doublet CT	453	MPR rate, EFS	OS, DFS, pCR rate, ORR, TRAEs, HRQoL
NCT04316364	SHR-1316-III-303	Ib/III	2020	II-IIIB	Three arms	Arm 1: adebrelimab (PD-L1 inhibitor) + carboplatin + paclitaxel (albumin-bound) Arm 2: adebrelimab (PD-L1 inhibitor) + platinum-doublet CT Arm 3: platinum-doublet CT	537	MPR rate, EFS	OS, DFS, pCR rate, ORR
NCT04158440	NEOTORCH	III	2020	II-III	Double arms	Arm 1: toripalimab (PD-1 inhibitor) + platinum-doublet CT Arm 2: platinum-doublet CT	500	MPR rate, EFS	OS, DFS, pCR rate, AEs
NCT04422392	—	II	2020	IIIA	Double arms	Arm 1: PD-1 inhibitor + platinum-doublet CT Arm 2: platinum-doublet CT	107	PFS	—
NCT04025879	CheckMate 77T	III	2019	II-IIIB	Double arms	Arm 1: nivolumab (PD-1 inhibitor) + platinum-doublet CT Arm 2: platinum-doublet CT	452	EFS	OS, pCR rate, ORR, AEs
NCT03456063	IMpower030	III	2018	II-IIIB	Double arms	Arm 1: atezolizumab (PD-L1 inhibitor) + platinum-doublet CT Arm 2: platinum-doublet CT	302	EFS	pCR rate, MPR rate, ORR, OS, DFS, HRQoL, AEs
NCT03425643	KEYNOTE-671	III	2018	II-IIIB	Double arms	Arm 1: pembrolizumab (PD-1 inhibitor) + platinum-doublet CT Arm 2: platinum-doublet CT	786	EFS, OS	pCR rate, MPR rate, AEs
NCT03800134	AEGEAN	III	2018	II-III	Double arms	Arm 1: durvalumab (PD-L1 inhibitor) + platinum-doublet CT Arm 2: platinum-doublet CT	825	EFS, pCR rate	OS, DFS, MPR rate, HRQoL

*Ongoing randomized controlled trials do not include the studies presented in this meta-analysis, but the studies that have not published any data before the deadline of literature search for the meta-analysis.

AE indicates adverse event; CT, chemotherapy; DFS, disease-free survival; EFS, event-free survival; HRQoL, health-related quality of life; MPR, major pathologic response; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, pathologic complete response; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; RCT, randomized controlled trial; TRAE, treatment-related adverse event.

neoadjuvant immunotherapy plus platinum-based CT or neoadjuvant immunotherapy alone.

The era of immunotherapy has provided important treatment means for operable lung cancer patients, especially for locally advanced lung cancer patients, and preoperative neoadjuvant therapy has brought an important opportunity for surgical treatment. How to maximize the benefits of downstaging will be an important area for us to explore. Furthermore, micrometastatic lesions can be effectively controlled through systemic therapy to achieve longer OS in patients with NSCLC after surgery.

This study multidimensionally and systematically evaluated the effectiveness and safety of neoadjuvant immunotherapy for patients with NSCLC with 17 outcomes. A total of 11 RCTs were included, including 7 studies of neoadjuvant immunochemotherapy versus CT, 3 studies of neoadjuvant double-immunotherapy versus single-immunotherapy, and 1 study of neoadjuvant immunoradiotherapy versus immunotherapy.

The results showed that neoadjuvant immunochemotherapy significantly improved ORR in patients with NSCLC compared with neoadjuvant CT (62.46% vs 41.88%, P = 0.003), indicating that neoadjuvant immunochemotherapy had better clinical efficacy. ORR of neoadjuvant double-immunotherapy was higher than that of neoadjuvant single-immunotherapy, but there was no significant statistical difference (15.74% vs 10.45%, P = 0.387). MPR rate and pCR rate of neoadjuvant immunochemotherapy and neoadjuvant double-immunotherapy were significantly superior to neoadjuvant CT alone and neoadjuvant single-immunotherapy, respectively. The CA209-8Y9 study showed that MPR or pCR achieved in patients with NSCLC was associated with better OS and EFS outcomes, and MPR and pCR could be considered as alternative endpoints for survival benefit of patients with resectable NSCLC.[32] Therefore, it was possible for patients with NSCLC to obtain better OS and EFS after neoadjuvant immunochemotherapy or neoadjuvant double-immunotherapy.

Compared with neoadjuvant CT alone, neoadjuvant immunochemotherapy increased the down-staging rate (40.16% vs 26.70%, P = 0.060), the surgical resection rate (83.69% vs 73.07%, P = 0.231), and R0 resection rate (86.19% vs 77.98%, P = 0.502), but there were no statistically significant differences. Neoadjuvant immunochemotherapy did not increase the postoperative complications rate compared with neoadjuvant CT alone (40.20% vs 41.30%, P = 0.920). In terms of safety, neoadjuvant immunochemotherapy and neoadjuvant double-immunotherapy did not increase the incidence of TRAEs and the grade 3 or higher TRAEs.

In some studies[7,20], subgroup analyses have been conducted in terms of PD-L1 expression level, smoking status, histology, PS, sex, and tumor stage, but the pooled analyses were not conducted due to incomplete data reports. Some of the included studies[7,22–24,26,28] had outcomes, including recurrence-free survival, EFS, disease-free survival, progression-free survival, or OS, but the relevant data were not reported in the corresponding studies, so the pooled analysis could not be performed.

The study still has many limitations, so these results need to be interpreted carefully. (1) The sample size of some included studies was small, and few original studies were included in some outcomes, which could potentially bias the results. (2) The included studies described less about the methods of random sequence generation and allocation concealment, which may have a certain degree of selection bias; many studies were open-labels, which may have a certain degree of implementation bias. (3) Neoadjuvant immunotherapy drugs or CT drugs were different between the included studies, which may have some influence on the results of the study. (4) The effectiveness and safety of neoadjuvant immunotherapy for patients with NSCLC may vary depending on ethnic and geographic differences of populations among included studies. (5) Due to the limited data available from included studies, subgroup analysis could not be conducted on tumor stage, pathologic type, sex, smoking status, PS, epidermal growth factor receptor and other gene expression status, and PD-L1 expression level. (6) Due to the insufficient follow-up time and the lack of mature survival outcome data in most studies, the long-term survival outcomes of neoadjuvant immunotherapy for patients with NSCLC need to be further confirmed.

Although there were many deficiencies and limitations in this meta-analysis, it is currently the first meta-analysis of neoadjuvant immunotherapy for patients with NSCLC based on RCTs. In addition, we summarized ongoing RCTs of neoadjuvant immunotherapy in patients with NSCLC, as shown in Table 5. We look forward to further updating and refining this meta-analysis when more high-quality RCT results are available.

CONCLUSION

In summary, neoadjuvant immunochemotherapy significantly improved the ORR of patients with NSCLC than neoadjuvant CT, indicating that neoadjuvant immunochemotherapy had better clinical efficacy. MPR rate and pCR rate of neoadjuvant immunochemotherapy and neoadjuvant double-immunotherapy were significantly superior to neoadjuvant CT and neoadjuvant single-immunotherapy, respectively, for patients with NSCLC, which showed that MPR rate and pCR rate were probably considered as alternative endpoints for survival benefit. TRAEs were comparable between the corresponding groups. The long-term survival outcome of neoadjuvant immunotherapy for patients with NSCLC needs to be further confirmed to better guide clinical practice.

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