Impact of Neoadjuvant Immune Checkpoint Inhibitors on Surgery and Perioperative Complications in Patients With Non–small-cell Lung Cancer: A Systematic Review

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Abstract

Several clinical trials are currently underway to evaluate immune checkpoint inhibitors (ICIs) as neoadjuvant treatment for patients with early-stage non–small-cell lung cancer (NSCLC), and their use in clinical practice is expected to increase in the future. Therefore, a proper assessment of surgical outcomes and perioperative complications after neoadjuvant ICIs is essential to establish recommendations and guidelines. We performed a systematic literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA), searching the PubMed and Scopus databases from the January 1, 2017, to the July 27, 2023, to identify potentially relevant published trials of neoadjuvant ICIs in patients with reseactable NSCLC with available information on surgical outcomes and perioperative complications. A total of 18 studies were included in the review. The rates of surgery cancellation ranged from 0% to 45.8%. Importantly, adverse events (AEs) were the least reported underlying cause, while disease progression caused from 0% to 75% of cancellations. Surgery delays ranged from 0% to 31.3% with AEs as the most frequently reported underlying cause. However, 6 out of 13 trials (46.2%) reported no surgery delays. Conversion rates from minimally invasive to open chest surgery were available for 7 trials and ranged from 0% to 53.8%. Thirty-day mortality rates ranged from 0% to 5.4%, with 11 out of 16 trials reporting 0%. A few reports described perioperative complications in detail. Considering the limited evidence available, we can preliminarily confirm that preoperative ICIs are safe and well tolerated even from the surgical perspective. Additional details on intraoperative findings from prospective controlled trials are needed to establish and disseminate guidelines and recommendations for thoracic surgeons.

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Central Message

The use of ICIs as neoadjuvant therapy in NSCLC is expected to increase. This systematic review preliminary confirms the surgical-safety profile of ICI-based regimens in this setting.

Introduction

In recent years, systemic treatments in oncology have seen remarkable advancements with the introduction of immune checkpoint inhibitors (ICIs), which have shown antitumor effects in many areas, and now represent the cornerstone of systemic therapy for several malignancies.

In non–small-cell lung cancer (NSCLC), the clinical efficacy of ICI-based regimens was first demonstrated in patients with advanced or recurrent disease,[1] although they are now mainly used as first-line treatment.[2] Subsequently, single-agent programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors have been investigated as adjuvant treatment following radical surgery for early-stage NSCLC, with and without prior adjuvant chemotherapy,[3,4] leading to the approval of atezolizumab as adjuvant treatment for completely resected stage II to III NSCLC with PD-L1 expression on tumor cells of ≥1% by the food and drug administration (FDA),[5] and with PD-L1 expression on tumor cells of ≥50% by the European Medicine Agency (EMA).[6]

With the publication of the positive efficacy results of the CheckMate 816 trial,[7,8] which assessed 3 cycles of neoadjuvant nivolumab in combination with platinum-based chemotherapy vs. chemotherapy alone, the FDA granted approval for neoadjuvant chemoimmunotherapy with nivolumab for stage IB to IIIA NSCLC.[9] In addition, several clinical trials are currently ongoing to evaluate ICI-based regimens as neoadjuvant treatment for early-stage NSCLC,[10] and their use in clinical practice as preoperative induction therapy is expected to increase in the future.

Considering this, thoracic surgeons will be increasingly called to assess efficacy outcomes and the safety profile of neoadjuvant ICI-bases regimens in the context of multidisciplinary clinical management of patients with resectable NSCLC, in order to assess the impact of these treatments on surgical procedures and perioperative complications.

In this systematic review, we summarized the information available to date on surgical outcomes and perioperative complications from clinical trials with neoadjuvant ICI-based systemic treatments and discussed their potential impact on surgical techniques and approaches.

Methods

Literature Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA).[11] We searched the PubMed (https://PubMed.ncbi.nlm.nih.gov) and Scopus (https://www.scopus.com) databases from the January 1, 2017 to the July 27, 2023, to identify potentially relevant studies. The search terms were "non-small cell lung cancer or non-small cell lung carcinoma or nonsmall cell lung cancer or nonsmall cell lung carcinoma or NSCLC," "immunotherapy or immuno-therapy or immunetherapy or immune-therapy or immune checkpoint inhibitor or nivolumab or ipilimumab or sintilimab or durvalumab or atezolizumab or pembrolizumab or avelumab or tremelimumab or camrelizumab or tislelizumab or toripalimab," and "neoadjuvant or perioperative or preoperative or peri-operative or pre-operative."

Study Selection Criteria

The inclusion criteria were as follows: 1) published studies including patients with stage I to IIIB, potentially resectable, non-metastatic NSCLC; 2) ICIs-based systemic therapy, either as monotherapy or combinations, given as neoadjuvant treatment prior to surgical resection; and 3) data availability about surgical outcomes and perioperative complications. The exclusion criteria were as follows: 1) published studies including patients with unresectable or metastatic NSCLC; 2) patients receiving other than ICIs (+/- chemotherapy) neoadjuvant systemic treatments prior to surgical resection, including chemo-radiation therapy; 3) information on the impact of neoadjuvant ICIs on surgical outcomes and perioperative complications not available; 4) studies not published in English; 5) duplicated studies; 6) study protocols, reviews, editorials, case reports/case series, retrospective studies, and meta-analyses. Because this study was a systematic review, ethical approval and informed consent to participate were not required.

The study protocol was registered in PROSPERO, an international, National Institute for Health and Research (NIHR) funded, prospective register of systematic reviews (registration code CRD42023393920; https://www.crd.york.ac.uk/prospero/#searchadvanced).

Data Extraction and Clinical Outcomes

Two authors (K.T. and S.T.) independently reviewed and extracted data from the published papers, including first author, journal name, year of publication, immunotherapy regimens, number of patients, sample size by clinical stage, surgery cancellation and surgery delay with their underlying reasons (when available), conversion from video-assisted thoracic surgery (VATS) or robot-assisted thoracic surgery (RATS) to conventional open surgery, sample size by surgical procedure, and perioperative complications, defined as: 30-day mortality, pneumonia, empyema, bronchopleural fistula, arrhythmia, prolonged air leaks, respiratory failure, and thromboembolic events. Surgery delays were defined by study authors. Disagreements between the 2 authors (K.T. and S.T.) were discussed and resolved with a third independent author (A.C.).

Results

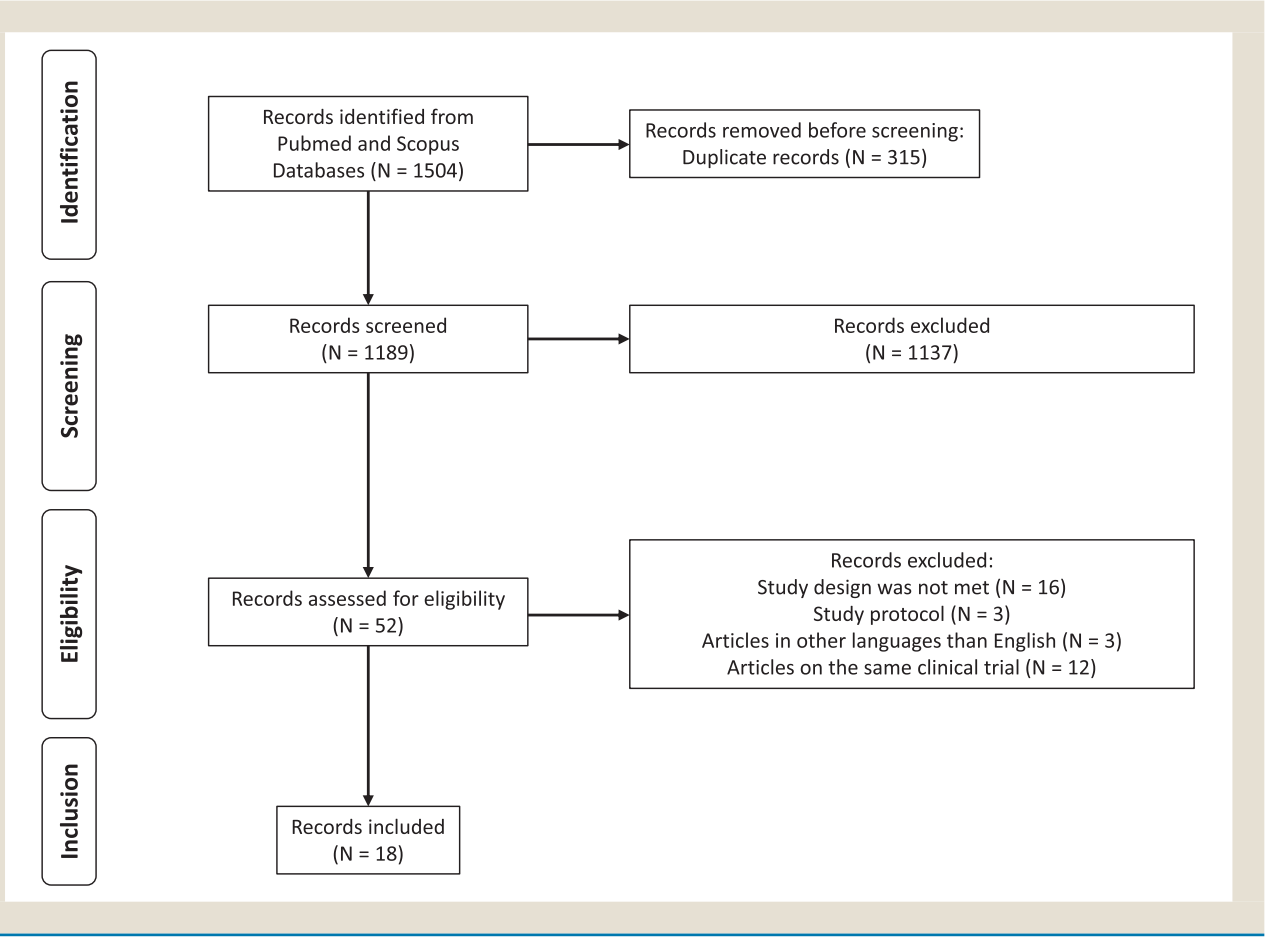
Study Selection

The initial search identified a total of 1504 potentially relevant records from the PubMed and Scopus online databases. After the exclusion of 315 duplicate records, 1189 were screened and 52 were subsequently assessed for eligibility, resulting in a total of 18 records eventually included in the analysis. A detailed PRISMA flow diagram of the study selection process is reported in Figure 1. Overall,11 trials (61.1%) included experimental treatments with chemo-immunotherapy combinations, 6 trials (33.3%) with chemo-free ICIs regimens, either PD-1/PD-L1 alone or in combination with Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) inhibitors, and 1 (5.5%) trial included single-agent PD-L1 monotherapy +/- stereotactic radiotherapy. The number of administered cycles ranged from 2 to 4, and 3 trials (16.7%) included a chemotherapy-based comparative arm. Table 1 summarizes the baseline characteristics of each study and surgical outcomes for each trial, including surgery cancellation, surgery delay, and conversion from VATS/RATS to open surgery.[8,12-28]

Surgery Cancellations

As reported in Table 1, surgery cancellation rates ranged from 0% to 45.8%. More specifically, among trials with chemo-

Figure 1 Flow diagram of the study selection process according to the PRISMA guidelines.



immunotherapy combinations, the cancellation rates ranged from 10.9% to 45.8%, while among trials with chemo-free ICIs regimens from 0% to 33.3%. Importantly, adverse events (AEs) were the least reported underlying cause, while disease progression caused from 0% to 75% of surgery cancellations. Among other underlying causes of surgery cancellations, patient's refusal, inadequate respiratory function, and difficult surgical procedure were also reported (Table 1).

Surgery Delay

Definition of surgery delay was not predefined for each clinical trial, and the surgical timing window was available for 15 trials (Supplementary Table II), ranging from 14 to 49 days after the last dose of systemic treatment. However, surgery delays according to the investigators were available for 13 trials, ranging from 0% to 31.3% (Table 1). More specifically from 0% to 20.9% among trials with chemo-immunotherapy combinations and from 0% to 31.3% among trials with chemo-free regimens. Of note, 6 trials reported no surgery delays. Treatment-related adverse events (TRAEs) were the most frequently reported underlying cause of surgery delays.

Conversion From VATS or RATS to Open Surgery

Conversion rates from minimally invasive surgery (eg, VATS or RATS) to open chest surgery were available for 7 trials only and ranged from 0% to 53.8% as summarized in Table 1.

Perioperative Complications

Table 2 summarizes available information on surgical procedures and perioperative complications. Overall, surgical procedures were available for 16 trials (88 .9%) and pulmonary lobectomy was the most performed surgery. Thirty days mortality ranged from 0% to 5.4%, with 11 trials (61.1%) reporting 0%. Few reports described perioperative complications in detail, with pneumonia ranging from 0% to 5.7%, empyema from 0% to 5%, bronchopleural fistula from 0% to 25%, arrhythmia from 0% to 30%, prolonged air leaks from 0% to 16%, respiratory failure from 0% to 3.8%, and thromboembolic events from 0% to 7.7% (Table 2).

Discussion

To the best of our knowledge, this is the first systematic review assessing the impact of neoadjuvant ICI-based systemic treatments on surgery and perioperative complications in patients with resectable NSCLC. Considering that ICIs and other immune-based treatments will be increasingly used as neoadjuvant therapy in this

Table 1 Summary of the Included Studies on Impact of Neoadjuvant Immune Checkpoint Inhibitors on Surgery in Patients With Non-Small Cell Lung Cancer. Full Details Including TNM Staging and AJCC Version is Presented as Supplementary Table 1

Study	Study Phase/Design	Immunotherapy	No. of Patients	Surgery Cancellation, n (%)	Surgery Delay, n (%)	Conversion from VATS or RATS to Open, n (%)
Yang CJ et al. Ann Thorac Surg 2018	Phase II Noncomparative	Cycle 1 paclitaxel (175 mg/m^2) + cisplatin (75 mg/m^2) or carboplatin (AUC 6) and cycles 2 and 3 of the same chemotherapy + ipilimumab (10 mg/kg) every 3 wk	24	11/24 (45.8) cancer progression 2, AE 1, others 8[e]	2/13 (15.4) TRAE 2	3/12 (25.0)
Bott MJ et al. J Thorac Cardiovasc Surg 2019	Phase II Noncomparative	2 cycles of nivolumab (3 mg/kg) every 2 wk	21	1/21 (4.8) cancer progression 1, AE 0, others 0	0/20 (0.0)	7/13 (53.8) -
Shu CA et al. Lancet Oncol 2020	Phase II Noncomparative	2 or 4 cycles of atezolizumab (1200 mg) + nab-paclitaxel (100 mg/m^2) + carboplatin (AUC 5) every 3 wk	30	4/30 (13.3) cancer progression 1, AE 0, others 3[f]	0/26 (0.0) -	NR
Reuss JE et al. J Immunother Cancer 2020	Phase Ib/II Noncomparative	3 cycles of nivolumab (3 mg/kg) every 2 wk + 1 dose of ipilimumab (1 mg/kg)	9	3/9 (33.3) cancer progression 3, AE 0, others 0	0/6 (0.0) -	NR
Tfayli A et al. Cancer Med 2020	Phase II Noncomparative	3 cycles of chemotherapy every 3 wk + 4 doses of avelumab (10 mg/kg) every 2 wk[a]	15	4/15 (26.7) cancer progression 1, AE 0, others 3[g]	NR	NR
Eichhorn F et al. Lung Cancer 2021	Phase II Noncomparative	2 cycles of pembrolizumab (200 mg) every 3 wk	15	0/15 (0.0) cancer progression 0, AE 0, others 0	1/15 (6.7) TRAE 1	NR
Tong BC et al. J Thorac Cardiovasc Surg 2022	Phase II Noncomparative	2 cycles of pembrolizumab (200 mg) every 3 wk	30	5/30 (16.7) cancer progression 1, AE 0, others 4[h]	1/25 (4.0) TRAE 1	5/23 (21.7)
Altorki NK et al. Lancet Oncol 2021	Phase II Comparative	2 cycles of durvalumab (1120 mg) every 3 wk	30	4/30 (13.3) cancer progression 2, AE 1, others 1[i]	1/26 (3.8) patient's wishes 1	NR
		2 cycles of durvalumab (1120 mg) every 3 wk + stereotactic body radiotherapy (8 Gy x 3 fractions)	30	4/30 (13.3) cancer progression 3, AE 1, others 0	1/26 (3.8) TRAE 1	NR
Rothschild SI et al. J Clin Oncol 2021	Phase II Noncomparative	3 cycles of chemotherapy every 3 wk + 2 doses of durvalumab (750 mg) every 2 wk[b]	67	12/67 (17.9) cancer progression 6, AE 3, others 3[j]	NR	NR
Zhao ZR et al. Oncoimmunology 2021	Phase II Noncomparative	3 cycles of chemotherapy + toripalimab (240 mg) every 3 wk[c]	33	3/33 (9.1) cancer progression 1, AE 0, others 2[k]	0/30 (0.0) -	1/6 (16.7)
Zhang P et al. Ann Thorac Surg 2022	Phase II Non comparative	2 or 4 cycles of chemotherapy + sintilimab (200 mg) every 3 weeks[d]	50	20/50 (40.0) cancer progression 2, AE 2, others 16[l]	0/30 (0.0) -	NR

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Table 1 (*continued*)

Study	Study Phase/Design	Immunotherapy	No. of Patients	Surgery Cancellation, n (%)	Surgery Delay, n (%)	Conversion from VATS or RATS to Open, n (%)
Sepesi B et al. J Thorac Cardiovasc Surg 2022	Phase II Comparative	3 cycles of nivolumab (3 mg/kg) every 2 wk	23	2/23 (8.7) cancer progression 1, AE 1, others 0	3/21 (14.3) TRAE 0, others 3[t]	1/6 (16.7)
		3 cycles of nivolumab (3 mg/kg) every 2 wk + 1 dose of ipilimumab (1 mg/kg)	21	5/21 (23.8) cancer progression 1, AE 1, others 3[m]	5/16 (31.3) TRAE 1, others 4[u]	1/4 (25.0)
Sun C et al. J Cancer Res Clin Oncol 2022	Phase II Noncomparative	2 or 3 cycles of nab-paclitaxel (135 mg/m^2) + carboplatin (AUC 5) + sintilimab (200 mg) every 3 wk	20	4/20 (20.0) cancer progression 1, AE 0, others 3[n]	0/16 (0.0) -	0
Forde PM et al. N Engl J Med 2022	Phase III Comparative	3 cycles of platinum-doublet chemotherapy + nivolumab (360 mg) every 3 wk	176	28/176 (15.9) cancer progression 12, AE 2, others 14o	31/148 (20.9) TRAE 6, others 25[v]	17/61 (27.9)
Gao S et al. J Thorac Oncol 2020	Phase Ib Noncomparative	2 cycles of sintilimab (200 mg) every 3 wk	40	3/40 (7.5) cancer progression 1, AE 0, others 2[p]	2/37 (5.4) TRAE 2	NR
Provencio M et al. Lancet Oncol 2020	Phase II Noncomparative	3 cycles of paclitaxel (200 mg/m^2) + carboplatin (AUC 6) + nivolumab (360 mg) every 3 wk	46	5/46 (10.9) cancer progression 0, AE 0, others 5[q]	NR	NR
Wakelee H et al. N Engl J Med 2023	Phase III Comparative	4 cycles of cisplatin (75 mg/m^2) + {gemcitabine (1000 mg/m^2) or pemetrexed (500 mg/m^2)} + pembrolizumab (200 mg) every 3 wk	397	71/397 (17.9) cancer progression 16, AE 25, others 30[r]	NR	NR
Provencio M et al. N Engl J Med 2023	Phase II Comparative	3 cycles of paclitaxel (200 mg/m^2) + carboplatin (AUC 5) + nivolumab (360 mg) every 3 wk	57	4/57 (7.0) cancer progression 0, AE 1, others 3[s]	NR	NR

Abbreviations: Ad = adenocarcinoma; AJCC = American joint committee on cancer; AE = adverse event; AUC = area under the curve; NR = not reported; RATS = robot-assisted thoracic surgery; Sq = squamous cell carcinoma; TRAE = treatment-related adverse event; VATS = video-assisted thoracic surgery.

[a] Chemotherapy = Sq, cisplatin (75 mg/m^2) or carboplatin (AUC 5) + gemcitabine (1000 mg/m^2); non-Sq, cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2)

[b] Chemotherapy = cisplatin (100 mg/m^2) + docetaxel (85 mg/m^2)

[c] Chemotherapy = Ad, carboplatin (AUC 5) + pemetrexed (500 mg/m^2); non-Ad, carboplatin (AUC 5) + nab-paclitaxel (260 mg/m^2)

[d] Chemotherapy = Sq, carboplatin (AUC 5) + gemcitabine (1000 mg/m^2); non-Sq, carboplatin (AUC 5) + pemetrexed (500 mg/m^2)

[e] Persistent N2 cancer (n = 5), inadequate pulmonary function (n = 2), location of tumor (n = 1)

[f] Unresectability (n = 3)

[g] Unresectability (n = 3)

[h] Unresectability (n = 4)

[i] Refusal (n = 1)

[j] Unresectability (n = 3)

[k] Refusal (n = 2)

[l] Refusal (n = 3), coronavirus disease 2019 (n = 13)

[m] Refusal (n = 1), inadequate lung perfusion and active smoking (n = 1), unresectability (n = 1)

[n] Refusal (n = 1), coronavirus disease 2019 (n = 1), unresectability (n = 1)[o]Refusal (n = 9), poor lung function (n = 2), unresectability (n = 2), unknown (n = 1)

[p] High surgery risk (n = 2)

[q] Refusal (n = 2), unresectability (n = 3)

[r] Refusal (n = 4), physician decision (n = 16), withdrawal of consent (n = 10)

[s] Refusal (n = 1), principal investigator's decision (n = 1), poor lung function (n = 1)

[t] Accidental fall (n = 1), pulmonary embolism (n = 1), pneumonia (n = 1)

[u] Scheduling issues (n = 1), accidental fall (n = 1), hyperthyroidism and hypoglycemia (n = 1), chest pain (n = 1)

[v] No details were provided.

Table 2 Perioperative Complications in Patients With Non–small-cell Lung Cancer Treated With Neoadjuvant Immune Checkpoint Inhibitors

Study	No. of Patients	Surgical Procedure, n (%)	Thirty-day Mortality, n (%)	Pneumonia, n (%)	Empyema, n (%)	Bronchopleural Fistula, n (%)	Arrhythmia, n (%)	Prolonged air Leaks, n (%)	Respiratory Failure, n (%)	Thromboembolic Event, n (%)
Yang CJ et al. Ann Thorac Surg 2018	13	lobectomy 10, pneumonectomy 1, bilobectomy 1, sublobar resection 1	0 (0.0)	0 (0.0)	NR	NR	1 (7.7)	2 (15.4)	0 (0.0)	1 (7.7)
Bott MJ et al. J Thorac Cardiovasc Surg 2019	20	lobectomy 16, pneumonectomy 2, bilobectomy 1, sublobar resection 1	0 (0.0)	1 (5.0)	1 (5.0)	NR	6 (30.0)	1 (5.0)	NR	1 (5.0)
Shu CA et al. Lancet Oncol 2020	26	lobectomy 19, pneumonectomy 3, bilobectomy 4, sublobar resection 0	1 (3.8)	NR	NR	NR	3 (11.5)	NR	NR	NR
Reuss JE et al. J Immunother Cancer 2020	6	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tfayli A et al. Cancer Med 2020	11	NR	NR	NR	NR	NR	NR	NR	NR	NR
Eichhorn F et al. Lung Cancer 2021	15	lobectomy 15, pneumonectomy 0, bilobectomy 0, sublobar resection 0	0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Tong BC et al. J Thorac Cardiovasc Surg 2022	25	lobectomy 21, pneumonectomy 3, bilobectomy 1, sublobar resection 0	0 (0.0)	1 (4.0)	NR	0 (0.0)	7 (28.0)	4 (16.0)	0 (0.0)	1 (4.0)
Altorki NK et al. Lancet Oncol 2021	26	lobectomy 21, pneumonectomy 4, bilobectomy 1, sublobar resection 0	0 (0.0)	NR	NR	NR	NR	NR	NR	NR
	26	lobectomy 17, pneumonectomy 5, bilobectomy 4, sublobar resection 0	0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Rothschild SI et al. J Clin Oncol 2021	55	lobectomy 43, pneumonectomy 5, bilobectomy 7, sublobar resection 0	1 (1.8)	3 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Zhao ZR et al. Oncoimmunology 2021	30	lobectomy 22, pneumonectomy 6, bilobectomy 1, sublobar resection 1	0 (0.0)	NR	NR	NR	3 (10.0)	1 (3.3)	NR	NR
Zhang P et al. Ann Thorac Surg 2022	30	lobectomy 26, pneumonectomy 4, bilobectomy 0, sublobar resection 0	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Table 2 (*continued*)

Study	No. of Patients	Surgical Procedure, n (%)	Thirty-day Mortality, n (%)	Pneumonia, n (%)	Empyema, n (%)	Bronchopleural Fistula, n (%)	Arrhythmia, n (%)	Prolonged air Leaks, n (%)	Respiratory Failure, n (%)	Thromboembolic Event, n (%)
Sepesi B et al. J Thorac Cardiovasc Surg 2022[a]	21	lobectomy 17, pneumonectomy 2, bilobectomy 0, sublobar resection 2	0 (0.0)	NR	NR	NR	NR	NR	NR	NR
	16	lobectomy 15, pneumonectomy 0, bilobectomy 1, sublobar resection 0	0 (0.0)	NR	NR	NR	NR	NR	NR	NR
Sun C et al. J Cancer Res Clin Oncol 2022	16	lobectomy 13, pneumonectomy 3, bilobectomy 0, sublobar resection 0	0 (0.0)	NR	NR	4 (25.0)	NR	NR	NR	NR
Forde PM et al. N Engl J Med 2022	149	lobectomy 97, pneumonectomy 25, bilobectomy 3, other 24	5 (3.4)	8 (5.4)	NR	NR	NR	NR	NR	NR
Gao S et al. J Thorac Oncol 2020	37	lobectomy 24, pneumonectomy 13, bilobectomy 0, sublobar resection 0	2 (5.4)	NR	NR	NR	NR	NR	NR	NR
Provencio M et al. Lancet Oncol 2020	41	lobectomy 38, pneumonectomy 3, bilobectomy 0, sublobar resection 0	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	4 (9.8)	2 (4.9)	1 (2.4)	1 (2.4)
Wakelee H et al. N Engl J Med 2023	325	lobectomy 256, pneumonectomy 37, bilobectomy 26, sublobar resection 2, other 4	6 (1.8)	NR	NR	NR	NR	NR	NR	NR
Provencio M et al. N Engl J Med 2023	53	lobectomy 42, pneumonectomy 6, bilobectomy 3, sublobar resection 2	1 (1.9)	3 (5.7)	NR	NR	1 (1.9)	3 (5.7)	2 (3.8)	1 (1.9)

Abbreviation: NR = not reported.
[a] In total = pnemonia (n = 2), empyema (n = 1), bronchopleural fistula (n = 1), atrial fibrillation (n = 4), prolonged air leaks (n = 8), respiratory failure (n = 1).

setting, it is essential to assess surgical outcomes and the safety profiles of these treatments even from the perspective of thoracic surgeons.

Almost all studies concluded that preoperative ICIs are safe and well tolerated compared to other treatment modalities such as chemotherapy. Despite that, no direct comparisons can be made between literature data on neoadjuvant chemotherapy and ICIs, as prior trials of preoperative chemotherapy date back as far as 20 years, including a variety of disease setting, tumor stages and chemotherapy regimens, with surgery cancellation rates ranging from 9% to 23.3% and postoperative deaths from 9.2% to 28%.[29-34]

Three comparative trials were included in our review,[8,27,28] which randomized patients to receive either neoadjuvant standard chemotherapy or chemotherapy plus neoadjuvant ICI[8]/perioperative ICI[27,28] (meant as ICI administered also in the adjuvant phase for the experimental arm). Along with significantly improved efficacy results, such as prolonged event-free survival and higher pathological response rate, overall improved surgical outcomes were reported for the experimental arms.[8,27,28] Moreover, 2 additional phase III trials comparing perioperative ICI plus chemotherapy with standard chemotherapy have been recently presented, further confirming that the addition of PD-1 checkpoint inhibition to the chemotherapy backbone improves efficacy outcomes with a manageable safety profile and preliminary comparable surgical outcomes.[35,36]

In the context of neoadjuvant treatments, efficacy, safety, and surgical outcomes are closely intertwined. Beside the risks of potential disease progression, toxicity and surgery cancellation, the theoretical advantages of the neoadjuvant approach were all well known, consisting in the early treatment of micrometastatic disease and reduction in drug resistance by early exposure, anticipate assessment of response to identify patients who will benefit from postsurgical treatments, and downstaging with improved resectability. Therefore, assuming a positive safety profile for ICIs monotherapy and for their addition to a chemotherapy backbone, it is legitimate to postulate that neoadjuvant ICIs are associated with improved surgical outcomes by increasing response rates compared to chemotherapy alone.

Preclinical evidence supports a specifically enhanced antitumor activity of checkpoint blockade when administered prior to surgery rather than as adjuvant treatments, findings that are not clearly replicated in the context of chemotherapy.[37] With the macroscopic presence of the primary tumor and without the confounding effect of other treatments, the repertoire of potential immunogenic tumor neo-antigens is larger and may enhance T-cell expansion and the antitumor immune response.[38] In addition, the concomitant administration of chemotherapy, may boost PD-L1 expression, immunogenic cell-death and intratumoral immune infiltrate.[39,40]

A point of great interest in the setting of surgical assessment after neoadjuvant ICIs are tissue reactions to immune-based treatments. In the context of metastatic disease immune-infiltration and tissue inflammation may significantly affect the radiological assessment,[41,42] similarly in the neoadjuvant setting tissue inflammation may affect resectability and other technical aspects. Conversion rates from VATS/RATS to open chest surgery are described in 6 reports,[8,12,13,22,23,25] with the highest conversion rate of 53.8%.[13] Assuming that surgery conversion is mainly based on safety reasons, this could be interpreted as a failure to ensure a safe and complete resection with minimally invasive techniques, with inherent implications for the postsurgical follow-up, such as prolonged hospitalization and increased risk of postoperative complications.[43]

Moreover, intraoperative findings after neoadjuvant ICI-based treatments may have an impact on technical aspects of pulmonary resection, as suggested by several reports.[13,44-46] Takamori and colleagues reported a case of left upper lobectomy after neoadjuvant chemo-immunotherapy in a patient with NSCLC, which was challenged by the adhesion of the left main pulmonary artery and left upper bronchus.[46] After securing and clamping the central and peripheral sides of the left main pulmonary artery, the adhesion was dissected, and the pulmonary artery and bronchus were divided and individually cut with staplers.[46] Similarly, Bott et al[44] reported a case of right upper lobectomy after preoperative ICI, which was similarly hampered by the adhesion between the truncus branch of the pulmonary artery and the right upper lobar bronchus, resulting in their resection en-bloc with a single staple fire, despite the attempt of detachment. Other reports mentioned adhesions and fibrosis in fissures, the chest wall, and hilum, although most of them reviewed the operative records retrospectively.[44,45]

Another typical intraoperative finding after neoadjuvant immunotherapy which thoracic surgeons will be increasingly called to deal with, is hilar/mediastinal immune nodal flare. Immune nodal flares seem to be restricted to patients who receive preoperative ICIs and has been reported in up to the 16% of cases.[47] Importantly, even though it is mainly due to an inflammatory response after neoadjuvant immunotherapy, some cases need pathological examination as it can mimic metastatic spread and may challenge the surgical procedure as described by Bott et al.[13]

Regarding perioperative complications, although most reports described 30 mortality, many of them did not provide details of other complications. In the Check-Mate 816 trial similar rates of surgery-related adverse events, including pain, wound complication and pneumonia, and median length of hospital stay by surgery type, were reported between the 2 arms, while the rates of minimally invasive surgery and conversion from minimally invasive to thoracotomy, favored the chemo-immunotherapy arm.[8] Considering this, special precautions in the postoperative management of patients who received neoadjuvant ICIs do not seem to be necessary, even though additional data from prospective randomized clinical trials are still needed to draw conclusive considerations.

This review has several limitations, mainly associated with the design of the included studies, as most of them were single-arm trials with limited sample sizes, with 3 comparative randomized trials. In addition, postsurgical and survival follow-up from most of the included trials are still immature, limiting our ability of assessing long term outcomes.

Despite these limitations, we can preliminarily conclude that preoperative ICIs are safe and well tolerated even from the surgical perspective. Additional details on intraoperative findings and their impact on technical aspects of the surgical approach from prospective trials are still needed to properly establish guidelines and disseminate recommendations for thoracic surgeons.

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CRediT authorship contribution statement

Kazuki Takada: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Writing – original draft. **Shinkichi Takamori:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Leonardo Brunetti:** Writing – review & editing. **Pierfilippo Crucitti:** Writing – review & editing. **Alessio Cortellini:** Data curation, Writing – review & editing.

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Supplementary Tables

Supplementary Table 1 Full details including TNM staging and AJCC version for the included studies

Study	Study phase/design	Immunotherapy	No. of patients	n, Stage I/II/III	AJCC version for staging	Surgery cancellation, n (%)	Surgery delay, n (%)	Conversion from VATS or RATS to open, n (%)
Yang CJ et al. Ann Thorac Surg 2018	Phase II Non comparative	Cycle 1 paclitaxel (175 mg/m2) + cisplatin (75 mg/m2) or carboplatin (AUC 6) and cycles 2 and 3 of the same chemotherapy + ipilimumab (10 mg/kg) every 3 weeks	24	0/5/19	7th edition	11/24 (45.8)	2/13 (15.4)	3/12 (25.0)
						cancer progression 2, AE 1, others 8[g]	TRAE 2	
Bott MJ et al. J Thorac Cardiovasc Surg 2019	Phase II Non comparative	2 cycles of nivolumab (3 mg/kg) every 2 weeks	21	4/10/7	7th edition	1/21 (4.8)	0/20 (0.0)	7/13 (53.8)
						cancer progression 1, AE 0, others 0	-	
Shu CA et al. Lancet Oncol 2020	Phase II Non comparative	2 or 4 cycles of atezolizumab (1200 mg) + nab-paclitaxel (100 mg/m2) + carboplatin (AUC 5) every 3 weeks	30	0/7/23	7th edition	4/30 (13.3)	0/26 (0.0)	NR
						cancer progression 1, AE 0, others 3[f]	-	
Reuss JE et al. J Immunother Cancer 2020	Phase Ib/II Non comparative	3 cycles of nivolumab (3 mg/kg) every 2 weeks + 1 dose of ipilimumab (1 mg/kg)	9	1/2/6	7th edition	3/9 (33.3)	0/6 (0.0)	NR
						cancer progression 3, AE 0, others 0	-	

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Supplementary Table 1 (*continued*)

Study	Study phase/design	Immunotherapy	No. of patients	n, Stage I/II/III	AJCC version for staging	Surgery cancellation, n (%)	Surgery delay, n (%)	Conversion from VATS or RATS to open, n (%)
Tfayli A et al. Cancer Med 2020	Phase II Non comparative	3 cycles of chemotherapy every 3 weeks + 4 doses of avelumab (10 mg/kg) every 2 weeks[a]	15	2/5/8	8th edition	4/15 (26.7)	NR	NR
						cancer progression 1, AE 0, others 3[g]		
Eichhorn F et al. Lung Cancer 2021	Phase II Non comparative	2 cycles of pembrolizumab (200 mg) every 3 weeks	15	0/6/9	7th edition	0/15 (0.0)	1/15 (6.7)	NR
						cancer progression 0, AE 0, others 0	TRAE 1	
Tong BC et al. J Thorac Cardiovasc Surg 2022	Phase II Non comparative	2 cycles of pembrolizumab (200 mg) every 3 weeks	30	9/13/8	7th edition	5/30 (16.7)	1/25 (4.0)	5/23 (21.7)
						cancer progression 1, AE 0, others 4[h]	TRAE 1	
Altorki NK et al. Lancet Oncol 2021	Phase II Comparative	2 cycles of durvalumab (1120 mg) every 3 weeks	30	11/5/14	7th edition	4/30 (13.3)	1/26 (3.8)	NR
						cancer progression 2, AE 1, others 1[i]	patient's wishes 1	
		2 cycles of durvalumab (1120 mg) every 3 weeks + stereotactic body radiotherapy (8 Gy x 3 fractions)	30	8/10/12		4/30 (13.3)	1/26 (3.8)	NR
						cancer progression 3, AE 1, others 0	TRAE 1	
Rothschild SI et al. J Clin Oncol 2021	Phase II Non comparative	3 cycles of chemotherapy every 3 weeks + 2 doses of durvalumab (750 mg) every 2 weeks[b]	67	0/0/67	7th edition	12/67 (17.9)	NR	NR
						cancer progression 6, AE 3, others 3[j]		

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Supplementary Table 1 (*continued*)

Study	Study phase/design	Immunotherapy	No. of patients	n, Stage I/II/III	AJCC version for staging	Surgery cancellation, n (%)	Surgery delay, n (%)	Conversion from VATS or RATS to open, n (%)
Zhao ZR et al. Oncoimmunology 2021	Phase II Non comparative	3 cycles of chemotherapy + toripalimab (240 mg) every 3 weeks[c]	33	0/0/33	8th edition	3/33 (9.1)	0/30 (0.0)	1/6 (16.7)
						cancer progression 1, AE 0, others 2[k]	-	
Zhang P et al. Ann Thorac Surg 2022	Phase II Non comparative	2 or 4 cycles of chemotherapy + sintilimab (200 mg) every 3 weeks[d]	50	0/0/50	8th edition	20/50 (40.0)	0/30 (0.0)	NR
						cancer progression 2, AE 2, others 16[l]	-	
Sepesi B et al. J Thorac Cardiovasc Surg 2022	Phase II Comparative	3 cycles of nivolumab (3 mg/kg) every 2 weeks	23	NR	7th edition	2/23 (8.7)	3/21 (14.3)	1/6 (16.7)
						cancer progression 1, AE 1, others 0	TRAE 0, others 3[t]	
		3 cycles of nivolumab (3 mg/kg) every 2 weeks + 1 dose of ipilimumab (1 mg/kg)	21	NR		5/21 (23.8)	5/16 (31.3)	1/4 (25.0)
						cancer progression 1, AE 1, others 3[m]	TRAE 1, others 4[u]	
Sun C et al. J Cancer Res Clin Oncol 2022	Phase II Non comparative	2 or 3 cycles of nab-paclitaxel (135 mg/m^2) + carboplatin (AUC 5) + sintilimab (200 mg) every 3 weeks	20	0/0/20	8th edition	4/20 (20.0)	0/16 (0.0)	0
						cancer progression 1, AE 0, others 3[n]	-	
Forde PM et al. N Engl J Med 2022	Phase III	3 cycles of platinum-doublet chemotherapy + nivolumab (360 mg) every 3 weeks	176	NR	7th edition	28/176 (15.9)	31/148 (20.9)	17/61 (27.9)
	Comparative					cancer progression 12, AE 2, others 14[o]	TRAE 6, others 25[v]	

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Supplementary Table 1 (*continued*)

Study	Study phase/design	Immunotherapy	No. of patients	n, Stage I/II/III	AJCC version for staging	Surgery cancellation, n (%)	Surgery delay, n (%)	Conversion from VATS or RATS to open, n (%)
Gao S et al. J Thorac Oncol 2020	Phase Ib Non comparative	2 cycles of sintilimab (200 mg) every 3 weeks	40	8/14/18	8th edition	3/40 (7.5)	2/37 (5.4)	NR
						cancer progression 1, AE 0, others 2[p]	TRAE 2	
Provencio M et al. Lancet Oncol 2020	Phase II Non comparative	3 cycles of paclitaxel (200 mg/m^2) + carboplatin (AUC 6) + nivolumab (360 mg) every 3 weeks	46	0/0/46	7th edition	5/46 (10.9)	NR	NR
						cancer progression 0, AE 0, others 5[q]		
Wakelee H et al. N Engl J Med 2023	Phase III Comparative	4 cycles of cisplatin (75 mg/m^2) + {gemcitabine (1000 mg/m^2) or pemetrexed (500 mg/m^2)} + pembrolizumab (200 mg) every 3 weeks	397	0/118/279	8th edition	71/397 (17.9)	NR	NR
						cancer progression 16, AE 25, others 30[r]		
Provencio M et al. N Engl J Med 2023	Phase II Comparative	3 cycles of paclitaxel (200 mg/m^2) + carboplatin (AUC 5) + nivolumab (360 mg) every 3 weeks	57	0/0/57	8th edition	4/57 (7.0)	NR	NR
						cancer progression 0, AE 1, others 3[s]		

[a] Chemotherapy = Sq, cisplatin (75 mg/m^2) or carboplatin (AUC 5) + gemcitabine (1000 mg/m^2); non-Sq, cisplatin (75 mg/m^2) or carboplatin (AUC 5) + pemetrexed (500 mg/m^2)
[b] Chemotherapy = cisplatin (100 mg/m^2) + docetaxel (85 mg/m^2)
[c] Chemotherapy = Ad, carboplatin (AUC 5) + pemetrexed (500 mg/m^2); non-Ad, carboplatin (AUC 5) + nab-paclitaxel (260 mg/m2)
[d] Chemotherapy = Sq, carboplatin (AUC 5) + gemcitabine (1000 mg/m^2); non-Sq, carboplatin (AUC 5) + pemetrexed (500 mg/m^2)
[e] Persistent N2 cancer (n = 5), inadequate pulmonary function (n = 2), location of tumor (n = 1)
[f] Unresectability (n = 3)
[g] Unresectability (n = 3)
[h] Unresectability (n = 4)
[i] Refusal (n = 1)
[j] Unresectability (n = 3)
[k] Refusal (n = 2)
[l] Refusal (n = 3), coronavirus disease 2019 (n = 13)
[m] Refusal (n = 1), inadequate lung perfusion and active smoking (n = 1), unresectability (n = 1)
[n] Refusal (n = 1), coronavirus disease 2019 (n = 1), unresectability (n = 1)
[o] Refusal (n = 9), poor lung function (n = 2), unresectability (n = 2), unknown (n = 1)
[p] High surgery risk (n = 2)
[q] Refusal (n = 2), unresectability (n = 3)
[r] Refusal (n = 4), physician decision (n = 16), withdrawal of consent (n = 10)
[s] Refusal (n = 1), principal investigator's decision (n = 1), poor lung function (n = 1)
[t] Accidental fall (n = 1), pulmonary embolism (n = 1), pneumonia (n = 1)
[u] Scheduling issues (n = 1), accidental fall (n = 1), hyperthyroidism and hypoglycemia (n = 1), chest pain (n = 1)
[v] No details were provided.Ad, adenocarcinoma; AJCC: American joint committee on cancer; AE, adverse event; AUC, area under the curve; NR, not reported; RATS, robot-assisted thoracic surgery; Sq, squamous cell carcinoma; TRAE, treatment-related adverse event; VATS, video-assisted thoracic surgery.

Supplementary Table 2 **Details of surgical timing windows.**

	Surgical window
Yang CJ et al. Ann Thorac Surg 2018	within 21 to 28 days after the last dose of chemotherapy
Bott MJ et al. J Thorac Cardiovasc Surg 2019	within 14 to 24 days after the last dose of nivolumab
Reuss JE et al. J Immunother Cancer 2020	14 days after the last dose of nivolumab
Tong BC et al. J Thorac Cardiovasc Surg 2022	within 29 to 56 days from the first dose of pembrolizumab (within 8 to 35 days from the last dose of pembrolizumab)
Altorki NK et al. Lancet Oncol 2021	within 14 to 42 days after the neoadjuvant treatment
Rothschild SI et al. J Clin Oncol 2021	within 14 to 28 days after the last dose of durvalumab
Zhao ZR et al. Oncoimmunology 2021	within 28 to 35 days after the first day of the third cycle of treatment
Zhang P et al. Ann Thorac Surg 2022	within 42 to 49 days after the last dose of chemotherapy
Sepesi B et al. J Thorac Cardiovasc Surg 2022	within 21 to 42 days after the last dose of nivolumab
Sun C et al. J Cancer Res Clin Oncol 2022	within 30 to 45 days after neoadjuvant treatment
Forde PM et al. N Engl J Med 2022	within 42 days after completing neoadjuvant treatment
Gao S et al. J Thorac Oncol 2020	within 29 to 43 days after the first dose of sintilimab (within 8 to 22 days after the last dose of sintilimab)
Provencio M et al. Lancet Oncol 2020	within 21 to 28 days after completing neoadjuvant treatment
Wakelee H et al. N Engl J Med 2023	no later than 20 weeks after the first dose of neoadjuvant treatment (no later than 140 days after the first dose of neoadjuvant treatment)
Provencio M et al. N Engl J Med 2023	within 3 to 4 weeks after completing neoadjuvant treatment (within 21 to 28 days after completing neoadjuvant treatment)