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Lung cancer surgery: innovations and future perspectives

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Abstract

Nine decades ago in 1933, Evarts A. Graham performed the first successful pneumonectomy in a patient with primary pulmonary squamous cell carcinoma. The patient survived for another 30 years, which drew the curtain on the surgical treatment of lung cancer. Surgical resection continues to be the cornerstone of multidisciplinary treatment for patients with early-stage non-small cell lung cancer and a proportion of those with locally advanced disease. Moreover, recent years have seen developments in automatic control, biomechanics, robotics, image transmission, artificial intelligence, three-dimensional reconstruction and printing, biological pharmacy, and molecular biology. Therefore, there is now an increasing focus on how to integrate these technologies into lung cancer surgery to improve quality of life, resect the tumor accurately, expand the population that is suitable for surgical management, predict disease recurrence with better accuracy, and ultimately achieve long-term survival. This article systematically reviews the innovative achievements that may be detrimental to current clinical practice and in future clinical trials, and simultaneously provides a brief overview of the polyvagal perspective in this field.

Keywords Lung cancer, Surgery, Innovations, Perspectives

Introduction

Lung cancer continues to be one of the most common malignancies and is the leading cause of cancer-related mortality in the Chinese population [1]. In developing countries, only a minority (20%–30%) of patients who present with early-stage lung cancer have the opportunity to benefit from surgical resection, mainly because of delays in diagnosis. As a result, the age-standardized 5-year relative survival rate is only 19.7% [1]. However, with the benefits accrued by public health prevention strategies, more widespread screening, and accurate diagnosis of lung cancer in the past two decades, an inflection point with respect to survival may be imminent [2]. Age-standardized mortality from lung cancer in China decreased by approximately 0.6% per annum between 2000 and 2016, with a decrease of 1.3% per year in urban areas [1]. However, in the era of perioperative cytotoxic therapy, there has been no further survival benefit in patients with locally advanced lung cancer. Hopefully, recent advances in our understanding of the molecular mechanisms underlying oncogene mutations and immunoregulation have led to several clinical trials assessing the benefit of perioperative targeted therapy or immunotherapy, which may improve survival in patients with potentially resectable non-small cell lung cancer (NSCLC) [3–6]. This narrative review summarizes the main innovations and advances in surgical strategies and multidisciplinary treatments for lung cancer and outlines the issues pertaining to high-quality studies that explore personalized therapy.

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Sublobar resection for early-stage lung cancer

With the increasing use of low-dose computed tomography (CT) as an imaging modality for lung cancer screening and respiratory disease pandemic, an increasing number of patients with early-stage lung cancer manifesting as ground-glass nodules (GGNs) are being detected and constitute the main population undergoing treatment in thoracic surgery departments [1, 7]. In terms of biological behavior, GGNs generally manifest as shallow or non-invasive lesions, grow slowly, and do not show vascular or lymphatic invasion and metastasis [7]. Moreover, long-term survival after surgical resection alone is better in patients with lung cancer that presents as GGNs than in those with lung cancer that presents as a solid lesion [8]. Furthermore, along with further clinical studies and practice, the ratio or size of solid component in radiology could efficiently distinguish per-invasive, non-invasive, less invasive, and invasive disease, which may direct the extent of resection (Table 1).

A series of studies by the Japanese Clinical Oncology Group (JCOG) has highlighted the importance of the consolidation-to-tumor ratio (CTR) not only for prediction of survival outcomes but also for selection of candidates for sublobar resection (Fig. 1) [9–11]. A prospective observational study of 545 patients with clinical T1N0M0 peripheral lung cancer from 31 Japanese institutions between December 2002 and May 2004 was performed to identify radiological predictors of pathological non-invasion (i.e., primary adenocarcinoma of lung without lymphatic, vascular, or lymphatic invasion). Suzuki et al. reported that a maximum radiological tumor size of ≤ 2.0 cm and a CTR of ≤ 0.25 corresponded well to pathological non-invasion (specificity, 98.7%; 95% confidence interval [CI] 93.2–100.0). They also found that patients with non-invasive radiological features had an excellent long-term prognosis after a median follow-up of 7.1 years (5-year overall survival [OS] rate, 97.1%; 10-year OS rate, 94.0%; 5-year relapse-free survival [RFS] rate, 97.1%) [12]. Therefore, these patients were considered suitable for sublobar resection. This hypothesis was confirmed by the JCOG 0804 study, in which all 333 prospectively enrolled patients with a radiological diagnosis of peripheral lung cancer measuring ≤ 2.0 cm and a CTR of ≤ 0.25 underwent sublobar resection (wide wedge resection, $n = 258$ [77.5%]; segmentectomy, $n = 56$ [16.8%]). The 5-year RFS rate was 99.7% (90% CI 98.3–99.9) with no cases of local recurrence detected (Fig. 1) [11]. Furthermore, based on the long-term survival outcomes of JCOG 0201, RFS and OS in patients with a maximum tumor size of ≤ 3.0 cm and a CTR of ≤ 0.50 were similar to those in patients with radiologically non-invasive lung cancer (5-year RFS rate, 95.3% and 97.1%, respectively; 5-year OS rate, 96.5% and 97.1%; and 10-year OS rate, 92.2% and 94.0%). The JCOG 1211 study targeted patients with a maximum tumor diameter of ≤ 3.0 cm and pure or predominant ground-glass opacities (≤ 0.50) who underwent anatomic segmentectomy and found a similar survival outcome (i.e., a 5-year RFS rate of 98.0% [95% CI 95.9–99.1]) [10]. Therefore, anatomic segmentectomy as performed in the JCOG 1211 study is recommended for this population of patients (Fig. 1).

According to the JCOG 0802, 0804, and 1211 studies, sublobar resection can achieve an excellent prognosis in patients with lung cancer measuring ≤ 2.0 cm in size regardless of the CTR (Table 1). Although another multicenter, randomized, non-inferiority, phase 3 trial investigated by the American Cancer and Leukemia Group B (CALGB) in North American patients had several baseline differences with JCOG 0802 (such as the constituent ratios of wedge resection, squamous cell carcinoma, solid adenocarcinoma, etc.), the concordance of results reconfirmed this trend (Table 1) [10]. In CALGB140503 study, the outcomes in patients diagnosed to have peripheral cT1N0M0 NSCLC with a maximum tumor size of ≤ 2 cm who underwent sublobar resection after intraoperative confirmation of N0 status were not inferior to those in patients who underwent lobar resection in terms of the 5-year DFS rate (63.6% vs. 64.1%), 5-year OS rate (80.3% vs. 78.9%), locoregional recurrence rate (13.4% vs. 10.0%), and distant recurrence rate (15.2% vs. 16.8%). However, there were subtle differences in the inclusion criteria and surgical procedures performed in the above-mentioned studies. Moreover, the evidence provided by these studies is insufficient to establish a professional standard with respect to the top priorities of sublobar resection (i.e., the safety margin and lymph node evaluation) to ensure each early-stage NSCLC patient receives a homogeneous managements and outcomes. A retrospective study by Weiss et al. found that 19.2% of all patients who underwent planned curative segmentectomy did not meet the criteria for standard segmentectomy, and an analysis of the National Cancer Database demonstrated an association between poor-quality segmentectomy and decreased survival [13, 14]. Therefore, in current clinical practice, if sublobar resection is planned for patients with GGNs, the surgical procedure should adhere strictly to that performed in the relevant studies to ensure an adequate safety margin and allow evaluation of lymph node status (Fig. 1). Furthermore, we propose that future studies should focus on establishing a generally accessible standard or qualitative platform to control the quality of sublobar resection in early-stage NSCLC rather than on interpretation or reproduction of the published data.

Table 1 High-level prospective clinical trials to evaluate the safety and efficacy of sublobar resection in patients with clinical stage IA NSCLC

Variables	JCOG 0201	JCOG 0802	JCOG 0804	JCOG 1211	CALGB 140503
Date of enrollment	December 2002-May 2004	August 2009-October 2014	May 2009-April 2011	September 2013-November 2015	June 2007-March 2017
Number of patients	545	1106	314	357	697
Number of institutions	31	70	51	42	83
Radiological diagnosis	cT1N0M0, peripheral NSCLC	cT1N0M0 (≤ 2 cm) NSCLC with CTR > 0.50	cT1N0M0 (≤ 2 cm), peripheral NSCLC with CTR ≤ 0,25	cT1N0M0 (≤ 3 cm) NSCLC including GGO	cT1N0M0 (≤ 2 cm), peripheral (outer third of the lung) NSCLC, not including pure GGOs
Study design	Single-arm trial: lobectomy	Randomized controlled trial (RCT): segmentectomy vs. lobectomy	Single-arm trial: sublobar resection	Single-arm trial: segmentectomy	RCT: sublobar resection vs. lobar resection
Extent of resection					
Lobectomy	544 (99.8%)	554 (50.1%)	0 (0%)	0 (0%)	357 (51.2%)
Segmentectomy	0 (0%)	552 (49.9%)	56 (17.8%)	357 (100%)	129 (18.5%)
Wedge resection	0 (0%)	0 (0%)	258 (82.2%)	0 (0%)	201 (28.8%%)
Intraoperative procedure	Lobectomy with lymph node dissection	Systematic or selective lymph node dissection was mandatory, and sampling was not allowed	Wide wedge resection was firstly selected; segmentectomy could be selected if wedge might result in insufficient margin	Hilar, interlobar, and intrapulmonary lymph node dissection was performed. A margin ≥ the maximum tumour diameter or ≥ 2 cm. Intraoperative frozen-section diagnosis was required, if no perioperative diagnosis.	Histologic confirmation of NSCLC and confirmation of N0 status by frozen-section examination (the right side: 4R, 7, and 10; the left side: 5 or 6, 7, and 10)
Primary endpoint	The predicting specificity using CTR	Overall survival	5-year Recurrence-free survival (RFS)	5-year RFS	Disease-free survival (DFS)
The intended purpose	Observational	Noninferiority	Confirmatory	Confirmatory	Noninferiority
Adenocarcinoma, n (%)	529 (97.1%)	1003 (90.7%) 501 (90.4%) vs. 502 (90.9%)	331 (88.3%)	350 (98.0%)	444 (63.7%) 218 (64.1%) vs. 226 (63.3%)
Median follow-up (years)	10.1 years	7.3 years	5.5 years	5.4 years	7 years
5-year DFS/RFS, hazard ratio (95% confidence interval)	All: 84.5% ≤ 2 cm, CTR ≤ 0.25: 97.1% ≤ 3 cm, CTR ≤ 0.50: 95.3% ≤ 2 cm, CTR > 0.50: 86.5% 2-3 cm, CTR > 0.50: 75.5%	88.0% vs. 87.9% 0.998 (0.7553–1.323)	99.7%	All: 98.0% 2-3 cm, CTR ≤ 0.50: 98.0%	63.6% vs. 62.1% 1.01 (0.83–1.24)
5-year OS, hazard ratio (95% confidence interval)	All: 90.4% ≤ 2 cm, CTR ≤ 0.25: 97.1% ≤ 3 cm, CTR ≤ 0.50: 96.5% ≤ 2 cm, CTR > 0.50: 91.8% 2-3 cm, CTR > 0.50: 85.0%	94.3% vs. 91.1% 0.663 (0.474–0.927)	99.4%	All: 98.2% 2-3 cm, CTR ≤ 0.50: 98.0%	80.3% vs. 78.9% 0.95 (0.72–1.26)
Median reduction in FEV_1 (%)					
At 6 months	Not available	8.5% vs.13.1%	Not available	7.9%	4.0% vs.6.0%
At 12 months	Not available	10.4% vs.12.0%	4.5%	7.3%	Not available

Table 1 (continued)

Variables	JCOG 0201	JCOG 0802	JCOG 0804	JCOG 1211	CALGB 140503
Median reduction in FVC (%)					
At 6 months	Not available	Not available	Not available	8.5%	3.0% vs. 5.0%
At 12 months	Not available	Not available	2.6%	6.6%	Not available

JCOG Japan Clinical Oncology Group, *CALGB* American Cancer and Leukemia Group B, *NSCLC* non-small cell lung cancer, *CTR* consolidation-to-tumor ratio, *GGO* ground-glass opacity, *HR* hazard ratio, *CI* confidence interval, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity

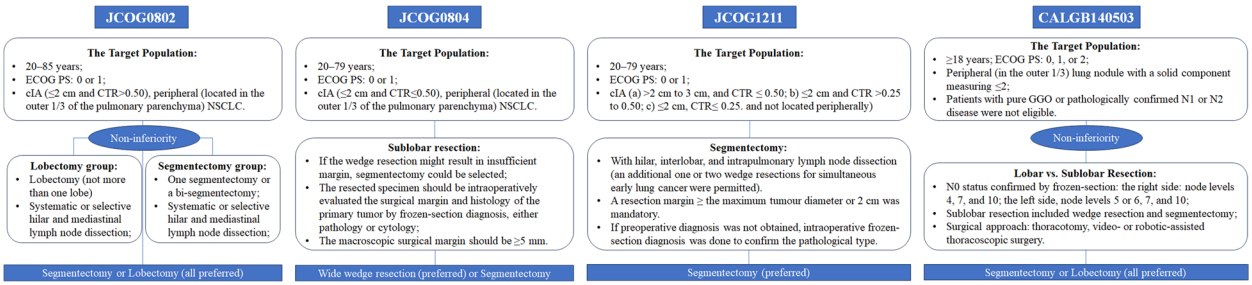

Fig. 1 Inclusion criteria and surgical procedures used in trials of sublobar resection for early-stage non-small cell lung cancer

Near-infrared fluorescence imaging in lung cancer surgery

In terms of theoretical perspectives, indocyanine green (ICG) binds rapidly to plasma proteins after intravenous injection, remains mainly in the vascular space, has a half-life of 4 min, and is excreted mostly into the small intestine through the biliary system. When intravascular ICG is illuminated with near-infrared (NIR) fluorescence, fluorescence is absorbed at wavelengths in the range of 800–810 nm and emitted at 835 nm. A camera sensor captures the specific fluorescence and converts it to a real-time output on a monitor. Therefore, ICG can be used in clinical practice to measure functional reserve in the liver before hepatectomy [15]. NIR fluorescence imaging was first used in the field of thoracic surgery in 2010 to visualize the intersegmental line during pulmonary segmentectomy. All eight patients in that pilot study underwent accurate segmentectomy with intravenous injection of ICG to mark the color zonation under an NIR system with no postoperative complications [16]. Advanced NIR staining using ICG has several advantages over the lung ventilation methods traditionally used to identify the intersegmental plane [15–18]. First, the operative procedure is simple to perform and does not need assistance from another department or additional equipment. The inflation-deflation method is that to inflate the whole lung through continuous positive-pressure ventilation after blocking the target segmental bronchus (or bronchi) or to precisely inflate the target segment(s) via jet ventilation, is a conventional but widely used technique in current clinical practice. However, this method is not always satisfactory for identifying the intersegmental line, especially in patients with chronic lung disease, or for removing the segmental specimen during minimally invasive thoracic surgery [18]. Furthermore, fluorescence staining with the aid of ICG not only allows the fluorescent green to disappear easily and quickly but also has no effect on the operation or the surgical field. After injecting ICG via a peripheral vein, the intersegmental line can be observed within several seconds or tens of seconds, marked by an electrosurgical knife, and subsequently cut by electrocautery or a stapler [17, 18]. This novel method allows a higher identification rate and better demarcation. Yotsukura et al. reported good depiction of the intersegmental line using ICG in 184 patients (88.0%) and that the identification rate was higher than that achieved by high-frequency jet ventilation (126/160, 78.8%) [17]. Sun et al. compared the modified inflation-deflation technique with the ICG fluorescence-based technique in uniport thoracoscopic segmentectomy and found that ICG fluorescence was superior with regard to the identification rate (98.0% vs. 89.8%, $P=0.015$) [18]. No perioperative adverse events that were caused directly by injection of ICG were observed.

Recently, thoracic surgeons have assessed the value of NIR imaging to terms of optimizing the surgical procedure and guiding lymph node dissection in patients with lung cancer. Owing to a sharp increase in small-sized peripheral pulmonary lesions detected by low-dose CT, there has been an increasing demand for accurate localization to allow radical resection or intraoperative diagnosis by frozen section. Several pilot and feasibility trials have investigated perioperative CT-guided percutaneous and intraoperative ICG injection under the guidance of a virtual navigation bronchoscope or fiberbronchoscope, and reported localization success rates in the range of 95.5%–100% [15, 19]. However, the above-mentioned alternative localization technique, which only includes a change in the localization material, has disadvantages similar to those of conventional localization methods under the guidance of CT, including hemothorax, pneumothorax, air embolus, and breakthrough pain, and requires skilled manipulation by an experienced bronchoscopy specialist. More recently, researchers in China have attempted to combine three-dimensional CT bronchography and angiography with injection of ICG to simplify and optimize localization of lung nodules during wide wedge resection and anatomical partial lobectomy. The key step in the operative procedure is to cut the target

segmental arteries and/or veins under the guidance of three-dimensional CT bronchography and angiography before intravenous injection of ICG, marking the pulmonary segment containing the lesion and finally achieving accurate resection with an acceptable safety margin. Furthermore, for patients with early-stage lung cancer, intraoperative pathological sentinel lymph node (SLN) evaluation may guide selective lymph node dissection or sampling such that systematic lymph node dissection may be omitted. However how to effectively map the lymphatic drainage route and identify the SLN is not clear. In the literature, the rate of SLN detection under ICG fluorescence ranges from 80.3% to 89.0%, with a low false-negative rate of 0%–2.9%, which is non-inferior to the rate reportedly achieved by radiotracer labelling [15].

Overall, although the safety and feasibility of NIR fluorescence imaging have been explored in various scenarios of lung cancer surgery in small-sized, prospective and retrospective pilot studies, they are regarded as experience-based medicine only with lower-level evidences. High-quality multicenter randomized controlled trials (RCTs) are warranted to systematically evaluate the indications for and standardization of NIR fluorescence imaging and accelerate its progression from experience-based to evidence-based medicine (EBM).

Perioperative immunotherapy in lung cancer

Immune checkpoint inhibitors (ICIs), which block programmed death-1 or programmed death ligand-1, have achieved a high objective response rate (ORR) and a survival benefit in patients with advanced or metastatic NSCLC. Investigators have recently attempted to use this novel therapeutic modality in patients with potentially resectable NSCLC [20, 21]. Several randomized Phase III trials have confirmed significantly higher radiological and pathological response, complete (R0) and definitive resection rates in patients with resectable NSCLC (stage II to IIIA/IIIB [T3N2] according to the eighth edition of the American Joint Committee on Cancer staging system) who are treated with neoadjuvant immunotherapy plus chemotherapy than in those treated with neoadjuvant chemotherapy alone (Table 2). However, owing to the various designs and therapeutic modalities used in the various trials (Table 2), confusion persists regarding individualized treatment decisions in real-world clinical practice.

First, it is unclear how many cycles of neoadjuvant immunochemotherapy are sufficient. In current clinical trials, 2–4 cycles of neoadjuvant immunochemotherapy have been used. For example, patients in the CheckMate-816 trial received three cycles of neoadjuvant therapy whereas those in the Keynote-671 study received four cycles. Through a horizontal comparison of the numerical number, the pathological response rates (i.e., the major pathological response [MPR] and pathological complete response [pCR]) were lower in patients who received four cycles than in those who received three cycles. Furthermore, 25.5% of patients in the Keynote-671 trial did not complete four full cycles of neoadjuvant immunochemotherapy, mainly because of adverse events, whereas the corresponding proportion in the Checkmate-816 trial was only 6.2%. Therefore, it is still unknown how many cycles of induction immunotherapy plus chemotherapy is optimal for NSCLC in terms of the balance between treatment-related toxicity and oncological response. The recent small-sized RCT known as neoSCORE evaluated the perioperative outcomes of two versus three cycles of neoadjuvant sintilimab plus platinum-based chemotherapy in patients with resectable stage IB–IIIA NSCLC. Although patients who received three cycles of neoadjuvant therapy had a higher MPR rate (41.4% vs. 26.9%), a higher pCR rate (24.1% vs. 19.2%), and a higher ORR (55.2% vs. 50.0%) without increases in the grade ≥ 3 treatment-related adverse event rate (29.0% vs. 31.0%) or postoperative complication rate (31.0% vs.23.1%), the differences were not statistically significant (all $P > 0.05$).

Second, a multicenter, retrospective study that spanned 20 years during the era of neoadjuvant chemoradiotherapy found that patients with locally advanced NSCLC who achieved a pCR on neoadjuvant chemoradiotherapy could still derive significant benefit from adjuvant therapy [22]. However, it is unknown whether adjuvant therapy is necessary in patients who reach a pCR after neoadjuvant immunotherapy ± chemotherapy. In the current randomized trials, non-differential adjuvant treatment was still administered according to the prespecified study design regardless of the pathological status reached. Further subgroup analyses in the Keynote-671 trial showed that adjuvant pembrolizumab therapy had a beneficial effect on event-free survival (EFS) independent of the MPR (hazard ratio 0.54, 95% CI 0.24–1.22) and pCR (hazard ratio 0.33, 95% CI 0.09–1.22); however, the differences were not statistically significant. Furthermore, it is not clear whether the complete response (CR) status in the primary tumor or that in the regional lymph nodes represents a cure. There is a need for further studies focusing on a combination of molecular residual disease, radiological response, and pathological status to guide cycles of neoadjuvant therapy and determine the need for adjuvant therapy [23].

The third question to be answered is whether patients with epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) translocation should receive neoadjuvant

Table 2 Advances in perioperative immune checkpoint inhibitors in patients with resectable NSCLC from the randomized, phase III trials

Variables	Checkmate-816	Keynote-671	Neotorch[a]	AEGEAN[a]
Neoadjuvant regimen	Nivolumb plus chemotherapy (CT) vs.CT alone: 3 cycles	Pembrolizumab plus CT vs.Placebo plus CT: 4 cycles	Toripalimab plus CT vs.Placebo plus CT: 3 cycles	Durvalumab plus CT vs.Placebo plus CT: 4 cycles
Adjuvant regimen	Up to 4 cycles of chemotherapy, radiotherapy, or both	Pembrolizumab vs. placebo: up to 13 cycles	Toripalimab or placebo plus CT: 1 cycle; and then toripalimab or placebo up to 13 cycles	Durvalumab vs. placebo: up to 12 cycles
Clinical TNM staging	cIB (≥ 4 cm)-IIIA, AJCC 7th	cII-IIIB (N2), AJCC 8th	cII-III, AJCC 8th	cII-IIIB (N2), AJCC 8th
Clinical stage III, n (%)	228 (64.2%): 113 (63.1%) vs. 115 (64.2%)	558 (70.0%) 279 (70.3%) vs. 279 (69.8%)	402 (99.5%) 202 (100%) vs. 200 (99.0%)	524 (70.8%) 261 (71.3%) vs. 263 (70.3%)
Smoking history, n (%)	318 (89.1%): 160 (89.4%) vs. 158 (88.3%)	696 (87.3%) 343 (86.4%) vs. 353 (88.3%)	355 (87.9%) 174 (86.1%) vs. 181 (89.6%)	633 (85.5%) 315 (86.1%) vs. 318 (85.0%)
Squamous cell carcinoma, n (%)	182 (50.8%): 87 (48.6%) vs. 95 (53.1%)	344 (43.2%) 171 (43.1%) vs. 173 (43.2%)	314 (77.7%) 157 (77.7%) vs. 157 (77.7%)	360 (48.6%)
***EGFR* mutation/*ALK* translocation, n (%)**	Not included	14 (3.5%) vs. 19 (4.8%) 12 (3.0%) vs. 9 (2.2%)	Not included	Not included
PD-L1 expression, n (%)				
< 1% or unevaluated	155 (43.3%): 78 (43.6%) vs. 77 (43.0%)	289 (36.3%) 138 (34.8%) vs. 151 (37.8%)	139 (34.3%) 69 (34.2%) vs. 70 (34.7%)	247 (33.4%) 122 (33.3%) vs. 125 (33.4%)
≥ 1%	178 (49.7%): 89 (49.7%) vs. 89 (49.7%)	508 (63.7%) 259 (65.2%) vs. 249 (62.3%)	265 (65.5%) 133 (65.8%) vs. 132 (65.3%)	493 (66.6%) 244 (66.7%) vs. 249 (66.6%)
Primary endpoints	EFS, pCR	EFS, OS	EFS, MPR	pCR, EFS
Completion rate of neoadjuvant regimen	93.8% vs. 84.7%	74.5% vs. 74.4%	Not available	86.9% vs. 88.5%
Completion rate of adjuvant regimen	11.9% vs. 22.2%	40.4% vs. 35.3%	Not available	Not available
Definitive surgery rate	83.3% vs. 75.4%	82.1% vs. 79.4%	82.2% vs. 73.3%	77.6% vs. 76.7%
Minimally invasive surgery rate	29.5% vs. 21.5%	Not available	Not available	Not available
R0 resection rate	83.2% vs. 77.8%	92.0% vs. 84.2%	95.8% vs. 92.6%	94.7% vs. 91.3%
Median follow-up months	41.4	25.3	18.25	11.7
2-year EFS rate	63.8% vs. 45.3%	62.4% vs. 40.6%	64.7% vs. 38.7%	63.3% vs. 52.4%
Hazard ratio for EFS, 95% *CI*	0.63, 0.43–0.91	0.58, 0.46–0.72	0.40, 0.28–0.57	0.68, 0.53–0.88
pCR rate	24.0% vs 2.2%	18.1% vs.4.0%	28.2% vs. 1.0%	17.2% vs. 4.3%
MPR rate	36.9% vs. 8.9%	30.2% vs. 11.0%	48.5% vs. 8.4%	33.3% vs.12.3%
Grade 3/4 AEs of any cause				
All, n (%)	72 (40.9%) vs. 77 (43.8%)	29 (10.0%) vs. 15 (5.6%)	36 (21.7%) vs. 30 (20.3%)	169 (42.3%) vs. 173 (43.3%)
Leading to discontinuation of treatment, n (%)	10 (5.7%) vs. 7 (4.0%)	Not available	11 (6.6%) vs. 2 (1.4%)	48 (12.0%) vs. 24 (6.0%)
Serious, n (%)	19 (10.8%) vs. 17 (9.7%)	16 (5.5%) vs. 7 (2.6%)	Not available	150 (37.5%) vs. 126 (31.6%)
Grade 3/4 treatment-related AEs				
All, n (%)	59 (33.5%) vs. 65 (36.9%)	178 (44.9%) vs. 149 (37.3%)	Not available	129 (32.3%) vs. 132 (33.1%)
Leading to discontinuation of treatment, n (%)	10 (5.7%) vs. 6 (3.4%)	50 (12.6%) vs. 21 (5.3%)	Not available	Not available
Serious, n (%)	15 (8.5%) vs. 14 (8.0%)	70 (17.7%) vs. 57 (14.3%)	Not available	Not available
Treatment-related death, n (%)	0 (0%) vs. 3 (1.7%)	4 (1.0%) vs. 3 (0.8%)	0 (0%) vs. 2 (1.4%)	7 (1.8%) vs. 2 (0.5%)

TNM, tumor-node-metastasis; AJCC, American Joint Committee on Cancer; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; PD-L1, programmed death ligand 1; EFS, event-free survival; pCR, pathological complete response; OS, overall survival; MPR, major pathological response; *CI*, confidence interval; AEs, adverse events

[a] results from the interim analysis

immunotherapy ± chemotherapy. Patients with advanced/metastatic lung cancer who have *EGFR* mutation or *ALK* translocation showed a low ORR (12% and 0%, respectively), median progression-free survival (2.1 months and 2.5 months), and median OS (10 months and 17 months) when treated with an ICI as monotherapy [24]. However, OS was better in patients with *EGFR*-positive NSCLC who were treated using a programmed death ligand-1 inhibitor plus bevacizumab plus carboplatin-based chemotherapy than in those treated with traditional first-line bevacizumab plus carboplatin-based chemotherapy [25]. Therefore, combined therapy is regarded as a promising strategy in driver mutated early or metastatic NSCLC. Among the currently published Phase III trials, only Keynote-671 included patients with known *EGFR* mutations or *ALK* translocations, and subgroup analysis showed that perioperative pembrolizumab therapy improved EFS in these patients [6]. However, a retrospective study that included propensity score matching analysis found that the MPR rate after neoadjuvant immunochemotherapy was lower in patients with driver gene mutated operable NSCLC than in those with oncogene-negative operable NSCLC (9% vs. 56.6%), as was the 1-year EFS rate (75.4% vs. 85.5%) [26].

Two recently reported large-scale RCTs found that the radiological response, pathological response, and EFS rates were significantly higher in patients who received neoadjuvant immunochemotherapy than in those who received neoadjuvant chemotherapy alone, potentially paving a way towards a new treatment modality. However, the recommendations for personalized therapy in real-world clinical practice remain unclear owing to the various designs and therapeutic modalities used and the limited evidence base for outcomes. More fundamental researches and clinical trials continue to focus on the hotspot direction and will hopefully change the treatment landscape and improve OS in patients with potentially resectable NSCLC.

Achievements and perspectives

> *"Where of what's past is prologue, what to come in yours and my discharge." William Shakespeare, The Tempest*

Anatomic lobectomy with adequate lymphadenectomy is still the gold standard of care for patients with potentially resectable NSCLC. However, several advanced, high-level EBMs have demonstrated that an increasing number of early-stage NSCLCs, especially those with GGNs, detected by low-dose CT may be sufficiently curable by limited resection, such as segmentectomy or wide wedge resection. Although procedures centered on quality of life could yield better preservation of pulmonary function and be non-inferior to lobectomy in terms of long-term survival in clinical trials, homogeneous criteria for true segmentectomy and the safety margin for wide wedge resection have yet to be established in clinical practice, which may cause a dilution of efficacy in the real-world situation. Given that the advent of novel fluorescence staining material can simplify the surgical procedure and precisely identify the intersegmental plane and location of the lesion, RCTs that investigate the safety and feasibility of fluorescence imaging in lung cancer surgery are now imperative. Furthermore, lung cancers that manifest as GGNs have been considered to be localized disease with limited lymph node invasion, and whether examination of lymph nodes can be omitted in this population has yet to be determined. Fluorescence imaging is also a promising tool that can guide SLN evaluation as an alternative to systematic lymphadenectomy, which is associated with increased risks of chylothorax, bronchopleural fistula, and prolonged air leak. However, there is still no high-level evidence base that can be used to select the optimal operative procedure and assess the clinical value and safety of this novel imaging method.

A treatment regimen that includes an ICI or a targeted agent could further improve the likelihood of cure in patients with locally advanced NSCLC. However, patients with NSCLC can be reclassified into various subpopulations according to histological subtype, genomic mutations and fusions, and molecular biomarkers (e.g., molecular residual disease and tumor mutation burden), lymph nodes involvement status (the 9th edition of TNM classification for lung cancer). Therefore, the available evidence base is insufficient for formulation of individualized treatment. Moreover, the majority of the reported and ongoing clinical trials have not only selected pathological response status as the primary endpoint but also included a short follow-up duration. Longer-term follow-up is needed to finally establish the role of perioperative ICI therapy in terms of decreasing the risk of relapse and curing NSCLC.

Authors' contributions
Xiangyang Yu and Feng Wang drafted and edited the manuscript. Kai Ma and Zhentao Yu designed the research and approved the final version. All authors have read, reviewed, and approved the final manuscript.

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Declarations

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Not applicable.

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The authors declare that they have no conflict of interest.

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