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Video-assisted surgery in oncology

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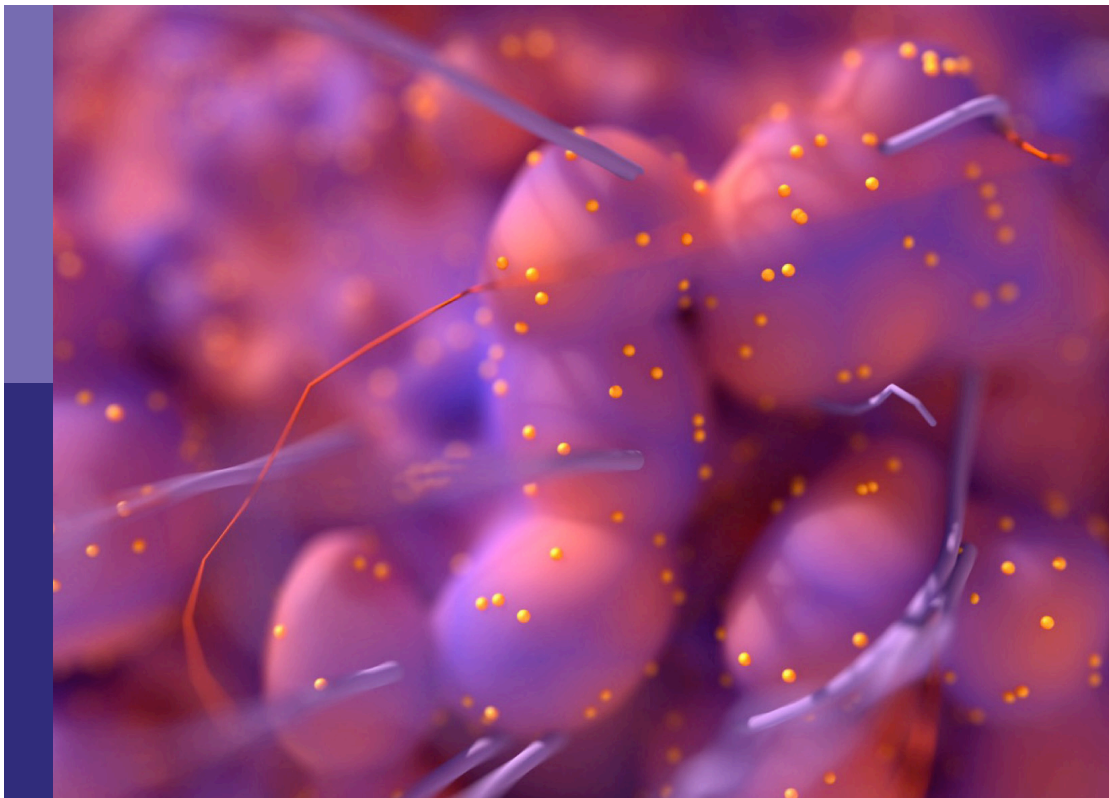

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Video-assisted surgery in oncology

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Editorial: Video-assisted surgery in oncology

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Editorial on the Research Topic
Video-assisted surgery in oncology

Video-assisted surgery (VAS) has emerged as a safe and effective approach to the treatment of diseases, including cancer. In contrast to open surgery, which is the traditional type of surgery, VAS allows resection to be minimally invasive for improved peri- and post-operative patient outcomes. Moreover, VAS can potentially enhance the effectiveness of healthcare service utilization (1). This Research Topic, "Video-Assisted Surgery in Oncology", aims to provide a transdisciplinary forum with rigorous evidence on the use of VAS in cancer.

Research comparing patient outcomes between VAS and open surgery, robotic-assisted surgery (RAS) and radiotherapy is a common focus. Two studies among the publications focus on the comparison between RAS and VAS. Specifically, a study by Zeng et al. in non-small-cell lung cancer (NSCLC) after neoadjuvant immunochemotherapy yielded positive results for RAS in terms of the conversion rate to open surgery (thoracotomy), number of lymph nodes (LNs) and the stations harvested, post-operative pain score, and importantly, higher pathological N1 and N2 staging. Another study, by Fu et al., revolved around the upper third of gastric cancer, with positive RAS results in the number of LNs and quality of life assessments within one year post-operatively. For this comparison, we observed the superiority of RAS mostly in operation experience, peri-operative and short-term post-operative outcomes in eligible patients. Its superiority in long-term outcomes needs to be confirmed by more studies. In observational studies, the analysis may consider how patient demographics, especially socioeconomic status, may interact with the comparison, given the high cost of RAS.

Similar conditions in the above peri-operative and post-operative outcomes were found in sleeve lobectomy via VAS and RAS combined versus thoracotomy for centrally located lung cancer, as reported by Chen et al. Of note, sleeve lobectomy for this type of cancer is a technically demanding procedure, especially via RAS and VAS, so comparable results on survival should be acceptable.

New and advanced VAS techniques are included in this Research Topic. In pre-operative settings, Zhang et al. reported the feasibility of applying three-dimensional computed tomography-bronchography and angiography (3D-CTBA) for basal segmentectomy via VAS to treat lung neoplasms, with the advantage of clearly displaying the anatomical structure of the bronchi, pulmonary arteries and veins for accurate resection. Wang et al. explored the safety and effectiveness of pre-operative (versus peri-operative) injection of a tracer agent carbon nanoparticles (CNs) to protect the parathyroid glands in patients receiving VAS for papillary thyroid cancer. In addition to precise surgery, better applications in imaging and biomarker testing are also needed for accurate staging and post-operative surveillance, particularly with positron emission tomography (PET)-CT scans, whole genome sequencing, and liquid biopsy.

In the peri-operative setting, a randomized controlled trial (RCT) by Fan et al. investigating opioid-free anesthesia (OFA) with esketamine versus opioid anesthesia in spontaneously ventilated video-assisted thoracic surgery (SV-VATS) for NSCLC, found 1) equivalent pain control within 24 hours post-operatively, 2) superior circulatory and respiratory stability, quality of pulmonary collapse but 3) a longer time to consciousness with higher doses of propofol and dexmetomidine. With respect to OFA, important research questions to be answered are the post-discharge outcomes. For example, longer-term pain control and adverse events, in addition to its association with opioid over prescribing, prolonged use, diversion, and human harm.

Therapeutic strategies with new indications are suggested in the following publications. Shen et al. proposed 4L LN dissection for left-sided NSCLC, especially lung adenocarcinoma, given the station metastasis with a prevalence of 25% and medium-term prognostic impact. Gao et al. explored the safety and feasibility of laparoscopic transduodenal ampullectomy (LTDA) in 9 cases with pre-malignant tumors of the ampulla of Vater (AoV). Wang et al. introduced a novel "zero-line" incision design in VAS gasless unilateral trans-axillary approach (GUA) thyroidectomy for thyroid cancer.

The state of the art also includes the extension of VAS indications to more advanced cancers with neoadjuvant or adjuvant treatment. We encourage studies aimed at improving the efficacy, postoperative safety and tolerability of neoadjuvant/adjuvant treatment. Comparing the neoadjuvant/adjuvant treatment regimens can be a promising option (2). In addition, we should point out the peri-operative adjuvant strategy with VAS and the use of VAS for cancer treatment regimens. Recent advances include hyperthermic intrathoracic chemotherapy (HITHOC) with VATS for malignant pleural mesothelioma (3) and laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for gastric cancer with peritoneal metastasis (4).

With many advances in VAS and further innovations to come, the implementation question should be how to scale utilization to benefit more patients. Understanding the learning curve is fundamental. Huang et al. found that 44 operations are needed to achieve acceptable perioperative outcomes for subsegmental resection via uniportal VATS for patients with early-stage lung cancer, including operative time, intraoperative bleeding, and length of hospital stay. Also, in uniportal VATS for early-stage lung cancer, Song et al. found reviewing recorded surgical videos to be beneficial for learning lobectomy, suggesting that 53 operations are necessary to achieve proficiency based on the above outcomes as well as complications and lymph nodes harvested. The next step is continuing medical education. It may need to be improved as differences in patient prognostic outcomes and hospital utilization may be impacted by surgeons and hospitals, even within developed countries. For example, better results have been found in high-volume surgeons and hospitals (5, 6).

Inequitable access is a central issue. Advanced VAS techniques have been well adopted in high-performance settings and regions. However, VAS is still poorly applied in low- and middle-income countries, mainly due to limited infrastructural capacity and clinical experience (7). VAS capacity and its studies in the countries must be further developed to meet the increasing demand due to the growing cancer burden (8). As VAS becomes the standard of care in cancer surgery, affordable VAS should be a goal, regardless of geographic or socioeconomic conditions. Along with feasibility and efficacy studies, efforts also need to be made to conduct cost-effectiveness studies and implementation studies on geographic and socioeconomic disparities.

Finally, the study of the timeliness to VAS in oncology is insufficient but essential (9), as delays in cancer care are still common worldwide (10). With the more frequent use of VAS with other cancer treatment, especially for more advanced cancer, studies investigating the optimal timing of the subsequent treatment are also warranted (9). As a transdisciplinary forum, this Research Topic celebrates the current advances and innovations in VAS and calls for more evidence to support its implementation.

Author contributions

JZ: Writing – original draft, Writing – review & editing. HL: Writing – review & editing. JC: Writing – review & editing. ZM: Writing – review & editing. LJ: Writing – review & editing.

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Conflict of interest

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

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Effects of robotic and laparoscopic-assisted surgery on lymph node dissection and quality of life in the upper third of gastric cancer: A retrospective cohort study based on propensity score matching

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Objective: The objective of this study was compare the effects of robot-assisted and laparoscopic-assisted surgery on lymph node dissection and quality of life in upper third gastric cancer patients undergoing radical total gastrectomy.

Methods: The clinical and follow-up data of 409 patients with upper third gastric cancer who underwent total gastrectomy from July 2016 to May 2021 were enrolled. The patients were divided into a robotic group ($n = 106$) and a laparoscopic group ($n = 303$). Age, sex, body mass index, American Society of Anesthesiologists score, tumor size and location, pathological type, cT, cN, and cTNM were adjusted to offset selection bias. The patient characteristics, operative procedures, surgical outcomes, oncologic and pathologic outcomes, number of lymph node dissections, quality of life assessment, and nutritional status were compared between the two groups.

Results: After propensity score matching, 61 cases were included in the robotic group and 122 cases were included in the laparoscopic group. The number of dissected lymph nodes (37.3 ± 13.5 vs. 32.8 ± 11.8, $P = 0.022$) significantly differed between the two groups. The number of lower mediastinal and subphrenic lymph nodes in the robotic group was greater than that in the laparoscopic group, and the difference was statistically significant ($P < 0.001$). Compared with the laparoscopic group, the total score of physical symptoms in the robotic group was significantly lower at 6 and 12 months after surgery ($P = 0.03$ and $P = 0.001$, respectively). The total social function score at 6 and 12 months after surgery was higher in the robotic group ($P = 0.006$ and $P = 0.022$). The quality of life scores were statistically significant only at 3 months after the operation ($P = 0.047$). A higher patient-generated subjective global assessment (PG-SGA) score is when the score significantly correlated ($P < 0.001$) with a higher related physical symptoms score, lower social function score, and lower quality of life score.

Conclusion: Compared with laparoscopic radical gastrectomy, robotic radical gastrectomy is safe and feasible. Compared with laparoscopic radical gastrectomy, robotic radical gastrectomy was more refined, was associated with less surgical bleeding, and increased the quality of lymph node dissection. In addition, patients in the robotic group showed better postoperative quality of life.

KEYWORDS

upper third gastric cancer, robotic surgery, laparoscopic surgery, lymph node dissection, quality of life

Introduction

In the past 40 years, the worldwide incidence rate of upper third gastric cancer (GC) has shown a significant upward trend (1, 2). Upper third gastric cancer is defined as adenocarcinoma of the upper third of the stomach, with or without esophagogastric junction adenocarcinoma, according to the Classification of the Japan Gastric Cancer Association (JGCA) (3). Although great progress has been made in targeting, immunological treatment, perioperative radiotherapy, and chemotherapy based on the molecular classification of upper third gastric cancer, surgery still plays an important role. Surgical methods, including traditional laparotomy and laparoscopy, represented by minimally invasive surgery and the Da Vinci robot, have become the main methods used to treat upper third gastric cancer cases worldwide. In 2002, Hashizume et al. carried out the world's first robot-assisted radical gastrectomy for gastric cancer (4). Robot-assisted surgery has a good 3D field of view, which is more suitable for narrow body cavity operations. The precise anatomy modified by the computer, the excellent suture technology under the microscope, and the movement of the 7-degree-of-freedom robot arm overcome the limits of the human body, which significantly reduced the dependence of the operator on the team. These unique advantages are unmatched by traditional laparoscopy. In addition, robotic surgery also has the advantages of a short learning curve, less surgical bleeding, an increased number of lymph node dissections, and other potential tumor control (5). However, few studies comparing laparoscopic and robotic lymph node dissection in upper third gastric cancer are currently available.

Radical gastrectomy combined with local lymph node dissection is the main treatment strategy for resectable gastric cancer (6). Especially for patients with advanced upper gastric cancer, radical total gastrectomy combined with D2 lymph node dissection is recommended. With the development of minimally invasive surgery and the improvement of postoperative quality of life (QOL), the recovery of postoperative somatic symptoms and social functions has gradually become the focus of attention for gastric cancer patients (7). The purpose of this study was to compare the effects of laparoscopic- and robotic-assisted gastrectomy combined with D2 lymph node dissection on the potential tumor control effect and quality of life of patients with upper third gastric cancer.

Materials and methods

Study design and participants

From July 2016 to May 2021, 409 patients with upper third gastric cancer consecutively received surgical treatment at the Gastrointestinal Surgery Department of Qingdao University Affiliated Hospital. Upper third gastric cancer is defined as adenocarcinoma of the upper third of the stomach, with or without esophagogastric junction adenocarcinoma, according to the Classification of the JGCA (3). The location of the primary carcinoma was determined by esophagogastroscopy.

Patients were divided into two groups based on whether they underwent robotic-assisted or laparoscopic-assisted surgery. Patients underwent propensity score matching analysis, and age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) score, tumor size, pathological type, cT, cN, and cTNM were adjusted to offset selection bias. The matched robot-assisted group was compared with the laparoscopic-assisted group based on preoperative basic information, perioperative complications, histopathological features, number of lymph nodes dissected during operation, postoperative quality of life, and nutritional status.

Preoperative tumor staging was assessed by computed tomography (CT) and gastroscopy. T stage and N stage were determined using the latest AJCC/UICC TNM staging system (8), and histological types were consistent with the Japanese classification of gastric cancer (3).

Patients' eligibility criteria

The patients' eligibility criteria were as follows: (1) 12-month follow-up was completed and the follow-up data were complete; (2) gastric cancer in the upper third of the stomach; (3) first-time gastrectomy; (4) age >20 years for both

sexes; (5) R0 gastrectomy; (6) no recurrence or distant metastasis; (7) performance status (PS) 0 or 1 based on the Eastern Cooperative Oncology Group scale; (8) sufficient capacity to understand and respond to the questionnaire; (9) no history of other diseases or operations that might influence the responses to the questionnaire; and (10) no organ failure or mental illness.

In addition, patients with a history of abdominal surgery, double primary tumors, and simultaneous resection of other organs were excluded.

Surgery procedure

All patients had undergone curative resection and D1+/D2 lymphadenectomy in accordance with the Japanese guidelines for treating GC (3).

To obtain a better prognosis, a sufficient tumor edge should be ensured by the surgeons before specimen resection. If the tumor margins cannot meet the requirement and may be positive, intraoperative frozen pathology of the margin needs to be performed to exclude positive results. We stipulate performing uncut Roux-en-Y reconstruction after tumor resection.

The surgical procedure of robotic gastrectomy (RG) was very similar to that of laparoscopic gastrectomy (LG) in terms of trocar placement, surgical anatomical sequence, and anastomosis technique. The surgeons chose the extracorporeal method and stapling instrument methods for anastomosis to reinforce the hand-sewing according to the intraoperative conditions and extracorporeal anastomosis using a minilaparotomy.

Perioperative management

The application of enhanced recovery after surgery (ERAS) has widely gained acceptance, and all patients were managed with the ERAS protocol during the perioperative period (9).

Before surgery, patients received education and exercise in lung function and prerehabilitation. For daily smokers and alcohol abusers, 1 month of abstinence was required before surgery. Chest, abdominal, and pelvic CT were performed to confirm the size and location of the tumor and imaging staging. Neoadjuvant chemotherapy was an option in cases with a large tumor or bulky lymph node metastasis. Cardiac ultrasound and pulmonary function tests were used to evaluate the tolerance of cardiopulmonary function for gastric cancer surgery. Lower extremity vascular ultrasound was used to evaluate the thrombus. Nutrition Risk Screening (NRS) 2002 was used to assess the nutritional status of patients: if the score was $\geq$3, the patient was given nutritional support (10). The correct evaluation of the patient's tolerance to surgery, reasonable treatment of other combined diseases, correction of anemia and water, and electrolyte disorders improved the patient's general condition.

On the day of surgery, the patients were allowed clear fluids for up to 2 h and solids for up to 6 h before the induction of anesthesia (11). A complex clear carbohydrate-rich drink designed for use within 2 h before anesthesia reduced hunger, thirst, anxiety and the length of stay, as well as postoperative insulin resistance.

After the surgery, the following measures were employed: (1) multimodal analgesia, including epidural analgesia and intravenous analgesia; (2) anasogastric tube, which should be removed on postoperative day 1 (POD1); (3) an abdominal drainage tube, which can be removed on POD3 when drainage fluid is clear and <100 ml/day, when the anastomotic status is good, or when no abdominal infection is found; (4) a urinary catheter, which should be removed on POD1; (5) venous thromboembolism (VTE) prevention, which included mechanical measures (intermittent pneumatic leg compression and elastic stockings) for patients with increased VTE risk; (6) oral feeding: we stipulated that patients can consume a clear fluid diet on POD1–2, semiliquid diet on POD3–4, and soft blended diet on POD5 if tolerable and then gradual transition to a normal diet based on the premise of patient's tolerance and no severe complication (including anastomosis leakage, ileus, high risk of gastroplegia, etc.); (7) movement: we encouraged early ambulation for 1 h/day on POD1 and prepared an appropriate scheme of movement for patients. The time of ambulation should properly increase to 4 h/day on POD7 based on the patient's status and need; (8) discharge: patients could be discharged from the hospital on POD7 according to the discharge criteria (without postoperative complications and primary disease that requires current intervention).

According to the postoperative pathological stage and Chinese Society of Clinical Oncology (CSCO) guidelines for the diagnosis and treatment of gastric cancer, patients with stage II/III gastric cancer were treated with 5-fluorouracil-based regimens, either XELOX or S-1, for six to eight cycles. The patients were followed up for 1 year and once at 3, 6, and 12 months. The follow-up included physical examination and laboratory examination. At each follow-up, the diet, physical symptoms, and social function recovery were collected by telephone contact. The deadline for follow-up was May 2022.

Data collection and clinical analysis

Patients were enrolled in this study, and two data management staff members were assigned to collect relevant data. The basic characteristics of patients collected before surgery were age, sex, body mass index, ASA score, and hematologic indices (complete blood count, blood biochemistry, tumor biomarkers, etc.). The operation was

characterized by estimated blood loss, operative time, and cost. Postoperative outcomes were mean maximum body temperature during the first 3 days, pain Numerical Assessment Scale (NAS) score on the first 3 days after surgery, days of bowel function recovery, time to start soft diet, complications, and adverse events. Morbidity was described based on the Clavien–Dindo classification of JOCG criteria for postoperative complications and according to the Common Terminology Criteria for Adverse Events (CTCAE 5.0) (12–15). The oncologic and pathologic outcomes were the number of lymph nodes removed, pathological proximal and distal margins, TNM stage, tumor size and location, Lauren classification, and tumor cell differentiation. After discharge, a 1-year follow-up, which included QOL questionnaires, periodic physicals, laboratory examinations, and abdominal CT every 3 months at the outpatient department, began on time.

Assessment of postoperative quality of life: The quality of life assessment scale was constructed with reference to the quality of life questionnaire-core 30 (QLQ-C30) (16, 17) and the gastric cancer specific module scale (quality of life questionnaire-stomach 22, qlq-sto22) (18, 19) designed by the European Organization for Research and Treatment of Cancer (EORTC) in Chinese. The new scale combines the advantages of the above two scales, mainly including physical symptom scores and social function evaluations. According to the scoring procedure of the EORTC scoring manual, the score is linearly converted into a score of 0–100. The higher the function score is, the better the function, and the higher the symptom score is, the more serious the symptoms (20). Quality of life score = (100 − score of physical symptom scale + score of social function scale)/2.

Nutritional parameters after gastrectomy were assessed on the basis of changes in serum prealbumin, albumin, hemoglobin, meal size and times, foods with different degrees of hardness and softness, prognostic nutritional index (PNI), and body weight at 3, 6, and 12 months after surgery (21). PNI was calculated using the following formula: 10 × serum albumin value (g/dl) + 0.005 × lymphocyte count in peripheral blood (22). On the CT images, the cross-sectional area of the psoas muscle was measured at the level of the third lumbar vertebra (L3). Psoas muscle index (PMI) = (area of the psoas muscle at L3 cm^2)/(height m^2). The 1-year change rate was calculated as follows: (nutrition-related indicators at one year after surgery − preoperative)/(preoperative × 100) (23, 24). Considering the relationship between nutritional status and quality of life, the patient-generated subjective global assessment (PG-SGA) score was used to assess the association with quality of life.

Statistical analysis

All data were processed using SPSS 26.0 and R software (version 4.0.2). To eliminate the potential deviation caused by the lack of equal distribution between the two groups, a logistic regression model with the following covariates was used to calculate the propensity score: age, sex, body mass index, American Society of Anesthesiologists score, tumor location, tumor size, pathological type, cT, cN, and cTNM. Matching was performed at a ratio of 1:2, and a caliper width of 0.01 standard deviation was specified (25). Categorical variables are expressed as examples (%), and the chi-square or Fisher exact test was used. Continuous variables conforming to a normal distribution are expressed as $X \pm s$, and a paired *t*-test was used for comparisons between groups. Nutrition-related indices were compared before the operation and at 1, 3, and 6 months after the operation, and repeated-measures ANOVA was used. $P < 0.05$ indicates that the difference is statistically significant.

Ethics statement

The data for this study were collected in the course of general clinical practice, so informed consent signed by each patient was obtained for any surgical and clinical procedure. This protocol was in line with the ethical guidelines of the World Medical Association Declaration of Helsinki adopted by the 18th World Medical Association Congress held in Helsinki, Finland, in June 1964. Institutional Review Board approval was not needed. Since this study was retrospective, patients' consent was not required for inclusion in the study.

Results

Patient characteristics

A total of 409 upper third gastric cancer patients underwent surgery (**Figure 1**). Among these patients, 37 patients were excluded from the study due to palliative surgery ($n = 7$), non-adenocarcinoma ($n = 4$), complications with other malignant tumors ($n = 6$), neoadjuvant chemotherapy ($n = 9$), and loss to follow-up ($n = 11$). Finally, a total of 372 patients who underwent laparoscopic-assisted surgery (278 patients) or robotic-assisted surgery (94 patients) were enrolled in this study. After 1:2 matching between the RG group and LG group, 61 patients were included in the RG group and 122 patients were included in the LG group.

The basic clinical characteristics of the patients in the two groups are shown in **Table 1**. Age, sex, BMI, preoperative nutritional indicators, or comorbidities did not significantly differ between groups in the entire cohort. The matched baseline features were well balanced.

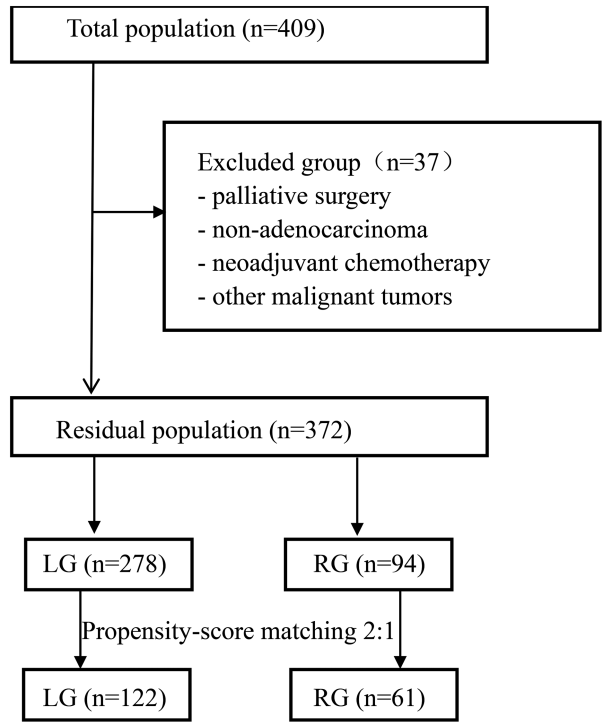

FIGURE 1
Selection schema of patients. LG, laparoscopic gastrectomy; RG, robotic gastrectomy.

Operative procedures and surgical outcomes

The operation time did not significantly differ between the two groups ($P = 0.531$). Compared with that in the laparoscopic group, the intraoperative blood loss in the robotic group was lower (45.7 ± 13.9 vs. 53.4 ± 21.6 ml, $P = 0.012$). In addition, the time to bowel function recovery (2.02 ± 1.21 vs. 2.63 ± 1.09, $P = 0.001$) and start of a soft diet (3.41 ± 1.64 vs. 4.07 ± 1.32, $P = 0.004$) in the robotic group were better than those in the laparoscopic group. The pain NAS score on the first postoperative day in the robotic group (1.51 ± 0.23 vs. 2.29 ± 0.28, $P < 0.001$) was lower than that in the laparoscopic group. No significant difference was detected in the highest temperature or complications. However, cost was higher in the robotic group than in the laparoscopic group ($79{,}810.6 \pm 7{,}126$ vs. $63{,}102.1 \pm 4{,}137$, $P < 0.001$) (Table 2).

Oncologic and pathologic outcomes

Tumor location and size, proximal and distal resection margins, histological type, or Lauren classification did not significantly differ between the two groups ($P > 0.05$). After propensity matching, no significant difference in pTNM staging was detected between the two groups ($P > 0.05$) (Table 3).

The number of dissected lymph nodes (37.3 ± 13.5 vs. 32.8 ± 11.8, $P = 0.022$) was significantly different between the two groups. The number of lower mediastinal and subphrenic lymph nodes in the robotic group was greater than that in the laparoscopic group, and the difference was statistically significant ($P < 0.001$) (Table 4). The total number of abdominal lymph nodes and the number of abdominal lymph nodes at each station between the two groups were not statistically significant ($P > 0.05$) (Figure 2).

The lymph node metastasis rates of No. 1, No. 2, No. 3, and No. 7 were the highest, all approximately 20%, followed by No. 8a, No. 9, No. 11p, and No. 110. The lymph node metastasis rate was close to 5%, and the lymph node metastasis probability of other stations was less than 5% (Figure 3).

Quality of life assessment

In the robotic group, the total scores of physical symptoms before surgery and 3, 6, and 12 months after surgery were 7.9 ± 5.1, 16.4 ± 7.3, 9.6 ± 5.3, and 6.7 ± 1.9, respectively. Compared with the laparoscopic group, the total score of physical symptoms in the robotic group was significantly lower at 6 and 12 months after surgery ($P = 0.03$ and $P = 0.001$, respectively). In the robotic group, the total social function scores were 94.7 ± 7.3, 71.6 ± 12.7, 81.6 ± 8.4, and 90.3 ± 7.8 before surgery and 3, 6, and 12 months after surgery, respectively. In the laparoscopic group, the scores were 93.9 ± 7.1, 69.2 ± 9.6, 77.4 ± 10.2, and 87.1 ± 9.3, respectively. Compared with the laparoscopic group, the total score at 6 and 12 months after surgery was higher in the robotic group ($P = 0.006$ and $P = 0.022$). The quality of life scores of the robotic group were 95.2 ± 8.1, 78.0 ± 13.1, 85.7 ± 9.4, and 92.9 ± 7.8 before surgery and 3, 6, and 12 months after surgery, respectively. The scores of the laparoscopic group were 94.9 ± 8.9, 74.4 ± 10.6, 83.4 ± 10.5, and 90.7 ± 8.6, respectively. The difference between the two groups at each time point was statistically significant only at 3 months after the operation ($P = 0.047$) (Table 5).

Nutritional status

The preoperative baseline data of the two groups were very balanced (Tables 6, 7). Although body weight did not significantly differ between the two groups during the same period after surgery, the 1-year change rate was statistically significant [(-8.1 ± 1.7) vs. (-8.7 ± 1.9), $P = 0.039$]. PMI significantly differed between the two groups at 3 and 6 months after the operation ($P < 0.05$), but no significant difference was detected in the 1-year change rate after the

TABLE 1 Patient characteristics.

Factor	Entire cohort		*P*	Matched cohort		*P*
	RG (*n* = 106)	LG (*n* = 303)		RG (*n* = 61)	LG (*n* = 122)	
Age, year ± SD	63.34 ± 7.91	64.08 ± 8.52	0.434	64.11 ± 8.03	64.42 ± 8.12	0.807
Sex			0.773			0.412
Male, *n* (%)	74 (69.8)	216 (71.3)		42 (68.9)	91 (74.6)	
Female, *n* (%)	32 (30.2)	87 (28.7)		19 (31.1)	31 (25.4)	
BMI, kg/m^2 ± SD	24.69 ± 4.01	25.15 ± 3.14	0.229	24.36 ± 4.12	25.01 ± 3.64	0.278
ASA physical status			0.808			0.909
0–1, *n* (%)	43 (40.6)	127 (41.9)		18 (29.5)	37 (30.3)	
≥2, *n* (%)	63 (59.4)	176 (58.1)		43 (70.5)	85 (69.7)	
Preoperative Hb, g/L ± SD	131.85 ± 12.01	130.41 ± 13.17	0.322	133.21 ± 13.41	133.76 ± 12.74	0.787
Preoperative albumin, g/L ± SD	41.21 ± 3.03	40.92 ± 2.78	0.367	42.17 ± 3.12	41.62 ± 2.61	0.210
Psoas muscle index, cm^2/m^2 ± SD	172.24 ± 29.12	171.26 ± 31.04	0.776	173.02 ± 31.95	171.27 ± 32.05	0.728
Lymphocyte count, 10^9/L ± SD	1.39 ± 0.42	1.42 ± 0.35	0.472	1.38 ± 0.43	1.41 ± 0.36	0.620
Preoperative prealbumin, g/L ± SD	239.52 ± 31.22	241.67 ± 34.21	0.569	242.86 ± 33.14	240.14 ± 32.19	0.594
NRS 2002 score			0.275			0.916
<3, *n* (%)	69 (65.1)	179 (59.1)		36 (59.0)	71 (58.2)	
≥3, *n* (%)	37 (34.9)	124 (40.9)		25 (41.0)	51 (41.8)	
Her2			0.560			0.929
0, *n* (%)	71 (67.0)	215 (70.9)		43 (70.5)	87 (71.3)	
+, *n* (%)	23 (21.7)	59 (19.5)		11 (18.0)	23 (18.9)	
++, *n* (%)	3 (2.8)	13 (4.3)		2 (3.3)	5 (4.1)	
+++, *n* (%)	9 (8.5)	16 (5.3)		5 (8.2)	7 (5.7)	
History of smoking, *n* (%)	67 (63.2)	184 (60.7)	0.652	33 (54.1)	69 (56.6)	0.752
FEV1.0, % ± SD	76.3 ± 8.7	75.4 ± 8.2	0.339	77.8 ± 9.5	76.3 ± 9.4	0.312
Number of comorbidities			0.612			0.991
0, *n* (%)	51 (48.1)	137 (45.2)		24 (39.3)	46 (37.7)	
1, *n* (%)	37 (34.9)	126 (41.6)		29 (47.5)	61 (50.0)	
2, *n* (%)	13 (12.3)	29 (9.6)		6 (9.8)	11 (9.0)	
3, *n* (%)	5 (4.7)	11 (3.6)		2 (3.3)	4 (3.3)	
Comorbidities			0.987			0.954
Hypertension	31 (29.2)	112 (37.0)		22 (36.1)	47 (38.5)	
Diabetes	18 (17.0)	61 (20.1)		15 (24.6)	27 (22.1)	
Hepatic disease	3 (2.8)	7 (2.3)		2 (3.3)	3 (2.5)	
Cardiac disease	4 (3.8)	9 (3.0)		3 (4.9)	5 (4.1)	
Cerebrovascular disease	3 (2.8)	10 (3.3)		1 (1.6)	4 (3.3)	
Asthma	1 (0.9)	5 (1.7)		1 (1.6)	2 (1.6)	
History of pulmonary tuberculosis	1 (0.9)	4 (1.3)		0 (0)	1 (0.8)	

RG, robotic gastrectomy; LG, laparoscopic gastrectomy; BMI, body mass index; ASA, American Society of Anesthesiologists; NRS, Nutrition Risk Screening.

operation ($P > 0.05$). The proportion of meal size change [(−16.4 ± 3.9)% vs. (−18.1 ± 4.3)%, $P = 0.001$] and the proportion of meal time change [(29.3 ± 6.5)% vs. (31.2 ± 7.1)%, $P = 0.081$] significantly differed between groups. At 3, 6, and 12 months after the operation, the proportion of solid diet in the robotic group was higher than that in the laparoscopic group, but this difference was not significant ($P > 0.05$). As seen in Table 8, a higher PG-SGA score significantly correlated ($P <$ 0.001) with a higher related physical symptom score, lower social function score, and lower quality of life score.

Discussion

A large number of studies have confirmed that robotic radical gastrectomy has the advantages of fewer complications,

TABLE 2 Operative procedures and surgical outcomes.

Factor	Entire cohort		*P*	Matched cohort		*P*
	RG (*n* = 106)	LG (*n* = 303)		RG (*n* = 61)	LG (*n* = 122)	
Operation time (min ± SD)	182.2 ± 36.4	174.3 ± 37.1	0.059	176.1 ± 39.1	172.3 ± 38.3	0.531
Estimated blood loss (ml ± SD)	48.4 ± 11.5	55.1 ± 24.8	0.008	45.7 ± 13.9	53.4 ± 21.6	0.012
Lymph node dissection, *n* (%)			0.268			0.221
D1+	21 (19.8)	46 (15.2)		14 (23.0)	19 (15.6)	
D2	85 (80.2)	257 (84.8)		47 (77.0)	103 (84.4)	
Bowel function recovery (days ± SD)	2.49 ± 1.34	2.89 ± 1.16	0.004	2.02 ± 1.21	2.63 ± 1.09	0.001
Start of soft diet (days ± SD)	3.74 ± 1.51	4.13 ± 1.62	0.031	3.41 ± 1.64	4.07 ± 1.32	0.004
Pain numerical assessment scale score						
Postoperative day 1	1.62 ± 0.41	2.03 ± 0.37	<0.001	1.51 ± 0.23	2.29 ± 0.28	<0.001
Postoperative day 2	1.54 ± 0.29	1.59 ± 0.33	0.167	1.47 ± 0.26	1.52 ± 0.31	0.138
Postoperative day 3	1.24 ± 0.22	1.26 ± 0.27	0.493	1.21 ± 0.25	1.18 ± 0.21	0.230
Body temperature during the first 3 days[a]						
Postoperative day 1	37.5°C ± 1.3°C	37.3°C ± 1.7°C	0.271	37.6°C ± 1.6°C	37.4°C ± 1.3°C	0.366
Postoperative day 2	37.8°C ± 1.5°C	37.6°C ± 1.4°C	0.215	37.5°C ± 1.4°C	37.6°C ± 1.6°C	0.679
Postoperative day 3	37.3°C ± 1.2°C	37.2°C ± 1.3°C	0.487	37.2°C ± 1.3°C	37.3°C ± 1.2°C	0.606
Overall complication, *n* (%)			>0.999			>0.999
Anastomotic leakage	1 (0.9)	2 (0.6)		0 (0)	0 (0)	
Anastomotic stenosis	3 (2.8)	7 (2.3)		1 (1.6)	1 (0.8)	
Cholecystitis	1 (0.9)	4 (1.3)		0 (0)	0 (0)	
Pancreatitis	2 (1.9)	5 (1.7)		0 (0)	2 (1.6)	
Pancreatic fistula	1 (0.9)	5 (1.7)		0 (0)	1 (0.8)	
Intraperitoneal hemorrhage	1 (0.9)	4 (1.3)		1 (1.6)	2 (1.6)	
Fluid abscess	2 (1.9)	5 (1.7)		0 (0)	2 (1.6)	
Wound infection	2 (1.9)	3 (0.9)		0 (0)	1 (0.8)	
Wound dehiscence	1 (0.9)	3 (0.9)		0 (0)	1 (0.8)	
Pneumonia	4 (3.8)	11 (3.6)		2 (3.3)	5 (4.1)	
Chyle leakage	1 (0.9)	3 (0.9)		0 (0)	2 (1.6)	
Ileus	2 (1.9)	4 (1.3)		1 (1.6)	2 (1.6)	
Adverse events, *n* (%)			0.847			0.744
Anemia[b]	27 (25.5)	78 (25.7)		11 (18.0)	23 (18.9)	
Lymphocytopenia[c]	4 (3.8)	6 (2.0)		1 (1.6)	2 (1.6)	
Creatinine increased[d]	2 (1.9)	4 (1.3)		1 (1.6)	1 (0.8)	
Hypo-pre-albuminemia[e]	23 (21.7)	63 (20.8)		13 (21.3)	24 (19.7)	
Hyperbilirubinemia[f]	7 (6.6)	19 (6.3)		3 (4.9)	7 (5.7)	
AST/ALT increased[g]	5 (4.7)	13 (4.3)		3 (4.9)	6 (4.9)	
Hypernatremia[h]	0 (0)	1 (0.3)		0 (0)	0 (0)	
Hyponatremia[i]	6 (5.7)	21 (6.9)		4 (6.6)	10 (8.2)	
Hyperkalemia[j]	3 (2.8)	7 (2.3)		1 (1.6)	3 (2.5)	
Postoperative hospital stay (days ± SD)	6.9 ± 4.4	7.3 ± 5.2	0.479	6.6 ± 4.1	7.2 ± 4.8	0.405
30-day reoperation, *n* (%)	1 (0.9)	4 (3.8)	>0.999	0 (0)	1 (0.8)	>0.999
30-day readmission, *n* (%)	5 (4.7)	12 (4.0)	0.737	1 (1.6)	3 (2.5)	>0.999
Medical cost (dollars ± SD)	81,942.7 ± 8,796	65,917.2 ± 5,138	<0.001	79,810.6 ± 7,126	63,102.1 ± 4,137	<0.001

RG, robotic gastrectomy; LG, laparoscopic gastrectomy; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]The highest body temperature.
[b]Male patients Hb < 120 g/L, female patients Hb < 110 g/L.
[c]Lymphocyte count <1.1 × 10^9/L.
[d]Creatinine > 132 μmol/L.
[e]Pre-albumin <200 mg/L.
[f]Total bilirubin >22 μmol/L.
[g]AST/ALT > 2.
[h]Na > 147 mmol/L.
[i]Na < 137 mmol/L.
[j]K > 5.3 mmol/L.

TABLE 3 Oncologic and pathologic outcomes.

Variable	Entire cohort		*P*	Matched cohort		*P*
	RG (*n* = 106)	LG (*n* = 303)		RG (*n* = 61)	G (*n* = 122)	
Tumor location, *n* (%)			0.854			0.919
EG junction	29 (27.4)	71 (23.4)		17 (27.9)	31 (25.4)	
Cardia	9 (8.5)	24 (7.9)		7 (11.5)	11 (9.0)	
Fundus	33 (31.1)	99 (32.7)		18 (29.5)	39 (32.0)	
Upper body	35 (33.0)	109 (36.0)		19 (31.1)	41 (33.6)	
Tumor size (cm ± SD)	4.1 ± 3.1	4.7 ± 2.9	0.073	4.2 ± 2.7	4.4 ± 3.2	0.676
Pathological proximal margin (cm ± SD)	2.3 ± 1.9	2.6 ± 2.1	0.195	2.1 ± 1.7	2.4 ± 1.5	0.224
Pathological distal margin (cm ± SD)	5.1 ± 1.7	5.3 ± 2.6	0.461	4.9 ± 1.4	5.2 ± 1.7	0.235
Histological type, *n* (%)			0.804			0.931
Poorly differentiated	64 (60.4)	197 (65.0)		34 (55.7)	73 (59.8)	
Moderately differentiated	31 (29.2)	82 (27.1)		21 (34.4)	40 (32.8)	
Well differentiated	7 (6.6)	16 (5.3)		4 (6.6)	6 (4.9)	
Undifferentiated	4 (3.8)	8 (2.6)		2 (1.9)	3 (2.5)	
Histology (Lauren classification), *n* (%)			0.848			0.989
Intestinal	30 (28.3)	87 (28.7)		17 (27.9)	36 (29.5)	
Diffuse	39 (36.8)	99 (32.7)		21 (34.4)	41 (33.6)	
Mixed	31 (29.2)	95 (31.4)		19 (31.1)	36 (29.5)	
Indeterminate	6 (5.7)	22 (7.3)		4 (6.6)	9 (7.4)	
T stage, *n* (%)			0.338			0.962
T1	20 (18.9)	42 (13.9)		7 (11.5)	15 (12.3)	
T2	16 (15.1)	33 (10.9)		12 (19.7)	27 (22.1)	
T3	58 (54.7)	189 (62.4)		37 (60.7)	69 (56.6)	
T4a	12 (11.3)	39 (12.9)		5 (8.2)	11 (9.0)	
N stage, *n* (%)			0.608			0.906
N0	38 (35.8)	97 (32.0)		23 (37.7)	42 (34.4)	
N1	59 (55.7)	185 (61.1)		33 (54.1)	69 (56.6)	
N2	9 (8.5)	21 (6.9)		5 (8.2)	11 (9.0)	
pTNM stage, *n* (%)			0.874			0.993
IA	17 (16.0)	44 (14.5)		9 (14.8)	21 (17.2)	
IB	14 (13.2)	30 (9.9)		7 (11.5)	16 (13.1)	
IIA	23 (21.7)	74 (24.4)		17 (27.9)	31 (25.4)	
IIB	34 (32.1)	104 (34.3)		19 (31.1)	36 (29.5)	
IIIA	13 (12.3)	32 (10.6)		7 (11.5)	13 (10.7)	
IIIB	5 (4.7)	19 (6.3)		2 (3.3)	5 (4.1)	

RG, robotic gastrectomy; LG, laparoscopic gastrectomy; EG, esophagogastric.

less bleeding, faster postoperative recovery, and shorter hospital stays compared with laparoscopic surgery (26–28). Moreover, robotic surgery can ensure that the surgical field is clean and clear, is easier to use for the surgeon and team, minimize the occurrence of vascular and organ side injuries, and increase the number of lymph nodes obtained. Lymph node dissection is the most complex and challenging part of radical gastrectomy. Some studies have shown that robots are more suitable for complex operations and lymph node dissection than laparoscopic radical gastrectomy for gastric cancer (29). This study shows that the average number of lymph nodes cleaned by robot surgery is 37.3, which is significantly higher than that of laparoscopic surgery is 32.8. This difference suggests that robot lymph node cleaning is superior to laparoscopic surgery, which may bring patients potential advantages in terms of better tumor treatment. This improvement may be related to the advantages of robot surgery, such as 10–15 times enlarged vision, distortion-free

TABLE 4 Comparison of lymph node dissection between robot and laparoscopic group.

Lymph node dissection	RG ($n = 61$)	LG ($n = 122$)	P
Retrieved lymph nodes	37.3 ± 13.5	32.8 ± 11.8	0.022
Subphrenic lymph nodes			
No.19	2.4 ± 0.9	1.1 ± 0.7	<0.001
No.20	2.3 ± 0.6	1.2 ± 0.5	<0.001
Inferior mediastinal lymph nodes			
No.110	3.3 ± 1.6	1.7 ± 0.8	<0.001
No.111	3.2 ± 1.4	1.9 ± 1.3	<0.001
Laparoscopic lymph nodes	23.4 ± 11.2	24.6 ± 12.6	0.530

RG, robotic gastrectomy; LG, laparoscopic gastrectomy.

3D display, and 7 degrees of freedom of surgical instruments, which make lymph node cleaning more accurate. Lee et al. (27) reported that patients with a high body mass index who underwent robotic-assisted distal gastrectomy plus D2 lymph node dissection had less blood loss and higher lymph node dissection quality. At the same time, since the operation time in this study does not include installation time, the operation time did not significantly differ between the two groups.

This study showed that the No. 1, No. 2, No. 3, and No. 7 lymph node metastasis rates were higher, followed by the metastasis rates of the No. 8, No. 9, No. 11, No. 19, No. 20, No. 110, and No. 111 lymph nodes; the lymph node metastasis rate of No. 4, No. 5, No. 6, and No. 12 were the lowest, which

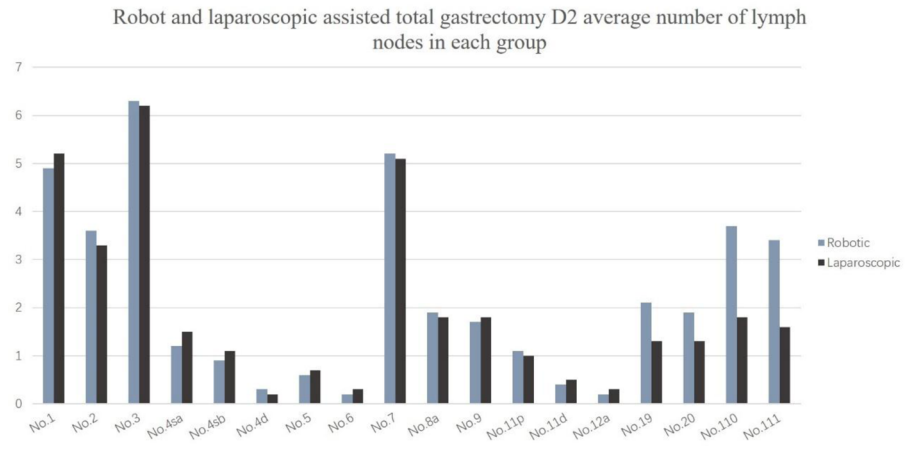

FIGURE 2
Robot and laparoscopic assisted total gastrectomy D2 average number of lymph nodes in each group.

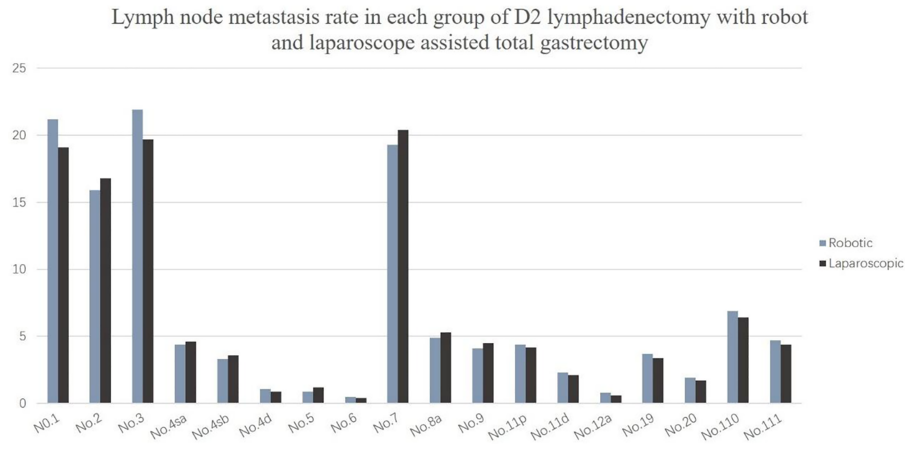

FIGURE 3
Lymph node metastasis rate in each group of D2 lymphadenectomy with robot and laparoscope assisted total gastrectomy.

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TABLE 5 Assessment of quality of life.

Factor	RG ($n = 61$)	LG ($n = 122$)	*P*	RG ($n = 61$)	LG ($n = 122$)	*P*
	Preoperative			Three months after surgery		
Physical symptoms	6.9 ± 3.1	7.2 ± 3.7	0.587	16.4 ± 7.3	18.7 ± 9.3	0.093
Dysphagia	10.3 ± 6.3	10.9 ± 5.7	0.518	27.8 ± 12.3	30.9 ± 10.8	0.082
Sour regurgitation	9.2 ± 7.1	8.9 ± 6.5	0.776	10.3 ± 6.3	12.4 ± 7.1	0.052
Belching	5.1 ± 4.2	5.4 ± 3.9	0.633	11.2 ± 6.1	14.1 ± 8.7	0.021
Abdominal pain	8.1 ± 4.9	8.3 ± 4.1	0.771	15.7 ± 6.8	19.1 ± 7.3	0.003
Diarrhea	6.9 ± 5.1	7.1 ± 5.2	0.805	13.4 ± 7.1	16.6 ± 8.7	0.014
Fatigue	7.1 ± 4.7	7.3 ± 4.4	0.777	18.7 ± 10.3	21.2 ± 9.8	0.111
Anxious	3.1 ± 1.2	2.9 ± 1.5	0.366	15.7 ± 9.2	18.4 ± 8.3	0.047
Insomnia	3.2 ± 1.4	3.7 ± 1.8	0.059	13.6 ± 8.7	16.2 ± 11.1	0.111
Social function	94.7 ± 7.3	93.9 ± 7.1	0.477	71.6 ± 12.7	69.2 ± 9.6	0.155
Independent living	96.3 ± 14.1	95.1 ± 15.2	0.607	82.1 ± 17.2	77.6 ± 18.1	0.109
Hobby	89.1 ± 15.7	90.4 ± 16.1	0.604	78.3 ± 16.8	73.4 ± 17.1	0.068
Exercise	93.1 ± 16.2	91.9 ± 17.3	0.652	74.3 ± 13.2	69.2 ± 12.7	0.012
Work efficiency	84.9 ± 19.2	86.1 ± 10.1	0.580	72.5 ± 17.4	64.7 ± 16.2	0.003
Quality of life score	95.2 ± 8.1	94.9 ± 8.9	0.825	78.0 ± 13.1	74.4 ± 10.6	0.047
	Six months after surgery			One year after surgery		
Physical symptoms	9.6 ± 5.3	11.4 ± 5.2	0.030	6.7 ± 1.9	7.8 ± 2.1	0.001
Dysphagia	16.4 ± 6.7	18.4 ± 9.7	0.150	12.3 ± 3.1	13.1 ± 2.9	0.087
Sour regurgitation	8.2 ± 4.3	8.6 ± 3.7	0.515	8.1 ± 3.3	8.3 ± 3.7	0.721
Belching	7.1 ± 3.9	9.4 ± 4.5	0.001	6.2 ± 2.2	6.7 ± 2.4	0.174
Abdominal pain	12.3 ± 4.9	14.4 ± 5.7	0.015	9.3 ± 3.6	10.6 ± 3.3	0.016
Diarrhea	12.9 ± 5.3	14.1 ± 4.9	0.130	9.9 ± 4.7	10.1 ± 4.6	0.783
Fatigue	11.3 ± 5.2	13.7 ± 6.5	0.013	8.4 ± 3.9	9.2 ± 3.1	0.134
Anxious	12.4 ± 3.3	14.2 ± 3.5	0.001	8.3 ± 2.6	10.4 ± 2.9	0.013
Insomnia	10.2 ± 3.7	11.8 ± 4.0	0.010	7.7 ± 2.4	8.6 ± 2.3	0.015
Social function	81.6 ± 8.4	77.4 ± 10.2	0.006	90.3 ± 7.8	87.1 ± 9.3	0.022
Independent living	87.6 ± 15.1	84.1 ± 13.7	0.117	91.4 ± 13.7	88.3 ± 11.6	0.111
Hobby	82.3 ± 14.2	77.6 ± 12.1	0.021	86.5 ± 12.9	83.7 ± 15.6	0.228
Exercise	83.7 ± 17.3	78.9 ± 14.7	0.051	88.3 ± 15.3	83.2 ± 14.4	0.028
Work efficiency	77.9 ± 16.2	72.1 ± 12.4	0.008	82.7 ± 13.6	78.1 ± 12.7	0.025
Quality of life score	85.7 ± 9.4	83.4 ± 10.5	0.150	92.9 ± 7.8	91.7 ± 8.6	0.360

RG, robotic gastrectomy; LG, laparoscopic gastrectomy.

was similar to findings reported in the Japanese literature (26). These results all suggest that upper third gastric cancer is characterized by a unique pattern of lymph node metastasis, which can flow to the lower mediastinum and abdominal lymph nodes. Furthermore, the abdominal lymph nodes are the main lymph nodes, while the lower mediastinum still experiences a certain proportion of lymph node metastasis. Therefore, lymph node dissection for upper third gastric cancer should consider these two regions. The number of abdominal lymph nodes cleaned did not significantly differ between the robotic and laparoscopic groups, but the main difference lies in the subphrenic lymph nodes (No. 19 and No. 20) and the lower mediastinal lymph nodes (No. 110 and No. 111), and robot surgery is superior to laparoscopy.

In addition to the quality of radical surgery, the postoperative quality of life of gastric cancer patients is also the focus of surgeons (30). A number of clinical studies have confirmed the minimally invasive advantages of laparoscopic radical gastrectomy and its exact oncological efficacy. This study integrated the scales of the European Cancer Research and Treatment Assistance Organization (EORTC QLQ—C30 questionnaire and EORTC QLQ—STO22 questionnaire) to evaluate the quality of life recovery of patients in the robotic and laparoscopic groups after surgery. The results showed that dysphagia, abdominal pain, fatigue, diarrhea, and other physical symptoms after surgery were significantly better in the robotic group than in the laparoscopic group, which may be due to the more sophisticated operation of the robotic

TABLE 6 Postoperative recovery of nutrition-related indicators in two groups.

Factor	RG ($n = 61$)	LG ($n = 122$)	*P*	RG ($n = 61$)	LG ($n = 122$)	*P*
	Preoperative			Three months after surgery		
Body weight (kg)	63.2 ± 9.7	62.9 ± 9.4	0.841	57.8 ± 6.5	56.1 ± 6.1	0.084
Psoas muscle index (cm^2/m^2)	15.2 ± 2.1	15.4 ± 2.3	0.569	10.5 ± 1.8	9.8 ± 1.6	0.008
Serum albumin (g/L)	42.7 ± 5.6	43.1 ± 6.2	0.672	37.5 ± 4.7	37.9 ± 4.3	0.566
Serum prealbumin (g/L)	278.3 ± 37.4	281.6 ± 39.8	0.590	211.6 ± 27.3	203.8 ± 23.1	0.044
Hemoglobin (g/L)	139.8 ± 13.6	141.2 ± 13.9	0.519	112.4 ± 9.6	110.7 ± 9.3	0.250
Meal size, *n* (g)	371.8 ± 67.3	367.5 ± 71.2	0.695	266.3 ± 40.2	253.6 ± 40.7	0.047
Meal times	2.3 ± 0.4	2.2 ± 0.5	0.176	3.1 ± 1.2	3.2 ± 0.9	0.528
Soft diet, *n* (%)	3 (4.9)	7 (5.7)	>0.999	32 (52.5)	59 (48.4)	0.601
Liquid diet, *n* (%)	28 (46.7)	62 (50.8)	0.530	25 (41.0)	56 (45.9)	0.528
Hard diet, *n* (%)	30 (49.2)	53 (43.4)	0.462	4 (6.5)	7 (5.7)	>0.999
Prognostic nutritional index	422.7 ± 75.3	437.02 ± 81.2	0.251	362.1 ± 61.4	369.5 ± 57.6	0.424
	Six months after surgery			One year after surgery		
Body weight (kg)	58.2 ± 6.8	57.3 ± 6.3	0.376	58.6 ± 7.2	57.8 ± 6.9	0.467
Psoas muscle index (cm^2/m^2)	11.3 ± 2.4	10.6 ± 1.9	0.033	12.1 ± 1.4	11.9 ± 1.7	0.428
Serum albumin (g/L)	37.9 ± 3.6	38.3 ± 4.7	0.560	38.7 ± 5.1	38.9 ± 5.4	0.810
Serum prealbumin (g/L)	237.1 ± 24.6	232.4 ± 21.7	0.188	247.2 ± 31.3	244.3 ± 30.2	0.546
Hemoglobin (g/L)	114.7 ± 8.5	115.5 ± 8.1	0.536	118.2 ± 8.7	117.1 ± 7.4	0.373
Meal size, *n* (g)	279.4 ± 49.2	264.4 ± 45.2	0.041	311.5 ± 59.2	301.3 ± 62.4	0.291
Meal times	2.7 ± 0.8	2.8 ± 0.2	0.260	2.4 ± 0.2	2.5 ± 0.7	0.276
Soft diet, *n* (%)	21 (34.4)	39 (32.0)	0.738	10 (16.4)	18 (14.8)	0.772
Liquid diet, *n* (%)	31 (50.8)	68 (55.7)	0.529	35 (57.4)	77 (63.1)	0.453
Hard diet, *n* (%)	9 (14.8)	15 (12.3)	0.642	16 (26.2)	27 (22.1)	0.538
Prognostic nutritional index	370.4 ± 53.5	373.6 ± 55.8	0.711	379.5 ± 51.2	383.4 ± 51.4	0.629

RG, robotic gastrectomy; LG, laparoscopic gastrectomy.

TABLE 7 One year change rate of nutrition-related indexes after operation.

One year change rate	RG ($n = 61$)	PG ($n = 122$)	*P*
Body weight loss	−8.1 ± 1.7	−8.7 ± 1.9	0.039
Psoas muscle index	−10.9 ± 1.7	−11.4 ± 2.1	0.108
Serum albumin	−6.5 ± 0.7	−6.4 ± 0.6	0.317
Serum prealbumin	−5.7 ± 1.1	−5.9 ± 1.4	0.331
Hemoglobin	−7.4 ± 1.7	−7.2 ± 1.9	0.488
Meal size	−16.4 ± 3.9	−18.1 ± 4.3	0.010
Meal times	29.3 ± 6.5	31.2 ± 7.1	0.081
Prognostic nutritional index	−9.8 ± 2.6	−10.4 ± 3.2	0.206

RG, robotic gastrectomy; LG, laparoscopic gastrectomy.

group (31). In addition, the amount of intraoperative bleeding was reduced in the robotic group, which may help reduce the formation of intra-abdominal adhesions and the resulting abdominal discomfort. These factors are conducive to the recovery of intestinal function after surgery.

TABLE 8 Correlation between nutritional status and quality of life in gastric cancer patients 1 year after surgery.

Categories	PG-SGA score			
	0–3	4–8	≥9	*P*
Physical symptoms				
Dysphagia	14.4 ± 6.1	15.2 ± 7.3	17.8 ± 9.2	<0.001
Sour regurgitation	7.2 ± 4.1	6.9 ± 3.4	7.7 ± 5.4	<0.001
Belching	8.4 ± 5.3	8.2 ± 4.6	8.9 ± 3.8	<0.001
Abdominal pain	16.3 ± 8.2	19.4 ± 7.7	22.6 ± 6.3	<0.001
Diarrhea	7.2 ± 5.2	9.3 ± 4.9	12.2 ± 6.4	<0.001
Fatigue	21.1 ± 9.3	22.5 ± 13.2	22.9 ± 12.6	<0.001
Anxious	6.3 ± 3.3	6.8 ± 4.1	7.4 ± 4.7	<0.001
Insomnia	23.6 ± 13.7	24.2 ± 12.9	23.9 ± 14.8	<0.001
Social function				
Independent living	92.2 ± 13.4	88.3 ± 16.2	82.4 ± 11.2	<0.001
Hobby	88.7 ± 12.3	84.2 ± 10.1	78.4 ± 9.8	<0.001
Exercise	89.3 ± 15.6	83.5 ± 11.2	80.1 ± 12.3	<0.001
Work efficiency	84.7 ± 14.4	80.3 ± 12.6	73.4 ± 10.7	<0.001
Quality of life score	94.7 ± 17.4	90.6 ± 15.9	83.9 ± 13.8	<0.001

The results of this study also showed that the social function scores of independent living, hobbies, fitness exercise, and work efficiency were better in the robotic group than in the laparoscopic group at 3–12 months after surgery, and the overall quality of life scores of the robotic group were better than those of the laparoscopic group. The reason may be that the robotic group has less intraoperative trauma, earlier bowel function recovery, an earlier return to a soft diet, a faster reduction of physical symptoms, less mental burden, and earlier physiological function recovery to the preoperative level (32). The results of this study also showed that the physical symptoms score of patients in the robotic group returned to the preoperative level at 6 months after surgery, and the improvement was more obvious at 12 months after surgery, while the physical symptoms score of patients in the laparoscopic group did not return to the preoperative level until 12 months after surgery. Therefore, compared with the laparoscopic group, patients in the robotic group were able to achieve self-care earlier, were more willing to resume leisure activities and fitness exercises, had higher work efficiency, and were better able to recover their social roles.

Due to the changes in the anatomical and physiological structure of the digestive tract and the impairment of gastrointestinal function after operation, patients undergoing radical gastrectomy are recommended to eat smaller and more frequents meals, mainly a liquid diet (33). However, this study found that more patients in the robotic group ate a solid diet and soft food than those in the laparoscopic group at 3, 6, and 12 months after surgery and had a greater tendency to recover to the proportion of preoperative dietary components. This finding indicated that patients in the robotic group were more able to tolerate a solid diet after surgery. Furthermore, the robotic group had a lower score of dysphagia, diarrhea, and other physical symptoms than the laparoscopic group, which further indicated that gastrointestinal symptoms in the robotic group recovered quickly in the early postoperative period.

The recovery of postoperative nutritional indicators is also an important standard to consider the quality of life of gastric cancer patients after surgery. Lower changes in nutritional indicators and faster nutritional recovery after surgery tend to promote a better prognosis, indicating better postoperative quality of life (34). The results of this study showed that the proportion of changes in body weight and meal size were significantly lower in the robotic group than in the laparoscopic group 1 year after surgery. This difference may be related to the fact that the patients in the robotic group have a higher tolerance to diet than those in the laparoscopic group and can quickly recover their preoperative eating habits after surgery. In addition, the patients in the robotic group consumed a solid diet as early as possible after the operation, which provided them with more energy and nutrients needed by the human body, thus promoting the maintenance of body weight after the operation.

We found that as the PG-SGA score increased, values from the functional category and for the overall health status of patients with a lower mean field rank and the symptoms category rank mean increased. Specifically, as functional abilities and quality of life worsened, symptoms or problems, such as fatigue, nausea, belching, diarrhea, and insomnia, worsened and added to the poor quality of life.

Learning curve

Although studies regarding the learning curve of robotic gastrectomy are scarce, all reported that the robotic system is more adaptable than the laparoscopic environment (35–37). Moreover, in contrast to the longer operation time, the robotic system makes surgeons rapidly overcome the learning curve for robotic gastrectomy, which may help less-experienced surgeons. The actual impact of the robotic system on the learning curve of robotic gastrectomy is difficult to evaluate without considering the experience of laparoscopic gastrectomy because the robotic gastrectomy procedure is identical to laparoscopic gastrectomy. Thus, the exact assessment of the learning curve effect would be difficult.

Cost

Studies have consistently reported that the costs of robotic gastrectomy are higher than those of laparoscopic gastrectomy. Robotic gastrectomy consistently costs more than laparoscopic gastrectomy. The high cost of robotic gastrectomy is mainly associated with the cost of robotic system installation and disposable drapes and instruments (38, 39). Moreover, since a longer operation time itself means another source of extra expense of robotic surgery, balancing the cost of robotic surgery with that of laparoscopic surgery is difficult. Thus, further studies to determine whether the benefits of robotic surgery would reduce the other costs related to postoperative care or readmission are necessary.

This research is subject to limitations. The malnourished patients did not receive further nutritional intervention, and we hope to clarify in future research whether an improvement in the nutritional status in gastric cancer patients will improve clinical outcome. In addition, the effect of nutritional status on the final clinical outcome after nutritional therapy was not followed up.

Conclusion

In summary, robotic-assisted radical total gastrectomy for upper third gastric cancer is safe and feasible. Compared with laparoscopic surgery, it is more sophisticated, has less

bleeding, and has a higher quality of lymph node dissection, especially for subphrenic and lower mediastinal lymph nodes. At the same time, patients in the robotic group also had better quality of life and faster postoperative nutritional recovery than patients in the laparoscopic group.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JF contributed to this study. ZN made substantial contributions to the conception and design for this study, YL and XJ acquired and analyzed data and JF drafted the article. HQ and YW gave many important suggestions for this study. ZN and XL participated in critical interpretation of important intellectual results. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Minimally invasive sleeve lobectomy for centrally located lung cancer: A real-world study with propensity-score matching

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Background: The safety, feasibility, and prognosis of sleeve lobectomy by minimally invasive surgery (MIS) remain to be validated. The purpose of this study was to investigate outcomes in real-world patients receiving minimally invasive sleeve lobectomy in a balanced large cohort.

Methods: Between January 2013 and December 2018, 578 consecutive patients undergoing sleeve resection at a high-volume center were retrospectively analyzed. Surgical and oncologic outcomes were compared between MIS and thoracotomy patients after propensity-score matching (PSM).

Results: MIS sleeve lobectomy was increasingly used as a time-trend in real-world. Before PSM, the MIS group had smaller tumor size, more T2-stage cases, and more right upper lobe sleeve lobectomies compared to the Open group. After 1:4 PSM by patient demographics and tumoral characteristics, 100 cases of MIS and 338 cases of Open sleeve lobectomy were further analyzed. Although median operation time was longer in the MIS group than in the Open group (170.5 minutes vs.149.5 minutes, $P < 0.001$), patients in MIS group had significantly less estimated intraoperative blood loss (100 ml vs. 200 ml, $P = 0.003$), shorter drainage duration (5 days vs. 6 days, $P = 0.027$) and less amount of drainage (1280 ml vs. 1640 ml, $P < 0.001$) after surgery. Complete resection rate, combined angioplasty, number of dissected lymph nodes, post-operative length of stay, postoperative morbidity and mortality rate, and application of adjuvant therapy were similar between the two matched groups. Conversion to open thoracotomy was necessary in 13.6% patients, but with similar perioperative outcomes compared to Open cases except for longer operation time. More lower lobe sleeve lobectomies were accomplished *via* robot-assisted thoracoscopic surgery than *via* video-assisted thoracoscopic surgery (40.0% vs. 12.0%, $P = 0.017$) in MIS patients. Five-year overall survivals (MIS vs. Open: 72.7% vs. 64.4%, $P = 0.156$) and five-year progression-free survivals (MIS vs. Open: 49.2% vs. 50.5%, $P = 0.605$) were similar between the two matched groups.

Conclusions: MIS sleeve lobectomy is associated with similar or even better perioperative results and oncologic outcomes to open thoracotomy. Conversion to thoracotomy does not compromise perioperative outcomes. Robot surgery may be preferable for more complex sleeve resections.

KEYWORDS

sleeve lobectomy, minimally invasive surgery, thoracotomy, robot-assisted thoracoscopic surgery, video-assited thoracoscopic surgery

Introduction

Lung cancer is currently one of the leading causes of cancer death in the world (1). Non-small cell lung cancers (NSCLCs) can be clinically divided into centrally located and peripheral ones according to their position in the lung. In 1933, Graham performed the first successful pneumonectomy (2) for a centrally located lung cancer. However, pneumonectomy is associated with high mortality and morbidity. A selected group of centrally located tumors can be completely resected by using bronchoplastic techniques with anastomosis of one lobar bronchus to the other to preserve lung parenchyma. These so-called sleeve resections were reported for the first time by Clement Price Thomas in 1956 (3). Compared to pneumonectomy, sleeve lobectomy has been shown to be associated with less morbidity and mortality but similar or even better long-term survival if the tumor could be completely removed (4–10). It has thus become the preferred surgical procedure for centrally located NSCLC, whenever technically feasible and when complete resection can be achieved (11).

Minimally invasive surgery (MIS), including video-assisted thoracoscopic surgery (VATS) and robot-assisted thoracoscopic surgery (RATS), is the preferred approach in the current guidelines for the surgical management of early-stage NSCLC (12). Its advantage over open thoracotomy includes less pain, decreased postoperative complications, less impaired pulmonary function, and better quality of life and compliance to adjuvant therapies after surgery (13–16). And similar oncologic outcomes in lymph node dissection and long-term survival have been demonstrated in MIS and open surgery (17, 18). But most sleeve lung resections are still accomplished *via* conventional open thoracotomy, as they are technically more demanding and are often applied in locally advanced tumors. Although Santambrogio et al. (19) reported the first successful case of VATS sleeve lobectomy in 2002, up till now, there have been only a few single-institutional reports with small numbers of cases showing its feasibility technically (20–30). Although the conversion rates reported in these series were generally higher than in standard lobectomy, converted cases were either excluded or their outcomes not studied in the previous reports. Most reported cases were accomplished *via* VATS, with very few RATS cases included (27, 29). Since most of the MIS sleeve lobectomies were done in recent years, follow-up time of MIS patients was unanimously short in these series. Therefore, the safety and efficacy of MIS in sleeve lobectomy for NSCLC remains largely unknown.

Our study thus aimed to find out the results of MIS for sleeve lobectomy in a real-world setting, with special attention paid to its potential benefits and surgical outcomes in conversion cases, and to the unique advantages of RATS.

Materials and methods

Patients with centrally located primary NSCLC receiving bronchial sleeve resection with or without pulmonary artery angioplasty at the Shanghai Chest Hospital between January 2013 and December 2018 were retrospectively identified from the institutional database. The study was approved by the Institutional Review Board of Shanghai Chest Hospital (No. KS(Y) 21268). Informed consent was waived as only de-characterized data were used for the study.

Designed as a real-world study, all consecutive patients receiving sleeve lobectomy for potentially resectable primary NSCLC *via* either MIS or Open thoracotomy were included. Exclusion criteria were concomitant carina resection or reconstruction of great vessels such as superior vena cava, patients with metastatic disease, small cell lung cancer, or benign diseases. All patients were confirmed of having central lung cancer by bronchoscopy. Pretreatment evaluation included chest computed tomography (CT) scan, brain magnetic resonance imaging, neck, and abdominal ultrasonography, bone scintigraphy, or positron emission tomography. Tumor stage was re-classified according to the 8th Edition TNM Classification of Malignant Tumors (31).

Patients were divided into two groups according to the planned surgery: the MIS group and the Open group. The approach was chosen according to the surgeons' decision. Those converted to open thoracotomy during the operation were included in the MIS group, using an intention-to-treat (ITT) analysis.

General anesthesia and double-lumen tube intubation were used in all patients. Open thoracotomy was performed using a postero-lateral incision at the fourth or fifth intercostal space. MIS was accomplished *via* one, two, three, or four-port VATS or RATS according to surgeons' preference. Frozen section was performed intraoperatively in all patients to assess the resected bronchial margins. In patients with poor pulmonary function or severe comorbidity, pneumonectomy was usually avoided even if the bronchial margin was positive, and postoperative radiotherapy would be recommended to these patients. Most of the surgeons in

our institution chose to do the running sutures using non-absorbable thread in MIS and Open sleeve lobectomy. But a few surgeons preferred absorbable thread to do interrupted sutures in open cases. Angioplasty would be added if the pulmonary artery trunk was also invaded by the tumor. In open sleeve cases, some surgeons preferred covering the anastomosis with muscle or pericardium flap or thymus. However, we do not routinely cover the anastomosis with any tissues in the MIS sleeve cases. We routinely did bronchoscopy right after finishing the bronchial anastomosis to control the anastomosis.

After surgery, adjuvant chemotherapy was recommended to patients with histologically proven stage II or III diseases who did not receive neoadjuvant therapy before surgery. Adjuvant radiation would also be suggested to patients with positive resection margin or pathological N2 disease. Patients were followed every three months after treatment in the first two years and 6-12 months afterwards. These routinely included serum tumor markers, chest CT scan, neck, and abdominal ultrasonography. Brain magnetic resonance imaging, bone scintigraphy, or positron emission tomography was conducted when disease progression was suspected.

Patients' demographics, tumoral characteristics, and treatment outcomes were compared between the two groups. Overall survival (OS) was defined as the duration from the date of operation to death of any cause or the date of last follow-up. Progression-free survival (PFS) was defined as the duration from the date of operation to the date of progress or death of any cause or the date of last follow-up.

Continuous variables were expressed as mean ± standard deviations (SD) if normally distributed, otherwise were exhibited as median with interquartile range (IQR). Student t-test or Mann-Whitney test was used for comparison. Comparison of categorical variables was performed by Chi-Squared test or Fisher's exact test when appropriate. Survival curves were plotted using the Kaplan-Meier method. Log-rank test was used to compare survivals between different groups. As the baseline characteristics in the MIS and Open cases were not balanced, a propensity-score matched (PSM) analysis was performed with R version 4.2.0. A 1:4 matching was performed by potential confounding factors including sex, age, body mass index (BMI), forced expiratory volume in one second (FEV1), percentage of diffusing capacity of the lung for carbon monoxide (DLCO%), comorbidity, smoking history, tumor size, tumor location, clinical T and N stage, histological classification, and neoadjuvant chemotherapy. Patients having MIS were ordered and sequentially matched to the nearest unmatched patients having thoracotomy. Surgical and postoperative outcomes were then compared between the matched groups. Univariable analysis was performed using the Cox univariate model to assess the impact of potential risk factors on survival and disease-progression. Multivariable analysis was performed with a Cox proportional model, using the enter method. The variables would be included into the multivariable analysis if their P-values were less than 0.05 in univariable analysis. Statistical significance was defined as $P < 0.05$ throughout the study.

Results

Between January 2013 and December 2018, 692 consecutive patients underwent sleeve lobectomy at the Shanghai Chest Hospital. Based on the exclusion criteria, 114 cases were excluded, leaving 578 patients for analysis, 103 (17.8%) in the MIS group and 475 (82.2%) in the Open group. The MIS group included 20 RATS cases and 83 VATS cases (Figure 1). There was an obvious trend

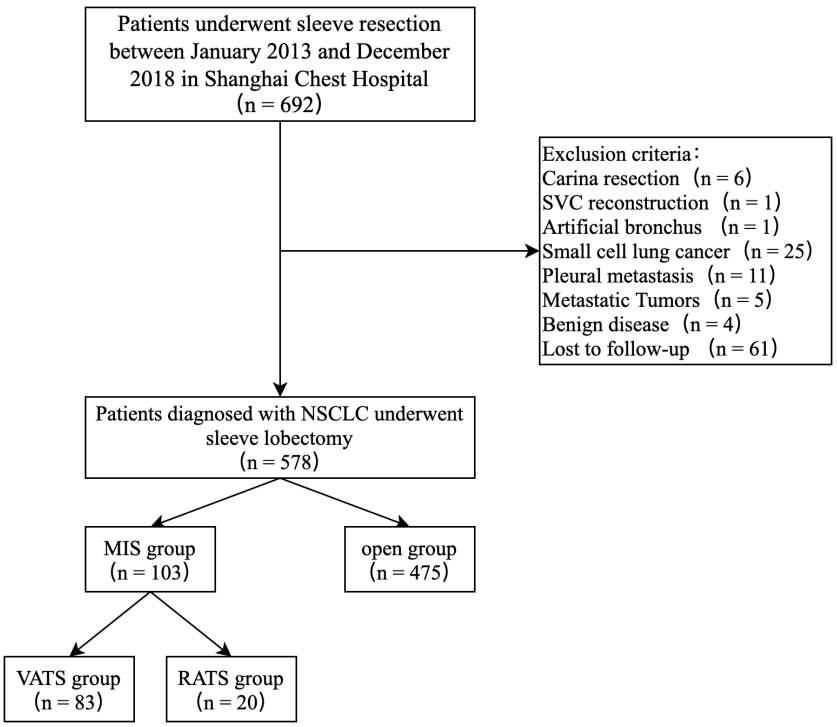

FIGURE 1
Study population flow diagram — patients who underwent sleeve lobectomy between 2013 and 2018.

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toward increasing use of MIS in sleeve lobectomy patients during the study period (7.7% in 2013 to 36% in 2018), as shown in Figure 2. Conversion to thoracotomy was found necessary in 14 patients (13.6%) due to difficult tumor or hilar lymph nodes, dense adhesion, or unexpected intraoperative bleeding. Details of patient demographics and oncologic characteristics are listed in Table 1. Demographic characteristics were similar between the MIS and the Open groups before PSM. There was no difference in patient age, sex,

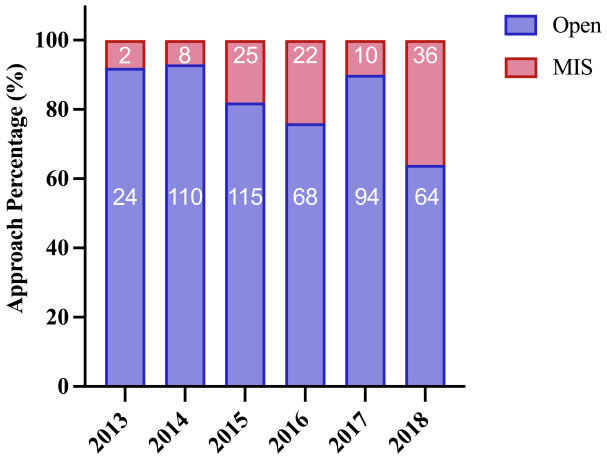

FIGURE 2
Annual numbers and percentage of patients underwent MIS and open sleeve lobectomy.

TABLE 1 Demographic and pathologic characteristics before and after propensity-score matching.

Characteristics	Unmatched cohort			Matched cohort		
	Open (n=475)	MIS (n=103)	*P*	Open (n=338)	MIS (n=100)	*P*
Sex, n (%)			0.601			0.907
Male	439 (92.4)	93 (90.3)		311 (92.0)	91 (91.0)	
Female	36 (7.6)	10 (9.7)		27 (8.0)	9 (9.0)	
Age (year), mean ± SD	61.2 ± 8.8	60.2 ± 8.5	0.290	60.6 ± 8.5	60.4 ± 8.4	0.861
BMI (kg/m^2), mean ± SD	23.3 ± 3.0	23.0 ± 3.1	0.333	23.2 ± 2.8	23.0 ± 3.0	0.691
CCI, n (%)			0.514			0.703
0	356 (74.9)	80 (77.7)		255 (75.4)	77 (77.0)	
1	86 (18.1)	19 (18.4)		62 (18.3)	19 (19.0)	
≥2	33 (6.9)	4 (3.9)		21 (6.2)	4 (4.0)	
Smoking history, n (%)			0.754			0.888
Never	252 (53.1)	57 (55.3)		181 (53.6)	55 (55.0)	
Ever	223 (46.9)	46 (44.7)		157 (46.4)	45 (45.0)	
FEV1%, mean ± SD	79.4 ± 14.9	81.9 ± 14.6	0.127	80.2 ± 15.2	81.9 ± 14.8	0.318
DLCO%, mean ± SD	86.7 ± 18.6	87.1 ± 16.0	0.859	86.0 ± 17.4	87.3 ± 16.2	0.503
Histology, n (%)			0.385			0.486
Squamous	372 (78.3)	76 (73.8)		270 (79.9)	76 (76.0)	
Non-suamous	103 (21.7)	27 (26.2)		68 (20.1)	24 (24.0)	
Location, n (%)			0.026			0.118
RUL	224 (47.2)	61 (59.2)		166 (49.1)	58 (58.0)	
others	251 (52.8)	42 (40.8)		172 (50.9)	42 (42.0)	

(Continued)

TABLE 1 Continued

Characteristics	Unmatched cohort			Matched cohort		
	Open (n=475)	MIS (n=103)	*P*	Open (n=338)	MIS (n=100)	*P*
Size (mm), mean ± SD	37.3 ± 16.2	32.0 ± 14.3	0.002	33.9 ± 13.5	32.7 ± 13.9	0.424
Clinical T stage, n (%)			0.022			0.508
cT2	408 (85.9)	97 (94.2)		311 (92.0)	94 (94.0)	
cT3 + cT4	67 (14.1)	6 (5.8)		27 (8.0)	6 (6.0)	
Clinical N stage, n (%)			0.251			0.612
cN0	214 (45.1)	55 (53.4)		162 (47.9)	52 (52.0)	
cN1	217 (45.7)	38 (36.9)		147 (43.5)	38 (38.0)	
cN2	44 (9.3)	10 (9.7)		29 (8.6)	10 (10.0)	
Neoadjuvant therapy, n (%)	76 (16.0)	11 (10.7)	0.224	42 (12.4)	11 (11.0)	0.834

MIS, minimally invasive surgery; SD, standard deviation; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, carbon monoxide diffusing capacity; CCI, Charlson Comorbidity Index; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

comorbidity or functional status between the MIS and the Open group. The proportion of patients receiving neoadjuvant therapy (10.7% vs. 16.0%, P = 0.224) were also similar. However, right upper lobe sleeve lobectomy accounted for only 47.2% of the cases in the Open group, while it was 59.2% in the MIS group (P = 0.026). There was only one (0.9%) case of sleeve bilobectomy in the MIS group but 17(3.6%) in the Open group. The MIS group also had more patients with smaller lesions and thus more cT2 tumors (94.2% vs. 85.9%, P = 0.022). The mean diameter of tumor was 32 mm in the MIS group and 37 mm in the Open group (P = 0.002).

In the unmatched cohort, median operation time was 171 minutes in the MIS group and 151 minutes in the Open group (P < 0.001). However, rate of angioplasty (7.8% vs. 8.4%, P = 0.983), R0 resection (84.5% vs. 84.6%, P = 0.966) and median number of harvested lymph nodes (15 vs. 15, P = 0.445) were similar between the two groups. The MIS group had shorter drainage duration (5 days vs. 6 days, P = 0.004), less drainage amount (1270 ml vs. 1670 ml, P < 0.001) and shorter length of postoperative hospitalization (7 days vs. 8 days, P = 0.007) compared to the Open group. In term of postoperative complications, there was only one patient diagnosed with bronchopleural fistula (BPF) after surgery in the MIS group who recovered after conservative treatment. Regarding the late complications, there was 1 patient in the MIS group and 2 in the Open group experiencing bronchial stenosis after surgery. These patients received balloon dilation *via* bronchoscopy. We did not see any patients with late dehiscence postoperatively. Five patients in the Open group died due to bronchopleural fistula or pulmonary infection, and one in the MIS group died due to empyema and sepsis during postoperative hospitalization. The in-hospital mortality was not significantly different (MIS vs. Open, 1.0% vs. 1.1%, P = 0.940).

After PSM, 100 MIS and 338 Open patients were retained for further analysis. There was no longer any significant difference in patient demographics or tumor characteristics between the two matched groups (Table 1). Potential confounders like tumor size, tumor location, tumor stage, and proportion of patients receiving neoadjuvant therapy before surgery were well-balanced after PSM. In the matched cohort, median operation time in the MIS group was still longer than in the Open group (170.5 minutes [IQR, 134–224.5] vs.149.5 minutes [IQR, 128–179], P < 0.001). However, the estimated intraoperative blood loss was significantly less in the MIS group (100 ml [IQR, 100–200] vs. 200 ml [IQR, 100–200], P = 0.003). There was no difference in complete resection rate, number of total or mediastinal lymph nodes dissected between the two groups. After surgery, chest drainage duration (5 days [IQR, 4–7] vs. 6 days [IQR, 5–7], P = 0.027) was significantly shorter, and total amount of drainage (1280 ml [IQR, 957.5–1695] vs. 1640 ml [IQR, 1200–2307.5], P < 0.001) was significantly less in the MIS group than in the Open group. Postoperative ICU stay and length of stay in hospital was similar (Table 2) between two groups. The overall postoperative complication rate was 18.0% in the MIS group and 20.7% in the Open group, which was also similar (Table 2). The BPF rate was 0% in the MIS group and 1.5% in the Open group in the matched cohort.

Perioperative outcomes were also compared between the conversion patients and the Open group. The conversion cases had longer operation time than the Open group (190.5 minutes [IQR, 153.25–306.25] vs. 151 minutes [IQR, 127–179], P = 0.004). However, intraoperative blood loss, number of total and mediastinal lymph nodes dissected, postoperative ICU stay, postoperative drainage duration or amount, postoperative length of hospitalization, or postoperative complication rates were similar between the two groups. No conversion cases died during hospitalization (Table 3).

Patient characteristics and perioperative outcomes were further compared between VATS and RATS cases (Table 4). Operation time, intraoperative blood loss, lymph node dissection, postoperative drainage, postoperative length of hospitalization and overall postoperative complication rates were similar between the two groups. However, significantly more lower lobe sleeve lobectomies were accomplished *via* RATS than *via* VATS (40.0% vs. 12.0%, P = 0.017).

The median follow-up time was 31 months in the Open group and 42 months in the MIS group before PSM. Five-year OS rate in the MIS group was significantly better than in the Open group (73.5% vs. 60.6%, P = 0.039) before PSM (Figure 3A). Five-year PFS rate was

TABLE 2 Perioperative outcomes before and after propensity-score matching.

Characteristics	Unmatched cohort			Matched cohort		
	Open (n=475)	MIS (n=103)	*P*	Open (n=338)	MIS (n=100)	*P*
Operating time (minute), (median (IQR))	151 (127, 179)	171 (134, 227)	<0.001	149.5 (128, 179)	170.5 (134, 224.5)	<0.001
Intraoperative blood loss (ml), (median (IQR))	200 (100, 200)	200 (100, 200)	0.001	200 (100, 200)	100 (100, 200)	0.003
Angioplasty, n (%)	40 (8.4)	8 (7.8)	0.983	25 (7.4)	8 (8.0)	0.841
R0, n (%)	402 (84.6)	87 (84.5)	0.966	282 (83.4)	84 (84.0)	0.893
LN numbers (median (IQR))	15 (11, 20)	15 (11, 20)	0.445	15.5 (11, 20.75)	15 (11, 20)	0.424
MLN numbers (median (IQR))	9 (6, 12)	8 (5, 12)	0.483	9 (6, 12)	8 (5, 12)	0.443
Pathological T stage, n (%)			0.010			0.179
pT0	0 (0.0)	1 (1.0)		0 (0.0)	1 (1.0)	
pT2	394 (82.9)	95 (92.2)		301 (89.1)	92 (92.0)	
pT3	63 (13.3)	6 (5.8)		28 (8.3)	6 (6.0)	
pT4	18 (3.8)	1 (1.0)		9 (2.7)	1 (1.0)	
Pathological N stage, n (%)			0.211			0.508
pN0	209 (44.0)	55 (53.4)		157 (46.4)	52 (52.0)	0.503
pN1	148 (31.2)	28 (27.2)		96 (28.4)	28 (28.0)	0.486
pN2	118 (24.8)	20 (19.4)		85 (25.1)	20 (20.0)	
ICU stay(day), (median (IQR))	1 (0, 3)	1 (0, 3)	0.237	1 (0, 3)	1 (0, 3)	0.338
Drainage duration (day), (median (IQR))	6 (5, 8)	5 (4, 7)	0.004	6 (5, 7)	5 (4, 7)	0.027
Drainage amount (ml), (median (IQR))	1670 (1235, 2350)	1270 (910, 1680)	<0.001	1640 (1200, 2307.5)	1280 (957.5, 1695)	<0.001
LOS (day), (median (IQR))	8 (7, 10)	7 (6, 9)	0.007	8 (7, 10)	7 (6, 9)	0.053
Complication in hospital, n (%)	97 (20.4)	18 (17.5)	0.587	70 (20.7)	18 (18.0)	0.651
Prolonged air leak	27 (5.7)	4 (3.9%)		19 (5.6)	4 (4.0)	
Arrhythmia	17 (3.6)	5 (4.9%)		13 (3.8)	5 (5.0)	
Pulmonary infection	15 (3.2)	2 (1.9%)		9 (2.7)	1 (1.0)	
Atelectasis	15 (3.2)	6 (5.8%)		12 (3.6)	6 (6.0)	
Bronchopleural fistula	9 (1.9)	1 (1.0%)		5 (1.5)	0 (0.0)	
Empyema	4 (0.8)	1 (1.0%)		4 (1.2)	1 (1.0)	
Respiratory failure	3 (0.6)	1 (1.0%)		2 (0.6)	0 (0.0)	
Hemothorax	3 (0.6)	0 (0.0%)		3 (0.9)	0 (0.0)	
Chylothorax	2 (0.4)	0 (0.0%)		1 (0.3)	0 (0.0)	
Mortality in hospital, n (%)	5 (1.1)	1 (1.0)	0.940	5 (1.5)	1 (1.0)	0.707
Adjuvant chemotherapy, n (%)	220 (46.3)	51 (49.5)	0.631	153 (45.3)	51 (51.0)	0.372
Adjuvant radiotherapy, n (%)	67 (14.1)	17 (16.5)	0.637	51 (15.1)	17 (17.0)	0.759

MIS, minimally invasive surgery; LN, lymph node; MLN, mediastinal lymph node; ICU, intensive care unit; LOS, length of stay.

47.9% in the MIS group and 50.7% in the Open group without significant difference before PSM (Figure 3B). As showed in Figure 3C, five-year OS remained better in the MIS group compared with the Open group after PSM, although without statistical significance (72.7% vs. 64.4%, P = 0.156). Five-year PFS was similar after PSM, 49.2% in the MIS group and 50.5% in the Open group (Figure 3D). To determine whether surgical approach would have any impact on OS and PFS, univariable and multivariable analyses were performed in the entire cohort (Supplemental Table S1). The multivariable results showed that surgical approach was not associated with OS or PFS in sleeve lobectomy patients (Figure 4). Interestingly, we also found that there was no significant difference in five-year OS rates (60.7% vs. 63.1%, P = 0.763) or PFS rates (39.1% vs. 49.9%, P = 0.205) between margin positive group and margin negative

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TABLE 3 Perioperative outcomes between conversion and open groups in unmatched cohort.

Characteristics	Conversion (n=14)	Open (n=475)	*P*
Operating time (minute), (median (IQR))	190.5 (153.25, 306.25)	151 (127, 179)	0.004
Intraoperative bleeding (ml), (median (IQR))	200 (200, 300)	200 (100, 200)	0.152
Angioplasty, n (%)	3 (21.4)	40 (8.4)	0.224
R0, n (%)	13 (92.9)	402 (84.6)	0.642
LN numbers (median (IQR))	15.5 (13, 20)	15 (11, 20)	0.600
MLN numbers (median (IQR))	8 (7, 11.5)	9 (6, 12)	0.849
Pathological T stage, n (%)			0.758
pT2	12 (85.7)	394 (82.9)	
pT3	2 (14.3)	63 (13.3)	
pT4	0 (0.0)	18 (3.8)	
Pathological N stage, n (%)			0.724
pN0	7 (50.0)	209 (44.0)	
pN1	3 (21.4)	148 (31.2)	
pN2	4 (28.6)	118 (24.8)	
ICU stay(day), (median (IQR))	1.5 (0.25, 3)	1 (0, 3)	0.738
Length of drainage (day), (median (IQR))	6 (4.25, 7.50)	6 (5, 8)	0.341
Drainage amount (ml), (median (IQR))	1435 (855, 1972.5)	1670 (1235, 2350)	0.122
LOS (day), (median (IQR))	7 (6, 8.75)	8 (7, 10)	0.065
Complication in hospital, n (%)	1 (7.1)	97 (20.4)	0.376
Mortality in hospital, n (%)	0 (0.0)	5 (1.1)	0.589
Adjuvant chemotherapy, n (%)	7 (50.0)	220 (46.3)	0.785
Adjuvant radiotherapy, n (%)	4 (28.6)	67 (14.1)	0.259

LN, lymph node; MLN, mediastinal lymph node; ICU, intensive care unit; LOS, length of stay.

TABLE 4 Perioperative outcomes between robot-assisted thoracic surgery and video-assisted thoracic surgery groups in unmatched cohort.

Characteristics	RATS (n=20)	VATS (n=83)	*P*
Operating time (minute), (median (IQR))	153 (118, 199.25)	172 (136.5, 233.5)	0.128
Intraoperative bleeding (ml), (median (IQR))	150 (100, 200)	200 (100, 200)	0.252
Angioplasty, n (%)	2 (10.0)	6 (7.2)	0.687
R0, n (%)	20 (100.0)	67 (80.7)	0.073
LN numbers (median (IQR))	15 (13, 18)	16 (10, 20)	0.655
MLN numbers (median (IQR))	9 (7.75, 11.25)	8 (5, 13)	0.496
Location, n (%)			0.017
RUL	7 (35.0)	54 (65.1)	
RML	0 (0.0)	1 (1.2)	
RLL or RML+RLL	1 (5.0)	0 (0.0)	
LUL	5 (25.0)	18 (21.7)	
LLL	7 (35.0)	10 (12.0)	

(Continued)

TABLE 4 Continued

Characteristics	RATS (n=20)	VATS (n=83)	*P*
Pathological T stage, n (%)			0.867
pT2	19 (95.0)	76 (92.7)	
pT3	1 (5.0)	5 (6.1)	
pT4	0 (0.0)	1 (1.2)	
Pathological N stage, n (%)			0.311
pN0	8 (40.0)	47 (56.6)	
pN1	6 (30.0)	22 (26.5)	
pN2	6 (30.0)	14 (16.9)	
ICU stay(day), (median (IQR))	0.5 (0, 2.25)	1 (0, 3)	0.344
Length of drainage (day), (median (IQR))	5 (4, 6)	5 (4, 7)	0.667
Drainage amount (ml), (median (IQR))	1140 (695, 1492.5)	1300 (955, 1680)	0.353
LOS (day), (median (IQR))	8 (6, 9)	7 (6, 9)	0.671
Complication in hospital, n (%)	3 (15.0)	15 (18.1)	0.742
Mortality in hospital, n (%)	1 (5.0)	0 (0.0)	0.437
Adjuvant chemotherapy, n (%)	6 (30.0)	45 (54.2)	0.091
Adjuvant radiotherapy, n (%)	2 (10.0)	15 (8.1)	0.591

RATS, robot-assisted thoracoscopic surgery; VATS, video-assisted thoracoscopic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LN, lymph node; MLN, mediastinal lymph node; ICU, intensive care unit; LOS, length of stay.

group. When we delved into the database, we found that 37(41.6%) patients received postoperative radiotherapy (PORT) in margin positive group for local control, but only 47(9.6%) patients in the margin negative group received PORT.

Discussion

In this real-world study, only 17.8% of the sleeve resections for NSCLC were performed by MIS. MIS including both VATS and RATS were increasingly used during the study period, although it was more often used for smaller tumors and relatively simpler right upper lobe sleeve resections. Our study showed that in a matched cohort, intraoperative blood loss and postoperative drainage after MIS sleeve lobectomy was significantly less than after open surgery, although operation time for sleeve lobectomy by MIS was about 20 minutes longer than by open surgery. And overall mortality and morbidity were comparable between the two groups. The conversion cases had similar postoperative outcomes compared to the Open cases. What is more, there was no significant difference between the MIS group and the Open group in OS or PFS. And surgical approach was not associated with long-term outcomes in multivariable analysis for survivals.

In the real-world, the application of MIS for sleeve lobectomy was still much less often used than open thoracotomy even at a high-volume thoracic surgery center. According to the annual report of the Shanghai Chest Hospital, the overall MIS rate for lung surgery was over 95% (32), but the MIS rate for sleeve lobectomy was only 17.8% in our study during the same time period. As a technically demanding procedure, surgeons tended to perform MIS sleeve lobectomy for smaller tumors in earlier stages or less complex right upper lobe sleeve lobectomy, as was shown in our study. However, pulmonary function and comorbidity had no influence on patient selection. Unlike most previous reports, patients with neoadjuvant therapies before surgery or requiring angioplasty were also included in our study. Even with such more difficult MIS cases (10.7% after neoadjuvant therapy and 7.8% of angioplasty), perioperative results and long-term survivals were not compromised or even better after MIS sleeve lobectomy than after open surgery in the real world.

To reduce potential selection bias, we performed PSM and ITT analysis to validate our findings. In the matched cohort, although operation time by MIS was around 20 minutes longer than that by open surgery, it did not bring any additional complication compared to open surgery. This was further supported by the very low rate of anastomotic complications, especially BPF, which occurred similarly between the MIS group and the Open group (1.0% vs. 1.9%). On the other hand, intraoperative blood loss and postoperative amount of drainage in the MIS group were significantly less than in the Open group, indicating that MIS sleeve lobectomy could render uncompromised recovery and carries with it certain benefits in selected patients with centrally located NSCLC. Recently a database study showed that the VATS approach was associated with shorter length of stay and decreased morbidity in sleeve lobectomy cases (33), which was consistent with our findings.

In this study, there were fourteen cases intended to receive MIS but were converted to open surgery. The conversion rate was 13.6%, which was similar to the 4.5%–21.1% conversion rates in the other published MIS sleeve lobectomy studies (28–30, 33). Unfortunately,

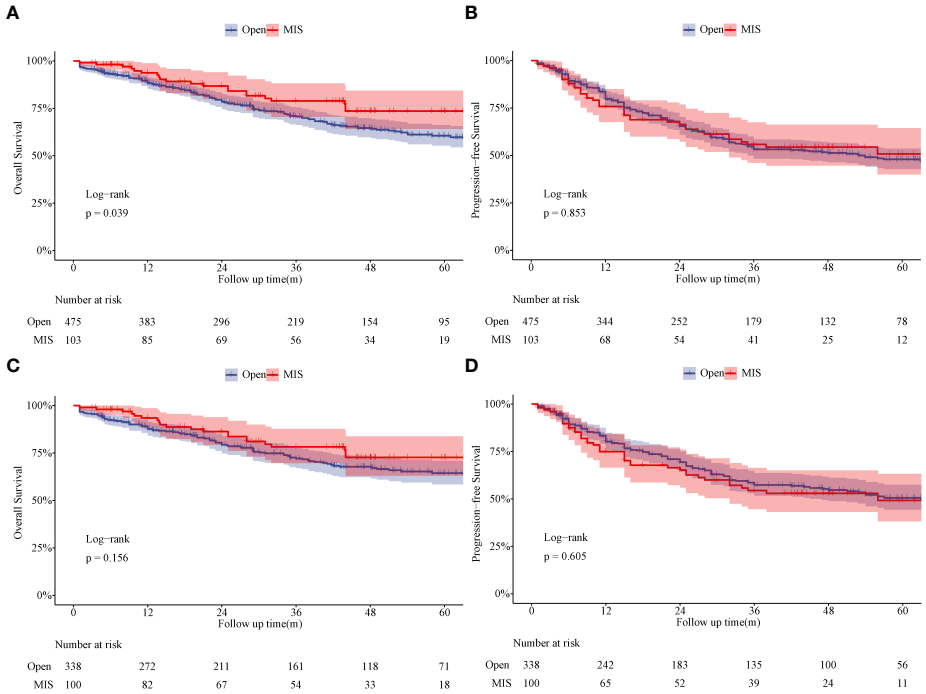

FIGURE 3
Comparison of overall survival and progression-free survival between the Open group and MIS group. **(A)** Comparison of overall survival between the Open group and MIS group (unmatched). **(B)** Comparison of progression-free survival between the Open group and MIS group (unmatched). **(C)** Comparison of overall survival between the Open group and MIS group (matched). **(D)** Comparison of progression-free survival between the Open group and MIS group (matched).

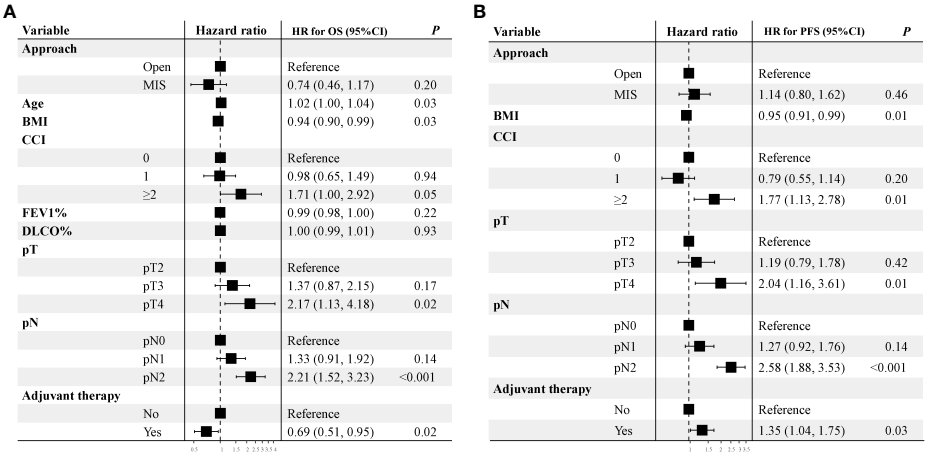

FIGURE 4
Multivariable analysis of overall survival and progression-free survival of unmatched cohort. A hazard ratio more than 1 implies a higher risk of overall survival and progression-free survival after sleeve lobectomy.

none of those studies reported the surgical outcomes in converted cases. Our results showed that although operation time was longer in the conversion cases than open surgery, intraoperative blood loss, postoperative drainage, length of hospital stays, and postoperative complication rates were similar between the two groups. No conversion patient died after surgery during hospital stay. Our results suggested that conversion to thoracotomy during the operation did not bring additional risks to the patients. It is thus safe and feasible to start sleeve lobectomy minimally invasively in well selected patients.

Robotic surgery has gradually become an integrated part of MIS. However, whether RATS had any advantages in sleeve lobectomy remains to be explored. Among all sleeve lobectomies, right upper lobe is the most straight forward. The lower lobe sleeve lobectomies

are comparatively more complex because of the anastomosis angles and greater size discrepancy between the proximal and distal bronchi. In addition to significantly more right upper sleeve lobectomies in the MIS group than in the Open group (59.2% vs. 47.2%), percentage of right upper sleeve lobectomy was the highest in VATS cases (65.1%) but was the lowest (35.0%) in RATS cases. Meanwhile 40.0% lower lobe sleeve lobectomies were done *via* RATS, but only 12.0% of them were done *via* VATS. This was in consistency with the findings in Qiu's study in which lower lobe sleeve lobectomies were most often accomplished *via* RATS than *via* VATS or open thoracotomy (26.5% vs. 21.9% vs. 16.7%) (29). There are two potential explanations for this. First, RATS is more flexible and feasible than VATS. The three-dimensional and magnified vision and the dexterous robotic arms are helpful in more demanding cases. Second, surgeons favoring robotic surgery may be more experienced in MIS and in handling anastomotic difficulties. According to our previous study, short-term and mid-term outcomes after RATS sleeve lobectomy were comparable to open surgery (27). Therefore, RATS may be an important alternative in complex MIS surgery such as lower lobe sleeve lobectomy.

Previous studies suggested that oncological outcomes after MIS might be similar to open surgery in patients with NSCLC needing sleeve lobectomy. But one of the major limitations in most such studies was the relatively short follow-up time in MIS patients, being 24–36.8 months in previous published reports (28–30). This was mostly because MIS sleeve lobectomies were often accomplished more recently, with open cases in earlier years as historical controls. The median follow-up time of the MIS group reached 42 months in our study. And it is by far the longest follow-up time in MIS sleeve lobectomy patients, with a control Open group during the same time period. OS turned out to be significantly better in the MIS group than in the Open group (73.5% vs. 60.6%, P = 0.039), probably because of more smaller tumors in MIS patients. Although OS in the MIS group was still better than in the Open group after PSM, PFS was similar between the two groups both before (47.9% vs. 50.7%, P = 0.853) and after PSM (49.2% vs. 50.5%, P = 0.605). Together with similar R0 resection rates and numbers of lymph node dissected, our results indicated that oncological outcomes after minimally invasive sleeve lobectomy were at least non-inferior to those after open thoracotomy. There have been studies showing that MIS approach could reduce level of cytokine responses and lead to better immune function than open surgery (34, 35). Hopefully with increasing experience in MIS, sleeve lobectomy patients may have benefit in both perioperative recovery as well as prolonged survival in the future.

There were certain limitations in our study. First, our study was retrospective in nature. Unknown confounding factors like surgeons' preference and expertise would still influence the results even though PSM was used to diminish potential impact from patient conditions and tumor characteristics. However, this study included all consecutive patients receiving sleeve lobectomy for potentially resectable primary NSCLC, using an ITT analysis. Our study results clearly revealed the surgical and oncological outcomes of MIS in the real world. Second, all patients included in this study were treated at a single institution, which has a very high surgical volume and has more experience in MIS for lung cancers. It would thus be interesting to use external data to validate our findings on the efficacy of MIS sleeve lobectomy. Third, the detailed information on conversion to pneumonectomy could not be accurately retrieved due to the retrospective nature of the study. However, we found that the positive margin did not compromise the long-term survival of sleeve lobectomy patients, probably because of the role of postoperative radiation for local control.

Conclusions

In conclusion, MIS sleeve lobectomy is still a technically demanding procedure currently. Nonetheless, it is safe and feasible in experienced hands, with similar or even better surgical and oncologic outcomes compared to open surgery in well-selected patients. And RATS may be preferable for more difficult sleeve cases. Conversion to thoracotomy does not compromise perioperative recovery of the patients. Therefore, it does little harm to try sleeve lobectomy minimally invasively first.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Shanghai Chest Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

(I) Conception and design: TC, WZ, WF. (II) Administrative support: WF. (III) Provision of study materials or patients: TC, CJ. (IV) Collection and assembly of data: WZ, TC. (V) Data analysis and interpretation: All authors. (VI) Manuscript writing: All authors. (VII) Final approval of manuscript: All authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

The reviewer MC declared a shared parent affiliation with the authors TC, WZ, CJ, LJ, YW, YL and WF to the handling editor at the time of review.

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Supplementary material

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Learning curve analysis of single-port thoracoscopic combined subsegmental resections

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Background: Combined subsegmental surgery (CSS) is considered to be a safe and effective resection modality for early-stage lung cancer. However, there is a lack of a clear definition of the technical difficulty classification of this surgical case, as well as a lack of reported analyzes of the learning curve of this technically demanding surgical approach.

Methods: We performed a retrospective study of single-port thoracoscopic CSS performed by the same surgeon between April 2016 and September 2019. The combined subsegmental resections were divided into simple and complex groups according to the difference in the number of arteries or bronchi which need to be dissected. The operative time, bleeding and complications were analyzed in both groups. Learning curves were obtained using the cumulative sum (CUSUM) method and divided into different phases to assess changes in the surgical characteristics of the entire case cohort at each phase.

Results: The study included 149 cases, including 79 in the simple group and 70 in the complex group. The median operative time in the two groups was 179 min (IQR, 159-209) and 235 min (IQR, 219-247) $p < 0.001$, respectively. And the median postoperative drainage was 435 mL (IQR, 279-573) and 476 mL (IQR, 330-750), respectively, with significant differences in postoperative extubation time and postoperative length of stay. According to the CUSUM analysis, the learning curve for the simple group was divided by the inflection point into 3 phases: Phase I, learning phase (1st to 13th operation); Phase II, consolidation phase (14th to 27th operation), and Phase III, experience phase (28th to 79th operation), with differences in operative time, intraoperative bleeding, and length of hospital stay in each phase. The curve inflection points of the learning curve for the complex group were located in the 17th and 44th cases, with significant differences in operative time and postoperative drainage between the stages.

Conclusion: The technical difficulties of the simple group of single-port thoracoscopic CSS could be overcome after 27 cases, while the technical ability of the complex group of CSS to ensure feasible perioperative outcomes was achieved after 44 operations.

KEYWORDS

subsegmental resection, learning curve, three-dimensional reconstruction and simulation, combined dimensionality reduction method, video-assisted thoracoscopy

Background

With the implementation of lung cancer screening programs using computed tomography (CT) and low-dose CT (LDCT) in high-risk patients, an increasing number of small early-stage lung cancers (≤2 cm) are being detected (1). Many studies have shown that sublobar resection produces the same oncological outcomes as lobectomy in patients with stage I non-small cell lung cancer (2). While wedge resection has been reported as a risk factor for local recurrence and poorer survival (3, 4), segmental resection or subsegmental resection benefits from its removal of venous and lymphatic drainage in the intersegmental plane, providing acceptable surgical outcomes (5, 6). Anatomical segmental resection is increasingly proposed as an alternative to lobectomy for small-sized lesions, particularly those presenting with ground glass opacity (GGO) (7). However, a large proportion of small-sized peripheral ground-glass shaded nodules in clinical practice are not located in the center of the lung segments, but between them, and it is difficult to meet their marginal requirements with segmental resection alone. Combined segmentectomy or lobectomy can remove these nodules, but too much normal lung tissue is excised. While combined subsegmental surgery (CSS) can preserve lung function as much as possible while ensuring tumor margins.

The CSS is usually considered more technically demanding than segmental lung resection, because of the variety of vessels and bronchi that need to be dealt with, generally in larger numbers and at a more dissected distance from the hilum. Therefore, CSS requires thorough preoperative reconstruction and surgical planning to ensure the safe performance of multiple subsegmental resections. Related studies have shown that thoracoscopic CSS with 3-dimensional (3D) navigation is a safe technique for intersegmental nodal resection, saving more lung parenchyma and ensuring safe margins for anatomical resection (8, 9). It was also shown that FEV1 in each lobe after CSS was higher than that after multisegmental resection (0.3 ± 0.2 vs. 0.2 ± 0.2 l, p=0.07), which is effective for maintaining lung function in each lobe (10). The CSS learning curve study reported by Zhang et al. showed that in single-port thoracoscopic subsegmental resection, a surgical procedure of 28 cases was required to achieve a level of surgical proficiency (11), but fewer cases of complex subsegmental resection were included, while the selected cases were not stratified for difficulty. Regarding the criteria for classifying simple and complex lung segment resections, scholars have proposed classifying them according to the type of intersegmental plane designed, i.e. whether they are complex segmental resections according to linear intersegmental planes or non-linear complex intersegmental planes (12, 13). On this basis, we believe that the combined subsegmental resection technique is characterized by a complex and variable intersegmental plane and can therefore be further classified for technical difficulty based on the number of intraoperative off-segmental target lung tissue vessels and bronchi.

In this study, the learning curve for CSS was investigated using cumulative sum (CUSUM) analysis to assess the surgical characteristics and postoperative outcomes of patients undergoing simple and complex combined subsegmental lung resection, and to analyze the pattern of the learning curve comparing simple and complex combined subsegmental lung resection, which can be used to guide the safe performance of subsequent procedures.

Method

Patients

The study population covered 149 patients who underwent CSS by the same surgeon at Fujian Medical University's Union Hospital between April 2016 and September 2019. Patients who received single-port thoracoscopic CSS for less than or equal to 2 cm GGO were included in the study and divided into simple and complex groups according to the difference in the number of arteries or bronchi which need to be dissected. A simple CSS is defined as a procedure in which the number of vessels dissected and the number of bronchi were both less than or equal to 3. In contrast, if one of the number of vessels or bronchi removed is greater than 3, it was considered complex CSS. Patients found to have intraoperative thoracic adhesions were excluded. Information was collected on age, gender, site of resection, duration of surgery, intraoperative bleeding, final pathological diagnosis, duration of chest tube placement, length of hospital stay, intraoperative and postoperative complications. Learning curves were constructed to analyze the differences in operative time and intraoperative and postoperative complications between periods in the consecutive surgical cohorts. The study was approved by the review committee of the Union Hospital of Fujian Medical University. The data are anonymous, and the requirement for informed consent was therefore waived.

Surgical procedure

The surgical approach is determined by the lesion characteristics on the preoperative CT scan of the chest. The extent of surgical resection and the final surgical plan are based on the size of the nodule and the adjacent structures of the lesion, with the principle of ensuring resection of the tumor margins and maximum preservation of lung function. The appropriate margin for resection should be greater than or equal to 2 cm or greater than or equal to the diameter of the lesion. Preoperatively, all patients are reconstructed in three dimensions using the IQQA-3D system (EDDA technology), using thin-section enhanced CT as the data source. In this system, the lung areas are planned and accurately reconstructed according to the tracheal branches and the trachea, arteries and veins of the lung lobes. The location and extent of the lung nodules are marked, the lung area is delineated and a resection margin sphere is created at 2cm from the lesion margin or greater than the tumor diameter. The reconstruction is analyzed to observe the relationship of the resection margin sphere to the bronchi and lung tissue, and the extent of resection is determined first, and then the target lung segment vessels to be resected are determined accordingly. In each case, an experienced surgeon discusses and formulates the resection plan and discusses its feasibility, assessing the structure of the target lung segment and the sequence of treatment.

After general anesthesia, the patient is operated with the assistance of a single-port thoracoscope. A 3.5-4.0 cm incision was

made in the fourth rib space in the mid-axillary line. The target arteries and bronchi were isolated to reveal them in the sequence planned preoperatively, ligated and then dissected with an ultrasonic knife. Both lungs are then inflated with 100% oxygen and the target lung tissue is atrophied by ventilating one lung for 15 min. For the management the inter-segmental plane, a "combined dimensional reduction method" (14) is used, whereby the subsegmental plane is treated according to the guidance of the intersegmental distension-atrophy divide, first separating the inter-segmental plane from the hilum distally with the ultrasonic knife, stretching the target lung segment to one side and meticulously separating nearly three-quarters of the proximal parenchyma so that the remaining unsegmented target parenchyma is sufficiently thin and lies in a two-dimensional plane. This allows the anastomosis to be quickly positioned in the resection plane to cut through the remaining parenchyma. Following sampling of the mediastinal lymph nodes, a lung leak test was performed. The bronchial stump was examined for significant air leaks and blood leakage, and hemostatic material was placed on the surgical wound.

Statistical analysis

SPSS Statistics 26.0 (IBM Corporation, Armonk, NY) was used for all statistical analyzes. Continuous variables were compared using t-tests or Wilcoxon rank sum tests. Categorical data were compared using the chi-square test. Differences in variables between the two groups were considered statistically significant at the $p<0.05$ level. In this study, the cumulative sum method was used to analyze the learning curve. Cumulative sums were used to analyze the duration of surgery for a series of consecutive operations to see if the operation was proficient and if the learning curve was overcome.

Results

One hundred and forty-nine consecutive patients underwent combined single-port thoracoscopic subsegmental resection, 79 in the simple group and 70 in the complex group. The median age in the two groups was 49 years (IQR, 39-57), 54 years (IQR, 45-60) $p<0.05$, median operative time was 179 min (IQR, 159-209), 235 min (IQR, 219-247) $p<0.001$, median postoperative drainage 435 ml (IQR, 279-573), 476 ml (IQR, 330-750) $p<0.05$, median postoperative extubation time 4 days (IQR, 3-4), 4 days (IQR, 3-5) $p<0.05$, median postoperative hospital stay 4 days (IQR, 3-4), 4 days (IQR, 3-6) $p<0.05$, and postoperative lung infection rates of 13.9% and 18.6%, respectively. Table 1 shows the baseline characteristics and other perioperative data for all cases. According to the CUSUM analysis, cut-off points were established in the curve area due to increasing and

TABLE 1 Comparisons of patient characteristics and operative parameters in simple and complex groups.

Characteristics	Simple group (n= 79)	Complex group (n= 70)	(P value)
Sex, n (%)			
Male	60 (75.9)	49 (70.0)	0.415
Age			
Median (IQR), y	49 (39-57)	54 (45-60)	0.020
ASA score			
Median (IQR)	2 (2-2)	2 (2-2)	0.929
History of hypertension, n (%)			0.103
Yes	14	6	
History of diabetes, n (%)			0.596
Yes	4	5	
History of cigarette smoking, n (%))			0.309
Yes	8	11	
History of alcohol consumption, n (%)			0.474
Yes	16	11	
Location, n (%)			0.074
RUL	37	19	
RML	0	0	
RLL	8	15	
LUL	31	33	

(Continued)

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TABLE 1 Continued

Characteristics	Simple group (n= 79)	Complex group (n= 70)	(P value)
LLL	3	3	
Tumor size, cm			<0.001
0 to ≤ 1	67	46	
1 to ≤ 2	11	23	
>2	1	1	
operative time			<0.001
Mean (SD), min	179 (159-209)	235 (219-247)	
Bleeding			0.370
Median (IQR), mL	50(20-50)	50(30-50)	
Drainage			
Median (IQR), d	4(3-4)	4(3-5)	0.002
Median (IQR), mL	435 (279-573)	476 (330-750)	0.028
Length of hospital stay			
Median (IQR), POD	4(3-4)	4(3-6)	0.004
Postoperative pulmonary infection, n (%)			0.443
Yes	11(13.9)	13(18.6)	
Pathologic diagnosis, n (%)			0.192
Minimally invasive	67	52	
Invasive adenocarcinoma	9	16	
Benign	3	2	

IQR, Interquartile range, ASA, American Society of Anesthesiologists; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; OT, operative time; SD, standard deviation; POD, postoperative day.

decreasing operative times, and the CUSUM OT for the simple group. Figure 1 suggests that the learning curve for the simple group was divided by inflection points into 3 phases: phase I, learning phase (1st to 13th operation); phase II, consolidation phase (14th to 27th operation), and phase III, experience phase (28th to 79th operation), with each The median operative time and intraoperative bleeding in each stage were 222 min (IQR, 191-260), 199 min (IQR, 160-226), 173 min (IQR, 155-187), 50 ml (IQR, 50-50), 30 ml (IQR, 30-50), 30 ml (IQR, 20-50), with statistically significant differences. Table 2 showed the basal characteristics and other perioperative data for cases in the simple group at each stage. Figure 2 demonstrated the operative time of simple CSS.

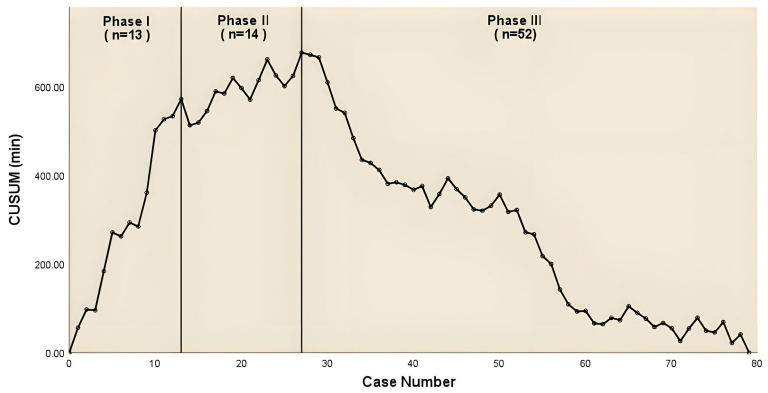

FIGURE 1
The CUSUM chat for operative time of simple combined subsegmental resecion.

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TABLE 2 Interphase comparisons of patient characteristics and operative parameters in all simple cases.

Characteristics	Phase I (n= 13)	Phase II (n= 14)	Phase III (n=52)	Phase I vs Phase II	Phase I & II vs Phase III	(P value)
Sex, n (%)						
Male	10 (76.9)	10 (71.4)	40 (76.9)	0.749	0.780	0.910
Age						
Median (IQR), y	41 (36-54)	52 (47-58)	49 (39-56)	0.120	0.605	0.201
ASA score				0.217	0.897	0.450
Median (IQR)	2 (1-2)	2 (2-2)	2 (2-2)			
History of hypertension, n (%)				0.692	0.894	0.912
Yes	2	3	9			
History of diabetes, n (%)				0.134	0.496	0.154
Yes	2	0	2			
History of cigarette smoking, n (%))				0.957	0.566	0.847
Yes	1	1	6			
History of alcohol consumption, n (%)				0.937	0.389	0.688
Yes	2	2	12			
Location, n (%)				0.228	0.416	0.405
RUL	9	5	23			
RML	0	0	0			
RLL	0	4	4			
LUL	4	5	22			
LLL	0	0	3			
Tumor size, cm				0.980	0.975	0.957
0 to ≤ 1	12	14	41			
1 to ≤ 2	0	0	11			
>2	1	0	0			
operative time				0.048	<0.001	<0.001
Mean (SD), min	222 (191-260)	199 (160-226)	173 (155-187)			
Bleeding				0.028	0.099	0.044
Median (IQR), mL	50 (50-50)	30 (30-50)	30 (20-50)			
Drainage						
Median (IQR), d	4 (3-4)	4 (4-5)	3(3-4)	0.080	0.025	0.020
Median (IQR), mL	445 (287-570)	459 (366-588)	425 (249-556)	0.771	0.264	0.496
Length of hospital stay						
Median (IQR), POD	4 (4-4)	4 (4-5)	4 (3-4)	0.325	0.015	0.033
Postoperative pulmonary infection, n (%)				0.937	0.870	0.983
Yes	2 (15.4)	2 (14.3)	7 (13.5)			
Pathologic diagnosis, n (%)				0.307	0.947	0.590

(Continued)

TABLE 2 Continued

Characteristics	Phase I (n= 13)	Phase II (n= 14)	Phase III (n=52)	Phase I vs Phase II	Phase I & II vs Phase III	(P value)
Minimally invasive	12	11	44			
Invasive adenocarcinoma	1	2	6			
Benign	0	1	2			

IQR, Interquartile range, ASA, American Society of Anesthesiologists; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; OT, operative time; SD, standard deviation; POD, postoperative day.

For the complex group (Figure 3), the curve inflection points of the learning curve for the complex group are located in the 17th and 44th cases, and we can distinguish 3 phases in the figure: phase 1, the learning phase (1st to 17th operation) suggests a longer than median operative time; phase 2, the consolidation phase (18th to 44th operation) remains dynamically stable and suggests an approximately equal to the median operation time. ; phase 3, the experience phase (45th to 70th operation) suggests a less than median operative time. The median operative time and median postoperative drainage in each phase were 250 min (IQR, 243-261), 240 min (IQR, 220-248), 222 min (IQR, 206-230), 855 ml (IQR, 360-1010), 500 ml (IQR, 369-738), 460 ml (IQR, 210-665). There were no significant differences between the stages of surgical bleeding, postoperative extubation time, postoperative hospital stay and postoperative lung infection rates. Table 3 showed the baseline characteristics and other perioperative data for cases in the complex group at each stage. Figure 4 illustrated the operative time of simple CSS.

Discussion

JCOG0802 and 0804 studies have shown that lung segments are preferable to lobes in early stage lung cancer (15). However, some nodules are not centrally located in the lung segment and are not suitable for segmental lung resection. Some studies have shown that CSS is safe and feasible for such nodules. For GGOs located between segments, CSS removes venous and lymphatic drainage in the intersegmental plane, and adjacent subsegmental resection rather than a larger wedge resection provides a safe margin (16, 17). In addition, CSS reduces the degree of lung volume reduction and is therefore considered more minimally invasive than segmental resection for smaller nodules, preserving lung function in each lobe by avoiding lobectomy or multiple segmental resections (18). The preservation of lung function associated with fewer resections may be particularly important in those patients with borderline lung function and in those who will require additional lung resections in the future to treat multiple lung cancer. The primary objective of this study was to analyze the learning curve pattern of CSS and to guide the safe operation of subsequent surgeries.

The surgical difficulty of CSS varies considerably from one individual to another, in two aspects: firstly, the intersegmental plane of CSS is usually irregular and varies widely; secondly, the number of vessels and airways to be dissected is variable. As the intersegmental plane of CSS is variable and difficult to quantify, we have therefore considered the number of vessels or tracheas to be treated as a criterion for simple or complex CSS, based on clinical experience. A simple CSS is defined as a procedure in which the number of vessels dissected and the number of bronchi are both less than or equal to 3, such as RS2b+S3a resection, LS1+2 (a+b) resection, etc. In contrast, if one of the number of vessels or bronchi removed is greater than 3, it is considered complex CSS, such as RS6b+S8ai+S9a resection, LS1+2(a+b) +S3c resection, etc. Compared to simple CSS, complex CSS requires the surgeon to identify segmental arteries and veins in greater detail, especially to differentiate between the numerous intersegmental and intra-segmental veins, to separate and divide appropriate bronchi more peripherally, and to identify and manage more complex intersegmental planes. To our best knowledge, this is the first study of CSS learning curves stratified by

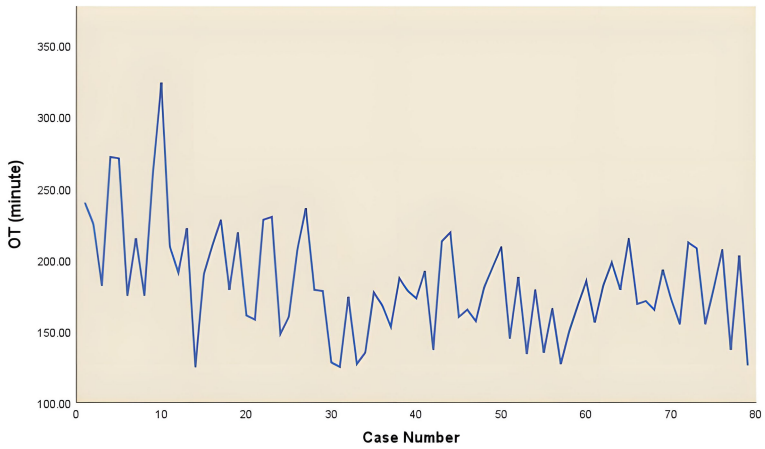

FIGURE 2
The operative time of simple combined subsegmental resecion.

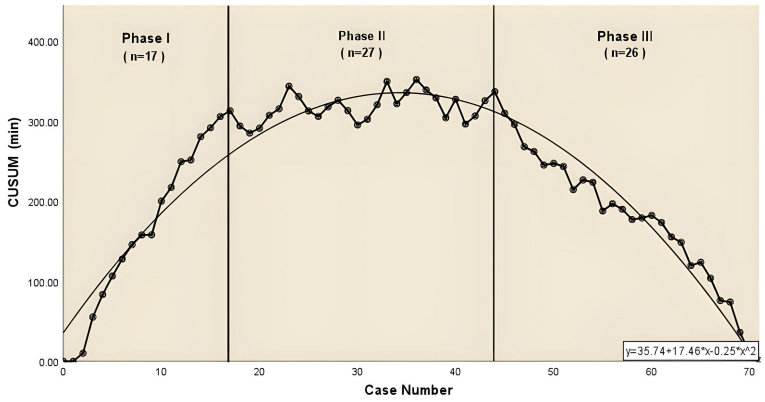

FIGURE 3
The CUSUM chat for operative time of complex combined subsegmental resecion. The dashed line represents the curve of best fit for the plot (a second-order polynomial with equation $CUSUM_{OT}$= −0.25×case number ^{2} + 17.46×case number +35.74.

TABLE 3 Interphase comparisons of patient characteristics and operative parameters in all complex cases.

Characteristics	Phase 1 (n= 17)	Phase 2 (n= 27)	Phase 3 (n=26)	(P value)
Sex, n (%)				
Male	11 (64.7)	16 (59.3)	22 (84.6)	0.077
Age				
Median (IQR), y	57 (47-62)	57 (46-60)	50 (43-58)	0.409
ASA score				
Median (IQR)	2 (2-2)	2 (2-2)	2 (2-2)	0.410
History of hypertension, n (%)				0.501
Yes	2	3	1	
History of diabetes, n (%)				0.498
Yes	1	1	3	
History of cigarette smoking, n (%))				0.066
Yes	3	7	1	
History of alcohol consumption, n (%)				0.681
Yes	3	5	3	
Location, n (%)				0.338
RUL	7	5	7	
RML	0	0	0	
RLL	1	8	6	
LUL	9	13	11	
LLL	0	1	2	
Tumor size, cm				0.668
0 to ≤ 1	11	16	19	
1 to ≤ 2	6	11	6	
>2	0	0	1	
operative time				<0.001

(Continued)

TABLE 3 Continued

Characteristics	Phase 1 (n= 17)	Phase 2 (n= 27)	Phase 3 (n=26)	(P value)
Mean (SD), min	250 (243-261)	240 (220-248)	222 (206-230)	
Bleeding				0.835
Median (IQR), mL	50(30-50)	50 (20-50)	30 (30-50)	
Drainage				
Median (IQR), d	5 (3-7)	4 (3-5)	3 (4-5)	0.151
Median (IQR), mL	855 (360-1010)	500 (369-738)	460 (210-665)	0.004
Length of hospital stay				0.080
Median (IQR), POD	5 (3-7)	4 (4-6)	4 (3-5)	
Postoperative pulmonary infection, n (%)				0.094
Yes	5 (29.4)	6 (22.2)	2 (7.7)	
Pathologic diagnosis, n (%)				0.829
Minimally invasive	13	19	20	
Invasive adenocarcinoma	4	8	4	
Benign	0	0	2	

IQR, Interquartile range, ASA, American Society of Anesthesiologists; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; OT, operative time; SD, standard deviation; POD, postoperative day.

surgical difficulty. Furthermore, our study is the first study to present an attempt to differentiate between Simple CSS and Difficult CSS.

The learning curve is a graphical representation of the temporal relationship between the surgeon's mastery of a given task and the amount of time spent performing the case. Cumulative sums (CUSUM) can help to visually identify trends in a data set and have proved particularly valuable when analyzing learning curves (19, 20). In the series presented in this study joint subsegmental resections were divided into simple and complex groups, where 27 cases were required in the simple group to become proficient in simple joint subsegmental resections and 32 cases were required in the complex group to gain technical proficiency in the application of complex subsegmental resections. Both in the simple and complex groups, the initial learning period showed a longer operative time, but intraoperative bleeding and postoperative complications were in a more acceptable range, which can be attributed to the correct preoperative 3D reconstruction and planning of the surgical procedure. Variations in vascular and bronchial structures may increase operative time and the risk of accidental bronchial injury, but with recent advances such as image processing and artificial intelligence 3D reconstruction allowing proof of the precise structure of the pulmonary arteries and veins, this allows surgeons to perform CSS more safely and effectively (21–23).

A physician with extensive experience in segmental resection can control the operative time and perioperative complications more quickly during the accumulation of CSS experience. Our results show that the learning curve for simple CSS requires a learning process of 27 cases before the experience phase can be entered, and

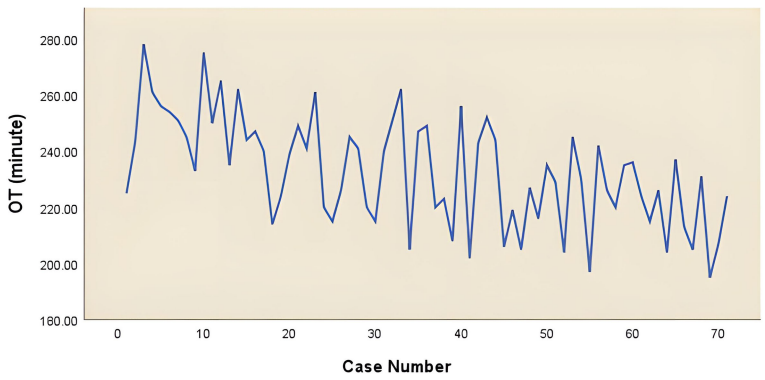

FIGURE 4
The operative time of complex combined subsegmental resecion.

the experience phase requires a cumulative experience process of 52 cases. We found no significant difference in intraoperative bleeding or postoperative drainage between the learning process (first 27 cases) and the experience-building process (second 52 cases). In the previous report, the number of cases for the learning curve of pulmonary segment surgery was 33, which is similar to the results of our study (24). We believe this is because simple CSS is similar in difficulty to segmental lung resection and requires similar numbers of vessels and bronchi to be dissected, so with prior experience in segmental lung surgery and preoperative 3D reconstruction, simple CSS can be mastered with only a smaller number of cases.

The application of a preoperative 3D reconstruction system for identification of lung segment structures and surgical planning can help to overcome the learning curve of complex CSS more smoothly. The learning curve for the complex group of combined subsegmental resections was divided into three phases, namely learning, plateau and experience, with 17 and 44 cases as the inflection points. In all cases, stage 1 represents the initial part of the learning curve and includes 17 cases. Meanwhile the Stage 2 plateau phase includes 27 cases, which means that once the initial phase of the learning curve has passed, more experience is gained and subsequently the experience phase is entered. The complex and diverse anatomy makes complex combined subsegmental resections technically more difficult. Our team, with the aid of the IQQA-3D system, identifies the segmental structures and locates the nodes while showing the 3D relationships between segmental bronchi, arteries and veins. The target subsegments were identified based on a 2cm marginal sphere constructed around the nodes, ensuring safe margins in surgical planning. Our research team has demonstrated in previous studies that IQQA can detect most arterial segmental, venous and bronchial variation in surgical planning, with a variable frequency of 61.6% and 17.8% for segmental arteries and veins respectively (25). We therefore believe that the use of 3D images for surgical simulation and intraoperative one-to-one correspondence between the actual anatomy and the virtual anatomy, enabling real-time navigation during the procedure, can reduce the difficulty of the technique on subsegmental or sub-subsegmental resection and improve the accuracy of the procedure.

There are a number of factors that can affect the learning curve of CSS. For example, pleural adhesions can have a significant impact on operative time, so in this study, we excluded patients with dense pleural adhesions. In patients with incomplete lung fissures this makes the procedure more difficult, but we have sufficient experience in single-port thoracoscopic surgery that there are no substantial difficulties at the technical level. The limitations of this study are its retrospective nature and the fact that it was performed in a single study center. Postoperative survival benefits of simple and complex CSS require long-term follow-up.

Conclusion

In summary, single-port thoracoscopic CSS is a safe and feasible for small lung lesions, with perioperative data on intraoperative bleeding and postoperative complications in the acceptable range. The technical difficulties in the simple group could be overcome after 27 of these cases, while the technical ability to ensure feasible perioperative outcomes with combined subsegmental resection in the complex group was achieved after 44 procedures.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was approved by the review committee of the Union Hospital of Fujian Medical University. The data are anonymous, and the requirement for informed consent was therefore waived (Lines 90 to 91 of the manuscript).

Author contributions

YH, MC, and CC contributed to conception and design of the study. BZ organized the database. MC performed the statistical analysis. YH wrote the first draft of the manuscript. SZ, TZ, GH, and BZ wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Clinical application of VATS combined with 3D-CTBA in anatomical basal segmentectomy

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Objective: This study aimed to summarize the clinical application experience of video-assisted thoracic surgery (VATS) combined with three-dimensional computed tomography-bronchography and angiography (3D-CTBA) in anatomical basal segmentectomy.

Methods: Clinical data of 42 patients who underwent bilateral lower sub-basal segmentectomy by VATS combined with 3D-CTBA in our hospital from January 2020 to June 2022 were retrospectively analyzed; the patients included 20 males and 22 females, with a median age of 48 (30–65) years. Combined with the preoperative enhanced CT and 3D-CTBA techniques to identify the altered bronchi, arteries, and veins during the operation, the anatomical resection of each basal segment of both lower lungs was completed through the fissure approach or inferior pulmonary vein approach.

Results: All operations were successfully completed without conversion to thoracotomy or lobectomy. The median operation time was 125 (90–176) min, the median intraoperative blood loss was 15 (10–50) mL, the median postoperative thoracic drainage time was 3 (2–17) days, and the median postoperative hospital stay was 5 (3–20) days. The median number of resected lymph nodes was 6 (5–8). There was no in-hospital death. Postoperative pulmonary infection occurred in 1 case, lower extremity deep vein thrombosis (DVT) in 3 cases, pulmonary embolism in 1 case, and persistent air leakage in the chest in 5 cases, all of which were improved by conservative treatment. Two cases of pleural effusion after discharge were improved after ultrasound guided drainage. Postoperative pathology showed 31 cases of minimally invasive adenocarcinoma, 6 cases of adenocarcinoma *in situ* (AIS), 3 cases of severe atypical adenomatous hyperplasia (AAH), and 2 cases of other benign nodules. All cases were lymph node-negative.

Conclusion: VATS combined with 3D-CTBA is safe and feasible in anatomical basal segmentectomy; consequently, this approach should be promoted and applied in clinical work.

KEYWORDS

VATS, 3D-CTBA, thoracic surgery, basal segment resection, lung cancer

1 Introduction

More than 70% of cases of lung cancer are non-small cell lung cancer (NSCLC). Early NSCLC has slow proliferation of cancer cells and late tumor spread; however, there are no obvious symptoms in the early stage and this cancer is not easily detected. Consequently, most patients with NSCLC are in the middle and late stages when diagnosed, and the mortality rate is high (1). Currently, lung cancer is the malignant tumor with the highest incidence and mortality worldwide. The improvement of health awareness in individuals and the popularization of chest high-resolution computed tomography (HRCT) scanning for physical examination have facilitated the detection of many sub-centimeter pulmonary nodules characterized by ground glass opacity (GGO) (2). Video-assisted thoracic surgery (VATS) is the preferred treatment for early lung cancer. Compared with lobectomy, anatomical segmentectomy can reduce the scope of lung tissue resection on the basis of ensuring adequate resection margin, protect lung function and postoperative quality of life, and achieve a long-term prognosis that is not inferior to that of lobectomy (3). However, owing to the complex anatomical structure of the lung, it is difficult to identify the segmental arteries, veins, and bronchi near the segmental hilum, especially in the case of anatomical variation. Surgeons often rely on their experience to transection blood vessels and segmental bronchi; however, incorrect transection of the bronchus will lead to atelectasis, and incorrect transection of the vein will lead to inaccurate intersegmental plane, resulting in poor surgical effect (4). Three-dimensional computed tomography-bronchography and angiography (3D-CTBA) technology has the advantage of clearly displaying the anatomical structure of bronchi, pulmonary arteries, and veins through 3D images, which allows determination of congenital variation, helps doctors accurately locate lesions before surgery, increases the chance of accurate surgical resection, and reduces operation errors and tissue damage during surgery (5, 6). Among all pulmonary segmental resections, basal segmentectomy of bilateral lower lobes is the most challenging because there are many vessels and bronchi with frequent variations, which easily lead to unclear identification of segmental hilum and intra-segmental structures, and the adjacent relationship between segmental planes is more complex (7). The application of auxiliary 3D-CTBA technology in basal segment resection can greatly reduce false injury and increase the probability of correct and precise resection. This study summarizes some short-term results that have been achieved using this approach.

2 Materials and methods

2.1 Clinical data

A total of 42 patients were enrolled in the study, including 20 males and 22 females, with a median age of 48 (30–65) years. Preoperative chest HRCT was routinely performed to determine the size, nature, and location of the lesion, and to complete the surgical plan (including target segment to be resected, the resection range, and the variation of the target segment bronchus and vessel, etc.). The indications for basal segment resection were: 1) diameter of nodule ≤2 cm, solid component <50%, and high suspicion of early lung cancer; 2) consider benign tumor or oligometastatic tumor, not suitable for wedge resection; 3) no surgical contraindications before operation, with cardiopulmonary function, blood test, etc. all meeting the surgical indications; 4) informed consent obtained from the patients. Exclusion criteria: 1) intraoperative frozen pathology suggested invasive carcinoma or positive sampling of lymph node; 2) previous history of ipsilateral thoracic surgery; 3) distant organ metastasis.

2.2 3D-CTBA image processing

Mimics 21.0 software was used to automatically calculate and generate the coronal and sagittal images after importing the original tomographic images. The transparency of each part was adjusted to determine the extent of resection after locating the position of the nodule in the target segment. Before the operation, the reconstructed images were transferred to a mobile computer. First, the presence of segmental vessel and segmental bronchus variation was determined. If there was variation, the precise location of the variation and whether it affected identification of the intersegmental plane was evaluated. In addition, whether the variation affected the margin was determined. During the operation, the 3D-CTBA images combined with a mobile computer can help surgeons complete the accurate segmentectomy (Figure 1).

2.3 Surgical methods

After the patient was properly fixed, routine disinfection and drapting were performed. Incisions were made in the patient as

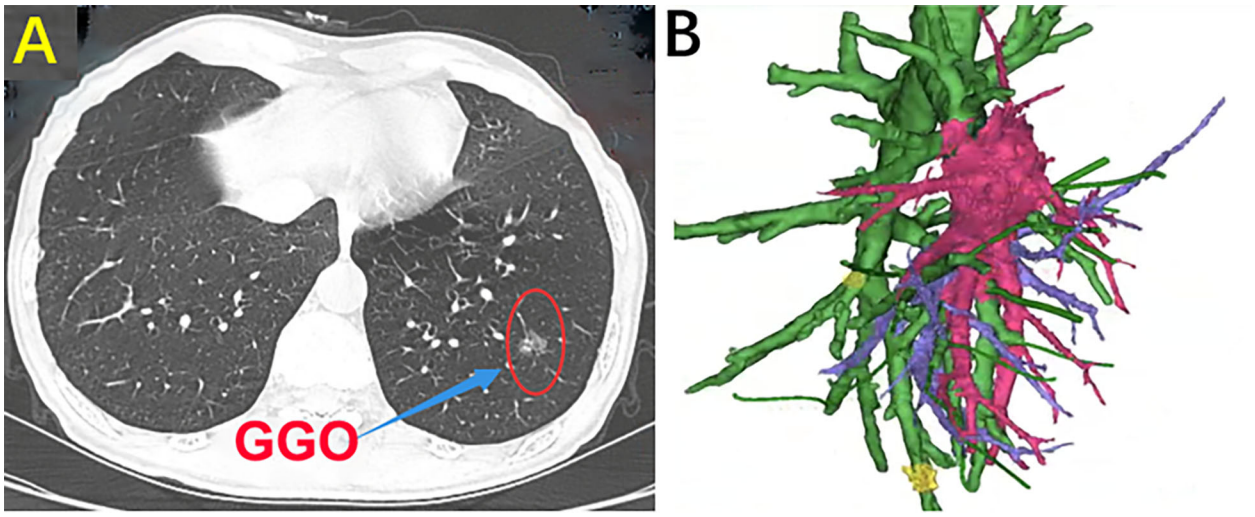

FIGURE 1
(A) Chest CT scan. **(B)** Three-dimensional computed tomography-bronchography and angiography (3D-CTBA).

follows: an incision of approximately 1 cm in the seventh intercostal space of the midaxillary line was used as the observation port; an incision of approximately 2–3 cm in the fourth or fifth intercostal space of the anterior axillary line (with or without an incision of approximately 1 cm in the ninth intercostal space of the posterior axillary line) was used as the operating port for multiportal VATS; an incision of approximately 4 cm in the fifth intercostal space of the anterior axillary line was made as the operating port for uniportal VATS (Figure 2). If there was adhesion, thoracolysis of pleural adhesion was initially performed, and then the situation of the lower pulmonary nodules was explored. After determining the general location of the nodules, the lower pulmonary ligament was routinely dissociated.

The choice of the oblique fissure approach or the inferior pulmonary vein approach depends on the development of the oblique fissure, and the order of treatment for the pulmonary

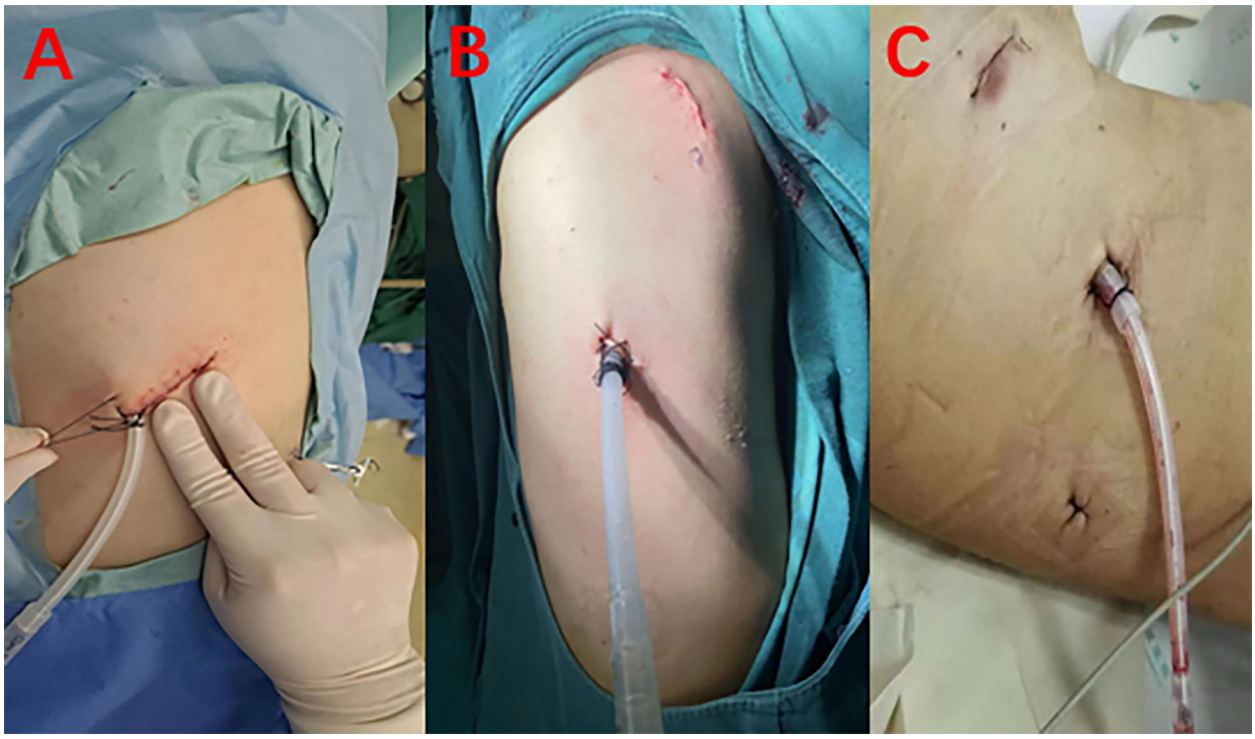

FIGURE 2
(A) Uniportal VATS. **(B)** Biportal VATS. **(C)** Triportal VATS.

artery, vein, and bronchus is also flexible according to the development of the fissure. In addition, the choice of the oblique fissure approach or inferior pulmonary vein approach corresponds to the anterior (anteromedial) basal segment or the lateral and posterior basal segment, respectively.

2.3.1 Resection of the lateral and posterior basal segment

In general, even if the oblique fissure is well developed, the inferior pulmonary vein approach will be routinely performed in the lateral and posterior basal segment resection. Combined with preoperative 3D-CTBA image processing technology, the thoracic surgeons can identify the vessels and bronchi, and know whether there is a variation of vessels and bronchi (Figure 3).

After confirming the dorsal branches of the inferior pulmonary vein (the dorsal veins often branch independently), the branches of the vein of the basal segment were fully dissociated, and then the location of the target segmental vein was identified. After ligation, the target segmental vein was removed by the ultrasonic scalpel. The target segmental bronchus was further explored and was transected with the endoscopic cutter stapler (if it was difficult to place the endoscopic cutter stapler, the target segmental bronchus could be ligated and the bronchial stump could be strengthened by Hem-O-Lok). The target segmental artery was further searched on the deep surface of the segmental bronchial stump. After ligation of No.7 surgical suture, the target segmental artery was removed with the ultrasonic scalpel. When it is difficult to identify the vessels and bronchi using the inferior pulmonary vein approach, the role of

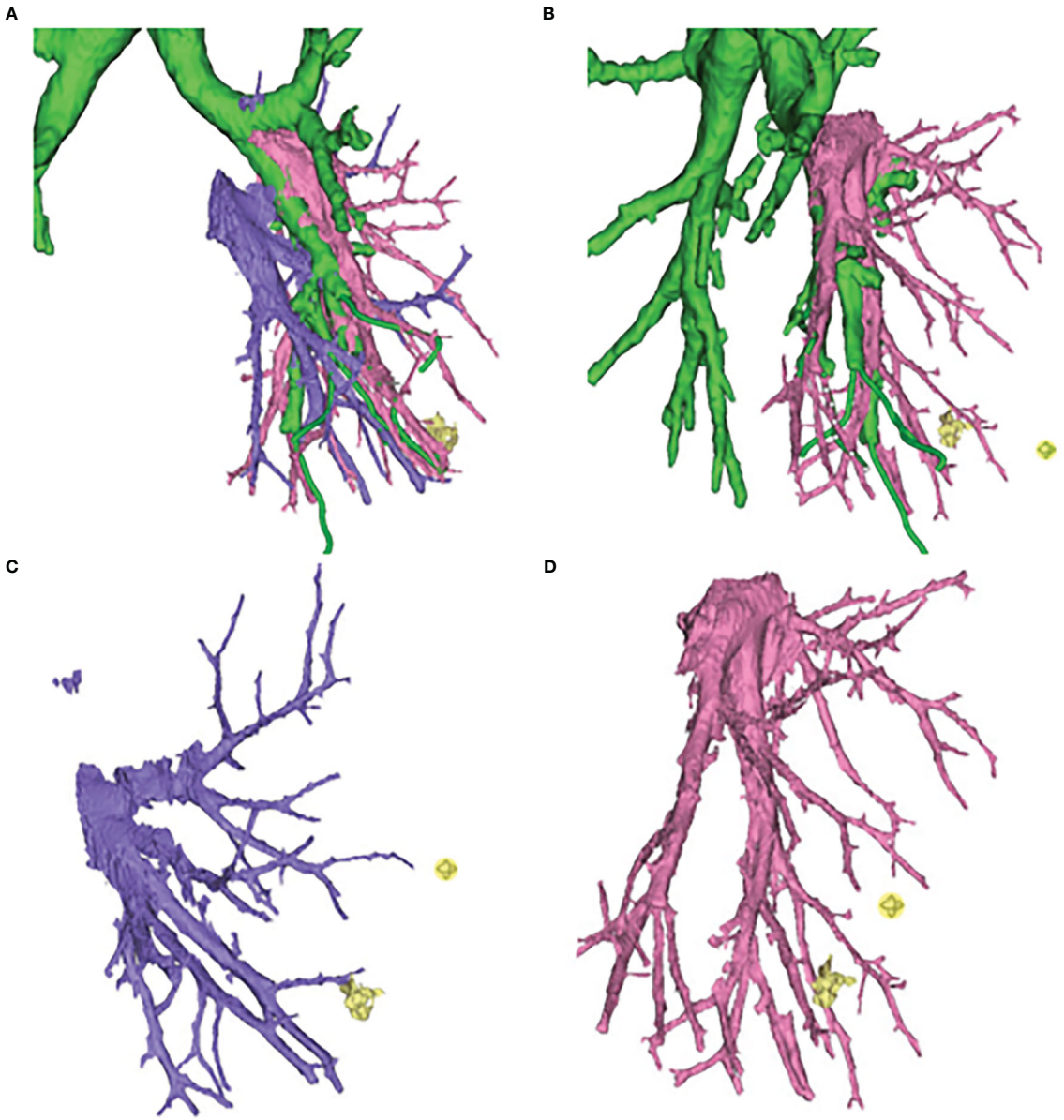

FIGURE 3
Three-dimensional computed tomography-bronchography and angiography (3D-CTBA) for GGO in S9. **(A)** Bronchi, artery and vein. **(B)** Bronchi and artery. **(C)** vein. **(D)** artery.

preoperative 3D-CTBA image processing technology will be significant, and the variation of vessels or bronchi can be located in advance to avoid accidental injury. Simultaneously, if the oblique fissure is well developed, the oblique fissure approach can be added to verify the vessels or bronchi that are difficult to identify. After separating the oblique fissure, the distribution of the segmental arteries and bronchi can be reconfirmed, so as to accurately remove the target segmental artery, vein, and bronchus, and accurately retain the intersegmental vein (the intersegmental vein is the natural boundary of the segments; separating the intersegmental lung tissue along the intersegmental vein can effectively reduce the air leakage and blood loss from lung tissue). Finally, at the end of these processes, accurate lateral and posterior basal segmentectomy is achieved (Figure 4).

2.3.2 Resection of anterior basal segment or anteromedial basal segment

Routine dissection of the oblique fissure makes it easier to identify the arteries and bronchi. First, the oblique fissure was dissected, the target segmental artery was identified, and the basal segmental artery was removed with an endoscopic cutter stapler. Usually, arteries and bronchi distribute together, therefore the target segmental bronchus can be located by continuing exploration on the deep surface of the segmental arterial stump. After routine separation, the segmental bronchus was removed by an endoscopic cutter stapler. For dissection of the target segmental vein, both inferior pulmonary vein approach and oblique fissure approach can be used. Usually with the assistance of 3D-CTBA, the target segmental vein can be accurately resected, the intersegmental vein can be accurately preserved, and the anterior basal segment or anteromedial basal segment can be accurately resected.

3 Results

The operation was successfully completed in all patients, and there was no conversion to thoracotomy or lobectomy. All 42 patients underwent thoracoscopic basal segmentectomy, including 26 cases of simple basal segmentectomy and 16 cases of combined basal segmentectomy (the nodule located between the two basal segments). The median operation time was 125 (90–176) min, the median intraoperative blood loss was 15 (10–50) mL, the median postoperative thoracic drainage time was 3 (2–17) days, and the median postoperative hospital stay was 5 (3–20) days. The median number of resected lymph nodes was 6 (5–8). There was no in-hospital death. Postoperative pulmonary infection occurred in 1 case, lower extremity deep vein thrombosis (DVT) in 3 cases, pulmonary embolism in 1 case, and persistent air leakage in the chest in 5 cases, all of which were improved by conservative treatment. Two cases of pleural effusion after discharge were improved after ultrasound guided drainage. Postoperative pathology showed 31 cases of minimally invasive adenocarcinoma (MIA), 6 cases of adenocarcinoma *in situ* (AIS), 3 cases of severe atypical adenomatous hyperplasia (AAH), and 2 cases of other benign nodules. All cases were negative for lymph nodes. The specific surgical procedures and other clinical data are shown in Table 1.

4 Discussion

GGO is a common feature of early lung cancer encountered in the clinic. This kind of lung cancer often has low invasiveness and malignancy, slow growth, and good prognosis after surgical resection (8). GGO is represented by pure ground glass nodules and partial solid ground glass nodules, among which, partial solid nodules—especially those with a solid component <50%—are the standard indicators for segmentectomy. Anatomical segmentectomy has a long-term prognosis that is not inferior to that of lobectomy, and is better than lobectomy in terms of minimal trauma and protection of lung function (9).

Surgery is the first choice for the treatment of early lung cancer and can significantly prolong the survival rate of patients, with some patients being completely cured. The operation of lung cancer has developed from open surgery in the early days to minimally invasive thoracoscopic surgery used currently. At present, the commonly

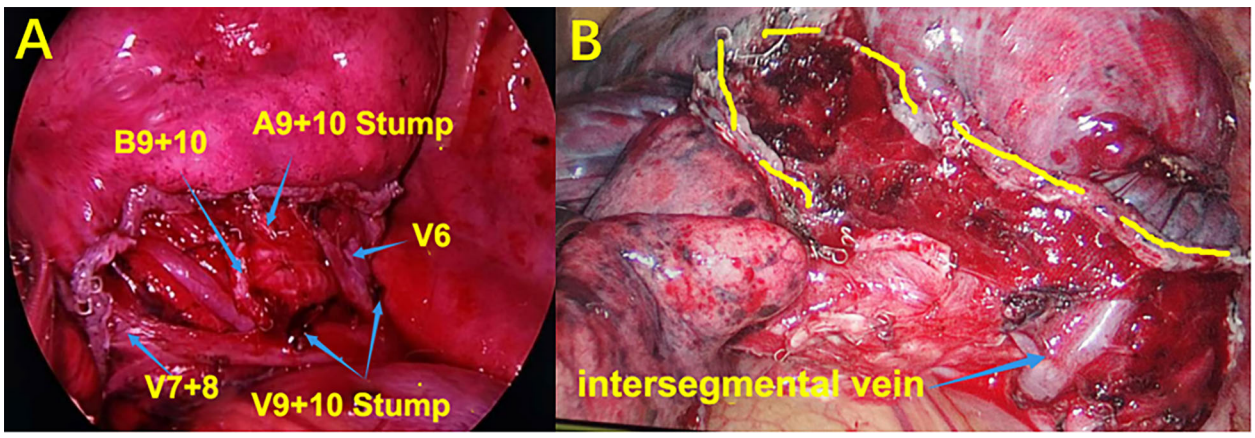

FIGURE 4
(A) S9+10 segmentectomy. **(B)** Intersegmental vein and intersegmental plane.

TABLE 1 The specific surgical procedures and other clinical data.

Clinical parameter	Data
Age	
Gender	
Male	20
Female	22
Surgical options	
RS7	1
RS8	5
RS9	2
RS10	3
RS7+8	5
RS9+10	5
LS8	9
LS9	1
LS10	5
LS9+10	6
Operation time (min)	125 (90–176)
Lymph nodes removed	6 (5–8)
Intraoperative blood loss (mL)	15 (10–50)
Postoperative drainage time (days)	3 (2–17)
Postoperative hospital stay (days)	5(3–20)
Postoperative complications	
Pulmonary infection	1
Deep vein thrombosis	3
Pulmonary embolism	1
Persistent air leakage	5
Pleural effusion	2
Postoperative pathology	
MIA	31
AIS	6
AAH	3
Other benign tumors	2

used minimally invasive thoracoscopic surgery for early GGO includes lobectomy, wedge resection, and segmentectomy. Pulmonary wedge resection is often used for the resection of benign lung tumors in clinical practice because it only targets superficial nodules, the scope of resection is limited, and it cannot be resected through the normal anatomical structure of the lung. For some elderly lung cancer patients with poor physical conditions, wedge resection can be the second-best choice. Lobectomy and lymph node dissection have played a long and unshakeable role in surgery for early lung cancer, and their effect and prognosis have been recognized for many years. However, this situation is changing as VATS is no longer a technical problem. The popularization of VATS in thoracic surgery and the advent of large data means there is no significant difference in the recurrence rate and prognosis survival rate between VATS and lobectomy for patients with early GGO (10). Under certain conditions, segmentectomy has the advantages of more precise resection, less trauma, more preservation of lung tissue, shorter recovery time, more preservation of lung function, and a significant decrease in the rate of infection. Okada et al. (11) found that for nodules less than 2 cm, there was no statistical difference in long-term survival rate between segmentectomy and lobectomy. Tsutani and colleagues (12) reported that for nodules less than 2 cm, there was no statistically significant difference in 3-year recurrence-free survival rate between segmentectomy and lobectomy. In addition, Zhao et al. (10) found that for nodules less than 2 cm, there was no statistically significant difference in 5-year recurrence-free survival rate between segmentectomy and lobectomy, and Altorki et al. (13) reported similar findings. From these studies, it can be concluded that the prognosis of thoracoscopic segmentectomy is not inferior to that of lobectomy. Therefore, for patients with early lung malignant tumors, anatomical segmentectomy has obvious effect and great significance (14). For the elderly and patients with normal basic cardiopulmonary function, thoracoscopic segmentectomy can retain more lung tissue in the anatomical scope and effectively protect lung function. Keenan et al. [30] retrospectively analyzed the pulmonary function of patients with stage I NSCLC and divided the surgical patients into two groups, who underwent lobectomy and segmentectomy, respectively. The mean preoperative forced expiratory volume in one second (FEV1) was 75.1% and 55.3% in the two groups, respectively, suggesting that the selected patients in the pulmonary segment group had relatively poor pulmonary function. One year after surgery, forced vital capacity (FVC) and FEV1 of patients in the lobar group decreased significantly, but there was no significant decline in the segmental group. Based on these two points, thoracoscopic segmentectomy has become a more popular surgical method by thoracic surgeons. In addition, the National Comprehensive Cancer Network, The National Health Commission of China (NCCN) guidelines also indicate that for most patients with early-stage NSCLC, anatomical segmentectomy is currently the main surgical method.

Previous scholars have questioned whether segmentectomy, compared with lobectomy, may increase the risk of tumor recurrence due to insufficient resection margin, resulting in a worse prognosis. Moreover, it has been reported that the recurrence rate after segmentectomy may be predominantly related to segmental location and margin width (15). Segmental surgery requires adequate safe resection margins. However, in thoracoscopic surgery, the lobe is in an atrophic state and it is difficult to identify the intersegmental veins and determine the safe resection margins. Simultaneously, compared with the lobar anatomy, the segmental anatomy of the lung is extremely complex, and there are many variations in the segmental arteries, veins, and bronchi, which are prone to accidental injury during surgery. Therefore, precise segmentectomy of the lung under a thoracoscope is difficult and risky. Moreover, there are many

variations in the basal segment of the lung, and it is difficult to identify the segmental veins; consequently, accurate basal segmentectomy is the most difficult of all pulmonary segmental resections. Such variations cause great confusion for the identification of the basal segment veins. Exact identification of the veins will provide the best basis for the accurate segmentation of the intersegmental plane (16, 17); it is known that the intersegmental veins are the natural boundary marks between two lung segments and only after these veins are identified can the resection of the lung segment be accurate. In addition, for the resection of the lateral and posterior basal segments, the inferior pulmonary vein approach is the natural preferred approach; however, owing to variation in the bronchus and artery, such as the phenomenon of common trunk, the bronchus should not be blindly cut off during the operation, so as to avoid atelectasis or inaccurate resection. Proficiency in pulmonary segmental anatomy is crucial to the success of anatomical segmentectomy, especially the resection of basal lung segments with more challenging anatomy (18).

For a mature thoracic surgeon, it is necessary to understand the normal anatomical structure of the lung segments, but the morphological and spatial variation of the lung fissure, bronchus, and blood vessels that are not normally developed also need the help of CT imaging. Traditional two-dimensional CT images are not accurate for the anatomical structure of lung segments and subsegments, and it is also difficult to show the relationship between bronchi, blood vessels, and tumors without a 3D approach. Therefore, it cannot match the increasingly precise anatomical segmentectomy, which is significantly more challenging. In the past, thoracic surgeons needed to carefully dissect and repeatedly confirm the pulmonary vessels and bronchus during the operation to accurately understand the anatomical morphology of the vessels and bronchus, which not only increased the operation time and risk, but also increased the blindness and inaccuracy of pulmonary segmentectomy. Nowadays, in the auxiliary technology of 3D-CTBA, the bronchi, vessels, and nodules can be directly reconstructed in three dimensions before the operation, showing the volume of each lobe and segment, non-invasively showing the distance and 3D relationship between the primary tumor and the intersegmental veins, and safely reflecting the relationship between the resection margin and the pulmonary vessels. Therefore, the assistance of 3D-CTBA will help doctors identify anatomical variations before surgery, make surgical plans in advance, achieve accurate separation of vessels and bronchus during surgery, and accurately identify the intersegmental plane. Collectively, these benefits to the surgeons can effectively reduce the occurrence of postoperative air leakage and blood loss, shorten the operation time (19), reduce the accidental injury rate, and achieve better treatment effects. The application of 3D-CTBA can also ensure that the lung tissue is accurately cut according to the intersegmental plane, which naturally improves the probability of accurate resection, retains more normal lung tissue, preserves the lung function of the patient to the greatest extent, and reduces the risk of postoperative hypoxemia and respiratory failure. Therefore, thoracoscopic segmentectomy under 3D-CTBA is beneficial to the recovery of pulmonary function and effectively reduces the occurrence of postoperative complications. In this study, the 3D-CTBA simulated preoperative imaging was not 100% consistent with the actual anatomy during the operation. This discrepancy may be explained by a number of possibilities. Firstly, in some patients who are bed-bound for a long time, some of the bronchi on the back of body, such as the posterior segment of the right upper lobe, are chronically compressed and may not be able to be imaged on 3D images. Secondly, during thoracoscopic surgery, we generally take the lateral position and one-side lung ventilation, and lobes on the surgical side are in a collapsed state. Therefore, there will be some differences between the preoperative evaluation images of 3D-CTBA and the actual bronchi, arteries, and veins seen during the operation. There is also the possibility that vessels smaller than 2 mm in diameter are missing in the imaging of 3D-CTBA. In these cases, thoracic surgeons need to have clear theoretical knowledge and considerable experience.

As mentioned above, the accurate preservation of intersegmental veins is a natural and potential dividing line between subsegments of the lung. Splitting the lung tissue along the intersegmental veins greatly reduces the risk of postoperative air leakage, coupled with the application of biological glue and resistance to block the air leakage of lung tissue. In some cases, there will still be persistent air leakage after surgery, even after the above process (20). At this time, if the lung is well inflated, a 50% glucose solution (combined with lidocaine for pain relief) is used for pleural injection to promote pleural adhesion to treat air leakage after segmentectomy.

Most reports of thoracoscopic segmentectomy are usually limited to the lung segments with relatively simple anatomy, and there are few introductions to the more difficult segmental resections such as that of the basal segment. Basal segment resection is challenging because there are adjacent lung segments between each lung segment. When dividing the subbronchus, especially B9 or B10, because the angle of dividing the subsegmental bronchus is tricky, it is often necessary to add an auxiliary surgical incision to complete the operation. Moreover, if there is accidental bleeding when separating the blood vessels, it is also necessary to add an auxiliary surgical incision to complete the operation. When performing S9 surgery, it is necessary to accurately locate the intersegmental plane between the adjacent S8 and S10. If there is a common trunk or abnormal development of S9, it is easy to mis-cut or multi-cut the bronchus, arteries, and veins. In addition, it is necessary to ensure the safety range of the surgical margin (the distance between the nodule and the cutting edge should be >2 cm), and this can be confirmed by preoperative 3D-CTBA. Segmentectomy of S9+10 is often performed because this only involves the intersegmental plane between S8 and S9 and the intersegmental plane between S6 and S10 (21), which can effectively reduce the operation time. Therefore, if anatomical variation or margin safety problems are encountered during segmentectomy of S9, the surgeon will actively seek resection of the combined segment S9+10. S7 and S8 of the left pulmonary lower lobe naturally share the same trunk, combined with the natural boundary of oblique fissure, so S7+8 resection of the left pulmonary lower lobe is relatively easy in all basal segmental resections. Generally, the anterior oblique fissure is still well developed, so LS7+8 resection

via oblique fissure approach is more common. Similarly, owing to the existence of the natural boundary of the oblique fissure, it is more convenient to take the oblique fissure approach in S8 of the right lung. Unlike B7 in the left lung, B7 in the right lung develops alone, "surrounded by mountains on three sides", and S7 has a small volume. Therefore, cases of S7 resection alone are rare, and the combined subsegmental resection of RS7+8 is more common. The approach for the resection of both S9 and S10 is still the inferior pulmonary vein approach, which is more reliable (22). If the oblique fissure is still well developed, the oblique fissure approach can be added to verify the course of blood vessels and bronchi in cases where preoperative 3D-CTBA indicate variation, so as to increase the success rate of surgery.

This study does have some limitations and biases. Firstly, the sample size was small. Furthermore, the short follow-up time makes it impossible to evaluate the long-term efficacy of 3D-CTBA in thoracoscopic segmentectomy, and to analyze whether there is a difference in the long-term efficacy between the two groups. In addition, some preoperative CT was not enhanced CT, which resulted in unclear display of small vascular branches reconstructed by 3D-CTBA. The following aspects should be strengthened in future research. (1) Increase the number of patients, establish a 3D-CTBA data model of patients, analyze the anatomical morphology of patients, and provide data and image reference for other relevant medical departments. (2) This study is a retrospective study, and it is the preliminary results and experience obtained from a small sample size. In the future, we will expand the sample size, reduce the error, and conduct prospective studies to further verify the recurrence rate and long-term efficacy of 3D-CTBA in thoracoscopic segmentectomy, and analyze whether there is any difference between the two groups. (3) Comparative studies between single lung segments should also be performed to avoid errors caused by anatomical and surgical differences between different lung segments. (4) Further research on the application of 3D-CTBA in thoracic surgery, especially in the field of training young doctors is also needed.

In conclusion, VATS combined with 3D-CTBA for basal segment resection of the lower lung is clear and relatively simple to operate. 3D-CTBA can clarify the variation of vessels and bronchi before the operation, increase the accuracy of surgical resection, effectively preserve lung function, and reduce postoperative complications. In this study, the assistance of 3D-CTBA combined with the inferior pulmonary vein approach or/and oblique fissure approach resulted in successful completion of all operations, without conversion to thoracotomy and lobectomy, and all patients were discharged safely. This study proved that the technology is safe and feasible and can be widely applied in clinical work.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of China–Japan Union Hospital of Jilin University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CH put forward the theoretical concept. CH and LZ established the methodology. LZ, TW, YF, YC, CF, and DQ wrote the manuscript. CH, and LZ supervised the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Publisher's note

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Safety and feasibility of robotic-assisted thoracic surgery after neoadjuvant chemoimmunotherapy in non-small cell lung cancer

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Objectives: This study aimed to evaluate the safety and feasibility of robotic-assisted thoracic surgery (RATS) after neoadjuvant chemoimmunotherapy in NSCLC.

Methods: We retrospectively collected data for NSCLC patients who received thoracic surgery after neoadjuvant chemoimmunotherapy from May 2020 to August 2022. Surgery details, pathological response, and perioperative outcome were compared between video-assisted thoracic surgery (VATS) group and RATS group. Inverse probability of treatment weighting (IPTW) was used to equal the baseline characteristics.

Results: A total of 220 patients were divided into 78 VATS patients and 142 RATS patients. There was no 90-day mortality in either group. RATS patients demonstrated better results in conversion rate to thoracotomy (VATS vs. RATS: 28.2% vs. 7.5%, $P < 0.001$), number of lymph node stations harvested (5.63 ± 1.75 vs. 8.09 ± 5.73, $P < 0.001$), number of lymph nodes harvested (13.49 ± 9.325 vs. 20.35 ± 10.322, $P < 0.001$), yield pathologic-N (yp-N) assessment (yp-N0, 88.5% vs. 67.6%; yp-N1, 7.6% vs. 12.6%; yp-N2, 3.8% vs. 19.7%; $P < 0.001$), and visual analog scale pain score after surgery (4.41 ± 0.93 vs. 3.77 ± 1.21, P=0.002). However, there were no significant differences in pathological response evaluation for neoadjuvant chemoimmunotherapy ($P = 0.493$) and complication rate ($P = 0.803$). After IPTW-adjustment, these results remained constant.

Conclusions: RATS reduced the risk of conversion to thoracotomy, provided a better yp-N stage evaluation, and improved pain score; this suggests that RATS is safe and feasible for NSCLC patients after neoadjuvant chemoimmunotherapy.

KEYWORDS

non-small-cell lung cancer, neoadjuvant chemoimmunotherapy, robotic-assisted thoracic surgery, video-assisted thoracic surgery, safety and feasibility

Introduction

Non-small cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer and is one of the leading causes of cancer-related mortality worldwide (1). Approximately 22% of NSCLC patients are diagnosed with a locally advanced stage of NSCLC; the five-year survival rate of these patients is less than 33% (2). Neoadjuvant chemoimmunotherapy has been recommended as an effective treatment to improve the survival outcome of locally advanced NSCLC patients (3). In the NADIM trial, 83% of patients who received neoadjuvant chemoimmunotherapy for NSCLC achieved major pathological response (MPR), including 63% who achieved pathological complete response (pCR). The 24-month progression-free survival rate among MPR patients was 88.4%, and the overall survival rate was 100% (4). The phase III clinical trial, Checkmate816, further showed the importance of neoadjuvant chemoimmunotherapy for locally advanced NSLC patients, with a pCR rate of 24% (5).

However, neoadjuvant chemoimmunotherapy might increase the difficulty and risk of surgery. In a study by Romero et al., approximately 20% of NSCLC patients who received video-assisted thoracic surgery (VATS) as initial surgery approach ultimately converted to open thoracotomy; this figure was significantly higher than for those without neoadjuvant chemoimmunotherapy (6). In Zhang et al.'s study, 44.2% of patients who received VATS after neoadjuvant chemoimmunotherapy for NSCLC converted to thoracotomy (7). Compared with VATS, robotic-assisted thoracic surgery (RATS) has shown advantages in surgery for lung cancer, with a larger number of removed lymph nodes and more accurate N-stage assessment (8). In a previous study, the safety of RATS after neoadjuvant chemoimmunotherapy was reported to have only a 4.5% conversion rate to thoracotomy (9). However, as a single-arm study, the result was incomplete. The difference in short-term outcomes between RATS and VATS after neoadjuvant chemoimmunotherapy remains unknown. Therefore, the main objective of this study was to analyze the safety and feasibility of RATS after neoadjuvant chemoimmunotherapy in NSCLC patients.

Materials and methods

Study design and patient selection

This research was a retrospective study conducted at Xiangya Hospital, Central South University, and was designed to evaluate the safety and feasibility of RATS after neoadjuvant chemoimmunotherapy in NSCLC patients.

Patients who received surgery for NSCLC from May 2020 to August 2022 were included if they met the following inclusion criteria: pathological types of NSCLC were confirmed by pathology results before neoadjuvant chemoimmunotherapy; NSCLC stages before neoadjuvant chemoimmunotherapy were diagnosed as IIA–IIIB (American Joint Committee on Cancer, 8th edition) (10); received three cycles neoadjuvant chemoimmunotherapy, with PD-1/PD-L1 immune checkpoint inhibitors plus platinum-based doublet chemotherapy; and their Eastern Cooperative Oncology Group performance-status score before neoadjuvant chemoimmunotherapy was 0 or 1. Patients were excluded if they met any of the exclusion criterion as follows: aged < 18 years old; stage IIIB patients who were diagnosed with N3 lymph node metastasis positive; chose thoracotomy as the initial surgical approach; received extra medicine for neoadjuvant chemoimmunotherapy at the same time; or clinical data was incomplete.

Therapy procedures

All patients received PD-1/PD-L1 immune checkpoint inhibitors combined with platinum-based doublet chemotherapy as neoadjuvant chemoimmunotherapy. Chemoimmunotherapy drugs were given on the first day of each treatment cycle (21 days per cycle). A standard staging evaluation was performed before and after neoadjuvant chemoimmunotherapy, including a computed tomography (CT) scan (11); 18-F-fluorodeoxyglucose positron emission tomography/CT scan; magnetic resonance imaging or CT for the brain; and a bronchoscopy examination. All patients received 18-F-fluorodeoxyglucose positron emission tomography/CT scan to assess the presence of mediastinal involvement before and after neoadjuvant chemoimmunotherapy. Surgery was planned 3–7 weeks after the first day of the last treatment cycle. If there were progressive M1 or N3 metastasis after neoadjuvant chemoimmunotherapy, patients would continue medical therapy and be excluded from this study. The type of resection for the primary tumor was determined according to standard institutional procedures, including lobectomy, bronchial or vascular sleeve lobectomy, bilobectomy, and pneumonectomy. Systematic lymphadenectomy was performed in every patient. Decisions of conversion to thoracotomy were made by surgeons during operation whenever they felt necessary. Pathological responses and yield pathologic stage (yp-stage) were determined by the Department of Pathology according to resected samples.

Patients were divided into the VATS or RATS groups according to the initial surgery approach. Surgery approach was determined by patients' will. All surgeries were performed by surgeons with extensive experience. VATS was performed in a two-port or three-port approach liberally. RATS was performed using the Da Vinci Xi surgery system (Intuitive Surgical, Inc., Mountain View, CA, USA), using the three-arm method. Patients without viable tumor cells in resected lymph nodes and primary lung cancer were defined as pCR, while less than 10% of viable tumor cells were defined as MPR, and more than 10% were defined as an incomplete pathological response (IPR) (12).

Abbreviations: NSCLC, Non-small cell lung cancer; MPR, Major pathological response; pCR, Pathological complete response; VATS, Video-assisted thoracic surgery; RATS, Robotic-assisted thoracic surgery; CT, Computed tomography; IPR, Incomplete pathological response; VAS, Visual analogue scale; ADL, Activities of daily living; PAL, Prolonged air leak; IQR, Interquartile range; SD, Standard deviation; SMD, Standardized mean difference; IPTW, Inverse probability of treatment weighting.

Clinical data collection

Patients' demographics data, clinical variables, surgical details, and pathological details were retrospectively collected. The tumor response after completing neoadjuvant chemoimmunotherapy was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (13). Pain evaluation was performed at 2 h after surgery and at discharge by a visual analog scale (VAS) (14). During hospitalization, non-steroidal anti-inflammatory drugs were used for pain relief. Recovery after surgery was evaluated at discharge according to the Activities of Daily Living scale (ADL) (15). Patients with an air leak longer than five days were defined as prolonged air leaks (PAL) (16). Surgery-related complications were defined according to the Society of Thoracic Surgeons database criteria (17).

Statistical analysis

Categoric variables were exhibited as absolute and relative frequencies. Differences between categoric variables were evaluated by $\chi 2$ test or Fisher's exact test. Continuous variables were presented as mean and standard deviation (SD) if normally distributed and analyzed using the Student's t-test. Otherwise, the median was used [25%–75% interquartile range (IQR)] and analyzed with a Mann–Whitney U-test. Baseline characteristics between RATS and VATS were balanced by the inverse probability of treatment weighting (IPTW). In IPTW analysis, multivariate logistic regression was used to estimate the propensity score for each patient and regress on baseline characteristics. The inverse of the predicted probability of receiving RATS was calculated as the weight (11, 18). A covariate was considered adequate balance when the standardized mean difference (SMD) score was < 0.20. A two-tailed *P*-value of < 0.05 was considered statistically significant. All data were analyzed using R version 4.1.3 software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics of patients

From May 2020 to August 2022, 261 patients were evaluated; a total of 220 patients were included in final analyses according to inclusion and exclusion criteria (Figure 1). Twenty-six patients were excluded due to missing data; they received neoadjuvant chemoimmunotherapy at local hospital, leading to a lack of data before neoadjuvant chemoimmunotherapy. Eight patients chose thoracotomy as the initial surgical approach. Five patients were diagnosed with positive N3 lymph node metastasis, and two received bevacizumab for neoadjuvant therapy simultaneously.

Baseline characteristics of the included patients were presented in Table 1. A total of 78 patients were assigned to the VATS group and 142 to the RATS group, according to the initial surgery

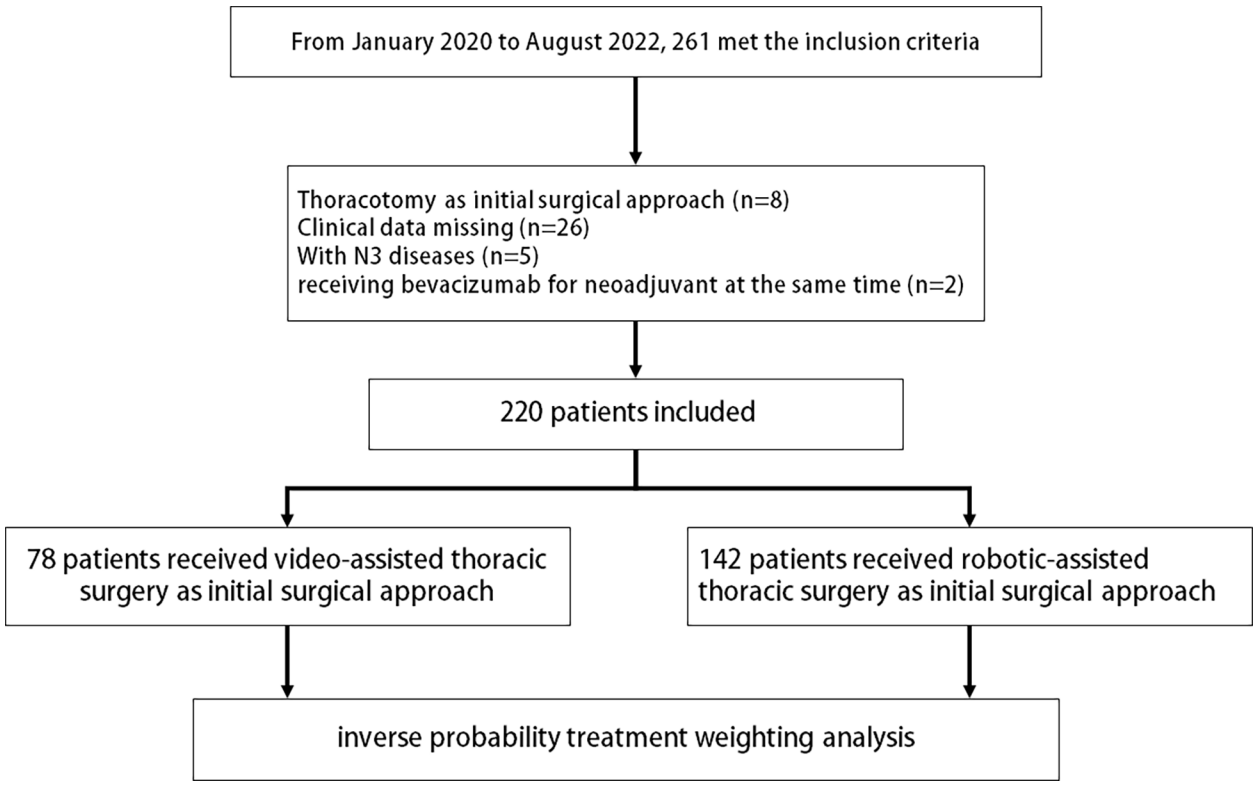

FIGURE 1
Flowchart of patient inclusion and exclusion criteria.

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TABLE 1 Unadjusted and IPTW adjusted patient baseline characteristics. .

Index	Without IPTW, NO. (%)				With IPTW, %			
	VATS (n=78)	RATS (n=142)	*P*	SMD	VATS	RATS	*P*	SMD
Age, mean (SD[a]), y	58.01 (8.96)	58.98 (7.56)	0.397	0.117	58.35 (8.50)	58.46 (7.66)	0.932	0.013
Gender, No. (%)			0.779	0.064			0.753	0.052
Female	15 (19.2)	31 (21.8)			23.0%	20.9%		
Male	63 (80.8)	111 (78.2)			77.0%	79.2%		
BMI, mean (SD), kg/m2	23.87 (2.88)	23.53 (3.02)	0.421	0.114	23.73 (2.65)	23.71 (3.05)	0.971	0.005
Smoking history			0.56	0.151			0.927	0.014
Never	28 (35.9)	41 (29.8)			30.6%	31.3%		
Former/current	50 (64.1)	101 (70.1)			69.4%	68.7%		
Surgery history			0.867	0.024			0.745	0.050
Never	63 (80.8)	116 (81.7)			83.1%	81.1%		
Former	15 (19.2)	26 (18.3)			16.9%	18.8%		
Tumor position			0.781	0.264			0.995	0.116
RUL	22 (28.2)	32 (22.5)			24.3%	25.0%		
RML	5 (6.4)	10 (7.0)			4.9%	5.7%		
RLL	17 (21.7)	23 (16.2)			18.5%	17.3%		
LUL	20 (25.6)	37 (26.1)			28.2%	26.4%		
LLL	2 (2.6)	1 (0.7)			0%	0.5%		
RCTC	10 (12.9)	33 (23.2)			21.2%	21.6%		
LCTC	2 (2.6)	6 (4.2)			3.0%	3.5%		
Histology			0.859	0.077			0.982	0.029
Squamous	52 (66.7)	99 (69.7)			68.1%	66.8%		
Adenocarcinoma	23 (29.5)	37 (26.1)			27.9%	29.2%		
Other[b]	3 (4.1)	6 (4.2)			4.1%	4.1%		
T stage before neoadjuvant treatment			0.979	0.062			0.959	0.085
T1	7 (9.0)	15 (10.6)			9.0%	9.8%		
T2	24 (30.8)	41 (28.9)			31.0%	29.4%		
T3	27 (34.6)	49 (34.5)			30.7%	34.0%		
T4	20 (25.6)	37 (26.1)			29.3%	26.8%		
N stage before neoadjuvant treatment			0.386	0.189			0.962	0.042
N0	8 (10.3)	8 (5.6)			6.9%	8.0%		
N1	30 (38.5)	52 (36.6)			36.3%	35.8%		
N2	40 (51.3)	82 (57.7)			56.8%	56.2%		
T stage before surgery			0.414	0.283			0.971	0.112
T0	1 (1.3)	5 (3.5)			2.3%	2.7%		
T1	25 (32.1)	56 (39.4)			35.9%	36.5%		
T2	28 (35.9)	35 (24.6)			30.2%	30.4%		
T3	12 (15.4)	21 (14.7)			12.3%	14.7%		
T4	12 (15.4)	25 (17.6)			19.3%	15.7%		

(Continued)

TABLE 1 Continued

Index	Without IPTW, NO. (%)				With IPTW, %			
	VATS (n=78)	RATS (n=142)	*P*	SMD	VATS	RATS	*P*	SMD
N stage before surgery			0.739	0.108			0.990	0.022
0	14 (17.9)	20 (14.1)			14.8%	15.5%		
1	26 (33.3)	48 (33.8)			32.6%	32.4%		
2	38 (48.7)	74 (52.1)			52.7%	52.0%		
RECIST evaluation			0.455	0.233			0.916	0.107
CR	1 (1.3)	5 (3.5)			2.3%	2.7%		
PR	41 (52.6)	85 (59.9)			55.2%	57.8%		
SD[c]	3 5 (44.9)	50 (35.2)			41.7%	37.9%		
PD	1 (1.3)	2 (1.4)			0.8%	1.7%		
Type of resection			0.248	0.297			0.930	0.110
Lobectomy	64 (82.1)	99 (69.7)			73.0%	74.3%		
Bilobectomy	7 (9.0)	24 (16.9)			14.4%	14.2%		
Sleeve lobectomy	2 (2.6)	6 (4.2)			5.8%	3.6%		
Pneumonectomy	5 (6.4)	13 (9.2)			6.8%	7.9%		

BMI, body mass index; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; RCTC, right central type carcinoma; LCTC, left central type carcinoma; RESIST, response evaluation criteria in solid tumors; CR, complete response; PR, partial response; PD, Progressive disease; IPTW, inverse probability treatment weight; VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery; SMD, standardized mean difference.
[a]SD, standard deviation;
[b]including: large cell carcinoma, lymphoepithelioma-like carcinoma, not otherwise specified.
[c]SD, Stable Disease.

approach. Patients were primarily male smokers, with over one-half of those in both groups being diagnosed as squamous carcinoma (SCC). Three patients had progressive disease (PD), and six patients achieved complete response (CR) before surgery, according to RECIST version 1.1. Lobectomy was the most common resection type. The two groups' baseline characteristics were relatively balanced before IPTW. However, SMDs of some baseline characteristics were more than 0.2. IPTW was used to further equal the baseline differences between the VATS and RATS groups. After IPTW analysis, there were no baseline characteristics with SMD > 0.2 (Table 1).

Surgery details results

A total of 22 (28.2%) patients who underwent VATS as the initial surgery approach converted to open thoracotomy. The conversion rate was higher than for RATS patients (respectively, 28.2% vs. 7.5%, $P < 0.001$). Dense adhesion and fibrosis after neoadjuvant chemoimmunotherapy and intraoperative bleeding were the most common reason for conversion. The surgical duration of VATS was shorter than RATS (respectively, 176.94 ± 74.974 min vs. 197.28 ± 70.945 min, $P = 0.048$). The bleeding volume, transfusion rate, and transfusion volume between these two groups were similar, without statistical significance. After IPTW, the difference in conversion rate remained statistically significant (VATS vs. RATS, 33.7% vs. 8.2%, $P < 0.001$). However, the surgery duration became similar (VATS vs. RATS, 190.24 ± 82.96 min vs. 196.87 ± 72.17 min, $P = 0.625$). The details were summarized in Table 2.

Pathological details and oncologic staging

The number of lymph node stations harvested was lower in VATS than RATS (respectively, 5.63 ± 1.75 vs. 8.09 ± 5.73, $P < 0.001$). Similarly, the lymph node harvested count in VATS group was lower than the RATS group (respectively, 13.49 ± 9.325 vs. 20.35 ± 10.322, $P < 0.001$). Overall yp-N staging was significantly higher in the RATS group (VATS vs. RATS; yp-N0, 88.5% vs. 67.6%; yp-N1, 7.6% vs. 12.6%; yp-N2, 3.8% vs. 19.7%; $P < 0.001$). However, there was no statistically significant difference in the yp-T staging and pathological response evaluation for neoadjuvant chemoimmunotherapy. After IPTW, these differences between these two groups were consistent, showing the stability of our results (Table 3).

Perioperative outcomes

No patients died within 90 days after surgery in these two groups. The VAS score at 2 h after surgery in VATS group was

TABLE 2 Unadjusted and IPTW adjusted surgery details.

Index	Without IPTW, NO. (%)			With IPTW, %		
	VATS (78)	RATS (142)	*P*	VATS	RATS	*P*
Surgery duration, mean (SD), min	176.94 (74.97)	197.28 (70.945)	0.048	190.24 (82.96)	196.87 (72.17)	0.625
Conversion to open, NO. (%)						
Total	22 (28.2)	10 (7.0)	<0.001	33.7%	8.2%	<0.001
Primary tumor invasion	4 (5.1)	2 (1.4)		7.1%	1.6%	
Dense adhesion and fibrosis	7 (8.9)	4 (2.8)		9.3%	3.2%	
Fibrocalcified lymph nodes	3 (3.8)	1 (0.7)		5.2%	0.5%	
Bleeding	8 (10.2)	3 (2.1)		12.1%	2.9%	
Transfusion, NO. (%)	10 (12.8)	8 (5.6)	0.063	19.3%	7.5%	0.054
Bleeding volume, Median (IQR), ML	100 (50 to 200)	50 (50 to 100)	0.053	112.3 (46.7 to 198.8)	121.7 (63.1 to 218.4)	0.184
Transfusion volume Median (IQR), ML	0 (0 to 0)	0 (0 to 0)	0.078	0 (0 to 0)	0 (0 to 0)	0.072

SD, standard deviation; IQR, interquartile range; IPTW, inverse probability treatment weight; VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

higher than for RATS group (respectively, 4.41 ± 0.93 vs. 3.77 ± 1.21, $P = 0.002$). However, the VAS score at discharge was not significantly different (VATS vs. RATS, 1.27 ± 0.57 vs. 1.71 ± 0.68, $P = 0.267$). Similarly, there were no statistical differences in length of stay (LOS) after surgery, activities of daily living (ADL) score at discharge, drainage volume, and drug cost between these two groups. After IPTW-adjustment, these trends remained constant (Table 4).

Complications outcomes

A total of 71 cases of complications were detected, including 26 cases in VATS group and 45 in RATS group. The overall complication rate was similar in patients with different initial surgery approaches (VATS vs. RATS, 33.2% vs. 31.7%, $P = 0.803$), and no difference was detected for individual complications. Pneumonia was the most common complication in both groups (VATS vs. RATS, 16.6% vs.

TABLE 3 Unadjusted and IPTW adjusted pathological details and oncologic staging.

Index	Without IPTW, NO. (%)			With IPTW, %		
	VATS(n=78)	RATS(n=142)	*P*	VATS	RATS	*P*
Lymph node station count, mean (SD)	5.63 (1.75)	8.09 (5.73)	<0.001	5.64 (1.89)	7.98 (5.40)	<0.001
Lymph nodes count, mean (SD)	13.49 (9.32)	20.35 (10.32)	<0.001	13.65 (9.44)	19.92 (10.05)	<0.001
yp-T stage			0.885			0.827
yp-T0	39 (50.0)	73 (51.4)		50.6%	50.9%	
yp-T1	23 (29.5)	42 (29.6)		24.4%	28.8%	
yp-T2	12 (15.4)	20 (14.1)		19.0%	15.2%	
yp-T3	3 (3.8)	3 (2.1)		4.1%	2.0%	
yp-T4	1 (1.3)	4 (2.8)		1.9%	3.2%	
yp-N stage			<0.001			0.015
yp-N0	69 (88.5)	96 (67.6)		86.5%	65.9%	
yp-N1	6 (7.7)	18 (12.7)		7.8%	14.8%	
yp-N2	3 (3.8)	28 (19.7)		5.6%	19.3%	
Pathology response			0.493			0.449
IPR	31 (39.7)	60 (42.3)		38.1%	44.7%	
MPR	9 (11.5)	23 (16.2)		12.1%	15.9%	
PCR	38 (48.7)	59 (41.5)		49.8%	39.4%	

SD, standard deviation; yp-, yield pathological-; IPR, incomplete pathological response; MPR, major pathological response; PCR, pathological complete response; IPTW, inverse probability treatment weight; VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

14.7%, $P = 0.194$). Results were similar after IPTW-adjustment based on the baseline characteristics (Table 5).

Discussion

This study compared the safety and feasibility of RATS and VATS as initial surgery approaches for NSCLC after neoadjuvant chemoimmunotherapy. The results depict that the conversion rate of VATS was significantly higher than that of RATS. Moreover, the numbers of lymph node stations harvested and lymph nodes harvested in RATS were significantly higher than VATS, leading to an overall yp-N upstaging. Furthermore, the VAS pain score at 2 h after surgery was lower in RATS. Through IPTW, we further balanced the baseline characteristics. These results remained consistent, indicating the stability of our results.

In recent years, neoadjuvant chemoimmunotherapy has dramatically changed the treatment for locally advanced NSCLC, with an extraordinary pathological response rate and survival improvement (19). However, increasing numbers of studies have demonstrated that neoadjuvant chemoimmunotherapy could cause vascular fragility, inflammatory changes in hilar structures, loss of planes, and adhesions, which increased the difficulty and risk of surgery (20). Although VATS after neoadjuvant chemoimmunotherapy was considered a safe and feasible approach, there were obvious disadvantages in the high conversion rate to thoracotomy (21). In the TOP1201 clinical trial, 25% of VATS after neoadjuvant chemoimmunotherapy converted to thoracotomy (22). In the NEOSTAR clinical trail, 40% of surgeries after neoadjuvant immunotherapy for NSCLC were considered more difficult (23). In the most recent trial, the conversion rate of VATS after neoadjuvant immunotherapy for NSCLC was 11% (5). Compared with traditional VATS equipment, the Da Vinci robotic-assisted system was designed for more complicated conditions, with a more flexible surgery system and multifaceted vision technologies (24). The flexibility and stability of this system allowed the surgeon to perform minimal surgery more smoothly, particularly in complicated operations. The study by Qiu et al. revealed the safety and feasibility of robotic-assisted sleeve lobectomy, which was considered to be the most complicated type of resection in NSCLC patients (25). Similarly, our results indicated that RATS reduced the conversion risk to thoracotomy in surgery after neoadjuvant chemoimmunotherapy for NSCLC.

In addition to the conversion rate, concerns about lymph node assessment have traditionally been a drawback for VATS in NSCLC, which was an important part of the surgical treatment. According to the guidelines for NSCLC surgery, at least three mediastinal stations and three hilar stations of lymph nodes should be harvested (26). The study by Liang et al. demonstrated that a higher number of lymph nodes harvested could improve lymph node assessment and improve the survival of stage I–III NSCLC (27). RATS was considered advantageous for lymph node assessment in NSCLC without neoadjuvant chemotherapy. In Shahin et al.'s study, RATS provided a better N2 lymph nodes metastasis assessment in I–II NSCLC patients (28). Veronesi et al. further compared the difference between RATS and VATS in lymph node assessment; RATS was found to associate with a higher number of removed lymph node stations, hilar lymph nodes, and mediastinal lymph nodes (29).

Our study demonstrated more numerous removed lymph nodes in RATS after neoadjuvant chemoimmunotherapy, which led to an overall yp-N upstaging. This might be because the surgeon could easily identify lymph nodes and resect them more completely in RATS. Although there was no significant difference in pathological response evaluation between these two groups, patients might still benefit from yp-N upstaging. For example, treatment after surgery for patients with residual cancer cells positive in lymph nodes but no residual cancer cells in the primary tumor was determined according to the yp-N stage alone. This was rare in the era of neoadjuvant chemotherapy, but pure residual cancer cells positive lymph nodes would become increasingly common with the clinical application of neoadjuvant chemoimmunotherapy. Thus, lymph node upstaging might ultimately affect the survival of NSCLC patients who have received neoadjuvant chemoimmunotherapy.

Complications have been a common problem in neoadjuvant therapy. In 2015, Yang et al. reported the surgery outcomes of 84

TABLE 4 Unadjusted and IPTW adjusted perioperative outcomes.

Index	Without IPTW			With IPTW		
	VATS(n=78)	RATS (n=142)	*P*	VATS	RATS	*P*
90-day mortality	0 (0)	0 (0)	>0.990	0%	0%	>0.990
LOS after surgery, mean (SD), d	6.01 (3.00)	6.78 (4.07)	0.145	6.18 (3.11)	6.75 (4.22)	0.298
VAS score after surgery, mean (SD)	4.41 (0.93)	3.77 (1.21)	0.002	4.47 (0.97)	3.7 1(1.22)	<0.001
VAS score at discharge, mean (SD)	1.71 (0.68)	1.27 (0.57)	0.267	1.69 (0.67)	1.31 (0.56)	0.375
ADL score at discharge, mean (SD)	59.49 (11.29)	62.22 (12.27)	0.106	59.60 (11.25)	62.27 (12.22)	0.138
Drainage volume, mean (SD), ML	452.05 (399.10)	439.33 (304.18)	0.791	459.00 (300.06)	431.37 (288.50)	0.461
Drug cost, mean (SD), $	1320.70 (638.73)	1579.58 (1178.16)	0.355	1336.06 (668.59)	1571.83 (1359.65)	0.087

SD, standard deviation; LOS, length of stay; VAS, visual analogue scale; ADL, activities of daily living; IPTW, inverse probability treatment weight; VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

TABLE 5 Unadjusted and IPTW adjusted postoperative complications.

Index	Without IPTW, NO. (%)			With IPTW, %		
	VATS(n=78)	RATS(n=142)	*P*	VATS	RATS	*P*
Total	26 (33.2)	45 (31.7)	0.803	33.8%	30.5%	0.434
Pneumonia	13 (16.7)	21 (14.8)	0.193	14.1%	9.1%	0.102
Pneumothorax	5 (6.4)	8 (5.6)	0.774	5.4%	5.2%	0.981
Prolonged air leak	4 (5.1)	9 (6.3)	0.169	10.6%	11.4%	0.769
Chylothorax	1 (1.3)	3 (2.1)	>0.990	1.0%	1.7%	0.417
Return to the OR	2 (2.6)	0 (0)	0.124	1.9%	0%	0.154
Pulmonary embolism	1 (1.3)	2 (1.4)	>0.990	0.9%	0.6%	0.927
Deep vein thrombosis	0 (0)	2 (1.4)	0.540	0	1.3%	0.162

OR, Operation room; IPTW, inverse probability treatment weight; VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

NSCLC patients who received neoadjuvant chemotherapy; the overall complication rate was 17.9% (30). A meta-analysis further confirmed the risk of complication after surgery in NSCLC patients who received neoadjuvant chemotherapy (31). In this study, we compared the perioperative outcome of VATS and RATS. The complication rate was similar in these two groups, which suggested that the surgery approach might not be the solution to the complication rate in NSCLC patients who received neoadjuvant chemoimmunotherapy.

In addition, several issues raised in this study should be noted. First, evaluation before surgery by CT imaging might underestimate the efficacy of neoadjuvant chemoimmunotherapy. Among all the included patients, only 6 out of 220 people achieved CR, according to RESIST 1.1. However, through pathology detection after surgery, there were 97 patients who reached pCR. Second, although no statistically significant differences were found for transfusion, amount of bleeding during surgery, and blood transfusion volume between the VATS and RATS groups, the latter patients might still benefit to some degree. Third, the surgery duration was longer in RATS. However, after IPTW, the two groups' results became similar, indicating that surgery duration might be associated with baseline characteristics.

Furthermore, this study was limited by its retrospective nature. On the one hand, potential biases remained in this study, although the baseline characteristics of the two groups were balanced by IPTW. On the other hand, we collected data for the lymph node count number from the pathological reports; this might be underestimated due to the difficulty of isolating them from lung tissue or overestimated as a result of nodal tissue fragmentation. In addition, the data for complications were prospectively extracted from the patient charts, some minor complications might have been unrecorded, such as cough or arrhythmia. Moreover, the surgical treatment of IIA–IIIB NSCLC patients after neoadjuvant chemoimmunotherapy remains probably open surgery considering the challenging of this type of surgery. However, minimally invasive surgery has become the first choice for NSCLC patients, with lower complication rate and shorter length of stay after surgery compared with open surgery, after several decades of development in modern medical technology.

The results of this retrospective study reveal that RATS was safe and feasible for IIA–IIIB NSCLC patients after neoadjuvant chemoimmunotherapy. RATS was found to have a lower conversion rate to thoracotomy, a higher count of lymph node stations and lymph nodes harvested, more-accurate yp-N staging, and a lower VAS pain score after surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board and Ethics Committee of Xiangya Hospital, Central South University, China (202210229). The patients/participants provided their written informed consent to participate in this study.

Author contributions

JZ: Conceptualization; Data collection; Formal analysis; Writing original draft; Writing—review and editing. BY: Conceptualization; Data collection; Formal analysis; Writing original draft; Writing—review and editing. RC: Data collection; Formal analysis; Writing—review and editing. YC: Data collection; Writing—review and editing. ZY: Data collection; Writing—review and editing. YG: Conceptualization; Writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Due to a production error, there was a mistake in Table 4 as published. The heading "Index" was incorrectly repeated and the subheadings "VATS(n=78)", "RATS (n=142)", "P", "VATS", "RATS", and "P" were positioned above the incorrect columns. The corrected Table 4 appears below.

The publisher apologizes for this mistake. The original version of this article has been updated.

TABLE 4 Unadjusted and IPTW adjusted perioperative outcomes.

	Without IPTW			With IPTW		
Index	VATS(n=78)	RATS (n=142)	*P*	VATS	RATS	*P*
90-day mortality	0(0)	0(0)	>0.990	0%	0%	>0.990
LOS after surgery, mean (SD), d	6.01(3.00)	6.78(4.07)	0.145	6.18(3.11)	6.75(4.22)	0.298
VAS score after surgery, mean (SD)	4.41(0.93)	3.77(1.21)	0.002	4.47(0.97)	3.71(1.22)	<0.001
VAS score at discharge, mean (SD)	1.71(0.68)	1.27(0.57)	0.267	1.69(0.67)	1.31 (0.56)	0.375
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Drug cost, mean (SD), $	1320.70(638.73)	1579.58(1178.16)	0.355	1336.06(668.59)	1571.83(1359.65)	0.087

SD, standard deviation; LOS, length of stay; VAS, visual analogue scale; ADL, activities of daily living, IPTW, inverse probability treatment weight; VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

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Modification and application of "zero-line" incision design in total endoscopic gasless unilateral axillary approach thyroidectomy: A preliminary report

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Introduction: Gasless unilateral trans-axillary approach (GUA) thyroidectomy has witnessed rapid development in technologies and applications. However, the existence of surgical retractors and limited space would increase the difficulty of guaranteeing the visual field and disturb safe surgical manipulation. We aimed to develop a novel zero-line method for incision design to access optimal surgical manipulation and outcomes.
Methods: A total of 217 patients with thyroid cancer who underwent GUA were enrolled in the study. Patients were randomly classified into two groups (classical incision and zero-line incision), and their operative data were collected and reviewed.
Results: 216 enrolled patients underwent and completed GUA; among them, 111 patients were classified into the classical group, and 105 patients were classified into the zero-line group, respectively. Demographic data, including age, gender, and the primary tumor side, were similar between the two groups. The duration of surgery in the classical group was longer (2.66 ± 0.68 h) than in the zero-line group (1.40 ± 0.47 h) ($p < 0.001$). The counts of central compartment lymph node dissection were higher in the zero-line group (5.03 ± 3.02 nodes) than that in the classical group (3.05 ± 2.68 nodes) ($p < 0.001$). The score of postoperative neck pain was lower in the zero-line group (1.0 ± 0.36) than that in the classical group (3.3 ± 0.54) ($p < 0.05$). The difference in cosmetic achievement was not statistically significant ($p > 0.05$).
Conclusion: The "zero-line" method for GUA surgery incision design was simple but effective for GUA surgery manipulation and worth promoting.

KEYWORDS

gasless endoscopic thyroidectomy, surgery, thyroid cancer, lymphadectomy, incision activity

Introduction

Endoscopic or minimal invasive thyroid surgery has rapidly spread in recent decades (1–3). Currently, the commonly applied techniques according to surgical approaches could be divided into trans-thoracic, trans-axillary, trans-oral, trans-cervical, and axillo-breast approaches (4). In Asian centers, especially in China, GUA has been widely

Abbreviation
GUA, Gasless unilateral trans-axillary approach; CO2, carbon dioxide; FNA, fine needle aspiration; cN0, no clinical involved; BMI, body mass index.

applicated and accepted since modified and improved in 2017 by Ge et al. (5). Compared with others, the gasless unilateral axillary approach (GUA) can establish a surgical space without carbon dioxide (CO2) insufflation and gas-related complications such as gas embolism and acidosis (6). Furthermore, the learning curve is relatively short for skilled surgeons to obtain, and surgical efficacy and cosmetic outcomes are as well as other techniques (7–9). However, the surgical space separation was achieved with a dedicated surgical retractor, which, together with the limited operating space, would increase the difficulty of guaranteeing the visual field and disturb the surgeon's manipulation. In addition, dissection of inferior thyroid areas, including recurrent laryngeal nerve and the inferior border of the VI area neck lymph node compartment, could be interfered with by the clavicular head of the sternocleidomastoid muscle. Hence, we modified the design of the incision approach and called it the "zero-line" method. Also, we compared the effects of zero-line incision and the classical incision approach in surgical outcomes.

Materials and methods

Inclusion and exclusion criteria

Patients who underwent GUA surgery in our hospital from October 2021 to August 2022 were included. All patients were diagnosed with thyroid cancer by fine needle aspiration (FNA) pathological examination and/or BRAF V600E before surgery. The further enrollment criteria were as below (10–12): first, the diameter of thyroid nodules was smaller than 2 cm; second, all lesions are unilateral, and intra-lobe, and the contralateral thyroid lobe could be preserved; third, no clinical involved cervical lymph nodes (cN0) was detected by imaging examination preoperatively; last, no obvious abnormality in coagulation, cardiopulmonary, liver, and kidney function preoperatively. The 217 patients were randomly classified into two groups (classical design or zero-line design). This research was approved by the Human Research Ethics Committee (No.1280) at the Hunan Provincial People's Hospital. All patients had completed the GUA operation by the same group of surgeons with informed consent obtained.

Surgical procedures

After generally anesthetized under tracheal incubation, the patient was placed in a supine position on a pad positioner, with the neck gently extended using a mildly sloping pillow under the shoulder and neck. Place the operated side body close to the edge of the surgical bed (**Figure 1A**), and the arm was naturally abducted at about 90 degrees at the arm board (**Figure 1B**), which could be adjusted if the clavicle is higher than the thyroid isthmus. The monitor was placed contralateral, and the surgeon and assistant were seated on either side of the patient's arm (**Figure 1C**).

For the classical design (5), the main oblique incision (about 3.5–4.5 cm in length) was made along the armpit's first or second natural skin fold. It should not exceed the anterior axillary line, whereby the endoscope and surgical instrument were placed. In addition, we made a 0.5 cm small incision at the intersection of the axillary front line and the upper edge of the breast; the location was 3.0–4.0 cm underneath the main incision, whereby a 5 mm trocar, and the cannula was then inserted (**Figures 2A,B**). For the zero-line design, an oblique incision (about 3.5–4.5 cm in length) parallel to the armpit stripes was made about 2 cm from the axillary top. The front end should not exceed the anterior axillary line. Define the line connecting the intersection of the incision with the lateral border of the pectoralis major and the highest point of the clavicle as the zero-line. After that, define the intersection of the reverse extension line of zero-line and the anterior midline of the chest (midline of the sternum) as the apex point, then draw a straight line along a 30-degree counterclockwise angle. A 0.5 cm trocar incision is then made at the intersection of this line and the lateral border of the pectoralis major; the 30-degree angle could be slightly different due to right-handed habit. When choosing the site of the trocar incision for a female patient, the breast should

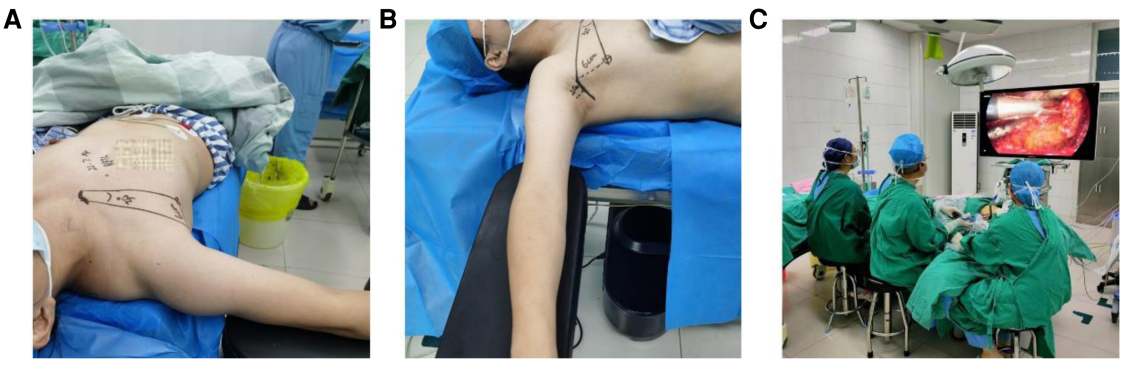

FIGURE 1
Patient's posture and surgeon's seat. (**A**) Place the operated side body close to the edge of the surgical bed. (**B**) The arm was abducted at 90°. (**C**) The HD monitor was placed contralateral, and the surgeon and assistant were then seated on either side of the patient's arm.

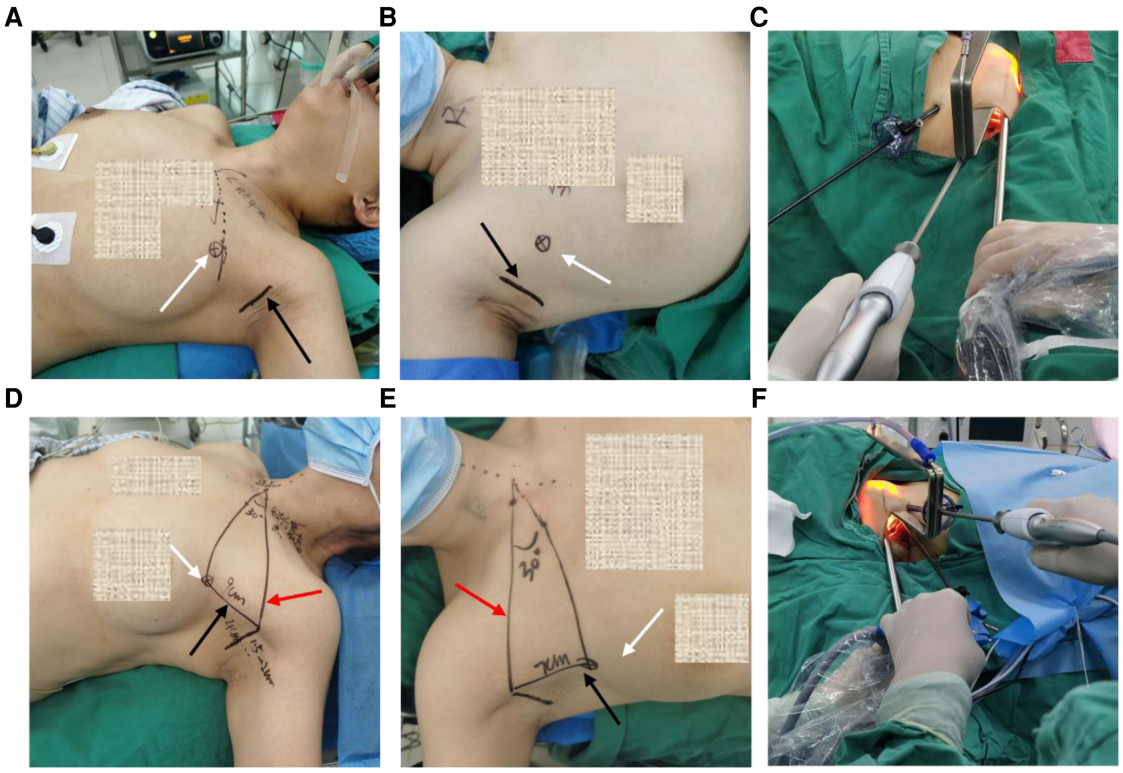

FIGURE 2
Representative photos of zero-line and classical incision design. (A,B) Classical designation on body surface for left-side and right-side thyroidectomy. (C) Endoscope, surgical clamp, and auxiliary clamp cooperation for left-sided thyroidectomy. (D,E) Zero-line designation on body surface for left-side and right-side thyroidectomy. (F) Endoscope, surgical clamp, and auxiliary clamp cooperation for right-sided thyroidectomy. Black row indicated the main incision, white row indicated the trocar incision, red row indicated the zero-line.

be retracted inferiorly, and kept the chest skin flattened (Figures 2D,E).

Data collection and outcomes

The gender, age, body mass index (BMI), size of largest tumor, primary tumor side, total operation time, intraoperative blood loss, postoperative pathological examination of central lymph nodes, and the score of postoperative neck pain were compared between the two groups of patients. Operative time was defined as the time from the initial skin incision to the point of final closure. Also, the postoperative neck pain was evaluated by the standard pain scoring method 48 h after surgery. Score 5 was defined as an extremely severe inability to complete daily activities. The evaluation of incision cosmetic achievement was evaluated by a visual analog scale after 30 days of leaving the hospital. A score of 0 was defined as extremely dissatisfied, and a score of 10 was defined as well satisfied.

Statistical analysis

We used SPSS 27.0 software (Armonk, NY: IBM Corp) for statistical analysis. Categorical variables were analyzed using the Chi-squared test. The normality of continuous data was analyzed using the Shapiro-Wilk test. Continuous data were analyzed using an unpaired t-test or Mann-Whitney test. A p-value of <0.05 was considered statistically significant.

Results

Completion of endoscopic surgery

Between October 2021 and August 2022, 217 enrolled participants diagnosed with thyroid cancer underwent GUA. Of all the 217 patients, one patient of the classical design group was converted to open surgery due to intraoperative bleeding, and the rest 216 patients completed the endoscopic surgery successfully. 111 patients (83 females and 28 males) in the classical design group had an average age of 36.84 ± 11.12 years, and 105 patients (82 females and 23 males) in the zero-line design group had an average age of 38.87 ± 10.95 years, respectively. Demographic data, including age, gender, BMI, size of the largest tumor, and the primary tumor side, were similar between the two groups (Table 1). There was no issue of postoperative bleeding, permanent hypoparathyroidism, recurrent laryngeal nerve or superior laryngeal nerve injury in both groups. In all cases, the scapula hyoid muscle was retained *in situ* successfully.

TABLE 1 General conditions of two groups.

Group (*n*)	Age	Gender	BMI	Size of largest tumor (cm)	Primary tumor side
Classical (111 cases)	36.84 ± 11.12	83 F and 28 M	23.36 ± 3.715	0.93 ± 0.39	42 L and 69 R
Zero-line (105 cases)	38.87 ± 10.95	82 F and 23 M	23.38 ± 3.802	0.89 ± 0.51	49 L and 56 R
p	>0.05	>0.05	>0.05	>0.05	>0.05

Operative duration, lymph node dissection, and bleeding

The operative time in the classical design group was longer than in the zero-line design group, with an average time of 2.66 ± 0.68 h and 1.40 ± 0.47 h ($p < 0.001$). The counts of central compartment lymph node dissection were higher in the zero-line design group (5.03 ± 3.02 nodes) than that in the classical design group (3.05 ± 2.68 nodes) ($p < 0.001$). The difference in the volume of intraoperative bleeding between the two groups was not statistically significant ($p > 0.05$) (Table 2).

Postoperative pain and cosmetic satisfaction

The score of postoperative neck pain was lower in the zero-line design group (1.0 ± 0.36) than that in the classical design group (3.3 ± 0.54) ($p < 0.05$). The difference in the visual analog scale of cosmetic achievement was not statistically significant in the two groups ($p > 0.05$) (Table 2). Representative photos of the comparison of recovery of the postoperative surgical incision in two groups were shown in Supplementary Figure S1.

Discussion

The significant advantages in the GUA approach for unilateral thyroidectomy included the excellent cosmetic effect. Also, the gasless method can effectively avoid CO2-related complications. Also, the technique is relatively easy for surgeons to master and promote, and the curative effect is also equivalent and satisfactory compared with other surgical methods (9, 13–16). Further, recent advances in neuromonitoring and energy-based device also made video-assisted sutureless thyroidectomy safe and effective (17, 18). In the GUA method, surgeons first accessed to the surgical field from the axillary, then dissected and exposed the unilateral thyroid in the space between the clavicular head and the sternal head of the sternocleidomastoid muscle. After that, adequate tension was kept using the retractors, which suspended the unilateral thyroid above the surgical field. Surgeons first separated the posterior of the thyroid, then dissected the thyroid gland from the lateral to the inferior. Therefore, avoiding interference between the forceps, the endoscope, and the retractor during the operation is pivotal. Further, how to avoid the operative blockage of the clavicle head on the lower pole of the thyroid gland, the recurrent laryngeal nerve, and the lower border of the central lymph node compartment remains significant for a successful operation (9, 19). However, the smoothness and difficulty of the operation often suffer due to the unreasonable design of the incision approach.

Our study provides a zero-line incision design method. The method uses relatively fixed markers on the human body, by which the operational space could be granted even with variation from gender, neck length, chest width, and weight status. In our experience, the zero-line method reduced the mutual interference of surgical instruments during the operation. As shown in Figure 3, the scope of the auxiliary clamp's activities was determined by the distance from the auxiliary trocar incision to the main incision. When the distance is longer, the incidence of surgical instruments' mutual interference will be reduced according to the lever principle, which would be the fundamental superiority of zero-line design. In zero-line design, the distance was determined by the location relationship of each anatomy marker and could be flexibly changed in a different patient, which was usually longer than in classical design. While in classical design, a settled distance (3–4 cm) makes the dissecting line relatively far from the superior margin of the mammary gland, and the activity space of the auxiliary clamp is more seriously restricted (9). In short, zero-line design enlarges the scope of surgical instruments' activity and leads to universally smoother operations.

At the same time, the ample operating space by zero-line approach significantly improved the lower thyroid gland separation and the central lymph node dissection. More tissues were dissected in the zero-line design group since the activity scope of the auxiliary clamp was significantly larger than the classical group. In many hospitals, including our center, prophylactic central neck dissection will be applied in patients with thyroid cancer to reduce the possibility of

TABLE 2 Operative indicators of two groups.

Group (*n*)	Operative duration (hours)	Counts of central lymphnode dissection	Bleeding volume (ml)	Score of postoperative neck pain	Score of cosmetic achievement
Classical (111 cases)	2.66 ± 0.68	3.05 ± 2.68	11.53 ± 7.32	3.3 ± 0.54	9.28 ± 0.41
Zero-line (105 cases)	1.40 ± 0.47	5.03 ± 3.02	10.86 ± 6.98	1.0 ± 0.36	9.55 ± 0.44
t	16.33	−5.10	0.69	31.61	−4.60
p	<0.001	*p* < 0.001	>0.05	<0.001	>0.05

F, female, M, male, L, left, R, right.

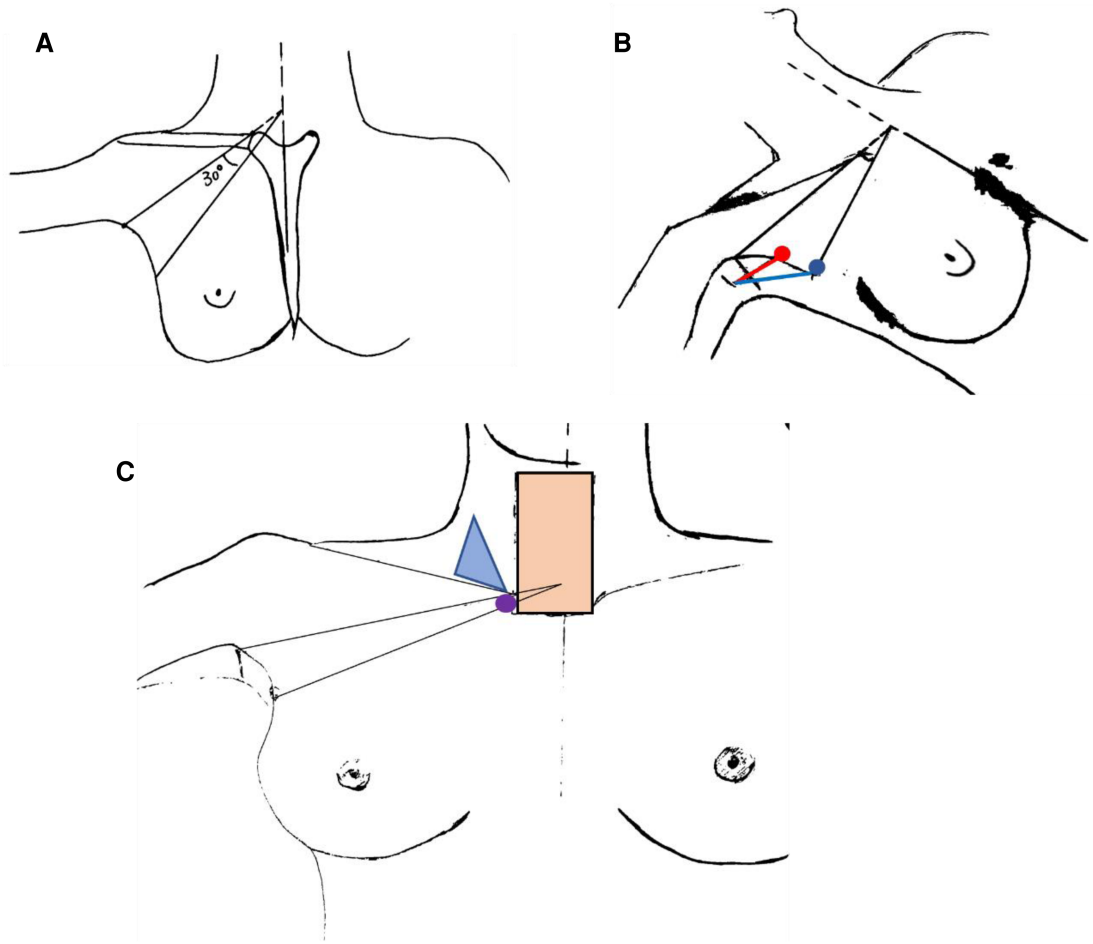

FIGURE 3
Schematic diagrams of zero-line and classical incision design. (A) Schematic diagram of zero-line incision design. (B) Comparative diagram of the two designs representing different positions of trocar incision. The red dot and line indicated the classical trocar incision and the distance to the main incision, and the blue dot and line indicated the zero-line ones. (C) Diagram representing the lever principle of zero-line incision design. The purple dot indicated the fulcrum (clavicular head of sternocleidomastoid). The light blue triangle indicated the supraclavicular fossa. The meat-colored square indicated the surgical lesion of thyroidectomy.

recurrence, and clinical uninvolved lymph nodes (cN0) by imaging examination but with cancer metastases will be diagnosed in postoperative pathological examination (20, 21). In GUA surgery, recognition and protection were usually easily handled for the superior parathyroid gland. Still, the inferior parathyroid gland in both groups was almost undetectable and protected in the endoscopic vision. However, by immediate auto-transplantation combined with unilateral surgery, no contemporary or persistent postoperative hypoparathyroidism in both group. Further, patients experienced less neck discomfort under zero-line design after surgery. We believe the main reason is the shorter operative time of the zero-line group, which leads to a slighter skin flap extraction and suspension in surgical field exposure.

Conclusion

In conclusion, we modified the "zero-line" method for incision design, and the method was simple but effectively facilitated GUA surgery and was worth promoting. The zero-line incision design enlarges the scope of surgical instruments' activity and leads to smoother operations, slighter skin flap extraction and more radical lymph node dissection. However, there were still limitations to our study. First, the sample size for the zero-line method cases we completed was still insufficient, and we hope that multi-center trials can be conducted and promoted. Second, patients reported their visual cosmetic achievement 30 days after hospitalization, which requires longer follow-ups. Also, we must pay attention to the technical requirements and difficulties of the GUA approach for bilateral thyroid surgery in the future. Last, the learning curve for the surgery should not be ignored.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Human Research Ethics Committee at the Hunan Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HW and CZ designed the study and obtained the data; HW, RL and CZ carried out operations and analyzed data: HW, RL, QF and ZZ wrote the manuscript; WW, SY, MF and JD revised and approved the manuscript; CZ provided acquisition of the financial support for the study. HW and RL contributed equally to the study. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1121292/full#supplementary-material.

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Preoperative application of carbon nanoparticles in transoral endoscopic thyroidectomy vestibular approach for papillary thyroid cancer

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Background: Carbon nanoparticles (CNs) have been widely used in the protection of the parathyroid gland and act as a tracer agent in central lymph node dissection. However, the right time for CN injection has not been well illustrated in the transoral endoscopic thyroidectomy vestibular approach (TOETVA). The purpose of this study was to evaluate the safety and feasibility of the preoperative injection of CNs in TOETVA for papillary thyroid cancer.

Methods: From October 2021 to October 2022, a total of 53 consecutive patients with PTC were retrospectively analyzed. All patients underwent unilateral thyroidectomy *via* the TOETVA. The patients were divided into the preoperative group (n = 28) and the intraoperative group (n = 25) according to CN injection time. In the preoperative group, 0.2 ml of CNs were injected into the thyroid lobules with malignant nodules 1 h before surgery. The numbers of total central lymph node (CLN) and metastatic central lymph node (CLNM), parathyroid autotransplantation, accidental removal of the parathyroid, and the parathyroid hormone level were recorded and analyzed.

Results: The leakage of CNs happened more frequently in the intraoperative group than in the preoperative group (P = 0.002). The mean number of retrieved CLN and CLNM was similar in the preoperative group and the intraoperative group. In parathyroid protection, more parathyroid was discovered in the preoperative group than in the intraoperative group (1.57 $\pm$ 0.54 *vs*. 1.47 $\pm$ 0.50, P = 0.002), but less parathyroid autotransplantation (P = 0.004) and accidental removal of the parathyroid (P = 0.036) were discovered in the preoperative group. However, the PTH level between the two groups was similar after the first day and the first month.

Conclusion: The preoperative injection of CNs is a safe and effective method to protect the parathyroid glands (PGs) in patients with PTC undergoing TOETVA. However, the value of preoperative injection of CNs in TOETVA for central lymph node dissection needs to be further studied.

KEYWORDS

preoperative injection, papillary thyroid cancer, transoral endoscopic thyroidectomy vestibular approach, carbon nanoparticles, intraopertive injection

Introduction

Papillary thyroid carcinoma is the most common endocrine tumor worldwide (1, 2). The transoral endoscopic thyroidectomy vestibular approach (TOETVA) provides easy access to the thyroid and central compartment and avoids skin scarring during thyroid surgery, which makes it a widely popular option in thyroidectomy (3).

Carbon nanoparticles (CNs) act as a novel lymph node tracer and have been used in the surgery of stomach carcinoma, breast cancer, and thyroid cancer (4, 5). In thyroidectomy, CNs are usually injected into the thyroid gland during operation and stain the gland and lymph node black, which facilitated the surgeons to identify the parathyroid and guide them to dissect the lymph nodes (6). However, CNs might leak out of the thyroid and stain the surrounding tissues during the intraoperative injection. Recent studies have shown that the preoperative injection of CNs is safe and feasible in thyroidectomy *via* traditional open thyroid surgery and bilateral axillo-breast approach robotic thyroidectomy (7–9). However, the effectiveness of the preoperative injection of CNs has not been well illustrated in TOETVA. Therefore, the purpose of this study was to discover the appropriate time to inject CNs in TOETVA.

Materials and methods

Patients

From October 2021 to October 2022, 53 consecutive adult papillary thyroid cancer (PTC) patients who underwent TOETVA with central lymph node dissection at the Department of Thyroid and Breast Surgery, Weifang People's Hospital, were retrospectively enrolled. Patients were divided into the preoperative CN injection group (preoperative group, n = 28) and the intraoperative CN injection group (intraoperative group, n = 25).

The inclusion criteria were as follows: patients with cosmetic requirements, patients with the longest diameter of tumor less than 20 mm, and patients with postoperative pathologically confirmed PTC.

The exclusion criteria include patients with a history of thyroid surgery or neck radiotherapy, patients younger than 18 years of age, and patients with postoperative pathology suggesting other types of tumors, such as benign tumor, follicular cancer, and medullary or undifferentiated cancer.

All the TOETVA was performed by the same professional thyroid surgeon (Yonghui Wang).

CN injection before the operation

Ultrasound-guided injection of CNs was performed 1 h before surgery in the preoperative group. Carbon nanoparticles (0.5 ml per ampoule, Chongqing LaiMei Pharmaceutical Co., Ltd., Chongqing, China) were used in this study. The special procedures were as follows: 0.2 ml of CNs were extracted with a 1-ml syringe, then a new needle was used, and the air inside it was expelled (Figure 1A). Patients were in the position of high shoulder with a pad, and disinfection around the puncture point was prepared before the injection of CNs. We chose a safe and short way to avoid puncturing into the vessels, tumor, and nerves under ultrasound guidance. A volume of 0.2 ml of CNs was injected into the normal thyroid gland tissues, and the needle was gently withdrawn with negative pressure (Figure 1B). After the injection, 1 h of observation was needed, so that timely disposal could be arranged once the patients felt unwell. Preoperative injection of CNs was conducted under ultrasound guidance by an experienced surgeon (Liquan Wang) 1 h before the operation.

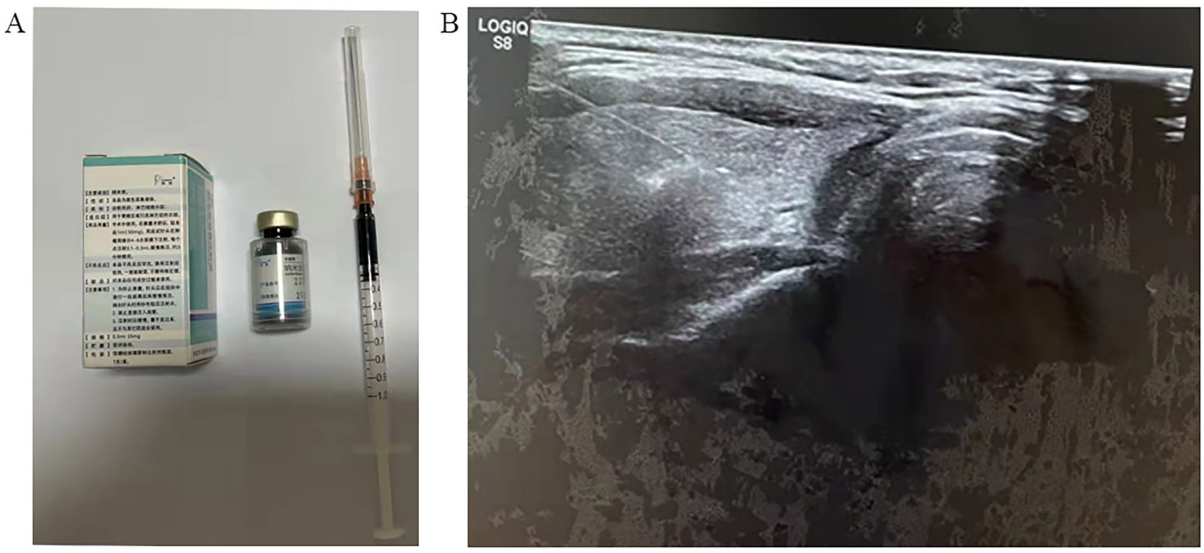

FIGURE 1
Carbon nanoparticle injection. **(A)** Preparation of carbon nanoparticles. **(B)** The ultrasound-guided carbon nanoparticle injection.

Injection of CNs during surgery

The CNs could not be injected under direct vision due to the endoscopic surgery. A percutaneous puncture was made by locating the CN puncture site on the ceiling skin of the working space. CNs (0.2 ml) were injected into the normal thyroid tissue by using a syringe (1 ml). Back-drawing should be performed during injection to avoid mistakenly injecting into the blood vessel. The needle puncture site was gently pressed using gauze for 10 min.

Surgical procedure

All the patients were diagnosed as unilateral PTC by preoperative fine-needle aspiration, and unilateral thyroid gland dissection was first performed followed by ipsilateral central neck lymph node dissection. The TOETVA operative procedures have been previously described (10).

Monitoring indicators

The general characteristics, complications of CNs (pain, hematoma, and CN leakage), pathological examinations, and parathyroid gland (PG)-related parameters [mean number of PGs *in situ*, mean number of PG autotransplantation, and postoperative parathyroid hormone level (PTH)] were collected and analyzed.

The level of PTH would be tested at three time points, i.e., during preoperation and 1 day and 1 month after the operation. Hypoparathyroidism is defined as a decline in serum PTH below 15 pg/ml. The patient was considered to have permanent hypoparathyroidism when the serum PTH level at 3 months after surgery was below 1.3 mmol/L.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared using independent samples *t*-tests. Chi-square tests were performed to analyze categorical data. Statistical analysis was performed using SPSS 17.0, and a value of $P < 0.05$ was considered statistically significant.

Results

Patients' characteristics

The process of patient selection based on the inclusion and exclusion criteria is shown in Figure 2. TOETVA was performed on a total of 70 consecutive patients. Fifty-three patients (28 patients in the preoperative group and 25 patients in the intraoperative group) were eligible and 17 patients were excluded. Clinical data were retrospectively collated from 53 patients. The ages of the patients ranged from 20 to 60 years, with a median age of 39 years. All patients underwent endoscopic unilateral thyroidectomy with central lymph node dissection (CND) (level VI), and no patient was converted to open thyroidectomy. PTC was confirmed by postoperative pathology for all patients. The clinicopathological characteristics of the patients enrolled in this study are summarized in Table 1. There was no significant difference between the preoperative group and the intraoperative group in terms of age, sex, Hashimoto's thyroiditis, extrathyroid extension, tumor size, and preoperative PTH.

Safety and tolerance of the CN injection

The injection time was approximately 2 min. No patient in the preoperative group has obvious systemic toxicity. In addition, there was no intolerable pain, bleeding, or hematoma during the injection procedure. One patient had skin marking at the puncture site after injection at the early stage, and we put the drainage tube in the marking site during the operation. CN leakage happened in two patients in the preoperative group and in 11 patients in the intraoperative group. The CN leakage rate was higher in the intraoperative group than in the preoperative group ($P = 0.002$) (Table 2).

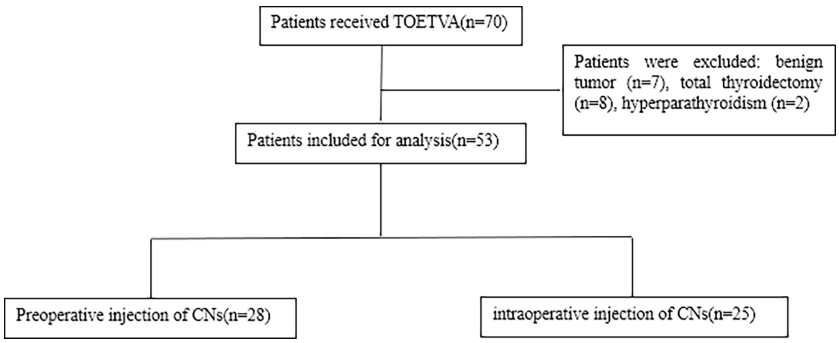

FIGURE 2
A CONSORT diagram showing the patient inclusion and exclusion criteria. TOETVA, transoral endoscopic thyroidectomy vestibular approach; CNs, carbon nanoparticles.

TABLE 1 Patients' clinical characteristics in the preoperative group and the intraoperative group.

Characteristics	Preoperative group (n = 28)	Intraoperative group (n = 25)	P-value
Age	40.14 ± 1.65	38.60 ± 2.41	0.593
Sex (male/female)			0.883
Male	3	3	
Female	25	22	
Extrathyroid extension			0.184
No	14	8	
Yes	14	17	
Hashimoto's thyroiditis			0.823
No	6	6	
Yes	22	19	
Tumor size (mm)	0.62 ± 0.45	0.55 ± 0.29	0.928
PTH (preoperative)	40.75 ± 2.47	38.37 ± 2.15	0.478

PTH, parathyroid hormone.

Lymph node dissection

As shown in Table 2, a total of 124 and 125 lymph nodes were dissected in the preoperative group and the intraoperative group, respectively. In the preoperative group, there were 1–12 lymph nodes per case with an average of 4.50 ± 0.49 lymph nodes per case, and 20 lymph nodes had metastases. In the intraoperative group, there were 1–13 lymph nodes per case with an average of 5.00 ± 0.56 lymph nodes per case, and 15 lymph nodes had metastases. However, there was no statistical difference in both total CLN (P = 0.502) and CLNM (P = 0.775) between the preoperative group and the intraoperative group.

Identification and protection of the parathyroid glands during the operation

The baseline of preoperative PTH was similar between the preoperative group and the intraoperative group (40.75 ± 2.47 *vs.* 38.37 ± 2.15, P = 0.478) (Figure 3). Although the postoperative PTH level dropped on the first day, no significant difference was found between the preoperative group and the intraoperative group, and it recovered to preoperative levels on the first month (Figure 3). Pathological results showed that one incident of accidental removal of PG occurred in the preoperative group, whereas seven instances of PG removal occurred in the control group (Table 3), which means that there was more frequent accidental PG removal in the intraoperative group (P = 0.036). In addition, there was a low ratio of PG autotransplantation in the preoperative group than in the intraoperative group (P = 0.004) (Table 3).

Discussion

CNs, with a diameter of 150 nm, can pass through the lymphatic vessels and accumulate in the lymph nodes and stain them (11). CNs have been widely used as a tracer for lymph node dissection in thyroid surgery. As they do not enter the blood capillaries, the other function of CNs is to discover the parathyroid which is not changed and left unstained unlike the thyroid and lymph nodes (11). More surgeons usually injected CNs during the operation and noticed the phenomenon of CNs leaking out during surgery which stained the surrounding tissue and affected the recognition of the parathyroid (12). Recent studies have shown that the preoperative use of CNs has more advantage in the protection of the parathyroid and in central lymph node dissection in open thyroidectomy and bilateral axillo-breast

TABLE 2 Central lymph node dissection and CN leakage in the preoperative group and the intraoperative group.

Variables	Preoperative group (n = 28)	Intraoperative group (n = 25)	P-value
Number of CLN	4.50 ± 0.49	5.00 ± 0.56	0.502
Metastatic CLN	0.75 ± 0.24	0.60 ± 0.19	0.775
CN leakage			0.002
No	2	11	
Yes	26	14	

CLN, central lymph node; CLNM, central lymph node metastasis.

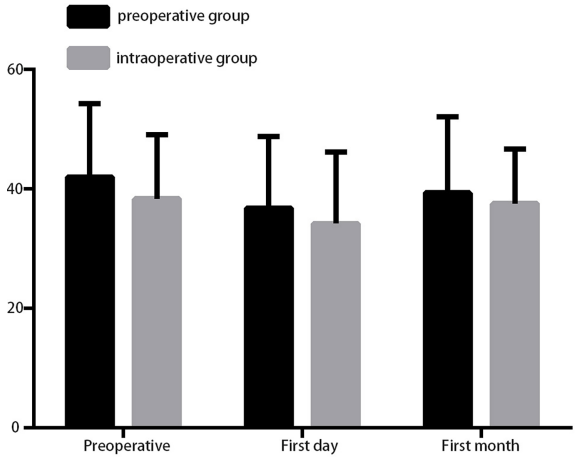

FIGURE 3
The parathyroid hormone was detected during preoperation and on the first day and first month after surgery.

approach robotic thyroidectomy (7, 8). However, the right time for CN injection has not been well illustrated in TOETVA.

Similar to previous studies with the preoperative injection of CNs, this study showed a few complications of CNs, which is also consistent with the intraoperative injection of CNs in other studies (7, 8). Skin staining after injection occurred in one patient during the early stage of our study, and this adverse event could be avoided by using a new needle before the injection. In addition, the leakage of CNs occurred in two patients in the preoperative group, which is much lesser than in the intraoperative group. There are some reasons for the less chance of leakage in the preoperative injection of CNs. Firstly, the capsule of the thyroid has not been destroyed before the surgery which can prevent the CNs from leaking. Secondly, the trap muscle is still in contact with the capsule and could compress the injection site to prevent leaking.

Due to less scarring in the neck, endoscopic thyroid surgery techniques including the transoral approach and the bilateral axillo-breast approach have been used all over the world (13). The transoral approach does not cause scarring in the skin and requires a smaller subcutaneous flap elevation than the bilateral axillo-breast approach; therefore, TOETVA attracted the attention of both surgeons and patients (3). A previous study showed that central lymph node metastasis occurred in nearly half of the patients and prophylactic central lymph node dissection was performed to reduce its recurrence (14). However, the central lymph node dissection has enhanced the injury of the parathyroid and induced the occurrence of postoperative hypoparathyroidism (14).

Injury to the parathyroid would lead to hypocalcemia, which is often caused by the accidental removal of the parathyroid gland or damage to the glandular blood supply. As a result of the surgeons' awareness of parathyroid protection and operative skills, the parathyroid injury rate has been reduced. However, the postoperative hypocalcemia rate is still up to 0.3%–49% (14). Therefore, protecting the blood supply and parathyroid is of primary importance in thyroid surgery. In terms of parathyroid protection, there was a low ratio of autotransplantation and accidental thyroid dissection in the preoperative group than in the intraoperative group. The plausible reason was that there was more leaking of CNs in the intraoperative group than in the preoperative group, which darkened the parathyroid and made it hard to distinguish the parathyroid from the adipose tissues. In our study, the accidental removal of the parathyroid happened in seven patients, and all of them had CN leakage. Therefore, it is important to prevent CN leakage by preoperative injection. Most people have four parathyroids. Once one or two parathyroids are injured in the operation, the other parathyroid could enhance the secretion

TABLE 3 Preserved PG *in situ*, PG autotransplantation, and accidental PG removal between the preoperative group and the intraoperative group.

Variables	Preoperative group (n = 28)	Intraoperative group (n = 25)	P-value
Identification of PG	50 (1.57 ± 0.54)	45 (1.47 ± 0.50)	0.002
Autotransplantation of the parathyroid			0.004
No	26	10	
Yes	2	15	
Accidental PG removal			0.036
No	27	18	
Yes	1	7	

PG, parathyroid gland.

function and act as a substitute for the injured parathyroid. Therefore, the PTH level was not significantly different between the two groups on day 1 in this study. This result was special for total thyroidectomy and bilateral central lymph node dissection which had more possibility to damage all the four parathyroids and develop permanent hypoparathyroidism.

Previous studies showed that CNs could help detect the lymph nodes and increase the discovery of metastatic lymph nodes. However, consistent with the recent study, the time of CN injection could not help in discovering more lymph nodes and metastatic lymph nodes, and this can be attributed to the fact that skillful surgeons could perform central neck dissection according to the requirements of the guidelines.

However, there are some limitations in this study. Firstly, this study was not a prospective randomized control one, which means that the evidence provided by the study was not as powerful as that of a multicentric pragmatic randomized control clinical trial. Secondly, the number of patients in our study was small, and unilateral thyroidectomy was performed which might influence temporary and permanent hypoparathyroidism. In addition, the time of preoperative injection was only 1 h before surgery. In a future study, we might consider more time points such as immediately after anesthesia which might alleviate anxiety.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by ethics committee of WeiFang people's hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

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

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The learning curve on uniportal video-assisted thoracoscopic lobectomy with the help of postoperative review of videos

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Objectives: Video-assisted thoracoscopic lobectomy has become the preferred surgical approach in experienced centers, and uniportal approaches are becoming increasingly used. But the uniportal approach is still not widely applied presumably due to the learning difficulties of this complex procedure. The use of surgical videos may be helpful to accelerate the learning of this new techniques as in other fields. In this study, we aimed to analyze the learning curve of uniportal video-assisted thoracoscopic lobectomy with the help of postoperative review of videos.

Methods: 114 patients with early-stage lung cancer who underwent uniportal video-assisted thoracoscopic lobectomy performed from 2020 to 2021 were reviewed in this study. We recorded the operation video for each patient and reviewed all the videos after surgery. The learning curves were assessed using cumulative sum analysis and the collected data of perioperative outcomes were assessed.

Results: The CUMSUM curve showed its inflection points were around case 38 and 53. It was less compared with previous studies, which about 57–140 cases are needed to attain the proficient phase. The perioperative outcomes were similar in each phase, which included intraoperative blood loss (79.00 ± 26.70 *vs* 70.67 ± 26.64 *vs* 70.56 ± 27.23, p=0.0119), the length of hospital stay (3.60 ± 1.52 days *vs*. 3.23 ± 0.90 days *vs*. 3.06 ± 0.88 days, p=0.053), the rate of prolonged air leak and conversion to open thoracotomy. There was also no significant difference in the numbers and station of lymph node dissection among the three phases.

Conclusions: Uniportal video-assisted thoracoscopic lobectomy is a safe and reliable approach. Recording and reviewing the operation video could help the surgeon to improve deficiencies and refine the procedure.

KEYWORDS

uniportal video-assisted thoracoscopic lobectomy, learning curves, review of videos, efficacy, proficiency

Introduction

With the full implementation of screening and the development of high-resolution computed tomography, the detection rate of early stage lung cancer has significantly increased (1). Minimally invasive surgery, which includes video-assisted thoracoscopic surgery (VATS), has become the preferred approach for the curative treatment of early stage lung cancer (2, 3).

In the last decade, VATS lobectomy has become the preferred surgical approach in experienced centers, and is usually performed through 2–4 ports. Uniportal VATS (U-VATS) is based on the conventional VATS with reduced auxiliary operation ports. However, the U-VATS technique is still not widely applied in most medical centers, presumably due to the learning difficulties of this complex procedure (4–8).

Video review has been proved to be a useful tool for learning new skills in many fields such as athletics, modern drama and aviation. The use of surgical videos is also emerging as a powerful tool to facilitate the acquisition of new surgical skills and to accelerate the learning of new techniques (9, 10). However, these studies are usually limited to the study of multiportal laparoscopic technology and there is no research report on the uniportal thoracoscopy technology. In this study, we aimed to describe our experience in 114 consecutive cases and to analyze the learning curve of uniportal video-assisted thoracoscopic lobectomy with the help of video-assisted operative feedback.

Materials and methods

Patients

This retrospective study was reviewed and approved by the ethics committee of the Shanghai Chest Hospital. All patients have signed the written informed consent before the operation. All operations were performed by the same surgeon (Dr. Xinghua Cheng) from Shanghai Chest Hospital, which had performed 88 cases of multiportal thoracoscopic lobectomy before. Totally 114 consecutive patients who underwent uniportal VATS lobectomy from May 2020 to August 2021 were reviewed in this study.

Surgical technique

The patients were maintained in the lateral decubitus position and 1-lung ventilated with double-lumen endotracheal intubation, received general anesthesia. The surgeon was on the patient's abdominal side, and the assistant was on the opposite side (the back of the patient). A 2.5 to 3 cm hole was made at the fifth intercostal space on the middle axillary line. Wound protectors were used at the incision to facilitate exposure and simplify instrumentation.

The camera was positioned on the posterior portion of the incision. The staplers were always introduced through the most anterior portion of the incision, below any other instrument, and fissures were always cut with energy sealing devices. The bronchus, vein and artery were divided anatomically, and dissected separately using endoscopic staplers or ligated by using hem-o-locks before dissection. 24 Fr chest tubes were inserted through the incision at the end of the operations, and we would remove the chest tube if the patient's volume of drainage was less than 200ml per day and there was no air leakage.

Video review of surgical skills

We recorded the operation video for each patient and reviewed the videos after surgery. The video recording was started with the introduction of a dissector and concluded with the removal of the target lobe and lymph nodes. All videos were assessed from three domains of bimanual dexterity, efficiency and tissue handling based on the surgical performance. Besides, all the operation videos were analyzed for frequency of minor technical errors and adverse events after surgery. Minor errors included insufficient exposure, wrong pass angle of cutting stapler, dropping tissue or suture. Examples of adverse events included excessive blood loss, tears of lung or bronchus requiring repair. Meeting quarterly, we reviewed the "typical" and "challenging" operation videos with senior surgeons to share best practices and identify where the technique could be improved.

Data collection

All patients were characterized by demographic and clinical variables, including sex, age, smoking history, body mass index (BMI), Charlson comorbidity index (CCI), forced expiratory volume in 1 s (FEV1), diffusion capacity of the lung for carbon monoxide (DLCO), pathology, tumor size, operation procedure, and lymph node (LN) status. Surgical outcomes included procedure time, intraoperative blood loss, postoperative hospital stay, complications, and lymph node retrieval. Procedure time was defined as the time from the first incision to complete closure of the skin. Prolonged air leakage was defined as air leakage lasting for >5 days postoperatively. Perioperative mortality included death during hospitalization or within the first 30 days after the operation.

Statistical analysis

Statistical analysis was performed using SPSS software (version 18.0; SPSS, Inc., Chicago, IL) and R (version 3.6.2). Data are shown as mean (standard deviation) or median (interquartile range) for

Abbreviations: VATS, video -assisted thoracoscopic surgery; BMI, Body mass index; ASA, American Society of Anesthesiology; CCI, Charlson comorbidity index; DLCO, Diffusion capacity of the lung for carbon monoxide; FEV1, Forced expiratory volume in 1 s; LN, Lymph node.

continuous variables and as n (%) for categorical variables. Differences between groups were analyzed using one-way analysis of variance or the Kruskal-Wallis *H* test. Fisher's exact test or chi-square test was used to classify variables. A two-sided P-value < 0.05 was considered statistically significant. The cumulative sum (CUSUM) analysis method was used to quantitatively assess the learning curve. CUSUM for operation time was calculated as follows: $CUSUM = \sum_{i=0}^{n}(x_i - u)$, where x_i and u respectively represent an individual and the mean overall operative time (6). In addition, we established a polynomial trend line to show the change in the slope of the learning curve. According to the learning curve obtained from the analysis, we divided it into three stages: the ascending phase (Phase I), the transition phase (Phase II), and the maturity phase (Phase III).

Results

Patient characteristics

Altogether, 114 patients who undergoing U-VATS lobectomy performed by a single surgeon between May 2020 and August 2021 were enrolled in this study. The baseline characteristics of the patients are shown in Table 1. Of the 114 patients, 50(43.86%) were men and 64(56.14%) were women. The median age of the patients was 61 years. Adenocarcinoma was the most frequent histologic type(87 patients, 76.3%), and the mean tumor diameter was 21.00 ± 12.80 mm. Detailed patient characteristics are presented in Table 1. When clinical demographics and characteristics were assessed for the three periods of the learning

TABLE 1 Patients' demographics and surgical outcomes according to learning curve phases.

Parameters	Total (n=114)	Phase I (n=35)	Phase II (n=18)	Phase III (n=61)	*P*
Patients number		1-35	36-53	54-114	
Gender, n (%)					
Male	50 (43.86%)	11 (36.7%)	13 (43.3%)	26 (48.15%)	0.113
Female	64 (56.14%)	19 (63.3%)	17 (56.7%)	28 (51.85%)	
Age, year					0.721
Mean ± SD	59.82 ± 9.99	59.73 ± 10.86	60.03 ± 8.82	59.74 ± 10.27	
BMI					0.553
Mean ± SD	23.16 ± 3.05	23.73 ± 3.00	22.62 ± 2.65	23.14 ± 3.27	
CCI					0.717
Median(IQR)	2.0(2.0-3.0)	2.0(2.0-3.0)	2.0(2.0-3.0)	2.0(2.0-3.0)	
FEV1(%)					0.348
Mean ± SD	98.48 ± 13.63	97.92 ± 13.50	97.80 ± 11.46	99.16 ± 14.95	
DLCO(%)					0.362
Mean ± SD	93.82 ± 17.33	93.54 ± 16.21	92.89 ± 17.72	94.48 ± 17.99	
Smoking history (%)	38(33.3%)	12(40%)	11(36.7%)	15(27.8%)	0.080
Pathology					0.291
Adenocarcinoma	87(76.3%)	21(70%)	23(76.7%)	42(77.8%)	
Squamous	11(9.6%)	4(13.3%)	3(10%)	6(11.1%)	
Others	16(14%)	5(16.7%)	4(13.3%)	6(11.1%)	
Tumor size					0.094
Mean ± SD	21.00 ± 12.80	21.93 ± 12.15	22.53 ± 14.78	19.63 ± 12.06	
Operation procedure					0.073
RUL	45(39.5%)	16(53.3%)	10(33.4%)	20(37%)	
RML	12(10.5%)	3(10%)	4(13.3%)	5(9.3%)	
RLL	21(18.4%)	7(23.3%)	6(20%)	8(14.8%)	
LUL	19(16.7%)	2(6.7%)	6(20%)	10(18.5%)	

(Continued)

TABLE 1 Continued

Parameters	Total (n=114)	Phase I (n=35)	Phase II (n=18)	Phase III (n=61)	*P*
LLL	17(14.9%)	2(6.7%)	4(13.3%)	11(20.4%)	
Operative time, min					<0.001
Mean ± SD	86.09 ± 21.23	99.40 ± 18.72	85.93 ± 20.93	78.78 ± 19.36	
Blood loss					0.119
Mean ± SD	72.81 ± 26.96	79.00 ± 26.70	70.67 ± 26.64	70.56 ± 27.23	
LN stations					0.521
Mean ± SD	5.82 ± 1.68	5.93 ± 1.98	5.67 ± 1.37	5.85 ± 1.68	
LN numbers					0.086
Mean ± SD	8.23 ± 3.63	7.93 ± 3.82	7.63 ± 2.86	8.72 ± 3.89	
Length of stay, days					0.053
Mean ± SD	3.25 ± 1.10	3.60 ± 1.52	3.23 ± 0.90	3.06 ± 0.88	
Prolonged air leak (%)	4(3.5%)	2(6.7%)	0	2(3.7%)	0.098
Conversion to open thoracotomy (%)	2(1.8%)	1(3.3%)	0	1(1.9%)	0.177

BMI, Body mass index; CCI, Charlson comorbidity index; FEV1%, forced expiratory volume in 1 second to forced vital capacity ratio; DLCO%, Diffusion capacity of the lung for carbon monoxide ratio; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LN, Lymph node.

curve, there were no significant differences between patients in each learning period.

Learning curve analysis

The raw operative time for all 114 patients is shown in Figure 1B. As the number of procedures increased, the operation time decreased and became stable eventually. The learning curve for operative time is shown in Figure 1A. According to the trend and inflection points of the curve, we obtained three well-differentiated phases: phase I (1–35 cases), phase II (36–53 cases), and phase III (54–114 cases). Phase I was the ascending slope of the curve, which represented the initial experience of the technique learning, and Phase II was the transition part of the curve, which represented further improvement in surgical skills. Phase III was the descending slope, which indicated that proficiency had been achieved.

Perioperative outcomes and subgroup analysis

In the all patients, the mean operative time and length of stay were 86.09 ± 21.23 minutes and 3.25 ± 1.10 days (Table 1). No patient died perioperatively, and two cases were converted to open thoracotomy due to severe adhesions in thoracic cavity (1 case) and vascular accident (1 case). Only four patients (3.5%) experienced prolonged air leak after surgery.

In the subgroup analysis, the operative time improved from a mean of 99.40 ± 18.72 minutes to 78.78 ± 19.36 minutes, with a significant difference (p<0.001). Intraoperative blood loss tended to decrease, but there was no significant difference between the three phases (P = 0.119) (Figure 2A). The length of hospital stay was reduced (3.60 ± 1.52 days *vs.* 3.23 ± 0.90 days *vs.* 3.06 ± 0.88 days), but this was not statistically significant (P = 0.053) (Figure 2B). There was no significant difference in the stations (p=0.521) or numbers (p=0.086) of lymph node dissection among the three phases (Figure 3).

Discussion

U-VATS lobectomy has been proven to be a safe and feasible surgical approach for early stage lung cancer (11–13). However, it is not widely applied in most medical centers because of technical difficulties. Currently, the use of surgical videos by surgeons facilitate the learning of new procedures and techniques (9, 10). Surgical videos could record the frequency of minor technical errors and adverse events. Surgeons can review these videos to continuously reduce and correct these errors, thereby reducing the incidence rate of potential patients' morbidity. There is always a sharp contrast between what the surgeons think they did and what actually happened, postoperative review of videos would be helpful for operators to addresses important cognitive limitations (14–17). Besides, reviewing the "typical" and "challenging" operation videos with senior surgeons allows accurate assessment and identifying where the technique could be improved. All of the above can help improve surgical techniques, thus to accelerate the learning curve of surgeons and improve the surgical safety. Nevertheless, most of the research on video learning is limited to laparoscopic technology,

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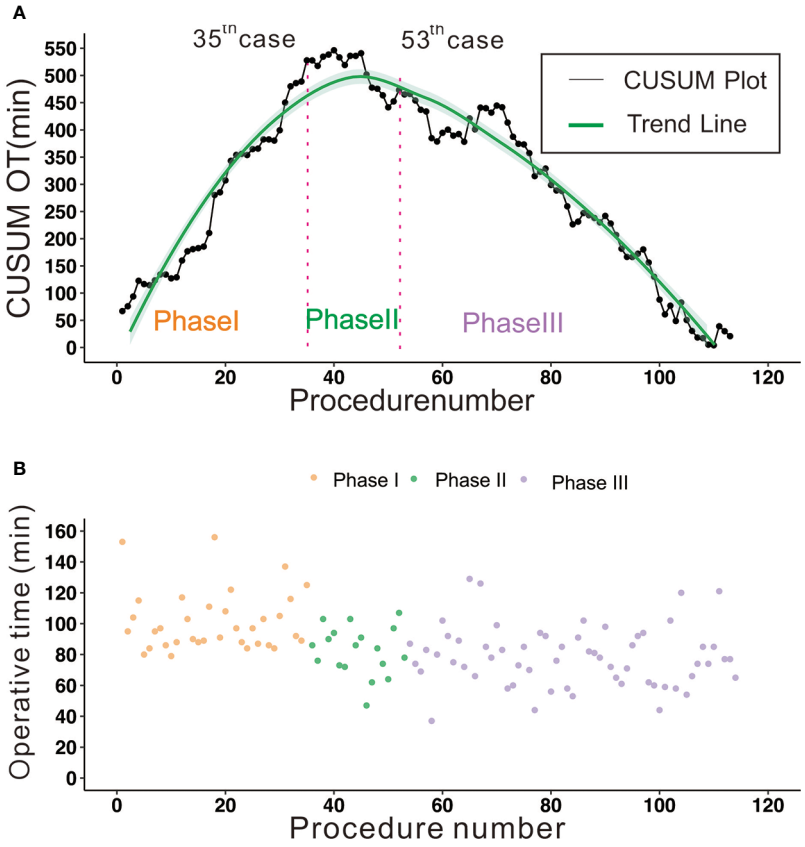

FIGURE 1
(A) The CUSUM curve of operative time; 35 cases were needed to lay the technical foundation and 53 cases were necessary to achieve proficiency. Phase I: 1-35 cases, learning phase. Phase II: 36-53 cases, transition phase. Phase III: 54-114 cases, proficiency phase. **(B)** The raw operative times were plotted in chronologic surgery order.

there is few research focus on the thoracoscopy technology, especially on the uniportal thoracoscopy technology.

In the present study, we analyzed 114 cases of U-VATS lobectomy performed by a single surgeon using the CUSUM method to evaluate how video review promotes the learning curve. It took 35 consecutive cases of U-VATS lobectomy to complete the ascending phase and 18 additional cases to overcome the transition phase. In other words, efficacy was achieved after 35 cases and proficiency was achieved after 53 cases. No patient died preoperatively, regardless of the phase of the learning curve. There was no significant difference between the three phases in terms of both intraoperative blood loss and length of hospital stay. There was also no significant difference in the number and station of lymph node dissection among the three phases. These results indicate that U-VATS lobectomy is safe and reliable, even during the initial phase of learning the technique.

So far, studies have been carried out in large-volume centers to analyze the learning curve of U-VATS lobectomy regardless of video review (Table 2) (7, 18–20). According to the results of these study, about 57–140 cases are needed to attain the proficient phase. Compared with our results, this number is obviously higher than required, which may indicate that video review can accelerate the learning curve of surgeons. Moreover, almost all previous studies showed that the amount of blood loss and length of hospital stay showed a downward trend among the three distinct periods of the learning curve. In other words, the other surgeons' operations were not sufficiently stable at the beginning of the learning curve. However, in our study, all the perioperative outcomes of patients in the three phases were comparable. This may be what was caused by the earlier mentioned video review that can help reduce intraoperative errors and improve surgical safety. Besides, in some of these previous studies (7), there was significant difference in the numbers or stations of lymph node removed because of performing lymph node dissection through the uniportal technique remains challenging. But there was no significant difference in the numbers and stations of lymph node dissection among the three phases of our study. The comparative analysis of these research results all suggest that video review can help surgeons learn uniportal thoracoscopy more quickly and safely.

Video review is associated with shortened learning curve and reduced intraoperative accidents such as bleeding probably implicates accelerated self-improvement of surgical skills. It is

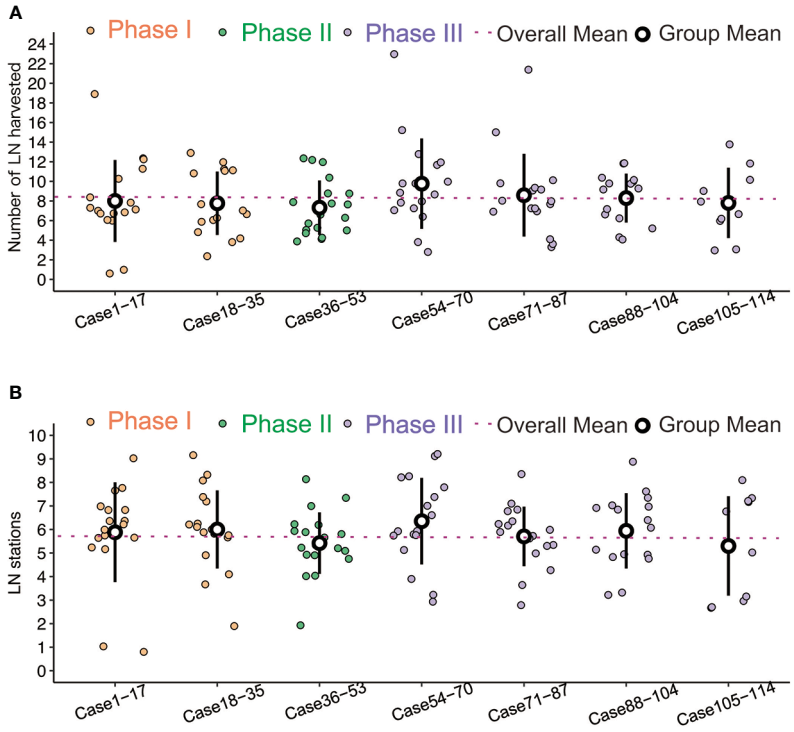

FIGURE 2
(A) Comparisons of blood loss, no significant difference between the three phases. **(B)** Comparisons of postoperative stay, no significant difference between the three phases.

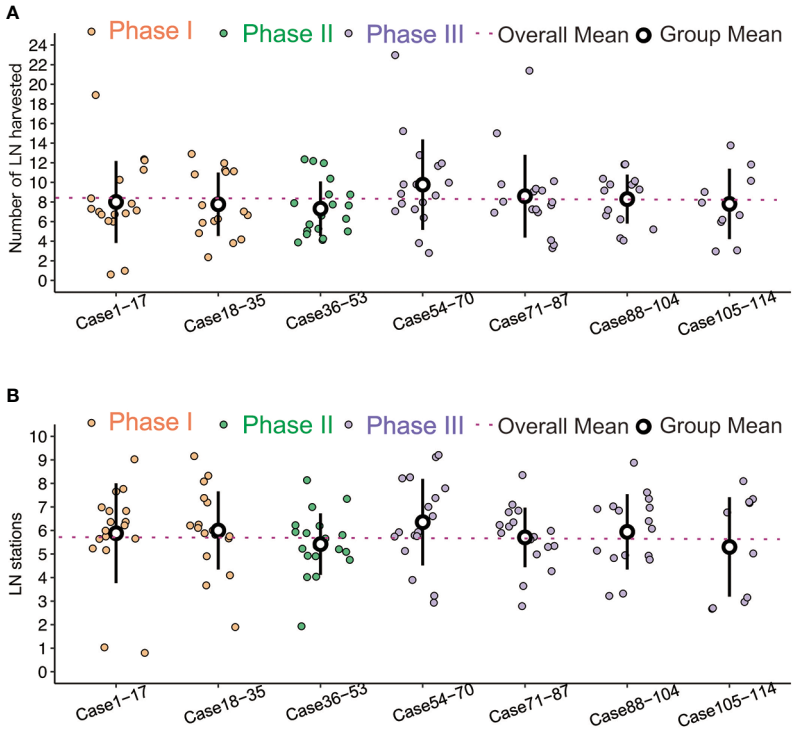

FIGURE 3
(A) Comparisons of LN harvested number, no significant difference between the three phases. **(B)** Comparisons of LN station, no significant difference between the three phases.

TABLE 2 Surgical outcomes of previous U-VATS research.

Author, year, country	Number of patients included	Number of cases needed to get the proficient phase	Mean or median operation time (min)
Xiaochuan Liu et al. (18), China	120	61	Phase1 92.1 ± 20.7 Phase2 65.9 ± 22.5 Phase3 52.6 ± 10.4
Liang Chen et al. 2020 (19), China	124	57	Phase1 130 Phase2 110 Phase3 105
Shenghui Li et al. (20), China	397	71	Phase1 140 Phase2 123 Phase3 116
Arthur Vieira et al. (7), Canada	274	140	Phase1 158.8± 52.2 Phase2 145.9± 43.8 Phase3 117.9 ± 32.6

particularly important when new technique is to be implemented or to be transferred to new trainees. By recording surgical videos, surgeons can not only review by themselves but also compare the videos with the operations from more experienced surgeons, and ask for suggestion from senior peers. For intraoperative accidents, it is easier for the surgeon to re-think how to confound and avoid similar situations after the surgery. Besides, a surgical video database is important for surgical education and generate future artificial intelligence guided surgical programs (21, 22). Video review is very practical and eliminates many inconveniences and risks associated with on-site surgical guidance. It can also be of great help in the training and education of surgical residents (23). The emergence of complex thoracoscopic and robotic surgeries transfers surgical experience from junior residents to more advanced trainees. Intraoperative learning is further limited by increasing concerns for patient safety and the possibility that resident teaching may prolong surgery time. These challenges indicate a need for innovative educational strategies to maximize the learning of operative skills (24). The electronic transmission of video is well suited for remote viewing without the limitations of location and environment. Surgical residents can use fragmented time to conduct video review and analysis freely. In addition, they can share videos with peers or more experienced surgeons to obtain feedback. Nowadays, most thoracoscopic equipment comes with video recording capability, making video recording of surgeries very easy. With the fast development of imaging and AI technologies, video review methods will become an increasingly valuable tool to accelerate innovation and promote safer surgeries.

Despite our best efforts, this study has some limitations. First, this study was a retrospective study, in which the selection bias is inevitable. Second, the residents, fellows, and nursing teams were not the same for every procedure. There was no definite evidence to demonstrate whether these could have impacted the learning curve. Third, there was no clear definition of a "learning curve" for this procedure, and there were varying definitions of proficiency (25–27).

Conclusion

In conclusion, uniportal VATS lobectomy is a safe and reliable approach, and the surgeon with the help of postoperative review of videos is better able to improve deficiencies and can better refine the procedure. In the results of our study, with the help of video review, efficacy was reached after 35 cases, and proficiency was achieved after 53 cases.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of the Shanghai Chest Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

XC and QL conceived and designed the study. ZS and YY wrote the paper. CC performed data analysis. ZS and XC reviewed and

edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Clinicopathological and survival outcomes of 4L lymph node dissection in left lung adenocarcinoma and squamous cell carcinoma

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Background: Whether 4L lymph node dissection (LND) should be performed remains unclear and controversial. Prior studies have found that station 4L metastasis was not rare and that 4L LND may provide survival benefits. The objective of this study was to analyze the clinicopathological and survival outcomes of 4L LND from the perspective of histology.

Methods: This retrospective study included 74 patients with squamous cell carcinoma (SCC) and 84 patients diagnosed with lung adenocarcinoma (ADC) between January 2008 and October 2020. All patients underwent pulmonary resection with station 4L LND and were staged as T1-4N0-2M0. Clinicopathological features and survival outcomes were investigated based on histology. The study endpoints were disease-free survival (DFS) and overall survival (OS).

Results: The incidence rate of station 4L metastasis was 17.1% (27/158) in the entire cohort, with 8.1% in the SCC group, and 25.0% in the ADC group. No statistical differences in the 5-year DFS rates (67.1% *vs*. 61.7%, *P*=0.812) and 5-year OS rates (68.6% *vs*. 59.3%, *P*=0.100) were observed between the ADC group and the SCC group. Multivariate logistic analysis revealed that histology (SCC *vs*. ADC: OR, 0.185; 95% CI, 0.049–0.706; *P*=0.013) was independently associated with 4L metastasis. Multivariate survival analysis showed that the status of 4L metastasis was an independent factor for DFS (HR, 2.563; 95% CI, 1.282–5.123; *P*=0.008) but not for OS (HR, 1.597; 95% CI, 0.749–3.402; *P*=0.225).

Conclusion: Station 4L metastasis is not rare in left lung cancer. Patients with ADC have a greater predilection for station 4L metastasis and may benefit more from performing 4L LND.

KEYWORDS

adenocarcinoma, squamous cell carcinoma, station 4L metastasis, prognosis, lymph node dissection

1 Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small-cell lung cancer (NSCLC) being the most frequent subtype (1). Lobectomy with systemic nodal dissection (SND) remains the fundamental approach for operable NSCLC patients because of its vital role in accurate staging and its therapeutic and prognostic implications (2). The National Comprehensive Cancer Network (NCCN) guidelines require the evaluation of a minimum of three N2 stations. For left-sided cancers, stations 4L, 5, 6, 7, 8, and 9 should be dissected (3). Often, station 4L is not routinely sampled or dissected during lung cancer resection out of concern for recurrent laryngeal nerve, thoracic duct, and aortic arch injury because of its anatomic location (4). Previous studies have shown that station 4L lymph nodes play a crucial role in the left bronchial-recurrent lymph node (LN) chain, an essential lymphatic pathway of the left lung (5, 6). Recently, some studies have assessed the clinical significance of 4L lymph node dissection (4L LND) in left lung cancer and found that station 4L metastasis was not rare and that 4L LND may provide survival benefits (7–12). However, whether 4L LND should be resected remains unclear and controversial because most guidelines have no detailed requirements. Furthermore, complete 4L LND is technically challenging and may cause postoperative complications. Thus, many surgeons choose not to perform 4L LND even in high-volume thoracic centers.

To the best of our knowledge, no study has been conducted to identify the clinicopathological features and survival outcomes of 4L LND in left lung cancer from a histological perspective. Therefore, the purpose of this study was to investigate the differences in clinicopathological features and survival outcomes between adenocarcinoma (ADC) and squamous cell carcinoma (SCC) after 4L LND.

2 Patients and methods

2.1 Study population

We retrospectively reviewed the records of all patients who underwent left NSCLC surgery at our hospital between January 2008 and October 2020. The inclusion criteria were as follows: patients who underwent pulmonary resection (lobectomy or pneumonectomy) with SND or lymph node sampling, tumor pathology of ADC or SCC, and pathological stage of T1-4N0-2M0. The following patients were excluded: those with metastatic lung tumors or distant metastasis, those who underwent partial resection or segmentectomy, those who had no LN resection or unknown lymph node status (pNx), and those who received neoadjuvant therapy. Finally, 158 patients were enrolled in this study, and their clinicopathological characteristics were collected from the hospital electronic medical record system (Figure 1). All patients were staged according to the 8th edition of the American Joint Committee on Cancer (AJCC) lung cancer staging system (13). The study was approved by the Ethics Committee of Chinese People's Liberation Army General Hospital. All patients signed the informed consent.

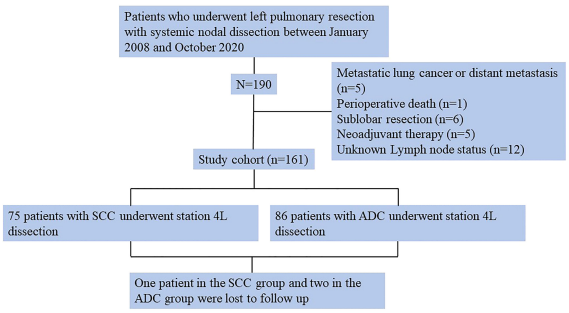

FIGURE 1
Study enrollment flow diagram.

2.2 Follow-up

Routine examinations after surgery were requested every 3 months for the first 2 years, and every 6 months thereafter for 5 years. After 5 years, the patients were assessed annually. The examinations included blood tumor marker testing, chest CT, ultrasound of the neck and abdomen, and head magnetic resonance imaging. Bone scans were performed in case of bone pain. Follow-up information was collected by official contact with patients or their relatives *via* telephone or from the hospital outpatient clinic records. The last follow-up was in May 2022. The primary endpoint was disease-free survival (DFS), which was defined as the time interval from the date of surgery to the first event (recurrence, metastasis, or NSCLC-related death) or last follow-up. Overall survival (OS) served as the secondary endpoint, defined as the time interval between the date of surgery and the date of death or the last follow-up. The DFS and OS were calculated in months.

2.3 Statistical analysis

All statistical analyses were performed using SPSS version 22 software (IBM Corporation, Armonk, NY, USA). Continuous variables are expressed as the mean with standard deviation as well as the median with a range of values. We used the Mann-Whitney U test to determine significant differences in continuous variables between the two groups. Every group with categorical variables is summarized with the frequency and percentage of the considered population, and statistical comparisons between the two groups were performed using the χ^2 test. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test was used to compare differences. The Cox proportional hazards model was applied in univariate analyses to determine the influence on patients' risk of death. Predictive variables were selected based on univariate models (P-value <0.05). A two-sided P<0.05 was considered statistically significant.

3 Results

3.1 Patients' clinical characteristics

Table 1 shows the clinical characteristics of the patients (n=158). A total of 74 (46.8%) and 84 (53.2%) patients were assigned to the SCC group and ADC group, respectively. Patients in the SCC group were older than those in the ADC group (P=0.001). Sixty-seven (90.5%) patients in the SCC group were male, whereas 38 (45.2%) male patients in the ADC group (P<0.001). The proportion of smoking history in the SCC group was significantly higher than that in the ADC group (P<0.001). Chest CT showed a central mass in 40 (54.1%) SCC cases and in 14 (16/7%) ADC patients (P<0.001). No differences were observed in terms of comorbidities, abnormality of tumor markers, tumor location, surgical procedure, surgical approach, lymph node dissection, postoperative complication, and adjuvant therapy.

3.2 Pathological findings

Comparisons of the pathological findings between the SCC group and the ADC group are shown in Table 2. Differences were observed in terms of tumor diameter (P=0.002), visceral pleural

TABLE 1 Clinical characteristics of patients in the squamous cell carcinoma and adenocarcinoma groups.

Variables	SCC	ADC	*P*
	N=74	N=84	
Age (years)	61.73 ± 9.51	57.55 ± 8.87	0.001
Sex			<0.001
Male	67(90.5%)	38(45.2%)	
Female	7(9.5%)	46(54.8%)	
Smoking history	56(75.7%)	38(45.2%)	<0.001
Comorbidities †	25(33.8%)	28(33.3%)	0.952
Abnormality of tumor markers ‡	8(10.8%)	17(20.2%)	0.105
Tumor location			0.348
Left upper lobe	44(59.5%)	56(66.7%)	
Left lower lobe	30(40.5%)	28(33.3%)	
Tumor area			<0.001
Central	40(54.1%)	14(16.7%)	
Peripheral	34(45.9%)	70(83.3%)	
Surgical procedure			0.809
Pneumonectomy	19(25.7%)	23(27.4%)	
Lobectomy	55(74.3%)	61(72.6%)	
Surgical approach			0.083
VATS	26(35.1%)	41(48.8%)	
Thoracotomy	48(64.9%)	43(51.2%)	
Lymph node dissection			
Stations	6.01 ± 0.94	6.23 ± 1.02	0.204
Numbers	16.41 ± 7.88	15.21 ± 7.22	0.371
Postoperative complications			
Hoarseness	5(6.8%)	4(4.8%)	0.735
Chylothorax	0	0	1.000
Adjuvant therapy	41(55.4%)	46(54.8%)	0.935

† indicates diabetes, hypertension, coronary disease, kidney failure, nervous system disease, and chronic obstructive pulmonary disease. ‡ indicates carcinoembryonic and squamous cell carcinoma antigens.
SCC, squamous cell carcinoma; ADC, adenocarcinoma; VATS, video-assisted thoracic surgery.

TABLE 2 Pathological findings in the squamous cell carcinoma and adenocarcinoma groups.

Variables	SCC	ADC	*P*
	N=74	N=84	
Tumor diameter(mm)	35(25.5, 50)	30(20, 45)	0.002
Visceral pleural invasion	19(25.7%)	42(50.0%)	0.002
Lymphovascular invasion	6(8.1%)	9(10.7%)	0.577
Ki-67 index (%)	50(32.5, 75)	25(10,50)	0.001
Cell differentiation			
Well	3(4.1%)	1(1.2%)	0.341
Moderate	39(52.7%)	47(56.0%)	0.682
Poor	32(43.2%)	36(42.9%)	0.961
pT stage			
T1	15(20.3%)	30(35.7%)	0.032
T2	41(55.4%)	44(52.4%)	0.704
T3	12(16.2%)	8(9.5%)	0.207
T4	6(8.1%)	2(2.4%)	0.148
pN stage			
N0	43(58.1%)	45(53.6%)	0.567
N1	24(32.4%)	31(36.9%)	0.556
N2	14(18.9%)	28(33.3%)	0.041
Station 4L metastasis	6(8.1%)	21(25.0%)	0.005
Station 5 metastasis	8 (10.8%)	18(21.4%)	0.072
Station 6 metastasis	1(1.4%)	5(6.0%)	0.131
Station 7 metastasis	6(8.1%)	5(6.0%)	0.595
Station 8 metastasis	0	1(1.2%)	1.000
Station 9 metastasis	0	3(3.6%)	0.101
Station 10 metastasis	18(24.3%)	18(21.4%)	0.665
Station 11 metastasis	13(17.6%)	14(16.7%)	0.881
Station 12 metastasis	2(2.7%)	2(2.4%)	1.000
pTNM stage			
I	29(39.2%)	36(42.9%)	0.640
II	24(32.4%)	17(20.2%)	0.080
III	21(28.4%)	31(36.9%)	0.255
IV	0	0	1.000

SCC, squamous cell carcinoma; ADC, adenocarcinoma.

(*P*=0.002), Ki-67 index (*P*=0.001), pT1 stage (*P*=0.032), and station 4L metastasis (*P*=0.005). The incidence of station 4L metastasis was 17.1% (27/158) in the entire cohort, with 8.1% in the SCC group and 25.0% in the ADC group. Two patients had skip station 4L metastasis in the ADC group and one patient had solitary station 4L metastasis in the SCC group. Four patients in the ADC group only had station 4L and 10 LN metastasis.

3.3 Risk factor analysis for 4L lymphatic metastasis

As shown in Table 3, the 4L metastasis was significantly correlated with abnormalities in tumor markers (*P*=0.031), histology (*P*=0.005), visceral pleural invasion (*P*<0.001), lymphovascular invasion (*P*=0.001), moderate and poor cell

TABLE 3 Univariate and multivariate analysis of the correlation between clinicopathological factors and station 4L metastasis.

Variables	Univariate Analysis			Multivariate Analysis		
	Station 4L Metastasis					
	positive	negative	*P*	OR	95% *CI*	*P*
Abnormality of tumor markers	8	17	0.031	0.623	0.069 to 5.650	0.674
Histology			0.005	3.778	1.432 to 0.706	0.007
SCC	6	68				
ADC	21	63				
Visceral pleural invasion	20	41	<0.001	4.284	0.573 to 32.011	0.156
Lymphovascular invasion	7	8	0.001	5.823	0.704 to 48.162	0.102
Station 5 metastasis	17	9	<0.001	20.567	5.520 to 76.6939	<0.001
Station 6 metastasis	4	2	0.008	0.297	0.013 to 6.741	0.446
Station 7 metastasis	5	6	0.010	11.479	0.812 to 162.330	0.071
Station 10 metastasis	17	19	<0.001	10.607	2.985 to 37.694	<0.001
Cell differentiation						
Well	0	4	1.000			
Moderate	7	79	0.001	0.000	NA	0.999
Poor	20	48	<0.001	6.080	1.655 to 22.340	0.007

SCC, squamous cell carcinoma; ADC, adenocarcinoma; OR, odds ratio; CI, confidence interval.

differentiation (P=0.001 and $P < 0.001$, respectively), and other stations (station 5, $P < 0.001$; station 6, P=0.008; station 7, P=0.010; station 10, P<0.001). These statistically significant factors were further analyzed by multivariate logistic analysis, and the results revealed that histology (SCC *vs.* ADC: OR, 0.185; 95% CI, 0.049–0.706; P=0.013), station 5 metastasis (OR, 20.567; 95% CI, 5.520–76.6939; P<0.001), station 10 metastasis (OR, 10.607; 95% CI, 2.985–37.694; P<0.001), and poor cell differentiation (OR, 6.080; 95% CI, 1.655–22.340; P =0.007) were independently associated with 4L LN metastasis.

3.4 Survival outcomes

The median follow-up time was 36 months (range: 1–152 months). Fifty-seven patients died and 54 had recurrence or metastasis at the last follow-up. In the ADC group, 20 patients died and 20 patients had recurrence or metastasis. The rates of local recurrence and distant metastasis were 28.6% (24/84) and 23.8% (20/84), respectively. In the SCC group, 30 patients died and 34 patients had recurrence or metastasis. The rates of local recurrence and distant metastasis were 32.4% (24/74) and 16.2% (12/74), respectively. The 5-year DFS rates were 67.1% and 61.7% in the ADC group and SCC group, respectively. The 5-year OS rates in the two groups were 68.6% and 59.3%, respectively. The log-rank test showed no statistical differences in DFS (P =0.812; Figure 2A) and OS (P =0.100; Figure 2B) between the two groups.

3.5 Analysis of survival factors

Some variables, such as sex, station 4L metastasis, station 7 metastasis, pT stage, and pTNM stage were significantly associated

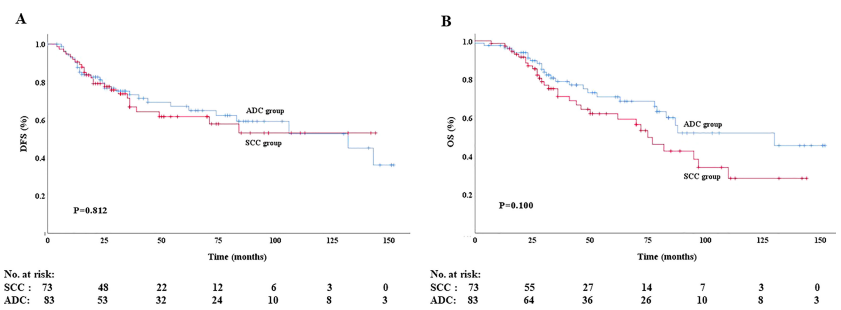

FIGURE 2
Disease-free survival **(A)** and overall survival **(B)** of patients in the ADC group and SCC group.

with DFS in the univariate analysis (P=0.042, P<0.001, P<0.001, P<0.001, and P<0.001, respectively). And the above five variables were also significantly associated with OS (P=0.003, P<0.001, P<0.001, P<0.001, and P<0.001, respectively). Additional multivariate analysis showed that status of 4L metastasis was an independent factor for DFS (HR, 2.563; 95% CI, 1.282–5.123; P=0.008), together with the status of station 7 LN metastasis, pT stage, and pTNM stage. Sex, status of station 7 LN metastasis, and pTNM stage were independent factors for OS (Table 4).

4 Discussion

Lymph node metastasis is a major metastatic pathway in NSCLC, which leads to poor prognosis. Thorough removal of lymph nodes is of great importance for precise stage assessment, prognosis prediction, and development of postoperative therapeutic strategies (14). The American College of Surgeons Oncology Group Z0030 trial suggested that all patients should undergo comprehensive lymph node evaluation (15). However, whether 4L LN should be resected remains unclear, as only the European Society of Thoracic Surgeons expert consensus guidelines and NCCN guidelines recommend 4L nodal evaluation for left-sided tumors, except in select circumstances (16) whereas others have no specific requirements (3, 17, 18). Wang et al. (7) raised the debate for a more comprehensive evaluation of the 4L station in patients with left-sided NSCLC.

In this study, we investigated the differences in clinicopathological features and survival outcomes between left-sided ADC and SCC after 4L LND. Our findings suggested that station 4L metastasis was not rare(17.1%), which is consistent with previous studies (7–12), and that patients with adenocarcinoma are more likely to have 4L lymph node metastasis. However, we found no difference in DFS and OS between the ADC and the SCC group. The status of station 4L metastasis was an independent factor for DFS, but not for OS.

A recent meta-analysis (12) and previous studies (7–11) had found that dissection of the 4L LN could significantly improve both the 5-year OS and DFS rates in patients with left-sided NSCLC. Specifically, Zhao et al. (9) found that patients with stage II, IIIA, and N2 disease in the 4L LND group had better survival outcomes than those without, whereas patients with stage I left-sided NSCLC had no survival benefit. Yang et al. (8) found that 4L LND only benefits patients with NSCLC in the left upper lobe, indicating that 4L LND may be unnecessary for left lower lobe tumors. From another perspective, our study found that patients with adenocarcinoma were more likely to have 4L lymph nodal metastasis than those with squamous cell carcinoma (25.0% *vs.* 8.1%; P=0.005), which may be the first report. We propose that it is of great necessity for left-sided adenocarcinoma to undergo 4L LND. To our knowledge, ADC develops and progresses quickly and has a poorer prognosis than SCC. However, no differences in DFS (P=0.812) and OS (P=0.100) between the ADC group and SCC group were observed in our cohort. We speculated that two main reasons may contribute to the contradictory results. First, dissection of 4L LN in the ADC group could yield more lymph nodes for examination and lead to more accurate node upstaging followed by adjuvant therapy, which might improve the DFS and OS. In our study, two patients (2.4%) had skip station 4L metastasis in the ADC group and one patient (1.4%) had single-station 4L metastasis in the SCC group, while four patients (4.8%) in the ADC group only had station 4L and 10 LN metastasis. This indicated that two patients were upstaged from N0 to N2 and four from N1 to N2 in the ADC group, and one patient was upstaged from N0 to N2 in the SCC group. Second, 4L LND could therapeutically clear lymph nodes with micrometastases, which might significantly reduce the risk of recurrence. Therefore, the poor prognosis in ADC patients may be compensated by the complete dissection of 4L LN and adjuvant treatment resulting from accurate node staging.

Fang et al. (11) demonstrated that cN2, stations 5 and 10 metastases were independent risk factors for station 4L metastasis, whereas Wang et al. (7) suggested that station 10 metastasis was independently associated with 4L metastasis. Our study revealed that histology, station 5 metastasis, station 10 metastasis, and poor cell differentiation were risk factors, implying that stations 5 and 10 metastases were common risk factors for station 4L metastasis. We speculate that this may be related to their transition zone (such as the aortopulmonary window and tracheobronchial angle) (19), which could explain the result that left upper lobe tumors had a greater preference for superior mediastinal LN metastasis than lower lobe tumors (20) and that 4L LND only benefits patients with NSCLC in the left upper lobe (8).

TABLE 4 Univariate and multivariate Cox regression analysis of prognostic factors in the SCC and ADC groups.

Predictor	Univariate Analysis				Multivariate Analysis			
	DFS		OS		DFS		OS	
	P	95% *CI*	*P*	95% *CI*	*P*	95% *CI*	*P*	95% *CI*
Sex	0.042	2.041 (1.026 to 4.061)	0.003	3.336 (1.511 to 7.365)	0.342	1.416 (0.691 to 2.901)	0.002	3.566 (1.607 to 7.917)
Station 4L metastasis	<0.001	3.870 (2.155 to 6.947)	<0.001	3.733 (2.116 to 6.585)	0.008	2.563 (1.282 to 5.123)	0.225	1.597 (0.749 to 3.402)-
Station 7 metastasis	<0.001	8.484 (3.876 to 18.569)	<0.001	NA	<0.001	7.138 (2.991 to 17.035)	0.001	4.631 (2.032 to 10.555)
pT stage	<0.001	2.122 (1.567 to 2.874)	<0.001	1.833 (1.372 to 2.449)	0.021	2.800 (1.168 to 6.708)	0.129	1.336 (0.919 to 1.941)-
pTNM stage	<0.001	3.087 (2.121 to 4.491)	<0.001	2.764 (1.956 to 3.905)	0.007	3.911 (1.464 to 10.450)	<0.001	0.144 (0.064 to 0.323)

DFS, disease-free survival; OS, overall survival. OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma.

Interestingly, our study suggested that the status of station 4L metastasis is an independent factor for DFS, but not for OS, while the status of station 7 metastasis and pTNM stage were both independent predictors for DFS and OS. We speculate that the following reason may contribute to this finding. Station 4L LN involvement changed the pathological stage and remodeled the postoperative regimens, which temporarily influenced the DFS. However, overall survival still needs to be elevated in locally advanced and metastatic NSCLC, even with the rapid progress in immunotherapy and targeted therapy (21, 22).

With the technical development of video-assisted thoracic surgery, the safety and thoroughness of 4L LND have been demonstrated in several studies (23, 24). The rate of hoarseness (5.7%, 9/158) caused by left recurrent laryngeal nerve injury in our study was acceptable and consistent with that in previous studies (9). Therefore, concern regarding hoarseness as a complication is not an obstacle in 4L LND, and the survival benefit should be taken into consideration and consensus regarding 4L LND should be reached.

Our study has several limitations. First, this single-center retrospective study inevitably had the possibility of uncontrolled confounding or selection bias, and we could not use the propensity score matching method to reduce them because of the relatively small number of enrolled patients with 4L LND left-sided tumors. This could be overcome by using a larger sample size and conducting a multicenter randomized clinical trial. Second, we focused on patients who received 4L LND without comparing them to patients who did not undergo 4L LND, as in some other studies. These findings should not be overinterpreted.

In conclusion, station 4L metastasis is not rare in left lung cancer. Patients with adenocarcinoma have a greater predilection for station 4L metastasis and may benefit more from performing 4L LND.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Chinese People's Liberation Army General Hospital. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

LS: Conceptualization, Methodology, Data curation, Writing-Original draft preparation. JG: Data curation, Writing-Review and Editing. HC: Formal analysis. WZ: Conceptualization, Writing-Review and Editing. YL: Conceptualization, Supervision, Writing-Reviewing and Editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Esketamine opioid-free intravenous anesthesia versus opioid intravenous anesthesia in spontaneous ventilation video-assisted thoracic surgery: a randomized controlled trial

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Background: Opioid-free anesthesia (OFA) provides adequate analgesia and can reduce postoperative opioid consumption, but its efficacy in spontaneous ventilation video-assisted thoracic surgery (SV-VATS) has not been demonstrated. We aimed to investigate the hypothesis that OFA could provide the same perioperative pain control as opioid anesthesia (OA), maintain safe and stable respiration and hemodynamics during surgery, and improve postoperative recovery.

Methods: Sixty eligible patients (OFA group: n=30; OA group: n=30) treated between September 15, 2022, and December 15, 2022, at The First Hospital of Guangzhou Medical University were included. They were randomized to receive standard balanced OFA with esketamine or OA with remifentanil combined with sufentanil. The primary outcome was the pain numeric rating score (NRS) at postoperative 24 h, and the secondary outcomes were intraoperative respiratory and hemodynamic data, opioid consumption, vasoactive drug dosage, and recovery in the post-anesthesia care unit and ward.

Results: There was no significant difference in the postoperative pain scores and recovery quality between the two groups. The OFA group had a significantly lower dose of phenylephrine (P=0.001) and a lower incidence of hypotension (P=0.004) during surgery. The OFA group resumed spontaneous respiration faster (P<0.001) and had a higher quality of lung collapse (P=0.02). However, the total doses of propofol and dexmetomidine were higher (P=0.03 and P=0.02), and the time to consciousness was longer (P=0.039) in the OFA group.

Conclusions: OFA provides the same level of postoperative pain control as OA, but it is more advantageous in maintaining circulatory and respiratory stability and improving the quality of pulmonary collapse in SV-VATS.

KEYWORDS

opioid-free anesthesia, opioid anesthesia, spontaneous ventilation, video-assisted thoracic surgery, mechanical ventilation

Introduction

Video-assisted thoracoscopic surgery (VATS) has become a minimally invasive choice for thoracotomy (1, 2). Traditional thoracoscopic surgery usually requires double-lumen endotracheal intubation and mechanical ventilation (MV), which is usually performed with the assistance of opioids and muscle relaxants (3). It is now feasible to perform spontaneous ventilation-VATS (SV-VATS) without intubation in the management of wedge resection (4, 5). SV-VATS is often combined with an intercostal nerve block. Intercostal nerve blocks can reduce the amount of opioids required and preserve spontaneous breathing to avoid respiratory failure due to respiratory-related muscle weakness after surgery (6). Current studies have shown that this technique can accelerate postoperative recovery, shorten hospital stay, and improve patient prognosis (7–9).

Previously, opioids were mostly required for analgesia in SV-VATS, which inevitably resulted in respiratory depression and deep breathing, increasing challenges in intraoperative respiratory management and surgical manipulation (10, 11). Esketamine is a non-opioid drug with a strong analgesic effect and the least possible effect on respiration and circulation. Therefore, it has high potential as an alternative intraoperative analgesic to opioids (12, 13). Studies have shown that opioids promote the production of inflammatory factors and tumor micrometastasis (7, 14, 15). Therefore, opioid-free anesthesia (OFA) has been attempted to explore its effectiveness for SV-VATS.

Several studies have shown that OFA can effectively control pain and reduce perioperative opioid consumption (11, 16). However, interpreting these studies is difficult because the definition of OFA varies between studies and institutions (17). Moreover, there is a lack of high-level clinical evidence on whether OFA is harmful or beneficial in SV-VATS procedures.

Therefore, we aimed to investigate the hypothesis that OFA could provide the same perioperative pain control as opioid anesthesia (OA), maintain the safety and stability of respiration and hemodynamics during surgery, and improve postoperative recovery.

Materials and methods

Study design

This study was a prospective, single-center, randomized controlled trial. All patients who underwent wedge resection for non-small-cell lung cancer (NSCLC) in the First Affiliated Hospital of Guangzhou Medical University from September 15, 2022, to December 15, 2022, and satisfied the inclusion and exclusion criteria were included. The study was conducted in accordance with the Helsinki Declaration (revised in 2013). The research scheme and methods were reviewed by the Ethics Committee (2020–69). Before inclusion in the study, all participating patients provided written informed consent.

Patients

Participants were screened, approached, and recruited by study staff, who evaluated patient eligibility.

The inclusion criteria were age between 18 and 64 years, thoracoscopic resection for NSCLC, single or multiple wedge resections, an American Society of Anesthesiologists score of I–II, a body mass index of 16–25 kg/m^2, and generally normal cardiopulmonary and other vital organ function indicating the patient could tolerate surgery.

The exclusion criteria were a history of previous thoracic surgery, uncontrolled hypertension, severe coronary artery disease, hepatic and renal insufficiency, hyperthyroidism, visual impairment, allergy to any of the drugs in this study, psychiatric disorders, severe cardiopulmonary impairment, history of chronic pain, or regular opioid use.

Elimination criteria were intraoperative blood loss >15% of the expected circulatory volume, thoracoscopy transferring to thoracotomy, intubation, failure to cooperate, or loss to follow-up.

Randomization and interventions

Patients were randomized in a 1:1 ratio to either the opioid-free group or the opioid group. Randomization was centralized using the SPSS25 random number generator, and each patient was given a unique randomization number (patient code), using sealed opaque envelopes to reveal the treatment arm on the morning of surgery. Each enrolled patient was grouped in the operating room on the day of surgery, and a designated anesthesiologist performed anesthesia management and intraoperative data collection. The surgeons were blinded to the group allocation of the patients. Postoperative follow-up was performed by study personnel who were trained but not involved in patient care.

Interventions

Opioid-free anesthesia group

Anesthesia was induced with dexmedetomidine (0.5 μg/kg for 15 minutes), target-controlled infusion (TCI) of propofol (2–3.5 μg/ml), and intravenous infusion of midazolam (0.05 mg/kg), esketamine (0.5 mg/kg), cisatracurium (0.05 mg/kg), and atropine (0.005 mg/kg). During maintenance of anesthesia, TCI dosages of propofol, esketamine, and dexmedetomidine were 1.5–4 μg/ml, 0.2–0.5 mg/kg/h, and 0.5–1.0 μg/kg/h, respectively. Dexmedetomidine was stopped directly after thoracic closure, and propofol and esketamine were stopped at the end of the procedure.

Opioid anesthesia group

Anesthesia was induced with dexmedetomidine (0.5 μg/kg for 15 minutes), TCI of propofol (2–3.5 μg/ml), and intravenous infusion of midazolam (0.05 mg/kg), sufentanil (0.2 μg/kg), cisatracurium (0.05 mg/kg), and atropine (0.005 mg/kg). During maintenance of anesthesia, TCI of propofol, remifentanil, and dexmedetomidine were administered at 1.5–4 μg/ml, 0.03–0.08 μg/kg/h, and 0.5–1.0 μg/kg/h, respectively. Dexmedetomidine was stopped directly after the pleural cavity closure, and propofol and remifentanil were stopped at the end of the operation.

Patients in both groups did not inhale volatile anesthetics and received betamethasone 5 mg plus ropivacaine 75 mg diluted to 20 ml for intercostal nerve block, of which 2 ml was injected into each intercostal area above and below the adjacent incision. Five ml of 1% lidocaine was used for vagal nerve block on the surgical side to reduce choking and maintain spontaneous breathing during pulmonary traction.

A third-generation double-tube laryngeal mask airway (LMA) was used for ventilation management. In both groups, if spontaneous breathing was not fully restored after anesthesia, manual ventilation or synchronized intermittent mandatory ventilation (SIMV) was used when the oxygen saturation was less than 94% or the $PaCO_2$ was more than 80 mmHg. The tidal volume in SIMV mode was set to 3–5 ml/kg, the peak airway pressure did not exceed 9 mmHg, and the frequency was 12–15 times/min to avoid the dilation of collapsed lungs due to excessive tidal volume. A bispectral index sensor (BIS) was maintained between 45 and 60 during the operation. Dopamine or phenylephrine was administered and recorded when the intraoperative blood pressure decreased to less than 20% of the baseline average. After the operation, the patient was transferred to the post-anesthesia care unit (PACU), and the patient could be sent back to the ward after meeting the departure requirements of the PACU (Supplementary Table 1).

Postoperatively, patients in both groups received oral imrecoxib 100 mg twice daily to maintain a resting pain numeric rating score (NRS) ≤ 3. If the resting pain NRS was > 3, tramadol 1 mg/kg was given intravenously as remedial analgesia.

Surgical process

Patients in both groups were operated on in the same manner. Patients were placed in the lateral position with the upper arm extended and secured on a hand rest. The operative procedure was performed with a single-port VATS, depending on the situation. The thoracoscope was inserted between the 5th and 6th ribs in the posterior axillary line with a soft incision protector over the thoracoscope to protect the skin, subcutaneous tissue, ribs, and pleura. Types of surgery included single or multiple wedge resections. The pulmonary expansion pressure on the operative side was 20 cmH_2O to detect air leakage in the lung tissue, and a 9F thoracic drainage tube was placed. The thoracic drainage tube was removed postoperatively after reexamination *via* chest radiograph if good lung expansion was observed and there was no obvious air leakage or active bleeding.

Primary outcome

The primary outcome was pain NRS evaluated at rest within 24 h after surgery.

Secondary outcomes

The secondary outcomes were intraoperative respiratory and circulatory parameters, opioids consumption, vasoactive drug dose, cardiovascular events, time to resume from spontaneous breathing, degree of lung collapse, incidence of body movements, arterial blood gas analysis, and the patient's overall recovery in the PACU and ward.

The Campos score criteria for lung collapse includes a classification for complete collapse (I), mostly collapsed (II), and partial or no collapse (III). Spontaneous respiratory recovery time was from the beginning of anesthesia induction to the resumption of spontaneous respiration during surgery. The criteria for nocturnal sleep time include a classification for more than 5 h of continuous sleep (I), continuous sleep time of 2–5 h (II), and less than 2 h of continuous sleep (III).

Sample size calculation and statistical analysis

The sample size was calculated based on the primary outcome. According to the pretest, the pain NRS at postoperative 24 h was 2.0 ± 1.3 in the OFA group and 3.0 ± 1.3 in the OA group. A sample size of 26 was deemed necessary to achieve a power of 80% with a type I error of 0.05. An additional 15% of participants were included to account for possible loss to follow-up. Therefore, the final sample size was 60 participants (30 in each group).

All primary and secondary data were analyzed according to the intention-to-treat principle. Normality was checked using the

Shapiro–Wilk test for continuous variables. We used an independent-sample t-test for continuous variables that were normally distributed and ANOVA for repeated measures or the Friedman test for non-normally distributed data. The χ^2 test or Fisher's exact test was used for categorical variables, if appropriate. Recovery-related indexes were drawn using the Kaplan–Meier curve and tested by the log-rank test. We used SPSS version 25.0 (IBM SPSS Inc., Armonk, NY) for all statistical analyses. GraphPad Prism 9.0 software (GraphPad Software Inc., La Jolla, CA) was used for drawing figures. PASS 15.0 (NCSS LLC, Kaysville, UT) was used to calculate the sample size.

Results

Patient characteristics

Sixty of the screened patients were included in the analysis (Figure 1). No patients were converted from SV-VATS to MV-VATS. The demographic and clinical characteristics of the two groups were similar (Table 1). The intraoperative doses of sufentanil and remifentanil in the control group were 7.5 ± 2.4 μg and 259.7 ± 91.7 μg, respectively. Patients in the OFA group did not receive sufentanil or any other opioids during induction or surgery. Patients in the OFA group had an esketamine dose of 57.9 ± 11.9 mg, with higher doses of propofol (489.7 ± 113.1 mg *vs.* 417.7 ± 137.1 mg, P=0.03) and dexmedetomidine (54.4 ± 50.7 μg *vs.* 43.0 ± 15.7 μg, P=0.02).

Regarding intraoperative cardiovascular events, one case of hypertension occurred in each group, but the incidence of hypotension (P=0.004) and the intraoperative dose of phenylephrine (P=0.001) were significantly higher in the opioid group than in the opioid-free group. The details of the intraoperative data are summarized in Table 2.

Primary outcome

Time significantly affected the pain score (P<0.001). Comparison within groups showed that the NRS at 6 h (P<0.001) and 24 h (P<0.05) was higher than NRS 2 h after surgery. The NRS was higher at 6 h than at 24 h after surgery (P<0.01), but the NRS was not significant between the groups (Table 3).

Secondary outcomes

In the comparison of intraoperative hemodynamics between the two groups, heart rate, diastolic blood pressure, and BIS values at T2, heart rate at T3, and BIS values at T5 were significantly higher in the OFA group than in the OA group (Figure 2, P<0.05). There were no significant differences in heart rate, diastolic blood pressure, and BIS values at any other observation periods. There were no significant differences in systolic blood pressure and oxyhemoglobin saturation at T1 to T8. The spontaneous respiratory rate was significantly faster in the OFA group than in the OA group both in wedge resection and after closing the pleura (P<0.001), but with no significant difference in tidal volume between the two groups (Table 4).

There were no significant differences in the indexes of arterial blood gas analysis at 5 min after anesthesia, immediately after wedge resection, and 5 min after removal of the laryngeal mask, but the oxygenation index was higher in the OFA group than in the OA group immediately after wedge resection (P=0.018). The arterial partial pressure of carbon dioxide was higher than 80 mmHg in three patients (10.0%) in the OA group and seven patients (23.3%) in the OFA group, but the oxygen saturation of the patients was maintained above 94%, and these individuals received SIMV-assisted ventilation (Table 5).

The levels of intraoperative lung collapse were higher (P=0.02), and the time of resumption of spontaneous breathing was shorter (P=0.001) in the OFA group than in the OA group. There was no

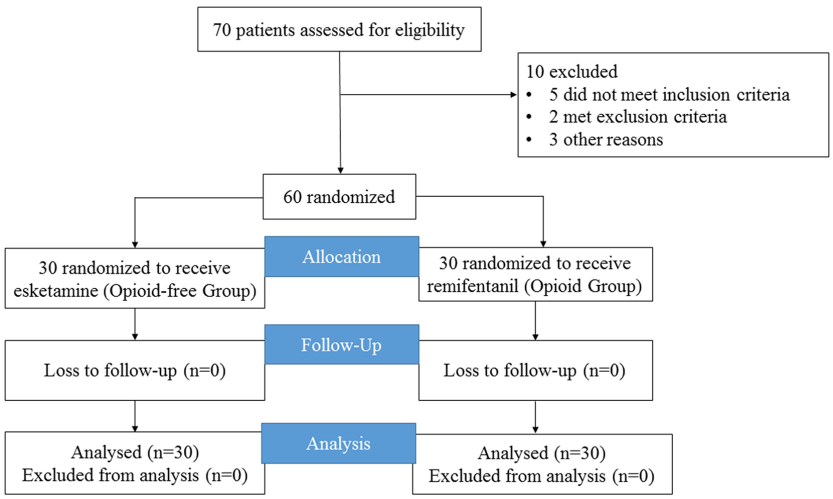

FIGURE 1
Flowchart of participants.

TABLE 1 Characteristics of the patients at baseline.

Characteristic	OA group (n=30)	OFA group (n=30)	*P*-value
Age (years)	48.4 ± 9.3	44.6 ± 6.7	0.07
Gender, n (%)			0.79
Male	11 (36.7)	12 (40.0)	
Female	19 (63.3)	18 (60.0)	
Weight (kg)	58.0 ± 6.9	58.0 ± 8.4	0.96
Body mass index, kg/m^2	22.6 ± 1.9	21.6 ± 2.4	0.08
ASA physical status*			0.75
I	6	7	
II	24	23	
center ventricular ejection fraction (%)	70.3 ± 5.3	69.4 ± 5.5	0.52
FEV1/FEV □	94.9 ± 10.5	99.7 ± 9.1	0.06
T stage, n (%)			0.72
T0	4 (13.3)	3 (10.0)	
Tis	2 (6.7)	3 (10.0)	
T1mi	19 (63.3)	22 (73.3)	
T1	5 (16.7)	2 (6.7)	
N stage			1
0	30 (100)	30 (100)	
1	0	0	
M stage			1
0	30 (100)	30 (100)	
1	0	0	
Lymphadenectomy	3 (10.0)	4 (13.3)	1

significant difference in cases of intraoperative somatic motion between the two groups.

In the PACU, the time to consciousness was significantly longer in the OFA group (P=0.039). There were no significant differences in the comparison of the occurrence of dizziness, cognitive dysfunction, pneumonia, pulmonary atelectasis, and duration of nocturnal sleep on the first and second postoperative days between the two groups (P>0.05) (Table 6). Remedial analgesia also showed no difference between the two groups (P>0.05) (Table 7).

No significant differences were observed regarding postoperative recovery between the two groups, including anal venting times (14.2 *vs.* 13.5 h, P=0.19) (Figure 3A), postoperative ambulation (P=0.61) (Figure 3B), feeding times (P=0.53) (Figure 3C), chest tube duration (P=0.24) (Figure 3D), and hospitalization (P=0.17) (Figure 3E).

Discussion

In this single-center randomized trial, compared with OA, OFA demonstrated similar pain control in the postoperative period. Moreover, it had more stable hemodynamics. The incidence of hypotension was lower, and the use of phenylephrine was significantly reduced. The quality of pulmonary collapse was better, and the time of resumption of spontaneous respiration was significantly shortened with OFA compared to OA. A higher oxygenation index was observed in the OFA group after wedge resection, possibly due to the mild respiratory excitatory and bronchodilatory effects of esketamine. However, in the OFA group, the intraoperative doses of propofol and dexmetomidine were significantly increased, and the recovery time in the PACU was significantly prolonged. There was no significant difference in postoperative complications and rehabilitation between the two groups.

Traditionally, VATS was performed by double-lumen endotracheal intubation for one-lung ventilation. Although endobronchial intubation allows for lung collapse on the side of the operation and gives the surgeon good maneuvering space, it is associated with complications, such as sore throat and hoarseness (8, 18). MV can also cause or aggravate volutrauma, barotrauma, atelectrauma, and biotrauma (19, 20). The application of SV-VATS has been proven in various thoracic surgeries, such as lobectomy,

TABLE 2 Intraoperative data.

Variable	OA group (n=30)	OFA group (n=30)	*P*-value
Dose of anesthetic drugs			
Propofol, mg	417.7 ± 137.1	489.7 ± 113.1	0.03*
Esketamine, mg	0	57.9 ± 11.9	
Remifentanil, μg	259.7 ± 91.7	0	
Sufentanil, μg	7.5 ± 2.4	0	
Dexmedetomidine, μg	43.0 ± 15.7	54.4 ± 50.7	0.02*
Dose of cisatracurium, mg	3.3 ± 1.1	3.6 ± 1.2	0.29
Vasoactive drugs			
Atropine, mg	0.4 ± 0.1	0.3 ± 0.2	0.07
Dopamine, mg	2.4 ± 6.2	0.20 ± 0.6	0.06
Phenylephrine, μg	152.7 ± 183.8	30.0 ± 61.0	0.001**
Hypertension △, n(%)	1 (3.3)	1 (3.3)	1
Hypotension ▽, n(%)	20 (66.7)	9 (30.0)	0.004**
Bradycardia ○, n(%)	7 (23.3)	1 (3.3)	0.06
Duration of surgery, min	56.3 ± 32.9	63.0 ± 29.9	0.42
Duration of anesthesia, min	91.8 ± 40.4	100.0 ± 38.2	0.42
Infusion volume, ml	546.7 ± 130.6	654.3 ± 281.3	0.06
Blood loss, ml	5.4 ± 2.8	9.1 ± 17.5	0.27

The data are presented as means ± SD. *P<0.05, **P<0.01.
△Hypertension was defined as the mean arterial blood pressure higher than 90 mmHg. ▽Hypotension was defined.
as mean arterial blood pressure lower than 65 mmHg. ○Heart rate less than 50 beats/min.

wedge resection, and tracheal carina reconstruction (4, 5, 7, 9). Spontaneous breathing in thoracic surgery can avoid the complications caused by tracheal intubation and lung injury induced by MV, even lead to residual relaxation (9, 21, 22). Intraoperative regional anesthesia can significantly reduce the dosage of opioids, which is important given that opioids have been proven to demonstrate tumor-promoting activity *in vitro* and accelerate tumor progression through immunosuppression, angiogenesis, and tumor cell migration (23). Previous clinical studies have confirmed that SV-VATS can lead to better survival outcomes than MV in invasive NSCLC (24). Moreover, a number of clinical studies have demonstrated that this method of anesthesia can promote rapid postoperative recovery (8, 22). Whether OFA in spontaneous breathing thoracoscopic surgery can bring more benefits to patients with NSCLC was the key point in that study.

SV-VATS still requires opioid drugs such as remifentanil, but OFA completely avoids the use of opioids during surgery. In this study, the postoperative scores of NRS were less than 3 in the two groups. The main reason may be that the two groups used long-acting hormone mixed with ropivacaine for intercostal nerve block, and some studies have shown that long-acting hormone can significantly prolong the time of analgesia (25–27). No significant differences were observed in NRS scores and rescue analgesia rates between the two groups at the same time after surgery. The pain scores were consistent with a recent meta-analysis by D'Amico that found no difference in pain scores between OFA and OA at 24 h after thoracic surgery (MD -1.69 [-3.82,0.43]; P = 0.12) (28). The NRS was the highest at 6 h after surgery due to the weakening of the analgesic effect of the intercostal nerve block and the stimulation of the pleura by the thoracic drainage tube. After the chest tube was removed 24 h after surgery, the degree of pain reduced, and the pain score was lower than that at 6 h after surgery, improving comfort and facilitating the postoperative lung rehabilitation training. Many regional nerve block methods can provide postoperative analgesia in thoracic surgery, such as epidural nerve block, thoracic paravertebral nerve block, and anterior serratus block. However, surgeons have also advocated intercostal nerve block, and the injection is performed by thoracic surgeons under direct thoracoscopic view, making it easy to operate and providing effective treatment. Therefore, regional nerve block was still used

TABLE 3 Resting numerical rating scale.

Variable	2h	6h	24h	Total
OA group (n=30)	0.9 ± 0.8	1.7 ± 0.9	1.2 ± 0.7	1.3± 0.13
OFA group (n=30)	1.0 ± 1.4	1.8 ± 1.2	1.4 ± 1.1	1.4 ± 0.13
Total	0.95 ± 0.14	1.73 ± 0.14***	1.30 ± 0.12*$^{\theta\theta}$	

The data are presented as mean ± standard deviation. Comparison with 2 hours after operation.
*P<0.05, ***P<0.001. Comparison with 6 hours after operation, $^{\theta\theta}$P<0.01.

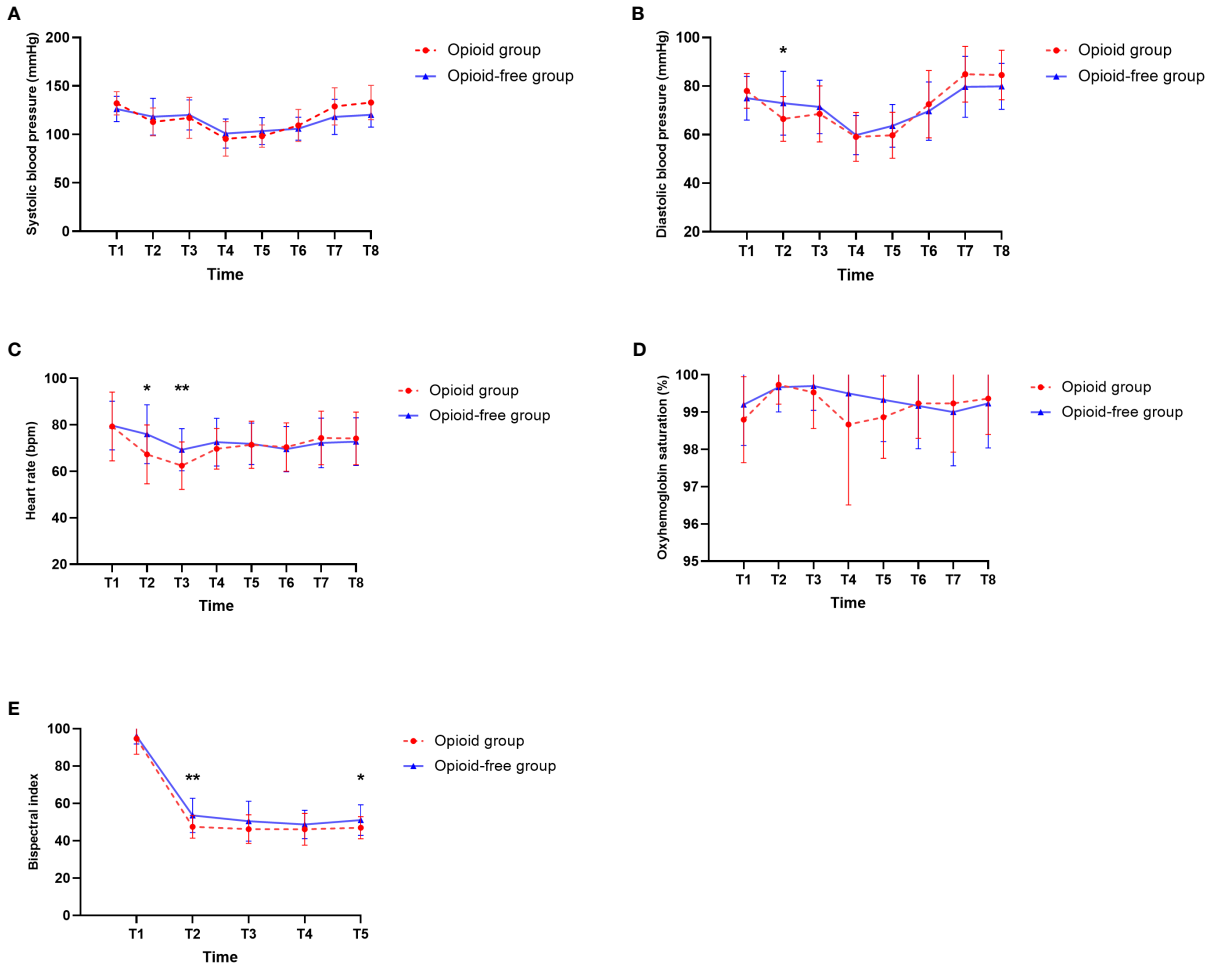

FIGURE 2
Intraoperative hemodynamic data, anesthetic depth. **(A)** Systolic blood pressure. **(B)** Diastolic blood pressure. **(C)** Heart rate. **(D)** Oxyhemoglobin saturation. **(E)** Bispectral index. T1, Baseline. T2, After the insertion of the laryngeal mask. T3, At the time of incision. T4, During the wedge resection. T5, At the end of surgery. T6, After transfer to PACU. T7, Immediately after removal of the laryngeal mask. T8, When ready to leave the PACU. *P<0.05, **P<0.01.

the intercostal nerve block method in this study. Esketamine demonstrates quasi-sympathetic activity in pharmacodynamics, and blood pressure decreases significantly after intercostal nerve block in the control group. The possible reason is that the local anesthetic solution blocks the sympathetic nerve along the parietal pleura, leading to decreased blood pressure. It is precisely because of the excitatory effect of esketamine on the circulatory system that the hemodynamics in the opioid-free group was more stable, the incidence of hypotension was reduced, and the amount of phenylephrine used during surgery was also reduced. It was

TABLE 4 Intraoperative ventilation characteristics.

Variable	OA group (n=30)	OFA group (n=30)	*P*-value
In wedge resection			
Spontaneous breathing rate (times/min)	7.5 ± 5.8	15.0 ± 4.5	<0.001***
Tidal volume (ml)	124.7 ± 94.9	147.7 ± 61.6	0.27
After closing pleura			
Spontaneous breathing rate (times/min)	12.6 ± 2.9	17.5 ± 3.6	<0.001***
Tidal volume (ml)	240.8 ± 99.5	233.6 ± 57.0	0.73

The data are presented as mean ± standard deviation or n (%). ***P<0.001.

TABLE 5 Intraoperative arterial blood gas indicators.

Characteristic	OA group (n=30)	OFA group (n=30)	*P*-value
Oxygenation index (mm Hg)			
After anesthesia	453.8 ± 84.0	458.2 ± 102.6	0.86
Immediately after wedge resection	261.2 ± 119.5	326.8 ± 86.2	0.018*
After awake 5min	386.1 ± 197.2	412.9 ± 160.8	0.57
Oxygen saturation (%)			
After anesthesia	98.8 ± 1.1	99.2 ± 1.1	0.17
Immediately after wedge resection	98.7 ± 2.2	99.5 ± 0.9	0.05
After awake 5min	99.2 ± 0.9	99.0 ± 1.4	0.51
Arterial carbon dioxide tension (mm Hg)			
After anesthesia	44.4 ± 4.5	45.3 ± 7.6	0.59
Immediately after wedge resection	75.8 ± 46.8	71.7 ± 10.1	0.65
After awake 5min	47.2 ± 4.5	47.0 ± 4.4	0.87
Arterial carbon dioxide tension >80 mmHg, n(%)			0.17
Yes	3 (10.0)	7 (23.3)	
No	27 (90.0)	23 (76.7)	
pH			
After anesthesia	7.4 ± 0.03	7.4 ± 0.05	0.64
Immediately after wedge resection	7.2 ± 0.06	7.2 ± 0.07	0.67
After awake 5min	7.3 ± 0.03	7.3 ± 0.03	0.87

Values are presented as mean ± standard deviation or n (%). Percentages are calculated for the whole population. *P<0.05.

TABLE 6 Secondary outcome analyses.

Variable	OA group (n=30)	OFA group (n=30)	*P*-value
Campos score, n (%)			0.02*
I	17 (56.7)	26 (86.7)	
II	13 (43.3)	4 (13.3)	
III	0	0	
Time to resume from spontaneous breathing$^{\Psi}$, min	38.7 ± 13.7	24.1 ± 9.4	<0.001***
Body movement, n (%)	3 (10.0)	9 (30.0)	0.053
Time to consciousness in the PACU, min	23.6 ± 13.3	31.8 ± 16.8	0.039*
Length of stay in the PACU, min	74.5 ± 20.1	74.0 ± 22.5	0.92
Postoperative Day 1, n (%)			
Dizzy	0	1 (3.3)	1.00
Cognitive dysfunction	0	0	1.00
Pneumonia / Atelectasis	1 (3.3)	3 (10.0)	0.61
Nocturnal sleep time			0.19
I	2 (6.7)	5 (16.7)	
II	13 (43.3)	17 (56.7)	
III	15 (50.0)	8 (26.7)	
Postoperative Day 2, n (%)			
Dizzy	0	0	1.00
Cognitive dysfunction	0	0	1.00
Pneumonia / Atelectasis	1 (3.3)	0	1.00
Nocturnal sleep time			0.80
I	13 (43.3)	15 (50.0)	

(Continued)

TABLE 6 Continued

Variable	OA group (n=30)	OFA group (n=30)	*P*-value
II	17 (56.7)	15 (50.0)	
III	0	0	

[Ψ]Spontaneous respiratory recovery time was from the beginning of anesthesia induction to the resuming spontaneous respiration during operation.
The data are presented as mean ± standard deviation or n (%). *P<0.05, ***P<0.001.

TABLE 7 Postoperative salvage analgesia.

Time	OA group (n=30)	OFA group (n=30)	*P*-value
2h	0	2 (6.7)	0.49
6h	3 (10.0)	9 (30.0)	0.05
24h	5 (16.7)	5 (16.7)	1.00

The data are presented as mean ± standard deviation or n (%).

similar to the Forget study that found that ketamine had no significant effect on heart rate but significantly reduced blood pressure variability (29).

At present, most of the commonly used anesthetic drugs can reduce brain metabolism and inhibit brain electrical activity. Esketamine increases the metabolic rate of the brain and inhibits the activity of the cerebral cortex, but the activity of the subcortical structure is enhanced. Some patients have muscle tension, which was verified in this study, and there were higher BIS values in the OFA group than in the OA group. Before completing the intercostal nerve block under direct vision, we increased the infusion of propofol and esketamine to deepen the sedation and enhance analgesia. However, the incidence of intraoperative body movement in the OFA was higher than in the opioid group, possibly due to the sensory-motor separation of esketamine (30). The process of pulmonary collapse during surgery is divided into two main stages. The first stage is the period of rapid lung collapse, due to the opening of the pleural cavity, and the inherent elastic retraction force of the lung tissue promotes lung collapse. The second stage is the period of gas absorption in the lung, in which the residual gas in the lung is diffused and absorbed by itself. Esketamine has the effect of dilating bronchial smooth muscle and improving pulmonary compliance, which promotes gas expulsion in the lung. In addition, the excitatory effect of esketamine in the circulatory system can accelerate the heart rate and increase cardiac output. The increase of blood volume per unit time through the pulmonary circulation also benefits gas absorption in the lung, enhancing the quality of lung collapse in the OFA group. The recovery time in the PACU was significantly prolonged in the OFA group, similar to the results of several studies that found that opioid-sparing anesthesia prolongs the recovery time of patients and increases the dose of sedatives (17, 31). The rate of

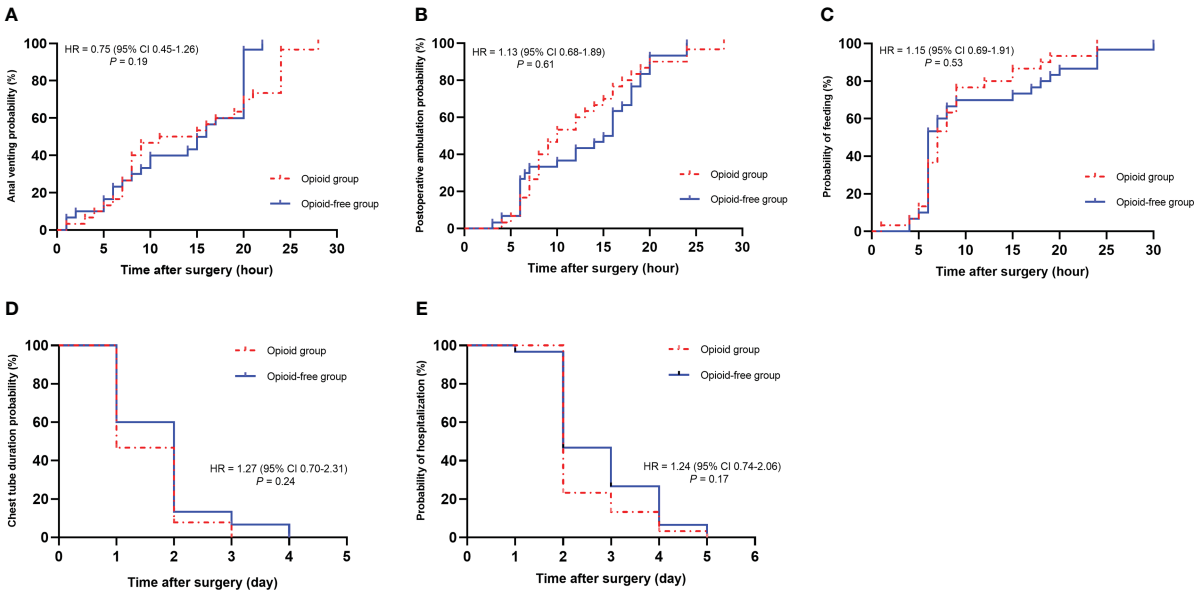

FIGURE 3
Recovery-related evaluation. **(A)**, Anal venting. **(B)**, Postoperative ambulation. **(C)**, Feeding times. **(D)**, Chest tube duration. **(E)**, Hospitalization.

continuous infusion of esketamine did not exceed 0.6 mg/kg/h during surgery, and the dosage of propofol and dexmedetomidine were significantly higher in the OFA group, which may delay awakening but not increase the total duration of stay in the PACU.

It is worth noting that, although the OFA strategy can avoid the slow down of gastrointestinal peristalsis caused by opioids such as sufentanil and remifentanil, this did not significantly shorten the anal exhaust time of patients. It was speculated that, first, both groups initiated regional nerve block to decrease the dosage of opioids during surgery. Second, the intraoperative analgesia was maintained by a rapidly metabolizing drug, such as remifentanil, in the opioid group, which would not weaken intestinal function after surgery. Finally, there was no significant difference in anal venting time between the two groups, which enabled the implementation of rapid rehabilitation strategies to encourage patients to eat and ambulate early. There was no significant difference in postoperative complications and recovery quality between the two groups.

There are several limitations to this study. First, the degree of analgesia is mainly determined by the change in hemodynamics and the values of BIS in SV-VATS. Thus, using an analgesia monitor would have provided a more objective measure. Second, to make the study more controllable, we mainly selected patients requiring single or multiple wedge resections, and there was no further comparison of other types of surgery. Because this type of thoracic surgery has less procedural heterogeneity, thereby minimizing the influence of differences in surgical procedures between surgeons, it can provide the best perspective for comparing these two different anesthetic modalities. Finally, this was a single-center study, and a larger sample of data is needed to confirm the findings regarding OFA.

Conclusion

Our findings indicated that compared with OA, OFA provides similar postoperative pain control and recovery quality, but the respiration and circulation were more stable, and the quality of lung collapse was higher. However, this increased the dosage of propofol and dexmedetomidine and prolonged the return to consciousness. Future clinical trials should aim to identify the most effective OFA regimen and pay attention to chronic pain and tumor recurrence after surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Guangzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conception and design: QF, LL, and LJ. Administrative support: LL. Provision of study materials or patients: QF, JHL, YZ, and XZ. Collection and assembly of data: QF, JHL, YZ, and XZ. Data analysis and interpretation: QF, QZ, and JHL. Manuscript writing: All authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1145953/full#supplementary-material

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Laparoscopic transduodenal ampullectomy: initial experience from a single center

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Background: Laparoscopic transduodenal ampullectomy (LTDA) is a function-preserving surgery for pre-malignant tumors of the ampulla of Vater (AoV). However, it is technically challenging, and only a few case reports of LTDA are available in the literature.

Methods: A total of 43 cases of pre-malignant tumors of AoV were operated in West China Hospital, Sichuan University between January 2017 and July 2022. Among these patients, 9 patients (group 1) underwent LTDA, 19 patients (group 2) underwent laparoscopic pancreaticoduodenectomy (LPD), and 15 patients (group 3) underwent open transduodenal ampullectomy (OTDA). Prospective collection and retrospective analysis of the demographic characteristics, intraoperative variables, and postoperative variables were carried out.

Results: The patients in the three groups were comparable in terms of sex, age, body mass index, tumor size, and preoperative blood tests. In comparison to the patients in group 2, the patients in group 1 were found to require less operative time (159.7 $\pm$ 47.5 min vs. 298.1 $\pm$ 62.6, $p < 0.01$) and suffered lower blood losses (23.3 $\pm$ 16.7 ml vs. 156.8 $\pm$ 112.1, $p = 0.002$) and complications. Moreover, the postoperative hospital stays (POHS) were significantly shorter for patients in group 1 (9.0 $\pm$ 5.3 days vs. 15.5 $\pm$ 7.3 days, $p = 0.04$). Compared to patients who underwent OTDA, the patients in LTDA suffered from less blood loss. The operative time and post-operative details were comparable.

Conclusion: Therefore, LTDA was found to be safe and feasible in the setting of pre-malignant tumors of AoV in well-selected patients. However, multidisciplinary preoperative planning is essential before the surgery.

KEYWORDS

laparoscopy, function-preserving surgery, ampullectomy, pancreaticoduodenectomy, ampulla of Vater

Introduction

Tumors of the ampulla of Vater (AoV) are relatively uncommon, accounting for only 5% of all cancers of the gastrointestinal system, with a prevalence of 0.04%–0.12% in cases of autopsy (1). There has been frequent identification of ampullary tumors owing to better imaging techniques and increasing endoscopic surveillance. Strategies for treating the tumors of AoV include endoscopic papillectomy (EP), transduodenal ampullectomy (TDA), and pancreaticoduodenectomy (PD) (2). PD is considered to be the standard treatment for cancers in AoV (3). However, the high degree of invasiveness associated with PD comes into question in the setting of pre-malignant lesions of the AoV. EP is considered to be a safer alternative for treating pre-malignant lesions of the AoV. Despite having lower rates of morbidity and mortality, EP is associated with a risk of incomplete resection (4). Compared with PD, TDA is a less invasive and function-preserving surgery. It has lower rates of peri-operative morbidity and mortality than PD and has been suggested as an alternative surgical treatment for ampullary adenoma (5). Laparoscopic transduodenal ampullectomy (LTDA) is more challenging than open surgery, and only a few case reports of LTDA are available in the literature (6–8). In this single-center study, we aim to evaluate the safety and effectiveness of LTDA for the treatment of ampullary tumors.

Materials and methods

A total of 118 cases of tumors of AoV were operated by a single surgeon (Prof. Peng) in West China Hospital, Sichuan University, Chengdu, China, between January 2017 and July 2022. Among these patients, 10 patients (group 1) underwent LTDA. One patient in group 1 converted to laparoscopic pancreaticoduodenectomy (LPD) was excluded from this study. LPD was performed on 19 patients (group 2) with benign or pre-malignant tumors of AoV. Eighty-nine cases of adenocarcinoma of AoV were excluded from this study. Fifteen cases of open transduodenal ampullectomy (OTDA) operated by other surgeons (group 3) were also included as a control group. Generally, multidisciplinary preoperative planning was routinely carried out for each patient. The final selection of the treatment modality was determined based on a consensus of the endoscope doctor, surgeon, pathologist, and patient. Surgery was considered in the case of malignant lesions, or tumors of AoV with intraductal involvement, or tumor size larger than 4 cm or other technical difficulty for endoscopic papillectomy. Each patient underwent endoscopic biopsy and endoscopic ultrasound examination preoperatively. For patients where the biopsy suggests malignancy or highly suspected malignancy, or for patients where the endoscopic ultrasound suggests intraductal involvement > 2 mm, PD was preferentially recommended. For patients with moderate to severe atypical hyperplasia and intraductal involvement > 2 mm, TDA was recommended. The decision to choose open surgery or laparoscopic surgery was a comprehensive decision made by the surgeon based on their surgical experience, technical proficiency, and a comprehensive assessment of the patient's condition. Demographic characteristics (age, gender, BMI, and pathological diagnosis), intraoperative variables (conversion, operative time, estimated blood loss, transfusion, pancreatic texture, and diameter of the main pancreatic duct), and postoperative variables (time for oral intake, postoperative hospital stay, and complications) were prospectively collected and retrospectively analyzed. Informed consent for participation was obtained from all the patients, and this study was ethically cleared by the Ethics Committee of Sichuan University.

Surgical techniques

Patient position and trocar distributions

Patients were placed in a supine position with two legs separated. The surgeon stood on the left side of the patient. The first surgeon stood on the right side of the patient. The scope assistant stood between the patient's two legs. The observing trocar was located at the inferior umbilicus. Four trocars were distributed symmetrically at the midclavicular line and anterior axillary line.

The operative procedure for LTDA

The operative procedures began with a careful exploration of the entire abdominal cavity. The hepatic flexure of the colon and mesocolon was fully taken down. A wide Kocher maneuver was performed, and the duodenum and pancreatic head were fully mobilized. Suturing of the anterior wall of the descending duodenum was carried out, and it was retracted to the left abdominal wall. The location of AoV was identified using palpation or intraoperative laparoscopic ultrasonography. A 3-cm longitudinal duodenotomy was performed, and the ampullary lesion was visualized and ligated for retraction. For lifting the lesion, physiological saline with noradrenaline (5 ml) was injected into the submucosa. The duodenal mucosa was incised at least 1 cm from the tumor to ensure a negative margin. The Wirsung duct was then identified, cut sharply with care to ensure an adequate margin, and a stent was placed into it. The reconstruction of the pancreatic duct to duodenum mucosa was carried out using 4-0 absorbable sutures. The mucosal defect at the distal side of AoV was also repaired using absorbable sutures. A cephalad dissection was continued, and the common bile duct was identified and opened. A 50-cm stent was placed into the common bile duct, and the other end of the stent remained outside the abdominal cavity. The bile juice was completely drained out to prevent bile juice contamination in the abdominal and duodenal cavities. The sphincteroplasty of the common bile duct to duodenum mucosa was carried out with 4-0 absorbable sutures at the 3, 6, and 9 o'clock positions. The specimen was then removed and sent for rapid frozen pathologic examination. Suturing of the common bile duct to duodenum mucosa was performed at the 12 o'clock position. While the stent in the pancreatic duct was preserved, the stent in the common bile duct was removed. The duodenal incision was then closed transversely with two-layer sutures, and two drainages were placed around the duodenal incision.

The operative procedure for LPD

The patient position and trocar distributions were the same as that for LTDA. The details of operative procedure and pancreaticojejunostomy were demonstrated in our previous study (9). Briefly, four layers of duct-to-mucosa pancreaticojejunostomy with an internal stent were performed. Running suturing was performed for the outer layer using 4-0 Prolene. A figure-eight suture plus running suturing was carried out for the inner layer by using 5-0 PDS suture.

Peri-operative management

Gastroscopy and biopsy of the lesion were performed for all patients. Endoscopic ultrasonography (EUS) was used to observe and assess the T factor and superficial bile or pancreatic duct progression. The nasogastric tube was removed on the first postoperative day (POD). Patients began the intake of water on the first POD, and the oral intake of liquid food was started to post the first passage of flatus. Computed tomography was performed on POD 3, and the drainages were removed on POD 5.

Statistical analyses

Statistical analyses were carried out using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA), and the numerical data were expressed as mean ±standard deviation. The chi-square test, or Fisher's exact test, was used to compare the categorical variables, and the independent *t*-test, or Mann–Whitney *U*-test, was used to compare the continuous variables. A value of $p < 0.05$ was considered statistically significant.

Results

The demographic characteristics of the patients are shown in Table 1. A total of 43 cases of surgery for pre-malignant tumor of AoV were included in this study, including 9 cases of LTDA, 15 cases of OTDA, and 19 cases of LPD. The median age of these patients was 62 years (range, 38 to 78 years). The age, sex, and BMI were comparable among the three groups.

The operative details and postoperative outcomes are shown in Tables 2, 3, respectively. One patient in group 1 was converted to LPD due to rapid frozen pathological examination indicating a malignant lesion. The patients required neither intraoperative blood transfusions nor the conversion to open surgery. Compared to the patients in group 2, the patients in group 1 required less operative time (159.7 ± 47.5 min vs. 298.1 ± 62.6 min, $p < 0.01$) and suffered from lesser blood loss (23.3 ±16.7 ml vs. 156.8 ±112.1 ml, $p = 0.002$). Compared to the patients in group 3, the patients in group 1 suffered from less blood loss (23.3 ± 16.7 ml vs. 123.7 ± 132.6 ml, $p = 0.03$). The operative time between two groups was comparable. All patients in this study achieved R0

TABLE 1 The demographic characteristics of patients.

Variables	LTDA	LPD	OTDA	p^1-value	p^2-value
No. of patients	9	19	15	–	
Age (years)	64.1 ± 13.2	63.1 ± 11.3	61.6 ± 9.5	0.76	0.34
Sex (F/M)	3/6	6/13	7/8	0.93	0.68
BMI (kg/m^2)	22.4 ± 2.4	21.6 ± 2.3	23.6 ± 1.8	0.66	0.78
Diagnosis				0.89	0.85
TVA	3	5	6		
Villous adenoma	2	3	2		
Tubular adenoma	1	2	2		
CIHGIN	1	1	2		
Stromal tumor	1	1	0		
NET	1	6	2		
P-J polypus	0	1	1		
Pre-HB	134.9 ± 18.8	129.8 ± 19.1	126.1 ± 30.5	0.23	0.15
Pre-TBIL	14.0 ± 6.8	29.5 ± 43.7	22.3 ± 13.2	0.12	0.44
Pre-DBIL	3.8 ± 2.1	21.6 ± 43.8	17.6 ± 15.8	0.32	0.51
CA19-9	19.1 ± 21.7	30.6 ± 39.9	22.6 ± 9.9	0.18	0.46
CEA	1.92 ± 1.4	4.1 ± 6.8	3.1 ± 1.6	0.27	0.61

LTDA, Laparoscopic transduodenal ampullectomy; LPD, Laparoscopic pancreaticoduodenectomy; OTDA, Open transduodenal ampullectomy; BMI, Body mass index; TVA, Tubulovillous adenoma; NET, Neuroendocrine tumor; CIHGIN, Chronic inflammation with high-grade intraepithelial neoplasia; P-J polypus, Peutz–Jeghers polypus; Pre-HB, Pre-operative hemoglobin; Pre-WBC, Pre-operative white blood cells; Pre-TBIL, Pre-operative total bilirubin; Pre-DBIL, Pre-operative direct bilirubin; CEA, Carcinoembryonic antigen; p^1-value, the p-value of comparison between group 1 and group 2; p^2-value, the p-value of comparison between group 1 and group 3.

TABLE 2 The operative outcomes.

Variables	LTDA	LPD	OTDA	p^1-value	p^2-value
No. of patients	9	19	15	–	–
OT (min)	159.7 ± 47.5	298.1 ± 62.6	138.2 ± 36.2	<0.01	0.37
EBL (ml)	23.3 ± 16.7	156.8 ± 112.1	123.7 ± 132.6	0.002	0.03
R0 resection	9, 100%	19, 100%	15, 100%	–	–
Depth of ductal invasion (mm)	1.5 ± 0.3	2.6 ± 0.8	1.5 ± 0.7	0.08	0.88
Conversion to open surgery (*n*, %)	0	0	–		–
Transfusion (*n*, %)	0	0	0	–	–
Tumor size (cm)	1.9 ± 0.5	2.0 ± 0.9	2.3 ± 0.9	0.87	0.65

LTDA, Laparoscopic transduodenal ampullectomy; LPD, Laparoscopic pancreaticoduodenectomy; OTDA, Open transduodenal ampullectomy; OT, Operative time; EBL, Estimated blood loss; p^1-value, the p-value of comparison between group 1 and group 2; p^2-value, the p-value of comparison between group 1 and group 3.

TABLE 3 The post-operative outcomes.

Variables	LTDA	LPD	OTDA	p^1-value	p^2-value
No. of patients	9	19	15	–	–
Time to oral intake (days)	1.3 ± 1.1	1.6 ± 0.8	2.8 ± 0.9	0.42	0.02
POHS (days)	9.0 ± 5.3	15.5 ± 7.3	9.3 ± 6.9	0.04	0.34
Overall complications (*n*, %)	2, 22.2%	7, 36.8%	6, 40%	0.67	0.66
Clavien–Dindo ≥ III (*n*, %)	1, 11.1%	1, 5.3%	1, 6.7%	1.0	1.0
Re-operation (*n*, %)	0	1, 5.3%	1, 6.7%	–	–
Pancreatic fistula (*n*, %)				0.53	–
Grade B	0	2, 10.6%	0		
Grade C	0	1, 5.3%	0		
Bile leakage (*n*, %)	0	1, 5.3%	0	1.0	–
DGE (*n*, %)	1, 11.1%	1, 5.3%	2, 13.4%	1.0	1.0
Abdominal bleeding (*n*, %)	0	1, 5.3%	0	1.0	–
Abdominal abscess (*n*, %)	0	1, 5.3%	2, 13.4%	1.0	0.51
Gastrointestinal bleeding (*n*, %)	1, 11.1%	0	1, 6.7%	0.32	1.0
90-day mortality	0	0	0	–	–

LTDA, Laparoscopic transduodenal ampullectomy; LPD, Laparoscopic pancreaticoduodenectomy; OTDA, Open transduodenal ampullectomy; POHS, Post-operative hospital stays; DGE, Delayed gastric emptying. p^1-value, the p-value of comparison between group 1 and group 2; p^2-value, the p-value of comparison between group 1 and group 3.

resection. Compared to that in group 2, the postoperative hospital stays (POHS) were significantly shorter for patients in group 1 (9.0 ± 5.3 days vs. 15.5 ± 7.3 days, p = 0.04). In terms of complications, one patient in group 1 and two patients in group 3 suffered from delayed gastric emptying, which was managed by conservative therapy. However, more patients in group 2 suffered from postoperative complications, including three cases of clinically relevant pancreatic fistula (grade B: 2 cases, grade C: 1 case), one case of delayed gastric emptying, one case of bile leakage, and one case of an abdominal abscess. One patient in group 1 reported gastrointestinal bleeding after discharge, which was managed by arterial-embolization therapy. One patient in group 2 discharged on POD 9 suffered from abdominal bleeding on the fourth day after discharge and required re-operations. The patient was finally discharged 32 days after the last operation. One patient in group 3 who suffered from abdominal abscess and gastrointestinal bleeding required re-operation. Another patient in group 3 who suffered from abdominal abscess required percutaneous drainage. The 90-day mortality of patients included in this study was 0. All patients included in this study were followed up by outpatient department visits or by telephonic assessment every 6 months and the median follow-up period was 17 months. No patients suffered from the recurrence of tumors during the follow-up period.

Discussion

The adenoma–carcinoma sequence is believed to be related to the malignant transformation of ampullary tumors, which is validated by histological observation of transitional stages from adenoma with mild, moderate, and severe cellular atypia to invasive carcinoma (10). Therefore, prompt recognition, diagnosis, and removal of these lesions have become the standard of care (11). There are three therapeutic strategies for tumors of AoV, including EP, TDA, and PD. For malignant ampullary tumors, PD is the standard treatment of choice. Apart from removing the primary tumor, PD can provide extensive lymphadenectomy, which is particularly important because nodal status is one of the most significant predictors of survival in patients with carcinoma of AoV (12). In the setting of benign ampullary lesions, EP was found to be equally effective with lower rates of morbidity and identical mortality when compared to surgical ampullectomies (SAs) (13). EP is now considered the gold standard for the treatment of benign tumors of AoV (14). According to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines for ampullary tumors, TDA should be considered when endoscopic resection is not feasible due to technicalities (e.g., diverticulum, size > 4 cm) or in the case of intraductal involvement (of >20 mm) (15). Multidisciplinary preoperative planning should be carried out before conducting the procedure (16).

Accurate preoperative diagnosis and staging of ampullary adenomatous lesions are critical for the prediction of prognosis and the determination of the most suitable therapeutic approach. Gastroscopy and biopsy of the lesion should be routinely performed in all patients. Performing preoperative endoscopic ultrasonography and/or abdominal magnetic resonance cholangiopancreatography (MRCP) is essential to confirm the diagnosis and depth of lesion invasion before performing TDA (15). However, the preoperative diagnostic accuracy is not very high, particularly in the diagnosis of adenoma (17). Sekine et al. reported an 83.3% preoperative diagnostic accuracy rate and stressed the importance of a complete excision biopsy (18). Intraoperative rapid frozen pathological examinations of an intact specimen are critical. All patients who underwent LTDA consented to the possibility of an LPD, with the intraoperative determination based on the frozen section results. One patient in this study was required to be converted to LPD.

Compared to open surgeries, laparoscopic surgeries can have several advantages, including earlier recovery, lower complications, and better cosmetic outcomes. However, it is challenging to perform transduodenal ampullectomy laparoscopically and only a few case reports are available in the literature. To the best of our knowledge, we reported the largest number of LTDA in the literature. The operative outcomes were also more favorable compared to that in the literature.

In open surgeries, the location of AoV can be easily identified by palpating the mass in the duodenal cavity. However, in laparoscopic approaches, the effectiveness of palpation is limited. Generally, the position of AOV is relatively fixed. In this study, the duodenum was opened at the lower third of the descending duodenum, and AoV was successfully located in the first two cases. However, AoV was not found when the duodenum was opened at the same position in the third patient. We were then forced to open the duodenum more widely, and finally, AoV was located at the beginning of the horizontal segment of the duodenum. In the process of searching for AoV, repeated clamping of the duodenal mucosa led to significant swelling of the duodenal mucosa, causing difficulties in performing ampullectomy. Furthermore, due to the duodenal incision being too large, it was also very difficult to close the duodenal incision. Therefore, it is critical to identify the accurate location of AoV. There are several strategies to locate the ampulla. A preoperative endoscopic retrograde biliary drainage catheter could assist in locating the AoV. However, the procedure may cause acute pancreatitis, which could interfere with ampullectomy. To locate the ampulla, Logarajah et al. performed a partial cystic ductotomy and fed a rubber tube through the cystic duct until it entered the duodenum (11). Intraoperative ultrasound is an atraumatic tool that can be used to locate the AoV. The precise opening of the duodenum can also reduce the difficulty of closing the duodenal incision.

It is very important to maintain good exposure and a clean surgical field for laparoscopic surgery. The mucosa of the duodenum is fragile and prone to bleeding. Physiological saline with noradrenaline was routinely injected into the submucosa of AoV, which can aid in lifting the lesion, thereby reducing mucosal bleeding. Ahn et al. did not carry out sphincteroplasty until they removed the tumor completely (6). However, we found that if the tumor was completely removed, the bile duct and pancreatic duct would shrink back into the parenchyma of the pancreas, increasing the difficulty of carrying out sphincteroplasty. Therefore, the pancreatic duct was first opened, and the common bile duct was retained for retraction. In the setting of the common bile duct to duodenum mucosa sphincteroplasty, the common bile duct was opened three-quarters circumferentially, retaining the cephalad common bile duct wall for retraction. Sphincteroplasty could then be carried out safely and speedily with good exposure.

Compared to LPD, the operative outcomes of LTDA were much more favorable, with significantly less operative time and lower blood losses. Patients with pre-malignant ampullary tumors often involve a soft pancreas with a small duct, increasing the risk of pancreatic fistula (19). Therefore, more patients in the PD group suffered from complications. Only one patient suffered from postoperative complications, which were managed by conservative therapy. The postoperative hospital stays were also significantly shorter in the LTDA group due to lower postoperative complications.

Local recurrence after ampullectomy is uncommon, but it does occur, even in benign adenomas. Logarajah et al. reported the development of recurrent adenomas in 2 out of 15 patients (13.3%) after OTDA (11). No patient suffered from tumor recurrence. However, the median follow-up period was only 17 months in this study, and longer follow-ups are required to establish a definite conclusion.

There are several limitations of this study. It is a retrospective study with a small sample size. A prospective, randomized controlled trial (RCT) comparing LTDA to LPD or EP can

provide valid pieces of evidence. However, an RCT is difficult to carry out in small numbers of patients undergoing these procedures. Therefore, the present study can substantially contribute to the available evidence despite its limitations.

Conclusion

In conclusion, LTDA is found to be a safe and feasible procedure in the setting of pre-malignant tumors of AoV in well-selected patients. Preoperative planning at the multidisciplinary level is essential before the surgery. Although these patients require continued follow-up, the benefits of organ preservation may outweigh the requirements of future endoscopic surveillance. However, high-volume, multi-center prospective studies are required to validate the findings of this study and to establish a definite conclusion.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee West China Hospital of Sichuan University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PG, HC, ZW, BP, and YC designed of the work; PG, HC, ZW and BP collected and analyzed the data for the work; PG, HC and ZW drafted the manuscript; BP and YC revised the manuscript. All authors published and agreed to be accountable for all aspects of the work. All authors approved the final manuscript.

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Conflict of interest

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

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