Review Article

Narrative review of non-intubated video-assisted thoracic surgery (Ni-VATS) for lung cancer: a focus on lobectomy

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Objective: To provide a narrative review of comparing Non-intubated video-assisted thoracic surgery (Ni-VATS) and intubated VATS (IVATS) lobectomy among patients with lung cancer.

Background: Ni-VATS is an evolving technique that provides a less invasive treatment option for patients undergoing thoracic surgery. However, few studies have investigated the role of Ni-VATS lobectomy in lung cancer.

Methods: We explored the current evidence on this topic by conducting a narrative review of studies on Ni-VATS lobectomy for lung cancer mainly using PubMed and Embase. The outcomes were summarized using descriptive statistics and vote counting based on the direction of effect. The risk of bias was assessed using the Jadad scale or the Newcastle-Ottawa Scale.

Conclusions: We retrieved five retrospective comparative cohort studies. Our review indicated that the non-intubated approach may provide faster postoperative recovery by ensuring faster oral intake, shorter chest tube duration, and a shorter hospital stay than intubated VATS. However, there is a paucity of data regarding the mid-term and long-term oncological outcomes. This study is also limited by a lack of consistency in the design of the individual studies and the retrospective nature of all reviewed articles. Based on current evidence, Ni-VATS lobectomy may represent an alternative for improving postoperative recovery among patients with lung cancer. Nonetheless, additional evidence is required to clarify the oncological impact of Ni-VATS lobectomy.

Keywords: Awake VATS; lung cancer; non-intubated VATS; video-assisted thoracic surgery (VATS)

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Background

Video-assisted thoracic surgery (VATS) lobectomy is now a standard treatment for lung cancer. Nonetheless, modifications to modern VATS, such as awake or non-intubated VATS (Ni-VATS), may allow thoracic surgeons to utilize a less invasive approach for cancer treatment. In 2004, Pompeo and colleagues first proposed that solitary lung nodules could be resected via awake VATS, with the goal of preventing intubation-related complications and ventilator-induced lung injury (1). Further, the successful use of awake VATS in major operations such as lobectomy has opened a new window for the treatment of lung cancer (2). Chen *et al.* first described the detailed techniques of Ni-

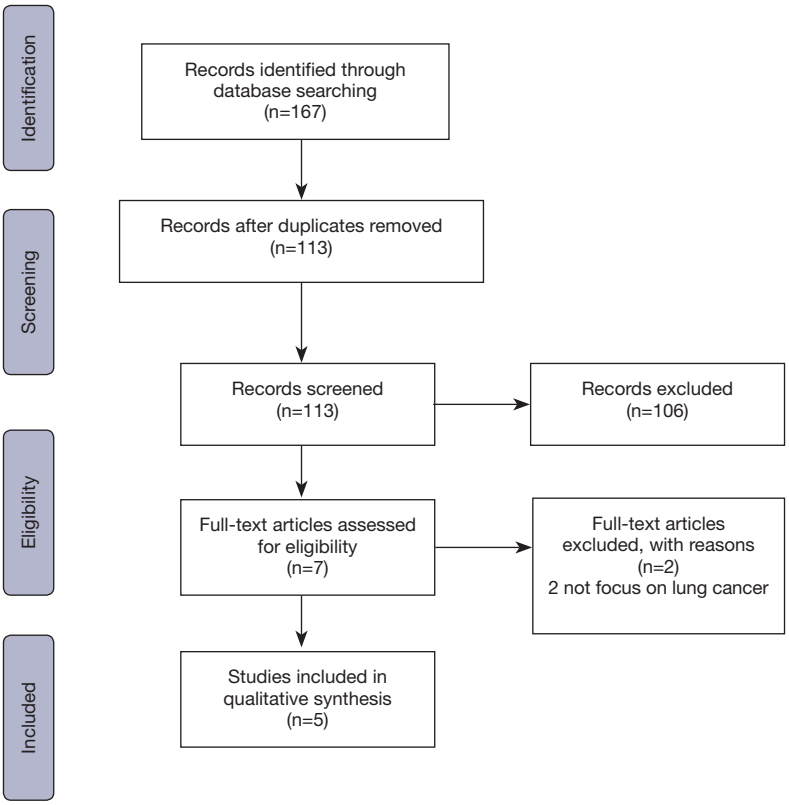

Figure 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram for the search and identification of included studies.

VATS lobectomy for lung cancer in 2011 (3). In the past few years, although awake VATS or Ni-VATS has been widely applied in minor thoracic surgeries such as pleural biopsy, wedge resection, lung volume reduction surgery, and bullectomy (4-6), reports concerning Ni-VATS lobectomy are much less common. To summarize current evidence and identify areas that warrant further study, we conducted a narrative review of eligible studies to compare perioperative outcomes and oncological outcomes of Ni-VATS and intubated VATS (IVATS) lobectomy among patients with lung cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/vats-21-20).

Methods

Search strategy and inclusion criteria

We performed a literature search for studies involving Ni-VATS lobectomy for lung cancer across PubMed, Embase, and the Cochrane library databases, from their earliest record to November 2020. The titles and abstracts were reviewed for relevant references. Only literature written in English or available in full was included. The search criteria were as follows: (video-assisted thoracic surgery OR VATS OR thoracoscopy OR thoracoscopic surgery) AND (nonintubated OR non-intubated OR awake) AND lobectomy. Only abstracts specifically addressing Ni-VATS as the main subject were enrolled for subsequent evaluation. Other inclusion criteria were as follows: (I) randomized controlled trials (RCTs) or observational studies comparing Ni-VATS with conventional IVATS in patients undergoing lobectomy for the treatment of lung cancer; (II) studies with sufficient data for extraction of main postoperative outcomes; and (III) the most recent study in a group among duplicate studies. We excluded (I) studies that did not compare Ni-VATS and IVATS; (II) studies in which patients in both groups underwent different surgical procedures; (III) studies in which patients were not diagnosed with lung cancer or did not undergo lobectomy; (IV) letters, editorials, case reports, expert opinions, and reviews; and (V)

Table 1 Summary of the retrieved studies investigating Ni-VATS and VATS lobectomy in patients with lung cancer

First author	Year	Study design	Diagnosis	Inclusion criteria	Exclusion criteria	Enrolled sample number		Quality assessment
						Ni-VATS	IVATS	
Chen	2011	Observational	Stage I or II NSCLC	Same as for IVATS: stage I or II peripheral NSCLC, tumors <6 cm, no evidence of chest wall/ diaphragm/main bronchus involvement	ASA >3, bleeding disorders, sleep apnea, or unfavorable airway or spinal anatomy	30	30	NOS: 6 stars
Wu	2013	Observational	Stage I or II NSCLC	>65 y/o, stage I or II NSCLC, without unfavorable airway or spinal anatomy, tumors <6 cm, no evidence of chest wall/diaphragm/ main bronchus involvement	Patients who underwent a thoracotomy or sublobar resection, those with stage III or IV cancer, and those who had received preoperative chemotherapy, radiotherapy, or both	36	48	NOS: 7 stars
Liu	2016	Observational	NSCLC	ASA ≤3, BMI <30, FEV1 ≥60% predicted, LVEF ≥50%, no coagulopathy	Combined with severe coronary heart disease, unstable asthma, history of thoracic surgery, history of tuberculosis or other diseases that could cause pleural adhesion or more pleural effusion and conversion from Ni-VATS to IVATS	116	116	NOS: 8 stars
AlGhamdi	2018	Observational	NSCLC	Stage I & II NSCLC, tumor size <6 cm, no evidence of bronchus involvement, and no regional or distantmetastasis.	BMI >30, bleeding diathesis, difficult airway, previous pulmonary resection, or cardiac dysfunction	30	30	NOS: 6 stars
Furák	2020	Observational	Stage IB-IIIB NSCLC	Stage IB-IIIB NSCLC and receipt of adjuvant chemotherapy after VATS	Suspicion of difficult intubation, full anti-coagulation, reflux disease, cardiac instability, or psychiatric disease	28	28	NOS: 6 stars

NIVATS, non-intubated video-assisted thoracic surgery; IVATS, intubated video-assisted thoracic surgery; NSCLC, non-small cell lung cancer; NOS, Newcastle-Ottawa Scale; ASA, American Society of Anesthesiologists score; BMI, body mass index; FEV1, forced expiratory volume in 1 second; LVEF, left ventricular ejection fraction.

studies from which relevant data could not be extracted.

Data extraction and assessment of risk of bias

Two authors assessed each retrieved article based on the eligibility criteria. When multiple studies contained overlapping data, the most informative study was included. Data were independently extracted by two authors onto a standardized data extraction sheet. The first authors, publication year, sample size, details of the Ni-VATS and IVATS approaches, and comparative outcomes were systematically recorded. The outcomes were summarized using descriptive statistics such as means and frequencies. Vote counting based on the direction of effect was also used for synthesis. The methodological quality of enrolled studies was evaluated using the Jadad scale for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies (7). The Jadad scale reflects randomization (2 points), blinding

Table 2 Comparison of anesthetic and surgical protocols used in the included studies

First author	Year	Ni-VATS anesthetic techniques				IVATS OLV technique	Surgical approach
		Analgesia	Sedation	Airway management	Vagal nerve block		
Chen	2011	TEA (lidocaine)	IV propofol + fentanyl/ Ramsey III	Oxygen face mask	Yes	DLC	3 port
Wu	2013	TEA (lidocaine)	IV propofol + fentanyl/ Ramsey III	Oxygen face mask	Yes	DLC	3 port
Liu	2016	TEA (lidocaine)	IV remifentanil + propofol	Nasopharyngeal airway, LMA, or oxygen mask	Yes	DLC	3 port
AlGhamdi	2018	ICNB (3rd–8th)	IV propofol + dexmedetomidine/BIS 40–60	Oxygen face mask	Yes	DLC	4 port
Furák	2020	ICNB (2nd to 5th, bupivacaine)	IV propofol/BIS 40–60	LMA	Yes	Not mentioned	Multiportal and uniportal VATS

Ni-VATS, non-intubated video-assisted thoracic surgery; IVATS, intubated video-assisted thoracic surgery; TEA, thoracic epidural analgesia; ICNB, intercostal nerve block; OLV, one-lung ventilation; DLC, double-lumen cannula; VATS, video-assisted thoracic surgery; LMA, laryngeal mask airway; BIS, bispectral index.

of the studies (2 points), and withdrawals (1 point). Scores range from 0 to 5, and a higher Jadad score indicates better methodological quality. The NOS contains three factors: participant selection, comparability of the study groups, and outcomes. NOS scores of 0–9 (allocated as stars) were assigned to each observational study.

Results

Characteristics of included articles

We retrieved 113 unique articles based on a review of their titles and abstracts; from these, seven articles were examined further (*Figure 1*). We excluded two studies that did not focus on lung cancer. Ultimately, the review included 502 patients from five retrospective cohort studies (*Table 1*) (3,8-11). Generally, in these studies, patients considered appropriate for Ni-VATS lobectomy met the same criteria required for intubated single-lung ventilation, including clinically early-stage lung cancer, tumors less than 6 cm, no evidence of chest wall/ diaphragm/main bronchus involvement, and American Society of Anesthesiologists score ≤3. One study by Wu *et al.* focused on geriatric patients with lung cancer and only included patients aged 65 years or older (9), while another study by Furák *et al.* included patients who had received adjuvant chemotherapy after VATS (10). Common exclusion criteria included expected pleural adhesion, unfavorable airway, and conditions inappropriate for thoracic epidural anesthesia (TEA) (e.g., unfavorable spinal anatomy and coagulopathy).

Anesthetic protocols of included studies

The anesthetic and surgical protocols of Ni-VATS varied among the study groups (*Table 2*) (3,8-11). In the non-intubated group, three studies applied TEA for regional analgesia and two studies used intercostal nerve blocks (ICNBs). Propofol infusion was used for sedation in all studies, with different adjuvants such as fentanyl, remifentanil, and dexmedetomidine. Four studies used oxygen face masks for breathing support, while two studies applied laryngeal mask airways (LMAs). All studies applied vagal nerve blocks for cough suppression. For the intubated group, four studies utilized double-lumen endotracheal tubes (DLTs) for single-lung ventilation and one study did not mention the type of tube used.

Perioperative outcomes of included studies

The results of perioperative assessments including anesthetic outcome, operative results, and postoperative recovery are summarized in *Table 3*. One study by Chen *et al.* (3) reported comparable induction duration between the

Table 3 Summary of outcomes for included studies

First author	Year	Anesthetic outcome			Operation results			Postop recovery				Oncological related outcome
		Induction duration	Conversion to intubation	Others	OP duration	Conversion to thoracotomy	Others	Chest tube duration	Complications	Hospital stay	Others	
Chen	2011	‡32.2 *vs.* 34.9 min, P=0.434	3 (10%)/ persistent hypoxemia, poor TEA pain control, bleeding	‡Comparable lowest SpO_2 and peak $ETCO_2$	‡161.9 *vs.* 161.3 min, P=0.955	‡3.3% *vs.* 3.3%, P=1.00	‡Comparable blood loss, and dissected LN number	‡3.6 *vs.* 5.0 d, P=0.085	‡10% *vs.* 33%/ P=0.057	‡5.9 *vs.* 7.1 d, P=0.078	†Ni-VATS had less sore throat, shorter NG tube insertion, and faster postop oral intake	NA
Wu	2013	†23.0 *vs.* 33.2 min, P=0.001	1 (2.8%)/ persistent hypoxemia	NI higher peak $ETCO_2$ 45.1 *vs.* 36.2 mmHg, P=0.013	‡184.6 *vs.* 212.6 min, P=0.334	‡0 *vs.* 0	‡Comparable blood loss and dissected LN number	NA	‡25% *vs.* 35%, P=0.489	‡6.7 *vs.* 7.2 d, P=0.31	NA	NA
Liu	2016	NA	9 in 128 (7.0%)	NA	‡177.8 *vs.* 182.0 min, P=0.508	‡0 *vs.* 0	‡Comparable blood loss (124.4 *vs.* 142.6 mL, P=0.613)	‡3.5 *vs.* 3.2 d, P=0.432	‡8.6% *vs.* 10.3 %, P=0.654	†7.4 *vs.* 8.6 d, P=0.035	†Ni-VATS less pleuraldrainage: 607.4 *vs.*766.7 mL, P=0.022, NI shorter postop fasting time (6.7*vs.* 12.3 h, P<0.001)	NA
AlGhamdi	2018	NA	1 (3.3%)/ dense adhesions and intraoperative bleeding	NA	‡130.9 *vs.* 146.0 min, P=0.144	NA	‡/§Comparable blood loss (82.3 *vs.* 78.3 mL, P=0.870); NI less LN dissection 12.6 *vs.* 18.0, P=0.003	‡5.6 *vs.* 5.4 d, P=0.943	‡6% *vs.* 6%, P=0.862	‡6.9 *vs.* 7.6 d, P=0.578		NA
Furák	2020	NA	NA	NA	†91 *vs.* 125 min, P<0.01	NA	NA	†2.12 *vs.* 4.33 d, P<0.01	†0% *vs.* 15.7%, P=0.027	NA		†NIVATS better compliance with adjuvant chemotherapy and less Gr. 1/2 chemotherapy-related toxicity and Gr. 4 neutropenia

†, NIVATS better; ‡, Ni-VATS and IVATS comparable; §, IVATS better. Comparative results are presented as "Ni-VATS" *vs.* "IVATS". OP, operation; NA, not available; SpO_2, oxyhemoglobin saturation by pulse oximetry; ETCO2, end-tidal CO2; LN, lymph node.

intubated and non-intubated groups, while another study (9) involving geriatric patients reported a shorter induction time in the non-intubated group (23.0 *vs.* 33.2 min; P=0.001). The available intraoperative physiological data were generally comparable between the two groups except for higher $PaCO_2$ without adverse effects noted in non-intubated geriatric patients (45.1 *vs.* 36.2 mmHg, P=0.013) in Wu *et al.*'s study (9). The conversion rate to intubation was between 2.8% and 10%, and the reasons for conversion included persistent hypoxemia or hypercapnia, significant mediastinal movement, bleeding, extensive pleural adhesions, and poor TEA pain control.

The operation duration was comparable in most studies, except for one study reporting shorter surgical duration in the non-intubated group (10). Blood loss was also comparable between the two groups in four studies (3,8,9,11). One study reported less lymph node dissection in the Ni-VATS group (8).

Two studies reported faster postoperative oral intake in non-intubated patients (3,11). Most postoperative recovery results were comparable between the two groups in all studies, except for the study by Furák *et al.* (10) that reported shorter chest tube duration (2.12 *vs.* 4.33 d; P<0.01) and fewer postoperative complications (0% *vs.* 15.7%; P=0.027) in the non-intubated group. In addition, Liu *et al.* (11) observed less pleural drainage and shorter hospital stays (7.4 *vs.* 8.5 d; P=0.035) among non-intubated patients. No postoperative mortality was reported in any of the included studies.

Oncological outcomes of Ni-VATS and IVATS

None of the studies compared mid-term or long-term oncological outcomes such as survival or recurrence between the two groups. Only one study by Furák and colleagues compared oncological treatment-related responses between non-intubated and intubated VATS (10). They retrospectively reviewed data for patients with stage IB-IIIB non-small-cell lung carcinoma (NSCLC) who had undergone non-intubated or intubated VATS lobectomy and received adjuvant chemotherapy. Their findings indicated that more non-intubated patients completed the planned chemotherapy protocol than intubated patients (92% *vs.* 71%, P=0.035). There was also a lower incidence of grade 1/2 toxicity (0% *vs.* 16%, P=0.03) and grade 4 neutropenia in the non-intubated group. They concluded that the non-intubated approach resulted in improved adjuvant chemotherapy compliance and lower toxicity rates after VATS lobectomy.

Discussion

In this review, we systematically explored current evidence concerning Ni-VATS and IVATS for lobectomy in patients with lung cancer. Five retrospective comparative cohort studies were included. The evidence shows that most perioperative outcomes were comparable between the non-intubated and intubated approaches. Some studies reported faster postoperative recovery in different aspects such as faster oral intake, shorter chest tube drainage duration, and shorter hospital stay in the non-intubated group. Only one study presented oncological treatment-related outcomes, reporting that a non-intubated approach may enhance compliance with adjuvant chemotherapy and decrease chemotherapy-related toxicity.

Patient selection for Ni-VATS lobectomy for lung cancer

There is no consensus regarding inclusion criteria specific for a non-intubated approach to VATS lobectomy. Although VATS lobectomy without tracheal intubation was first reported by Al-Abdullatief *et al.* in 2007 (2), the first study reporting detailed inclusion and exclusion criteria for Ni-VATS lobectomy was published by Chen *et al.* (3) in 2011. Subsequently, other studies generally followed their criteria, with some modifications (8-14). The reported inclusion criteria are generally the same as those for conventional IVATS lobectomy for lung cancer. However, exclusion criteria are more important when considering Ni-VATS lobectomy. Indeed, conditions that may increase the risk for conversion to tracheal intubation and the difficulty of conversion should be taken into account. For example, in a study by Hung *et al.* involving 1,025 patients who underwent Ni-VATS for lung tumor resections, the authors found that a BMI ≥ 25 kg/m^2 was a risk factor for conversion (15). Those with expected increases in the difficulty of operation, such as extended pleural effusion and coagulopathy, should also be excluded. However, some other feasibility studies have suggested that the non-intubated approach may not be contraindicated for some groups traditionally considered to be high-risk for IVATS, such as patients with impaired lung function (16) and geriatric patients (9).

Anesthetic protocols

In non-intubated VATS, endotracheal intubation and muscle relaxants are waived for thoracoscopic surgery. In addition, the anesthetic and operative protocols vary among different studies and institutes.

The common methods for achieving regional analgesia are TEA and ICNBs. Although TEA was used in initial studies, ICNB provides a simpler, safer, and more effective alternative for intraoperative pain control (17-20). Given the recent development of uniportal VATS that decreases postoperative pain (21,22), the role of TEA may be decreasing. Propofol is most commonly used for sedation, likely due to its fast induction, the ease with which the level of sedation can be altered, and its quick recovery (23). Opioids such as fentanyl or remifentanil are commonly combined with propofol to achieve better analgesia and sedation with a lower dosage, thereby decreasing side effects. Airway and breathing supports can be applied using an oxygen mask or LMA, although the latter may provide better oxygenation and positive pressure ventilation if needed (24,25) and may be a better approach for less experienced surgeons.

Feasibility and safety of Ni-VATS lobectomy for lung cancer

Ni-VATS was initially used in minor operations such as wedge resection for lung nodules or lung volume reduction surgery (1). Due to several concerns such as hypoxemia and hypercapnia induced by prolonged spontaneous single-lung ventilation, coughing induced during manipulation of proximal airways, and lung movement during delicate hilar dissection, it was not until 2011 that Chen and colleagues first reported the comparable safety and short-term results of Ni-VATS lobectomy for the treatment of early NSCLC (3). The studies included in this review also demonstrated the feasibility and safety of the Ni-VATS approach for lobectomy in patients with lung cancer. Induction time, operation time, intraoperative physiological data, and blood loss were similar in the intubated and non-intubated groups. Although one study reported higher peak hypercapnia in the geriatric non-intubated group, the authors believe that this was not clinically significant (9). Surgical techniques, such as the implementation of the single-port approach, have also evolved over time. The feasibility and satisfactory early postoperative outcomes of uniportal Ni-VATS lobectomy have also been reported in other noncomparative studies (13,26,27). Low rates of conversion to tracheal intubation were reported (range, 2.8–10%), and no conversion-related complications were observed. The risk of conversion may also be reduced with careful patient selection and preparation of the medical team, which should include experienced anesthesiologists and surgeons with prior technical practice in minor operations such as wedge resection (15).

Potential benefits of Ni-VATS lobectomy for lung cancer

General intubated anesthesia often causes gastrointestinal dysfunction and increases the risk of postoperative nausea and vomiting (28). This may explain the faster recovery of postoperative oral intake in the Ni-VATS lobectomy group in two studies (3,11). Given that other studies have reported positive findings such as less pleural drainage, fewer complications, and shorter hospital stay in the non-intubated group (10,11), our analysis suggests that non-intubated anesthesia enhances postoperative recovery in patients with lung cancer undergoing VATS lobectomy. Possible mechanisms include avoidance of the side effects of inhalational anesthetics, residual effects of muscle relaxants, possible injury due to endotracheal intubation, and positive pressure-related trauma (29,30). However, due to diversity in anesthetic protocols for Ni-VATS lobectomy, further studies are required to compare different drug choices and airway management techniques, in order to define the best protocol for a non-intubated approach.

Mid-term and long-term oncological outcomes

Since VATS lobectomy is still the standard treatment for lung cancer, the oncological outcomes of Ni-VATS lobectomy are of great importance. Although no perioperative mortality was observed in this review, we are also interested in mid-term and long-term oncological outcomes. Some studies hypothesized that Ni-VATS reduces ventilator-related stress and the need for opioids, which may preserve perioperative anticancer immunosurveillance (29,30). Others also observed a lower impact on postoperative immunological response in awake or Ni-VATS (31-34). In this review, although most studies reported comparable numbers of dissected lymph nodes (3,9,11), AlGhamdi *et al.* (8) observed significantly fewer dissected lymph nodes in the non-intubated group. It is unclear whether the finding was oncologically significant. Unfortunately, no studies have been able to answer this question. One of our included studies attempted to

indirectly compare oncological outcomes with respect to adjuvant chemotherapy compliance and toxicity, proposing that a non-intubated procedure may result in improved adjuvant chemotherapy compliance and lower toxicity rates after lobectomy (10). However, in that study, the comorbidity and pathological staging in the two groups differed, which may have also affected compliance with adjuvant chemotherapy (35,36). Moreover, the potential impact on long-term survival was also unknown.

Limitations

The lack of consistent anesthetic/surgical protocols and outcome reporting is the greatest limitation of this study that prevents detailed analysis. Heterogeneity between the included studies exists in terms of the included population. All studies are retrospective observational studies and therefore suffer from possible bias.

Conclusions

Current evidence consistently demonstrates that Ni-VATS lobectomy for lung cancer may improve postoperative recovery. Potential benefits of Ni-VATS include faster oral intake, less chest tube drainage and duration, and shorter hospital stay. However, there is a paucity of data related to mid-term and long-term oncological outcomes. Studies providing comparable or better oncological results may encourage more thoracic surgeons to perform Ni-VATS lobectomy. Future studies should aim to identify an optimal indication for a specific group who may benefit most from a non-intubated approach, as well as the mid-term and long-term oncological outcomes of Ni-VATS.

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Footnote

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