Non-intubated VATS for lung cancer—a focus on segmentectomy: a narrative review

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Abstract: Traditionally, lobectomy is the gold standard for early-stage non-small-cell lung cancer (NSCLC) treatment but in recent years lung segmentectomy is gaining a key role in small-sized or subsolid peripheral lung lesion <2 cm. It can be performed with minimally invasive approaches leading to better pulmonary function preservation, less postoperative pain and shorter hospitalization. Although for decades general anesthesia with tracheal intubation was considered mandatory, non-intubated video-assisted thoracic surgery (NiVATS) has been proposed as an alternative to traditional surgery. Its role in more challenging thoracoscopic procedures such as VATS anatomical lung resections is currently being evaluated. NiVATS applied to lung resections for early-stage NSCLC treatment, even if technically more challenging than conventional intubated thoracic surgery, is an innovative and promising surgical strategy allowing less intubation-related adverse effects and a faster recovery; several encouraging results have recently been reported, proving that minimally invasive surgical and anesthetic approaches could be a valid alternative to more invasive procedures in selected patients also in technical challenging anatomical resections. The aim of this review is to describe various technical aspects of NiVATS procedures and to investigate the combination of thoracoscopic segmentectomy and non-intubated anesthesia in terms of feasibility, safety, intra and perioperative complications, short-term outcomes and oncological adequacy.

Keywords: Segmentectomy; non-intubated thoracic surgery (NITS); lung cancer

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Introduction

For many years pulmonary lobectomy has been considered the gold standard treatment for localized non-small-cell lung cancer (NSCLC) even in early stage, despite the critical points shown in the only randomized trial published in 1995 by Lung Cancer Study Group: above all, lung segmentecomy and wedge resection were both included in the sublobar resection group (1). In the last decade the role of segmentectomy has been significantly reconsidered especially for selected cases with small ground-glass opacity (GGO) tumours or sub-centimeter solid nodules, even if the patients could tolerate a lobectomy (2). These "parenchyma sparing" procedures are usually conducted by video-assisted thoracic surgery (VATS) with relevant benefits for the patients (3).

In this scenario non-intubated thoracic surgery (NITS) can represent a further step toward a less invasive approach, although more technically challenging than traditional tracheal intubation. The purpose of this article is to describe the current clinical practice in NITS segmentectomy and to evaluate its role in terms of feasibility, complications and short-term outcomes. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/vats-21-9).

Methods

A literature search was conducted by the authors to identify all English-written published articles on NITS. PubMed, EMBASE and Web of Science databases were consulted matching the terms "Non intubated" and "segmentectomy" and "thoracoscopy" with "AND" until 31st August 2020. The search was extended by consulting the listed references of each article.

All the articles, case reports and case series were included in this narrative review. Abstracts were excluded. The extracted data included study characteristics, number of operated patients, clinical data, type of surgical procedure, short-term outcomes and postoperative complications.

Indications

From an oncological point of view indications for NITS segmentectomy do not differ from intubated procedures, as reported in the NCCN guidelines (2).

Segmentectomy for NSCLC is considered adequate in case of N0 disease and peripheral lung nodules less than 2 cm in major diameters with at least one of the following conditions:

- Ground glass appearance on computed tomography (CT) scan (for more than 50% of their size);
- Long doubling time (more than 400 days between two sequent CT scans);
- Pure adenocarcinoma *in situ* histology.

The tumour must be contained within the anatomical edges of the proper segment, with the circumferential margin free from disease for at least its size. It is crucial to assess the resection margins during segmentectomies by frozen sections analyses that must confirm the oncological radicality. In case of inadequate resection margins, N1 disease or single station N2 disease, the surgical strategy should be modified to a completion lobectomy (4). According with these indications, a recent meta-analysis by Winckelmans *et al.* concluded for a non-inferior oncological long-term outcome (overall survival, cancer-specific survival, recurrence free-survival) between segmentectomy and lobectomy for stage IA <2 cm NSCLC. This could be particularly important in case of recurrence, because the lung sparing obtained by segmentectomies could allow a lung resection at a later stage (5).

Segmentectomies are common in case of poor pulmonary reserve (3) or major comorbidities that contraindicate lobectomy (6) especially with low performace status and patients older than 75 years old (7,8) because several studies have shown that segmentectomies are affected by fewer complications (9,10). However, these indications are still on debate and not worldwide accepted because of the lack of data on long-term overall survival and disease-free survival (11).

Segmentectomy can also be recommended in case of metastasectomy if adequate margins can not be obtained with a wedge resection (12).

Anesthesiologic indications for NITS segmentectomies are similar to those for other lung resections, including patients with ASA score I–III, BMI less than 25, Mallampati grade I–II and little airway secretions (13). Due to the potential technical complexity of anatomical sublobar resections, it is important to evaluate the side effects of a non-intubated procedure. General contraindications to NITS are: impossibility to perform epidural puncture, mainly for spinal anatomy; sleep apnoea, obesity, supraelevated or paralyzed diaphragm, chest wall deformity, unfavourable airways anatomy, bleeding disorders, evidence or clinical history of possible pleural adhesions (14).

Technical aspects

Planning surgery

Preoperative three-dimensional CT (3D-CT) angiography/bronchography or a 3D printing technology can help to detect detailed arterial, venous, and bronchial anatomy and to find whether variation occurred to the target segment of vessels and bronchi. These methods allow planning resection margins based on the patient's segmentation and simulate anatomical segmentectomy prior to the resection. The benefit of simulation on the theoretical and practical learning of health professionals was clearly demonstrated. 3D reconstruction on the intraoperative view could also help the surgeon in the detection of non-palpable nodule or GGO.

Unfortunately many disadvantages have been described: small vessel branches are commonly missed using this technology; misidentification of an artery as a vein and vice versa; 3D model does not reflect the deflation of the lung. For these reasons thoracic surgeons should use this technology to plan and simulate anatomical surgical resection, recognizing its limitations (15,16).

The peripheral small nodule in the target segment can be located by CT-guided coil or patent blue vital dye labeling for confirmation of its complete resection, while the deeply located nodules could be labeled by the

vital dye as described by Lin *et al.* (17). This localization method enables surgeons to resect small, deeply located, GGO predominant, synchronous, multiple, indeterminate pulmonary nodules by VATS.

Anesthesia

As premedication, intramuscular midazolam and atropine can be used for sedation and secretion reduction. Several methods of anesthesia have been described, combining local and regional anesthesia of the chest wall and intercostal nerves: among selective intercostal nerve blockade, serratus anterior plane block (18), thoracic paravertebral blockade (19,20), lidocaine administration in the pleural space (21) and vagus nerve block in the pulmonary hilum (22,23), the choice falls on the team.

Thoracic epidural analgesia is usually reserved to more invasive and time-consuming procedures (24). The pharmacological sedation with continuous intravenous propofol or fentanyl, using a target-controlled infusion (TCI) is also useful to relieve patients' anxiety (21,25).

In most NiVATS patients SpO_2 could be maintained above 90% with a face mask, as described by Chen *et al.* in a pilot study (23). Laryngeal mask is a solution to hypoxia and hypoventilation which occurs especially in prolonged operations or in patients with higher respiratory risk. This supraglottic airway device also facilitates conversion to tracheal intubation in a lateral decubitus position, if necessary.

Recently, Starke *et al.* reported 88 patients scheduled for non-intubated VATS (NiVATS) who underwent minor and major pulmonary resections, including segmentectomies: epidural anesthesia was performed more frequently in major surgery (70.0% *vs.* 18.8%) and during the procedure oxygen was applied more often with laryngeal mask than face mask especially in major resection (62.5% *vs.* 22.9%) (26).

There is currently no published randomized evidence-based study comparing laryngeal mask and oxygen mask in NiVATS.

Surgical technique

In general, segmentectomy is performed with division of segmental vessels and bronchi in a manner similar to the open approach. Accurate hilar and mediastinal lymph nodes dissection is mandatory, due to its relevant impacts on recurrence free survival. The most commonly performed segmental resections are lingula-sparing left upper lobectomy, lingulectomy, apical lower segmentectomy and basilar segmentectomy. Bi- or trisegmentectomy is performed when tumours are close to intersegmental fissures.

The chance of segmentectomy decreases if the tumour is located between neighboring segments. Lung segmentectomy can be classified into two types: typical segmentectomy and atypical segmentectomy. Typical segmentectomy includes upper segmentectomy of the left upper lobe, lingulectomy, apical lower segmentectomy, and basilar segmentectomy of both sides. Atypical segmentectomy includes resection of individual segments of the upper lobe, middle lobe, or basilar segments. Atypical segmentectomy is technically feasible but remains challenging, considering that it is more complicated than typical segmentectomy and therefore requires a longer operation time (27).

Hilar dissection

Before starting with hilar dissection, the block of vagus nerve is performed with injection of 4 mL Ropivacaine in the Barety's space for the right side or in the aorto-pulmonary window for the left side. Moreover, a selective intercostal space blockage is done with 3 mL of Ropivacaine 0.5% at each level.

During NITS segmentectomy hilar dissection is performed in a similar manner to the intubated procedures: it usually begins with ligation of the segmental pulmonary vein, followed by either the bronchus or the artery, depending on the segment. When beginning the hilar dissection, usually the segmental vein is easily identified and stapled. Subsequently, it is often advisable to remove all visible hilar lymph nodes related to the adjacent segmental bronchus and artery. It is mandatory to sample with frozen section hilar lymph nodes, because in case of positive result, segmentectomy must be converted to lobectomy. After division of hilar structures, one of the major challenges is the identification of the intersegmental plane to guide the parenchymal section strictly to the proper segment to be removed.

Identification of the intersegmental plane

Several techniques have been described for the identification of the intersegmental plane during VATS segmentectomy. The "inflation and deflation" is the most conventional method to develop an intersegmental plane. In this

technique mechanical ventilation is essential because the segment to be resected can be either deflated or inflated, therefore is not possible during NITS.

An alternative method of bronchial inflation during NITS segmentectomy has been described by Kamiyoshihara, using a butterfly-needle in the target bronchus after its stapling (28): one of the limits of this technique is due to collateral ventilation that can cause the inflation of the adjacent segments. Moreover it must be taken into account that two cases of massive air embolism have been reported due to direct injection of air into an adjacent pulmonary vein (29). Considering this potentially severe complication, it is recommended to use an "open-cut" selected segmental inflation technique without the use of a needle.

The widely used intraoperative localization technique is provided by a combination of indocyanine-green (ICG) and infrared thoracoscopy. ICG is a green dye visible under regular white light and visible as fluorescence by near-infrared. Once the pulmonary artery is clamped or resected, the intravenous ICG injection perfuses the target segment and it helps to identify the intersegmental planes. The dividing line is marked by a fluorescent boundary between viable (bright area) and devascularized segments (dark area) (30). Misleading ICG staining could result from an accessory branch of the pulmonary artery (e.g., an accessory artery to S10a branching from S6 with regular bronchial branching) (31): basic anatomy and variations of accessory arteries need careful examination with 3D images especially if the resection margin is strictly dependent on the intersegmental plane. Intrabronchial marking by ICG injection under bronchoscopy or electromagnetic navigation bronchoscopy (ENB) allows identification of the intersegmental lines and planes: injection into the segmental bronchus and the ligation of the segmental vein creates a demarcation line, that easily allows to identify the parenchyma (32). Compared with intravenous injection, dye marking administered by intrabronchial injection lasts longer in the alveoli and no repeated injection in required. As described in inflation-deflation technique, airway secretions and collateral ventilation could create heterogeneous staining and obscure intersegmental lines.

Zhang *et al.* reported a hypothetical segmental labeling procedure for non-intubated segmentectomy: after the ICG or methylene blue is injected into the target bronchus, a one-way endobronchial valve is delivered by ultrathin bronchoscope to achieve a complete atelectasis. The remaining coloured gas is extracted to avoid staining of the other lobes and then the collapsed segment is confirmed under real-time CT. The collapsed target segments assisted with artificial pneumothorax by carbon dioxide insufflation are usually cone-shaped. The cutting edge is sealed using fibrin glue to decrease air leakage, especially in emphysematous patients (33).

Lymph node dissection

Systematic mediastinal lymph node dissection should be performed to complete the pulmonary resection under spontaneous breathing.

As reported by Chen *et al.* in 2011 the number of lymph nodes dissected in the non-intubated versus intubated group was 13.8±6.0 *vs.* 14.0±6.0 in 30 cases of NSCLC patients (23) and similar results were confirmed in 2013 in lung cancer patients older than 65 years old (34). According to Liu *et al.* in 2016 the number of lymph nodes dissected in the non-intubated versus intubated group was 7.8±5.4 *vs.* 6.4±5.3, and the stations of lymph nodes dissected were 3.2±1.4 *vs.* 2.7±1.5, showing no significant difference (35). These results proved that non-intubated segmentectomy did not negatively affect the completeness of lymph node dissection compared to intubated segmentectomy.

Discussion

In recent years, lung segmentectomy has been assessed as a valid alternative to lobectomy for the treatment of early-stage NSCLC in selected patients, a viable option for elderly patients and in case of impaired pulmonary function (36,37). Ongoing international multicenter randomized phase III controlled clinical trials (CALGB 140503 in the United States and JCOG0802/WJOG4607L in Japan) (38,39) are evaluating the non-inferiority in overall survival of segmentectomy compared to lobectomy in patients with small-sized (diameter <2 cm) peripheral NSCLC.

Several minimally invasive surgical techniques are applied to segmentectomy, such as uniportal, multi-port, totally endoscopic or robotic approach. Since the advent of thoracoscopic surgery, tracheal intubation with single-lung selective ventilation has been considered mandatory in VATS anatomical lung resections, to obtain an optimal thoracoscopic view of the hilar structures and to manipulate safely the lung in a small pleural space. In recent years several NITS techniques have been proposed as a safe and feasible alternative to the traditional tracheal-intubated surgery: since the late 1990s, NITS has been performed as

a less invasive procedure for pneumothorax, pleural biopsies and atypical lung resections, with similar surgical results and complication rates compared to traditional surgery (40).

In our review we explored the role of NITS applied to lung segmentectomies in terms of feasibility, intra and perioperative complications and short-term outcomes. At present, just few surgical groups published papers on anatomical pulmonary resections performed via NiVATS: most of the reviewed studies reported encouraging results of non-intubated techniques and VATS lobar/sublobar resections, proving that minimally invasive surgical and anesthetic approaches could be an alternative to more invasive procedures in selected patients also in technical challenging anatomical resections.

A retrospective review by Guo *et al.* comparing 48 NiVATS with 92 intubated segmentectomies reported no significant differences between the two groups in terms surgical duration (2.81±0.96 *vs.* for NITS group *vs.* 2.74±0.87 for intubated group; P=0.643), intraoperative blood loss (75.10±206.88 *vs.* 56.65±71.56; P=0.441), postoperative chest tube drainage (2.25±1.36 days *vs.* 3.16±3.93; P=0.047), and postoperative hospital stay (6.04±3.60 *vs.* 7.83±5.89; P=0.057). Comparable postoperative complication rates between the two groups were described (8.3% *vs.* 15.2%; P=0.248), mainly represented by pneumonia and chylothorax (13).

Liu *et al.* reported similar intraoperative results comparing NITS and intubated anatomical lung resections (282 lobectomies and 57 segmentectomies); in particular considering short-term outcomes in lung segmentectomies, significant differences were shown in favour of NITS procedures in terms of postoperative fasting time (6.5±2.1 *vs.* 13.8±2.3 h; P<0.001), mean volume of pleural fluid drainage (354.5 *vs.* 723.0 mL) and mean duration of hospital stay (6.0 *vs.* 8.3 days). In this retrospective analysis only one case of vascular accident requiring tracheal intubation was described; conversion to tracheal intubation was also required in case of broad mediastinal movements, dense pleural adhesions and hypercapnia/hypoxaemia (total conversion rate of 7%) (41).

Liu and colleagues recently reported a retrospective study comparing uniportal and multiportal NITS segmentectomies with similar complication rates and short-term outcomes. Conversion rate to multi-port procedure was 6.3%, mostly when was difficult to identify the nodule (preoperatively marked with dye in the uniportal group) or in presence of dense pleural adhesions. No conversion to tracheal intubation or thoracotomy was needed in the uniportal group, proving that also challenging procedures can be performed safely without endotracheal intubation (42). In terms of oncological adequacy of lung resections and lymph nodes dissection, Chen *et al.* reported no significant differences between procedures performed under general anaesthesia and non-intubated lung resections, proving that a satisfactory nodal sampling or dissection is feasible also during NITS (23).

Several technical aspects should be considered in the approach to NiVATS segmentectomies, above all the careful selection of patients undergoing the procedure: nearly all studies dealing with anatomical lung resections and NITS recommend avoiding patients with BMI >25 kg/m^2, because of the wide diaphragmatic and mediastinal movements associated with obeses' respiratory pattern which can make hazardous the anatomical dissection. Non-intubated thoracoscopic surgery is longer applicable in small-sized females, distinguished by a favourable breathing pattern and a suitable anatomical setting for sublobar VATS resection (43). They also have small tracheal caliber and therefore they are more exposed to potential tracheal damages during intubation.

The most evident advantages using a NiVATS technique for lung surgery are represented by the reduced rates of post-operative adverse effects of conventional general anaesthesia, such as vomiting and headache, often requiring more medications. Moreover, the residual neuromuscular blockade is avoided: this is a significant risk factor for the development of early post-operative respiratory complications (hypoxemia, impaired ventilation, atelectasis and pneumonia). The absence of a double-lumen endotracheal tube minimizes intubation-related airway lesions and reduces the adverse effects of intubation including sore throat, tracheal traumas and ventilator-induced lung injuries. In addition, minor airway irritation diminishes the risk of bronchospasm in predisposed patients, such as COPD or asthmatic subjects. Furthermore, Liu *et al.* have recently shown significantly lower levels of post-operative inflammatory factors (in particular TNF-α and s-CRP) in NiVATS procedures compared to patients treated with conventional intubated surgery: one of the possible mechanisms involved is the inhibition of the sympathetic system and the consequent reduced release of inflammatory factors due to epidural anaesthesia, commonly used to manage analgesia during NITS (41).

Despite the encouraging results and the several advantages of NITS described above, some concerns may arise especially considering NITS for VATS major

pulmonary resections. First, iatrogenic pneumothorax obtained through thoracoscopic incisions during spontaneous breathing may affect pulmonary ventilation, leading to hypoxemia and hypercapnia, in particular during time-consuming operations. Hypoventilation due to partial collapse of the non-dependent lung and to pendular ventilation between lungs may cause hypercapnia: it is typically well tolerated and may occasionally be regulated using intraoperative manual control or synchronized intermittent mandatory ventilation (SIMV) (13). Regarding hypoxemia, it is generally well responsive to O_2 supplementation using face masks or trans-nasal O_2 high-flow devices. However, in conventional intubated thoracic surgery, monopulmonary ventilation and atelectasis of the dependent lung have been described as a contributing factor for ventilation-perfusion mismatch and consequent severe hypoxiemia (44).

From a technical point of view, some limits should be considered approaching NITS segmentectomy. During anatomical dissections, the manipulation of lung and airway can trigger cough reflex: in this regard, vagal blockade with local anesthetics (i.e., Ropivacaine, Lidocaine, Bupivacaine) has been proved as an effective and safe method to minimize cough reflex and to reduce broad mediastinal movements (23).

The management of cough reflex triggered by lung and airway manipulation can be critical, performing anatomical dissections, in particular in close proximity to vascular structures. In addition, the identification of the intersegmental planes can be challenging during NITS procedures: inflation-deflation technique can not be used without tracheal intubation, therefore some alternatives such as labeling techniques with ICG may be applied during NITS segmentectomies.

Even if most of the studies considered in this review reported very low intraoperative conversion rates to intubated surgery, there are some situations in which a rapid conversion to intubated general anaesthesia is needed: uncontrolled bleeding and unstable haemodynamic conditions are the main causes of immediate conversion. Other technical reasons for conversion are an unsatisfactory surgical field due to an insufficient lung deflation, the presence of dense pleural adhesions, deep mediastinal movements due to spontaneous breathing and severe persistent hypoxemia. In these cases, a close cooperation between a highly trained anaesthesiologists' team and the surgeon is mandatory to manage a quick and efficient conversion especially in emergency situations such as uncontrolled bleeding.

Despite the interesting results of NITS segmentectomies, some recommendations should not be forgotten in order to minimize intraoperative risks and severe complications; above all, an adequate learning curve and a wide experience with non-intubated minor thoracic procedures such as pleural biopsies and non-anatomical resections is pivotal to approach more complex NITS.

In conclusion, NITS for anatomical resections such as segmentectomies could be considered a feasible and safe alternative to conventional intubated surgery in selected patients, with comparable short-term outcomes.

Although the encouraging results, more studies and a longer follow up are needed to evaluate the oncological value of these procedures in terms of disease-free survival and overall survival.

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Footnote

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