VATS segmentectomy: an underused option?

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Abstract: It is well known that the "gold standard" procedure for surgically resectable early-stage non-small cell lung cancer (NSCLC), is pulmonary lobectomy. Even though sublobar resections (SLR), particularly segmentectomy, seem attractive as an alternative to lobectomy in early stage lung cancers, they are still debated procedures. The aim of this study is to answer to the question: "Is VATS lung segmentectomy an underused option?" To obtain an answer to this query, the authors carried out a review of the "state of the art" as follows: (I) performing a non-systematic review of the literature; (II) analyzing the review articles published; (III) looking at the ongoing studies, the results of which have not yet published; (IV) scanning the technical aspect of lung segmentectomy. After completing the multi-step revision, we can conclude that there is a lack of evidence about the oncological value of segmentectomy in early stage NSCLC. Although VATS segmentectomy is feasible and performed by many thoracic surgeons, it's currently not yet world-wide adopted. Among the trials now being recruited in some countries and, aimed to clarify the role of SLR in the treatment of early stage lung cancer, a European prospective randomized study is advocated to implement the scientific knowledge on this issue.

Keywords: Lobectomy; lung cancer; segmentectomy; sublobar; video-assisted

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Background

It is accepted that the "gold standard" procedure for surgically resectable early-stage non-small cell lung cancer (NSCLC) still remains pulmonary lobectomy, either with thoracotomy or thoracoscopic approach.

Such belief comes from multiple considerations: (I) the majority of thoracic surgeons are convinced that the lobectomy is "oncologically safer", because the anatomical sub-unit represented by lobe has its own arteries, veins, bronchi and fissures; (II) the conviction that "we always performed this way"; (III) the results of the first randomized trial published in 1995 by Ginsberg *et al.* on behalf to the Lung Cancer Study Group (1). Such manuscript showed a high loco-regional recurrence rate (17.2% *vs.* 6.4%) and a

worse survival in patients submitted to sublobar resections (SLR). This was the only randomized trial published at present that compared survival between sublobar resection with lobectomy in stage I NSCLC. Unfortunately, the study had strong limitations: "sublobar" resections included lung segmentectomies and wedge resections, many of the operators were general surgeons with limited thoracic experience, the sample size was underpowered, but, most importantly, T1 comprised tumors up to 3 cm in diameter. In addition, the conclusions of Ginsberg's study have been confirmed in a non-randomized prospective trial published by Landreneau *et al.* in 1997 (2).

From 1995 to nowadays several articles have been published, but most of them are retrospective analysis. The results published were contradictory, depending to the point

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Table 1 Selected studies

Author, year	Type of study	Sample size	Source	Sublobar	Results
Deng, 2014	Retrospective	2,547	Monocentric	S	T1a: OS and DFS n.s.; T1b: worse OS and DFS in segmentectomy
Schuchert, 2012	Retrospective	899	Monocentric	S	OS and DFS: n.s.
Carr, 2012	Retrospective	429	Monocentric	S	OS and DFS: n.s.
Schuchert, 2007	Retrospective	428	Monocentric	S	OS and DFS: n.s.
Whitson, 2011	Retrospective	14,473	Database (SEER)	S	OS and CSS worse in segmentectomy
Nakamura, 2011	Retrospective	411	Monocentric	S and WR	OS n.s. in lobectomy and segmentectomy but worse in WR
Zhang, 2016	Retrospective	12,324	Database (SEER)	S	OS and LCSS worse in segmentectomy
Landreneau, 2014	Retrospective, propensity matched	624	Monocentric	S	OS and DFS n.s.
Khullar, 2015	Retrospective, propensity matched	2,961	Database (NCDB)	S and WR	OS worse in segmentectomy and WR
Okada, 2006	Retrospective	567	Multicentric	S or WR	OS and DFS n.s.

S, segmentectomy; WR, wedge resection; OS, overall survival; DFS, disease-free survival; SEER, Surveillance, Epidemiology and End Results Program; CSS, cancer-specific survival; LCSS, lung cancer-specific survival; NCDB, National Cancer Database; n.s., not statistically significant.

of view and the population analyzed, but most of them are in favour of segmentectomy in early stage NSCLC, in particular regarding the overall survival (OS) and cancerspecific survival.

The research question

To answer the question "Is VATS lung segmentectomy an under-used option?" the authors decided to look at the literature with a non-systematic review of what is published and what is in progress now.

Methods

The authors carried out a "four-step" non-systematic review in the field of sublobar pulmonary resections versus pulmonary lobectomies for early stage of lung cancer. The revision was conducted as follows:

- (I) The authors made a non-systematic review, with MEDLINE as primary source. The search string was as follows: ((("lung"[All Fields] OR "pulmonary"[All Fields]) AND "segmentectomy"[All Fields]) AND "lobectomy"[All Fields]) AND "cancer"[All Fields]);
- (II) The second part consisted in the analysis of review articles published about the comparison between

SLR and lobectomy for early stage lung cancer;

- (III) The third part was the overview of the ongoing studies registered on line;
- (IV) The final part is an analysis of the technical aspects of wedge resection and segmentectomy.

Results

Non-systematic review

The results of the search have been filtered excluding papers with the following criteria: (I) survival data not reported; (II) comparison with lobectomy not reported; (III) case reports/case series; (IV) review paper; (V) expert opinions/editorials; (VI) non-English language. The papers found with the result search were 248. After a manually review of title and abstract and/or full text of each citation, the authors screened 40 papers. Of which, 10 papers were considered providing the "best evidence" in answering the authors' question (*Table 1*).

Among retrospective studies, Deng *et al.* compared 212 segmentectomies with 2,336 lobectomies for stage I NSCLC: OS and disease-free survival (DFS) were not statistically different for T1a, but worse for T1b in segmentectomy (3). Other retrospective monocentric

studies from USA published by Schuchert et al. and Carr et al. showed no differences in OS and DFS between segmentectomy and lobectomy for stage I NSCLC (4-6). Analyzing stages I to III NSCLC, Okumura et al. confirmed no differences in OS and DFS, with a long-term followup (7). On the contrary an important retrospective study published by Whitson et al. in 2011 showed OS and cancer-specific adjusted survival worse in segmentectomy than lobectomy for stage I NSCLC, analyzing a sample of 14,473 patients extracted from the Surveillance, Epidemiology, and End Results (SEER) Database (8). Nakamura et al. in a retrospective study compared wedge resection, segmentectomy and lobectomy for stage I NSCLC, revealing no differences between segmentectomy and lobectomy but worse 5-year OS in wedge resections (9). A Chinese work based on SEER Database enrolling more than 12,000 cases, found worse overall and lung cancer specific survival in segmentectomy compared to lobectomy in elderly patients (10).

Propensity matched studies included the Landreneau *et al.* paper, published in 2014, that showed the same OS and DFS in an enrolling 312 segmentectomies and 312 lobectomies (11). In 2015, an analysis from National Cancer Database (NCDB) was published by Khullar *et al.* comparing wedge, segmentectomy and lobectomy for pT1aN0 NSCLC with the propensity match method. The results reported in this paper established worse OS in wedge resections and segmentectomies compared with lobectomies (12).

Ongoing studies

Searching for registered ongoing studies, we found 6 trials based on different subsets of patients. In particular, four trials were registered from Chinese researchers: (I) "Comparison of Different Types of Surgery in Treating Patients with Early-stage Non-small Cell Lung Cancer" is a prospective, matched, controlled, open, multicenter trial. Patients with NSCLC <2 cm are matched according to age and groundglass opacity (GGO) component ratio. Among SLR, wedge resection is permitted. The outcome of this non-randomized trial is the DFS but the planned 630 patients appears to be an underpowered sample size. (II) "Comparison of cVATS Segmentectomy Versus Lobectomy for Lung Adenocarcinoma in Situ and With Microinvasion" is a prospective, open-label, parallel, multi-center, randomized trial recruiting patients with <2 cm pure ground-glass or mixed ground-glass nodules (solid areas <0.5 cm). Considerations on sample size are similar to those expressed for the previous trial. (III)

"Comparison of Lobectomy and Segmentectomy for cT1aN0M0 Peripheral NSCLC" is a randomized, parallel, open label trial with DFS as end-point. Even in this case the sample size (610 patients) looks as underpowered. (IV) "Surgical Treatment of Elderly Patients with cT1N0M0 Non-small Cell Lung Cancer Comparison between Sublobar Resection and Lobectomy (STEPS)" is a randomized, parallel, open label trial recruiting patients (\geq 70 years old) with \leq 2 cm NSCLC; DFS is the end-point. The sample size is limited to 339 patients.

A multi-continental study (USA, Canada and Australia), enrolling an estimate number of 1,288 adult patients affected by stage I NSCLC, is aimed to compare lobectomy with SLR. The primary end-point of this study is DFS; a concern on sample size adequacy is present considering that wedge resections are permitted among the SLR.

Finally, a multicenter Japanese trial named "A Phase III Randomized Trial of Lobectomy Versus Limited Resection for Small-sized Peripheral Non-small Cell Lung Cancer" is recruiting patients with ≤ 2 cm peripheral NSCLC (13). Pulmonary lobectomy is the standard treatment and segmentectomy is the experimental one. Unlike previous studies, this trial has OS as primary end-point; this detail could make the sample size questionable.

The scientific community is looking forward to having the results from the mentioned studies but it is notable the absence of any European project.

Technical aspects

SLR include various types of limited excision of parenchyma, with considerable differences from a technical, anatomical and oncological point of view.

Depending from the hilum dissection, SLR are divided into non-anatomic (wedge resections) and anatomic (segmentectomies).

A wedge resection is the removal of a triangle-shaped slice of tissue, usually for small peripheral lung lesions, without dissection of pulmonary hilum. This makes the procedure technically simple, even in VATS. On the other hand, the distance between the nodule and the surgical margin is usually inferior to the anatomic procedures, as well as the assessment of hilar lymph nodes, which is frequently limited.

An anatomical segmentectomy is the removal of one or more pulmonary segments, after individual dissection of vein, artery and bronchus. After division of hilar structures, intersegmental plan is identified, to guide the parenchymal section strictly to the proper segment to be removed.

Segmentectomy allows a wider parenchymal resection

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than wedge resections, with a lower risk of inadequate surgical margins. Moreover, segment specific lymphatics are removed, ensuring a valid radicality in early stage NSCLC. The total number of resected lymph nodes is significantly higher than in wedge resections, as reported in several studies (14-16).

Hilum dissection in anatomical segmentectomies can be technically more complex than a lobectomy, because of the extended and more distal isolation of segmental vessels and bronchi.

Moreover, some segments can be difficult to be removed for the very deep location of vessels and bronchi into the parenchyma (i.e., dorsal and lateral basal segments of lower lobes). For this reason, the majority of segmentectomies performed are left upper lobe trisegmentectomy, lingulectomy, and apical segmentectomy of lower lobes.

In case of suspect hilar adenopathy, it's mandatory to have a frozen section on segment-specific lymph nodes: if the response is positive, we don't consider segmentectomy radical from an oncological point of view. In that case, if the patient's respiratory function is permissive, the strategy change in favor of lobectomy is advisable.

After hilum division, intersegmental plane can be challenging to be identified. Usually we ask to the anesthesiologist to inflate the lung before segmental bronchial closure, keeping the proper bronchus closed with a clamp. This helps to identify the limit between the involved segment, that remains deflated, and the parenchyma to be preserved. If collateral ventilation is relevant, the intersegmental plane can be difficult to be identified.

Other techniques for distinguishing the intersegmental plane have been proposed. Tsubota in 2000 described the inflation of the lobe followed by the bronchus closure, in order to maintain gas inside the segment to be removed (17). Okada in 2007 described the application of jet ventilation under bronchoscopic guide to cause selective segmental inflation (18). Sekine in 2012 reported the transbronchial injection of indocyanine green, followed by infrared thoracoscopy (19). Zhang in 2015 described a staining technique with methylene blue injection into the segmental bronchus (20).

After intersegmental plane identification, parenchyma division is usually performed with stapler, as in our centre. Some authors reported use of cautery cutting (18) or energy based devices. In case of thick lung resection, autologous or synthetic tissue reinforce on the staple line can be useful to prevent air leakage.

Although technically demanding, most of anatomic segmentectomy are now performed with VATS or RATS. We believe the mini-invasive procedure is feasible and safe, even in uniportal VATS, if surgeon's experience is adequate (21,22).

The Italian point of view

Looking at the Italian situation, analyzing the case series reported and papers published, attending National meetings on Thoracic Surgery and speaking with colleagues, the feedback is that several Thoracic Surgery Departments sometimes carried out segmentectomy in early stage NSCLC, but without a precise rule. In fact, often segmentectomy is proposed to patients that cannot be undertaken to lobectomy because of age, poor cardiopulmonary function or relevant comorbidities, and previous thoracic surgery, especially for recurrent tumors. Therefore, as mentioned before, the choice to decide for segmentectomy, either by thoracotomy or by VATS, is a "non-intentional" one.

Regarding the "non-intentional" choice of sublobar resection, Fiorelli *et al.* published a multicenter retrospective propensity matched analysis comparing sublobar resection (comprehending both wedge resection and segmentectomy) with lobectomy in elderly patients. The results showed no differences in long term survival between two populations (23).

In 2004 Campione *et al.* published a retrospective analysis where results showed no differences in survival but high incidence of local recurrence in segmentectomy compared to lobectomy for stage Ia NSCLC (24).

The Padua group, concerning surgical treatment of second primary cancers, concludes that lobectomy should be considered the treatment of choice, but sublobar resection remains a valid option in high-risk patients (25). In addition, Pardolesi *et al.* published in 2012 their initial experience about robotic segmentectomy, analyzing surgery outcome of 17 lung segmentectomies performed in two different centers. The authors concluded that robotic lung segmentectomy is feasible and safe (26).

Discussion

Interest in sub-lobar resections has been growing in recent years. Some authors have tried to summarize the evidence in the literature: Cao *et al.* published a review and meta-analysis in 2015; the results emphasized the patient selection between "intentionally selected" or "compromised" patients, and suggested segmentectomy as a feasible alternative to lobectomy in selected patients with peripherally <2 cm tumors with favorable histopathology and with ground glass imaging (27). On the contrary, a review published by Sihoe and Van Schil in 2014, pointed out that evidences regarding survival outcomes between "intentional" segmentectomy and lobectomy were too low; therefore, waiting ongoing randomized trials results, they considered lobectomy as standard therapy for early stage NSCLC (28). A meta-analysis published by Bao *et al.* in 2014 suggest that segmentectomy provides worse survival than lobectomy in NSCLC from 2 to 3 cm of diameter, but equivalent survival in tumors smaller than 2 cm (29).

Completing our multi-step narrative revision, we observed a lack of evidence about the oncological value of segmentectomy in early stage NSCLC. In fact, several authors published papers with contradictory results; this is not surprising considering that almost all of the papers were retrospective cohort studies with limited population and that studies based on large national database frequently suffer from incomplete record. Data that are difficult to find in retrospective studies are why and when the sublobar resection has been performed. In other words, segmentectomy or wedge resection can be "intentional" or "not intentional". An "intentional" sublobar resection is done in patients that could tolerate a major resection (i.e., lobectomy). If the sublobar resection was "not intentional", probably the parenchyma sparing procedure was chosen due to poor postoperative pulmonary and/or cardiac function or other reasons that inevitably could impact on survival. Some retrospective studies were propensity matched, that adds statistical value to the results, but unfortunately, they were not powered enough to analyzing a survival-based outcome.

The lack of randomized prospective studies is probably due to different reasons: firstly, the "ethical problem" for randomization: in fact it's quite difficult to propose a segmentectomy to a fitting patient, that can tolerate a lobectomy; secondly, proper sample size for a non-inferiority study on this issue requires thousands of patients; thirdly, a large scale multicenter randomized study has important economic and organizing impact. Nevertheless, both in Asia and North America, prospective randomized studies are ongoing; a European study would be desirable for the racial and socio-economic diversity of the Old Continent.

Certainly SLR, particularly segmentectomy, could be attractive for many reasons. Firstly, the growing incidence of GGO tumors, especially in Asiatic people; the main features of these tumors are to be "multi-focal" and have low rate of local recurrences, that potentially require multistep or redo surgery (as "intentional" procedures). Secondly the rising in expectancy of life requires lung resections in elderly patients who could benefit from parenchymasparing, "non-intentional" procedures; thirdly, the ongoing lung cancer screening programs allow detections of more early-stage lung opacities in high-risk patients, who, once more, can functionally benefit from "not intentional" segmentectomy.

Although VATS segmentectomy is performed by experienced thoracic surgeons, it's not yet world-widely adopted. The main technical obstacle is the long learning curve of VATS segmentectomy and the difficulty to resect all pulmonary segments.

Of course, the interest in this field is increasing, both from oncological and technical point of view.

To conclude, our impression is that segmentectomy is mainly adopted as "not intentional" procedure, in high risk patients who cannot tolerate lobectomy. The surgical scientific community is looking forward to receiving the results of ongoing and future randomized trials, that could answer to our dilemma: "to do or not to do 'intentional' segmentectomy in early NSCLC?" In the meantime, we are confident that VATS segmentectomy could become widely adopted among thoracic surgeons.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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