Review Article

Post-operative and oncological outcomes of minimally-invasive simple and complex segmentectomy: a narrative review

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Background and Objective: The recent two randomized controlled trials (RCTs) (JCOG0802/WJOG4607L and CALBG/Alliance 140503) have definitively removed the belief that segmentectomy is the surgical treatment of patients not able to tolerate lobectomy, but some arguments remained without a clear answer such as the adequacy of the minimally invasive approach, the effectiveness in the treatment of cIA (<2 cm) non-small cell lung cancer (NSCLC) and also the long-term functional impact of segmentectomy. The purpose of this narrative review is to clarify the role of sublobar resection by presenting the most important scientific papers on this topic, focusing on the minimally-invasive approach.

Methods: PubMed, Embase and Scopus were searched for "lung segmentectomy", "minimally-invasive lung segmentectomy", "Video Assisted Thoracic Surgery (VATS) segmentectomy", and "Robot Assisted Thoracic Surgery (RATS) segmentectomy" in January 2023.

Key Content and Findings: Four RCT studies, five systematic reviews and meta-analyses, one prospective and 12 retrospective studies published from 1995 to 2023 that compared the oncological and functional outcomes of lobectomy and segmentectomy were included. Seven retrospective papers compared the results of minimally-invasive simple or complex segmentectomy. The two recent large RCT (JCOG0802/WJOG4607L and CALBG/Alliance 140503) demonstrate the non-inferiority of segmentectomy on the overall survival (OS) and disease-free survival (DFS) and partial functional advantage 6 months after surgery. The oncological adequacy of segmentectomy was demonstrated also by several retrospective studies in which the functional impact of segmentectomy was more evident. The retrospective studies on simple and complex segmentectomy showed that these procedures are feasible, associated with an increased risk of post-operative prolonged air leak, but complex segmentectomy considered oncologically sound option for clinical stage IA NSCLC.

Conclusions: Segmentectomy could become the standard surgical approach for small and peripheral clinical IA NSCLC guaranteeing adequate oncological outcomes and a more preserved lung function.

Keywords: Segmentectomy; minimally-invasive segmentectomy; early-stage non-small cell lung cancer (early-stage NSCLC); complex segmentectomy; simple segmentectomy

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Introduction

Lung tumors are one of the leading causes of death in the world, and the number of cases is increasing worldwide (1). It is generally accepted (2) that surgical resection of early-stage lung cancer is curative and lobectomy with systematic nodal dissection has long been considered the best option and mainstay for early-stage non-small cell lung cancer (NSCLC). The first randomized controlled trial (RCT) comparing oncologic outcomes between lobectomy and sublobar resection, including segmentectomy and wedge resection, was started in 1982, the accrual concluded in 1988 and the results were published in 1995 by the Lung Cancer Study Group (LCSG) (3). The study stated that lobectomy was superior to limited pulmonary resections in terms of both overall survival (OS) and recurrence rate; furthermore, compared to lobectomy, sublobar resection did not result in better perioperative and postoperative outcomes (morbidity, mortality, and pulmonary function). Consequently, sublobar resection was a compromise surgery reserved only for patients with impaired pulmonary function who could not tolerate lobectomy.

However, with recent technological advances in radiological imaging and the advent of computed tomography (CT) low-dose screening programs, the diagnosis of early-stage lung cancer and ground glass opacity (GGO) has improved significantly (4). Therefore, many physicians wondered whether it was more appropriate to perform segmentectomy rather than lobectomy in patients with small peripheral lung cancer at an early stage. In the last 20 years, several studies have emphasized the feasibility and oncologic appropriateness of sublobar resection for stage I lung cancer and demonstrated its equivalence to lobectomy (5-8).

The turning point regarding the exact role of limited pulmonary resections came recently with the publication of two RCTs (JCOG0802/WJOG4607L and CALBG/Alliance 140503) that definitively confirmed and demonstrated the noninferiority of sublobar resection compared with lobectomy in terms of OS (9,10).

The JCOG0802/WJOG4607L was a Japanese multicenter (70 institutions), phase III, randomized, controlled trial designed to demonstrate noninferiority of segmentectomy versus lobectomy for treatment clinical stage IA small-sized (≤2 cm; consolidation-to-tumor ratio >0.5) peripheral NSCLC, regardless of the patient's respiratory function and other clinical factors. This study led to two main conclusions: first, segmentectomy is superior than lobectomy in terms of OS, and secondly, patients at stage IA who are operated with curative intent (whether lobectomy or segmentectomy) can expect a 5-years survival rate of 90% or more.

Also, the recently published CALGB/Alliance 140503 was a multicenter (83 institutions), randomized noninferiority trial that enrolled 697 patients with cT1a (2 cm) N0 NSCLC without hilar and mediastinal lymph node metastases. Participants were randomly assigned to the sublobar resection arm (segmentectomy or wedge resection at the surgeon's discretion) or lobectomy arm. Analysis of the results showed that OS and 5-year disease-free survival (DFS) were comparable between sublobar resection and lobectomy. Data from these two studies suggest that sublobar resections should be the standard treatment for patients with early-stage NSCLC (cT1aN0 peripheral, <2 cm) without nodal metastases. In addition, sublobar resections could also provide an important advantage in terms of preserving postoperative lung function (11).

From a technical point of view, sublobar resections include both wedge resection and segmentectomy, but the surgical difficulties differ considerably: wedge resection involves nonanatomic excision of the lung parenchyma where the tumor is located, whereas segmentectomy involves anatomic excision of the lung segment after isolation, suturing, and incision of veins, bronchi, and segmental arteries.

The segmentectomy in turn, in accordance with Handa and colleagues, can be divided into simple and complex segmentectomy (12). The authors define a simple segmentectomy as a segmental resection which requires a single linear dissection of the intersegmental plane as the right and left S6 segments, lingula segment or left upper division. Instead, complex segmentectomy requires the creation of two or more intersegmental planes and the surgical procedure is objectively more complicated; the resection of the left S1+S2, the right S3, right S2 or the single pyramidal segments could be considered as complex segmentectomy. Furthermore, the minimally-invasive approach [both thoracoscopic—video-assisted thoracic surgery (VATS) or robot-assisted thoracic surgery (RATS)] is nowadays widely accepted for lung resection for cancer (2) and it could be considered absolutely more complex than thoracotomy almost during the creation of the intersegmental plane due to the limits of the rib cage and the lack of three-dimension.

To date, sublobar resection should be the standard surgical treatment for early-stage NSCLC IA, but

Table 1 The search strategy summary

Items	Specification
Date of search	January 2023
Databases and other sources searched	PubMed, Embase, Scopus
Search terms used	Lung segmentectomy, minimally-invasive lung segmentectomy, VATS segmentectomy, RATS segmentectomy
Timeframe	1995 to 2023
Inclusion criteria	Meta-analysis, retrospective and prospective studies, systematic reviews and randomized controlled trials in English language were included
Selection process	The selection was conducted by S.B. and A.S. independently

VATS, video-assisted thoracic surgery; RATS, robot-assisted thoracic surgery.

lobectomy remains the surgical technique preferred by many surgeons, as anatomical segmentectomy is still a major technical challenge, especially with the minimally-invasive approach.

The aim of this narrative review is to summarize the current literature on sublobar resection and its role in lung cancer surgery evaluating postoperative outcomes and OS compared with lobectomy. We present this article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-23-45/rc).

Methods

PubMed, Embase and Scopus were searched for "lung segmentectomy", "minimally-invasive lung segmentectomy", "VATS segmentectomy", and "RATS segmentectomy" in January 2023 as shown in the search strategy table (*Table 1*). This research was focused on original papers about segmentectomy, minimally invasive segmentectomy (systematic reviews and papers about hybrid procedures were excluded) and the comparison between lobectomy sublobar resection in the English language. Articles were independently screened by authors (S.B. and A.S.) for type and year of publication, first author, number of patients involved, pre-operative and post-operative characteristics, post-operative complications and oncological outcomes. Characteristics for all included studies on the comparison between lobar and sublobar resection are summarized in *Table 2* (3,6-10,13-28). Four RCT studies, five systematic reviews and meta-analyses, one prospective and 12 retrospective studies published from 1995 to 2023 were included.

Table 3 (12,29-34) depicted the selected published papers (all retrospective and single center) on minimally invasive segmentectomy. No formal statistical procedures (meta-analysis) were performed.

Adoption of minimally-invasive segmentectomy

In the last twenty years, with the improvement of technologies and the development of new devices, the use of minimally invasive surgery, VATS and RATS, have increased significantly and have thus fully entered the surgical routine (2). However, sublobar resection, especially anatomical segmentectomy, is still largely performed in open surgery (lateral or postero-lateral thoracotomy) because of the technical difficulties in handling the intersegmental planes and segmental hilum. Effectively, the large part of segmentectomy performed in the JCOG0802/WJOG4607L RCT were conducted with a hybrid technique, whereas in the CALGB/Alliance 140503 RCT a more consistent rate of minimally invasive sublobar resection was reported (81%), but we need to consider the large adoption rate of wedge resection in this RCT. Furthermore, the multi-institutional analysis of the ESTS database confirmed that minimally invasive segmentectomy (35) was performed in a third of patients (31.9%) in the period 2007–2018.

VATS has shown comparable oncological outcomes to thoracotomy, but is associated with less postoperative pain and a shorter hospital stay (36). The studies published to date show no differences between VATS lobectomy and VATS segmentectomy in terms of operative time, hospital stay, postoperative complications, and duration of chest drainage (16,22,23,37). Recently, the RCT VIOLET study (38) compared the post-operative results

Table 2 Clinical studies comparing sublobar resection and lobar resection in lung surgery

Authors	Country	Type	Period	No. patients	Wedge resection	NSCLC stage	Conclusion
Ginsberg *et al.* 1995, (3)	USA	RCT	1982–1988	247	Yes	T1N0 (≤3 cm)	Lobectomy superior *vs.* segmentectomy
Harada *et al.* 2005, (13)	Japan	Retrospective (propensity score matching)	2005	83	No	cT1N0M0 (≤2 cm)	Segmentectomy superior *vs.* lobectomy
Nakamura *et al.* 2005, (14)	Japan	Meta-analysis	1970–2004	14 studies analyzed	Yes	IA/IB	Sublobar resection noninferior *vs.* lobectomy
Okada *et al.* 2006, (15)	Japan	Retrospective	1992–2001	313	Yes	T1aN0 (≤2 cm)	Sublobar resection noninferior *vs.* lobectomy
Kilic *et al.* 2009, (8)	USA	Retrospective	2002–2007	184	No	I	Sublobar resection noninferior *vs.* lobectomy
Shapiro *et al.* 2009, (16)	USA	Retrospective	2002–2008	144	No	I	Segmentectomy noninferior *vs.* lobectomy
Whitson *et al.* 2011, (17)	USA	Retrospective	1998–2007	14,473	No	I	Lobectomy superior *vs.* segmentectomy
Fan *et al.* 2012, (18)	China	Meta-analysis	1990–2010	24 studies analyzed	Yes	I (≤2 cm)	Segmentectomy noninferior *vs.* lobectomy; wedge resection inferior *vs.* lobectomy
Yendamuri *et al.* 2013, (19)	USA	Retrospective	1988–2008	8,797	Yes	I (≤2 cm)	Lobectomy superior *vs.* sublobar resection
Altorki *et al.* 2014, (20)	USA	Retrospective	1993–2001	347	Yes	I	Sublobar resection noninferior *vs.* lobectomy
Tsutani *et al.* 2014, (7)	Japan	Prospective	2005–2010	610	Yes	IA (GGO dominant)	Sublobar resection noninferior *vs.* lobectomy
Zhang *et al.* 2015, (21)	China	Meta-analysis	1980–2014	21,926	Yes	I	Lobectomy superior *vs.* segmentectomy
Hwang *et al.* 2015, (22)	South Korea	Retrospective (propensity score matching)	2005–2013	1,149	No	T1aN0 (≤2 cm)	Segmentectomy noninferior *vs.* lobectomy
Gu *et al.* 2017, (6)	USA	Retrospective (propensity score matching)	2004–2013	188	Yes	IA	Sublobar resection noninferior *vs.* lobectomy
Song *et al.* 2018, (23)	Japan	Retrospective (propensity score matching)	2007–2016	163	No	IA	Segmentectomy noninferior *vs.* lobectomy
Stamatis *et al.* 2019, (24)	Germany	RCT	2013–2016	108	No	I (≤2 cm)	Segmentectomy superior *vs.* lobectomy in terms of postoperative outcomes and quality of life
Ijsseldijk *et al.* 2020, (25)	Netherlands	Meta-analysis/ systematic review	2000–2018	28 studies analyzed	Yes	T1aN0	Sublobar resection noninferior *vs.* lobectomy

Table 2 (*continued*)

Table 2 (*continued*)

Authors	Country	Type	Period	No. patients	Wedge resection	NSCLC stage	Conclusion
Wen *et al.* 2020, (26)	China	Retrospective (propensity score matching)	2008–2018	1,108	No	I (≤2 cm)	Segmentectomy noninferior *vs.* lobectomy
Yu *et al.* 2021, (27)	China	Retrospective	1998–2016	9,580	No	IA (size of 21–30 mm)	Segmentectomy superior *vs.* lobectomy in terms of postoperative outcomes and quality of life
Saji *et al.* 2022, (9)	Japan	RCT	2009–2014	1,106	No	IA (≤2 cm; CTR >0.5)	Segmentectomy superior *vs.* lobectomy
Xu *et al.* 2022, (28)	China	Meta-analysis	1999–2018	14 studies analyzed	No	I	Segmentectomy superior *vs.* lobectomy in terms of postoperative outcomes and quality of life
Altorki *et al.* 2023, (10)	USA	RCT	2007–2017	697	Yes	T1aN0 (≤2 cm)	Sublobar resection noninferior *vs.* lobectomy

NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; GGO, ground glass opacity; CTR, consolidation-to-tumor ratio.

Table 3 Clinical retrospective studies reporting and comparing simple and complex minimally-invasive segmentectomy

Authors	Country	Type	Period	N. patients	NSCLC stage	Surgical approach
Handa *et al.* 2019, (12)	Japan	Retrospective	2007–2017	209	I	Hybrid VATS/RATS
Bédat *et al.* 2019, (29)	Switzerland	Retrospective	2014–2018	232	Primary and metastatic tumor	VATS
Okubo *et al.* 2021, (30)	Japan	Retrospective	2012–2018	538	I (nodule ≤3 cm)	VATS
Handa *et al.* 2021, (31)	Japan	Retrospective	2007–2018	580	I	Hybrid VATS/VATS/RATS/ open
Ohtaki *et al.* 2022, (32)	Japan	Retrospective	2010–2021	118	Primary and metastatic tumor	VATS/open
Zhou *et al.* 2022, (33)	USA	Retrospective	2004–2019	222	Primary and metastatic tumor	VATS/RATS/open
Bongiolatti *et al.* 2023, (34)	Italy	Retrospective	2015–2020	163	IA	VATS

NSCLC, non-small cell lung cancer; VATS, video-assisted thoracic surgery; RATS, robot-assisted thoracic surgery.

of lobectomy preformed with the minimally invasive thoracoscopic approach with thoracotomy and the authors demonstrated comparable post-operative results in terms of mortality, post-operative complications and severe adverse events, length of stay, number of dissected lymph nodes, rate of complete resection, percentage of adjuvant therapy delivered and 1-year OS and DFS. Thoracoscopic lobectomy was associated with less post-operative pain and the authors stated that the advantages of minimally-invasive surgery "*extended after discharge, with superior physical function, continued less pain, fewer serious adverse events (SAEs) and hospital readmissions, and improved general quality of life*".

Several studies have confirmed the feasibility and safety of RATS in the treatment of NSCLC (2). However, these studies are often monocentric, with small samples. Therefore, the equivalence between the two techniques, the advantages and disadvantages in the treatment of lung cancer are not yet clear. In a recent meta-analysis,

perioperative outcomes were compared between VATS and RATS in the treatment of NSCLC (39). The analysis included 18 studies with a total of 60,349 patients (RATS =8,726 and VATS =51,623) and found no significant differences in perioperative outcomes between VATS and RATS. The authors argue that the two surgical techniques are equivalent.

Surgical classification of segmentectomies

Anatomical lung segmentectomy is frequently still performed by thoracotomy or with a hybrid approach (9,12) and also the surgical-technical difficulties in performing segmentectomy minimally-invasively are depending on the segment to be resected and then Handa proposed a classification differentiating segmentectomy into simple and complex (12). Complex segmentectomy refers to a surgical procedure that requires the creation of multiple segmental planes and is technically more difficult. Simple segmentectomies are parenchymal resections that require the creation of only one intersegmental plane including the removal of the basal pyramid (right and left), the apical segment of the lower lobes (S6), lingula, and tri-segmentectomy of the left upper lobe. Few studies have been performed comparing the oncological outcomes of simple and complex segmentectomy (32-39). A recent expert consensus (40) between European Society of Thoracic Surgeons (ESTS) members suggested to distinguish segmentectomy into single (removal of a single segment) and multiple (removal of more than one segment) almost because this classification have a functional implication.

Post-operative outcomes of segmentectomy

Several studies investigated perioperative outcomes after sublobar resection and compared them with those of lobectomy. Already in 2005, Harada and coworkers (13) compared the degree postoperative functional loss of segmentectomy with lobectomy. They analyzed forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and anaerobic threshold measured preoperatively at 2 and 6 months after surgery in 45 patients undergoing lobectomy and 38 patients undergoing intentional segmentectomy for NSCLC. The postoperative loss of function was directly related to the amount of lung parenchyma removed, and segmentectomy showed better functional preservation than lobectomy even 6 months after surgery.

A prospective, randomized phase III trial was recently published by Stamatis *et al.* (24) that evaluated perioperative complications and quality of life in patients undergoing segmentectomy for early-stage IA NSCLC (<2 cm). One hundred and eight patients were enrolled and randomly assigned to segmentectomy (n=54) or lobectomy (n=54). The 90-day mortality was the same in both groups, 0%. Perioperative complications were slightly lower after segmentectomy than after lobectomy, but did not reach statistical significance. However, patients who have undergone lobectomy, at an interval of 12 years after surgery, have significant worsening of physical health (P<0.001), cognitive functioning (P=0.025), pulmonary function such as dyspnea (P<0.001) and fatigue (P=0.003). Instead, patients undergoing segmentectomy recover from dyspnea faster than the lobectomy group (P=0.016 after 12 months) and had a better quality of life.

Functional impact of segmentectomy

A recent meta-analysis (28) examined postoperative lung function in patients with NSCLC after lobectomy or segmentectomy. In this analysis 14 studies were included and clinical outcomes [ΔFEV1, ΔFVC, ΔFEV1/FVC, Δ diffusing capacity of the lung for carbon monoxide (DLCO)] were analyzed. The results showed that patients in the segmentectomy group had better pulmonary function with a smaller decrease in FEV1, FVC, FVC%, FEV1/FVC and DLCO compared with the lobectomy group.

Preservation of respiratory function, measured as FEV1, by sublobar resection was also reported in JCOG0802 and CALGB 140503 trials. These studies reported that the reduction of FEV1 to 6 and 12 months was greater in patients who underwent lobectomy (9,10).

Is prolonged air leak (PAL) a real issue after segmentectomy?

Several (9,12,41,42) authors reported that parenchymal-sparing resection is associated with PAL, an important postoperative complication that can slow the recovery, increase hospital stay, chest tube duration, costs and could also postpone adjuvant treatments if needed.

The JCOG0802 study reported a significantly higher rate of PAL in the segmentectomy group compared with lobectomy group (6.5% *vs.* 3.4%, P=0.004) and the authors

considered this percentage acceptable especially for the presence of complex segmentectomies in which the risk of PAL is higher (9). Gonzalez *et al.* (41) reported a prevalence of air leak of 14.1% in patients treated with segmentectomy for NSCLC. The retrospective cohort study conducted by Gooseman and colleagues (42) also yielded similar results, with PAL occurring in 19% of patients. According to some authors, the increased rate of PAL in segmentectomies is due to the more use of electrocautery to complete the pulmonary fissure and the intersegmental plane (9) and in order to minimize postoperative air leakage, some authors suggest that the intersegmental plane should therefore constructed with a stapler device or apply an absorbable mesh on the new plane (43).

Post-operative results of simple and complex segmentectomies

Bongiolatti *et al.* (34) in their retrospective analysis evaluated the postoperative results after simple and complex segmentectomies performed with minimally invasive techniques. The data of 123 patients (n=65 simple segmentectomy and n=58 complex segmentectomy) operated for lung cancer with VATS were analyzed and no difference was found between segmentectomy types in 5-year OS and DFS. According to the authors, minimally invasive surgery to perform segmentectomies, both simple and complex, is an appropriate option for patients with early-stage lung cancer (stage IA, 2 cm).

Another large retrospective study published in 2021 by Okubo and coworkers (30) compared the perioperative outcomes of 538 patients after simple (n=287) and complex (n=251) segmentectomy. The results showed that complex segmentectomy provides good surgical and postoperative results and is not inferior to simple segmentectomy, moreover patients who undergo complex segmentectomy have a shorter hospital stay and less persistent air leak. *Table 4* depicted the post-operative results of complex and simple minimally-invasive segmentectomy.

The more critical aspect of minimally-invasive complex segmentectomy is the feasibility of a lower lobe single segmentectomy (excluding apical segments) for small tumoral lesion because several issues could raise: first of all, the small lesion is hard to identify and frequently not palpable and then the precise construction of an oncologically safe intersegmental plane could be challenging. Moreover, the creation of two or more intersegmental plane in thoracoscopy could be a strenuous and demanding procedure exposing also to a theoretically increased risk of surgical complications such as a post-operative PAL and a consequent longer length of stay. At the last, the segmental branches of the pulmonary artery and vein are small and delicate and this frailty could determine intraoperative injuries during dissection that lead to more extensive resection. Considering these issues, VATS multiple segmentectomies of the lower lobes could be considered easier, safer and oncologically more adequate due to wider margins and also these resections showed a functional advantage in comparison with VATS lobectomy (11).

Although further clinical studies are needed, minimally invasive surgery to perform both simple and complex segmentectomies appears to be a feasible, safe, and satisfactory procedure. To date, no studies have reported the post-operative or oncological results of RATS complex segmentectomies.

Several techniques are available to construct the intersegmental plane (44), but the indocyanine-green administration with near-infrared fluorescence seem reliable, accurate and time saving despite the higher costs of the instrumentation (45). The indocyanine-green administration could be more accurate than inflation techniques especially in the construction of complex intersegmental plane of the upper lobes during segmentectomy in emphysematous lungs, but more research are need to clarify the role of the florescence in this field.

Oncological outcomes of segmentectomy

The LCSG (3) was the first prospective, multi-institutional RCT comparing oncologic outcomes between lobectomy and limited resection (segmentectomy or wedge resection) for early-stage NSCLC (T1N0). Two hundreds and forty-seven patients were enrolled in this study, of whom 122 underwent sublobar resection, while 125 received lobectomy. The study failed to demonstrate the oncologic equivalence between lobectomy and sublobar resection; patients who received limited resection had a 75% increased recurrence rate, in addition, sublobar resection was associated with a 30% increase in the overall mortality rate. However, several limitations affected the study by Ginsberg and colleagues, including the inclusion of tumors up to 3 cm in diameter, a large number of wedge resections in the limited resection group (32.8%), and also the nonroutine use of CT in the preoperative evaluation and postoperative follow-up (46).

Table 4 Comparison of the post-operative outcomes after simple and complex segmentectomy

Authors	Operative time (min)		Blood loss (mL)		Hospital stay (days)		Prolonged air leak (days)		Pneumonia		Bleeding		30-days mortality	
	Median [IQR] or mean (± SD)	P value	Median [IQR]	P value	Median [IQR] or mean (± SD)	P value	N (%)	P value	N (%)	P value	N (%)	P value	N (%)	P value
Handa *et al.* 2019, (12)		<0.0001		0.43		0.17		0.83	Not reported	–		–		>0.99
Complex segmentectomy (n=117)	180 [153–209]		50 [25–84]		7 [6–9]		14 (12.0)				2 (1.7)		0	
Simple segmentectomy (n=92)	143.5 [126–182]		40 [20–90]		6 [5–8]		10 (10.9)				0		0	
Bédat *et al.* 2019, (29)	Not reported		Not reported	–		0.026	Not reported	–		0.064		0.51		0.14
Complex segmentectomy (n=111)					5 [1–36]				8 (7.2)		2 (1.8)		2 (1.8)	
Simple segmentectomy (n=121)					7 [2–31]				18 (14.9)		1 (0.8)		0	
Okubo *et al.* 2021, (30)		0.51		0.76		0.0001		0.035		0.63		>0.99		>0.99
Complex segmentectomy (n=251)	113 [102–127]		20 [11–35]		3 [3–4]		5 (2.0)		1 (0.4)		0		0	
Simple segmentectomy (n=287)	113 [101–125]		20 [10–34]		4 [3–5]		10 (3.5)		3 (1.0)		1 (0.3)		1 (0.3)	
Handa *et al.* 2021, (31)	Not reported	–	Not reported	–		0.7	Not reported	–	Not reported	–	Not reported	–	Not reported	–
Complex segmentectomy (n=135)					7 [6–9]									
Simple segmentectomy (n=83)					7 [6–10]									
Ohtaki *et al.* 2022, (32)		0.76		0.023	Not reported	–		0.24		0.44	Not reported	–		–
Complex segmentectomy (n=53)	230 [190–270]		12 [0–70]				2 (3.8)		2 (3.8)				0	
Simple segmentectomy (n=65)	218 [181–248]		36 [8–112]				6 (9.2)		1 (1.5)				0	
Bongiolatti *et al.* 2023, (34)		0.11	Not reported	–		0.38		–		–		–		–
Complex segmentectomy (n=58)	181.9 (±49.6)				6.07 (±3.47)		0		3 (5.1)		0		0	
Simple segmentectomy (n=65)	156.9 (±36.6)				6.58 (±3.11)		3 (4.6)		2 (3.1)		1 (1.5)		0	

IQR, interquartile range; SD, standard deviation.

From that RCT, lobectomy was defined as the standard treatment for resectable early-stage NSCLC, leading to the assumption that lobectomy was associated with a higher survival rate and a lower recurrence rate. Subsequent studies have further supported the LCSG data and confirmed the inferiority of sublobar resection in terms of oncological outcomes; Whitson *et al.* concluded after database Surveillance Epidemiology and End Results (1998 to 2007) analysis that lobectomy offered greater benefits than segmentectomy in terms of 5-year OS (P<0.0001) and 5-year cancer-specific survival (P=0.0053) (17).

A recent meta-analysis examined the survival difference after lobectomy, segmentectomy, and wedge resection in stage I NSCLC; 42 studies published between 1980 and 2014 for a total of 21,926 patients were considered (21). This analysis showed that lobectomy was superior to sublobar resection with a combined hazard ratio (HR) of 1.530 (95% confidence interval: 1.402–1.671, P<0.001).

Despite the results of these studies, in recent years many authors have tried to prove the feasibility and non-inferiority of sublobar resection of lung cancer.

In 2006, a non-randomized study by Okada *et al.* (15) compared sublobar resection (segmentectomy and wedge resection) with lobectomy for the treatment of peripheral cT1N0M0 NSCLC of 2 cm or less. Patients who underwent segmentectomy or wedge resection had OS and DFS of 85.9% and 83.4%, respectively, compared with 89.6% and 89.1% in the lobectomy group. The multivariate analysis confirmed these results showing that the prognosis of sublobar resection was not worse than that of lobectomy. Finally, the study concluded that limited resection should be considered a viable alternative to lobectomy because DFS and OS were comparable.

In their systematic review and meta-analysis, Ijsseldijk *et al.* (25) compared oncological outcomes between parenchymal-sparing resection (segmentectomy and wedge resection) and standard lobectomy for T1a NSCLC. The authors identified 11,195 articles, of which 28 were included in the analysis; the results of this study show that segmentectomy and wedge resection have equivalent 5-year OS and DFS as lobectomy.

The same results demonstrating the oncologic equivalence of sublobar resection and lobectomy have also been reported by other authors (47).

In a large retrospective analysis, Landreneau *et al.* (47) performed propensity score matching of 1,192 patients who had undergone lobectomy (n=800) or segmentectomy (n=392) for early-stage lung cancer (T1 <3 cm in diameter). The primary end point of this analysis was to compare segmentectomy with lobectomy by evaluating clinical outcomes (DFS and OS); no statistically significant differences in 5-year survival and recurrent disease rates were observed between the two groups. OS was 54% for segmentectomy and 60% for lobectomy (P=0.258) and freedom from recurrence were also 70% and 71%, respectively (P=0.467); The 30-day and 90-day mortality rates were also comparable between the two groups.

Similar oncological results were also reported by Altorki *et al.* The authors analyzed the International Early Lung Cancer Action Program (I-ELCAP) database and identified 347 patients with clinical stage IA NSCLC (cT1N0M0) who underwent sublobar resection (n=53) and lobectomy (n=294), and no differences in survival rates were observed (20). Despite an increasing number of articles (14,18,19,26) suggesting the usefulness and validity of sublobar resection for peripheral stage I NSCLC, resection of even the smallest lung carcinoma is still considered by many surgeons as a compromise option to be considered only for physiologically compromised patients who are not candidates for lobectomy (27).

Recently, however, the results of two large RCTs comparing lobectomy with sublobar resection have been published: JCOG0802/WJOG4607L (9) and CALGB/ALLIANCE 140503 (10). The results of these two studies definitely demonstrated the fundamental role of sublobar resection in clinical stage IA NSCLC.

Unlike the LCSG, the JCOG0802/WJOG4607L study showed that 5-year OS is better in the segmentectomy (94.3%) group than in the lobectomy group (91.1%) and 5-year recurrence-free survival was 88% and 87.9%, respectively. However, it is important to note that locoregional recurrences were greater in patients who underwent segmentectomy (11%) than in those who underwent lobectomy (5%). Based on these results, the authors recommend performing anatomic segmentectomy in patients with small peripheral NSCLC (early clinical stage IA) and also argue that segmentectomy should be the standard surgical treatment in these patients.

The CALGB/ALLIANCE 140503 RCT was published in 2023 and the results were similar to those JCOG0802: the authors showed a 5-year OS of 80.3% after sublobar resection and 78.9% after lobectomy; the 5-year DFS was 63.6% and 64.1%, respectively. The recent RCTs JCOG0802 and CALGB 140503 data showed unambiguously that patients undergoing sublobar resection have comparable OS to patients undergoing lobectomy.

For these reasons, sublobar resection is likely to become the standard treatment for peripheral and small early-stage NSCLC.

Conclusions

The two large RCTs (JCOG0802 and CALGB 140503) definitively demonstrated the non-inferiority of sublobar resection in the treatment of early-stage lung cancer (IA, <2 cm, peripheral). On this basis, parenchymal-sparing surgery should be considered the standard treatment for patients with early-stage lung cancer, regardless of respiratory function and concomitant diseases. Controversies in the application of segmentectomy could arise in the use of this procedure for cT1c, IA3 NSCLC, for completely solid nodules, for more aggressive adenocarcinoma subtypes and an argument of debate is if the segmentectomy is adequate in the presence of spread through air spaces (STAS) (48-52).

In conclusion, it is very likely that in the near future, with the increasing use of lung cancer screening programs, the detection of small peripheral nodules will increase and sublobar resection will take a leading position and become the surgical strategy of first choice.

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Footnote

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