



Current indications and outcomes for thoracoscopic segmentectomy for early stage lung cancer

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Contributions: (I) Conception and design: SJ Swanson; (II) Administrative support: All authors; (III) Provision of study materials or patients: SJ Swanson; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Management of early stage non-small cell lung cancer (NSCLC) is evolving as the epidemiology of NSCLC has changed due to decreased rates of smoking in the general population, the development of screening programs and advancements in imaging modalities. Surgical technique is also evolving as a result of changes in instrumentation. Segmentectomy for early stage NSCLC has the advantage of preservation of lung function. Video-assisted thoracic surgery (VATS) segmentectomy is a safe option for surgeons already experienced in VATS lobectomy and offers comparable oncological benefit with better quality of life in selected patients. In this article, we will examine the role of segmentectomy and VATS for early stage NSCLC.

Keywords: Video-assisted thoracic surgery (VATS); segmentectomy; non-small cell lung cancer (NSCLC)

Submitted Apr 19, 2019. Accepted for publication Jul 02, 2019.

doi: 10.21037/jtd.2019.07.06

View this article at: <http://dx.doi.org/10.21037/jtd.2019.07.06>

Introduction

The best treatment of stage I non-small cell lung cancer (NSCLC) over three decades was established as lobectomy following Ginsberg *et al.*'s study in 1995 (1), showing a clear survival advantage of lobectomy over limited resections. Video-assisted thoracic surgery (VATS) is superior to open anatomic resections due to equivalent oncological outcome and better quality of life parameters (2,3).

Since Ginsberg's report, the epidemiology of early stage lung cancer has changed. Increased use of computerized tomography (CT) scans both as a diagnostic and a screening tool, led to increased detection of early stage NSCLC (4,5). Also due to easier/widespread access to medical care and better management algorithms, more patients now present with small lung nodules and many patients are older (e.g., octogenarians) or have later stages of well managed chronic disease [chronic obstructive lung disease (COPD), cardiovascular disease] (6). As a result, parenchymal sparing operations have been proposed as a viable alternative to

lobectomy, with comparable survival (7-9).

The role of segmentectomy in early stage NSCLC is still controversial in terms of selection criteria (patients with limited cardiopulmonary reserve *vs.* general patient population), oncologic efficacy of the resection, technical considerations such as surgical margins and effective lymph node dissection/sampling. Also, segmentectomy may minimize patient morbidity, be associated with better quality of life and allow for potential multimodality treatment protocols.

Contemporary outcomes

Contemporary literature has many reports as to whether thoracoscopic segmentectomy is the best lung-sparing operation for early stage lung cancer, both in terms of oncologic efficacy and morbidity. Wedge resections were also evaluated against both lobectomies and segmentectomies, offering comparable survival with some caveats (size of the margins, histologic type, solid component, lymph node

dissection) (9-11). National database studies demonstrating worse outcomes for sub-lobar resections often note that a patient receiving a sub-lobar resection is more likely to have undergone a less extensive mediastinal lymph node dissection (11,12). Surgeons who choose proper sized tumors, achieve adequate margins and lymph node assessment report comparable outcomes for sub-lobar resections (13-15) (Table 1).

Altorki *et al.* (17) reported their institutional experience with sublobar resections and compared wedge resections (n=160) with anatomic segmentectomies (n=129). In his article, 30% of the patients were deemed to be able to tolerate lobectomy but received sublobar resection (37 wedge, 48 segmentectomy). Three- and 5-year survival and disease-free survival were found to be comparable between those groups, with similar patterns of recurrence, despite less extensive lymph node assessment in the wedge resection group. The ability to tolerate lobectomy was not found to be a determinant in terms of oncologic outcomes.

In a meta-analysis done by Fan *et al.* (18), 24 studies involving 11,360 patients between 1990 and 2010, compared lobar with sub-lobar resections, overall survival was similar between the groups for tumors smaller than 2 cm.

Risk factors for locoregional recurrence were examined by Koike *et al.* (19). Three hundred and twenty-eight patients with stage 1a NSCLC without invasive pre-operative mediastinal node sampling were included in the study (216 segmentectomies and 112 wedge resections). Wedge resection, microscopic positive surgical margin, visceral pleural invasion and lymphatic permeation were identified as independent predictors of locoregional recurrence and poor disease-specific survival. One hundred sixty patients received sub-lobar resection due to their compromised status, the rest of the sub-lobar resections were intentional. The segmentectomy group was found to have a 5-year recurrence-free survival probability of 93% versus 66% in the wedge resection group. They also noted that the extent of lymph node resection (systematic dissection versus sampling) and tumor size (<2 *vs.* >2 cm) were significant predictors for 5-year freedom from locoregional recurrence (19).

For ground glass opacity (GGO) dominant nodules, a case series of 239 patients (identified from 610 consecutive early stage NSCLC resections) who had a lobectomy, segmentectomy or wedge resection were reported by Tsutani *et al.* (16). They observed no difference in 3-year recurrence-free survival between stage IA patients who received lobectomy, segmentectomy or wedge resection. Lymphatic, vascular and pleural invasion were rare and only 2 out of 84 T1b patients were found to have lymph node metastasis.

Patient selection

Since lobectomy remains the gold standard approach for operable NSCLC in terms of disease specific outcomes, patient selection for segmentectomy carries the utmost importance. Existing studies mostly concentrate on segmentectomy as a comparable alternative to lobectomy in patients with limited cardiopulmonary reserve who would not tolerate a lobectomy. Segmentectomy in those patients can offer a better chance for disease specific and overall survival for tumors <2 cm, as long as proper deep margins and sufficient nodal evaluation/clearance are achieved (20).

Segmentectomy and wedge resection of NSCLC combined with LVRS in 14 patients with severely impaired lung function due to emphysema was identified as an alternative to SBRT in patients meeting LVRS criteria by Caviezel *et al.* (21). Median pre-operative forced expiratory volume in one second was observed to have increased to 37% from 32.5% (P=0.002) 3 months following surgery. Three and 5-year survival rates were reported as 50% and 35%.

There are several considerations regarding segmentectomy versus lobectomy for stage 1a NSCLC. For example, Stiles *et al.* (22) report that among 266 patients deemed to have clinical stage 1a NSCLC (with Chest CT and PET), only 65% were pathological stage 1a after pathological staging. Tumor size >2 cm was associated with upstaging (49% *vs.* 29%). So, depending on the functional status of the patient, clinical under-staging may result in segmentectomies in patients who would be otherwise better served with lobectomy. Tumors bigger than 2 cm are more likely to have local recurrence and overall worse results with sublobar resection of any kind (1,16,18,22) so sublobar resection in this group of patients should be avoided if lobectomy is tolerable.

In terms of PET-avid early stage lesions Kamel *et al.* (23), report a retrospective review of a prospective database, comparing lobectomy to segmentectomy, including 414 PET-avid (SUV >3) clinical stage 1a NSCLC. A propensity score match from that database, reveals no 5-year recurrence-free survival benefit despite more thorough mediastinal lymph node dissection in the lobectomy group when compared with the segmentectomy group.

Technical considerations

VATS segmentectomy requires excellent understanding of the hilar/mediastinal anatomy and satisfactory comfort with instrumentation and surgical manipulation. Following

Table 1 Summarizes selected studies comparing lobectomy and segmentectomy

Study	Patient population	Operation (n)	Tumor classification	Results and survival
Tsutani <i>et al.</i> [2014] (16)	239 GGO dominant NSCLC	Lobectomy =90 Segmentectomy =56 Wedge resection =93	Wedge resection (cT1a/cT1b) =79/14 Segmentectomy (cT1a/cT1b) =37/19 Lobectomy(cT1a/cT1b) =39/51	Patients with LN metastasis cumulative: T1a/T1b =0/2 Three-year RFS Wedge resection =98.7%; mean RFS, 69.8 mo; 95% CI, 68.6–70.9 mo Segmentectomy =96.1%; mean RFS, 70.3 mo; 95% CI, 67.3–73.4 mo Lobectomy =96.4%; mean RFS, 71.4 mo; 95% CI, 61.9–73.7 mo P=0.44
Subramanian [2018] (12)	1,354 Stage 1A NSCLC	Lobectomy =1,354 Sublobar resection =333 Wedge =285 Segmentectomy =48	Lobectomy (Stage I/II/III) =298/17/10 Sublobar resection (Stage I/II/III) =309/9/7	Positive surgical margin unmatched lobectomy vs. sublobar resection =34/22, P=0.003 Positive surgical margin matched lobectomy vs. sublobar resection =8/22, P=0.013 Unmatched 5-year overall survival: Lobectomy =66.8% Sublobar resection =55.5% P=0.147 Matched 5-year overall survival: Lobectomy =56.5% Sublobar resection =55.6% P=0.561

Table 1 (continued)

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Study	Patient population	Operation (n)	Tumor classification	Results and survival
Cao [2018] (13)	16819 Stage 1A NSCLC, SEER database	Lobectomy =13,303	Lobectomy: <1 cm =1,160; 1.1–2.0 cm =6,586; 2.1–3.0 cm =5,257	Tumors <1 cm:
	Propensity matching:	Segmentectomy =809	Segmentectomy: <1 cm =127; 1.1–2.0 cm =461; 2.1–3.0 cm =221	Unmatched: equivalent lung cancer specific survival (LCSS), lobectomy and segmentectomy superior to wedge resection in overall survival (OS)
	segmentectomy versus lobectomy (n=126 pairs)	Wedge =3,007	Wedge: <1 cm =626; 1.1–2.0 cm =1,714; 2.1–3.0 cm =6,670	Matched: all three equal in LCSS and OS
	wedge resection versus lobectomy (n=514 pairs)			Tumors 1.1–2.0 cm:
	wedge resection versus segmentectomy (n=126 pairs)			Unmatched: equivalent LCSS, lobectomy superior to segmentectomy in OS
				Matched: lobectomy and segmentectomy have better LCSS and OS than wedge resections
				Tumors 2.1–3.0 cm:
				Lobectomy with better OS and LCSS than segmentectomy or wedge resection, for both univariate and multivariate unmatched and matched analyses

GGO, ground glass opacity; NSCLC, non-small cell lung cancer; RFS, recurrence-free survival.

the same general principles, a VATS segmentectomy can be completed as easily as a VATS lobectomy when the surgeon has adequate training. Placement of the ports, triangulation of the lesion, the type of surgical instruments are all important considerations. Identifying and exposing that particular segment's artery, bronchus and vein are crucial. While staplers can be used for smaller segmental vessels, energy-based ligation is also a safe alternative (24) as low-profile devices are easier to use when the dissection does not allow for adequate length of the vessel for proper stapler placement. Powered staplers are also potential alternatives to conventional staplers due to their lower profile and stability while firing. The intersegmental plane and fissure can be divided by staplers, cautery or energy devices. Usually segmental arteries and bronchi are the best anatomical guide for intersegmental planes.

A wedge resection rather than segmentectomy or a lobectomy can be another option for small subpleural nodules straddling the segment border as long as sufficient margins can be achieved and lymph node staging is completed (1,11,18).

Over the years, several investigators have tried to establish mapping protocols together with advanced imaging to help with both localizing the intersegmental plane and the draining lymph nodes. For example, Sato *et al.* used a combination of virtual bronchoscopy via high-resolution CT, navigational bronchoscopy and marking with indigo-carmin to aid in lesion detection and adequate surgical margin (25). While their technique did help with lesion detection, results were less impressive for surgical margin adequacy.

Lymph node assessment

Lymph node dissection during segmentectomy is very important in terms of recurrence free survival and postoperative treatment planning. White *et al.* report 10% of the cT1N0M0 of NSCLC patients, recruited from a 11,663 cases database, has at least one lymph node metastasis (26).

The quality of lymph node dissection and overall number of examined lymph nodes have been reported as important variables for both accurate staging for possible adjuvant treatments and overall survival. Liang *et al.* (27) reported outcomes of a SEER cohort [2001–2008] and Chinese multi-institutional registry and determined that 16 examined lymph nodes is the cut-off for accuracy of N0 prognosis. Upstaging and overall survival is improved as the number of lymph

nodes removed is increased. Overall survival improvement with more extensive lymph node assessment was seen in all pN groups. This finding is especially important since outcomes reported from a study that encompassed over ninety thousand patients who underwent resection for NSCLC from the National Cancer Database showed that only 23%, 27% and 39% of all resections done in community cancer programs, community comprehensive cancer programs and academic teaching centers respectively had more than 9 lymph nodes assessed (28).

One downside of segmentectomy is the difficulty in dissecting/sampling level 13 lymph nodes, especially when they are located in juxtaposition to the resected segment but within non-resected segments. For this problem, Nomori *et al.* evaluated sub-segmental lymph nodes in both resected and preserved segments during segmentectomy and concluded that segmental/subsegmental nodes can be reached and resected in 42 of the 94 cT1N0 patients (29).

Although rarely necessary, hybrid approaches (thoracoscopy with muscle sparing mini thoracotomy without retraction) have been described to help with both adequate surgical margins and a meticulous lymph node dissection (30).

Prognostic relevance of tumor margins and tumor size

Tumor size and margins are important factors for tumor recurrence, therefore they should be taken into consideration when deciding on the type of surgical resection. For tumors smaller than 2 cm and taken out with a wedge resection, patients with 1 cm margin were 45% less likely to have a local recurrence, when compared to patients with 5 mm margin. Beyond 15 mm, no additional benefit was seen (11,31).

In a Nomori *et al.* (32) study with a cohort of 179 patients who underwent open segmentectomy with systematic lymph node dissection for peripheral cT1N0M0 NSCLC, frozen section was used to achieve at least 2 cm surgical margin. Five-year disease-free survival was found to be 95% for patients with tumors smaller than 2 cm and 79% for those who had tumors between 2.1 and 3 cm.

Okada *et al.* (33) pooled 1,272 cases who had complete resection of stage I NSCLC via lobectomy, segmentectomy or wedge resection. Five-year cancer-specific survivals of patients with tumors of <20 and 21–30 mm were 92.4% and 87.4% after lobectomy, 96.7% and 84.6% after segmentectomy, and 85.7% and 39.4% after wedge resection.

Pulmonary function tests

Segmentectomy may be the more advantageous type of resection when compared to lobectomy for early stage NSCLC, regarding preservation of pulmonary function. Harada *et al.* (34) evaluated preoperative pulmonary function tests (PFT) and compared them at 2 and 6 months after radical segmentectomy (n=38) and lobectomy (n=45). The segmentectomy group was found to have significantly better preservation of lung volumes (FEV1 and FVC). Comparable results were also seen in Keenan *et al.*'s (35) retrospective analysis of patients undergoing lobectomy (n=147) or segmentectomy (n=54) for stage I NSCLC. While lobectomy patients exhibited both volumetric and diffusion capacity declines (FVC from 85.5% to 81.1%, FEV1 from 75.1% to 66.7%, diffusing capacity from 79.3% to 69.6%), segmental resection patients only exhibited decline of diffusion capacity without clinical deterioration (FVC from 72.8% to 69.1%, FEV1 from 55.3% to 52.2%). The decline in lung function was found to be correlated with the number of segments resected in the Nomori *et al.* study (36).

Conversely, Suzuki *et al.* (37) reported equivalent results for segmentectomy and lobectomy patients, for pulmonary function measured six months after surgery. In his study no functional differences were found at the end of 6 months with lobectomy patients recovering faster than predicted. Particularly for patients with limited pulmonary reserves (predicted postoperative FEV1 under 70, Kashiwabara *et al.* (38) found no functional advantage of segmentectomy over lobectomy.

As a result, larger series of patients, especially of patients with impaired lung function are needed for exploration and definition of the lower functional limits for surgery.

Future directions and ongoing trials

Thoracoscopic segmentectomy offers excellent oncological outcomes in patients with stage IA NSCLC, provided that adequate parenchymal margins are achieved and a complete lymph node dissection is done. Just like lobectomy, an oncologically sound segmental resection can be done via VATS, with the advantages of preservation of pulmonary capacity and quality of life. With the advent of targeted therapies, limited resections have the advantage (over SBRT or ablative methods) of providing a representative tissue sample for genetic analysis.

Even though large database studies and meticulously

done propensity score matching articles report comparable outcomes, the retrospective nature of these studies comparing lobar and sub-lobar resections cause ongoing controversy about the optimal management of small, peripheral NSCLCs. The Cancer and Leukemia Group B 140503 trial (Alliance trial) (39) finished enrollment in 2017 and randomly allocated 697 physically fit T1aN0 patients into lobar and sublobar resection (59% wedge) groups. Early perioperative results were published and notable for comparable mortality and morbidity in both groups. Prolonged air leak was more frequent in sublobar resections. This trial is notable for including both wedges and segmentectomies chosen at the discretion of the surgeon after randomization, so survival data may be limited regarding the oncologic non-inferiority issue. Another randomized controlled trial JCOG0802/WJOG4607L (40) also recently published perioperative results from 1,106 randomized patients between lobectomy or segmentectomy. Patients who had a lobectomy and segmentectomy had comparable postoperative complication profiles with the exception of complex segmentectomies (segmentectomies other than resection of the right or left segment 6, left superior, or lingular segment were considered complex, e.g., individual right upper lobe segments or basilar segmentectomy) having more pulmonary complications.

Our own institutional experience shows that, for NSCLC less than 2 cm, a segmentectomy is the best parenchymal preserving resection. A VATS approach can be used for this operation in a safe and standard fashion. A wedge resection is only reasonable for patients with very small nodules (<1 cm) that are located at segmental borders. Lymph nodes should be dissected regardless of the resection method (lobectomy, segmentectomy or wedge resection).

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Bilgi Z, Swanson SJ. Current indications and outcomes for thoracoscopic segmentectomy for early stage lung cancer. *J Thorac Dis* 2019;11(Suppl 13):S1662-S1669. doi: 10.21037/jtd.2019.07.06