Keynote Lecture Series

Open, thoracoscopic and robotic segmentectomy for lung cancer

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While lobectomy is the standard procedure for early stage lung cancer, the role of sublobar resection is currently under investigation for selected patients with small tumors. In this review, studies reporting outcomes on open, thoracoscopic and robotic segmentectomy were analyzed. In patients with stage I lung cancer, with tumors <2 cm in diameter and within segmental anatomic boundaries, segmentectomy appears to have equivalent rates of morbidity, recurrence and survival when compared to lobectomy. Segmentectomy also resulted in greater preservation of lung function and exercise capacity than lobectomy. It appears reasonable to consider segmentectomy for patients with stage I lung cancer (particularly in air-containing tumors with ground glass opacities) where tumors are <2 cm in diameter and acceptable segmental margins are obtainable, especially in patients with advanced age, poor performance status, or poor cardiopulmonary reserve. The results of two ongoing randomized controlled trials (CALGB 140503 and JCOG0802/WJOG4607L) and additional well-designed studies on open, thoracoscopic, and robotic segmentectomy will be important for clarifying the role of segmentectomy for lung cancer.

Keywords: Lung cancer surgery; minimally invasive surgery; thoracoscopy/video-assisted thoracoscopic surgery (VATS); segmentectomy

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Introduction

The first segmentectomy, a lingulectomy, was performed by Churchill and Belsey in 1939 for the treatment of bronchiectasis (1). Over the subsequent decades, segmentectomy was increasingly applied to small primary lung cancers (2,3). However in 1995, the Lung Cancer Study Group (LCSG) performed a randomized controlled trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer (NSCLC) and found that limited pulmonary resection for tumors <3 cm in size resulted in increased locoregional recurrence compared to lobectomy (4). Subsequently in North America, the use of segmentectomy for NSCLC was generally limited to patients with marginal cardiopulmonary function (5).

The LCSG trial is the only randomized controlled trial of lobectomy versus limited resection for lung cancer to date, and is indeed a landmark study. However, it enrolled patients from 1982-1988 (4) and the landscape of thoracic oncology has changed considerably. Since then, there have been new developments leading to renewed interest in segmentectomy for small primary lung cancer tumors (5). Firstly, there is now strong evidence that low-dose computed tomography (LDCT) screening in high-risk patients reduces lung cancer deaths. Importantly, the screening protocols have identified greater numbers of smaller lung tumors (<2 cm), which are more frequently operable and curable (6,7). Of note, the LCSG trial did not specifically assess the effect of lobectomy versus segmentectomy on smaller tumors, as 30% of patients in that study had tumors that were larger than 2 cm (4). Secondly, since 1995, newer staging modalities have emerged which will likely improve patient selection for anatomic lung resection (4). Thirdly, surgeons have advanced the fields of video-assisted thoracoscopic surgery (VATS) and robotic surgery, with increasing experience at applying those approaches to segmentectomy. These new developments have led to a growing number of studies investigating the use of open, minimally invasive and robotic segmentectomy for carefully selected patients with smaller tumors less than 2 cm in size, especially in patients with marginal cardiopulmonary function (5).

A previous review of these studies demonstrated that when compared to thoracoscopic lobectomy, thoracoscopic segmentectomy had equivalent rates of morbidity, recurrence and survival in selected patients (5). When compared to open segmentectomy, thoracoscopic segmentectomy was found to have equivalent oncologic results, with shorter length of stay, reduced rates of morbidity, and lower cost. There have since been additional studies on segmentectomy, including further reports on uniportal and robotic approaches. This review is an update on the current role of segmentectomy and will focus on the most relevant recent studies on open, minimally invasive and robotic segmentectomy for lung cancer.

Open segmentectomy *vs.* open lobectomy

Since the LCSG study, although there have been no new randomized trials, there have emerged several retrospective studies comparing open segmentectomy to open lobectomy (8). In contrast to the LCSG trial, which enrolled patients from 1982-1988 and included 30% of patients with tumors >2 cm, these studies reflected a more current medical and surgical practice, and focused on examining the role of segmentectomy for tumors >2 cm in diameter. These studies reported similar outcomes and have found no significant differences in morbidity, mortality, locoregional recurrence or survival between segmentectomy and the lobectomy (8).

Most of these studies had groups well-matched for pulmonary function, but an important limitation of these studies is that many did not include information on preoperative co-morbidities. Three recent retrospective studies on segmentectomy *vs.* lobectomy did however include preoperative comorbidities and pulmonary function tests in their analysis. In 2011, Schuchert and colleagues compared the results of 107 patients undergoing resection for stage IA NSCLC (≤1 cm) via lobectomy (n=32), segmentectomy (n=40) or wedge resection (n=35) (9). Preoperative forced expiratory volume in 1 second (FEV1) was significantly lower in the sublobar resection (segmentectomy, wedge) groups compared with the lobectomy group; but age, sex distribution, tumor size, histology and preoperative comorbidities were similar between groups. Mean follow-up was 42.5 months and there was no statistically significant difference in overall disease recurrence or estimated 5-year disease-free survival (lobectomy, 87%; segmentectomy, 89%; wedge, 89%; P>0.402). While the authors note that a VATS approach was used more often than an open approach (57% *vs.* 43%) they did not specifically study the effects of open *vs.* VATS approach on outcomes.

Carr and colleagues conducted a retrospective study comparing the outcomes of 429 patients undergoing resection of stage I NSCLC via lobectomy or anatomic segmentectomy (10). The segmentectomy group (n=178) was older and had more co-morbidities—more likely to have coronary artery disease (18.5% *vs.* 12.8%, P=0.036) or chronic obstructive pulmonary disease (26.4% *vs.* 14.4%, P=0.0001)—than the lobectomy group (n=251). The segmentectomy group also had worse pulmonary function than the lobectomy group (FEV1 81.1±17.6 *vs.* 71.8±25.6, P=0.02). The authors found no difference in 30-day mortality (1.1% *vs.* 1.2%), recurrence rates (14.0% *vs.* 14.7%, P=1.00), or 5-year cancer-specific survival (T1a: 90% *vs.* 91%, P=0.984; T1b: 82% *vs.* 78%, P=0.892) when comparing segmentectomy and lobectomy for pathologic stage IA non-small cell lung cancer, when stratified by T stage. Of note, this study included patients who underwent both open and VATS approaches, and an open approach was used less often with segmentectomy than with lobectomy (41% *vs.* 60.6%, P=0.0001). The authors did not specifically evaluate outcomes by type of approach.

With regard to the role of open segmentectomy in the elderly, Kilic and colleagues conducted a retrospective review of 78 patients >75 years of age who underwent segmentectomy *vs.* lobectomy for stage 1 NSCLC. The segmentectomy group included more patients with chronic obstructive pulmonary disease (COPD) and diabetes. The tumors were significantly larger in the lobectomy group (3.5 *vs.* 2.5 cm, P<0.0001). The authors found no significant difference in 5-year disease-free survival between segmentectomy and lobectomy (11). Outcomes associated with an open *vs.* VATS approach were not specifically evaluated.

In addition to the single-institution retrospective studies described above, there has been one population-based study of open segmentectomy and lobectomy for stage I NSCLC. In 2011, Whitson and colleagues analyzed 14,473 patients undergoing anatomic segmentectomy or lobectomy for stage I NSCLC derived from the Surveillance Epidemiology and End Results (SEER) database. The authors were unable to stratify by open or VATS approach, but presumably most of the operations were performed open. Lobectomy was demonstrated to be associated with improved overall ($P<0.0001$) and cancer-specific ($P=0.0053$) 5-year survival compared with segmentectomy. After adjusting for tumor size, this improvement in survival remained. However, it is difficult to draw specific conclusions from this study because, in addition to its retrospective nature, the study did not have data on patient preoperative co-morbidities and pulmonary function—important variables which may have significantly affected both procedure selection and postoperative outcomes.

Advantages of open segmentectomy *vs.* open lobectomy

Since the 1995 LCSG randomized trial, there have been numerous retrospective studies that have shown that there are no differences in recurrence and survival between open segmentectomy and open lobectomy, even in patients with greater co-morbidities and worse pulmonary function (10), patients older than 75 years of age (11), and patients with larger tumors between 2 and 3 cm in size (10). Furthermore, in one study, open segmentectomy was found to preserve postoperative pulmonary function at 90%±12% of preoperative levels (12). There is one recent population-based analysis which found that patients undergoing anatomic segmentectomy had a decreased survival rate when compared to those undergoing lobectomy for stage I NSCLC. However, this study did not include information about patient comorbidities or cardiopulmonary function; patients in segmentectomy could have had reduced cardiopulmonary function, greater co-morbidities or other factors that affected survival.

Advantages of segmentectomy *vs.* wedge resection

With regard to the outcomes of patients undergoing an open segmentectomy versus wedge resection for stage I NSCLC, multiple reports show a decreased risk of recurrence and equivalent or improved survival in patients undergoing open segmentectomy compared to those undergoing wedge resections (8). When compared with the wedge resection, segmentectomy has also been shown to be associated with a larger parenchymal margin (13,14), a higher yield of lymph nodes and rate of nodal upstaging (14), and reduced risk of locoregional recurrence (15). Based on these studies, segmentectomy would be the preferred procedure for patients considering sublobar resection.

Predictors for prognosis and recurrence

With regard to predictors for prognosis and recurrence for patients with NSCLC who underwent segmentectomy, Koike and colleagues found age >70 years, gender (male), >75% consolidation/tumor ratio on high-resolution CT, and lymphatic permeation to be independent poor prognostic factors, and lymphatic permeation to be an independent predictor for recurrence (16). Yamashita and colleagues found KI-67 proliferation index to be a predictor of early cancer death (17). Traibi and colleagues have also shown male gender, FEV1 ≤60% and open (as opposed to VATS) surgery to be risk factors for postoperative complications (18).

In 2013, Koike and colleagues reported risk factors for locoregional recurrence and survival in patients undergoing sublobar resection (patients who underwent segmentectomy or wedge resection in the analysis) (15). They found four independent predictors of locoregional recurrence: wedge resection, microscopic positive surgical margin, visceral pleural invasion, and lymphatic permeation. Independent predictors of poor disease-specific survival were smoking status, wedge resection, microscopic positive surgical margin, visceral pleural invasion, and lymphatic permeation.

Thoracoscopic segmentectomy *vs.* open segmentectomy

Since the 1995 LCSG randomized trial, there have been significant advancements in thoracoscopic surgical techniques, including a better understanding of the potential advantages of the thoracoscopic lobectomy and segmentectomy for anatomic pulmonary resection (5). The studies included in the present review will use the definition of thoracoscopic segmentectomy as the completion of sublobar anatomic pulmonary resection, with individual vessel ligation and without the use of a utility thoracotomy, retractors or rib-spreading (5). Studies using a "hybrid" segmentectomy with mini-thoracotomy fall into the category of open surgery and are not included in this section.

The first retrospective study comparing outcomes of thoracoscopic and open segmentectomy was performed by Shiraishi and colleagues in 2004 (19). The authors selected patients with clinical stage IA peripheral tumors (<2 cm) and reviewed the outcomes of 34 patients who underwent VATS segmentectomy versus 25 who underwent open segmentectomy. They found no significant differences in postoperative complications and perioperative deaths. Long-term survival was not evaluated in this study.

In 2007, Atkins and colleagues conducted a retrospective study comparing the results of 48 patients who underwent VATS versus 29 who underwent an open approach (20). The authors found no significant differences in preoperative co-morbidities, pulmonary function, operative time, estimated blood loss, nodal stations sampled and chest tube duration between the two groups. In addition, no significant differences were seen in locoregional recurrences between the open (8.3%) and the VATS (7.7%) approaches (P=1.0). However, there was a significantly decreased length of hospital stay for the VATS group when compared to the thoracotomy group (4.3±3 *vs*. 6.8±6 days; P=0.03). At approximately 30 months postoperatively, it was found that the VATS group had improved long-term survival when compared with the thoracotomy group (P=0.0007), although the groups were not matched oncologically.

Schuchert and colleagues performed a retrospective review of patients who underwent VATS segmentectomy (n=104) versus those who underwent thoracotomy (n=121) (21). There were no significant differences between the two groups in age, gender, histology, and pulmonary function as measured by FEV1 and DLCO. The VATS group had slightly smaller tumor sizes than the thoracotomy group (2.1±1.1 *vs*. 2.4±1.2 cm, P=0.05) and there were fewer lymph nodes harvested during VATS segmentectomy when compared with open segmentectomy (6.4. *vs*. 9.1, P=0.003). The VATS group also had a decreased length of hospital stay compared to the thoracotomy group (5 *vs*. 7 days, P<0.001). There were significantly fewer perioperative pulmonary complications in the VATS group as well (15.4% *vs*. 29.8%; P=0.012) but both groups, VATS and open, had similar rates of postoperative complications. Most importantly, regarding margins, it was demonstrated that a margin: tumor size ratio >1 was associated with a decrease in recurrence (14.7%) when compared to a ratio <1 (28.9%, P=0.037). In addition, the authors performed a propensity analysis that showed no significant difference in recurrence-free or overall survival. Interestingly, there were also no significant differences in locoregional or overall survival between groups with tumors >2 cm and tumors <2 cm.

In another analysis, Leshnower and colleagues conducted a retrospective review of 17 patients who underwent VATS segmentectomy versus 26 who underwent a thoracotomy approach for patients with primary lung cancer and metastatic disease (22). The two groups were similar with regards to age, tumor size, gender, body-mass index, co-morbidities and pulmonary function. An average of 3 lymph node stations were sampled in both groups and there were no significant differences in numbers of lymph nodes sampled (VATS 4.0±3 *vs*. open 6.1±5, P=0.40). There was also no significant difference between the groups in operative time. There were 2 (4.8%) deaths within 30 days after surgery in the thoracotomy group but none in the VATS group. Furthermore, the VATS group had decreased chest tube duration (VATS 2.8±1.3 *vs*. open 5.2±3 days, P=0.001) and reduced hospital length of stay (VATS 3.5±1.4 *vs*. open 8.3±6 days, P=0.01). In addition, the authors found that average hospital costs were approximately $1,700 less for the VATS group, although this finding was not statistically significant.

Advantages of thoracoscopic segmentectomy *vs.* open segmentectomy

In summary, the above studies comparing VATS segmentectomy with open segmentectomy show that VATS segmentectomy for stage I NSCLC is feasible and safe (19-22). VATS segmentectomy appears to be associated with an equivalent survival rate when compared to the open approach: all studies report 0% 30-day mortality for the VATS group, compared to 1.7-7.7% 30-day mortality for open segmentectomy, and there is no apparent difference in long-term survival. The VATS approach was also found to be associated with shorter length of stay, lower costs, reduced rates of overall complications, including fewer cardiopulmonary complications and reduced length of chest tube duration (5). At this time, it appears that there are no significant differences in operative times between the VATS *vs*. open approach: one study has shown a longer operative time (19), and the other three have shown similar operative times (20-22).

Thoracoscopic segmentectomy *vs.* lobectomy *vs.* wedge resection

Evaluation of thoracoscopic segmentectomy *vs*. thoracoscopic lobectomy or wedge resection for NSCLC is also under current investigation. Harada and colleagues conducted an analysis of pulmonary function for patients undergoing VATS segmentectomy (n=38) or VATS lobectomy (n=45) for stage I NSCLC (23). The authors found that 50% fewer segments were resected in the segmentectomy group and that the number of resected segments was associated with reduced forced vital capacity (FVC) and FEV1 at 2-

and 6-month postoperatively (P<0.0001). Consequently, at six months after surgery, the segmentectomy group had regained exercise capacity while the lobectomy group continued to have a 10% loss in exercise capacity.

In 2004, Iwasaki and colleagues performed a retrospective review of patients who underwent VATS lobectomy (n=100) or VATS segmentectomy (n=40) for stage I and II NSCLC (24). The authors found no significant differences in 5-year survival between the segmentectomy and lobectomy groups (77.8% *vs*. 76.7%, P=0.47). Shapiro and colleagues also conducted a retrospective study of VATS segmentectomy (n=31) *vs*. VATS lobectomy (n=113) but solely for stage I NSCLC (25). The segmentectomy group was found to have a longer smoking history and reduced pre-operative pulmonary function when compared to the lobectomy group (FEV1 83% *vs*. 92%, P=0.04). Despite differences in baseline patient fitness between the segmentectomy and lobectomy groups, there were no significant differences in complication rates, perioperative mortality, hospital length of stay, local recurrence (3.5% *vs*. 3.6%) and total recurrence rate (17% *vs*. 20%). In terms of lymph nodes dissected, segmentectomy was equivalent to lobectomy, with both groups having approximately five nodal stations sampled and ten lymph nodes resected. Mean follow-up for the segmentectomy and lobectomy groups were 21 and 22 months respectively, and both groups had similar overall and disease-free survival rates (P>0.5).

In 2010, Sugi and colleagues conducted a retrospective study of 159 patients who underwent VATS wedge resection (n=21), VATS segmentectomy (n=43) or VATS lobectomy (n=95) for stage I NSCLC (26). The lobectomy group had a higher percentage of patients with pathological stage greater than pT1N0 when compared to the segmentectomy group (18% *vs*. 8%, P=0.07). Follow-up was five years and the groups had similar 5-year recurrence-free and overall surviva, although there were differences in tumor size between the groups—the VATS wedge group had tumors <1.5 cm, the segmentectomy group had tumors <2 cm and the lobectomy group had tumors >2 and <3 cm. Yamashita and colleagues compared the results of VATS segmentectomy (n=38) or VATS lobectomy (n=71) with systemic lymphadenectomy (27). Both groups had similar recurrence-free and overall survival, although there were differences in tumor size between the segmentectomy and lobectomy groups (1.5 *vs*. 2.5 cm, P<0.0001).

Nakamura and colleagues performed a retrospective review of patients undergoing VATS lobectomy (n=289), VATS segmentectomy (n=38) or VATS wedge resection (n=84) for stage I NSCLC (28). The authors found differences in the mean tumor size between the lobectomy (2.57 cm), segmentectomy (1.98 cm) and wedge resection groups (1.85 cm). In this study, 5-year survival was lower for the wedge resection group (71.2%), compared to the lobectomy (90%) and segmentectomy (100%) groups. However, compared to the other groups, the wedge resection group comprised sicker patients with more co-morbidities.

Yamashita and colleagues evaluated the results of patients undergoing VATS segmentectomy (n=90) or VATS lobectomy (n=124) for stage IA NSCLC (29). There was a higher percentage of T1a tumors in the segmentectomy group when compared with the lobectomy group (84% *vs*. 58%, P<0.001). The segmentectomy group had a smaller median tumor size (15 *vs*. 20 mm). However, both groups were similar with regards to operative time, intraoperative blood loss, chest tube duration, and hospital stay. There were fewer numbers of dissected lymph nodes in the segmentectomy group when compared to the lobectomy group (12.1 *vs*. 21, P<0.0001) but both groups were also similar with regards to morbidity, 30-day mortality, recurrence, disease-free and overall survival.

Zhong and colleagues conducted a retrospective review of patients undergoing VATS segmentectomy (n=81) or VATS lobectomy (n=120) for stage IA NSCLC (30). There were no significant differences between the groups in pre-operative co-morbidities, pulmonary function, tumor size or histology. Both groups had similar operative times, similar rates of postoperative complications and no perioperative deaths. There were no differences between VATS segmentectomy and lobectomy with regards to lymph nodes resected (11.2±6.5 *vs*. 14.5±8.1, P=0.18). Length of hospital stay was also similar between both groups. There were no significant differences in local recurrence rates and 5-year overall or disease-free survivals. Multivariate Cox regression analyses also showed that tumor size was the only independent prognostic factor for disease-free survival. Another study compared the results of 73 VATS trisegmentectomies for stage IA (n=45) and IB (n=11) lung cancer with 266 VATS left upper lobe lobectomies for stage IA (n=105) and IB (n=73) lung cancer (31). There were no significant differences in overall complication rates or survival between patients undergoing VATS trisegmentectomy and those undergoing lobectomy for either stage IA lung cancer or stage IB lung cancer.

A retrospective review of patients undergoing VATS segmentectomy (n=26) or VATS lobectomy (n=28) for stage

IA NSCLC was also conducted by Zhang and colleagues (32). Again, there were no significant differences in operative time, estimated blood loss, number of lymph nodes resected and postoperative complications. Both groups had similar local recurrence rates and 3-year survival. Of note, the authors did find a significantly decreased length of hospital stay in the VATS segmentectomy group by approximately three days (P=0.03). Postoperative FEV1 was also decreased to a lesser degree in the VATS segmentectomy group. Tumor size, however, was not reported in this study.

Zhao and colleagues compared the results of patients undergoing VATS segmentectomy (n=36) or VATS lobectomy (n=138) for stage I NSCLC (33). There were no significant differences in blood loss, operative time, chest tube duration and length of hospital stay between the two groups. There was also no significant difference in local recurrence and in recurrence-free survival between the two groups, although the study was limited by a relatively short follow-up of less than one year and by not including tumor size data.

Advantage of thoracoscopic segmentectomy over thoracoscopic lobectomy and wedge resection?

These studies demonstrate that although thoracoscopic segmentectomy is a more complex procedure than the thoracoscopic lobectomy (5), the rates of morbidity, recurrence and survival are similar among patients with tumors >2 cm in diameter. Specifically, there were no significant differences in overall complication rates (25,26,29,30,32,33), local recurrence rates (25,26,29,30,32,33), 5-year recurrence-free survival (26,27,29,30) and 5-year survival rates (24,26,27,29,30). The studies also show no difference in operative time between the two groups (29,30,32,33). In addition, the segmentectomy groups had similar (25,29,30,33), or reduced lengths of hospital stay (32) when compared to the lobectomy groups. It appears that thoracoscopic segmentectomy is able to preserve more lung function (23,32) and exercise capacity (23) than thoracoscopic lobectomy, although long-term follow-up data is needed.

There are, however, important limitations to the abovementioned studies. Firstly, some studies did not report the tumor size data (31-33). Of the studies that did, most found that the lobectomy groups had significantly larger tumors than the segmentectomy groups (23-29). This difference in tumor size limits interpretation of results because tumor size is known to be a prognostic factor of survival for NSCLC (30,34). However, in one recent study where both thoracoscopic segmentectomy and lobectomy groups were well-matched in tumor size, histology, preoperative co-morbidities and pulmonary function (30), both groups had similar local recurrence rates, disease-free and overall survival. This is consistent with previous data from the open segmentectomy literature. For example, in 2006, Okada and colleagues conducted a multi-center study of 567 patients with tumor size <2 cm who underwent open segmentectomy or lobectomy (35). Mean tumor size for the segmentectomy and lobectomy groups were 1.57 cm and 1.62 cm (P=0.056), respectively. The segmentectomy was associated with equivalent 5-year survival when compared to the lobectomy (83.4% *vs.* 85.9%, respectively).

Another limitation of the above-referenced studies is that many of them, with the exception of four studies (27,29,30,33), did not report the percentage of patients with bronchoalveolar carcinoma or adenocarcinoma *in situ*. This is an important variable to account for (5), as demonstrated by a study performed by Nakayama and colleagues that examined the results of 63 patients with adenocarcinoma who underwent open sublobar resection of clinical stage IA NSCLC (36). The authors classified the patients' tumors as either "air-containing type" (n=46) or "solid-density type" (n=17) according to the tumor shadow disappearance rate on high-resolution CT. After resection, 38 of the 46 air-containing tumors were identified as bronchoalveolar carcinomas whereas all solid-density type tumors were non-bronchoalveolar carcinomas. Air-containing tumors were associated with better overall 5-year survival than solid-density tumors (95% *vs.* 69%, P<0.0001).

The VATS wedge resection procedure yields a smaller parenchymal margin, reduced number of resected lymph nodes and reduced sampling of nodal stations when compared to segmentectomy (14). There have also been two studies comparing the survival outcomes of this procedure with that of the VATS segmentectomy and lobectomy. However, in the wedge resection group, the tumors were smaller (26,28) or the patient population had greater co-morbidities, which limits interpretation of results (28); further studies with groups that are better matched will be needed prior to making any conclusions regarding the role of VATS wedge resection role in NSCLC.

Further study is also needed regarding selection criteria for the thoracoscopic segmentectomy. Based on the reviewed evidence, it appears reasonable to consider segmentectomy for patients with small, peripheral tumors (in particular air-containing tumors with ground glass opacities suggesting bronchoalveolar histology) that are less than 2 cm in diameter when an acceptable segmental margin is obtainable (margin ≥ tumor diameter), especially in patients with advanced age, poor performance status, or poor cardiopulmonary reserve. Future retrospective studies would benefit from controlling for tumor size, operative co-morbidities, type of cancer, tumor location (including distance from the margin to the edge of the tumor and resection margin) and propensity score matching. There are two ongoing randomized trials (discussed below) that will clarify the role of the thoracoscopic segmentectomy in lung cancer.

Feasibility of mediastinal lymph node dissection (MLND)

Mediastinal lymph node assessment is a critical component of segmentectomy for NSCLC. Mattioli and colleagues reported that open segmentectomy procures an adequate number of N1 and N2 nodes for pathologic examination (37). When comparing the thoracoscopic segmentectomy to the thoracoscopic lobectomy, two studies preliminarily demonstrate no significant differences in lymph nodes harvested or nodal stations sampled (25,30) while one reported fewer lymph nodes harvested with the segmentectomy (29). When comparing open *vs.* thoracoscopic segmentectomy, one study found no difference in lymph nodes harvested (22), while another reported fewer lymph nodes harvested with the VATS approach (21).

In addition, two studies compared the completeness of lymph node evaluation during anatomic resection of primary lung cancer by open and VATS approaches (38,39). Most of the analyses performed in these studies grouped segmentectomies together with lobectomies, thereby limiting the ability to draw any conclusions specifically regarding segmentectomy. However, in one of the studies which reported analyses of nodal upstaging from the Society of Thoracic Surgery national database, the authors did report one subset analysis that showed off the 170 VATS segmentectomies analyzed, upstaging from cN0 to pN1 was seen in 4% of patients compared with 5.3% among 280 open segmentectomies (38). The authors noted that the differences in upstaging between VATS and open approaches may have been the result of approach bias, and that equivalent nodal staging may be possible with increasing experience with VATS (38).

Preliminarily, based on the available evidence, it appears that it is possible to achieve adequate lymph node dissection with segmentectomy, but that surgeon experience does play an important role, particularly in the case of the thoracoscopic segmentectomy. More detailed investigation on lymph node evaluation in VATS versus open segmentectomy and VATS segmentectomy *vs.* VATS lobectomy is therefore needed.

Other types of thoracoscopic segmentectomy

Totally thoracoscopic segmentectomy

There have been a few small case series reported on the "totally thoracoscopic" or "complete VATS" technique for segmentectomy (39-46). In this technique, there is no access incision, and the specimen is retrieved through one of the port sites that is enlarged at the end of the procedure; only video-display and endoscopic instrumentation are used (47). There is no evidence that there are advantages associated with this approach, although it does allow the surgeon to use carbon dioxide insufflation. The largest series reported is from Gossot and colleagues, who performed totally thoracoscopic anatomic segmentectomy on 117 patients (48). The authors reported five conversions to thoracotomy with mean operative time of 181±52 minutes, mean intraoperative blood loss of 77±81 mL, and postoperative complication rate of 11.7%. The mediastinal lymph node harvested and nodal stations sampled were 21±7 and 3.5±1. The average length of hospital stay was 5.5±2.2 days. Preliminarily, it appears that totally thoracoscopic segmentectomy is feasible and safe, although further studies with longer follow-up that compare this technique with traditional open and VATS approaches are needed.

Uniportal segmentectomy

VATS segmentectomies are typically performed via two to three incisions, but Gonzalez-rivas and colleagues presented the first case report demonstrating that the procedure is feasible with one incision and through one port (49). Subsequently, they reported their initial results for 17 uniportal VATS anatomic segmentectomies. Mean operative time was 94.5±35 minutes, 4.1±1 nodal stations were sampled and 9.6±1.8 lymph nodes were resected. There were no conversions. Median tumor size was 2.3±1 cm, chest tube duration was 1.5 days (range, 1-4 days) and the median length of stay was 2 days (range, 1-6 days) (50). Wang and colleagues also demonstrated their experience, performing thoracoscopic lobectomy (n=14) and segmentectomy (n=5) with radical MLND through a single small (3- to 5-cm) incision (51). Mean operative time was 156±46 minutes, median number of lymph nodes harvested was 22.9±9.8, and blood loss was 38.4±25.9 mL. There were no conversions and 30-day mortality was 0%. The authors did not assess for differences by type of operation and there was no long-term follow-up. Preliminarily, it appears that single-incision segmentectomy is feasible and safe, although further studies comparing single-port to traditional open and VATS approaches are needed.

Robotic segmentectomy

A recent review of a national database demonstrated that robotic pulmonary resections have increased from 0.2% in 2008 to 3.4% in 2010 (52). The vast majority of robotic procedures are lobectomies, but there has been a small increase in robotic segmentectomies performed as well.

A retrospective study of 35 patients who underwent robotic thoracoscopic segmentectomy was performed, including 12 patients who had stage IA NSCLC (53). In this series, median age was 66.5 years, tumor size was 1.4 cm, operative time was 146 minutes and number of lymph node stations sampled was 5 (54). Four patients had perioperative complications, and 60-day mortality was 0%, while length of hospital stay was two days. Pardolesi and colleagues reported the initial results of 17 patients who underwent robotic segmentectomy at three institutions (55). The authors used a 3- or 4-incision strategy with a 3-cm utility incision in the anterior fourth or fifth intercostal space. Mean age was 68.2 years and mean duration of surgery was 189 minutes. There were no major intraoperative complications and no conversions were needed. Postoperative morbidity rate was 17.6%, median postoperative stay was five days and postoperative mortality was 0%.

Based on these reports, robotic segmentectomy appears to be a safe and feasible operation although additional studies comparing the outcomes of the robotic segmentectomy with the open and VATS approaches, as well as with the lobectomy, will be needed.

Limitations

There were several key limitations to the studies discussed above. Firstly, because the studies were retrospective in nature, there was the potential for surgeons' bias to affect the type of operation a patient received, which could have affected outcomes. In addition, often, the studies did not compare groups that were well-matched—which could have affected results. For example, in studies where patients in the VATS segmentectomy group were sicker than those in the comparison group (9-11,21,25), the benefits of VATS segmentectomy could have been underestimated. In studies where the VATS group had slightly smaller tumors than those in the comparison group (21,24,26-29), there may have been an overestimation of the benefits of VATS segmentectomy.

To reduce the impact of treatment-selection bias and confounding in estimating the effects of segmentectomy *vs.* lobectomy, randomized controlled trials should continually be performed (described below). Future retrospective studies should also aim to match variables that have confounding effects, use stratification or multivariate regression analysis where appropriate, and incorporate propensity score matching when possible (56,57).

Future research

In the studies reviewed above, there was no data reported on the tolerance of patients for resection of secondary cancers. This would be an important area for future research because up to 11.5% of patients who undergo pulmonary resection for stage I NSCLC develop additional primary lung cancers (25,58). By causing less trauma than open segmentectomy, and preserving more lung function than lobectomy, VATS segmentectomy theoretically would offer patients higher tolerance for resection of secondary cancers when compared to the open segmentectomy or open or VATS lobectomy (5).

In addition, future studies should aim to include data on the number and type of nodal stations sampled or lymph nodes dissected. Only four of the studies in this review (22,25,29,30) reported specific information on lymph node sampling with segmentectomy. The effect of surgeon experience on outcomes in segmentectomy also deserves attention, as there is currently no published data on the topic.

There are two ongoing large-scale randomized controlled trials that will improve our understanding of the outcomes of limited resection for NSCLC: CALGB 140503 and JCOG0802/WJOG4607L (59,60). CALGB 140503, sponsored by the Alliance for Clinical Trials in Oncology, will evaluate the outcomes of patients who are randomly assigned to undergo limited resection (segmentectomy or wedge resection) or lobectomy, with the VATS or thoracotomy approach determined by the surgeon (60). JCOG0802/WJOG4607L, sponsored by the Japan Clinical Oncology Group and the West Japan Oncology Group, will evaluate outcomes of patients who are randomly assigned to undergo segmentectomy (wedge resections are excluded) or lobectomy (59). Both studies will clarify the role of segmentectomy for NSCLC but will have some limitations as well. CALGB 140503 may be limited in its final analysis because the limited resection group includes not only patients undergoing segmentectomy, but also patients undergoing wedge resection. And in both CALGB 140503 and JCOG0802/WJOG4607L, the operative approach—VATS *vs*. open—will not be a primary outcome variable.

Conclusions

Based on the reviewed evidence, it appears reasonable to consider segmentectomy for patients with stage I NSCLC tumors (particularly in air-containing tumors with ground glass opacities) that are <2 cm in diameter when an acceptable segmental margin is obtainable (at least 2 cm), especially in patients with advanced age, poor performance status, or poor cardiopulmonary reserve. The outcomes of CALGB 140503 and JCOG0802/WJOG4607L and additional well-designed studies on open, thoracoscopic, and robotic segmentectomy will be important for further clarifying the role of segmentectomy for NSCLC.

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