Perspective

T1a lung carcinoma: the place of segmentectomy in the treatment array

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Abstract: Contemporary management of early stage non-small cell lung cancer (NSCLC) is evolving and can be attributed to a change in size and histology of lung cancer, advancements in imaging modalities, instrumentation and surgical techniques. The emergence of segmentectomy has further challenged the existing treatment landscape, with promising results. Despite limited widespread adoption, video-assisted thoracoscopic surgery (VATS) segmentectomy is a safe option in the treatment of patients with small stage I lung cancers, with excellent oncologic results and improved morbidity relative to open techniques. In this paper, we critically examine the utility of segmentectomy, and the emerging role of VATS, including technical tips and tricks, in the management of T1a lung carcinoma.

Keywords: Segmentectomy; thoracoscopy/video-assisted thoracoscopic surgery (VATS)

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Introduction

Over the last 20 years, management of early stage non-small cell lung cancer (NSCLC) has substantially evolved. Following the Ginsberg's landmark trial in 1995 (Lung Cancer Study Group), lobectomy has become widely adopted as the standard of care for optimal oncologic resection of NSCLC (1,2). Over time, many clinicians have challenged this dogma and demonstrated promising results with segmentectomy for stage IA NSCLC. In recent years, video-assisted thoracoscopic surgery (VATS) has emerged as a viable alternative to open approaches, and demonstrated superior oncologic efficacy (2,3). This progress is largely attributed to advancements in imaging modalities, instrumentation, and institutional experiences in thoracoscopic technique (2,4-6).

The changing epidemiology of tumor patterns, and increasing ability of high-resulted imaging techniques in the current era has improved our ability to detect sub-centimeter malignant lesions. This ability has led to many surgeons re-examining their stance on the extent of surgical resections (i.e., sublobar resections) or malignant disease processes. However, the role of parenchymal-sparing operations such as segmentectomy in the treatment of T1a lung carcinoma, is still of much debate, in part because of the retrospective nature of existing published studies (7-9). Two randomized control trials however, both of which have currently finished enrollment, will hopefully shed further light on this topic (10,11). Understanding the nuances of segmentectomy is essential to minimize patient morbidity and improve overall oncologic efficiency, and a crucial skill for today's thoracic surgeon. In this perspective, we examine the utility of segmentectomy, and the role of VATS segmentectomy, including technical considerations, in the management of early stage NSCLC using our extensive single center experience.

Contemporary outcomes

Significant debate exists in the contemporary era as to whether segmentectomy is the best lung-sparing operating for early stage lung cancer. However, in many studies, VATS segmentectomy has been shown to be equal to VATS lobectomy for small lung cancers (7-9,12). For instance, Shapiro *et al.* compared 31 VATS segmentectomy to 113 VATS lobectomy in patients with mostly stage I lung cancer over a median follow-up of 22 months. The study found no difference in chest tube duration, length of stay (LOS), complications (major or minor), perioperative mortality and rates of locoregional or distant recurrences. Cumulative survival was also similar between the two groups (P=0.52) (7). Fan *et al.* performed a meta-analysis of 24 studies (11,360 patients) from 1990 to 2010 comparing sub-lobectomy *vs.* lobectomy, and found no differences in overall survival in stage 1A patients with tumor size ≤2 cm (13). A similar relationship was observed when comparing segmentectomy *vs.* lobectomy in stage I NSCLC (13).

Likewise, Altorki *et al.* (14) examined outcomes of cT1N0 patients from 2000 to 2014 at a single institution in patients with poor performance status and limited cardiopulmonary reserve over a median follow-up of 34 months. The study found that anatomical segmentectomy patients were more likely than wedge resection patients to have nodal sampling/dissection (95% *vs.* 70 %; P<0.001), more stations sampled (3% *vs.* 2%; P<0.001), and more lymph nodes removed (7% *vs.* 4%; P=0.001). N1/N2 disease was present in 13 (4.5%) patients. On multivariable analysis, only maximum standardized uptake value of tumor was associated with worse outcomes. Overall, local recurrence and 5-year disease-free survival was similar (P>0.05). In a propensity matched cohort, 3- and 5-year disease-free survival was 65% *vs.* 68%, and 49% *vs.* 49% between wedge resection and anatomical segmentectomy patients, respectively (14). In another study, which examined trends in survival following surgery for lung cancer in France between 2005 and 2012, overall 3-year survival had increased significantly from 80.5% to 81.4% among 34,006 patients. Interestingly, during the first 2 periods, lobectomy had better 3-year survival than segmentectomy. However, over the last two periods, overall 3-year survival between the procedures was similar. Systematic nodal dissection was also shown to increase overall 3-year survival (15).

Another study examined the impact of histology (adenocarcinoma or squamous cell carcinoma) following limited resection *vs.* lobectomy in patients over 65 years with stage IA NSCLC in the surveillance, epidemiology, and end results (SEER) registry. Twenty-seven percent of the 2008 patients with adenocarcinoma, and 32 of the 1,130 patients with squamous cell carcinoma had limited resection. The study found that segmentectomy was equivalent to a lobectomy for adenocarcinoma but not for squamous cell carcinoma (16). Likewise, according to another study, wedge resection with nodes approximates to lobectomy with no survival difference observed after 10 years (17).

Patient selection

While lobectomy remains the gold standard approach, the efficacy of segmentectomy, in terms of oncologic and survival outcomes, is largely dependent on appropriate patient selection. Existing literature suggests segmentectomy is a viable approach for patients with limited cardiopulmonary reserve, or who would otherwise be unable to tolerate lobectomy (7,14). Compared to wedge resection, segmentectomy is regarded as the superior sublobar option, and provides better deep margins as well as sufficient nodal evaluation and clearance. In general, segmentectomy is indicated in patients with peripheral T1N0 (≤2 cm) lesions and with either limited cardiopulmonary reserve, or synchronous lung primary tumors, or concern for metachronous primary tumors (i.e., following a small contralateral lesion). Moreover, the lesion must be centered in the segment of interest, as determined preoperatively using high resolution, multimodality imaging techniques. Wedge resection on the other hand, is adequate for peripheral (sub-pleural), small (<1 cm) lesions, or when the tumor margin is wide (i.e., margin of 10–15 mm is preferred) as detailed later, or if the lesion straddles segmental boundary (for example. between lingula and upper division). Attention to lymph nodes is important in call cases.

Technical considerations

Despite advances in instrumentation and imaging platforms, VATS segmentectomy requires a certain amount of finesse and a thorough understanding of the associated anatomy. The approach to performing a successful VATS segmentectomy is generally similar to that of a VATS lobectomy, in terms of port placement, surgical instruments, hilar dissection and lung ventilation. In terms of technique, meticulous isolation and division of appropriate segmental bronchus, artery and vein is critical. The fissure is carefully divided using a stapler, cautery, other energy devices or finger fracture. While mechanical staplers are widely employed during thoracoscopic approaches, energy-based ligation of small-diameter pulmonary vessels is a safe and useful adjunct in anatomic VATS resection and a viable alternative. Based on our institutional experience, the narrow profile and thin blades of ultrasonic shears make it ideal for ligation of pulmonary vasculature, particularly where the size and necessary clearance of mechanical staplers prohibit safe dissection (18).

Furthermore, full nodal dissection/sampling is essential and if draining or sump node is positive on rapid intraoperative analysis, conversion to a lobectomy should be considered. Segmentectomy may include adjacent segments depending on spatial location of tumor. It is also very important for the surgeon to perform a safe and effective surgery without compromising any oncologic principles. While technically VATS segmentectomy can be challenging, the surgeon must be prepared to proceed with a lobectomy if segmentectomy is not feasible, or consider conversion to open if patient safety or oncologic outcome is to be compromised.

Over the years, several Japanese investigators have also studied the role of sublobar resection especially in terms of extended segmentectomy. This technique involves the development of the intersegmental plane, by keeping inflated the segment to be resected after ligation of the segmental bronchus, while the adjacent segments are collapsed. The resection is then performed on the side of the collapsed segments in order to optimize lateral margins, and a complete lymph node dissection including segmental, hilar and mediastinal lymph nodes is undertaken, as is performed during lobectomy (19).

Lymph node assessment

Lymph node dissection during segmentectomy is extremely pivotal. According to one study of 11,663 cases from the Japanese lung registry, the frequency of lymph node metastasis in patient with cT1N0M0 NSCLC is approximately 10% (20). One theoretical disadvantage of segmentectomy versus lobectomy is the potential presence of metastatic disease in level 13 lymph nodes especially in the preserved adjacent segments. For instance, Nomori *et al.* investigated the distribution of sub-segmental lymph nodes in resected and preserved segments during segmentectomy and interestingly found that segmental nodes at both the resected and non-resected segments (especially for tumors in the anteriorly located segment) could be dissected in 42 of the 94 cT1N0 patients (21). Thus, lymph node dissection can be performed as effectively during segmentectomy as lobectomy (7).

The draining or sump lymph node should always be checked during surgery, and if positive, conversion to lobectomy should be strongly considered. Similar to VATS lobectomy, lymph node dissection is also performed during VATS segmentectomy for accurate tumor staging. While mediastinal lymph node assessment is an important component of VATS segmentectomy, advantage of complete mediastinal lymph node dissection as opposed to systematic sampling is unclear.

Prognostic relevance of tumor margins and tumor size

With improvements in imaging techniques and modalities, our ability to detect small-sized lung cancer in clinical practice has increased remarkably. In most circumstances, tumor size and tumor margins have become important factors in determining operability and treatment selection (i.e., lobar versus sublobar) given their role in tumor recurrence. Schuchert *et al.* first examined the impact of margin and tumor size in 182 patients undergoing segmentectomy over a mean follow-up period of 14.4 months. Notably, 89% of recurrences were seen when tumor margins were 2 cm or less, and margin/tumor diameter ratios >1 were associated with a significant reduction in recurrence rates (almost 4-fold) compared with ratios <1 (22). Nomori *et al.* also examined the outcomes of 179 patients who underwent open radical segmentectomy with systematic lymph node dissection for peripheral cT1N0M0 NSCLC between 2005 and 2009 at a single institution. Intraoperative frozen section was done to ensure that surgical margins were at least 2 cm. Notably, the 5-year disease-free survival was 95% for patients with tumors ≤2 cm and 79% for those who had tumors between 2.1 and 3 cm (23).

Our institution further investigated this relationship in patients who underwent pulmonary wedge resection for elective surgical resection for NSCLC tumors (≤2 cm), performed either via thoracotomy or VATS. We excluded patients with other non-cutaneous malignancies, bronchoalveolar carcinoma, lymph node or distant metastasis at diagnosis, multiple/multifocal/metastatic or patients with prior chemoradiation or positive resection margin (24). Importantly, we found that an increase in margin length is beneficial for over all local recurrence. In terms of thresholds, as margin length/tumor size ratio increases, the risk of local recurrence decreases although the trend was clinically but not statistically significant. Thus, in wedge resection for small (≤2 cm) NSCLC, increased margin length up to 15 mm is associated with decreased

Figure 1 Right upper lobe posterior segmentectomy (31). Available online: http://www.asvide.com/article/view/24362

local recurrence with no evidence of additional benefit beyond 15 mm (24).

Likewise, Okada *et al.* examined the relation between tumor dimensions and clinical outcomes in 1,272 patents who underwent complete resection for NSCLC. Multivariate analysis demonstrated that male sex, older age, larger tumor, and advanced pathologic stage adversely affected survival (25). Furthermore, the 5-year cancer-specific survivals of patients with pathologic stage I disease with tumors of 20 mm or less and 21 to 30 mm in diameter were 92.4% and 87.4% after lobectomy, 96.7% and 84.6% after segmentectomy, and 85.7% and 39.4% after wedge resection, respectively (25). For tumor size greater than 30 mm in diameter, survivals were 81.3% after lobectomy, 62.9% after segmentectomy, and 0% after wedge resection, respectively. These findings suggest that lobectomy should be chosen for larger tumors sizes while segmentectomy may be acceptable for patients with smaller tumor sizes (<20 mm) without nodal involvement (25).

And finally, more recently, Zhao *et al.* examined 7,989 patients in the SEER database with stage IA (T1b) and found that patients who underwent segmentectomy had similar outcomes to those who underwent lobectomy for pathological stage IA adenocarcinomas at least 10 but no larger than 20 mm in size (26).

Pulmonary function tests

With regards to the functional advantage of a limited resection (i.e., segmentectomy), Harada *et al.* (27) analyzed pulmonary function tests (PFT) preoperatively and at 2 and 6 months after radical segmentectomy in 38 patients and lobectomy in 45 patients. Notably, statistically significant differences were observed between the two groups in the ratio of postoperative to preoperative forced vital capacity (FVC) and forced expiratory volume after 1 second (FEV1; P<0.01). Similarly, another study retrospectively analyzed patients undergoing lobectomy (n=147) or segmentectomy (n=54) for stage I NSCLC, and examined PFT preoperatively and at one-year follow-up. Lobectomy patients experienced significant declines in FVC (85.5% to 81.1%), FEV1 (75.1% to 66.7%), and diffusing capacity (79.3% to 69.6%), while a decline in diffusing capacity was the only significant change seen after segmental resection (28).

Nomori *et al.* recently examined functional outcomes in patients undergoing segmentectomy (117 patients) and stratified according to the number of segments resected (<2 *vs.* ≥2), and left upper division (LUD). Left upper lobectomy was used as a control for the LUD group. The study found that segmentectomy decreased the pulmonary function with increasing number of resected segments. LUD segmentectomy decreased both systemic and lobar function significantly, with a similar decrease as lobectomy (29). Similar findings were demonstrated by Macke and his colleagues who demonstrated that parenchymal-sparing resections resulted in better preservation of 1-year PFT with small anatomic segmental resections (1–2 segments) (30).

Our institutional technique

While there may be subtle variations in the number of ports utilized or the approach (open, VATS, or robotic) between different institutions, fundamentally, hilar dissection is technically similar. The most important segments of interest for the VATS approach include the LUD (tri-segment), lingula, superior segment (either lower lobe), composite basilar segments (either lower lobe), and posterior segment of the right upper lobe. The conduct of the operation for the different segments is also similar. We have provided a video to demonstrate our technique of VATS right upper lobe posterior segmentectomy (*Figure 1*).

Implications of ongoing randomized clinical trials (RCTs)

Existing controversy on the optimal management of small, peripheral NSCLC ≤2 cm has been an impetus for two multicenter prospective RCTs. Both trials just completed enrollment and they are similar in design in that they randomized patients to either lobectomy or sub-lobar resection for peripheral cancer less than 2 cm in diameter after adequate mediastinal staging. The procedures could be done open or VATS. The Cancer and Leukemia Group B 140503 trial (known as the Alliance Trial) finished enrollment of 637 patients. This trial required a negative frozen section analysis of draining lymph nodes prior to randomization (11). The Japanese trial (JCOG0802/WJOG4607L) included 1,100 patients accrued from 71 institutions within 3 years (10). All randomized patients will be followed for at least 5 years. Tumor markers, chest X-ray and chest computed tomography will be evaluated at least every 6 months during the first 2 years and at least every 12 months for the duration of follow-up.

Future directions

Thoracoscopic segmentectomy is a safe option for experienced thoracoscopic surgeons treating patients with small stage I lung cancers. Moreover, even though existing literature is based on retrospective studies, segmentectomy yields excellent oncological results with comparable morbidity, mortality, locoregional recurrence, and overall survival compared to lobectomy in patients with T1a NSCLC. Moving forward, understanding the importance of lesser resections via minimally invasive approaches is becoming more crucial, especially given changes in pathology of tumors (type, size, location), quality of life considerations, and availability of alternate treatment options such as stereotactic body radiation therapy (SBRT) in select patients.

From our experience, for small lung cancers, 2 cm range, segmentectomy is the best sublobar treatment, and can be done safely via VATS. For very small sub-pleural lung cancers [1 cm range or those that straddle segmental boundaries (upper division/lingula for example)], a wedge resection is reasonable but lymph nodes must be dissected. Importantly, both approaches are good or better than SBRT (a reasonable second choice) due to documentation of pathology, removal of lymph nodes and clear measurable margins. Furthermore, lobectomy is better than sublobar resection when done in standard fashion without regard to margins, lymph nodes while segmentectomy is superior to wedge resection when anatomically appropriate. Hopefully, the results of the two RCTs will shed further light in determining the most optimal treatment approach moving forward. In the meantime, certain preoperative and intraoperative considerations should be taken into account when considering segmentectomy for the treatment of early-stage non-small cell lung cancers.

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Footnote

Conflicts of Interest: Dr. Swanson serves as an educational consultant to Covidien and Ethicon. Dr. Hirji has no conflicts of interest to declare.

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