Comprehensive narrative review of segmentectomy for lung cancer

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Abstract: Pulmonary lobectomy has been historically the gold standard oncologic resection for early stage non-small cell lung cancer (NSCLC). Pulmonary segmentectomy has gained popularity as technological advances and improved understanding of segmental anatomy have allowed the use of minimally invasive surgery for parenchymal sparing resections. Oncologic equivalency between segmentectomy and lobectomy remains under investigation. In this manuscript, we aim to review existing literature with regards to oncologic and functional outcomes comparing lobectomy *vs.* segmentectomy, and comparisons among different surgical approaches: open, traditional video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery. When compared with lobectomy, segmentectomy appears to provide equivalent oncologic outcomes in appropriately selected patients, as long as adequate lymphadenectomy and negative margins are achieved. The robotic platform, with its improved visualization and use of wristed instruments may allow for a more complete lymphadenectomy during a segmental resection. The following manuscript serves as a guide for clinicians on recent literature for open, video-assisted and robotic thoracoscopic pulmonary segmentectomy.

Keywords: Robotic segmentectomy; video-assisted thoracoscopic surgery segmentectomy (VATS segmentectomy); sublobar resection (SLR); lung cancer

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Introduction

The first pneumonectomy for lung cancer was performed by Dr. Evarts Graham in 1933 (1). Since then, thoracic surgeons have acquired a variety of diagnostic and therapeutic tools, knowledge, and technical skills that have not only better defined the role of surgery for lung cancer, but also the extent of resection necessary to obtain an optimal oncologic outcome. In 1960, Dr. William Cahan established radical lobectomy as the new gold standard for lung cancer surgery, leading to improved patient outcomes and avoiding higher morbidity associated with pneumonectomy. Cahan delineated the principles of lymph node (LN) dissection during lobectomy that were necessary to achieve an equivalent oncologic resection to pneumonectomy (2). Approaching the current surgical era, Dr. Robert Jensik pioneered the first segmentectomy for lung cancer in 1973; he reported similar oncologic outcomes to lobectomy with the advantage of sparing more lung parenchyma, appropriate for patients with poor pulmonary function unable to tolerate lobectomy (3).

Lung segmentectomy is considered a more technically complex operation than lobectomy, in part due to the high variability of the segmental anatomy. The advent of the robotic platform with a tridimensional high-definition camera and seven degrees of freedom in wristed instruments provides thoracic surgeons with tools for precise dissection during complex segmentectomies. We seek to review the reported functional and oncologic outcomes of segmentectomy for early stage lung cancer and discuss the implications of utilizing video-assisted thoracoscopic surgery (VATS) and robotic surgical techniques during this type of operation.

In order to establish fair comparisons between lobectomy and segmentectomy, it is important to be familiar with the following terms described in the literature: sublobar resection (SLR) includes both wedge resection and segmentectomy. A wedge resection is a non-anatomic removal of lung tissue containing a tumor. Segmentectomy involves the individual ligation and division of bronchi, arteries, and at times veins corresponding to a well-defined lung segment. Perhaps more importantly, it also includes dissection of the inter-segmental LNs. Intentional segmentectomy indicates patients are candidates for lobectomy, in contrast to segmentectomy performed to reduce potential surgical risk associated with poor pulmonary function, advanced age, frailty or comorbidities. In the case of non-small cell lung cancer (NSCLC), intentional segmentectomy is typically reserved for peripherally located tumors up to 2 cm in size with no radiologic evidence of LN involvement (N0). Simple (typical) segmentectomy includes segments with a single inter-segmental parenchymal division (superior segment or common basilar segmentectomy of the left or right lower lobe, lingulectomy, left upper lobe trisegmentectomy). Complex (atypical) segmentectomy includes segments that require more than one inter-segmental parenchymal division (individual segments of either left or right upper lobe, individual basilar segments, bi-segments or combinations of segments and subsegments).

PubMed and MEDLINE databases were queried between 2000 and 2020 with key words that included the following in the writing of this review: robotic segmentectomy, VATS segmentectomy, thoracoscopy, NSCLC, complication, oncologic resection.

Comparison of oncologic outcomes between lobectomy and segmentectomy

The Lung Cancer Study Group (LCSG) remains the only randomized controlled trial (RCT) with reported oncologic outcomes comparing lobectomy and SLR. Results published by the LCSG in 1995 established lobectomy as the standard of care for clinical stage I NSCLC (4). This multi-institutional RCT between 1982 and 1988 by Ginsberg and Rubinstein analyzed 247 patients (SLR =122, lobectomy =125) and reported SLR was associated with an increase in local recurrence and death. Data against segmentectomy derived from this trial has been criticized for the following reasons: a large proportion (32.8%) of wedge resections in the SLR group, inclusion of tumors between 2 to 3 cm in size, and the absence of routine computed tomographic (CT) examination for preoperative management or for postoperative surveillance (5).

Since the LCSG, there has been conflicting literature comparing oncologic outcomes between lobectomy and SLR. We highlight key publications below.

Several single-institution studies have reported similar oncologic outcomes between segmentectomy and lobectomy. Okada *et al.* in 2001 evaluated intentional segmentectomy (n=70) *vs.* lobectomy (n=139) in clinical (c) T ≤2 cm N0M0 NSCLC and found 5-year survival similar between the segmentectomy (87.1%) and lobectomy group (87.7%, P=0.8) (6). A few years later in 2006, a Japanese multi-center non-randomized study reported similar oncologic outcomes between intentional SLR (n=305) and lobectomy (n=262) for cT ≤2 cm N0 NSCLC with similar 5-year survival for each resection type (95% wedge, 93.9% segmentectomy, 95% lobectomy, P=0.42) for pathologic (p) T ≤3 cm N0 NSCLC (7).

A number of other publications comparing segmentectomy *vs.* lobectomy lack detail regarding segmentectomy indication; some, however use propensity-matching analysis in order to account for different characteristics between groups. Landreneau *et al.* compared lobectomy *vs.* segmentectomy for cT ≤3 cm N0 NSCLC tumors (312 patients in each group) and reported equivalent 5-year disease-free recurrence (DFR) (71% *vs.* 70%, P=0.467) and 5-year survival (60% *vs.* 54%, P=0.258), similar perioperative mortality and no significant difference in loco-regional, distant, or overall recurrence (8). A similar trend held in their propensity-matched analysis of their institutional database for cT2–3 cm N0 NSCLC (90 patients in each group) in which there were no significant differences in overall survival (OS) (HR: 1.034, P=0.764) or recurrence-free survival (RFS) (HR: 1.168, P=0.1391) (9). Wen *et al.* in 2020 described equivalent OS and RFS between segmentectomy and lobectomy for cT ≤2 cm N0 invasive adenocarcinoma after propensity-matching 214 patients in each group (10).

Equivalent oncologic outcomes between segmentectomy and lobectomy have also been found in large database analyses. Altorki *et al.* analyzed the International Early Lung Cancer Action Program (I-ELCAP) database and reported similar recurrence for SLR (n=50) and lobectomy (n=256) in patients with solid tumors cT ≤2 cm N0 (20% *vs.* 10%, P=0.21) (11). Yendamuri and associates examined the Surveillance, Epidemiology, and End Results (SEER) database and stratified patients with cT ≤2 cm N0 by three time periods: early [1988–1998], intermediate [1994–2004], and late [2005–2008]. In the early period, SLR, including wedge resection and segmentectomy, was inferior to lobectomy (HR: 1.4, 95% CI: 1.21–1.65). In the intermediate period, segmentectomy was equivalent to lobectomy (HR: 1.04, 95% CI: 0.8–1.36); wedge resections remained inferior to lobectomy (HR: 1.19, 95% CI: 1.01–1.41). In the Late Period, all three resections had similar trends for OS and DFS (wedge *vs.* lobectomy HR: 1.09, 95% CI: 0.79–1.5; segmentectomy *vs.* lobectomy HR: 0.83, 95% CI: 0.47–1.4) (12).

A series of meta-analyses have been performed comparing the two operative techniques. Nakamura and associates in 2005 reviewed 14 studies for cT ≤5 cm N0 NSCLC and found no significant difference in OS between SLR and lobar resections at 1, 3, and 5 years (13). Fan *et al.* performed a meta-analysis of 24 studies for T ≤5 cm N0 NSCLC between 1990 and 2010 and reported no difference in OS or CSS between the two groups (14). Ijsseldijk *et al.* also found no difference in 5-year OS between lobectomy (n=15,003) and SLR (n=1,224), (RR: 0.92, 95% CI: 0.84–1.01) in a review of 28 papers including wedge resections, segmentectomy and lobectomy for cT ≤2 cm N0 NSCLC (15).

In contrast to the publications previously described, several studies have reported inferior oncologic outcomes for segmentectomy in comparison to lobectomy. A propensity-matched study (987 patients in each group) of the National Cancer Data Base (NCDB) between 2003 and 2011 found superior 5-year OS for lobectomy 70.4% (95% CI: 69–71.7%) *vs.* segmentectomy 59.6% (95% CI: 53.5–65.2%), and wedge resection 54.5% (95% CI: 52.3–56.9%) (P<0.001). Median OS was 95 months for lobectomy, 74 months for segmentectomy, and 68 months for wedge resections (P<0.001) (16).

Meta-analyses data have also been conflicting. Zhang *et al.* in 2015 included 16 studies for cT ≤5 cm N0 NSCLC comparing segmentectomy and lobectomy and reported inferior OS and CSS for segmentectomy *vs.* lobectomy (HR: 1.231, 95% CI: 1.070–1.417, P=0.004) (17).

Comparisons in the literature between lobectomy and segmentectomy are not limited to early stage NSCLC; however, sample size for more advanced stages is much smaller. Roman and associates matched 64 patients undergoing segmentectomy or lobectomy for stage I–III NSCLC according to the AJCC 7th edition and found no difference in 5 year survival for stage I tumors; 3 year survival for stage II/III NSCLCs was lower, but not statistically significant, segmentectomy (n=18, 20%) *vs.* lobectomy (n=13, 68%, P=0.07) (18). An analysis of the SEER database between 1998 and 2007 for NSCLC cT <7 cm found lobectomy associated with superior OS (P<0.0001) and CSS (P<0.0053) as compared to segmentectomy, independent of tumor size (19).

Historically, nodal disease has mandated a lobectomy for appropriate oncologic resection. A 2004 to 2015 query of the NCDB for cT <3 cm N0 NSCLC with unsuspected nodal disease described equivalent 5-year OS between segmentectomy (n=9,118) and lobectomy (n=132,604) for unsuspected N1 (41.9% *vs.* 44.3%, P=0.35) and N2 (41.6% *vs.* 37.2%, P=0.99) disease. Adjuvant chemotherapy was noted to be associated with improved survival in patients with N1 and N2 disease, independent of anatomic lung resection type (20). A similar analysis of the NCDB between 2004 and 2014 for patients with cT ≤3 cm N0 with pathological nodal disease described no difference in 3-year OS between segmentectomy and lobectomy (66.3% *vs.* 68.1%, P=0.723) (21).

Role of LN dissection, segment location, and surgical margins

Associating lobectomy with improved OS may be confounded by the adequacy of LN harvest in SLRs. Some literature suggests that segmentectomy has equivalent oncologic outcomes to lobectomy as long as adequate margins and LN dissection are accomplished.

The presence of positive LNs has been directly correlated with larger tumor size (22). Mattioli *et al.* in a case-matched study reported equivalent LN dissection between lobectomy and segmentectomy in patients with cT ≤2 cm N0 NSCLC (46 patients in each group) with similar median number of total nodes (13 *vs.* 12, P=0.68), N1 nodes (7 *vs.* 6, P=0.43), and N2 nodes (5 *vs.* 5.5, P=0.88) and no difference in CSS at 36 months (93.5% *vs.* 100%, P=0.33) (23). Huang *et al.* reported ≥6 LNs harvest during segmentectomy as independent factor for improved RFS (90.2% *vs.* 73.7% for patients with <6 LN harvest, P=0.038) (24). In a subgroup analysis of the previously described NCDB study, there was no difference in OS between lobectomy and segmentectomy in patients with negative margins and similar LN dissection (16).

Segment location may also play a role in surgical outcomes. Aprile *et al.* retrospectively evaluated oncologic outcomes for NSCLC pT ≤7 cm in a single institution study, comparing patients undergoing lingulectomy (n=33) and trisegmentectomy (n=21) *vs.* left upper lobectomy (n=105). Between lobectomy and multi-segmentectomy groups, mean OS (87 *vs.* 89 months, P=0.895) and DFS (91 *vs.* 96 months, P=0.565) were similar and there was no difference in local recurrence rate (P=0.337) (25). In a similar pair-matched case-control study, comparing trisegmentectomy (n=15) and lingulectomy (n=7) *vs.* left upper lobectomy (n=44) for tumors ≤6.3 cm in size in the segmentectomy group, there were no significant differences in 5 year RFS (RR =2.22, P=0.3) and OS (RR =1.09, P=0.9) (26). Sienel *et al.* compared recurrence for segmentectomy (n=49) and lobectomy (n=150) in pT ≤3 cm N0 NSCLC and found local recurrence rate higher in the segmentectomy *vs.* lobectomy group (16% *vs.* 5%, P=0.005). In a subgroup analysis, when segmentectomies were stratified by location, there was an increase in local recurrence in the S1-3 region as compared to S4-10 (23% *vs.* 5%, P=0.08) (27).

Different outcomes related to segment location may also be related to differences in distribution of sentinel LNs. Nomori and colleagues reviewed 94 patients with cT ≤3 cm N0 NSCLC and described a significantly higher number of sentinel nodes in resected segments as compared to non-resected segments (64% *vs.* 29%, P=0.001). Hence, the authors advocated for a complete LN dissection including both resected and unresected segments. There were more unresected sentinel nodes in non-resected segments in an anterior segmentectomy *vs.* a posterior segmentectomy (47% *vs.* 17% respectively, P=0.04) and more sentinel LNs were identified in the intersegmental LNs (47% in station 12 and 53% in station 13) as compared to hilar (23%) and interlobar (40%) LNs (28).

Schuchert and coworkers, in two analyses, emphasized the importance of surgical margins. They compared 182 segmentectomy and 246 lobectomy patients with NSCLC pT ≤7 cm who underwent resections between 2002 and 2006 and found similar DFR and survival rates. When evaluating all recurrences between both resection types, they noted margin/tumor diameter ratios (MTR) >1 had lower recurrence rates as compared to MTR <1 (6.2% *vs.* 25%, P=0.0014) (29). In their 2019 paper, they found no significant difference in recurrence between the segmentectomy (n=384) and lobectomy (n=748) groups for NSCLC cT ≤4 cm. Independent predictors of recurrence included lymphatic invasion, tumor size, grade and MTR (30).

Role of tumor biology for recurrence and survival

Although there has been an emphasis on tumor size, staging, and patient comorbidities as selection criteria for lobectomy *vs.* segmentectomy, the impact of tumor biology on outcomes for segmentectomy *vs.* lobectomy is a focus of active research.

Consolidation to tumor ratio (CTR) has been associated with risk of recurrence for lung adenocarcinoma. Hattori and colleagues reviewed 353 cases of T ≤2 cm N0 NSCLC treated with segmentectomy and stratified the tumors into solid (CTR =1.0) and part-solid (CTR 0.5 to 1.0). Three-year loco-regional RFS was significantly worse in the segmentectomy *vs.* lobectomy group (82.2% *vs.* 90.6% respectively, P=0.0488) for pure solid tumors whereas in part-solid tumors the two groups with adequate hilar and mediastinal dissection had similar oncologic outcomes (31). Tsutani *et al.* reviewed 610 patients with adenocarcinoma up to 3cm who underwent wedge resection, segmentectomy, or lobectomy and reported similar three-year RFS in ground glass opacity (GGO) dominant lesions groups (wedge 96.4%; segmentectomy 96.1%; lobectomy 98.7%, P=0.44) (32). Tsubokawa and colleagues retrospectively analyzed RFS and OS after segmentectomy (n=52) and lobectomy (n=44) between 2007 and 2015 for pure solid T ≤2 cm N0 NSCLC and described no significant differences in 3-year RFS (82.2% *vs.* 84.1%, P=0.745) and 3-year OS (92.0% *vs.* 94.2%, P=0.723) (33).

Koike *et al.* retrospectively studied 179 patients who underwent segmentectomy for N0 NSCLC up to 5 cm in size and identified solid tumor size as an independent significant risk factor for recurrence (HR: 3.5, 95% CI: 2.244–5.459). Stratified by tumor size greater than and less than 1.5cm, the recurrence free probability (RFP) was 73% and 100% (P<0.001) at 3 years and 69.5% and 97.2% (P<0.001) at 5 years, respectively (34). A meta-analysis of 7 studies between 2014 and 2018 of segmentectomy (n=441) *vs.* lobectomy (n=987) for pure-solid or solid-dominant tumors T ≤3 cm N0 NSCLC concluded segmentectomy had a worse RFS as compared to lobectomy (HR: 1.46, 95% CI: 1.05–2.0.3, P=0.024) with no significant difference in OS (HR: 1.52, 95% CI: 0.95–2.43, P=0.08) (35).

Tumor maximum-standard uptake value (SUVmax) on PET scan has been correlated with higher incidence of occult pathologic nodal metastases and worse DFS (36,37). Kamel and colleagues reported no difference in 5 year RFS (72% *vs.* 69%, P=0.679) or CSS (92% *vs.* 83%, P=0.557) between lobectomy and segmentectomy for T ≤3 cm N0 NSCLC with SUV ≥3 g/dL (38).

The presence of lymphovascular invasion has also been associated with higher risk of recurrence after resection of lung cancer. A retrospective study of 312 patients with cT ≤2 cm N0 NSCLC who underwent a segmentectomy (n=80) or lobectomy (n=232) between 1997 and 2010 described no significant difference in five and ten year survival rates and segmentectomy was not independent prognostic factor for loco-regional recurrence. Lymphatic (P<0.001) and vascular invasion (P<0.001) were independent, significant prognostic factors for loco-regional recurrence (39).

Histologic type has been recognized as an important factor for prognosis after lung cancer surgery. Large cell neuroendocrine carcinoma (LCNEC) is associated with poor prognosis. A propensity-matched study of the NCDB between 2004 and 2014 for LCNEC tumors ≤3 cm found SLR (151 wedge, 34 segmentectomy) had worse 5-year OS as compared to lobectomy (n=185) (41.5% *vs.* 60.3%, HR: 1.59, 95% CI: 1.20–2.12, P=0.001) (40). The presence of spread through air spaces (STAS) may play a role in selecting appropriate candidates for SLR. STAS is defined as tumor cells within air spaces in the surrounding lung parenchyma, beyond the edges of the main tumor. Eguchi and colleagues included the presence of STAS in their propensity score matching of patients who underwent lobectomy *vs.* SLR for T ≤3 cm N0 adenocarcinoma (349 matched-pairs) and found in STAS-positive tumors SLR was associated with higher recurrence (HR: 2.84, P<0.001) and cancer specific death (HR: 2.63, P=0.021). This association remained significant in subgroup analysis of segmentectomy *vs.* lobectomy. Importantly, STAS-positive tumors had higher loco-regional recurrence for SLR, irrespective of margin-to-tumor ratio. For STAS-negative tumors, recurrence after SLR was rare for MTR >1 (41). Similarly, a study of T ≤2 cm N0 adenocarcinomas found a significantly higher 5-year cumulative incidence of recurrence (CIR) for SLR when STAS was present *vs.* absent (42.6% *vs.* 10.9%, P<0.001), while in the lobectomy group STAS had no impact on CIR (12.7% *vs.* 9.5%, P=0.50) (42). There is no effective or reliable method to detect STAS by using frozen section. Suh *et al.* reported that GGO percentage ≥75% on CT scan, SUV tumor to liver ratio <0.65 on PET and pathologic lepidic predominance are predictive of STAS-negative tumors (43).

Comparison of postoperative complications and functional outcomes between lobectomy and segmentectomy

Differences in perioperative outcomes between lobectomy and segmentectomy have been evaluated. Gulack *et al.* queried the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database and determined a multivariable logistic regression model for factors associated with 30-day mortality including age, chronic obstructive pulmonary disease (COPD), previous cerebrovascular event, functional status, recent smoking status, and minimally invasive surgery *vs.* open as significant risk factors. Their risk model to predict operative mortality compared SLR and lobectomy and found a risk score greater than 5 had higher perioperative mortality after lobectomy (4.9%) as compared to segmentectomy (3.6%) or wedge resection (0.8%, P<0.01) (44).

Recent results of the JCOG0802/WJOG4602 RCT trial demonstrated a significantly increased rate of air leaks in segmentectomy as compared to lobectomy (6.5% *vs.* 3.8%, P=0.04). The authors hypothesized the use of electrocautery to divide the lung parenchyma during complex segmentectomy may have contributed to an increased rate of air leaks (45). Chen and colleagues have previously reported the association between prolonged air leak and use of electrocautery. They conducted a single institution RCT between June 2017 and March 2018 to evaluate outcomes using stapling devices (n=35) *vs.* electrocautery (n=95) for segmentectomies. They stopped the trial early, as the rate of air leaks was significantly higher in the electrocautery group as compared to the stapler device group (34.4% *vs.* 6.1%, P=0.004) (46). In contrast, Bédat and coworkers compared VATS lobectomy (n=450) and segmentectomy (n=240) in a multicenter study and found similar rates of complications and complication grades between the two procedures; the rate of air leaks between lobectomy (11.3%) and segmentectomy (8.8%) was not significantly different (P=0.36). Instead, they noted American Society of Anesthesiologists (ASA) score >2 (OR 1.55; 95% CI: 1.10–2.19, P=0.011) and FEV1 <80% (OR 1.61; 95% CI: 1.11–2.30, P=0.009) were significantly associated with complications but not with complication severity (47). Bédat *et al.* evaluated the effect of complex versus simple segmentectomies on perioperative outcomes and found similar complication rates, chest tube duration, and operative times and noted decreased length of stay for complex segmentectomy [CS, median: 5 days (range, 1–36)] *vs.* simple segmentectomy [SS, median 7 days (range, 2–31); P=0.026] (48)

Lobectomy or segmentectomy may result in differences in pulmonary function tests (PFTs). Harada and colleagues analyzed intentional segmentectomy (n=38) *vs.* lobectomy (n=45) for clinical T ≤2 cm N0 NSCLC and reported that the number of resected segments significantly correlated to loss of forced vital capacity (P<0.0001) and forced expiratory volume in 1 s (FEV1) (P<0.0001) at two and six months. For tumors located in large volume lobes (left upper lobe and bilateral lower lobes), exercise capacity at 6 months was regained for segmentectomy patients while patients with lobectomy continued to experience a 10% loss of exercise capacity (P=0.03) (49).

More recently, Stamatis and associates conducted a prospective randomized multicenter phase III trial to evaluate quality of life for patients with NSCLC T ≤2 cm N0 who underwent a lobectomy (n=54) or segmentectomy (n=54). Twelve months after resection, lobectomy patients had significantly diminished physical health (P<0.001) and cognitive functioning (P=0.025), increased dyspnea (P<0.001) and fatigue (P=0.003). Shortness of breath improved at a faster rate for segmentectomy patients (P=0.016) a year after resection (50).

Minimally invasive segmentectomy

Minimally invasive surgery via traditional VATS has been associated with equivalent oncologic outcomes and decreased post-operative pain and length of stay in comparison to thoracotomy. The majority of studies reviewed above comparing segmentectomy *vs.* lobectomy include both open and VATS cases. Few studies, outlined below, compare strictly VATS segmentectomy to VATS lobectomy.

Hwang *et al.* compared VATS segmentectomy and VATS lobectomy (94 propensity matched-pairs) between 2005 and 2013 and described no difference in terms of operative time and hospital stay. A non-statistically significant higher rate of postoperative complications was noted for the lobectomy group (17.2% *vs.* 10.6%, P=0.1) while mortality was higher for the segmentectomy group (2.1% *vs.* 1.1%, P=0.56). Postoperative FEV1 was also similar in both groups (P=0.36). The 3-year OS and RFS was also similar between the two groups (94% and 87%, P=0.62 in the segmentectomy group and 96% and 94%, P=0.69 in the lobectomy group (51).

VATS lobectomy and VATS segmentectomy for cT ≤3 cm N0 NSCLC have no significant differences in recurrence rates or perioperative outcomes including length of stay, complications, or chest tube duration (52,53). Bédat and co-workers performed a retrospective analysis of VATS segmentectomy (n=102) for two university hospitals in Switzerland and noted post-operative complications were largely associated with COPD (OR: 2.54; 95% CI: 1.18–5.47) and smoking >50 pack-years (OR 5.27, 95% CI: 1.68–16.55); nodules greater than or equal to 2 cm had decreased DFS (P=0.04) (54). Notably, surgeon experience did not contribute to complications or disease free survival outcomes. Shapiro *et al.* noted a similar trend when comparing VATS lobectomy (n=113) and VATS segmentectomy (n=31) for T ≤3 cm N0 NSCLC between 2002 and 2008 with the segmentectomy group found to have had a more extensive smoking history and worse pulmonary function reserve preoperatively (83% *vs.* 92% FEV1, P=0.04) (53).

Robotic segmentectomy

The first reported use of robotic technology in for primary lung cancer in thoracic surgery was in the early 2000s (55). Robotic surgery allows for multiple degrees of freedom, decreased tremor, and improved visualization. Thoracic surgeons have increasingly adapted the use of the robotic platform.

There is a lack of studies that evaluate oncologic outcomes of robotic segmentectomy. In contrast, a few studies have compared oncologic outcomes between robotic and VATS lobectomy. A propensity match of patients with T ≤5 cm N0 NSCLC undergoing robotic (n=172), VATS (n=141), and open (n=157) lobectomy between 2002 and 2012 found all techniques had similar 5-year OS rates (77.6%, 73.5%, 77.9% respectively, P=0.53); VATS and robotic surgery had shorter lengths of stay; robotic surgery was associated with greater LN harvest (5 for robotic, 3 for VATS, 4 for open P<0.001) (56). A propensity-matched analysis of the NCDB by Yang and colleagues in 2016 reported the robotic group (n=1,938) was not significantly different from VATS lobectomy (n=1,938) with regard to nodal upstaging, 30-day mortality, and 2-year survival (57).

A major limitation to the application of robotic surgery has been the perception of increased cost. Nguyen *et al.* queried the Premier Healthcare Database between 2008 and 2015 and after propensity matching compared clinical outcomes and cost for robotic, VATS and open lobectomy for malignancy found in the early period [2008–2012] robotic lobectomies (RL) had longer operating room times and more admissions to intensive care units as compared to open (OL) and VATS lobectomies (VL) (P<0.0001). In the Late period [2013–2015], RL was associated with lower rates of complications (P<0.05), conversions, and shorter length of stay than VL and OL. When hospital volume was not considered, costs were higher for RL than VL and

OL. In hospitals where >25 lobectomies were performed annually, the total cost of RL was comparable to VL (P=0.09) and OL (P=0.11) (58).

Some studies comparing operative techniques combined both segmentectomy and lobectomy as a single group in their outcome assessment. Mungo *et al.* evaluated clinical T ≤5 cm N0 NSCLC patients undergoing VATS (n=80) or robotic (n=53) lobectomy or segmentectomy between 2007 and 2014. The robotic-assisted group had more segmentectomies (11.3% *vs.* 1.2%, P=0.016), a lower rate of conversion to open surgery as compared to VATS (12.2 *vs.* 26.2%, P=0.25) and a higher number of LNs retrieved (9 *vs.* 7, P=0.049). All VATS patients remained stage I; 5 robotic patients (9.4%) were upstaged. There were no differences in postoperative morbidity or mortality (59).

A meta-analysis of 14 studies evaluating oncologic outcomes between robotic and VATS lobectomy/segmentectomy reported lower 30-day mortality, lower rates of conversion to open surgery for the robotic group, and no significant difference in operative time, length of hospital stay, chest tube duration, LN retrieval, or perioperative morbidity (60).

A few studies have exclusively compared outcomes between robotic and VATS segmentectomy. Xie *et al.* evaluated NSCLC tumors ≤2 cm resected with VATS (n=85) versus robotic (n=81) segmentectomy between January 2016 and April 2017 and described a higher number of LNs dissected in robotic *vs.* VATS cases (13 *vs.* 10 LNs respectively, P=0.01) with no significant differences in perioperative outcomes (61). Similarly, other authors report a higher number of LNs obtained in robotic *vs.* VATS segmentectomies (52,54,62).

Zhang and coworkers in their retrospective analysis of robotic (n=298) and VATS (n=476) segmentectomies for T ≤2 cm N0 NSCLC at three institutions between 2015 and 2019 found similar rates of complications and length of stay. The robotic group had a greater number of N1 LNs (4 *vs.* 3, P<0.01) and N1 stations (3 *vs.* 2, P<0.01) dissected; there were no significant differences for N2 nodal harvest. The robotic approach was associated with increased cost (63).

A few studies have compared robotic segmentectomy *vs.* RL. Echavarria *et al.* retrospectively evaluated patients with NSCLC who underwent robotic segmentectomy (n=43) and lobectomy (n=208) between 2010 and 2013. Only two individual complications were significantly higher in the segmentectomy group: pneumothorax after chest tube removal requiring chest tube reinsertion (10.3% *vs.* 1.9%, P=0.032) and effusion or empyema requiring drainage (16.3% *vs.* 1.0%, P=0.011). Post-operative changes in FEV1 and DLCO were significantly less (P<0.001) after segmentectomy (64).

Nguyen and associates retrospectively reviewed 71 patients who underwent robotic segmentectomy for cT ≤2 cm N0 NSCLC between 2004 and 2013 and reported 55% 5-year OS and 73% 5-year CSS, which was comparable to survival outcomes previously published in the open segmentectomy literature. Advanced age and pathological upstaging were significant risk factors for cancer specific death (65).

Our group recently used the NCDB to compare perioperative outcomes and OS for robotic, open and VATS segmentectomies in patients with clinical T ≤3 cm N0 NSCLC between 2010 and 2015. The VATS group had a significantly higher rate of conversion to open (8%) *vs.* the robotic group (4.9%, P=0.036). LN yield was higher for the robotic group (mean =7.07) as compared to the VATS (mean =6.33) and open groups (mean =5.33, P<0.001); LN upstaging however was not significantly different among robotic (3.0%), VATS (3.0%), and open cases (4.3%, P=0.106). Notably, increase in LN yield did not translate to better survival; OS at 80 months was similar (P=0.181) in all three groups (66). The associated video presentation serves as a visual instructional guide, highlighting key steps of a robotic-assisted right lower lobe basilar posterior and lateral (S9+10) segmentectomy performed at our institution (*Video 1*).

Ongoing trials

There are currently two RCTs that seek to evaluate outcomes between SLR and lobectomy in patients with T ≤2 cm N0 peripheral NSCLC. The Japanese JCOG0802/WJOG4602 trial includes two treatment arms—segmentectomy and lobectomy—while the CALGB/Alliance 140503 includes wedge resection and segmentectomy in the SLR group.

Perioperative morbidity and mortality for the CALGB 140503 study did not differ significantly between segmentectomy and lobectomy (67). In the JCOG0802/WJOG4602 study, there were no significant differences in intraoperative or post-operative complications between groups. The segmentectomy group had higher air leak rates as described above (45). Oncologic outcomes have not yet been reported for either trial.

Conclusion and future directions

The widespread use of chest CT scan for a variety of indications has resulted in earlier detection of NSCLC. The decision to perform a SLR in place of the historically gold-standard lobectomy is a paradigm shift. A significant number of prospective and retrospective studies suggest that segmentectomy provides equivalent oncologic outcomes to lobectomy for small (≤2 cm) NSCLC as long as adequate margins and LN dissection are achieved. Segmentectomy is particularly beneficial for patients considered high-risk to undergo lobectomy. In addition, preserving lung parenchyma may be important for multifocal synchronous tumors, for future metachronous primary cancers, and for cancers with multiple and recurrent lung metastases. Leroy *et al.* have reported a cumulative incidence of second primary lung cancer of 25.2% at 14 years (68).

In the past, a focus on size criteria has determined the indication for segmentectomy *vs.* lobectomy. Selection criteria may be more complex when accounting for tumor biology and location, in addition to size. It appears that for large cell carcinomas and STAS-positive tumors, lobectomy should remain the standard of care. Segmentectomy may be associated with higher locoregional recurrence for segments S1-S3.

Interestingly, recent data suggests that the presence of unsuspected nodal disease may not mandate completion lobectomy; adjuvant chemotherapy may play a more significant role than the type of anatomic lung resection.

Technological advances have allowed for an improved patient experience. The use of thoracoscopic procedures, as compared to open resection, is associated with decreased postoperative pain, decreased length of stay, and faster return to baseline function.

In the continuum of improving technology, the introduction of robotic surgery has allowed for improved visualization and dexterity of surgical instruments. Robotic segmentectomy has been found to be a safe procedure, providing equivalent oncologic outcomes to VATS and open segmentectomy. The precision of wristed instruments with seven degrees of motion may allow for a more complete lymphadenectomy; it may also facilitate resection of complex segments that are challenging to perform with inflexible VATS instruments. A high case volume could mitigate the cost associated with the use of a robotic platform.

Limitations to our narrative review include the retrospective nature of the published data and the few RCTs in the literature. With regards to future directions, the thoracic community awaits the oncologic results of the CALGB140503 and JCOG0802/WJOG4602 trials in order to further delineate outcome differences between SLR and lobectomy for stage I NSCLC. As our knowledge of cancer biology improves, a clinical algorithm encompassing preoperative and intraoperative factors including patient factors, tumor size, tumor biology, and segmental anatomy may be useful to better guide surgeons for an optimal patient-specific oncologic resection and technique. Further development of navigational software that allows for clear mapping of segments and sub-segments, in conjunction with the use of robotic technology, may allow thoracic surgeons to perform increasingly complex segmentectomies and sub-segmentectomies that spare more lung parenchyma with equivalent oncologic outcomes.

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Footnote

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