Lobectomy was established in 1995 as the standard of care for optimal oncologic resection of stage I non-small cell lung cancer (NSCLC), after the results of the Lung Cancer Study Group (LCSG) reported a significantly higher rate of recurrence and associated trend toward lower cancer-specific survival in patients undergoing sublobar resections (1). Since then, several investigators have challenged this dogma by demonstrating equivalent oncologic outcomes of segmentectomy and lobectomy for peripheral clinical T1N0M0 NSCLC 2 cm or smaller in size. The majority of these publications are retrospective studies. Two ongoing RCTs aim to resolve this debate, one in Japan and the other in the United States. This manuscript is a comprehensive review of the literature that compares lobectomy to segmentectomy for peripheral clinical T1N0M0 NSCLC 2 cm or smaller in size. Until data from the ongoing RCTs become available, this literature review provides the best evidence to guide the thoracic surgeon in the management of these patients.

**Keywords:** Segmentectomy; lobectomy; lung cancer; 2 cm

Lobectomy was established in 1995 as the standard of care for optimal oncologic resection of stage I non-small cell lung cancer (NSCLC), after the results of the Lung Cancer Study Group (LCSG) reported a significantly higher rate of recurrence and associated trend toward lower cancer-specific survival in patients undergoing sublobar resections (1). Since then, several investigators have challenged this dogma by demonstrating equivalent oncologic outcomes of segmentectomy and lobectomy for stage IA NSCLC. A large proportion of studies have integrated segmentectomy and wedge resection under the category of limited resection when making comparisons to lobectomy (2). However, recent publications have focused on comparisons between segmentectomy and lobectomy excluding cases of wedge resection (3-6).

Potential advantages of segmentectomy over lobectomy include preservation of lung function and reduced morbidity and disability. Preservation of lung function may be particularly important for elderly patients, those with borderline preoperative cardiopulmonary function, and patients with synchronous or metachronous cancers that would require repetitive resections over the course of their lifespan. The incidence of a second primary lung cancer may be as high as 3% per year (7); thus, patients who survive five or more years after their first resection would face a significant cumulative risk of second cancers. On the other hand, lobectomy may provide a lower recurrence rate that could translate into longer disease free survival, particularly in young patients who are good surgical candidates.

The main objective of this manuscript is to review the literature that compares lobectomy versus segmentectomy for peripheral clinical T1N0M0 NSCLC 2 cm or smaller in size. Until data from the ongoing RCTs become available, this literature review provides the best evidence to guide the thoracic surgeon in the management of these patients.

**Lung Cancer Study Group (LCSG) trial**

This randomized controlled trial (RCT) enrolled patients from February 1982 through November 1988 and compared open lobectomy to sublobar resection for patients with lung cancer ≤3 cm with absence of lymph node involvement (1). There were 247 patients eligible for analysis: 122 received a limited resection and 125 underwent lobectomy. Of the 122
patients who underwent a limited resection, 40 (32.8%) had a wedge resection and 82 (67.2%) had a segmentectomy. There were no significant differences for all stratification variables, selected prognostic factors, perioperative morbidity, mortality, or late pulmonary function. The rate of local recurrence in the limited resection group was 6.3%, which was significantly higher than the 2.1% observed in the lobectomy group (P=0.008), and the 5-year survival rate in the limited resection group was 83.1%, which was slightly poorer than the 89.1% observed in the lobectomy group. In addition, postoperative pulmonary function was not significantly different in the two groups, even at one year after surgery. The authors concluded that, compared with lobectomy, limited pulmonary resection does not confer improved perioperative morbidity, mortality, or late postoperative pulmonary function. Furthermore, due to higher death rates and locoregional recurrence rates associated with limited resection, lobectomy must be considered the surgical procedure of choice for patients with peripheral T1N0 NSCLC.

It must be acknowledged that a considerable number of wedge resections (32.8%) were included in the limited resection group; tumor sizes ranging from 2 to 3 cm were included in the analysis; and routine computed tomographic examination of the lung was not required either preoperatively or for postoperative surveillance. Several publications have demonstrated a lower rate of loco-regional recurrence after segmentectomy compared to wedge resection for stage I NSCLC (8-10). An adequate body of literature has also demonstrated that T1b tumors (2-3 cm) have lower survival rates than T1a tumors (≤2 cm) (11,12). Moreover, advances in imaging and optimal pre-resection surgical mediastinal staging have improved staging accuracy since the LCSG trial was published (13). This trial was done in an earlier era when tumors were often more central, many were squamous cell cancers, and they were larger stage I tumors (14).

Extended segmentectomy for stage I lung cancer

Since the results of the LCSG were published, several Japanese investigators have studied the role of sublobar resection for stage I NSCLC. The Study Group of Extended Segmentectomy for Small Lung Tumors was created and their final report was published in 2002 (15). This prospective multicenter study enrolled 55 patients with peripheral clinical T1N0M0 (cT1N0M0) NSCLC (≤2 cm) from January 1992 to December 1994. All patients were in physical conditions to tolerate a lobectomy. Extended segmentectomy 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 (16). The patients were followed up at 1- or 3-month intervals for five years or more. The 5-year disease-free survival (DFS) rate was 91.8%. Postoperative loss of lung function was 11.3% in forced vital capacity (FVC) and 13.4% in forced expiratory volume in one second (FEV1). The authors concluded that extended segmentectomy is viable as a standard operation for patients with small peripheral lung tumors, and causes minimal loss of lung function.

More recently, Nomori et al. (17) also examined the outcomes of 179 patients who underwent intentional open radical segmentectomy with systematic lymph node dissection for peripheral cT1N0M0 NSCLC between 2005 and 2009 at a single institution. All analyzed patients had intraoperative frozen section to demonstrate surgical margins of at least 2 cm. Of these 179 patients, 134 (75%) had tumors ≤2 cm, and 45 (25%) had tumors 2.1 to 3 cm. The 5-year DFS was 95% for patients with tumors ≤2 cm and 79% for those who had tumors 2.1 to 3 cm. Postoperative pulmonary function (measured at least six months after surgery) was preserved at 90%±12% of preoperative levels.

The importance of lymph node dissection during segmentectomy has been demonstrated. The frequency of lymph node metastasis in patient with cT1N0M0 NSCLC is approximately 10% (18). A theoretical disadvantage of segmentectomy versus lobectomy is the potential presence of metastatic disease in level 13 lymph nodes in the preserved adjacent segments. Nomori et al. (19) investigated the distribution of subsegmental lymph nodes in resected and preserved segments during segmentectomy. Out of 94 patients with cT1N0M0 NSCLC treated with segmentectomy, segmental nodes at both the resected and nonresected segments could be dissected in 42 of the 94 patients. The authors concluded that segmental lymph nodes should be dissected at both the resected and nonresected segments during segmentectomy, especially for tumors in the anteriorly located segment.

Another factor that appears to play an important role in recurrence after segmentectomy is the surgical margin. Schuchert and colleagues (20) performed a retrospective review of 182 consecutive patients undergoing anatomic...
Segmentectomy versus lobectomy for cT1N0M0 NSCLC ≤ 2 cm

In order to elucidate factors associated with survival, Okumura et al. (12) analyzed 144 patients who underwent segmentectomy and 1,241 who underwent lobectomy. The authors concluded that a favorable outcome would be obtained by a segmentectomy in patients with a maximum diameter of the tumor smaller than 2 cm, no nodal involvement, and non-large cell carcinoma. Five- and 10-year overall survival (OS) in patients who met those criteria were both 83%, which was significantly higher than that for those who did not (41%) (P<0.0001). In comparison, 5- and 10-year OS in patients who underwent lobectomy meeting the same criteria (non-large cell carcinoma at stage IA ≤ 2 cm) was 81% and 64% respectively (P=0.66). There were no 5-year survivors among the six patients with large cell carcinoma who underwent a segmentectomy. In contrast, there was no difference in survival among different histologic types when a lobectomy was performed. The authors concluded that lobectomy, but not a segmentectomy, is recommended for large cell carcinomas, even when the tumor diameter is 2 cm or smaller.

In another retrospective study, Yamato and colleagues (21) reviewed 523 cases of cT1N0M0 peripheral adenocarcinomas ≤ 2 cm between 1991 and 2004. The surgical procedure was a lobectomy in 277 patients, segmentectomy in 153 patients and wedge resection in 93 patients. The limited resection was intentional in 140 cases, and it was performed for compromised patients in 106 cases. The 5-year survival rate of the patients who underwent a wedge resection was 70.6%, which was significantly worse than the 87.5% after a segmentectomy and the 85.5% after a lobectomy.

A multicenter nonrandomized study comparing lobectomy to sublobar resection was conducted by Okada et al. (22) from 1992 to 2001 for patients with a first peripheral cT1N0M0 NSCLC ≤ 2 cm who were able to tolerate a lobectomy. During the operation, the tumor status was confirmed to be T1N0 on the basis of frozen-section analysis of sampled segmental, lobar, hilar, and mediastinal lymph nodes. For segmentectomy, a margin of at least 2 cm of healthy lung tissue was required. It was specified that when the surgical margin was less than 2 cm or a lymph node was positive, lobectomy had to be performed instead. Of the 567 patients enrolled, 214 patients underwent curative segmentectomy, 30 underwent wedge resection and 236 had lobectomy. DFS and OS were similar in all groups. Five-year DFS was 92.2% after segmentectomy and 91.5% after lobectomy (P=0.64). Five-year OS was 93.9% after segmentectomy and 95.3% after lobectomy (P=0.43).

More recently, Carr and coworkers (11) performed a retrospective review of 429 patients undergoing resection of pathologically confirmed stage IA NSCLC via lobectomy (251 patients) or anatomic segmentectomy (178 patients) from 2002 to 2009. Video-assisted thoracoscopic surgery (VATS) was the approach utilized in 59% of segmentectomies and 39.4% of lobectomies during the study period. The margin:tumor ratio was similar whether performing an anatomic segmentectomy or lobectomy for T1a or T1b tumors. There was no difference in mortality, recurrence rates (14% segmentectomy vs. 14.7% lobectomy, P=1.00), or 5-year cancer-specific survival (CSS) for T1a tumors (90% vs. 91%, P=0.984) when comparing segmentectomy and lobectomy. The authors concluded that anatomic segmentectomy may achieve equivalent recurrence and survival compared with lobectomy for patients with stage IA NSCLC.

A criticism of the literature comparing the efficacy of segmentectomy and lobectomy since 1995 is that the majority of publications have been limited to single-institution retrospective reviews. However, more recently some investigators have used the Surveillance Epidemiology and End Results (SEER) database to compare survival after lobectomy and limited resection in patients with stage IA NSCLC. Whitson et al. (23) analyzed the SEER database for stage I adenocarcinoma or squamous cell carcinoma in patients 40 years and older from 1998 through 2007. The analysis included 13,892 patients who underwent lobectomy and 581 who underwent segmentectomy. Even after stratifying by tumor size, the authors found that lobectomy was associated with more favorable 5-year OS (P=0.0002) and CSS (P=0.0047) rates for tumors ≤ 2 cm.

Yendamuri and coworkers (13) also used the SEER database to identify surgically treated patients with stage I NSCLC ≤ 2 cm in size from 1988 to 2008. The cohort included 2,161 patients undergoing sublobar resection and 6,636 patients undergoing lobectomy or greater resection. They grouped these patients into three temporal cohorts.
the first included patients from 1988 to 1997 (early), the second was from 1998 to 2004 (intermediate) and the third was from 2005 to 2008 (late). In the early group, sublobar resection was associated with worse outcome. In the intermediate group, wedge resection but not segmentectomy was associated with a worse outcome compared with lobectomy. The association between extent of resection and OS completely disappeared in the late subgroup, in which neither wedge resection nor segmentectomy had an outcome worse than did lobectomy. The authors concluded that the survival advantage offered by lobectomy over sublobar resection in NSCLC patients with tumor size ≤2 cm has incrementally decreased over the past two decades.

A recent meta-analysis (24) included 24 studies (11,360 patients) published from 1990 to 2010 to compare OS and CSS of stage I NSCLC after sublobectomy or lobectomy. In stage IA patients with tumor ≤2 cm, there were no differences in OS between lobectomy and sublobectomy (HR 0.81; 95% CI, 0.39-1.71; P=0.58). For the comparison between lobectomy and segmentectomy, there was no significant difference on OS (HR 1.09; 95% CI, 0.85-1.40; P=0.45) and CSS (HR 0.99; 95% CI, 0.72-1.38; P=0.97) in stage I NSCLC.

Several studies have specifically limited their objective to compare outcomes between lobectomy and segmentectomy for NSCLC ≤2 cm, excluding larger tumors or wedge resections. Mattioli et al. (25) performed a retrospective investigation to compare anatomical segmentectomy and lobectomy for peripheral cT1N0M0 NSCLC ≤2 cm on preoperative CT scan, with regard to the number/station of lymph nodes resected, as well as survival. In this case-matched study, 46 intentional segmentectomy patients were matched with 46 lobectomy patients for age, anatomical segment, and size of the tumor. All patients were able to tolerate a lobectomy as evaluated by cardiopulmonary functional tests. Starting in January 2001, the authors offered anatomical segmentectomy as an alternative to lobectomy to patients affected by a peripheral cT1aN0M0 NSCLC. The cases in which lobectomy was performed within the same time period were retrospectively retrieved from the institutional electronic medical record system database. The approach for the resection was an axillary muscle-sparing thoracotomy. Radical dissection of lymph node stations 4, 5, 6 and 7 was identical in segmentectomies and lobectomies. Node stations 10, 11, 12 and the segmental 13 were also dissected carefully during segmentectomy and in the pathology laboratory after lobectomy. The median number of total dissected lymph nodes was 12 in anatomical segmentectomy compared with 13 in lobectomy (P=0.68), with the number of N1 nodes being 6 and 7, respectively (P=0.43), and N2 nodes 5.5 and 5 (P=0.88). No perioperative mortality was observed. Complications occurred in 13% of segmentectomies and in 15% of lobectomies (P=0.76). The median follow-up was 25 months for the segmentectomy group and 32 months for the lobectomy group. Freedom from recurrence at 36 months was 100% for anatomical segmentectomy and 93.5% for lobectomy (P=0.33).

**Thoracoscopic segmentectomy vs. lobectomy**

The vast majority of the evidence described above involves open procedures. However, a few recent studies have compared the outcomes of thoracoscopic segmentectomy and thoracoscopic lobectomy for small-sized stage IA lung cancer. Shapiro et al. (6) analyzed patients between January 2002 and February 2008. Indications for segmentectomy were tumor smaller than 3 cm, limited pulmonary reserve, comorbidities, and peripheral tumor location. Thirty-one patients underwent a segmentectomy and 113 had a lobectomy. Patients undergoing a segmentectomy had worse mean FEV1 than those having a lobectomy (83% vs. 92%, P=0.04). There were no differences in mean number of nodes (10) and nodal stations (5) resected. The mean follow-up was 21 months. There were 5 (17.2%) recurrences after segmentectomy and 23 (20.4%) after lobectomy (P=0.71), with locoregional recurrences rates of 3.5% and 3.6%, respectively. OS and DFS were similar between the groups. Zhong and colleagues (26) also compared outcomes between thoracoscopic segmentectomy and thoracoscopic lobectomy. Their inclusion criterion was limited to stage IA NSCLC ≤2 cm. The study period was between March 2006 and August 2011. A total of 39 segmentectomies and 81 lobectomies were analyzed. The two groups had a similar incidence of postoperative complications. The median follow-up was 26.5 months. Local recurrence rates were similar after segmentectomy (5.1%) and lobectomy (4.9%). No significant difference was observed in 5-year OS (79.9% vs. 81%) or DFS (59.4% vs. 64.2%).

**Segmentectomy for clinical T1N0M0 ≤2 cm and ≥50% ground glass opacity component (GGO-dominant)**

Tumor characteristics may also play an important role in deciding the extent of surgical resection. Tsutani et al. (27)
evaluated 239 patients with GGO-dominant clinical stage IA lung adenocarcinoma from four institutions between August 2005 and June 2010. All patients underwent HRCT and FDG-PET/CT followed by curative R0 resection. The inclusion criteria were absence of >1 cm enlargement in mediastinal or hilar lymph nodes and an absence of >1.5 accumulation for maximum standardized uptake values (SUVmax) in these lymph nodes. Sublobar resection was allowed for a peripheral cT1N0M0 intraoperatively assessed as N0, using frozen section evaluation of enlarged lymph nodes or by ensuring that there was no obvious enlargement of lymph nodes in the thoracic cavity. Systematic lymph node dissection was performed during segmentectomy, but not during wedge resection. Follow-up included a chest CT every six months for the first two years postoperatively, and every year thereafter. Median follow-up period after surgery was 42.2 months. Lobectomy was performed in 90 patients, segmentectomy in 56, and wedge resection in 93. A total of 155 tumors were classified as T1a and 84 as T1b. There was no significant difference in 3-year DFS among patients with GGO-dominant tumors who underwent lobectomy (96.4%), segmentectomy (96.1%), and wedge resection (98.7%; P=0.44). A multivariate Cox proportional hazards model for DFS included variables of age, gender, clinical T descriptor, solid tumor size, SUVmax, and surgical procedure. However, none of these variables were independent prognostic factors.

**Pulmonary function tests**

With regards to the functional advantage of a limited resection, Harada et al. (28) analyzed PFT preoperatively and at two and six months after radical segmentectomy in 38 patients and lobectomy in 45 patients. Both groups were able to tolerate a lobectomy and had cT1N0M0 NSCLC ≤2 cm. The anatomic segmentectomy was made through video-assisted approach with minithoracotomy. They performed segmentectomy if the patient consented to the sublobar resection, and lobectomy if the patient did not. During the postoperative course, statistically significant differences were observed between the two groups in the ratio of postoperative to preoperative FVC (P=0.0006) and FEV1 (P=0.0007), whereas a marginal difference was seen in the ratio of postoperative to preoperative anaerobic threshold (P=0.616). Keenan and colleagues (29) retrospectively analyzed patients undergoing lobectomy (n=147) or segmentectomy (n=54) for stage I NSCLC between March 1996 and June 2001. From the pathologic analysis, there were 126 stage IA and 21 stage IB patients in the lobectomy group, and 47 stage IA and 7 stage IB patients in the segmentectomy group. PFT was obtained preoperatively and at one year. At one year, 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%). In contrast, a decline in diffusing capacity was the only significant change seen after segmental resection. Actuarial survival in both groups was similar (P=0.406), with a 1-year survival of 95% for lobectomy and 92% for segmentectomy. Four-year survivals were 67% and 62%, respectively. Overall, the risk of any recurrence, whether local, regional, or systemic, was identical in the two groups (20.4% segmentectomy, 19% lobectomy). The authors concluded that for patients with stage I NSCLC, segmental resection offers preservation of pulmonary function compared with lobectomy and does not compromise survival.

**Ongoing prospective RCTs**

The controversy about the optimal extent of surgical resection for peripheral NSCLC ≤2 cm has led to several multicenter prospective RCTs. The JCOG0802/WJOG4607L trial (30) began in August 2009 in Japan to evaluate the non-inferiority in OS of segmentectomy compared with lobectomy in patients with peripheral NSCLC ≤2 cm. A total of 1,100 will be accrued from 71 institutions within three years. The inclusion criteria include age 20-79 years old, sufficient organ function, single tumor, ≤2 cm in maximum diameter, proportion of maximum diameter to consolidation >25%, center of tumor located in the outer third of the lung field, tumor not located at middle lobe, and no lymph node metastasis. The secondary endpoints include postoperative respiratory function, relapse-free survival, and proportion of local recurrence. The distance from the dissection margin to the tumor edge must be evaluated intra-operatively. If the distance is less than 2 cm, the absence of cancer cells in the resection margin must be histologically or cytologically confirmed before finishing surgery. When lymph node metastasis is present or resection margin is not cancer-free, the surgical procedure must be converted to a lobectomy. All randomized patients will be followed for at least five years. Tumor markers, CXR and chest CT is evaluated at least every six months during the first two years and at least every 12 months for the duration of follow-up.

Similarly, the CALGB 140503 study (31) aims to determine whether DFS after sublobar resection (segmentectomy or
wedge) is non-inferior to that after lobectomy in patients with NSCLC ≤2 cm. A total of 692 patients will be accrued to the study and randomized intra-operatively to either lobectomy or limited resection. Prior to registration, patients must have a lung nodule measuring ≤2 cm on CT scan, presumed to be lung cancer and located in the outer third of the lung. Intraoperative histological confirmation of NSCLC must be obtained (if not done preoperatively), as well as confirmation of N0 status by frozen examination of levels 4, 7, and 10 on the right side and 5 or 6, 7 and 10 on the left side, either at the time of surgery or pre-operatively by mediastinoscopy within six weeks of the definitive procedure. Patients must also have a performance status of 0–2. Exclusion criteria include prior malignancy within five years, prior chemotherapy or radiation, and age <18 years.

Conclusions

The increasing use of CT scans and improvement in CT resolution has been associated with earlier detection of NSCLC with smaller tumor size. Also, the location and type of lung cancer has evolved over time such that smaller, peripheral adenocarcinomas are now among the most common presentation. An extensive body of literature mainly composed of retrospective studies supports the use of radical anatomical segmentectomy for peripheral cT1N0M0 NSCLC ≤2 cm, certainly for older patients with limited cardiopulmonary function. However, caution should be taken to promote a widespread indication for intentional segmentectomy in young good surgical candidates until the results of the ongoing RCTs become available. When expertise exists, the surgeon should use a minimally invasive approach to realize perioperative and functional patient benefits.

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Villamizar and Swanson. Lobectomy vs. segmentectomy for NSCLC <2 cm


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