

History of Limited Resection for Non-small Cell Lung Cancer

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A retrospective study of limited resection for lung cancer in a large number of patients was first reported in the 1970s. The reported outcome of segmentectomy was comparable to that of standard lobectomy. The North American Lung Cancer Study Group (LCSG) performed a randomized controlled clinical trial to compare limited resection (segment or wedge) with lobectomy for T1N0 (stage IA) non-small cell lung cancer (NSCLC) in the 1980s. The study revealed a significant excess of intrathoracic recurrence rate and a tendency to poorer survival in the limited resection group. Since then, limited resection has not been considered the standard operation for lung cancer. However, this situation is gradually changing, because the recent introduction of chest computed tomography (CT) to mass surveys has made peripherally located lung cancer detectable at the earliest stage. Several recent non-randomized studies of intentional limited resection from Japan demonstrated good outcomes comparable to those of lobectomy. Organ-sparing wedge resection without systematic dissection of lymph nodes may be suitable for some types of small lung cancers detected only by CT. Our meta-analysis of published data comparing survival rates after limited resection and lobectomy for stage I lung cancer revealed that limited resection was comparable to lobectomy. Further studies are necessary to define precise targets of intentional limited resection for lung cancer. (Ann Thorac Cardiovasc Surg 2005; 11: 356–62)

Key words: lung cancer, limited resection, lobectomy, segmentectomy, wedge resection

Introduction

In the 1960s, lobectomy with systematic dissection of mediastinal lymph nodes became the standard operation for lung cancer.^{1,2} However, a question remained as to whether less invasive limited resection sometimes might be curative. An excellent outcome of segmentec-

tomy first was reported in a large number of patients by Jensik et al. in the 1970s.³ A randomized controlled clinical trial comparing limited resection with lobectomy for T1N0 non-small cell lung cancer (NSCLC) was carried out by the North American Lung Cancer Study Group (LCSG) in the 1980s. The results of this trial were published in 1995 by Ginsberg and Rubinstein.^{4,5} Although this randomized trial concluded that limited resection should not be the standard operation even for small peripheral NSCLC, other surgeons still believed that this procedure was suitable for selected patients. Some clinical studies showed excellent outcome for patients undergoing intentional limited resection.⁶⁻⁸ Although these studies were non-randomized, the results of limited resection seemed acceptable.⁹ We review here the past history and present status of limited resection for NSCLC.

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Early Experience of Limited Resection (1970s)

Jensik et al. first reported the results of segmentectomy for 119 patients in 1973.³⁾ The patients were categorized into three groups; previous resection (n=16), palliative resection (n=37), and curative resection (n=69). In the 69 patients who underwent a curative resection, the survival rate was 56.4% at 5 years. This 5-year survival rate was comparable to that for lobectomy at that time. Later, Jensik¹⁰⁾ reported 296 patients with stage I or II peripheral lung cancers, obtaining a survival rate of 52% at 5 years and 31% at 10 years after surgery. These survival rates were considered comparable to those for lobectomy. In 1994, however, a study from the same institution demonstrated a higher recurrence rate with segmentectomy than with lobectomy in stage I lung cancer.¹¹⁾ In that study, 173 patients with stage I NSCLC underwent either a segmental resection (n=68) or lobectomy (n=105) from 1980 to 1988. Patients undergoing lobectomy had a statistically significant survival advantage over patients undergoing segmentectomy (p=0.035). The survival differences varied according to the size of the tumor. No survival advantage of lobectomy over segmental resection was noted for patients with tumors 3.0 cm in diameter or smaller. However, a survival advantage was apparent for patients undergoing lobectomy for tumors larger than 3.0 cm (p=0.006). In addition, the rate of locoregional recurrence was 22.7% (15/66) after segmentectomy vs. 4.9% (5/103) after lobectomy. This remarkable excess of locoregional recurrence in the limited resection group was similar to the result of a randomized trial⁴⁾ reported by the LCSG in 1995.

A Randomized Controlled Clinical Trial by the Lung Cancer Study Group (1980s)

A randomized controlled trial comparing limited resection (segment or wedge) with lobectomy for T1N0 (stage IA) NSCLC was initiated by the North American LCSG in 1982.⁴⁾ Entry to the study was concluded in November 1988. After a minimum follow-up period of 4.5 years, the results of the trial were reported. Segmental resection or large adequate wedge resection was used, and at least 2 cm of normal lung tissue was required to be resected beyond the tumor. After completion of the resection, the surgeon confirmed that all required lymph node stations were negative for metastatic disease by frozen section analysis. A total of 276 patients were entered into this study. Although an additional 495 pa-

tients were registered for the study before operation, these patients were ineligible at operation for various reasons (benign disease 40%, larger resection needed because of tumor location or configuration 25%, more advanced stages 25%, or other than non-small cell histologies). Finally 247 patients, 122 limited resections and 125 lobectomies, were eligible. Total recurrence, excluding second primary (p=0.02) and locoregional recurrence (p=0.008), was significantly higher in the limited resection group. Both death rates and death with cancer rates were lower after lobectomy than after limited resection. Limited resection was associated with a 30% increase in the overall death rate and a 50% increase in the observed death with cancer rate. Although pulmonary function tests were significantly better for patients receiving limited resection at 6 months after surgery, these differences lost statistical significance at 12 to 18 months. On this point, Keenan et al.⁹⁾ reported that segmentectomy patients were able to maintain pulmonary function in the postoperative period in contrast to the lobectomy group. However, precise comparison of the postoperative lung function between both groups was difficult in most non-randomized studies^{11,18,20,23)} because limited resection has been done usually for patients with poor pulmonary function. The randomized trial clearly found the outcome with limited resection to be inferior to that with lobectomy in terms of both survival and locoregional recurrence. We think that the results in this trial were not surprising because positivity of mediastinal lymph nodes are 15% to 25%, even in NSCLC less than 2 cm in size.^{12,13)} Systematic removal of lymph drainage routes by lobectomy presumably prevents locoregional recurrence better than wedge resection or segmentectomy. The results of this trial became the most reliable evidence for considering lobectomy the gold standard, since this is the only randomized trial existing.

Intentional Limited Resections (2000 to the Present)

Although the randomized trial showed limited resection to be less effective for NSCLC, several promising results of intentional limited resection have been reported from Japan.⁶⁻⁸⁾

Kodama et al.⁶⁾ compared survival after lobectomy or limited resection for stage IA NSCLC. Limited resection with curative intent was performed for 63 patients, including 46 patients who underwent segmentectomy. These

patients had good pulmonary function and could tolerate lobectomy. The other 17 patients underwent wedge resection or segmentectomy as a compromised limited resection because of poor pulmonary reserve or other limiting factors. The 5-year survival was 93% in the intentional resection group. The survival curve for this group was not different from that for 77 patients who underwent lobectomy for stage IA NSCLC during the same period. The frequency of locoregional recurrence in the intentional limited resection group was 8.7%, whereas that in the lobectomy group was 1.3%. According to multivariate analysis, limited resection was not associated with poorer survival. The authors concluded that segmentectomy with regional lymph node dissection, including the mediastinum, should be considered as an acceptable alternative treatment for selected patients with stage IA disease.

Okada et al.⁷⁾ prospectively enrolled 89 patients able to tolerate lobectomy in a trial of limited resection. The limited procedure consisted of segmentectomy in which the resection line was extended beyond the involved segment. Exploration of lymph nodes by frozen sectioning guided resection; node positivity determined whether a different procedure was needed. This extended node-guided procedure was called extended segmentectomy. Of 89 patients initially assigned to the limited resection group, 19 had to receive other procedures, because of nodal involvement in 12 and tumor location or invasion in 7. Among patients with cT1N0M0 NSCLC of 2 cm or less, the 5-year survival rate was 87.3% after extended segmentectomy and 77.7% after lobectomy. They found no significant difference between the groups. Interestingly, they reported no local recurrences in the limited resection group. In intentional segmentectomy studies, nodal disease is carefully sought during the operation, and such cases are strictly excluded from limited resection. This procedure would yield a limited resection group different from that obtained by simple wedge resection without intraoperative nodal examination. They concluded that extended segmentectomy should be considered as an alternative for patients with cT1N0M0 NSCLC of 2 cm or smaller.

Koike et al.⁸⁾ performed limited resection for patients with c-stage IA peripheral NSCLC whose maximum tumor diameter was 2 cm or less. Patients who could tolerate lobectomy were treated with limited resection if the patient consented to the procedure. Lobectomy was performed if consent to limited resection was not obtained. Survival and clinical outcome of the patients

whose tumors were postoperatively staged as p-stage IA were compared between the limited resection group (n=74) and the lobectomy group (n=159). The limited resection group consisted of 60 patients treated with segmentectomy and 14 patients treated with wedge resection. Among patients followed up for a mean period of 52 months after the operation, the 5-year survival rates were 89.1% in the limited resection group and 90.1% in the lobectomy group. Postoperative tumor recurrence was found in 5 patients after limited resection and in 9 patients after lobectomy, showing no significant difference between the groups. The authors concluded that in patients with peripheral NSCLC less than 2 cm, the outcome of limited resection is comparable with that of lobectomy.

Results of Wedge Resection without Systematic Dissection of Mediastinal Lymph Nodes

The prognosis of patients after simple wedge resection according to tumor size and pathologic features is unclear. We examined the outcome of 100 patients who underwent limited resection (wedge or segmentectomy) without systematic dissection of lymph nodes as potentially curable surgery for lung cancer.¹⁴⁾ There were 44 women and 56 men, and ages ranged from 40 to 92 years. Histologic types included 76 adenocarcinomas, 21 squamous cell carcinomas, and 3 large cell carcinomas. Clinical stages included 83 stage IA and 17 stage IB. From computed tomography (CT) findings, tumors were classified into two groups; pure ground-glass opacity (PGGO) and non-PGGO. By high-resolution CT, 27 tumors (27%) showed PGGO. Postoperative pathologic examination showed that all of these tumors showing PGGO were localized bronchioloalveolar carcinomas. Overall and lung cancer-specific 5-year survival rates in all patients were 58.0% and 64.8%, respectively (Table 1). Overall 5-year survival with small adenocarcinomas (≤ 2 cm) was 93.7%, significantly better than the 24.8% rate with larger adenocarcinomas ($p < 0.0001$) (Table 2). Since no locoregional recurrence or distant metastasis has been observed in PGGO tumors, wedge resection appears to be the best operation for localized bronchioloalveolar carcinoma showing localized PGGO (≤ 2 cm). From these results, we believe that lung cancers with PGGO detectable only by CT can be completely resectable by simple wedge resection, and wedge resection is highly curable for most well-differentiated small-size (≤ 2 cm) adenocarcinomas.

Table 1. Univariate analysis for 100 patients who underwent limited resection for non-small cell lung cancer (Nakamura et al. Lung Cancer J-IASLC 2004; 44: 61–8)¹⁴

Prognostic factor	Overall		Lung cancer-specific	
	5-year survival rate (%)	p value	5-year survival rate (%)	p value
Histologic type		0.0382		0.7567
Ad (n=76)	63.2		66.4	
Sq (n=21)	42.1		58.7	
Tumor size (1 cm)		0.0384		0.0403
≤1 cm (n=36)	65.6		75.0	
>1 cm (n=64)	52.4		58.2	
Tumor size (2 cm)		0.0002		<0.0001
≤2 cm (n=73)	78.2		87.6	
>2 cm (n=27)	33.2		37.6	
Tumor size (3 cm)		0.0047		0.0057
≤3 cm (n=83)	64.6		72.5	
>3 cm (n=17)	37.2		42.1	
Differentiation		0.0007		0.0041
WD (n=52)	79.7		83.9	
MD+PD (n=45)	38.0		45.7	

Ad, adenocarcinoma; Sq, squamous cell carcinoma; WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated.

Table 2. Univariate analysis for 76 patients who underwent limited resection for lung adenocarcinoma (Nakamura et al. Lung Cancer J-IASLC 2004; 44: 61–8)¹⁴

Prognostic factor	Overall		Lung cancer-specific	
	5-year survival rate (%)	p value	5-year survival rate (%)	p value
Tumor size (1 cm)		0.0321		NC
≤1 cm (n=29)	94.4		100.0	
>1 cm (n=47)	51.6		53.9	
Tumor size (2 cm)		<0.0001		<0.0001
≤2 cm (n=60)	93.7		98.2	
>2 cm (n=16)	24.8		26.5	
Tumor size (3 cm)		0.0101		0.0180
≤3 cm (n=66)	71.5		74.6	
>3 cm (n=10)	35.0		38.9	
Differentiation		0.0003		0.0006
WD (n=50)	81.2		83.9	
MD+PD (n=26)	30.7		33.3	

WD, well-differentiated; MD, moderately differentiated; PD, poorly differentiated; NC, not calculated.

Meta-analysis Comparing Survival Rates between Limited Resection and Lobectomy

As mentioned above, the sole randomized controlled trial, reported by the LCSG, advised against limited resection as standard surgery even for small peripheral NSCLCs (≤3 cm), because of frequent local recurrences and worse survival. Some surgeons still believe that limited resection is comparable to lobectomy. We therefore conducted a meta-analysis of reported studies to compare survival of stage I patients between limited resection and stan-

dard lobectomy.¹⁵) A MEDLINE search for computer-archived bibliographic data yielded 14 articles suitable for analysis (Table 3).^{4,6-9,11,16-23}) Combined survival differences (survival rate with lobectomy minus that with limited resection) at 1, 3, and 5 years after resection according to the DerSimonian-Laird random effects model were 0.7% (95% CI, -0.8 to 2.1; p=0.3659), 1.9% (95% CI, -3.7 to 7.4; p=0.5088), and 3.6% (95% CI, -0.4 to 10.5; p=0.3603), respectively. None of these survival differences were significant, indicating that survival after limited resection for stage I lung cancer was comparable

Table 3. Studies comparing the outcome of limited resection and lobectomy (Nakamura et al. Br J Cancer 2005; 92: 1033–7)¹⁵⁾

Author	Stage	Number of limited resection	Number of lobectomy	Survival difference
Hoffmann (1980) ¹⁶⁾	IA	33	40*	NS
Read (1990) ¹⁷⁾	IA	113	131	NS (CSS)
Date (1994) ¹⁸⁾	IA	16	16	Lobectomy better
Warren (1994) ¹¹⁾	IA+B	66	103	Lobectomy better
Harpole (1995) ¹⁹⁾	IA+B	75	193	NS (CSS)
LCSG (1995, 1996) ⁴⁾	IA	122	125	NS
Kodama (1997) ⁶⁾	IA	46**	77	NS
Landreneau (1997) ²⁰⁾	IA	102	117	NS
Pastorino (1997) ²¹⁾	IA+B	53	367	NS
Kwiatkowski (1998) ²²⁾	IA+B	58	186***	Lobectomy better
Okada (2001) ⁷⁾	IA ≤2 cm	70	139	NS
Koike (2003) ⁸⁾	IA ≤2 cm	74	159	NS
Campione (2004) ²³⁾	IA	21	100	NS
Keenan (2004) ⁹⁾	IA+B	54	147	NS

LCSG, Lung Cancer Study Group; NS, not significant; CSS, cancer-specific survival.

*Tumours peripherally located; **only intentional resection; ***including 13 pneumonectomies.

Table 4. Extent of lymph node metastasis in small size non-small cell lung cancer (≤2 cm)

Author	Limited to clinical N0	Histologic type	Number of patients	N0	N1	N2	N3	Patients with positive nodes
Asamura (1996) ¹²⁾	No	Ad	152	78.9%	8.6%	12.5%	0%	21.1%
		Sq	16	93.7%	0%	6.3%	0%	6.3%
		NSCLC	174	80.5%	8.0%	11.5%	0%	19.5%
Konaka (1998) ²⁴⁾	No	NSCLC	171	83.0%	5.8%	11.1%	0%	17.0%
Ohta (2001) ²⁵⁾	Yes	Ad	106	78.3%	ND	ND	ND	21.7%*
		Sq	6	100%	0%	0%	0%	0%
		NSCLC	112	79.5%	ND	ND	ND	20.5%*
Watanabe (2001) ²⁶⁾	No	Ad	170	77.6%	7.6%	11.8%	2.9%	22.4%
		Sq	20	90.0%	10.0%	0%	0%	10.0%
		NSCLC	225	76.9%	7.6%	13.3%	2.2%	23.1%
Nonaka (2003) ²⁷⁾	No	NSCLC	46	71.7%	8.7%	19.6%	0%	28.3%

Ad, adenocarcinoma; Sq, squamous cell carcinoma; NSCLC, non-small cell lung cancer; ND, not described.

*Detected by immunohistochemistry using anti-cytokeratin antibody.

to that after lobectomy. However, since most studies included were non-randomized and inter-study heterogeneity was detected, caution is required in interpretation of these results.

Conclusion

Regarding limited resection for lung cancer, the sole randomized controlled study indicated that wedge resection or segmentectomy was inferior to lobectomy concerning both locoregional recurrence and survival in stage IA NSCLCs. Further, involved lymph nodes are found in association with 15% to 25% of small lung cancers. Thus, tumor size in itself is not a good criterion for limited re-

section. Different authors have reported the positivity of dissected lymph nodes (Table 4).^{12,24-27)} Even for clinical N0 tumors (≤2 cm), metastatic nodes have been frequently found in adenocarcinomas. However, in squamous cell carcinomas (≤2 cm), nodal metastases have been rarely seen.^{12,25,26)}

Two clinical studies^{28,29)} comparing systematic lymph nodal dissection to lymph nodal sampling revealed that survival after lung resection combined with systematic dissection was significantly better. Although a conflicting result³⁰⁾ exists, importance of systematic nodal dissection cannot be ignored even for small size lung cancers.

Without addressing the problems above, reliably cura-

tive limited resection cannot be performed. Protocols for limited resection must include careful exclusion of cases with lymph node metastasis by rapid examination of intraoperative frozen sections, such as was reported by Tsubota's group in Japan.^{7,31} However, this method would be difficult to apply reliably to all institutions. Biologic characteristics of lung cancers that can be removed safely by limited resection should be determined. As a classic pathologic feature, we think differentiation grade may be useful if this information can be obtained from a preoperative biopsy specimen. We believe that small (≤ 2 cm) well-differentiated adenocarcinomas or squamous cell carcinomas are good candidates for wedge resection. Genetic markers favoring limited resection should be determined. Screening for lung cancer using chest CT is becoming more prevalent, and small peripheral lung cancers are being detected more frequently. For peripheral localized bronchioloalveolar carcinoma showing PGGO, wedge resection appears to be the best option.

We believe that the precise subset of NSCLCs curable by limited resection is likely to be determined in the near future.

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