

Pulmonary wedge resection for clinical stage I non-small cell lung cancer: a review of a mini-invasive treatment

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ABSTRACT

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related deaths in the world. Therefore, there is a need to intensify treatments of these tumors. Because stage I NSCLC is a nonmetastatic disease, local therapies are indicated, among which surgery is the most commonly deployed strategy. Pulmonary wedge/sublobar resection is therefore discussed in comparison to stereotactic body radiation therapy for stage I lung cancer. Review of retrospective and prospective clinical trials reveal similar outcomes for both strategies, while a multicenter randomized prospective study comparing the efficacy of both therapies is on-going. Because the results of pulmonary wedge/sublobar resection may depend on tumor size, tumor-distance from surgical margin, tumor size-to-margin distance ratio, and margin cytology, prospective studies to evaluate the clinical implications of these factors, so as to inform patient prognostication, are recommended.

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INTRODUCTION

The need for less invasive treatment strategies has been increasing, partly due to the increase in the ageing population.^[1] Because stage I lung cancer is a localized disease without evidence of metastases^[2] and is associated with low morbidity and mortality, minimally invasive (mini-invasive) local therapies are central to managing the high-risk or medically unfit patient such as the elderly. The various types of mini-invasive

local therapies for stage I lung cancer are defined by the amount of lung tissue targeted or resected. These include segmentectomy and wedge resection (wedge/sublobar resection), radiation, radiofrequency ablation,^[3,4] and cryoablation therapies.^[5] Currently, the most commonly used strategies are wedge/sublobar resection and radiation therapy, including stereotactic body radiation therapy (SBRT). We therefore review pulmonary wedge/sublobar resection in comparison to SBRT for stage I lung cancer.



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In order to retrieve articles, the author (N. S.) searched “PubMed” using key words relevant to the context of this review. Specifically, in addition to “lung cancer” and “stage I”, either “wedge” or “SBRT” was chosen as key words. Incorporating the terms “wedge” and “SBRT”, found a total of 169 and 250 articles, respectively. The author read the abstracts to select appropriate articles, which were then read in full. Article references were checked for useful studies that were not detected via “PubMed” searches.

Limited pulmonary resection varies such that making a distinction between segmentectomy and wedge resection can sometimes be difficult. Some segmentectomies fall under wedge resection; however, others with large amounts of resected pulmonary parenchyma are similar to lobectomy. Therefore, in this review, sublobar and wedge resections are discussed together. All contributors read the draft manuscript for comments, and when necessary, issues presented in the text were rewritten after discussion.

RETROSPECTIVE STUDIES

Pulmonary wedge resection for solid lesions

Stage I lung cancer comprises tumors that are not larger than 5 cm in diameter. It is usually technically difficult to achieve complete tumor removal by wedge resection for stage I tumors that are 5 cm in size (T2AN0M0; stage IB). It has therefore been speculated that such cases were excluded from retrospective analyses of pulmonary wedge resections for solid lesions. In addition, although the main subtypes of non-small cell lung cancer (NSCLC), adenocarcinoma, squamous cell carcinoma, and large-cell neuroendocrine carcinoma are associated with different prognosis, there are a few studies of pulmonary wedge resections for these tumors.

Among patients with early stage NSCLC, the rates of operative morbidity and mortality were reported to be lowest in those who underwent wedge resection, followed by segmentectomy, and then lobectomy. This was the conclusion of a study that aimed at investigating the grade of invasiveness of pulmonary wedge resection, segmentectomy, and lobectomy using registry data. Linden *et al.*^[6] therefore state that the Society of Thoracic Surgery database was reviewed for stage I and II NSCLC patients undergoing wedge resection and anatomic resection to analyze postoperative morbidity and mortality. Propensity scores were estimated using a logistic model adjusted for a variety of risk factors. Between 2009 and 2011, 3,733 wedge resection and 3,733 anatomic resection patients were matched. The operative mortality was

1.21% for wedge resection versus 1.93% for anatomic resection ($P = 0.0118$). Major morbidity occurred in 4.53% of wedge resection patients versus 8.97% of anatomic resection patients ($P < 0.0001$).^[6] They concluded that wedge resection has a 37% lower mortality and 50% lower major morbidity rate than anatomic resection and these perioperative benefits must be carefully weighed against the increase in loco-regional recurrence and possible decrease in long-term survival associated with the use of wedge resection for primary lung cancers.^[6]

Reports before 2000 that studied stage I NSCLC patients who received wedge/sublobar pulmonary resection provide a calculated 5-year overall survival rate (5-YSR) of 60-70%, and a local recurrence rate of approximately 25%.^[7-9] Errette *et al.*^[8] reported in 1985 that the 5-YSR of wedge resection and lobectomy cases were 69% and 75%, respectively, which was not statistically significant. In the 1997 study of the efficacy of thoracoscopic surgery for stage I NSCLC, Landreneau *et al.*^[9] reported a 5-YSR of 58%, 65%, and 70% for patients who received open wedge resection, video-assisted wedge resection, and lobectomy, respectively. Although the calculated survival rate was not statistically significant between the open and video-assisted wedge resection groups, there was a difference in the 5-YSR between the wedge resection and lobectomy groups due to a significantly greater non-cancer-related deaths that occurred within 5 years among the wedge resection group (38% vs. 18%, $P = 0.014$).

The results of retrospective institutional studies of pulmonary wedge resections for stage I NSCLC published in the 2000s are summarized in [Table 1](#). The mortality rate was very low; however, the long-time survival rate was inferior to reports before 2000, which were investigations based on non-biased patient populations,^[10-13] while the rate of local recurrence did not change.^[13,14] In addition, the 5-YSR was not different between the wedge/sublobar resection and lobectomy groups.^[10,12,15] There have also been detailed analyses based on parameters speculated to be indicators of prognosis. Kraev *et al.*^[12] reported on the long-time survival of patients who underwent pulmonary wedge resection and lobectomy. Of 215 lobectomy and 74 wedge resection patients matched for age, tumor size, and other comorbidities, there was a non-significant overall trend towards better survival times (mean survival time, 5.8 vs. 4.1 years, respectively; $P = 0.112$). However, this trend gained significance in analysis of smaller cancers, where patients who underwent lobectomy had better survival times than those who underwent wedge resection for tumors less than 3 cm

Table 1: Retrospective institutional study of pulmonary wedge resection for clinical stage I NSCLC from 2000 to 2010

Author	Year	n	Age, years	T1a < 2 cm, n (%)	GGO dominant	OP	Margin positive	Mortality, n (%)	Local relapse, n (%)	5-YSR (%) [3-YSR (%)], RR	Sublobar/wedge	Seg	Lob	P
Griffin <i>et al.</i> ^[10]	2006	31	Mean 69	NA	NA	Wedge	NA	NA	NA	(35)	NA	(35)	0.8	
Yendamuri <i>et al.</i> ^[11]	2007	68	NA	NA	NA	Wedge	NA	0 (0)	NA	(58)	NA	NA	0.08	
Kraev <i>et al.</i> ^[12]	2007	74	NA	31 (42)	NA	Wedge	NA	NA	NA	(37)	NA	(52)	0.1	
						T > 3 cm				(35)	NA	(35)	0.9	
						T < 3 cm				(35)	NA	(60)	0.01	
El-Sherif <i>et al.</i> ^[14]	2007	81	Mean 70	NA	NA	Sublobar (wedge 55; 68%)	NA	0 (0)	6 (7)	NA (RFS)	NA	NA	NA	
		40				MD > 1		0 (0)	3 (8)	(35) [80]	NA	NA	0.2	
		41				MD < 1		0 (0)	6 (15)	(58) [78]	NA	NA	(0.7)	
Grills <i>et al.</i> ^[13]	2010	69	0 (0%)	NA	NA	Wedge	NA	0 (0)	20 (29)	(52) [79]	NA	NA	0.01	
Wisnivesky <i>et al.</i> ^[15]	2010	196	> 75 (62%)	196 (100)	NA	Sublobar	NA	NA	NA	1.1	NA	Ref	NS (Cox)	

NSCLC: non-small cell lung cancer; GGO: ground glass opacity; OP: operation; YSR: year survival rate; RR: relative risk; NA: not assessed or not available; MD: margin distance; RFS: relapse free survival rate; NS: not significant; Seg: segmentectomy; Lob: lobectomy; Ref: reference

in size ($P = 0.029$). They concluded that tumor size appears to be an important factor to be considered in preoperative planning.^[12] Based on these findings, the authors recommended randomized trials to confirm the superiority of lobectomy over wedge resection for stage IA lung cancers.^[12] The implications of tumor distance from surgical margin (margin-distance) in mini-invasive surgery have also been addressed. El-Sherif *et al.*^[14] demonstrated that margin-distance had a significant impact on local recurrences. In their report, 14.6% (6/41) of the patients with margin-distances of less than 1 cm developed local recurrences compared to 7.5% (3/40) of patients with margin-distances equal to or greater than 1 cm ($P = 0.04$). Segmentectomy was the choice of surgery for 17% (7/41) and 47.5% (19/40) of the patients with margin-distances of less than 1 cm and equal to or greater than 1 cm, respectively. The authors concluded that margin-distance was an important consideration after sublobar resection of NSCLC, because wedge resection was frequently associated with margins less than 1 cm and a high-risk for loco-regional recurrence.^[14] Although the clinical implications of tumor size and margin-distance were evaluated, margin cytology and ground glass opacity (GGO) did not receive much attention in the 2000s.

Investigations published in the 2010s are summarized in Table 2. The mortality rate was also very low during this period, with a 5-YSR of 55-65% (median, 61%) for all ages^[16-20] and 41% for aged patients.^[21] The 5-YSR seems to have improved in the 2010s, and this may be because the detection rate of small stage I tumors had increased for every decade as shown in the report from the Japanese Joint Committee of Lung Cancer Registry.^[22]

The status of surgical margin of wedge resected clinical

stage I NSCLC and patient outcomes has often been a consideration in the 2010s. This critical observation may have led to the designation of “occult margin malignancy” (malignant positive cytological surgical margin without histological positive result), which was introduced by Sawabata *et al.*^[23] This “occult margin malignancy” occurs not only in wedge resections, but also in segmentectomies and lobectomies.^[24] Furthermore, it had been revealed that insufficient margin-distance correlated with positive margin cytology results.^[25] Therefore, in order to achieve clean surgical margins (negative for malignancy) recent wedge resection may be carried out with sufficient margin-distance. Sawabata *et al.*^[17] reported that both M/T and margin cytology findings were indicators of cancer recurrence and survival. In their series, all seven cases of surgical margin recurrences were associated with positive margin cytology results. Additionally, the 5-year survival rate was 54.2% ($n = 24$) for M/T less than 1, and 84.6% for M/T more than 1 ($n = 13$, $P = 0.05$), while it was 38.5% for positive margins ($n = 13$) and 79.2% for negative margins ($n = 24$, $P = 0.001$). The authors therefore concluded that a pulmonary wedge resection for peripheral NSCLC should result in a negative malignant margin, which might be achieved with an M/T of more than 1. However, Maurizi *et al.*^[26] reported that among 243 consecutive patients with a functional contraindication to major lung resection, and who therefore underwent wedge resection with systematic lymph node (LN) dissection for clinical stage I NSCLC, loco-regional (lung parenchyma, hilum, mediastinum) recurrence rate was 26.4% ($n = 48$), distant recurrence rate was 11% ($n = 20$), 5-YSR was 70.4%, and 5-year disease-free survival (DFS) rate was 51.7%. When the first 3 groups were compared, there was no statistically significant difference in loco-regional recurrence ($P = 0.9$), distant

Table 2: Retrospective institutional study of pulmonary wedge resection for clinical stage I NSCLC after 2011

Author	Year	n	Age, years	T1a < 2 cm, n (%)	GGO dominant, n (%)	OP	Margin positive, n (%)	Mortality, n (%)	Local relapse, n (%)	5-YSR (%) {4-YSR (%)}, RR	Sublober/wedge	Seg	Lob	P
Nakamura et al. ^[16]	2011	84	NA	NA	28 (33)	Wedge	NA	0 (0)	NA	(55)	(82)	(87)	NA	
Sawabata et al. ^[17]	2012	37		25 (67)	NA	Wedge	13 (35)	0 (0)	9 (23)	(64)	NA	NA		
		24				MNMC	0 (0)		0 (0)	(79)	NA	NA	0.01	
		13				MPMC	13 (100)		8 (62)	(39)	NA	NA		
		13				MD/TS > 1	0 (0)		0 (0)	(85)	NA	NA	0.05	
		24				MD/TS < 1	12 (50)		8 (33)	(54)	NA	NA		
Matsuo et al. ^[18]	2014	65	Median 65	NA	NA	Sublober	NA	0 (0)	NA	(61)	NA	NA	NA	
Mediratta et al. ^[19]	2014	540	Median 72	NA	NA	Wedge	NA	NA	NA	(65)	NA	NA	NA	
Mohiuddin et al. ^[27]	2014	479	> 80 (10%)	118 (25)	NA	Wedge	NA	1 (0)	NA	(RFS)				
		169				MD < 0.5 cm				{63}			0.03	
		123				0.5 cm < MD < 1.0 cm				{70}				
		NA				1.0 cm < MD < 1.5 cm				{80}				
		NA				1.5 cm < MD				{82}				
Ambrogi et al. ^[20]	2015	59	Median 70	NA	NA	Wedge	NA	0 (0)	NA	(55)	NA	NA	NA	
Maurizi et al. ^[26]	2015	182	Mean 70	138 (76)	NA	Wedge	NA	2 (1)	48 (26)	NA	NA	NA		
		30		24		MD < 1 cm				(47)	NA	NA	NS	
		80		63		1 cm < MD < 2 cm				(54)	NA	NA		
		72		51		2 cm < MD			(58)	NA	NA			
Fiorelli et al. ^[21]	2016	90	> 75 (100%)	40 (44)	1 (2)	Sublober	NA	0 (0)	12 (13)	(41)	NA	(61)	0.1	
Altorki et al. ^[28]	2016	160	Median 74	136 (85)	22 (14)	Wedge	2 (1)	0 (0)	15 (9)	Ref	1.1		0.7 (Cox)	
		58				MD/TS > 1	NA							
		84				MD/TS < 1	NA							
Stiles et al. ^[36]	2016	166	Median 72	159 (95)	27 (16)	Wedge	NA	0 (0)	16 (10)	NA	NA	NA		
		138	Median 72	111 (80)	20 (14)	LN	NA	0 (0)	8 (7)	(83)	NA	NA	0.04	
		58	Median 72	48 (83)	7 (12)	NLN	NA	0 (0)	8 (7)	(56)	NA	NA		
Moon et al. ^[41]	2017	91		67 (74)	52 (57)	Sublober (wedge 63; 69%)	NA	0 (0)	NA	(RFS)				
		14	Mean 66	13	14	MD < 0.5 cm	NA		0 (0)	(100)				
		38	Mean 61	35	38	MD > 0.5 cm	NA		0 (0)	(100)				
		11	Mean 71	6		MD < 0.5 cm	NA			(24)				< 0.001
		28	Mean 69	23		MD > 0.5 cm	NA			(80)				

NSCLC: non-small cell lung cancer; OP: operation; GGO: ground glass opacity; YSR: year survival rate; RR: relative risk; NA: not assessed or not available; RFS: relapse free survival rate; MNMC: malignant negative margin cytology; MPNC: malignant positive margin cytology; MD: margin distance; TS: tumor size; Ref: reference; NS: not significant; Seg: segmentectomy; Lob: lobectomy

recurrence ($P = 0.3$), and overall survival ($P = 0.07$) rates. It was therefore concluded that wedge resection is a viable option for the surgical treatment of stage I NSCLC when lobectomy is contraindicated, while the distance between the tumor and the parenchymal suture margin does not influence recurrence or the survival rate when an R0 resection is achieved.^[26] In contrast, Mohiuddin et al.^[27] after reviewing 497 non-biased adult patients who had undergone wedge resections for small (less than 2 cm) NSCLC reported that the overall unadjusted 1 and 2 year local recurrence rates were 5.7% and 11.0%, respectively. However, from the adjusted analyses, an increased margin-distance was significantly associated with a lower risk of local recurrence ($P = 0.033$), and patients with a 10 mm margin-distances had a 45% lower local recurrence risk than those with a 5 mm distance [hazard ratio (HR) 0.55, 95% confidence interval (CI): 0.35-0.86], while beyond 15 mm, no evidence of additional benefit was achieved. It was therefore

concluded that in wedge resection for small NSCLC, increasing the margin distance 15 mm significantly decreased the local recurrence risk, with no evidence of additional benefit beyond 15 mm.^[27] However, both Maurizi et al.^[26] and Mohiuddin et al.^[27] did not consider surgical margin cytology in their studies.

In view of the clinical implications of surgical margin cytology and distance, Altorki et al.^[28] compared the outcomes of pulmonary wedge resection to segmentectomy for peripheral small sized lung cancers by examining both parameters. With a median follow-up of 34 months, there was no difference between patients who underwent wedge resection and anatomical segmentectomy in regards to local recurrence (9% vs. 11%; $P = 0.68$) and 5-year DFS (51% vs. 53%; $P = 0.7$). On the other hand, Smith et al.^[29] reported inferior survival outcome for wedge resection to segmentectomy using registry data. Analyses with adjustment for propensity scores of 3,525 patients

Table 3: Retrospective study of pulmonary wedge resection for clinical stage I NSCLC using registry data

Author	Year	n	Age, years	T1a < 2 cm, n (%)	GGO dominant, n (%)	OP	Margin positive	Mortality	Local relapse	5-YSR (%) {4-YSR (%), RR			
										Sublobar/wedge	Seg	Lob	P
Mery <i>et al.</i> ^[35]	2005	1,403	NA	NA	NA	Wedge	NA	NA	NA	NA	NA	NA	0.03
		NA	< 60							(50)	NA	(67)	
		NA	60-75							(40)	NA	(54)	
Kates <i>et al.</i> ^[30]	2011	688	> 70 (43%)	688 (100) (< 1 cm)	NA	Sublobar	NA	NA	NA	1.1	NA	Ref	NS (Cox)
		768	> 80 (12%)	407 (53)	NA	Wedge	NA	NA	NA	(47)	(69)	(68)	< 0.001
		361 (1998-2004)	NA	361 (100)	61 (17)	Wedge	NA	NA	NA	{50}	{60}	{75}	< 0.05 (wedge vs. Lob)
Yendamuri <i>et al.</i> ^[31]	2013	737 (2005-2008)	NA	737 (100)	115 (16)	Wedge	NA	NA	NA	{64}	{73}	{80}	NS
		1,568	Mean 70	Mean size 1.82 cm	187 (12) (pure)	Wedge	NA	NA	NA	Ref	0.8	NA	< 0.05 (Cox)
Warwick <i>et al.</i> ^[33]	2013	210	Median 72	NA	NA	Wedge	NA	NA	NA	(45)	NA	(68)	0.003
Khullar <i>et al.</i> ^[34]	2015	7,297	Mean 68.9	NA	NA	Wedge	292 (4%)	11 (2%)	NA	(54)	(58)	(71)	< 0.001 (wedge vs. Lob)

NSCLC: non-small cell lung cancer; OP: operation; GGO: ground glass opacity; YSR: year survival rate; RR: relative risk; NA: not assessed or not available; RFS: relapse free survival rate; Ref: reference; NS: not significant; Seg: segmentectomy; Lob: lobectomy

from the Surveillance, Epidemiology and End Results (SEER) registry revealed that, segmentectomy was associated with significant improvement in overall survival (HR 0.80, 95% CI: 0.69-0.93) and lung cancer-specific survival (HR 0.72, 95% CI: 0.59-0.88) compared to wedge resection. Thus, it was concluded that these results suggest that segmentectomy should be the preferred technique for limited resection of patients with stage IA NSCLC.^[29] However, margin status of wedge resection was not registered in the SEER registry.

In addition, it is reported that survival outcome of pulmonary wedge resection is similar to lobectomy for patients with tumors of less than 2.0 cm.^[30,31] The registry data shows that demonstrate inferior^[29,32-34] or non-inferior^[30,31] survival outcomes of pulmonary wedge resection to lobectomy [Table 3]. Furthermore, there is a report showing that the outcome of surgery was age-dependent.^[35]

Lymph node (LN) dissection is also worthy of consideration because this is a standard procedure performed during lobectomy. However, because of potential side effects, caution should be exercised in choosing to perform this procedure. Stiles *et al.*^[36] evaluated all patients undergoing wedge resection for peripheral clinical stage IA NSCLC, and grouped them into those with and without LN dissection. Of 196 patients undergoing wedge resection, of whom 138 (70%) had LNs (median = 4 nodes) resected and the remainder did not, there were no significant differences in the clinical or pathologic characteristics between the two groups. Additionally, no difference in terms of

operating room time, estimated blood loss, chest tube duration or length of hospital stay was uncovered. However, the LN dissected group had higher probability of freedom from loco-regional recurrence compared to the no lymph node (NLN) group (5-year: 92% vs. 74%, $P = 0.025$) and higher probability of freedom from local recurrence ($P = 0.024$) in propensity matched groups. The conclusion therefore was that LN removal appears to decrease loco-regional recurrence and may be associated with a survival benefit.^[36]

Intentional pulmonary sublobar resection for solid lesions

As a standard practice, lung cancer patients with limited pulmonary function undergo limited resections, such as wedge resection or segmentectomy, which are referred to as “compromised resections”. However, some surgeons prefer ‘intentional’ sublobar resections in patients with normal lung functions.

In 1997, Kodama *et al.*^[37] conducted a 10-year study of 63 patients who received limited resections (46 segmentectomies and 17 wedge resections) and 77 patients who underwent the standard operation (lobectomy plus complete mediastinal LN dissection) as curative-intent treatments for T1N0M0 NSCLC. The 5-year survival rate was 93% in the intentional/limited resection group, and this was not different from that of the 77 patients who underwent the standard operation. The frequency of local/regional recurrence in the intentional resection group was 8.7% (4/46), with mediastinal involvement in 3 patients. It was thus concluded that sublobar resection should be considered

an acceptable alternative treatment for selected patients with T1N0M0 disease. Koike *et al.*^[38] studied 74 patients who received intentional limited resections for T1N0M0 (< 2 cm) disease, and uncovered that the calculated 3-year and 5-year survival rates were 94.0% and 89.1%, respectively, which did not significantly differ from those of a lobectomy group. They therefore concluded that in patients with peripheral T1N0M0 NSCLC whose maximum tumor diameter was 2 cm or less, the outcome of limited pulmonary resection is comparable with that of pulmonary lobectomy. Okada *et al.*^[39] also examined 260 sublobar resections, including 30 wedge resections, in comparison to 260 lobectomies, and found that DFS and overall survivals were similar in both groups. The 5-year DFS and overall survival were 85.9% and 89.6%, respectively for the sublobar resection group, and 83.4% and 89.1%, respectively for the lobar resection group. The conclusion was that sublobar resection should be considered as an alternative for stage IA NSCLC 2 cm or less, even in low-risk patients.^[39] These results could lay the foundation for starting new randomized controlled trials, which could revolutionize lung cancer surgery in this era of early detection. In this context, a phase III randomized trial of lobectomy versus limited resection (segmentectomy) for small (2 cm or less) peripheral NSCLC (JCOG0802/WJOG4607L) has been conducted in Japan.

Pulmonary wedge resection for GGO predominant lesions

In the 2010s, there was an increase in the number of articles that examined GGO lesions in regard to surgery. Asamura *et al.*^[40] conducted a prospective multi-institutional study whereby image diagnosis was used to define early (noninvasive) adenocarcinomas of the lung (Japan Clinical Oncology Group 0201). This study demonstrated that a consolidation/tumor ratio on thin-section computed tomography (CT) scans of 0.25 or less for cT1a (less than or equal to 2.0 cm) lesions was a better radiologic criterion for early pathology than a ratio of 0.50 or less for T1a-b (less than or equal to 3.0 cm) tumors. This criterion was used for prognostic evaluation of 545 patients with adenocarcinoma who underwent lobectomy and lymph node dissection. Using a consolidation/tumor ratio of 0.25 or less, the overall survival and 5-year relapse-free survival of the patients were 90.6% and 84.7%, respectively. With a ratio 0.5 or less for T1a-b lesions, the 5-year overall survival for radiologic noninvasive (121 patients, 22.2%) and invasive (424 patients, 77.8%) adenocarcinomas was 96.7% and 88.9%, respectively, and this difference was statistically significant ($P < 0.001$, log-rank test). However, when a consolidation/tumor ratio of 0.25 or less for clinical T1a was used, the 5-year overall survival rates of radiologic

noninvasive (35 patients, 12.1%) and invasive (254 patients, 87.9%) adenocarcinomas were 97.1% and 92.4%, respectively, and the difference was not statistically significant. It is currently widely accepted that the radiologic criteria of a consolidation/tumor ratio of 0.25 or less in clinical T1a and 0.50 in clinical T1a-b are both able to define a homogeneous group of patients with an excellent prognosis before surgery.

Margin-distance is an indicator of recurrence among patients with solid but not GGO predominant lesions. In the study by Moon *et al.*,^[41] there was no recurrence in GGO-predominant tumors after sublobar resection, and this was not influenced by margin-distance. However, for solid-predominant tumors, the 5-year recurrence-free survival after sublobar resection according to margin-distances of less than 5 mm and more than 5 mm were 24.2% and 79.6%, respectively ($P = 0.001$). The conclusion therefore was as follows that the distance between the tumor and resection margin does not affect the recurrence after R0 sublobar resection in patients with clinical N0 GGO-predominant lung cancer less than 3 cm but margin distance is a significant risk factor for recurrence after sublobar resection in patients with clinical N0 solid-predominant lung cancer.^[41]

Stereotactic body radiation therapy

Because conventional 2-dimensional radiation therapy of lung cancer has resulted in inadequate rates of local control and adverse effects, it is being replaced by SBRT, which is mainly administered for stage I lung cancer with acceptable morbidity and local control rates.^[42,43] Among inoperable patients, the mortality and severe morbidity from SBRT were few, and the 5-year survival rate was less than 20% (17-19%).^[44-46] Additionally, in non-biased patients with stage IA NSCLC, mortality and severe morbidity seldom occurred, but controllable radiation pneumonitis developed in up to 20% of the patients, and the median 5-year survival rate was 39% (ranged, 30-73%).^[47-50] It has also been reported that the outcome of surgery is superior to SBRT.^[51-53]

Comparison of pulmonary wedge resection and radiation therapy

Clinical observational studies that compared the outcomes of pulmonary wedge resection to SBRT suggest SBRT is inferior^[11,13,18] but comparable to wedge/sublobar pulmonary resection among operable^[53] and elderly^[54] patients.

PROSPECTIVE CLINICAL STUDIES

Pulmonary wedge resection

The Lung Cancer Study Group (LCSG) conducted the

first multicenter prospective study in 1995 that compared wedge/sublobar pulmonary resection to lobectomy.^[55] In this study, the rate of local recurrence was 17% in patients who received wedge/sublobar resections (40 wedge resections) in contrast to 6% for the lobectomy group ($P = 0.008$). The 3- and 5-year survival rates of the wedge/sublobar resection group were 79% and 48%, respectively. Although the survival rate was not statistically significant between the groups ($P = 0.1$), wedge/sublobar resection has not been accepted as a standard therapy for clinical stage I NSCLC.

A number of clinical trials have now been conducted to evaluate the usefulness of various surgical strategies for treating early stage lung cancer. Recently, a phase III randomized trial (JCOG0802/WJOG4607L) was conducted in Japan to evaluate the non-inferiority of overall survival of limited resection (segmentectomy) over lobectomy in patients with small peripheral NSCLC (2 cm or less, the proportion of maximum diameter of the tumor itself to consolidation > 0.5).^[56] In addition, a non-randomized confirmatory study (JCOG0804/WJOG4507L) has been conducted to evaluate the efficacy and safety of limited resection (wedge resection in general) in patients with small (2 cm or less) peripheral radiological noninvasive lung cancer, diagnosed by preoperative thin-section CT scan images.^[57] Another confirmatory trial (JCOG1211) has been conducted to confirm the efficacy of limited resection (lung segmentectomy) in patients with GGO-predominant lung cancers of less than or equal to 3 cm in diameter based on thin-section CT scans.^[58] In South America, a randomized phase III trial has also been conducted to compare the efficacy of different types of surgeries used to treat patients with stage I NSCLC.^[59] Wedge resection or segmentectomy may be less invasive surgeries with fewer side effects and improve recovery than lobectomy for NSCLC, but it is not yet known whether wedge resection or segmentectomy are more effective than lobectomy in treating stage IA NSCLC. However, there have been only three completed multicenter prospective studies of pulmonary wedge resections, including the LCSG study.^[55,60,61]

The American College of Surgeons Oncology Group (ACOSOG) completed a multicenter prospective study named Z4032.^[60] The ACOSOG Z4032 was a randomized phase III trial comparing sublobar resection to sublobar resection plus brachytherapy (wire of I-125 implantation at the site of surgical margin) in patients with stage I NSCLC who were considered high-risk for lobectomy. The study was closed to accrual in January 2010 after a planned enrollment of 222 evaluable patients. Although the study failed to reveal the efficacy of I-125 brachytherapy, its results are important

reference data of pulmonary wedge/sublobar resection of NSCLC. The ASOCOG Z4032 results revealed a local control rate of 71% and a 3-year survival rate of 76% in the wedge/sublobar resection group. Although the local control rate was not different regardless of brachytherapy administration, it was higher among cases with cytological malignant positive surgical margins that receive I-125 brachytherapy. Thus I-125 brachytherapy was proven to be effective.

The Kanetsu Lung-cancer Study Group (KLSG) conducted a one arm multicenter prospective study (KLSG0801) to investigate the feasibility of wedge/sublobar pulmonary resection among patients with limited cardio-pulmonary preservation in Japan.^[61] This study uncovered grade 3 morbidity in only 2 cases (7%), a calculated 3-year surgical margin control rate of 97%, a calculated 3-year local recurrence control rate of 76%, and a calculated 3-year overall survival rate of 79%, supporting the feasibility of wedge/sublobar pulmonary resection for NSCLC. In the KLSG0801 study, surgical margin cytology was carried out in 21 (67%) and margin-distance was measured in all (100%) cases. The calculated 3-year overall survival rate was 88% for negative margin cytology in contrast to 20% for those with positive margins. This finding suggests the importance of determining surgical margin cytology during pulmonary wedge resection of NSCLC. Furthermore, 80% of cases that revealed malignant positive margin cytology possessed M/T ratio of greater than 1, which further emphasizes the importance of performing pulmonary wedge resection with sufficient parenchymal surgical margin-distance. The results of a prospective study of wedge/sublobar resection for clinical stage I NSCLC are summarized in Table 4.

Stereotactic body radiation therapy

A prospective multicenter study of SBRT demonstrated a 3-year recurrence-free survival rate of 48-80%, 3-year overall survival rate of 56-90%, and tumor control rate of 86-98% with acceptable rates of adverse effects [Table 5].^[62-64] In addition, a recent prospective phase III study with SBRT and lobectomy arms suggests SBRT could be an option for treating operable stage I NSCLC; however, a limitation of this study was the small sample size.^[64]

Besides, there are technical limitations associated with SBRT such as “no-fly-zone” and irradiation of hilar tumors, and complications such as pulmonary fibrosis and hemoptysis, which should be considered when comparing surgery to SBRT. In addition, patients with unknown histologic diagnosis received SBRT in most of the studies.

Table 4: Prospective studies of pulmonary wedge/sublobar resection for clinical stage I NSCLC (%)

Study	Year	n	Operation Margin exploration					3-year recurrence free rate						3-year overall survival rate		
			Seg	Wed	MD	All	MC(+)	Margin recurrence free			Recurrence free			All	MC(+)	MC(-)
								All	MC(+)	MC(-)	All	MC(+)	MC(-)			
LCSG ^[55]	1995	122	82	40	NA	NA	NA	NA	NA	NA	78	NA	NA	79	NA	NA
ASCOG Z4032 ^[60]	2014	222	47	155	100	NA	7	NA	NA	NA	71	< 60	NA	76	< 70	NA
KLSG 0801 ^[61]	2016	32	1	31	100	67	16	97	80	100	76	NA	NA	79	20	88

NSCLC: non-small cell lung cancer; NA: not assessed or not available; MD: margin distance; MC: margin cytology; (+): malignant positive; (-): malignant negative; Seg: segmentectomy; Wed: wedge

Table 5: Prospective studies of stereotactic body radiation therapy for clinical stage I NSCLC

Study	Year	Design	Operability	n	Age (median, years)	Tumor size (median, cm)	3-year recurrence free rate (%)	3-year overall survival rate (%)	Tumor control rate (%)	Mortality (%)
RTOG0236 ^[62]	2010	Phase II	In-operable	55	72	T1, 2	48	56	98	0
JCOG0403 ^[63]	2015	Phase II	Operable	65	79	2.1	69	76	86	0
			In-operable	104	78	2.1	50	60	88	0
STARS ROSEL ^[64]	2015	Randomized	Operable	58						
			SBRT	31	67	NA	86	95	96	0
			Surgery	27	66	NA	80	79	100	0

NSCLC: non-small cell lung cancer; SBRT: stereotactic body radiation therapy; NA: not assessed or not available

Comparison of pulmonary wedge resection and stereotactic body radiation therapy

Investigators from both ACOSOG and the Radiation Therapy Oncology Group (RTOG) embarked on a randomized phase III study of SBRT vs. pulmonary wedge resection for high-risk operable NSCLC patients (ACOSOGZ4099/RTOG1021) that opened for accrual in 2012.^[65] The ACOSOG Z4099 is a randomized phase III study that will compare sublobar resection (SR) and SBRT for high-risk operable NSCLC patients. Eligible patients will have clinical stage I disease with tumors of 3 cm or less in the maximum diameter. Invasive lymph node staging will not be mandatory for all patients. However, patients with clinically suspicious lymph nodes (defined as > 1 cm on the short axis by CT scan and/or positive by positron emission tomography) will require biopsy to confirm N0 status before registration. Biopsy methods can include mediastinoscopy, anterior mediastinotomy, endoscopic ultrasonography, endobronchial ultrasonography, CT-guided techniques, and video-assisted thoracic surgical biopsy. It is possible that in the surgical arm of the study, the diseases of some patients will be upstaged. However, the primary analysis will be an “intent-to-treat” analysis, and all patients registered and randomized will be included in that analysis. Tumors will have to be in locations that will permit sublobar resection, and also not within 2 cm of the proximal bronchial tree in all directions. Tumors in close proximity to the bronchial tree have previously been demonstrated to have a high incidence of grade 4 and 5 toxicity with

standard-dose SBRT.^[66] Additionally, tissue diagnosis confirming NSCLC will be required for all patients before registration. Eligible patients will be defined as high-risk using the ACOSOG Z4032 criteria.^[60] The ACOSOG Z4032 was a randomized study undertaken to compare wedge/sublobar resection alone to wedge/sublobar resection plus brachytherapy for stage I lung cancer. Although closed to accrual, the primary endpoint data was not yet available at the time ACOSOG Z4099 opened. Brachytherapy is not a requirement in the surgical arm of ACOSOG Z4099, and the decision to use brachytherapy will be determined by institutional preference. The primary endpoint for the study will be 3-year overall survival. The secondary endpoint will include comparisons of loco-regional recurrence (using a uniform definition), DFS, grade 3 or higher adverse effects during a 1-year period, the effect of therapy on pulmonary function, and adverse effects and pulmonary function test results in patients with high or low Charlson comorbidity index scores. In addition, some correlative studies will be undertaken to consider patients' quality of life, as well as molecular studies using tissue and blood samples. The target accrual for ACOSOG Z4099 is 420 patients. Unfortunately this study seems to have been closed due to very slow patient accrual.

COMMENTS

The outcome data of clinical studies of pulmonary wedge/sublobar resection and/or SBRT were not different, and both had acceptable morbidity and

mortality rates. However, technical limitations and complications associated with SBRT, including “no-fly-zone”, irradiation of hilar tumors, pulmonary fibrosis, and hemoptysis should be considered when comparing surgery to SBRT. Moreover, in many studies, patients with unknown histologic diagnosis received SBRT. However, in order to perform SBRT, the lesion should be diagnosed cytologically and/or pathologically. Because diagnosing a cancer lesion involves some interventions, it is necessary to consider the merits and demerits of each diagnostic procedure.

There are three main methods used to diagnose lung cancer are transbronchial biopsy with flexible fiberoptic bronchoscopy (FFB), CT-guided fine needle aspiration biopsy (FNAC), and surgical resection.^[67] Each method is important but has some drawbacks. FNAC has potential to disseminate cancer cells through the needle tract.^[68] In a clinical settings, it has been reported that the relapse rate due to pleural recurrences is higher in FNAC than other diagnostic methods.^[69,70] There are also reports that reveal a prognostic disadvantage of biopsy using FFB.^[71,72] Pulmonary wedge resection is also a useful diagnostic technique for pulmonary nodules suspicious of malignancy, in addition to complete lesion resection with sufficient margin. As such, wedge/sublobar resection may be more suitable than SBRT in operable patients with no pathological diagnosis, and a select group of patients even if the cytological and/or pathological diagnosis is attained. In addition, if surgeons decide to carry out sampling of suspicious lymph nodes as in ACOSOG Z4032, knowledge of lymph node metastasis can inform adjuvant therapy.^[60]

Even if the results of ACOSOGZ4099/RTOG1201 is affirmative for SBRT, it would be important for selecting a subgroup of patients for wedge/sublobar resection based on tumor size, location, margin-distance, M/T ratio, and margin cytology. In addition, it has been reported that pure GGO and mixed GGO lesions are different from pure solid lesions in regards to surgical and radiation therapies.^[40,73,74] Therefore the proportion of GGO in a tumor is a very important parameter for choosing a treatment method. The International Lung-Clinical-Study Organization/Kanetsu Lung Cancer Study Group therefore embarked on a multicenter prospective study of wedge pulmonary resection for clinical stage I NSCLC (ILO1502/KLSG1602, UMIN000024303) that opened in October 2016, with mandatory assessment of GGO, resection type, tumor location, tumor size, margin-distance, M/T ratio, and margin cytology with the primary end-point of local control.^[75]

In conclusion: (1) patient survival after wedge/

sublobar resection of stage I NSCLC is improving, and is not significantly different globally for peripheral small-sized tumors; (2) there are phase III studies comparing lobectomy and segmentectomy but not wedge resection; (3) survival probability of wedge resection seems to be similar to that of SBRT, but SBRT has limitations such as “no-fly-zone”, irradiation of hilar tumors and associated complications such as pulmonary fibrosis and hemoptysis; and (4) a suitable subgroup of patients for wedge/sublobar resection may be found based on tumor size, location, margin-distance, M/T ratio, and margin cytology.

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Organizing this review and writing: N. Sawabata
Making a discussion and comments on the context of this review: A. Kawase, N. Takahashi, T. Kawaguchi, N. Matsutani

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