Long-term outcomes after a variety of video-assisted thoracoscopic lobectomy approaches for clinical stage IA lung cancer: A multi-institutional study

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Background: Although video-assisted thoracic surgery (VATS) has been in use for more than a decade, its application to major lung resection for lung cancer is still not widely practiced. The success of a cancer operation is judged by the long-term survival of the treated patients. Therefore, the goal of the present study was to evaluate long-term outcomes associated with various video-assisted lobectomy techniques and conventional surgery in patients with peripheral non–small cell lung cancer less than or equal to 2 cm in diameter (stage IA).

Methods: A multi-institutional, retrospective review was performed in 145 consecutive patients. Patients with clinical stage IA disease, with tumor size less than or equal to 2 cm in diameter, from three institutions underwent a complete VATS (c-VATS, n = 56), an assisted VATS (a-VATS, n = 34), or a conventional open (open, n = 55) approach for pulmonary lobectomy and lymph node dissection.

Results: Patients undergoing lobectomy and lymph node dissection with c-VATS had less blood loss, faster recovery, shorter hospitalization, and longer operating times than did patients undergoing the lobectomy with the a-VATS and open approaches. At a mean follow-up of 38.8 months, Kaplan-Meier probabilities of survival at 5 years were as follows: c-VATS, 96.7%; a-VATS, 95.2%; open, 97.2%. There was no significant difference in the rate of recurrence among the 3 different procedures.

Conclusion: VATS lobectomy, a safe procedure with earlier return to normal activities, can be regarded as an acceptable cancer operation for the patients with peripheral non–small cell lung cancer less than or equal to 2 cm in diameter (clinical stage IA) with the same long-term survivals as open surgery.

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Although video-assisted thoracoscopic (VATS) lobectomy with hilar and mediastinal lymph node dissection has been used for more than a decade in the management of patients with lung cancer,[1,2] this technique is still not widely practiced.[3,4] Many surgeons have expressed concerns about the adequacy of VATS lobectomy as a cancer operation. An early, small, multi-institutional randomized study of lobectomy failed to demonstrate any benefit of VATS over thoracotomy.[5] However, one problem with this type of study is that the VATS lobectomy procedures include a broad spectrum of operative techniques that range from complete endoscopic surgery to minithoracotomy with a thoracoscope serving only as a light source.[6] This variability in VATS techniques may contribute to confusion regarding the benefits of VATS lobectomy for management of lung cancer. Indeed, we[7] previously demonstrated that different VATS lobectomy techniques yielded different perioperative outcomes. Nonetheless, enough evidence to suggest that VATS lobectomy as a treatment for lung cancer is not compromised in

Abbreviations and Acronyms

ACT = Active Tracer AC-301
a-VATS = assisted video-assisted thoracic surgery
CI = confidence index
CT = computed tomography
c-VATS = complete video-assisted thoracic surgery
NSCLC = non–small cell lung cancer
VATS = video-assisted thoracic (thoracoscopic) surgery

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terms of long-term benefits has yet to be proven, because the success of a cancer treatment is judged only by the long-term survival of the treated patients.

Therefore, the goal of the present study was to evaluate long-term outcomes of various VATS lobectomy techniques and conventional surgery in patients with clinical stage IA lung cancer.

Materials and Methods

A retrospective review of 145 consecutive patients with clinical stage IA non–small cell lung cancer (NSCLC) less than or equal to 2 cm in diameter undergoing VATS and conventional thoracotomy for lobectomy and systematic nodal dissection was conducted at three centers from January 1999 and January 2004.

All patients underwent noninvasive staging with thoracic, upper abdominal, and brain computed tomography (CT) to verify absence of multiple pulmonary lesions and hepatic, adrenal, or brain metastases. Supplementary hepatic ultrasound and bone scintigraphic scans were ordered when clinically indicated. Standard criteria including adequate functional status and pulmonary reserve were uniformly used to identify operative candidates at all study sites. Patients were included in the study only if their preoperative CT scans showed the primary tumor to be amenable to complete VATS (c-VATS) resection according to predetermined criteria. These criteria included stage IA disease on CT, primary tumor smaller than 2 cm in long-axis diameter, tumor situated at least 2 cm from hilar vessels or interlobar fissures, no history of previous thoracic surgery or pleurodesis, and preoperative pulmonary function tests suggesting ability to tolerate one-lung ventilation. These criteria were agreed on by the senior surgeons from all participating centers before this study. Once each patient had been selected as a potential candidate for c-VATS, the surgical approach used was decided by the preference of the surgeon.

The technical aspects of VATS lobectomy were described previously.[7] In brief, c-VATS used purely endoscopic techniques with 100% monitor vision without rib-spreading minithoracotomy, whereas assisted VATS (a-VATS) involved performing the main procedures via rib spreading and used minithoracotomy (10 cm long) with monitor and direct vision. The open method (open) was performed via thoracotomy (20 cm long) with direct vision only. The differences among the 3 approaches are illustrated in Figure 1. A systematic nodal dissection was performed in all cases, and when VATS techniques were applied, the procedures were identical to those used with thoracotomy. Nine patients required conversion of the intended procedure to an alternate procedure (c-VATS to a-VATS, n = 4; c-VATS to open, n = 2; a-VATS to open, n = 3) secondary to adhesions surrounding the pulmonary arteries (n = 3), stapler malfunction (n = 2), severe intrathoracic adhesions (n = 2), or failure of lung collapse (n = 2). These cases were excluded from analysis.

Regarding the postoperative pain control, patients in all 3 groups were offered the same analgesic regimens and all patients were studied with a similar degree of pain. Otherwise, common protocols were also used for postoperative management at all study

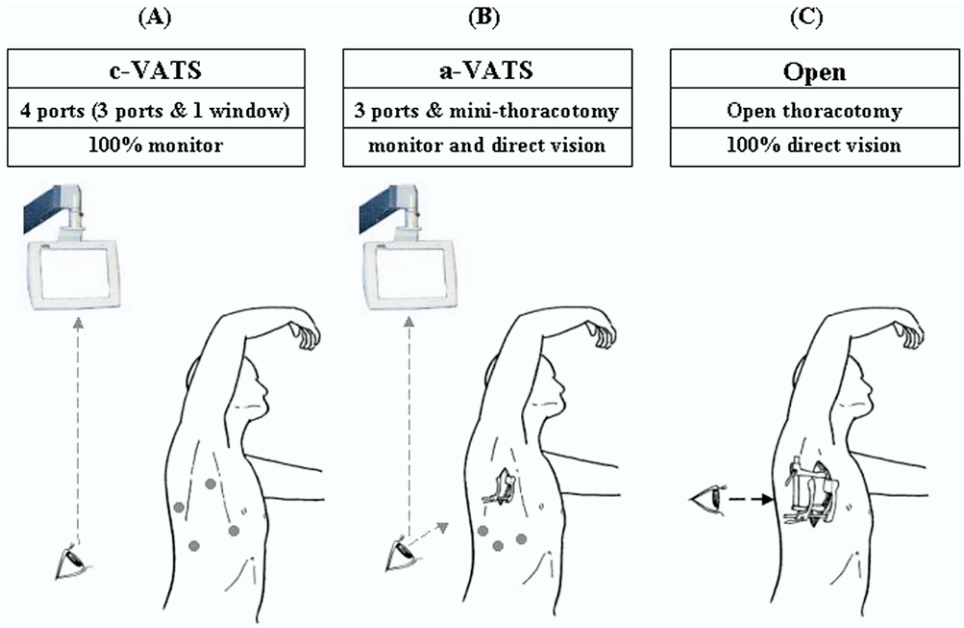

Figure 1. Descriptions of 3 different approaches for pulmonary lobectomy with systematic lymph node dissection. A, Complete VATS lobectomy *(c-VATS):* 3 ports and a window (4 cm in length to be used as the utility thoracotomy) were made. Standard commercially available endoscopic surgical tools were used, and all operative work was performed under thoracoscopy. B, Assisted VATS lobectomy *(a-VATS):* major manipulation, including dissection of the mediastinal lymph nodes, was performed with video assistance and under direct vision via a 10-cm long minithoracotomy. C, Open conventional thoracotomy *(open):* all procedures were performed under direct vision via a 20-cm-long thoracotomy.

TABLE 1. Patient characteristics

	c-VATS	a-VATS	Open
Male/female	26/24	14/17	29/26
Age (y)	66 ± 10	64 ± 11	62 ± 9
$FEV_{1.0}$ (L)	2.28 ± 0.65	2.32 ± 0.58	2.45 ± 0.93
$FEV_{1.0}$ (%)	72.6 ± 9.8	74.9 ± 7.6	76.0 ± 8.8
Histology			
Adenocarcinoma	34	26	38
Squamous cell carcinoma	8	2	6
Bronchioloalveolar carcinoma	5	3	7
Adenosquamous carcinoma	1	0	1
Large cell carcinoma	2	0	3
Lobectomy site			
RUL	16	10	17
RML	5	2	3
RLL	11	7	12
LUL	11	8	16
LLL	7	4	7
Total	50	31	55

$FEV_{1.0}$, Forced expiratory volume in 1 second; *RUL*, right upper lobe; *RML*, right middle lobe; *RLL*, right lower lobe; *LUL*, left upper lobe; *LLL*, left lower lobe.

sites. An accelerometer (Active Tracer AC-301 [ACT]; GMS Inc, Tokyo, Japan) was used for measurement of postoperative physical activity, as previously described.[8] In brief, the ACT is a device that continuously measures the gravitational acceleration of body movement using built-in acceleration sensors and hence permits a quantitative evaluation of integrative physical activity. The data were collected in consecutive preoperative 24-hour periods up to postoperative day 7, and these postoperative values were expressed as a percentage of the preoperative value. Then, we called a parameter recovery time, defined as the number of days required for restoration to more than 90% of the preoperative value, to assess the duration of recovery quantitatively.

All data are expressed as mean ± standard error. Statistical analysis was performed with StatView version 5 (SAS Institute, Inc, Cary, NC). Continuous and categorical variables were analyzed with the Student *t* test and Fisher exact test, respectively. Postoperative survival was plotted according to the Kaplan-Meier method, and any difference in survival between the groups was evaluated with the log-rank test.

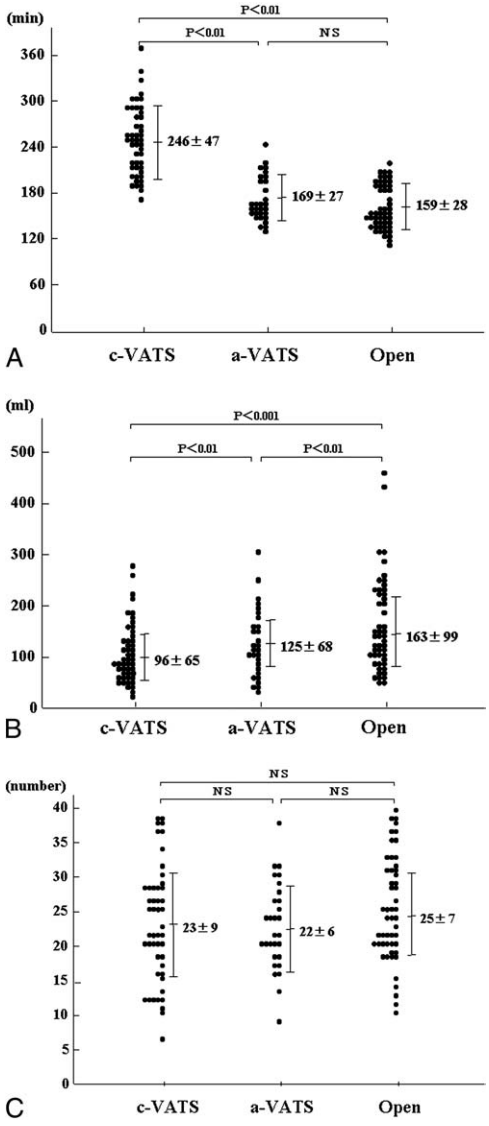

Figure 2. Operative outcomes after pulmonary lobectomy and systematic lymph node dissection by c-VATS, a-VATS, and open approach. A, Operative time. B, Blood loss. C, Number of lymph nodes dissected during surgery. *c-VATS*, Complete video-assisted thoracoscopic surgery (VATS) lobectomy; *a-VATS*, assisted VATS lobectomy; *open*, open conventional thoracotomy; *NS*, not significant. Values are mean ± standard deviation.

Results

Patient characteristics are summarized in Table 1. There was no significant difference in age, gender distribution, pulmonary function, histology, or tumor distribution when comparing the 3 study groups. Complete follow-up was obtained in all patients, and none of the patients received adjuvant or neoadjuvant treatment.

Operative time was longer for c-VATS (246 ± 47 minutes) than for a-VATS (169 ± 27 minutes) or open surgery (159 ± 28 minutes) ($P < .05$; c-VATS vs other approach) (Figure 2, *A*). Estimated blood loss was lower for c-VATS (96 ± 65 mL) than for other approaches (Figure 2, *B*), and massive bleeding (eg, >500 mL of blood loss or need for intraoperative transfusions) did not occur in any case. In all patients with a preoperative diagnosis of clinical stage I disease, there was no significant difference in the number of dissected lymph nodes (Figure 2, *C*). Recovery time ana-

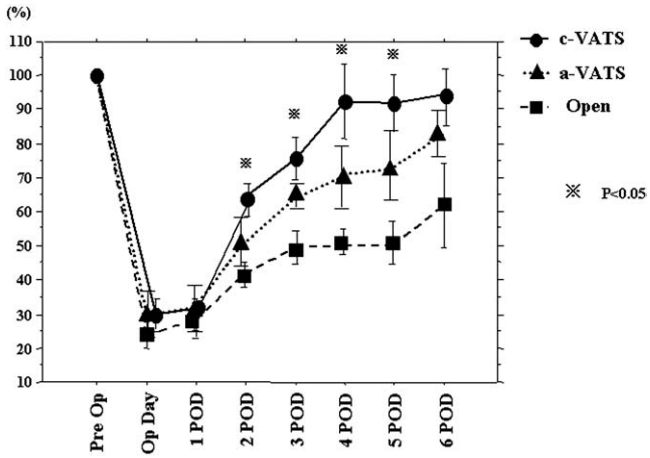

Figure 3. Comparison of the postoperative physical ability as determined by Active Tracer and expressed as the percentage of the preoperative 24-hour value. Time points included are before surgery and 0, 1, 2, 3, 4, 5, and 6 days postoperatively. Each value represents the mean ± standard error at each time point. *$P < .05$ for complete VATS *(c-VATS)* versus assisted VATS *(a-VATS).*

lyzed by ACT was shorter in patients undergoing c-VATS than in patients undergoing a-VATS or open surgery ($p < 0.05$) (Figure 3). There was no postoperative mortality. Complications (Table 2) were recorded in fewer than 3 patients in each group, but there was no significant difference in complication rate when comparing the 3 groups. Median length of hospitalization was shorter for patients undergoing c-VATS (11.8 ± 2.7 days) than for patients undergoing a-VATS and open procedures ($P < .05$) (Figure 4).

TABLE 2. Complications after the operation

Complication	No. of cases
c-VATS (50 cases)	
Prolonged air leak	1
Chylothorax	1
Arrhythmia	1
Total	3/50 (6%)
a-VATS (31 cases)	
Prolonged air leak	1
Arrhythmia	1
Total	2/31 (6%)
Open (55 cases)	
Prolonged air leak	1
Pneumonia	1
Liver dysfunction	1
Total	3/55 (5%)

c-VATS, Complete video-assisted thoracic surgery; *a-VATS,* assisted video-assisted thoracic surgery.

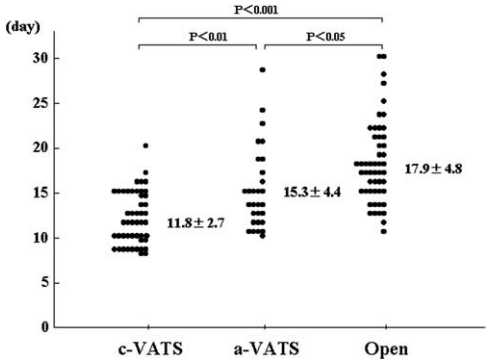

Figure 4. Length of hospitalization. Values are mean ± standard deviation. *c-VATS,* Complete VATS; *a-VATS,* assisted VATS.

On the basis of pathologic evaluation, upstaging was noted in 8 of 136 (5.9%). These patients were included in both the survival and recurrence analyses. Mean follow-up was 38.8 months (range, 10 months to 5 years), and there was no significant difference in follow-up time when comparing the 3 groups. The overall 5-year survival was 96.4% ± 5% (Figure 5). Of the deaths to date, only 1 death was related to lung cancer. Four patients are alive with recurrent disease at 13 to 36 months after resection (Table 3). Kaplan-Meier survival at 5 years for peripheral small lung cancer less than or equal to 2 cm in diameter (stage IA) was 96.7% (95% confidence index [CI] 7.5) for those who underwent c-VATS, 95.2% (95% CI, 8.0) for those who underwent a-VATS, and 97.2% (95% CI, 8.7) for those who underwent open surgery. However, there was no statistical difference between survivals when comparing the 3 groups (Figure 6).

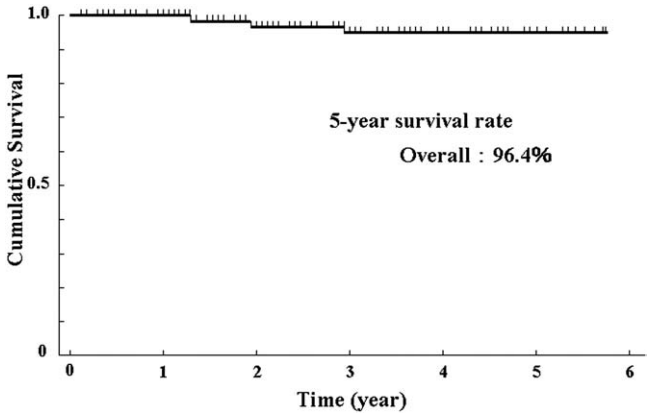

Figure 5. Kaplan-Meier survival curve showing the overall survivals after surgery for stage IA non–small cell lung cancer. Causes of death included brain metastasis (n = 1), other cancers (n = 2), and different disease (n = 1).

TABLE 3. Recurrent diseases

	Local recurrence	Metastasis	Other disease
c-VATS (50 cases)	No	Brain metastasis, 1 case; dead Bone metastasis, 1 case; dead	Pancreatic cancer, 1 case; dead
a-VATS (31 cases)	No	Bone metastasis, 1 case; alive	Colon cancer, 1 case; dead
Open (55 cases)	Local recurrence, 1 case; alive	Liver metastasis, 1 case; alive	Pneumonia, 1 case; dead

Discussion

There is now a growing body of evidence to suggest that the body's immune function is better preserved after VATS than after thoracotomy, as documented by decreased cytokine release and activated lymphocyte function.[9-11] Since immunosurveillance is believed to be important, surgically induced immunosuppression may predispose to increased tumor growth and recurrence. It is widely recognized that most cases of lung cancer recurrence arise at sites distant from the primary tumor site, and most cancers that recur are likely to be metastatic at initial exploration.[9] Taken together, these findings seem to support the use of the VATS approach for lung cancer in terms of preserving host immunity and optimizing long-term survival. Inasmuch as major resection for early lung cancer is a common operation (one of the most common for a general thoracic surgeon), even a slight advantage of one technique over another could have far-reaching implications. However, there is a notable lack of data in the published literature regarding long-term survival after VATS lobectomy, which has limited the widespread use of this technique.[12] The present study evaluated long-term outcome data in patients with early lung cancer after the use of various lobectomy techniques and conventional thoracotomy in different institutions, whereas outcomes after VATS lobectomy in past reports have been compared with historical controls from other studies.[12,13] This trial could be performed because all attending institutions own the common programs for operative indication, preoperative and postoperative schedule, and training their registrars for the patients with lung cancer.

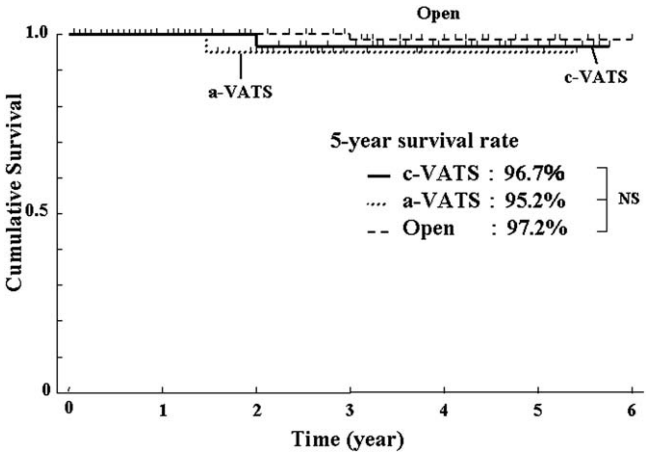

Figure 6. Kaplan-Meier survival curves for patients with clinical stage IA disease who underwent lobectomy under complete VATS *(c-VATS),* assisted VATS *(a-VATS),* or open conventional thoracotomy.

To assess the postoperative recovery status, we applied the method of measuring the changes of the acceleration in physical activity with the ACT for the patients who underwent thoracic surgery for the first time, successfully demonstrating the differences among a variety of VATS lobectomy and conventional approaches. It has been difficult to compare the benefits of purely endoscopic approaches to the other approaches regarding the postoperative recovery status, because a variety of factors may affect these results, such as pain, drainage period, and the response in cytokine and endocrine related to the invasiveness of the procedure.[8] However, the ACT appears to be useful for quantitatively expressing those benefits. The better results in the early postoperative period of c-VATS as compared with a-VATS and conventional thoracotomy, including less intraoperative bleeding, faster recovery, and shorter hospitalization, may be attributed to minimization of immune disturbance and preservation of host immunity at the time of resection. These data may support the use of complete endoscopic surgery for patients with stage IA lung cancer, although more evidence should be accumulated to clarify those contributions.[7]

In the past several years, there have been tremendous advancements in the field of adjuvant chemotherapy for patients with lung cancer, and this therapeutic modality is expected to play an increasing role in optimizing outcomes.[14,15] Since chemotherapy produces better outcomes in patients with better functional status, the use of surgical techniques that preserve near-term functional status (eg, c-VATS) may allow earlier institution of adjuvant chemotherapy and ultimately result in even better outcomes. Although this study was conducted in patients with stage IA lung cancer, c-VATS may also be of use in advanced cases that require adjuvant chemotherapy.

This study design was limited to retrospective investigation, and a prospective randomized controlled study on a larger scale is required to reach definitive conclusions regarding the efficacy of c-VATS relative to other techniques.[12] In our experience, the 5-year survival of patients with peripheral NSCLC less than or equal to 2 cm in diameter (stage IA) was 96.7% after c-VATS, 95.2% after

a-VATS, and 97.2% after open surgery, revealing that long-term survival was comparable among 3 different approaches. The improved long-term survival seen in the present study relative to previous studies may be related to selection bias of patients with better prognostic factors, such as a larger number of female patients, adenocarcinomas, or bronchioloalveolar carcinomas. Recently, a growing body of evidence has shown that patients with a tumor of 2 cm or less in diameter have a better survival than those with a tumor of 2.1 to 3.0 cm in diameter and that smaller tumor size at diagnosis is associated with improved curability within stage IA NSCLCs, which we speculate is one of the reasons for the better survivals in our study.[16-18] In addition, the better outcomes may be further exaggerated by the limited number of patients available.[12,19] Therefore, comparisons between the present data and previous studies should be performed with caution and only in the context of recognizing differences in patient characteristics. Regardless, this use of a retrospective multi-institutional comparison with common surgical programs yields higher-order data than simple comparison of outcomes reported by different institutions without standardized protocols. We appreciate that using the retrospective format may not be the ideal approach, but we think that it is a fair way to combine the data from three affiliated institutions and to assess the results from a larger combined population.

In conclusion, these data suggest that in experienced hands, VATS lobectomy is a safe procedure that may go well beyond the early postoperative period. Further, more importantly, VATS lobectomy can be regarded as an acceptable cancer operation for patients with peripheral NSCLC less than or equal to 2 cm in diameter (clinical stage IA) with the same long-term survivals as open surgery.

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