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# Ten-year Survival and Clinical Course After Video-assisted Thoracoscopic Lobectomy for Pathological Stage I Non-small Cell Lung Cancer

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***Background:*** There are limited reports of follow-up >5 years for lung cancer after minimally invasive surgery. This study examined the 10-year outcomes. ***Methods:*** There were 98 eligible patients with pathological stage I non-small cell lung cancer who had undergone video-assisted thoracoscopic surgery lobectomy between 2007 and 2011. Patients' perioperative factors and clinical course were evaluated retrospectively. ***Results:*** Of the patients, 71 had pathological stage IA, and 27 had pathological stage IB. The 10-year overall, relapse-free, and lung cancer-specific survival were 74.4%, 72.4%, and 89.7% for pathological stage IA and 57.4%, 55.9%, and 80.7% for pathological stage IB, respectively. The median time from surgery to recurrence and the diagnosis of second primary lung cancer（SPLC）was 22.0 and 61.0 months, respectively. ***Conclusion:*** This study was able to show the 10-year survival outcomes. The incidence of recurrence after 5 years is low in this population. However, it may be necessary to pay attention to SPLC.

Keywords: long-term survival, non-small cell lung cancer, second primary lung cancer, video-assisted thoracoscopic surgery, minimally invasive surgery

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## INTRODUCTION

Video-assisted thoracoscopic surgery（VATS）is one of the major minimally invasive surgeries and has been proven to provide a better 5-year survival for early-stage non-small cell lung cancer（NSCLC）compared to open thoracotomy［1］. However, there are few reports of long-term（>5 years）outcomes. In addition, there are still many issues of postoperative follow-up for NSCLC that remain to be elucidated. Postoperative follow-up for NSCLC is routinely performed to check for postoperative complications and recurrence, as well as due to patient demand. Regular postoperative follow-ups with contrast-enhanced chest computed tomography（CT）for up to 2 years are recommended after radical resection［2, 3］. However, the ideal duration of follow-up has not been determined. Regarding the method of postoperative follow-up for lung cancer, some studies report no improvement in prognosis whether the patient is followed up intensively or not［4］, while others report that survival improves when patients are followed up intensively［5］. Therefore, the present study examined the 10-year survival and clinical course of patients with pathological stage I NSCLC who had undergone VATS lobectomy.

## PATIENTS AND METHODS

This study was approved by the institutional review board of Shimane University Hospital（study number: 20200916-2）. Opt-out consent was provided because of the retrospective study design.

Cases of NSCLC that had undergone resection between October 2007 and March 2011 were assessed. During the study period, 136 patients with NSCLC underwent VATS lobectomy. Of these, 20 patients had pathological stage IIA or higher NSCLC, and 18 patients with missing perioperative data were excluded. Finally, 98 patients were considered eligible.

All patients underwent lobectomy with lymphadenectomy via hybrid VATS [6]. The indications for VATS were limited to NSCLC with clinical stages IA–IIIA, and chest wall and major vascular reconstruction, pulmonary artery and bronchial plasty, and pneumonectomy were not indicated. Patients were followed up regularly after discharge. A plain or contrast-enhanced CT was performed every 6 months. After 5 years postoperatively, CT was performed once a year. Additional examinations were performed as appropriate for patients with suspected recurrence or new lesions on routine examinations. The primary endpoint of this study was set at 10-year survival. The secondary endpoint was set at development of recurrence or secondary primary lung cancer (SPLC). Overall survival (OS) was defined as the time from the day of surgery to death, and patients who were alive were censored at the last follow-up. Relapse-free survival (RFS) was defined as the time from the day of surgery to the day of confirmed recurrence or death, and patients who were alive were censored at the last follow-up. Cancer-specific survival (CSS) was defined as the time from the day of surgery to lung cancer-related death, and patients who were alive were censored at the last follow-up. Recurrence was diagnosed by imaging or histological findings. Local recurrence included regional lymph node metastases, dissemination and malignant effusion. SPLC was diagnosed based on the pathologist's diagnosis with reference to the histology at the time of the initial surgery. If histology was unknown or unable to be collected, the patient was determined to be SPLC on the basis that there was clear evidence of primary lung cancer with no other metastases clinically or on imaging findings according to the doctor's conference. The pathological stage was defined by the seventh TNM classification [7]. The performance status was grouped using the Eastern Cooperative Oncology Group classification [8]. Comorbidity was enumerated using the Charlson comorbidity index [9]. The OS, RFS, and CSS curves were described using the Kaplan–Meier method. Prognostic factors were assessed using multivariate analyses (Cox proportional hazard model). A p value of less than 0.05 was considered statistically significant. EZR software was used for statistical analyses [10].

## RESULTS

Table 1 shows the characteristics of the patients. The median age was 73 years. There were 46 males and 52 females. Forty-six patients were current or past smokers. Many patients had good performance status and low Charlson comorbidity index. The most common tumor localization was in the right upper lobe. Adenocarcinoma was found in 83 patients (84.7%). Imaging findings revealed a solid tumor in 63 patients (64.3%). Pathological stages IA and IB were found in 71 and 27 patients, respectively. Table 2 shows the postoperative clinical course. Recurrence was observed in 13 patients (13.3%). Local recurrences were all regional lymph node metastases. The most common pattern of recurrence was distant metastasis. One of these patients had a distant metastatic recurrence after the fifth postoperative year. Systemic drug therapy was administered to nine of the recurrent patients. SPLC was observed in 12 patients (12.2%). Six patients developed SPLC after the fifth postoperative year, and 10 patients with SPLC were treated surgically. The median time from surgery to recurrence and SPLC was 22 and 61 months, respectively. There were three patients with cancer and 26 deaths, 10 of which were from lung cancer-related causes and 16 from other diseases. Table 3 reveals multivariate analyses of variables associated with OS and RFS. The significant prognostic factors for poor survival were older age (≥75 years) and recurrence. Between the recurrence patients and SPLC patients, the 5-year overall survival rates were 40.0% and 91.7% ($p < 0.01$). The factors such as solid tumor and pathological stage were not prognostic factors. Fig. 1 demonstrates the OS, RFS, and CSS curves. In patients with pathological stage IA and IB, the 10-year OS, RFS, and CSS rates were 74.4%

Table 1. Patient characteristics

| | N = 98 |
|---|---|
| Age (year): median (range) | 73.0 (33.0–89.0) |
| Sex | |
| Male | 46 (46.9%) |
| Female | 52 (53.1%) |
| Performance status | |
| <2 | 94 (95.9%) |
| ≥2 | 4 (4.1%) |
| Smoking history | |
| Non-smoker | 52 (53.1%) |
| Current or past smoker | 46 (46.9%) |
| Charlson comorbidity index | |
| <3 | 87 (88.8%) |
| ≥3 | 11 (11.2%) |
| Histology | |
| Adenocarcinoma | 83 (84.7%) |
| Squamous cell carcinoma | 13 (13.3%) |
| Large cell carcinoma | 1 (1.0%) |
| Adenosquamous cell carcinoma | 1 (1.0%) |
| Tumor location | |
| Right upper lobe | 42 (42.9%) |
| Right middle lobe | 4 (4.1%) |
| Right lower lobe | 21 (21.4%) |
| Left upper lobe | 16 (16.3%) |
| Left lower lobe | 15 (15.3%) |
| Maximum tumor size (cm) | |
| ≤3 | 74 (75.5%) |
| >3 | 24 (24.5%) |
| Tumor finding with imaging | |
| Solid[1)] | 63 (64.3%) |
| Non-solid | 35 (35.7%) |
| CEA (ng/ml) | |
| ≤5 | 57 (58.2%) |
| >5 | 41 (41.8%) |
| Clinical stage (seventh) | |
| IA | 74 (75.5%) |
| IB | 19 (19.4%) |
| IIA | 3 (3.1%) |
| IIB | 1 (1.0%) |
| IIIA | 1 (1.0%) |
| Pathological stage (seventh) | |
| IA | 71 (72.4%) |
| IB | 27 (27.6%) |

CEA, Carcinoembryonic antigen. [1)] including consolidation tumor ratio ≥0.5.

Table 2. Postoperative clinical course

| | N = 98 |
|---|---|
| Recurrence | 13 (13.3%) |
| (After 5 years postoperatively) | 1 (1.0%) |
| Recurrence pattern | |
| Local | 4 (4.1%) |
| Distant | 8 (8.2%) |
| Both (local + distant) | 1 (1.0%) |
| Treatment after recurrence | |
| Chemotherapy | 4 (4.1%) |
| Target therapy | 5 (5.1%) |
| Local control | 2 (2.0%) |
| Best supportive care | 2 (2.0%) |
| Second primary lung cancer | 12 (12.2%) |
| (After 5 years postoperatively) | 6 (6.1%) |
| Treatment for second primary lung cancer | |
| Wedge resection | 8 (8.2%) |
| Segmentectomy | 2 (2.0%) |
| Radiotherapy | 1 (1.0%) |
| Best supportive care | 1 (1.0%) |
| Time to recurrence (month): median (range) | 22.0 (10.0–99.0) |
| Time to second primary lung cancer (month): median (range) | 61.0 (8.0–120.0) |
| Alive with lung cancer | 3 (3.1%) |
| All deaths | 26 (26.5%) |
| Cause of death | |
| Lung-cancer related death | 10 (10.2%) |
| Other death | 16 (16.3%) |

Table 3. Multivariate analyses of variables associated with survival

| Variables | Overall survival<br>Hazard ratio (95% CI), p value | Relapse-free survival<br>Hazard ratio (95% CI), p value |
|---|---|---|
| Age (≥75 years/<75 years) | 3.396 (1.399–8.246), <0.01 | 2.360 (1.099–5.067), 0.028 |
| Sex (female/male) | 0.470 (0.075–2.939), 0.420 | 0.911 (0.182–4.562), 0.910 |
| Smoking history (current or former/non) | 0.888 (0.134–5.903), 0.902 | 1.304 (0.252–6.748), 0.752 |
| Charlson comorbidity index (≥3/<3) | 0.720 (0.143–3.622), 0.690 | 0.579 (0.123–2.732), 0.490 |
| Histology (non-Ad/Ad) | 0.861 (0.240–3.082), 0.818 | 0.599 (0.178–2.019), 0.408 |
| Solid tumor[1)] (yes/no) | 1.132 (0.410–3.125), 0.811 | 1.497 (0.613–3.658), 0.376 |
| CEA (>5/ ≤5) | 0.778 (0.318–1.905), 0.583 | 1.901 (0.880–4.106), 0.102 |
| Pathological stage (IB/IA) | 1.550 (0.637–3.775), 0.335 | 1.280 (0.555–2.952), 0.563 |
| Recurrence (yes/no) | 16.21 (5.302–49.59), <0.01 | NA |
| Second primary lung cancer (yes/no) | 0.640 (0.204–2.003), 0.443 | NA |

Ad, Adenocarcinoma; CEA, Carcinoembryonic antigen; CI, Confidence interval; NA, Not applicable. [1)] including consolidation tumor ratio ≥0.5.

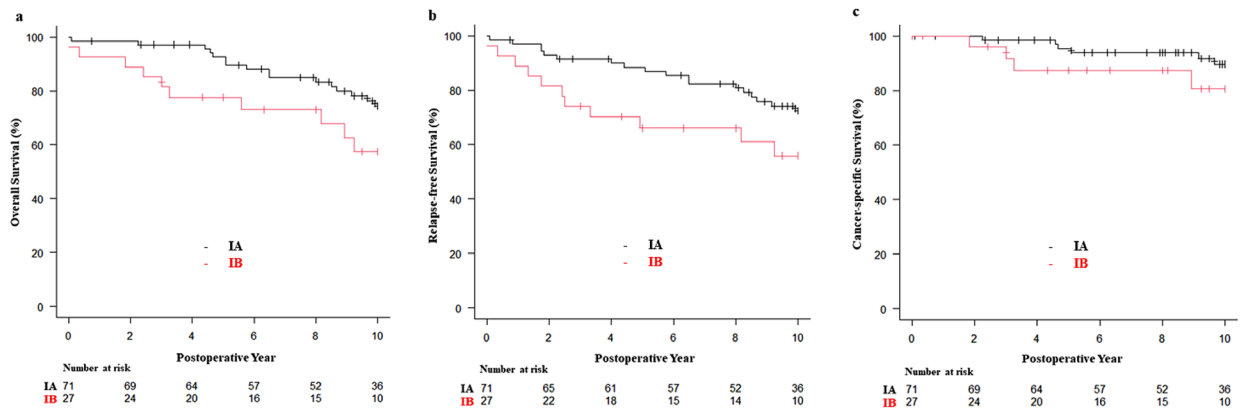


Fig. 1. Kaplan–Meier survival curves.
(a) Overall survival (OS) curve. (b) Relapse-free survival (RFS) curve. (c) Cancer-specific survival (CSS) curve.

(95% confidence interval [CI]: 61.5–83.5%) and 57.4% (95% CI: 34.5–74.8%), 72.4% (95% CI: 59.6–81.7%) and 55.9% (95% CI: 34.0–73.1%), and 89.7% (95% CI: 78.2–95.3%) and 80.7% (95% CI: 55.2–92.6%), respectively. The median follow-up period was 123.0 months.

## DISCUSSION

VATS as a surgical approach for early-stage NSCLC has been reported to have good perioperative outcomes and a good 5-year survival rate [11, 12]. In recent years, several reports have demonstrated favorable 10-year survival after resection for early-stage NSCLC [13, 14]. However, there are few reports of long-term outcomes beyond 5 years postoperatively in patients for whom the surgical approach is limited to VATS. This study demonstrated the 10-year survival of patients with pathological stage I NSCLC who had undergone VATS lobectomy. This study's results are difficult to evaluate because of single arm study. Nevertheless, the 10-year survival rate in this study was similar to the overall postoperative Japanese outcomes [15]. Notably, the 5-year OS in this study was 92.6% for pathological stage IA and 77.6% for pathological stage IB. In Japan during the same period, the 5-year OS was reported to be 88.9% for pathological stage IA and 76.7% for IB [16]. Although not comparable to this study, we believe that the results of the current study were favorable. In addition, the 10-year CSS in this study was 89.7% and 80.7% for pathological stages IA and IB, respectively. The most common cause of death was not lung cancer-related. This reaffirms that VATS lobectomy is sufficient for curing early-stage NSCLC.

The follow-up period after NSCLC resection is controversial. There have been several reports of long-term outcomes (>5 years) after early-stage NSCLC surgery. Patients with T1N0 NSCLC who have undergone surgery have reported recurrence or the appearance of new malignancies after 5 years postoperatively in some populations [17]. Cut-end recurrence or SPLC was also observed 5 years after surgery in adenocarcinomas with ground-glass opacity lesions that were treated with limited resection [18, 19]. Therefore, follow-up observation may be necessary even 5 years postoperatively. On the other hand, a report on stage IA–IIIB patients who have survived more than 5 years postoperatively suggests that recurrence is more common within 5 years and that 5 years may be a reasonable time frame for determining cure [20]. Furthermore, another report found that adenocarcinoma in situ and minimally invasive adenocarcinoma more than 5 years after the initial surgery did not relapse thereafter [21]. This study may serve as an indicator in this area. In the present study, the older age (≥75 years) and recurrence were significant poor prognostic factors. Older patients often did not receive systemic treatment after recurrence. Additionally, recurrence was observed in 13 patients (13.3%). Recurrence primarily occurred within 5 years postoperatively. Only one patient had recurrence (multiple lung metastases) after 5 years postoperatively. The recurrence rate after 5 years postoperatively was 1.0%, and it is low.

Therefore, we believe that 5 years is a reasonable period to determine a cure for resected pathological stage I NSCLC. However, the SPLC is problematic. In this study, SPLC was observed in 12 patients (12.2%). The median time from surgery to SPLC diagnosis was 61 months. In addition, half of the patients had been diagnosed after 5 years postoperatively. This study was unable to identify any factors associated with the development of SPLC. However, SPLC was not a poor prognostic factor. Furthermore, the prognosis for the SPLC patients was favorable. In this respect, there is a major difference between recurrence and SPLC. Many cases diagnosed with SPLC received some form of treatment in this study. We believe that positive treatment for SPLC is important. However, patients with SPLC may also be limited in their possible treatment by previous lung resections. Therefore, we believe that early detection of SPLC is significant and that follow-up with CT helped detect SPLC early and lead to treatment. Normally, it is difficult to detect early-stage lung cancer, such as ground-glass opacity dominant lung cancer by x-ray examination. Hence, it may be possible to take advantage of the recent focus in this area. The effectiveness of low-dose CT (LDCT) is already being proven in the field of health screening. LDCT has been reported to significantly reduce lung cancer mortality compared to chest x-rays [22]. Furthermore, it has been reported that LDCT reduces lung cancer mortality in high-risk patients [23]. We believe that LDCT may be useful for early screening of SPLC after lung surgery. In summary, postoperative follow-up for NSCLC should be terminated after 5 years, and screening with LDCT should be recommended thereafter, depending on the patient's self-motivation.

The current study had several limitations. First, this was a retrospective observational study with a small sample size. Second, the diagnoses with clinical and pathological stages were based on the seventh edition of the TNM classification. Third, two patients with SPLC were not proven histologically, and the diagnosis of SPLC was made comprehensively based on imaging findings and the clinical course.

## CONCLUSION

This study demonstrated the favorable 10-year survival of patients with pathological stage I NSCLC who had undergone VATS lobectomy. A 5-year follow-up period is sufficient for patients with pathological stage I NSCLC who had undergone VATS lobectomy. However, screening for SPLC is necessary.

### *Ethical Approval and Consent to Participate*

This study was approved by the institutional review board of Shimane University Hospital (study number: 20200916-2). We provided opt-out consent for patients.

### *Author's Contributions*

Tomohiro Fujita and Masaomi Yamane conceived the study. Tomohiro Fujita collected data, conducted statistical analyses, contributed to the interpretation of the results, and drafted the original manuscript. Masaomi Yamane reviewed the manuscript and revised it critically. All authors are in agreement with the content of the final version of the manuscript being published.

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### *Conflicts of Interest*

The authors declare no conflict of interest.

### *Data Availability Statement*

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

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