Results of video-assisted thoracic surgery for stage I/II non-small cell lung cancer

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Abstract

Objective: The best indicators for VATS are not well known. Therefore, we review here a series of patients who underwent VATS lobectomy and segmentectomy at our hospital, and we attempt to identify the factors that influence the survival of VATS patients and the backgrounds of such patients.

Methods: A thoracoscopic curative approach was attempted in 140 patients (100 lobectomy, 40 segmentectomy) from January 1994 to December 2002. We retrospectively reviewed the VATS patients with non-small cell lung cancer (NSCLC). All patients were subject to lobectomy or segmentectomy, including dissection of hilar and mediastinal lymph nodes that were in pathological stage (p-Stage) I or II. Our VATS approach was a hybrid technique, employing three ports and a small (7 cm diameter) utility thoracotomy to allow access for the instrument and a view.

Results: The Kaplan–Meier probabilities of survival at 5 years were VATS, 77.3%. According to a univariate analysis of survival curves, the significant prognostic factors (P < 0.05) in the patients with VATS in p-Stage I and II were gender, type of histology, and T factor. In addition, the grades of differentiation, surgical procedure (lobectomy vs. segmentectomy), and extent of metastasis to the hilar lymph node (N0 vs. N1) in VATS were not found to be significant prognostic factors. A multivariate prognostic factor in VATS showed that the histologic cell type, gender, and T factor were predominant. All of the VATS cases that included these three favorable factors (adenocarcinoma, T1, female) were alive. Conclusion: Stringent selection of candidates for VATS in NSCLC at pathological stages I and II could be an acceptable and valuable approach.

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Keywords: Video-assisted thoracic surgery; Indication; Stages I and II in NSCLC

1. Introduction

Currently the technique of video-assisted thoracic surgery (VATS) has become available for the treatment of early lung cancer [1]. However, the approaches that use this technique to treat early lung cancer have not been widely accepted because of VATS’s questionable oncological efficacy. During a VATS lobectomy, Yamashita et al. found tumor cells circulating perioperatively in the peripheral blood [2]. And significant questions remain major advantages of VATS over open thoracotomy. The VATS technique has many approaches, depending on the surgeon performing it. Examples include minithoracotomy, the use of a rib spreader, positioning of the access port, and looking down the thorax in partly through a videomonitor. Limited resection (segmentectomy or wedge resection) have been demonstrated as an alternative method of treating early lung cancer [3,4]. Some papers have reported that the 5-year survival rate of VATS lobectomy was 90 or 97% significantly favorable in stage I. Selection bias may occur in indications that select VATS or conventional open thoracotomy (COT). However, few studies have attempted to determine the true influences of these factors in VATS. In addition, we attempt to clarify the role of VATS in stage II NSCLC. The object of this study was to evaluate the characteristics of this bias in both the selection of and the surgical approach to VATS for NSCLC, and to do so more precisely, in view of our clinical experiences.

2. Materials and methods

From January 1994 to December 2002, 640 patients underwent pulmonary surgical resection for NSCLC at Fukuoka University Hospital. Of these patients,
we retrospectively selected 375 patients with histologically confirmed NSCLC at pathological stage I or stage II, for which the primary treatment was surgical resection. Patients were excluded if they had undergone chemotherapy or radiotherapy, or if they had exhibited adenosquamous or rare histological results. All patients were subject to lobectomy or segmentectomy with mediastinal lymphadenectomy. The patients received complete resections and were considered to be potentially cured by the surgical approach. Among these 375 patients, 140 were treated with the VATS approach.

2.1. Indications for approach

Our inclusion criteria for VATS lobectomy were as follows: clinical stage I disease, tumor size less than 3 cm, located within one-third of the periphery, histologically confirmed NSCLC, well-isolated intralobar fissure, and nearly free from adhesion in the thoracic cavity. Furthermore, patients with tumors that were 2 cm or less in diameter and suspected of being perfectly within a segment were registered for a VATS segmentectomy. Conventional lobectomy or segmentectomy via open thoracotomy was selected in patients who did not meet the VATS criteria, who did not provide informed consent for VATS, or who were suspected of having clinical hilar node involvement on CT scanning.

2.2. Operative technique

One-lung ventilation was used and the patient was placed in the lateral decubitus position. The surgical technique for VATS lobectomy was basically the same as that for segmentectomy. Briefly, we placed a thoracoscope in the six or seventh intercostal space in a midaxillary line (1.5 cm), as well as a main access portion (a 7 cm incision) placed anteriorly or in the midaxillary in the fifth intercostal space; this gave us easy access to the bleeding problem and allowed for the insertion of multiple instruments simultaneously or the removal of a lobe or segment of lung tissue. Anterior incisions, were made for an upper or middle approach, whereas midaxillary incisions were made for a lower approach. An additional access port (1.5 cm) was placed on either side of this main access portion. First, hilar dissection was performed peri-vascularly and bronchial structures were dissected. If the pulmonary vein or artery were retracted perfectly and could be easily positioned for vascular stapling, the stapler was used. In cases with anatomical problems, the vessels were ligated and the bronchus was then stapled by an automatic stapling device. Fig. 1 shows an example of a right upper lobectomy by our method. In cases of segmentectomy, the segmental border was isolated after the segmental bronchus has been cut, and either the stapler or an ultrasonically activated device is used to cut within a sufficient surgical margin. Mediastinal lymphnode

Fig. 1. Surgical techniques of VATS: (a) Pulmonary artery is identified at right upper lobe and retracted before positioning the endovascular. (b) Pulmonary vein is stapled separately. (c) Branch of the pulmonary artery is sometimes ligated and dissected by scissors. (d) Right upper bronchus is subsequently retracted and stapled.
dissection was performed by removing the lymphnode through the same procedure as was used in the COT (Fig. 2a). Fig. 2b is a schematic of a patient with a VATS lobectomy. In case of segmentectomy, the N1 node removed with the segment.

2.3. Statistical analysis

All statistical analyses were performed with the StatView 5.0.1 software package (SAS Institute Inc.). Survival rates were calculated by the Kaplan–Meier method, while survival curves were compared using a log-rank test. Statistical comparisons were made using the $\chi^2$ test. For multivariate analysis, a Cox’s proportional hazards regression model was used to evaluate variables that were significant predictors of survival by SPSS.

3. Results

The mean age of the patients was $66 \pm 9.4$ years. Of the 140 VATS resections, there were 100 lobectomies and 40 segmentectomies. In three cases treatment was changed from VATS to open thoracotomy, because of bleeding in one case and anatomical difficulties in two others. All cases displayed uneventful postoperative courses. Of the 140 patients, 125 were at pathologic Stage I, and 15 were at Stage II. Histological distribution of tumor types included 110 adenocarcinomas and 30 squamous cell carcinomas. Pathological differentiation included 76 well type, 63 moderately or poor type. Pulmonary function were normal (FVC, 3.15L; %FVC, 109.79%; FEV1, 2.21; %FEV1, 104.13). There were 81 male and 59 female in this study, and average age was 67 years. These characteristics are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics in VATS</th>
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<td>Gender</td>
<td>Male</td>
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<td></td>
<td>Female</td>
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<tr>
<td>Age</td>
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<td>&gt;70</td>
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Characteristic of VATS with pathological stage I and II.
3.1. Survival analysis

To show the relationship between each factor and prognosis, Fig. 3a shows Kaplan–Meier survival plots generated on the basis of curves stratified by the VATS approach. Actual survival for the VATS was 77.3% at 5 years. The 5-year survival rate of patients in stage I group was 80.9%, vs. 70.3% for patients in stage II group (Fig. 3b). There was no significant difference in the survival rate of pathological stage I patients vs. that of pathological stage II patients \((P = 0.7671)\). The 5-year survival rate for VATS patients at pathological stage IA (pIA) was 90.9%, vs. 78.3% for those at clinical stage IA (cIA). A comparison of 5-year survival between cIA and pathological pIA shows a remarkable 12.6% advantage for pIA in VATS, although this difference was not statistically significant \((P = 0.4667)\) at pathological stages I and II (Fig. 4b). A comparison of the 5-year survival curves between the genders shows that males had worse prognoses than females; for the p-Stage I and II group, 94.2% of females had survived at 5 years, compared to 63.0% of males (Fig. 5a). A significant difference between genders \((P = 0.0051)\) was seen in the VATS cases.

The patients with adenocarcinoma had better prognoses than patients with squamous cell carcinoma for the p-Stage I and II group: the 5-year survival rates were 87.3% for the former and only 28.6% for the latter (Fig. 5b). Statistically significant histological differences were also seen between the two groups \((P = 0.0001)\). The survival rates of patients according to differentiation pattern were 79.9% for well-differentiated patients at 5 years, compared with 72.9% for patients with moderate to poor differentiation (Fig. 6a). There was thus no significant difference between these two differentiation groups \((P = 0.3240)\). The survival rates of the patients according to \(T\) factor (Fig. 6b), the 5-year survival rate with \(T1\) was 85.1%, while that with \(T2\) was 70.5%. This difference was statistically significant \((P = 0.0443)\).

Multivariate analysis was performed to evaluate the independent prognostic roles of these factors in VATS. All variables that significantly affected survival were introduced for analysis by the Cox proportional-hazard models (Table 2). At the end of the stepwise process, histology \((P = 0.0049)\) and \(T\) factor \((P = 0.0199)\) each displayed an independent prognostic influence on overall survival. Gender was also an independent factor \((P = 0.0405)\). With these data, we compared VATS patients at stages I and II with COT patients at the same stages. We further

**Fig. 3.** (a) Kaplan–Meier survival curves for patients with VATS. (b) Kaplan–Meier survival curves for VATS patients at pathological stage I and stage II.

**Fig. 4.** (a) Kaplan–Meier survival curves for VATS patients at clinical stage IA and pathological stage IA. (b) Kaplan–Meier survival curves for VATS patients with lobectomy and for those with segmentectomy.
analyzed the survival rates of the patients according to three factors: adenocarcinoma, T1, and female gender. VATS patients ($n = 27$) showed survival rates of 100% at 5 and 7 years.

4. Discussion

Recently the thoracoscopic technique has been used in cases of lung cancer as an alternative to open thoracotomy [5]. But there have been very few prospective randomized controlled trials that compared VATS lobectomy with COT. Some researchers have reported that the prognosis after VATS lobectomy was superior to that after open thoracotomy [6]. The excellent survival rate of 97% may have been unintentionally affected by selection. We previously reported that lymph node dissection can be technically the same procedure regardless of whether it is performed under VATS or COT [7]. In our study, the 5-year or longer survival rate of the VATS group was superior as our expectation. The chance of completer node clearance of VATS which is able to get the clear view with spread may be superior to COT.

The VATS group included a large number of females. This suggested a possible influence on the overall survival rate VATS. In general, female lung cancer patients are thought to have a better prognosis factor than male patients [8]. It is thought that the best surgical results were observed in women who were operated on at an early stage of the disease. Alexiou et al. reported that women had a significant survival advantage at pathological stage I and relatively better survival at stages II and III [9]. They differed significantly from males in exposure to smoke and in smoking habits. This may be related to exposure to carcinogens. Ahrendt et al. showed a strong link between cigarette smoking and K-ras mutations in adenocarcinoma of the lung; this supports the idea that specific tobacco carcinogens play a role in the etiology of this malignancy [10]. Wang et al. reported that XRCC3 polymorphism appeared to be associated with an increased risk of lung carcinoma in certain subgroups, depending on the extent of the smoking habit [11]. Sex hormones may contribute to the pathogenesis of a disease or serve as protective factors. Kreuzer et al. presented evidence for a possible role of hormonal factors in the aetiology of lung cancer in women [12]. In our study, unlike the others, histology was a distribution factor. Our VATS group included a large number of adenocarcinomas. This factor also affected the survival rate of VATS patients. Adenocarcinoma is the major histologic type in NSCLC, and has a more favorable

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**Fig. 5.** (a) Kaplan–Meier survival curve for VATS patients by gender (female vs. male). (b) Kaplan–Meier survival curves for VATS patients by histologic cell type (adenocarcinoma vs. squamous cell carcinoma).

**Fig. 6.** (a) Kaplan–Meier survival curve for patients with VATS in histologic grade. (b) Kaplan–Meier survival curves for patients by $T$ factor ($T1$ vs. $T2$).
prognosis than squamous cell carcinoma at an early stage [13]. Furthermore, histological grade may be affected in our VATS. Ichinese reported that the grade of differentiation was one of the predominant prognostic factors in stage I NSCLC [14]. Poorly differentiated tumors in squamous cell lung cancers had metastases that were significantly more distant than were seen in the other grade, and poorly differentiated adenocarcinomas had a significantly higher incidence of local recurrence [15]. As shown in Fig. 5b, VATS patients at pathological stages I and II had a survival advantage in curative operations for adenocarcinoma (P = 0.0001). The adenocarcinomas of females were more likely to be well differentiated than those of men (data not shown). The curative VATS procedures are compared in Fig. 4b. The VATS segmentectomy group had a 77.8% survival rate at 5 years, whereas the rate was 76.8% for VATS lobectomy patients. This difference was not statistically significant for patients at pathological stages I and II. These data suggested that both VATS procedures for lung cancer at pathological stages I and II may be feasible. Recently, one paper showed the possibility of using segmentectomy as an alternative to the standard operation for small size in NSCLC [4]. Jones et al. reported that segmentectomy is an acceptable procedure as judged by its morbidity rate. Locoregional recurrence was not a reason for cancer-related death in that study [16]. Reports of intentional segmentectomy for early lung cancer have been rare. Kodama et al. reported that intentional segmentectomy for patients selected with T1 N0 M0 NSCLC was comparable outcome to the lobectomy [17]. VATS segmentectomy may be an acceptable oncologic procedure in patients with pulmonary reserve, and it is less invasive to the chest wall than conventional procedure. As shown Fig. 4a, a survival difference was observed between clinical and pathological stages I A. A difference that must be upstaged by nodal stage IA. Charagozloo et al. reported that in a series of VTAS lobectomies, upstaging was noted in 7.8% [18]. In their data, however, patients with squamous cell carcinoma did not differ significantly in their rate of survival from patients with nonsquamous cell carcinoma. This may indicate that the histological distribution may be different in Japan than in other parts of the world; in Japan, adenocarcinoma predominates over squamous cell carcinoma. Daniel et al., reviewing 90 primary lung cancer patients who received thoracoscopic lobectomies, showed an upstage rate of 11.1% from clinical stage I based on pathology. In our VATS study, the patients with pathological N1 did not show a survival difference vs. the patients with pathological N0. These data may suggest that, in the presence of N1 and of an upgrade from clinical stage I, the indication of VATS for clinical stage I is notably favorable. We previously reported that hilar and mediastinal lymph node dissections via VATS lobectomy are comparable in outcome to conventional open lobectomy [7]. We have shown a favorable overall survival in T1 compared to T2, but this better survival rate is also related to the worsening of factors as the tumor grows. In multivariate analysis of complete resections for our 140 patients via the VATS procedure, histologic type, T factor, and gender were shown to be significant predictors of survival, as shown in Table 2. From these data, we decided temporarily on new criteria for VATS: tumor size less than 3 cm (T1), histologically or cytologically confirmed or CT suspected as adenocarcinoma, female gender. VATS was demonstrated to increase the survival rate. Careful selection of VATS in NSCLC at pathological stages I and II may be an inclusion criterion in the future.

A prospective study will be needed to further compare VATS with COT, but in the meantime at least VATS trials should be indicated for females with adenocarcinomas of less 3 cm in diameter. In any case, since our study used a small series, additional prospective randomized controlled trials with the same background need to be done in larger series.

References


### Table 2

<table>
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<tr>
<th>Factors</th>
<th>Relative risk ratio</th>
<th>95% Confidence limit</th>
<th>P-value</th>
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<td>0.081–0.806</td>
<td>0.0199</td>
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<tr>
<td>Gender (male)</td>
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<td>0.044–0.934</td>
<td>0.0405</td>
</tr>
<tr>
<td>Histology (SQ)</td>
<td>4.505</td>
<td>0.078–0.634</td>
<td>0.0049</td>
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Multivariate analyses of various factors in VATS.