Video-Assisted Thoracic Surgery Lobectomy for Non-small Cell Lung Cancer in Patients with a Charlson Comorbidity Index Score of Two or More

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Introduction: We evaluated the feasibility and safety of the video-assisted thoracic surgery (VATS) lobectomy for non-small cell lung cancer (NSCLC) in patients with comorbidity.

Methods: Between April 2000 and December 2006, a prospective database of 58 consecutive patients undergoing a VATS lobectomy for NSCLC, who had a Charlson comorbidity index score of 2 or more, was retrospectively analyzed. The demographic, perioperative, histopathologic, and outcome variables, including the recurrence and survival, were assessed.

Results: The VATS lobectomy was successfully performed in 57 patients (16 women and 41 men; median age, 70 years). Twenty-three patients (40.4%) were aged 75 years or older. The total score of the Charlson comorbidity index was as follows: 2 in 26 patients, 3 in 13 patients, 4 in 12 patients, 5 in five patients, and 6 in one patient. None of the patients required a blood transfusion during surgery or during the postoperative course. We observed no intraoperative or in-hospital deaths, and no complications occurred in the 45 patients (78.9%). At a median follow-up of 34 months, a recurrence was observed in five patients who had advanced stages: a local recurrence in one and a distant recurrence in four. The overall 5-year survival rates for postoperative stage IA ($n = 25$) and IB ($n = 16$) were 100% and 94%, respectively.

Conclusions: We believe that a VATS lobectomy is a feasible and safe procedure for NSCLC in patients with comorbidity because this modality demonstrates an acceptable morbidity and a favorable oncologic outcome.

Key Words: Video-assisted thoracic surgery (VATS), Non-small cell lung cancer, Lobectomy, Comorbidity.

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The number of surgical candidates with comorbidity increases as the aged population increases. Especially in patients with lung cancer, comorbidity is more frequently observed due to the large number of patients who smoke. Many investigators have reported that the comorbidity is one of the important predictors of survival in patients with non-small cell lung cancer (NSCLC).[1–4] Furthermore, the surgical treatment for NSCLC in patients with comorbid diseases always poses a dilemma regarding whether to perform a limited resection to achieve an uneventful recovery or an curative resection to achieve an oncologic cure.

Recently, many video-assisted thoracic surgery (VATS) lobectomies have been performed as minimally invasive surgery, since the earliest reports of a videoendoscopic pulmonary lobectomy for lung cancer were published a decade and a half ago.[5] This treatment modality seems to be the preferred method for patients with comorbidity because it provides the benefits of decreased pain-related morbidity[6] while also achieving oncologic efficacy for early NSCLC.[7] Although evidence in the literature is increasing that a VATS lobectomy may be a safe and efficacious procedure for NSCLC,[8–15] such evidence regarding patients with comorbidity is still sparse.

To resolve the dilemma regarding the optimal surgical treatment for patients with comorbidity, a VATS lobectomy has always been applied to such patients with NSCLC at our hospital.[16] The purpose of this study is to evaluate the feasibility and safety of performing a VATS lobectomy for NSCLC in patients with comorbidity.

PATIENTS AND METHODS

Patients

Between April 2000 and December 2006, 160 patients underwent a VATS major lung resection for NSCLC at our hospital. The indications for a VATS major lung resection were based on the standard criteria for an open thoracotomy, including tumors up to 6 cm in diameter. The preoperative staging included a chest roentgenogram, computed tomographic scan of the body with intravenous contrast, flexible bronchoscopy, brain magnetic resonance, and bone scintigraphy. Mediastinoscopy was not routinely performed, whereas positron emission tomography was frequently used. The status of comorbidity was objectively assessed using the Charlson comorbidity index (CCI), which takes into account both the number and

seriousness of comorbid diseases. Components of the weighted index are published in Charlson's manuscript.[17] The assigned weights for each comorbid condition that a patient has was estimated, and the sum of the weighted index of the patient was calculated. The patients with comorbidity were identified as those with total score of the CCI of 2 or more, which has been reported to be closely associated with the morbidity and mortality.[3,4]

Of the 160 patients, a prospective electronic database of 58 consecutive patients (36.3%) undergoing a VATS lobectomy for NSCLC, with the CCI score of 2 or more, was retrospectively analyzed. This series includes consecutive patients for whom the preoperative intention was to perform a VATS major pulmonary resection including a lobectomy or a bilobectomy. Any patient demonstrating primary NSCLC with direct invasion of the vessels, main bronchus, or surrounding organs was excluded. The Institutional Review Board of Clinical Research of our hospital ethically approved this study, and informed consent for this prospective study was obtained from all patients.

Surgical Technique

Under single-lung anesthesia, four incisions were used in the majority of the patients in this series. A utility thoracotomy was placed in the third or fourth intercostal space and consisted of a 5- to 7-cm incision. The remaining three incisions for the 5.5-mm or 12-mm trocars were made. The pulmonary vessels and bronchi were individually divided and an extensive dissection of the mediastinal lymph nodes was performed, as previously reported.[16] All VATS procedures were performed without the use of a rib spreader.

Data Acquisition and Follow-Up

The demographic, perioperative, histopathologic, and outcome variables, including recurrence and survival, were analyzed. In addition, a subset analysis was performed that excluded minor comorbidities such as a history of a prior cancer, stage I chronic obstructive pulmonary disease (COPD), and a history of congestive heart failure showing an ejection fraction of more than 40% from the CCI because these conditions probably have little effect on morbidity or mortality. The CCI score of these conditions was regarded as 0, and then the patients with total score of the CCI of 2 or more were studied. The operative mortality included all patients who died within the first 30 days after surgery or during the hospitalization, regardless of the length of stay. The postoperative morbidity included all patients who suffered complications during the hospitalization and after discharge from the hospital. The complete follow-up data were obtained from the records of the post discharge visits, from the regular radiographic follow-up, and from telephone interviews. Computed tomographic scans of the body were obtained in all patients at 12 months postoperatively and thereafter at yearly intervals. Recurrence was defined as local when the disease recurred in the hilar or mediastinal lymph nodes, in the pleural space, or at the surgical margins. Recurrence was defined as distant when the disease developed in a separate lobe or in the contralateral lung, in addition to a remote metastatic disease.

Statistical Analysis

Standard descriptive statistics and Kaplan-Meier survival analyses were used. The χ^2 test and Fisher's exact test were used to test whether relationships existed between the nominal variables. The continuous variables were analyzed by the Mann-Whitney U test. Comparisons of the survival were made using the log-rank test. The differences were considered to be statistically significant when the p value was less than 0.05.

RESULTS

Demographic and Comorbidity Data

One of the 58 consecutive patients with the CCI score of 2 or more was excluded from this study because the patient was converted from VATS to an open thoracotomy to perform angioplasty of the pulmonary artery. The subjects included 16 women (28.1%) and 41 men (71.9%). The median age was 70 years (range, 52–90); 23 patients (40.4%) were aged 75 years or older, and 10 (17.5%) of those were aged 80 years or older. A smoking history was present in 41 patients (median pack-year of tobacco smoking: 42). The preoperative clinical stage of NSCLC included stage IA in 28, IB in 20, IIB in six and IIIA in three patients.

The comorbid conditions are listed in Table 1. The malignant disease group included 10 patients with colorectal cancer, nine patients with gastric cancer, four patients with prostatic cancer, nine patients with other cancers, and one patient with malignant lymphoma. Twenty-nine of 33 patients with previous disease of malignancy (87.9%) had an early-stage NSCLC, and the ratio was slightly more than that of the remaining 24 patients without prior malignancy. The patients with chronic pulmonary disease included 14 patients with COPD, four patients with both COPD and restrictive pulmonary disease such as tuberculous pleuritis, three patients with restrictive pulmonary disease, two patients with both COPD and interstitial lung disease such as interstitial pneumonia, two patients with interstitial lung disease, two patients with bronchial asthma requiring steroid medication, and one patient with both COPD and bronchial asthma. The 21 patients with COPD had the following stages: stage I (80 $\leq$ predicted % forced expiratory volume in 1 second [FEV1]) in 13 patients, stage II (50 $<$ predicted % FEV1

TABLE 1. Comorbidity (n = 57)

Comorbid Conditions (Assigned Weights for Diseases)	No. of Patients (%)
Any malignant tumor or lymphoma (2)	33 (57.9)
Chronic pulmonary disease (1)	28 (49.1)
Cerebrovascular disease (1)	18 (31.6)
Diabetes (1)	13 (22.8)
Ulcer disease (1)	9 (15.8)
Myocardial infarct (1)	7 (12.3)
Mild liver disease (1)	7 (12.3)
Peripheral vascular disease (1)	4 (7.0)
Congestive heart failure (1)	4 (7.0)
Hemiplegia (2)	1 (1.8)

≤80) in seven patients, and stage III (30 < predicted % FEV1 ≤50) in one patient.[18] Four patients who had a diagnosis of congestive heart failure showed 40 to 50% of cardiac ejection fraction as determined by echocardiography. The total score of the CCI was as follows: 2 in 26 patients, 3 in 13 patients, 4 in 12 patients, 5 in five patients, and 6 in one patient.

Perioperative and Histopathologic Data

The thoracoscopic exploration showed a broad adhesion in 10 patients (17.5%) and a broad fused fissure in 43 patients (75.4%). In particular, seven patients (12.3%) presented with a severe pleural adhesion and fused major fissure. The treatment modality was a lobectomy in 54 patients and a bilobectomy in three patients. The distribution of the lobectomies was as follows: right upper lobe in 16 patients, right lower lobe in 15, right upper and middle lobe in one, right middle and lower lobe in two, left upper lobe in 13, and left lower lobe in 10. The combined resections performed were as follows: the involved ipsilateral lung in two patients, a part of the contralateral lung in one patient, and the involved parietal pleura in one patient. The median number of total dissected nodes (only mediastinal nodes) was 33 (16) nodes. The median operation time was 305 minutes, and the bleeding volume was 114 ml. No patients required a blood transfusion during the surgery or the postoperative course. The median chest tube duration was 2 days, and the median length of hospitalization was 12 days (range, 7–57 days). There were no differences in hospital stay between the lower (2–3) and higher (4–6) groups of CCI score and among types of comorbidity.

The histologic types of the primary NSCLC resected included adenocarcinoma in 38 patients (including one patient with bronchioloalveolar carcinoma), squamous cell carcinoma in 18, and adenosquamous carcinoma in one. The postoperative stages were as follows: IA in 25, IB in 16, IIA in one, IIB in two, IIIA in six, and IIIB in seven patients. All surgical margins were clear, and the most frequent histologic subtype was adenocarcinoma (66.7%). Three patients with stage IIIA disease preoperatively had a single N2 station consisting of subcarinal node enlargement. Because the increasing experience with the VATS lobectomy has allowed an expansion of the indications for lobectomy, this series included nine patients (15.8%) with a preoperative stage II or greater NSCLC. The additional patients with stage IIIA postoperatively had pathologic N2 disease, which was found after surgery. Seven patients with stage IIIB postoperatively were found to have metastasis within the same resected lobe (T4).

Morbidity and Mortality

There were no complications in 45 patients (78.9%), and 14 complications were observed in the remaining 12 patients (21.1%) (Table 2). Three of five patients (60.0%) who presented with prolonged air leaks had some pulmonary comorbidity, such as COPD and/or restrictive pulmonary disease, whereas all patients who presented with sputum retention had some pulmonary comorbidity. There were no differences in development of complication between the lower (2–3) and higher (4–6) groups of CCI score (17.9% versus 27.8%, respectively; $p = 0.4893$). There were no intraoperative or in-hospital deaths.

TABLE 2. Postoperative Complications ($n = 57$)

Complication	No. of Patients (%)
None	45 (78.9)
Air leak (lasting >7 d)	5 (8.8)
Atelectasis and/or sputum retention requiring bronchoscopy	3 (5.3)
Atrial fibrillation	2 (3.5)
Late pleural effusion requiring thoracentesis	1 (1.8)
Pneumothorax	1 (1.8)
Chylothorax	1 (1.8)
Recurrent nerve injury	1 (1.8)

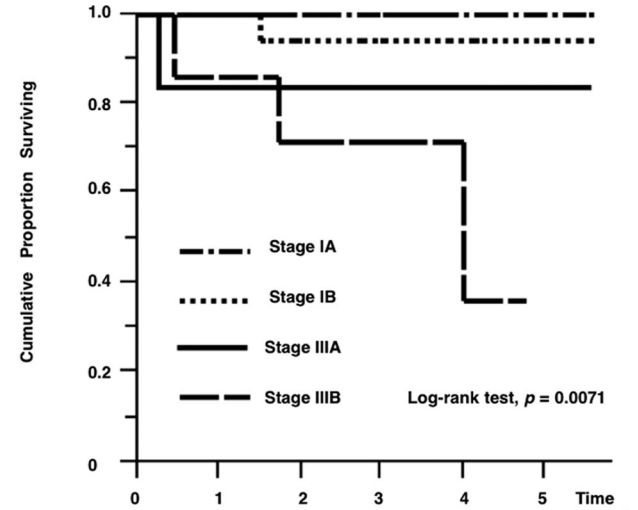
Two patients who had sputum retention requiring bronchoscopy developed multiple complications.

Recurrence and Survival

No patients were lost to follow-up. A total of one local recurrence and four distant recurrences have been identified in the follow-up period. Patients with postoperative stage I (A and B) showed neither local nor distant recurrence. The local recurrences included a subcarinal lymphadenopathy in one patient with postoperative stage IIIA who underwent a right upper lobectomy. There were no instances of wound implantation. The first relapse site of the distant organs included the residual lung in three patients with postoperative stage IIIB and the bone in one patient with stage IIIA. At a median follow-up of 34 months, six patients have died. Of them, four patients died of cancer. Of the remaining two patients, one died of pneumonia, whereas the other died of a brain infarction. The Kaplan-Meier survival according to the postoperative stage is shown in Figure 1. There were no differences in survival between the lower (2–3) and higher (4–6) groups of CCI score ($p = 0.2341$).

Subset Analysis

In a subset analysis that excluded minor comorbidities from the CCI, 30 patients with the CCI score of 2 or more were analyzed. The subjects included six women (20.0%) and 24 men (80.0%). The median age was 72 years. The comorbid conditions included chronic pulmonary disease ($n = 15$), cerebrovascular disease ($n = 11$), diabetes ($n = 8$), ulcer disease ($n = 8$), liver disease ($n = 7$), myocardial infarct ($n = 5$), peripheral vascular disease ($n = 3$), and hemiplegia ($n = 1$). The total score of the CCI was as follows: two in 24 patients, three in five patients, and four in one patient. The median operation time was 315 minutes, and the bleeding volume was 110 ml. The median length of hospitalization was 14 days. The histologic types included adenocarcinoma in 15 patients, squamous cell carcinoma in 14, and adenosquamous carcinoma in one. The postoperative stages were as follows: IA in nine, IB in 12, IIB in one, IIIA in four, and IIIB in four patients. There were 10 complications in eight patients (26.7%). Postoperative complications included sputum retention requiring bronchoscopy ($n = 3$, 10.0%), atrial fibrillation ($n = 2$, 6.7%), prolonged air leak ($n = 1$, 3.3%), pleural



Patients at risk

Stage IA	25	24	16	13	7	1
Stage IB	16	15	11	9	6	4
Stage IIIA	6	4	3	0	0	0
Stage IIIB	7	5	4	2	1	0

FIGURE 1. Kaplan-Meier analysis of the overall survival after a video-assisted thoracic surgery lobectomy for non-small cell lung cancer according to the postoperative stage (log-rank $p = 0.0071$).

effusion ($n = 1$), pneumothorax ($n = 1$), chylothorax ($n = 1$), and recurrent nerve injury ($n = 1$). There was no operative mortality. The overall 5-year survival rates for postoperative stage IA and IB were 100% and 91.7%, respectively.

DISCUSSION

There are two broadly applicable methods for rating comorbid diseases. One is the method of Kaplan and Feinstein developed by consensual criteria for use in a longitudinal study of patients with diabetes.[19] The other is the CCI,[17] which evolved the method of Kaplan and Feinstein. The CCI excludes the following comorbid conditions as angina, arrhythmia, hypertension, and severe obesity, which are included in the Kaplan-Feinstein index, because their conditions presented a low relative risk of death. Wang et al.[3] have suggested that the CCI has a great impact on the perioperative mortality than the Kaplan-Feinstein index in patients with stage I lung cancer. Thus, the CCI seems to be more reliable than the Kaplan-Feinstein index because the comorbidity is confined to only serious conditions. Birim et al.[2] reported that the CCI is a better predictor of survival than individual comorbid conditions in lung cancer surgery. Asmis et al.[4] suggested that the presence of comorbid conditions with the CCI score of one or more was associated with a poor survival in large prospective randomized trials of systemic chemotherapy for NSCLC. Wang et al.[3] demonstrated that patients with the CCI score of 2 or more had higher perioperative mortality compared with those with the CCI score of less than 2. Such reports support the notion that patients with comorbidity can be identified as those with a total CCI score of 2 or more in this study. However, there remains a problem that a history of a tumor such as prostatic cancer may be only a minor medical issue, despite the high comorbidity score assigned to it. This may be a subject of future investigation. The eligibility criteria for surgery include the assessment of performance status according to either the Karnofsky index or the Eastern Cooperative Oncology Group performance scale. The CCI offers a more objective measurement of the patient's physiologic reserve than the performance status because these measures of performance status address the activity levels of the patient and are often affected by the mental condition of the patient.[1]

There are two reports on a VATS lobectomy for high-risk patients. One is a case-control study designed comparison between VATS and an open thoracotomy,[20] and the other is a case series.[21] Such reports have strongly affected the thoracic surgeons, although both studies were limited to showing short-term survival in a small number of high-risk patients. When compared with the high morbidity rate of 49 to 70% found in the open thoracotomy studies of high-risk patients,[22] the morbidity of 15.8 to 46.2% of both studies of the VATS procedures is favorable. Lower pain scores and decreased narcotic use associated with VATS lobectomy may benefit high-risk patients. Although the risk factors of our study patients may be lower than those of the patients in the high-risk studies, our results of morbidity (21.1%) and mortality (0%) are acceptable when compared with those (15.3–22.6% and 0.5–1.8%, respectively) of the many studies without explicit statements as to the surgical risk of the study patients.[8–15] Additionally, because a subset analysis of high-risk patients in this study showed a satisfactory morbidity (26.7%) and mortality (0%), a VATS lobectomy is considered to be almost a safe procedure for NSCLC in patients with comorbidity.

With respect to the number of dissected nodes, this study using VATS obtained the same number or more nodes than the other studies did by an open thoracotomy and achieved an equivalent rate of lymphadenectomy-related morbidity, including recurrent nerve injury and chylothorax.[23] A randomized and multiinstitutional study also showed that the complete mediastinal lymphadenectomy added little morbidity to a pulmonary resection for lung cancer.[24] The morbidity rate of this study is acceptable for patients with comorbidity because of the absence of serious complications and because of a lower morbidity than that found in other studies using an open thoracotomy.[23,24] Although several pulmonary complications often were found in patients who had some pulmonary comorbidity, the number of CCI score may not be associated with development of postoperative complication. Reduced bleeding volume, careful control of air leak, neuroprotective procedures, and an effective physiotherapy are considered to be needed to keep complications low in high-risk patients.

The one conversion (1.8%) and postoperative hospitalization (12 days) in this study are considered to be acceptable in comparison with those (0–22.2% and 3–24 days, respectively) of the many studies on VATS lobectomy for preoperative stage I NSCLC, because this study included not only patients with comorbidity but also nine patients (15.8%) with preoperative

stage II disease or greater. The length of stay after a VATS lobectomy in this series was obviously shorter than the hospitalization (range, 32–115 days) after an open thoracotomy lobectomy in our earlier study.[23] Hospitalization generally tends to be longer in Japan because the majority of patients are not imposed with an excessive financial burden by the National Health Insurance System.[14]

Both of the outcomes of local recurrence and of long-term survival are believed to judge the oncological efficacy of a VATS lobectomy for a NSCLC. Martini et al.[25] demonstrated local recurrence in 7% (systemic recurrence of 20%) and a 5-year survival of 75% for stage I lung cancer (82% for stage IA and 68% for stage IB) with an overall median follow-up of 91 months in the open thoracotomy study (n = 598). The recurrence (0%) and 5-year survival rates (100% for stage IA and 94% for stage IB) of comorbid patients with postoperative stage I reported in this series of a VATS lobectomy were compared favorably with those of the open thoracotomy study, despite the smaller number of patients with a shorter follow-up in our study. In comparison with the outcomes dealing with similar surgery, our results also compared favorably with those (recurrence rate, 2.6–27.4%; 5-year survival rate, 70.2–88.0% for stage IA, and 56.1–77.0% for stage IB) without comorbidity published in other reports. The patients with previous disease of malignancy accounted for approximately 60% of all patients in this study. In such patients, the latest lung cancer may be detected as a consequence of cancer surveillance and therefore may be found at an earlier stage. This could explain the high survival in a risky population.

If the oncological efficacy of a VATS lobectomy can be established, then this surgical procedure should also be applicable to patients with advanced stage NSCLC. Walker et al.[13] reported that a 5-year survival rate of stage III disease in eight patients (stage IIIA in five and stage IIIB in three patients) was 28.6%. McKenna et al.[8] have shown a 5-year survival of more than 30% in 109 patients with a postoperative stage IIIA. It seems that a VATS approach does not compromise the survival for patients with advanced stage NSCLC, although the number of patients in this study was small (Figure 1). Further study of advanced stage NSCLC with a large number of patients and with a long-term oncologic follow-up is required.

In conclusion, we believe that a VATS lobectomy is a feasible and safe procedure for NSCLC in patients with comorbidity because it demonstrates an acceptable morbidity and a favorable oncologic outcome, although the limitations of this study includes the small number of patients and the short term of observation. Independently of CCI, a VATS lobectomy might be optimal for other special populations including patients with orthopedic problems, advanced age, and reduced performance status caused by angina, arrhythmia, hypertension, and severe obesity because of shorter hospitalizations, chest tube durations, and earlier return to full preoperative activities than an open lobectomy. Because this study population is a series of complication-prone patients, the salutary effect of VATS lobectomy should be magnified.

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