Editorial

A natural way to extend the indications for video-assisted thoracoscopic surgery in patients with advanced lung cancer

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Video-assisted thoracoscopic surgery (VATS) was first reported by Levi *et al*. in 1990 (1). VATS has become an attractive surgical procedure for benign diseases because of its low invasiveness (2,3). As experience performing VATS for benign diseases has accumulated, VATS has gradually begun to be used for lung cancer surgery. Since Roviaro *et al*. reported the first lobectomy using a videoendoscope for lung cancer, many investigators have used VATS for lung cancer operations and have reported the resulting outcomes (4). VATS is obviously superior to an open thoracotomy (Open) in terms of postoperative pain and cosmesis. However, the safety and adequacy of VATS for cancer operations needs to be confirmed.

VATS for early lung cancer

As the first step in applying VATS for lung cancer, VATS has been used in patients with an early disease stage. Two prospective randomized trials have compared VATS and Open in patients with stage I lung cancer, although the sizes of both trials were relatively small. Kirby *et al.* randomized 55 patients with stage I disease into two groups, a VATS lobectomy group and muscle-sparing lobectomy group, and compared the operative time, volume of bleeding, period of chest tube use, postoperative pain, period of hospital stay, and rate of postoperative complications. They reported that there were no significant differences between the two groups in terms of operative time, volume of bleeding, period of chest tube use, postoperative pain, or period of hospital stay, while more postoperative complications occurred in the muscle-sparing lobectomy group (24% in the VATS group and 53% in the muscle-sparing group, $P<0.05$) (5). Sugi *et al*. also conducted a similar randomized control study in 100 patients with stage IA NSCLC (6). They reported that there were no significant differences between the VATS group and the Open group with regard to the number of resected lymph nodes (21.2 in the VATS group and 21.8 in the Open group), the rate of recurrence (10% in VATS and 17% in Open), or the 5-year survival rate (90% in VATS and 85% in Open). They concluded that VATS with lymph node dissection enabled an excellent 5-year survival outcome comparable to that achieved in the Open group.

There are many observational cohort studies and several meta-analyses in patients with early lung cancer (*Table 1*). Yan *et al*. conducted a systemic review and meta-analysis comparing VATS and Open. They included two randomized studies described above and 19 observational cohort studies and evaluated the safety and efficacy of VATS in patients with stage I disease (7). They reported that there were no significant statistical differences between VATS and Open in terms of postoperative prolonged air leakage, arrhythmia, pneumonia, or mortality. On the other hand, VATS was superior in terms of the systemic recurrence rate (relative risk =0.57; 95% confidential interval, 0.34–0.95; P=0.03) and had an improved 5-year mortality rate (relative risk =0.72; 95% confidential interval, 0.45–0.97; P=0.04), while no difference in locoregional recurrence was seen. Taioli *et al*. conducted a meta-analysis that included 2,106

Table 1 Summary of the meta-analyses in patients with early lung cancer

Study	Year	Included studies		No. of patients	Stage	Conversion rate	Complication	Survival data
		RCT	OC					
Yan *et al.*	2009	2	19	2,641	I	8.1%	VATS lower	VATS favorable
Taioli *et al.*	2013	0	20	4,764	I, II in 1 study	N/A	N/A	VATS favorable
Cai *et al.*	2013	2	21	2,104	I	N/A	VATS lower	VATS favorable

RCT, retrospective control study; OC, observational cohort; VATS, video-assisted thoracoscopic surgery; N/A, not available.

patients with VATS and 2,661 patients with Open from among 20 observational cohort studies and evaluated the 5-year survival (8). They demonstrated an advantage in long-term mortality for patients who underwent VATS, compared with the patients who underwent Open, although a large degree of heterogeneity existed among the studies. Cai *et al*. also conducted a meta-analysis comparing VATS and Open in patients with Stage I disease and reported that VATS was associated with a longer 5-year survival, higher local recurrence rate, similar distant recurrence rate and lower total complication rate, compared with Open (9). VATS was also associated with lower rates of arrhythmias, prolonged air leakage, and pneumonia, although the differences were not statistically significant. Three meta-analyses similarly concluded that VATS was superior to Open in terms of survival and was equivalent in terms of perioperative complications, but it should be noted that the papers to which the three meta-analyses referred mostly overlapped. It was, therefore, natural that the three meta-analyses reached similar conclusions.

As described above, two RCTs and three meta-analyses evaluated VATS in early lung cancer, but the study sizes of the two RCTs were relatively small and the three meta-analyses utilized overlapping studies. Thus, it is difficult to make a clear conclusion with a high quality and high level of evidence based on these studies. A large multi-institutional prospective randomized-controlled trial would be optimal, but such a study comparing VATS *vs.* Open for lung cancer is unlikely to ever be completed, since the advantages of VATS, such as less pain and superior pulmonary function during the early postoperative phase, are already well known and VATS is now being performed in clinical practice (10). In this scenario, observational studies remain the most reliable source of scientific information. Under this circumstance and judging from the available data, it seems reasonable to accept that both the short-term and long-term outcomes of VATS for the treatment of early lung cancer might be equivalent to those of Open, making VATS a feasible alternative method.

VATS for advanced lung cancer

With the accumulation of experience performing VATS for early lung cancer, it was natural to expand the indications for VATS to advanced lung cancer as the next step. Several studies have addressed the feasibility of VATS for advanced lung cancer; three single arm observational cohort studies and four observational cohort studies comparing VATS and Open have been performed, but an RCT or meta-analysis comparing VATS and Open has not yet been done (*Table 2*). Huang *et al*. reported the outcomes of VATS following neoadjuvant chemotherapy in patients with stage II–IIIB disease (11). The perioperative complication rate was 9.5% and the mortality rate was 2.4%. They concluded that VATS following neoadjuvant chemotherapy was safe and feasible for the treatment of advanced lung cancer. Gonzales-Rivas *et al*. conducted a comparison of uniportal VATS between early lung cancer and advanced lung cancer (12). The median number of resected lymph nodes (14 for early lung cancer and 16 for advanced lung cancer) was significantly higher for the advanced cases, and the complication rate (17.2% for early lung cancer and 14% for advanced lung cancer) was similar in both groups. They concluded that uniportal VATS for advanced cases was as safe and feasible as that for early cases. Chen *et al*. conducted a comparison between VATS and Open in patients with stage II–IIIA disease (13). They included 250 patients with VATS and 161 patients with Open and compared the perioperative outcomes and survival. Furthermore, interestingly, they performed propensity-matched analysis in the selected 240 patients to remove patient bias. In total, 11.7% of the patients in the VATS group required a conversion to an open thoracotomy because of bleeding, a large tumor size, lymph node calcification, margins that needed to be extended, and failed fissure dissociation. The hospital stay in the VATS group was shorter than that in the Open

Table 2 Summary of observational cohort study in patients with advanced lung cancer

Study	Year	Study type	Study design	No. of patients	Stage	Comment	Conversion rate	Complications	Survival data
Hennon *et al.*	2011	OC	VATS *vs.* open	113	I–IV	–	23.0%	38.9% in VATS, 36.8 in Open equivalent	Equivalent
Huang *et al.*	2013	OC	VATS	43	IIA–IIIB	Following NAC	16.7% concerted to hybrid VATS	9.50%	–
Gonzales-Rivas *et al.*	2014	OC	VATS	130	Early-advanced	Uniport	1.1% in early stage, 6.5% in advanced stage	17.2% in early stage, 14% in advanced stage	–
Pischik *et al.*	2014	OC	VATS	92	I–III	–	3.2%	21.90%	–
Yang *et al.*	2015	OC	VATS *vs.* open	272	IB–IV	Following NAC propensity-matched	10.0%	40% in VATS, 57% in Open	Equivalent
Fan *et al.*	2016	OC	VATS *vs.* open	132	IB–IV	Uniport	3.1%	Air leak lower in VATS	N/A
Chen *et al.*	2017	OC	VATS *vs.* open	411	II–III	Propensity-matched	11.7%	25% in VATS, 28.3% in Open	Equivalent

OC, observational cohort; VATS, video-assisted thoracoscopic surgery; NAC, neoadjuvant chemotherapy; N/A, not available.

group, while the number of resected lymph nodes and the perioperative complication rates were similar between the two groups. Disease-free survival and overall survival were also similar between the two groups. They concluded that VATS can be performed in most cases of advanced lung cancer without compromising the perioperative outcome or oncological efficacy.

The mean conversion rate of the seven studies evaluating VATS in advanced lung cancer was 10.6%, which is likely to be slightly higher than that for early-stage disease. This result is understandable because lymph node dissection in patients with N1 or N2 or vessel isolation in patients whose tumors are located close to a large vessel might be more difficult and might often require conversion to an open thoracotomy.

All seven studies supported that VATS for advanced lung cancer was feasible and equivalent to Open. However, it should be noted that a patient selection bias was likely present, since VATS was likely to be performed in patients who were expected to be capable of undergoing VATS and Open was likely to be performed in other patients and that this selection bias surely had favorable influence on the outcomes of VATS.

Decaluwe *et al.* evaluated intraoperative complications during VATS in 3,076 patients from six European centers (14). Conversion to Open was observed in 5.5% of the cases: 21.8% were for oncological reasons, 29.4% were for technical reasons, and 48.8% were for complications. Vascular injuries were reported in 2.9% of the patients. In 1.5%, major intraoperative complications were identified. These consisted of the erroneous transection of bronchovascular structures or injuries to gastrointestinal organs or the proximal airway. Twenty-three percent of the in-hospital mortalities were related to major intraoperative complications. Interestingly, the authors evaluated the correlation between the surgeon's experience and the incidence of intraoperative complications and reported that surgeon experience was not correlated with the incidences of vascular injuries or major complications. Byun *et al.* also evaluated intraoperative complications and reported that the intraoperative complications and conversion to Open might be associated with postoperative respiratory complications (15). Once intraoperative complications occur during VATS, their repair can be difficult and time-consuming, and the risk of postoperative complications might increase. Thus, the decision to convert should be made promptly to reduce the potential risk of postoperative complications and to maintain curability, especially in

patients with advanced lung cancer.

With the accumulation of further experience performing VATS, the indications for VATS have been extended to include advanced lung cancer. The outcomes of VATS in advanced cancer are likely to be comparable to those of Open in the selected patients. Patient selection and the timing of conversion to Open should be carefully and promptly decided, especially in patients with advanced lung cancer.

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