Video-assisted mediastinoscopic lymphadenectomy combined with minimally invasive pulmonary resection for left-sided lung cancer: feasibility and clinical impacts on surgical outcomes

Ho Jin Kim, Yong-Hee Kim*, Se Hoon Choi, Hyeong Ryul Kim, Dong Kwan Kim and Seung-Il Park

Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

* Corresponding author. Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea. Tel: +82-2-30103580; fax: +82-2-30106966; e-mail: kimyh67md@hotmail.com (Y.-H. Kim).

Received 28 September 2014; received in revised form 22 January 2015; accepted 27 January 2015

Abstract

OBJECTIVES: Although video-assisted mediastinoscopic lymphadenectomy (VAML) has greatly increased the accuracy of mediastinal staging, its clinical value as a therapeutic tool for complete mediastinal lymph node dissection in the treatment of left-sided lung cancer is not well elucidated.

METHODS: We identified the consecutive 649 patients with left-sided lung cancer undergoing minimally invasive pulmonary resection between July 2002 and June 2013. Among them, 225 patients underwent VAML combined with pulmonary resection (VAML + VATS group), while the remaining 424 patients underwent VATS procedure only (VATS group). Operative outcomes including procedural time, removed lymph nodes and node stations, complications and the final pathological mediastinal staging in the both groups were evaluated and compared.

RESULTS: There was no significant difference in the baseline profiles between the two groups. The patients in the VATS + VAML group showed significantly shorter operative time (116.8 ± 39.8 vs 159.8 ± 44.0 min; P < 0.001), more extensive lymph node dissection (total number of removed lymph nodes, 29.7 ± 10.8 vs 23.0 ± 8.6; P < 0.001) and the higher rates of patients with mediastinal lymph nodes removed: Station 2 on the right (12.4 vs 0.2%), Station 2 on the left (15.1 vs 0.2%), Station 4 on the right (42.7 vs 0.9%), Station 4 on the left (87.6 vs 57.3%) and Station 7 (100 vs 99.3%), while maintaining comparable surgical morbidities compared with the VATS group. Also, the patients in the VATS + VAML group tended to have higher rates of being upstaged with mediastinal involvement (8.0 vs 5.7%; P = 0.31).

CONCLUSIONS: VAML is a clinically feasible procedure safely performed as a therapeutic tool for complete mediastinal lymph node dissection (MLND), and can be a good complement to minimally invasive pulmonary resection in left-sided lung cancer, where optimal MLND is not always feasible with VATS approach. Further studies are required to investigate the long-term clinical impacts of VAML with regard to survival and tumour recurrence.

Keywords: Video-assisted mediastinoscopic lymphadenectomy • Video-assisted thoracic surgery • Lung cancer

INTRODUCTION

Accurate mediastinal staging of resectable lung cancer is clinically important in the prediction of postoperative prognosis and the guidance for the adoption of adjuvant therapy. Among the three components of TNM staging system, the nodal stage is the most difficult to determine correctly owing to the limited specificity with imaging modalities [1]. Several invasive staging techniques have been developed to improve on the accuracy of mediastinal nodal staging. Conventional mediastinoscopy, introduced by Carlens [2] in 1959, has been widely used to sample the mediastinal lymph nodes, and contributed to more accurate nodal staging. However, its limited visualization of the mediastinal structures has forbidden the complete resection of the mediastinal lymph nodes.

Video-assisted mediastinoscopic lymphadenectomy (VAML), pioneered by Hurtgen et al. [3] in 2002, has greatly increased the exposure and the imaging of the mediastinal structures, thus allowed the complete resection of lymph nodes instead of nodal sampling [4]. The advent of VAML has enabled the minimally invasive approach to be equivalent to open lymphadenectomy in terms of diagnostic accuracy and surgical radicality, and has widened its clinical applications from preoperative inspection...
and sampling to a therapeutic tool for intraoperative complete mediastinal dissection. In addition, with a growing number of minimally invasive pulmonary resection, where oncologically optimal mediastinal lymph node dissection (MLND) is not always feasible, especially in left-sided lung cancer [5], VAMLA is emerging as a complement to video-assisted thoracic surgery (VATS) lobectomy [6].

Though previous clinical series has advocated the clinical efficacy and safety of VAMLA in the assessment of mediastinal nodal staging [6–8], its clinical role as a therapeutic tool in combination with minimally invasive pulmonary resection in left-sided lung cancer, has not been fully elucidated. In these regards, we sought to evaluate the clinical outcomes in the 225 consecutive patients undergoing VAMLA combined with VATS pulmonary resection for left-sided lung cancer.

MATERIALS AND METHODS

Patients

All patients undergoing surgery for lung cancer are prospectively registered in our institution’s database, which records baseline characteristics, detailed information about surgery and postoperative results. By the review of our institutional database, we identified 649 patients with left-sided lung cancer who underwent either a combination of concomitant VAMLA and thoracoscopic procedure (VATS + VAMLA group) or anatomical lobar resection and mediastinal lymphadenectomy using only thoracoscopic (VATS group) from July 2002 to June 2013. These patients were enrolled in the present study, and formed the study population.

Concomitant VAMLA was mainly indicated for the patients with left-sided lung cancer who is suspicious for clinical N0, N1 or single station N2 involvement. Otherwise, VAMLA was rarely indicated for the patients with right-sided lung cancer suspicious for clinical N3 involvement, but the decision to perform the intraoperative VAMLA was made mainly at the discretion of operating surgeons who have clinical expertise with minimally invasive pulmonary resection and mediastinoscopic procedures, and have different attitudes towards VAMLA. We assumed that mediastinal lymphadenectomy in the left-side is more difficult than the right-side because of the inferior accessibility to lymph nodes in the left side due to anatomical barrier, and the addition of VAMLA would not influence the extent of MLND in the minimally invasive pulmonary resection for right-sided lung cancer. Therefore, the patients with right-sided lung cancer were not included in this study. The study was approved by the institutional ethics committee/review board, which waived the requirements for informed consent due to the retrospective nature of the study.

Surgical technique

A detailed procedural description about VAMLA was explained in the previous literature [9]. A Linder-Dahan video mediastinoscope (Richard Wolf, Knittlingen, Germany) has been used for VAMLA since July 2004. In brief, the patient is intubated with a single-lumen endotracheal tube under general anaesthesia, and placed in a supine position with a neck hyper-extended. After the paratracheal fascia is opened and blunt dissection is performed, the two-bladed video mediastinoscope is inserted and advanced into the pretracheal space. After the inferior valve of the video mediastinoscope is opened to create the wide operative field enough for bimanual manoeuvre, the node stations including Station 2 on the right (2R) and left (2L), Station 4 on the right (4R) and left (4L), and Station 7 were explored. Wherever possible, we usually performed en bloc resection along with neighbouring fatty tissue for all accessible lymph nodes in the right paratracheal and subcarinal compartments. For the excision of left-sided node stations, careful dissection was made not to injure the adjacent recurrent laryngeal nerve. The frozen section biopsies during VAMLA were mainly obtained when multiple N2 or N3 lesions are suspected of being involved. The patients who were confirmed to have lymph node involvement in the N3 lesion did not undergo subsequent VATS lobectomy, or rarely had VATS wedge resection for peripherally located mass only to reduce tumour burden. Following VAMLA, a single-lumen endotracheal tube was changed into a double-lumen catheter, and the patient was switched into the full lateral position for subsequent thoracoscopic pulmonary resection.

Outcomes of interest and statistical analysis

The primary outcomes of interest were operation-related data: operative profiles including VAMLA, and the number of lymph nodes and nodal stations removed by thoracoscopy and VAMLA. The secondary outcomes of interest were the early surgical outcomes in the both groups: mortality and morbiditys including pneumonia/acute respiratory distress syndrome (ARDS), atrial fibrillation, chylothorax, prolonged air leakage >7 days and vocal cord palsy. Finally, pathological mediastinal nodal staging in both the groups was compared with investigate the patients upstaged or downstaged with VAMLA.

Categorical variables, presented as percentages or frequencies, were compared with the $\chi^2$ test or Fisher’s exact test. Continuous variables, expressed as either mean ± standard deviation or median and interquartile range, were compared with Student’s t-test. All reported P-values were two-sided, and a value of $P < 0.05$ was considered statistically significant. The SPSS software, version 20 (IBM, Armonk, NY, USA) was utilized for statistical analysis.

RESULTS

Patients and baseline characteristics

Of a total of 649 patients, 225 patients underwent a combination of VAMLA and minimally invasive pulmonary resection mainly by a single surgeon, whereas 424 underwent lobectomy and mediastinal lymphadenectomy using thoracoscopic only. The subsequent pulmonary resections following VAMLA were as follows: pneumonectomy ($n = 2$), lobectomy ($n = 201$), segmentectomy ($n = 16$) and wedge resection ($n = 2$). The remaining 4 patients were found to have pleural dissemination on thoracoscopic exploration, so subsequent pulmonary resection was aborted.

Table 1 demonstrates the baseline clinical characteristics of all patients in both the groups. In summary, there were no significant differences in the baseline characteristics including age, gender, tumour locations and clinical nodal stage between the two groups. In the VATS + VAMLA group ($n = 225$), there were 138 (61.3%) males with a mean age of $61.3 ± 10.1$ years, whereas there were 238 (56.1%) males with a mean age of $60.7 ± 10.3$ years in
Comparison of operative profiles between the two groups

The operative profiles including VAMLA between the two groups are summarized in Table 2. The operative time for lobectomy was significantly longer in the VATS group (116.8 ± 39.8 vs 159.8 ± 44.0 min; P < 0.001). The procedural time for VAMLA was 38.0 ± 12.3 minutes. The total number of lymph nodes removed during the entire surgery was significantly higher in the VATS + VAMLA group, compared with the VATS group (29.7 ± 10.8 vs 23.0 ± 8.6; P < 0.001). The lymph node stations 2R and 2L were removed in 28 (12.4%) and 34 (15.1%) patients, whereas the stations 4R, 4L and 7 were removed in 96 (42.7%), 197 (87.6%) and 225 (100%) patients in the VATS + VAMLA group, respectively. The corresponding node stations 2, 4, 7 were significantly higher in the VATS + VAMLA group. The number of lymph nodes (13.2 ± 6.9 vs 6.6 ± 4.5; P < 0.001) and node stations (2.6 ± 0.8 vs 1.6 ± 0.5; P < 0.001) in the stations of 2, 4 and 7 were significantly higher in the VATS + VAMLA group.

Comparison of early operative outcomes between the two groups

We compared the early operative outcomes between the two groups; to maintain the homogeneity of surgical procedure, 201 patients undergoing VATS lobectomy in the VATS + VAMLA group were selected and compared with the VATS group. There was no in-hospital mortality in the VATS + VAMLA group, and the rate of in-hospital mortality after surgery was 0.5% (n = 2) in the VATS group. The procedural time for VAMLA was 38.0 ± 12.3 minutes. The total number of lymph nodes removed during the entire surgery was significantly higher in the VATS + VAMLA group, compared with the VATS group (29.7 ± 10.8 vs 23.0 ± 8.6; P < 0.001). The lymph node stations 2R and 2L were removed in 28 (12.4%) and 34 (15.1%) patients, whereas the stations 4R, 4L and 7 were removed in 96 (42.7%), 197 (87.6%) and 225 (100%) patients in the VATS + VAMLA group, respectively. The corresponding node stations 2, 4, 7 were significantly higher in the VATS + VAMLA group. The number of lymph nodes (13.2 ± 6.9 vs 6.6 ± 4.5; P < 0.001) and node stations (2.6 ± 0.8 vs 1.6 ± 0.5; P < 0.001) in the stations of 2, 4 and 7 were significantly higher in the VATS + VAMLA group.
group. Table 3 presents the comparative data of early mortality and morbidities between the two groups. On the crude comparisons, the rates of early complications were similar in the both groups: pneumonia/ARDS (2.9 vs 1.2%; P = 0.16), atrial fibrillation (1.9 vs 1.9%; P = 0.92), chylothorax (0.5 vs 0.5%; P = 0.96), prolonged air leakage lasting >7 days (1.5 vs 1.2%; P = 0.87) and vocal cord palsy (4.9 vs 2.4%, P = 0.14). Also, there was no difference in the length of hospital or intensive care unit (ICU) stays between the two groups.

Comparison of the final pathological nodal staging between the two groups

Table 4 demonstrates the comparative data of pathological lymph nodal staging between the two groups. In the VATS + VAMLA group, there were 28 (12.5%) patients who were diagnosed with ≥pN2, whereas 33 (7.7%) were diagnosed with ≥pN2 in the VATS group. In the VATS + VAMLA group, 18 patients (8.0%) were upstaged from cN0/1 to pN2/3, whereas 24 patients (5.7%) were upstaged from cN0/1 to pN2/3 in the VATS group. The pathological downstaging was observed in 17 patients, and the rate of downstaging was significantly higher in the VATS + VAMLA group (4.4 vs 1.7%; P = 0.04). The rate of mediastinal downstaging (cN2 to pN0/1), however, was comparable for the both groups (1.3 vs 1.2%; P>0.99).

DISCUSSION

In the present study, we demonstrated that VAMLA is a clinically feasible procedure that can be performed with an acceptable safety profile. In addition, VAMLA allowed a removal of more mediastinal lymph nodes than VATS approach, suggesting that VAMLA can be a good complement to minimally invasive pulmonary resection for complete MLND in the surgical treatment for left-sided lung cancer. Accurate mediastinal nodal staging of lung cancer is a prerequisite for the selection of adequate treatment strategies and the prediction of treatment outcomes. Computed tomography (CT) and positron emission tomography (PET) scan have been the preferred non-invasive diagnostic modalities for nodal staging. However, their sensitivity and specificity have not been satisfactory. Conventional mediastinoscopy, despite its invasive nature and requirement for general anaesthesia, has remained the gold standard for the exclusion of mediastinal lymph node involvement with higher sensitivity and specificity than non-invasive imaging modalities. However, from a perspective of complete MLND, conventional mediastinoscopy also has not been satisfactory owing to its technical limitations of tight operative field and one-hand manoeuvre.

On the other hand, VAMLA allowed the operating surgeon to perform a more extensive MLND with the employment of two-bladed expandable speculum, which freed the surgeon to bimanual manoeuvre and wider operative filed. Given that the sensitivity of mediastinoscopy is mainly affected by the amount of removed lymph nodes and the number of removed lymph node stations [3], we can speculate that the sensitivity of VAMLA is higher than a conventional mediastinoscopy, as reported in the previous literature [10]. As mediastinal staging by VAMLA is known to be as accurate as by open lymphadenectomy, the clinical application of VAMLA is not only limited to a diagnostic mediastinal staging but also evolves to a therapeutic tool for complete MLND, and it gains wider acceptance as a complement to minimally invasive pulmonary resection for lung cancer, especially in the left side [4,6].

From a surgical perspective, MLND in the left side is more difficult than the right side with thoracoscopic because aorta and pulmonary artery get in the way of reaching to mediastinal lymph nodes. Complete MLND with thoracoscopy in the left side, therefore, necessitates the division of ligamentum arteriosus for the exposure of node stations 2 and 4. Especially node station 2 is almost inaccessible by thoracoscopy. Such shortcomings can be overcome by the combination of VAMLA, which can allow easy access to node stations 2 and 4. In addition, as the dissection in the right side can be easily performed with VAMLA, it has enabled a simultaneous evaluation of N3 lesion intraoperatively if necessary.

The employment of VAMLA can allow the operating surgeons to decrease the procedural complexity of VATS pulmonary resection by obviating the need for MLND thoracoscopically, and especially benefit the starting surgeons and trainees by avoiding technical difficulties of MLND with thoracoscopy in their early learning periods. Furthermore, we demonstrated that the operative time is significantly shorter in the VATS + VAMLA group (116.8 ± 39.8 vs 159.8 ± 44.0 min; P < 0.001), and the shortened time may account for the one saved for MLND with VAMLA. This result implies that VAMLA can save the one-lung ventilation time by reducing the time for MLND with thoracoscopy. Because the prolonged one-lung ventilation time is known to be related to major postoperative complications after pulmonary resection [11], the combination of VAMLA might decrease the incidence of postoperative morbidities. However, there was no significant difference in the rates of early morbidity between the two groups in this study, possibly owing to their low incidence of morbidities, which resulted in the lack of statistical power. Also, the aforementioned clinical benefits of VAMLA in terms of reduced morbidities might be offset by more extensive...
mediastinal dissection. It is noteworthy that the incidence of vocal cord palsy was higher in the VATS + VAMLA group, though it did not reach the statistical significance. Owing to the combined fashion of VAMLA and VATS, we could not attribute vocal cord palsy in this group to VAMLA solely, but careful manoeuvre is required to avoid the injury of the recurrent laryngeal nerve during VAMLA.

We also compared the incidence of upstaging from cN0/1 to pN2/3 between the two groups, which demonstrated that the VATS + VAMLA group tended to have a higher incidence of upstaging (7.6 vs. 5.7%; P = 0.40). The feasibility of oncologically optimal MLND with thoracoscopy in the preoperative clinical N0/1 patients has always been a concern owing to the possibility of overlooking the patients with mediastinal involvement [6, 12]. This result, although statistically not significant, implicates that VAMLA may be a better method in detecting mediastinal involvement than thoracoscopy in left-sided lung cancer, and lead patients to a more adequate stage-oriented adjuvant treatment. Among the patients upstaged by VAMLA, there were 2 patients diagnosed with pN3. Those patients were incidentally upstaged to pN3 because VAMLA was not used for diagnostic purpose, so we obtained frozen section biopsies during VAMLA for the patients highly suspicious of N3 or multiple N2 involvement only. In case VAMLA is used for therapeutic MLND combined with pulmonary resection, meticulous mediastinal staging needs to be performed intraoperatively to identify the patients with advanced stage who will not benefit from surgery.

This study demonstrated that the combination of VAMLA yielded more extensive systemic nodal dissection (29.7 ± 10.8 vs. 23.0 ± 8.6; P < 0.001) including mediastinal LN (13.2 ± 6.9 vs. 6.6 ± 4.5; P < 0.001) and mediastinal nodal stations (2.6 ± 0.8 vs. 1.6 ± 0.5; P < 0.001) for left-sided lung cancer. Although there is a controversy with regard to the extent of intraoperative mediastinal lymph node exploration (sampling versus complete dissection) [5], it is generally agreed that complete lymph node dissection is a significant predictor for a long-term survival [13–16]. Complete lymph node dissection is the consensus strategy in our institution, and a sufficient number of lymph nodes were dissected as recommended by the guidelines [5] in both the groups. However, insufficient node dissection in the paraatracheal compartment with VATS approach for left-sided lung cancer should raise the controversy whether MLND via left-sided VATS is oncologically adequate. On the other hand, further investigations are warranted whether extensive MLND with VAMLA can be translated into the improved long-term survival and the reduced tumour recurrence in left-sided lung cancer.

This study has several limitations. It is a retrospective and non-randomized study with observational data, so the study results may have been affected by unmeasured confounders. Because VAMLA was mainly performed by a single surgeon, the operative outcomes may have been influenced by ‘surgeon bias’, but it should be considered that the use of VAMLA combined with pulmonary resection is a relatively new area in the surgical treatment of lung cancer. Also, this study incorporates the surgical experience of the 12-year period, and the technical advances in surgical procedure and nodal staging by CT or PET scan were not adequately reflected.

In conclusion, VAMLA is a clinically feasible procedure that can be safely performed as a therapeutic tool for complete MLND, as well as a staging purpose. The procedural benefits of VAMLA in terms of complete MLND and the simplification of pulmonary resection can be demonstrated more evidently in left-sided lung cancer where optimal MLND is not always feasible with VATS approach, and enabled VAMLA to be a good complement to minimally invasive pulmonary resection. Further studies are required to investigate the long-term clinical impacts of VAMLA with regard to survival and tumour recurrence.

Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr K. Athanassiadis (Athens, Greece): To tell you the truth, reading the paper, I was a little bit confused. I understand that you decided to do that for left-sided...
lung cancer, but I could imagine that VAMLA or a simple mediastinoscopy could be enough for the left lower lobe cancers, and not for the upper lobe cancers due to the lymphatic drainage, and not due to the difficulty of the VATS lobectomy, doing a lymphadenectomy during VATS lobectomy, which is not mentioned in the literature.

Can you please comment on that?

Dr Kim: We did not decide whether to use VAMLA depending on the location of the lung cancer.

In the case of left-sided lung cancer, we try to use VAMLA because we believe systemic mediastinal lymph node dissection is the best surgical treatment strategy in the treatment of lung cancer, which made us take an aggressive strategy.

Dr Athanassiadi: Since you are an aggressive group, that probably explains my next question.

Within these 225 patients, 221 were operated on, also with N2 and N3 disease. You had four cases where there was pleural invasion, and practically, you did not include them in the study. There were 20, 21 patients, that some of them, they had N2 and N3 disease, as you mentioned, after your VAMLA procedure. But although you had N2 and N3 disease, you proceeded to surgery. Can you please comment on that?

Dr Kim: We performed the surgery on the patients in whom single N2 involvement is suspected. I will check on the patients with N3 lesion.

Dr Athanassiadi: Okay, and in the preoperative staging, I can believe everything you are telling us about the literature, about PET and CT, but why not EBUS? I mean, you could save yourself from some cases like that, where N3 or N2 diseases were operated.

Dr Kim: Usually, N2 and N3 disease was not operated.

Dr Athanassiadi: My last comment would be that you take lymph nodes from three stations, and the three stations are exactly the same, with mediastinoscopy.

Why not do the mediastinoscopy in advance giving you time for the pathologist to review, not having a quick intraoperative biopsy, since they can miss micrometastasis especially if they can get, according to your paper, 29.7 lymph nodes as a mean number.

Dr Kim: Yes.

Dr Athanassiadi: I would like you to comment, also, on the operative time. I congratulate you on the operative time as a whole, VAMLA plus VATS together, but the operative time is something else; concerning the time the patient is under anaesthesia.

If you take the time that you have the VAMLA, you have the waiting for the lymph nodes, 30 lymph nodes from your pathology department. If you have the time to turn the patient in order to have a VATS procedure, the whole hour, the patient having anaesthesia is far too long.

Dr Kim: Usually, we perform VAMLA procedure; we do not wait for the result of frozen biopsy, because VAMLA was used for a treatment modality rather than diagnostic purpose.

Therefore, the average operative time for VAMLA plus VATS group, when compared with VATS only group the difference in the overall operative time between the two groups was not so high.