Experience of Simultaneous Bilateral Open Surgery and VATS for Pulmonary Metastasectomy

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Abstract

Background Resection is the current treatment of choice for resectable bilateral pulmonary metastases. This study aimed to compare the differences in outcomes between simultaneous bilateral open and video-assisted thoracic surgery (VATS) for pulmonary metastasectomy.

Methods Forty-three patients underwent pulmonary metastasectomy through one-stage bilateral open thoracotomy ($n = 16$) and VATS ($n = 27$) between 2011 and 2020. Perioperative and oncological data were analyzed.

Results The predominant primary tumor histology in both groups was colorectal cancer. The operative time, blood loss, and pain score on postoperative day 1 (POD1) were higher in the open group ($p < 0.001$, 0.009, and 0.03, respectively). No significant differences in pain score on POD2 and POD3, postoperative length of stay, or complications were found. Notably, numbers of the resected metastatic lung nodules were significantly greater in the open group (median number: 9.5 vs. 3, $p < 0.001$). Recurrence-free survival (RFS) and overall survival (OS) were comparable. The median RFS was 15 months (interquartile range [IQR], 6–22) in the open group and 18 months (IQR, 8–47) in the VATS group. The median OS was 28 months (IQR, 14–44) and 29 months (IQR, 15–54) in the open group and VATS group, respectively.

Conclusion One-stage bilateral pulmonary metastasectomy is safe and reduces medical expenditures in selected patients regardless of surgical approach. Although the open group harbored a greater number of metastatic foci, perioperative and oncological outcomes were similar to that of the VATS group.

Keywords
- metastases/metastasectomy
- thoracoscopy/VATS
- surgery/incisions

Introduction

Pulmonary metastasectomy is safe and has curative potential for properly selected patients with lung metastases.[1,2] However, there is controversy with regard to whether open surgery or video-assisted thoracoscopic surgery (VATS) is a better approach in terms of metastatic foci harvested, complications, recovery, recurrence, and survival.[3–14]

Recently, VATS has been more widely utilized due to its numerous benefits. Studies have shown VATS to be associated with less postoperative pain, fewer postoperative complications, faster recovery, and better quality of life compared with open thoracotomy, as reported in both nonrandomized and randomized studies for primary lung cancer.[15–17]

Few studies thus far on one-stage bilateral pulmonary metastasectomy have reported the feasibility, safety, and

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additional financial benefits compared with staged operations in the relevant cohorts.[18–21] Furthermore, none of these studies described the differences in outcome between open surgery and VATS. It is unknown whether these two surgical approaches employed in patients with bilateral pulmonary metastases would produce similar efficacy.

Therefore, we performed a retrospective cohort study to explore patients undergoing simultaneous bilateral pulmonary metastasectomy by comparing open surgery against VATS. Similar articles were not found in the literature. The primary objective was to investigate the perioperative safety and morbidity, while the secondary aim was to analyze the oncological results including recurrence-free survival (RFS) and overall survival (OS).

Materials and Methods

Study Design

This retrospective cohort study was conducted from January 2011 to April 2020 at a single medical center. The Institutional Review Board of Kaohsiung Medical University Hospital approved this study and the requirement for written informed consent was waived (KMUHIRB-E(I)-20200228). Fifty patients were consecutively enrolled receiving simultaneous bilateral surgery for pulmonary metastases. Seven patients were excluded, four with surgical approaches combined sternotomy or ipsilateral thoracotomy and contralateral VATS, and three with diagnostic purposes of suspected metastatic lesions. After exclusion, 43 patients surgically treated with therapeutic intent were divided into two groups, (1) sixteen patients receiving simultaneous bilateral open thoracotomy (open group) and (2) twenty-seven patients receiving simultaneous bilateral VATS (VATS group) (►**Fig. 1**). Patients' data including demographic characteristics, perioperative data, and postoperative oncological outcomes from electronic medical records were collected. High-resolution computed tomography (HRCT) scan examinations were performed using the Optima CT660 system (GE, Tokyo, Japan) throughout the study period. Although the reconstruction thickness had been 5 mm in axial sections before 2016, it had been adjusted to thinner 1 to 2 mm slices in the past 5 years (2016–2020). The positron emission tomography and computed tomography(CT) scan was performed when needed. All patients were evaluated preoperatively in an interdisciplinary tumor board setting to reach a consensus on surgical treatment. In addition, indications for metastasectomy were evaluated with Rusch's criteria[22]: (1) the primary tumor is controllable, or it can be resected totally at the time of resecting the metastases; (2) metastatic disease can be resected completely; (3) the patient can tolerate the extent of pulmonary resection required to remove all lesions; (4) no extrathoracic metastases are present.

Operative Procedure

Open thoracotomy with ~12 cm incisions via posterolateral approach and thoracoscopic assistance had been the standard surgical approach for pulmonary metastasectomy, which allowed for the complete inspection and palpation of the whole lung. Since 2013, two-port VATS (no rib spreading) has been implemented in our center for pulmonary metastasectomy in selected patients. One lung anesthesia via

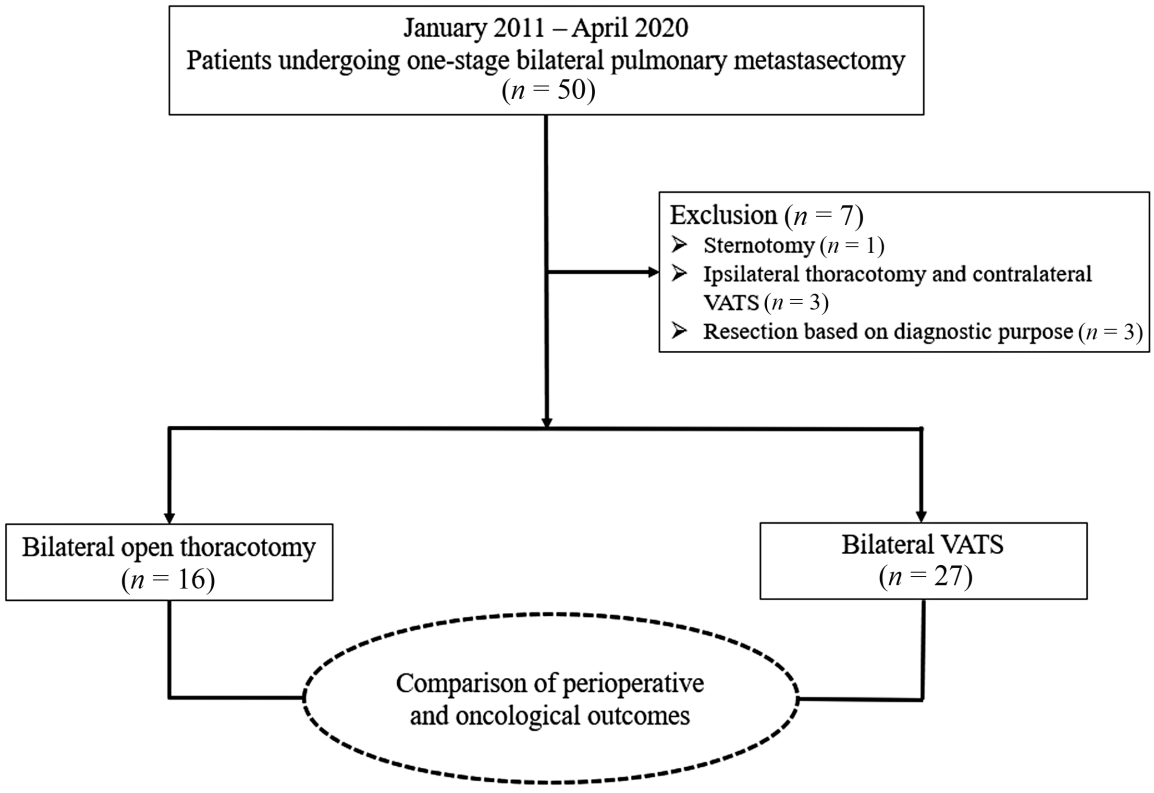

Fig. 1 Flow diagram of patient recruitment. VATS, video-assisted thoracic surgery.

a double-lumen endotracheal tube has also been routinely performed. The bilateral operations were all performed in the lateral decubitus position and sequentially repositioned either in the open group or in the VATS group. The plan was to prioritize the side requiring lesser lung parenchyma sacrifice, permitting a safe resection of the contralateral side afterwards. Wedge resections via stapler devices were performed mostly in both surgical approaches, unless the lesions were centrally located and adequate margin cannot be ensured. Additionally, in a handful of patients from the open group with tiny metastatic foci identified with finger palpation, pneumotomy was performed using electrocautery followed by direct suture. However, mediastinal lymph node dissection or sampling was not routinely performed. For the most part, case selection for open surgery or VATS was down to the following factors; the surgeon's preference, technical considerations, and the aim of preserving as much lung parenchyma as possible, in which preoperative radiological imaging was utilized.

Perioperative Management

In 2012, we implemented the enhanced recovery after surgery (ERAS) protocol for the improvement of postoperative recovery of patients who received major thoracic operations as previously reported for esophagectomy and reconstruction.[23] Therefore, patients with planned one-stage bilateral pulmonary metastasectomy were advised to receive thoracic epidural analgesia (TEA), and respiratory rehabilitation program was routinely performed. For patients without TEA, intravenous patient-controlled anesthesia was administered. It should be noted that although available on request, both analgesic options were paid out of pocket by the patients themselves. Additional doses of intravenous Parecoxib were used for intolerable pain during postoperative hospital stay. Pain scores were assessed using a numerical rating scale (NRS), 0 (no pain) to 10 (excruciating pain), every 8 hours with the patient at rest on postoperative day 1 (POD1) and then on each day until discharge. Chest drains were removed in both groups if there were no air leaks and if the drainage was $<$200 mL within 24 hours.

Postoperative Follow-Up

All patients were advised to receive outpatient clinic follow-up. For each patient, a base-line HRCT scan was conducted after metastasectomy at 3 months postoperatively and every 3 months for 2 years, then every 6 months for each subsequent year. RFS and OS after metastasectomy were assessed as well as the site of first recurrence. In June 2021, an investigation was performed regarding either death or date of last follow-up for living patients.

Statistical Analysis

Categorical variables were expressed as numbers with percentages and compared by the chi-squared test. Non-normally distributed data were described by medians with interquartile range (IQR) and were analyzed using Mann–Whitney U test. Survival was estimated by the Kaplan–Meier method. Log-rank test was used to examine the differences between treatment groups. All statistical operations were performed using MedCalc Statistical Software version 19.2.6 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2020). A p-value from two-tailed test and less than 0.05 was considered significant.

Results

As shown in ►**Table 1**, patient characteristics in the two groups with regard to age, body mass index, sex, smoking, or preoperative pulmonary function test were found to be similar. Among patients in both groups, regarding the American Society of Anesthesiologists (ASA) physical status and primary tumor histology, a slight majority were ASA grade III (75 vs. 63%, open vs. VATS, $p = 0.51$) and colorectal cancer (38 vs. 38%, open vs. VATS, $p = 0.44$). The time period of surgery regarding operated cases throughout the study cohort (early vs. late) was analyzed (►**Fig. 2**). Although no significant differences were identified, it appeared that more cases tend to be operated on in VATS group (14/27, 52%) than that of open group (6/16, 37%) over the recent years. This finding may demonstrate the change of our surgical policy due to advancements in VATS technique and CT imaging within this time period. In terms of perioperative variables (►**Table 2**), all patients in open group underwent wedge resections, while most patients in VATS group underwent wedge resections except for 4 patients who received a greater extent of ipsilateral resections (2 lobectomies and 2 segmentectomies, respectively). The operative time and estimated blood loss were greater in the open group than those in the VATS group (median 280 vs. 180 minutes, $p < 0.001$ and 30 vs. 20 mL, $p = 0.009$). When the percentage of TEA usage in the open group was compared with the VATS group, the difference was significant (88 vs. 30%, $p < 0.001$). However, the early postoperative NRS pain score was higher in the open group than in the VATS group on POD1 (median 6 vs. 5, $p = 0.03$), but insignificant on POD2 and POD3.

Prior pulmonary resection was not an absolute contraindication for performing bilateral simultaneous metastasectomy, although not statistically different, the open group entailed a higher number of previous lung resections than those in the VATS group (31 vs. 11%, $p = 0.13$), and delineated the concern of open surgery due to the probable intrapleural adhesions. There were no significant differences in length of hospital stay, intensive care unit stay, and complications between the groups. Furthermore, the most frequent Clavien-Dindo grade I-II complication was persistent air leakage (persisting for $>$5 days postoperatively), followed by arrhythmia, poor wound healing, and urinary tract infection. However, there was no need to reoperate for any of these complications. Comparing medical expenditures, hospital charges were similar between the two groups (open: 10,713 USD and VATS: 10,107 USD). While another 36 patients who underwent two-stage bilateral metastasectomy via VATS were added to the study for further analysis, the median hospital charges for the group of two-stage VATS were 16,464 USD. Interestingly, this group was significantly costlier than the other one-stage groups ($p = 0.006$) (►**Fig. 3**).

Table 1 Demographic data

Variables	Open ($n = 16$)	VATS ($n = 27$)	*p*-Value
Age, y	59 (36–65)	58 (49–66)	0.37
BMI, kg/m^2	23 (21.3–28)	25 (23–26.8)	0.48
Sex			0.22
Male	11 (69)	13 (48)	
Female	5 (31)	14 (52)	
Ever smoker	2 (13)	6 (22)	0.43
FEV_1, L	2.6 (2–2.9)	2.4 (1.8–2.8)	0.37
FEV_1 (% predicted)	86 (83.5–93.2)	85 (79–99.5)	0.93
ASA physical status			0.51
Grade II	4 (25)	10 (37)	
Grade III	12 (75)	17 (63)	
Time period of surgery			0.37
2011–2015	10	13	
2016–2020	6	14	
Primary tumor histology			0.44
Colorectal cancer	6 (38)	10 (38)	
Sarcoma	4 (25)	3 (11)	
Renal cell cancer	1 (6)	5 (18)	
Liver cancer	3 (19)	2 (7)	
Breast cancer	1 (6)	3 (11)	
Head and neck cancer	0	2 (7)	
Testicular cancer	1 (6)	0	
Ovarian cancer	0	1 (4)	
Thymic cancer	0	1 (4)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; FEV_1, forced expiratory volume in the first second of expiration; VATS, video-assisted thoracic surgery.
Data are expressed as median (interquartile range, IQR) for continuous variables and number (%) for categorical variables, unless specified otherwise.

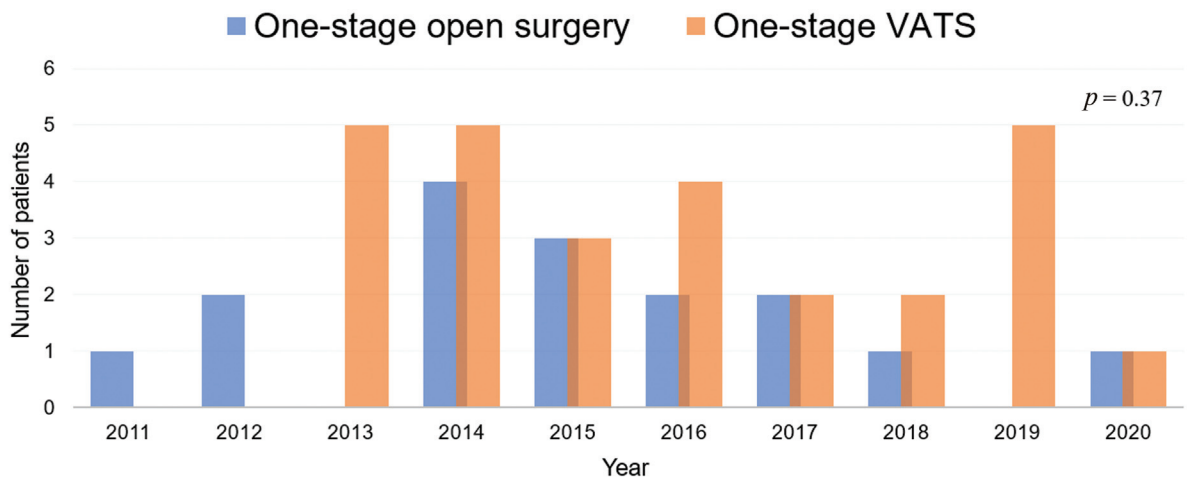

Fig. 2 Patients of bilateral one-stage metastasectomy per year. VATS, video-assisted thoracic surgery.

Table 2 Perioperative outcome

Variables	Open ($n = 16$)	VATS ($n = 27$)	*p*-Value
Extent of resection			0.28
W/W	16 (100)	23 (86)	
W/S + W	0	2 (7)	
W/L + W	0	2 (7)	
Operation time (min)	280 (240–310)	180 (145–248)	<0.001
Estimated blood loss (ml)	30 (27.5–50)	20 (20–30)	0.009
NRS pain score on POD1	6 (5–6.5)	5 (4–6)	0.03
NRS pain score on POD2	4 (4–5)	4 (3–4.75)	0.45
NRS pain score on POD3	3 (2.5–4)	3 (3–4)	0.06
Thoracic epidural analgesia	14 (88)	8 (30)	<0.001
Mean ICU stay (day) (range)	0.3 (0–4)	0.3 (0–3)	0.87
Postoperative length of stay (day)	6 (6–8)	5 (4–7)	0.05
Previous lung resection	5 (31)	3 (11)	0.13
Unilateral	1	3	
Bilateral	4	0	
In-hospital mortality	0	0	1.0
Complication (Clavien–Dindo classification)	2 (12)	3 (11)	1.0
Grade I and II	2	3	
Prolonged air leak (> 5 days)	0	2	
Atrial fibrillation	0	1	
Poor wound healing	1	0	
Urinary tract infection	1	0	
Grade III and IV	0	0	
Surgical margin status			0.37
R_0 resection	15 (94)	27 (100)	
R_1 resection	1 (6)	0	
Hospital charges (USD)	10,713 (9928–13,214)	10,107 (9611–11,553)	0.52

Abbreviations: ICU, intensive care unit; L, lobectomy; NRS, numerical rating scale; POD, postoperative day; S, segmentectomy; VATS, video-assisted thoracic surgery; W, wedge resection.
Data are expressed as median (interquartile range, IQR) for continuous variables and number (%) for categorical variables, unless specified otherwise.

As described in ►**Table 3**, the median number of the preoperatively image-detected, intraoperatively resected, and pathologically confirmed metastatic lung nodules were significantly greater in the open group than those in the VATS group (9.5 vs. 3, 12.5 vs. 3, 9.5 vs. 3, respectively, all $p < 0.001$). However, the maximum diameter of the metastatic lesions did not substantially differ between the two groups. ►**Fig. 4** demonstrated the representative cases receiving simultaneous bilateral metastasectomy either in open surgery or VATS. It is worth mentioning that the highest number of resected metastatic nodules in our series was 42 and the patient is still disease free after 114 months. Moreover, Kaplan–Meier analysis in ►**Fig. 5** showed that RFS and OS were comparable between open and VATS groups (Log-rank test, $p = 0.52$ and $p = 0.73$, respectively). Median RFS was 15 months (IQR: 6–21.6) vs. 18 months (IQR, 7.5–47.4) and median OS was 27.6 months (IQR, 13.8–43.8) vs. 28.8 months (IQR, 14.7–54.3) during the similar follow-up periods (28 vs. 29 months, $p = 0.73$). Comparing recurrence patterns, no difference was found regarding the pulmonary

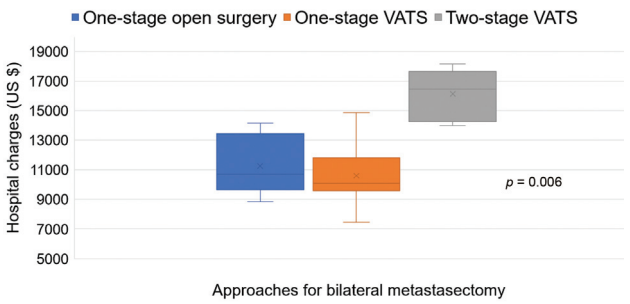

Fig. 3 Box plot of hospital charges per treatment groups. VATS, video-assisted thoracic surgery.

Table 3 Oncological outcome between the two surgical approaches

Variables	Open ($n=16$)	VATS ($n=27$)	*p*-Value
Preoperatively image-detected nodules on HRCT			<0.001
Bilateral single lesions ($n=2$)	0	7 (26)	
Number of lesions (3–5)	3 (19)	14 (52)	
Number of lesions (6–10)	5 (31)	4 (15)	
Number of lesions (11–20)	7 (44)	2 (7)	
Number of lesions (>20)	1 (6)	0	
Intraoperatively resected nodules			0.004
Bilateral single lesions ($n=2$)	0	5 (18)	
Number of lesions (3–5)	4 (25)	15 (56)	
Number of lesions (6–10)	4 (25)	6 (22)	
Number of lesions (11–20)	4 (25)	1 (4)	
Number of lesions (>20)	4 (25)	0	
Pathologically confirmed metastatic nodules			<0.001
Bilateral single lesions ($n=2$)	0	11 (41)	
Number of lesions (3–5)	4 (25)	13 (48)	
Number of lesions (6–10)	4 (25)	2 (7)	
Number of lesions (11–20)	5 (31)	1 (4)	
Number of lesions (>20)	3 (19)	0	
Number of image-detected nodules, (range)	9.5 (3–28)	3 (2–16)	<0.001
Number of resected nodules, (range)	12.5 (3–42)	3 (2–12)	<0.001
Number of confirmed metastatic nodules, (range)	9.5 (3–39)	3 (2–12)	<0.001
Diameter of largest lesion			0.75
< 10 mm	3 (19)	4 (15)	
10–19 mm	8 (50)	13 (48)	
20–29 mm	5 (31)	6 (22)	
≧30 mm	0	4 (15)	
Pattern of first recurrence after surgery			0.42
Lung only	7 (44)	8 (29)	
Lung and other sites	7 (44)	14 (52)	
Free from recurrence	2 (12)	5 (19)	
Reoperated metastasectomy	4 (25)	5 (19)	0.71
Follow-up (month)	28 (14–44)	29 (15–54)	0.73

Abbreviations: HRCT, high-resolution computed tomography; VATS, video-assisted thoracic surgery.
Data are expressed as median (interquartile range, IQR) for continuous variables and number (%) for categorical variables, unless specified otherwise.

recurrence (44 vs. 29%, $p=0.42$) and the reoperated pulmonary metastasectomies (25 vs. 19%, $p=0.71$).

Discussion

In recent years, simultaneous bilateral surgery has gained popularity and proven to be efficacious for thoracic diseases including the treatment of primary spontaneous pneumothorax (PSP) with contralateral blebectomy and resecting bilateral multifocal ground-glass nodules suggestive of early primary lung cancer.[24–26] The literature suggested that not only was the psychological burden circumvented, but reductions were observed in contralateral occurrence in PSP, progression of the contralateral tumor as well as medical expenditures.

In patients with bilateral disease, the original indications for pulmonary metastasectomy have been broadened. Although the prognosis deteriorates as the number of pulmonary metastases increases, if all lesions are potentially resectable, surgical treatment should be considered.[2,27] Consequently, several studies have suggested that one-stage surgery in managing bilateral pulmonary metastases is as

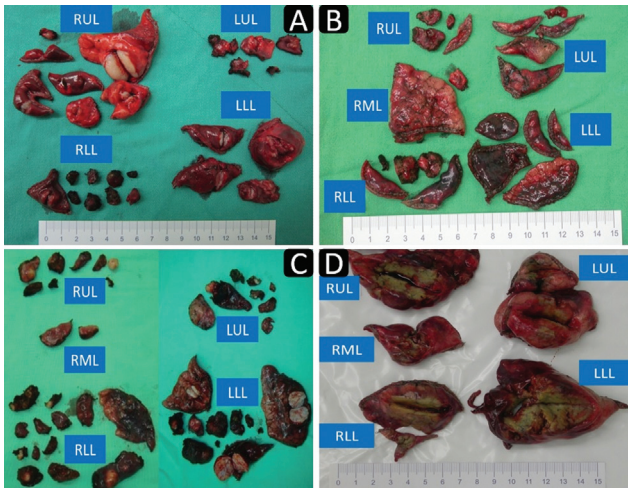

Fig. 4 The representative cases receiving simultaneous bilateral metastasectomy in either open surgery or VATS. (**A**) One patient received bilateral open thoracotomy for pulmonary metastases from sarcoma with 25 resected nodules and overall survival of 12.2 months. (**B**) One patient received bilateral open thoracotomy for pulmonary metastases from sarcoma with 21 resected nodules and overall survival of 66.8 months. (**C**) One patient received bilateral open thoracotomy for pulmonary metastases from testicular cancer with 42 resected nodules, overall survival of 114 months, and he is still living well at the time of paper submission. (**D**) One patient received bilateral VATS for pulmonary metastases from breast cancer with six resected nodules and overall survival of 15.4 months. The largest lesion was 4.5 cm. VATS, video-assisted thoracic surgery; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

safe as unilateral-side surgery.[18–21] Despite this, an increased operative time was observed in the bilateral groups compared with the unilateral groups, while the length of postoperative hospital stays and complications were comparable between groups. Furthermore, in properly-matched comparisons, one-stage surgery may confer benefits to the reduced hospitalization costs and also to the medical resources restrained by the coronavirus disease 2019 pandemic.[18,19]

To the best of our knowledge, our study was the first to compare the outcomes between open surgery and VATS in simultaneous bilateral pulmonary metastasectomy. Traditionally, one-stage bilateral thoracotomy is not preferred because of the potential for increased postoperative morbidity. Conversely, VATS enables minimally invasive resection of lung metastases and is associated with less patient discomfort with smaller incisions, absent rib spreading, and shorter hospitalization. In particular, we ensured all the surgical candidates had good pulmonary function reserves and were of appropriate physical fitness for either approach. Regarding the extent of resection, only four patients in the VATS group (4/27) had pulmonary segmentectomy or lobectomy, all others in both groups received a smaller extent of resection (wedge resection or pneumotomy in some of the open group). Hence, there was no respiratory insufficiency or pneumonia in complications with the aforementioned measures in place.

From our perspective, pain control plays a vital role in postoperative care. Based on our ERAS protocol implemented for major thoracic operations, more patients in the open group received TEA than in the VATS group, which could explain the subtle differences in the early postoperative pain scores, whereby only greater pain on POD1 in the open group was present but insignificant on POD2 and POD3. Bayman et al[28] reported no differences between the average NRS pain score for the 3 days after surgery in thoracotomy patients compared with patients undergoing VATS. Likewise, Feldman et al[18] demonstrated that pain was not significantly different in the cohort undergoing simultaneous resection when compared with pain experienced by individuals undergoing staged procedures. With this in mind, it is feasible to attain an equivalent outcome on postoperative wound pain following aggressive pain control even for patients receiving simultaneous bilateral open metastasectomy. Nonetheless, conditions such as borderline cardiopulmonary reserve, poor performance status, or patient's requests should be taken into consideration as indicators of lacking suitability for one-stage bilateral surgery. Due to the rigorous selection

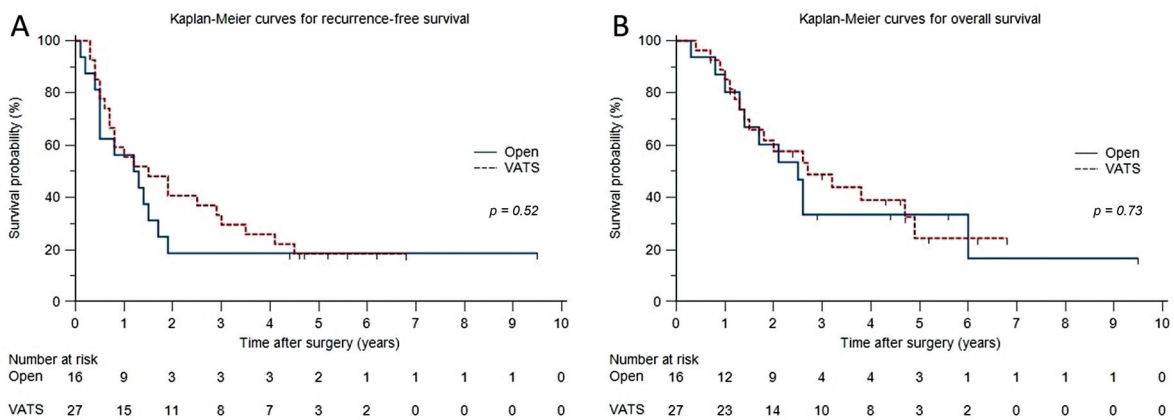

Fig. 5 Kaplan–Meier analysis showing recurrence-free and overall survival of patients receiving bilateral pulmonary metastasectomy in open and VATS group. VATS, video-assisted thoracic surgery

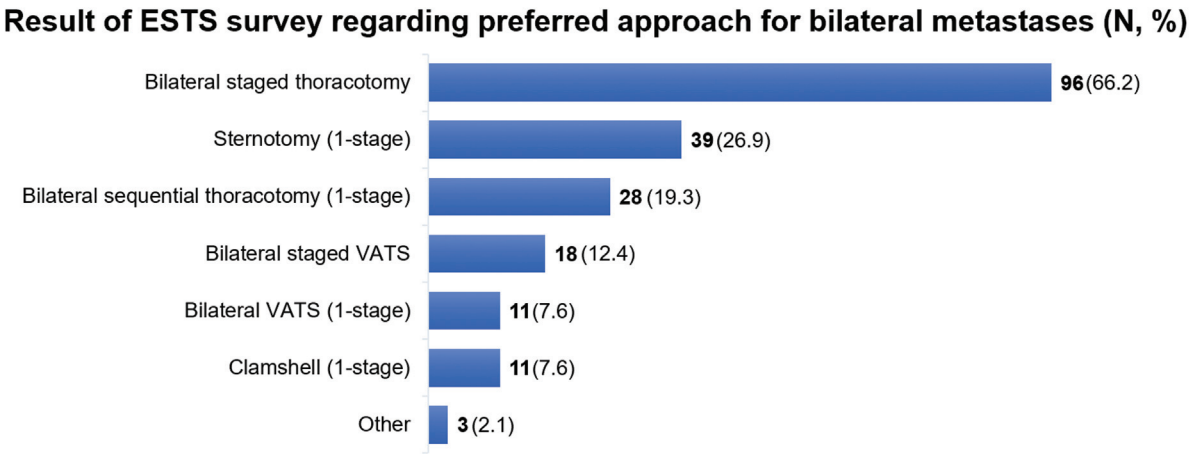

Fig. 6 Result of ESTS survey regarding preferred approach for bilateral pulmonary metastasectomy. ESTS, European Society of Thoracic Surgeons; VATS, video-assisted thoracic surgery.

of surgical candidates and ERAS implementation in our patient cohort, findings were comparable between the open and VATS group in terms of postoperative recovery, complications, postoperative length of stay, and even the hospital charges.

Interestingly, there were significantly more resected metastatic nodules in the open group than those in VATS group in our study (median: 9.5 vs. 3, $p < 0.001$). Essentially, this finding may be associated with the effectively decreased tumor burden and disease severity. However, our OS in both groups was comparable (►**Fig. 5**) and not inferior to survival results of studies entailing patients with four or more metastases (27–33.7% at 5 years).[2,27] From our perspective, the comparable oncological findings reflect a stronger inclination toward metastasectomy, regardless of the greater number of image-detected nodules in the open group. Moreover, there is consensus among thoracic surgeons that a high number of metastases should not preclude patients from surgery if they are otherwise good candidates for pulmonary resection. As demonstrated in ►**Fig. 6**, up to 27% of thoracic surgeons from the European Society of Thoracic Surgeons perform one-stage surgery either by open thoracotomy or VATS for bilateral metastases.[29]

Recently, the number of lesions found in HRCT scans was almost the same as those found during the open surgery. The reason may be due to the better resolution of newer CT imaging technologies or setting adjustments to thinner slice thicknesses. On a practical note, we were able to resect more undetected nodules (from imaging) in the open group. This result is consistent with findings in the literature favoring open thoracotomy over VATS, because a substantial number of image-undetected metastatic nodules were found during thoracotomy despite advancements in VATS and CT imaging.[7–9] The aforementioned prospective trials have also demonstrated the merits of manual palpation in open surgery and indicated the limitations of VATS. However, there are still difficulties in determining whether aggressive resection of small image-undetected nodules could improve survival outcomes,[10–14] not to mention the more complex condition of bilateral metastases.

The main limitation of this study is its retrospective design without randomization of subjects. Therefore, some selection bias does invariably exist, including the variation of HRCT slice thickness, interpretation for occult metastatic foci, operation method (open thoracotomy vs. VATS), and patients' or surgeons' sentiments toward one-stage bilateral surgery. Additionally, we did not analyze the subgroup risk factors associated with different tumor histologies due to the small sample size.

In conclusion, one-stage surgery for managing a wide array of thoracic diseases has proven its safety and efficacy,[18–21,24–26,30] with the advantages of circumventing the risk of progression of contralateral tumor, comparable wound pain to the unilateral-side surgery, decreased medical expenditures, and lessened psychologic burden. Despite receiving simultaneous bilateral metastasectomy in the open group, patients seemed to harbor greater tumor burden than those in the VATS group. The RFS and OS outcomes did not differ according to Kaplan–Meier survival analyses between the two groups. Our findings suggest that one-stage bilateral pulmonary metastasectomy from either open or VATS to be a viable option for selected patients with noncompromised perioperative safety and reduced medical expenditures.

Conflict of Interest

The authors declare that they have no conflict of interests.

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