ANTICANCER RESEARCH *38*: 1715-1719 (2018)
doi:10.21873/anticanres.12406

Safety of Simultaneous Bilateral Pulmonary Resection for Metastatic Lung Tumors

TAICHI MATSUBARA, GOUJI TOYOKAWA, FUMIHIKO KINOSHITA, NAOKI HARATAKE, YUKA KOZUMA, TAKAKI AKAMINE, SHINKICHI TAKAMORI, FUMIHIKO HIRAI, TETSUZO TAGAWA, TATSURO OKAMOTO and YOSHIHIKO MAEHARA

Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Abstract. *Aim: We investigated the safety of simultaneous bilateral lung resection for lung metastases. Patients and Methods: We retrospectively analyzed 185 patients with pulmonary metastases who underwent unilateral or bilateral pulmonary resection from August 2009 to December 2016 at a single institution. Results: Single-stage bilateral lung resection was undertaken in 19 patients, and the other 166 patients underwent unilateral pulmonary resection, including 20 patients who underwent repeated resections for synchronous or metachronous metastases. Operative time and drainage days in the bilateral group were significantly longer than those in the unilateral group (220±20 vs. 152±6.9 min: p<0.01, and 2.79±0.3 vs. 2.08±0.1 days: p<0.01). Incidence of postoperative complications and postoperative in-hospital days did not differ between the two groups (p=0.33 and 0.66, respectively). The bilateral group was further divided into two groups, namely, those who underwent wedge resection on both sides (WW) and those who underwent wedge resection on one side and segmentectomy or lobectomy on an opposite side (WSL). Operative time in the WSL group was significantly longer than that in the WW group (260±19 vs. 201±18 min: p=0.03). However, there was no significant difference in duration of chest tube use and postoperative hospital days between the two groups (p=0.26 and p=0.89). No severe postoperative complications occurred in either group. Conclusion: One-stage bilateral pulmonary metastasectomy appears to be safe as long as only wedge resection is performed on at least one side.*

Correspondence to: Testuzo Tagawa, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan. Tel: +81 926425466, Fax: +81 926425482, e-mail: tetagawa@yahoo.co.jp

Key Words: Bilateral resection, lung metastases, pulmonary resection, safety.

Since the first case of pulmonary metastasectomy was reported in 1927 (1), surgical resection has been shown to be the most effective method to cure or control one or more pulmonary metastases (2). In 1965, Thomford *et al*. advocated indications for pulmonary metastasectomy, which were limited metastatic lesions located in only one side (3). However, the indications for pulmonary metastasectomy have been broadened owing to the spread of video-assisted thoracoscopic surgery (VATS) (4-5) and prolonged survival as a result of progress in chemotherapy. In terms of bilateral multiple metastases, a multidisciplinary treatment approach including systemic chemotherapy is basically taken into account; however, bilateral pulmonary resection is sometimes indicated when the tumors are considered resistant to chemotherapy or the number of target lesions is limited. However, it remains to be fully elucidated whether simultaneous bilateral pulmonary metastasectomy can be safely performed.

In the present study, we analyzed the safety of simultaneous bilateral lung resection for lung metastases by comparing with unilateral lung metastasectomy.

Patients and Methods

Patients. We retrospectively analyzed patients who underwent pulmonary resection for histopathologically diagnosed pulmonary metastasis from other organs at our Department from August 2009 to December 2016. We use the following criteria for bilateral pulmonary metastasectomy: i) cardiopulmonary function is sufficient to undergo operation, ii) the primary tumor is controlled, iii) there are no other lesions except for those of the lung, and iv) pulmonary resection can possibly lead to control of the disease. In terms of the indications for simultaneous bilateral pulmonary resection, the tumors on at least one side should be resected by wedge resection. Nineteen cases who underwent simultaneous bilateral pulmonary resection were categorized as the bilateral group, while 166 patients who underwent unilateral pulmonary metastasectomy were categorized as the unilateral group. Twenty-one out of 166 patients in the unilateral group underwent repeated pulmonary resections for synchronous or metachronous multiple pulmonary metastases. To analyze the safety and efficacy of

bilateral resection, we examined patient data including Eastern Cooperative Oncology Group Performance Status (ECOG PS), age, forced expiratory volume in 1 second (FEV1.0), operative time, bleeding loss, complications, duration of drainage days, and postoperative hospital stay.

Preoperative diagnostic method. For imaging diagnosis, chest X-ray and computed tomography (CT) were performed for all patients. Newly identified pulmonary nodules without ground-glass opacity by CT were followed-up several times. Enlarged pulmonary nodules were suspected as lung metastases, and relevant patients underwent restaging by whole-body examination, including positron-emission tomography (PET)/CT. Imaging was evaluated by an expert radiologist at our hospital and we decided to perform pulmonary metastasectomy based on the above indications. After that, general preoperative examinations such as electrocardiogram and lung function test were carried out, and tolerability to surgical resection was assessed.

Surgical procedures. When patients were found to have bilateral lung tumors which are doubted to be metastatic lung tumors, we basically performed simultaneous bilateral pulmonary metastasectomy when the tumors did not require anatomical resections on both sides. We performed wedge resections to remove as much tumor tissue as possible for tumors that were small and located under the pleura. When tumors located close to the hilum or a surgical margin could not be secured by wedge resection, we performed anatomical resections such as segmentectomy or lobectomy. The bilateral group was further divided into two groups, namely, those who underwent wedge resection on both sides (WW) and those who underwent wedge resection on one side and segmentectomy or lobectomy on an opposite side (WSL). For the WSL group, we first performed wedge resection on one side and then performed the contralateral segmentectomy or lobectomy at one stage.

To resect bilateral metastatic lung tumors simultaneously, we did not select median sternotomy or clamshell thoracotomy. After resection on one side was completed, the patients were changed to the opposite-side lateral *decubitus* position. Wedge resection was performed by VATS with a maximum wound size less than 8 cm and no rib separation. In all cases of wedge resection, we used staplers. Segmentectomy or lobectomy was performed by thoracotomy or VATS.

Statistical analysis. Continuous variables are expressed as mean values±standard deviation (SD), and categorical variables are expressed as numbers. We performed statistical evaluation using the JMP software version 13 (SAS Institute Inc., Cary, NC, USA). For continuous variables, differences were evaluated using two-sided Student's *t*-test. For categorical variables, statistical differences between groups were tested using chi-square test or Fisher's exact test. A *p*-value under 0.05 was regarded as significant.

Results

Characteristics of patients who underwent lung metastasectomy. Table I shows the characteristics of the cases in this study. A total of 19 patients (12 men and 7 women; mean age, 54.8 years, range=19-77 years) who underwent single-stage bilateral lung metastasectomy (bilateral group) were identified, and patients of the unilateral group (102 men and 64 women; mean age, 58.9 years [range-18-84 years]) were also verified. In the unilateral group, there were six patients who underwent two-stage bilateral metastasectomy for simultaneous bilateral metastatic lung tumors due to a need for bilateral anatomical pulmonary resection, and 17 patients who underwent repeated lung resection for metachronous lung metastases (bilateral tumors in 10 patients and ipsilateral in seven patients). ECOG PS of all cases were 0 or 1, and there was no significant difference between the groups (p=1.00). The mean values of preoperative FEV1.0 were 2700

Table I. *Characteristics of 185 cases who underwent unilateral or bilateral pulmonary resection for lung metastases*.

Factor (n=185)	Bilateral group (n=19)	Unilateral group (n=166)	*p*-Value
Age (years)			
Mean (SD)	54.8 (3.7)	58.9 (1.2)	0.86
Gender			
Male (n=114)	12	102	1.000
Female (n=71)	7	64	
Smoking history (BI)			
Mean (SD)	412 (129)	444 (45)	0.59
Performance status			
0 (n=165)	17	148	1.000
1 (n=20)	2	18	
FEV1.0 (ml)			
Mean (SD)	2700 (0.16)	2462 (0.06)	0.08
FEV1.0%			
Mean (SD)	80.5 (2.4)	76.6 (0.8)	0.06
Primary tumor, n			
Carcinoma	13	141	0.10
Sarcoma	6	25	
Surgical procedure, n	W+P: 10	W: 116	
	W+S: 3	S: 20	
	W+L: 6	L: 30	

BI: Brinkman index (the number of cigarettes smoked per day multiplied by the number of years of smoking); FEV1.0: Forced expiratory volume in 1 second; W: wedge resection; S: segmentectomy; L: lobectomy.

Table II. *The types of primary tumor lesion patients who underwent unilateral or bilateral pulmonary resection for lung metastases*.

	Bilateral group (n=19)	Unilateral group (n=166)
Colorectal	5	48
Head and neck	5	32
Skeletal	3	13
Renal	2	10
Other	4	63

Table III. *Perioperative comparison between patients who underwent unilateral or bilateral pulmonary resection for lung metastases.*

Factors (n=185)	Bilateral group (n=19)	Unilateral group (n=166)	*p*-Value
Operative time (min)			
Mean (SD)	228 (20)	152 (6.9)	<0.01
Duration of drainage (days)			
Mean (SD)	2.79 (0.3)	2.08 (0.1)	<0.01
Postoperative complications			
None (n=177)	19	158	0.33
Occurred (n=8)	0	8	
Postoperative hospital stay (days)			
Mean (SD)	8.7 (0.9)	8.3 (0.3)	0.66

Table IV. *Intraoperative and postoperative variables for the bilateral group.*

Variables (n=19)	WW (n=10)	WSL (n=9)	*p*-Value
Operation time (min)			
Mean (SD)	201 (18)	260 (19)	0.03
Blood loss (g)			
Mean (SD)	35 (19)	50 (20)	0.58
Approach (most invasive)			
Thoracotomy	3	9	<0.01
VATS	7	0	
Duration of drainage (day)			
Mean (SD)	2.3 (0.3)	2.8 (0.3)	0.26
Postoperative complications	None	None	1.0
Postoperative hospital stay (day)			
Mean (SD)	8.6 (1.4)	8.9 (1.5)	0.89

VATS: Video-assisted thoracic surgery; WW: wedge resection + wedge resection; WSL: wedge resection + segmentectomy (n=3) or wedge resection + lobectomy (n=6).

(range=1,400-4,720) ml and 2462 (range=570-4,280) ml in the bilateral and unilateral groups, respectively, with the FEV1.0% being 80.5% and 76.6%, respectively. There was no significant difference with regard to FEV1.0 and FEV1.0%. Sarcoma accounted for 32% (6/19) of primary lesions in the bilateral group and 15% of lesions (25/166) in the unilateral group. These details are shown in Table II. In all cases in the bilateral group, wedge resection was performed on one side, and on the opposite side, wedge resection was performed for 10 cases, segmentectomy for three cases, and lobectomy for six cases.

Comparison of perioperative safety between unilateral and bilateral groups. We investigated the safety of synchronous bilateral lung resection by comparing perioperative variables, including operative time, duration of drainage and postoperative course between the bilateral and unilateral groups. As shown in Table III, operative time and duration of chest drain tube use were significantly longer in the bilateral group than those in the unilateral group (220±20 *vs*. 152±6.9 min and 2.79±0.3 *vs*. 2.08±0.1 days; both p<0.01). However, there was no significant difference in postoperative hospital stay between the two groups (8.7±0.9 *vs*. 8.3±0.3; *p*=0.66). In addition, postoperative complications were not observed in the bilateral group, while in the unilateral group, complications were found in eight cases (4.8%). Prolonged lung fistula, pneumonia and wound trouble were observed in three, two and three patients, respectively.

Intraoperative and postoperative variables for the bilateral group. Next, we examined whether segmentectomy or lobectomy could be safely performed on one side in patients undergoing simultaneous bilateral pulmonary resection (Table IV). We divided the bilateral group into the aforementioned WW (n=10) and WSL (n=9) groups. As a matter of course, operative time in the WSL group was significantly longer than that in the WW group (*p*=0.03). In the WSL group, mean blood loss was 50±20 g (range=1-203 g), and no significant difference was found in comparison with the WW group (*p*=0.58). We investigated the most invasive surgical approach: for example, the most invasive approach for wedge resection under VATS on one side and lobectomy under thoracotomy on the opposite side is thoracotomy. For the WW group, 70% (7/10) of procedures were VATS performed on both sides. As mentioned in the previous section, postoperative complications were not identified in either group and there were no incidents of perioperative death. Despite segmentectomy or lobectomy having been performed, the mean drainage days in the WSL groups was 2.8±0.3 days and was not significantly longer than that of the WW group (*p*=0.26). Moreover, postoperative hospital days did not significantly differ between groups (WW *vs*. WSL; 8.6±1.4 *vs*. 8.9±1.5 days: *p*=0.89).

Discussion

In the present study, we showed that compared with unilateral pulmonary resection for metastatic lung tumors, simultaneous bilateral pulmonary resection is a safe procedure as long as only wedge resection is performed on at least one side. Surgical resection for metastatic lung tumor contributes not only to confirming an exact diagnosis (6) but is also a potentially curative treatment (7-11). However, until the 1960s, patients with bilateral lung lesions were believed to have a poor prognosis, and therefore were not indicated for surgery (12). Advances in preoperative radiographic imaging modalities and improvement of surgical instruments

Table V. *Previous studies which is analyzed safety and efficacy for one-stage bilateral pulmonary resection.*

	Number of cases	Complications	Duration of drainage days	Postoperative in-hospital stay (days)
Mun M. *et al*. 2008 (18)	19	3/19 (15.8%)	Not mentioned	14.3
Mizuno Y. *et al*. 2014 (20)	24	4/24 (16.7%)	3.4±1.2	10.0±4.7
Yao F. *et al*. 2016 (19)	29	9/29 (31%)	4.0±1.2	7.3±1.8
Present study	19	0/19 (0%)	2.8±0.3	8.7±0.9

have contributed to an increased applicability of operation for bilateral lung lesions (13). However, it remains unclear whether it is safe to resect bilateral pulmonary metastases simultaneously.

According to a web-based questionnaire by the European Society of Thoracic Surgeons (ESTS) Pulmonary Metastasectomy Working Group in 2008 (14), in the case of bilateral disease, 146 members of ESTS responded that the most favorable approach was bilateral two-staged thoracotomy (66.2%). The second most popular approach, one-stage median sternotomy, was selected by 39 members (26.9%). When approaching bilateral lesions simultaneously, median sternotomy was evaluated as an effective approach in the 1980s (15-17). Roth *et al*. researched patients who underwent sternotomy for metastatic soft-tissue sarcoma tumors of the lung and concluded that median sternotomy allowed exploration for unsuspected diseases on the opposite side, which avoided the need for a second operation (15). Furthermore, Van der Veen *et al*. suggested that median sternotomy was chosen for the pulmonary resection because it allows a one-stage complete operation, lower morbidity, and the discovery of hidden metastases (16). However, recent progress in surgical procedures and instruments have encouraged surgeons to perform simultaneous bilateral pulmonary metastasectomy for patients with synchronous bilateral metastatic lung tumors. Previous reports on the risk of bilateral simultaneous pulmonary resection for pulmonary metastases or primary lung tumors are summarized in Table V. Mun *et al*. surveyed 19 cases with synchronous bilateral multiple lung cancer (18). Five cases underwent median sternotomy and another 14 cases underwent VATS, and all cases underwent wedge resection on at least one side. In two out of 19 cases, postoperative complications (pneumonia and interstitial pneumonia progression) occurred. The report demonstrated that mean postoperative hospitalization was 14.3 days (range=4-113 days); however, it did not mention the duration of chest drainage, which seems critical in considering the safety of simultaneous bilateral lung resection. In addition, Yao *et al*. reviewed 29 patients who underwent single-stage pulmonary resection under VATS (19) compared to two-stage resections. In terms of postoperative complications, they concluded that the one-stage strategy was more tolerable compared with the two-stage operation (p=0.944). The mean duration of chest tube drainage in patients who underwent the one-stage operation was 4.0±1.2 days, which was not different from that in patients who underwent the two-stage operation. There was a significant decrease in postoperative in-hospital stay for patients who underwent one-stage bilateral pulmonary resection in comparison with that in patients who underwent a two-stage operation (mean=7.3±1.2 *vs*. 7.3±3.2 days: p=0.009). In our study, the mean operative time and duration of chest tube drainage in the bilateral group was significant longer than that in the unilateral group (both p<0.01). There were no postoperative complications in the bilateral group, and there was no statistical difference in postoperative hospital stay after surgery (p=0.66). These results and previous reports indicate that simultaneous bilateral lung metastasectomy has been a tolerable surgical option compared with two-staged lung metastasectomy.

Table VI. *Proposed indication criteria for single-stage bilateral pulmonary resection for bilateral metastatic lung tumors.*

1. The patient must be a good risk for pulmonary resection
2. The primary lesion must be controlled
3. No other metastatic disease; or if present, it can be controlled by surgery or another treatment modality
4. All pulmonary lesions are resectable by wedge resection on at least one side

We also showed that simultaneous bilateral pulmonary metastasectomy with anatomical resection in one side can be safely performed in selected patients. Mean operative time was significantly longer in the WSL group than in the WW group (p=0.03), but there was no statistical difference in blood loss between the groups (50±20 *vs*. 35±19 g, p=0.58). In terms of postoperative course, duration of drainage and postoperative in-hospital days were not significantly different (p=0.26 and 0.89, respectively). In the present series, we performed two-stage operations for the patients who need bilateral anatomical resections. As Mun *et al*. suggested (18), we presently think that

simultaneous bilateral lobectomy should be performed in two stages because of the invasiveness and risk.

Thomford *et al*. established the four operative indications for pulmonary metastases from malignant tumors (3). We propose a modified version of Thomford *et al*.'s criteria for simultaneous bilateral lung metastasectomy in Table VI. The above three indications in Table VI, which are almost same as Thomford *et al*.'s criteria, are important factors for undertaking pulmonary metastasectomy. The most important indication for undertaking simultaneous bilateral pulmonary metastasectomy is that all pulmonary lesions should be resectable by wedge resection on at least one side. Anatomical pulmonary resection can be performed if the lesion on at least one side is resectable by wedge resection.

Limitations

The retrospective design of this study to analyze the safety of single-stage pulmonary metastasectomy is a limitation because the patient background is biased.

Conclusion

Simultaneous bilateral pulmonary resection can be performed safely. A prospective study is needed to compare one-stage and two-stage resection for bilateral pulmonary metastases.

Funding

This study was not funded externally.

Conflict of Interest

None declared.

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Received December 21, 2017
Revised January 18, 2018
Accepted January 25, 2018