Original Article

Surgical approach and outcomes for treatment of pulmonary metastases

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Abstract:

AIMS: To investigate the surgical approach and outcomes, as well as prognostic factors for pulmonary metastasectomy.

METHODS: Clinical data of 201 patients treated by pulmonary metastasectomy between January 1990 and December 2009 were retrospectively reviewed. One hundred thirty three patients were received an approach of thoracotomy while 68 with video-assisted thoracoscopic surgery (VATS). There were 54 lobectomies, 139 wedge resections and 8 pneumonectomies. Hilar or mediastinal lymph nodes dissection or sampling was carried out in 38 patients with lobectomy. The Kaplan-Meier method was used for the survival analysis. Cox proportional hazards model was used for multivariate analysis.

RESULTS: The 5 years survival rate of patients after metastasectomy was 50.5%, and the median survival time was 65.9 months. The median survival time of patients with hilar or mediastinal lymph nodes metastasis was 23 months. By univariate analysis, significant prognostic factors included disease-free interval (DFI), number of metastases, number of affected lobe, surgical approach (open vs. VATS) and pathology types. DFI, number of metastases, and pathology types were revealed by Cox multivariate analysis as independent prognostic factors.

CONCLUSION: Surgical resection of pulmonary metastases is safe and effective. Palpation of the lung is still seen as necessary to detect the occult nodule. More accurate and sensitive pre-operative mediastinal staging are required.

Key words:

Prognosis, pulmonary metastasis, surgery

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The lung is a common site of malignant tumor metastasis. Surgical resection of pulmonary metastases is a safe and effective treatment.[1,2] However, the use of video-assisted thoracoscopic surgery (VATS) in surgical approaches to lung metastases is a controversial topic.[3] For example, the differences in therapeutic effect between VATS and conventional thoracotomy are unknown. Furthermore, it is not yet determined whether hilar or mediastinal lymph node dissection should be performed.[4] We retrospectively analyzed clinical and follow-up data from patients with lung metastases who underwent surgical resection in our hospital from January 1990 to December 2009 to evaluate surgical approaches and outcomes, as well as prognostic factors in the lung metastases.

Methods

The records of all patients with pulmonary metastases who underwent a pulmonary metastasectomy between January 1990 and December 2009 at Cancer Hospital, Sun Yet-Sen University were reviewed. This study was officially approved by the Ethics Committee of our hospital. There were 217 patients. Of these, 12 patients had pulmonary metastases and the primary tumor surgically removed simultaneously (1 case of tracheocarcinoma, 6 cases of esophageal carcinoma, 3 cases of malignant thymoma, 1 case of colorectal cancer, and 1 case of liver cancer). In 4 of other patients, non-pulmonary primary tumors were discovered after the pulmonary metastasectomy (1 case of testicular cancer, 1 case of ovarian cancer, 1 case of renal cancer, and 1 case of nasopharyngeal carcinoma). These 16 cases were excluded from our analysis. The remaining 201 patients were included in this study and their clinical and follow-up data were analyzed retrospectively: All patients who underwent pulmonary metastasectomy met the following criteria: (1) The primary tumor had been controlled; (2) all metastases were surgically resectable; (3) no extrapulmonary metastases were detected; (4) no other effective treatment methods were available; (5) the patients were healthy enough to tolerate surgery. Pre-surgical testing included chest and abdominal computed tomography (CT), brain CT or magnetic resonance imaging (MRI), fiberobronchoscopy, pulmonary function tests, and in some cases some patients receive positron emission computed tomograpy (PET-CT).

Surgical approach included posterolateral thoracotomy or VATS. Surgical resection consisted lobectomy, wedge resection or pneumonectomy. Some other patients who underwent lobectomy also underwent hilar and mediastinal lymph node dissection or sampling at the same time Of the 15 (7.5%) cases of bilateral lung metastases, one patient underwent bilateral metastasectomy by an approach of median sternotomy, and the remaining 14 cases underwent resection through hand-assisted thoracoscopic surgery (HATS).[5] Lung metastasis recurred in 17 (8.5%) patients. These patients underwent secondary resection of lung metastases. There were no perioperative deaths or serious complications, and 88 cases underwent postoperative chemotherapy (1-6 courses).

Follow-up

The full-time staff of the follow-up department in the hospital telephoned every treated patient. Patients who were absent from outpatient review after pulmonary metastasectomy and who did not respond to telephone follow-up with unknown survival conditions were considered as lost to follow-up. The follow-up ended on June 30, 2012. Nine cases were lost to follow-up, producing a follow-up rate of 95.5%. Disease-free interval (DFI) refers to the time from the date of the primary tumor treatment to the time at which lung metastases was found. The endpoint for our study was overall survival (OS) time, measured from the day of lung metastases surgery to the date of death or of last follow-up.

Statistical methods

In the univariate analysis, factors potentially affecting OS included the following: DFI (≤36 months vs. >36 months); number of metastases (1 vs. 2 vs. ≥3); number of lobes with metastases (single lobe vs. multiple lobes); tumor pathology (adenocarcinoma, squamous cell carcinoma, sarcoma, hepatocellular carcinoma, and others); type of surgical resection (lobectomy, wedge resection, and pneumonectomy); use of adjuvant chemotherapy after surgery (with vs. without); recurrence of lung metastases (with vs. without); and surgical approach (VATS vs. thoracotomy). SPSS 16.0 was used for statistical analysis. The Kaplan-Meier method was used for survival analysis. The log rank test was used to compare survival rates. Cox proportional hazard model was used for analyzing statistically significant factors found in the univariate analysis. A *P* value of 0.05 or less was considered statistical significance.

Results

There were 128 (63.7%) male patients and 73 (36.3) female patients, all aged between 11 and 79 years (median age of 45 years). The clinic-pathological features of all patients are shown in Table 1. There were total of 338 lesions of lung metastases resection, with a median of 1 (range: 1-8).

One hundred thirty-three (66.2%) patients underwent posterolateral thoracotomy, 68 (33.8%) VATS. Fifty four (26.9%) patients were received lobectomy, 139 (69.1%) wedge resection and 8 (4.0%) pneumonectomy. In 38 cases of lobectomy with hilar and mediastinal lymph node dissections or sampling, 11 (28.9%) cases were lymph node metastasis, of which only 7 (18.4%) cases were N1 metastasis, 4 (10.5%) cases were N1 and N2 metastasis [Table 2]. The median survival time of hilar or/and mediastinal lymph node metastasis patients (11 cases) was 23 months and the mean was 26.4 months.

The 5 years survival rate of all patients was 50.5%, with a median survival time of 65.9 months. The survival curve is shown in Figure 1. In the univariate analysis, factors potentially affecting survival are shown in Table 3. Differences caused by DFI, the number of metastases, the number of involved lobes, pathological type, and surgical approach were found to be

Table 1: Clinicopathological features of 201 cases of lung metastases

	Number of cases	%
Gender		
Male	128	63.7
Female	73	36.3
Age (year)		
Average (SD)	45.1 (14.0)	
Median (rang)	45.0 (11-79)	
Primary site		
The large intestine	51	25.4
Breast	21	10.4
Nasopharynx	26	12.9
Limbs and trunk	33	16.4
Liver	21	10.4
Uterus	13	6.5
Kidney	12	6.0
Esophagus	8	4.0
Testis	7	3.5
Bladder	2	1.0
Thymus	2	1.0
Oral cavity	2	1.0
Thyroid	1	0.5
Stomach	1	0.5
Throat	1	0.5
Total	201	100
Pathological type		
Adenocarcinoma	76	37.8
Squamous cell carcinoma	40	19.9
Sarcoma	37	18.4
Hepatocellular carcinoma	20	10.0
Others	28	13.9
Total	201	100

SD = Standard deviation

Table 2: Hilar or mediastinal lymph node metastasis

Primary tumor	Number of cases	*N*0	*N*1	*N*2
Breast cancer	6	4	2	1
Nasopharyngeal cancer	10	4	6	3
Colon cancer	8	7	1	
Gastric cancer	2	2		
Hepatic carcinoma	3	3		
Kidney cancer	3	1	2	
Cervical cancer	2	2		
Sarcoma	4	4		
Total	38	27	11	4

Table 3: Univariate analysis of factors potentially affecting survival

Influencing factors	Number of cases (%)	5-years survival rate (%)	*P* value
DFI			
≤36 months	126 (62.7)	40.5	0.000
>36 months	75 (37.3)	65.0	
Number of metastases			
1	139 (69.2)	57.8	0.000
2	35 (17.4)	49.1	
≥3	27 (13.4)	14.5	
Metastases involving the lobe			
Single lobe	151 (75.1)	57.6	0.001
Multiple lobes (including bilateral lungs)	50 (15) (24.9)	26.6	
Pathological type			
Adenocarcinoma	76 (37.8)	64.0	0.019
Squamous cell carcinoma	40 (18.9)	50.5	
Sarcoma	37 (18.4)	42.2	
Hepatocellular carcinoma	20 (10.0)	39.4	
Others	28 (13.9)	35.7	
Surgical resection type			
Lobectomy	54 (26.9)	51.4	0.927
Wedge resection	139 (69.1)	51.4	
Pneumonectomy	8 (4.0)	46.9	
Postoperative adjuvant chemotherapy			
Without	108 (53.7)	48.2	0.261
With	93 (46.3)	53.3	
Recurrence of the lung metastases			
Without	172 (85.6)	49.1	0.771
With	29 (14.4)	58.0	
Surgical methods			
Thoracotomy	133 (66.2)	56.4	0.004
VATS	68 (33.8)	37.9	

DFI = Disease-free interval, VATS = Video-assisted thoracoscopic surgery

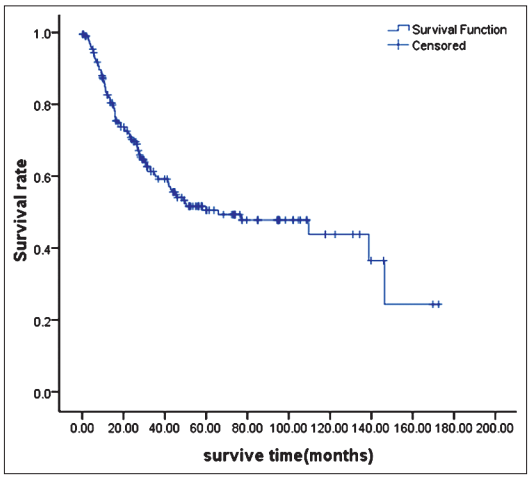

Figure 1: Overall survival curves in patients underwent pulmonary metastasectomy

statistically significant. When various factors were incorporated into the Cox proportional hazards model for multivariate analysis, DFI, number of metastases, and pathological type remained as independent prognostic factors [Table 4].

Table 4: Multivariate analysis of factors affecting survival

Influencing factors	Exp. (β) (HR)	95% CI for Exp. (β)	*P* value
DFI (≤36 months vs. >36 months)	0.446	0.273-0.727	0.001
Number of metastases (1 vs. 2 vs. ≥3)	1.602	1.220-2.104	0.001
Pathological type*	1.106	1.011-1.209	0.028

*Adenocarcinoma versus squamous cell carcinoma versus sarcoma versus hepatocellular carcinoma versus other, DFI = Disease-free interval, Exp. = Experiences, CI = Confidence interval, HR = Hazard ratio

Discussion

The lung is one of the most common sites of metastases in many malignancies. For metastases that are insensitive to chemotherapy or radiotherapy, surgery is the main treatment. In patients in whom the primary tumor can be controlled and who can tolerate surgery, complete resection of the metastases can significantly improve the survival rate. The results of this study show the 5 years survival rate after complete resection of lung metastases to be 50.5%. The 5 years survival rates of the surgical resection of lung metastases from epithelial malignancies were reported by Monteiro, *et al.* and Rena, *et al.* to be 47.4% and 43%, respectively.[6,7] Among the 5206 cases of the internationally registered patients with lung metastases, the 5, 10 and 15-years survival rates after complete resection were 36%, 26%, and 22%, respectively.[1]

The emergence of VATS has led to its widespread usage in the resection of lung metastases. In the present group, 33.8% of patients underwent VATS resection. The survival rate of these patients was significantly different from that of patients who underwent traditional thoracotomy, when evaluated using univariate analysis, but this statistical significance disappeared under multivariate analysis. This is consistent with most reports.[1,6] Some retrospective studies found survival for patients through VATS lung metastases resection was better than that through thoracotomy.[8,9] The efficacy between traditional thoracotomy and VATS in the lung metastasis resection is still controversial. What is uncertain is whether VATS can detect small lesions, which are usually located through manual palpation during open chest thoracotomy. With the help of CT or PET-CT, the number and location of metastases can be determined preoperatively. However, Fortes, *et al*. found that 32.5% of malignant nodules went undetected by PET-CT (sensitivity of 67.5%)[10] and that 50% could not be detected by CT.[5] McCormack, *et al*. reported that VATS could only find 22% of pulmonary nodules.[11] These results showed that the use of VATS cannot completely detect nodules hidden in the lung parenchyma, resulting in incomplete resection and ultimately affecting curative. Based on these shortcomings, the working group of the European society of thoracic surgeon recommended that VATS only be used as a diagnostic tool and that intraoperative manual palpation remain the primary means of detecting pulmonary nodules, facilitating complete resection of metastases.[3] In one case, our group had found metastatic nodules as small as 2 mm using HATS.[5]

Pulmonary wedge resection is the most common surgical procedure for the lung metastases. Hilar and mediastinal lymph node dissections are not convention. Only suspicious enlarged lymph nodes found during surgery are resected using this method. This causes the large differences in the rates of hilar and mediastinal lymph node metastasis reported in the literature.[4] There were 38 cases of hilar and mediastinal lymph node dissection or sampling in our patient group and a lymph-node-positive rate of 28.9%. Due to the small number of cases, the survival rates were not compared. The median survival period was only 23 months. Garcia-Yuse summed up 742 patients in relevant studies in which 163 patients (22%) had hilar or mediastinal lymph node metastasis, neither of which had previously been considered associated with these types of the primary tumor.[4] Pulmonary metastases accompanied by mediastinal or hilar lymph node metastasis have a poor prognosis. Veronesi, *et al*. reported a group of patients who underwent resection of lung metastases with simultaneous mediastinal and hilar lymph node dissection or sampling. Among these patients, 20% had hilar or mediastinal lymph node metastasis, 8% had N1 metastasis, and 12% had N2 metastasis.[12] The 5 years survival rate of patients with N0, N1, and N2 metastases were 60%, 17%, and 0%, respectively. In undergoing resection of pulmonary metastases from the colorectal cancer, Welter, *et al*.[13] found hilar and mediastinal lymph node involvement can affect prognosis: The 5 years survival rate for patients without lymph node involvement was 78.5%, 0% for those with hilar or/and mediastinal lymph node involvement. These patients did not appear to benefit from surgery. However, whether hilar or mediastinal lymph node metastases are contraindications for surgical resection remains controversial. Pfannschmidt found resection of lymph node metastases to prevent further spread of tumor cells and maintains that surgery should remain an important part of systemic treatment.[14] However, most scholars believe that the surgery does not change the development of the disease and advocate pre-operative assessment of mediastinal lymph nodes, including PET-CT or mediastinoscopy. They believe that surgical resection is not suitable for cases in, which lymph node metastases have been found.[4,15] Resection was not found to be efficacious in our group of hilar and mediastinal lymph node metastasis patients. For this reason, we also maintain that other multidisciplinary modality should be used in these patients.

The results of this study showed the DFI and the number of metastases to be independent prognostic factors. Short DFI was found to be associated with the high rates of malignancy, fast metastasis, and poor prognosis. The survival rate for patients with DFI greater than 3 years was significantly higher than those with DFI less than 3 years. This is consistent with most previous reports.[1,6,7] The prognosis of patients with a single metastasis was significantly better than that of patients with the multiple metastases.[16] There is no clear standard for the minimum number of metastases necessary to undergo surgery. It is generally believed that surgical resection may be performed as long as the tumor can be completely removed and patients can physically tolerate surgery.[17]

As in some previous reports, the pathological type of the tumor is a prognostic factor.[1,18,19] However, there are also reports indicating that pathological type is irrelevant to prognosis.[6,7]

In summary, the surgical removal of lung metastases is safe and effective. It seems that intraoperative manual palpation is still necessary to detect minor pulmonary nodules. Further clinical study is needed to seek a suitable alternative method instead of palpation. Accurate assessment of the mediastinal lymph nodes before surgery is necessary to determine if surgical intervention is indicated.

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