

Management of Lung Metastases from Colorectal Cancer: Video-Assisted Thoracoscopic Surgery versus Thoracotomy—A Case-Matched Study

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Abstract

Objectives The benefits of video-assisted thoracoscopic surgery (VATS) for performing pulmonary metastasectomy are considered controversial. This case-matched study aimed to compare long-term outcomes after surgical resection of pulmonary metastases from colorectal cancer using different approaches (VATS vs. thoracotomy).

Methods Between 1997 and 2008, 143 patients with colorectal cancer who had received their first pulmonary metastasectomy were selected. Fifty-three patients underwent a surgical procedure that utilized a thoracotomy approach (Group 1), and 90 patients underwent a surgical procedure that used a VATS-based approach (Group 2). After being matched for tumor number, diameter (measured by computed tomography), and surgical procedure (wedge resection or lobectomy), 35 pairs of patients were finally enrolled. Study endpoints included tumor recurrence and survival.

Results There was no hospital mortality in both groups. Within the mean follow-up period of 50 months, 47.1% patients developed a recurrence (52% at the pulmonary level and 48% at systemic level), and 52.9% of the patients were alive at the time of analysis. There was no difference between Groups 1 and 2 in terms of overall recurrences (54 vs. 40%, $p = 0.23$), all pulmonary recurrences (25.7 vs. 22.9%, $p = 0.78$), and same side lung recurrences (14.3 vs. 20%, $p = 0.75$). The 5-year overall survival (OS) after lung resection was 43 and 51% in Groups 1 and 2, respectively ($p = 0.21$).

Conclusions Our case-matched study showed that survival outcome of pulmonary metastasectomy using VATS is not inferior to that of open thoracotomy in selected cases.

Keywords

- ▶ VATS
- ▶ thoracotomy
- ▶ pulmonary metastasectomy

Surgical treatment for patients with pulmonary metastasis from colorectal cancer has been well documented, with a 5-year survival rate of ~30 to 40%.^{1–3} A number of key factors are thought to influence a patient's postoperative survival following pulmonary metastasectomy in colorectal carcino-

ma. These factors include aspects such as the extent of lung lesion (size and number), serum titer of carcinoembryonic antigens(CEA), and disease-free interval(DFI) between treatment of the primary lesion and detection of pulmonary metastasis.^{1–6} However, few studies have evaluated the

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efficacy of alternative surgical approaches (thoracotomy or video-assisted thoracoscopic surgery [VATS]).

Thus far, open thoracotomy is the most commonly used surgical approach for colorectal pulmonary metastasectomy (► **Table 1**).^{4,6-10} This approach allows manual palpation of the lung parenchyma, thus enabling detection of occult metastases that may have been undetected by preoperative computed tomography (CT). In contrast, the VATS approach is highly dependent on preoperative image localization and intraoperative instrumental palpation. The potential of missing small metastatic lesions with the VATS approach has often been discussed.¹¹⁻¹³

Despite these limitations, VATS is being utilized more and more frequently because of the benefit of a smaller, less painful incision, and a shorter hospital stay. Oncological concerns in terms of pulmonary recurrence and survival supporting this approach are weak. Few studies have directly compared the survival outcome after VATS to that of open thoracotomy.^{14,15} Patient characteristics (tumor number, laterality, and surgical procedure) between VATS and thoracotomy groups in the existing studies were different and selection bias could not be avoided.^{14,15} Moreover, none of the previous studies focused on colorectal cancer.

To eliminate factors that could influence the results, we conducted a case-matched study that allowed us to select patients according to the tumor characteristics (number, size, and laterality defined by preoperative CT) and surgical procedure (lobectomy or wedge resection). We compared tumor recurrence rate and overall survival to assess whether our belief, that VATS is not an oncological compromise, was true.

Material and Methods

Patients

This study recruited patients receiving pulmonary metastasectomy due to colorectal cancer in the Division of Thoracic Surgery from 1997 to 2008. We excluded patients who had previous pulmonary metastasectomy, incomplete resection, or biopsy procedure.

Patients included in the study were then divided into two groups based on the surgical approach used. Patients in Group 1 received thoracotomy and those in Group 2 received VATS. The clinical information was gathered from the computerized

database, medical charts, and telephone interviews. The exemption for retrospective review and data collection methods was made by the Institutional Review Board on July 1, 2010 (CGMH IRB: 99-3022B).

Case-Match Methods

Group 1 patients were individually matched to Group 2 patients on the bases of image characteristics (tumor number, size, laterality) and surgical procedure (wedge resection or lobectomy). The greatest difference in diameter allowed in each pair was limited to 5 mm.

Chest CT has been a crucial preoperative diagnostic tool for identifying the number, location, and size of pulmonary metastases. Chest CT also plays an important role in determining the surgical approach. Thus, our case-match was based on preoperative CT imaging but not on postoperative pathological findings.

VATS has been the preferred approach for most metastatic origin lung cancer since 1993.¹² Preoperative CT-guided hook-wire localization for tiny nodules was also used since 1998 to facilitate VATS resection.¹⁶ Thoracotomy was mostly reserved for cases with central or large lesions. Occasionally, some patients may choose the thoracotomy approach despite the tumor being operable by VATS due to economical concerns because the mechanical stapler used for thoracoscopic lung resection was not covered by the National insurance system in Taiwan until June 2008. It was this choice that allowed us to perform case-matching in our study.

Operative Technique

In Group 1, either posterolateral thoracotomy or lateral thoracotomy (10 to 20 cm, in the fourth or fifth intercostals thoracotomy without rib resection) was performed in patients with bilateral and unilateral lung metastases. We palpated the whole lung to detect all nodules before pulmonary resection in the open operation.

In Group 2, we used three-port VATS in the standard "inverted triangle" position (with two 10-mm working ports in the fifth intercostal space between the scapula tip and anterior axillary line and a 10-mm 0° video thoracoscope in the sixth or seventh intercostal space in the anterior axillary line or approximately midway between the working ports) along with one-lung ventilation and lateral decubitus

Table 1 Published Series and Specified VATS/Thoracotomy Numbers for Colorectal Metastectomy

Year/author	Study Period	Case Number	Solitary/Multiple Metastases	Thoracotomy/VATS/Others	Unilateral/Bilateral Resection	Limited Resection/Lobectomy	Survival (5-Year OS)
2003/Pfannschmidt ⁴	1985-2000	167	84/83	104/2/61	85/80	141/74	32%
2006/Yedibela ⁹	1978-2003	141	101/40	135/6/0	120/21	87/54	37%
2007/Nakajima ⁸	1999-2005	122	77/45	43/79/0	129/17	120/26	NA
2007/Welter ⁷	1993-2003	175	NA	169/0/6	NA	199/65	39%
2009/Rama ⁶	1988-2005	61	37/24	93/0/1	79/15	75/19	48%

OS, overall survival; NA, not available.

Table 2 Clinical Characteristics of Group 1 and 2 (Before Case-Matching)

	Group 1 (Thoracotomy)	Group 2 (VATS)	<i>p</i> Value
Case number	53	90	NA
Male: Female	35/18	49/41	0.17
Largest Tumor size	3.86 ±1.93	2.58 ±1.19	< 0.001
Tumor number			
Single	39	71	0.47
Multiple	14	19	
Unilateral/Bilateral	48/5	84/6	<0.001
Surgical procedure			< 0.001
Pneumonectomy	1	0	
Lobectomy	17	5	
Wedge resection	35	85	

NA, not available.

position. Preoperative CT-guide hook localization was performed if the nodule was small or deep in the parenchyma in patients in the VATS group. In all cases, the wedge resection or lobectomy was performed using linear staplers (Endo-GIA, USCC-Tyco Healthcare).

Either through open thoracotomy or VATS, pulmonary wedge resection was performed to resect peripherally located pulmonary nodules with a safety margin. If the pulmonary nodule was located deep in the parenchyma, we performed lobectomy to remove the nodule, either through thoracotomy or VATS. Lymph node sampling was not routinely performed unless mediastinal lymphadenopathy found on preoperative image or intraoperatively.

Postoperative Surveillance

After the operation, patients received adjuvant chemotherapy following our colorectal cancer treatment guideline. Follow-up protocol included chest radiograph every 3 months and CT scans every 6 months. The recurrence was radiographically documented and histologically confirmed, if feasible. Follow-up data was obtained from medical records and referring physicians. Survival data was updated every 3 months. For missing cases, the National Cancer Registry Database of Taiwan was used to update follow-up information. Data analysis was closed on July 1, 2010.

Statistical Analysis

The data are presented as median (range) and number (%) unless stated. A Student's *t*-test was used for continuous data and a Pearson χ^2 test or Fisher χ^2 exact test was used for categorical data. OS was calculated from the date of pulmonary metastectomy to the date of last follow-up or death. Postoperative survival was plotted according to the Kaplan-Meier method and any difference in survival between the groups was evaluated using the Log-Rank test. Statistical significance was defined by *p*-values of <0.05 throughout the study. All statistical analyses were performed using SPSS 12.0 software (SPSS Inc., Chicago, IL).

Results

General Characteristics of the Groups (Before and After Matching)

In all, there were 143 cases. Fifty-three patients were in Group 1 (thoracotomy) and 90 patients were in Group 2 (VATS). Thirty-five patients in Group 1 were able to match to another 35 patients in Group 2 according to the selection criteria stated above. Thus, 70 patients were enrolled finally.

The demographic data of the two groups before and after case matching were presented in ► **Tables 2** and **3**, respectively. Before matching (► **Table 2**), tumor sizes were bigger and more pneumonectomy/lobectomy and bilateral procedures were performed in the thoracotomy group. After case-matching (► **Table 3**), the two groups became homogenous. Twenty-eight pairs of patients had single lesions; four pairs with two lesions, two pairs with three lesions and two pairs with four lesions. There were no differences in the initial stage, disease-free interval between resection of primary tumor and lung metastases, and preoperative CEA level between two groups.

Surgical Details of the Two Groups

All patients in Group 2 underwent complete tumor resection by VATS without the need of conversion to thoracotomy. Three cases in the thoracotomy group had additional pulmonary nodules detected by intraoperative manual palpation. Sixteen patients in Group 1 and 11 patients in Gr2 received lymph node sampling (*p* > 0.05). With similar tumor size, the nearest resection margin (measured from tumor edge to staple line) on wedge-resection specimen was significantly shorter in VATS group (*p* < 0.05).

The perioperative course was smooth and there was no hospital mortality in either group. Only three patients did not receive postoperative adjuvant chemotherapy (two in Group 1 and one in Group 2)

Survival and Tumor Recurrence

With the mean follow-up of 50 months, 37 patients (52.9%) were alive at the time of the study. The 5-year OS was 50.7%.

Table 3 Clinical Characteristics and Recurrence Pattern of Group 1 and 2 (After Case-Matching)

	Group 1 (Thoracotomy)	Group 2 (VATS)	p Value
Case number	35	35	NA
Male: Female	22/13	17/18	0.23
Initial stage			0.385
Duke B	8	13	
Duke C	22	19	
Duke D	5	3	
DFI			1.00
<36 month	19	20	
≥36 months	16	15	
Preop CEA level			0.56
<5 ng/mL	17	13	
≥5 ng/mL	15	17	
unknown	3	5	
Tumor size (cm)	3.25 ± 1.56	3.17 ± 1.25	*
Tumor number			*
Single	28	28	
Multiple	7	7	
Unilateral/Bilateral	32/3	32/3	*
Surgical procedure			*
Lobectomy	6	4	
Wedge resection	29	31	
Lymph node sampling			0.326
Yes	16	11	
No	19	24	
Lymph node metastases			0.47
Positive	6	4	
Negative	10	7	
Unknown	19	24	
Mean Tumor number resected	1.46 ± 1.19	1.43 ± 1.03	0.82
Nearest staple margin (cm)	0.89 ± 0.54	0.44 ± 0.28	0.01
Postop adjuvant therapy			1.0
Yes	33	34	
No	2	1	
Ipsilateral lung recurrence (%)	5(14.3)	7(20)	0.75
All pulmonary recurrence (%)	9(25.7)	8(22.9)	0.78
All recurrence (%)	19(54)	14(40)	0.23

*Case match item.

NA, not available; DFI, disease free interval; CEA, carcinoembryonic antigens.

There was no significant difference observed in OS (42 vs. 58%, $p = 0.22$) between the two groups (► **Fig. 1**).

Total 47.1% of patients developed tumor recurrence (52% at pulmonary and 48% at systemic). There was no difference between Groups 1 and 2 in terms of overall recurrences (54 vs. 40%, $p = 0.23$), all pulmonary recurrences (25.7 vs. 22.9%, $p = 0.78$), and same side lung recurrences (14.3 vs. 20%, $p = 0.75$) (► **Table 3**).

Surgical Approach for Repeat Pulmonary Metastasectomy

Among the 17 patients that developed pulmonary recurrence following their operation, 10 received repeat pulmonary

metastasectomy (four in the thoracotomy group and six in the VATS group). Four ipsilateral pulmonary recurrences were resected via VATS and two by thoracotomy.

Discussion

VATS is a well-established surgical approach for use in the thoracic cavity. It has been shown to have similar oncological results and lesser operative pain when compared with the thoracotomy approach in early stage primary lung cancer.¹⁷ In contrast, despite the common use of VATS in pulmonary metastasectomy during our daily practice, oncological evidences supporting the application of this

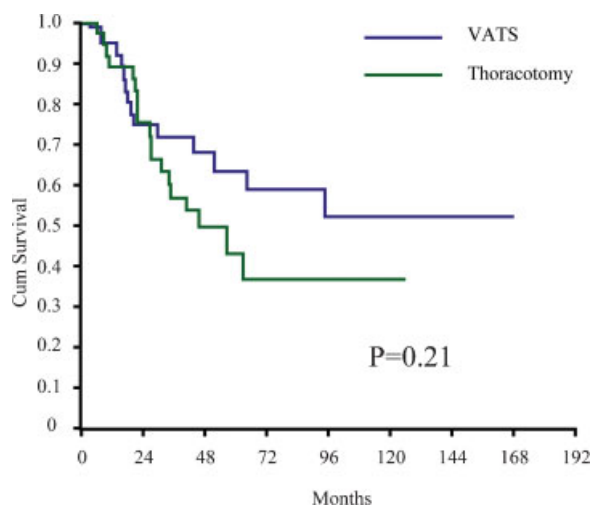


Figure 1 Overall survival between VATS and thoracotomy group.

approach to pulmonary metastasectomy were limited. To the best of our knowledge, there were two larger studies that directly compared the oncological outcomes after different surgical approaches (►Table 4).^{14,15} Unfortunately, these studies had important caveats, including diverse primary cancer type and significant intergroup tumor size/number/laterality variation. It was thought that these factors may have had a significant influence on the survival outcome of the patients included in these studies (►Table 4).^{14,15} Indeed, as shown in our prematched data (►Table 2), they could not be compared directly because of the possible underlying selection bias. In the current study, we focused on colorectal cancer to eliminate the diverse characteristics of pulmonary metastases from the other organs. More importantly, through our case-matched design, we showed that VATS is not inferior to thoracotomy in terms of disease recurrence and survival.

Open thoracotomy offers reasonable access to all areas of the hemithorax. This allows surgeons to accomplish wedge resections and anatomic resections with direct observation of the affected tissues. On the contrary, the major problem with VATS is that the thoroughness of the exploration may be called into question.^{11,13} Although lung parenchyma palpation during VATS could be accomplished by inserting finger through one of the ports assisted by placing instrument through another port to move the lung toward the examining finger, there were still limitations in palpating small and deep lesions. Our earlier report showed a high rate of conversion from VATS to thoracotomy because of a failure to localize small pulmonary nodules ≤ 10 mm in size or ≥ 5 mm deep.¹² Other studies also have shown that an inability to perform hand palpation through VATS incision might cause small pulmonary nodules, which were not detected by the chest CT, to be missed.^{11,13} Some authors further postulated that the use of VATS would result in early pulmonary recurrence but statistical evidence supporting this hypothesis was weak.¹¹ Interest-

ly, all previous studies showed a higher percentage (10~30%) of ipsilateral side pulmonary recurrence after thoracotomy than was observed in VATS.^{8,14,15} Because they applied thoracotomy for multiple and bilateral nodules and VATS for single peripheral nodule, the 30% difference in favor of VATS could not be attributed only to the use of a different surgical approach. In our study, after precise case-matching, we found that 20.2% of the patients included in the VATS group and 14.8% of the patients included in the open thoracotomy group showed new pulmonary metastases at the same side of lung that had been operated on. An unexpected finding was the closer surgical resection margin in the VATS group. This finding has not been recorded in any previous studies. We could not conclude that the 5% difference was related to a missing nodule or a shorter margin. But with the emerging advances in medical devices and surgical techniques, we believed the benefit of thoracotomy might be limited. First, the use of helical CT has been shown to improve detection of smaller pulmonary nodules when compared with conventional CT. Overestimation of the number of intrapulmonary nodules has recently become more problematic than underestimation. Preoperative CT guide hook-wire localization or methyl-blue injection also facilitates the resection of deep or tiny nodules without finger palpation.^{16,18} Second, despite the very small possibility of missing small metastatic nodules, the well-documented equal survival benefit after a second-resection and the smaller amount of postoperative adhesion made repeat surgery much less detrimental to the patient.^{1,19,20} Third, the introduction of new mechanical staples with wider proximal-to-distal jaw aperture and a flexible articulation angle also helps us to resect thicker lung parenchyma and provided an adequately large safe margin during wedge resection.

Another important finding that supports the VATS approach was the disease recurrence pattern after metastasectomy. As contralateral and extra-pulmonary recurrence accounted for the majority of postoperative recurrence in most studies, survival could not be improved significantly using only manual palpation of the ipsilateral lung parenchyma through thoracotomy. From a tumor biology standpoint, lung involvement in cancer patients is always the sign of systemic tumor spread. Pulmonary metastasectomy should be regarded as an essential part of the combined treatment. Thus, the goals of surgery would be faster recovery and an earlier return to adjuvant therapy. VATS has the well-known benefits of lesser postoperative pain, shorter length of stay, fewer adhesions at reoperation, and better compliance with adjuvant therapies.²¹ Together with the similar oncologic results documented by the current study, we believed VATS could become the standard treatment of pulmonary metastasis.

We acknowledge that there are potential sources of bias in our work. This is the result of our study being retrospective and not randomized, although being able to match individually patients in the two groups makes our study more powerful.

Table 4 Details of Published Series Which Comparing VATS and Thoracotomy for Pulmonary Metastectomy and Result of Current Study

	2001 Nakajima ¹⁵		P	2009 Carballo ¹⁴		P	2010 Chao		P
	VATS	Thoracotomy		VATS	Thoracotomy		VATS	Thoracotomy	
Case number	45	55		36	135		35	35	
Primary tumor type	Various(>6)	Various(>6)	NS	Various(>6)	Various(>6)	*	Single	Single	NS
Laterality									
Unilateral	43	27	*	34	90	*	32	32	NS
Bilateral	2	28		2	45		3	3	
Tumor number									
Single	34	14	*	20	28	*	7	7	NS
Multiple	11	41		16	107		28	28	
Surgical procedure									
Wedge resection	42	17	*	30	88	*	31	29	NS
Others	3	38		6	47		4	6	
Ipsilateral pulmonary recurrence (%)	9	18	NS	NA	NA	NA	20	14.3	NS
All pulmonary recurrence (%)	49	62	NS	28	43.7	NS	22.9	25.7	NS
5-year Survival (%)	62.3 [†]	52.7 [†]	NS	69.6	58.8	NS	42	58	NS

[†]p < 0.05.

[‡]3-year survival.

NS, not significant; NA, not available.

Conclusions

The similar oncological results documented by the current case-matched study show that VATS is not inferior to open thoracotomy for treating pulmonary metastasis from colorectal cancer in selected cases.

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