

The prognostic impact of pulmonary metastasectomy in recurrent gynecologic cancers: a retrospective single-institution study

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ABSTRACT

The aim was to examine the impact of pulmonary metastasectomy in patients with recurrent gynecologic cancers. Thirty-seven patients with isolated lung metastases (< 3 nodules) in recurrent epithelial gynecologic cancers were treated at Nagoya University Hospital between 1985 and 2013. The clinicopathological data for the 23 patients who underwent surgical resection were retrospectively analyzed, and their survival was compared with patients who received chemotherapy only. The median age at the time of surgery was 56 years (range 28–77). The studied population comprised 7 patients with 2 or 3 nodules and 8 patients with chemoresistant tumors, including fourteen cervical, 4 endometrial, and 5 ovarian primary tumors, with 5-year overall survivals (OSs) after surgery of 61, 100, and 100%, respectively. The survival of recurrence-free interval after initial treatment (>2 years) was significantly favorable (5-year OS 100% vs. 41.7%, $p=0.006$). Among the 6 patients with re-recurrence of lung metastases, 5 patients underwent a second pulmonary metastasectomy, and all of the patients are currently alive without disease. None of the 29 operations yielded severe complications. Although the survival rate showed a tendency to be higher in the surgery group than in the chemotherapy-only group, no significant difference was observed (5-year OS 81.7% vs. 49.5%, $p=0.072$). Our results indicate that pulmonary metastasectomy contributed to long-term survival with a low-risk of complications. Surgery to remove isolated lung metastases might provide a favorable prognosis for patients with long recurrence-free intervals and for patients with chemoresistant or re-recurrent tumors.

Key Words: pulmonary metastasectomy, lung metastasis, prognosis, uterine cancer, ovarian cancer

INTRODUCTION

Metastatic lung cancers, with the exception of sarcomas, have been reported to primarily originate in the colon, rectum, kidney, and breast, whereas the rate of metastasis of gynecologic cancers is relatively low.^{1, 2)} In gynecologic cancers, the rate of lung metastasis is higher in

Received: February 17, 2015; accepted: April 22, 2015

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patients with choriocarcinoma³⁾ or sarcoma^{4, 5)} than in patients with epithelial gynecologic cancers, such as cervical, endometrial or ovarian carcinoma.⁶⁻¹⁰⁾ In addition, the frequency of cases with isolated lung metastasis is low in patients with recurrent epithelial tumors because most tumors in these patients metastasize to the pelvis, vagina, peritoneum, or lymph nodes. Therefore, the first line of treatment for these patients is often chemotherapy.¹¹⁾ As a surgical treatment for patients with recurrent endometrial carcinoma, it has been reported that reductive surgery of the central pelvis-vagina area, when it is the only site of recurrence other than the lungs, is significantly associated with survival.¹²⁾ However, some authors have shown a favorable prognosis after surgery for lung metastases in uterine malignancies, including sarcomas and epithelial tumors.^{2, 13, 14)} Therefore, the prognosis for patients with recurrent gynecologic epithelial cancers and isolated lung metastasis is unclear, especially regarding whether they would benefit from pulmonary resection.

The aim of our study was to analyze the long-term outcomes of pulmonary metastasectomy at a single institution with respect to clinicopathological factors in patients with recurrent gynecologic epithelial cancers.

METHODS

Between January 1985 and December 2013, 3,110 patients with epithelial gynecologic cancers were registered and treated at Nagoya University Hospital. We analyzed all patients with epithelial gynecologic cancers, including cervical, endometrial, and ovarian cancer, except germ cell tumors, choriocarcinomas, and sarcomas. Approval from the Ethics Committee of our hospital was obtained before the study was registered. A total of 166 (5.3%) of the 3,110 patients were diagnosed with lung metastasis. In this study, a lung nodule that measured more than 1 cm according to computed tomography (CT) images that were obtained over time was defined as a lung metastasis. Of the 166 patients, those who had multiple lung metastases (i.e., more than 3 nodules), those who had metastasis in multiple organs, and those who had synchronous primary disease were excluded. Thirty-seven patients with lung metastases (<3 nodules) during recurrence remained; of these patients, 23 (62.2%) underwent surgical treatment, 12 (32.4%) received chemotherapy only, and 2 received radiotherapy (5.4%). One patient who had already been treated for other metastases was included in each treatment group. The prognoses for the 23 patients were retrospectively evaluated according to their clinicopathological factors. Pathological staging was assessed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria, and all of the tumors were histologically classified according to the World Health Organization classification.

All of the surgical patients received standard treatment for each primary cancer as an initial treatment, including 18 patients (78.2%) who underwent radical surgery with or without adjuvant therapy and 5 patients (21.7%) who received primary chemoradiation. With regard to chemotherapy, a platinum-based regimen was used for all patients as first-line chemotherapy. All of the patients achieved remission after the initial treatments.

Each patient underwent surgery with a conventional thoracotomy or a video-assisted thoracic surgery (VATS) approach for pulmonary metastasectomy. Conventional thoracotomy consisted of a wedge resection, lobectomy, or segmentectomy via open thoracotomy. After the diagnosis of lung metastases, whether the patients received preoperative chemotherapy was determined individually for each case. With regard to the chemotherapy regimen, patients with a recurrence-free interval longer than 6 months received platinum-based chemotherapy, whereas patients with a recurrence-free interval of less than 6 months received non-platinum chemotherapy. Complications and side

effects were estimated with the Common Terminology Criteria for Adverse Events (CTCAE, version 4).

All of the responses to treatment were evaluated according to the guidelines of the Response Evolution Criteria in Solid Tumors (RECIST, version 1.1). To evaluate the re-recurrence rate after pulmonary metastasectomy, a CT scan was performed every six months for the first year and then once a year for five years. The patients who received chemotherapy only underwent a CT scan every 3–6 months during treatment, then every year for five years thereafter to confirm whether a complete response (CR) had been achieved.

Survival was measured from the date of diagnosis until the date of death or the date of the final follow-up visit, whichever occurred first. Disease free-survival (DFS) and overall survival (OS) curves were calculated using the Kaplan-Meier method, and the significance was determined using log-rank tests. Categorical data were analyzed using the chi-squared test or Fisher's exact test for comparisons of each group; p -values less than 0.05 were considered statistically significant. All of the statistical analyses were performed using the Statistical Package for Social Science (SPSS) software package for Windows®, version 21.

RESULTS

Patient characteristics and survival

The characteristics and survival of the 23 patients who underwent pulmonary metastasectomy are summarized in Table 1. The interval between the initial treatment and recurrence as lung metastases ranged from 7 to 117 months (median 28.5 months). The median age at the time of surgery was 56 years old (range 28–77). Fifteen patients, including 11 with only one pulmonary nodule and 4 patients with 2 nodules, first underwent pulmonary metastasectomy after confirmation that no other recurrent tumors were present. Eight patients received first-line chemotherapy, 2 patients with advanced primary cancers, 2 patients with re-recurrent tumors, and 3 patients with 2 pulmonary nodules each. The mean number of chemotherapy cycles was 5.1 (range 3–8). The disease control rate was 62.5% (1 with a CR, 1 with a partial response (PR), and 3 with stable disease (SD)); of the remaining 37.5%, all 3 patients had progressive disease (PD). Therefore, pulmonary metastasectomy was selected for these patients as the next mode of treatment. The 1 patient with a CR underwent this surgery due to a re-recurrence at the same site within 1 year. A total of 5 patients (21.7%) underwent 3 cycles of post-surgery chemotherapy, whereas the remaining 18 patients received no treatments after surgery.

The median follow-up duration was 47 months (range 9.9–180) after pulmonary metastasectomy. In the 23 patients who underwent the surgery, 10 patients (43.4%) experienced recurrence, three of the 10 patients died from their disease, and the 5-year OS rate was 81.7% among all 23 patients. The primary disease in the 3 patients who died was cervical cancer, and all of these patients experienced recurrence within six months of surgery. Table 1 shows that no significant differences were observed in OS with respect to age, primary disease, stage, or surgical procedure. However, a significant difference was observed between the histological types mucinous adenocarcinoma and endometrioid adenocarcinoma (5-year OS 50% vs. 100%, respectively, $p=0.044$, Figure 1-A). The survival rate in patients who were diagnosed with a recurrence more than 2 years after their initial treatment was significantly higher than in patients who were diagnosed within 2 years (100% vs. 41.7%, respectively, $p=0.006$, Figure 1-B).

Re-recurrence after pulmonary metastasectomy

The medical data for the 10 cases of re-recurrence are summarized in Table 2. The interval

Table 1 Patient characteristics and survival after pulmonary metastasectomy

Variables	Number	5-year OS	P
Age(years)			
<60	13	65.6%	0.109
>60	10	100.0%	
Primary disease			
Cervical cancer	14	61.0%	0.145
Endometrial cancer	4	100.0%	
Ovarian cancer	5	100.0%	
Histological type			
Squamous carcinoma	9	75.0%]*
Mucinous adenocarcinoma	5	50.0%	
Endometrioid adenocarcinoma	8	100.0%	
Serous adenocarcinoma	1	100.0%	
FIGO Stage			
I	13	80.0%	0.640
II	5	100.0%	
III, IV	5	66.7%	
Number of pulmonary metastases			
1	16	77.1%	0.366
2 or 3	7	100.0%	
Recurrence-free interval			
<2 years	8	41.7%	0.006
>2 years	15	100.0%	
Chemotherapy before pulmonary metastasectomy			
Yes	9	68.6%	0.271
No	14	90.9%	
Pulmonary metastasectomy			
VATS	13	90.0%	0.446
Conventional thoracotomy	10	71.4%	

OS: Overall survival, Recurrence-free interval: the interval between initial treatment and recurrence in the lung, VATS: video-assisted thoracic surgery. Conventional thoracotomy included 5 lobe, 4 segment, and 1 wedge resection.

* Mucinous vs. endometrioid adenocarcinoma; $p=0.044$

between surgery and re-recurrence ranged from 2.2 to 41.6 (median 18.8) months, and the 5-year DFS rate was 44.7%. Of the 10 patients, 6 (60%) tumors appeared in the lung, 2 (20%) in a pelvic organ, 1 (10%) in distant lymph nodes, and 1 (10%) in the muscles. Five of 6 patients with lung metastasis underwent pulmonary metastasectomy again, and the remaining 1 patient with multiple bilateral lung metastases received chemotherapy. Of these 5 patients, 1 patient with

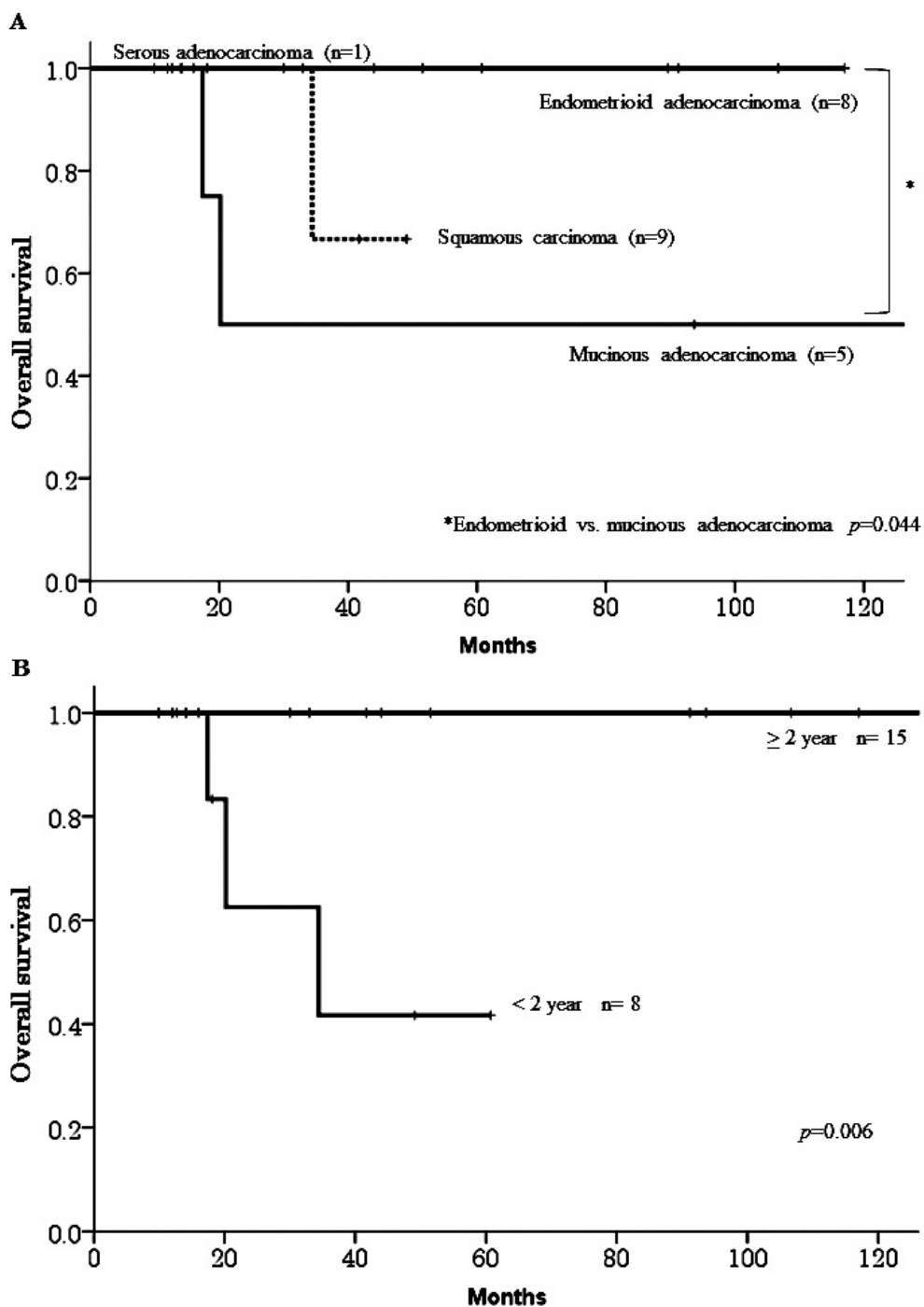


Fig. 1A Overall survival curves according to histological type.

Fig. 1B Overall survival curves according to the disease-free interval after initial treatment.

Table 2 Re-recurrence after pulmonary metastasectomy

Variables	Number	%
Re-recurrence		
Yes	10	43.5%
No	13	56.5%
Time to diagnosis of re-recurrence		
Median time (range)	18.8 (2.2–41.6) months	
Re-recurrence site		
Lung	6	60.0%
Ipsilateral side	3	
Contralateral side	1	
Both sides	2	
Others	4	40.0%
Treatment for re-recurrence		
Pulmonary surgery with/without chemotherapy	5	50.0%
Chemotherapy only	5	50.0%

3 nodules on both sides underwent pulmonary surgery in two steps. All 5 of the patients were alive at the time of this writing, although 1 patient had experienced a third recurrence in the lung.

Complications of pulmonary metastasectomy

Of the 23 patients who underwent a total of 29 surgeries, 24.1% of the patients were older than 70 years of age. Among them, no serious complications or extended hospitalizations after surgery were observed except in 1 patient who underwent 3 pulmonary metastasectomies. This particular patient, who was 79 years old, required temporary home oxygen therapy postoperatively, but her condition improved within 6 months.

Chemotherapy for lung metastasis

The survival rates were compared between the pulmonary metastasectomy group and the chemotherapy-only group. The chemotherapy-only group comprised patients with 3 or fewer lung metastases who were extracted from the same population. Table 3 shows the characteristics of the patients in the pulmonary metastasectomy versus the chemotherapy-only groups. No differences were observed between the 2 groups after performing an analysis of the categorical data using the chi-squared test. Of the 12 patients who received chemotherapy, only 6 (50%) had a CR, 1 (8.3%) had a PR, 3 (25%) had SD, and 2 (16.7%) had PD. One of the 6 patients with a CR experienced recurrence in 1 lung. Although the survival rate in the patients in the pulmonary metastasectomy group tended to be higher than in the patients in the chemotherapy-only group, no significant differences were observed (5-year OS 81.7% vs. 49.5%, respectively, $p=0.072$, Figure 2).

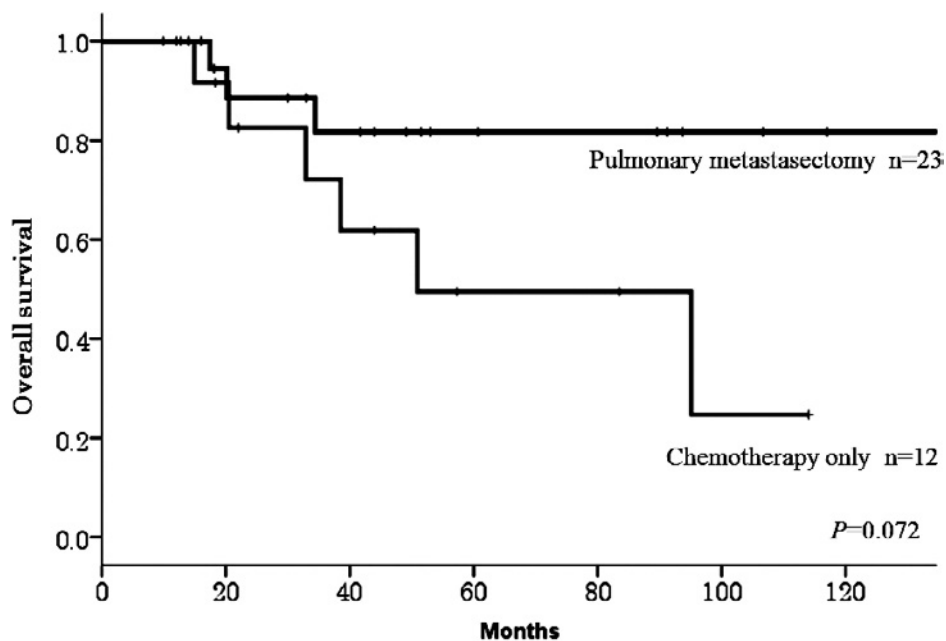
DISCUSSION

Few reports have been published regarding pulmonary metastasectomy for patients with recurrent gynecologic epithelial carcinoma. In an analysis of 5,206 patients who underwent the

Table 3 Characteristics of the patients in the pulmonary metastasectomy versus chemotherapy only groups

Variables	Total	Number of patients				P
		Surgery* (n=23)		Chemotherapy (n=12)		
Age (years)						
Median age (range) in years		56 (28–77)		58.5 (44–76)		
<60	20	13	60.9%	7	58%	0.884
>60	15	10	41.7%	5	42%	
Primary disease						
Cervical cancer	21	14	60.9%	7	58%	0.607
Endometrial cancer	8	4	17.4%	4	33%	
Ovarian cancer	6	5	21.7%	1	8%	
Histological type						
Squamous carcinoma	15	9	39.1%	6	50%	0.797
Mucinous adenocarcinoma	8	5	21.7%	3	25%	
Endometrioid adenocarcinoma	11	8	34.8%	3	25%	
Serous adenocarcinoma	1	1	4.3%	0	0%	
Number of lung metastases						
1	22	16	69.6%	6	50%	0.256
2 or 3	13	7	30.4%	6	50%	
Diagnosis time of pulmonary metastasis post initial treatment						
<2 years	13	7	30.4%	6	50%	0.256
>2 years	22	16	69.6%	6	50%	

Surgery*: pulmonary metastasectomy

**Fig. 2** Overall survival curves according to treatment for recurrent lung metastasis.

surgery, Pastorino *et al.*¹⁾ reported that the number of uterine cancer cases was 83 (3.6%) out of the 2,273 female patients, but the number of breast cancer cases was 396 (17.4%). In patients with cervical cancer, which has the highest rate of lung metastasis among cervical, endometrial and ovarian cancer,^{13, 14)} the rate of isolated lung metastasis was founded to be 1.5 to 6%.^{11, 15, 16)} According to our data, the rate of isolated lung metastasis among 35 epithelial carcinomas was 1.1% among the 3,110 patients with gynecologic cancers.

In general, pulmonary metastasectomy is accepted for patients with the following conditions: (1) the patient must have adequate pulmonary reserve and be at low risk for surgical intervention; (2) the primary malignancy must be either controlled or controllable; (3) there must be no evidence of extra-thoracic metastatic disease; and (4) a complete resection of the pulmonary metastases must be possible.^{1, 2, 17)} In our study, all of the patients also underwent pulmonary resection according to these criteria after an evaluation for extra-thoracic metastatic disease. In most of these patients, a pathological diagnosis of lung tumor was made after a CT-guided biopsy or a biopsy with bronchoscopy prior to surgery, but the histologic diagnosis was made by VATS in some patients.

Various results have been reported for survival after pulmonary metastasectomy due to the different populations studied, including patients with epithelial tumors and patients with non-epithelial tumors. The 5-year OS rate was 10 to 46.8% in patients with mixed epithelial carcinomas and sarcomas.^{14, 16)} In addition, this report also showed a significant difference between adenocarcinoma and sarcoma in 17 patients with uterine cancer (median survival; 46 months vs. 25 months, respectively, $p=0.02$). With respect to the survival of patients with cervical cancer, the 5-years OS rate ranged from 0 to 45.7%.^{13, 14, 16)} An analysis of the histological types of this cancer showed that the 5-year OS rate of patients with squamous cell carcinoma (SCC) showed a tendency to be higher than that in patients with adenocarcinoma^{13, 18)}. Yamamoto *et al.*¹⁹⁾ reported data from a multicenter study and found a significant difference in the DFS between the 20 patients with SCC and the 9 patients with adenosquamous cell carcinoma or adenocarcinoma in both a univariate analysis (5-year DFS: 47.4% vs. 0%, respectively, $p=0.0141$) and a multivariate analysis (hazard ratio: 3.775, 95% confidence interval 1.271–11.212, $p=0.0168$). In contrast, in Anraku's report¹³⁾ on a large number of patients enrolled from more than 20 institutions, no statistically significant difference was found between the 5-year OS rates of the 2 groups (58 SCCs vs. 13 adenocarcinomas: 46.8% vs. 40.3%, respectively, $p=0.92$). Our single-institution study indicated a favorable prognosis for patients with SCC in comparison with adenocarcinoma, but no significant difference was observed. Regarding endometrial cancer, the 5-year OS rate has been reported to be 27.8% to 75.5% in previous studies^{1, 2, 14, 16)} and was 100% in our study. Furthermore, the endometrioid adenocarcinoma subtype of endometrial or ovarian cancer had a significantly better prognosis than the mucinous adenocarcinoma subtype of cervical cancer ($p=0.044$). Our data featured higher survival rates than other studies, and there are two possible reasons for this result: first, most patients had 1 or 2 lung nodules, and no patient had more than 4 nodules; second, most patients underwent a complete pulmonary metastasectomy. Many authors have demonstrated that complete resection is a significant prognostic factor.^{1, 2, 14, 16)}

Prognostic factors are also important indicators for the selection of pulmonary resection or chemotherapy for patients. Some authors have reported that the disease-free interval (DFI) from the initial treatment does not significantly influence survival.^{18, 19)} In contrast, it has also been reported that a longer DFI is a strong prognostic factor for the survival of patients after pulmonary resection (>12 vs. <12 months, 5-year OS 59.8 vs. 17.1%, $p<0.001$,¹³⁾ >24 vs. <24 months: approximately 65 vs. 25%, $p=0.004$ ¹⁴⁾). Our data were similar to these results in that we also found that a favorable prognosis was associated with a longer recurrence-free interval.

In cervical cancer, the response rates (CR plus PR) for a single chemotherapy agent for

patients with recurrent tumors have been reported to be 14 to 40% for cisplatin or ifosfamide,⁶⁾ and 46% for paclitaxel-cisplatin regimens for patients with recurrence after radiotherapy.²⁰⁾ In endometrial cancer, the response rates have been reported to be 20 to 42% for cisplatin or doxorubicin²¹⁾ and to be 60% for paclitaxel-carboplatin regimens in recurrent and advanced cancers.²²⁾ In our study, a total of 20 patients received chemotherapy for recurrent lung tumors, including patients who underwent surgery after chemotherapy because of tumor chemoresistance. The response rate for cervical cancer (33.3%) was lower than that for endometrial cancer (83.3%), similarly to previous reports. Although there was no significant difference between chemotherapy only and surgery, patients who underwent surgery were more likely to have a favorable long-term outcome (8-year OS rate 81.7% vs. 24.8%, $p=0.072$). There may have been some bias because the chemotherapy-only group included patients who were not able to undergo surgery to remove even just one nodule, such as patients who refused treatment or who had 5 cm tumors in the hilar region. However, our data suggested that even patients who did not achieve remission after chemotherapy were helped by surgery. Anderson's study¹⁶⁾ also indicated that pulmonary resection could provide a survival advantage even for patients with isolated lung metastases with chemoresistance.

Furthermore, we examined re-recurrence rates after pulmonary metastasectomy. Few reports have been published on this topic. Of the 23 total patients who underwent surgery, 6 patients (26%) had re-recurrent lung tumors, 5 of which (83%) underwent lung surgery again.

Most authors have reported that pulmonary metastasectomy is safe and effective and that it is associated with very low perioperative morbidity and mortality.^{1, 2, 13, 16)} In our study, approximately 25% of the patients at the time of surgery were older than 70 years of age. No severe complications higher than grade 3 were observed, except in one patient. Many authors have suggested that pulmonary metastasectomy provides a survival advantage for selected patients with isolated lung metastases.^{16, 18, 23)} With respect to the therapeutic management of recurrence, it is necessary to consider various conditions when choosing among surgery, chemotherapy, and radiation therapy.

In conclusion, our results indicated that pulmonary metastasectomy contributed to the long-term survival and was a low-risk treatment. Surgery for isolated lung metastasis might provide a favorable prognosis not only for patients with a long RFI but also for patients with chemoresistant tumors or re-recurrent tumors. Our study has several limitations due to the small number of patients and the retrospective nature of the study. It will be necessary to evaluate the benefits and complications of the surgery in a larger sample in the future.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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