

## Result of Surgical Resection for Pulmonary Metastasis from Urothelial Carcinoma

Woo Sik Han, M.D.<sup>1</sup>, Kwahnmien Kim, M.D.<sup>2</sup>, Joon Suk Park, M.D.<sup>1</sup>

**Background:** Treatment of pulmonary metastasis from urothelial cell carcinoma has been mostly palliative chemotherapy and the role of pulmonary metastasectomy has not been investigated much. **Materials and Methods:** This study is a retrospective interim review of pulmonary metastasectomy from urothelial carcinoma at single institution between 1998 and 2010. Overall 16 patients underwent pulmonary metastasectomies. **Results:** There was no post-operative complication or hospital mortality. Mean hospital stay was 6 days. Overall and disease-free 5-year survival were 65.3% and 37.5%, respectively. **Conclusion:** In selected patients with pulmonary metastasis from urothelial carcinoma, surgical treatment is feasible and could contribute to long-term survival in selected patients.

Key words: 1. Lung neoplasms  
2. Metastasectomy

### INTRODUCTION

Although systemic chemotherapy is the mainstay of treatment for distant metastasis of cancer, there are several cancers known to have survival benefit from pulmonary metastasectomy, which include colorectal carcinoma, renal cell carcinoma, and osteosarcoma. But in relatively chemosensitive malignancies, role of metastasectomy is not well established [1].

Systemic chemotherapy remains the standard treatment for metastatic urothelial cancer since cisplatin-based combination chemotherapy introduced in the 1980s. Despite relatively high response rate of chemotherapy (range, 50% to 70%), patients frequently experiences recurrence and have poor prognosis [2]. Surgical resections of lung metastases from urothelial carcinoma are not common, and there are limited data for role

of metastasectomy on long-term survival.

In this study, we retrospectively reviewed our experience to identify the feasibility and benefits of pulmonary metastasectomy from urothelial cancer.

### MATERIALS AND METHODS

Between 1998 and 2010, 16 patients of urothelial carcinoma with lung metastasis underwent metastasectomy at Samsung Medical Center. Eligible criteria for surgical resection are as follows: 1) the pulmonary lesion must be completely resectable; 2) metastasis was limited to the lung; 3) primary tumor had been or could be completely controlled; and 4) patient was medically operable and had sufficient expected pulmonary reserve after resection [3].

After surgery for primary tumor, adjuvant chemotherapy

Department of Thoracic and Cardiovascular Surgery, <sup>1</sup>Samsung Medical Center, Sungkyunkwan University School of Medicine, <sup>2</sup>Seoul National University Bundang Hospital, Seoul National University College of Medicine

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Corresponding author: Kwahnmien Kim, Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro, Bundang-gu, Seongnam 463-707, Korea  
(Tel) 82-31-787-7131 (Fax) 82-31-787-4050 (E-mail) kmkim0070@snuh.org

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was administered according to the guidelines of National Comprehensive Cancer Network, unless pathologic stage was T2 or less and there was no nodal involvement or lymphovascular invasion. Palliative chemotherapy was administered when there was evidence of disease progression like distant metastasis or unresectable loco-regional recurrence [4]. Regimens for adjuvant chemotherapy were generally 3 cycles of gemcitabine and cisplatin (GP). Palliative regimens were mostly 4 to 6 cycles of GP, but sometimes methotrexate, vinblastine, doxorubicin, and cisplatin were used. Same policies and regimen were used after pulmonary metastasectomy, considering patients condition.

After initial surgery for primary tumor, chest computed tomography (CT) for the surveillance of pulmonary metastasis was performed by 6 month interval generally. Since 2004, positron emission tomography (PET) was routinely performed 1 year after surgery for primary tumor. After pulmonary metastasectomy, chest CT was performed at every 3 months for the first year, every sixth months for the next 2 years, and annually thereafter. Recently, integrated PET-CT has substituted annual chest CT.

Surgery was generally targeted to limited resection such as wedge resection and segmentectomy. However, in case that tumor was located centrally or could not be differentiated from primary lung cancer by intraoperative frozen section biopsy, lobectomy or more extended resection was considered. The same indications and surgical strategies were used for pulmonary recurrence after pulmonary metastasectomy.

Patients' medical records and follow-up information were retrospectively reviewed. Descriptive statistics for categorical variables are reported as frequency and percentage, and continuous variables are reported as mean or median as appropriate. Survival was estimated by Kaplan-Meier survival plot using SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). This study was reviewed and approved by institutional review boards in Samsung Medical Center.

## RESULTS

Patient demographics and clinicopathologic characteristics were illustrated in Table 1. Complete resection was achieved in all patients. Sublobar resection was performed in 10 pa-

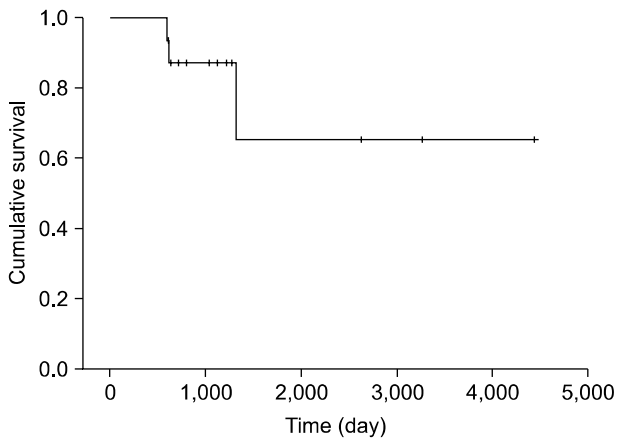
**Table 1.** Patient demographics and clinicopathologic data

Characteristics	Number
Sex	
Male	10
Female	6
Age (yr)	
Mean	61
Range	36–72
Extent of resection	
Wedge	8
Segmentectomy	2
Lobectomy	6
Operative approach	
Video-assisted thoracoscopic surgery	12
Lateral thoracotomy	1
Posterolateral thoracotomy	3
No. of resected nodules	
1	12
2	3
≥3	1
Size of resected nodules (cm)	
Mean size	1.9
<3	11
≥3	5
Perioperative chemotherapy	
Done	14
Not done	2
Disease free interval (mo)	
<12	13
12–24	2
≥24	1

tients (8 wedge resections and 2 segmentectomies). Lobectomy was performed in 6 patients. In 3 patients, intraoperative frozen section of nodule could not differentiate it from primary lung cancer due to very poor differentiation of tumor, and therefore, lobectomy was performed with mediastinal lymph node dissection. In the other 3 patients, nodule was centrally located and sublobar resection was not possible.

The median hospital stay was 5 days (range, 2 to 10 days). There were neither postoperative complications nor hospital mortality.

The 5-year overall survival and disease free survival were 65.3% and 37.5%, respectively (Fig. 1). Eight patients have experienced recurrence after pulmonary metastasectomy. Site of recurrence included lung (n=5), loco-regional relapse in bladder with lung metastasis (n=1), liver (n=1), and multiple



**Fig. 1.** Kaplan-Meier survival plot for overall survival of 16 patients.

mediastinal and cervical lymph nodes (n=1). In all the 5 patients with pulmonary recurrence, newly detected pulmonary nodules were found to be resectable again, and repeated metastasectomy was performed, which included 4 wedge resections and 1 lobectomies. Median disease free interval between the first metastasectomy and repeated resection was 10 months (range, 1 to 56 months). In addition, two of these 5 patients experienced another resectable pulmonary recurrence. One patient with 1 nodule after 3 months from second metastasectomy underwent wedge resection, and the other with 6 nodules after 4 months from second metastasectomy underwent bilateral wedge resection. Both patients are alive without evidence of tumor recurrence for 24 and 5 months. Patient with loco-regional relapse in bladder with lung metastasis underwent transurthral resection of the bladder tumor and metastasectomy simulataneously but spine metastasis relapsed 7 months later and radiation therapy applied.

Total 3 patients expired after initial pulmonary metastasectomy, one patient was who recurred at cervical and mediastinal lymph nodes, another was recurred at liver and last one was not known because of follow-up loss but confirmed by telephone interview. All five patients with recurrence limited to lung without extrathoracic metastasis who underwent repeated metastasectomy are alive for median survival length of 31 months (range, 5 to 39 months).

## DISCUSSION

Despite distant metastasis is regarded as systemic disease, there are some malignancies such as colorectal cancers, renal cell carcinoma, or various types of sarcoma in which pulmonary metastasectomy contributes to prolong survival. Furthermore, in these tumors, even repeated metastasectomy has been shown to have favorable outcomes. We also reported favorable outcomes after repeated metastasectomy from colorectal carcinoma [5]. However, there are limited studies for efficacy of pulmonary metastasectomy from urothelial carcinoma. Urothelial cell carcinoma is known to be relatively chemosensitive, and standard treatment for systemic metastasis from urothelial carcinoma has been palliative combination chemotherapy. However, despite that systemic chemotherapy promises high response rate (range, 50% to 70%) in metastatic urothelial carcinoma, its effect lasts transiently and the disease eventually progresses with poor prognosis.

Several authors reported favorable outcomes regarding pulmonary metastasectomy in combination with chemotherapy for urothelial carcinoma. In 2004, Siefker-Radtke et al. [6] reported result of 31 patients who underwent metastasectomy, which included 24 metastasis to the lung, 4 to distant lymph nodes, and 2 to the brain. Five year overall survival after metastasectomy was about 33% and median overall survival time was 23 months [6]. In 2007, Abe et al. [7] reported experience of multimodal treatment of 48 patients with metastatic urothelial cancer. They found median survival time was significantly different (42 vs. 10 months) in metastasectomy group and the number of chemotherapy cycle, sites of metastasis, and resection of metastasis were independent predictors on survival [7]. Recently Matsuguma et al. [8] reviewed 32 patients with urothelial cancer who underwent pulmonary metastasectomy for curative intent. They reported 5-year overall survival rate of 50% and size of metastasis greater than 3 cm was a significant poor prognostic factor [8]. In 2010, Kanzaki et al. [1] reviewed data from 18 patients who underwent pulmonary metastasectomy from transitional cell carcinoma and reported cumulative 3 and 5-year survival rate of 59.8% and 46.5%. They also found solitary metastasis is associated with good prognosis [1]. In our series, we also observed favorable survival in after metastasectomy from ur-

othelial cell carcinoma. Overall and disease-free 5-year survival were 65.3% and 37.5%, respectively. We also observed favorable survival after repeated pulmonary metastasectomy. Those 5 patients in our series had recurrent pulmonary metastasis but not in other organs. All of them underwent repeated resection and two of them underwent third resection for recurrent disease. All these patients are alive until now without recurrence.

Our study has some obvious limitations. First, just as mentioned above, patient population is too small. We could have only 16 cases of pulmonary metastasectomy for 12-years period. Second, it was very difficult to compare the results of surgery with those of non-surgical treatment because of differences in patient characteristics between the two groups. Patients without metastasectomy usually had much advanced disease with multiple metastases to the lung or various organs, or their physical performance or pulmonary reserves are not sufficient for additional surgery. Therefore, we could not find comparable groups without metastasectomy to those with it. Third, many patients in Samsung Medical Center who could have been potentially candidates of pulmonary metastasectomy might not have referred to surgery due to lack of agreements for pulmonary surveillance and treatment strategy for pulmonary metastasis after surgery of urothelial cell carcinoma, and these can lead to selection bias.

## CONCLUSION

Although there is still limitation, pulmonary metastasectomy

can be applied in patients who have pulmonary metastasis from urothelial carcinoma with favorable outcomes.

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