

# Disease-Free Interval Length Correlates to Prognosis of Patients Who Underwent Metastasectomy for Esophageal Lung Metastases

Satoshi Shiono, MD,\* Masafumi Kawamura, MD,† Toru Sato, MD,\* Ken Nakagawa, MD,‡ Jun Nakajima, MD,§ Ichiro Yoshino, MD,|| Norihiko Ikeda, MD,¶ Hirotohi Horio, MD,# Hirohiko Akiyama, MD,\*\* and Koichi Kobayashi, MD†; The Metastatic Lung Tumor Study Group of Japan

**Background:** Pulmonary metastasectomy is a standard method for treatment of selected pulmonary metastases cases. Nevertheless, because prognosis for patients with lung metastases from esophageal cancer who have undergone pulmonary metastasectomy is poor, candidates for this method of treatment are rare. Therefore, the efficacy of surgical treatment for pulmonary metastatic lesions from esophageal cancer has not been thoroughly examined.

**Methods:** Between March 1984 and May 2006, 57 patients underwent resection of pulmonary metastases from primary esophageal cancer. These cases were registered in the database developed by the Metastatic Lung Tumor Study Group of Japan and were retrospectively reviewed from the registry. After excluding eight cases because of missing information, we reviewed the remaining 49 cases and examined the prognostic factors for pulmonary metastasectomy for metastases from esophageal cancer.

**Results:** There were no perioperative deaths. After pulmonary metastasectomy, disease recurred in 16 (33%) of the 49 patients. The overall 5-year survival was 29.6%. Median survival time was 18 months. The survival of patients with a disease-free interval (DFI) less than 12 months was significantly lower than patients with a DFI greater than 12 months. Through multivariate analysis, we identified DFI as a clinical factor significantly related to overall survival ( $p = 0.04$ ).

**Conclusions:** We identified that patients with a DFI less than 12 months who underwent pulmonary metastasectomy for metastases from esophageal cancer had a worse prognosis. Pulmonary metas-

ectomy for esophageal cancer should be considered for selected patients with a DFI  $\geq 12$  months.

**Key Words:** Esophageal cancer, Pulmonary metastasis, Metastasectomy.

(*J Thorac Oncol.* 2008;3: 1046–1049)

Pulmonary metastasectomy is a standard method of treatment for selected pulmonary metastases cases.<sup>1</sup> When patients are appropriately selected for this treatment, the overall 5-year survival after pulmonary metastasectomy is about 30 to 40%.<sup>1,2</sup> In general, because prognosis for patients who have undergone this method of treatment is poor with disease frequently recurring, pulmonary metastasectomy is not a frequently chosen method of treatment for lung metastases from esophageal cancer. Consequently, survival after surgery for pulmonary metastases from esophageal cancer has not been thoroughly examined. In Japan, the annual report by the Japanese Association for Thoracic Surgery does not document patients who underwent metastasectomy for metastasized esophageal cancer.<sup>3</sup> Because the outcome of pulmonary metastasectomy for metastases from esophageal cancer has not been thoroughly investigated, it is controversial whether surgery is an effective treatment for metastatic esophageal cancer. To identify prognostic factors of pulmonary metastasectomy for metastases from esophageal cancer, in the present study, we reviewed cases registered in the Metastatic Lung Tumor Study Group of Japan database of patients who underwent metastasectomy for metastasized esophageal cancer.

## PATIENTS AND METHODS

The Metastatic Lung Tumor Study Group of Japan developed a database for registration of lung metastases cases. These patients all underwent surgical resection. The database documents the following parameters: gender; age; histology; status of the primary tumor; treatment for the primary tumor; date of primary surgery; kind of surgery; curability; date of metastasis; disease-free interval (DFI); side, size and numbers of resected metastases; date of metas-

\*Department of Thoracic Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan; †Department of Thoracic Surgery, Keio University School of Medicine; ‡Department of Chest Surgery, Cancer Institute Hospital; §Department of Cardiothoracic Surgery, University of Tokyo, Tokyo, Japan; ||Department of Thoracic Surgery, Chiba University, Chiba, Japan; ¶Department of First Surgery, Tokyo Medical University; #Department of General Thoracic Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; and \*\*Department of Thoracic Surgery, Saitama Cancer Center, Saitama, Japan.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Satoshi Shiono, MD, Department of Thoracic Surgery, Yamagata Prefectural Central Hospital, 1800, Ozaaoyagi, Yamagata 990-2292, Japan. E-mail: sshiono@ypch.gr.jp

Copyright © 2008 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/08/0309-1046

tasectomy; and follow-up. Between March 1984 and May 2006, 57 patients underwent resection of pulmonary metastases from primary esophageal cancer. These cases were registered in the Metastatic Lung Tumor Study Group of Japan database and were retrospectively reviewed from the registry. Preoperative examination, surgical indication, and operative procedure were at the discretion of each institution.

After excluding eight cases because of missing information such as number of resected metastases, age, or DFI, we examined the remaining 49 cases (46 males and 3 females) in our study. Surgery alone for the primary tumor was performed in 26 cases (53%), surgery and chemoradiotherapy were performed in 7 cases (14%), surgery and radiotherapy were performed in 6 cases (12%), surgery and chemotherapy were performed in 3 cases (6%), radiotherapy alone was performed in 2 cases (4%), and treatment data were not available for 5 cases (10%). We examined the following variables (Table 1): age ( $\geq 70$  or  $< 70$ ), number of resected metastases (solitary or multiple), resected side (unilateral or bilateral), tumor size ( $\geq 3$  or  $< 3$  cm), DFI ( $\geq 12$  or  $< 12$  months), surgical procedure (partial resection, segmentectomy, or lobectomy), and curability (complete or incomplete).

The present study was analyzed using anonymized data that were collected in each institution. Therefore, informed consent was not specifically obtained and institutional review board approval was not necessary.

### Statistical Analysis

Overall survival was analyzed by the Kaplan-Meier method, and differences in variables were calculated by the

log-rank test. The date of pulmonary resection was defined as the starting point. Cox's proportional hazards model was used for multivariate analysis. The data were calculated using version 5.0 of the StatView software package (SAS Institute Inc, Cary, NC). A  $p$  value of less than 0.05 was defined as indicative of statistical significance.

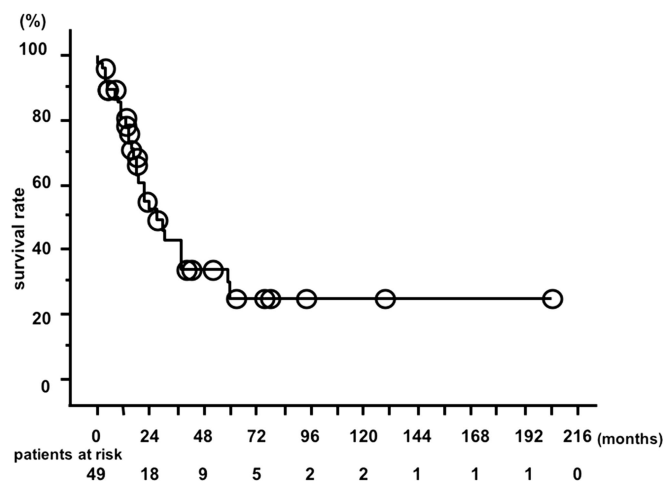
### RESULTS

The median interval between treatment of esophageal cancer and diagnosis of pulmonary metastasis (disease-free interval) was 14 months (range: 0–124 months). There were no perioperative deaths. The median age of patients at the time of pulmonary metastasectomy was 65 years (range: 35–82). The median number of resected metastatic lesions per patient was one (range: 1–5). The metastases ranged in size from 0.4 to 5.5 cm, and the median size was 2.0 cm. The metastases were squamous cell carcinoma in 48 cases and adenocarcinoma in one case. The surgical procedure was wedge resection in 23 cases (47%), lobectomy in 16 cases (33%), segmentectomy in 8 cases (16%), and bilobectomy in 2 cases (4%). The median follow-up period after the first pulmonary resection was 18 months (range: 0–206 months). Recurrence developed in 16 (33%) of the 49 patients. Recurrences were as follows: lung, nine; lymph node, three; neck, one; distant metastasis, one; stomach, one; and unknown, two. The overall 5-year survival after pulmonary metastasectomy was 29.6% (Figure 1). Median survival time was 27 months. We investigated the relationships between prognostic factors and survival (Table 1). Patients with a DFI less than 12 months had a significantly worse prognosis, as assessed by survival rates, than patients with a DFI greater than 12 months (Figure 2). Multivariate analysis of these variables was performed using Cox's proportional hazards model for disease-specific survival. A DFI less than 12 months was shown to be an independent prognostic factor ( $p = 0.04$ ) (Table 2). At the time of submission, 28 patients examined in our study have died. Although 23 patients died of esophageal cancer, 7 patients were not available for recurrent sites. Five patients have died of other diseases (two cases

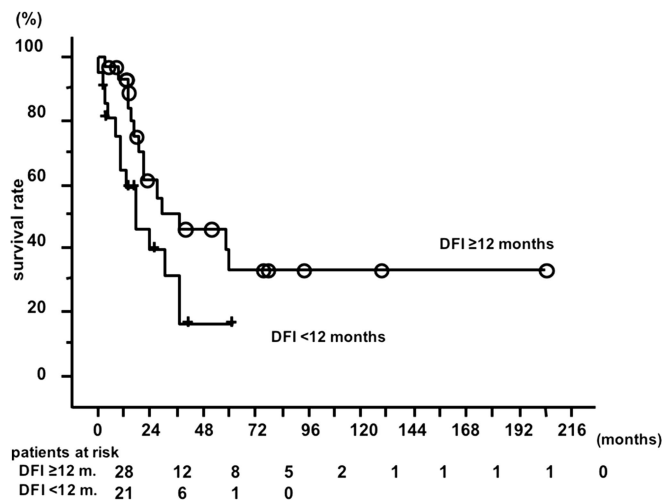
**TABLE 1.** Survival of 49 Patients According to Clinical Factors of Pulmonary Metastases

Variables	n (%)	5-yr Survival (%)	p
Age (yr)			
$\geq 70$	13 (27)	32.9	0.928
$< 70$	36 (73)	27.8	
Number			
Solitary	39 (80)	27.4	0.797
Multiple	10 (20)	42.9	
Resected side			
Unilateral	44 (90)	29.3	0.621
Bilateral	5 (10)	30.0	
Tumor size <sup>a</sup>			
$\geq 3$ cm	10 (21)	40.0	0.640
$< 3$ cm	38 (79)	26.7	
DFI			
$\geq 12$ mo	28 (57)	39.2	0.048
$< 12$ mo	21 (43)	15.7	
Surgical procedure			
Partial and segment	31 (63)	36.4	0.338
Lobectomy	18 (37)	22.9	
Curability			
Complete	45 (92)	31.4	0.990
Incomplete	4 (8)	25.0	

<sup>a</sup> No cases were available.  
DFI, disease-free interval.



**FIGURE 1.** Overall survival of the 49 patients after pulmonary metastasectomy. The 5-year survival was 29.6%.



**FIGURE 2.** Overall survival after pulmonary metastasectomy according to DFI. Survival curves of patients with DFI <12 months and  $\geq$ 12 months. DFI, disease-free interval.

**TABLE 2.** Relationships of Individual Variables to Survival (Cox's Proportional Hazards Model)

Variable	Risk Ratio	95% CI	<i>P</i>
$\geq$ 70 yr	1.01	0.41–2.50	0.983
Multiple metastasis	1.67	0.30–9.19	0.557
Bilateral metastasis	1.19	0.19–7.53	0.853
Tumor size $\geq$ 3 cm	0.76	0.25–2.35	0.635
DFI <12 mo	2.30	1.04–5.09	0.040
Partial and segment	0.60	0.22–1.65	0.180
Incomplete resection	1.00	0.22–4.56	0.881

CI, confidence interval; DFI, disease-free interval.

were pneumonia, two cases were cerebral infarction, and one case was myocardial infarction).

## DISCUSSION

Patients who are candidates for pulmonary metastasectomy for metastases from esophageal cancer are a minority. Analysis of the outcomes of surgery for pulmonary metastases from esophageal cancer has not been published. Quint et al.<sup>4</sup> showed that 29 of 147 (20%) patients with newly diagnosed metastasized esophageal cancer had lung metastasis. Although autopsy studies showed that the frequency of esophageal lung metastasis was 50%,<sup>5</sup> there was not a high percentage of esophageal cancer relapse after esophagectomy. Kyriazanos et al.<sup>6</sup> revealed that 12 of 151 (8%) patients who underwent a curative esophageal resection had lung metastases. Within our study the number of adenocarcinoma of the esophagus was very small. Because the frequency of adenocarcinoma of the esophagus is low in Japan, we do not speculate about the scarce incidence of lung metastasis from adenocarcinoma of the esophagus.

Matsubara et al. showed that 38 of 230 patients (17%) who underwent surgery for esophageal cancer with extended lymph node dissection had distant metastases and 14 (6%)

patients had lung metastases. In their article, the outcomes after recurrence were dismal, and no patients were alive 5 years after detection of recurrence. Nevertheless, they showed that the 1-year survival of the patients who had recurrent lesions and were treated with resection and adjuvant therapy was 83%. They concluded that when recurrent lesions were localized macroscopically, surgical removal of the recurrent lesions was an effective treatment.<sup>7</sup> Through our analysis, we found a 5-year survival of 29.6% after pulmonary metastasectomy, which indicates that pulmonary metastasectomy is a promising treatment for metastases from esophageal cancer. Nevertheless, as it is not easy to differentiate esophageal metastases from primary lung squamous cell carcinomas, it is possible that our data might include primary lung squamous cell carcinoma. Survival after metastasectomy might be lower than what our data indicate. Virgo et al mentioned that genetic markers are needed to confidently distinguish between metastases and primary solitary nodules.<sup>8</sup> Further investigation is needed to clarify this matter.

An article from the international registry of lung metastases states that the 5-year survival was 37% after pulmonary metastasectomy. In addition, the article showed that among cases of complete resection, the 5-year survival was 33% for patients with a DFI of 0 to 11 months and 45% for those with a DFI of more than 36 months. Furthermore, the 5-year survival was 43% for single lesions and 27% for 4 or more lesions.<sup>1</sup> DFI and number of pulmonary metastases are significant prognostic factors. Because our present data show that the median DFI is 14 months, we categorized DFI as  $\geq$ 12 or <12 months. Regarding the DFI, our study suggests that patients with a DFI less than 12 months have a poor prognosis. Osugi et al. showed that 83% of recurrences presented within 24 months after esophagectomy and that the chance of survival of patients whose disease recurred within 24 months after esophagectomy was better than that of patients who suffered recurrence within 24 months. Regarding follow-up studies after esophagectomy, meticulous care should be taken to detect hematogenous recurrence.<sup>9</sup>

In general, incomplete resection is a dismal prognostic factor in lung metastasectomy. We could not demonstrate whether surgical curability is a prognostic factor. McDonald et al. reported that incomplete resection appeared to have no influence on overall survival in metastatic breast cancer. They suggested that this could be due to the systemic nature of the disease at the time of thoracotomy with unsuspected occult metastasis in other areas.<sup>10</sup> Nevertheless, in our study, only four patients underwent incomplete resection. Because the report from The International Registry of Lung Metastases stated that cases with incomplete resection clearly had worse prognoses,<sup>1</sup> we speculate that patients with lung metastases from esophageal cancer have the same tendency.

Although our present study was multi-institutional, we could not analyze in detail all of the records for each patient. From this point of view, because our findings were based on a limited number of cases, pulmonary metastasectomy for lung metastases from esophageal cancer is still highly controversial. Nevertheless, we identified that patients with a DFI less than 12 months had a worse prognosis, as assessed by

survival rates, than patients with a DFI greater than 12 months.

Consequently, although metastases from esophageal cancer are a minority, we think that pulmonary metastasectomy for esophageal cancer should be considered for selected patients with a DFI  $\geq$ 12 months. As this study is small, further clinical studies will be needed.

#### REFERENCES

1. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997;113:37–49.
2. Kondo H, Okumura T, Ohde Y, Nakagawa K. Surgical treatment for metastatic malignancies. Pulmonary metastasis: indications and outcomes. *Int J Clin Oncol* 2005;10:81–85.
3. Kazui T, Osada H, Fujita H. Thoracic and cardiovascular surgery in Japan during 2004. *Jpn J Thorac Cardiovasc Surg* 2006;54:363–385.
4. Quint LE, Hepburn LM, Francis IR, Whyte RI, Orringer MB. Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. *Cancer* 1995;76:1120–1125.
5. Anderson LL, Lad TE. Autopsy findings in squamous-cell carcinoma of the esophagus. *Cancer* 1982;50:1587–1590.
6. Kyriazanos ID, Tachibana M, Shibakita M, et al. Pattern of recurrence after extended esophagectomy for squamous cell carcinoma of the esophagus. *Hepatogastroenterology* 2003;50:115–120.
7. Matsubara T, Ueda M, Takahashi T, Nakajima T, Nishi M. Localization of recurrent disease after extended lymph node dissection for carcinoma of the esophagus. *J Am Coll Surg* 1996;182:340–346.
8. Virgo KS, Naunheim KS, Johnson FE. Preoperative workup and postoperative surveillance for patients undergoing pulmonary metastasectomy. *Thorac Surg Clin* 2006;16:125–131.
9. Osugi H, Takemura M, Higashino M, et al. Causes of death and pattern of recurrence after esophagectomy and extended lymphadenectomy for squamous cell carcinoma of the thoracic esophagus. *Oncol Rep* 2003;10:81–87.
10. McDonald ML, Deschamps C, Ilstrup DM, Allen MS, Trastek VF, Pairolero PC. Pulmonary resection for metastatic breast cancer. *Ann Thorac Surg* 1994;58:1599–1602.