

Original
Article

Impact of Perioperative Chemotherapy on Prognosis of Patients with Esophageal Carcinoma Undergoing Pulmonary Metastasectomy

Hiroaki Komatsu, MD, PhD, Nobuhiro Izumi, MD, PhD, Takuma Tsukioka, MD, PhD, Hidetoshi Inoue, MD, PhD, Hikaru Miyamoto, MD, and Noritoshi Nishiyama, MD, PhD

Purpose: To evaluate prognosis of patients with esophageal carcinoma undergoing pulmonary metastasectomy, and help determine appropriate therapeutic strategies.

Methods: We retrospectively studied 16 patients (15 men and one woman; median age 66.5 years) with esophageal carcinoma, who underwent curative resection of pulmonary metastases. Clinical characteristics and surgical outcomes were analyzed.

Results: In all, 11 patients underwent wedge resection, three segmentectomy, and two lobectomies. The average operating time and blood loss were 147 min and 103 mL, respectively. There were no perioperative deaths or severe complications. Five-year overall survival rate was 40.2% and 2-year disease-free survival rate was 35.2%. All recurrences occurred within 2 years. Univariate and multivariate analyses revealed that absence of adjuvant chemotherapy after therapy for esophageal carcinoma was a significant predictor of poor prognosis and recurrence, respectively ($p < 0.05$). The prognosis of seven patients who underwent esophagectomy with adjuvant chemotherapy was better than that of the other nine patients ($p = 0.0166$).

Conclusion: Pulmonary metastasectomy in patients with esophageal carcinoma was only one choice of multimodal treatment, and perioperative chemotherapy was important for long-term survival after pulmonary metastasectomy. Pulmonary metastasectomy was effective in patients undergoing esophagectomy with adjuvant chemotherapy.

Keywords: esophageal carcinoma, pulmonary metastasis, metastasectomy, prognostic factors, perioperative chemotherapy

Department of Thoracic Surgery, Osaka City University Hospital, Osaka, Osaka, Japan

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Corresponding author: Hiroaki Komatsu, MD, PhD. Department of Thoracic Surgery, Osaka City University Hospital, 1-4-3 Asahi-machi, Abeno-ku, Osaka, Osaka 545-8585, Japan
Email: m1111276@med.osaka-cu.ac.jp



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Introduction

Recent advances in multimodal treatment have improved the prognosis of patients with esophageal carcinoma.¹⁾ Pulmonary metastasis from esophageal carcinoma is one of the major recurrence patterns, and patients with hematogenous recurrence have poorer prognosis than those with locoregional recurrence.²⁾ Pulmonary metastasectomy is reported to be effective in patients with several types of cancer, including colorectal cancer.³⁾ However, there are few reports on the prognosis of

pulmonary metastasectomy for patients with esophageal carcinoma.^{4–7)} The aims of this study were to evaluate the prognosis of patients with esophageal carcinoma who underwent pulmonary metastasectomy, and help determine appropriate therapeutic strategies.

Methods

We retrospectively studied 16 patients (15 men and one woman, median age 66.5 years) who underwent curative resection for pulmonary metastases from esophageal carcinoma, at Osaka City University Hospital between January 2008 and December 2017. Patients who underwent resection for biopsy or diagnosis were excluded. Informed consent regarding the use of examination outcomes and clinical data were obtained before surgery from all patients. The local Institutional Ethics Committee approved this study. Pathological diagnosis of esophageal carcinoma and its metastasis was performed by at least two pathologists at our hospital in accordance with the criteria of the World Health Organization. Cancer stage was classified according to the 7th edition of the International Union Against Cancer (Union for International Cancer Control [UICC]) TNM classification of esophageal carcinoma.

Clinical characteristics and surgical outcomes were analyzed statistically. Survival curves were calculated from the day of pulmonary resection to death or to final follow-up using the Kaplan–Meier method, and differences in survival curves were assessed with the log-rank test. Multivariate Cox regression analyses were calculated to determine associations between clinical characteristics and postoperative survival. Clinical characteristics with a *p* value of <0.05 in the univariate analysis were entered into the multivariate Cox regression analysis. *p* < 0.05 was considered statistically significant. All statistical analyses were performed using JMP version 9 (SAS Institute, Cary, NC, USA).

Results

The patients' clinical characteristics are summarized in **Table 1**. As initial treatment for esophageal carcinoma, 12 patients underwent esophagectomy, three chemoradiotherapy, and one endoscopic resection. Seven patients underwent adjuvant chemotherapy after esophagectomy, including a combined regimen of 5-fluorouracil (5-FU) and cisplatin in six, and 5-FU alone in one. In all, 16 patients underwent curative resection of pulmonary

metastases, including wedge resection in 11, segmentectomy in three, and lobectomy in two patients. The median disease-free interval (DFI) between primary esophageal carcinoma and pulmonary metastasis was 23.3 months (range: 0–48.6 months). No patients had extrapulmonary metastases. In all, 12 patients (75%) had single pulmonary metastasis, whereas four had multiple pulmonary metastases. Among the latter, two patients had synchronous multiple metastases in one lung and underwent multiple wedge resections. One had synchronous multiple metastases in both lungs and underwent two-stage surgery. The first stage was segmentectomy for metastasis of the left lung, and the second stage was wedge resection of right pulmonary metastasis. The other patient had metachronous multiple metastases of one lung and underwent repeated wedge resections. The average operating time was 147 min and average blood loss was 103 mL. The surgical procedure, operating time, and blood loss did not differ between surgery of the right and left lungs. There were no perioperative deaths or severe complications. Only one patient had prolonged air leakage after segmentectomy of the right lung, and the leakage was stopped by drainage without additional treatment.

The median follow-up period was 34.5 months (range: 4–105 months). One-year, 3-year, and 5-year overall survival rates were 93.8, 40.2, and 40.2%, respectively (**Fig. 1A**). According to univariate survival analysis, absence of adjuvant chemotherapy after therapy of esophageal carcinoma and presence of chemotherapy before pulmonary metastasectomy were significant predictors of poor prognosis (*p* = 0.0166 and 0.0240, respectively; **Table 2**). The prognosis of seven patients who underwent esophagectomy with adjuvant chemotherapy was better than that of the other nine patients (*p* = 0.0166, **Fig. 1B**). Although tumor diameter ≥ 2 cm was not a significant predictor of poor prognosis, two patients with pulmonary metastases of diameter > 3 cm had poorer prognosis than patients with metastases < 3 cm (*p* = 0.0026). Multivariate survival analysis revealed that absence of adjuvant chemotherapy after therapy of esophageal carcinoma was an independent predictor of poor prognosis (hazard ratio 7.58, *p* = 0.0247). Two-year disease-free survival rate was 35.2% (**Fig. 2**). All recurrences occurred within 2 years after pulmonary metastasectomy. According to univariate analysis, absence of adjuvant chemotherapy after therapy of esophageal carcinoma and presence of chemotherapy before pulmonary metastasectomy were also significant predictors of recurrence (*p* = 0.0173 and 0.0186, respectively; **Table 3**). Multivariate

Table 1 Clinical characteristics of patients with esophageal carcinoma who underwent pulmonary metastasectomy

Age (years)	Median (range)	66.5 (52–77)
Gender	Male	15
	Female	1
Therapeutic modality for esophageal carcinoma	Surgery	12
	Chemoradiotherapy	3
	Endoscopic resection	1
Histology of esophageal carcinoma	Squamous cell carcinoma	13
	Adenocarcinoma	2
	Basaloid carcinoma	1
T status of esophageal carcinoma	1	3
	2	5
	3	7
	4	1
N status of esophageal carcinoma	0	5
	1	3
	2	5
	3	3
Pathological stage of esophageal carcinoma	1	2
	2	5
	3	7
	4	2
Disease-free interval (months)	Median (range)	23.3 (0–48.6)
Chemotherapy after esophagectomy	Yes	7
	No	9
Number of pulmonary metastasis	Solitary	12
	Multiple (bilateral)	4 (1)
Tumor side of pulmonary metastasis	Right	7
	Left	8
	Bilateral	1
Tumor size of pulmonary metastasis (mm)	Median (range)	12 (4–73)
Surgical procedure for pulmonary metastasis	Wedge resection	11
	Segmentectomy	3
	Lobectomy	2
Chemotherapy before pulmonary metastasectomy	Yes	2
	No	14
Chemotherapy after pulmonary metastasectomy	Yes	12
	No	4

analysis revealed that absence of adjuvant chemotherapy after therapy of esophageal carcinoma was an independent predictor of recurrence (hazard ratio 4.70, $p=0.0399$). Ten (62.5%) of 16 patients had recurrence after pulmonary metastasectomy, and the site of recurrence was additional pulmonary metastasis in five patients (50%). The recurrence sites of the other five patients were esophagus, mediastinal lymph node, and pleural in one each, and distant metastasis, but not lung, in two. The cause of death of all patients was esophageal carcinoma.

Discussion

There are few reports on the prognosis of patients with esophageal carcinoma undergoing pulmonary

metastasectomy.^{4–7)} Five-year overall survival is reported to be 29.6%–43.5%, and short DFI, nodal involvement of primary tumor, or extrapulmonary metastases are reported to be significant predictors of poor prognosis. Although our study did not include patients with extrapulmonary metastases or incomplete resection, the surgical outcome was consistent with that in previous studies. We focused on the impact of perioperative chemotherapy on prognosis of patients with esophageal carcinoma who underwent pulmonary metastasectomy.

Chemotherapy before pulmonary metastasectomy was associated with poor prognosis. This might be because the patients who underwent chemotherapy before pulmonary metastasectomy were poor responders to chemotherapy and they may have missed the best

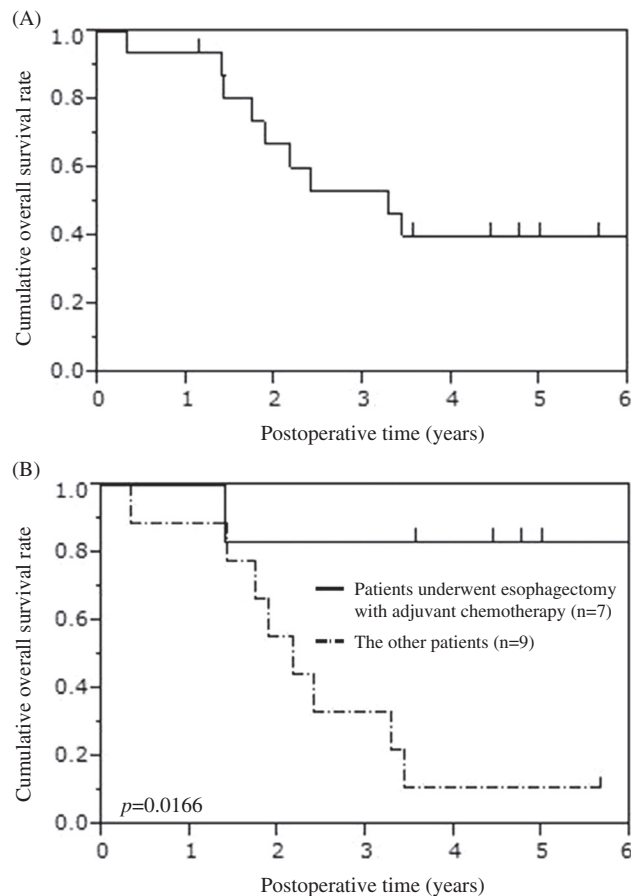


Fig. 1 (A) Kaplan–Meier curves for postoperative overall survival of 16 patients with esophageal carcinoma who underwent pulmonary metastasectomy. (B) Kaplan–Meier curves for postoperative overall survival of seven patients who underwent esophagectomy with adjuvant chemotherapy and the other nine patients. Prognosis of patients who underwent esophagectomy with adjuvant chemotherapy was significantly better than that of the other patients ($p = 0.0166$).

timing for surgery. In fact, the two patients who underwent chemotherapy before pulmonary metastasectomy had large metastases, one of which had a diameter of 73 mm. In patients who underwent resection of pulmonary metastases, tumor diameter >3 cm was associated with hilar and mediastinal lymph node metastasis or poor prognosis.⁸⁾ In the present study, the two patients with pulmonary metastases >3 cm in diameter had poorer prognosis than the patients with metastases <3 cm diameter. Pulmonary metastases >3 cm in diameter might have malignant potential to cause additional metastasis and spread to other locations. When we find large pulmonary nodules suspected as metastases from esophageal carcinoma, resection without preoperative chemotherapy

should be considered until the nodule does not grow unresectable with multiple mediastinal lymph node metastases. By contrast, when the pulmonary nodule is small, preoperative chemotherapy might be acceptable to re-evaluate additional occurrences of metastases during chemotherapy because of high rate of early recurrence. In the present study, 10 (62.5%) of 16 patients had recurrences within 2 years after pulmonary metastasectomy. Previous studies have also reported high recurrence rates of 66.7%–82.6%.^{5,7)} Preoperative whole body examination and exclusion of other metastases are important to determine surgical indications for undergoing curative resection.

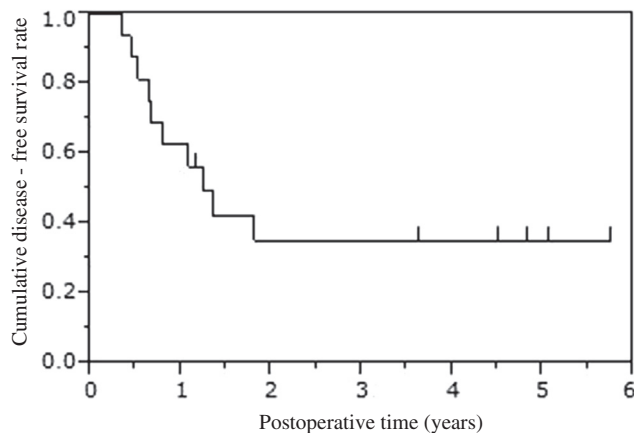
Adjuvant chemotherapy of esophageal carcinoma was associated with good prognosis with regard to overall survival and disease-free survival. In a previous study of patients with pulmonary metastases of colorectal cancer, perioperative chemotherapy was associated with good disease-free survival or progression-free survival,⁹⁾ whereas the current evidence does not support an independent prognostic effect of perioperative chemotherapy on overall survival. In patients who undergo postoperative adjuvant chemotherapy after esophagectomy, the resection of pulmonary metastases that had a poor response to chemotherapy might lead to good prognosis. Adjuvant chemotherapy after esophagectomy might be useful to select patients who survive long term without recurrences after pulmonary metastasectomy.

Chemotherapy after pulmonary metastasectomy was not significantly associated with good prognosis with regard to overall survival and disease-free survival in our study. This was because of the selection bias that chemotherapy after pulmonary metastasectomy was performed in patients with multiple or large metastases, who were expected to have a high risk of recurrence. All five patients who did not undergo chemotherapy after pulmonary metastasectomy had solitary small lesions, and four of them are surviving without recurrence. It is possible that they might have included primary lung squamous cell carcinoma because it is not easy to differentiate esophageal metastases from primary lung squamous cell carcinoma.⁴⁾ This might be one of the reasons why the prognosis of patients who underwent solitary metastasectomy without perioperative chemotherapy was better than expected.

Thus, our data demonstrated that perioperative chemotherapy had an impact on the prognosis of patients with esophageal carcinoma who underwent pulmonary

Table 2 Univariate analyses of postoperative overall survival in patients with esophageal carcinoma who underwent pulmonary metastasectomy

Characteristics			3-year survival rate (%)	5-year survival rate (%)	p value
Age (years)	≥67	8	85.7	57.1	0.0974
	<67	8	25.0	25.0	
Therapeutic modality for esophageal carcinoma	Surgery	13	58.7	42.0	0.8207
	Other	3	33.3	33.3	
Histology of esophageal carcinoma	Squamous cell carcinoma	13	50.4	33.6	0.3109
	Other	3	66.7	66.7	
T status of esophageal carcinoma	1, 2	8	62.5	62.5	0.1202
	3, 4	8	42.9	14.3	
N status of esophageal carcinoma	0	5	60.0	40.0	0.8888
	1–3	11	50.0	40.0	
Pathological stage of esophageal carcinoma	1, 2	7	71.4	57.1	0.3025
	3, 4	9	37.5	25.0	
Disease-free interval	≥2 years	8	57.1	57.1	0.7842
	<2 years	8	50.0	37.5	
Chemotherapy after esophagectomy	Yes	7	83.3	83.3	0.0166
	No	9	33.3	11.1	
Number of pulmonary metastasis	Solitary	12	55.0	45.8	0.5087
	Multiple	4	50.0	25.0	
Tumor size of pulmonary metastasis	≥2 cm	6	40.0	40.0	0.6652
	<2 cm	10	60.0	40.0	
Surgical procedure for pulmonary metastasis	Wedge resection	11	50.5	40.4	0.9741
	Anatomical resection	5	60.0	40.0	
Chemotherapy before pulmonary metastasectomy	Yes	2	0	0	0.0240
	No	14	61.9	46.4	
Chemotherapy after pulmonary metastasectomy	Yes	11	45.5	27.3	0.1329
	No	5	75.0	75.0	

**Fig. 2** Kaplan–Meier curves for postoperative disease-free survival of 16 patients with esophageal carcinoma who underwent pulmonary metastasectomy.

metastasectomy, and was important to long-term survival after pulmonary metastasectomy. There are no reports about the impact of perioperative chemotherapy on the prognosis of patients who underwent resection of pulmonary metastases from esophageal carcinoma. Kanamori et al. recommended adjuvant systematic chemotherapy after pulmonary resection because of the high recurrence rate.⁷⁾ Among several timings of perioperative chemotherapy, adjuvant chemotherapy after esophagectomy was the most useful for long-term survival in this study. Chemotherapy before pulmonary metastasectomy, including adjuvant chemotherapy after esophagectomy, has some possibility to be useful for surgical indication in patients with pulmonary metastases from esophageal carcinoma by evaluating response to chemotherapy or additional occurrences of metastases.

Table 3 Univariate analysis of postoperative disease-free survival in patients with esophageal carcinoma undergoing pulmonary metastasectomy

Characteristics		p value
Age (years)	≥67 vs <67	0.1826
Therapeutic modality for esophageal carcinoma	Surgery vs others	0.8635
Histology of esophageal carcinoma	Squamous cell carcinoma vs others	0.7889
T status of esophageal carcinoma	1, 2 vs 3, 4	0.2845
N status of esophageal carcinoma	0 vs 1–3	0.8672
Pathological stage of esophageal carcinoma	1, 2 vs 3, 4	0.7159
Disease-free interval	≥2 years vs <2 years	0.7571
Chemotherapy after esophagectomy	Yes vs no	0.0173
Number of pulmonary metastasis	Solitary vs multiple	0.2349
Tumor size of pulmonary metastasis	≥3 cm vs <3 cm	0.5808
Surgical procedure for pulmonary metastasis	Wedge resection vs anatomical resection	0.9455
Chemotherapy before pulmonary metastasectomy	Yes vs no	0.0186
Chemotherapy after pulmonary metastasectomy	Yes vs no	0.0802

Whereas short DFI has been reported to be a significant prognostic factor,^{4,6,7)} DFI was not significant predictor of poor prognosis and recurrence in the present study. Based on results of the previous studies, we have performed pulmonary metastasectomy in patients with long DFI and no extrapulmonary metastases. Therefore, our study consisted of only selected patients who have longer DFI than the previous studies. Although DFI less than 12 months was unfavorable prognostic factor,^{4,6)} only 4 (25%) of 16 patients had DFI less than 12 months. This is why DFI was not a significant prognostic factor.

All recurrences in our patients occurred within 2 years after pulmonary metastasectomy. Osugi et al. also showed that 83% of recurrences presented within 2 years after esophagectomy, and that the chance of survival was better in patients with recurrence after than within 2 years after esophagectomy.¹⁰⁾ In patients without recurrence within 2 years after pulmonary metastasectomy, long-term survival can be expected. Even the prognosis of patients who underwent bilateral or metachronous metastasectomy was not poorer than that in patients who underwent solitary metastasectomy, and resection should be considered in patients with bilateral or metachronous metastases.

In patients undergoing esophagectomy, metastasectomy of the right lung is expected to be difficult because they have a reconstructed gastric tube and adhesion in their thoracic cavity.⁶⁾ In the present study, operating time, blood loss, and perioperative complications did not differ between patients with right and left pulmonary metastases. However, one patient had prolonged air leakage after segmentectomy of the right lung, which was due to dissection of severe adhesion in the thoracic cavity. In the selected patients whose primary esophageal

carcinoma is well controlled by surgery and chemotherapy, resection was acceptable for metastases even in the right lung, although it was necessary to exercise caution about the intrathoracic adhesion and postoperative prolonged air leakage.

Our study had some limitations. This was a single-institution retrospective study conducted in Japan and the sample size was small. Despite the recent improvement in the prognosis of patients with esophageal carcinoma, the previous studies included patients treated >20 years ago, whereas the present study consisted only of patients treated in the past 10 years. Further study of recent patients from multiple institutions is needed to confirm the effectiveness of resection of pulmonary metastases from esophageal carcinoma.

Conclusion

Our data suggest that pulmonary metastasectomy in patients with esophageal carcinoma is only one choice of multimodal treatment, and perioperative chemotherapy is important for long-term survival after pulmonary metastasectomy. Pulmonary metastasectomy for esophageal carcinoma should be considered in selected patients. Pulmonary metastasectomy is particularly effective in patients undergoing esophagectomy with adjuvant chemotherapy.

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Disclosure Statement

The authors have no conflict of interest to declare.

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