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

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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

Introduction

Recent advances in multimodal treatment have improved the prognosis of patients with esophageal carcinoma. 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. Pulmonary metastasectomy is reported to be effective in patients with several types of cancer, including colorectal cancer. However, there are few reports on the prognosis of
pulmonary metastasectomy for patients with esophageal carcinoma. 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 extrapolmonary 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 synchronous 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
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

| 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 |
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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).

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, 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. 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 metastasectomy.
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.
Whereas short DFI has been reported to be a significant prognostic factor, 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, 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. 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. 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.

| 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 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 metastectomy                 | Yes vs no   | 0.0186 |
| Chemotherapy after pulmonary metastectomy                  | Yes vs no   | 0.0802 |

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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