Prognostic Factors for Survival after Resection of Pulmonary Metastases from Colorectal Carcinoma

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Purpose: As chemotherapy has improved, the survival of patients with metastatic colorectal carcinoma has reached up to 2.5 years. Many of these patients experience pulmonary metastases; however, the prognosis after pulmonary metastasectomy is not satisfying. In this study, we analyzed the prognostic factors for survival in patients who underwent pulmonary metastasectomy.

Methods: Eighty-seven patients with colorectal carcinoma received pulmonary metastasectomy. The pathological status of the primary tumor, outcome of the pulmonary metastasectomy, disease-free interval, perioperative carcinoembryonic antigen (CEA) level and history of liver metastases were assessed.

Results: The five-year survival was 42.5% after pulmonary metastasectomy. A univariate analyses revealed that the CEA level (p = 0.043) and the number of pulmonary metastases (p = 0.047) were prognostic factors for survival. The CEA level was an independent prognostic factor in a multivariate analysis (relative risk = 2.01, p = 0.037). Among cases with elevated preoperative CEA levels, those whose CEA level normalized after metastasectomy had a better prognosis compared with those whose CEA level decreased but was still high, or whose level increased after metastasectomy (median survival time of 41.8 months compared with 28.1 or 15.7 months, respectively p = 0.021).

Conclusion: The CEA level can be a predictive marker for the prognosis in patients with pulmonary metastases from colorectal carcinoma.

Keywords: pulmonary metastasis, colorectal carcinoma, carcinoembryonic antigen

Introduction

Recent advances in systemic chemotherapy have prolonged the survival in patients with metastatic colorectal carcinoma. The combination of oxaliplatin, fluoropyrimidine and CPT-11, along with other newly developed molecular targeting agents like bevacizumab, cetuximab/panitumumab and regorafenib has led to the median overall survival reaching approximately 2.5 years.

Nearly half of the patients with colorectal carcinoma experience distant metastases, mainly in the liver and lungs. From the pathological view with regard to the cascade hypothesis, these two metastatic sites develop in discrete steps, which supports the idea that these hematogenous metastases are limited diseases. Several retrospective studies have shown that patients with isolated pulmonary metastases from colorectal carcinoma benefit from resection. The published five-year survival rates after pulmonary resection of colorectal carcinoma metastases range from 25% to 30%.
metastasectomy range from 30.5% to 61.4%,15–23) including the study from our institution reported in 1993.24) In this study, we evaluated the survival after resection for patients with pulmonary metastases from colorectal origin, and assessed the prognostic factors for survival among these patients.

Methods

Patients
From February 1986 through June 2007, 87 consecutive patients with colorectal carcinoma underwent pulmonary metastasectomy at our institution. The reason why this time period was chosen was that (1) almost complete follow-up data could be obtained and (2) perioperative chemotherapy using oxaliplatin, fluoropyrimidine and bevacizumab had not been performed routinely during this time period. The criteria for surgical resection were as follows: (1) control of the primary tumor, or ability to resect the primary tumor completely simultaneously with the resection of metastases; (2) the capability to resect the metastatic disease completely; (3) the ability of the patient to withstand the extent of pulmonary resection required to remove all gross tumor; (4) with extrathoracic metastases controlled or resected.25) At the period of this study, we did not set a limit by the tumor number or the tumor size, as long as the tumor was considered to be resectable by the criteria above. As a rule, we performed limited resection (i.e., wedge resection, segmentectomy) for metastatic nodules, but we performed lobectomy or pneumonectomy when the tumor was centrally located, when the tumor was larger than 3 cm or the tumor was indistinguishable from primary lung cancer. Lymph node sampling was performed when hilar or mediastinal lymph nodes were swollen, but systematic lymph node dissection was performed only when the tumor was larger than 3 cm or when primary lung cancer could not be ruled out.

Table 1 is a summary of pertinent patient demographics. The median age was 64 years old, and 48% of the patients were male. In 67% of the cases, the tumor originated from the colon, and 82% had advanced pathological stage disease (III/IV). Limited resections were performed in 62% of patients, lobectomies were performed in 33% of patients and pneumonectomies were performed in 5% of patients. The average number of pulmonary metastasis was 2.3 (range 1–10) at the first thoracotomy, and the average number of thoracotomies was 1.4 (range 1–5). The median pre-thoracotomy carcinoembryonic antigen (CEA) level

<table>
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1Pathological stage when the primary colorectal cancer was resected. Data were not available for 27 patients. 2Wedge resection or segmentectomy. 3Data were not available for six patients. CEA: carcinoembryonic antigen
Pulmonary Metastasectomy from Colorectal Carcinoma

The overall survival after pulmonary metastasectomy (A) was compared according to the CEA levels (B) or number of pulmonary metastases at first thoracotomy (C). CEA: carcinoembryonic antigen; MST: median survival time.

was 3.8 ng/ml (with 5.0 ng/ml used for the cut-off line). The median disease-free interval (DFI) was 23.1 months, and liver metastases were observed in 37% of patients (seven synchronous metastases and 23 metachronous metastases).

Statistical analysis

All patients were retrospectively analyzed for age and sex, the location (colon or rectum) and pathological stage of the primary tumor by the UICC-TNM classification, the number and type of pulmonary resections, number of pulmonary metastases, DFI (between the resection of the primary tumor and the first pulmonary metastasectomy), perioperative CEA level, history of liver metastases and long-term survival. The postoperative CEA level for each patient was measured about one month after pulmonary metastasectomy.

The event used for the assessment of efficiency was death. The follow-up period ranged from 0.5 to 305 months (average 56, median 28.8 months). The probability of survival was analyzed by the Kaplan-Meier method using the date of the first pulmonary resection as the starting point. The
significance of differences between subgroups was calculated using the log-rank test.\textsuperscript{29} The Cox model\textsuperscript{29} was used for the multivariate analysis of prognostic factors for survival. The factors analyzed included the age, sex, pre-thoracotomy serum CEA level, number of metastases and DFI. The results of the analysis were regarded to be statistically significant at a probability value \( < 0.05 \). The EZR software program was used for the statistical analyses.\textsuperscript{30}

### Results

#### Overall survival and prognostic factors

The median survival time (MST) after the first pulmonary metastasectomy was 33.9 months, and the five-year survival rate was 42.5\% (Fig. 1A). Among the factors analyzed, the pre-thoracotomy CEA level, and the number of metastases at the first thoracotomy were statistically significant in the univariate analyses (Table 2). Patients with a pre-thoracotomy CEA level less than 5 ng/ml had better survival than those with a CEA level higher than 5 ng/ml (MST 95.0 months vs. 28.1 months, \( p = 0.043 \), Fig. 1B). Patients with a single metastasis at the first metastasectomy lived longer than those with multiple metastases (MST 66.3 months vs. 27.7 months, \( p = 0.047 \), Fig. 1C). However, the survival difference became insignificant when we compared the survival curves between those with one or two metastases and those with more than three metastases, not to mention when we used higher cut-offs for comparison. The pathological stage of the primary tumor, primary site of the tumor, DFI, the presence of liver metastases, the surgical procedure for pulmonary metastases, the size of the pulmonary metastasis, the laterality (unilateral or bilateral) of pulmonary metastases and the patient sex had no significant impact on the overall survival (data not shown).

#### Multivariate analysis of prognostic factors for survival

A multivariate regression analysis was performed to identify independent factors predicting the survival using a Cox proportional hazards model (Table 2). Among the factors analyzed, a pre-thoracotomy CEA level higher than 5 ng/ml was the most significant prognostic factor, with a relative risk of 2.01 (95\% confidence interval: \( 1.04–3.89, p = 0.037 \)).

#### Overall survival according to the postoperative CEA level

In order to identify a subgroup of patients who might benefit from metastasectomy, even though they had a high pre-thoracotomy CEA level, the survival differences according to the post-operative CEA level were estimated. Among 35 patients with a high pre-thoracotomy CEA level, the postoperative CEA level was available for 27 patients. Twenty-one patients experienced a CEA decline after metastasectomy, and furthermore, the postoperative CEA level in 14 patients became normal after the operation. The survival curves were significantly better in the patients whose CEA level returned to normal (MST 41.7 months) than in patients whose CEA level did not return to the normal level or increased after the surgery (MST 28.1 and 15.7 months, respectively, \( p = 0.021 \), Fig. 2).

### Discussion

When we consider pulmonary metastasectomy for cancers from various origins, the most important factor is how

\begin{table}
\centering
\caption{The prognostic factors for survival}
\begin{tabular}{|l|c|c|c|c|}
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Factors (n) & MST (months) & Univariate \( p \)-value & RR (95\% CI) & Multivariate \( p \)-value \\
\hline
Sex & Male (42) & 29.0 & 1 & \\
& Female (45) & 37.5 & 0.85 & 0.762 (0.398–1.46) & 0.41 \\
Age & & & & & \\
CEA\textsuperscript{*1} & \( \leq 5 \) ng/ml (43) & 95.0 & 1 & \\
& >5 ng/ml (37) & 28.1 & 0.043 & 2.01 (1.04–3.89) & 0.037 \\
Disease-free interval\textsuperscript{*2} & \( \leq 12 \) months (15) & 41.8 & 1 & \\
& >12 months (67) & 33.9 & 0.97 & 0.688 (0.318–1.49) & 0.34 \\
Number of nodules at first thoracotomy & 1 (46) & 66.3 & 1.75 (0.894–3.42) & 0.10 \\
& >1 (41) & 27.7 & & \\
\hline
\textsuperscript{*1}Data not available for seven patients. \textsuperscript{*2}Data not available for five patients. MST: median survival time (after the first pulmonary resection); RR: relative risk; CI: confidence interval; CEA: carcinoembryonic antigen.
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effective chemotherapy is for the particular type of cancer. Colorectal carcinoma is thought to be a relatively chemotherapy-insensitive tumor, as metastatic breast cancer used to be until about 20 years ago.\textsuperscript{25,31–33} As chemotherapy for colorectal carcinoma is improving,\textsuperscript{1–3,5,7,8} it is necessary to be able to properly select patients who would benefit from pulmonary metastasectomy. In this study, we have shown that CEA negative (or low level) cases and those with a single metastasis would benefit most from resection. These factors are in agreement with previous studies.\textsuperscript{15,21–23} The pre-thoracotomy CEA level was the most prognostic factor for survival in a multivariate analysis, and has been reviewed in other reports.\textsuperscript{34,35} It has been reported that 70\% of patients with recurrent or metastatic colorectal carcinoma are CEA-positive.\textsuperscript{30} The indications for surgery should be considered carefully in these “high-risk” patients.

CEA is a soluble glycoprotein, which has been reported to be markedly elevated in patients with several cancers, especially with digestive tract cancers. The higher serum CEA levels correlate with more advanced stages in patients with colorectal carcinoma. Therefore, our result showing that patients with a higher pre-thoracotomy CEA level have a worse prognosis is reasonable. However, the impact of a decrease or normalization of the CEA levels after pulmonary metastasectomy has been unclear. There have been few studies that have examined this point. It can be speculated that if the postoperative CEA level would become normal, the remnant cancer might be small or eliminated, leading to a better prognosis. We herein reported that the postoperative CEA level could affect the patient’s prognosis.

In conclusion, we have shown a survival benefit of pulmonary metastasectomy in selected patients with colorectal cancer. The serum CEA level can be a useful indicator for determining the indications for a surgery, predicting the postoperative prognosis and for selecting patients suitable for adjuvant chemotherapy after pulmonary metastasectomy.

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**Disclosure Statement**

Atsushi Osoegawa and other co-authors have no conflict of interest.

**References**


