Outcomes after repeated resection for recurrent pulmonary metastases from colorectal cancer

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Background: It remains controversial whether metastasectomy is still feasible in patients with pulmonary recurrence from colorectal cancer, after initial metastasectomy. The aim of this study was to evaluate outcomes of repeated metastasectomy in these patients.

Materials and methods: From 1995 to 2007, 202 patients had received a pulmonary metastasectomy from colorectal cancer at our institution. Over a median follow-up of 28.9 months, 48 patients received second metastasectomy (29 wedge resections, 5 segmentectomies, 13 lobectomies, and 1 completion pneumonectomy). The median disease-free interval was 9.6 months. Among these 48 patients, 28 showed pulmonary recurrence again and of those, 10 patients received third metastasectomy (two wedge resections, two segmentectomies, four lobectomies, and two completion pneumonectomies).

Results: There was no postoperative mortality. Of the 48 patients who underwent second metastasectomy, overall and disease-free 5-year survivals were 79% and 49%, respectively, after second operation. Of the 10 patients who received third metastasectomy, overall survival was 78% at 5 years after last operation.

Conclusions: Repeated resection after initial metastasectomy can be carried out safely and provides long-term survival in patients with recurrent pulmonary metastasis from colorectal cancer. Our findings indicate that close follow-up for the early detection of recurrence and parenchyma-saving resection can improve the results after repeated resection.

Key words: colorectal cancer, pulmonary metastasis, repeated metastasectomy

Introduction

The role of metastasectomy for the treatment of pulmonary metastasis from colorectal carcinoma is widely accepted [1]. Surgical resection is now indicated for multiple metastases, including metastasis with bilateral involvement, simultaneous hepatic metastasis, and even for advanced diseases in which pulmonary metastasis is found at initial presentation.

However, no consensus has been reached concerning the optimal treatment strategies for patients that have already undergone pulmonary metastasectomy, and are later found to have recurrent pulmonary metastasis, despite efforts, like systemic chemotherapy, to overcome the disease. Furthermore, no standard has been proposed that enables adequate answers to questions frequently encountered under clinical conditions regarding the benefits actually conferred by repeated resection under the following circumstances: (i) pulmonary recurrence found within a year after initial metastasectomy, (ii) multiple but resectable pulmonary recurrence including bilateral metastasis, or (iii) the feasibility of a third or even fourth resection of pulmonary metastasis.

We follow a policy of undertaking metastasectomy regardless of the number of resections already carried out and bilaterality or multiplicity of the lesions, if the following criteria are fulfilled: (i) the primary tumor has been controlled or is believed to be controllable, (ii) the patient can tolerate the operation, (iii) there is no evidence of uncontrollable extrathoracic metastasis, (iv) there is no better alternative systemic treatment, and most of all, (v) complete resection of recurrent disease is believed to be possible at presentation [2].

This analysis was carried out with an emphasis on the interval between initial metastasectomy and repeated resection, the multiplicity of lesion, and the number of metastasectomies carried out. The aim of this study was to evaluate the operative outcomes of repeated resection and to establish standards for the treatment of recurrent pulmonary metastasis.

Materials and methods

From January 1995 to December 2007, 202 patients underwent surgical resection for pulmonary metastasis from colorectal carcinoma at our
metastasectomy and subsequent death without records of treatment or recurrence (n = 1), and (iv) loss of follow-up immediately after initial metastasectomy and subsequent death without records of treatment or recurrence (n = 1). The median follow-up period was 28.9 months. Overall 5-year survival for the 195 patients was 71.2%, and median disease-free survival (DFS) and 5-year DFS were 27.4 months and 33.3%, respectively.

Patients were closely observed after the initial resection. Chest computed tomography (CT) was routinely carried out every 3 months for the first year, every 6 months for the next 2 years, and annually thereafter. Chest X-ray and serum carcinoembryonic antigen (CEA) level were routinely checked at every outpatient visit. When the extrapulmonary recurrence was suspected, we tried to obtain histological or unequivocal radiological proof. If pulmonary recurrence was considered resectable, aggressive surgical resection was carried out.

Of the 195 patients, 98 patients developed recurrent pulmonary metastasis. Median disease-free interval (DFI) between initial resection and the recurrence of pulmonary metastasis was 9.6 months. Median disease-free interval (DFI) between initial metastasectomy and subsequent death without records of treatment or recurrence (n = 1). The median follow-up period was 28.9 months. Overall 5-year survival for the 195 patients was 71.2%, and median disease-free survival (DFS) and 5-year DFS were 27.4 months and 33.3%, respectively.

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Of the 195 patients, 98 patients developed recurrent pulmonary metastasis. Median disease-free interval (DFI) between initial metastasectomy and the recurrence of pulmonary metastasis was 9.6 months. Fifty patients could not undergo second metastasectomy because of the following: (i) metastasis to other organs (brain, liver, bone, and others) (n = 21), (ii) multiple unresectable pulmonary recurrence (n = 20), (iii) relapse of primary tumor (n = 1), (iv) patient’s refusal to undergo further treatment, including surgery and even chemotherapy (n = 8), and (v) poor general condition after systemic chemotherapy (n = 3). The adjuvant chemotherapy for these patients was conducted under the guidelines of National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO). Briefly, the chemotherapeutic regimens included oxaliplatin/leucovorin/5-fluorouracil (FOLFOX), capecitabine–irinotecan, or irinotecan–leucovorin–5-fluorouracil (FOLFIRI), capecitabine–irinotecan with or without bevacizumab. The duration of chemotherapy varied among patients but was decided in compliance with the NCCN/ASCO guidelines.

The other 48 patients (27 male and 21 female, median age 58 years) underwent second metastasectomy. Of these 48 patients, pulmonary recurrence occurred in 28, and 10 patients (five male and five female and median age of 58) underwent third metastasectomy for pulmonary metastasis. The median follow-up period was 42.3 months (7.9–76.7 months) after the second metastasectomy and 67.7 months (26.8–108.6 months) after the third metastasectomy.

We retrospectively reviewed the surgical technique and postoperative outcomes, including recurrence and survival of repeated metastasectomy.

This study was reviewed and approved by Institutional Review Boards in Samsung Medical Center (Table 1).

results

Of the 48 patients with second metastasectomy, parenchyma-saving resection was carried out in 34 cases (29 wedge resections and 5 segmentectomies). Lobectomy was carried out in 13 cases and completion pneumonectomy in 1 case. Bilateral simultaneous resection was carried out in six patients. In one patient with five lesions bilaterally, sequential resection (left completion pneumonectomy and following right upper lobe wedge resection) was planned, but due to postpneumonectomy empyema, resection of the right side lesion could not be done. Twenty-eight patients had a single lesion, and 20 had multiple lesions. The mean number of metastatic nodules was 1.3. Three patients had lesions >4 cm. Complete resection was achieved in all patients except one patient with postpneumonectomy empyema. In the 10 patients with third metastasectomy, two wedge resections, two segmentectomies, four lobectomies, and two completion pneumonectomies were carried out. Two of these patients had multiple lesions, and those were less than five. No patient had bilateral metastasis in third metastasectomy.

Thirty-one patients received postoperative treatments following the initial metastasectomy, which included 28 oxaliplatin- or irinotecan-based standard chemotherapies,
Two chemoradiations, and 1 radiotherapy. Seventeen patients did not receive any further postoperative treatment. After second metastasectomy, 24 patients received additional oxaliplatin- or irinotecan-based chemotherapy, 2 received chemoradiation, and 1 received additional radiation. Twenty-one patients were closely followed up with periodic evaluations for recurrence without further postoperative treatment.

**mortality and morbidity**
No operative mortality occurred. Delayed postpneumonectomy empyema occurred in three patients that received completion pneumonectomy. Additional resection of a contralateral lesion could not be carried out in one of these patients, and this patient died of tumor recurrence. There was one patient with a prolonged air leak at right side after bilateral segmentectomy.

**survivals**
The overall survival (OS) of the 48 patients with second metastasectomy was 79.3%, and their median DFS and 5-year DFS were 42.8 months and 48.7%, respectively. OS of the 10 patients that underwent third metastasectomy was 77.8% (Table 2 and Figure 1).

**Table 2. Survival according to number of resections**

<table>
<thead>
<tr>
<th>Survival</th>
<th>Initial metastasectomy</th>
<th>Second metastasectomy</th>
<th>Third metastasectomy</th>
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<tbody>
<tr>
<td>Overall 5-year survival (%)</td>
<td>71.17</td>
<td>79.32</td>
<td>77.78&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>DFS</td>
<td></td>
<td></td>
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<tr>
<td>Median survival (months)</td>
<td>27.43</td>
<td>42.8</td>
<td>Not calculated&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5-year survival (%)</td>
<td>33.30</td>
<td>48.69</td>
<td>Not calculated&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup>The number of patients that underwent third metastasectomy was too small for statistical analysis.
<sup>b</sup>OS, overall survival; DFS, disease-free survival.

Figure 1. Kaplan–Meier survival curve for the patients who received second metastasectomy. The number of patients at risk is shown.

The DFI between initial metastasectomy and repeated resection for the 20 of these 48 patients was <1 year, but this DFI was not found to have a significant influence on survival.

The potential prognostic factors were age, sex, primary tumor pathology, primary tumor stage, DFI, extent of resection, the surgical approach used, numbers and sizes of metastases, bilaterality of the lesion, and preoperative CEA level. The only significant risk factor for patients' survival, identified by univariate analysis, was elevated preoperative CEA level above the normal range (P = 0.028). Multivariate analysis did not show any significant prognostic factor for recurrent metastasis.

**performance and quality of life after repeated resection**
Patients were asked for details of subjective symptoms and of their abilities to carry out daily activities (such as 30-min walk or light jog and climbing up two stairs without significant dyspnea) 2–3 months postoperatively. Recently, in patients of concern, their performance status was evaluated by 6-min-walk test. All patients with repeated metastasectomy were able to carry out daily activities without discomfort. Two patients had New York heart association class II dyspnea on exertion, but were able to tolerate adjuvant chemotherapy, and this symptom subsequently resolved. In particular, all three patients that suffered from postpneumonectomy empyema recovered sufficiently to carry out normal daily activities. Adjuvant therapy was not hindered by the general conditions of patients.

**discussion**
In our institution, we maintained a constant policy on the treatment of pulmonary metastasis from colorectal cancer. We carried out surgical resection aggressively in all patients who would be afforded additional surgical resection following the same criteria applied in initial metastasectomy [2]. Even in cases with extrathoracic metastasis (e.g. to the liver), if we consider it to be controlled, we actively carry out pulmonary metastasectomy. In addition, bilateral metastasis was resected, in almost all cases, simultaneously via bilateral approach of thoracotomy, thoracoscopic surgery, or sternotomy. The OS of the 48 patients that underwent second metastasectomy in our institution was 79.3% and of those that underwent third metastasectomy, it was 77.8%. The median DFS and 5-year DFS of those that underwent second metastasectomy were 42.8 months and 48.7%, respectively. These results were favorable when compared with those of initial metastasectomy in our institution and were a lot better when compared with previous reports regarding the feasibility of repeated pulmonary metastasectomy from colorectal cancer, where 5-year survivals were <50% [3–6].

There are some points that can explain the better survival in our study. First, for the early detection of recurrent metastasis, we closely followed up the patients. It includes tightly scheduled radiological examination and biochemical tests. Simple chest X-ray is inadequate for the early detection of small metastases, and chest CT is the most effective diagnostic modality for the pulmonary metastatic surveillance [7–9]. The
or by a combination of the two in presented preoperatively, by wedge resection, segmentectomy, residual tumor. In the present series, we removed all lesions patients and concluded that 11 (33.3%) had microscopic metastases and local recurrences of primary tumors [10, 11]. Secondly, in addition to ensuring a safe resection margin, we always attempt to retain as much pulmonary reserve as possible because future repeated resections might be necessary. Parenchyma-saving resections, such as wedge resection, precision excision, and segmentectomy, are our primary choice for pulmonary metastasectomy, and we view lobectomy and precision excision, and segmentectomy, are our primary choice for pulmonary metastasectomy, and we view lobectomy and more extensive resection as modalities of last resort. Welter et al. [3] reported outcomes for repeated resection in 33 patients and concluded that 11 (33.3%) had microscopic residual tumor. In the present series, we removed all lesions presented preoperatively, by wedge resection, segmentectomy, or by a combination of the two in >75% of cases. However, in terms of the initial 195 metastasectomies, incomplete resection was suspected in only five cases. In four of these, a contralateral nonoperated lesion, initially considered benign, was found to have increased in size by chest CT conducted immediately after surgery, and thus, these lesions were considered as metastases. Three of these patients later underwent repeated resection after adjuvant chemotherapy. In the remaining patient, the pathological report described microscopic residual tumor at the bronchial stump after lobectomy. Thirdly, vigorous multimodal approach, consisting of surgery and preoperative and postoperative chemotherapies, was applied for these patients. There has been a great advance in adjuvant therapies since the concept of pulmonary metastasectomy had been first adopted. In our institution, most of the patients receive adjuvant chemotherapy not only after the operation of primary tumor but also after metastasectomies, if only they could tolerate. As we mentioned above, the adjuvant therapy was conducted under the guidelines of NCCN and ASCO. It was mainly on the basis of the combination regimen, which involved the combination of infusional FOLFOX with bevacizumab or infusional FOLFIRI with bevacizumab. Various kinds of newly developed combination chemotherapy have been vigorously applied or under clinical trial [12, 13].

Beside the colorectal cancer, the efficacy of repeated pulmonary resection of pulmonary metastasis from sarcoma was already proven to be effective [19] and has been appraised in other malignancies, such as renal cell carcinoma and hepatocellular carcinoma [20–22]. Our result would imply that in the management of recurrent pulmonary metastasis from colorectal cancer, surgical resection must be considered at first, and even in multiple or bilateral pulmonary recurrence, or even in patients that have already received multiple operations for the pulmonary metastasis, repeated metastasectomy followed by chemotherapy can be helpful for the patients’ survival.

Many different prognostic factors have been proposed to influence the survival of patients with pulmonary metastasis from colorectal carcinoma [14–18]. Main factors identified in these previous studies are DFI after resection, thoracic lymph node involvement, numbers of metastases, and preoperative CEA level. However, in the present study, the first three factors were not found to have a significant influence on survival after repeated resection for recurrent pulmonary metastasis from colorectal carcinoma. In fact, the only significant risk factor identified was preoperative CEA level (P = 0.028). This is probably because the current study was carried out for the patients with repeated metastasectomy and previous studies were carried out mainly for the patients with initial metastasectomy. Accordingly, the patients with high preoperative CEA level must be kept in tight surveillance of recurrence.

In conclusion, we consider that repeated resection after initial metastasectomy can be safely carried out and that it prolongs survival in patients with recurrent pulmonary metastasis from colorectal cancer. Our findings indicate that close follow-up to detect recurrence at an early stage and meticulous parenchyma-saving resection can increase the likelihood of a successful result after repeated resection of pulmonary recurrence.

disclosure
The authors have nothing to disclose for conflict of interest.

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