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Prognostic markers for metastatic colon cancer patients undergoing multiple metastasectomies

COLON

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ABSTRACT

Background/Aims: Following metastasis resection, 5-year survival rate has been reported as approximately 40%. There is no consensus regarding prognostic factors related to progression-free survival after repeated metastasectomies.

Materials and Methods: A total of 21 patients with metastatic colorectal cancer who underwent repeated metastasectomies were retrospectively analyzed. The periods between the first and second metastasectomies and that between the second metastasectomy and progression were defined as metastasis-free survival 1 (MFS1) and metastasis-free survival 2 (MFS2), respectively. Univariate analysis was used to analyze factors related to MFS1 and MFS2.

Results: Approximately two-thirds of the patients had synchronous metastasis, which were localized mostly in the liver (90%). During a 49-months follow-up, MFS1 was 15.7 (8.4–23) months and MFS2 was 26.3 (12.3–40.4) months. Systemic chemotherapy followed the first metastasectomy (p=0.01), and the recurrence site (p=0.03) was found to be related to MFS1. Furthermore, the number of metastases during the first metastasectomy (p=0.02), the type of the chemotherapy regimen administered following the first metastasectomy (p=0.04), and the number of metastases before the second metastasectomy (p=0.03) were significantly related to MFS2.

Conclusion: Surgical resection is currently the most effective and curative form of therapy for colorectal metastasis, whenever possible. Repeated metastasectomies can be achieved safely in experienced centers; thus, the operability of the patients should be evaluated by a multidisciplinary approach during treatment.

Keywords: Colon cancer, metastasectomy, metastasis-free survival

INTRODUCTION

One-fourth of the colon cancer patients have metastases at the time of diagnosis, and 35%–45% develop metachronous metastases during the course of the disease (1). The liver is the most common site of metastasis followed by the lung (2). Metastasectomy is the standard treatment for the resectable metastasis of colon cancer, and if untreated, median survival time is less than a year (1,2). With improved surgical techniques and radiological methods to detect metastases in early stages, metastasectomy has become more prevalent among colorectal cancer patients.

In the presence of a potentially resectable liver metastasis, preoperative chemotherapy can facilitate metastasectomy with clear margins (3). Preoperative 5-fluorouracil (5-FU)-, irinotecan-, oxaliplatin-, bevacizumab (Avastin; Roch, USA)-, and cetuximab (Erbitux, Merck, USA)-based chemotherapy regimens can be used to facilitate metastasectomy (2). Response rates exceed 50% with combinations (1).

With liver metastasectomy, a 5-year survival rate of metastatic colon cancer has been reported to be ranging from 12% to 58%, and median survival ranged from 42 to 68

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months (2-6). After pulmonary metastasis resection, 5-year survival rates ranged from 24% to 63% (7). Surgical margins, the number of metastases, carcinoembryonic antigen (CEA) level, disease-free interval, and the presence of locoregional lymph nodes are known as prognostic factors for metastatic colon cancer after metastasectomy (8). Approximately two-thirds of the patients had recurrence after the first metastasectomy in the first 2 years (8,9). Recurrence following liver metastasectomy indicates poor prognosis, showing a tendency of the disease to be systemic (10). Only 20%–30% of the patients can be referred for re-resection. In well-selected patients, more than one metastasectomy has been demonstrated to provide long-term survival (10,11).

The aim of our study was to evaluate the outcome of multiple metastasectomies in colorectal cancer patients after recurrence and to define the prognostic factors related to metastasis-free survival (MFS).

MATERIALS AND METHODS

We retrospectively reviewed data from 156 metastatic colorectal cancer patients who were treated with metastasectomy in the Haydarpaşa Numune Education and Research Hospital between 2009 and 2013. Of these, 21 patients underwent liver, lung, or abdominal lymph node metastasectomy more than one time, and these patients constituted the study group. All patients were metastatic at presentation or developed metachronous metastasis during the course of the disease. Patients who had secondary malignancies or distant metastases other than the liver, lung, and abdominal lymph node metastases were excluded. A total of 13 patients had synchronous metastasis; metastasis developed metachronously in eight patients during the follow-up period.

If the primary disease was under control, metastasectomy was performed, aiming to remove all tumors completely with an acceptable amount of residual hepatic reserve. Prior to surgery, metastases were evaluated with ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI), and colonoscopy was also performed to exclude local recurrence. Initially, all patients underwent liver metastasectomies and subsequently during the follow-up period; 13 liver, seven lung, and one abdominal lymph node re-metastasectomies were performed. Only two patients had both lung and liver metastases before the first metastasectomy.

The study was performed retrospectively based on the medical records of the patients in our institution. Because the study was a retrospective analysis, we did not obtain the approval of the ethical committee. Clinical information as well as data regarding pathological parameters such as lymphovascular invasion (LVI), perineural invasion (PNI), surgical margins, and grade and stage during diagnosis were obtained from patients' charts after receiving informed consent from the patient. Oxaliplatin-, irinotecan-, or 5-FU-based regimens were used as chemotherapy to convert inoperable metastases to operable states.

Statistical analysis

Statistical analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software. The period between the first and second metastasectomies was defined as metastasis-free survival 1 (MFS1), and that between the second metastasectomy and progression was referred to as metastasis-free survival 2 (MFS2). Factors related to MFS1 and MFS2 were analyzed using both univariate and multivariate analyses. In addition, overall survival (OS) was described as the time from the diagnosis to the date of the patient's death or last-known contact. Survival analysis and curves were established according to the Kaplan–Meier method and compared using the log-rank test. A 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values in the tests were two-sided, and p values less than or equal to 0.05 were considered to be significant.

RESULTS

There were six females and 15 males with a median age of 54 (range: 34–78) years during diagnosis. The primary tumor was located at the right colon in five patients (23.8%), in the left colon in 16 patients (76.2%), and in the rectum in six patients. Primary tumors were associated with lymph node metastasis in 12 patients. The median number of metastatic and resected lymph nodes was two (range: 0–4) and 17 (range: 7–35), respectively (Table 1). LVI was present in 12 patients (60%), and PNI was detected in six primary tumors (31.5%). KRAS status could be evaluated in 57.1% of the primary tumors, and mutation was detected in seven patients (33.3%).

None of the tumors were grade 3, but 18 (85.7%) were grade 2. Approximately more than half of the patients (61.9%) were metastatic (13 patients) at the time of diagnosis, and others were staged pathologically as follows: 3 (14.3%), stage II and 5 (23.8%), stage III. Before the first metastasectomy, all metastases were located in the liver; moreover, two patients had simultaneous lung metastasis. Metastases occurred metachronously in these eight patients during follow-up. Six of these eight patients had liver metastasis, one had metastasis in both the liver and lung at the same time, and one had abdominal lymph

Table 1. The clinicopathological factors

Characteristics age (year)	Median	Range
	54	34-78
Primary tumor size (cm)	4.5	2-8
Operated lymph node	17	7-35
Metastatic lymph node	2	0-4
Follow-up time (months)	48.7	9.4-100.7
OS (months)	78.4	na
MFS1 (months)	15.7	8.4-23
MFS2 (months)	26.3	12.3-40.4

OS: overall survival; MFS: metastasis-free survival

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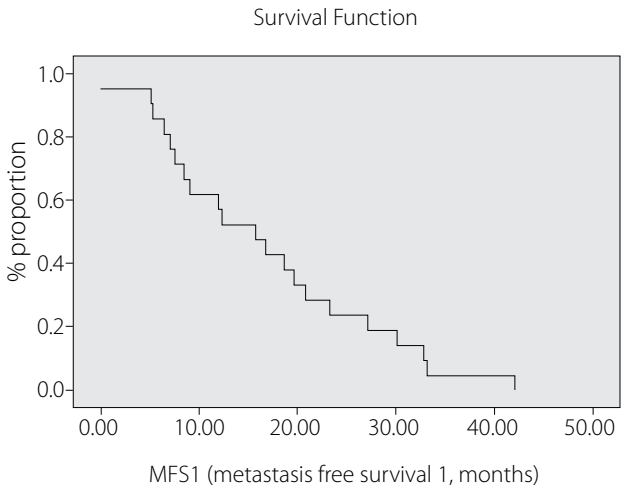

Figure 1. The curve of metastasis-free survival 1 (MFS1).

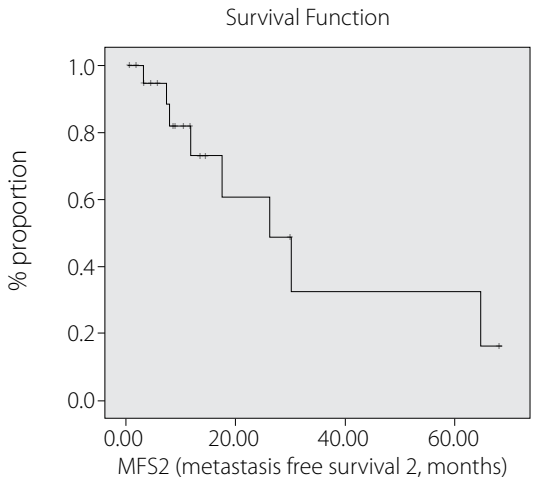

Figure 2. The curve of metastasis-free survival 2 (MFS2).

node metastasis. We did not observe any mortality or serious morbidity during metastasectomies. The median number of metastases was two (1-4), and 10 patients had one metastasis (47.6%), six had two metastases (28.6%), and 5 (23.8%) had more than two metastases before metastasectomy. Ten patients (46%) simultaneously underwent primary tumor resection with liver metastasectomy. The first metastasectomy was followed by systemic chemotherapy, including oxaliplatin (four patients)-, irinotecan (three patients)-, or 5-FU (two patients)-based regimens for nine patients. Two patients with both lung and liver metastases underwent liver metastasectomy followed by lung metastasectomy within a median period of 1 month. Negative surgical margins could be achieved during the first metastasectomy in 17 patients, but four patients underwent R1 resection. Fifteen patients (71.7%) received chemotherapy, including oxaliplatin (XELOX or FOLFOX) in 10 patients, but the other five patients were given capecitabine after the first metastasectomy.

Median OS time was 78 months, and median MFS1 and MFS2 were 15.7 (8.4–23.5) months and 26.3 months (12.3-40.4), respectively, (p=0.2). Figures 1 and 2 show the Kaplan–Meier curve. All patients progressed during a median follow-up period of 48.70 months; 3-year OS rate was 94%. Systemic chemotherapy following the first metastasectomy (p=0.01), and the recurrence site after the first metastasectomy (p=0.03) was found to be related to MFS1. The median MFS1 was 18.6 months for patients who were treated with chemotherapy after the first metastasectomy, whereas it was 5.3 months for patients who were not treated with chemotherapy. Patients with recurrent liver metastases had worse MFS1 compared with other metastases (median, 11.9 months vs. 23.3 months). Furthermore, the number of metastases during the first metastasectomy (p=0.02), the type of chemotherapy regimen administered subsequently (p=0.04), and the number of metastases before the second metastasectomy (p=0.03) were significantly related to MFS2. Patients with more metastases during both the first and second metastasectomies had worse MFS2 compared with those with fewer metastases. Patients receiving oxaliplatin-based chemotherapy after the first metastasectomy had better MFS2 than 5-FU-based regimens (1-year MFS2 rates: 87.5% vs. 37.5%). Recurrence sites after the first metastasectomy were mostly the liver (13 patients), followed by the lung in seven patients and abdominal lymph node in one patient. None of the factors was found to be related to OS. Table 2 shows the results obtained on conducting univariate analysis. We could not find any independent prognostic factor related with MFS1 or MFS2 by multivariate analysis. After second metastasectomies, eight recurrence were detected; because of systemic recurrence, re-operation was not considered.

DISCUSSION

Approximately 25% of colon cancer patients have metastatic disease at the time of diagnosis, and metastases develop during the course of the disease in 40% of the patients (1). Potential long-term survival for metastatic colon cancer patients can only be achieved with liver or lung metastasectomy. To date, numerous studies have reported the OS or progression-free survival (PFS) benefit after liver metastasectomy. Combining more effective chemotherapy with safer surgical techniques has rendered multiple and extensive metastasectomies possible for recurrent colon cancer patients; however, prognostic markers for determining suitable patients have not been documented. Accordingly, we analyzed our metastatic colon cancer patients who underwent multiple metastasectomies.

The aim of our study was to analyze the factors related to the MFS of metastatic colon cancer patients who underwent multiple metastasectomies. A total of 21 patients were included; 13 patients (61.9%) had liver metastasis at the time of diagnosis, and nine of these 13 patients underwent metastasectomy at the same time as that of primary resection without receiving preoperative chemotherapy. On the other hand, preoperative 5-FU-based chemotherapy was administered to four patients.

Table 2. The results of the univariate analysis

Characteristics	Number (%)	5-year OS (%)	p	2-year MFS1 (%)	p	2-year MFS2 (%)	p
Gender			0.5		0.6		0.3
Female	6 (28.6)	N/A		16		80	
Male	15 (71.4)	78.6		26		58.2	
Metastasis at diagnosis			0.7		0.8		0.5
Synchronous	13 (61.9)	75		23		66.7	
Metachronous	8 (38.1)	87.5		25		29.2	
Metastasis number			0.06		0.4		0.3
1	10 (47.6)	80		30		55.6	
2	6 (28.6)	50		16		40	
>2	5 (23.8)	66		20		N/A	
localization			0.8		0.1		0.9
Right	5 (23.8)	N/A		40		N/A	
Left	16 (76.2)	76.4		18.8		60.9	
Surgical margin			0.1		0.9		0.8
R0	17 (81)	92.9		29.4		55.5	
R1	4 (19)	N/A		0		N/A	
Metastatic site			0.1		0.5		0.5
Liver	19 (90.5)	77.4		22.2		65.1	
Liver+lung	2 (9.5)	N/A		33.3		N/A	
MADJ			0.1		0.01		0.1
Present	15 (71.7)	16.4		33.3		44.3	
Absent	6 (28.6)	N/A		0		50	
T stage			0.4		0.7		0.3
3	19 (90.5)	81.7		26.3		51.2	
4	2 (9.5)	N/A		0		N/A	
Stage at diagnosis			0.9		0.4		0.01
2	5 (23.8)	50		25		N/A	
3	3 (14.3)	66.7		33			
4	13 (61.9)	75		16.7			
grade			0.6		0.8		0.2
1	3 (14.3)	N/A		na		N/A	
2	18 (85.7)	82		27.8		55.5	
Lymphovascular invasion			0.7		0.2		0.8
Present	12 (60)	75		16.7		58.3	
Absent	8 (30)	83.3		37.5		55.6	
Perineural invasion			0.4		0.9		0.6
Present	6 (31.5)	N/A		0		75	
Absent	13 (68.5)	75		30.8		44.9	
Neodjuvant treatment			0.2		0.1		0.2
Present	15 (71.4)	87.5		33		70	
Absent	6 (28.6)	76.7		41.7		56.3	
MADJ oxaliplatin			0.1		0.6		0.04
Irinotekan	10 (66.7)	80		30		65.6	
5FU	1 (6.7), 4 (26.7)	66.7		25		N/A	
Recurrence side after metastasectomy		0.3		0.2		0.8	
Liver	13 (61.9)	88.9		7		68.2	
Other	8 (38.1)	66.7		50		40	
Second metastasectomy surgery			0.8		0.5		0.2
R0	19 (90.5)	83.3		26.3		64.4	
R1	2 (9.5)	N/A		N/A		N/A	
MADJ			0.8		0.2		0.2
Present	19 (90.5)	93.3		26.3		51.2	
Absent	2 (9.5)	50		N/A		N/A	
MADJ type			0.3		0.5		0.5
5-FUFA	5 (23.8)	N/A		20		33.3	
Oxaliplatine	5 (23.8)	N/A		40		N/A	
Irinotekan	9 (42.9)	87.5		22.2		50.8	

OS: overall survival; MFS: metastasis-free survival; RF: radiofrequency ablation; MADJ: adjuvant treatment after metastasectomy

Furthermore, six liver metastases and 2 lung and liver metastases developed during the course of the disease. All patients underwent hepatic resection during the first metastasectomy. In two patients, additional lung metastasectomy was performed at a median period of 1month after the first metastasectomy.

Recurrence following liver metastasectomy is associated with poor prognosis, and only 20%–30% of these patients may be amenable to re-resection (10). A review of 584 metastasectomies in colorectal cancer patients, surgical margins and extrahepatic disease resection were associated with a poor prognosis (1). The most common site of recurrence was the lung (32%) followed by the liver (28%). Thirty-three (34%) patients underwent re-resection, 20 for lung recurrence and 13 for liver recurrence. Resection of recurrence is associated with longer DFS (1). In our study, after the first metastasectomy, 13 patients progressed with liver metastases, six with lung metastases, and two with lymph node metastases, and second metastasectomies for the liver, the lung, or lymph nodes were performed. Two-year MFS1 and MFS2 rates were 23.8% and 60.8%, respectively. In a study by Hsu, the initial stage at the time of diagnosis was reported to be related to PFS after liver metastasectomy, and patients had recurrence within 30 months (2). In our study, the reason for shorter MFS period after the first metastasectomy (15.7 months) may be associated with metastases other than liver metastasis, and the R0 resection rate was also lesser in our study (80.9% vs. 90.8%). We could not find any patient-related factors, such as age and sex, or tumor characteristics, such as primary tumor location, LVI, PNI, or grade, to be associated with MFS1 or 2, which were similar to those documented in the literature (10). In the literature, 39 colon cancer patients with lung metastasectomy were evaluated, and 21 of them had undergone liver metastasectomy previously. OS and DFS were comparable in both groups with 5-year OS rates of 20% and 30%, respectively, for the lung-only metastasectomy group (12). Takahashi et al. (13) also retrospectively analyzed 30 patients who received multiple resection for both hepatic and pulmonary metastases of colorectal cancer. They defined DFS time as the time period from the first metastasectomy for the first organ to the second metastasectomy, which was similar to the definition of MFS1 in our study. They reported the 2-year DFS rate after the first metastasectomy as 24% with a median of 13 months, which was again similar to our study (23.8% and 15.7 months). Shah et al. (14) also reported a 5-year survival rate of 74% after multiple metastasectomy for colorectal cancer patients. In our study, 3-year OS was reported as 94% because of the shorter follow-up time of 48 months. Although systemic chemotherapy after metastasectomy was not used in the study by Takahashi et al. (13), in the study by Shah, all patients were administered chemotherapy after metastasectomy. We also applied chemotherapy after the first metastasectomy in 15 of 21 patients (71.4%). There is no consensus regarding adjuvant chemotherapy after metastasectomy. In the analysis of two randomized clinical studies, 5-FU-based chemotherapy had marginal statistical significance associated with both PFS and OS after metastases resection (15). Brandi et al. (8) also reported that adjuvant chemotherapy was the independent prognostic factor for DFS after the first resection of liver or lung metastasectomy in 78 metastatic colon cancer patients. They reported a median DFS of 16 months with chemotherapy compared with 9.7 months without adjuvant chemotherapy. Although our study group was smaller than that of the reported study, patients who were given adjuvant chemotherapy following metastasectomy had better MFS1 compared with those who were not (18.6 vs. 5.3 months, p=0.01); this result was also in accordance with the literature.

Nishio et al. (16) analyzed 44 patients who underwent a second liver resection for colorectal liver metastasis. At the time of repeat resection, 13 patients (24%) had extrahepatic disease, and five of them had lung metastases. Three-year survival rates following repeat resection was 53%, and the size of metastasis, preoperative CEA levels, and surgical margins were found to be related to survival. Eight out of our 21 patients (38%) had progressed from the extrahepatic site after the first metastasectomy, and six had lung metastases; the 3-year survival rate was 94%. Only adjuvant chemotherapy and recurrence site were related to metastasis-free survival after the first metastasectomy.

We consider our study group to be small. None of the clinicopathological factors were found to be associated with survival. Contrary to the literature, we also analyzed factors related to MFS2. The number of metastases during the first metastasectomy (p=0.02), the type of chemotherapy regimen administered following the first metastasectomy (p=0.04), and the number of metastases before the second metastasectomy (p=0.03) were significantly related to MFS2.

The median survival following liver and lung metastasectomies have been reported as 68 and 38 months, respectively (6). Hsu et al. (2) reported the 5-year survival rate of patients who underwent liver metastasectomy as 42.1%. We found longer survival periods, resulting in a median of 78 months. Our study indicates that in selected patients, surgery for metastases occurring during the course of the disease contributed to survival. Therefore, all relapsed patients should be evaluated for resection, and those fit for surgery should be considered for a second metastasectomy.

Zabaleta et al. (17) reviewed lung metastasectomy in 84 colorectal cancer patients. Seventeen of them (20%) had undergone liver metastasectomy previously, and previous liver metastasis was reported as a negative prognostic factor. They found that the disease-free interval between primary tumor and liver metastasectomy was an important prognostic factor. We found no correlation between MFS1 and MFS2 and survival.

In conclusion, we have shown that repeated metastasis resection in metastatic colon cancer patients can positively affect MFS. Systemic chemotherapy should be considered after me-

tastasectomy for all patients; we think that aggressive metastasectomy can be an option for some selected patients, even if the patient has previously undergone hepatic metastasis.

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