

# Hepatic resection margin predicts survival in colorectal cancer with hepatic metastasis

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**Backgrounds/Aims:** Prognostic factors for colorectal cancer with hepatic metastasis are not well-established. We investigated the factors that predicted survival following surgical resection of hepatic metastases in patients with colorectal cancer. **Methods:** Fifty-three patients underwent resection of hepatic metastases of colorectal cancer between January 2000 and December 2005, with follow-up periods that ranged from 3 to 119 months. In this retrospective study, the effects of sex, age, type of hepatic resection, T stage and N stage of the primary cancer, number and size of metastatic hepatic tumors, synchronicity or metachronicity of the liver metastases, surgical resection margins, and preoperative carcinoembryonic antigen (CEA) levels on 1-year and 3-year survival were analyzed using the Kaplan-Meier method and the log rank test. **Results:** Median survival was 39.9 months and the 3-year survival rate was 62.2%. Twenty patients died during the follow-up period of 3 to 119 months (mean, 48.8±34.24). In univariate analysis, only the surgical margin of the hepatic metastasis resection correlated significantly with 3-year survival. Sex, age, T stage and N stage of the primary cancer, synchronicity or metachronicity of the metastases, number and size of hepatic metastases, type of hepatic resection and preoperative CEA levels did not predict long-term outcome. **Conclusions:** Hepatic resection provides a safe and effective treatment in patients with hepatic metastasis from colorectal cancer. In this study, only the surgical resection margin of the hepatic metastasis of colorectal cancer significantly predicted survival. ([Korean J Hepatobiliary Pancreat Surg 2012;16:55-58](#))

**Key Words:** Colorectal cancer; Hepatic metastasis; Prognostic factor

## INTRODUCTION

The incidence of colorectal cancer is increasing in Korea as like in Western countries. Up to 50% of patients with colorectal cancer will develop hepatic metastasis from the disease.<sup>1</sup> Up to 25% of patients with colorectal cancer will have hepatic metastasis at diagnosis; more than 70% of all patients will develop hepatic metastasis; and almost 90% of patients who die from colorectal cancer have hepatic metastases.<sup>2</sup>

Hepatic resection currently presents the only potentially curative treatment for patients with hepatic metastases from colorectal cancer, although this approach is feasible in fewer than 25% of patients.<sup>3</sup> Surgical resection for hepatic colorectal metastases favors long-term survival, with 5-year survival rates ranging from 30% to 40%, and with median survival between 39 and 46 months. Patients with untreated hepatic metastasis have a median survival of

6-12 months, and the median survival with chemotherapy is 12-18 months.<sup>4-6</sup>

The factors that predict outcomes in colorectal cancer with hepatic metastasis are not well established, although resection margin, number and size of metastatic hepatic tumors, preoperative carcinoembryonic antigen (CEA) levels and stage of the primary tumor show significant associations with survival.<sup>5-7</sup> In this study, we analyzed the factors that may predict outcome of colorectal cancer with hepatic metastasis.

## METHODS

Between January 2000 and December 2005, 53 patients underwent resection for hepatic metastasis from colorectal cancer, with follow-up periods that ranged from 3 to 119 months. The diagnosis of hepatic metastasis was determined by preoperative abdominal ultrasonography and

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abdominal computed tomography, and was confirmed histologically.

Thirty six hepatic metastases were resected in the same operation as the primary tumor, and 17 metachronous hepatic metastases were confirmed during the follow-up period. We excluded patients with multiple distant metastases.

We analyzed the following factors for relationships to patient outcome: sex, age, T and N stage of the primary cancer, synchronicity or metachronicity of the liver metastasis, number and size of hepatic metastases, type of hepatic resection and preoperative CEA levels.

Survival was analyzed by the Kaplan-Meier method and differences in survival were compared using the log-rank test. Fisher's exact test or the chi-square test was used in univariate comparisons. Statistical analysis was performed using SPSS Version 17.0 for Windows (IBM Corporation, Armonk, NY, USA). Differences were considered significant for  $p$ -values < 0.05.

## RESULTS

Thirty-six (67.9%) of 53 patients were male and 17 (32.1%) were female. The mean age was  $63.1 \pm 10.3$  years (range: 45-81). The mean follow-up period was  $48.8 \pm 32.4$  months and the median, 39.9 months. Thirty-six (67.9%) of 53 patients had synchronous metastasis and 17 (32.1%) had metachronous metastasis. Of all liver resections performed, 41.5% (n=22) were wedge resections, 47.1% (n=25) were segmentectomies and 11.3% (n=6) were lobectomies. Based on TNM classification, the primary tumor was staged T3 in 45 patients (84.9%), T4 in 8 patients (15.1%), and N0, N1, N2, N3 in 15 patients (28.3%), 22 patients (41.5%), 13 patients (24.5%), and 3 patients (5.6%), respectively. Forty-seven patients (88.7%) had tumors with largest diameter of more than 5 cm and 46 patients (86.6%) had solitary tumors or two tumors. Seven patients (13.4%) had three or more tumors. The mean preoperative CEA level was  $17.9 \pm 43.1$  ng/ml (range: 0.76-302 ng/ml). Twenty patients (37.7%) had higher than normal (< 5 ng/ml) preoperative CEA levels and 13 patients (24.5%) had highly elevated preoperative CEA levels ( $\geq 20$  ng/ml) (Table 1).

The overall survival rate was 81.0% at 1 year and 62.2% at 3 years after hepatic resection. Sex, age, syn-

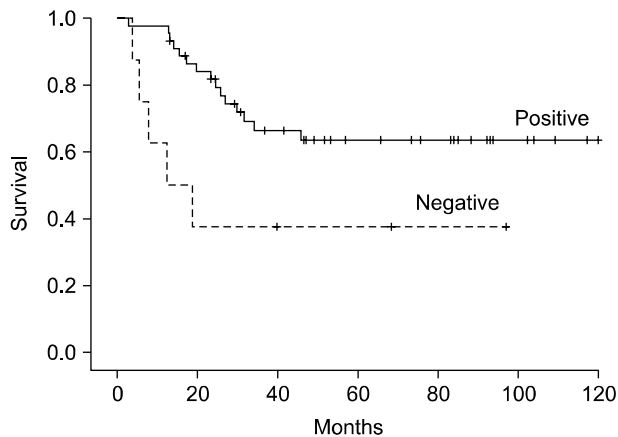
**Table 1.** Prognostic factors for survival in patients with hepatic metastasis from colorectal cancer

Parameters	No. of patients	3-year survival (%)	Median survival (months)	$p$ -value
Overall	53	62.2	38.3	
Sex				NS
Male	36	66.8	41.5	
Female	17	52.9	31.6	
Age				NS
< 60	19	62.2	31.6	
> 60	34	62.4	36.7	
Metastasis				NS
Synchronous	36	65.7	45.8	
Metachronous	17	54.0	56.7	
Primary T-stage				NS
T3	45	67.0	39.9	
T4	8	37.5	24.5	
Primary N-stage				NS
N0	15	57.4	41.5	
N1	22	75.4	38.3	
N2	13	46.2	19.7	
N3	3	66.7	75.6	
Pre-op CEA level				NS
> 20 ng/ml	13	66.6	35.9	
$\leq 20$ ng/ml	40	60.7	43.7	
Operation				NS
Wedge resection	22	67.9	51.7	
Segmentectomy	25	56.6	24.5	
Lobectomy	6	62.5	25.7	
Number of tumor				NS
> 2	7	57.1	36.7	
$\leq 2$	46	63.1	36.5	
Largest tumor size				NS
> 5 cm	6	83.3	35.3	
$\leq 5$ cm	47	60.2	39.9	
Resection margin				0.024
Negative	45	66.5	45.8	
Positive	8	37.5	12.4	

NS, not significant

chronicity or metachronicity of metastasis, type of resection, T stage and N stage of primary cancer, number and size of tumors and preoperative CEA levels did not predict long-term outcome.

Eight patients (15.1%) had positive surgical margins and 45 patients (84.9%) had negative margins. Survival rates for patients who had positive resection margins were 87.5% and 37.5% at 1 and 3 years, respectively, and 95.6% and 66.5% at 1 and 3 years for patients who had negative resection margins (Fig. 1). During follow-up periods, 5 out of 8 patients who had positive margins were died, and all of them were caused by multiple recurrence



**Fig. 1.** Cumulative survival curves of the groups between surgical resection margin positive and negative.

of hepatic metastasis.

## DISCUSSION

The hematogenous spread of colorectal cancer leads into the liver through the portal vein. Because of this anatomical characteristic, a high proportion of colorectal cancers produce hepatic metastases,<sup>8</sup> and accordingly, the resection of hepatic metastases concurrently with the primary tumor is standard surgical procedure.<sup>9,10</sup> Studies support the survival benefit of this surgery for the patients with hepatic metastasis.<sup>6,11</sup>

Studies conducted to identify the factors most likely to benefit from surgical resection give inconclusive results. Some authors believe that age may increase the risk of surgery and reduce long-term survival, but in our study age did not correlate significantly with mortality. While some studies report lower survival rates for patients over 70 years old,<sup>7,12</sup> most studies report no significant correlation of age with either surgical or cancer-related mortality. In the few studies conducted on differences in survival between male and female patients, some found more favorable prognosis for women,<sup>13,14</sup> but the opposite finding was also reported.<sup>15,16</sup> In our study, gender did not influence the survival rate.

Hughes et al.<sup>17</sup> reported a 5-year survival rate of 37% following resection of one or two lesions and an 18% rate for three or more lesions. In the report by Cady et al.<sup>19</sup> none of the patients having three or more metastatic cancers experienced a disease-free period of 48 months or longer. Fong et al.<sup>6</sup> reported a 5-year survival rate of 44%

in patients with a single lesion and 28% in those with multiple lesions. In our study, however, the number of metastatic cancers did not affect the survival rate.

In the report of Fong et al.<sup>6</sup> the 5-year survival rate was 31% when the size of metastatic cancer was over 5 cm but 40% when it was under 5 cm. Scheele et al.<sup>5</sup> and Ahn et al.<sup>18</sup> also reported a lower survival rate in patients whose cancer size was over 5 cm. According to Nordlinger et al.<sup>7</sup> postoperative mortality was higher when the size of metastatic cancer was over 5 cm than when it was under 5 cm. In our study, the size of metastatic cancer did not affect the survival rate.

Preoperative CEA may indicate the risk for relapse after resection of the primary lesion, but the value of CEA in prognosis is controversial. Cady et al.<sup>19</sup> observed no patient with a 5-year disease-free interval among those with CEA concentration greater than 200 ng/ml; however, the 5-year disease-free rate was greater than 50% among those with CEA levels under 5 ng/ml. Based on this report, a CEA concentration higher than 200 ng/ml may be one of the most powerful prognostic indicators following resection of hepatic metastases. Oussoultzoglou et al.<sup>20</sup> divided patients into groups with normal CEA levels before and after surgery, high levels before and normal after surgery, and high levels both before and after surgery. Surveying the overall and disease-free survival of these groups, they observed the lowest rates in the group with high CEA both before and after the operation. Younes et al.<sup>21</sup> reported that the frequency of relapse was higher when preoperative CEA was high, and Hughes et al.<sup>17</sup> reported more favorable prognosis for patients with low CEA. On the contrary, however, Doci et al.<sup>22</sup> reported that survival did not differ according to preoperative CEA. We stratified our patients based on a preoperative CEA level of 20 ng/ml and observed no difference in the survival rates between the two groups.

Scheele et al.<sup>5</sup> reported that radical resection and the presence of residual cancer cells in the resection margin were the most important factors in predicting survival. Cady et al.<sup>23</sup> reported that an adequate resection margin was important for reducing relapse. Recent studies lend further support to the view that the resection margin correlates closely with relapse and survival. In our study as well, the presence of residual cancer cells in the resection margin was significantly related to the 3-year survival

rate.<sup>23</sup>

We could not perform multivariate analysis in this study because we lacked a sufficient number of cases with adequate follow-up time. In univariate analysis, however, the presence of residual cancer cells in the resection margin reflected adversely on survival. Hence, for hepatic metastasis in colorectal cancer, we may expect a higher survival rate through adequate hepatic resection, if primary tumor resection is possible.

In this study, surgical resection margin was significantly associated with postoperative survival in patients with colorectal cancer and hepatic metastasis. The significance of this result may be limited by the small number of patients included in the analysis and the relatively short follow-up periods recorded. The findings are nevertheless consistent with previous observations that careful resection of hepatic metastases may promote survival in patients with colorectal cancer.

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