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Risk Factors for the Development of Metachronous Liver Metastasis in Colorectal Cancer Patients After Curative Resection

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Abstract
Background Metachronous liver metastasis (MLM) occurs in 20–40% of colorectal cancer (CRC) patients following surgical treatment. The aim of the present study was to determine the risk factors affecting the development of MLM in CRC patients following curative resection.
Methods A total of 1,356 patients who underwent curative intent resection for CRC were retrospectively studied. Of these patients, those who with 30 days postoperative mortality ($n = 23$), incomplete medical record ($n = 32$), synchronous liver metastasis ($n = 148$) and UICC stage IV ($n = 54$) were excluded, and finally 1,099 patients were analyzed, including 977 patients without liver metastasis and 122 patients with MLM-only. Clinical and pathological records for each patient were reviewed from medical charts. The clinicopathologic characteristics of 1,099 patients were investigated.
Results The median timing of developing MLM was 13 months with a range of 4 to 79 months. Univariate

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analysis identified that preoperative serum carcinoembryonic antigen (CEA) level, depth of invasion, lymph nodes metastasis, vascular invasion, and perineural invasion were significantly correlated with the development of MLM (all $P < 0.05$). Meanwhile, a multivariate analysis showed that preoperative serum carcinoembryonic antigen (CEA) level > 5 ng/ml (Odds Ratio [OR] = 1.591; 95% Confidence Interval [CI], 1.065–2.377; $P = 0.024$), tumor depth (OR = 2.294; 95% CI, 1.103–4.768; $P = 0.026$), positive lymph node metastasis (OR = 2.004; 95% CI, 1.324–3.031; $P = 0.001$) and positive vascular invasion (OR = 1.872; 95% CI, 1.225–2.861; $P = 0.004$) were independent prognostic factors contributing to the occurrence of MLM. *Conclusions* The present study demonstrates that preoperative serum CEA level, tumor depth, lymph node metastasis, and positive vascular invasion could affect the occurrence of MLM in CRC patients following curative resection, and thus could help to define these high-risk patients who would benefit from enhanced surveillance and therapeutic program(s).

Introduction

Colorectal carcinoma (CRC) is the most common malignancy and the third leading cause of cancer-related death in Taiwan [1]. In recent decades, the incidence of CRC has significantly increased and approaches that of Western countries (http://www.doh.gov.tw/statistic/index.htm; accessed in March 2010). Despite improved cancer screening methods, aggressive resection, and advanced adjuvant regimens, distant metastasis from CRC remains the major determinant of survival. Liver is the most common site for metastatic spread. In 30–40% of CRC patients, liver is the only site of metastasis [2]. Of new cases, 20–25% of patients will have clinically detectable liver metastasis at the time of the initial diagnosis (synchronous liver metastasis, SLM), and a further 40–50% of patients will eventually develop liver metastasis after resection of the primary CRC (metachronous liver metastasis, MLM) [3, 4]. On the natural history for the colorectal liver metastasis (CLM), if there is no treatment, median survival is 19 months and the 5-year survival is less than 1% [5, 6]; however, if patients undergo R0 resection, median survival is 30 months and the 5-year survival is 15–67% [7]. Survival time is mainly dependent on the extent of tumor involvement and the tumor recurrence. Unfortunately, only 20–30% patients are suitable for hepatic resection, and the 5-year survival and operative mortality rates are 25–44% and 0–6.6% respectively [7, 8]. Therefore, early identification of high-risk MLM patients is essential for effective treatment to provide the greater chance of prolonging survival. However, there is little information about identifying risk factors related to developing MLM-only in CRC following curative resection [9]. The aim of the present study was to identify clinical and pathologic variables that could predict the development of MLM in CRC patients following curative resection of primary tumor.

Materials and methods

This retrospective cohort study included 1,356 consecutive patients with histologically proven CRC receiving surgical treatment at the Department of Surgery, Kaohsiung Medical University Hospital between January 2001 and December 2007. All patient clinical outcomes and survival status were regularly followed until December 2009 or until death, with a mean follow-up time of 39.0 ± 24.2 months (1.3–94.9 months). Patients who died postoperatively (postoperative mortality was defined as death within the first 30 days after operation) ($n = 23$), those having an incomplete record of medical charts ($n = 32$), those with synchronous liver metastasis ($n = 148$), and those with International Union Against Cancer (Union International Contra Cancer—UICC stage IV ($n = 54$) were excluded. A brief telephone follow-up was carried out by case managers if the patient could not adhere to the postoperative follow-up scheme. However, there were 32 patients lost to follow-up who were excluded on the basis of "incomplete record of medical charts." A total of 1,099 patients were finally analyzed, including 977 patients without liver metastasis and 122 patients with MLM-only (Fig. 1). Clinical and pathological records for each patient were abstracted from medical charts. The clinical

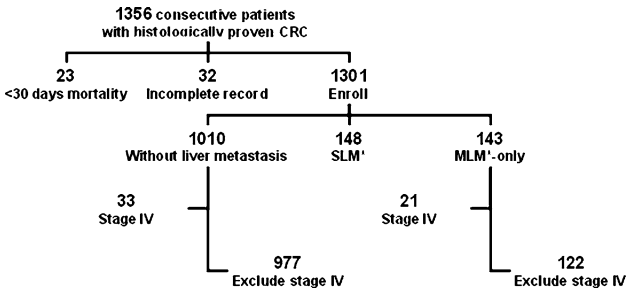

Fig. 1 The illustration of 1,356 consecutive CRC patients stratified in the study. *SLM* synchronous liver metastasis, *MLM* metachronous liver metastasis

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information included the demographics (age, gender) and clinical manifestations, such as preoperative serum carcinoembryonic antigen (CEA) level; postoperative adjuvant chemotherapy; size, location, and timing of developing liver metastasis; and maximum size, number, and distribution of liver metastases. The TNM classification was defined according to the criteria of the American Joint Commission on Cancer/International Union Against Cancer (AJCC/UICC) [10]. The following histopathologic features were assessed for each tumor specimen: depth of tumor invasion (classified as T1, T2, T3, and T4), tumor histologic grade (classified as well, moderately, and poorly differentiated), and lymph node (LN) metastasis, vascular invasion, and perineural invasion. We dichotomized continuous variables into two categories for statistical analysis including age: <65 and ≥65 years; serum CEA level: <5 and ≥5 ng/ml; colon cancer tumor size: <5 and ≥5 cm; and tumor depth: T1–2 and T3–4. MLM-only was defined as liver metastasis that was noted more than 3 months after resection of the primary CRC and confirmed by both triphasic helical abdominal-computed tomography (CT) or/and positron emission tomography-CT scan and pathological findings. The study was approved by the Institutional Review Board of the Kaohsiung Medical University Hospital.

Postoperative surveillance consisted of medical history, physical examination, and laboratory studies including serum CEA levels every 3 months. Abdominal ultrasonography or computed tomography was performed every 6 months, and chest radiography and total colonoscopy were performed once a year. Patients were followed at 3-monthly intervals for 2 years and at 6-monthly intervals thereafter. All data were statistically analyzed with SPSS version 14.0 (SPSS Inc., Chicago, IL). Values are presented as mean ± standard deviation for continuous variables and are compared by Student's *t*-test. The univariate analysis of clinicopathologic features between the two groups was compared using the chi-square test to determine the unadjusted relative risks and their 95% confidence intervals (CI). Then, the multivariate analysis of independent prognostic factors in which all the factors suggested by the univariate analysis ($P < 0.05$) were entered into the model to identify the potential risk factors for MLM was calculated, as were odds ratios (OR) and their 95% confidence intervals. All probability values were two-tailed, and probability values of 0.05 or less were considered to be statistically significant.

Results

The clinicopathologic characteristics of 1,099 patients including 977 without liver metastasis and 122 MLM-only are summarized in Table 1. The mean age of these patients was 64.4 ± 12.9 years, with a range of 19–93 years. With regard to the histological type of these tumors, 105 (9.6%)

Table 1 Clinicopathologic characteristics of colorectal cancer patients

Characteristic	Patients (n = 1,099)
Age, mean	64.4 ± 12.9
Male sex, No. (%)	597 (54.3)
Metachronous liver metastasis-only	122 (11.1)
Preoperative CEA level (ng/ml)	
CEA > 5	450 (40.9)
CEA > 10	269 (24.5)
Tumor size > 5 cm	443 (40.3)
Tumor location	
Cecum	17 (1.5)
Ascending colon	143 (13.0)
Transverse colon	75 (6.8)
Descending colon	98 (8.9)
Sigmoid	381 (34.7)
Rectum	385 (35.0)
Histology	
WD	105 (9.6)
MD	866 (78.8)
PD	128 (11.6)
Depth of invasion	
T1	77 (7.0)
T2	179 (16.3)
T3	800 (72.8)
T4	43 (3.9)
Positive lymph nodes, No. (%)	407 (37.0)
Positive vascular invasion, No. (%)	318 (28.9)
Positive perineural invasion, No. (%)	343 (31.2)
UICC Stage I/II/III	208/483/408

WD well differentiated, *MD* moderately well-differentiated, *PD* poorly differentiated, *UICC* International Union Against Cancer

Table 2 The characteristics of liver metastasis in colorectal cancer patients

	MLM (n = 122)
Liver meta post op, median (months)	13.0 (4–79)
Maximum size of tumor (cm)	3.5 ± 2.9 (0.7–13.0)
No. metastasis	*n* (%)
1–3	84 (68.9)
4–6	18 (14.7)
>6	20 (16.4)
Tumor distribution	
Right lobe	65 (53.3)
Left lobe	20 (16.4)
Bilobar	37 (30.3)

Table 3 Univariate analysis of risk factors for metachronous liver metastasis

Demographics	Without liver metastasis (n = 977)	MLM-only (n = 122)	P value
Age, years			0.036
<65	470 (48.1)	71 (58.2)	
>65	507 (51.9)	51 (41.8)	
Gender			0.528
Male	534 (54.7)	63 (51.6)	
Female	443 (45.3)	59 (48.4)	
Preoperative CEA level			<0.001
<5 ng/ml	594 (60.8)	51 (41.8)	
>5 ng/ml	383 (39.2)	71 (58.2)	
Tumor size			0.254
<5 cm	589 (60.3)	67 (54.9)	
>5 cm	388 (39.7)	55 (45.1)	
Tumor location			0.093
Colon	288 (29.5)	45 (36.9)	
Rectosigmoid	689 (70.5)	77 (63.1)	
Tumor depth of invasion			0.001
T1–2	247 (25.3)	9 (7.4)	
T3–4	730 (74.7)	113 (92.6)	
Lymph node metastasis			<0.001
Negative	645 (66.0)	47 (38.5)	
Positive	332 (34.0)	75 (61.5)	
Vascular invasion			<0.001
Negative	721 (73.8)	60 (49.2)	
Positive	256 (26.2)	62 (50.8)	
Perineural invasion			<0.001
Negative	692 (70.8)	64 (52.5)	
Positive	285 (29.2)	58 (47.5)	
Histology			0.592
WD + MD	865 (88.5)	106 (86.9)	
PD	112 (11.5)	16 (13.1)	
Adjuvant chemotherapy			
Yes	587 (60.1)	69 (57)	0.518
No	390 (39.9)	52 (43)	

patients were well differentiated carcinoma, 866 (78.8%) patients were moderately well-differentiated carcinoma, and 128 (11.6%) patients were poorly differentiated carcinoma. There were 318 (28.9%) patients with vascular invasion, and 343 (31.2%) patients with perineural invasion. Table 2 reveals the characteristics of patients with MLM-only. The median timing of MLM was 13 months, with a range of 4–79 months. The mean maximum size of liver tumor was 3.5 ± 2.9 cm. Regarding the number of liver tumors, 84 (68.9%) patients had one to three liver tumors, 18 (14.7%) patients had four to six liver tumors, and 20 (16.4%) patients had more than six liver tumors. For the distribution of liver tumors, 65 (53.3%) patients had tumors in the right lobe, 20 (16.4%) patients had tumors in the left lobe, and 37 (30.3%) patients had tumors in the bilobar region. Table 3 shows the univariate analysis of risk factors for the development of MLM. We found that age younger than 65 years ($P = 0.036$), preoperative serum CEA level higher than 5 ng/ml ($P < 0.001$), tumor depth of T3–4 invasion ($P = 0.001$), positive LN metastasis ($P < 0.001$), positive vascular invasion ($P < 0.001$), and positive perineural invasion ($P < 0.001$) were statistically significantly related to the occurrence of MLM. After adjustments in a multivariate logistic regression model, preoperative serum CEA level more than 5 ng/ml (OR = 1.591; 95% CI, 1.065–2.377; $P = 0.024$), tumor depth (OR = 2.294; 95% CI, 1.103–4.768; $P = 0.026$), positive LN metastasis (OR = 2.004; 95% CI, 1.324–3.031; $P = 0.001$), and positive vascular invasion (OR = 1.872; 95% CI, 1.225–2.861; $P = 0.004$) were significantly independent factors contributing to the development of MLM (Table 4).

Table 4 Multivariate analysis with age and gender adjusted in model of risk factors for metachronous liver metastasis

Effect	Odds ratio	95% CI	P value
Age (≤65 years vs. >65 years)	0.726	0.488–1.081	0.115
Gender (male vs. female)	1.149	0.778–1.698	0.485
CEA >5 ng/ml vs. CEA <5 ng/ml	1.591	1.065–2.377	0.024
Depth of invasion (T3–4 vs. T1–2)	2.294	1.103–4.768	0.026
Lymph node metastasis (yes vs. no)	2.004	1.324–3.031	0.001
Vascular invasion (yes vs. no)	1.872	1.225–2.861	0.004
Perineural invasion (yes vs. no)	1.233	0.807–1.886	0.333
Adjuvant chemotherapy (yes vs. no)	0.894	0.637–1.255	0.647

Discussion

Hepatic metastasis significantly influences the prognosis and survival of CRC patients who have undergone curative intent resection of CRC [11–13]. Before the 1980 s, liver metastasis from CRC was considered an incurable disease; the 5-year survival rate was less than 1% with supportive treatment [5, 14]. However, with the advances of adjuvant regimens treatment and aggressive surgical hepatectomy, the outcome of CLM has greatly improved over recent decades. Some large series have shown 5-year survival of

patients following resection of CLM ranges from 33.1 to 69% [13, 15, 16]. Scheele et al. reported actuarial 5-, 10-, and 20-year survival was 39, 28, and 18%, respectively, in 207 potentially curative liver resections performed between 1960 and 1988 for metastatic CRC. In contrast, for 983 patients thought to have unresectable tumor, the median survival was 6.9 months without any 5-year survivors [17]. Xu et al. demonstrated that the hepatic resection rate and 5-year survival rate were 32.5 and 36.6% in their SLM patients, as well as 44.8 and 33.1% in the MLM patients, respectively [15]. For raising the resectability rate, the exploration of the risk factors for the development of MLM is an important first step.

Various factors are known to influence the occurrence of CLM following surgical resection. Hoshino et al. defined lymph node metastasis, depth of invasion, and extramural lymphatic invasion as being significant influences on the incidence of MLM in univariate analysis, and only lymph node metastasis was an independent recurrent factor based on a multivariate logistic analysis [9]. Furthermore, Iizasa et al. reported using clinical factors that elevated CEA level and the quantity of metastasis were both considered to be independent prognostic factors [18]. In the present study, we comprehensively investigated the more clinicopathologic characteristics in 1,099 CRC cases within a 7-year period and followed these patients for a longer period than previous studies. Therefore, our observation could provide more information to predict the risk of developing MLM in CRC patients. We have demonstrated that six factors: age, preoperative serum CEA level, tumor depth of invasion, lymph node metastasis, vascular invasion, and perineural invasion, were the risk factors for MLM on univariate analysis. According to a multivariate logistic analysis, preoperative serum CEA level, depth of tumor invasion, lymph node metastasis, and vascular invasion were ultimately proven to be independent factors.

Carcinoembryonic antigen has been postulated to be a tumorigenicity-enhancing factor. It is used for the surveillance in CRC patients following curative resection for primary cancer [19]. Previously, it has been demonstrated that there was an association between CEA secretion and the growing ability of 10 different CRC cell lines in nude mouse models [20]. This result implies that CEA is involved in the development of hepatic metastasis of human CRC. In an experimental metastasis model of CRC in athymic nude mice, a systemic injection of CEA enhanced experimental liver metastasis and implantation in liver by a weakly metastatic CRC. This CRC also selectively bound to CEA that was attached to plastic. Thus, CEA may function as an attachment factor for CRC [21]. In addition, metastatic human colon cancer cell lines were shown to acquire a highly metastatic potential when transfected with the cDNA coding for CEA, suggested that CEA expressed on the cell surface may play an important role in hepatic metastasis from CRC, possibly through its cell adhesion activity [22, 23].

In our series, the incidence of elevated serum CEA levels was 60.7% in patients with MLM when compared to 42.7% in patients without liver metastasis. Furthermore, our recent investigation demonstrated that preoperative serum CEA level was the significant prognostic factor for patients with stage II and III CRC in both cancer-specific and overall survival rates [24].

Depth of tumor invasion and lymph node metastasis are two components of the TNM system that are regarded as the prognostic determinants for patients with CRC [9]. In the present study, both the depth of tumor invasion and lymph node invasion were demonstrated to be independent predictive factors for the development of MLM on multivariate analysis. Therefore, patients with positive lymph node invasion and deeper invasion of tumor are considered to be at a higher risk for developing hepatic metastasis, and they may be good candidates for postoperative adjuvant chemotherapy. In the series reported here, four patients with stage I (1.9%), 42 with stage II (8.7%), and 76 with stage III (18.6%) disease developed MLM. These results suggest that if patients are positive for these risks, then a more intensive follow-up may be necessary, even if the stage is relatively early and the curability rate of metastasis and the overall survival are potentially improved.

The presence of vascular invasion has often been considered as a risk factor for increased incidence of distant metastasis and unfavorable prognosis; therefore it is associated with a decrease in survival [25]. Consistent with this finding, the present results show that vascular invasion has an increased probability of liver metastasis when compared to those cases without vascular invasion. In contrast, perineural invasion was found to be a significant MLM risk factor in univariate analysis but not in multivariate analysis. The possible explanation may be owing to perineural invasion from some investigators being defined as intra-/extraneural perineural invasion or intraneural perineural invasion [26, 27]. Consequently, a more clarified definition of the positive perineural invasion is necessary by pathologists. In the present study, we found that most MLM (84/122, 68.9%) were 1–3 liver metastases that had high possibility for corrective intent liver resection.

In summary, the present study demonstrates that four independent factors (preoperative serum CEA level more than 5 ng/ml, depth of tumor invasion, positive LN invasion, and positive vascular invasion) significantly affect the development of MLM. These parameters could be useful in identifying patients with higher-risk MLM who might be considered for enhanced follow-up and even the administration of adjuvant therapy.

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