Survival after Curative Resection for Stage I Colorectal Mucinous Adenocarcinoma

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Research

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Abstract

Background : The prognostic value of the mucinous adenocarcinoma histotype on the early stages especially for stage I colorectal cancer (CRC) is still unclear. This study determined the clinicopathologic characteristics and long-term outcome of stage I colorectal mucinous adenocarcinomas (MAC).

Methods : Among the total of 503 patients with stage I CRC (56 having MAC and 447 having non-MAC) who underwent radical resection, the correlation between clinicopathological factors and MAC was analyzed. Multivariate analysis was performed to determine whether mucinous histotype itself was an independent prognostic impact in stage I patients.

Results : MACs were observed more frequently located in the colon than rectum (p =0.046), more frequently displayed the microsatellite instability (MSI) phenotype (p =0.023) and had a greater frequency of T2 stage (p =0.001). The rate of recurrence was 13.5% and the cancer-specific mortality was 4.3% among all stage I CRC patients. There was no difference in disease-free survival and overall survival between MACs and non-MACs. On multivariate analysis, older age (p =0.030), rectal cancer (p =0.025), lymphovascular invasion (LVI) (p <0.001), and microsatellite stability (MSS) phenotypes (p =0.023) were independently associated to poor survival of stage I CRC. A high carcinoembryonic antigen (CEA) level (p =0.031), LVI (p =0.002) and MSS phenotypes (p =0.012) were independently related to short disease-free survival of stage I CRC.

Conclusions : Compared with non-MAC, MAC patients had more T2 patients and more MSI phenotypes in stage I CRC at presentation, but the mucinous histology is not a significant predictor of recurrence and prognosis in stage I CRC.

Background

Colorectal cancer (CRC) can be classified by histological evaluation of tumor specimens [1]. Colorectal mucinous adenocarcinomas (MAC) were defined when the tumor mass consisted 50% or more of mucinous ingredient, mostly extracellular; while the other tumors were defined as non-mucinous adenocarcinomas (non-MAC). Non-MAC is the most common type of CRC (> 85%), while 10–15% of CRC patients are MAC [2]. MAC differs from non-MAC for its special clinicopathological characteristics, compared with non-MAC, MAC has long been associated with an inferior response to treatment, especially radiotherapy and chemotherapy [3]. The debate on the prognostic value of MAC in patients is ongoing, MAC is still considered to be a poor prognosis and refractory subtype of the disease. MAC presents a high microsatellite instability (MSI) status, young age and advanced stage at presentation [4, 5]. But the prognostic impact of MAC is controversial, some studies shown that mucinous histology was an independent negative prognostic factor [6, 7], but not in others [8, 9].

In general, MAC patients present a more advanced stage than non-MAC as shown in previous studies [10, 11]. It is well known that the inferior prognostic impact of MAC can be close related to the more advanced progression at presentation [12]. However, most previous studies focused on its clinicopathological

characteristics and prognosis of stage III and IV diseases. Moreover, the mucinous pathological subtype can also be a negative factor even for stage II CRC patients [13]. Few studies have focused the impact in survival between MAC and non-MAC of stage I CRC.

Thus, our study aimed to clarify the prognostic impact of MAC focusing on stage I CRC and correlate the mucinous histology with clinicopathological features of stage I CRC.

Patients And Methods

The study protocol was reviewed and approved by the institutional review board of of the Sixth Affiliated Hospital, Sun Yat-sen University, China. This study was carried out in accordance with the recommendations of the Declaration of Helsinki for biomedical research involving human subjects.

Patient

Between January 2011 to May 2016, 5753 patients have undergone radical resections due to CRC. The following exclusion criteria were applied: patients with familial adenomatous polyposis (FAP), hereditary non-polyposis CRC (HNPCC); patients with synchronous or metachronous cancer; death due to non-cancer causes such as heart disease and cerebral infarction; patients underwent local excision or neoadjuvant therapy were also excluded. Among them, 542 patients (9.42%) were diagnosed as stage I CRC on histopathologic examination and met the criteria for enrollment. Of the 542 patients, 12 patients refused radical resections, and 27 patients died from non-cancer causes. Therefore, 503 patients were analyzed in this study.

Clinicopathologic evaluation

Before surgery, patients underwent a baseline assessment of demographics and disease characteristics, blood carcinoembryonic antigen (CEA) tests, and tumor imaging. At least two pathologists, who are specialized in CRC, assessed the surgical specimens. Among the 503 patients, 56 were defined as MAC when the tumor mass consisted 50% or more of mucin ingredient, mostly extracellular; and the other tumors were defined as non-MAC. Hematoxylin and eosin staining was used to assess lymph nodes metastasis and lymphovascular invasion (LVI). Immunohistochemically (IHC) assessment of mismatch repair (MMR) genes in tissue samples were performed as described by Förster et al. [14]. The clinicopathological features of all 503 patients are shown in Table 1. All patients were staged by TNM classification criteria [15].

Treatment

All patients underwent radical surgery. Colon cancer is completely removed by mesocolic excision with Lymph node (LN) dissection at R0-resection level. Resection of rectal cancer were performed by total mesorectal excision as described [16]. Recurrence occurred in 68 of 503 patients during follow-up and 25 patients underwent re-radical surgery. Laparoscopic surgery is performed for most patients.

Data collection

The follow-up information of 503 patients was collect and analyzed. The median follow-up period of all cases was 59 months (2 to 103 months). According to the mucinous histology, patients were divided into two groups: the MAC group and the non-MAC group. Clinicopathologic factors (age, sex, preoperative CEA lever, tumor location, tumor size, T stage, histologic subtype, the number of obtained lymph nodes, LVI, MSI status) were analyzed. We selected the 5-year disease-free survival (DFS) as the primary endpoint, which defined as the time from the date of radical resection to the diagnosis of cancer recurrence. The 5-year overall survival rate (OS) was selected as the second endpoint, defined as the time from the date of radical resection to death caused by cancer.

Statistical analysis

The associations between the discrete variables were analyzed by Spearman rank correlation test. p value < 0.05 was regarded as statistically significant. Univariate analyses were performed by χ^2 tests to evaluate the associations between clinical variables and the tumor histology. The survival probability was analyzed by Kaplan–Meier procedure, and the distribution differences were assessed by the log-rank test. Clinicopathologic factors such as age, sex, preoperative CEA lever, tumor location, tumor size, T stage, histologic subtype, the number of obtained lymph nodes, LVI, MSI status were analyzed. In multivariate analysis, cox proportional risk model was also used to evaluate the predictive value of various factors. The statistical analysis was carried out by using IBM SPSS ver. 20.0(IBM, Armonk, NY, USA).

Results

Table 1 summarized the clinicopathologic characteristics, all of the 503 stage I CRC patients were classified as the MAC group and non-MAC group. MAC was identified in 56 (11.1%) patients by pathology. MAC was found in 33 males (58.9%) and 23 females (41.1%); non-MAC was found in 243 males (54.4%) and 204 females (45.6%). The mean ages of patients with MAC and non-MAC were 54.7 ± 13.2 years and 59.1 ± 11.8 years, respectively (p = 0.277). 49 (87.5%) of the 56 patients with MAC had tumors classified as T2 and only 7 (12.5%) as T1. In contrast, 290 (64.8%) of the 447 non-MAC were classified as T2 (p = 0.001). The MAC appeared to be found significantly more locate at colon than the non-MAC (p = 0.046). MSI status was found in 5 (8.9%) patients with MAC and 13 (2.9%) with non-MAC (p = 0.023). There were nearly significantly more LVI in MAC patients than non-MAC patients (7.1% vs. 2.6% percent; p = 0.073).

During the following period, 22 of all stage I patients (503) died of cancer. Relationships between clinicopathological factors and overall survival in all stage I CRC are shown in Table 2. On univariate and multivariate analysis, patients with rectal cancer, being older, LVI positive, MSS status were found to relate to poorer cancer specific overall survival significantly, however, mucinous histology itself had no significant prognostic effect on OS (Table 2, Figs. 1a, 2).

68 (13.5%) of the 503 stage I patients experienced recurrence, including 20 (3.9%) with local recurrence and 48 (9.6%) with distant metastasis. On univariate and multivariate survival analysis, patients with

rectal cancer, higher CEA lever, LVI positive, MSS status were independently related to short DFS, while mucinous histology was also not a significantly predictor for recurrence (Table 3, Fig. 1b, Fig. 3).

Discussion

It is difficult to determine the clinicopathologic characteristics and long-term outcome of stage I MAC. Even though the long-term survival of stage I CRC is thought to be much better, it is still unclear whether mucinous histology had significant prognostic effect on stage I CRC. Previous research shows poor survival for CRC patients with a higher mucinous content [17, 18], but there were also reports with opposite conclusions [19, 20]. Here, we analyzed the prognostic value of MAC focusing on stage I CRC and correlated the mucinous histology with clinical and pathological features of stage I CRC. Compared with non-MAC patients, MAC had more T2 patients in stage I at presentation, more colon cancers and a higher MSI status. Many independent risk factors for recurrence and long-term survival were found in our study, including abnormal CEA level, LVI and MSS phenotypes. However, there was no correlation between mucinous histology and survival in stage I CRC.

In our study, univariate and multivariate analyses showed that that the histology pattern of MAC was not a prognostic factor for DFS or OS. Although the pathological T2-classification of MAC was higher in stage I patients than in non-MAC patients (87.5% vs 64.9%, $p = 0.001$), distinct clinical results were not observed. Du et al. [21] also reported that patients with MAC in stage III alone shown poorer DFS and OS compared with the non-MAC group, which means the worse survival of MAC patients might be due to regional lymph node metastasis.

Serum CEA is the most widely used tumor markers for diagnosis and recurrence monitoring of CRC. Several studies have investigated the ability of CEA to predict tumor recurrence and metastasis [22–24]. However, in stage I CRCs, there has been a paucity of evidence for it being a predictive factor for recurrence. Here, we found abnormal pretreatment CEA was an independent risk factor for recurrence even in stage I CRC. It suggests that if the serum CEA level is high preoperative in patients, the recurrence of CRC should be closely monitored, even in stage I CRC.

LVI is considered to be an early event in lymph node metastasis, and it has been proved to be an independent predictor of survival in CRC. The LVI group showed a higher risk of recurrence and a significantly lower overall survival rate in advanced CRC compared with the non-LVI group[25]. Meanwhile, LVI also has an independent predictor power for poor prognosis rectal cancer after neoadjuvant therapy and surgery [26]. However, the prognostic value of LVI in stage I CRC patient has not been well studied. Our study confirms that LVI is an important risk factor for stage I CRC recurrence. This suggests that LVI might be a sensitive marker for local recurrence and distant metastasis, even the patients without LN metastases.

The effect of MSI on the prognosis of CRC is controversial. MSI status influences the prognosis of CRC only in specific stages [27, 28]. Compared to MSS patients, MSI patients were found to possess worse survival in stage III colon cancer [29]. While opposite conclusion was found that MSI status was related to a better survival in stage II CRC [30]. Our study revealed that stage I CRC patients with MSI status showed a much better survival compared with the MSS group. MSI tumors were also found significantly associated with mucinous histology in stage I CRC patients, suggesting patients of MC are suitable for immunotherapy when recurrence and metastasis occur in the future.

Declarations

Abbreviations: Not applicable.

Ethics approval and consent to participate: The study protocol was reviewed and approved by the institutional review board of the Sixth Affiliated Hospital, Sun Yat-sen University, China [E2019052]. This study was carried out in accordance with the recommendations of the Declaration of Helsinki for biomedical research involving human subjects.

Consent to publication: Not applicable.

Availability of data and materials: Please contact the corresponding author for data on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Conceived and designed the study: LH, SLL, LPW, LK. Implemented the surgery: LH, SLL, SCL, YC, ZL. Patients follow-up: HH, ZZ. Analyzed and interpreted the data: LH. Wrote the manuscript: LH, JD, CX, LPW, LK. All authors read and approved the final manuscript.

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Tables

Table 1. The relationship between clinicopathological characteristics and mucinous adenocarcinoma in stage I colorectal cancer

Variable	MAC (n=56)	non-MAC (n = 447)	*p* value
Sex			
Male	33	243	0.518
Female	23	204	
Age			
≤ 65	39	278	0.277
> 65	17	169	
Preoperative CEA			
≤5 ng/dL	51	390	0.413
> 5 ng/dL	5	57	
T classification			
1	7	157	**0.001***
2	49	290	
Location			
Colon	24	133	**0.046***
Rectal	32	314	
Size			
<3cm	27	266	0.107
≥3cm	29	181	
LVI			
(–)	52	435	0.073
(+)	4	12	
Less than 12 lymph nodes			
Yes	9	82	0.678
No	47	365	
MSI			
Yes	5	13	**0.023***
No	51	433	

MAC: mucinous adenocarcinomas

CEA : carcinoembryonic antigen

MSI : microsatellite instability

Table 2. Univariate and multivariate analyses for overall survival in stage I colorectal cancer

Variable	Univariate analysis		Multivariate analysis	
	Mean OS (95% CI)	P-value	HR (95% CI)	P-value
Gender				
Male	94.7(92.1-97.3)	0.155		
Female	99.7(96.7-102.7)			
Age				
≤ 65	99.9(97.3-102.4)	**0.032***	2.620(1.100-6.238)	**0.030***
> 65	94.0(90.3-97.8)			
Preoperative CEA				
≤5	99.0(96.7-101.2)	0.082		
> 5	95.5(89.4-101.6)			
T classification				
T 1	90.1(86.1-95.1)	0.414		
T 2	98.6(95.8-100.7)			
Lesion location				
Colon	98.6(97.1-100.2)	**0. 042***	5.418(1.243-23.626)	**0.025***
Rectal	97.1(94.6-100.0)			
Size				
<3cm	98.8(95.8-101.8)	0.691		
≥3cm	97.9(95.1-100.7)			
Mucinous histology				
MAC	93.8(89.5-98.2)	0.748		
non-MAC	98.6(96.1-100.7)			
LVI				
(–)	99.2(97.1-101.3)	**<0.001***	9.735(3.072-30.853)	**<0.001***
(+)	76.2(57.5-95.0)			
Less than 12 lymph nodes				
Yes	95.1(91.3-98.7)	0.585		
No	98.4(96.1-100.7)			
MSI				
Positive	99.3(97.5-101.2)	**0.018***	4.213(1.216-14.60)	**0.023***
Negative	82.9(71.2-94.6)			

MAC: mucinous adenocarcinomas

CEA : carcinoembryonic antigen

MSI : microsatellite instability

Table 3. Univariate and multivariate analyses for disease free survival in stage I colorectal cancer

Variable	Without recurrence (n=435)	With recurrence (n=68)	Univariate P-value	Multivariate HR (95% CI)	P-value
Gender					
Male	233	43	0.100		
female	202	25			
Age					
≤ 65	277	40	0.422		
> 65	158	28			
Preoperative CEA					
≤5	388	53	**0.010***	1.947(1.065-3.562)	**0.031***
> 5	47	15			
T classification					
T 1	146	18	0.298		
T 2	289	50			
Lesion location					
Colon	142	14	**0.045***	1.646(0.919-2.949)	0.094*
Rectal	293	54			
Size					
<3cm	255	38	0.790		
≥3cm	180	30			
Mucinous histology					
MAC	47	9	0.618		
non-MAC	388	59			
LVI					
(–)	425	62	**0.021***	3.950(1.670-9.343)	**0.002***
(+)	10	6			
Less than 12 lymph nodes					
Yes	73	18	0.081		
No	362	50			
MSI					
Positive	13	6	**0.020***	2.975(1.277-6.932)	**0.012***
Negative	422	62			

MAC: mucinous adenocarcinomas

CEA : carcinoembryonic antigen

MSI : microsatellite instability

Figures

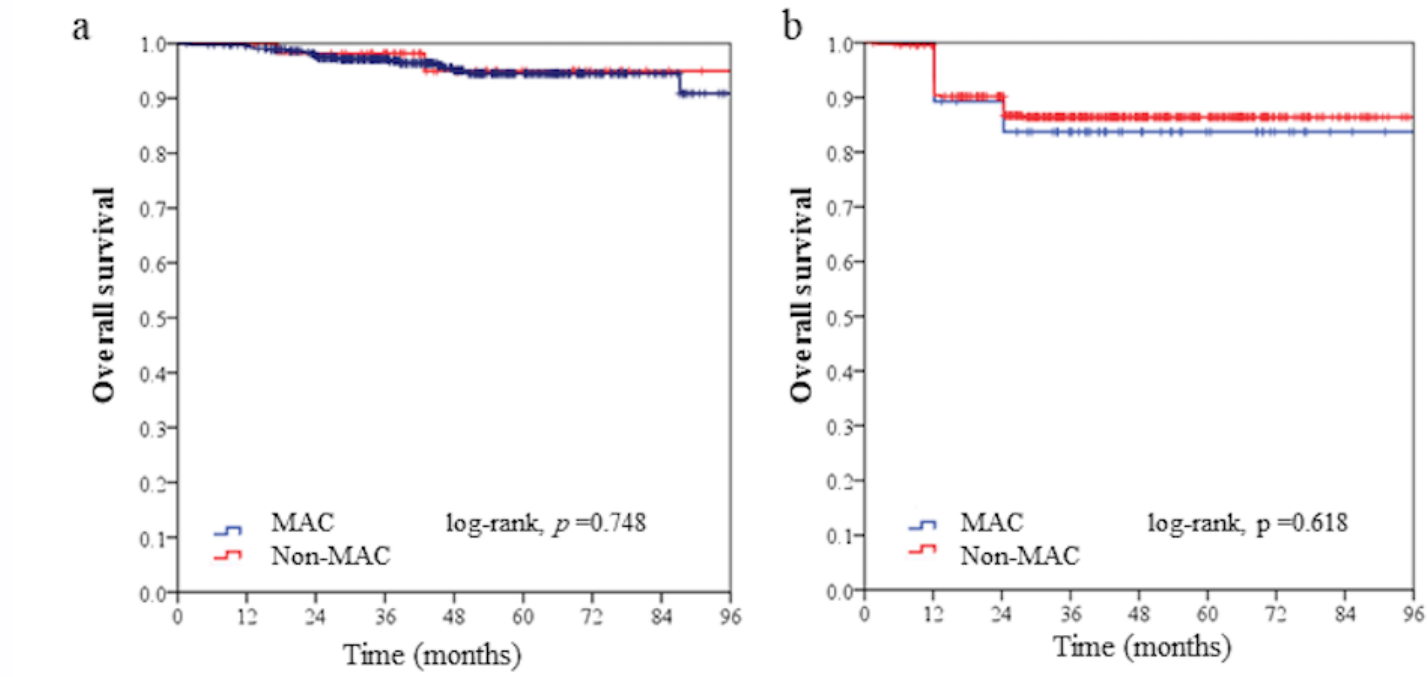

Figure 1

Univariate and multivariate survival analyses, which showed no significant differences in patient survival between mucinous adenocarcinomas (MAC) and non-MAC colorectal cancer, overall survival (a) and disease free survival (b).

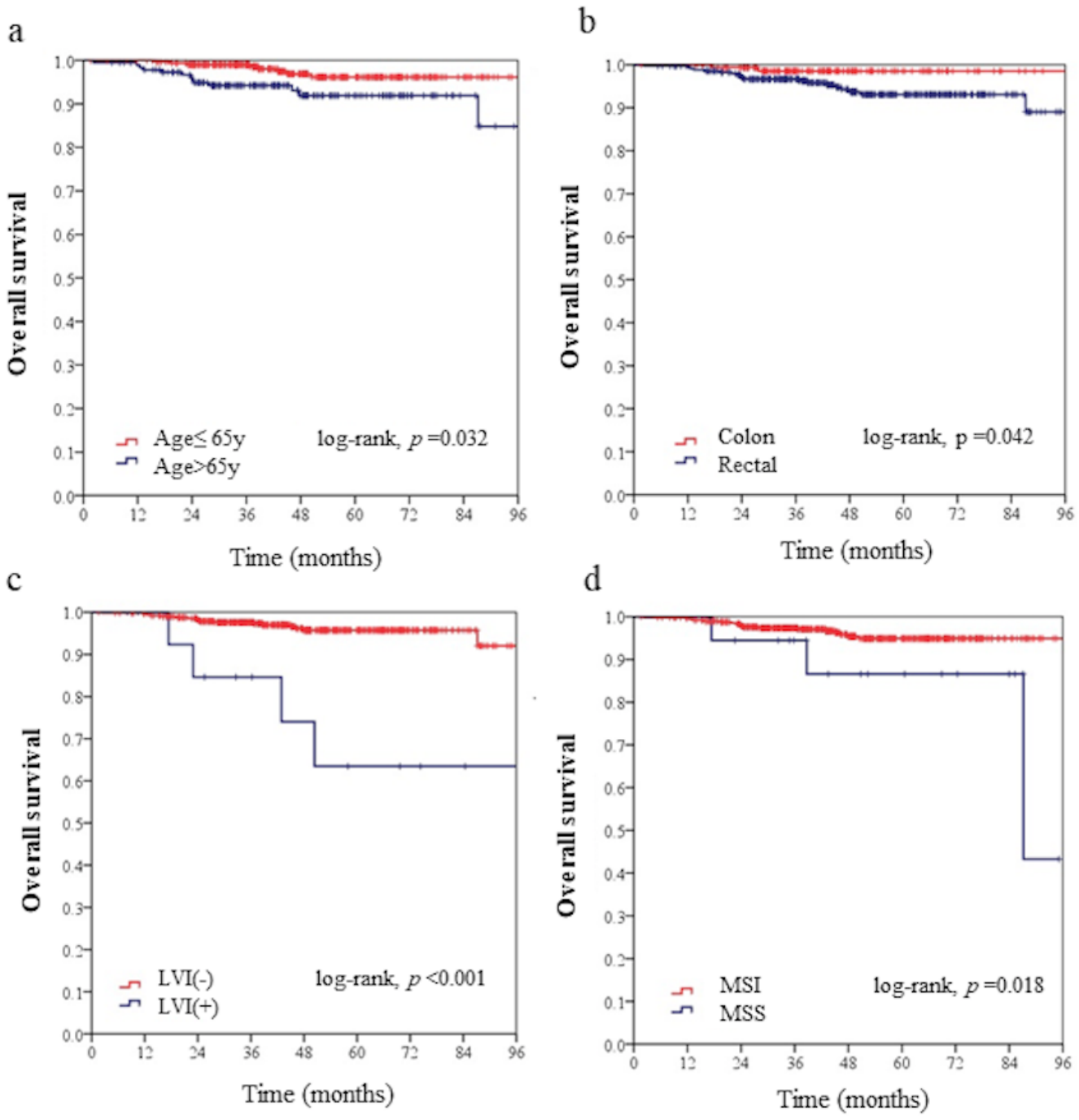

Figure 2

Kaplan-Meier survival curves show that patients being older (a), with rectal cancer (b), lymphovascular invasion (LVI) positive (c), and microsatellite stability (MSS) status (d) are significantly related to a poorer overall survival.

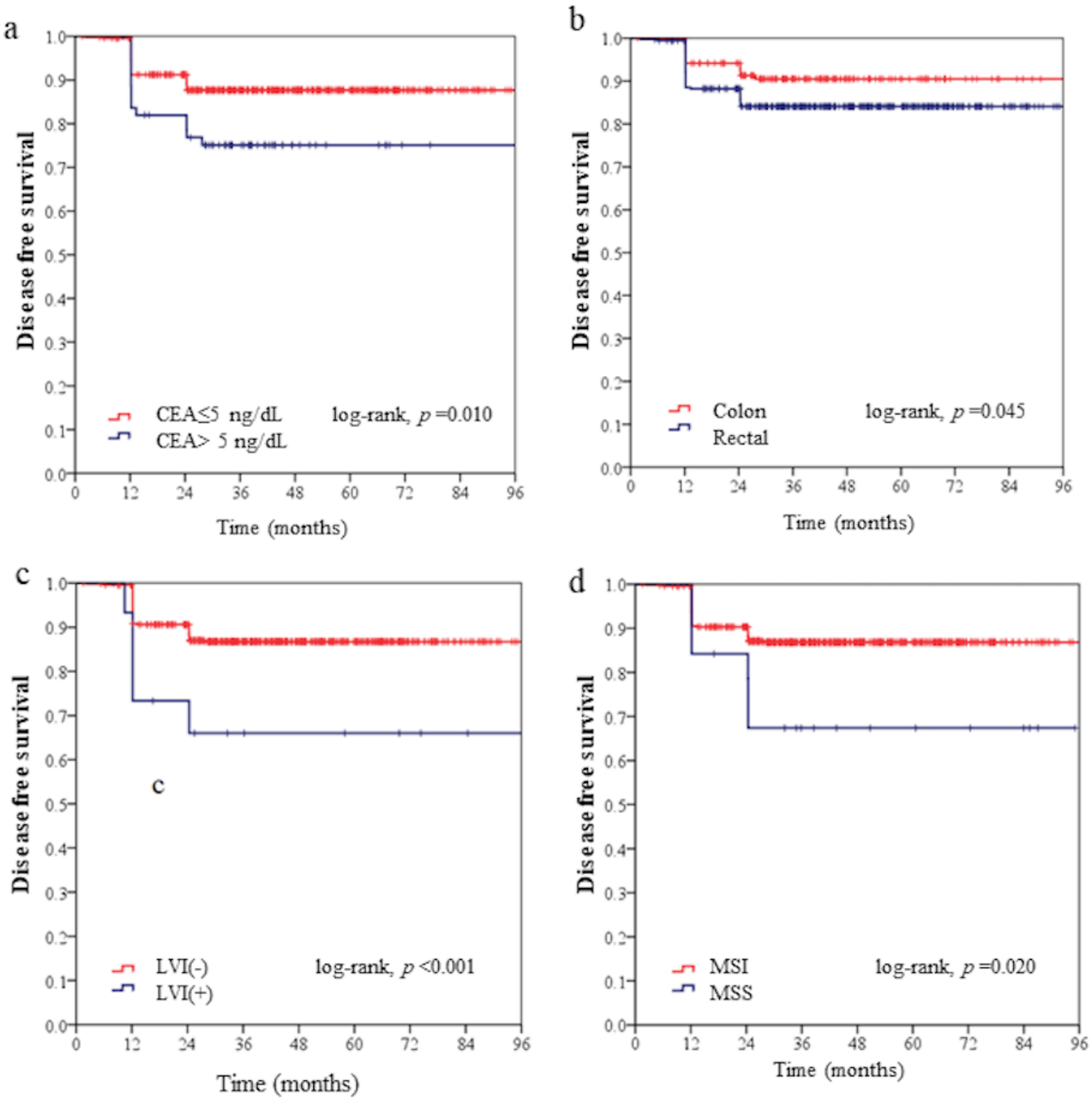

Figure 3

Kaplan-Meier survival curves show that patients with a higher carcinoembryonic antigen (CEA) lever (a), rectal cancer (b), LVI positive (c), and microsatellite stability (MSS) status (d) are independently related to disease free survival