Risk factors for recurrence of radically resected mucinous colorectal adenocarcinoma

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Research Article

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Abstract

Background Local recurrence and distant metastasis are major challenges to overcome in order to improve the survival of patients with colorectal cancer (CRC) after surgery. Mucinous adenocarcinoma (MA) is a subtype of CRC associated with a higher incidence of local extension and worse survival compared to non-mucinous adenocarcinoma, but few studies have investigated predictors for poor clinical outcome of MA. Therefore, we aimed to elucidate the predictors for local recurrence and remote metastasis of MA after surgery.

Methods This study retrospectively analyzed 162 patients with mucinous colorectal adenocarcinoma (MAC) after radical resection. Analysis variables included demographics, clinical indicators, pathologic stage, surgical procedure, adjuvant therapy, and recurrence. Univariate and multivariate analyses were performed to investigate the risk factors for local and distant tumor relapse.

Results A total of 162 patients (86 male) with a mean age of 58.26 years were included; 70.37% of patients had colonic tumors, and 29.63% had rectal tumors. The 5-year disease-free survival (DFS) rates for these patients were as follows: 100% for TNM stage I, 71.2% for stage II, and 47.8% for stage III. Five-year DFS rates of MAC, colonic and rectal MA were 62.0%, 65.8%, and 51.7%, respectively. Local recurrence occurred in 38 patients (23.5%) and distant metastasis in 33 patients (20.4%). In univariate analysis, predictors for local recurrence of MAC were intra-operative blood loss (p=0.004, OR=1.005), intra-operative transfusion (p=0.002, OR=5.179), and N2 stage (p=0.000, OR=4.643), and predictors for distant metastasis were male sex (p=0.035, OR=2.410), CA199 (p=0.011, OR=1.004), CEA (p=0.020, OR=1.010), intra-operative blood loss (p=0.022, OR=1.003), T4 stage (p=0.007, OR=4.125), and N2 stage (p=0.018, OR=3.4). In multivariate analysis, predictors for local recurrence of colorectal MA were intra-operative transfusion (p=0.04, OR=4.175) and N2 stage (p=0.000, OR=5.291), and predictors for distant metastasis were male sex (p=0.049, OR=2.410), CA199 (p=0.02, OR=1.003), and T4 stage (p=0.007, OR=4.006).

Conclusions Intra-operative transfusion and N2 stage were significant predictors for local recurrence. Male sex, CA199, and T4 stage were significant predictors for distant metastasis. Knowledge of the risk factors for postoperative recurrence provides a basis for logical approaches to treatment and follow-up of mucinous colorectal adenocarcinoma.

1. Introduction

Colorectal cancer (CRC), the third most diagnosed cancer and the fourth leading cause of cancer-related deaths[1], is a malignant tumor with a high prevalence: an estimated 1.2 million people develop CRC worldwide every year. Mucinous colorectal adenocarcinoma (MAC) is a special type of CRC with distinct pathological features. MAC tumors are composed of more than 50% extracellular mucin produced by tumor acinar cells[2]. Cases of MAC account for 1.6%-25.4% of primary CRC. Large population-based studies of the prevalence of CRC have shown lower rates (4%-5%) of MAC among Asians with CRC[3-5].

Given the rarity of the disease, relatively little is known about the best approaches to treatment and the prognosis of MAC.

Compared with non-mucinous adenocarcinoma, MAC is more frequently found in female and younger patients[6], and has a worse prognosis[7-10]. The worse prognosis of MAC may be due to its diagnosis at more advanced stages, its greater propensity for early spread to regional lymph nodes and peritoneal implants, and its resistance to chemotherapy. MAC is considered poorly differentiated (grade 3) according to the WHO tumor grade criteria based on the extent of glandular formation. Guidelines for CRC indicate that MAC is a risk factor for CRC[11]; for example, surgical resection with lymph node dissection is recommended for additional treatment after endoscopic resection of pT1 CRC when mucinous adenocarcinoma (MA) is observed[11]. Adjuvant chemotherapy is recommended for patients with stage II CRC with poor histological differentiation (grade 3-4) accompanied by MMR-proficient or microsatellite stable tumors[12]. However, there are still no current guidelines for the treatment of MA, even though individualized and precise treatment is critical for cancer therapy. We and others believe that specialized, precision therapy is needed for MAC[13]. Thus, it is of significant clinical importance to investigate MAC.

In previous reports, the distinctive clinicopathologic features of MA and their implication on the therapeutic strategy and prognosis were investigated. However, there are few studies that have conducted analyses of clinical, pathologic, and surgery-related risk factors. This retrospective study aimed to elucidate clinical, pathologic, and surgery-related risk factors for local and distant relapse of MAC after surgical resection.

2. Materials And Methods

2.1 Patients

All CRC patients enrolled in this study were treated at the Third Affiliated Hospital of Sun Yat-Sen University and Guangzhou First People's Hospital from 2009 to 2018. Local Institutional Review Boards (IRB) approved the data acquisition. The data included demographics, clinical indicators, pathologic stage, surgical procedure, adjuvant therapy, and recurrence. All patients were staged according to the AJCC 6^{th} or 7^{th} edition manual for colorectal cancer.

Inclusion criteria were as follows[14]: (1) history of primary colorectal cancer; (2) histologically confirmed MA; (3) undergoing radical surgery. Exclusion criteria were as follows: (1) MA with peritoneal or visceral metastasis (M1 stage); (2) multiple primary tumors of the colorectum; (3) palliative resection.

2.2 Surgical Technique, Histopathological Examination, Postoperative Adjuvant Chemotherapy and Follow-up

All surgeries were performed by qualified, experienced colorectal surgeons. All operations assisted were radical resections with a complete mesocolic excision (CME), which were performed according to protocol guidelines. All resected specimens were examined and confirmed by pathologists and surgeons

shortly after surgery. MAC is a histological subtype of colorectal cancer which is typically characterized by pools of extracellular mucin containing malignant epithelium. The TNM classification was defined by the criteria of the 6th or 7th edition manual of the AJCC/UICC. Post-operative adjuvant chemotherapy was recommended for patients with TNM high-risk stage Ⅱ disease and stage Ⅲ disease, unless the patient's physical status was unsuitable for chemotherapy administration or a patient was unwilling to receive chemotherapy. The Follow-up is according to the National Comprehensive Cancer Network (NCCN) guideline.

2.3 Observation Indexes

Preoperative indexes included age, gender, American Society of Anesthesiology (ASA) score, tumor location, comorbidity, and the tumor markers carbohydrate antigen 199 (CA199) and carcinoembryonic antigen (CEA). The intraoperative indexes included operation time, blood loss, blood transfusion, combined organ resection, postoperative complications, and number of lymph nodes harvested. Postoperative indexes included tumor size, pathological T stage, pathological N stage, tumor grade (TNM), positive lymph numbers, and postoperative complications. The follow-up indexes included adjuvant chemotherapy received, disease-free survival (DFS), local recurrence, and distant metastasis. For DFS, the follow-up time was recorded from the date of surgery to the first recurrence date. The classifications of local recurrence and distant metastasis were based on where the recurrence was first found by colonoscopy, CT, MRI, or PET-CT[14].

2.4 Statistical Analyses

All statistical analyses were performed using SPSS, release 26.0. Quantitative data are expressed as mean ± standard deviation (SD) or median. Categorical data were compared using $\chi 2$ tests or Fisher's exact test. Comparison of continuous variables was performed using the Mann-Whitney U test. Survival curves for DFS data were constructed using Kaplan-Meier method, and the curves were compared by the log-rank test. Significant prognostic factors identified using univariate analysis were further evaluated by logistic regression analysis. When the P-value was less than 0.05 in univariate analysis, it would be included in the multivariate analysis. Multivariate analysis was performed using an enter method. A P-value < 0.05 was considered statistically significant.

3. Results

3.1 Demographics

During the period from 2009 to 2018, we collected a total of 162 MAC cases according to a pathological database from 4527 cases of CRC at the Guangzhou First People's Hospital and the Third Affiliated Hospital of Sun Yat-Sen University. There were 60 cases with relapse (27 cases with local recurrences, 22 cases with distant metastases, and 11 cases with both) (Fig. 1).

Patients included a total of 76 men (46.91%) and 86 women (53.09%) with a mean age of 58.26±14.91 years (range, 15-87). There were 61 (37.65%) patients with comorbidities. The American Society of Anesthesiology scores were as follows: □ (n= 73; 45.06%), □ (n=68; 41.98%) and □ (n=21; 12.96%). There were 69 patients (42.59%) with right colonic MA, 45 patients (27.78%) with left colonic MA, and 48 (29.63%) with rectal MA. The mean preoperative levels of CEA and CA199 were 16.03±42.08 ng/mL and 57.53±152.61 U/mL, respectively. There were 76 patients (46.91%) with above-threshold levels of CEA (+, ≥5 ng/mL) and 49 patients (30.25%) with above-threshold levels of CA 199 (+, ≥34 U/mL). Most patients 114 (70.37%) received adjuvant chemotherapy. Most MAC cases (93.8% of colonic cancers and 87.5% of rectal cancers) were T3-T4 stage. 50% of patients with colonic MA and 39.5% of patients with rectal MA did not have any LN metastasis (N0). According to the TNM classification by UICC, there were 6.79% at stage □ (n=11), 40.12% at stage □ (n=65), and 53.09% at stage □ (n=86) (Table 1)

There were 79 (48.77%) patients that underwent open surgery and 83 (51.23%) that underwent laparoscopic surgery. The mean operation time was 211.01±78.34 min and the mean blood loss was 130.74±108.29 ml. There were 14 (8.64%) patients with multivisceral resection, including abdominal wall (n=2, 1.23%), small bowel (n=5, 3.09%), urinary organs (n=1, 0.62%), gynecologic organs (n=3, 1.85%), and gallbladder (n=3, 1.85%). There were 26 (16.05%) patients with postoperative complications, including anastomotic hemorrhage (n=3, 1.85%), intraabdominal bleeding (n=2, 1.23%), leakage (n=5, 3.09%), gastroplegia (n=2, 1.23%), infection of the incision or abdomen (n=12, 7.41%), pulmonary infection (n=6, 3.7%), obstruction (n=9, 5.56%), and renal insufficiency (n=1, 0.62%). Mean follow-up time for the endpoint of relapse free period (RFP) was 4 years (range 0–11), and the study endpoints were local recurrence or distant metastasis of the disease. The pattern of local recurrence was as follows: recurrent abdominal or pelvic masses (n=13, 8.02%), peritoneal dissemination (n=12, 7.41%), recurrent enlarged LNs (n=5, 3.09%), and recurrent masses with peritoneal nodules (n=8, 4.94%). The distant metastases included isolated liver metastasis (n=13, 8.02%), lung metastasis (n= 8, 4.94%), bone metastasis (n=6, 3.7%), brain metastasis (n=1, 0.62%), liver with lung metastasis (n=4, 2.47%), and liver with bone and brain metastasis (n=1, 0.62%) (Table 2).

3.2 The 5-year disease-free survival of MAC

The Kaplan-Meier plot showed that the 5-year disease-free survival (DFS) rates of patients were as follows: 100% for TNM stage I, 71.2% for TNM stage II, and 47.81% for TNM stage III. There were significant differences among these three groups (p=0.001) (Fig. 2A). Five-year DFS rates of MAC, colonic MA, and rectal MA were 62.0%, 65.8%, and 51.7%, respectively. There were no significant differences among these three groups (p=0.504, Fig. 2B).

3.3 Univariate analysis the predictive factors

Univariate analysis showed that the predictive factors for local recurrence of MAC were intra-operative blood loss (p=0.004, OR=1.005), intra-operative transfusion (p=0.002, OR=5.179) and N2 stage (p=0.000, OR=4.643) (Table 3A). Subgroup analysis showed that the predictors for local recurrence of colonic MA were intra-operative blood loss (p=0.008, OR=1.006), intra-operative transfusion (p=0.043,

OR=3.952), N2 stage (p=0.004, OR=5.044) and T4 stage (p=0.029, OR=3.752) (Table 3B). The main predictor for local recurrence of MAC was intra-operative transfusion (p=0.014, OR=7.857) (Table 3C).

Using univariate analysis, we found that the predictive factors for distant metastasis of MAC were male sex (p=0.035, OR=2.410), CA199 (p=0.011, OR=1.004), CEA (p=0.020, OR=1.010), intra-operative blood loss (p=0.022, OR=1.003), T4 stage (p=0.007, OR=4.125), and N2 stage (p=0.018, OR=3.4) (Table 4A). Subgroup analysis of the predictors for distant metastasis of colonic MA and rectal MA revealed that CA199 (p=0.022, OR=1.003), CEA (p=0.004, OR=1.017), T4 stage (p=0.022, OR=4.628), N2 stage (p=0.006, OR=6.568), and TNM stage Ⅲ (p=0.019, OR=5.308) were predictors for distant metastasis of colonic MA (Table 4-B), and CA199 (p=0.050, OR=1.013) and intra-operative blood loss (p=0.027, OR=1.007) were predictors for local recurrence of rectal MA (Table 4-C).

3.4 Multivariate analysis the independent predictors

Using multivariate analysis, we found that the independent predictors for local recurrence of MAC were intra-operative transfusion (p=0.04, OR=4.175) and N2 stage (p=0.000, OR=5.291) (Table 5A). The Hosmer-Lemeshow test had a P value of 0.00, indicating good fit of the data to the model. The AUC of the model was 0.771 (95% CI: 0.688–0.855) with standard error of 0.43. Calibration Plot showed that the model expected curve is close to the observed curve, indicating that the model has good predictive capabilities (Supplemental Fig 1A). Subgroup analysis showed that the independent predictor for local recurrence of colonic MA was N2 stage (p=0.028, OR=3.592) (Supplemental Table 1A). The independent predictor for local recurrence of rectal MA was intra-operative transfusion (p=0.014, OR=7.857) (Supplemental Table 1C). Overall, the independent predictors of distant metastasis of MAC were male sex (p=0.049, OR=2.410), CA199 (p=0.02, OR=1.003), and T4 stage (p=0.007, OR=4.006) (Table 5B). The Hosmer-Lemeshow test had a P value of 0.00, indicating good fit of the data to the model. The AUC of the model was 0.826 (95% CI: 0.758–0.894) with standard error of 0.035. Calibration Plot showed that the model expected curve is close to the observed curve, indicating that the model has good predictive capabilities(Supplemental Fig 1B). Subgroup analysis showed that the independent predictor for distant metastasis of colonic MA was T4 stage (p=0.043, OR=3.627) (Supplemental Table 1B). In contrast, none of the examined variables rose to the level of independent predictor for distant metastasis of rectal MA (Supplemental Table 1D).

4. Discussion

MA is a unique pathologic entity first described by Parham in 1923[15]. Compared with colorectal adenocarcinoma, MAC often has a worse prognosis[7, 16, 17] and microsatellite instability-high(MSI-H) [18], and is also more likely to lead to lymphovascular invasion, perineural invasion[3], lymph node metastasis, and peritoneal implants[5]. Considering the particularity of MAC, some researchers believe that patients with MAC may require adjustments in treatment[13]. Therefore, a thorough evaluation of the predictors of local disease recurrence and distant metastasis of MAC can serve to identify patients with a higher risk of future relapse, and thus improve the individualized management of patients with MAC.

MAC exhibits variation in geographical distribution, accounting for about 5% of CRC in studies from Asian countries[3-5] and 10-20% in studies from Western countries[6, 19-21]. Consistent with other studies, *our data* showed that the incidence rate of MAC is 5.24%. Previous studies showed that MAC is more frequently found in female patients and is predominantly located in the proximal colon[22-24]. Our data showed that 42.59% patients had right colonic MA, consistent with previous studies. However, there was one major difference compared to prior work, which was that our data showed that the proportion of female patients (53.09%) was not dominant.

Over ninety percent of patients (93%) had stage II or stage III disease, in agreement with previous reports that showed that MAC is often diagnosed at an advanced stage[13, 25, 26]. There were 91.98% patients with pathological T3 stage or T4 stage. More than half of patients (53.09%) had lymph node metastasis. A more advanced stage of MAC is attributed to many factors, including the more aggressive nature of MAC compared to colorectal adenocarcinoma and the tendency to form tumors in the proximal colon, which serves to delay clinical symptoms until a more advanced stage has been reached. Perhaps the advanced stage of tumors in this patient cohort contributed to the relatively high rate of cancer recurrence (37.04%). Our results showed that the five-year DFS rate for stage I tumors was 100%, and DFS rates for stage □ and □ were 71.2% and 47.81%, respectively (Fig. 2, $p<0.05$). Therefore, early and accurate diagnosis plays a critical role in the prevention and treatment of MAC.

The method of surgery did not affect the prognosis of MAC. Our previous study showed that laparoscopic and open surgery for MAC had similar prognoses[27]. There were many stage T4b tumors in this group, which led to more radical organ resection, including abdominal wall, small bowel urinary organs, gynecologic organs, and gallbladder. The rate of postoperative complications (16.05%) in this group was lower compared with previous reports[26], and most of them were mild complications according to the Clavien-Dindo scale. Studies have shown that postoperative complications can affect the prognosis of CRC patients[28]. However, our results showed that postoperative complications did not influence the prognosis of MAC.

The present study aimed to explore the predictors for poor outcome of MA in terms of local recurrence and distant metastasis after surgery. Many researchers have focused on the prognostic implications of the mucinous histologic phenotype, but few studies have explored the prognostic factors of MAC. The clinicopathological significance of a mucinous CRC subtype is well appreciated but remains controversial. Some studies have shown that MA has a worse prognosis than non-mucinous adenocarcinoma[23, 29-31], whereas others have shown no prognostic difference compared to conventional CRC[32, 33]. Although there was no direct comparison with non-mucinous adenocarcinoma in the present study, compared with previous published data[11, 34], the 5-year OS rate of this group (67.3%) of mucinous adenocarcinoma was lower. We therefore believe that MAC has a worse prognosis.

We found that the local recurrence of MAC mainly manifested as recurrent masses and peritoneal nodules. The independent risk factors for local metastasis were N2 stage and intra-operative transfusion. Patients with N2 stage in this group had higher pathological stages, which suggests that this high-

recurrence group should receive extra attention in the process of treating MAC. The local recurrence of MAC was related to intraoperative bleeding and intraoperative blood transfusion, which has important clinical significance. We think that the main reasons behind this may be as follows. First, more intraoperative bleeding may be caused by the higher T stage and the associated clinical infiltrative growth, leading to difficulty in tumor resection and surgical separation of tumor. These difficulties may have resulted in residual viable tumor cells. Second, studies have shown that MAC is associated with higher peritoneal metastasis and the cells of mucous tumors have a more aggressive nature[13]. Intraoperative blood loss may facilitate local transplantation of tumor cells. Third, more intraoperative bleeding may lead to slower perioperative recovery and poor immunity of patients, which may result in more postoperative complications that lead to a delay in the start of chemotherapy. Based on these factors that may lead to poor prognosis, we suggest the following guidelines. First, strictly follow the no-touch concept of surgical oncology and perform resection according to total mesorectal excision (TME); this will ensure that the intraoperative operation is conducted carefully and with clear surgical levels. Second, if patients with MAC experience excessive intraoperative bleeding can be flushed with distilled water in the abdominal cavity, intraperitoneal infusion chemotherapy and hyperthermic perfusion can also be considered. Third, if there is no neoadjuvant radiotherapy for rectal MA patients with excessive intraoperative bleeding, adjuvant radiotherapy can be used after surgery. Fourth, for these patients, adjuvant chemotherapy in combination with targeted drugs, or, if their MSI are unstable, immunotherapy should be considered. Additionally, close postoperative follow-up should be emphasized for these patients.

In the group with distant metastasis, the most common type was liver metastasis, followed by lung metastasis. The independent predictors of distant metastasis of MAC were T4 stage and CA199. For the patients with T4 stage, the tumor may invade local blood vessels, causing tumor cells to enter the blood. We believe that the distant metastasis of MAC is closely related to the high tumor markers, which is a sign of tumor cells entering the blood before surgery. To address this, clinicians should consider using stronger or more specific adjuvant therapy based on the results of genetic testing, such as adding targeted drugs and immune drugs. Studies have shown that MAC has a higher probability of microsatellite instability. 22.64% of patients in our study group had tumors with high microsatellite instability (MSI-H) (12/53, only 53 patients were tested for MSI status). Recent work showed that MSI detection of mucinous adenocarcinoma requires caution[35]. Second, it warrants close observation of the progress of the disease and the level of tumor markers after operation, and close follow-ups should be scheduled for all these patients.

Our study showed that male sex was an independent risk factor for distant metastasis. This finding goes against the findings of another study[26] that reported female sex to be an influential predictor of poor outcome of MAC. In our opinion, there are several reasons that male sex might be a risk factor: men are more likely to engage in unhealthy lifestyles such as consuming alcohol or smoking and in aggressive strategies to cope with stress in our country. We found that male relapsed patients had a higher rate of smoking and drinking habits in the present study. It also suggests that that tumor treatment should involve not only medical treatment, but primary prevention (healthy diet, healthy

lifestyle, etc.), implemented throughout the course of treatment for MAC. In a large multicenter study, patients with CRC who followed a healthy lifestyle were more likely to survive[36]. The review suggests that we should also attach importance to the factors for primary prevention after treatment of colorectal cancer[37].

5. Conclusions

In brief, the present study revealed significant predictors for local recurrence and distant metastasis in MAC. Interestingly, the risk factors that predicted local recurrence and distant metastasis of MAC were available before adjuvant treatment. They can therefore provide a basis for well-directed and timely follow-up treatment of MAC. This study is not without limitations. The small number of patients studied, and the retrospective nature of the study are important limitations that must be considered. Large-scale studies and multicenter studies are needed for more extensive analyses.

Declarations

Ethics approval and consent to participate: The study was approved by the the Ethics Committee of Guangzhou First People's Hospital. Because of the retrospective nature of the study, the data were anonymous and the requirement for informed consent was waived.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no conflict of interest.

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Tables

Table 1: Clinical and Pathologic information of 162 MAC

Clinical and Pathologic information		
Age	(mean ±SD)	58.26±14.91
Gender	Male/female	76/86
Comorbidities	Yes/no	61/101
ASA score	□/□/□	73/68/21
Tumor location	Right/left/rectal	69/45/48
Tumor size(cm)	mean ± SD	4.36±12.081
CA199 (U/mL)	(mean ±SD)	57.53±152.61
CEA (ng/mL)	(mean ±SD)	16.03±42.08
Adjuvant therapy	Yes/no	114/48
Number of LNs	(mean ±SD)	19.22±9.528
T stage	T1/T2/T3/T4	1/12/74/75
N stage	N0/N1/N2	76/36/50
TNM stage	□/□/□	11/65/86

ASA: American Society of Anesthesiology; CA199: Carbohydrate antigen 199; CEA: Carcinoembryonic antigen; LN: lymph node; SD: Standard deviation.

Table 2: Surgical and prognosis outcome of 162 MAC.

Surgical and prognosis outcome		
Surgical method	LAP/OPEN	83/79
Operative time (min)	mean ± SD	211.01±78.34
Blood loss (ml)	mean ± SD	130.74±108.29
Multivisceral resection	Total (%)	14(8.64)
	Abdominal wall (%)	2(1.23)
	Small bowel (except duodenum) (%)	5(3.09)
	Urinary organs (%)	1(0.62)
	Gynecologic organs (%)	3(1.85)
	gallbladder (%)	3(1.85)
Postoperative complication	Total (%)	26(16.05)
The frequency of appearance	Anastomotic Hemorrhage (%)	3(1.85)
	Intraabdominal bleeding (%)	2(1.23)
	Leakage (%)	5(3.09)
	Gastroplegia (%)	2(1.23)
	Infection (incision and abdomen) (%)	12(7.41)
	Pulmonary infection (%)	6(3.7)
	Obstruction (%)	9(5.56)
	Renal insufficiency (%)	1(0.62)
Local recurrence	Total (%)	38(23.46)
	Recurrent abdominal or pelvic masses (%)	13(8.02)
	Peritoneal dissemination (%)	12(7.41)
	Recurrent enlarged LNs (%)	5(3.09)
	Recurrent masses + peritoneal nodules (%)	8(4.94)
Distant metastasis	Total (%)	33(20.37)
	Liver metastasis (%)	13(8.02)
	lung metastasis (%)	8(4.94)
	bone metastasis (%)	6(3.7)
	Liver and lung metastasis (%)	4(2.47)

	Liver, bone and brain metastasis (%)	1(0.62)
	brain metastasis (%)	1(0.62)

LAP: Laparoscopic surgery group; OPEN: Open surgery group. LN: lymph node [a] Some patients have multiple postoperative complications.

Table 3-A: Univariate analysis of the risk factors for local recurrence of MAC

Variable (MAC)		Local recurrence N=38	No local recurrence N=124	P	OR
Age	(mean ±SD)	56.87±15.39	58.69±14.79	0.510	
Gender	Male/female	19/19	67/57	0.663	
Comorbidities (%)	□	14(36.8)	47(37.9)	0.906	
ASA score	□	16(42.1)	57(46.0)	0.180	
	□	20(52.6)	48(38.7)		
	□	2(5.3)	19(15.3)		
CA199 (U/mL)	mean ± SD	65.62±127.00	55.05±160.02	0.709	
CEA (ng/mL)	mean ± SD	15.34±32.45	16.24±44.73	0.908	
Tumor location	Colonic/rectal	26/12	94/36	0.764	
Tumor size(cm)	mean ± SD	4.057±1.670	4.454±2.189	0.305	
LAP and OPEN		17/21	66/58	0.361	
Operative time(min)	mean ± SD	213.89±80.21	210.12±78.06	0.795	
Blood loss(mL)	mean ± SD	178.68±138.49	116.04±93.01	0.004*	1.005
Transfusion (%)	Yes	10(26.3)	8(6.5)	0.002*	5.179
Multivisceral resection (%)	Yes	2(5.3)	12(9.7)	0.404	
Complications (%)	Yes	7(18.4)	19(15.3)	0.649	
No. of lymph nodes resected	mean ± SD	17.5±9.29	19.75±9.574	0.205	
T stage	T1-T2	0	13(10.5)	0.093	
	T3 (R)	13(34.2)	61(49.2)		
	T4a+T4b	25(65.8)	50(40.3)		
N stage	N0 (R)	11(28.9)	65(52.4)	0.000*	
	N1	5(13.2)	31(25.0)		
	N2	22(57.9)	28(22.6)		4.643
TNM stage	I	0	11(8.9)	0.062	
	□(R)	10(26.3)	55(44.4)		

	□	28(73.7)	58(46.8)	
Adjuvant therapy	Yes	27(71.1)	86(69.4)	0.842

ASA: American Society of Anesthesiology; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; OR, risk ratio, R: Reference group; *□p<0.05; LAP: Laparoscopic surgery group; OPEN: Open surgery group.

Table 3-B: Subgroup analysis of the risk factors for local recurrence of Colonic MA.

Variable (Colonic MA)		Local recurrence N=26	No local recurrence N=88	P	OR
Age	(mean ±SD)	56.92±17.25	59.20±14.96	0.540	
Gender	Male/female	13/13	50/38	0.508	
Comorbidities (%)	□	9(34.6)	36(40.9)	0.565	
ASA score	□	10(38.5)	38(43.2)	0.412	
	□	14(53.8)	36(40.9)		
	□	2(7.7)	14(15.9)		
CA199 (U/mL)	mean ± SD	75.25±150.13	60.46±182.58	0.706	
CEA (ng/mL)	mean ± SD	18.46±38.72	16.98±40.93	0.868	
Tumor location	Right/left	14/12	55/33	0.429	
Tumor size(cm)	mean ± SD	4.192±1.701	4.911±2.244	0.137	
LAP and OPEN		11/15	45/43	0.430	
Operative time(min)	mean ± SD	202.69±54.58	199.30±67.34	0.813	
Blood loss(mL)	mean ± SD	181.54±134.96	112.62±87.14	0.008*	1.006
Transfusion (%)	Yes	5(19.2)	5(5.7)	0.043*	3.952
Multivisceral resection (%)	Yes	1(3.8)	11(12.5)	0.234	
Complications (%)	Yes	5(19.2)	13(14.8)	0.585	
No. of lymph nodes resected	mean ± SD	18.73±10.04	20.19±9.969	0.510	
T stage	T1-T2	0	7(8.0)	0.029*	
	T3 (R)	7(26.9)	47(53.4)		
	T4a+T4b	19(73.1)	34(38.6)		3.752
N stage	N0 (R)	8(30.8)	49(55.7)	0.004*	
	N1	4(15.4)	22(25.0)		
	N2	14(53.8)	17(19.3)		5.044
TNM stage	I	0	7(7.9)	0.077	
	□(R)	7(26.9)	43(48.9)		
	□	19(73.1)	38(43.2)		

Adjuvant therapy	Yes	20(76.9)	58(65.9)	0.292

ASA: American Society of Anesthesiology; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; OR, risk ratio, R: Reference group; *p<0.05; LAP: Laparoscopic surgery group; OPEN: Open surgery group.

Table 3-C: Subgroup analysis of the risk factors for local recurrence of Rectal MA.

Variable (Rectal MA)		Local recurrence N=12	No local recurrence N=36	P	OR
Age	(mean ±SD)	56.75±10.96	57.42±14.51	0.882	
Gender	Male/female	6/6	17/19	0.868	
Comorbidities (%)	□	5(41.7)	11(30.6)	0.481	
ASA score	□	6(50.0)	19(52.8)	0.799	
	□	6(50.0)	12(33.3)		
	□	0(0)	5(13.9)		
CA199 (U/mL)	mean ± SD	44.76±48.28	41.82±82.92	0.906	
CEA (ng/mL)	mean ± SD	8.569±7.739	14.42±53.49	0.719	
Tumor size(cm)	mean ± SD	3.764±1.635	3.336±1.584	0.417	
LAP and OPEN		6/6	21/15	0.615	
Operative time(min)	mean ± SD	238.16±118.02	236.58±95.54	0.962	
Blood loss(mL)	mean ± SD	172.5±151.84	124.44±106.89	0.242	
Transfusion (%)	Yes	5(41.7)	3(8.3)	0.014*	7.857
Multivisceral resection (%)	Yes	1(8.3)	1(2.8)	0.427	
Complications (%)	Yes	2(16.7)	6(16.7)	1.000	
No. of lymph nodes resected	mean ± SD	14.83±7.056	18.67±8.569	0.172	
T stage	T1-T2	0	6(16.7)	0.981	
	T3 (R)	6(50.0)	14(38.9)		
	T4a+T4b	6(50.0)	16(44.4)		
N stage	N0 (R)	3(25.0)	16(44.0)	0.102	
	N1	1(8.3)	9(25.0)		
	N2	8(66.7)	11(30.6)		
TNM stage	I	0	4(11.1)	0.742	
	□(R)	3(25.0)	12(33.3)		
	□	9(75.0)	20(69.0)		
Adjuvant therapy	Yes	7(58.3)	28(77.8)	0.197	

ASA: American Society of Anesthesiology; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; OR, risk ratio, R: Reference group; *p<0.05; LAP: Laparoscopic surgery group; OPEN: Open surgery group.

Table 4-A: Univariate analysis of the risk factors for local distant metastasis of MAC.

Variable (MAC)		Distant metastasis N=33	No distant metastasis N=129	P	OR
Age	(mean ±SD)	60.00±13.81	57.81±15.20	0.452	
Gender	Male/female	23/10	63/66	0.035*	2.410
Comorbidities (%)	□	13(39.4)	48(37.2)	0.817	
ASA score	□	13(39.4)	60(46.5)	0.438	
	□	17(51.2)	51(39.5)		
	□	3(9.1)	18(14.0)		
CA199 (U/mL)	mean ± SD	141.92±244.32	35.94±109.84	0.011*	1.004
CEA (ng/mL)	mean ± SD	33.91±62.21	11.45±34.00	0.020	1.010
Tumor location	Colonic/rectal	22/11	92/37	0.602	
Tumor size(cm)	mean ± SD	4.331±2.398	4.368±2.001	0.928	
LAP and OPEN		17/16	67/62	0.723	
Operative time(min)	mean ± SD	225.45±77.54	207.31±78.41	0.240	
Blood loss(mL)	mean ± SD	171.21±117.49	120.39±103.77	0.022*	1.003
Transfusion (%)	Yes	6(18.2)	12(9.3)	0.155	
Multivisceral resection (%)	Yes	3(9.1)	11(8.5)	0.918	
Complications (%)	Yes	5(15.2)	21(16.3)	0.875	
No. of lymph nodes resected	mean ± SD	19.27±8.137	19.21±9.881	0.973	
T stage	T1-T2	0	13(10.1)	0.007*	
	T3 (R)	8(24.2)	66(51.2)		
	T4a+T4b	25(75.8)	50(38.8)		4.125
N stage	N0 (R)	10(30.3)	66(51.2)	0.018*	
	N1	6(18.2)	30(23.3)		
	N2	17(51.5)	33(25.6)		3.4
TNM stage	I	0	11(8.5)	0.126	
	□(R)	9(27.3)	56(43.4)		

	□	24(72.7)	62(48.1)	
Adjuvant therapy	Yes	23(69.7)	90(69.8)	0.994

ASA: American Society of Anesthesiology; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; OR, risk ratio, R: Reference group; *□p<0.05; LAP: Laparoscopic surgery group; OPEN: Open surgery group.

Table 4-B: Subgroup analysis of the risk factor of distant metastasis of Colonic MA.

Variable (Colonic MA)		Distant metastasis N=22	No distant metastasis N=92	P	OR
Age	(mean ±SD)	61.82±15.69	57.93±15.40	0.290	
Gender	Male/female	16/6	47/45	0.073	
Comorbidities (%)	□	9(40.9)	36(39.1)	0.878	
ASA score	□	8(36.4)	40(43.6)	0.504	
	□	12(54.5)	38(41.3)		
	□	2(9.1)	14(15.2)		
CA199 (U/mL)	mean ± SD	165.12±283.26	39.61±128.53	0.022*	1.003
CEA (ng/mL)	mean ± SD	46.49±73.20	10.34±22.86	0.004*	1.017
Tumor location	Right/left	15/7	54/38	0.415	
Tumor size(cm)	mean ± SD	4.781±2.507	4.739±2.066	0.932	
LAP and OPEN		9/13	47/45	0.393	
Operative time(min)	mean ± SD	207.95±67.01	198.18±64.04	0.522	
Blood loss(mL)	mean ± SD	147.72±113.64	123.70±101.09	0.333	
Transfusion (%)	Yes	3(13.6)	7(7.6)	0.376	
Multivisceral resection (%)	Yes	2(10.5)	10(10.9)	0.807	
Complications (%)	Yes	4(18.2)	14(15.2)	0.732	
No. of lymph nodes resected	mean ± SD	19.86±9.578	19.86±10.1	0.998	
T stage	T1-T2	0	7(7.6)	0.022*	
	T3 (R)	5(22.7)	49(53.3)		
	T4a+T4b	17(77.3)	36(39.1)		4.628
N stage	N0 (R)	5(22.7)	52(56.5)	0.006*	
	N1	5(22.7)	21(22.8)		
	N2	12(54.5)	19(20.7)		6.568
TNM stage	I	0	7(7.6)	0.019*	
	□(R)	4(18.2)	46(50.0)		

	□	18(81.8)	39(42.4)		5.308
Adjuvant therapy	Yes	14(63.6)	64(69.6)	0.592	

ASA: American Society of Anesthesiology; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; OR, risk ratio, R: Reference group; *□p<0.05; LAP: Laparoscopic surgery group; OPEN: Open surgery group.

Table 4-C: Subgroup analysis of the risk factor of distant metastasis of Rectal MA.

Variable (Rectal MA)		Distant metastasis N=11	No distant metastasis N=37	P	OR
Age	(mean ±SD)	56.36±8.488	57.51±14.88	0.804	
Gender	Male/female	7/4	16/21	0.241	
Comorbidities (%)	□	4(36.4)	12(32.4)	0.808	
ASA score	□	5(45.5)	20(54.1)	0.826	
	□	5(45.5)	13(35.1)		
	□	1(9.1)	4(10.8)		
CA199 (U/mL)	mean ± SD	95.53±137.77	26.81±31.86	0.050*	1.013
CEA (ng/mL)	mean ± SD	8.771±9.464	14.20±52.72	0.743	
Tumor size(cm)	mean ± SD	3.431±1.966	3.446±1.493	0.977	
LAP and OPEN		7/4	20/17	0.575	
Operative time(min)	mean ± SD	260.45±88.25	230.00±103.69	0.382	
Blood loss(mL)	mean ± SD	218.18±115.82	112.16±111.16	0.027*	1.007
Transfusion (%)	Yes	3(27.3)	5(13.5)	0.292	
Multivisceral resection (%)	Yes	1(9.1)	1(2.7)	0.380	
Complications (%)	Yes	1(9.1)	7(18.9)	0.453	
No. of lymph nodes resected	mean ± SD	18.09±4.11	17.59±9.248	0.861	
T stage	T1-T2	0	6(16.2)	0.309	
	T3 (R)	3(27.3)	17(45.9)		
	T4a+T4b	8(72.7)	14(37.8)		
N stage	N0 (R)	5(39.6)	14(37.8)	0.579	
	N1	1(20.8)	9(24.3)		
	N2	5(39.6)	15(37.8)		
TNM stage	I	0	4(10.8)	0.660	
	□(R)	5(45.5)	10(27.0)		
	□	6(54.5)	23(62.2)		

Adjuvant therapy	Yes	9(81.8)	26(70.3)	0.454

ASA: American Society of Anesthesiology; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; OR, risk ratio, R: Reference group; *p<0.05; LAP: Laparoscopic surgery group; OPEN: Open surgery group.

Table 5-A: Multivariate analysis of the significant independent predictors for local recurrence of MAC.

Variable (MAC)	OR	95% CI	P value
Blood loss(mL)	1.002	0.998-1.006	0.305
Transfusion	4.175	1.069-16.298	0.04*
N1 Stage	1.095	0.331-3.617	0.882
N2 Stage	5.291	2.132-13.131	0.000*

CI, confidence interval; OR, risk ratio. *p<0.05, The risk ratio (OR) of N1 or N2 stage is relative to N0 stage.

Table 5-B: Multivariate analysis of the significant independent predictors for distant metastasis of MAC.

Variable (MAC)	OR	95% CI	P value
Male sex	2.630	1.006-6.875	0.049*
CA199 (U/mL)	1.003	1.001-1.006	0.02*
CEA (ng/mL)	1.005	0.996-1.014	0.322
Blood loss(mL)	1.004	1.000-1.007	0.053
T4 Stage	4.006*	1.468-10.935	0.007*
N1 Stage	0.832	0.217-3.189	0.789
N2 Stage	2.13	0.792-5.727	0.134

CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; OR, risk ratio; CI, confidence interval; * p<0.05. The risk ratio (OR) of T4 stage is relative to T3 stage. The risk ratio (OR) of N1 or N2 stage is relative to N0 stage.

Figures

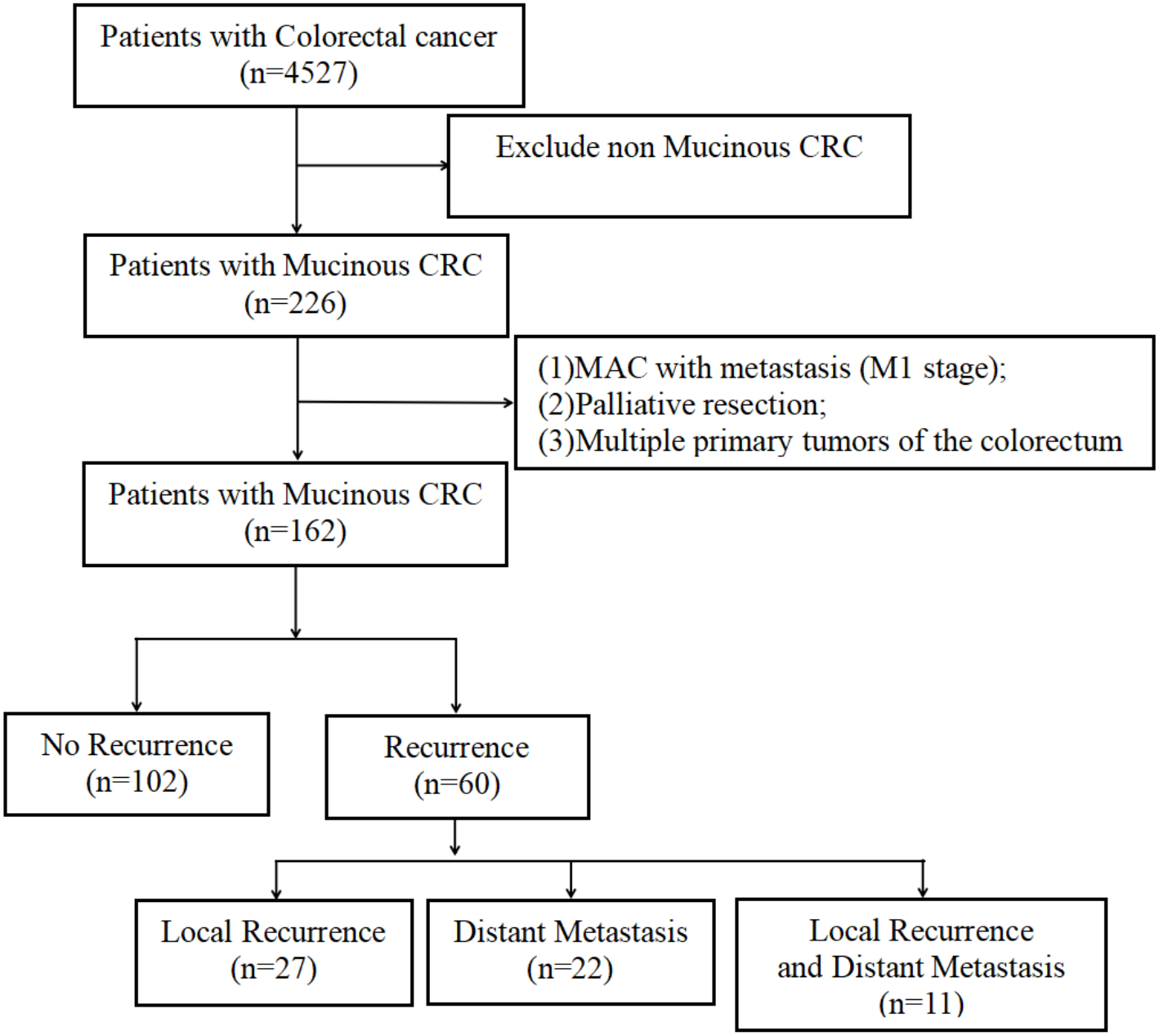

Figure 1

Flow diagram showing patient selection and exclusion process. CRC, colorectal cancer.

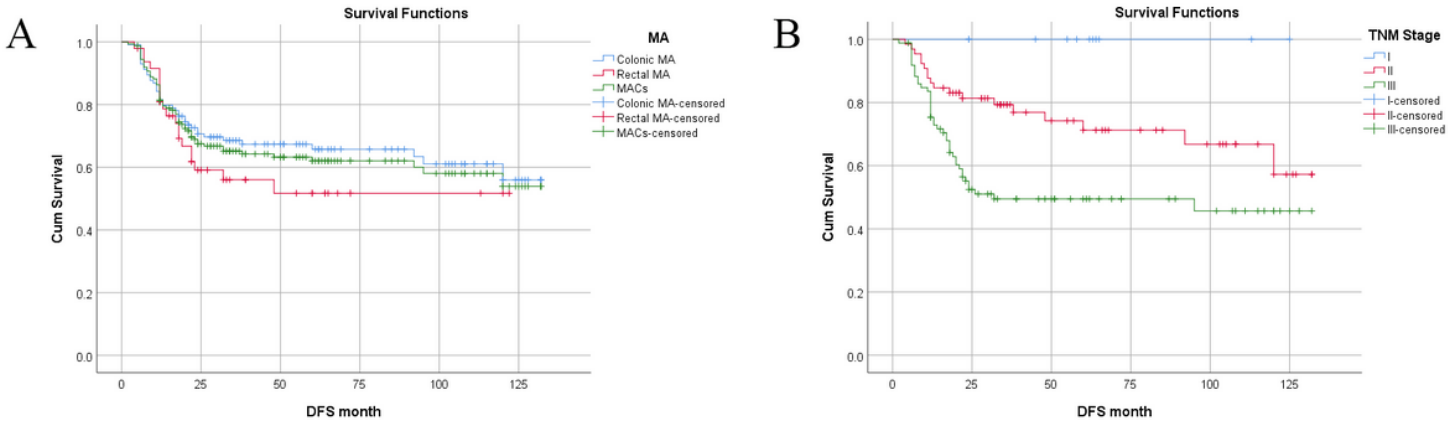

Figure 2

A: Log Rank (Mantel-Cox) test=1.371, p=0.504. Five-year DFS rates of MAC, colonic MA, and rectal MA were 62.0%, 65.8%, and 51.7%, respectively. B: Log Rank (Mantel-Cox) test=14.290, p=0.001. Five-year DFS rates of TNM stage Ⅰ, TNM stage Ⅱ, and TNM stage Ⅲ were 100%, 71.2%, and 47.81%, respectively.

Supplementary Files

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