Original Paper

Predictors of Lymph Node Metastasis and Prognosis in pT1 Colorectal Cancer Patients with Signet-Ring Cell and Mucinous Adenocarcinomas

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Key Words

Colorectal cancer • Signet-ring cell carcinoma • Mucinous carcinoma • Treatment • Prognosis

Abstract

Background/Aims: The local excision of early colorectal cancer is limited by the presence of lymph node metastasis (LNM). Signet-ring cell carcinomas (SRC) and mucinous adenocarcinomas (MAC) are two relatively infrequent histological subtypes. However, little is known about the predictors of LNM and prognosis to support the feasibility of local excision in early-stage SRC and MAC. **Methods:** The Surveillance Epidemiology and End Results Database were used to identify all patients with pT1 adenocarcinomas, including conventional adenocarcinoma (AC), MAC, and SRC. The prevalence of LNM was assessed, and the long-term survival rate in the above three types of colorectal cancer was calculated. **Results:** SRC accounted for 0.3% and MAC accounted for 4.4% of the entire cohort of colorectal adenocarcinomas. Compared to AC, MRC and SRC were more often located in the proximal colon, and exhibited a higher grade. The incidence of LNM in AC, MAC, and SRC was 10.6%, 17.2%, and 33.3% for colon cancers and 14.8%, 25.9%, and 46.2% for rectal cancers, respectively. In patients with lymph nodes resected no less than 12, incidence of LNM in AC, MRC, and SRC was 12%, 21%, and 44% for colon tumors and 17%, 30%, and 14% for rectal tumors, respectively. Although, colon patients MAC showed an entirely worse survival rate than AC, rectum patients MAC showed a similar prognosis to AC. We found that in patients with rectal tumors, SRC had a worse 3 and 5-year prognosis than AC. However, for colon cancers, the prognosis of SRC was similar to that of AC. Histology was not found to be an independent prognostic factor in multivariate survival analysis. **Conclusions:** MAC and SRC are two distinct subtypes of colorectal cancer that require special attention despite their relatively rare prevalence. pT1 patients with SRC of the rectum and patients with MAC of the colon have higher incidences of LNM, and with these adverse outcomes, local excision is not recommended. Although MAC of the rectum and SRC of colon have a high rate of LNM, the prognosis of these types are similar to that of AC.

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Introduction

Primary colorectal signet-ring cell and mucinous carcinoma were first described by Laufman in 1951 and Parham in 1923, respectively [1, 2]. SRC and MAC are distinct from the conventional adenocarcinomas defined by the World Health Organization colorectal histology classification in 1979. SRCs are relatively rare, accounting for approximately 0.1-2.4% of all primary colorectal cancers, and are characterized by predominantly intracytoplasmic mucin deposition that pushes the nucleus eccentrically. In contrast, MACs (approximately 1.6-25.4%) are composed of an abundant extracellular mucin pool [3, 4]. Although these histological subtypes may represent entities with unique biological behaviors, aggressiveness, and prognosis, in contrast to the TNM staging and grading system, they are currently not included in the clinical classification system or the guidelines for indications of minimally invasive treatment for early colon and rectal cancer, which simply classify SRC and MAC as undifferentiated cancers [5, 6]. SRC is not a simple form of undifferentiated adenocarcinoma. Many studies have shown that patients with early signet-ring cell gastric cancer have a more favorable prognosis than patients with other undifferentiated adenocarcinomas [7, 8]. This phenomenon has been explained by the low possibility of LNM, and it might be considered an indication for endoscopic resection for early gastric cancer with SRC. However, there are few data regarding the indications for local excision of early SRC of colorectal cancer. The present retrospective study based on the surveillance, Epidemiology, and End Results (SEER) database aimed at determining the appropriate management for patients with early SRC and MAC colorectal cancer by analyzing the clinicopathological and long-term survival features of SRC and MAC in early-stage colorectal cancer.

Materials and Methods

Patient selection strategy and tumor characteristics

The study population was obtained from the records of the SEER database (reference number 12224-Nov2013), a program of the National Cancer Institute, which covers approximately 28% of the population of the United States. Cases of colon (C18.0-18.9, C26.0) and rectal cancer (C19.9, C20.9) from 1988 to 2006

Table 1. Corresponding SEER code of the pathological T1 tumor (TNM7 Map)

SEER extension code	Colon	Rectum
Prior to 2003		
13	Head of polyp	Head of polyp
14	Stalk of polyp	Stalk of polyp
15	Polyp, NOS	Polyp, NOS
16	Submucosa (superficial invasion)	Submucosa (superficial invasion)
20	Muscularis propria invaded	Muscularis propria invaded
30	Localized, NOS/confined to colon, NOS	Localized, NOS/confined to colon, NOS
Since 2004		
130	Confined to head of polyp, NOS	Confined to head of polyp, NOS
140	Confined to stalk of polyp, NOS	Confined to stalk of polyp, NOS
150	Invasive tumor in polyp, NOS	Invasive tumor in polyp, NOS
160	Invades submucosa (superficial invasion), including submucosa in the head or stalk of a polyp	Submucosa (superficial invasion), including submucosa in the head or stalk of a polyp
165		For rectum: Tumor invading submucosa with intraluminal extension to colon and/or anal canal/anus
170	Stated as T1 with no other information on extension	Stated as T1 with no other information on extension
300	Localized, NOS; Confined to colon, NOS	Confined to rectosigmoid junction, NOS; Confined to rectum, NOS
		Localized, NOS

Table 2. Corresponding SEER code of the radical surgical Resection

SEER Site Specific Surgery Code	Colon	Rectum(includes rectosigmoid)
Prior to 1998		
30	Partial or subtotal colectomy, but less than hemicolectomy	Anterior/posterior resection, wedge or segmental resection, transsacral rectosigmoidectomy, Hartmann's operation, partial proctectomy, rectal resection, NOS
40	Hemicolectomy or greater (but less than total); right/left colectomy (all of right or left colon and a portion of transverse)	Pull-through resection WITH sphincter preservation
50	Total colectomy	Abdominoperineal resection
60	Colectomy, NOS	Any of codes 30-50 PLUS partial or total removal of other organs
70	Colectomy PLUS partial or total removal of other organs	Pelvic Exenteration (partial or total);
Since 1998		
30	Partial colectomy, but less than hemicolectomy (with or without permanent colostomy)	Wedge or segmental resection; partial proctectomy; proctosigmoidectomy, NOS
40	Hemicolectomy or greater (but less than total); right or left colectomy	Pull through WITH sphincter preservation (colo-anal anastomosis)
50	Total colectomy	Total proctectomy
51		Total colectomy
60	Total proctocolectomy	Total proctocolectomy, NOS
70	Colectomy or coloproctectomy WITH an en bloc resection of other organs; pelvic exenteration	Colectomy, Proctectomy or proctocolectomy WITH an en bloc resection of other organs; pelvic exenteration
80	Colectomy, NOS	Colectomy, NOS; Proctectomy, NOS

Fig. 1. (A) study flow diagram from the SEER database.

were identified from the SEER database (SEER*Stat 8.1.5) according to the Site Recode Classifications. Only histologically confirmed malignant tumors of colorectal cancer were included, and lesions were confined to the submucosa (T1). The definition of tumor extension in SEER database can be seen in Table 1. We also limited our analysis to patients underwent surgical resection, corresponding detail have been shown in Table 2. Non-first tumors (those involving more than a single primary tumor or in which the primary cancer was not the first of 2 or more primary malignancies), patients treated with preoperative radiation (downstage Tstage), without information of LNs involvement, and with distant metastasis were excluded. For further details, see Fig. 1. Cancer-specific survival was used as the primary outcome parameter. The histological type groups were categorized as follows using the ICD-O-3 (International Classification of Disease for Oncology, 3rd edition), (ICD-10) coding schema: conventional adenocarcinoma (8010, 8020-

8022, 8140-8141, 8144-8145, 8210-8211, 8220-8221, 8230-8231, 8260-8263), referring to nonmucinous and nonsignet-ring cell tumors; MAC (8470, 8472-8473, 8480-8481); and SRCC (8490) [3, 9]. The “colon” location was defined as cecum, ascending colon, hepatic flexure of the colon, transverse colon, splenic flexure of the colon, descending colon, sigmoid colon, overlapping lesion of the colon, and colon NOS (not otherwise specified). The “rectum” location was defined as the rectosigmoid and rectum [3]. The colon tumors were further divided into three categories: right colon (cecum, ascending colon, and hepatic flexure), transverse colon, and left colon (splenic flexure, descending, and sigmoid colon) tumors. The tumor grades were grouped as follows: Grade I (well differentiated); Grade II (moderately differentiated); Grade III (poorly differentiated); Grade IV (undifferentiated or anaplastic lesions). This study was based on public data from the SEER database, and it did not include interaction with human subjects or the use of personal identifying information. The study was approved by the Review Board of Fudan University Huadong Hospital, Shanghai, China.

Statistical analysis

Clinicopathological variables in the analysis included age at diagnosis, gender, race, tumor site, therapy (radiation and surgery), tumor size, and tumor grade. Univariate analysis was performed using the Pearson chi-squared method or Fisher’s exact test for categorical variables and a Kruskal-Wallis test for continuous variables. The Kaplan-Meier method was employed to calculate the cancer-cause-specific death rate, and the difference between the survival curves was analyzed using a log-rank test. Meanwhile, 3 and 5 year survival rates between groups were calculated by log-log transformation for survival function. A Cox proportional hazards model was used in the multivariate analysis [10]. All of the reported tests were 2-sided, and p values < 0.05 were considered statistically significant. All statistical analysis was conducted using R statistical software, version 3.1.3, with survival and rms libraries and SPSS version 17.0 for windows (SPSS Inc. Chicago, IL, USA).

Results

Study cohort

A total cohort of 21,463 patients matching the inclusion criteria were analyzed in this study, most of whom had AC (95%). The incidence of SRC was extremely rare and accounted for 0.3% (62) of all of the patients, whereas that of MAC was 4.4% (934). The patients’ median age was 68 years (range: 20-100 years). The median numbers of resected lymph nodes during the surgery were ten. Lymphadenectomy of 9777 patients (45.5%) was considered to be adequate (with lymph nodes examined no less than 12). Among the entire cohort, males ($n = 11,016$) were more common than females ($n = 10,447$) and more tumors were located in the colon ($n = 15,987$, 74%) than in the rectum ($n = 5,339$, 25%). The race of the population-based study was predominantly white and made up of 81.2% in AC, 88.4% in MAC, and 88.7% in SRC, respectively. For further details, see Table 3.

Clinicopathological characteristics of the patients and the tumors

SRC were found more frequently to present with younger age compared to AC and MAC, more common in patients younger than 40 years old ($p < 0.021$; Table 3), and this comparison was similar in colon patients after stratifying the lesion by tumor location (Table 4). There was a propensity for MAC (72.6%) and SRC (77.1%) to be located in the proximal colon (large bowel proximal to the splenic flexure) in contrast to AC (56.5%; $p < 0.001$). Compared to AC, the percentage of tumor size exceeding 20 mm of MAC was higher, however, there was a similar distribution with regard to the tumor size between SRC and AC. Colon MAC exhibited a female predominance and rectal SRC cancers was more frequently diagnosed in male (Table 4), compared with the AC group. In terms of tumor differentiation grade, the SRC patients (80.7%) were diagnosed with high-grade tumors (Grades III and IV) more frequently than the MAC (10.5%) and AC (7.5%; $p < 0.001$) patients.

Table 3. Characteristics of the SEER database T1 CRC patients by histological type (n = 21,463)

Factor	AC n=20,467(100%)	MAC n=934(100%)	p(MAC vs.AC)	SRC n=62(100%)	p(SRC vs.AC)
Age(yr)			0.001		0.021
20-39	330(1.6)	13(1.4)		3(4.8)	
40-59	5267(25.7)	208(22.2)		16(25.8)	
60-79	11624(56.8)	522(55.9)		27(43.5)	
80+	3246(15.9)	191(20.4)		16(25.8)	
Gender			0.003		0.303
Male	10544(51.5)	436(46.7)		36(58.1)	
Female	9923 (48.5)	498 (53.3)		26(41.9)	
Race			0.009		0.512
White	16612 (81.2)	788(84.4)		55(88.7)	
Black	2105(10.3)	93(10.0)		3(4.8)	
Others*	1658(8.1)	49(5.2)		4(6.5)	
Unknown	92(0.4)	4(0.4)		0(0)	
Primarysite			<0.001		<0.001
Right colon	7200(35.2)	501(53.6)		31(50.0)	
Transversecolon	1216(5.9)	70(7.5)		6(9.7)	
Left colon	6737(32.9)	215(23.0)		11(17.7)	
Rectum	5183 (25.3)	143(15.3)		13(21.0)	
Unknown	131(0.6)	5(0.5)		1(1.6)	
Tumorsize(mm)			<0.001		0.931
0-20	12233(59.8)	460(49.3)		38(61.3)	
21-30	4145(20.2)	195(20.9)		12(19.4)	
31-40	1942(9.5)	108(11.5)		6(9.7)	
41-50	1040(5.1)	73(7.8)		2(3.2)	
51-60	502(2.4)	29(3.1)		2(3.2)	
61-80	404(2.0)	37(4.0)		1(1.6)	
80+	201(1.0)	32(3.4)		1(1.6)	
Grade			<0.001		<0.001
I	4152(20.3)	189(20.2)		2(3.2)	
II	13514(66.0)	537(57.5)		6(9.7)	
III	1445(7.1)	94(10.1)		44(71.0)	
IV	89(0.4)	4(0.4)		6(9.7)	
Unknown	1267(6.2)	110(11.8)		4(6.4)	
No. of LNsdissected			0.968		0.085
<12	11151(54.5)	508(54.4)		27(43.5)	
≥12	9316(45.5)	426(45.6)		35(56.5)	
Nstage			<0.001		<0.001
N0	18088(88.4)	762(81.6)		40(64.5)	
N1	2112(10.3)	138(14.8)		19(30.7)	
N2	267(1.3)	34(3.6)		3(4.8)	

Risk factors for lymph node metastasis

Univariate analysis of risk factors for lymph node metastasis (LNM) found age, grade, tumor size and histological type to be significant factors regardless of tumor location (Table 5). Overall, the rate of LNM was 12.0% (2,573 out of 21,463). Among these 2,573 patients, 2,379 (92.5%) patients had AC, 22patients (0.8%) had SRC and 172 patients (6.7%) had MAC. SRC had a higher rate of LNM (35.5%) than MAC (18.4%) and AC (11.6%). When patients were stratified by site, a similar phenomenon was also seen. In the colon, SRC had an LNM rate of 33.3%, MAC had a rate of 17.2%, and AC had a rate of 10.6%. In the rectum, SRC had an LNM rate of 46.2%, MAC had a rate of 25.9%, and AC had a rate of 14.8% (Table 6). The multivariate analysis revealed that the age, race, tumor size, location, histological type, and grade were independent factors predicting LNM (Table 7). When patients were stratified by site, similar results were found in the colon patients. However, race was not an independent factor in the patients with rectal tumors (data not shown).

Table 4. Tumor site-specific demographics

Characteristic	Tumor site					
	Adeno carcinoma (n=15,153)	Colon Mucinous (n=786)	Signet ring (n=48)	Adenocarcinoma (n=5,183)	Rectum Mucinous (n=143)	Signet ring (n=13)
Age(yr)						
20-39	197(1.3)	8(1.0)	3(6.3)	132(2.5)	5(3.5)	0(0)
40-59	3544(23.4)	162(20.6)	12(25.0)	1698(32.8)	44(30.8)	4(30.8)
60-79	8760(57.8)	440(56.0)	21(43.7)	2784(53.7)	81(56.6)	6(46.2)
80+	2652(17.5)	176(22.4)	12(25)	569(11.0)	13(9.1)	3(23.0)
Gender						
Male	7636(50.4)	351(44.7)	25(52.1)	2841(54.8)	82(57.7)	11(84.6)
Female	7517(49.6)	435(55.3)	23(47.9)	2342(45.2)	61(42.3)	2(15.4)
Race						
White	12175(80.3)	665(84.6)	44(91.7)	4324(83.4)	120(83.9)	10(76.9)
Black	1758(11.6)	75(9.5)	3(6.3)	334(6.4)	16(11.2)	0(0)
Others	1149(7.6)	42(5.3)	1(2.0)	504(7.8)	7(4.9)	3(23.1)
Unknown	71(0.5)	4(0.5)	0(0)	21(0.4)	0(0.2)	0(0)
Tumor location						
Right	7200(47.5)	501(63.7)	31(64.6)	-	-	-
Transverse	1216(8.0)	70(8.9)	6(12.5)	-	-	-
Left	6737(44.5)	215 (27.4)	11(22.9)	-	-	-
Tumor size						
0-20	9350(61.7)	383(48.7)	31(64.5)	2800(54.0)	73(51.0)	7(53.8)
21-30	2844(18.8)	165(21.0)	9(18.8)	1283(24.8)	30(21.0)	3(23.1)
31-40	1390(9.2)	93(11.8)	3(6.2)	539(10.4)	15(10.5)	3(23.1)
41-50	772(5.1)	62(7.9)	2(4.2)	263(5.1)	11(7.7)	0(0)
51-60	358(2.4)	24(3.1)	2(4.2)	140(2.7)	5(3.5)	0(0)
61-80	293(1.9)	32(4.1)	0(0)	106(2.0)	5(3.5)	0(0)
80+	146(0.9)	27(3.4)	1(2.1)	52(1.0)	4(2.8)	0(0)
Grade						
I	3340(22.0)	168(21.4)	2(4.2)	774(14.9)	19(13.3)	0(0)
II	9738(64.3)	442(56.2)	3(6.3)	3698(71.3)	93(65.0)	2(15.4)
III	1019(6.7)	80(10.2)	34(70.8)	419(8.1)	14(9.8)	10(76.9)
IV	61(0.4)	4(0.5)	5(10.4)	27(0.5)	0(0)	1(7.7)
Unknown	995(6.6)	92(11.7)	4(8.3)	265(5.1)	17(11.9)	0(0)

Survival analysis

Cancer-specific survival (CSS) was calculated and stratified by histological subtypes and tumor location. The median follow-up interval was 60 months (range: 0-287 months). In total, 1,547 (7%) patients died from colorectal cancer during the follow-up period. The 3-year CSS rate was 96.0% for AC (colon: 96.0%; rectum: 95.8%), 94.3% for MAC (colon: 94.1%; rectum: 95.2%), and 90.1% for SRC (colon: 92.4%; rectum: 82.5%). The 5-year CSS rate was 93.3% for AC (colon: 93.8%; rectum: 92.2%), 90.7% for MAC (colon: 90.5%; rectum: 91.6%), and 85.6% for SRC (colon: 89.2%; rectum: 73.3%) (Table 8). For all patients MAC showed an entirely worse survival rate than AC (Fig. 2A). For colon patients, MAC also showed an entirely worse survival rate than AC (Fig. 2B). However, for rectum patients, MAC showed a similar prognosis to AC (Fig. 2C). Comparison of entire survival curves between SRC and AC failed to pick up significant differences. Low incidence of SRC could attribute to the intersection of two curves, which caused the log-rank testis negative and Grambsch-Therneau test also demonstrated the proportional hazards assumption of Log-rank test is not available. So, we used cloglog transformation for survival function and focused our interest on the comparison at fixed point in time. Adjusted for tumor location, we found that in patients

with rectal tumors, SRC had a worse 3 and 5-year prognosis than AC. However, for colon cancers, the prognosis of SRC was similar to that of AC ($p = 0.218$ for 3 year; $p = 0.204$ for 5 year; Table 8). Adjusted for histology, we found that patients with AC, tumors located in rectum had a worse 5-year prognosis than those located in colon (Fig. 3A). Differently, tumors located in rectum from patients with MAC and SRC had a similar prognosis to tumors located in colon (Fig. 3B and 3C). The patients with MAC, prognosis of these patients in proximal lesion was worse than in distal (Fig. 4).

Multivariate survival analysis

After adjusting for age, race, tumor size and grade, we performed a multivariate survival analysis stratified by tumor site and histological type was not an independent prognosis factor regardless of tumor site (Table 9). For patients with colon or rectal tumors, African Americans had a higher risk of death compared with whites and other races. High-grade adenocarcinomas, larger tumor size and older patients tended to increase the risk of death in either the colon or the rectum.

Discussion

Achievement of cure and a better quality of life should both be considered when devising a treatment strategy. Although traditional surgical resection TME (total mesorectal excision) and CME (complete mesocolic excision) achieve excellent oncological control and long-term survival for colorectal cancer patients, these approaches are also associated with substantial morbidity and mortality [11, 12].

Table 5. Prevalence of LNM according to histological type and site

Histology type	N0		N1		N2a		N2b	
	No	%	No	%	No	%	No	%
AC								
colon	13547	89.4	1443	9.5	117	0.8	46	0.3
rectum	4418	85.2	663	12.8	71	1.4	31	0.6
unknown	123		6		2		0	
MAC								
colon(total)	651	82.8	111	14.1	14	1.8	10	1.3
right	409	81.6	73	14.6	11	2.2	8	1.6
transverse	60	85.7	7	10.0	2	2.9	1	1.4
left	182	84.7	31	14.4	1	0.5	1	0.5
rectum	106	74.1	27	18.9	8	5.6	2	1.4
unknown	5		0		0		0	
SRC								
colon	32	66.7	14	29.2	1	2.1	1	2.1
rectum	7	53.8	5	38.5	1	7.7	0	0
unknown	1		0		0		0	

Table 6. Tumor site-specific clinical variables correlated with LNM in T1colorectal cancer

Characteristic	Lymph node metastasis					
	Positive (n=1,757)	Colon Negative (n=14,230)	p-value	Positive (n=808)	Rectum Negative (n=4,531)	p-value
Age(yr)			<0.001			<0.001
20-39	38(18.3)	170(81.7)		35(25.5)	102(74.5)	
40-59	524(14.1)	3194(85.9)		306(17.5)	1440(82.5)	
60-79	956(10.4)	8265(89.6)		407(14.2)	2464(85.8)	
80+	239(8.4)	2601(91.6)		60(10.3)	525(89.7)	
Gender			0.122			0.317
Male	850(10.6)	7162(89.4)		377(15.7)	2028(84.3)	
Female	907(11.4)	7068(88.6)		431(14.7)	2503(85.3)	
Race			<0.001			0.3506
White	1329(10.3)	11555(89.7)		662(14.9)	3792(85.1)	
Black	253(13.8)	1583(86.2)		61(17.4)	289(82.6)	
Others	167(14.0)	1025(86.0)		83(16.1)	431(83.9)	
Unknown	8(10.7)	67(89.3)		2(9.5)	19(90.5)	
Histology			<0.001			<0.001
AC	1606(10.6)	13547(89.4)		765(14.8)	4418(85.2)	
MAC	135(17.2)	651(82.8)		37(25.9)	106(74.1)	
SRC	16(33.3)	32(66.7)		6(46.2)	7(53.8)	
Tumor location						
Right	765(9.9)	6967(90.1)		-	-	
Transverse	120(9.3)	1172(90.7)		-	-	
Left	872(12.5)	6091(87.5)		-	-	
Tumor size(mm)			<0.001			0.050
0-20	975(10.0)	8789(90.0)		397(13.8)	2483(86.2)	
21-30	319(10.6)	2699(89.4)		216(16.4)	1100(83.6)	
31-40	191(12.9)	1295(87.1)		87(15.6)	470(84.4)	
41-50	127(15.2)	709(84.8)		56(20.4)	218(79.6)	
51-60	62(16.1)	322(83.9)		23(15.9)	122(84.1)	
61-80	57(17.5)	268(82.5)		19(17.1)	92(82.9)	
80+	26(14.9)	148(85.1)		10(17.9)	46(82.1)	
Grade			<0.001			<0.001
I	224(6.4)	3286(93.6)		72(9.1)	721(90.9)	
II	1152(11.3)	9031(88.7)		567(14.9)	3266(85.1)	
III	289(25.5)	844(74.5)		130(29.3)	313(70.7)	
IV	18(25.7)	52(74.3)		5(17.9)	23(82.1)	
Unknown	74(6.8)	1017(93.2)		34(12.1)	248(87.9)	

Table 7. Logistic regression analysis of the risk factors for LNM in T1 colorectal cancer

	P-value	Odds ratio	95% confidence interval	
			Lower	Upper
Age (ref.=<45 years)				
45-65 years	<0.001	0.71	0.59	0.86
>65 years	<0.001	0.50	0.42	0.61
Race(ref.=Black)				
Other	0.930	1.01	0.84	1.21
Unknown	0.233	0.66	0.33	1.26
White	<0.001	0.76	0.66	0.86
Location(ref.=Colon)				
Rectum	<0.001	1.36	1.24	1.50
Unknown	0.08	0.52	0.26	1.08
Histology (ref.=AC)				
MAC	<0.001	1.78	1.50	2.12
SRC	0.01	2.06	1.19	3.56
Tumor size(ref.>20 mm)				
0-20 mm	<0.001	0.77	0.71	0.84
Grade (ref.=I-II)				
III-IV	<0.001	2.80	2.48	3.16
Unknown	<0.001	0.67	0.54	0.82

Table 8. Cause-specific long-term survival rate according to histological subtypes

	Cause-Specific Survival						P value					
	AC		MAC		SRC		3-year		5-year		SRC vs. AC	vs. AC
	3 year	5 year	3 year	5 year	3 year	5 year	MAC vs. AC	MAC vs. SRC	SRC s. AC	MAC vs. SRC	MAC vs. SRC	
All	0.960	0.933	0.943	0.907	0.901	0.856	0.013	0.177	0.023	0.002	0.177	0.013
Colon	0.960	0.938	0.941	0.905	0.924	0.892	0.008	0.225	0.218	<0.001	0.078	0.204
Rectum	0.958	0.922	0.952	0.916	0.825	0.733	0.741	0.051	0.011	0.075	0.015	0.002

Particularly for distal rectal cancer patients, permanent colostomy is distressing and some patients develop inferiority or depression.

The management of early-stage colorectal cancer remains controversial and lacks sufficient evidence to guide decision making. Although local excision, as an alternative to TME and CME, shows advantages in terms of preserving anal function, fewer complications and shorter hospital stays compared with the curative procedure, it is inferior to radical resection for oncological outcomes and does not adequately remove the regional lymph nodes. Previous studies reported that LNM occurs in 6.3% to 17% of T1 and 10% to 22% of T2 colorectal cancers [13, 14]. Our analysis, based on population data, demonstrated that the rate of lymph node metastasis of T1 colorectal cancers was 12.0%. The risk of LNM in patients with colon cancers is 11.0%, with a similar rate for patients with rectal cancer (15.1%), which was consistent with previous reports [15-17]. Identifying a subgroup of patients for whom local excision would be safe is crucial when planning a tailored strategy. The National Comprehensive Cancer Network describes malignant lesions with T1, Grades I or II, no angiolymphatic invasion, and negative margin of resection as safe for endoscopic removal. However, the guidelines do not mention the histology subtypes. The JSCCR Guideline (Japanese Society for Cancer of the Colon and Rectum) simply classifies mucinous adenocarcinoma and signet-ring cell carcinoma into the poorly differentiated group [18].

Because of the rare occurrence of SRC and MAC, the clinical evaluation of these cancer types is difficult, in particular at the early stage. The SEER database provides a sufficiently

Fig. 2. Cancer-specific survival (CSS) was calculated and stratified by histological subtypes. (A) CSS for patients with cancer of all locations, stratified by histology of AC (solid black line), MAC (dot red line), and SRC (solid blue line). (B) CSS for patients with cancer of the colon, stratified by AC, MAC and SRC. (C) CSS for patients with cancer of the rectum, stratified by AC, MAC, and SRC.

large sample size to conduct such an evaluation. To our knowledge, our study is the only large-cohort study to investigate the possibility of local excision in early-stage colorectal patients with MAC and SRC.

Consistent with a majority of previous large-cohort retrospective analyses from the US, Europe and Asia, MAC and SRC had a propensity to be located in the proximate colon, to present in younger patients, to exhibit a worse differentiated grade and higher likelihood of LNM, and to be found in advanced TNM stages [5, 6, 9, 19]. In contrast to these studies, we focused our analysis on patients, whose lesions were confined to the submucosa and aimed to expand the indication for local excision, enabling individually tailored regimens for these patients. Our study will aid in the planning of individually tailored regimens. For example, a subgroup of patients had a chance to preserve their bowel function, reduce their morbidity or mortality rates and lead a better quality of life. With an increasing number of patients having early cancers of the colon and rectum, it is imperative to alter how we assess colorectal cancers. There are many methods for treating colorectal cancer patients, including endoscopic submucosal dissection, transanal endoscopic microsurgery, laparoscopically assisted endoluminal resection, laparoscopic colectomy, and open radical resections, each of which has specific indications. Patients with colorectal cancer should be evaluated by a multidisciplinary team and subjected to the least invasive treatment modality required to obtain cost-effective, patient-friendly cancer remedies.

SRC of colorectal adenocarcinomas share common features of those that are typically expressed in SRC of gastric cancer [19]. However, as opposed to our expectation based on early gastric SRC research, the incidence of LNM in patients with MAC and SRC is high. LNM is associated with 18.4% of patients with MAC and 35.5% of patients with SRC, with similar rates when the patients are divided by site (MAC: colon 17.2%, rectum 25.9%; SRC: colon 33.4%, rectum 46.2%). Moreover, this result may underestimate the true incidence of LNM because of inadequate lymphadenectomy. Of all of the patients, 54.5% represented an insufficient number of resected lymph nodes (fewer than 12). When limiting our analysis in patients with adequate lymph node removed, the incidence of LNM was higher.

Fig. 3. Cancer-specific survival (CSS) was calculated and stratified by histological subtypes. (A) CSS for patients with AC, stratified by tumor location. (B) CSS for patients with MAC, stratified by tumor location. (C) CSS for patients with SRC, stratified by tumor location.

Patients with SRC experienced reduced 3 and 5 survival rates in rectum patients, and the patients with MAC showed reduced 3 and 5 survival rates in colon patients. Rectum patients with MAC and colon patients with SRC showed no difference compared to those with AC. After adjusting for age, race, grade, tumor size, N stage, therapy regimen and site, a multivariate analysis also did not find histology to be an independent prognostic factor.

The aggressive behavior and reduced survival associated with SRC has been demonstrated by many previous studies, and many researchers attribute this phenomenon to a greater propensity of SRC histology to reach advanced stage, driven by the absence of the expression of adhesive molecules such as E-cadherin and β -catenin, which causes the tumor cells to have a more aggressive behavior and to disperse to other organs [20, 21]. Our research demonstrated high prevalence of LNM of SRC in both colon and rectum tumor, while didn't find the adverse prognosis of SRC in colon cancer.

However, the prognostic implications of MAC remain controversial. It has been reported that MAC was associated with a poorer prognosis, but others did not find that MAC adversely influenced the clinical outcomes [22]. An increasing number of studies have found that the prognostic role for MAC is more dependent on the tumor stage or the specific tumor site [3, 9].

Fig. 4. Cancer-cause-specific survival (CSS) for colon patients with MAC, stratified by specific tumor location of colon.

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Table 9. Independent prognostic factors in the multivariate survival analysis

Variable	Tumor Site						
	Colon				Rectum		
	P-value	HR	95% CI		P-value	HR	95% CI
Age(ref.=<45 years)							
45-65years	0.457	0.85	1.25	1.29	0.367	1.25	0.77 2.00
>65years	0.002	1.88	0.56	2.83	<0.001	2.69	1.68 4.30
Race(ref.=Black)							
Other	<0.001	0.53	0.38	0.72	<0.001	0.38	0.25 0.58
White	<0.001	0.72	0.60	0.86	0.502	0.50	0.37 0.66
Unknown	0.325	0.50	0.12	2.00	<0.001	0.51	0.07 3.67
Tumor size(ref.=>20 mm)							
0-20 mm	<0.001	0.57	0.50	0.64	<0.001	0.69	0.57 0.82
Grade(ref.=I-II)							
III-IV	0.029	1.25	1.02	1.53	0.006	1.43	1.10 1.87
Unknown	0.707	0.95	0.75	1.22	0.309	0.80	0.52 1.23
Adjuvant Radiation (ref.=No)							
Yes	0.008	2.10	1.21	3.66	<0.001	1.67	1.50 1.85
Nstage(ref.=N0)							
N1	<0.001	2.52	2.16	2.95	<0.001	2.01	1.67 2.51
N2	<0.001	4.47	3.30	6.07	<0.001	4.25	2.91 6.21
No. of LNs dissected(ref.=<12)							
≥12	<0.001	0.77	0.68	0.88	-	-	- -

Some researchers attribute these discrepancies to geographical variations, patient selection, differences in the defined histological criteria for MAC, and molecular alterations [19, 23]. Leopoldo et al. and Liu et al. identified two subtypes of mucinous adenocarcinoma of colorectal cancer [23, 24]. The MAC with MSI (microsatellite instability) phenotype presented an earlier TNM stage, a lower frequency of cancer recurrence and better survival compared with conventional adenocarcinoma and MSS (microsatellite stable) mucinous tumors. Compared to MAC in rectal lesions, MAC in colon lesions is associated with a higher MSI, a loss of hMlh1 expression, and a lower or absent p27 expression, and MSI mucinous adenocarcinomas tend to be located in the proximal colon [25-27]. Interestingly, in contrast to previous studies, we analyzed the rate of LNM according to the subdivided colon sites and found the proximal lesion to be associated with a higher incidence of LNM, and prognosis of these patients was worse than in distal.

Several inherent limitations of the SEER database were involved in this study. First, the white race predominated, and the lack of groups such Asians and Hispanics in this study requires that the findings be generalized with caution. Second, the SEER database does not contain information on the adjuvant therapy and the family history, which may be directly related to patients' outcomes. HNPCCs (hereditary nonpolyposis colorectal cancers) have a propensity to exhibit colloid pathology, and compared with the matched stage of sporadic cancer, these specific tumors are associated with improved survival rates [28]. The status of angioinvasion and lymphatic invasion, recurrence and MSI data are also not captured in the SEER database, and therefore, the impact of this information were not included in this study. Third, preoperative radiation may increase the proportion of mucin in primary tumors. The increasing component of mucin reflects the sensitivity to radiotherapy and improves prognosis.

Conclusion

MAC and SRC are not common forms of adenocarcinomas, especially early-stage colorectal carcinomas. The histological subtypes and differentiated grades should be

considered separately. Pre- and postoperative routine pathological reports should include information about the histology. Our data suggest that pT1 patients with SRC and patients with MAC of the rectum have a high incidence of LNM, and with these adverse outcomes, local excision is not recommended. Although MAC of the rectum and SRC of the colon have a high rate of LNM, the prognosis of these types is similar to that of AC.

Disclosure Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the reported research.

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