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Risk factors of recurrence in TNM stage I colorectal cancer

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Purpose: TNM stage I colorectal cancer (CRC) can recur, although the recurrence rate is low. Few studies have evaluated the risk factors for TNM stage I CRC recurrence. This study aimed to evaluate the TNM stage I CRC recurrence rate, as well as risk factors for recurrence.
Methods: In this retrospective study, we reviewed the database of patients who had undergone surgery for TNM stage I CRC between November 2008 and December 2014 without receiving neoadjuvant therapy or transanal excision for rectal cancer. Our analysis included 173 patients. Primary lesions were found in the colon of 133 patients and in the rectum of 40 patients.
Results: The CRC recurrence rate was 2.9% (5 out of 173 patients). For colon cancer patients, tumor size was not associated with higher recurrence risk (P = 0.098). However, for rectal cancer patients, both tumor size (≥3 cm) and T stage were associated with higher recurrence risk (P = 0.046 and P = 0.046, respectively). Of the 5 recurrent cases, 1 patient exhibited disease progression despite treatment, 1 patient maintained stable disease status after recurrence treatment, and 3 patients had no evidence of a tumor after recurrence treatment.
Conclusion: Our findings suggest that tumor size and T stage are predictors of stage I rectal cancer recurrence, and careful monitoring and follow-up of patients with larger tumors may be warranted.
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Key Words: Colorectal neoplasms, Neoplasm staging, Prognosis, Risk factors

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer (10%) with the second highest mortality rate (9.4%) worldwide [1]. In 2019, CRC was indicated as the fourth most common cancer in Korean men and women [2]. The incidence of early-stage CRC increased from 5.8% in the late 1990s to 8.9% in the early 2000s [3,4]. Increased diagnosis of early-stage CRC may also be attributed to medical screening, such as colonoscopy [2,3]. The 5-year cancer-specific survival for TNM stage I CRC is over 90% [5]. As TNM stage I CRC has a low recurrence rate, few studies have evaluated the risk factors for its recurrence.

According to the National Comprehensive Cancer Network (NCCN) guidelines, surgical resection is the primary treatment for TNM stage I CRC. In most cases, a segmental resection of the colon or rectum is performed to achieve negative surgical margins. Adjuvant chemotherapy is not typically recommended for stage I CRC due to the low risk of recurrence [6]. However, subgroups of patients with stage I CRC at higher risk of recurrence, such as those with lymphovascular invasion or poorly differentiated tumors [7], may benefit from adjuvant chemotherapy. Several studies have investigated the role of surveillance after surgical resection of stage I CRC. The NCCN recommends regular surveillance with colonoscopy every

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3–5 years for patients with stage I CRC, as well as regular monitoring of CEA levels [6]. In addition to surgical resection, lifestyle modifications, such as maintaining a healthy weight, engaging in regular physical activity, and consuming a balanced diet rich in fruits, vegetables, and whole grains, may help reduce the risk of recurrence and improve overall survival in patients with early-stage CRC [8].

This study investigated the rate and risk factors of TNM stage I CRC recurrence following surgical resection. In addition, we evaluated the prognosis of patients with recurrent CRC.

METHODS

Patient database

This study was approved by the Institutional Review Board of Konkuk University Medical Center (No. 2022-08-041) and the need for informed consent was waived. We retrospectively reviewed the patient database to identify patients diagnosed with TNM stage I CRC following colon or rectal cancer surgery. In total, 841 patients underwent CRC resection between November 2008 and December 2014. Eleven patients treated with neoadjuvant therapy were excluded, thereby excluding most patients with lower rectal cancer. Nine patients underwent transanal excision (TAE) for rectal cancer were excluded. Risk factors for recurrence were compared between the colon cancer, rectal cancer, and CRC groups.

Surgical treatment

All patients underwent curative surgery, including right or left hemicolectomy or anterior resection for colon cancer, lower anterior resection or abdominoperineal resection (APR) for rectal cancer. Colon surgery was performed via open surgery or hand-assisted laparoscopic surgery. If there were positive or transected margins, or unfavorable histologic features after endoscopic resection of the malignant polyp, additional surgery was performed. Tumor lesions were classified as colon or rectal cancer based on operation record descriptions.

Surveillance

All patients were followed up at 6-month intervals during the first 2 years after surgery, and at 12-month intervals for up to 5 years after surgery. Follow-up evaluations included a physical examination, serum CEA, abdominopelvic and chest CT, and colonoscopy within 12 months after surgery. The mean follow-up was 65 months (median, 66 months; range, 1–121 months).

Statistical analyses

Disease-free survival (DFS) was defined as the time from surgery until diagnosed recurrence by imaging or death. DFS for patients who survived with no recurrence until the end of the follow-up period was defined as the time from surgery until the last follow-up visit. Data were analyzed using the IBM SPSS Statistics ver. 28.0 (IBM Corp.). The Student t-test and the chi-square test were used to compare recurrent and nonrecurrent groups. DFS rates were calculated using the Kaplan-Meier curve and compared using the log-rank test. We could not use Cox analysis for overall survival as the coefficients did not converge due to low death rates. A P-value of <0.05 was considered statistically significant.

RESULTS

Of the 841 patients who underwent CRC resection, 193 patients were diagnosed with pathologic TNM stage I colon or rectal cancer between November 2008 and December 2014. Eleven patients received preoperative chemoradiotherapy and 9 patients underwent TAE for rectal cancer and were therefore excluded from this study. The remaining 173 patients were included in this study, of which 133 had colon cancer and 40 had rectal cancer; 100 were male and 73 were female, with a mean age of 62 years (range, 20–84 years). The 173 patients underwent curative resection, including 28 laparoscopic surgeries, and 145 open surgeries with D2 lymph node dissection as they exhibited early-stage cancer lesions. In 128 cases, primary curative resection was achieved,

Table 1. The patient's clinical characteristics

Characteristic	Data
No. of patients	173
Sex, male:female	100:73
Age (yr)	62.1 ± 11.5 (20–84)
Family history, yes	13 (7.5)
Tumor size (mm)	23.4 ± 14.4 (2–71)
No. of retrieved LN	17.0 ± 8.8 (2–58)
Location of primary cancer	
Colon	133 (76.9)
Rectum	40 (23.1)
Cell type	
MD	138 (79.8)
WD	34 (19.7)
PD or mucinous	1 (0.6)
T stage	
1	100 (57.8)
2	73 (42.2)
Invasion	
Lymphatics	8 (4.6)
Perineural	2 (1.2)
Venous	2 (1.1)
Follow-up (mo)	65.0 ± 27.4 (1–121)
Recurrence	5 (2.9)

Values are presented as number only, mean ± standard deviation (range), or number (%).
LN, lymph node; MD, moderately differentiated; WD, well differentiated; PD, poorly differentiated.

whereas 45 cases required additional curative resection after primary endoscopic resection. Tumor diameters in patients requiring additional curative resection were smaller than those in patients who achieved primary curative resection (mean diameter 12.0 mm and 27.4 mm, respectively; P < 0.001).

The median follow-up period was 66 months. The recurrence rate for CRC was 2.9% (Table 1). Based on clinical characteristics, tumor size (P = 0.030) and T stage (P = 0.012) were related to CRC recurrence (Table 2). Tumor size (≥3 cm *vs.* <3 cm) and T stage were identified as prognostic factors for DFS (P < 0.001 and P = 0.007, respectively) (Fig. 1). Evaluation of the clinical characteristics of the CRC, colon, and rectal cancer groups revealed no significant risk factors for recurrence (Tables 3, 4). However, for patients with colon cancer, evaluation of the DFS curve revealed that tumor size (≥3 cm *vs.* <3 cm) is a risk factor for recurrence (P = 0.035), whereas T stage is not a recurrence risk factor (P = 0.102) (Fig. 2). In patients with rectal cancer, evaluation of the DFS curve revealed that both tumor size (P = 0.014) and T stage (P = 0.014) are risk factors for recurrence (Table 5; Fig. 3).

Of the 173 patients, CRC recurred in 5 patients. Three patients were diagnosed with rectal cancer, while 2 were

Table 2. The clinical characteristics of recurrence in colorectal cancer patients

Characteristic	Recurrence		P-value
	No	Yes	
No. of patients	168	5	
Age (yr)	62.3 ± 11.6	56.8 ± 6.1	0.291
Sex, male:female	97:71	3:2	>0.999
Location of primary cancer, colon:rectum	131:37	2:3	0.082
Family history, yes	156:12	4:1	0.327
Tumor size (cm)	23.0 ± 14.4	37.2 ± 6.8	0.030
No. of retrieved LN	17.0 ± 8.8	17.6 ± 6.4	0.876
Cell type			0.521
MD	133	5	
WD	34	0	
PD or mucinous	1	0	
T stage			0.012
1	100	0	
2	68	5	
Invasion			
Lymphatics	8	0	>0.999
Vascular	2	0	>0.999
Perineural	2	0	>0.999

Values are presented as number only or mean ± standard deviation.
LN, lymph node; MD, moderately differentiated; WD, well differentiated; PD, poorly differentiated.

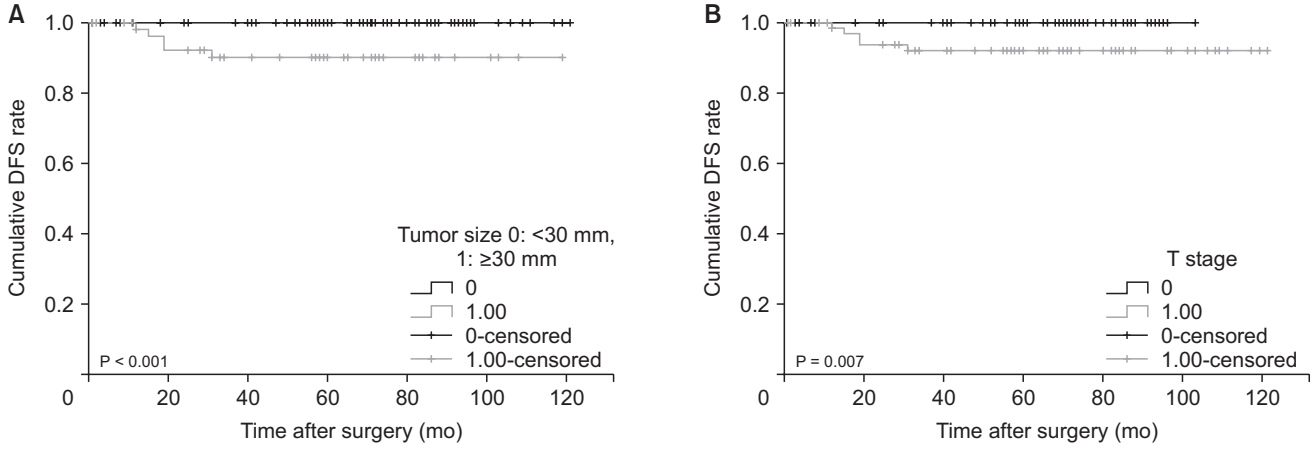

Fig. 1. The disease-free survival (DFS) rate in colorectal cancer according to the tumor size (A) and T stage (B).

Table 3. The patient's clinical characteristics in colon *vs.* rectal cancer

Characteristic	Colon	Rectum	P-value
No. of patients	133	40	
Sex, male:female	73:60	27:13	0.201
Age (yr)	61.3 ± 11.7	65.1 ± 10.6	0.067
Family history, yes	11	2	0.735
Tumor size (mm)	22.7 ± 14.9	25.6 ± 12.8	0.268
No. of retrieved LN	17.5 ± 9.3	15.2 ± 6.7	0.135
Cell type			0.178
MD	102	36	
WD	30	4	
PD or mucinous	1	0	
T stage			0.585
1	75	25	
2	58	15	
Invasion			
Lymphatics	6	2	>0.999
Vascular	1	1	0.410
Perineural	1	1	0.410
Recurrence	2 (1.2)	3 (1.7)	0.082

Values are presented as number only, mean ± standard deviation, or number (%).
LN, lymph node; MD, moderately differentiated; WD, well differentiated; PD, poorly differentiated.

Table 4. The clinical characteristics of recurrence in colon cancer patients

Characteristic	Recurrence		
	No	Yes	P-value
No. of patients	131	2	
Age (yr)	61.3 ± 11.7	60.5 ± 9.2	0.923
Sex, male:female	72:59	1:1	>0.999
Family history, yes	11	0	>0.999
Tumor size, ≥3 cm	40	2	0.098
No. of retrieved LN	17.6 ± 9.3	13.5 ± 7.8	0.536
Cell type			0.735
MD	100	2	
WD	30	0	
PD or mucinous	1	0	
T stage			0.188
1	75	0	
2	56	2	
Invasion			
Lymphatic	6	0	>0.999
Vascular	1	0	>0.999
Perineural	1	0	>0.999

Values are presented as number only or mean ± standard deviation.
LN, lymph node; MD, moderately differentiated; WD, well differentiated; PD, poorly differentiated.

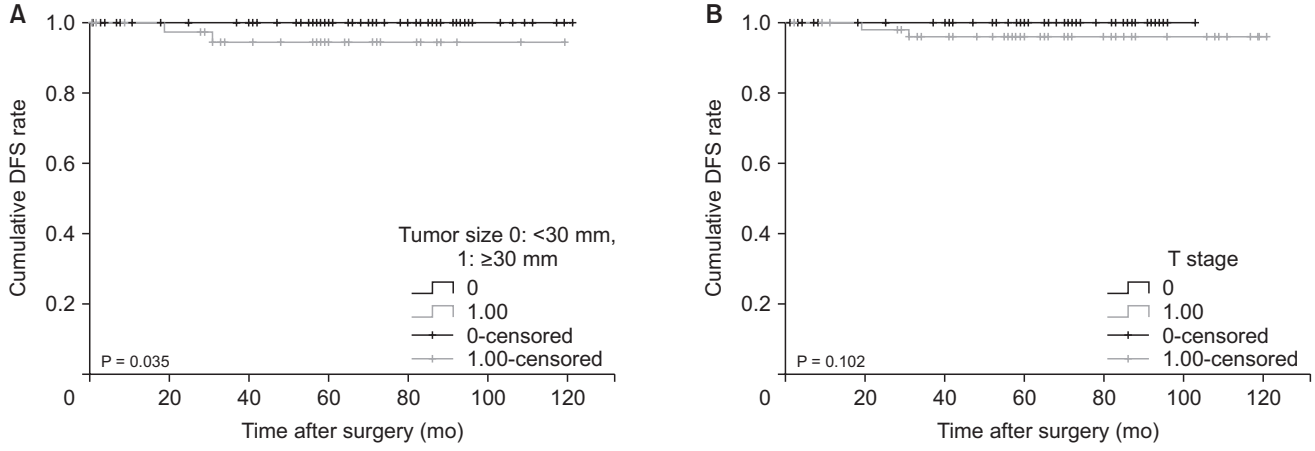

Fig. 2. The disease-free survival (DFS) rate in colon cancer according to the tumor size (A) and T stage (B).

diagnosed with rectosigmoid junction cancer. One systemic lymph node recurrence, 1 local recurrence, and 3 pulmonary metastases occurred within 3 years. These patients underwent total mesorectal excision. All patients with recurrence exhibited T2 stage and a tumor size of ≥3 cm. The distance from the anal verge to the primary tumor site was at least 9 cm (Table 6).

Two patients with rectal cancer recurrence underwent received chemoradiotherapy and 1 underwent APR. The 3 patients with pulmonary metastases without metastasis to other organs underwent pulmonary wedge resection and received chemotherapy. Disease progression was observed in only 1 patients. Three patients exhibited no evidence of disease during the follow-up period of this study. One patient with systemic lymph node metastasis maintained stable disease status during the follow-up period of this study.

DISCUSSION

Early CRC recurrence is rare, with reported recurrence rates of 2.4%–4.6% in early-stage CRC [9-12]. Leijssen et al. [13] reported recurrence rates of 2.3% and 4.7% for TNM stage I colon and rectal cancer, respectively. Without preoperative combined chemotherapy and radiation therapy (CCRT), the recurrence rate for rectal cancer was 7% [14]. Rectal cancer recurrence rates following TAE range from 1.8% to 14.1%. In this study, the recurrence rates for CRC, colon cancer, and rectal cancer were 2.9%, 1.2%, and 1.7%, respectively.

In this study, we found that tumor size and T stage are risk factors for TNM stage I colorectal and rectal cancer recurrence, but not for colon cancer recurrence. Previous studies also reported T stage as a risk factor for colorectal [9,11,15] and rectal cancer recurrence [13,16,17]. Peng et al. [18] reported that in patients with rectal cancer, radical resection is recommended to prevent local recurrence if the tumor diameter is greater than 2.5 cm. Although several studies reported lymphovascular and perineural invasion as risk factors for CRC recurrence [12,13,15,19-21], we did not observe an association between lymphovascular and perineural invasion and CRC recurrence.

Patients with early rectal cancer located on the lower rectum were not included in this study as patients who received neoadjuvant therapy for lower rectal cancer were excluded. All patients included in this study therefore had a tumor location of at least 9 cm from the anal verge. Of the relapsed patients, 1 patient had a primary tumor located 15 cm from the anal verge and 4 patients had primary tumors located 9 cm from the anal verge (Table 6).

Of the relapsed patients, 3 developed pulmonary metastases and 2 developed local recurrence. The 3 patients who had pulmonary metastases underwent pulmonary wedge resection for metastatic lung lesions and chemotherapy and exhibited a stable disease status after aggressive treatment. Of the 2 patients with local recurrence, 1 underwent CCRT and was subsequently stable. The other patient received APR and palliative chemotherapy but died due to progressive disease with pulmonary metastasis, suggesting that aggressive treatment should be recommended for patients with recurrent stage I CRC. The interval for recurrence in this study was 3 years, which corresponds to previous reports [22,23].

This study had some limitations, including the potential for selection bias in the patient recruitment process as the study relied on data from a single center, and a small size, which

Table 5. The clinical characteristics of recurrence in rectal cancer patients

Characteristic	Recurrence		
	No	Yes	P-value
No. of patients	37	3	
Age (yr)	66.0 ± 10.6	54.3 ± 2.9	0.067
Sex, male:female	25:12	2:1	>0.999
Family history, yes	1	1	0.146
Tumor size, ≥3 cm	12	3	0.046
No. of retrieved LN	14.8 ± 6.7	20.3 ± 4.9	0.166
Cell type			
MD	33	3	>0.999
WD	4	0	
T stage			
1	25	0	0.046
2	12	3	
Invasion			
Lymphatic	2	0	>0.999
Vascular	1	0	>0.999
Perineural	1	0	>0.999

Values are presented as number only or mean ± standard deviation.
LN, lymph node; MD, moderately differentiated; WD, well differentiated.

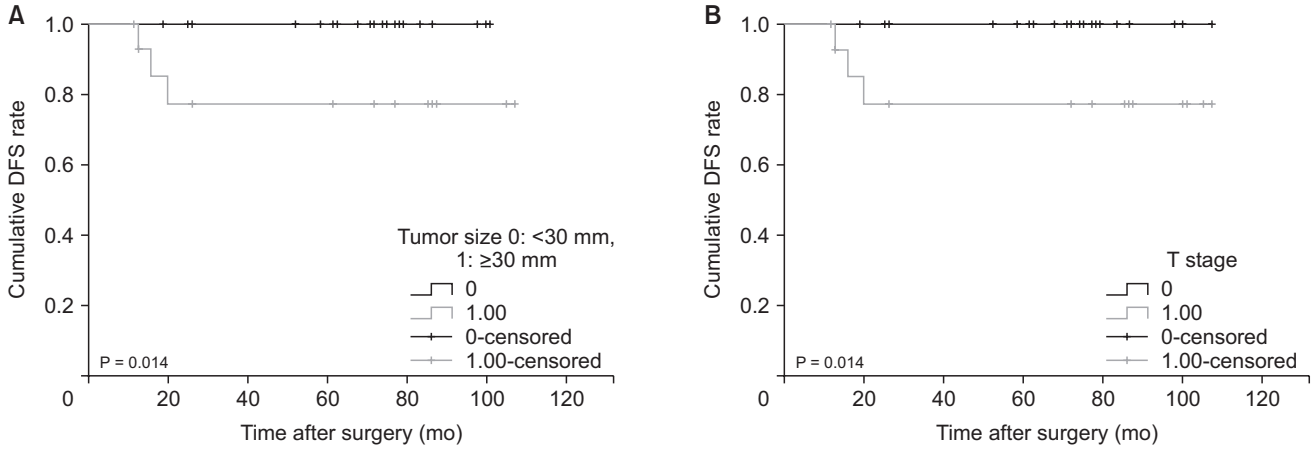

Fig. 3. The disease-free survival (DFS) rate in rectal cancer according to the tumor size (A) and T stage (B).

Table 6. Recurrent cases

Case No.	Sex/age (yr)	Tumor location	Distance from AV (cm)	Tumor size (mm)	T stage	Operation type	Disease-free period (mo)	Recurrence site	Additional treatment	rpTNM stage	Current status
1	Male/56	Rectum	9	40	T2	TME	19	Right internal iliac LN meta	RTx		Alive
2	Male/54	Rectosigmoid	9	48	T2	TME	19	Lung	Wedge resection of RLL + CTx		Alive
3	Male/56	Rectum	9	33	T2	TME	15	Local	APR + CTx	T2N0M0	Dead
4	Female/67	Rectosigmoid	15	32	T2	TME	31	Lung	Wedge resection of RLL/LLL + CTx		Alive
5	Female/51	Rectum	9	33	T2	TME	12	Lung	Wedge resection of LUL + CTx		Alive

AV, anal verge; rpTNM, pathological TNM stage of recurrent tumor; TME, total mesorectal excision; LN, lymph node; RTx, radiation therapy; RLL, right lower lobe; CTx, chemotheraphy; APR, abdominoperineal resection; LLL, left lower lobe; LUL, left upper lobe.

may limit the generalizability of the results. In addition, the study was conducted retrospectively, which may have resulted in incomplete or inconsistent data collection. Furthermore, as the study only evaluated patients who underwent surgery for TNM stage I CRC, the findings may not apply to patients with different disease stages or who receive different treatment modalities. Additionally, the study was unable to compare overall survival and cancer-specific survival, which may be important outcomes to evaluate in future studies.

In conclusion, although the recurrence rate of TNM stage I CRC is low, tumor size and T stage are risk factor for recurrence, and patients with recurrent disease may benefit from aggressive therapy.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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