Original Article

Risk Factors for Recurrence in Stage I Colorectal Cancer after Radical Resection

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Key Words
Stage I colorectal cancer;
Recurrence;
Risk factor

Purpose. Colorectal cancer (CRC) is the third most common cancer worldwide but the most common cancer in Taiwan. Early-stage CRC detection has improved because of various screening programs. Radical resection is the standard treatment for stage I CRC. Although the rate of recurrence after radical resection in patients with stage I CRC is low, CRC recurrence remains a concern. This study analyzed the rate of recurrence after curative radical resection in patients with stage I CRC and identified independent risk factors for CRC recurrence.

Methods. This retrospective study included patients with stage I CRC who had undergone surgical resection at Changhua Christian Hospital, Taiwan, between 2011 and 2021. Patients who had undergone local excision or polypectomy or received neoadjuvant chemotherapy were excluded. Likely associations between CRC recurrence and patients' clinicopathologic characteristics were analyzed.

Results. A total of 566 patients had undergone radical resection during the study period. Within an average follow-up period of 21.7 months, 31 (5.5%) patients had CRC recurrence. T2 stage, vascular invasion, and rectal tumor were significantly associated with an increased risk of stage I CRC recurrence. Tumor size was also likely to be associated with a high risk of recurrence; however, this association was nonsignificant. A multivariate analysis revealed that T2 stage (hazard ratio: 2.16; 95% confidence interval: 0.96 to 4.87) and rectal tumor (hazard ratio: 1.94; 95% confidence interval: 0.95 to 3.99) were likely to be associated with an increased risk of recurrence.

Conclusion. T2 stage, vascular invasion, and rectal tumor are likely to be associated with an elevated risk of CRC recurrence.

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Colorectal cancer (CRC) is the third most common cancer in the world[1] but the most common cancer in Taiwan.[2] CRC incidence and associated mortality have decreased, which may be attributable to the introduction of screening programs such as those involving the fecal occult blood test and colonoscopy.[3] These programs may facilitate the early resection of some benign neoplastic lesions that would otherwise turn into malignant ones; therefore, screening programs enable the early detection of asymptomatic malignancies. In Taiwan, 1100 cases of stage I CRC were reported in 2011; this number increased to 1653 in 2020.[4]

The standard treatment for stage I CRC is radical resection. For patients with stage I CRC, adjuvant chemotherapy is not recommended because it does not improve patient survival.[5] These patients generally

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have a favorable prognosis after curative resection, with a 5-year overall survival rate of > 90%.[6] However, tumor recurrence, either local or distal, can still occur after radical resection. The rate of CRC recurrence ranges from 4% to 13%.[7,8] Because of the relatively low rate of recurrence, few studies have explored the risk factors for the recurrence of stage I CRC. This study analyzed the rate of recurrence after curative radical resection in patients with stage I CRC and identified independent risk factors for CRC recurrence.

Patients and Methods

Fig. 1 presents the flowchart for patient selection. Between 2011 and 2021, 862 patients received a diagnosis of stage I CRC at Changhua Christian Hospital, Taiwan. Patients with familial adenomatous polyposis CRC, hereditary nonpolyposis CRC, synchronous CRC, or recurrent CRC; those who had undergone only local excision or polypectomy; those who had received neoadjuvant concurrent chemoradiotherapy; and those whose pathologic reports did not indicate adenocarcinoma were excluded. A total of 566 patients were included in this study. The Institutional Review Board number (IRB) was 220619.

The patients were divided into 2 groups: recurrence and nonrecurrence. The patients' clinical (eg, age, sex, preoperative carcinoembryonic antigen [CEA] level, and body mass index [BMI]) and pathologic (T stage, tumor size, histologic grade, harvested lymph node count, vascular invasion, lymphatic invasion, and perineural invasion location) data were collected.

Follow-up duration was defined as the interval between the day of surgery and that of the last outpatient visit. Recurrence was either local or distal. Local recurrence was defined as tumor recurrence at the previous anastomosis site or near the previous resection site. Distal recurrence was defined as tumor recurrence in the liver or lung or on the peritoneum. The primary outcomes were the risk factors for stage I CRC recurrence after radical resection.

SPSS (version 23.0) for Windows was used for statistical analysis. Categorical and continuous variables were analyzed using the chi-square and nonparametric t tests, respectively. Cox regression was performed to identify the significant factors for multivariate analysis.

Results

Clinicopathologic characteristics of the patients

Table 1 summarized the clinicopathologic characteristics of the 566 patients who were diagnosed with stage I colorectal cancer after a radical resection. There mean age was 63.9 ± 11.5 years, with 42.2% being female. The patients' mean BMI was 24.88 ± 3.84 kg/m^2. The median follow-up duration was 46 ± 31.5 months. The mean preoperative CEA level was 3.1 ± 3.9. An analysis of the patients' pathologic data revealed that 45.4% of all patients had stage T1 tumors and that 94.3% had histologic grade 2 tumors. The mean tumor size was 26.5 ± 17 mm. Of the patients, 1.8% had vascular invasion, 27.9% had lymphatic invasion, and 5.8% had perineural invasion. The mean number of harvested lymph nodes was 19.2 ± 9.1. For approximately 13.4% of all patients, < 12 lymph nodes were harvested. A total of 387 (68.4%) patients developed colon tumors, whereas 179 (31.6%) patients developed rectal tumors.

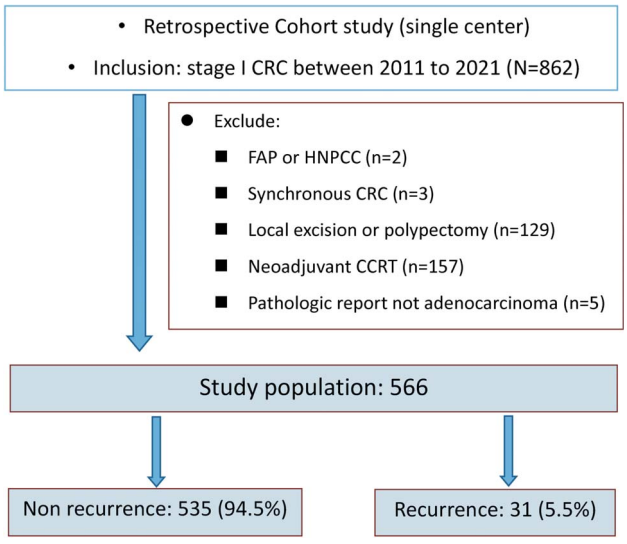

Fig. 1. Flowchart of patient selection.

Table 2 presents the characteristics of the patients with cancer recurrence. The mean time to recurrence was 21.7 months. A total of 7 (22.6%) patients had local recurrence, 23 (74.2%) had distal recurrence, and 1 (3.2%) had both local and distal recurrence. Among the patients with distal recurrence, 8 (34.8%) had liver metastasis, 11 (47.8%) had lung metastasis, and 4 (17.4%) had both liver and lung metastases.

Table 3 presents the recurrence patterns in relation to primary tumor site. In colon cancer recurrence group

Table 1. Characteristic of patients (N = 566)

Variation	Value	Non recurrence (N = 535)	Recurrence (N = 31)	*p*-value
Age	63.9 ± 11.5	63.8 ± 11.5	65.6 ± 11.1	0.34
Sex				0.25
Female	239 (42.2)	229 (42.8)	10 (32.3)	
Male	321 (57.8)	306 (57.2)	21 (67.7)	
BMI (kg/m^2)	24.88 ± 3.84	24.88 ± 3.80	24.80 ± 4.48	0.92
Follow up time (month)	46 ± 31.5	46 ± 31.6	45.9 ± 29.4	0.95
CEA	3.1 ± 3.9	3.0 ± 3.8	4.2 ± 4.3	0.08
T stage				0.02
T1	257 (45.4)	249 (46.5)	8 (25.8)	
T2	309 (54.6)	286 (53.5)	23 (74.2)	
Histology grade				0.72
Grade 1	22 (3.9)	21 (3.9)	1 (3.2)	
Grade 2	534 (94.3)	504 (94.2)	30 (96.8)	
Grade 3	10 (1.8)	10 (1.9)	0 (0)	
Tumor size	26.5 ± 17	26.3 ± 17.2	30.7 ± 15.2	0.06
Vascular invasion				0.04
No	556 (98.2)	527 (98.5)	29 (93.5)	
Yes	10 (1.8)	8 (1.5)	2 (6.5)	
Lymphatic invasion				0.17
No	408 (72.1)	389 (72.7)	19 (61.3)	
Yes	158 (27.9)	146 (27.3)	12 (38.7)	
Perineural invasion				0.35
No	533 (94.2)	505 (94.4)	28 (90.3)	
Yes	33 (5.8)	30 (5.6)	3 (9.7)	
Harvest LN	19.2 ± 9.1	19.3 ± 9.1	16.3 ± 6.8	0.08
≥ 12	490 (86.6)	463 (86.5)	27 (87.0)	0.93
< 12	76 (13.4)	72 (13.5)	4 (13.0)	
Location				0.04
Colon	387 (68.4)	371 (69.3)	16 (51.6)	
Rectum	179 (31.6)	164 (30.7)	15 (48.4)	

Table 2. Detail of recurrent patient (N = 31)

Variation	Value
Time to recurrence (month)	21.7 (1.9-87.6)
Recurrence pattern	
Local	7 (22.6)
Distal	23 (74.2)
Both	1 (3.2)
Distant metastasis	
Liver	8 (34.8)
Lung	11 (47.8)
Both	4 (17.4)

Table 3. Patterns of recurrence site vs. primary tumor location

Variation	Value
Colon cancer recurrence	16
Local	1 (6.2)
Distal	15 (93.8)
Both	0 (0)
Rectal cancer recurrence	15
Local	6 (40.0)
Distal	8 (53.3)
Both	1 (6.7)

(n = 16), 1 (6.2%) was local recurrence and 15 (93.8%) was distal recurrence. In rectal cancer recurrence group (n = 15), 6 (40.0%) was local recurrence, 8 (53.3%) was distal recurrence and 1 (6.7%) had both local and distal recurrence.

Risk factors for CRC recurrence

Of the 566 patients, 31 (5.5%) had recurrence. We observed that T2 stage (p = .02), vascular invasion (p = .04), and rectal tumor (p = .04) were significantly associated with CRC recurrence. A larger tumor size was likely to be associated with CRC recurrence, but this association was nonsignificant. No significant association was observed between CRC recurrence and age, sex, BMI, follow-up duration, CEA level, histologic grade, lymphatic invasion, perineural invasion, or harvested lymph node count.

Table 4 presents the results of the multivariate analysis, which was performed to identify the risk factors for stage I CRC recurrence. Cox regression revealed that tumor stage, vascular invasion, and tumor location were not significantly associated with CRC recurrence. T2 stage (hazard ratio: 2.16; 95% confidence interval: 0.96 to 4.87) and rectal tumor (hazard ratio: 1.94; 95% confidence interval: 0.95 to 3.99) were likely to be associated with an increased risk of CRC recurrence.

Discussion

In our cohort, the rate of CRC recurrence was 5.5%. Other studies have reported that the rate of stage I CRC recurrence ranges from 4% to 13%.[7,8] We excluded patients who had received preoperative concurrent chemoradiotherapy and those whose pathologic reports did not indicate adenocarcinoma. The design of our study might have influenced the outcomes.

In our study, major distant recurrence site of stage I colorectal cancer after curative resection was liver and lung. No distant metastases were found in brain, bone or other location. According to previous study, the liver is the most common site of distant recurrence, followed by lung and peritoneal cavity. Brain metastasis (2%) and bone metastasis (2%) were reported in the pattern of distant recurrence.[20]

According to Table 2, distant metastasis of recurrent group is 74.2%. In previous report, lymphatic invasion was indicated as risk factor of tumor recurrence and poor prognosis factor. Also, lymphatic invasion was correlated to skip metastasis.[21,22] In our study, the rate of lymphatic invasion (38.7%) was higher than vascular invasion (6.5%) and perineural invasion (9.7%) in recurrence group. We may hypothesize that lymphatic invasion is related to distant recurrence of colorectal cancer.

The standard treatment for early-stage CRC is total mesorectal excision (TME); ensuring high TME quality is crucial to the prevention of local recurrence.[18] However, sometimes, standard TME is challenging because of the small pelvic area in male patients or history of abdominal surgery. This explains why the rate of local recurrence was higher in patients with rectal tumors than in those with colon tumors (37.8% vs. 5.8%, respectively).

Our findings suggest that T2 stage, vascular invasion, and rectal tumor seemed to be significantly associated with an increased risk of stage I CRC recurrence. Tumor size exhibited a tendency to be associated with a high risk of CRC recurrence; however, this association was nonsignificant. Cox regression revealed that T2 stage and rectal tumor site were likely to be associated with an increased risk of CRC recurrence, although these associations were nonsignificant. This might have been due to our small sample size and inadequate follow-up duration. Other studies have indicated that T2 stage, male sex, vascular inva-

Table 4. Multivariate analysis of prognostic factors in stage I CRC

Variation	HR (95% CI)	p value
T stage		
T1	-	-
T2	2.16 (0.96-4.87)	0.06
Vascular invasion		
No	-	-
Yes	2.21 (0.44-11.17)	0.34
Location		
Colon	-	-
Rectum	1.94 (0.95-3.99)	0.07

sion, lymphatic invasion, high preoperative CEA level, and poor differentiation are associated with an increased risk of CRC recurrence.[9,10]

We observed that vascular invasion (6.5% vs. 1.5%; $p = .04$) was significantly associated with recurrence. The invasion of tumor cells into blood vessels is a crucial step in the dissemination and metastasis of these cells; thus, vascular invasion is a key factor for predicting cancer recurrence.[11] It is also an independent prognostic factor for distant metastasis.[12] However, in the present study, we did not investigate the association between vascular invasion and distant metastasis.

Patients with obesity are at increased risks of mortality and poor disease-free survival.[13] These patients have high levels of adipose tissue; a high level of adipose tissue is strongly associated with insulin resistance, hypertension, and dyslipidemia. Hormonal changes affect both immune functions and growth factors, promoting tumor growth.[14] However, in our study, BMI was not associated with CRC recurrence.

A high preoperative CEA level and a large tumor size have been associated with cancer recurrence.[15] A high preoperative CEA level is associated with tumor recurrence likely because CEA facilitates tumor invasion and metastasis.[16] Thus, a high level of CEA is associated with high degrees of invasiveness and metastatic propensity.[17] A tumor size of > 5 cm has been associated with an increased risk of cancer recurrence. Furthermore, a CEA level of > 6 was identified to be a risk factor for cancer recurrence.[8,9] In our study, the associations of recurrence with preoperative CEA level (4.2 vs. 3.0; $p = .08$) and tumor size (30.7 vs. 26.3; $p = .06$) were nonsignificant. However, we still recommend monitoring patients with high CEA levels for CRC recurrence.

The National Comprehensive Cancer Network guideline recommends adjuvant chemotherapy for preventing recurrence in patients with stage II CRC and various risk factors for cancer recurrence. However, for patients with stage I CRC, adjuvant chemotherapy is not recommended because of its limited range of benefits.[19] However, cancer recurrence may occur in patients with stage I CRC. We identified T2 stage, vascular invasion, and rectal tumor to be independent risk factors for CRC recurrence. Thus, careful postoperative monitoring of these patients is imperative. Additional studies are required before adjuvant chemotherapy can be indicated for these patients.

The limitations of this study include its single-center retrospective design, small sample, and inadequate follow-up duration for some patients. In addition, for some patients, only image data were available, with no further follow-up data; therefore, the rate of CRC recurrence might have been underestimated.

Conclusion

T2 stage, vascular invasion, and rectal tumor are likely to be associated with an elevated risk of CRC recurrence.

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原　著

第一期大腸直腸癌術後復發的危險因子

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目的　整理彰化基督教醫院的第一期大腸直腸癌病人術後復發率、並探討復發的危險因子。

方法　透過回溯性病歷收集，分析西元 2011 年到西元 2021 年診斷為第一期大腸直腸癌且接受手術治療的病人。我們記錄了病人的生理特徵，病理特徵並且分析復發危險因子。

結果　總共有 566 個病人，平均追蹤時間為 46 個月。有 31 (5.5%) 個病人復發，平均復發時間是術後 21.7 個月，統計發現，T2 stage、血管侵犯及直腸腫瘤是復發的危險因子，腫瘤大小有比較高的復發趨勢但是沒有統計上的顯著差異，根據 COX 多變量分析發現 T2 stage (HR: 2.16, 95% CI 0.96-4.87) 及直腸腫瘤 (HR: 1.94, 95 CI 0.95-3.99) 有比較高復發趨勢，但沒有到達統計的顯著差異。

結論　T2 stage、血管侵犯及腫瘤位置在直腸等，在第一期大腸直腸癌術後的病人有比較高的復發趨勢。

關鍵詞　第一期大腸直腸癌、復發率、危險因子。