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PREDICTORS OF INTRALUMINAL RECURRENCE AT THE ANASTOMOSIS SITE AFTER CURATIVE RESECTION FOR COLON CANCER*

REZEKTABL KOLON KANSERİNDE ANASTOMOZ HATTI NÜKSÜNE ETKİ EDEN PREDİKTİF FAKTÖRLER

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ABSTRACT

Objective: The increase in the number of patients recovering from colon cancer after primary resection inevitably increases the number of patients with local recurrence. This study was conducted to investigate the predictors of intraluminal recurrence at the anastomosis site in patients who underwent curative resection for colon cancer.

Material and Method: This study included 160 patients who underwent curative resection for colon cancer and had completed follow-up colonoscopy and surveillance for at least two years at our tertiary referral hospital. Patients with intraluminal recurrence were compared with those without locally recurrent disease. Patient data, including demographics, tumor characteristics, surgery type, and reconstruction technique, were reviewed.

Result: The median age of the study group was 61 years, and 60% were men. A total of 25 (15.6%) patients had only intraluminal recurrence at the anastomosis site. The median time to intraluminal recurrence was 21.3 months (range, 3–71 months). Univariate analysis revealed the histopathological type, histological grade, T stage, number of metastatic lymph nodes, tumor margins, presence of tumor budding, perineural invasion, and anastomosis type as risk factors for intraluminal recurrence. Multivariate analysis revealed handsewn anastomoses (odds ratio [OR]: 45.532; 95% confidence interval (CI): 5.278–392.778), T stage (OR: 3.593; 95% CI: 1.378–9.371), and the presence of

ÖZET

Amaç: Rezeksiyon sonrası kolon kanserinden (KK) iyileşen hastaların sayısındaki artış, lokal nüks olabilecek hastaların sayısını da artırmaktadır. Bu çalışmada, onkolojik prensiplere uygun yapılan cerrahi sonrası, cerrahi sınırlar negatif olmasına rağmen anastomoz hattında nükslerin gelişebilmesi nedeniyle, nüksün ortaya çıkmasına etki eden risk faktörlerini araştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya, kolon kanseri için küratif rezeksiyon uygulanmış ve en az iki yıl boyunca takip kolonoskopisi yapılan 160 hasta dahil edildi. İntraluminal nüksü olan hastalar, lokal nüks olmayan hastalarla karşılaştırılarak; hastaların demografik bilgileri, tümör özellikleri, cerrahi tipi ve rekonstrüksiyon tekniği gibi veriler incelendi.

Bulgular: Çalışma grubunun medyan yaşı 61 olup, %60'ı erkek hasta idi. Toplamda 25 (%15,6) hastada sadece anastomoz bölgesinde nüks görüldü. Anastomoz hattı nüksünün gelişimindeki medyan süre 21,3 ay (aralık, 3–71 ay) olarak hesaplandı. Tek değişkenli analiz, intraluminal nüks için risk faktörleri olarak histopatolojik tip, histolojik derece, T evresi, metastatik lenf nodu sayısı, tümör kenarları, tümör tomurcuklanması varlığı, perinöral invazyon ve anastomoz tipini ortaya koydu. Çok değişkenli analiz, el ile yapılan anastomozlar (odds oranı [OR]: 45.532; %95 güven aralığı (GA): 5.278–392.778), T evresi (OR: 3.593; %95 GA: 1.378–9.371) ve tümör tomurcuklanmasının varlığı (OR: 3.912; %95 GA: 1.306–11.715) olarak bağımsız risk faktörlerini ortaya

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tumor budding (OR: 3.912; 95% CI: 1.306–11.715) as independent risk factors. Adjuvant chemotherapy did not affect the rate of intraluminal recurrence.

Conclusion: This study suggests a relationship between tumor biology and intraluminal recurrence, and the T stage and tumor budding were the predictors.

Keywords: Colon cancer, intraluminal recurrence, risk factors

koydu. Adjuvan kemoterapinin, anastomoz hattı nüks oranını etkilemediği görüldü.

Sonuç: Anastomoz hattı nüksüne etki eden prediktif faktörler arasında, tümörün histopatolojik özellikleri ve T evresi ön plana çıkmaktadır.

Anahtar Kelimeler: Kolon kanseri, anastomoz hattı nüksü, risk faktörü

INTRODUCTION

Colon cancer (CC) is the most frequent cancer of the gastrointestinal tract and one of the major cause of cancer-related deaths worldwide, affecting women and men equally. Although recent improvements in both diagnosis and treatment have improved survival, the increasing number of CC survivors has posed a high risk for subsequent disease recurrence, either local or metastatic (1). Disease recurrence is detected in up to 30% of CC cases, with the highest expected probability found within the first two years after primary surgery (2, 3). Most cases of recurrence are hepatic or pulmonary metastases, whereas up to 13% of patients have isolated locoregional recurrence (4-7). Locoregional recurrence is mostly extramurally defined as intraabdominal, whereas intramural recurrence occurring in 12% of cases is defined as mucosal involvement (8). Although the disease burden of only intraluminal recurrence (IR) at the anastomosis site has not been well established, it is classified distinctively from locoregional recurrence or second primary CC (9, 10). Theoretically, locoregional recurrence has been believed to develop due to either exfoliation of cancer cells during primary resection or metachronous carcinogenesis (11, 12). In a recent case series, Costi et al. suggested a persistent, patient-specific alteration as the trigger of colorectal cancer IR (13). Subsequently, they performed a similar genetic analysis for microsatellite instability (MSI) and loss of heterozygosity and could not identify any potential risk factor (8).

A precise understanding of IR and predicting the intervals and patterns of recurrence determine effective treatment and follow-up strategies. The poor outcome of disease recurrence necessitates early diagnosis to perform salvage surgery. Cross-sectional imaging is the most widely used diagnostic tool for extraluminal recurrence, whereas endoscopy is primarily used for IR. Nonetheless, there is still a lack of consensus regarding the perfect timing for diagnostic workup after primary surgery. The commonly scheduled endoscopy or imaging is performed in the first year after primary surgery, which may be too late in the case of early recurrence without symptoms or signs. Therefore, identifying the risk factors for IR after primary resection may be helpful in determining high-risk patients in the postoperative follow-up. Considering these data, we conducted this study to explore the possible predictors of IR in patients with CC.

MATERIALS and METHODS

Study design and study population

This single-center, retrospective study was conducted at a general surgery outpatient clinic of a tertiary care center between January 2013 and December 2018. Patients who underwent curative-intent resection for CC were screened. We excluded patients in whom the proximal part of the tumor could not be reached by endoscopy; patients with peritoneal recurrence, pelvic recurrence, or systemic disease; and patients with less than 24 months of follow-up or in whom cancer surveillance was performed at an external center. Patients aged <30 years or those with a family history of cancer affecting at least two generations or with polyposis syndromes were also excluded to avoid the bias of hereditary cancer syndromes. We also excluded patients with synchronous primary cancer, those who underwent nonanastomotic surgery, patients who died within 30 days of surgery, those with incomplete data, and patients with primary rectal tumors. Finally, of 883 patients, we included 160 patients who met the inclusion criteria. All patients were informed about the diagnostic and therapeutic procedures, and written informed consent was obtained. The study protocol was approved by the Istanbul University, Istanbul Faculty of Medicine, Clinical Research Ethics Committee (Date: 22.02.2019, No: 04). This study was conducted according to the principles of the Declaration of Helsinki.

Assessment and data collection

Colon cancer was defined as a primary tumor developing between the cecum and rectosigmoid junction. All patients were evaluated and staged by colonoscopy and imaging techniques before surgery. Tumors were categorized anatomically according to the site of development as right-sided (cecum and ascending colon), transverse colon, descending colon, and sigmoid colon. All patients underwent primary surgery according to oncological principles and *en-bloc* resection of the invaded adjacent organs, if applicable to achieve R0 resection. Data, including primary tumor resection, patient demographics, surgery

type, pathology records, and the adjuvant therapy used, were recorded. The following clinical and pathological features were included for risk analysis: age at the time of surgery, sex of the patient, tumor location, surgery type, surgical approach, anastomosis type, histopathological type and grade, tumor diameter, disease stage according to the Tumor, Node, Metastasis (TNM) classification, total/positive/negative lymph node number, tumor margin, resection margin (infiltrative/expansive), distance of the tumor to the proximaistal and radial margin on the specimen, angiolymphatic invasion, venous invasion, peritumoral budding, perineural invasion, mesenteric tumor nodules, and receiving adjuvant chemotherapy.

Postoperative follow-up

Postoperative follow-up was performed at our institution in the outpatient setting. Patients were scheduled for physical examination, routine blood chemistry, serum carcinoembryonic antigen screening, and complete blood count every 3–6 months for the first three years and every six months in the 4th and 5th years. Colonoscopy along with thoracic, abdominal, and pelvic computed tomography was conducted annually, otherwise earlier depending on the patient's complaints. IR was diagnosed by mucosal biopsy at the anastomosis site.

Statistical analysis

Statistical analysis was conducted using the NCSS version 2007 software (NCSS LLC, Kaysville, UT, USA). Continuous data were expressed as mean±standard deviation (SD) or median (minimum–maximum), whereas categorical data were expressed as numbers and frequency. Categorical variables were analyzed using the chi-square or Fisher's exact test. Univariate and multivariate regression analyses were performed to identify risk factors. The backward stepwise logistic regression analysis was also conducted to determine the relationship between the statistically significant factors and recurrence. The Kaplan–Meier method was used to estimate survival regarding the T stage, and the log-rank test was used for the statistical comparison of the groups. A p value of <0.05 was considered statistically significant.

RESULTS

Of 883 patients with CC who underwent curative resection, 160 met the inclusion criteria. The median age of the cohort was 61 (range, 30–84) years, and 96 patients (60%) were men. The mean age at the time of surgery was 60.1±11.8 (range, 30–84) years. The mean follow-up period was 42.1 (range, 3–71) months, and 25 (15.6%) patients had only IR at the anastomosis site. The mean time to IR was 21.3 (range, 3–71) months. More than half of the tumors were located in the sigmoid colon (53.8%). Laparoscopic surgery was performed in 107 (66.9%) patients. Anterior resection (n=72) was the most common form of surgery type in both laparoscopic and open surgery, followed by right hemicolectomy (n=58). Anastomoses using a circular stapler (n=92, 57.5%) and linear stapler (n=57, 35.6%) were more common than handsewn anastomoses (n=11, 6.9%) (Table 1).

Table 1: Demographic characteristics and surgical data of patients

Variable		
Age (years)	Median (min–max)	61 (30–84)
		n (%)
Sex	Female	64 (40.0)
	Male	96 (60.0)
Tumor location	Sigmoid colon	86 (53.8)
	Right colon (cecum and ascending colon)	57 (35.6)
	Descending colon	14 (8.7)
	Transverse colon	3 (1.9)
Surgery type	Laparoscopic anterior resection	54 (33.7)
	Laparoscopic right hemicolectomy	40 (25.0)
	Laparoscopic low anterior resection	9 (5.6)
	Laparoscopic left hemicolectomy	4 (2.5)
	Anterior resection	18 (11.3)
	Low anterior resection	4 (2.5)
	Right hemicolectomy	18 (11.3)
	Left hemicolectomy	9 (5.6)
	Subtotal colectomy	3 (1.9)
	Total colectomy	1 (0.6)
Surgical approach	Open	53 (33.1)
	Laparoscopic	107 (66.9)
Anastomosis type	Circular stapler	92 (57.5)
	Linear stapler	57 (35.6)
	Handsewn anastomosis	11 (6.9)

Data are expressed as median (min–max) or numbers and percentage, unless otherwise stated.

According to the TNM classification, the most common T and N stages were T3 (n=103, 64.4%) and N0 (n=100, 62.5%), respectively. The majority of patients (n=80, 50%) had Stage II CC (Table 2).

We compared patients with IR with those without locally recurrent or metastatic disease and found that age (p=0.662), sex (p=0.182), tumor location (p=0.771), and

Table 2: Histopathological features of study group

		n (%)
Histopathological type	Adenocarcinoma	138 (86.3)
	Mucinous adenocarcinoma	19 (11.8)
	Signet ring cell adenocarcinoma	2 (1.3)
	Medullary adenocarcinoma	1 (0.6)
Histological grade (n=140)	Well–moderately	133 (95.0)
	Poorly	7 (5.0)
T stage	T1	7 (4.4)
	T2	21 (13.1)
	T3	103 (64.4)
	T4	29 (18.1)
N stage	N0	100 (62.5)
	N1	33 (20.6)
	N2	25 (15.6)
	Nx	2 (1.3)
Stage	I	22 (13.8)
	II	80 (50.0)
	III	58 (36.2)
Lymph nodes	Min–Max (Median)	5–83 (27)
	Total	4664
Lymph node metastatic patients		55 (34.4)
Metastatic lymph node #	Min–Max (Median)	1–24 (12.5)
	Total	298
Tumor border	Infiltrative	107 (66.9)
	Expansive	53 (33.1)
Tumor diameter (cm)	Min–Max (Median)	1–19 (4)
Proximal distance (cm)	Min–Max (Median)	1–114 (10.5)
Distal distance (cm)	Min–Max (Median)	1–38 (9)
Peritoneal distance (mm)	Min–Max (Median)	0–20 (2)
Angiolymphatic invasion		87 (54.4)
Venous invasion		19 (11.9)
Peritumoral budging		59 (36.9)
Perineural invasion		39 (24.4)
Mesenteric tumor nodules		24 (15.0)
Surgical margin	Negative	160 (100.0)
Adjuvant treatment		82 (51.3)
Time until anastomotic recurrence (months) (n=25)	Min–Max (Median)	3–71 (17)

SD: Standard deviation, Nx: Regional lymph nodes cannot be evaluated. Data are expressed as mean±SD or numbers and percentage, unless otherwise stated

surgery type (p=0.502) exerted no effect on the IR rate. However, the preferred anastomosis technique exerted a statistically significant effect on the IR rate (p=0.003, $p < 0.01$). The rate of IR also varied depending on the tumor type. A significant difference was observed in the IR rate between poorly and moderately well-differentiated tumors (p=0.012). The T stage was identified as a significant factor for IR (p=0.017). As anticipated, patients with stage T4 had a higher recurrence rate than those with stages T1, T2, and T3. However, there was no significant

difference in lymph node metastasis and disease stage between the groups (p>0.05) (Table 3).

We also found no significant differences in the tumor diameter, total number of dissected lymph nodes, angiolymphatic and venous invasion rates, presence of mesenteric nodules, and proximal and distal margin distance values between the groups. Nevertheless, having a higher number of metastatic lymph nodes (p=0.025), closer radial margin values (p=0.006), infiltrative surgical margins (p=0.048), peritumoral budding (p=0.009), perineural invasion (p=0.013), and receiving adjuvant therapy (p=0.024) exerted a statistically significant effect on the IR rate (Table 4).

In the backward stepwise logistic regression analysis, we evaluated the reconstruction technique, histology, T stage, N stage, tumor margins, distal distance, distance to the peritoneal surface, status of peritumoral budding, perineural invasion, presence of mesenteric tumor nod-

Table 3: Risk factors for anastomotic recurrence

Variable		No IR	IR	p value
Age (years)	Min–Max (Median)	32–82 (61)	27–84 (61)	[a]0.662
Sex, n (%)	Female	57 (89.1)	7 (10.9)	[b]0.182
	Male	78 (81.3)	18 (18.7)	
Tumor location, n (%)	Sigmoid colon	70 (81.4)	16 (18.6)	[c]0.771
	Right colon	50 (87.7)	7 (12.3)	
	Descending colon	12 (85.7)	2 (14.3)	
	Transverse colon	3 (100)	0 (0)	
Surgery type, n (%)	Anterior resection	69 (81.2)	16 (18.8)	[c]0.502
	Hemicolectomy	62 (87.3)	9 (12.7)	
	Total / subtotal colectomy	4 (100)	0 (0)	
Anastomosis type, n (%)	Circular stapler	75 (81.5)	17 (18.5)	[c]0.003**
	Linear stapler	54 (94.7)	3 (5.3)	
	Hand sewn	6 (54.5)	5 (45.5)	
Histopathological type, n (%)	Adenocarcinoma	118 (85.5)	20 (14.5)	[c]0.006**
	Mucinous adenocarcinoma	17 (89.5)	2 (10.5)	
	Signet cell carcinoma	0 (0)	2 (100)	
	Medullar carcinoma	0 (0)	1 (100)	
Histological type, n (%) (n=140)	Well–moderately	115 (86.5)	18 (13.5)	[d]0.012*
	Poorly	3 (42.9)	4 (57.1)	
T stage; n (%)	T1	7 (100)	0 (0)	[c]0.017*
	T2	20 (95.2)	1 (4.8)	
	T3	89 (86.4)	14 (13.6)	
	T4	19 (65.5)	10 (34.5)	
N stage; n (%)	N0	86 (86.0)	14 (14.0)	[c]0.106
	N1	30 (90.9)	3 (9.1)	
	N2	17 (68.0)	8 (32.0)	
	Nx	2 (100)	0 (0)	
Stage; n (%)	I	21 (95.5)	1 (4.5)	[c]0.305
	II	67 (83.8)	13 (16.3)	
	III	47 (81.0)	11 (19.0)	

[a]: Student's t-test, [b]: Pearson Chi-square test, [c]: Fisher-Freeman-Halton Test, [d]: Fisher's exact test, *: p<0.05, **: p<0.01, IR: Intraluminal recurrence, SD: standard deviation, Nx: Regional lymph nodes cannot be evaluated

ule, and adjuvant therapy. The multivariate analysis revealed handsewn anastomoses (odds ratio [OR]: 45.532; 95% confidence interval (CI): 5.278–392.778), T stage (OR: 3.593; 95% CI: 1.378–9.371), and presence of tumor budding (OR: 3.912; 95% CI: 1.306–11.715) as independent risk factors for IR. The risk of IR increased 12,479 times in the presence of anastomosis performed using a circular stapler compared with that performed using a linear stapler (95% CI: 2.435–63.945). The risk of recurrence increased 45,532 times in the presence of handsewn anastomosis (95% CI: 5.278–392.778) (Table 5).

DISCUSSION

Experience with only IR at the anastomosis site after curative resection for CC is limited due to the relatively low number of cases observed. The literature lacks risk

Table 4: Anastomotic recurrence and histopathological characteristics

Variable		No IR	IR	p value
Lymph nodes	Min–Max (Median)	10–83 (27)	5–72 (27)	[e]0.895
Lymph node metastasis, n (%)	Negative	92 (87.6)	13 (12.4)	[b]0.118
	Positive	43 (78.2)	12 (21.8)	
Metastatic lymph node #	Min–Max (Median)	0–22 (11)	0–24 (12)	[e]0.025*
Tumor diameter (cm)	Min–Max (Median)	1–19 (4)	2–15 (5)	[e]0.261
Proximal distance (cm)	Min–Max (Median)	1–114 (10)	4–35 (11)	[e]0.728
Distal distance (cm)	Min–Max (Median)	0–38 (10)	1–25 (6)	[e]0.092
Peritoneal distance (mm)	Min–Max (Median)	0–20 (2)	0–7 (1)	[e]0.006**
Tumor margin, n (%)	Infiltrative	86 (80.4)	21 (19.6)	[b]0.048*
	Expansive	49 (92.5)	4 (7.5)	
Angiolymphatic invasion, n (%)	Negative	63 (86.3)	10 (13.7)	[b]0.539
	Positive	72 (82.8)	15 (17.2)	
Venous invasion, n (%)	Negative	121 (85.8)	20 (14.2)	[d]0.183
	Positive	14 (73.7)	5 (26.3)	
Peritumoral budging, n (%)	Negative	91 (90.1)	10 (9.9)	[b]0.009**
	Positive	44 (74.6)	15 (25.4)	
Perineural invasion, n (%)	Negative	107 (88.4)	14 (11.6)	[b]0.013*
	Positive	28 (71.8)	11 (28.2)	
Mesenteric tumor nodules, n (%)	Negative	118 (86.8)	18 (13.2)	[d]0.065
	Positive	17 (70.8)	7 (29.2)	
Adjuvant treatment, n (%)	Negative	71 (91.0)	7 (9.0)	[b]0.024*
	Positive	64 (78.0)	18 (22.0)	

[b]: Pearson Chi-square test, [d]: Fisher's exact test, [e]: Mann–Whitney U Test, *: p<0.0, **: p<0.01, IR: Intraluminal recurrence, SD: Standard deviation.

Table 5: Logistic regression analysis of factors affecting anastomotic recurrence

	p value	OR	95% CI	
			Lower	Upper
Anastomosis type (linear stapler)	0.002**			
Anastomosis type (circular stapler)	0.002**	12.479	2.435	63.945
Anastomosis type (handsewn)	0.001**	45.532	5.278	392.778
T stage	0.009**	3.593	1.378	9.371
Peritumoral budding	0.015*	3.912	1.306	11.715

*: p<0.05, **: p<0.01, OR: odds ratio, CI: confidence interval

factor demonstration of prospective studies reporting outcomes of large cohorts. Herein, we report our results of only IR at the anastomosis site on follow-up and the associated risk factors. We detected 25 (15.6%) patients with IR at the anastomosis site on an average follow-up of 42 months. The median time to IR was 21.3 months. The univariate analysis revealed the histopathological type, histological grade, T stage, number of metastatic lymph nodes, tumor margins, presence of tumor budding, perineural invasion, and anastomosis type as risk factors for IR. The multivariate analysis revealed handsewn anastomoses (OR: 45.532), T stage (OR: 3.593), and presence of tumor budding (OR: 3.912) as independent risk factors. Adjuvant chemotherapy did not affect the IR rate.

Although the definition of local recurrence in rectal cancer is well established, it is complex for CC. Peritoneal recurrence is considered a metastatic disease in the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual. In contrast, the peritoneal carcinomatous condition is accepted as locoregional recurrence in several studies, which precludes an accurate interpretation of the findings. Furthermore, it is not possible to distinguish macroscopically or microscopically whether peritoneal tumors (implant) are locally recurrent or peritoneal metastatic entities.

Locoregional or local recurrence occurs in the resection area or near the anastomosis site. The currently proposed reasons for local recurrence are inadequate surgical technique, aggressive tumor biology, and the inability to remove tumor cells that are sewn during the resection. Galandiuk et al. described the first classification of CC local recurrence in 1992 (14), which consists of four patterns of recurrence, venous invasion, anastomosis, mesenteric/nodal, retroperitoneal, and peritoneal. Because several studies have investigated recurrences of colon and rectal cancer together, it is difficult to comment only on CC recurrences. The published studies describe a very wide range (0.4%–34%) for locoregional recurrence of CC (6, 15-21).

In the present study, we explored the predictors of IR occurrence after primary surgery according to oncological principles, although the surgical margins in all patients were negative. We excluded other intraabdominal recurrences, such as peritoneal, retroperitoneal, and nodal recurrences, which are considered local, and identified factors that only directly affect IR. Our results revealed the anastomosis technique (p=0.003), histopathological type (p=0.006), histological grade (p=0.012), T stage (p=0.017), peritoneal distance (p=0.006), tumor margin (p=0.048), peritumoral budding (p=0.009), perineural invasion (p=0.013), and receiving adjuvant therapy (p=0.024) as risk factors that exerted a significant or almost significant effect on IR. Nevertheless, in the multivariate analysis, the anastomosis technique (p=0.001), T stage (p=0.009), and peritumoral budding (p=0.015) were identified as independent risk factors for IR.

The current knowledge regarding the localization of primary colonic tumors is that the right-sided tumor has a worse prognosis in advanced stages, whereas right- versus left-sided tumors exert no effect on local recurrence, consistent with our findings (22, 23). Moreover, in laparoscopic/open surgery, more than one operator was among the features investigated in previous studies, and none of them were associated with IR. Nevertheless, because we could not evaluate these variables in our study, we cannot conclude the presence of causality in these correlations.

Liska et al. reported a higher locoregional recurrence rate in patients with lymphovascular invasion (p<0.001), positive surgical margin (p<0.001), and local tumor invasion (p<0.001) among 1397 patients over an average follow-up of 7.8 years (24). The recurrence rate was also higher in poorly differentiated tumors (p=0.012). Unlike that in previous reports, the study demonstrated no effect of angiolymphatic invasion on recurrence (23, 25). Other parameters, such as peritumoral budding and perineural invasion, have not yet been investigated. Therefore, our study is the first to explore these variables in CC. Despite the low proportion of patients with a tumor pathology of medullary carcinoma or signet ring cell carcinoma in the study group, the authors demonstrated a higher recurrence rate (23, 24). Another feature not investigated in previous studies is the tumor margin (infiltrative/expansive). In our study, the recurrence rate was higher in patients with infiltrative characteristics (p=0.048), indicating an aggressive tumor feature.

As mentioned in the 8th edition of the AJCC Staging Manual, at least 12 lymph nodes must be removed from colon specimens for formal resection (26). In our study, the mean number of lymph nodes dissected was 29.2±12.1, because all patients underwent radical surgery and wide resection to the tumor margin with an average of 13.3 and 11.2 cm for proximal and distal to the tumor margin, respectively. This wide resection refers to complete mesocolic excision under the threat of lymphatic spread. The number of lymph nodes dissected in our study, which can be counted among surgical-related factors, did not directly affect the development of recurrence, which is consistent with previous studies (24). More intriguingly, positive lymph nodes and the N stage did not increase the IR rate, whereas the higher number of positive lymph nodes in dissection increased the probability of IR. The preferred anastomosis type was another surgeon-related factor, where we found that recurrence was significantly higher in handsewn anastomoses than in stapled anastomoses. This high rate can be attributed to the prolonged duration of contamination with tumor cells during man-

ual anastomosis after the surgeon's contact with the tumor tissue. Tsikitis et al. investigated the clinicopathological-specific predictors of recurrence for Stage II–III CC and reported a higher recurrence rate in the group receiving adjuvant therapy and no effect of chemotherapy on IR (27), which is similar to our findings.

Nonetheless, there are some limitations in this study. The single-center, retrospective design of the study may have inevitably resulted in an inherent bias. Moreover, because we excluded patients without long-term follow-up or those who underwent surveillance colonoscopy at an external center, the recurrence rate in our series could not be described accurately. The number of cases in the control group (nonrecurrent) was relatively low, because we included only patients who were followed up at our clinic and had long-term data. The effect of genetic mutations (*i.e.*, *RAS* or *RAF* gene mutations, or MSI) on recurrence at the anastomosis site could not be investigated because of the high cost of these kits as they are not routinely performed for every patient.

CONCLUSION

CC remains an important health issue with a high mortality rate. Our study demonstrated a relationship between tumor biology and IR, and the results were comparable with those from other centers. Although a sufficient distance of clear margins or dissection of a large number of lymph nodes is of utmost importance for both distant metastases and local recurrences, whether they are a predictor of IR remains unclear. In local relapses, the tumor histopathology, stage, and tumor biology are critical factors that should be considered. In the light of our study, as the T stage of the disease increases and in the presence of peritumoral budding, the frequency of follow-up with postoperative colonoscopy should be tightened or revised. Tumor stage and tumor biology may increase the probability of early treatment of high-risk patients without the need for late-diagnosed recurrences necessitating multivisceral resections. Further studies are required to better understand IR in CC and identify its possible predictors.

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