ORIGINAL CONTRIBUTION

Significance of Radial Margin in Patients Undergoing Complete Mesocolic Excision for Colon Cancer

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BACKGROUND: Comparable to circumferential resection margin in rectal cancer, radial margin is a potential prognostic factor in colon cancer that has just begun to be studied. No previous studies have investigated the influence of radial margin in the context of complete mesocolic excision.

OBJECTIVE: This study aimed to examine the impact of radial margin on oncologic outcomes after complete mesocolic excision for colon cancer.

DESIGN: We retrospectively reviewed patients with stage I to III colon cancer who underwent curative resection from October 2010 to March 2013.

SETTINGS: This study was conducted using the prospective colorectal cancer registry of Severance hospital.

PATIENTS: A total of 834 consecutive patients who underwent complete mesocolic excision for colon adenocarcinoma were included.

INTERVENTIONS: We assigned patients into 3 groups according to radial margin distance: group A, radial margin ≥2.0 mm; group B, 1.0 ≤ radial margin < 2.0 mm; group C, radial margin <1 mm.

MAIN OUTCOMES AND MEASURES: Overall survival and disease-free survival were estimated.

RESULTS: On adjusted Cox regression analysis, only group C was predictive of reduced overall survival (HR, 1.90; 95% CI, 1.11–3.25; $p = 0.018$) and disease-free survival (HR, 1.93; 95% CI, 1.28–2.89; $p = 0.001$). We thereby defined radial margin threatening as radial margin <1 mm. Postoperative 5-fluorouracil (HR, 0.86; 95% CI, 0.35–2.10; $p = 0.743$) and FOLFOX (HR, 1.23; 95% CI, 0.57–2.64; $p = 0.581$) chemotherapy did not affect disease-free survival in patients with radial margin threatening.

LIMITATIONS: This study has the limitations inherent in all retrospective, single-institution studies.

CONCLUSIONS: Even with complete mesocolic excision, radial margin <1 mm was an independent predictor of survival and recurrence. This finding suggests that special efforts for obtaining a clear radial margin may be necessary in locally advanced colon cancer. See **Video Abstract** at http://links.lww.com/DCR/B125.

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IMPORTANCIA DEL MARGEN RADIAL EN PACIENTES SOMETIDOS A ESCISIÓN MESOCÓLICA COMPLETA PARA CÁNCER DEL COLON

ANTECEDENTES: Comparable al margen de resección circunferencial en cáncer rectal, el margen radial en cáncer de colon, es un factor pronóstico potencial, que recientemente comienza a estudiarse. Ningún estudio previo ha investigado la influencia del margen radial, en el contexto de la escisión mesocólica completa.

OBJETIVO: Examinar en cáncer de colon, el impacto del margen radial en los resultados oncológicos, después de la escisión mesocólica completa.

DISEÑO: Revisión retrospectiva de pacientes con cáncer de colon en estadio I-III, sometidos a resección curativa de octubre 2010 a marzo 2013.

AJUSTES: Este estudio se realizó utilizando un registro prospectivo de cáncer colorrectal del hospital Severance.

PACIENTES: Se incluyeron un total de 834 pacientes consecutivos con adenocarcinoma de colon, sometidos a escisión mesocólica completa. Dividimos a los pacientes en 3 grupos según la distancia del margen radial: grupo A, margen radial ≥ 2.0 mm; grupo B, 1.0 ≤ margen radial <2.0 mm; grupo C, margen radial <1 mm.

PRINCIPALES MEDIDAS DE RESULTADOS: Se estimó la supervivencia general y la supervivencia libre de enfermedad.

RESULTADOS: En el análisis de regresión de Cox ajustado, solo el grupo C fue predictivo de supervivencia global reducida (HR, 1.90; IC 95%, 1.11–3.25; $p = 0.018$) y supervivencia libre de enfermedad (HR, 1.93; IC 95%, 1.28–2.89; $p = 0.001$). Definimos como margen radial amenazante, un margen radial <1 mm. La quimioterapia posoperatoria con 5-FU (HR, 0,86; IC 95%, 0,35–2,10; $p = 0.743$) y FOLFOX (HR, 1,23; IC 95%, 0,57–2,64; $p =$ 0,581), no afectó la supervivencia libre de enfermedad en pacientes con riesgo de margen radial.

LIMITACIONES: Este estudio tiene limitaciones inherentes a todos los estudios retrospectivos de una sola institución.

CONCLUSIONES: Aun con la escisión mesocólica completa, el margen radial <1 mm fue un predictor independiente de supervivencia y recurrencia. Este hallazgo sugiere que pueden ser necesarios esfuerzos especiales para obtener un claro margen radial, en cáncer de colon localmente avanzado. Consulte **Video Resumen** en http://links.lww.com/DCR/B125. (*Traducción—Dr. Fidel Ruiz Healy*)

KEY WORDS: Colonic cancer; Complete mesocolic excision; Radial margin; Survival.

The key principle of surgical resection for malignancy is complete removal of the tumor to achieve a negative resection margin. Since the introduction of total mesorectal excision (TME) by Heald et al,[1] surgical treatment of rectal cancer has achieved significant success with respect to oncologic outcomes. Total mesorectal excision emphasizes dissection along the mesorectal plane, which provides an intact unit containing the primary tumor and the surrounding potential area of tumor spread. Complete mesocolic excision (CME) is comparable to TME; it involves en bloc removal of the tumor and nearby lymph node bearing soft tissue enveloped within the visceral fascia.[2] Similar to TME, CME has been shown to reduce the recurrence of colon cancer and thereby improve survival, compared with non-CME.[3]

In rectal cancer, the involvement of circumferential resection margin (CRM) is a powerful prognostic factor affecting both distant metastasis and local recurrence. Previous studies showed that tumors with <1 mm CRM have an increased risk of local recurrence.[4,5] On the basis of these results, efforts have been made to obtain a CRM >1 mm in the TME era. Preoperative concurrent chemoradiation, as well as dissection beyond the mesorectal plane, are the main methods of achieving CRM distance.[6,7]

Contrary to the established relationship between CRM and rectal cancer, the implications of a radial margin (RM) in colon cancer are poorly understood. Because part of the colon and rectum share similar spatial relationships between tumor and the dissection plane, RM likely influences oncologic outcomes of colon cancer. A few studies demonstrated that the presence of tumor cells at the cut edge of a specimen, which was defined as RM positivity, was an independent prognostic factor for recurrence and deaths in colon cancer.[8,9] However, research regarding the significance of RM in colon cancer is still at an early stage; even the concept of RM is not widely accepted, compared with the well-established concept of CRM in rectal cancer. The impact of RM in the patients who received CME remains vague.

To date, no published study has investigated the impact of RM in the context of CME. The current study aimed to evaluate the prognostic importance of RM for long-term outcomes in colon cancer after CME with central vessel ligation.

METHODS

Study Design and Population

From a prospective colorectal cancer registry, we selected consecutive patients who underwent CME with central vessel ligation for stage I to III colon cancer at Yonsei University Health System Severance Hospital, Seoul, Korea, from October 2010 to March 2013. We included subjects with a tumor in the cecum to sigmoid colon, excluding those with rectal cancer. We also excluded patients with surgical resection for palliation (n = 55), colon tumors other than adenocarcinoma (n = 28), and hereditary colon cancer syndromes (n = 17).

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Surgery

The surgical procedure has been described previously.[10] In brief, it involved en bloc resection, including the removal of the tumor and the surrounding soft tissue enveloped by intact visceral fascia. The extent of lymph node dissection in right colon cancer included the mesenteric nodes along the superior mesenteric vessels. The supplying vessels were ligated at their origin. For ascending and descending colon cancer, if the tumor was suspected to invade or threaten the CME plane on the retroperitoneal side, we extended our dissection deeper to include the retroperitoneal soft tissue in the en bloc specimen to achieve an adequate margin.

Assessment of RM

All en bloc specimens from the operating room were immediately sent for pathological examination, and a team of specialized colorectal pathologists processed the specimens for macro- and microscopic examination.

Radial margin was defined as the adventitial soft tissue margin from the cut edge of the mesentery or retroperitoneal surface to the deepest tumor infiltration, as suggested by the National Comprehensive Cancer Network.[11] The serosal surface or visceral peritoneum was not regarded as part of the RM. Only the mesenteric resection margin was appropriate for the assessment of RM for transverse and sigmoid colon, which are intraperitoneal organs. Assessment of RM included both tumor-bearing lymph nodes and direct tumor extension. Before initiation of the pathological examination, the nonserosal surface for RM assessment was dyed with ink by the pathologists. After opening the specimen longitudinally along the antimesenteric side of the colon, the specimen was fixed in formalin. The most deeply invaded tumor site was sectioned, and the colorectal pathologists assessed the RM according to protocol. If the enlarged lymph node or tumor deposit near the surface for RM was visible, assessment for RM was performed without dissection of lymph nodes. Radial margin was finally determined after more than 2 pathologists cross-checked on the slides.

Statistical Analysis

Patient characteristics, operative outcomes, and postoperative outcomes were compared by using the χ^2 test for categorical variables or the Kruskal-Wallis test for continuous variables. Univariate analyses of survival and recurrence were performed by using the Kaplan-Meier method, and the log-rank test was used to evaluate differences. Cox proportional hazards methods were used to assess the effect of RM and possible confounders on survival. Variables with $p < 0.2$ in univariate analysis were selected for the multivariate model. All tests were 2-tailed, and $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS version 20.0 (SPSS Institute, Chicago, IL).

Ethics Approval

The study protocol was approved by the Institutional Review Board at Human Research Protection Center, Severance Hospital, Seoul, South Korea (4-2017-1220).

RESULTS

Baseline Characteristics and Perioperative Outcomes

A total of 834 patients satisfying eligibility criteria were included in the final analysis. They were assigned to 3 groups according to RM distance: group A, RM ≥2.0 mm; group B, 1.0 ≤ RM < 2.0 mm; and group C, RM <1 mm.

Patients with BMI <19 kg/m^2 were observed more frequently in groups B and C than in group A (group A vs group B: $p = 0.020$; group A vs group C: $p < 0.001$). Prognostic Nutritional Index <50, which is a known predictor of worse short- and long-term outcomes,[12,13] was more frequently associated with group C than with group A ($p = 0.009$). There was no difference in the surgical approach method and conversion-to-open rate for patients in whom minimally invasive surgery was attempted. Combined resection of tumor-invaded adjacent organs was significantly more common in group C than in group A ($p = 0.001$). More aggressive pathological features were observed in group C than in group A. Distribution of pathological T (pT) stage differed among groups. It is notable that group C contained patients with only pT3 or pT4 lesions. There were no differences in mortality, morbidity rates, and the median postoperative hospital stay among groups. Postoperative FOLFOX (folinic acid/fluorouracil/oxaliplatin) chemotherapy was more frequently administered in patients in group C than in patients in group A ($p < 0.001$) (Table 1).

Impact of RM on Oncologic Outcomes

Overall survival, disease-free survival (DFS), and cumulative rates of local recurrence (LR) and systemic recurrence (SR) were assessed. Log-rank tests revealed that group A had superior overall survival (group A vs group C: $p < 0.001$), DFS (group A vs group C: $p < 0.001$, group A vs group B: $p = 0.007$), LR (group A vs group C: $p < 0.001$, group A vs group B: $p = 0.009$), and SR (group A vs group C: $p < 0.001$), compared with the other groups. Multivariate Cox regression analysis showed that group C was independently associated with a worse prognosis, after adjusting age, sex, BMI, ASA, Prognostic Nutritional Index, surgeon, tumor location, obstruction, American Joint Committee on Cancer stage, tumor size, histology, lymphovascular invasion, and postoperative chemotherapy. Although the Kaplan-Meier curve showed a tendency toward superior oncologic outcomes in group A and similar outcomes in groups B and C, multivariate analysis revealed that, after adjusting for other confounding variables, only group C exhibited significantly worse oncologic outcomes, compared with group A (Table 2). Therefore, we used RM <1 mm (group C) to

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TABLE 1. Baseline characteristics, perioperative outcomes, and treatment for all patients

	Radial margin, n (%)			
Variables	*Group A (n = 592)*	*Group B (n = 63)*	*Group C (n = 179)*	*p value*
Age >65 y	256 (43.2)	31 (49.2)	93 (52.0)	0.102
Male	360 (60.8)	38 (60.3)	104 (58.1)	0.810
BMI < 19 kg/m^2	26 (4.4)	7 (11.1)	25 (14.0)	<0.001
ASA physical status class 3 or 4	69 (11.7)	16 (25.4)	35 (19.6)	0.001
PNI <50	245 (41.4)	36 (58.1)	94 (52.5)	0.003
Obstruction	13 (2.2)	1 (1.6)	6 (3.4)	0.614
Tumor location				0.179
Cecum	27 (4.6)	0 (0.0)	5 (2.8)	
Ascending colon	195 (32.9)	25 (39.7)	69 (38.5)	
Transverse colon	64 (10.8)	2 (3.2)	21 (11.7)	
Descending colon	43 (7.3)	7 (11.1)	15 (8.4)	
Sigmoid colon	263 (44.4)	29 (46.0)	69 (38.5)	
Surgeon[a]				0.886
A	183 (68.3)	25 (9.3)	60 (33.5)	
B	77 (72.0)	9 (14.3)	21 (11.7)	
C	114 (72.6)	10 (6.4)	33 (21.0)	
D	107 (69.9)	11 (7.2)	35 (22.9)	
E	111 (74.5)	8 (5.4)	30 (20.1)	
T stage				<0.001
1	134 (22.6)	0 (0.0)	0 (0.0)	
2	113 (19.1)	4 (6.3)	0 (0.0)	
3	322 (54.4)	57 (90.5)	115 (64.2)	
4	23 (3.9)	2 (3.2)	64 (35.8)	
N stage				<0.001
0	410 (69.3)	34 (54.0)	87 (48.6)	
1	144 (24.3)	17 (27.0)	50 (27.9)	
2	38 (6.4)	12 (19.0)	42 (23.5)	
Tumor size ≥5 cm	184 (31.1)	33 (52.4)	95 (53.1)	<0.001
Histologic grade 3 or 4	38 (6.4)	7 (11.1)	26 (14.5)	<0.001
LVI (+)	91 (15.6)	14 (22.6)	55 (30.7)	<0.001
Postoperative CTx				<0.001
No CTx	340 (57.5)	28 (44.4)	61 (34.1)	
5-FU	79 (13.4)	9 (14.3)	32 (17.9)	
FOLFOX	172 (29.1)	26 (41.3)	86 (48.0)	
Operative details and immediate outcomes				
Minimally invasive surgery	516 (87.2)	53 (84.2)	149 (83.3)	0.552
Open conversion	10 (1.9)	0 (0.0)	3 (2.0)	0.589
Multiorgan resection	15 (2.5)	4 (6.3)	14 (7.8)	0.003
Duration of surgery, median (IQR), minutes	200 (94)	223 (84)	204 (76)	0.198
EBL ≥200 mL	117 (19.8)	16 (25.4)	36 (20.1)	0.571
30-day mortality	1 (0.2)	1 (1.6)	0 (0.0)	0.191
30-day morbidity	79 (13.3)	8 (12.7)	26 (14.5)	0.913
Major complications[b]	30 (5.1)	2 (3.2)	6 (3.4)	0.541
Hospital stay, median (IQR), days	7 (4)	7 (4)	7 (3)	0.089

CTx = chemotherapy; EBL = estimated blood loss; FOLFOX = folinic acid/fluorouracil/oxaliplatin; 5-FU = 5-fluorouracil; IQR = interquartile range; LN = lymph node; LVI = lymphovascular invasion; PNI = Prognostic Nutritional Index .

[a]Represents the percentages for each surgeon.

[b]Major complications were defined as complications with a Clavien-Dindo grade of III or higher.

define radial margin threatening (RMT) for subsequent analyses. To illustrate the difference in covariate-adjusted survival between patients with RMT and other groups, survival curves based on Cox proportional hazards survival models adjusted for the aforementioned clinicopathological characteristics are demonstrated in Figure 1.

Risk Factors for RMT

We performed multiple logistic regression analyses to identify risk factors for RMT. As shown in Table 3, pT4, pN2, tumor size ≥5 cm, and BMI <19 kg/m^2 were significant independent risk factors for RMT.

Effect of Postoperative Chemotherapy in Patients With RMT

Among 179 patients with RMT, 118 (65.9%) were treated with postoperative chemotherapy. The most common chemotherapy regimen was FOLFOX (72.8%). To investigate whether postoperative chemotherapy salvaged patients with RMT, we compared clinical features and

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TABLE 2. Multivariate analysis of risk factors for overall survival, disease-free survival, local recurrence, and systemic recurrence for all patients

	OS[a]		DFS[a]		LR[a]		SR[a]	
Covariates	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Age > 65 y	2.28 (1.30–3.97)	0.004	1.40 (0.94–2.08)	0.096			1.12 (0.65–1.93)	0.664
ASA class ≥3	2.07 (1.17–3.68)	0.012	1.68 (1.07–2.64)	0.024	2.15 (0.90–5.12)	0.083		
PNI <50	1.93 (1.11–3.35)	0.019	1.45 (0.97–2.15)	0.063	1.02 (0.46–2.25)	0.952	1.53 (0.88–2.67)	0.126
TNM stage								
1	1		1		1		1	
2	1.38 (0.47–4.01)	0.553	2.36 (1.08–5.14)	0.030	5.09 (0.60–43.23)	0.136	2.44 (0.65–9.06)	0.182
3	1.15 (0.33–4.03)	0.821	3.18 (1.27–7.91)	0.013	4.28 (0.62–44.77)	0.127	5.21 (1.22–22.25)	0.026
LVI	1.36 (0.75–2.45)	0.298	1.59 (1.02–2.46)	0.037			1.85 (1.02–3.35)	0.042
Radial margin								
RM ≥2 mm	1		1		1		1	
1 ≤ RM < 2 mm	1.44 (0.62–3.34)	0.390	1.56 (0.84–2.89)	0.154	2.84 (0.85–9.50)	0.089	1.27 (0.48–3.31)	0.620
RM <1 mm	1.90 (1.11–3.25)	0.018	1.93 (1.28–2.89)	0.001	3.63 (1.58–8.34)	0.002	1.97 (1.12 –3.44)	0.017

Covariates are age, sex, BMI, obstruction, tumor location, surgeon, histologic grade, tumor size, examined lymph nodes, postoperative chemotherapy.
DFS = disease-free survival; LR = local recurrence; LVI = lymphovascular invasion; OS = overall survival; PNI = Prognostic Nutritional Index; RM = radial margin; SR = systemic recurrence.
[a]Results of multivariate analysis for each long-term outcome. Variables that were not shown as significant for at least one outcome are not listed in this table.

oncologic outcomes in this subgroup according to postoperative chemotherapy status. The patients with RMT were thereby categorized into 3 groups: no chemotherapy (CTx) group, patients who received regular follow-up without CTx; 5-fluorouracil (5-FU) group, patients who received 5-FU only; and FOLFOX group, patients who received FOLFOX.

The following characteristics were more common in the No CTx group: age >65 years (No CTx, 77.0%; 5-FU, 59.4%; FOLFOX, 31.4%; $p < 0.001$), ASA class ≥3 (No CTx, 29.5%; 5-FU, 21.9%; FOLFOX, 11.6%; $p = 0.025$), stage II (No CTx, 85.2%; 5-FU, 62.5%; FOLFOX, 17.4%; $p < 0.001$), and absence of lymphovascular invasion (No CTx, 18.0%; 5-FU, 28.1%; FOLFOX, 40.7%; $p = 0.013$).

Unadjusted analysis for oncologic outcomes in patients with RMT showed no difference according to postoperative CTx regimen (Fig. 2). In multivariate Cox regression analysis, neither the 5-FU nor FOLFOX CTx groups exhibited superior results for DFS, compared with the No CTx group (5-FU: HR, 0.86, 95% CI, 0.35–2.10, $p = 0.743$; FOLFOX: HR, 1.23, 95% CI, 0.57–2.64, $p = 0.581$). Furthermore, LR (5-FU: HR, 0.52, 95% CI, 0.10–2.53, $p = 0.424$; FOLFOX: HR, 0.76, 95% CI, 0.27–2.10, $p = 0.603$) and SR (5-FU: HR, 0.94, 95% CI, 0.27–3.23, $p = 0.922$; FOLFOX: HR, 0.56, 95% CI, 0.16–1.95, $p = 0.369$) were not affected by 5-FU or FOLFOX CTx.

DISCUSSION

Because of the anatomic variance of the mesocolon and its adjacent peritoneum, the concept of RM is more complicated than CRM in rectal cancer. Unlike the rectum, which is a cylindrical shape facing the mesorectum in all directions, the colon faces the mesocolon to varying degrees, depending on the part of the colon being considered. The ascending and descending colon face the mesocolon over the largest area, whereas the transverse and sigmoid colon face it to a lesser extent. Different from ascending and descending colon cancer, mesenteric resection margin may be accurate for sigmoid and transverse colon cancer, whereas the term "radial margin" may be more intuitive. Therefore, for colon, the term "mesocolon" margin seems to be more appropriate and easier to understand than "radial" margin.

Amri et al[9] reported previously that RM involvement was strongly associated with worse survival in patients with colon cancer. In the current study, we further investigated whether, as with CRM, the RM distance was related to oncologic outcomes. In rectal cancer, Wibe et al[14] demonstrated that, as the distance of CRM decreases, LR and mortality increase. This is similar to our findings that oncologic outcomes were inversely related to the RM distance. Group C (RM <1 mm) had the worst outcomes, and group A (RM ≥2 mm) had the best outcomes, whereas group B (1 mm ≤ RM < 2 mm) had intermediate outcomes. Furthermore, we found that after filtering out other confounding factors, an RM distance <1 mm alone, even if the margin was not directly involved, can adversely affect oncologic outcomes.

The proportion of patients with RMT (RM <1 mm) was 21.4% in the current study. Considering that the study was conducted at a tertiary referral hospital, where patients tend to have more aggressive and advanced tumors, this is still a relatively high percentage. This high RMT rate may be attributed, at least in part, to our definition. A previous study reported an RMT of 5.3% when RMT included only direct involvement of the edge of the RM.[9] The BMI of our patients might also be part of the reason for our RMT rate. We found that patients with advanced pT and pN stages and with a low BMI had a higher risk of RMT. In comparison with previous reports, our study population had a similar proportion of patients with advanced pT and pN,

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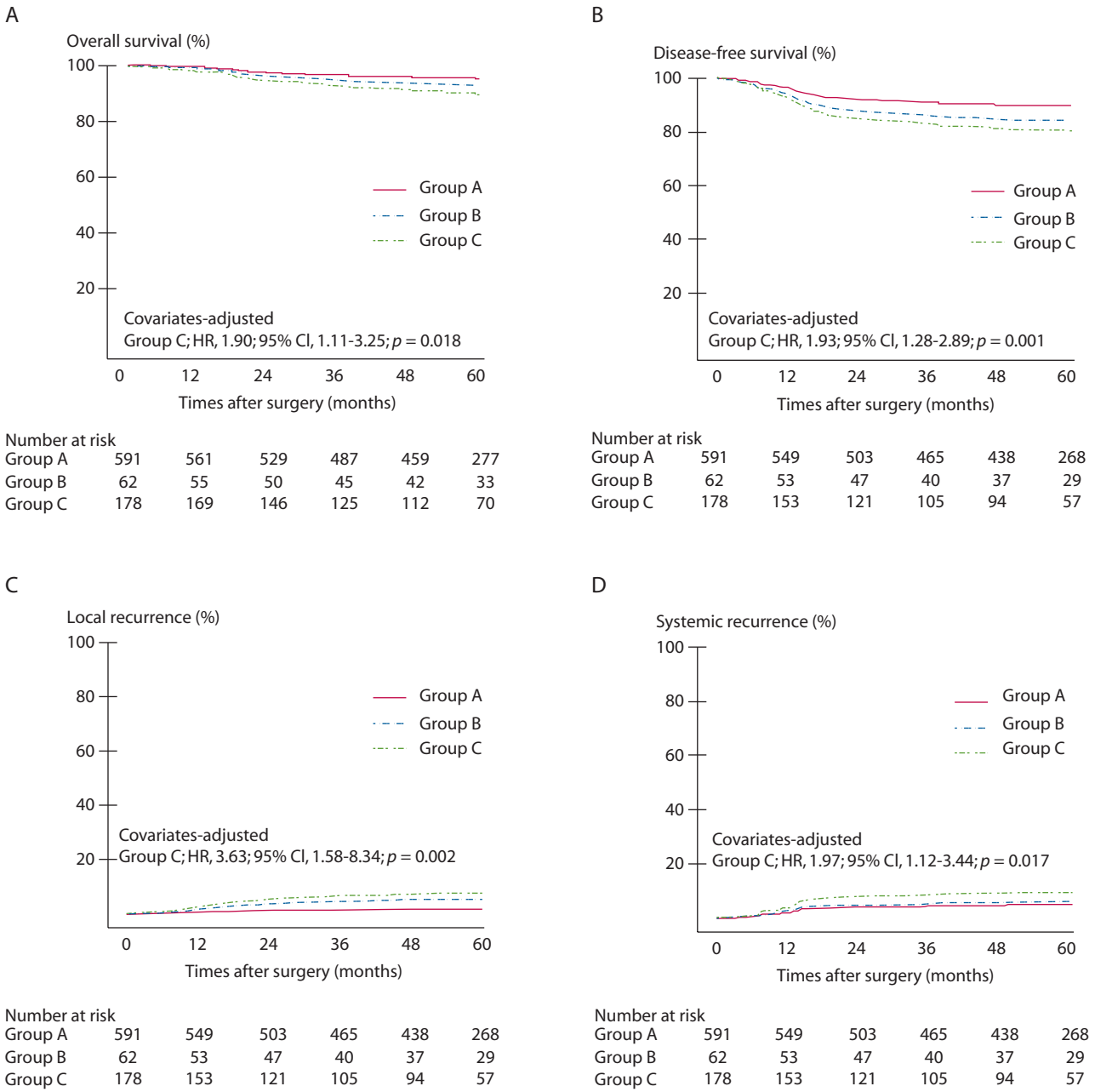

FIGURE 1. Survival and recurrence rates according to radial margins (covariates-adjusted Cox proportional hazards curves). A, Overall survival. B, Disease-free survival. C, Local recurrence. D, Systemic recurrence.

but a substantially lower BMI. The association between low BMI and increased rate of RMT is not unexpected when patterns of RMT are considered. The majority of patients with RMT had tumors in the ascending and sigmoid colon, where a tumor could invade posteriorly into the retroperitoneal surface. In patients with a low BMI, the retroperitoneal fat plane is relatively thin; this anatomical difference may result in a higher incidence of RMT.

To assess whether postoperative CTx can reverse the adverse effects of RMT, we performed a risk-adjusted analysis and found that postoperative CTx did not improve DFS in patients with RMT. This observation may suggest that postoperative CTx was not effective enough to reduce the risks of RMT. Thus, more efforts seem to be mandatory for the treatment of the patients who are suspected of having RMT colon cancer. For tumors in the ascending or descending colon, en bloc resection of retroperitoneal soft tissue anterior to the Gerota fascia should be considered for RMT tumors. For tumors in the sigmoid colon, metastatic lymph nodes along the inferior mesenteric artery or a posteriorly infiltrating tumor margin could be the point of RMT. Preaortic sympathetic nerves lie on the retroper-

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TABLE 3. Clinicopathological factors associated with radial margin threatening (radial margin <1 mm)

	Univariate		*Multivariate*	
Covariates	*OR (95% CI)*	*p value*	*OR (95% CI)*	*p value*
Age > 65 y	1.38 (0.99–1.93)	0.053	1.32 (0.88–1.98)	0.180
Male	0.89 (0.64–1.25)	0.519		
BMI < 19 kg/m^2	3.06 (1.76–5.29)	<0.001	2.52 (1.33–4.77)	0.004
ASA class ≥3	1.63 (1.05–2.51)	0.027	1.65 (0.98–2.77)	0.057
PNI < 50	1.73 (1.28–2.35)	<0.001	0.88 (0.58–1.34)	0.572
Obstruction	1.58 (0.60–4.19)	0.351		
Tumor location				
Cecum	1			
Ascending colon	1.69 (0.62– 4.56)	0.298		
Transverse colon	1.71 (0.58–5.02)	0.323		
Descending colon	1.62 (0.53–4.94)	0.396		
Sigmoid colon	1.27 (0.47–3.43)	0.629		
Surgeon				
A	1			
B	0.84 (0.48–1.47)	0.558		
C	0.92 (0.57–1.49)	0.742		
D	1.02 (0.64–1.65)	0.908		
E	0.87 (0.53–1.43)	0.592		
T stage				
1–3	1		1	
4	14.02 (8.47–23.19)	<0.001	9.69(5.70–16.48)	<0.001
N stage				
0	1		1	
1	1.58 (1.07–2.34)	0.021	1.18 (0.76–1.85)	0.450
2	4.28 (2.67–6.86)	<0.001	2.21 (1.22–4.01)	0.009
Histologic grade				
1	1		1	
2	3.59 (1.78–7.27)	<0.001	2.13 (0.88–4.64)	0.145
3 or 4	7.19 (3.12–16.54)	<0.001	3.09 (0.73–7.94)	0.437
Tumor size ≥5 cm	2.28 (1.63–3.19)	<0.001	1.58 (1.04–2.40)	0.030
Examined LNs	1.21 (1.13–1.30)	<0.001	1.00 (0.98–1.02)	0.686
LVI	2.27 (1.55–3.33)	<0.001	1.45 (0.90–2.34)	0.120

LN = lymph node; LVI = lymphovascular invasion; PNI = Prognostic Nutritional Index.

itoneal connective tissue and surround the origin of inferior mesenteric artery, and surgeons have been warranted to keep their dissection plane 1 to 2 cm away from this area to prevent nerve damage. To achieve a wider retroperitoneal margin in these cases, a surgeon should perform deeper dissection beyond the posterior (retroperitoneal) CME plane. For sigmoid colon cancer, the distal part of the CME plane continues as the TME plane. Hypogastric nerve plexus is embedded in a sheet of loose connective tissue within the presacral area, just below the mesorectal fascia plane.[15,16] Caution is necessary, because dissection deeper than the TME might damage the hypogastric nerve (Supplemental Figure, http://links.lww.com/DCR/B126).

Nonetheless, obtaining an adequate RM beyond CME resection may have limits. For example, in patients with a low BMI, the retroperitoneal soft tissue pad may not be sufficient to obtain a safe RM. Recent clinical trials investigating the effects of neoadjuvant CTx for colon cancer may provide a solution for obtaining an adequate RM. Observations that RMT is associated with a poor prognosis (especially higher SR and LR rates), and that more extensive surgical resection beyond CME may not improve RMT at some locations, may serve as a rationale for preoperative treatment of RMT colon cancer. In patients with RMT tumors, preoperative CTx may shrink the tumor enough to produce an adequate RM and may reduce the risk of systemic failure. Although ongoing clinical trials do not specifically list RMT cancer as an eligibility criterion, they have mostly enrolled patients with clinically T3 or T4 tumors with some aggressive radiological features. For example, a European trial (NCT01918527) has enrolled patients with T3 or T4 cancer with extramural tumor invasion >5 mm. Although this does not specifically meet the definition of RMT, it likely includes the majority of RMT tumors (RM distance < 1mm) in patients with a low to normal BMI.

This study has the limitations inherent in all retrospective, single-institution studies. One of the limitations of this study was that the analysis on the effect of postoperative CTx was conducted in a relatively small number of patients. The lack of CME grading is another drawback. Nonetheless, to the best of our knowledge, few, if any,

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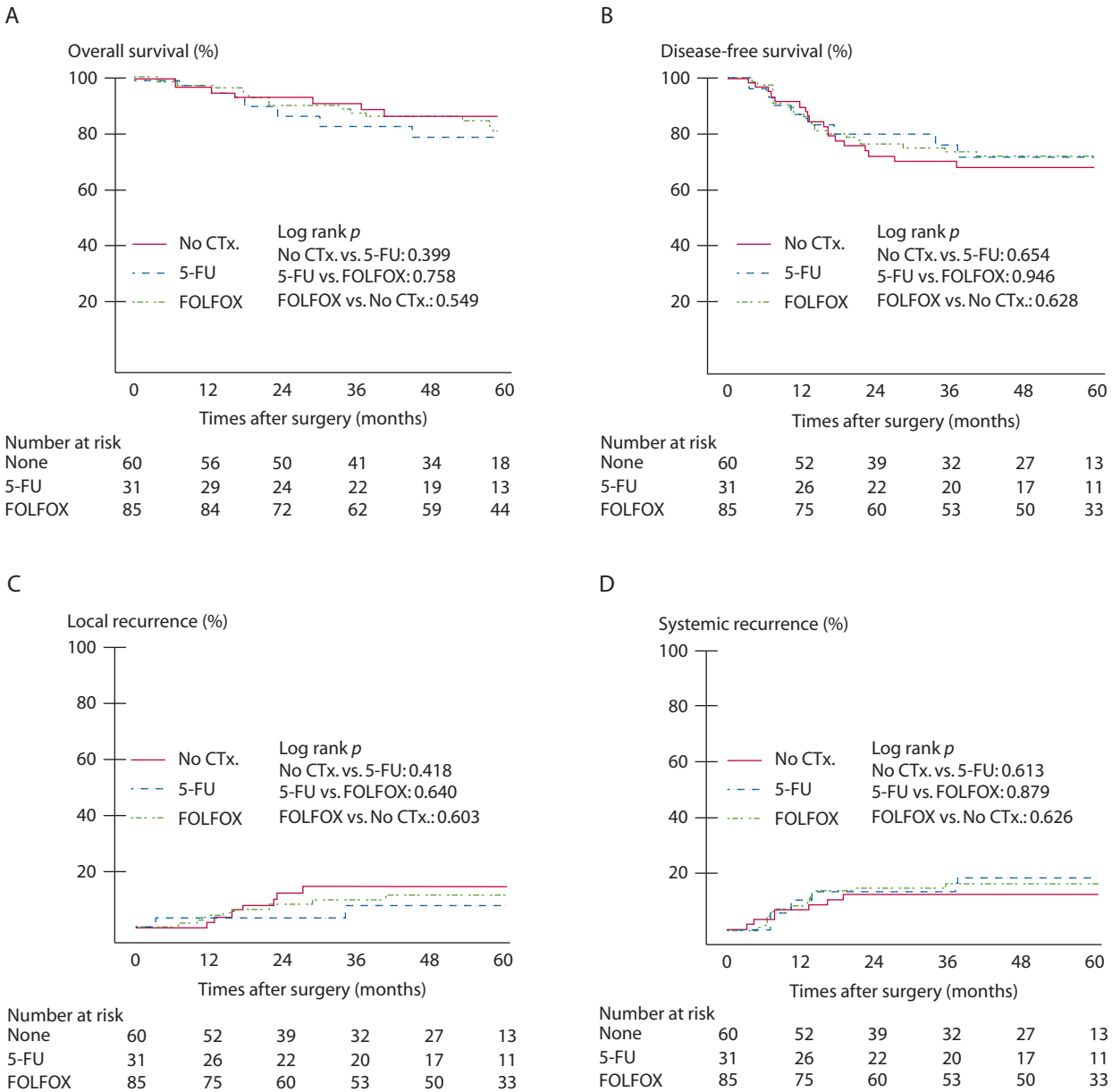

FIGURE 2. Survival and recurrence rates according to regimen of postoperative chemotherapy in patients with radial margin threatening (Kaplan-Meier plots). A, Overall survival. B, Disease-free survival. C, Local recurrence. D, Systemic recurrence. CTx = chemotherapy; FOLFOX = folinic acid/fluorouracil/oxaliplatin; 5-FU = 5-fluorouracil.

studies have heretofore examined the impact of RMT in the context of CME. Moreover, our comprehensive analysis provided valuable discussion points regarding the definition of RMT and the potential necessity for preoperative treatment in locally advanced colon cancer.

CONCLUSIONS

In conclusion, inadequate RM is a strong risk factor for recurrence and death even in patients with CME for colon cancer. Therefore, special efforts to secure an adequate RM are necessary. Reports from on-going clinical trials regarding preoperative CTx for locally advanced colon cancer suggest that this therapy is another option when surgery alone has limits.

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