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ORIGINAL SCIENTIFIC REPORT

Anastomotic Recurrence After Curative Resection for Colorectal Cancer

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Abstract

Background A precise understanding of anastomotic recurrence (AR) permits efficient surveillance and treatment strategies. This study aimed to evaluate the clinicopathologic characteristics of patients with AR undergoing curative resection for colorectal cancer (CRC), compare colonic with rectal tumors and investigate the risk factors related to AR.

Methods A single-institution, retrospective cohort of 9024 patients who underwent curative surgery for CRC between 2000 and 2010 was enrolled. Patients were classified into AR group ($n = 53$) or non-AR group ($n = 8971$) and were also characterized by tumor location.

Results The AR group was independently associated with old age ($p = 0.046$), advanced N stage ($p = 0.003$), the rectum ($p = 0.001$), a large tumor ($p = 0.001$) and mucinous differentiation (MU) ($p = 0.026$). In colon cancers, the AR group ($n = 20$) was independently associated with MU ($p = 0.022$) and lymphovascular invasion (LVI) ($p = 0.001$). In rectal cancers, the AR group ($n = 33$) was independently associated with N2 stage ($p = 0.007$) and a large tumor ($p < 0.001$). AR is a burden to patients and physicians because these tumors have a poor prognosis and more advanced pathologic stages than the primary tumors. However, N0 stage and curative resection of an AR tumor ($p = 0.001$ and $p < 0.001$, respectively) were found to be independently associated with improved survival in a Cox regression model.

Conclusion AR is independently associated with the rectum. In colon cancers, MU and LVI are independent risk factors for AR. In rectal cancers, a large tumor and N2 stage are independent risk factors for AR. Although AR shows a poor prognosis, early detection and curative resection may lead to an improved survival.

Introduction

A specific type of local recurrences in colorectal cancer (CRC), anastomotic recurrence (AR, also known as suture line recurrence) develops in 1.5–15.0 % of cases after curative resection [1–4]. AR cannot be easily diagnosed and controlled. Furthermore, salvage operation is a significant burden for these patients, both physically and economically [5, 6].

AR is thought to be caused by an inadequate resection margin [7] or the implantation of exfoliated cancer cells. Viable tumor cells, shed from the surface of solid tumor tissue in the lumen of the colon or rectum during an operation, may be responsible for AR [8–10]. Alternative mechanisms for AR include metachronous carcinogenesis at a perianastomotic site with proliferative instability and adaptive hyperplasia of the epithelium at the suture line might play an important role [11, 12].

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Despite the hypothetical mechanisms and alleged RFs for AR, relevant clinicopathologic variables are not readily available because of the low incidence of AR.

Our present study aimed to evaluate the clinicopathologic characteristics of AR patients undergoing curative resection for CRC, investigate the RFs related to AR, compare colon with rectum and identify potentially effective treatment strategies.

Materials and methods

Patients

Patients who received curative surgery for CRC at our institute between 2000 and 2010 were retrospectively reviewed. We excluded cases who had positive resection margins including circumferential resection margin (CRM) in frozen section and/or final pathological examination. We also excluded cases of hereditary CRC, mucosal cancer, concurrent unresectable distant metastasis at diagnosis and any patients who had undergone non-anastomotic surgery. This study was approved by Institutional Review Board. A total of 9024 patients were included. Patients were classified into AR group ($n = 53$) and non-AR group ($n = 8971$). A total of 649 (7.2 %) were lost during the follow-up periods. The median follow-up interval was 71.2 months (interquartile range 59–86).

Surgery

Curative surgery was defined as complete resection of any measurable disease without involvement of the resection margin. Depending on tumor location and number, right or left colectomy, anterior resection, low anterior resection, total colectomy were performed by seven experienced colorectal surgeons who perform more than 150 colorectal operations annually. Tumor location was defined as colon [>15 cm from the anal verge (AV)] or rectum (≤15 cm from the AV). In rectal cancers, we performed total mesorectal excision (TME) or tumor-specific mesorectal excision (TSME) according to tumor location. In addition, we routinely irrigated the proximal colonic and distal rectal stump with a 1 % povidone/iodine solution before anastomosis. Although complete mesocolic excision (CME) was highlighted in recent years for oncological outcome [13], we did not performed CME routinely in right colon cancers. However, we divided the ileocolic vessels and midcolic vessels at their origin and ligated the principal lymphovascular pedicles. If tumor located from cecum to proximal ascending colon, we divided ileocolic vessels and right branch of midcolic vessels. Performing of irrigation depended on the anastomotic methods.

Postoperative chemotherapy and concurrent chemoradiation therapy (CCRT)

After recovery from surgery, adjuvant therapy was provided to selected stage II and all stage III patients who were physically capable of receiving treatment. Postoperative chemotherapy regimen was mainly 5-Fluorouracil (5-FU) and leucovorin. Some patients received capecitabine-, irinotecan- and/or oxaliplatin-based chemotherapy. Preoperative CCRT was recommended for clinically T3–T4 and/or N positive. After surgery, postoperative CCRT was recommended for patients who had stage II or III rectal cancers without preoperative CCRT. The CCRT regimen consisted of a 45-Gy dose of pelvic external beam radiation delivered in 25–28 fractions. Concurrent chemotherapy was delivered as two cycles via an intravenous bolus of 5-FU (375 mg/m^2/day) and leucovorin (20 mg/m^2/day) for 3 days during the first and fifth weeks of radiotherapy or as oral capecitabine (1650 mg/m^2/day), administered twice daily during radiotherapy.

Pathology

After surgery, a pathological examination was performed by gastrointestinal pathologists. Staging was performed according to the American Joint Committee on Cancer (AJCC) 7th TNM classification of malignant tumors [14]. In addition, CRM, proximal and distal resection margin, lymphovascular invasion (LVI), perineural invasion (PNI) and differentiation were documented. A positive CRM was defined as the presence of tumor cells within 1 mm of the resection margin [15, 16]. LVI and PNI were defined by current practice guidelines [17–19].

Follow-up and surveillance

Follow-up investigations included clinical examination, routine blood chemistry, serum CEA screening, colonofiberscopy, chest radiography and abdominopelvic and chest computed tomography (CT). We performed a physical examination together with blood chemistry and CEA screening every 3 months for 2 years after the operation and every 6 months thereafter. We performed colonofiberscopy 6–12 months after the operation and then every 2–3 years. Abdominopelvic and chest CT were performed every 6 and 12 months, respectively.

Recurrence was generally determined by CT, magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT) or colonofiberscopy; then, a biopsy was performed whenever feasible. In our present study, AR was defined as tumor growth in the previous anastomotic suture line irrespective of whether it was accompanied by systemic and/or other local recurrence as nodal or regional

Table 1 Clinicopathologic characteristics of the study patients according to AR of colorectal cancer

Clinicopathologic parameters Number of patients and mean ± SE	AR group $n = 53$ (%)	Non-AR group $n = 8971$ (%)	p value
Sex, M/F	39 (73.6)/14 (26.4)	5506 (61.4)/3565 (38.6)	0.069
Age (≤65/>65, years)	27 (50.9)/26 (49.1)	5987 (66.7)/2984 (33.3)	0.015
Preoperative CEA (≤6.0/>6.0, ng/mL)	38 (71.7)/15 (28.3)	7253 (82.4)/1551 (17.6)	0.042
Tumor location			0.027
Colon/rectum	20 (37.7)/33 (62.3)	4750 (52.9)/4221 (47.1)	
Synchronous adenoma	22 (41.5)	3186 (35.5)	0.552
T stage			0.020
T1	1 (1.9)	1042 (11.6)	
T2	4 (7.5)	1350 (15.0)	
T3	44 (83.0)	6004 (66.9)	
T4	4 (7.5)	351 (3.9)	
N stage			<0.001
N0	22 (41.5)	5325 (59.4)	
N1	11 (20.8)	2214 (24.7)	
N2	20 (37.7)	1195 (13.3)	
Grade of differentiation			0.094
WD + MD/PD + MU	45 (84.9)/8 (15.1)	7929 (88.4)/747 (8.3)	
MU	6 (11.3)	377 (4.3)	0.014
LVI	18 (34.0)	1787 (19.9)	0.015
PNI	9 (17.0)	929 (10.4)	0.150
Longest diameter of tumor (≤5/>5, cm)	25 (47.2)/28 (52.8)	6013 (67.1)/2958 (32.9)	0.002
Intraoperative luminal irrigation	48 (90.6)	7924 (88.4)	0.432
Anastomotic leakage	2 (3.8)	105 (1.2)	0.081
Obstruction	3 (5.7)	975 (5.5)	0.965
Tumor perforation	1 (1.9)	130 (1.4)	0.791
Emergency surgery	2 (3.8)	170 (1.9)	0.319
Minimal invasive approach	3 (5.6)	1380 (15.4)	0.054
Number of harvested LN	18.7 (± 1.2)	19.4 (± 0.1)	0.600
PRM [cm, mean (±SE)]	17.5 (± 2.8)	16.2 (± 0.2)	0.578
DRM (<2 cm)	11 (20.8)	1478 (16.5)	0.466
DRM (<1 cm)	5 (9.4)	424 (4.7)	0.132

SE standard error, *N* number, *M* male, *F* female, *CEA* carcinoembryonic antigen, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *MU* mucinous, *LVI* lymphovascular invasion, *PNI* perineural invasion, *LN* lymph node, *PRM* proximal resection margin, *DRM* distal resection margin

recurrence. A diagnosis of AR was confirmed by a colonoscopic biopsy or the resected specimen. A total of 10 cases, who had radiologically recurrent tumors in suture line, were excluded because they were not pathologically confirmed by colonoscopic biopsy or surgery.

Statistical analysis

Categorical variables were compared using a Chi-square test or Fisher's exact test and continuous variables were compared using independent sample t tests. Incidence by during the follow-up period was analyzed using a histogram. Independent RFs associated with AR were determined by multivariate logistic regression analysis. Overall survival rates (OS) are expressed as percentages and were analyzed using the Kaplan–Meier method. Survival curves were compared using the log-rank test. Comparisons of AR tumors and primary tumors were performed using Wilcoxon's signed-rank test. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. All statistically significant factors for improving survival after AR were conducted using multivariate analysis with the Cox proportional hazards regression model with a forward selection of variables.

Table 2 Clinicopathologic characteristics of the study patients according to AR of colon cancer

Clinicopathologic parameters Number of patients and mean ± SE	AR group $n = 20$ (%)	Non-AR group $n = 4750$ (%)	p value
Sex, M/F	14 (70.0)/6 (30.0)	2863 (60.3)/1887 (39.7)	0.376
Age (≤65/>65, years)	8 (40.0)/12 (60.0)	3047 (64.1)/1704 (35.9)	0.025
Preoperative CEA (≤6.0/>6.0, ng/mL,)	13 (65.0)/7 (35.0)	3846 (81.0)/885 (19.0)	0.050
Tumor location			0.373
Right colon (CE, AC, TC)	6 (30.0)	1891 (39.8)	
Left colon (DC, SC)	14 (70.0)	2859 (60.2)	
T stage			0.247
1	0 (0)	529 (11.1)	
2	1 (5.0)	470 (9.9)	
3	17 (85.0)	3440 (72.4)	
4	2 (10.0)	226 (4.8)	
N stage			0.102
0	10 (50.0)	3001 (63.2)	
1	5 (25.0)	1175 (24.7)	
2	5 (25.0)	491 (10.3)	
Grade of differentiation			0.444
WD + MD	17 (85.0)	4174 (87.9)	
PD + MU	3 (15.0)	459 (9.7)	
MU	3 (15.0)	230 (4.9)	0.040
LVI	11 (55.0)	907 (19.1)	<0.001
PNI	7 (35.0)	492 (10.4)	0.001
Intraoperative luminal irrigation	15 (75.0)	4162 (87.6)	0.083
Anastomotic leakage	0 (0)	17 (0.3)	0.789
Obstruction	1 (5)	229 (4.8)	0.971
Tumor perforation	0 (0)	77 (1.6)	0.566
Emergency surgery	0 (0)	170 (1.8)	0.541
Longest diameter of tumor (≤5/>5, cm)	8 (40.0)/12 (60.0)	2725 (57.4)/2025 (42.6)	0.119
Minimal invasive approach	1 (5)	1033 (21.7)	0.098
Number of harvested LN	21.2 (± 2.4)	22.0 (± 0.2)	0.750
Postoperative chemotherapy	14 (70.0)	2581 (54.3)	0.169
PRM [cm, mean (±SE)]	12.3 (± 1.8)	15.9 (± 0.3)	0.379
DRM (<2 cm)	1 (5)	138 (2.9)	0.457
DRM (<1 cm)	0 (0)	32 (0.7)	0.708

SE standard error, *N* number, *M* male, *F* female, *CEA* carcinoembryonic antigen, *CE* Cecum, *AC* ascending colon, *TC* transverse colon, *DC* descending colon, *SC* sigmoid colon, *WD* well differentiated, *MD* moderate differentiated, *PD* poorly differentiated, *MU* mucinous, *LVI* lymphovascular invasion, *PNI* perineural invasion, *LN* lymph node, *PRM* proximal resection margin, *DRM* distal resection margin

Statistical analyses were performed with a dedicated computer software.

Results

Clinicopathologic characteristics of the study patients

Among the 9024 patients included in our present study, 1593 (17.7 %) had systemic recurrences, 284 (3.0 %) had locoregional recurrences and 53 (0.6 %) had ARs. Of 53 ARs, 22 (41.5 %) had concurrent systemic recurrences and 18 (34.0 %) had synchronous local recurrences except ARs. Of the AR cases, three received total colectomy due to multiple polyps or synchronous cancer. There was a significant difference in the AR rate according to tumor location (colon vs. rectum, 0.4 vs. 0.8 %, $p = 0.027$) (Table 1). Although there was no significant difference in differentiation grade between AR and non-AR group, the MU rate was significantly higher in the AR group (11.3 vs. 4.3 %, $p = 0.014$) (Table 1). The colonic AR group

Table 3 Clinicopathologic characteristics of the study patients according to AR of rectal cancer

Clinicopathologic parameters Number of patients and mean ± SE	AR group $n = 33$ (%)	Non-AR group $n = 4221$ (%)	p value
Sex, M/F	25 (75.8)/8 (24.2)	2643 (62.6)/1578 (37.4)	0.121
Age (≤65/>65, years)	19 (57.6)/14 (42.4)	2939 (69.6)/1282 (30.4)	0.135
Preoperative CEA (≤6.0/>6.0, ng/mL)	25 (75.8)/8 (24.2)	3415 (80.9)/806 (19.1)	0.640
Tumor location			0.644
Above reflection/below reflection	11 (33.3)/22 (66.7)	1573 (37.3)/2648(62.7)	
T stage			0.111
1	1 (3.0)	513 (12.1)	
2	3 (9.1)	880 (20.8)	
3	27 (81.8)	2564 (60.7)	
4	2 (6.0)	125 (3.0)	
N stage			<0.001
0	12 (36.4)	2302 (54.5)	
1	6 (18.2)	1061 (25.1)	
2	15 (45.4)	704 (16.7)	
Grade of differentiation			0.078
WD + MD	28 (84.8)	3755 (89.0)	
PD + MU	5 (15.2)	288 (11.0)	
MU	3 (9.1)	147 (3.6)	0.097
Postoperative chemotherapy	19 (57.6)	2122 (50.3)	0.418
Preoperative CCRT	8 (24.2)	1108 (26.2)	0.620
TRG to preoperative CCRT			0.483
Total regression/Near total regression	0/2 (25.0)	123/287 (37.0)	
Moderate regression/Minimal change	5/1 (75.0)	519/179 (63.0)	
Postoperative CCRT	5 (15.2)	1057 (25.0)	0.191
LVI	7 (21.2)	880 (20.8)	0.809
PNI	2 (6.1)	437 (0.9)	0.402
Anastomotic leakage	2 (6.1)	88 (2.1)	0.114
Obstruction	2 (6.1)	266 (5.5)	0.955
Tumor perforation	1 (3.0)	130 (1.3)	0.364
Emergency surgery	2 (6.1)	83 (2.0)	0.094
Longest diameter of tumor (≤5/>5, cm)	17 (51.5)/16 (48.5)	3374 (79.9)/847 (20.1)	<0.001
Minimal invasive approach	2 (6.1)	347 (8.2)	0.999
Number of harvested LN	17.2 (± 1.2)	16.4 (± 0.2)	0.472
PRM [cm, mean (±SE)]	16.4 (± 2.8)	16.6 (± 1.7)	0.950
DRM (<2 cm)	10 (30.3)	1340 (31.7)	0.853
DRM (<1 cm)	5 (15.2)	405 (10.2)	0.892

SE standard error, *N* number, *M* male, *F* female, *CEA* carcinoembryonic antigen, *WD* well differentiated, *MD* moderate differentiated, *PD* poorly differentiated, *MU* mucinous, *CCRT* concurrent chemoradiotherapy, *TRG* tumor regression grade, *LVI* lymphovascular invasion, *PNI* perineural invasion, *LN* lymph node, *PRM* proximal resection margin, *DRM* distal resection margin

($n = 20$) was older ($p = 0.025$), had a higher rate of MU ($p = 0.040$) and significantly higher rates of LVI and PNI ($p < 0.001$ and $p = 0.001$, respectively) than the non-AR group ($n = 4750$) (Table 2). The rectal AR group ($n = 33$) had more advanced N stage and larger tumors ($p < 0.001$ for both) than the non-AR group ($n = 4221$) (Table 3). In addition, pre-/postoperative CCRT and tumor regression grade to preoperative CCRT were not associated with AR ($p = 0.620$, $p = 0.418$ and $p = 0.483$, respectively) and postoperative chemotherapy were not associated with AR (colon and rectum, $p = 0.169$ and $p = 0.418$, respectively).

By multivariate logistic regression model, old age ($p = 0.046$), advanced N stage [N2 vs. N0, $p = 0.003$],

Table 4 Multivariate analyses of significant variables for AR

Factors	Colorectal cancer				Colon cancer				Rectal cancer			
	Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis		
	p	OR	95 % CI	*p*	*p*	OR	95 % CI	*p*	*p*	OR	95 % CI	*p*
Age (years)	0.084			0.046	0.073			0.063	0.295			
≤65		1				1						
>65		1.756	1.010–3.054			2.364	0.954–5.858					
Preop. CEA (ng/mL)	0.052				0.075				0.221			
≤6.0												
>6.0												
T stage	0.060				0.230				0.184			
N stage	<0.001			0.003	0.161				0.014			0.007
N1 versus N0				0.802								0.778
N2 versus N0		2.635	1.396–4.972	0.003						2.967	1.351–6.519	0.007
Tumor location	0.004			0.001								
Colon		1										
Rectum		2.650	1.453–4.832									
Tumor size (cm)	0.003			0.001	0.123				<0.001			<0.001
≤5		1								1		
>5		2.737	1.536–4.877							3.946	1.949–7.992	
MU	0.003			0.026	0.017			0.022	0.043			
Negative		1				1						
Positive		2.762	1.129–6.757			4.418	1.236–15.785					
LVI	0.028				0.001			0.001	0.797			
Negative						1						
Positive						4.325	1.768–10.580					
PNI	0.875				0.022				0.109			
Negative												
Positive												

Preop. CEA preoperative carcinoembryonic antigen, *MU* mucinous, *LVI* lymphovascular invasion, *PNI* perineural invasion

Table 5 Treatment of AR tumors

Treatment of AR tumors	$n = 53$ (%)
Surgery	46 (%)
Curative resection for AR (R0)	21 (39.6)
AR tumor resection with re-anastomosis	9 (17.0)
APR	6 (11.3)
Tumor resection with permanent diversion	5 (9.4)
Total pelvic exenteration	1 (1.9)
Resection for AR with microscopic involvement of resection margin (R1)	8 (15.1)
AR tumor resection with re-anastomosis	3 (5.7)
APR	3 (5.7)
Tumor resection with permanent diversion	2 (3.8)
Palliative surgery (R2)	17 (32.1)
Palliative diversion	10 (18.9)
Tumor resection with permanent diversion	3 (5.7)
Total pelvic exenteration	1 (1.9)
APR	1 (1.9)
AR tumor resection with re-anastomosis	1 (1.9)
Diagnostic laparotomy	1 (1.9)
Chemotherapy for AR	39 (73.6)
Radiotherapy for AR	19 (35.8)

AR anastomotic recurrence, *APR* abdominoperineal resection

rectum ($p = 0.001$), a large tumor ($p = 0.001$) and MU ($p = 0.026$) were independent RFs for AR in CRCs. In colon cancers, MU ($p = 0.022$), LVI ($p = 0.001$) were independent RFs of AR. In rectal cancers, advanced N stage [N2 vs. N0, $p = 0.007$] and a large tumor ($p < 0.001$) were identified as independent RFs for AR (Table 4).

Treatment of AR

Curative resection for ARs was first considered. If ARs seemed non-resectable or patients refused operation, neoadjuvant chemo- and/or radiotherapy were recommended. If tumors were resected, adjuvant chemotherapy and radiotherapy were recommended.

In the AR group, eight (15.1 %) colonic and thirteen (24.5 %) rectal ARs underwent curative resection for AR and ten (18.9 %) are free of disease. Eight (15.1 %) underwent resection with microscopic involvement of the resection margin. There was no statistically significance between tumor location and rate of R0 resection for AR in our study. Seventeen (32.1 %) underwent palliative surgery because of combined systemic recurrences, adjacent organ invasion with the recurrent tumor or severe intraabdominal invasion (Table 5). Seven (13.2 %) did not undergo an operation for AR. Two refused the surgery due to old age,

Table 6 Characteristics of AR tumors and comparison with primary tumors by Wilcoxon's signed-rank test

Clinicopathologic parameters	Acquired specimen *n* (%)	
T stage		
1/2/3/4	1 (2.0)/2 (3.9)/25 (49.0)/23 (45.1)	
N stage		
0/1/2	34 (65.4)/13 (25.0)/5 (9.6)	
M stage		
0/1	33 (56.9)/25 (43.1)	
Differentiation		
WD/MD/PD/MU	3 (6.7)/33 (73.3)/3 (6.7)/6 (13.3)	
LVI	22 (45.7)	
PNI	11 (32.4)	
Clinicopathological parameters	Recurred tumor—primary tumor (Z)	*p* value
T stage	3.654	<0.001
N stage	3.160	0.002
M stage	3.873	<0.001
Differentiation	0.541	0.589
LVI	1.155	0.248
PNI	2.333	0.020

WD well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *MU* mucinous, *LVI* lymphovascular invasion, *PNI* perineural invasion

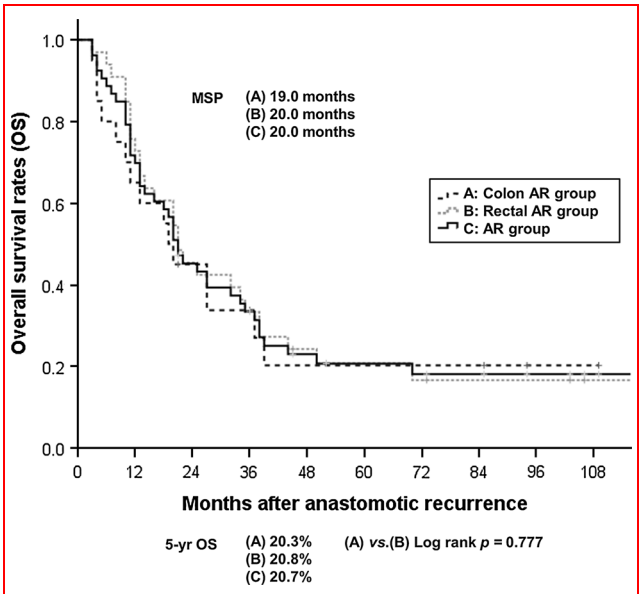

Fig. 1 Overall survival rates of patients in the AR group (colon cancer vs. rectal cancer)

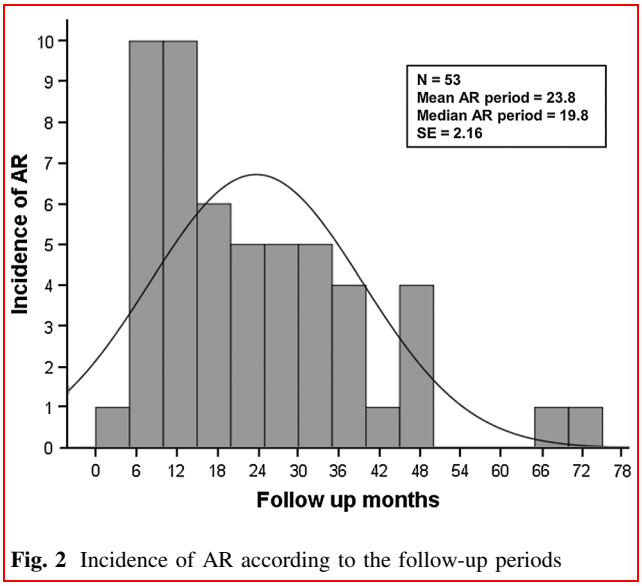

Fig. 2 Incidence of AR according to the follow-up periods

one due to a severe compromised lung resulting from tuberculosis, two were lost during follow-up and two preferred CCRT without surgery. Two underwent multivisceral resection (MVR) as total pelvic exenteration (TPE). Forty-six with surgery for AR showed 22.4 % rate of 5-year OS and 23 months of median survival period (range 1–130). After surgery for AR, one deceased within a month due to intracranial hemorrhage and other two due to pelvic sepsis within 6 months. Nine postoperative ileus and one acute kidney injury occurred within 6 month, and these problems were resolved with conservative treatment. After three pelvic fluid collection and one wound dehiscence occurred within 1 month, percutaneous drainage and reoperation were performed. Two incisional hernias, one stoma prolapse occurred within 6 months and revisions were performed. One had urethral anastomosis site leakage after TPE, and he received glue injection.

Except pathologically confirmed ARs, staging for ARs was retrospectively performed by authors considering intraoperative and radiologic findings. Differentiation, LVI and/or PNI of ARs were able to be collected in some patients. As a result, ARs showed more advanced pathologic stage and a higher rate of PNI ($p = 0.02$) than the primary tumors (Table 6).

Survival

In the AR group, the median survival period was 20.0 months and the 5-year OS was 20.7 % after AR (Fig. 1). There was no significant difference in survival between the colon and rectal AR groups ($p = 0.777$). From the primary tumor operation, 29 (54.7 %) ARs occurred within 2 years and 2 ARs arose after more than 5 years (Figure 2). Two late ARs (later 5 years) occurred following surgery for stage II rectal cancer. Tumor stage was not statistically related with the late AR in our study. By univariate analysis, factors that influenced OS were T and N stage of recurrent tumor ($p = 0.012$ and $p = 0.009$, respectively), curative resection for AR ($p < 0.001$) and adjuvant chemotherapy ($p = 0.047$). However, radiotherapy was not significantly associated with OS. By

Table 7 Univariate analyses and Cox regression analyses of variables for overall survival rates after AR

Factors	Univariate analysis		Multivariate analysis	
	p	HR	95 % CI	*p*
T stage of recurrent tumor	0.012	1.991	0.974–4.071	0.059
N stage of recurrent tumor	0.009	2.339	1.309–4.178	0.004
Curative resection for recurrent tumor	<0.001	0.326	0.139–0.766	0.010
Chemotherapy for recurrent tumor	0.047			0.230
Radiotherapy for recurrent tumor	0.367			

multivariate analysis, advanced N stage of the recurrent tumor ($p = 0.004$) and curative resection ($p = 0.010$) were prognostic factors for survival (Table 7).

Discussion

Pihl et al. [20, 21] previously reported a 2 % AR rate of in 440 colon cancers and another retrospective study reported a 3.5 % AR rate in 282 colon cancers. Recently, Kim et al. [15] described a 4.2 % AR rate for rectal cancer. Our present investigation found AR rates of 0.4 % for colon cancer and 0.8 % for rectal cancer. Our results may have been affected by selection bias, and the fact that only R0 resected patients were enrolled in the present study.

Previous studies have revealed that a left-sided colon, elevated CEA levels, a tumor margin $\leq$2 cm and anastomotic leakage were RFs for AR and that intraoperative luminal irrigation reduced the incidence of AR [4, 15, 22–27]. However, a CEA level, anastomotic leakage and tumor margin were not found to be associated with AR in our present study, and we did not analyze relationship between margin positivity and AR due to inclusion criteria. Moreover, the location of the tumor and intraoperative luminal irrigation were not associated with AR in colon cancer in our current analyses. We found that AR was more associated with rectum than colon. Rectal cancer patients have more frequent chances for tumor manipulation due to narrow pelvic cavity and considerably shorter distal resection margin than colon cancer patients. This in turn may create more chances of intraluminal seeding of exfoliated tumor cells. The independent RFs for rectal ARs were advanced N stage, especially N2 and a large tumor size. The ARs seems likely to be associated with the numbers of exfoliated tumor cells in proportion to the size of the tumor. In addition, large rectal tumors may involve more frequent chances for tumor manipulation due to the narrow nature of the pelvis. Although TME or TMSE reduce local recurrence after rectal cancer surgery, patients who have extensive lymph node metastases like N2 group cases may have metastatic tumor cell deposit in the residual mesorectum or outside of the mesorectal excision plane. This may well be the nidus for AR in the narrow pelvic cavity.

By contrast, we found in our current analysis that independent RFs for colonic ARs were pathologically aggressive factors such as MU and LVI (but not T, N pathologic stage and PNI). Park et al. [28] previously reported that peritoneal metastasis was found more often with the mucinous CRC. John et al. [29] revealed that LVI was associated with adverse locoregional recurrence in colon ($p = 0.002$) but not rectal adenocarcinoma ($p = 0.13$). These pathologic aggressive factors might enable AR to overcome relatively safe resection margin. Interestingly, these factors were not independently associated with rectal ARs in our present study. We have to concede the limited power of our current statistical analysis due to the small number of AR cases analyzed from our single institute. However, it seems that different mechanisms between colonic ARs and rectal ARs may exist and have yet to be clarified.

After surgery, intensive colonoscopy is recommended for CRC surveillance [30, 31]. Our present study findings suggest that rectal cancer patients need to receive more frequently surveillance endoscopy than colon cancer patients. Fortunately, an endoscopy to inspect the suture line is more comfortable in rectal cancer patients. In addition, our present findings suggest that there is a need to shorten the interval of repeated colonoscopy in colon cancer patients who have MU and/or LVI, as well as in rectal cancer patients with N2 pathologic stage and/or large tumors. Furthermore, surveillance colonoscopy is needed as we detected 2 recurrences up to 5 years after surgery in our patient series.

Hallet et al. [32] revealed that neoadjuvant chemotherapy and MVR is a feasible option for the treatment of AR; however, we had no AR patients underwent surgical resection with neoadjuvant chemotherapy for AR. Although William et al. [33] previously reported that en bloc surgical resection with radiotherapy and chemotherapy affords some AR patients for long-term survival, and our current findings indicated that N0 pathologic stage and R0 resection were independent factors for improved survival in ARs. Hence, early detection by strict surveillance and curative resection is recommended to optimize the prognosis of AR patients.

To our knowledge, this current study is the first to compare colon and rectum in terms of the pathophysiology of AR. One potential weakness of our present report is that it was not a randomized controlled study of the clinical relevance of AR. We performed a retrospective, observational cohort study at a single institution that may have been subject to referral and selection bias. Other limitations of our current analysis were the use of clinical TNM staging in cases who received neoadjuvant chemoradiation therapy and the small AR sample size. However, it must be remembered that the incidence of AR was very low. Future multicenter trials can possibly overcome these limitations and produce further meaningful results.

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Compliance with ethical standards

Conflicts of interest The authors declare no competing interests in relation to this study.

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