ORIGINAL

How many times can patients tolerate reoperation for the local recurrence of colorectal cancer in terms of complications?

Koji Komori, Takashi Kinoshita, Yusuke Sato, Akira Ouchi, Seiji Ito, Tetsuya Abe, Kazunari Misawa, Yuichi Ito, Seiji Natsume, Eiji Higaki, Tomonari Asano, Masataka Okuno, Hironori Fujieda, Satoshi Oki, Tsukasa Aritake, Kakeru Tawada, Satoru Akaza, Hisahumi Saito, Kiyoshi Narita, Hiroki Kawabata, and Yasuhiro Shimizu

Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Aichi, Japan

Abstract : The frequency of resection for the recurrence of colorectal cancer has not been investigated in previous studies. Likewise, the related postoperative complications and the limit for indicating surgical resection has not been reported. Herein, we reported the complications of a highly frequent surgical approach for rectal cancer recurrence, i.e., exceeding three reoperations, based on our clinical experience. We included 15 cases exceeding two operations for the local recurrence of colorectal cancer from 2014 to 2019. We examined the postoperative complications classified as Clavien–Dindo IIIb. The positive rates of the complications were 0 (0.0%), 0 (0.0%), 2 (13.3%), 3 (37.5%), and 0 (0.0%) for the primary, 1st recurrent, 2nd recurrent, 3rd recurrent, and 4th recurrent operation group (p = 0.027), respectively. It is important to exercise caution in handling cases exceeding two reoperations (exceeding three reoperations including the primary operation). J. Med. Invest. 70 : 369-376, August, 2023

Keywords **:** *reoperation, local recurrence of colorectal cancer, complications*

INTRODUCTION

We previously reported that frequent and multiple but resectable peritoneal recurrences can be aggressively treated by surgical removal to improve the long-term survival of patients with colorectal cancer (1). Likewise, we aggressively resected recurrent rectal cancer in our hospital when possible (2, 3). Additionally, we reported that ensuring adequate surgical margins prevents the local recurrence of rectal cancer (4).

However, the frequency of resection for recurrent colorectal cancer has not been investigated in previous studies. Likewise, related postoperative complications and the limit for indicating surgical resection has not been reported. Most importantly, the tolerable number of reoperations for patients with locally recurrent colorectal cancer has not been determined in terms of complications.

Herein, we reported the complications of a highly frequent surgical approach for rectal cancer recurrence, i.e., exceeding three reoperations, based on our clinical experience.

METHODS

Study design

Our inclusion criteria included cases exceeding two reoperations for locally recurrent colorectal cancers, i.e., exceeding three reoperations including the initial operation, at the Department of Gastroenterological Surgery, Aichi Cancer Center Hospital from 2014 to 2019. There was no case that we could resect completely before operation but could not resect recurrent lesion intraoperatively. But if unresectable distant recurrent lesion is recognized, we do not select the surgical therapy.

Received for publication January 3, 2023 ; accepted April 20, 2023.

Address correspondence and reprint requests to Koji Komori, Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa, Nagoya, Aichi 464-8681, Japan and Fax : +81-52-763-5233. E-mail : kkomori@aichi-cc.jp

This research project was approved by the Ethics Committee of our institution (2022-0-061) and conformed to the provisions of the Declaration of Helsinki. Comprehensive informed consent was obtained from all patients prior to surgery. Fifteen cases were eligible : six primary operations were performed at our hospital, and nine primary operations were performed at other hospitals. All cases underwent either a high or low anterior resection in the primary operation.

Figure 1 shows the eligible 15 cases. We classified five groups, primary operation group, 1st recurrent operation group, 2nd local recurrent operation group, 3rd local recurrent operation group, and 4th local recurrent operation group with overlapping. Seven cases were "2nd recurrent operation group", i.e., 3 times operations (primary operation + 1st recurrent operation + 2nd recurrent operation). Six cases were "3rd recurrent operation group", i.e., 4 times operations (primary operation + 1st recurrent operation + 2nd recurrent operation + 3rd recurrent operation). Two cases were "4th recurrent operation group", i.e., 5 times operations (primary operation + 1st recurrent operation + 2nd recurrent operation + 3rd recurrent operation + 4th recurrent operation). The number of primary operation group, 1st local recurrent operation group, 2nd local recurrent operation group, 3rd local recurrent operation group, and 4th local recurrent operation group were 15 cases, 15 cases, 15 cases, 8 cases, and 2 cases, respectively.

The surgical procedures included local resection (LR), high anterior resection + low anterior resection (HAR + LAR), abdominoperineal resection (APR), and total pelvic exenteration (TPE). Clinicopathologic factors, such as age, gender (male / femal), operation place (our hospital / another hospital), surgical procedures (LR / HAR + LAR / APR / TPE / others), operative time (minute), operative bleeding (ml), complication (Clavien–Dindo IIIb) (present / absent), and hospital mortality (present / absent) were estimated between operations (primary operation group / 1st local recurrent operation group / 2nd local recurrent operation group / 3rd local recurrent operation group / 4th local recurrent operation group).

Statistical analysis

All data are expressed as the mean ± standard deviation

(S.D.). The chi-squared test and non-parametric test were subsequently performed to identify factors that may influence clinicopathologic variables. The level of statistical significance was set at $p<0.05$.

RESULTS

Table 1 shows the detailed outcomes. The total numbers of LR, HAR+LAR, APR, TPE, and others were 0 (0.0%), 15 (100.0%), 0 (0.0%), 0 (0.0%), and 0 (0.0%) for the primary operation group ; 8 (53.3%), 3 (20.0%), 2 (13.3%), 1 (6.7%), and 1 (6.7%) for the 1st recurrent operation group ; 8 (53.3%), 1 (6.7%), 0 (0.0%), 5 (33.3%), and 1 (6.7%) for the 2nd recurrent operation group ; 7 (77.8%), 0 (0.0%), 0 (0.0%), 1 (1.1%), and 1 (1.1%) for the 3rd recurrent operation group ; and 1 (50.0%), 0 (0.0%), 0 (0.0%), 1 (50.0%), and 0 (0.0%) for the 4th recurrent operation group ($p<0.001$), respectively. The frequency of TPE was grown in the 2nd and 3rd recurrent operation group.

Five patients suffered complications once (Complication

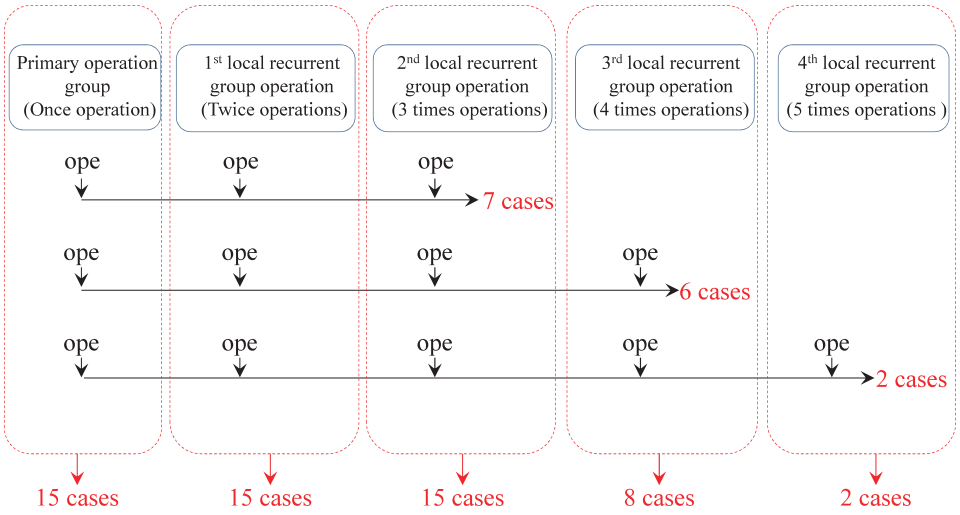

Figure 1. We classified five groups, such as primary operation group (Once operation), 1st local recurrent group operation (Twice operations), 2nd local recurrent group operation (3 times operations), 3rd local recurrent group operation (4 times operations), and 4th local recurrent group operation (5 times operations) with overlapping.

Table 1. The detailed outcomes of clinicopathologic factors

		Primary operation group (n=15)	1st recurrent operation group (n=15)	2nd recurrent operation group (n=15)	3rd recurrent operation group (n=8)	4th recurrent operation group (n=2)	*p*
Age		61.4±7.7	64.7±7.6	66.5±7.6	66.6±7.3	64.0±11.0	0.436
Gender	male	7 (46.7%)	7 (46.7%)	7 (46.7%)	5 (62.5%)	1 (50.0%)	0.953
	female	8 (53.3%)	8 (53.3%)	8 (53.3%)	3 (37.5%)	1 (50.0%)	
Operation place	Our hospital	6 (40.0%)	14 (93.3%)	15 (100.0%)	8 (100.0%)	2 (100.0%)	0.455
	Another hospital	9 (60.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Surgical procedure	LR	0 (0.0%)	8 (53.3%)	8 (53.3%)	6 (75.0%)	1 (50.0%)	<0.0001
	HAR+LAR	15 (100.0%)	3 (20.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	
	APR	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	TPE	0 (0.0%)	1 (6.7%)	5 (33.3%)	1 (12.5%)	1 (50.0%)	
	others	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (12.5%)	0 (0.0%)	
Operative time (min)		371.9±98.7	266.4±112.5	401.8±159.6	434.2±172.6	359.5±655.5	0.072
Operative bleeding (ml)		1396.4±2111.1	876.8±923.6	2573.7±2951.6	2777.8±2499.9	1000.0±800.00	0.219
Complication Clavien–Dindo IIIb	present	0 (0.0%)	0 (0.0%)	2 (13.3%)‡	3 (37.5%)‡	0 (0.0%)	0.027
	absent	15 (100.0%)	15 (100.0%)	13 (86.7%)	5 (62.5%)	2 (100.0%)	
Hospital mortality	present	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
	absent	15 (100.0%)	15 (100.0%)	15 (100.0%)	8 (100.0%)	2 (100.0%)	

(mean±S.D.)

LA : local resection, LAR : low anterior resection of rectum, HAR : high anterior resection of rectum, APR : abdominoperineal resection, TPE : total pelvic exenteration

‡Small intestinal perforation

Clavien–Dindo IIIb), but no patient suffered complications twice. The positive rates of the complications were 0 (0.0%), 0 (0.0%), 2 (13.3%), 3 (37.5%), and 0 (0.0%) for the primary, 1st recurrent, 2nd recurrent, 3rd recurrent, and 4th recurrent operation group (p = 0.027), respectively. A statistically significant difference was observed ; the rate of complications increased with the number of operations.

The operative times of the primary operation group, 1st recurrent operation group, 2nd recurrent operation group, 3rd recurrent operation group, and 4th recurrent operation group were 371.9±98.7, 266.4±112.5, 401.8±159.6, 434.2±172.6, and 359.5±655.5 minutes (p = 0.072), respectively. The number of operations increased with the operative time. However, the 4th recurrent operation had the shortest operative time in 2nd, 3rd, and 4th recurrent operation group.

Operative bleeding from the primary, 1st recurrent operation group, 2nd recurrent operation group, 3rd recurrent operation group, and 4th recurrent operation group were 1396.4±2111.1 ml, 876.8±923.6 ml, 2573.7±2951.6 ml, 2777.8±2499.9 ml, and 1000.0±800.0 ml (p = 0.219), respectively. No statistically significant difference was observed among the primary, 1st recurrent operation group, 2nd recurrent operation group, 3rd recurrent operation group, and 4th recurrent operation group. However, the 4th recurrent operation group had the least operative bleeding.

In terms of age and gender, no statistically significant difference was observed among the primary, 1st recurrent operation group, 2nd recurrent operation group, 3rd recurrent operation group, and 4th recurrent operation group.

There was no hospital mortality in all cases.

There was no relation between the present or absent of neoadjuvant therapy and complications (Clavien–Dindo IIIb). And there was no relation between the laparoscopic surgery or laparotomy of surgical procedure and complications (Clavien–Dindo IIIb). (Table 2)

5-year disease free survival (5y-DFS) from the primary operation was 66.7% and 5-year overall survival rate (5y-OS) from the primary operation was 79.4% (Fig. 2). And 5-year disease free survival (5y-DFS) from the 1st recurrent operation was 33.3% (Fig. 3).

Most complications (Clavien–Dindo IIIb) (5) were raptures and intestinal leakages due to intestinal thinning caused by organ detachment. In 2nd recurrent operation group, the raptures and intestinal leakages occurred on postoperative day (POD) 4 in all cases. In 3rd recurrent operation group, the raptures and intestinal leakages occurred on POD 3 in one case, POD 4 in one case, and POD 42 in one case (Table 3). The detail description of the cases are as follows :

Table 2. The detailed outcomes of clinicopathologic factors

		Primary operation (n = 15)		1st recurrent operation (n = 15)		2nd recurrent operation (n = 15)		3rd recurrent operation (n = 8)		4th recurrent operation (n = 2)	
		Clavien–Dindo IIIb		Clavien–Dindo IIIb		Clavien–Dindo IIIb		Clavien–Dindo IIIb		Clavien–Dindo IIIb	
		present	absent	present	absent	present	absent	present	absent	present	absent
Neoadjuvant therapy	present	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	2 (25.0%)	0 (0.0%)	0 (0.0%)
	absent	0 (0.0%)	15 (100.0%)	0 (0.0%)	14 (%)	2 (13.3%)	11 (73.4%)	3 (37.5%)	3 (37.5%)	0 (0.0%)	2 (100.0%)
	p	–		–		0.5513		0.2059		–	
Surgical procedure	Laparoscopic	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	laparotomy	0 (0.0%)	13 (87.6%)	0 (0.0%)	15 (100.0%)	0 (0.0%)	15 (100.0%)	0 (0.0%)	8 (100.0%)	0 (0.0%)	2 (100.0%)
	p	–		–		–		–		–	

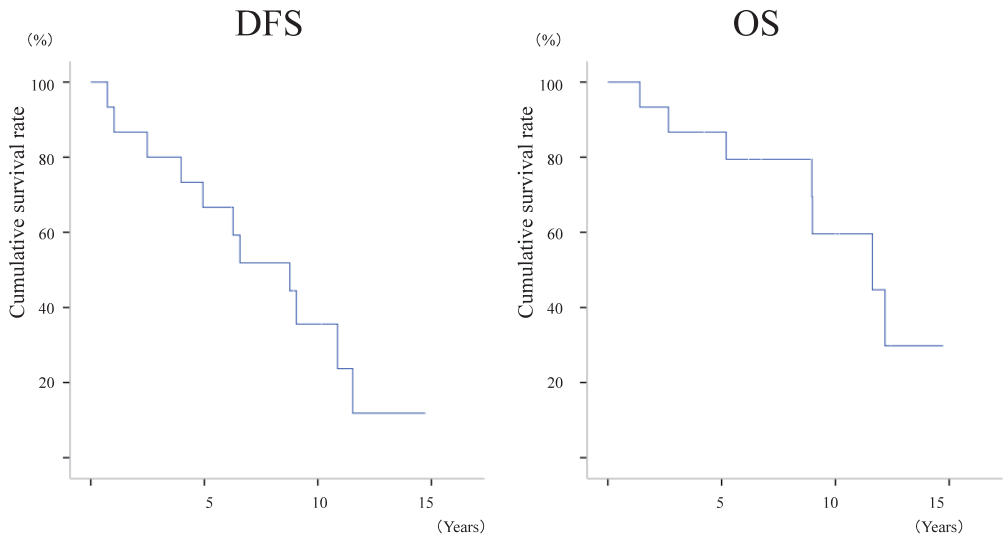

Figure 2. The prognosis from the primary operation
Left side : 5-year disease free survival (5y-DFS) from the primary operation was 66.7%.
Right side : -year overall survival rate (5y-OS) from the primary operation was 79.4%.

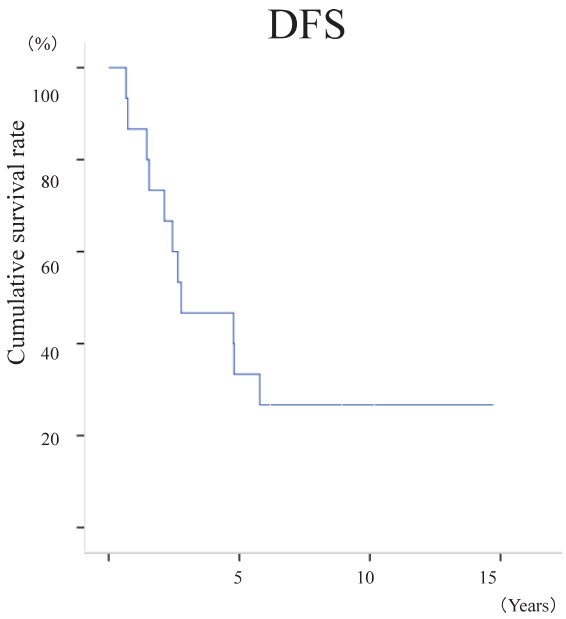

Figure 3. The prognosis from from the 1st recurrent operation 5-year disease free survival (5y-DFS) from the 1st recurrent operation was 33.3%.

Table 3. The onset of complications (Clavien–Dindo IIIb)

	2nd recurrent operation group (n=2)	3rd recurrent operation group (n=3)
POD3	0 (0.0%)	1 (33.3%)
POD4	2 (100.0%)	1 (33.3%)
POD42	0 (0.0%)	1 (33.3%)

Case 1

A 63-year-old male with a history of lower abdominal distension and a cancer pathological status of stage I : T1aN0M0 (6) underwent LAR as a primary operation at another hospital in February 2008. However, the patient had a local recurrence on the coccyx, with an approximate diameter of 2 cm and lymph node metastasis in the bifurcation of the common iliac artery. The patient underwent APR as the 1st recurrent operation at another hospital in November 2014, as well as postoperative adjuvant chemotherapy with capecitabine (7). The patient had a 2nd local recurrence on the sacrum without distant recurrence upon examination at another hospital in December 2015.

The patient was referred to our hospital and underwent TPE with sacrum (S5) resection as the 2nd recurrent operation in March 2016. The pathological finding was adenocarcinoma of the lymph node with no cancer in the surgical margin of the resected sacrum. However, in July 2016, the patient had a 3rd local recurrence on the residual sacrum without distant recurrence. Subsequently, radiation therapy (45 Gy/18 Fr) followed by chemotherapy with eight cycles of intravenous S-1 and oxaliplatin (SOX) (8) were administered. In May 2018, an ileal conduit was exteriorized to the skin, i.e., cutaneous fistula. Subsequently, a bilateral percutaneous nephrostomy tube was placed in the lumbar area, and 40 cycles of intravenous folinic acid plus irinotecan (FOLFIRI) were administered (9). However, in March 2019 the size of the locally recurrent tumor increased.

Surgical technique

In April 2019 the patient underwent resection of the sacrum (S3), ileal conduit, and a part of the ileum as the 3rd recurrent operation (Fig. 4). The ileum was reconstructed by an Albert–Lembert end-to-end anastomosis.

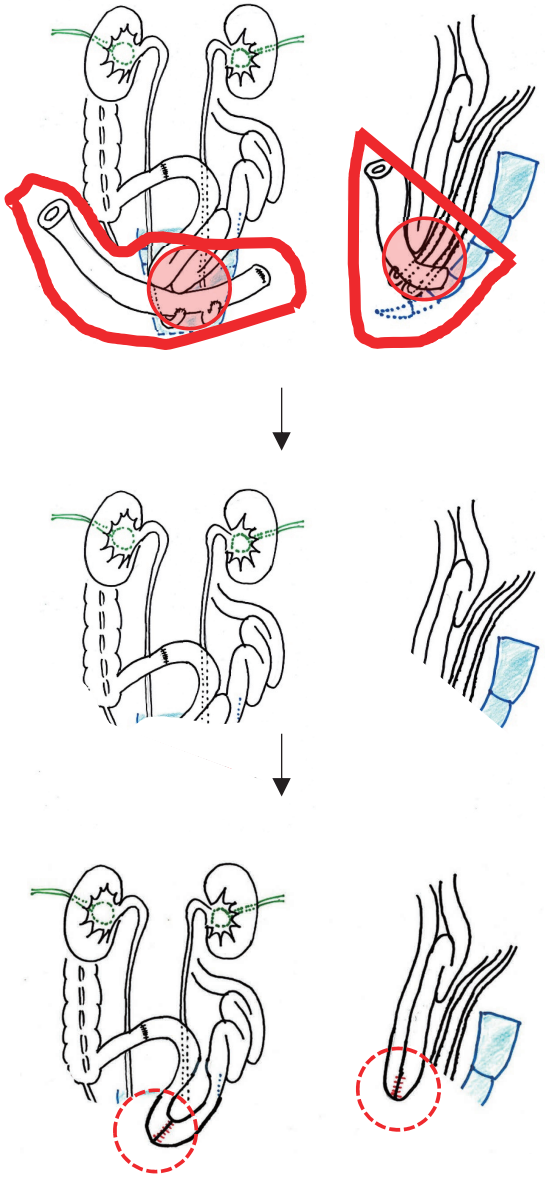

Figure 4. Upper and middle side : For the 3rd recurrent operation, the patient underwent sacrum resection (S3), ileal conduit creation (red circle : the locally recurrent tumor, red thick frame : the resected area), and partial ileum resection to remove the locally recurrent tumor
Lower side : Ileum reconstruction by Albert–Lembert end-to-end anastomosis (red dotted circle)

Surgical technique for the complication

POD 3, the ileum-to-ileum anastomosis leaked. An emergent operation was performed : the patient underwent an ileostomy at the oral side of the leakage and drainage (Fig. 5).

On POD 33, diffuse peritonitis occurred, perforating the ileum and left ureter. An emergent operation was performed : the

patient underwent a side-to-end anastomosis of the jejunum and transverse colon and ligation of the left ureter (Fig. 6).

On POD 90, a computed tomography (CT) scan revealed a pseudoaneurysm in the right common iliac artery (Fig. 7). Embolization of the right internal iliac artery was performed using coils (Fig. 8). The postoperative course was uneventful.

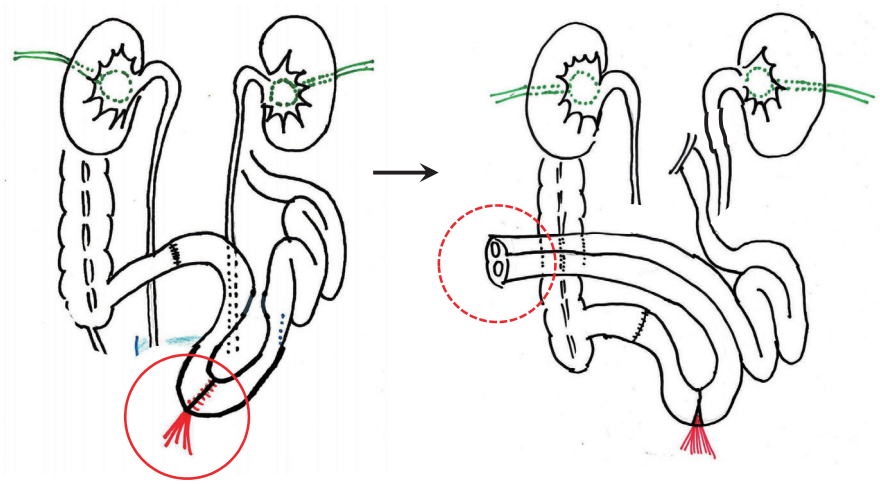

Figure 5. Left side : Leakage from the ileum-to-ileum anastomosis (red circle).
Right side : An emergent operation was performed : the patient underwent ileostomy at the oral side of the leakage and drainage (red dotted circle)

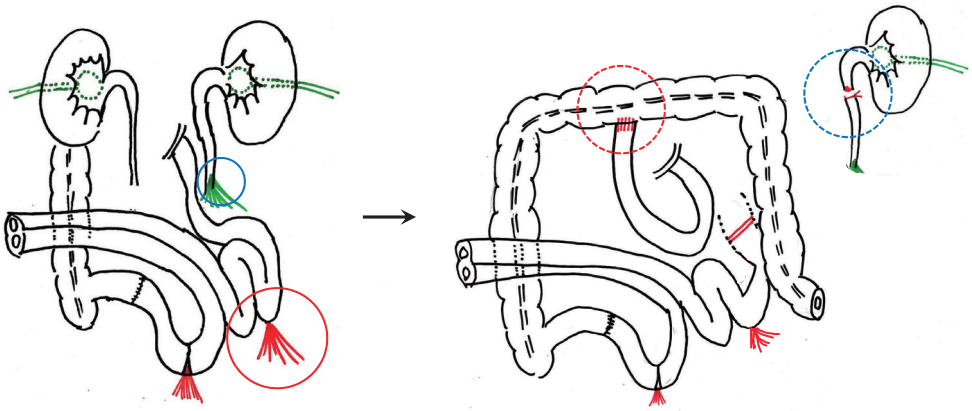

Figure 6. Left side : Diffuse peritonitis (red circle) perforating the ileum and left ureter (blue circle)
Right side : An emergent operation was performed : the patient underwent a side-to-end anastomosis of the jejunum and transverse colon (red dotted circle) and left ureter ligation (blue dotted circle)

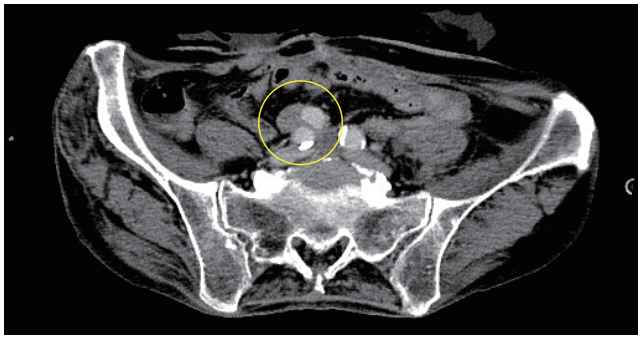

Figure 7. A CT scan revealed a pseudoaneurysm in the right common iliac artery (yellow circle)

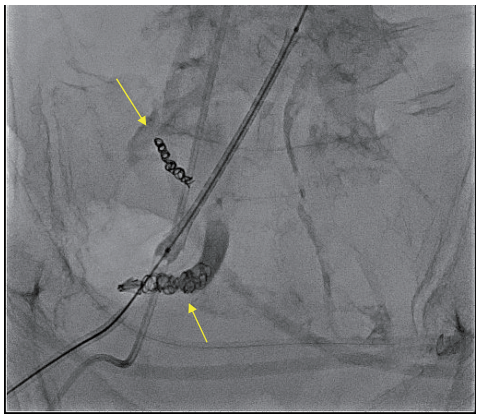

Figure 8. Embolization of the right internal iliac artery was performed using coils (yellow arrow)

Case 2

A 61-year-old female with a history of lower abdominal pain and a cancer pathological status of stage IIIC : T2N3M0 underwent LAR with lateral pelvic lymph node dissection. The primary operation was performed at our hospital in September 2010. We administered adjuvant chemotherapy with four cycles of modified intravenous FOLFOX (10). In May 2018, a CT scan detected a single, left lateral lymph node recurrence. For the 1st recurrent operation, the recurrent lymph node was excised in the left lateral obturator area through an intra and extraperitoneal approach. The patient rejected the subsequent chemotherapy administration. In February 2019, a positron emission tomography (PET) scan revealed a single, left lateral lymph node recurrence.

Surgical technique

For the 2nd recurrent operation, we excised the 2nd recurrent lymph node in the left lateral obturator area by partially resecting the ileum. The maximum diameter of the 2nd locally recurrent tumor was approximately 2 cm.

Surgical technique for the complication

On POD 4, the patient remained febrile, and diffuse peritonitis occurred. An emergent operation was performed. The operative findings indicated that intestinal juice flowed out through the ileal perforation. The perforation was sutured, and drainage tubes were placed. The postoperative course was uneventful.

Case 3

A 48-year-old female with a history of lower abdominal pain and a cancer pathological status of stage IIIC : T2N3M0 underwent LAR as a primary operation at another hospital in September 2010. Adjuvant chemotherapy (SOX) was also administered.

In February 2015, a single, left lateral lymph node recurrence was detected, and the patient was referred to our hospital. A PET scan revealed that the locally recurrent tumor was approximately 2 cm in diameter and was located on the left common iliac artery. For the 1st recurrent operation, we excised the recurrent lymph node on the left common iliac artery.

Surgical technique

In July 2015, A CT scan detected the 2nd locally recurrent tumor on the left ureter. For the 2nd recurrent operation, we performed LAR and left nephrectomy with left ureter resection and covering ileostomy formation.

Surgical technique for the complication

On POD 4, the patient complained of severe abdominal pain, and a CT scan revealed a significant amount of free air in the abdomen. An emergent operation was performed. The operative findings indicated that intestinal juice flowed out through the ileal perforation approximately 150 cm from the ileocecal valve. The perforation was sutured, and drainage tubes were placed. The postoperative course was uneventful.

Case 4

A 58-year-old male with a cancer pathological status of stage IIIB : T4aN1M0 underwent HAR as a primary operation at another hospital in December 2012. The patient was started on postoperative adjuvant chemotherapy with capecitabine plus oxaliplatin (CapeOX) (11) ; however, the treatment had side effects and was subsequently discontinued.

In February 2016, CT and PET scans revealed local recurrence. For the 1st recurrent operation, the patient underwent excision of the locally recurrent tumor and partial resection of the bladder, descending colon, and ileum. The operative finding indicated that the locally recurrent tumor was located in among the bladder, descending colon, and ileum.

In December 2017, CT and PET scans revealed the 2nd local recurrence. For the 2nd recurrent operation, the patient underwent excision of the locally recurrent tumor and partial resection of the bladder and ileum. The operative finding indicated that the 2nd locally recurrent tumor was located between the bladder and ileum.

In December 2018, CT and PET scans revealed the 3rd local recurrence. The patient was preoperatively catheterized with double-J stents for palpating the ureters easily during the 3rd recurrent operation (2). The operative finding indicated that the three locally recurrent tumors were located between the bladder and ileum.

Surgical technique

The patient underwent excision of three locally recurrent tumors with partial resection of the bladder and ileum. The maximum diameters of the three locally recurrent tumors were approximately 4 cm, 2 cm, and 2 cm.

Surgical technique for the complication

On POD 4, the patient complained of severe abdominal pain and became febrile. An emergent operation was performed. The operative finding indicated a leakage in a longitudinal fissure along the ileum, particularly on the anastomotic site. The diameter of the hole through which the leakage occurred was extremely small, making closure difficult. The drainage tubes were placed in the intraperitoneal space. The postoperative course was uneventful.

Case 5

A 74-year-old female with a cancer pathological status of stage IIa : T3N0M0 underwent LAR as a primary operation in July 2019. Subsequently, an anastomotic stricture and a rectovaginal fistula formed. These were not treated conservatively. The resection of anastomotic stricture and reanastomosis of the colon-anus were performed on October 2019. The histopathological diagnosis revealed adenocarcinoma in the anastomotic stricture line. The 1st recurrent operation was performed on the 1st locally recurrent tumor.

The 2nd locally recurrent tumor was found in the dorsal side of the anastomosis. An endoscopic ultrasound-guided fine needle aspiration of the tumor revealed adenocarcinoma. In February 2020, the patient underwent TPE as the 2nd recurrent operation. The operative finding indicated that the tumor was in two portions of the small intestine. Subsequently, inflammation of the pelvic dead space persisted and was managed conservatively. The patient consistently rejected chemotherapy.

In May 2020, the 3rd locally recurrent tumor was detected on the sacrum. It may have invaded the sacrum directly.

Surgical technique

In May 2020, TPE with sacral resection was attempted ; however, the tumor occupied a significant portion of the small intestine. Additionally, a complete resection entails resecting a significant portion of the small intestine, resulting in short bowel syndrome. In this regard, exploratory laparotomy was selected as the 3rd recurrent operation.

Surgical technique for the complication

On POD 4, intestinal juice flowed through the drainage tube, suggesting small intestinal perforation. However, the patient did not become febrile and did not complain of abdominal pain because the drainage was extremely effective. A conservative follow up was undertaken for a short period but with no improvement. In July 2020, the patient underwent a side-to-end

anastomosis of the jejunum and transverse colon. The postoperative course was uneventful.

DISCUSSION

The 2019 JSCCR guidelines recommend resection for the local recurrence of rectal cancer when R0 resection is possible (12). Many previous studies have reported cases of recurrent lesion resection and their corresponding prognoses (13), particularly that of hepatic, para-aortic lymph node, and peritoneal metastases secondary to colorectal cancer (14-16).

In previous years, chemotherapy had little to no effect. Thus, most cases of colorectal cancer recurrence were aggressively treated through surgery. However, in recent years, significant advancements have been made in colorectal cancer chemotherapy, making it an ideal alternative to surgical treatment. Additionally, reoperation for the local recurrence of colorectal cancer is difficult due to organ adhesion. As such, most surgeons do not select this option. Nevertheless, choosing between chemotherapy and surgery for the frequent recurrence of colorectal cancer remains debatable. If chemotherapy was ineffective, the patient was unable to receive the treatment, and severe side effects occurred in relation to the treatment, then surgery could be the next choice of treatment. The data from this study was invaluable in selecting the treatment method for colorectal cancer recurrence.

Previous studies have not explored repeated resection for the local recurrence of colorectal cancer. Further, the 2nd and 3rd recurrence of rectal cancer cannot be determined without distant recurrence, when R0 resection is possible. Additionally, the tolerable number of reoperations for patients with locally recurrent colorectal cancer has not been determined in terms of complications. Thus, elucidating complications from frequent reoperation is highly significant.

In this study, the prognoses were not investigated. Few surgeons aggressively performed frequent reoperation because few participants were eligible for the operation and the cases were of various stages, making statistical analysis difficult. Thus, analyzing the prognoses may not be possible in the future.

Additionally, no apparent evidence supports the superiority of either surgery or chemotherapy over the other in the local recurrence of colorectal cancers. Both reoperations and recurrent cases referred for surgical treatment are very few. Thus, conducting a prospective study to investigate the local recurrence of colorectal cancer is difficult.

Complications (Clavien–Dindo IIIb) were more frequent in the 2nd recurrent operation than in the 1st recurrent operation because the degree of adhesion was more severe in the 2nd recurrent operation than in the 1st recurrent operation. Similarly, the complications (Complication Clavien–Dindo IIIb) were more frequent in the 3rd recurrent operation than in the 2nd recurrent operation because the degree of adhesion was more severe in the 3rd recurrent operation than in the 2nd recurrent operation.

Likewise, the 2nd recurrent operation had a longer operative time and more severe operative bleeding than the 1st recurrent operation, and the 3rd recurrent operation had a longer operative time and more severe operative bleeding than the 2nd recurrent operation because the 3rd recurrent operation had the most severe degree of adhesion among all recurrent operations.

In contrast, the 4th recurrent operation had no complications (Clavien–Dindo IIIb). Further, it had a shorter operative time and milder operative bleeding than the 1st, 2nd, and 3rd recurrent operations. However, this outcome is expected in cases exceeding 5 resections (6 resections including the primary operation) because the 4th recurrent operation does not usually involve severe adhesion.

The diverting (covering) ileostomy is prevent leakage of anastomosis, but in the case of frequent operation, the lesion of the diverting (covering) ileostomy will be made on the upper small intestine, thus we do not intentionally make the diverting (covering) ileostomy.

It is important to exercise caution in handling "2nd recurrent operation group", "3rd recurrent operation group", and "4th recurrent operation group" to prevent complications (Clavien–Dindo IIIb).

ACKNOWLEDGEMENTS

The authors have no conflicts of interest to disclose and received no financial support for this report.

ETHICAL STATEMENTS

The Ethics Committee of Aichi Cancer Center Hospital approved this manuscript and agreed to submission to The Journal of Medical Investigation. The subject gave informed consent, and patient anonymity was preserved.

REFERENCES

1. Komori K, Kinoshita T, Taihei O, Ito S, Abe T, Senda Y, Misawa K, Ito Y, Uemura N, Natsume S, Kawakami J, Ouchi A, Tsutsuyama M, Hosoi T, Shigeyoshi I, Akazawa T, Hayashi D, Tanaka H, Shimizu Y : Aggressive resection of frequent peritoneal recurrences in colorectal cancer contributes to long-term survival. Nagoya J Med Sci 78(4) : 501-506, 2016
2. Komori K, Suda H, Kinoshita T, Sato Y, Ouchi A, Shimizu Y : Resection of the external iliac artery with axillofemoral bypass for local recurrence of rectal cancer. Tech Coloproctol 25(12) : 1329-1331, 2021
3. Komori K, Kinoshita T, Sato Y, Ouchi A, Ito S, Abe T, Misawa K, Ito Y, Natsume S, Higaki E, Okuno M, Fujieda H, Shoji K, Kunitomo A, Oki S, Maeda S, Nagao T, Aritake T, Tawada K, Akaza S, Shimizu Y : Repair of antegrade anastomosis between ileal segment and amputated ureter for recurrent rectal cancer. Clin J Gastroenterol 14(6) : 1687-1691, 2021
4. Komori K, Kimura K, Kinoshita T, Ito S, Abe T, Senda Y, Misawa K, Ito Y, Uemura N, Natsume S, Kawakami J, Iwata Y, Tsutsuyama M, Shigeyoshi I, Akazawa T, Hayashi D, Shimizu Y : Adequate Margins to Prevent Local Re-recurrence of Rectal Cancer : Viewpoint of Pathological Findings. Anticancer Res 35(12) : 6747-54, 2015
5. Dindo D, Demartines N, Clavien PA : Classification of surgical complications : a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240(2) : 205-13, 2004
6. Japanese Research Society for Cancer of the Colon and Rectum : General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus. 9th ed, revised version. Tokyo, Japan : Kanahara Shuppan : 2019
7. Hamaguchi R, Tsuchiya T, Miyata G, Sato T, Takahashi K, Miura K, Oshio H, Ohori H, Ariyoshi K, Oyamada S, Iwase S : Efficacy of oral administration of cystine and theanine in colorectal cancer patients undergoing capecitabine-based adjuvant chemotherapy after surgery : a multi-institutional, randomized, double-blinded, placebo-controlled, phase II

trial (JORTC-CAM03). Support Care Cancer 28(8) : 3649-3657, 2020
8. Yamada Y, Takahari D, Matsumoto H, Baba H, Nakamura M, Yoshida K, Yoshida M, Iwamoto S, Shimada K, Komatsu Y, Sasaki Y, Satoh T, Takahashi K, Mishima H, Muro K, Watanabe M, Sakata Y, Morita S, Shimada Y, Sugihara K : Leucovorin, fluorouracil, and oxaliplatin plus bevacizumab versus S-1 and oxaliplatin plus bevacizumab in patients with metastatic colorectal cancer (SOFT) : an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol 14 : 1278-1286, 2013
9. Muro K, Boku N, Shimada Y, Tsuji A, Sameshima S, Baba H, Satoh T, Denda T, Ina K, Nishina T, Yamaguchi K, Takiuchi H, Esaki T, Tokunaga S, Kuwano H, Komatsu Y, Watanabe M, Hyodo I, Morita S, Sugihara K : Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer : a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol 11(9) : 853-60, 2010
10. Inaba Y, Yamaura H, Sato Y, Najima M, Shimamoto H, Nishiofuku H, Ura T, Muro K : Central venous access port-related complications in outpatient chemotherapy for colorectal cancer. Jpn J Clin Oncol 37(12) : 951-4, 2007
11. Iwai M, Kimura M, Usami E, Yoshimura T, Teramachi H : Pharmaco-economic analysis of adjuvant chemotherapy for stage II and III colorectal cancer. Mol Clin Oncol 6(5) : 794-798, 2017
12. Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajioka Y, Hamaguchi T, Hasegawa K, Hotta K, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kinugasa Y, Murofushi K, Nakajima TE, Oka S, Tanaka T, Taniguchi H, Tsuji A, Uehara K, Ueno H, Yamanaka T, Yamazaki K, Yoshida M, Yoshino T, Itabashi M, Sakamaki K, Sano K, Shimada Y, Tanaka S, Uetake H, Yamaguchi S, Yamaguchi N, Kobayashi H, Matsuda K, Kotake K, Sugihara K : Japanese Society for Cancer of the Colon and Rectum : Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 25(1) : 1-42, 2020
13. Nakai N, Yamaguchi T, Kinugasa Y, Shiomi A, Kagawa H, Yamakawa Y, Numata M, Furutani A : Long-term outcomes after resection of para-aortic lymph node metastasis from left-sided colon and rectal cancer. Int J Colorectal Dis 32(7) : 999-1007, 2017
14. Sahara K, Watanabe J, Ishibe A, Suwa Y, Suwa H, Ota M, Kunisaki C, Endo I : Long-term outcome and prognostic factors for patients with para-aortic lymph node dissection in left-sided colorectal cancer. Int J Colorectal Dis 34(6) : 1121-1129, 2019
15. Komori K, Kinoshita T, Oshiro T, Ouchi A, Ito S, Abe T, Senda Y, Misawa K, Ito Y, Natsume S, Higaki E, Okuno M, Hosoi T, An B, Hayashi D, Uchino T, Kunitomo A, Oki S, Takano J, Suenaga Y, Maeda S, Dei H, Numata Y, Shimizu Y : Prognostic predictions based on pathological findings of peritoneal dissemination in patients with stage IV colorectal cancer without residual disease (R0 status). Surg Today 49(9) : 755-761, 2019
16. Saiura A, Yamamoto J, Hasegawa K, Koga R, Sakamoto Y, Hata S, Makuuchi M, Kokudo N : Liver resection for multiple colorectal liver metastases with surgery up-front approach : bi-institutional analysis of 736 consecutive cases. World J Surg 36(9) : 2171-8, 2012