

## ORIGINAL

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

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**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, 1<sup>st</sup> recurrent, 2<sup>nd</sup> recurrent, 3<sup>rd</sup> recurrent, and 4<sup>th</sup> 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.

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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, 1<sup>st</sup> recurrent operation group, 2<sup>nd</sup> local recurrent operation group, 3<sup>rd</sup> local recurrent operation group, and 4<sup>th</sup> local recurrent operation group with overlapping. Seven cases were “2<sup>nd</sup> recurrent operation group”, i.e., 3 times operations (primary operation + 1<sup>st</sup> recurrent operation + 2<sup>nd</sup> recurrent operation). Six cases were “3<sup>rd</sup> recurrent operation group”, i.e., 4 times operations (primary operation + 1<sup>st</sup> recurrent operation + 2<sup>nd</sup> recurrent operation + 3<sup>rd</sup> recurrent operation). Two cases were “4<sup>th</sup> recurrent operation group”, i.e., 5 times operations (primary operation + 1<sup>st</sup> recurrent operation + 2<sup>nd</sup> recurrent operation + 3<sup>rd</sup> recurrent operation + 4<sup>th</sup> recurrent operation). The number of primary operation group, 1<sup>st</sup> local recurrent operation group, 2<sup>nd</sup> local recurrent operation group, 3<sup>rd</sup> local recurrent operation group, and 4<sup>th</sup> 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 / female), 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 / 1<sup>st</sup> local recurrent operation group / 2<sup>nd</sup> local recurrent operation group / 3<sup>rd</sup> local recurrent operation group / 4<sup>th</sup> local recurrent operation group).

### *Statistical analysis*

All data are expressed as the mean  $\pm$  standard deviation

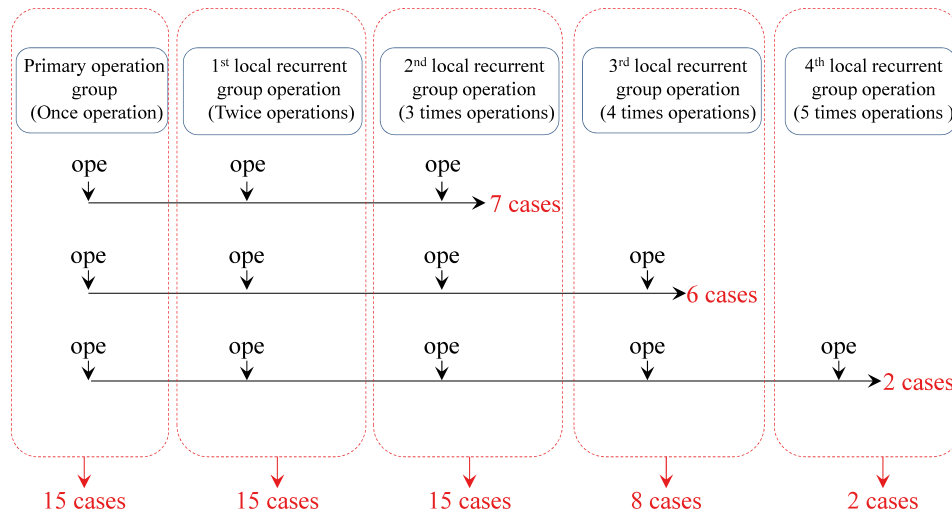
(S.D.). The chi-squared test and non-parametric test were subsequently performed to identify factors that may influence clinicopathologic variables. The level of statistical significance was set at  $p < 0.05$ .

**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 1<sup>st</sup> recurrent operation group ; 8 (53.3%), 1 (6.7%), 0 (0.0%), 5 (33.3%), and 1 (6.7%) for the 2<sup>nd</sup> recurrent operation group ; 7 (77.8%), 0 (0.0%), 0 (0.0%), 1 (1.1%), and 1 (1.1%) for the 3<sup>rd</sup> recurrent operation group ; and 1 (50.0%), 0 (0.0%), 0 (0.0%), 1 (50.0%), and 0 (0.0%) for the 4<sup>th</sup> recurrent operation group ( $p < 0.001$ ), respectively. The frequency of TPE was grown in the 2<sup>nd</sup> and 3<sup>rd</sup> recurrent operation group.

Five patients suffered complications once (Complication



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

**Table 1.** The detailed outcomes of clinicopathologic factors

		Primary operation group (n = 15)	1 <sup>st</sup> recurrent operation group (n = 15)	2 <sup>nd</sup> recurrent operation group (n = 15)	3 <sup>rd</sup> recurrent operation group (n = 8)	4 <sup>th</sup> 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%) <sup>‡</sup>	3 (37.5%) <sup>‡</sup>	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

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

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

In terms of age and gender, no statistically significant difference was observed among the primary, 1<sup>st</sup> recurrent operation group, 2<sup>nd</sup> recurrent operation group, 3<sup>rd</sup> recurrent operation group, and 4<sup>th</sup> 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 1<sup>st</sup> 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 2<sup>nd</sup> recurrent operation group, the raptures and intestinal leakages occurred on postoperative day (POD) 4 in all cases. In 3<sup>rd</sup> 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)		1 <sup>st</sup> recurrent operation (n = 15)		2 <sup>nd</sup> recurrent operation (n = 15)		3 <sup>rd</sup> recurrent operation (n = 8)		4 <sup>th</sup> 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%)
	<i>p</i>	–		–		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%)
	<i>p</i>	–		–		–		–		–	

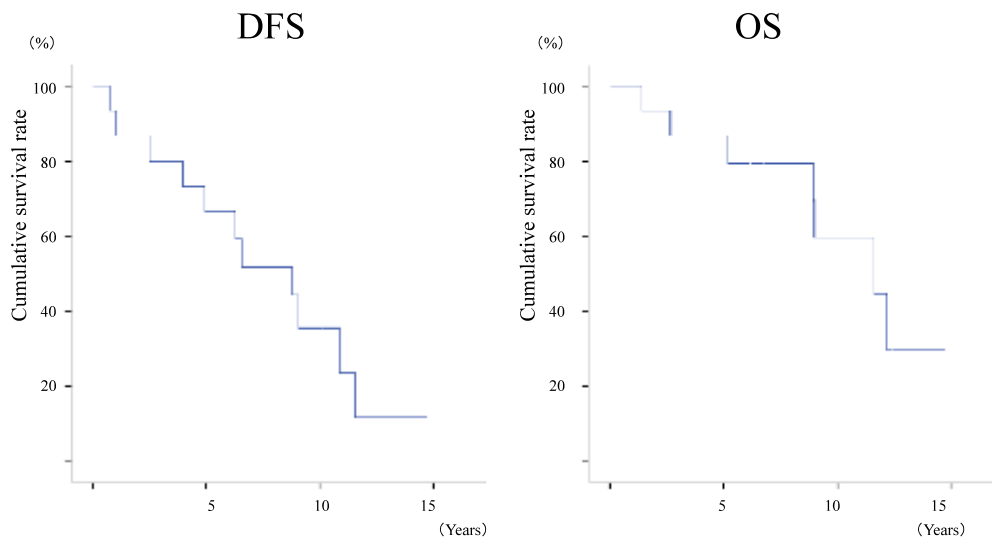
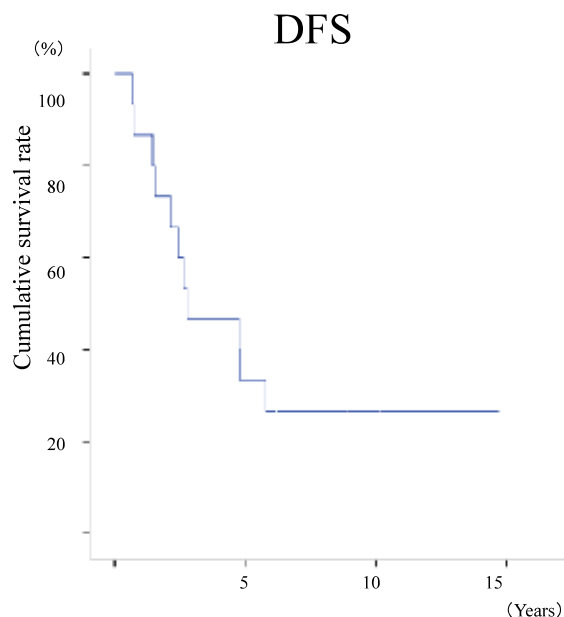


Figure 2. The prognosis from the primary operation  
 Left side : 5-year disease free survival (5y-DFS) from the primary operation was 66.7%.  
 Right side : 5-year overall survival rate (5y-OS) from the primary operation was 79.4%.



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

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

	2 <sup>nd</sup> recurrent operation group (n=2)	3 <sup>rd</sup> 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%)

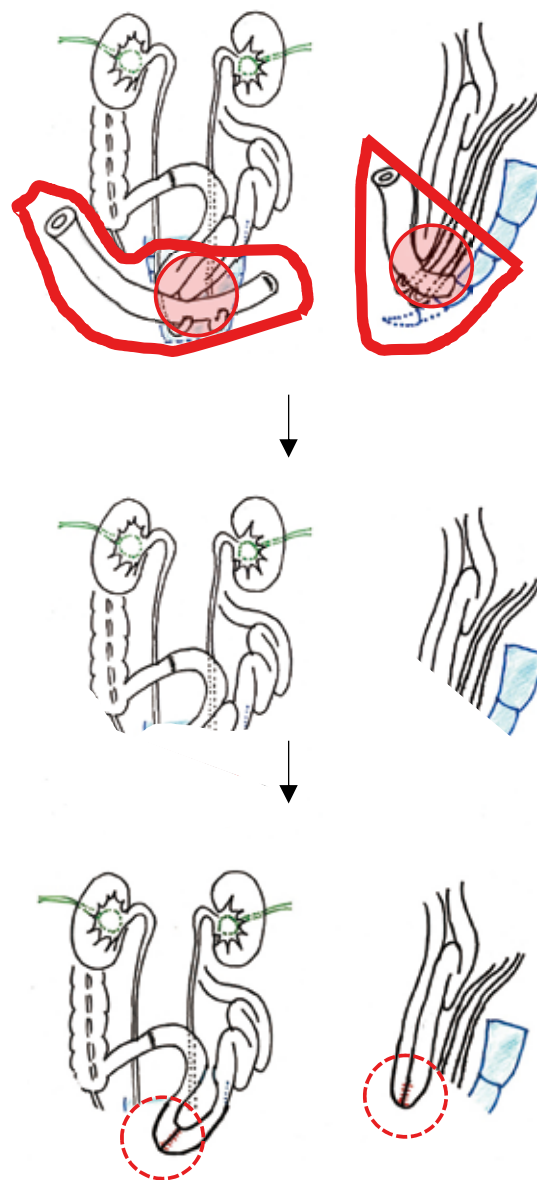
### Case 1

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 1<sup>st</sup> recurrent operation at another hospital in November 2014, as well as postoperative adjuvant chemotherapy with capecitabine (7). The patient had a 2<sup>nd</sup> 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 2<sup>nd</sup> 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 3<sup>rd</sup> 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 3<sup>rd</sup> recurrent operation (Fig. 4). The ileum was reconstructed by an Albert–Lembert end-to-end anastomosis.



**Figure 4.** Upper and middle side : For the 3<sup>rd</sup> 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.

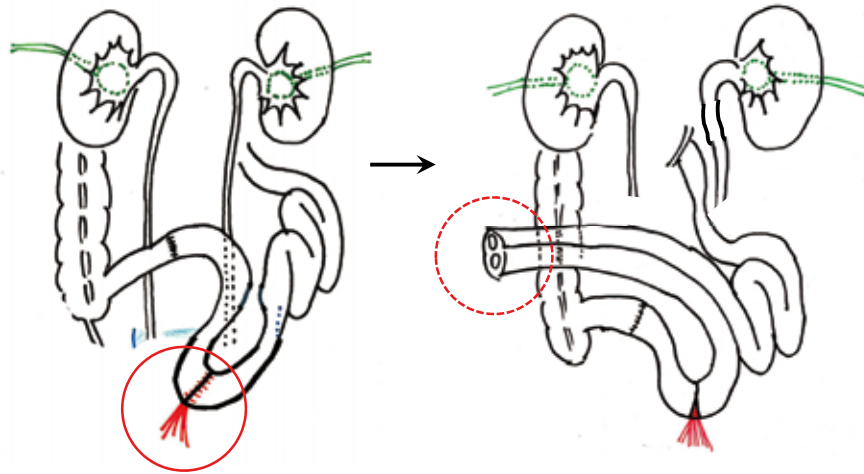


Figure 5. Left side : Leakage from the ileum-to-ileum anastomosis (red circle). Right side : An emergent operation was performed : the patient underwent ileostomy at the oral side of the leakage and drainage (red dotted circle)

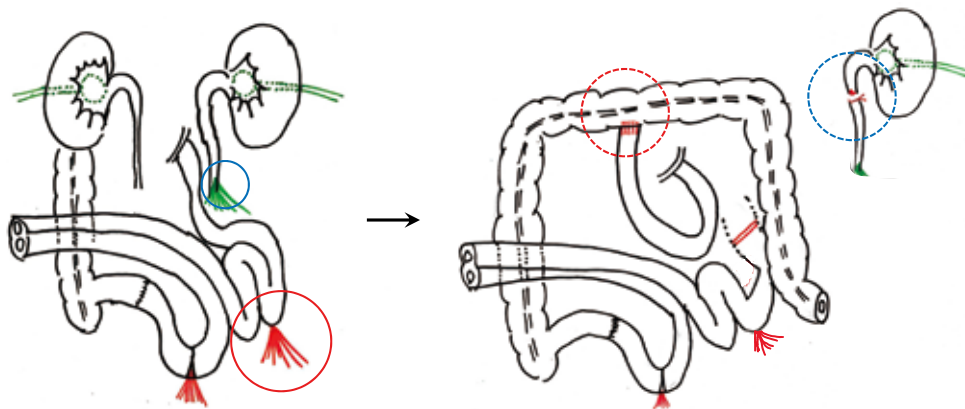


Figure 6. Left side : Diffuse peritonitis (red circle) perforating the ileum and left ureter (blue circle) Right side : An emergent operation was performed : the patient underwent a side-to-end anastomosis of the jejunum and transverse colon (red dotted circle) and left ureter ligation (blue dotted circle)

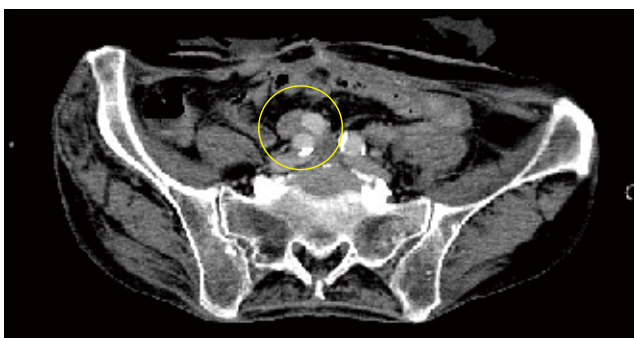


Figure 7. A CT scan revealed a pseudoaneurysm in the right common iliac artery (yellow circle)

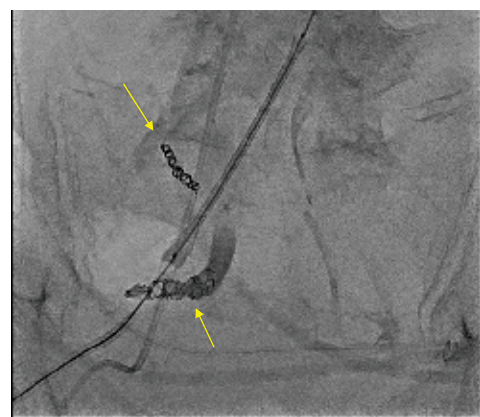


Figure 8. Embolization of the right internal iliac artery was performed using coils (yellow arrow)

**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 1<sup>st</sup> 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 2<sup>nd</sup> recurrent operation, we excised the 2<sup>nd</sup> recurrent lymph node in the left lateral obturator area by partially resecting the ileum. The maximum diameter of the 2<sup>nd</sup> 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 1<sup>st</sup> recurrent operation, we excised the recurrent lymph node on the left common iliac artery.

*Surgical technique*

In July 2015, A CT scan detected the 2<sup>nd</sup> locally recurrent tumor on the left ureter. For the 2<sup>nd</sup> 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 1<sup>st</sup> 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 2<sup>nd</sup> local recurrence. For the 2<sup>nd</sup> 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 2<sup>nd</sup> locally recurrent tumor was located between the bladder and ileum.

In December 2018, CT and PET scans revealed the 3<sup>rd</sup> local recurrence. The patient was preoperatively catheterized with double-J stents for palpating the ureters easily during the 3<sup>rd</sup> 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 1<sup>st</sup> recurrent operation was performed on the 1<sup>st</sup> locally recurrent tumor.

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

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

In contrast, the 4<sup>th</sup> recurrent operation had no complications (Clavien–Dindo IIIb). Further, it had a shorter operative time and milder operative bleeding than the 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> recurrent operations. However, this outcome is expected in cases exceeding 5 resections (6 resections including the primary operation) because the 4<sup>th</sup> 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 “2<sup>nd</sup> recurrent operation group”, “3<sup>rd</sup> recurrent operation group”, and “4<sup>th</sup> recurrent operation group” to prevent complications (Clavien–Dindo IIIb).

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## 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.

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