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ORIGINAL ARTICLE

Retrospective Study

Recurrent colorectal cancer after endoscopic resection when additional surgery was recommended

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Abstract

AIM: To evaluate the type of recurrence after endoscopic resection in colorectal cancer patients and whether rescue was possible by salvage operation.

METHODS: Among 4972 patients who underwent surgical resection at our institution for primary or recurrent colorectal cancers from January 2005 to February 2015, we experienced eight recurrent colorectal cancers after endoscopic resection when additional surgical resection was recommended.

RESULTS: The recurrence patterns were: intramural local recurrence (five cases), regional lymph node recurrence (three cases), and associated with simultaneous distant metastasis (three cases). Among five cases with lymphatic invasion observed histologically in endoscopic resected specimens, four cases recurred with lymph node metastasis or distant metastasis. All cases were treated laparoscopically and curative surgery was achieved in six cases. Among four cases located in the rectum, three cases achieved preservation of the anus. Postoperative complications occurred in two cases (enteritis).

CONCLUSION: For high-risk submucosal invasive colorectal cancers after endoscopic resection, additional surgical resection with lymphadenectomy is recommended, particularly in cases with lympho-



vascular invasion.

Key words: Colorectal neoplasms; Colorectal surgery; Laparoscopy; Endoscopy; Recurrence

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Core tip: This is a retrospective study to evaluate the type of recurrence after endoscopic resection in colorectal cancer patients and whether rescue was possible by salvage operation. All cases were treated laparoscopically and curative surgery was achieved in six cases. Among five cases with lymphatic invasion observed histologically in endoscopic resected specimens, four cases recurred with lymph node metastasis or distant metastasis. For highrisk submucosal invasive colorectal cancers after endoscopic resection, additional surgical resection with lymphadenectomy is recommended, particularly in cases with lymphovascular invasion.

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INTRODUCTION

Following recent advances in endoscopic diagnosis and techniques, the number of T1 [tumor node metastasis (TNM) cancer staging] colorectal cancer cases initially treated by endoscopic resection has been increasing^[1]. Lymph node metastasis occurs in approximately 10% of cases with submucosal invasive colorectal cancers^[2]. In Japan, according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines^[3], when any high-risk findings are observed in histological examination of a resected specimen after endoscopic resection, additional surgical resection with lymphadenectomy is recommended. Patients with submucosal invasive colorectal cancers treated by surgical or endoscopic resection, or both, according to the JSCCR, had good clinical outcomes^[2].

However, certain patients cannot undergo operation because of factors such as the patient's age and comorbid state. Particularly, in cases of rectal cancer, additional surgical resection with lymphadenectomy may cause dyschezia and a diverting stoma is sometimes necessary, which may decrease a patient's quality of life. Little is known about outcomes during follow-up in cases with endoscopic resection alone. Although some studies reporting local recurrence after endoscopic resection in T1 colorectal cancer patients for whom additional surgical resection was not

indicated have been published^[4-7], few reports discuss outcomes in these patients^[8].

In the present study, we retrospectively reviewed eight recurrent colorectal cancer cases after endoscopic resection, for which additional surgical resection including lymphadenectomy was recommended because of high-risk submucosal invasive cancer. Our aim was to evaluate the type of recurrence and whether the patient could be rescued by a salvage operation.

MATERIALS AND METHODS

Among 4972 patients who underwent surgical resection at our institution for primary or recurrent colorectal cancers at our institution from January 2005 to February 2015, we experienced eight recurrent colorectal cancers after endoscopic resection. Additional surgical resection with lymphadenectomy had been recommended in these patients because of high-risk submucosal invasive colorectal cancer. High-risk submucosal invasive colorectal cancer after ER is defined according to the JSCCR Guidelines, when any of the following findings are observed in histological examination of the endoscopic resected specimen: (1) depth of submucosal invasion \geq 1000 µm; (2) lymphovascular invasion was positive; (3) signet-ring cell carcinoma, mucinous carcinoma, or poorly differentiated adenocarcinoma; (4) Grade 2/3 budding; and (5) vertical tumor margin was positive. All cases had undergone endoscopic resection at another hospital and were referred to our institution after cancer recurred. The study was approved by our local institutional review board and signed consent was obtained from all patients to use data from their medical records in the study.

We retrospectively reviewed the patient characteristics including age, sex, American Society of Anesthesiologists physical status, body mass index, tumor location, and pathological data. Pathological data in six of eight cases were re-examined in our institution. All specimens from endoscopic resection were examined microscopically for resection margin status and tumor characteristics as identified above. Treatment and analysis information for recurrence after ER included the use of adjuvant therapy, followup interval, recurrence pattern, time to recurrence, and treatment to recurrence. Surgical outcome information in our institution included the surgical procedures, harvested lymph nodes, estimated blood loss, operating time, and complications. Postoperative outcome data included pathological findings, therapy after surgery, and survival outcome.

RESULTS

Patients' demographic data, including the primary cancer, are shown in Table 1. The median age was 60 years (range, 39-76 years) and the proportion of male patients was higher than female (six vs two cases, respectively). The median body mass index of all



Table 1 Characteristics of patients and primary tumors

Age BMI						Pathological data						
Case	(yr)	Sex	ASA	(kg/m^2)	Location	Invasion depth	Differentiation	ly	v	VM	Budding	
1	39	F	1	19.7	Rectum	sm (≥ 1000 µm)	Well	+	+	-	Grade 2	
2	43	M	1	19.4	Rectum	sm (≥ 1000 µm)	Well	+	+	+	Unknown	
3	71	F	1	17.0	Rectum	sm (< 1000 μm)	Well	+	+	-	Unknown	
4	75	M	1	25.3	Transverse	sm (= 1000 µm)	Well	-	-	-	Grade 0	
5	76	M	2	21.7	Rectum	un clear	Moderate	-	-	+	Grade 0	
6	42	M	1	18.8	Rectum	sm (≥ 1000 µm)	Well	+	+	-	Grade 0	
7	74	M	2	25.4	Rectum	sm (≥ 1000 µm)	Moderate	-	+	-	Grade 3	
8	49	M	2	22.4	Sigmoid	sm ($\geq 1000 \ \mu m$)	Moderate	+	-	-	Grade 1	

Table 2 Follow up and recurrence after endoscopic resection

		Use of adjuvant therapy								
Case	After ESD	Follow up interval	Recurrence pattern	Time to recurrence						
1	-	3 mo	Distant	8 mo						
			metastasis (lung,							
			PALN)							
2	-	Every year	Local + regional	10 mo						
			lymphnode							
3	-	No follow	Distant	7 yr						
			metastasis (lung,							
			liver)							
4	-	8 mo	Local	4 yr						
5	-	No follow	Local + regional	18 mo						
			lymphnode							
6	XELOX 6 mo	No follow	Local	2 yr						
7	-	Every year	Local + regional	4 yr						
			lymphnode							
8	-	No follow	Peritoneal	4 yr						
			dissemination							

Local: Intra mural; PALN: Para aortic lymphnode.

patients was 20.7 (range, 17.0-25.4) and the primary cancer was located in the rectum in six patients. Pathological examination in the previous hospitals showed that all cases indicated a need for additional surgical resection including lymphadenectomy, with the following findings: deep submucosal invasion (6 cases), lymphatic invasion positive (five cases), vascular invasion positive (five cases), vertical margin positive (2 cases), poor differentiation (0 case), and grade 2/3 budding (2 cases).

Follow-up and recurrence after endoscopic resection

Adjuvant chemotherapy after ER was performed in only one case. Four patients were followed up once every 3-12 mo after ER but another four cases were not followed up. The recurrence patterns were intramural local recurrence in five cases, regional lymph node recurrence in three cases, and associated with simultaneous distant metastasis in three cases (Table 2). Among five cases with lymphatic invasion observed histologically in the ER specimen, four cases recurred with lymph node metastasis or distant metastasis, and one case receiving adjuvant chemotherapy after ER experienced only local recurrence. Surgical

outcomes are shown in Table 3. All cases were treated laparoscopically, curative surgery was achieved in six cases, and there was no conversion to open surgery. The median operating time was 284 min (range, 205-440 min) and the median estimated blood loss was 168 mL (range, 10-285 mL). Among four cases located in the rectum, three cases achieved preservation of the anus. Postoperative complications occurred in two cases (enteritis).

Among three cases with distant metastasis, laparoscopic sigmoidectomy and excision of peritoneal dissemination were performed in one case. The remaining two cases received systemic chemotherapy after staging laparoscopy or laparoscopic sigmoid colostomy.

Postoperative outcomes are shown in Table 4. Macroscopically complete resection was achieved in five cases and no recurrence occurred during the 3-106-mo follow-up. Adjuvant chemotherapy was performed in three patients who had lymph node metastasis.

DISCUSSION

Of the eight cases in our study, three experienced recurrence with distant metastasis. Follow-up was not performed for all of the patients for whom additional resection after endoscopic treatment was recommended and some cases presented with distant metastasis at the time of recurrence. Yoshii et al^[8] compared outcomes between patients who underwent additional surgery (ER + SURG) and those who did not (ER only) and reported that the cumulative risks of recurrence was 3.7% (5/180) in the ER + SURG group vs 20.1% (13/96) in the ER only group (P =0.001). The authors also emphasized 6 of 13 recurrent cases in the ER only group were associated with concurrent distant metastasis. These findings support the JSCCR guidelines that additional surgery should be performed. However, additional surgical resection with lymphadenectomy in cases of rectal cancers can be associated with permanent stoma or some degree of anal dysfunction. Certain risks of surgical complications related to the operation have also been reported. Because of these concerns as well as patient age and comorbid state, some cases were followed up by ER

Table 3 Surgical outcomes

Case	Surgical procedures	Operating time	Estimated blood loss	Harvested	Lymphadenectomy	Complication	
		(min)	(mL)	lymph nodes			
1	Staging laparoscopy	139	10	-	-	-	
2	Laparoscopic LAR	205	10	15	D3	Enteritis	
3	Laparoscopic Sigmoid colostomy	-	-	-	-	-	
4	Laparoscopic TCR	339	135	12	D2	-	
5	Laparoscopic LAR	440	285	10	D3	Enteritis	
6	Laparoscopic APR	403	200	18	D3	-	
7	Laparoscopic LAR	227	20	13	D3	-	
8	Laparoscopic SCR+	230	350	-	-	-	
	Excision of peritoneal dissemination						

LAR: Low anterior resection; TCR: Transverse colon resection; APR: Abdominoperineal resection; SCR: Sigmoid colon resection.

	ostoperati	

Case_	Pathological data									Surviva	Last follow-up	
	Invasion depth	ly	V	ew	ow	aw	Lymphnode metastasis, n	Surgical margins	Therapy after surgery	Recurrence	(alive/death)	(mo)
1								R2	Systemic chemotherapy		Death	25
2	a	2	0	-	-	-	2	R0	Follow-up	-	Alive	106
3								R2	Systemic chemotherapy		Death	12
4	sm (700 µm)	0	0	-	-	-	0	R0	Follow-up	-	Alive	24
5	a	1	1	+	-	-	1	R1	Adjuvant chemotherapy	-	Alive	3
6	a	1	1	-	-	-	0	R0	Follow-up	-	Alive	7
7	a	0	1	-	-	-	1	R0	Adjuvant chemotherapy	-	Alive	23
8	Adenocarcinon	na (re	curre	nce of	sigm	oid		R0	Follow-up	-	Alive	33

without additional surgical resection.

Oka *et al*^[9] reported that the incidence of lymph node metastasis was only 2.2%, regardless of the degree of submucosal invasion depth. Other studies also reported that patients with deep submucosal invasion only had a low cumulative risk of recurrence even without surgery^[8,10,11]. Similarly, in our series, one case with deep submucosal invasion only, that experienced intramural local recurrence after ER, underwent curative surgery. Therefore, patients with only the single risk factor of deep submucosal invasion could be rescued by salvage if they are followed up.

In contrast, some studies have reported that lymphatic invasion was an independent risk factor for lymph node metastasis^[2] and that venous invasion and lymph node metastasis were independent factors for a poor prognosis^[2,12]. In our series, all cases with lymphatic invasion in the ER specimen recurred with distant metastasis. In patients with lymphovascular invasion, additional surgical resection is strongly recommended.

All of our cases were treated laparoscopically. Similar to findings in previous randomized clinical trials^[13-15], laparoscopic surgery had less blood loss and associated with shorter hospital stay, and earlier recovery of bowel function compared with the open surgery. These results indicate that laparoscopic surgery is a feasible procedure with short-term benefits compared with open surgery.

Regarding adjuvant therapy after ER, our patient with lymphovascular invasion experienced only local recurrence after adjuvant chemotherapy. Studies of additional alternative therapy in rectal cancers have reported the effectiveness of chemoradiotherapy for patients with high-risk submucosal invasive colorectal cancers who declined additional surgery^[16,17].

Surveillance after endoscopic resection is important. Some studies have reported recurrence within three to five years after curative $\mathrm{ER}^{[18-21]}$; however, the ideal follow-up period after ER with indication for additional surgery has not been determined. Yoshii $et\ al^{[8]}$ suggested a recommended follow-up period of at least 5 years based on the finding that their 13 cases of recurrence after ER occurred over 69 mo. Because the longest interval to recurrence was seven years in our series, it is difficult to recommend an ideal follow-up period.

In our study, two of three cases with simultaneous distant metastasis were not followed up using any modality. If ER is performed without additional surgery, we recommend monitoring closely for recurrence. Because the shortest interval to recurrence was 8 mo in our study, we recommend a follow-up interval of at least every 6 mo.

In conclusion, for high-risk submucosal invasive colorectal cancers after ER, we recommend additional surgical resection with lymphadenectomy particularly in cases with lymphovascular invasion. Patients with



high-risk submucosal invasive colorectal cancers should be adequately advised of the outcome of recurrence.

COMMENTS

Background

In Japan, according to the Japanese Society for Cancer of the Colon and Rectum guidelines, when any high-risk findings are observed in histological examination of a resected specimen after endoscopic resection, additional surgical resection with lymph node dissection is recommended. However, some patients refuse the operation because of the patient's will and comorbid state. Particularly, in cases of rectal cancer, additional surgical resection including lymph node dissection may cause dyschezia and a diverting stoma resulting decrease of patient's quality of life is sometimes necessary. Little is known about outcomes during follow-up in cases with endoscopic resection alone. Thus, it is important to evaluate the type of recurrence of these patients and whether they could be rescued by a salvage operation.

Research frontiers

Although some studies reporting local recurrence after endoscopic resection in T1 colorectal cancer patients for whom additional surgical resection was not indicated have been published, few reports discuss outcomes in the patients with endoscopic resection alone. The results of this study was persuasive and helpful for clinical.

Innovations and breakthroughs

In this study, all cases were treated laparoscopically and curative surgery was achieved in six cases. Among five cases with lymphatic invasion observed histologically in endoscopic resected specimens, four cases recurred with lymph node metastasis or distant metastasis. For high-risk submucosal invasive colorectal cancers after endoscopic resection, additional surgical resection with lymphadenectomy is recommended, particularly in cases with lymphovascular invasion

Applications

This study suggests that for high-risk submucosal invasive colorectal cancers after endoscopic resection, additional surgical resection with lymphadenectomy is recommended, particularly in cases with lymphovascular invasion. Due to lack of cases only by this retrospective study, another case series of prospective study design or randomized control study with multicenter cooperation for correcting data will be required.

Peer-review

The authors evaluated the type of cancer recurrence after endoscopic resection in 8 colorectal cancer (CRC) patients and whether rescue was possible by salvage operation. The reviewer absolutely agrees with the main conclusion of the authors, namely for high-risk submucosal invasive CRCs additional surgical resection with lymphadenectomy is highly recommended after EMR/EMD, particularly in cases with lymphovascular invasion. Though the number of cases is small, that was persuasive and helpful for clinical.

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