ORIGINAL

Comparative study on recurrence pattern and treatment method after radical esophagectomy for esophageal cancer

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Abstract : Background : With regard to the recurrence of esophageal cancer after surgery, the prognosis has improved with the progress of multimodal perioperative treatment. In this study, the recurrence pattern, treatment method, and prognosis of recurrent cases following esophageal cancer surgery were retrospectively examined. Materials and Methods : Three hundred seven patients with histologically proven squamous cell carcinoma, adenocarcinoma, and others were enrolled in the study. With respect to clinicopathologic factors and recurrence patterns, recurrence risk factors, recurrence period, treatment for recurrence, and prognosis were investigated. Results : Ninety two percent of all recurrent cases were observed within two years after radical esophagectomy. Locoregional recurrence, distant recurrence, and mixed recurrence were observed in 38 (35%), 56 (51%), and 16 (14%) cases, respectively. Patients with lymph node metastasis showed a significantly longer survival in comparison to those with metastasis to other organs (p = 0.0032). When analyzed using the treatment method, patients who underwent surgery (only surgery or additional postoperative chemotherapy) exhibited better survival in comparison to those who underwent other treatments. Discussion : Detailed and strict follow-up within two years are necessary in cases with deeper than muscular invasion, cases with extensive lymph node metastasis, or cases with lymphatic or vascular invasion. J. Med. Invest. 68 : 129-135, February, 2021

Keywords **:** *esophageal cancer, recurrence pattern, esophagectomy*

INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related mortality worldwide due to its high malignant potential and poor prognosis (1). The prognosis of this cancer is one of the worst among malignant digestive neoplasms. Its poor survival can be elucidated by its aggressive tumor biology and delayed detection of early esophageal cancer. The survival time in patients with advanced esophageal cancer is, therefore, unsatisfactory despite the development of operative procedures and perioperative managements (2, 3). Esophagectomy is traditionally considered the standard treatment for esophageal cancer. In Japan, the survival rate after esophagectomy has remarkably improved in recent years. Although the overall five-year survival rate exceeds 50%, recurrence still develops within two years after resection in more than 80% of these patients (4). In addition, Kunisaki C *et al*. reported that more than 50% of tumor recurrences occurred within 12 months of curative esophagectomy (5). According to the type of recurrence, the metachronous lesions are classified as locoregional, distant (including hematogenous metastasis within a solid organ, abdominal paraaortic lymph node metastasis, and peritoneal metastasis), and combined types (5). For such patients, chemotherapy or chemoradiotherapy (CRT) are the main treatments for recurrence (5-8). However, the role of adjuvant treatments, such as chemotherapy and radiotherapy, for esophageal cancer patients after radical esophagectomy remains controversial, although adjuvant therapy for the improvement of prognosis is important.

Therefore, understanding the predictive factors and assessing the pattern and timing of recurrence after curative esophagectomy plays a significant role in ameliorating therapeutic outcomes. These data can also aid in the administration of appropriate treatments according to recurrence pattern and improvement of prognosis after recurrence. With regard to the recurrent treatment of esophageal cancer, Shimada H *et al*. discussed that the status of serum p53 antibody and serum CRP may predict response and outcome of patients with recurrent esophageal cancer after radical operation (9). Moreover, Kunisaki C *et al*. have reported a significant difference in survival after recurrence between treatment methods (no treatment vs chemoradiotherapy, $p = 0.0063$; chemotherapy, $p = 0.0247$; and radiotherapy, $p < 0.0001$).

In this study, the recurrence pattern, treatment method, and prognosis of recurrent cases after esophageal cancer surgery were retrospectively examined, and risk factors for recurrence and favorable prognosis factors after recurrence were investigated.

PATIENTS AND METHODS

Patients

This was a single-center retrospective study. Between January 2004 and December 2015, 307 patients with histologically proven squamous cell carcinoma (n = 256 : 83.4%), adenocarcinoma (n = 31 : 10.1%), and others (n=20 : 6.5%) were successfully enrolled in the study. The patient population was composed of 267 men and 40 women from ages 39 to 86 years old [mean age ± standard deviation (SD), 66.3 ± 7.9 years]. The patients underwent transthoracic esophagectomy followed by esophagogastric anastomosis or esophagojejunal anastomosis using

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the gastric conduit or jejunal Roux en-Y at the Department of General Surgical Science, Gunma University Graduate School of Medicine, Japan. Preoperative diagnoses involving endoscopic examination with biopsy, endoscopic ultrasonography, computed tomography (CT), and positron emission tomography (PET) were routinely performed on all patients. Clinical staging and pathological examination for resected specimens were performed in accordance with the Guidelines for Clinical and Pathological Studies on Carcinoma of the Esophagus of the Japanese Society for Esophageal Diseases (10). Furthermore, tumor stage was classified according to the seventh edition of the tumor-node-metastasis classification system developed by the International Union Against Cancer (11). Lymph node metastasis was observed in 179 patients (58.3%). All lymph nodes were defined in accordance with the TNM Classification of Malignant Tumors.

Surgical procedure

All patients underwent radical esophagectomy with three-field lymphadenectomy (Mckeown : 265) or with two-field lymphadenectomy (Ivor-Lewis : 42). Gastric tubes, the jejunum, and the colon were utilized for the reconstruction of the digestive tract for esophagectomy. Additionally, the anastomotic mode was normally performed using stapling technique anastomosis. Post-mediastinal route was mostly preferred in this study than retrosternal and ante-thoracic routes. Retrosternal route was chosen to avoid interference of the mediastinal tumor recurrence with alimentary tract function. There were no cases of video-assisted thoracoscopic surgery involved in this study. Also, we performed chemoradiotherapy (CRT) for patients with tumors suspected to be T4 or to be associated with extended lymph node metastasis. Adjuvant chemotherapy was performed in 143 (46.6%) patients with pathologically identified lymph node metastasis, had good performance status, and who gave informed consent.

Follow-up and Definition of recurrence

Patients were assessed one month after completing treatment and every three months for the first three years and every 6 months until the fifth year. Additional examinations were made on other timings as necessary. Routinely, CT from the neck to the lower abdomen and FDG-PET/CT were carried out at least twice a year for three years after surgery and then once each year for five years after surgery. Blood sampling, including tumor marker, was performed at the same time as CT and FDG-PET examinations, and X-rays were also performed at appropriate times. Endoscopy was suggested at least every year. The mode of recurrence was classified into three patterns : locoregional, hematogenous, and mixed type (4, 5, 12). Locoregional recurrence was defined as tumors occurring on lymph nodes in the neck ; mediastinum, including anastomotic site ; or upper abdomen at the site of initial esophagectomy and lymph node dissection. Distant recurrence was described as hematogenous metastasis within the solid organ, abdominal paraaortic lymph nodes, or peritoneal metastasis. Mixed type was defined as recurrence which consisted of locoregional recurrence concomitant with hematogenous recurrence in the same patient, simultaneously. Overall survival (OS) indicated the interval between recurrence and death from any cause, loss to follow-up, or last follow-up. The disease-free survival time was the interval between surgery and first recurrence.

Statistical Analysis

We performed all statistical analyses using the JMP Pro Version 14 software (SAS Institute Japan, Tokyo, Japan). We employed the Student's t-test or the Mann–Whitney U test to assess continuous data and Person's Chi-squared test, Fisher's exact test, or the Mann–Whitney U test for categorical data, as appropriate. Univariate and multivariate logistic regression analyses were performed to examine the relationship between several clinical factors and recurrence. P values < 0.05 were considered statistically significant.

RESULTS

Examination of recurrence-related factors

Recurrence was observed in 110 patients (35.8%) among all patients included in the study. Table 1 demonstrated the relationship between patient characteristics and recurrence. There were significant correlations between depth of invasion ($p < 0.001$), lymph node metastasis ($p < 0.001$), distant lymph node metastasis ($p < 0.001$), lymphatic invasion ($p < 0.001$), vessel invasion ($p < 0.001$), and recurrence. Moreover, the recurrence rate was significantly higher in cases where poorly differentiated components were contained in a pathological specimen ($p = 0.001$). In addition, recurrence was significantly higher in cases with postoperative adjuvant therapies compared with cases who underwent surgery alone ($p = 0.001$). However, there were no significant difference in other clinicopathological factors. Furthermore, comparison of surgical techniques did not yield any significant difference in the recurrence rate ($p = 0.061$) or recurrence site ($p = 0.101$) between two-field and three-field lymphadenectomy. Table 2 summarizes the univariate and multivariate logistic regression analyses of factors associated with recurrence. The depth of invasion ($p = 0.0027$), distant lymph node metastasis ($p = 0.026$), lymphatic invasion ($p = 0.0036$), and vessel invasion ($p = 0.023$) were independent recurrence factors after radical esophagectomy.

Recurrence pattern and Survival

Table 3 illustrates the recurrence pattern in this study. Locoregional recurrence was observed in 38 cases (35%), and most cases manifested regional lymph node metastases. Distant recurrence was observed in 56 cases (51%), and 67% of distant metastasis were organ metastasis. Furthermore, mixed recurrence was exhibited in 16 (14%) cases. As regards median times until recurrence, locoregional, distant, and mixed were 260 days (38–1549), 198 days (32–2917), and 171 days (range 78–451), respectively. Ninety two percent of all recurrence cases were observed within two years after radical esophagectomy.

Figure1A demonstrates the OS of each pattern after recurrence. There was no significant difference in terms of survival in each pattern ($p = 0.988$). However, this data confirmed that there was a small number of long-term survivals in each group after recurrence. Figure1B shows the OS after recurrence in lymph node (regional lymph node metastasis plus distant lymph node metastasis) and organ recurrence. Cases of lymph node metastasis had significantly longer survival compared with cases of organ metastasis (median survival time, 1.59 year vs 0.69 year, $p = 0.0032$). Figure 2 describes OS by treatment for recurrence cases. As a result of extensive classification into four categories, there was a significant difference in survival among each treatment ($p < 0.0001$). Cases who were performed operation (only operation or plus postoperative chemotherapy) exhibited most better survival among these groups (median survival time, 3.8 year).

Characteristics of long-term survival cases after recurrence

Cases that survived more than one year after recurrence treatment were defined as favorable case ($n = 13$), and other cases were defined was poor cases ($n = 97$). Table 4 shows the relationship between patient characteristics and prognosis in

recurrent cases. The progression of vessel invasion was significantly a poor prognostic factor for survival over one year after treatment of recurrence ($p = 0.015$). In addition, local treatment, such as operation or radiotherapy, can significantly lead to the elongation of prognosis ($p = 0.037$). However, no significant difference was found in other factors, such as age, sex, disease progression, or recurrence type. Table 5 exemplifies a list of favorable cases. It was shown that some patients had long-term survival by excision for cervical lymph node recurrence and CRT for mediastinal lymph node recurrence, although statistical analysis was not possible due to a few numbers of cases in each treatment group.

Table 1. Relationship between patient characteristics and recurrence

		Recurrence		p-value
		Negative (n=197)	Positive (n=110)	
Age		66.8(42-86)	65.2(39-80)	0.95
Sex	Male	173	94	0.55
	Female	24	16	
Localization	Upper	21	11	0.46
	Middle	90	43	
	Lower	86	56	
Histrogical type	SCC	160	96	0.36
	Adeno	23	8	
	Others	14	6	
por component	-	151	65	0.001
	+	46	45	
ly	-	71	2	<0.001
	+	126	107	
v	-	103	12	<0.001
	+	94	97	
pT	0/Tis	12	1	<0.001
	1	101	16	
	2	29	17	
	3	51	66	
	4	4	10	
pN	0	109	19	<0.001
	1	58	26	
	2	24	35	
	3	6	30	
pM	0	192	92	<0.001
	1	5	18	
pStage	0	11	1	<0.001
	1	78	8	
	2	56	20	
	3	47	63	
	4	5	18	
Preoperative treatment	Present	26	21	0.17
	None	171	89	
Adjuvant therapy	Present	78	65	0.001
	None	119	45	

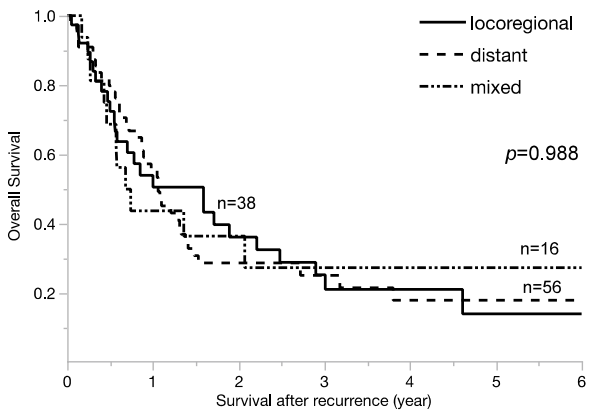
Table 2. Univariate and Multivariate logistic regression analyses of factors associated with recurrence

Characteristic	Objective variables	Control	Univariate analysis			Multivariate analysis		
			OR	95%CI	p-value	OR	95%CI	p-value
Age	>66	≤65	1.3	0.82-2.09	0.25			
Sex	M	F	1.2	0.61-2.40	0.55			
Pathological T	T2/3/4	T0/1	7.3	4.17-13.6	<0.0001	2.9	1.44-5.96	0.0027
Pathological N	N1/2/3	N0	5.9	3.42-10.7	<0.0001	1.7	0.71-4.34	0.22
Pathological M	M1	M0	7.5	2.89-23.3	<0.0001	3.1	1.13-10.3	0.026
Pathological Stage	St 2/3/4	St 0/1	9.2	4.64-20.6	<0.0001	1.1	0.33-3.65	0.86
por component	positive	negative	2.2	1.37-3.76	0.0014	1.3	0.74-2.43	0.32
Lymptaic invasion	ly 1/2/3	ly 0	30.1	9.16-186.0	<0.0001	6.9	1.78-46.0	0.0036
Vessel invasion	v 1/2/3	v 0	8.8	4.72-17.9	<0.0001	2.3	1.11-5.21	0.023

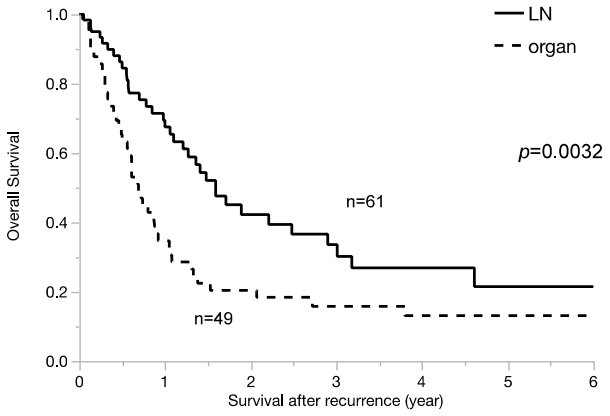
Table 3. Recurrence pattern in this study

Pattern	Number (%)	
Local	1(1)	Locoreginal recurrence
Regional LN	37(34)	
Distant LN	19(17)	Distant recurrence
Distant metastasis other than LN	37(34)	
Mixed	16(14)	Mixed recurrence

LN: lymph node metastasis



A. Survival comparison among each recurrence pattern
Median survival times (years) of locoregional, distant, and mixed patterns were 1.59, 1.06, and 0.71 years, respectively.



B. Survival comparison between lymph node metastasis and distant metastasis cases
Median survival times (years) of cases of lymph node metastasis and cases of distant metastasis were 1.59 and 0.69 years, respectively.

Figure 1. Overall survival after recurrence

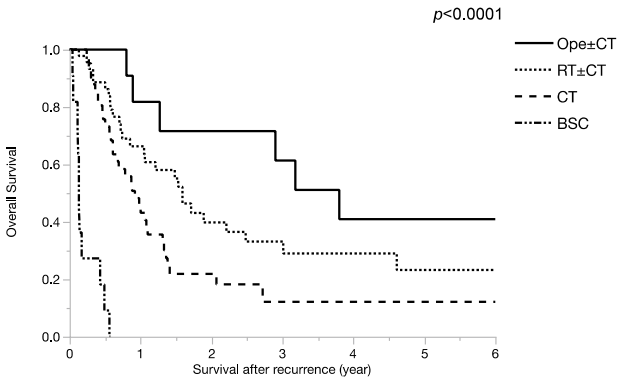


Figure 2. Overall survival by treatment for recurrent cases
Median survival times (years) of operation, radiation, and chemotherapy groups and BSC were 3.8, 1.59, 0.92, and 0.13 years, respectively.

Table 4. Relationship between patient characteristics and prognosis in recurrence cases

		Prognosis		
		Poor (n=97)	Favourable (n=13)	p-value
Age		65.2(39-86)	65.2(57-74)	0.98
Sex	Male	84	10	0.38
	Female	13	3	
Time to recurrence (day, median)		218 (38 - 1549)	309 (42 - 2917)	0.63
Localization	Upper	10	1	0.51
	Middle	36	7	
	Lower	51	5	
Histrogical type	SCC	83	13	0.34
	Adeno	8	0	
	Others	6	0	
por component	+	45	5	0.84
	-	57	8	
ly	+	94	13	0.47
	-	2	0	
v	+	88	9	0.015
	-	8	4	
pT	0/Tis	1	0	0.15
	1	12	4	
	2	13	4	
	3	62	4	
	4	9	1	
pN	0	17	2	0.55
	1	21	5	
	2	31	4	
	3	28	2	
pM	0	81	11	0.91
	1	16	2	
pStage	0	1	0	0.73
	1	6	2	
	2	17	3	
	3	57	6	
	4	16	2	
reccurrence lesion	locoregional	33	5	0.93
	distant	50	6	
	mixed	14	2	
Preoperative treatment	Present	20	1	0.22
	None	77	12	
Adjuvant therapy	Present	57	8	0.84
	None	40	5	
Treatment	Ope±CT	8	3	0.037
	RT±CT	38	8	
	CT	40	2	
	BSC	11	0	

BSC: best supportive care
CT: chemotherapy
RT: radiotherapy

Table 5. list of favorable cases after recurrence treatment.

case	age	sex	location	pT	pN	pM	pStage	preoperative treatment	initial operation	adjuvant therapy	time to recurrence	recurrence organ	recurrence treatment	suvival after recurrence (day)
1	73	M	Mt	1a	0	0	IA	-	Ivor Lewis	-	673	cervical LN	lymphadenectomy→DNF②	2946
2	57	M	Ut	1a	1	0	IIB	-	Mckeown	FP	154	lung cervical LN	partial resection lymphadenectomy →FP④	3307
3	64	M	Mt	2	2	1	IV	-	Mckeown	TXT	120	cervical LN	lymphadenectomy→DNF②	2011
4	64	F	Lt	4	1	0	IIIC	CRT	Mckeown	UFT	42	lung, 16	CDDP⑩+ UFT→ RT	3279
5	57	M	Mt	1b	1	0	IIB	-	Ivor Lewis	UFT	2917	8a, 9	heavy-ion to 8a, 9→DNF④ heavy ion to 16	923
6	67	F	Mt	1b	3	1	IV	-	Mckeown	TXT	1578	16	DCF-RT→UFT	1935
7	65	M	Mt	3	2	0	IIIB	-	Mckeown	DNF	1300	106pre	DCF-RT→UFT	1091
8	56	M	LtMt	3	2	0	IIIB	-	Mckeown	DNF	309	106tbL	FP-RT	1510
9	64	M	Lt	2	0	0	IB	-	Mckeown	-	371	mediastinum LN	DCF-RT→FP②	1364
10	73	F	Mt	2	2	0	IIIA	-	Mckeown	FP	407	mediastinum LN	DCF-RT→FP②	450
11	62	M	Mt	2	1	0	IIB	-	Mckeown	-	140	chest wall	DCF-RT→DNF④	1835
12	74	M	Lt	3	1	0	IIIA	-	Mckeown	-	64	multiple liver	DNF④→TXT⑩	2896
13	72	M	Lt	3	3	0	IIIC	-	Mckeown	FP	118	112Ao, 16	DNF④	1295

DCF: docetaxel, cisplatin, fluorouracil
DNF: docetaxel, nedaplatin, fluorouracil
FP: fluorouracil, cisplatin
UFT: tegaful, uracil
TXT: docetaxel
CDDP: cisplatin

DISCUSSION

After radical surgery, cancer progression is characterized as either a locoregional recurrence or a distant metastasis, and sometimes it includes both. In this study, we reported the current status and treatment of recurrent cases after esophagectomy. Surgical resection has constituted the main treatment option in esophageal cancer management. In Japan, cervical lymph node dissection, in addition to conventional thoraco-abdominal lymph node dissection, a three-field lymph node dissection, has been advocated for the improvement of surgical outcomes at many institutions (13). However, the use of surgery alone still results in high rates of locoregional recurrence and distant metastasis (14, 15). Despite advances in surgical methodologies, long-term survival after surgery alone for advanced esophageal cancer has remained poor. High rates of locoregional and distant recurrence resulted in the death of resected esophageal cancer patients and have leaded to intense exploration on the application of multidisciplinary approaches in esophageal cancer treatment. The implementation of perioperative chemotherapy has improved survival rates. The standard chemotherapy and treatment regimen of each institutions change with time.

In this study, we examined the correlation between patient characteristics after esophagectomy and recurrence. As a result, tumor progression, lymphatic invasion, and vessel invasion in resected specimens demonstrated significantly higher recurrence in a univariate analysis. These results are consistent with previous reports (16). Moreover, it is natural that postoperative recurrence is likely to occur in advanced cancer with a high mortality rate, even in cases after radical esophagectomy. In addition, our data also showed cases with poorly differentiated component in the pathological specimen which manifested a significantly higher recurrence rate in this study. Previous reports revealed that patients with poorly differentiated squamous cell carcinoma had higher recurrence rate in a similar review (16). However, this result was a different study because it was a report on the degree of differentiation of the whole tumor, while our study was a study on whether or not poorly differentiated components are contained. Recurrence will be frequently observed if a poorly differentiated component is partially included in the pathological specimen, even if the final pathological diagnosis after esophageal cancer is not poorly differentiated.

Kuwano H *et al*. revealed the depth of invasion, tumor length, and intramural metastasis as independent prognostic factors in multivariate analysis (17). Mariette *et al*. (18) also reported that a multivariate analysis identified the depth of tumor invasion as a predictive recurrence factor. Thus, patients harboring these pathological risk factors should be monitored closely for any signs of recurrence. In this study, our data described that the depth of invasion, distant lymph node metastasis, lymphatic invasion, and vessel invasion were independent recurrence factors after radical esophagectomy. This result is consistent with results of previous studies, and it is necessary to consider more powerful chemotherapy in order to suppress recurrence, as much as possible, in cases possessing these recurrence factors. However, it is necessary to consider the recovery state after surgery and the advantages and disadvantages.

Moreover, in this study, distant recurrence was observed in 56 cases (51%), and 67% of distant metastases were organ metastasis. Results indicated that the efficacy of adjuvant chemotherapy is not sufficient enough to reduce organ metastases after esophageal cancer surgery. We hope that the accumulated data on the use of triple-drug chemotherapy (19) and the introduction of nivolumab (20) will show improved outcomes after esophagectomy. Also, in this study, 92% of all recurrence cases were observed within two years after radical esophagectomy. This data was also consistent with previous reports, and detailed and strict follow-up is recommended two years after esophagectomy.

In favorable cases of this study, it was illustrated that some patients had long-term survival by excision for cervical lymph node recurrence and CRT for mediastinal lymph node recurrence. With regard to patients with isolated tumor recurrence, salvage therapeutic options include systemic chemotherapy, irradiation, surgical resection, or a combination of the above. Due to poor prognosis, only a few retrospective studies with small series of selected patients and several case reports showing results of surgical treatment exist. Therefore, the benefit of surgical resection as part of multimodality treatment for patients with isolated distant recurrence in solid organs is controversial. However, it is true that there are cases where long-term prognosis is obtained by local treatment among recurrent cases, and it is important to establish a method for selecting recurrent cases that are cured by such local treatment.

Our study has several limitations. This is a single-center

retrospective study, and results may, therefore, have been influenced by selection and statistical bias. Patients who did not receive treatment had a poor performance status, were older, or gave no informed consent were excluded from the study. Moreover, chemotherapy was frequently performed in patients with distant metastasis, whereas chemoradiotherapy was mainly employed in patients with locoregional recurrence. As the selection criteria for treatment were controlled by the physician, future work should focus on a randomized controlled trial conducted in patients who do and do not receive treatment. Due to the lack of strict guidelines on the therapeutic approach in each recurrence site, well-organized prospective multicenter studies may offer a possibility to draw firmer conclusions.

In conclusion, most esophageal cancer recurrences develop within two years after esophagectomy. Therefore, a detailed and strict follow-up within two years are needed in cases with deeper than muscular invasion, cases with extensive lymph node metastasis, or cases with lymphatic or vascular invasion. It is confirmed that there are cases in which long-term prognosis can be obtained by local treatment among recurrent cases. Thus, it is important to establish a method for selecting recurrent cases that are cured by such local treatment.

CONFLICT OF INTEREST

The authors have no financial conflicts of interest to disclose concerning the study.

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