ORIGINAL CONTRIBUTION

Features of Late Recurrence Following Transanal Local Excision for Early Rectal Cancer

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BACKGROUND: Transanal local excision has recently received attention as an alternative to radical surgery for early rectal cancer. Recurrence usually occurs within 5 years after surgery, but recurrences later than this have also been reported.

OBJECTIVE: The aim of this study was to investigate the incidence and risk factors of recurrence in patients who have early rectal cancer 10 years after transanal local excision.

DESIGN: Patients with early rectal cancer who underwent transanal local excision from October 1994 to December 2010 were retrospectively reviewed. We reviewed the demographics and clinicopathologic features of primary lesions and analyzed the incidence and risk factors of recurrence.

SETTINGS: This investigation was conducted at a tertiary university hospital.

PATIENTS: A total of 295 patients who underwent transanal local excision for pTis (n = 155) or pT1 (n = 140) early rectal cancer were included in the analysis.

INTERVENTION: Transanal local excision was performed for each patient to excise primary rectal lesions.

MAIN OUTCOME MEASURES: The primary end point of this study was the incidence of recurrence, especially late recurrence. The secondary end point was risk factors for recurrence.

RESULTS: The 10-year cumulative local recurrence rate was 6.7% in pTis and 18.0% in pT1 patients. The rate of late local recurrence was 2.8% in pTis and 3.7% in pT1 patients. There was no evidence of late systemic recurrence 5 years after transanal local excision. In pT1 patients, a higher risk of recurrence was associated with an invasion depth of sm3, the presence of lymphovascular invasion, and a positive resection margin.

LIMITATION: The main limitation of this study is its retrospective nature.

CONCLUSIONS: Late recurrence can occur in patients with early rectal cancer who have undergone transanal local excision. Transanal local excision can be performed in selective patients with biologically favorable tumors, and 10-year postoperative surveillance should be considered for these patients.

KEY WORDS: Early rectal cancer; Local excision; Recurrence; Survival.

Rectal cancer is a common malignancy for which total mesorectal excision is currently considered the standard of treatment.[1,2] The recent popularization of colorectal cancer screening is expected to lead to a

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dramatic increase in the detection of early rectal cancer.[3,4] Therefore, transanal local excision (TAE) has received attention as an alternative to radical surgery for early rectal cancer. TAE for early rectal cancer has several advantages, such as lower rates of sexual and urinary dysfunction and permanent stoma. In addition, it has been associated with shorter hospital stays and low morbidity and mortality rates.[2,5,6]

Early rectal cancer is usually defined as pT1 and pT2 in many Western countries.[7,8] However, some publications have defined pTis and pT1 to be early rectal cancers.[6,9] Several reports have confirmed that, as a clinically applicable modality, TAE of pTis and select pT1 rectal cancers has shown oncologic outcomes similar to radical surgery.[5,10] However, local and systemic recurrences of pTis and pT1 rectal cancers following TAE have been reported.[9,11] Recurrence usually occurs within 5 years after TAE, but later recurrences have also been reported.[12] The features of these late recurrences following TAE for early rectal cancer are currently unclear, and future work exploring this area is warranted.

In this study, we aimed to investigate the incidence and risk factors of recurrence in patients with early rectal cancer 10 years after TAE.

MATERIALS AND METHODS

Patients

The records from a total of 413 patients with early rectal cancer who underwent TAE from October 1994 to December 2010 were retrospectively reviewed. We defined early rectal cancer as pTis and pT1 rectal cancers. All patients had confirmed primary adenocarcinoma with a pTis-T1 and cN0 rectal cancer located less than 15 cm from the anal verge. Patients were excluded if they had any of the following criteria: recurrent disease, distant metastases, synchronous malignancies, hereditary colorectal cancer, preoperative chemoradiotherapy, or follow-up duration less than 2 years. Most patients with invasion depth of sm2 to sm3, lymphovascular invasion (LVI), poorly differentiated cell type, or positive resection margin received additional treatments following primary TAE. Of these, 30 patients received adjuvant concurrent chemoradiotherapy (CCRT), and 29 patients underwent additional radical surgery. These 29 patients were excluded from this study. This study was approved by the Samsung Medical Center Institutional Review Board.

Treatments and Histopathologic Examination

Preoperative clinical TNM stage was assessed radiologically by using colonoscopy, endorectal ultrasonography, abdominopelvic CT, chest CT, or pelvic MRI. All patients underwent local excision via transanal endoscopic microsurgery with a large-diameter proctoscope 12 or 20 cm in length (Richard Wolf, Knittlingen, Germany). With the use of general or spinal anesthesia, TAE was performed under direct vision with or without CO_2 insufflation of the rectum. In all cases, a full-thickness excision of the rectal wall up to perirectal fat was performed, and the excision site was closed with one or more running sutures. After the operation, we performed histologic examination of the specimen. Classification as adenocarcinoma included lesions with intramucosal cancer (pTis) and invasive carcinoma to the level of the submucosa (pT1). pT1 rectal cancer was subclassified by using the Kikuchi submucosal staging system (sm1–3).[13] To achieve standardization of submucosal staging, a single pathologist reanalyzed the depth of submucosal invasion of the primary cancer. For large benign lesions with a small invasive cancer, tumor size was considered to be the maximum diameter of the malignant tissue. Negative resection margin was defined as the absence of tumor cells within 1 mm of the surgical lateral resection margin.[14]

Follow-up

At our hospital, a 5-year postoperative surveillance program was offered to the patients. The patients were scheduled for follow-up visits every 3 months for the first 2 years and then every 6 months for up to 5 years. For most patients, the follow-up evaluation at each visit included physical examination, measurement of CEA level, and chest x-ray. Abdominopelvic CT and chest CT scans were performed every 6 months. Colonoscopy was performed at the first, third, and fifth years, and patients underwent additional regular sigmoidoscopy in the second and fourth years. After 5 years, we recommended that abdominopelvic and chest CT scans be performed annually and colonoscopy be performed biennially, if possible. Local recurrence was defined as cancer at the primary excision site, confirmed by colonoscopic biopsy. Systemic recurrence was defined as pathological or radiological evidence of metastasis. In addition, early and late recurrence was defined as recurrence less than or more than 5 years postoperatively.

Analysis for pT1 Patients With Radical Surgery

To compare the outcomes of recurrence after TAE and radical surgery, we further analyzed the outcomes of recurrence in patients with pT1 rectal cancer who underwent radical surgery. All patients underwent radical surgery in the same period for the TAE group, and confirmed pT1 rectal cancer located less than 15 cm from the anal verge. A total of 205 patients were included according to the same criteria used for the TAE group. The same postoperative surveillance program was offered to patients.

Outcome Assessment

Based on the inclusion criteria, we reviewed the data for sex, age, and clinicopathologic features of primary lesions.

In addition, we analyzed incidence and risk factors of recurrence. The primary end point of this study was the incidence of recurrence, especially late recurrence, in patients with pTis and pT1 rectal cancer following TAE. The secondary end point was risk factors for recurrence.

Statistical Analysis

Statistical analysis was performed by using SPSS for Windows (Version 20.0; IBM SPSS Statistics, IBM Corporation, Armonk, NY). Categorical variables were compared by using the χ^2 test and Fisher exact probability. Kaplan-Meier analyses were used for the determination of actuarial recurrence probabilities. Multivariate analyses for independent predictors of recurrence were performed in a Cox proportional hazards model with stepwise inclusion of variables. A p value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The records of a total of 413 patients who underwent TAE for early rectal cancer were analyzed. Of these, 295 patients (155 patients with pTis and 140 patients with pT1) met the inclusion criteria. Patient characteristics are summarized in Table 1. The patients included 160 men and 135 women with a median age of 58.3 (range, 28–83) years. The median follow-up duration was 72.9 (range, 24.9–216.1) months. Of 413 patients, 111 (45 in pTis and 66 in pT1) were followed for 5 to 10 years and 43 (27 in pTis and 16 in pT1) were followed for more than 10 years. Mean tumor distance from the anal verge was 6.2 cm, and mean tumor size was 1.9 cm. Thirty patients with pT1 cancer received adjuvant CCRT after TAE.

TABLE 1. Patient characteristics

Characteristic	*pTis (n = 155)*	*pT1 (n = 140)*
Age, n (%)		
<60 y	85 (54.8)	68 (48.6)
≥60 y	70 (45.2)	72 (51.4)
Sex, n (%)		
Male	80 (51.6)	80 (57.1)
Female	75 (48.4)	60 (42.9)
Preoperative CEA level, n (%)		
<5 ng/mL	133 (85.8)	123 (87.8)
≥5 ng/mL	3 (1.9)	6 (4.3)
Unknown	19 (12.3)	11 (7.9)
Distance from anal verge, n (%)		
≤8 cm	120 (77.4)	113 (80.7)
>8 cm	35 (22.6)	27 (19.3)
Aspect of tumor, n (%)		
Anterior	27 (17.4)	37 (26.4)
Posterior	61 (39.4)	52 (37.2)
Lateral	67 (43.2)	51 (36.4)
Tumor size, n (%)		
<3 cm	96 (61.9)	105 (75.0)
≥3 cm	59 (38.1)	35 (25.0)
Depth of invasion, n (%)		
sm1		60 (42.9)
sm2		30 (21.4)
sm3		30 (21.4)
Unknown		20 (14.3)
Cell type, n (%)		
WD/MD	132 (85.2)	133 (95.0)
PD/MUC	2 (1.3)	7 (5.0)
Unknown	21 (13.5)	0 (0.0)
Lymphovascular invasion, n (%)		
Yes		25 (17.9)
No		115 (82.1)
Lateral margin, n (%)		
<1 mm	5 (3.2)	9 (6.4)
≥1 mm	150 (96.8)	131 (93.6)
Adjuvant treatment, n (%)		
Yes	0 (0.0)	30 (21.4)
No	155 (100.0)	110 (78.6)

WD = well differentiated; MD = moderately differentiated; PD = poorly differentiated; MUC = mucinous carcinoma.

pTis Rectal Cancer

Local recurrence occurred in 6 patients with pTis. The cumulative incidence of local recurrence was 2.6% at 5 years and 6.7% at 10 years (Fig. 1A). Of these 6 patients, 4 and 2 patients had local recurrence less than and more than 5 years postoperatively, suggesting a late local recurrence rate of 2.8% (2/72). The 4 patients with early recurrence underwent repeated TAE. Of these, 1 patient experienced local recurrence again 5 years after the second TAE, for which the patient underwent abdominoperineal resection and received adjuvant CCRT. The 2 patients with late recurrence were both characterized by a well-differentiated cell type, absence of LVI, and a negative resection margin. Local recurrence in these patients was observed at 68 and 97 months. Both patients underwent repeated TAE, and the pathology results were identical to those from the first surgery, indicating pTis.

Systemic recurrence occurred in 1 patient with pTis. The cumulative incidence of systemic recurrence was thus 0.8% at 5 years (Fig. 1A); no late systemic recurrence occurred in patients with pTis. The patient with systemic recurrence had a moderately differentiated cell type and negative resection margins. Liver and lung metastases were detected 38 months after TAE, and the patient was treated with palliative chemotherapy.

The Cox proportional hazards model was used to identify risk factors for local or systemic recurrence. Analysis revealed no significant risk factors for recurrence in patients with pTis who underwent TAE.

pT1 Rectal Cancer

Local recurrence occurred in 17 patients with pT1 who underwent TAE. The cumulative incidence of local recurrence was 11.1% at 5 years and 18.0% at 10 years (Fig. 1B). Of these 17 patients, 14 and 3 patients had local recurrence less than and more than 5 years postoperatively, indicating

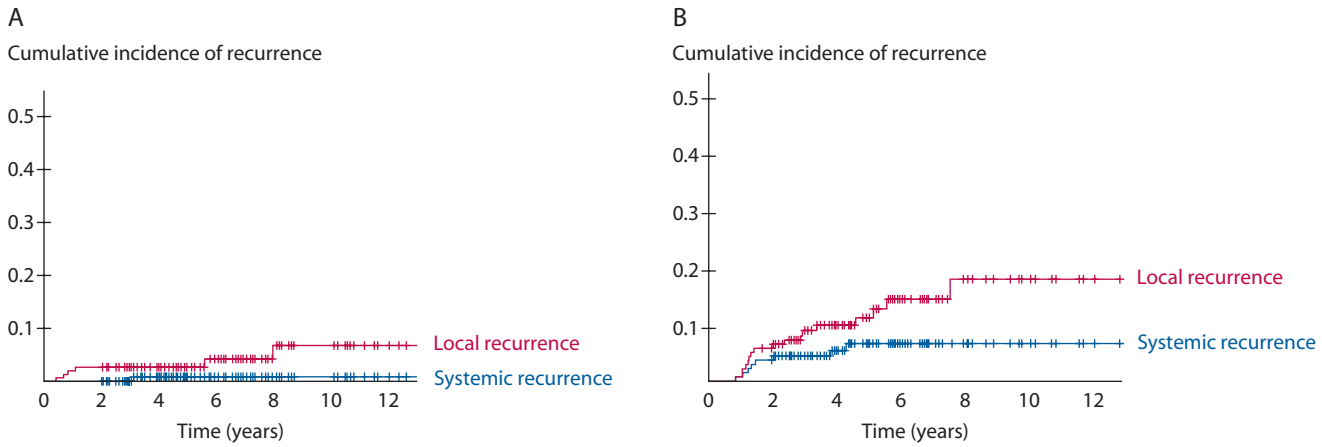

FIGURE 1. Cumulative incidence of recurrence in patients with early rectal cancer following transanal local excision. A, pTis rectal cancer. B, pT1 rectal cancer.

a late local recurrence rate of 3.7% (3/82). Among the 14 patients with early recurrence, 2 were treated with repeated TAE and adjuvant CCRT. Of these, 1 patient experienced local recurrence again 28 months after the second TAE, for which the patient underwent radical surgery. Ten of the 14 patients with early recurrence were treated with radical surgery and adjuvant therapies. The remaining 2 patients with early recurrence exhibited both local and systemic recurrence, and were treated with abdominoperineal resection and metastasectomy followed by adjuvant treatment. With regard to the 3 patients with late recurrence, the first was characterized by a moderately differentiated cell type, an invasion depth of sm3, presence of LVI, and negative resection margin. The patient experienced local recurrence at 63 months after TAE. However, the patient refused further treatment and died at 21 months from local recurrence. The second patient had a moderately differentiated cell type, an invasion depth of sm1, absence of LVI, and a positive resection margin. The patient experienced local recurrence at 68 months after TAE. The patient was treated with neoadjuvant CCRT and repeated TAE, but pathology results identified the tumor as ypT2. Thus, the patient underwent additional surgery with abdominoperineal resection and is currently alive. The third patient had a well-differentiated cell type, an invasion depth of sm3, presence of LVI, and a negative resection margin. The patient experienced local recurrence at 92 months after TAE, for which the patient underwent low anterior resection (pT3N2) and received adjuvant CCRT.

Systemic recurrence occurred in 8 patients with pT1. The cumulative incidence of systemic recurrence was 6.6% at 5 years, and all cases occurred within 5 years after TAE (Fig. 1B). Lung and liver metastases occurred in 3 patients and 1 patient, and these patients were treated with metastasectomy followed by adjuvant chemotherapy. One patient exhibited distant lymph node (LN) metastasis and received adjuvant chemotherapy. In addition, 1 patient had peritoneal seeding, but she did not undergo adjuvant treatment because of a poor general condition. Of the 8 total patients with systemic recurrence, the remaining 2 patients experienced both local and systemic recurrence; 1 patient had lung metastasis 15 months after TAE, and the other had liver metastasis 25 months after TAE. As previously described, both patients were treated with abdominoperineal resection and metastasectomy.

Using a multivariate analysis of risk factors for recurrence in pT1 patients who underwent TAE, we found that an invasion depth of sm3 and positive resection margin were associated with a higher risk of local recurrence ($p = 0.007$, HR = 4.916 and $p = 0.005$, HR = 7.167) (Table 2) (Figs. 2A and B). In addition, the presence of LVI was the only significant risk factor of systemic recurrence in these patients ($p = 0.003$, HR = 8.865) (Fig. 2C).

In addition, we compared the TAE and radical surgery pT1 patient groups. An invasion depth of sm3, poorly differentiated cell type, presence of LVI, negative resection margins, and greater distance from the anal verge were more frequent in the radical surgery group. Of the 205 patients with pT1 who underwent radical surgery, 62 were followed for 5to 10 years and 16 were followed for more than 10 years. The median follow-up duration was 50.6 (range, 24.2–218.4) months. Local recurrence occurred in 4 patients. The cumulative incidence of local recurrence was 1.7% at 5 years and 3.3% at 10 years. Of these 4 patients, late local recurrence occurred in 1 patient who had pT1N0, the absence of LVI, and a well-differentiated cell type. He experienced both local and systemic recurrence 66 months after radical surgery and was treated with palliative chemotherapy; however, the patient died 7 months after recurrence. Systemic recurrence occurred in 5 patients. The cumulative incidence of systemic recurrence was 2.1% at 5 years and 3.6% at 10 years. Late systemic recurrence occurred in only 1 patient, as previously described, indicating a late systemic recurrence rate of 1.3% (1/78).

TABLE 2. Risk factors for local recurrence of pT1 rectal cancer

	Univariate analysis		*Multivariate analysis*	
Variable	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*
Age				
≥60 y vs <60 y	2.076 (0.766–5.630)	0.15		
Sex				
Female vs male	1.038 (0.394–2.734)	0.94		
Preoperative CEA				
≥5 ng/mL vs <5 ng/mL	1.062 (0.762–3.195)	0.96		
Distance from anal verge				
>8 cm vs ≤8 cm	1.450 (0.501–4.198)	0.49		
Tumor size				
≥3 cm vs <3 cm	1.712 (0.633–4.631)	0.29		
Depth of invasion				
sm3 vs sm1–2	3.738 (1.225–11.130)	0.02	4.916 (1.556–15.536)	0.007
Cell type				
PD/MUC vs WD/MD	2.995 (0.680–13.194)	0.15		
Lymphovascular invasion				
Yes vs no	2.491 (0.920–6.740)	0.07		
Lateral margin				
<1 mm vs ≥1 mm	3.497 (1.003–12.192)	0.049	7.167 (1.830–28.071)	0.005
Adjuvant treatment				
Yes vs no	1.000 (0.260–3.841)	0.99		

WD = well differentiated; MD = moderately differentiated; PD = poorly differentiated; MUC = mucinous carcinoma.

DISCUSSION

In this study, we investigated the incidence of and risk factors related to recurrence, particularly late recurrence, in patients with pTis and pT1 rectal cancer following TAE. We observed a 10-year cumulative local recurrence rate of 6.7% in pTis patients and 18.0% in pT1 patients. The late local recurrence rate was 2.8% in pTis patients and 3.7% in pT1 patients. We found no evidence of late systemic recurrence 5 years after TAE. In pT1 patients who underwent TAE, an invasion depth of sm3 and a positive resection margin were associated with a higher risk of local recurrence, and the presence of LVI was a significant risk factor of systemic recurrence.

Many previous studies have reported the oncologic feasibility of TAE for early rectal cancer. These reports showed that TAE provides remarkable oncologic results with a local recurrence rate between 4% and 14%.[15,16] In contrast, some reports have shown higher local recurrence rates after TAE.[17,18] Stipa et al[19] reported a 5-year recurrence rate of 0% in pTis and 13.0% in pT1 rectal cancer after TAE. Wei et al[10] reported a 5-year recurrence rate of 6.1% in pTis rectal cancer after TAE. Morino et al[14] and Mellgren et al[8] reported a 5-year recurrence rate of 10.4% and 18.0% in pT1 rectal cancer after TAE. Most studies regarding oncologic outcomes of TAE have reported 5-year results, and there are few studies investigating the results of patients with early rectal cancer 10 years after surgery.

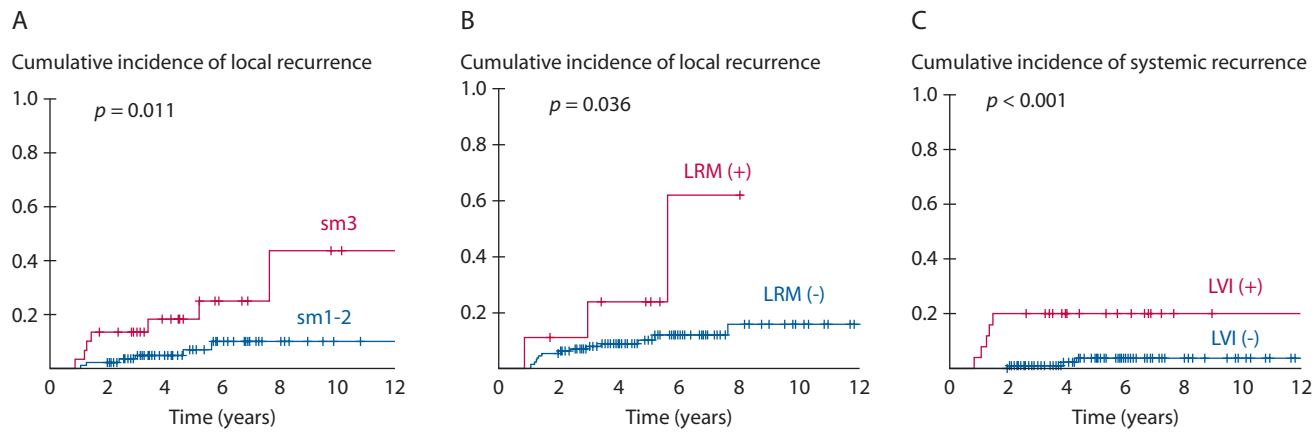

FIGURE 2. Cumulative incidence of recurrence in patients with pT1 rectal cancer following transanal local excision. A, Local recurrence according to depth of submucosal invasion (sm). B, Local recurrence according to lateral resection margin (LRM). C, Systemic recurrence according to lymphovascular invasion (LVI).

One such study reported an 11% cumulative recurrence rate at 10 years after TAE in patients with pT1 rectal cancer.[12] In addition, a report about the long-term survival of patients with pT1 rectal cancer after TAE revealed that the peak period for cancer recurrence is between 4 and 8 years.[18] There are, to date, no reports about late recurrence of pTis rectal cancer.

Many studies have been performed to identify risk factors for recurrence in patients with early rectal cancer following TAE. Wei et al[10] reported that recurrence in patients with pTis rectal cancer after TAE was significantly associated with a large diameter and sessile growth. Some previously published data showed independent predictors for the local recurrence of pT1 rectal cancer, such as depth of submucosal invasion, LVI, tumor grade, tumor budding, tumor size, location of tumors, and resection margin.[20–22] The National Comprehensive Cancer Network guidelines indicate that local excision can be conducted for pT1 rectal cancers that are <30% in bowel circumference, <3 cm in size, mobile, well to moderately differentiated cell type, and without lymphovascular or perineural invasion.[23]

Transanal local excision is being increasingly performed for early rectal cancer because it is a less invasive procedure and has similar oncologic outcomes to radical surgery. However, there is still controversy about local recurrence rates after TAE. In this study, we compared TAE and radical surgery pT1 patient groups. Despite unfavorable histologic features, the recurrence rate was lower in the radical surgery group than in the TAE group, and the late recurrence rate was only 1.3% in the radical surgery group.

Lymph node metastasis was observed in 27 patients in the radical surgery group, and 14 of these 27 patients had cN0 rectal cancer. The major limitation of TAE is the omission of LN dissection. Therefore, the risk of recurrence for early rectal cancer after TAE may be closely associated with occult LN metastasis. In addition, the depth of submucosal invasion has been reported to be a significant predictive factor for LN metastasis. Some studies have reported that the rate of LN metastasis was 0% to 1.8% when the depth of submucosal invasion was less than 1000 μm, compared with a metastasis rate of 12.8% to 13.8% for submucosal invasion beyond 1000 μm.[24–26] Similarly, another study showed that the rate of LN metastasis was 0.7% if the depth of submucosal invasion was less than 2000 μm and 15.5% for an invasion depth greater than 2000 μm.[27] Likewise, Kikuchi et al[13] showed 3.2% and 12.0% LN metastases in sm1 and sm3 invasion. Lymphovascular invasion and tumor grade were also considered significant predictive factors for LN metastasis in several studies.[20,21,24–27] In addition, factors such as tumor budding, tumor location, or tumor size may be associated with LN metastasis.[13,20,28] In patients with unfavorable features, adjuvant treatments after TAE can be performed to prevent recurrence. However, there are many reports that additional adjuvant treatments have limited effects on preventing recurrence in pT1 patients with unfavorable features.[18,28,29] In our study, overall recurrence was confirmed in 5 (3 local and 2 systemic recurrences) of 30 patients who received adjuvant CCRT. However, adjuvant CCRT did not reduce the recurrence rate of pT1 patients. Therefore, it is important to properly select patients for TAE and perform close follow-up after TAE to increase the early detection of recurrence.

The current study has several limitations: such as retrospective study by a single institution, our inability to review the Kikuchi submucosal staging for all included patients, and the presence of censoring cases. However, this study is meaningful because it is the first focusing on late recurrence in patients with pTis and pT1 rectal cancer following TAE. In our institution, 5-year postoperative surveillance after surgery for rectal cancer is the current standard of care. In this study, however, we observed recurrences between 5 and 10 years, and these later recurrences were not rare. Therefore, extending postoperative surveillance up to 10 years after surgery to detect recurrence is a valid strategy to improve outcomes. In particular, a more stringent postoperative surveillance schedule may be needed for patients who have early rectal cancer with unfavorable histologic features. Physical examination and sigmoidoscopy may be appropriate for surveillance beyond 5 years, because all cases of late recurrence occurred only locally, thus providing a more cost-effective standard of care.

CONCLUSION

We found late recurrences occurring in patients with early rectal cancer who previously underwent TAE. Thus, TAE is recommended selectively for patients with biologically favorable tumors, and 10-year postoperative surveillance should be considered for these patients.

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