and planes of dissection. Furthermore, the radicality of oncologic surgery was maintained [24].

Conclusions

Surgeons who have completed basic surgical residency but have limited colorectal surgery experience can learn both open and laparoscopic colorectal surgery simultaneously in an effective manner under supervision by well-experienced surgeons.

Disclosures Authors Maeda, Tan, Konishi, Tsujinaka, Mizokami, Sasaki, and Kawamura have no conflicts of interest or financial ties to disclosure.

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ORIGINAL ARTICLE – COLORECTAL CANCER

Is Total Mesorectal Excision Always Necessary for T1–T2 Lower Rectal Cancer?

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ABSTRACT

Background. The goal of this multicenter study was to clarify the determinants of local excision for patients with T1–T2 lower rectal cancer.

Methods. Data from 567 consecutive patients who underwent radical resection for T1–T2 lower rectal cancer at 12 institutions between 1991 and 1998 were reviewed. Rates of lymph node metastasis were investigated using a tree analysis, which was hierarchized using independent risk factors for nodal involvement.

Results. The independent risk factors for lymph node metastasis were female gender, depth of tumor invasion, histology other than well-differentiated adenocarcinoma, and lymphatic invasion. According to the first three parameters that can be obtained preoperatively, only 0.99% of the patients without risk factors had lymph node metastasis. On the other hand, even if the lower rectal cancer was at stage T1, women with histological types other than well-differentiated adenocarcinoma had an approximately 30% probability of having lymph node metastasis. Lymphatic invasion was most useful to predict nodal involvement among patients with T2 lower rectal cancer. The rates of lymph node metastasis in T2 patients with and without lymphatic invasion were 32.9% and 9.1%, respectively.

Conclusions. Gender is one of the most important predictors for lymph node metastasis in patients with early distal rectal cancer. Three parameters, including depth of tumor invasion, histology, and gender, are useful determinants for local excision. Additional studies are required to establish the minimum optimal treatment for T2 lower rectal cancer.

Total mesorectal excision (TME) has recently achieved excellent oncological outcomes for patients with rectal cancer.[1] The oncological outcome of rectal cancer is usually worse than that of colon cancer; one reason for this is the higher local recurrence rate after curative resection for rectal cancer.[2] Although TME has decreased the risk of local recurrence, some patients with rectal cancer undergo abdominoperineal resection (APR) followed by permanent colostomy. Some patients develop complications after radical resection for rectal cancer, despite sphincter-sparing procedures.

Local excision is an important treatment option for early distal rectal cancer, because complications can arise after

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radical resection. However, one of the problems associated with local excision for rectal cancer is the unsatisfactory oncological outcome. The reported local recurrence rates after local excision for T1 and T2 tumors range from 6.6% to 18% and from 17% to 37%, respectively.[3–7] A recent study found that patients with T1 rectal cancer treated by local excision have a threefold to fivefold higher risk of tumor recurrence than those treated by radical resection.[3]

Criteria for local excision to treat early rectal cancer have not been established. In this study, the indication of local excision for patients with T1–T2 lower rectal cancer was examined using a model hierarchized with independent risk factors for lymph node metastasis.

PATIENTS AND METHODS

We enrolled 567 patients with T1–T2 lower rectal cancer who underwent curative resection at 12 institutions (all members of the Japanese Society for Cancer of the Colon and Rectum) between 1991 and 1998. The local ethics committee of each institution approved this study. Lower rectal cancer was defined as the distal margin of tumor located below the peritoneal reflection. All patients received tumor-specific mesorectal excision (TSME), meaning that the rectum and mesorectum were removed with an appropriate distal resection margin of >2 cm. Patients who underwent transanal local excision or endoscopic mucosal resection were excluded from this study. Other exclusion criteria were cancers associated with ulcerative colitis, Crohn's disease, or familial adenomatous polyposis.

Preoperative investigations included barium enema examination, colonoscopy, endoscopic ultrasonography, chest x-ray, ultrasonography (US), and/or computed tomography (CT) of the liver, as well as blood tests for carcinoembryonic antigen (CEA). Five- to 10-year postoperative follow-up at most of the participating institutions comprised serum tumor marker measurements every 3 months for the first 3 years and every 6 months for the next 2 years, hepatic imaging (US and/or CT) and chest x-rays every 3 to 6 months, and annual or biennial pelvic CT and colonoscopy.

We analyzed the risk factors for lymph node metastasis in 567 patients who underwent radical resection. To determine the criteria for local excision in patients with T1–T2 lower rectal cancer, the rates of lymph node metastasis were compared according to the number of risk factors for lymph node metastasis.

STATISTICAL ANALYSIS

Data were statistically analyzed using the StatView 5.0 statistical package (Abacus Concepts, Inc., Berkeley, CA). All data are expressed as median ± standard deviation. Associations between each parameter and lymph node metastasis were analyzed using the χ^2 test. Independent risk factors for lymph node metastasis were determined using logistic regression analysis. Differences in numbers of lymph node metastases were analyzed using the Mann–Whitney U test between two groups and by the Kruskal–Wallis test among three or more groups. The actuarial survival of the patients was calculated using the Kaplan–Meier method, and overall survival rates in all groups were compared using the log-rank test. Statistical significance was established at $P < 0.05$ for all results.

RESULTS

Table 1 shows the characteristics of the participating patients. Surgical procedures, tumor size, histology of the primary rectal tumor, rate of lymph node metastasis, and lymphatic and venous invasion significantly differed between patients with T1 and T2 rectal cancer.

Risk Factors for Lymph Node Metastasis

The rates of lymph node metastasis in patients with T1 and T2 lower rectal cancer were 8.6% and 25.7%, respectively. Parameters, such as gender, age, tumor size and histology, T-factor, lymphatic invasion, and venous invasion, were analyzed as potential risk factors for lymph node metastasis in 567 patients with T1–T2 lower rectal cancer scheduled for radical resection. Univariate analysis revealed that female gender ($P = 0.0006$), histology ($P < 0.0001$), T factor ($P < 0.0001$), lymphatic invasion ($P < 0.0001$), and venous invasion ($P < 0.0001$) were risk factors for lymph node metastasis (Table 2). Multivariate analysis revealed that female gender ($P = 0.0009$), histology ($P = 0.017$), T-factor ($P = 0.0085$), and lymphatic invasion ($P < 0.0001$) were independent risk factors for lymph node metastasis in patients with early lower rectal cancers (Table 2).

Tree Analysis of the Rate of Lymph Node Metastasis

The 567 patients with T1–T2 lower rectal cancer were hierarchized for tree analysis according to preoperatively ascertainable T-factor, gender, and histology (in that order) among the independent risk factors for lymph node metastasis (Fig. 1). The rates of lymph node metastasis according to the number of risk factors were 0.99%, 10.6–15.5%, 26.3–30.4%, and 37.3% in patients with zero, one, two, and all three risk factors, respectively. Only 1 of 101 patients without any factors had lymph node metastasis. On the other hand, even if women had T1 lower rectal cancer, 30.4% of those with histological types other than well-differentiated adenocarcinoma had lymph node metastasis.

TABLE 1 Clinicopathologic characteristics of 567 patients with T1–T2 lower rectal cancer

Parameters	T1 (%)	T2 (%)	*P* value
Gender			
Male	144/346 (41.6)	202/346 (58.4)	NS
Female	89/221 (40.3)	132/221 (59.7)	
Age (yr)			
<61	118/288 (41.0)	170/288 (59.0)	NS
≥61	115/278 (41.4)	163/278 (58.6)	
Unknown		1	
Surgical procedure			
APR	28/141 (19.9)	113/141 (80.1)	<0.0001
Hartmann	3/9 (33.3)	6/9 (66.7)	
LAR	202/417 (48.4)	215/417 (51.6)	
Size (cm)			
≤2	128/173 (74.0)	45/173 (26.0)	<0.0001
>2	98/386 (25.4)	288/386 (74.6)	
Unknown	7	1	
Histology			
Well-differentiated Adenocarcinoma	167/327 (51.1)	160/327 (48.9)	<0.0001
Others	64/238 (26.9)	174/238 (73.1)	
Unknown	2		
Lymph node metastasis			
Absent	213/461 (46.2)	248/461 (53.8)	<0.0001
Present	20/106 (18.9)	86/106 (81.1)	
Lymphatic invasion			
Absent	142/241 (58.9)	99/241 (41.1)	<0.0001
Present	86/320 (26.9)	234/320 (73.1)	
Unknown	5	1	
Venous invasion			
Absent	169/317 (53.3)	148/317 (46.7)	<0.0001
Present	59/244 (24.2)	185/244 (75.8)	
Unknown	5	1	

APR abdominoperineal resection, *LAR* low anterior resection, *Others* moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, or mucinous adenocarcinoma

Multivariate analysis revealed that female gender, histological type other than well-differentiated adenocarcinoma, and venous invasion were independent risk factors for lymph node metastasis in patients with T1 lower rectal cancer (Table 3). Lymphatic invasion and gender were independent risk factors for nodal involvement among patients with T2 lower rectal cancer (Table 4). Figure 2 shows a tree analysis of the lymph node metastasis rate, including lymphatic invasion as a risk factor. The rate of lymph node metastasis in patients without lymphatic invasion was 9.1%.

Number of Lymph Node Metastases

We examined a median of 19 lymph nodes in 87 (15.3%) and 20 (3.5%) patients with N1 and N2 metastases, respectively. The numbers of lymph node metastases in 567 patients with T1–T2 lower rectal cancer and zero, one, two, and three risk factors (Fig. 3) were 0 ± 0.1 (0–1), 0 ± 1.1 (0–11), 0 ± 1.8 (0–13), 0 ± 3.2 (0–26), respectively. The number of lymph node metastases significantly differed among the four groups according to the number of risk factors ($P < 0.0001$) but not between patients with two and three risk factors.

Recurrence in Patients with T1–T2 Lower Rectal Cancer

During a median follow-up period of 4.9 ± 2.3 years, the local recurrence rates among patients with T1 and T2 lower rectal cancer were 2.1% (5/233) and 6.0% (20/334), respectively. Among these 25 patients, 12, 1, 3, 3, and 4 of them underwent curative resection, palliative resection, radiotherapy, and chemoradiotherapy together with chemotherapy, respectively. Two patients did not receive any treatment. The median survival after recurrence was 19

TABLE 2 Risk factors for lymph node metastasis in 567 patients with T1–T2 lower rectal cancer determined by univariate and multivariate analysis

Parameters	No. of lymph node metastasis (%)	Univariate analysis			Multivariate analysis		
		P value	OR	95% CI	*P* value	OR	95% CI
Gender							
Male	49/346 (14.2)	0.0006	1		0.0009	1	
Female	57/221 (25.8)		2.50	1.62–3.85		2.18	1.38–3.46
Age (yr)							
<61	57/288 (19.8)	NS	1				
≥61	49/278 (17.6)		0.867	0.57–1.32			
Unknown	1						
Size (cm)							
≤2	25/173 (14.5)	NS	1				
>2	80/386 (20.7)		1.55	0.95–2.53			
Unknown	8						
Histology							
Well-differentiated adenocarcinoma	39/327 (11.9)	<0.0001	1		0.017	1	
Others	67/238 (28.2)		2.89	1.87–4.48		1.79	1.11–2.88
Unknown	2						
T-factor							
T1	20/233 (8.6)	<0.0001	1		0.0085	1	
T2	86/334 (25.7)		3.69	2.20–6.21		2.13	1.22–3.77
Lymphatic invasion							
Absent	15/241 (6.1)	<0.0001	1		<0.0001	1	
Present	91/320 (28.4)		5.99	3.37–10.65		3.95	2.11–7.46
Unknown	6						
Venous invasion							
Absent	40/317 (12.6)	<0.0001	1		NS	1	
Present	66/244 (27.0)		2.57	1.66–3.97		1.25	0.76–2.07
Unknown	6						

OR odds ratio, *CI* confidence interval, *Others* moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, or mucinous adenocarcinoma

(range, 3–61) months. Total recurrence rates in this study were 3.4% (8/233) and 12.3% (41/334) among patients with T1 and T2 lower rectal cancer, respectively.

Prognosis of Patients with T1–T2 Lower Rectal Cancer

Relapse-free ($P = 0.0016$) and overall ($P = 0.011$) survival significantly differed between patients with T1 and T2 rectal cancer (Fig. 4). The 5-year relapse-free and overall survival rates were 90.6% and 91.7% in patients with T1 tumors and 82.6% and 86.8% in those with T2 tumors, respectively.

DISCUSSION

The oncological outcome of radical resection for rectal cancer has improved since the adoption of TME.[8] A reasonable quality of life and curability is required to treat patients with rectal cancer, especially those with lower rectal cancer. Therefore, early distal rectal cancer has been treated by local excision in some patients, despite the absence of definitive criteria for local excision. Because the rates of lymph node metastasis in rectal cancer range from 6.5–18% in T1 and 17–38% in T2, respectively, selecting the appropriate surgical procedure for patients with early rectal cancer by predicting lymph node metastasis is important.[6,9–11]

The present study demonstrated that gender, in addition to depth of tumor invasion, histological type, and lymphatic invasion, is a predictive marker for lymph node metastasis in early lower rectal cancer. Approximately 1% of men with well-differentiated T1 adenocarcinoma of the lower rectum had lymph node metastasis. Such patients are suitable candidates for local excision. On the other hand, the rate of lymph node metastasis in women with histological types other than

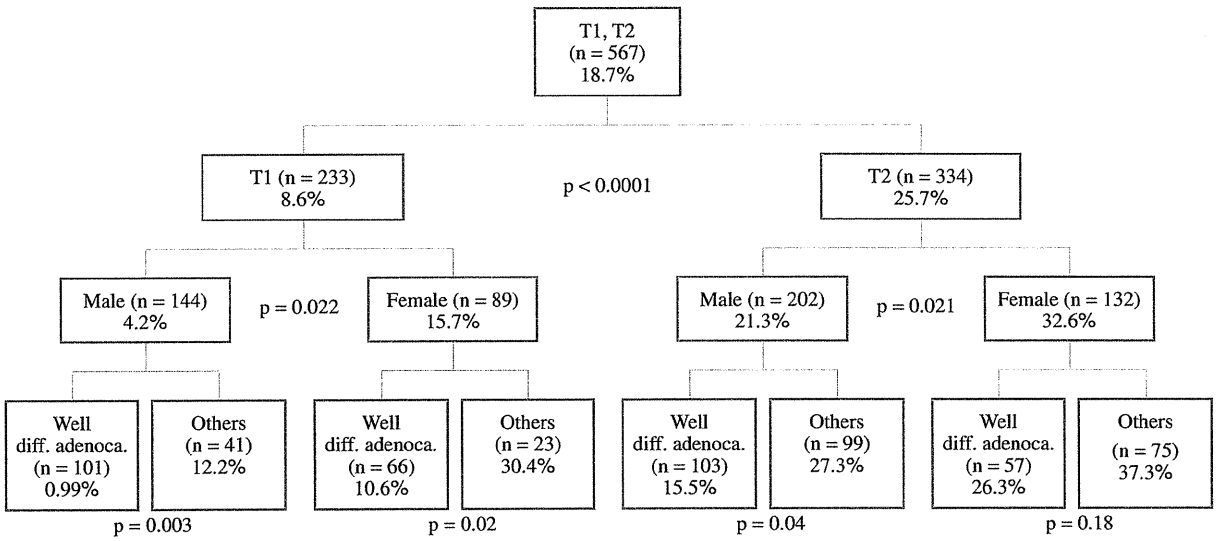

FIG. 1 Rates of lymph node metastasis in patients with T1–T2 lower rectal cancer hierarchized by depth of tumor invasion, gender, and histologic type as risk factors

TABLE 3 Risk factors for lymph node metastasis in 233 patients with T1 lower rectal cancer

Parameters	No. of lymph node metastasis (%)	Univariate analysis *P* value	Multivariate analysis		
			P value	OR	95% CI
Gender					
Male	6/144 (4.2)	0.0022	0.0019	1	
Female	14/89 (15.7)			5.68	1.90–16.9
Age (yr)					
<61	13/118 (11.0)	NS			
≥61	7/115 (6.1)				
Size (cm)					
≤2	14/128 (10.9)	NS			
>2	5/98 (5.1)				
Unknown	7				
Histology					
Well-differentiated adenocarcinoma	8/167 (4.8)	0.0007	0.010	1	
Others	12/64 (18.8)			1.5	1.4–11.1
Lymphatic invasion					
Absent	6/142 (4.2)	0.0018	0.059	1	
Present	14/86 (16.3)			2.87	0.96–8.62
Unknown	5				
Venous invasion					
Absent	9/169 (5.3)	0.0018	0.041	1	
Present	11/59 (18.6)			2.99	1.04–8.55
Unknown	5				

OR odds ratio, *CI* confidence interval, *Others* moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, or mucinous adenocarcinoma

well-differentiated adenocarcinoma was 30.4%, even when the tumor did not invade the muscularis propria. Therefore, radical resection should be indicated for these patients. The reason why female gender is one of the risk factors for nodal involvement in T1–T2 rectal cancer is unclear in the present study. One of the possible

TABLE 4 Risk factors for lymph node metastasis in 334 patients with T2 lower rectal cancer

Parameters	No. of lymph node metastasis (%)	Univariate analysis *P* value	Multivariate analysis *P* value	OR	95% CI
Gender					
Male	43/202 (21.3)	0.021	0.033	1	
Female	43/89 (32.6)			2.18	1.38–3.46
Age (yr)					
<61	44/170 (25.9)	NS			
≥61	42/163 (25.8)				
Unknown	1				
Size (cm)					
≤2	11/45 (24.4)	NS			
>2	75/288 (26.0)				
Unknown	1				
Histology					
Well-differentiated adenocarcinoma	31/160 (19.4)	0.011	0.14	1	
Others	55/174 (31.6)			1.5	0.88–2.56
Lymphatic invasion					
Absent	9/99 (9.1)	<0.0001	0.0001	1	
Present	77/234 (32.9)			4.65	2.11–10.2
Unknown	1				
Venous invasion					
Absent	31/148 (20.9)	0.069	0.92	1	
Present	55/185 (29.7)			0.97	0.55–1.71
Unknown	1				

OR odds ratio, *CI* confidence interval, *Others* moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, or mucinous adenocarcinoma

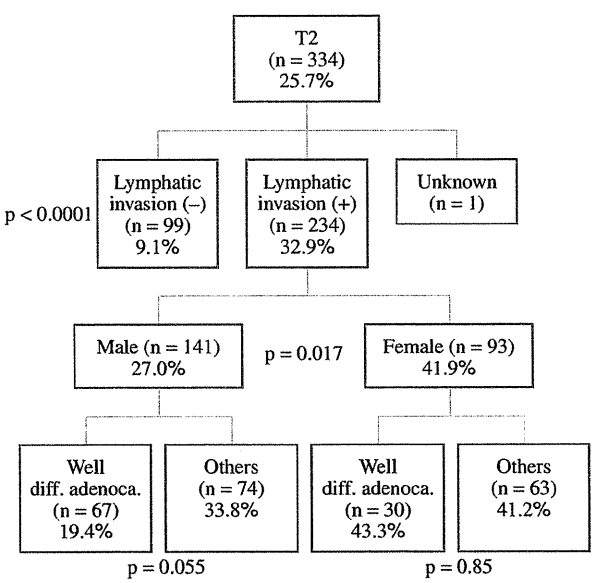

FIG. 2 Classification tree for risk of lymph node metastasis in patients with T2 lower rectal cancer

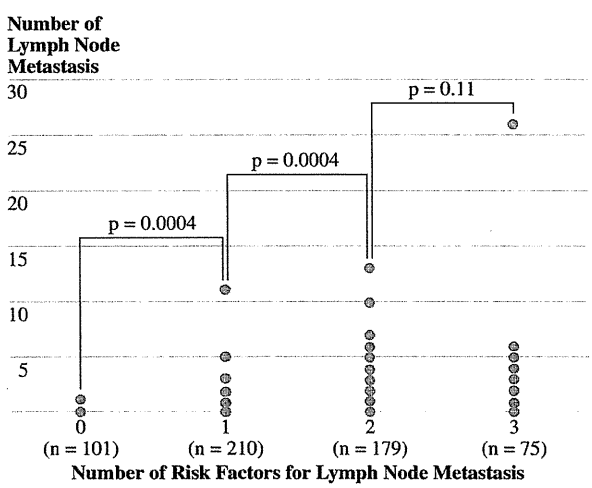

FIG. 3 Number of lymph node metastases according to numbers of risk factors

explanations might be a hormone, such as estrogen. Estrogen receptor is expressed in approximately 70% of colorectal adenocarcinoma.[12] Moreover, a previous study demonstrated that tamoxifen inhibited metastasis from colorectal cancer in a murine model.[13]

Further studies are required to determine therapeutic strategies for patients with T1 lower rectal cancer. Radical resection might be feasible from the viewpoint of

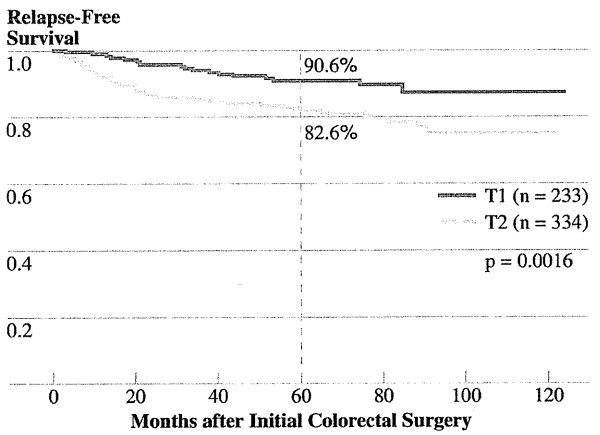

FIG. 4 Relapse-free survival after radical resection for T1 and T2 lower rectal cancer

oncological outcome, although the quality of life worsens after radical surgery compared with that after local excision. Local excision with informed consent would be one option for such patients.

Others have reported local recurrence rates of 4% to 18% after local excision alone for T1 rectal cancer, although those rates were >10% in most studies.[3,4,14–18] Furthermore, local recurrence rates after the local excision with adjuvant therapy in patients with T1 rectal cancer were 0% to 38%.[14,18–21] An optimal indication for local excision in patients with T1 rectal cancer is urgently required. The present study suggests that approximately 40% of patients with T1 lower rectal cancer could have avoided radical resection if the present classification had been applied. Additional studies are necessary to validate our data along with a large-scale, randomized, controlled study to compare the outcomes of radical resection and local excision with adjuvant therapy, such as radiation.

The present study also demonstrated that risk factors for lymph node metastasis, such as gender, histologic type, and the depth of tumor invasion, also are useful to predict numbers of lymph node metastases. Fewer risk factors for lymph node metastasis mean less development of lymph node metastasis. These findings also suggest that gender, histologic type, and depth of tumor invasion are useful to distinguish which patients should be indicated for local excision of early distal rectal cancer.

Lymphatic invasion was the most relevant risk factor to lymph node metastasis in patients with T2 lower rectal cancer. The rates of lymph node metastasis in men and women with T2 lower rectal cancer without lymphatic invasion were 8.3% and 10.3%, respectively. The feasibility of local excision for these patients should be carefully considered, because the present standard therapy for T2 lower rectal cancer seems to be radical resection. However, an initial option for these patients could be local excision. After a pathological examination, careful follow-up under informed consent or chemoradiotherapy might be indicated for patients without lymphatic invasion. On the other hand, radical resection should be added for patients with lymphatic invasion, because the rate of lymph node metastasis for such patients in this study was >30%. Others have reported 5-year local recurrence rates of 15% to 24% in patients with T2 rectal cancer after local excision and adjuvant therapy.[14,18–20,22,23]

The American College of Surgeons Oncology Group is presently conducting a phase II trial of neoadjuvant chemoradiation and local excision for uT2uN0 rectal cancer. The purpose of that study is to determine the rate of disease-free survival at 3 years in patients with ultrasound-staged uT2uN0 rectal cancer treated with chemoradiotherapy followed by local excision.[24] While the results of that study are anticipated, more effective therapeutic strategies are clearly required for patients with T2 lower rectal cancer from the perspective of posttreatment quality of life.

CONCLUSIONS

Gender is an independent determinant of lymph node metastasis in patients with early distal rectal cancer. The combination of gender, histologic type, and depth of tumor invasion is useful to determine indications for local excision in these patients. However, radical resection ought to be recommended for patients with T2 lower rectal cancer. Additional studies should establish the minimum optimal treatment for early distal rectal cancer.

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