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Feasibility of Transanal Local Excision Following Chemoradiation for Lower Rectal Cancer

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Abstract. *Background: The aim of this study was to evaluate the clinical outcome of transanal local excision for cT1/cT2 lower rectal cancer following pre-operative chemoradiation therapy (CRT). Patients and Methods: Eleven patients who underwent pre-operative CRT for cT1/cT2 lower rectal cancer were retrospectively enrolled in this study. Surgical outcomes were compared between the group that underwent trasanal local excision (TLE) (n=6) and that which underwent total mesorectal excision (TME) (n=5). Results: Regarding surgical outcomes, there were significant differences between the two groups in operative time, rate of anal preservation and post-operative hospital stay. There were no differences between the two groups in the disease-free or overall survival rates. Conclusion: The TLE following CRT had acceptable surgical outcomes. Surgeons should consider TLE following CRT for cT1/cT2 lower rectal cancer as a treatment option in selected patients.*

Colorectal cancer is the most common cancer in the world (1), and the second most common cause of cancer-related deaths in Japan (2). For decades in Japan, surgery was the recommended first approach for the treatment of localized lower rectal cancer. However, patients with lower rectal cancer who underwent radical surgery had a poorer quality of life because of anal dysfunction (3).

In Western countries, patients with locally advanced rectal cancer are routinely treated with pre-operative chemoradiotherapy (CRT) or chemotherapy. Randomized phase III trials have shown that pre-operative CRT significantly improves the local control of cancer as compared to pre-operative radiation alone or post-operative CRT (4, 6). With an increased benefit for CRT patients and advancements in surgical techniques, the possibility of anal preservation for selected patients has increased.

In 2005, Habr-Gama *et al.* first reported the results of non-operative management after CRT for early rectal cancer (7). They concluded that surgical resection may not improve the long-term outcome after CRT. Since then, a watch-and-wait approach is considered to be one of the management options (8).

Transanal local excision (TLE) has an acceptable surgical outcome when performed as a less invasive treatment for mucosal rectal cancer. In massive submucosal (SM) or *muscularis propria* (MP) lower rectal cancer, TLE is contra-indicated due to the risk of non-radical surgery (lymph node metastasis, positive surgical margin, vessel invasions). cT1/cT2 lower rectal cancer would be shrunk to a cCR state or mucosal invasion after CRT. Some studies have demonstrated the feasibility of TLE for cT1/cT2 lower rectal cancer after CRT (9, 10). Compared to a watch-and-wait approach, TLE provides the advantage of allowing pathological assessment of the tumor with less invasiveness. The treatment strategy for such down-staged cases has not been fully established, and risk factors associated with post-operative recurrence of cancer after TLE should be clarified.

The aim of this study was to evaluate the clinical outcome of TLE for cT1/cT2 lower rectal cancer following pre-operative CRT.

Patients and Methods

Patients. Eleven patients who underwent pre-operative CRT for cT1/cT2 lower rectal cancer between 2006 and 2013 at the Tokushima University Hospital were retrospectively enrolled in this study. These 11 patients comprised seven men and four women with a median age of 64.0 years (range=52-76 years). The patient characteristics are shown in Table I. The patients were divided into

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Key Words: Chemoradiation therapy, local excision, total mesorectal excision, disease-free survival, overall survival, clinical complete response, low anterior resection.

Table I. *Comparison of variables between trasanal local excision (TLE) and total mesorectal excision (TME) groups.*

Variable	TLE (n=6)	TME (n=5)	p-Value
Patient factors			
Age (years)	63±11 (52-78)	65±13 (47-76)	0.82
Gender (M/F)	4/2	3/2	0.82
CEA (ng/ml)	1.3 (0.9-6.0)	1.1 (0.8-2.8)	0.65
CA19-9 (U/ml)	15 (5-33)	9 (5-34)	0.86
Tumor location (Rb/P)	5/1	5/0	0.34
Tumor diameter (mm)	28±17 (15-60)	18±9 (7-28)	0.25
cT1/2 (SM/MP)	4/2	0/5	<0.05
Operative factors			
Surgical procedure (LE/LAR) (n)	6/0	0/5	<0.01
Intraoperative bleeding (ml)	46.7±35.7	19.0±5.0	0.17
Operative time (min)	80.2±58.7	289.6±48.2	<0.05
Rate of anal preservation (%)	100	40	<0.05
Pathological factors (n)			
Grade (0/1a/1b/2/3)	2/3/0/0/1	0/1/1/1/2	0.26
ypT0/1/2 (0/M/SM/MP)	1/2/2/1	2/0/3/0	0.32
ypStage (0/1/2/3)	3/3/0/0	1/3/0/1	0.38
ly (0/1)	5/1	5/0	0.34
v (0/1)	5/1	4/1	0.89
Differentiation (tub1/tub2)	5/1	3/2	0.91
Margin (negative/positive)	5/1	5/0	0.34
Postoperative. variables			
Morbidity (%)	0	40	0.09
Anastomotic bleeding (%)	0	20	0.25
Anastomotic stenosis (%)	0	20	0.25
Mortality (%)	0	0	UA
Length of hospital stay (days)	9.3±4.0	22.4±6.2	<0.05

Data are mean with range. M: Male; F: female; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; Rb: rectum below the peritoneal reflection; P: proctodeum; SM: submucosa; MP: *muscularis propria*; LE: local excision; LAR: low anterior resection; UA: unanalyzable.

two groups, the TLE group (n=6) and the total mesorectal excision (TME) group (n=5). The patient characteristics and the short- and long-term outcomes, including local recurrence, were compared between the two groups. Principally, neoadjuvant CRT followed by transabdominal surgery with TME was performed for patients with locally advanced lower rectal cancer. However, if the patients in whom down-staging of the tumor (cT1/cT2→T1 or cCR) was achieved refused transabdominal resection, TLE was performed after obtaining informed consent.

Follow-up. All the patients were followed-up after discharge using a serum tumor marker test every 3 months, enhanced CT scan every 6 months, and by colonoscopy every year. The follow-up period ranged from 4 years to 10 years and 5 months (median: 5 years and 0 months).

Pre-operative CRT. The protocol for CRT was previously reported (8). Patients received CRT with a total dose of 40 Gy of pelvic irradiation, which was administered 5 times per week with a daily fraction of 2 Gy using a four-field technique. Radiation was delivered concomitantly with TS-1 (tegafur/gimeracil/oteracil) (80 mg/m^2) or UFT (tegafur) (300 mg/m^2). Ten patients received the TS-1 or UFT regimen and one received the SOX-Bv regimen, which consisted of the TS-1 regimen with the addition of oxaliplatin (50 mg/m^2) administered on days1, 8, 15 and 22, and bevacizumab (5 mg/kg) administered on days1 and 15. Surgery was performed 6-8 weeks after completion of pre-operative CRT.

Statistical analysis. All statistical analysis was calculated through JMP 8 software (SAS Institute, Cary, NC, USA). The clinicopathological variables were analyzed with the chi-square test and Mann–Whitney *U*-test. Survival curves were calculated using the Kaplan–Meier method and compared using the Wilcoxon test. Statistical significance was defined as differences with $p<0.05$.

Results

Table I shows a comparison of variables between the TLE and TME groups. There were no significant differences with regard to age, gender, tumor marker, tumor location, and tumor diameter between the two groups, although the TLE group had tumors that were at an earlier cT stage ($p<0.05$). All patients in the TME group underwent low anterior resection (LAR). Regarding surgical outcomes, using TLE the operative time was significantly shortened by two-thirds to 80.2±58.7 minutes ($p<0.05$), and the rate of anal preservation was absolute ($p<0.05$) compared with TME. Morbidity was 0% in the TLE group, and 40% in the TME group (anastomotic bleeding: n=1; anastomotic stenosis n=1). Moreover, the post-operative hospital stay was more than halved by TLE compared with TME ($p<0.05$).

Disease-free (DFS) (Figure 1a) and overall (OS) (Figure 1b) survival rates were not significantly different between the two groups. Table II shows an overview of the patients who underwent TLE. Two out of six patients had post-operative local recurrence of cancer of the rectum after TLE. One recurrent case (case 2) had a 6 cm diameter tumor in the lower rectum pre-CRT (Figure 2a) and received CRT (S-1 regimen). Down-staging of the tumor was achieved (Figure 2b) and a TLE was performed. However, the surgical margin was positive for malignant cells in the pathological examination. Additional resection was not performed due to patient's refusal to undergo further surgery. Local recurrence was found by colonoscopy 1 year after TLE (Figure 2c) and a salvage laparoscopic LAR was performed. The patient died of gastric cancer 9 years after salvage surgery without recurrence of rectal cancer. In another recurrent case (case 6), the patient had cT1 lower rectal cancer (Figure 3a) with a high level of carcinoembryonic antigen (CEA) (6.0 ng/ml), and received CRT (SOX-Bv regimen). However, down-staging of the tumor was not achieved (Figure 3b), and CEA did not normalize after CRT (CEA 5.7 ng/ml). The patient refused transabdominal resection and TLE was performed. Pathological examination revealed SM invasion with ly1 and

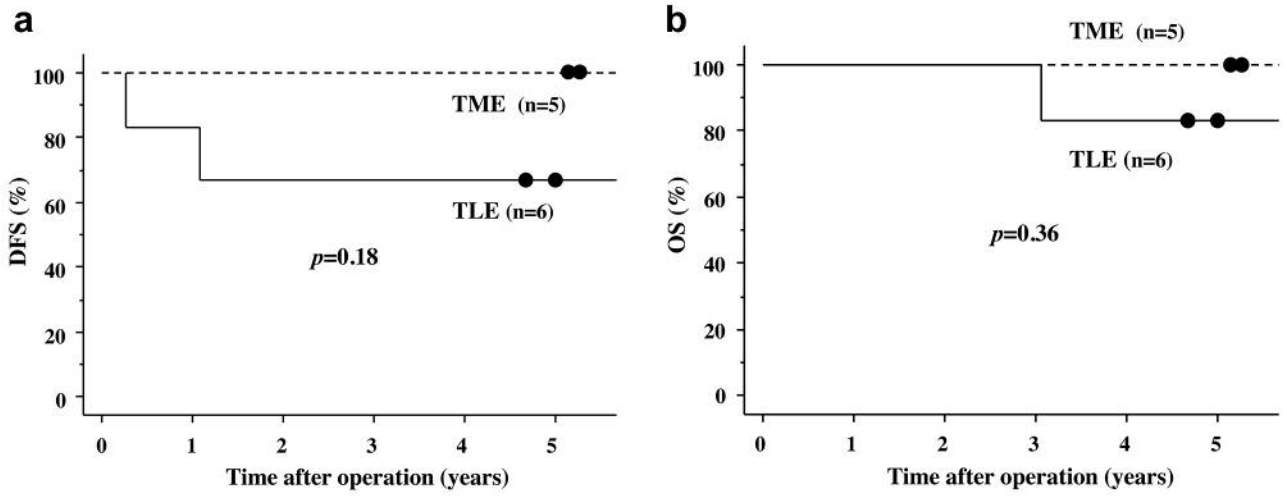

Figure 1. *Long-term outcomes: Disease-free (DFS) (a) and overall (OS) (b) survival.*

Table II. *Overview of the patients who underwent transanal local excision.*

Case	Age, years	Gender	Chemotherapy	Tumor grade	cT	ypT	Differentiation	ly	v	Surgical margins	Recurrence
1	57	F	TS-1	0	SM	M	tub1	0	0	Negative	No
2	66	M	TS-1	1b	SM	M	tub1	0	0	Positive	Yes
3	76	M	TS-1	NA	MP	MP	tub1	0	0	Negative	No
4	54	M	TS-1	0	SM	SM	tub1	0	1	Negative	No
5	52	F	TS-1	3	MP	CR	tub1	0	0	Negative	No
6	74	M	SOX+Bv	1a	SM	SM	tub2	1	0	Negative	Yes

M: Male; F: female; TS-1: tegafur/gimeracil/oteracil; SOX+Bv: TS-1, oxaliplatin and bevacizumab regimen; NA: not available; SM: submucosa; MP: *muscularis propria*; CR: complete response.

v0 and the surgical margin was negative. Local recurrence was found 1 year and 5 months after TLE (Figure 3c). Histological findings revealed widespread venous invasion from the mucosa to the sub-serosal layer. Salvage laparoscopic abdomino-perineal resection was performed. However, the patient had multiple lung metastases and died 3 years after TLE.

Discussion

This study demonstrated the surgical outcomes of TLE for clinical cT1/cT2 lower rectal cancer after pre-operative CRT. TLE has a clinical benefit in operative time and in preservation of the anus. Regarding the long-term outcome, TLE led to similar survival rates in DFS and OS compared to TME following CRT.

TLE or trans-abdominal resection for cT1/cT2 lower rectal cancer is recommended in the National Comprehensive Cancer Networkguideline (12). In patients with pT1 with high-risk features or pT2 after TLE, trans-abdominal resection or CRT are proposed. In pT1 lower rectal cancer, the rate of lymph node metastasis was 13.6% (13). TheJapanese Society for Cancer of the Colon and Rectum guidelines recommend D2 lymph node dissection for cT1(SM) and cT2 rectal cancer (14). However, trans-abdominal resection with lymph node dissection induces anal incontinence (3).

TLE was used as a treatment option for patients with severe co-morbidity or who refused to undergo trans-abdominal resection. Recently, use of TLE has been increasing. However, the local recurrence rate after TLE was found to be relatively high for cT1/cT2 tumor compared to that after trans-abdominal resection (15).

Pre-operative CRT is standard therapy for locally advanced lower rectal cancer (T3/T4) in Western countries. Because there is concern regarding good local control, TLE has also been performed for early rectal cancer. Recently,

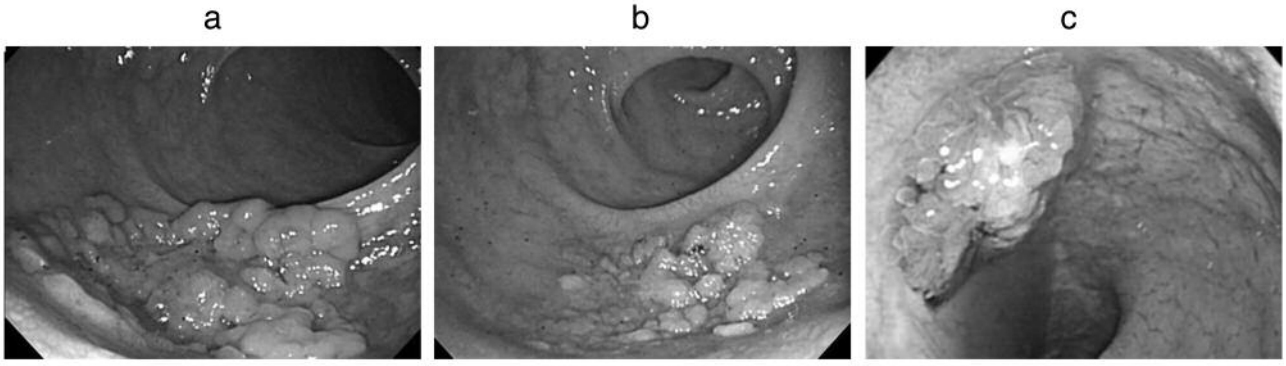

Figure 2. *Colonoscopy findings of case 2 before (a) and after (b) chemoradiotherapy, and recurrence after chemoradiotherapy (c).*

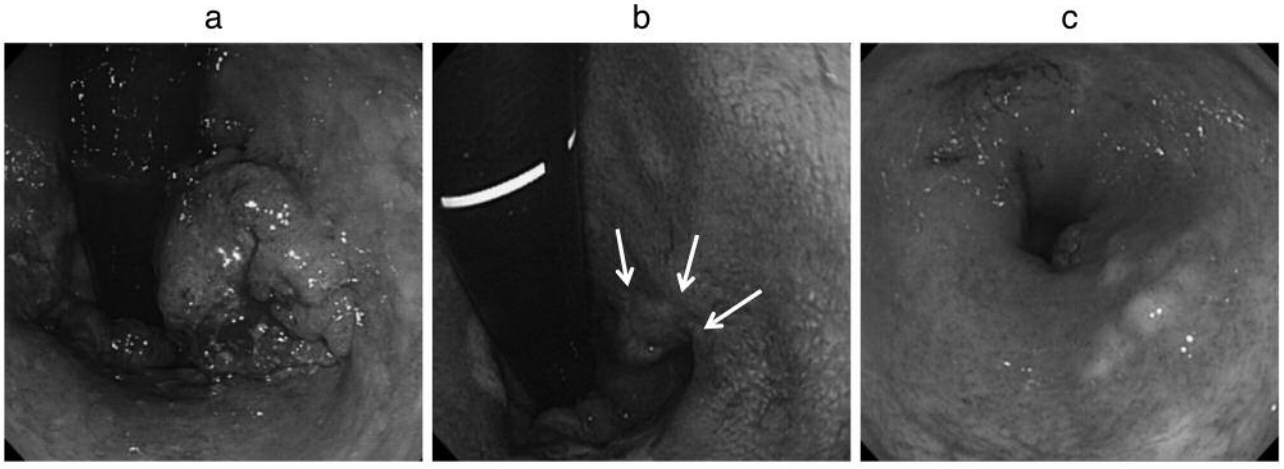

Figure 3. *Colonoscopy findings of case 6 before (a) and after (b) chemoradiotherapy, and recurrence after chemoradiotherapy (c). Arrows indicate reduced tumor.*

investigation of the oncological and functional outcomes of neoadjuvant CRT following TLE for stage I rectal cancer was reported (16). TLE achieved organ preservation without deterioration of the patient's quality of life. The estimated 3-year DFS rate was within the defined margin of efficacy. Another randomized controlled trial for cT2 rectal cancer showed the local recurrence rate was 6% in the TLE group and 7% in the TME group, respectively. As well, the DFS was not significantly different between the two groups (17).

With the advent of pre-operative therapy, some patients could be cured or almost cured of cancer after CRT. The watch-and-wait approach is proposed for selected patients. A propensity score-matched cohort analysis revealed a high local regrowth rate (24%) and 88% of these cases were salvaged after surgery (8). In the watch-and-wait approach, the definition of cCR was challenging. The diagnosis of cCR as an indication of the watch-and-wait approach requires correlation of: digital rectal examination (no palpable scar); endoscopy (flat scar without ulceration); magnetic resonance imaging (regression with no or minimal residual tumor or no extra-rectal disease); and negative biopsy (18). TLE after CRT is less invasive surgery, has a diagnostic value, and confirms the tumor status.

In this study, the local recurrence rate was relatively high (33%, n=2). One patient had a positive surgical margin. After CRT, appropriate evaluation of the tumor distribution is the key to achieving negative surgical margins, contributing to the long-term outcomes. In the other patient, moderately differentiated adenocarcinoma invaded to the SM layer with lymphatic invasion. Pathological examination of salvage surgery for the local recurrence revealed widespread venous invasion. Vessel invasion may be a factor indicating recurrence after TLE.

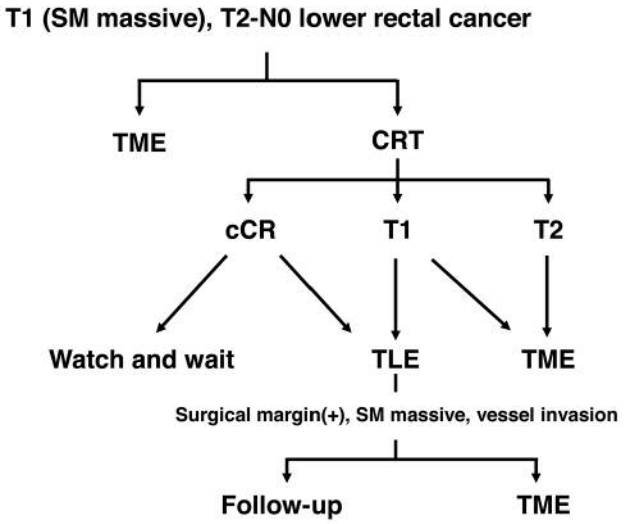

Figure 4. *Treatment strategy for cT1/cT2 lower rectal cancer. cCR: Clinical complete response; CRT: chemoradiotherapy; SM: submucosal; TLE: trasanal local excision; TME: total mesorectal excision.*

The treatment strategy is shown in Figure 4. Trans-abdominal resection or CRT is proposed for cT1 /cT2 lower rectal cancer. After CRT, trans-abdominal resection is recommended as a standard treatment. If patients with T1 tumor refuse trans-abdominal resection, TLE is proposed. In cCR cases, the watch-and-wait approach or TLE are considered. After TLE, if the patients have a positive surgical margin, SM massive invasion, or vessel invasion, additional trans-abdominal resection is considered.

Conclusion

In conclusion, TLE following CRT had acceptable surgical outcomes. Thus, surgeons should consider TLE following CRT as a treatment option for cT1/cT2 lower rectal cancer.

Conflicts of Interest

The Authors declare that they have no conflict of interest in regard to this study.

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