Clinical Study

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Clinical T2N0 Rectal Cancer Treated with Neoadjuvant Chemoradiotherapy plus Local Excision

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Abstract

Introduction: Total mesorectal excision is the standard treatment for clinical T2 (cT2) rectal cancer; however, this procedure can result in postoperative dysfunction, decreased quality of life, and stoma creation in some patients. We investigated neoadjuvant chemoradiotherapy (nCRT) plus local excision (LE) as an alternative treatment strategy for patients with cT2N0 rectal cancer. Method: Fifty-six patients with cT2N0M0 rectal cancer who exhibited the following characteristics (an anal verge of ≤8 cm, tumor size of <30 mm, well- or moderately differentiated adenocarcinoma on biopsy) underwent LE following nCRT. Chemoradiotherapy was administered at 40 or 45 Gy in 20–25 fractions with concurrent oral UFT (tegafur/uracil; 400 mg/m²) or S-1 (tegafur/gimeracil/oteracil; 80 mg/m²). Results: Fifty-five patients (98%) completed nCRT as planned. Histologically, the excision margin was negative in all patients, and four patients with ypT3 disease underwent total mesorectal excision. Recurrence was observed in 15 patients (27%), local recurrence in 7 (13%), and distant recurrence in 10 (18%). The salvage surgery was possible for the local recurrence group. The 5-year disease-free and overall survival rates were 68.4% and 84.9%, respectively. Multivariate analysis showed that only the tumor regression grade (TRG) was an independent risk factor for recurrence (p = 0.025). Although 7 (26%) out of 27 patients with a TRG of 3 or 4 developed local recurrence and 6 (22%) had distant metastasis, 25 patients with a TRG of 1 or 2 did not exhibit local recurrence, and only 1 (4%) experienced distant metastasis. Conclusion: nCRT plus LE may be an alternative treatment for patients with cT2N0 rectal cancer who achieved a TRG of 1 or 2. However, additional treatment was required in patients who achieved a TRG of 3 or 4.

Introduction

The standard treatment for early rectal cancer (clinical T1N0) is transanal local excision (LE), followed by observation if no high-risk features are histologically present. The treatment for clinical T1–2N0 rectal cancer is transabdominal resection followed by observation. After LE, patients with a pathological T1 (pT1) or pT2 disease who exhibit histologically high-risk features can also undergo additional transabdominal resection, radiotherapy, and/or chemoradiotherapy (CRT) [1].

Radical surgery (RS) with total mesorectal excision (TME) is associated with a relatively high morbidity rate as well as a risk of postoperative low anterior resection syndrome, urinary and sexual dysfunction, permanent...
stomata, and decreased quality of life [2–6]. It has been reported that there was no difference in local recurrence and survival rates between TME and LE followed by CRT for pT1 rectal cancer [7–10]. In patients with clinical T2 (cT2) rectal cancer, the local recurrence rate is reportedly high, even when CRT is performed following LE [8, 9, 11]. However, favorable results have been reported among patients who underwent LE after neoadjuvant CRT (nCRT) [12, 13]. The effectiveness of nCRT followed by LE for cT2 rectal cancer remains controversial given the lack of definitive data. Therefore, we performed this study to investigate the outcomes of patients with cT2N0 rectal cancer who underwent transanal full-thickness LE after nCRT.

Methods

We investigated 56 patients with rectal adenocarcinoma treated between October 2000 and March 2018 who exhibited the following characteristics: an anal verge of ≤8 cm, tumor size of <30 mm, well or moderately differentiated adenocarcinoma on biopsy, M0 (no distant metastasis) on abdominal ultrasonography or chest/abdominal/pelvic computed tomography, and cT2N0 on digital rectal examination or pelvic magnetic resonance imaging and endoscopic ultrasonography.

After providing informed consent, the patients underwent nCRT followed by transanal full-thickness LE. Patients who had pT3 disease or evidence of poorly differentiated adenocarcinoma or mucinous carcinoma in the resected specimen underwent TME.

Neoadjuvant CRT

Preoperative radiotherapy was performed using a 15-MV X-ray with a linear accelerator (Clinac 21EX; Varion Med System Inc., Palo Alto, CA, USA) using the 4-field technique. Irradiation (1.8 or 2 Gy) was performed 5 days per week for a total dose of 40–45 Gy.

Oral UFT (uracil-tegafur; 400 mg/m²) was simultaneously administered with radiotherapy on 5 weekdays, followed by a 2-day rest on the weekends; this cycle was repeated during irradiation. Alternatively, oral S-1 (tegafur/gimeracil/oteracil; 80 mg/m²) was started simultaneously with radiotherapy and administered for 2 consecutive weeks, followed by a 1-week rest and administration for another 2 weeks [14, 15].

Surgery

LE was performed 6–8 weeks (range, 31–63 days) after the completion of irradiation. Transanal full-thickness LE was performed while ensuring a horizontal margin of 1 cm from the tumor.

Evaluation of the Tumor Response

Treatment effectiveness was evaluated based on histologic and colonoscopy findings. Histologic regression was classified according to the tumor regression grade (TRG), which was classified as grade 1 (complete regression), grade 2 (presence of rare residual cancer cells), grade 3 (increased number of residual cancer cells), grade 4 (residual cancer outgrowing fibrosis), or grade 5 (absence of regressive changes) [16]. A grade of 1 or 2 was considered marked regression. Colonoscopy was performed immediately before surgery. Patients in whom the tumor mound flattened remarkably or disappeared (i.e., produced a scar) were considered responders, whereas the remainder were considered nonresponders.

Survveillance

Post-LE surveillance was performed on an outpatient basis every 3–4 months during the first 2 years and every 6 months thereafter until 5 years. During these visits, patients underwent physical examination, digital rectal examination, blood tests (including serum carcinoembryonic antigen levels), and abdominal ultrasonography. Computed tomography of the chest, abdomen, and pelvis were performed every 6 months, whereas colonoscopy was performed at 6 months and 1, 3, and 5 years after LE.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 26 (IBM Japan, Ltd., Tokyo, Japan). Categorical variables were analyzed using the χ² or Fisher’s exact test, and continuous variables were analyzed using the Student’s t test. Multivariate analysis was performed using a logistic regression model. Actuarial survival curves were calculated according to the Kaplan-Meier method, and disease-free survival (DFS) and overall survival (OS) probabilities were determined using the log-rank analysis.

Results

Patient Characteristics

Fifty-six patients were included in the present study. The characteristics of the patients are presented in Table 1. The median age of patients was 65 years, and most (75%) were men.

CRT-Related Adverse Events

CRT was discontinued for 1 patient who was treated with 38 Gy, owing to grade 3 liver dysfunction (Table 1). The remaining 55 patients (98%) completed CRT as planned.

Histological Findings in the Excised Specimens

The margin of excision was histologically negative in all patients. The ypT stage was pathological complete response (pCR) in 8 patients (14%); ypTis was observed in 6 patients (11%), ypT1 in 14 (25%), ypT2 in 24 (43%), and ypT3 in 4 (7%). The T downstaging rate was 50%. Furthermore, four patients with ypT3 stage additionally underwent TME according to our protocol.

Survival Analysis

Table 2 presents the oncological outcomes of the 56 patients, including 4 patients with ypT3 who additionally underwent TME. The median follow-up period was 65 (range, 2–174) months, with 15 patients (27%) exhibiting...
recurrence. Overall, 7 patients (13%) experienced local recurrence, and 10 (18%) had distant metastasis; the metastatic sites were the liver in 3 patients (5%), the lung in 4 (7%), and the lymph node in 3 (5%). The 1-year, 3-year, and 5-year DFS rates were 87.5%, 80.1%, and 68.4%, respectively (Fig. 1a). A total of 14 patients died, 8 from cancer recurrence and 6 due to other causes. The 1-year, 3-year, and 5-year OS rates were 98.2%, 94.3%, and 84.9%, respectively (Fig. 1b).

Risk Factors for Recurrence
Fifty-two patients who underwent LE after nCRT for cT2N0 rectal cancer were investigated after excluding four patients with ypT3 disease. Univariate analysis showed no association between recurrence and sex, age, pre-CRT histology, post-CRT tumor size, or colonoscopy findings. However, the recurrence rate was significantly lower among patients who achieved histological downstaging than in those who did not \((p = 0.026)\). Moreover, the recurrence rate was significantly higher among patients who exhibited lymphatic invasion and venous invasion than in those who did not \((p = 0.014 \text{ and } p = 0.005, \text{ respectively})\), whereas it was significantly lower among patients with TRGs of 1 or 2 than in those with TRGs of 3 or 4 \((p < 0.001)\).

Multivariate analysis showed that only the TRG was an independent risk factor for recurrence \((p = 0.025)\) (Table 3). Among the 27 patients with TRGs of 3 or 4, 7 (26%) exhibited local recurrence and 6 (22%) had distant metastasis. However, the 25 patients with TRGs of 1 or 2 did not exhibit local recurrence, and only 1 (4%) experienced distant metastasis.

Outcomes of Patients with Local Recurrence
The local recurrence occurred at the suture line in 7 patients. 2 patients underwent LE again and are currently alive without additional recurrence, and 4 patients

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**Table 1. Patient characteristics**

|                      | n (%) |
|----------------------|-------|
| Sex                  |       |
| Male                 | 42 (75)|
| Female               | 14 (25)|
| Age, median (range), years | 65 (44–89) |
| Tumor size before CRT, median (range), mm | 25 (11–29) |
| Distance from the anal verge before CRT, median (range), mm | 30 (10–80) |
| Histologic type before CRT |       |
| Wel                  | 46 (82)|
| Mod                  | 10 (18)|
| Radiation dose       |       |
| 38 Gy                | 1 (2)  |
| 40 Gy                | 16 (29)|
| 45 Gy                | 39 (69)|
| Concurrent CT        |       |
| UFT                  | 35 (63)|
| 5-1                  | 21 (38)|

**Table 2. Oncological outcomes**

|                      | n (%) |
|----------------------|-------|
| Death from rectal cancer | 8 (14) |
| Death from intercurrent disease | 6 (11) |
| Recurrence site        |       |
| Local                 | 7 (13) |
| Distant               | 10 (18)|
| Liver                 | 3 (5)  |
| Lung                  | 4 (7)  |
| Intraabdominal lymph node | 3 (5) |

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CRT, chemoradiotherapy; wel, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; UFT, tegafur/uracil; 5-1, tegafur/gimeracil/oteracil; CT, chemotherapy.
who underwent abdominoperineal resection (APR) developed distant metastases after surgery. The remaining patient refused surgery after local recurrence and underwent chemotherapy instead; this patient developed distant metastasis 2 months later (Table 4).

### Discussion

The rate of lymph node metastasis in patients with T2 rectal cancer reportedly ranges between 12.7% and 19.6% [17–19], whereas that of local recurrence following LE alone ranges from 11.4 to 37.0% [20–24]. Among patients with pT2 rectal cancer, You et al. [25] found that the local recurrence rate among 164 patients who underwent LE was 22.1%, which was significantly higher than the rate of 15.1% found among 866 patients who underwent RS (p = 0.01). Moreover, the 5-year OS rate was 67.6% for those who underwent LE, which was significantly worse than the rate of 76.5% following RS (p = 0.01). The National Comprehensive Cancer Network guideline indicates that LE is an option for patients with early rectal cancer (i.e., those with an anal verge of ≤8 cm and tumor size of <30 mm), and CRT may be added for patients with pT1 exhibiting high-risk features and with pT2.

Borstlap et al. [8] conducted a meta-analysis of 19 studies covering patients with pT2 rectal cancer and found that the local recurrence rate among those who underwent additional CRT following LE (14.3%) was higher than that among those who underwent TME (6%); however, there

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**Table 3. Risk factors for recurrence**

| Recurrence, n | Univariate analysis | | Multivariate analysis |
|---------------|---------------------|-----------------|----------------------|
|               | Recurrence, n | Univariate analysis | | Multivariate analysis |
|               | odds ratio | 95% CI | p value | odds ratio | 95% CI | p value |
| Gender | | | | | | |
| Men | 13/40 (32.5) | 1 | | | | |
| Female | 1/12 (8.3) | 0.189 | 0.22–1.623 | 0.098 | | |
| Age (median), years | | | | | | |
| <65 | 9/23 (39.1) | 1 | | | | |
| ≥65 | 5/29 (17.2) | 0.324 | 0.090–1.162 | 0.077 | | |
| Tumor size post-CRT (median), mm | | | | | | |
| <12 | 4/22 (18.2) | 1 | | | | |
| ≥12 | 10/30 (33.3) | 2.250 | 0.599–8.447 | 0.224 | | |
| Histologic type before CRT | | | | | | |
| Wel | 11/44 (25.0) | 1 | | | | |
| Mod | 3/8 (37.5) | 1.800 | 0.369–8.789 | 0.463 | | |
| Pathological result | | | | | | |
| ypT stage | | | | | | |
| Downstage (+) | 4/28 (14.3) | 1 | | | | |
| Downstage (–) | 10/24 (41.7) | 4.286 | 1.129–16.266 | 1.277 | 0.237–6.894 | 0.776 |
| Lymphatic invasion | | | | | | |
| (+) | 5/8 (62.5) | 1 | | | | |
| (–) | 9/44 (20.5) | 6.481 | 1.298–32.358 | 1.571 | 0.252–9.794 | 0.629 |
| Venous invasion | | | | | | |
| (+) | 7/12 (58.3) | 1 | | | | |
| (–) | 7/40 (17.5) | 6.600 | 1.615–26.977 | 2.954 | 0.515–16.955 | 0.224 |
| TRG | | | | | | |
| 1,2 | 1/25 (4.0) | 1 | | | <0.001 | 1 | 0.025 |
| 3,4 | 13/27 (48.1) | 22.286 | 2.627–189.054 | 13.699 | 1.396–134.426 | |
| Colonoscopic findings | | | | | | |
| Responder | 5/25 (20.0) | 1 | | | | |
| Nonresponder | 9/27 (33.3) | 2.000 | 0.564–7.087 | 0.588 | | |
| Scar | 3/14 (21.4) | 1 | | | | |
| Other | 11/38 (28.9) | 1.494 | 0.348–6.409 | | | |

CRT, chemoradiotherapy; wel, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; TRG, tumor regression grade; CI, confidence interval
was no difference in the rates of distant metastasis (8.2% and 7.7%, respectively). Xu et al. [26] conducted a meta-analysis of five randomized controlled trials of patients with pT2 rectal cancer and found that transanal endoscopic microsurgery (TEM) was associated with a higher local recurrence rate \( (p = 0.02) \) and worse OS \( (p = 0.01) \) than TME alone, but exhibited similar local recurrence and OS rates when TEM was combined with nCRT or neoadjuvant radiotherapy. These analyses suggest that administering CRT to patients with pT2 rectal cancer after LE is still associated with a high recurrence rate; however, conducting CRT before LE improves local recurrence, distant metastasis, and OS. Therefore, nCRT ought to be administered to patients with cT2 rectal cancer before LE.

In our protocol, patients with cT2N0 rectal cancer were administered nCRT followed by LE conducted 6–8 weeks after the final irradiation session. We had used the same nCRT for locally advanced rectal cancer and performed TME after 6–8 weeks after the final irradiation session [14, 15]. In the present study, 8 patients (14%) achieved pCR, whereas 28 (50%) achieved T downstaging. nCRT was completed in 55 of the 56 patients (98%). Garcia-Aguilar et al. [13] reported that 3 (4%) out of 76 patients were found to have pT3 in the resected specimen; 1 refused surgery, whereas the remaining 2 underwent APR and experienced no postoperative recurrence. We also performed APR on four patients with ypT3 disease, and no patient has experienced intra-pelvic recurrence to date.

Habr-Gama et al. [27] conducted nCRT on 183 patients with locally advanced rectal cancer and obtained a clinically complete response in 90 patients (49%). Factors that increase the likelihood of pCR in patients with locally advanced cancers who receive nCRT include female sex, no macroscopic ulcers, a small tumor circumference, small tumor diameter, low tumor grade, early cT stage, early cN stage, long radiation-to-surgery interval, and non-elevated carcinoembryonic antigen levels before treatment [28, 29]. Gerard et al. [30] reported that a cT2 stage, pre-treatment tumor size of <4 cm, and tumors spanning less than half the rectal circumference are predictive factors of pCR. An even higher clinical complete response rate is expected for cT2 tumors, which generally have smaller diameters than their cT3–T4 counterparts.

Garcia-Aguilar et al. [13] observed local recurrence in 3 of 76 patients with cT2N0 (4%) who underwent LE after nCRT, whereas 7 of 52 patients (13%) experienced recurrence in our cohort. One explanation for the higher local recurrence rate in our study may be that Garcia-Aguilar
et al. [13] used oxaliplatin and capecitabine for combined chemotherapy (50 mg/m² on weeks 1, 2, 4, and 5; and 825 mg/m², twice daily on days 1–14 and 22–35, respectively) with a total radiation dose of 50.4 or 54 Gy, whereas we administered only oral fluorinated pyrimidine with a total radiation dose of 40–45 Gy.

In the present study, patients with TRGs of 1 or 2 in the excised specimens developed no local recurrence, and only 4% developed distant metastasis. However, patients with TRGs of 3 or 4 revealed high recurrence rates both in local and distant metastases. Therefore, nCRT plus LE may be an alternative treatment strategy for patients with cT2N0 rectal cancer. No further treatment was necessary for patients who achieved a TRG of 1 or 2, whereas additional TME surgery may be required for patients with a TRG of 3 or 4.

This study was limited by its small sample size and the fact that the data were derived from a single institution. Going forward, our findings ought to be validated in multicenter prospective trials with a large sample sizes.

Conclusions

LE after nCRT for patients with cT2N0 rectal cancer was associated with a high recurrence rate. However, patients with TRGs of 1 or 2 in the excised specimen may be a definitive treatment, and patients with TRGs of 3 or 4 should receive additional therapy. Therefore, nCRT plus LE may be an alternative treatment strategy for patients with cT2N0 rectal cancer who achieved a TRG of 1 or 2.

Statement of Ethics

This study was approved by the Institutional Review Board of Tokai University (08R-032), and all patients provided written informed consent.

Conflicts of interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design of study: Toshiyuki Suzuki and Sotaro Sadahiro. Acquisition of data: Lin Fung Chan and Yutaro Kamei. Analysis and interpretation of data: Hiroshi Miyakita and Takeshi Ogimi. Drafting the manuscript: Toshiyuki Suzuki and Sotaro Sadahiro. Revising the manuscript critically for important intellectual content: Kazutake okada and Seiichiro Yamamoto. Approval of the version of the manuscript to be published: all the authors.

Data Availability Statement

Data are available on request due to privacy/ethical restrictions. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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