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Original Article

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Outcome of Local Excision Following Preoperative Chemoradiotherapy for Clinically T2 Distal Rectal Cancer: A Multicenter Retrospective Study (KROG 12-06)

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Purpose
The aim of this study was to examine the clinical implications of a pathologically complete response after neoadjuvant chemoradiotherapy (CRT) followed by local excision for patients with cT2 rectal cancer who refused radical surgery.

Materials and Methods
Seventeen patients with cT2 primary rectal cancer within 6 cm from the anal verge who received neoadjuvant CRT and local excision because of patient refusal of radical surgery or poor performance status were included. Two patients had clinical involvement of a regional lymph node. Preoperative radiotherapy was delivered to the whole pelvis at a dose of 44 to 50.4 Gy in 22 to 28 fractions. All patients underwent transanal excision and eight patients (47%) received postoperative chemotherapy.

Results
Ten patients (59%) achieved ypT0. At a median follow-up period of 75 months (range, 22 to 126 months), four (24%) patients developed recurrence (two locoregional and two distant). The 5-year disease-free survival of all patients was 82%, and was higher in patients with ypT0 (90%) than in patients with ypT1-2 (69%, p=0.1643). Decreased disease-free survival was also observed in patients receiving capecitabine compared with 5-fluorouracil (54% vs. 100%, p=0.0298).

Conclusion
Local excision could be a feasible alternative to radical surgery in patients with ypT0 after neoadjuvant CRT for cT2 distal rectal cancer without further radical surgery.

Key words
Rectal neoplasms, Neoadjuvant therapy, Local excision, Complete remission

Introduction

Neoadjuvant chemoradiotherapy (CRT) followed by total mesorectal excision (TME) is a standard treatment in patients with locally advanced rectal cancer [1,2]. In addition to improved local control, reduced toxicity, increased sphincter preservation, and tumor downstaging have been demonstrated after neoadjuvant CRT [1]. Complete pathologic response (ypCR) of approximately 15% has been reported after CRT [3,4]. Patients with ypCR after CRT tend to have decreased local or distant recurrence and improved survival [4-6]. Some authors have reported that a wait-and-see policy without surgical resection could be possible with strict selection criteria [7,8].

Radical surgery is associated with significant morbidity, especially in cases of low rectal cancer [9,10], therefore, local excision might be an alternative treatment to radical surgery after neoadjuvant CRT in selected cT2-3 cases [11-13]. However, cautious and strict patient selection is crucial in

this approach [14]. Higher risk of recurrence has limited the routine application of local excision alone in cT2 rectal cancer [15]. The incidence of local recurrence was 24% in T2 rectal cancer after local excision alone [15]. In addition, salvage treatment for failure after local excision is difficult and is often associated with treatment-related morbidity [16]. Under National Comprehensive Cancer Network (NCCN) guidelines, the standard treatment for cT2N0 rectal cancer is radical surgery, and adjuvant treatments are recommended according to pathological status [17]. For patients with cT2 distal rectal cancer whose sphincteric muscles cannot be preserved with abdominoperineal resection (APR), local excision after neoadjuvant CRT is an alternative approach to preserving the sphincter with equivalent oncologic outcomes [18,19]. A recent randomized clinical trial of local resection versus TME after neoadjuvant therapy showed equivalent disease-free survival (DFS) in patients with cT2N0, a diameter no larger than 3 cm, and histological grade G1-2 rectal cancer [20]. The probability of developing recurrence was 12% after local excision. Recurrence occurred only in low or non-responders to neoadjuvant CRT.

In this study, to elucidate the clinical implication of ypCR after neoadjuvant CRT in patients with cT2 distal rectal cancer, the Korean Radiation Oncology Group (KROG) conducted a multicenter retrospective study that examined the DFS according to ypT status.

Materials and Methods

Seventeen patients with cT2 primary rectal adenocarcinoma who were treated by neoadjuvant CRT and local excision between 2002 and 2009 were enrolled from four institutions. After approval by the KROG (KROG 12-06), the medical and radiotherapy (RT) records of the patients were reviewed retrospectively. The median age of patients was 63 years (range, 38 to 79 years). There were 11 (65%) men and six (35%) women. All tumors were located within 6 cm from the anal verge as measured by digital examination. For clinical staging, computed tomography (CT, n=15), magnetic resonance imaging (n=8), or transrectal ultrasound (n=11) was performed. Three patients were diagnosed by CT scan only. When positive lymph node involvement was defined as a lymph node ≥ 0.5 cm in the short-axis diameter, two patients had clinical involvement of a regional lymph node. The tumor characteristics at diagnosis are summarized in Table 1.

Patient refusal of radical surgery (n=16) and poor performance status (n=1) were the reasons for undergoing local excision following neoadjuvant CRT. Patients who chose local excision were fully informed about the tumor response to neoadjuvant CRT and the options of surgical modalities between radical resection and local excision. RT was delivered to the whole pelvis at a dose of 45 Gy in 25 fractions (n=8), 50.4 Gy in 28 fractions (n=5), or 44 Gy in 22 fractions (n=4) by 6-15 MV photon beams. The regimens of concurrent chemotherapy included 5-fluorouracil (5-FU; n=9, 53%), capecitabine (n=7, 41%), and S-1 plus irinotecan (n=1, 6%). There was no incidence of grade 3 or higher toxicity associated with neoadjuvant CRT. The median interval between completion of CRT and surgery was 53 days (range, 40 to 75 days). All patients underwent transanal tumor excision. Postoperative chemotherapy was delivered to eight (47%) patients, and six received four cycles of 5-FU.

The median follow-up duration calculated from the initiation of CRT was 75 months (range, 24 to 126 months). The primary endpoint of this study was DFS according to ypT-classification, which was divided into ypT0 or not. DFS was defined as the time from the initiation of the CRT to rectal cancer relapse or death, while second primary cancers were not included. DFS was estimated using the Kaplan-Meier test. DFS according to ypT-classification was compared using the log-rank test. The secondary endpoint was pattern of disease recurrence. SAS ver. 9.1.3 (SAS Institute Inc., Cary, NC) was used for statistical analysis. A $p < 0.05$ was chosen for statistical significance.

Results

1. Surgical pathology after CRT

The primary tumor included ypT0 (n=10, 59%), ypT1 (n=6, 35%), and ypT2 (n=1, 6%). All of the ypT1-2 tumors were adenocarcinoma. Histologic grade was well-differentiated in one tumor, and moderately-differentiated in six tumors. Lymphovascular invasion, perineural invasion, and involvement of the resection margin were not observed. Resection margins were not involved in pathologically residual tumors, although the distances of resection margins were not described, except two patients. There was no pathologic involvement of regional lymph node (n=4). Among the seven patients with ypT1-2 disease, five received postoperative chemotherapy, while three of the 10 patients with ypT0 received adjuvant chemotherapy. The clinicopathologic characteristics according to ypT-classification are summarized in Table 2.

Table 1. Tumor characteristics at diagnosis

Characteristic	No. (%)
Distance from anal verge (cm)	
Median	3
Range	1-6
Histologic grade	
Well	5 (29)
Moderate	11 (65)
Unknown	1 (6)
Clinical N-classification	
N0	15 (88)
N1	2 (12)
Tumor size (cm)	
Median	2.0
Range	1.4-4.0
Serum carcinoembryonic antigen (ng/mL)	
Median	1.3
Range	0.7-30.6

Table 2. Clinicopathologic characteristics according to ypT-classification

Characteristic	ypT0 (n=10)	ypT1-2 (n=7)
Gender		
Male	6	5
Female	4	2
Median age (yr)	64 (38-79)	53 (41-64)
Median pre-CRT CEA (ng/mL)	1.4 (0.8-4.5)	1.1 (0.7-30.6)
Median post-CRT CEA (ng/mL)	1.1 (0.5-5.0)	1.8 (0.3-3.0)
Histologic grade (pre-CRT)		
Well	2	3
Moderate	8	3
Clinical N-classification		
0	10	5
1	0	2
Chemotherapy (preoperative)		
5-FU	6	3
Capecitabine	4	3
S-1+irinotecan	0	1
Chemotherapy (postoperative)		
5-FU (+leucovorin)	3	5
No	7	2

CRT, chemoradiotherapy; CEA, carcinoembrynonic antigen; 5-FU, 5-fluorouracil.

2. Survival rates according to tumor response

During the follow-up period, four patients (24%) experienced recurrence (Table 3). Locoregional and distance recurrences each occurred in two patients, respectively. Among the patients who achieved ypT0 after neoadjuvant CRT, one patient (10%) experienced regional recurrence after 14 months. Three (43%) out of the seven ypT1-2 patients experienced a recurrence. One patient had locoregional recurrence and two had distant metastasis. The 5-year DFS of all patients was 82% (Fig. 1A). DFS in patients with ypT0 tumors was higher than in patients with ypT1-2 tumors (90% vs. 69%) (Fig. 1B), however, the difference was not significant (p=0.1643). Lower DFS was observed in patients who

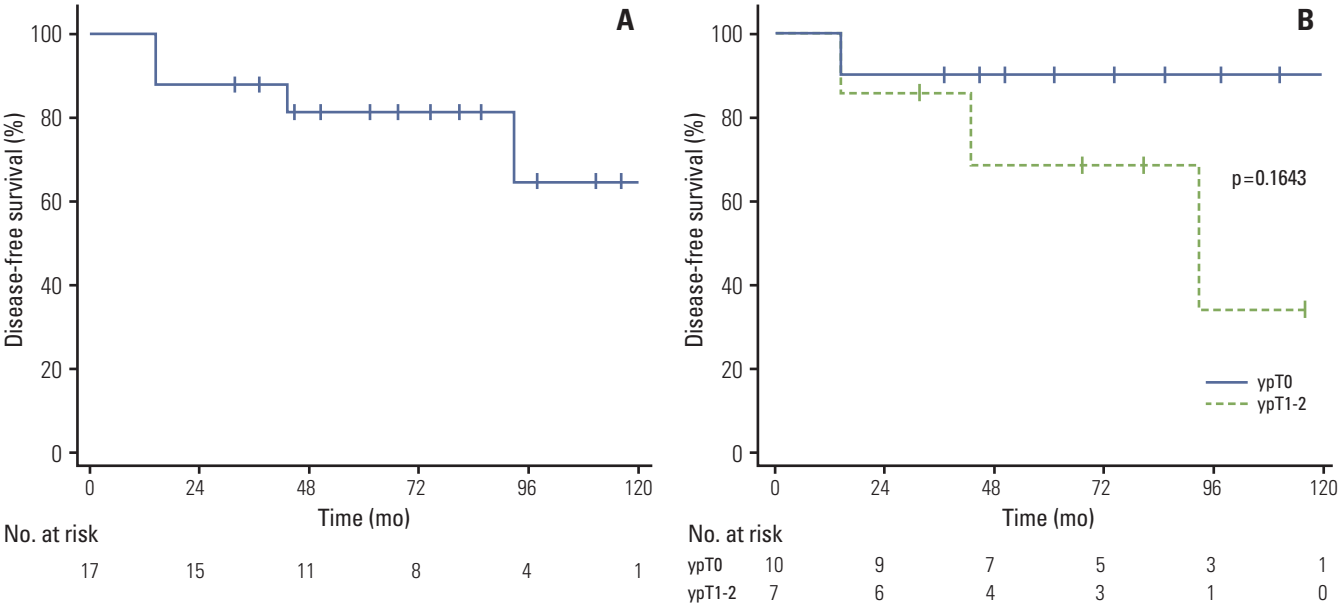

Fig. 1. (A) Disease-free survival of all patients. (B) Disease-free survival according to ypT-classification.

Table 3. Characteristics of patients who experienced disease recurrence

Age (yr)	Gender	AV (cm)	Grade	cN	Preoperative chemotherapy	ypT	Postoperative chemotherapy	Site of failure	DFS (mo)
53	Male	6	Well	0	Capecitabine	1	5-FU	Distant	14
49	Female	1	Well	0	Capecitabine	0	5-FU	Locoregional	14
41	Female	2	Unknown	1	Capecitabine	1	5-FU	Distant	43
62	Male	2	Moderate	0	5-FU	1	No	Locoregional	93

AV, anal verge; DFS, disease-free survival; 5-FU, 5-fluorouracil.

received capecitabine as neoadjuvant CRT, compared with patients treated with 5-FU (54% vs. 100%, p=0.0298). Among the seven patients with tumors close to the anal verge (< 3 cm), three patients had disease relapse (p=0.1434) (Table 4). No significant difference in DFS was observed for other clinicopathologic characteristics (Table 4). None of the patients died during the follow-up period.

Discussion

ypCR after neoadjuvant CRT is known to be associated with favorable long-term oncologic outcomes [4-6]. According to results of a pooled analysis, the ypCR rate is 16% [4]. Local control, distant metastasis-free survival, DFS, and overall survival were favored in patients with ypCR. The adjusted hazard ratio by Cox proportional hazards model was 0.41 (95% confidence interval [CI], 0.21 to 0.81), 0.49 (95% CI, 0.34 to 0.71), 0.54 (95% CI, 0.40 to 0.73), and 0.65 (95% CI, 0.47 to 0.89) for the outcomes, respectively. However, most studies included patients with cT3 rectal cancer who underwent radical surgery. Similar findings were observed in patients who underwent local excision following neoadjuvant CRT for cT2-3 rectal cancer [12]. The prevalence of ypT0 was 22% (53 of 237). After local excision, none of the patients with ypT0 experienced local recurrence, while 2%, 7%, and 21% of patients with ypT1, ypT2, and ypT3, respectively, experienced local recurrence. Although 34% of the patients had cT2 rectal cancer, the relationship between ypT-classification and clinical outcome in cT2 disease was not evaluated.

Table 4. Disease-free survival according to clinicopathologic characteristics

Variable	No.	5-Year rate (%)	p-value
Gender			
Male	11	91	0.4132
Female	6	67	
Age (yr)			
< 60	13	76	0.3320
≥ 60	14	100	
Tumor size (cm)			
< 2	5	80	0.7369
≥ 2	12	81	
Distance from AV (cm)			
< 3	7	69	0.1434
≥ 3	10	90	
Histologic grade			
Well	5	60	0.2056
Moderate	11	100	
Clinical N-classification			
0	15	87	0.2018
1	2	100	
Chemotherapy[a)]			
5-FU	9	100	0.0298
Capecitabine	7	54	
ypT-classification			
0	10	90	0.1643
1-2	7	69	

AV, anal verge; 5-FU, 5-fluorouracil. [a)]The patient who received S-1 plus irinotecan was excluded from comparison.

A recent randomized trial reported equivalent DFS to TME after local excision following neoadjuvant CRT [20]. The trial included patients with cT2N0, histologic grades 1-2 with tumors < 3 cm in diameter and within 6 cm of the anal verge, similar to the current study. After local resection, ypT0 was observed in 28% of patients, comparable to that of patients who received TME (26%). The probability of developing disease recurrence at the end of follow-up was 12% after local resection, and the corresponding overall survival rate was 72%. Although the duration of follow-up was shorter and the number of patients was smaller, the rate of ypT0 (59%) and overall survival rate were higher in the current study. In addition, the randomized trial did not evaluate the clinical implication of ypT0 after local resection. In the current study, ypCR after neoadjuvant CRT for cT2 rectal cancer showed an association with favorable outcomes in patients who underwent local excision. After neoadjuvant CRT, ypT0 showed an association with improved DFS compared with ypT1-2 in cT2 distal rectal cancer. The small number of patients limited the power of the study, and higher rate of ypT0 might be influenced by potential selection bias, which could be caused by patient's choice of local excision after they were informed about the clinical tumor response and the option of avoidance of radical resection. However, local excision could be a feasible alternative to radical surgery in properly selected patients with ypCR after neoadjuvant CRT for cT2 distal rectal cancer, which is located within 6 cm of the anal verge.

Of particular interest, most cases of disease recurrence occurred in patients who had received capecitabine as neoadjuvant therapy, regardless of postoperative chemotherapy. However, no difference in the proportion of patients with ypCR after neoadjuvant CRT was observed between the two chemotherapeutic regimens (67% vs. 57%, p=1). Compared to 5-FU, oral capecitabine demonstrated comparable or improved tumor response, local control, DFS, and overall survival in patients who received neoadjuvant CRT for locally advanced rectal cancer [21,22]. In addition to the convenience of oral administration and lesser toxicities, capecitabine has several advantages, including preferential activation in

tumor tissue and a synergistic effect with X-ray [23]. Oral capecitabine is currently a valid option in neoadjuvant CRT for rectal cancer, as investigated in previous studies [21,22]. However, most previous studies regarding local excision following neoadjuvant CRT used 5-FU as a chemotherapeutic regimen [12,13,20]. Efficacy of oral capecitabine in this setting has not been well established. Whether capecitabine is still as effective as 5-FU in patients receiving neoadjuvant CRT followed by local excision should be clarified. However, due to the small sample size, different DFS according to neoadjuvant chemotherapeutic regimen in the current study is not sufficient to answer this question.

In the current study, most of the enrolled patients refused radical surgery such as APR because the tumors were located in the distal rectum. Although a meta-analysis showed no difference in general quality of life (QoL) following APR or anterior resection [24], a sphincter-preserving procedure is preferred in terms of QoL for patients [25]. In this regard, local excision combined with neoadjuvant CRT could be the first treatment option in patients with cT2 distal rectal cancer for whom the anal sphincter cannot be preserved. After local excision, patients with residual tumors in the specimen should consider radical surgery. Because local excision alone is associated with increased risk of disease recurrence, it should be applied cautiously to patients with residual disease after neoadjuvant CRT.

Conclusion

In conclusion, local excision could be a feasible alternative to radical surgery in patients with ypCR after neoadjuvant CRT for cT2 distal rectal cancer. Future studies including a large patient population are needed in order to confirm the efficacy of local excision in this setting.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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