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Local Excision Following Pre-operative Chemoradiotherapy-induced Downstaging for Selected cT3 Distal Rectal Cancer

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Objective: To investigate the long-term outcomes of selected patients with cT3 distal rectal cancer treated with local excision following pre-operative chemoradiotherapy.
Methods: Between January 2003 and February 2008, 11 patients with cT3 distal rectal cancer received a local excision following pre-operative chemoradiotherapy. The median age of the patients was 61 years (range, 42–71). The median tumor size was 3 cm (range, 2–5), and the median distance of the caudal tumor edge from the anal verge was 3 cm (range, 1–4). Clinical lymph node status was positive in five patients. Pre-operative chemoradiotherapy consisted of a 50.4 Gy in 28 fractions with concurrent chemotherapy. A transanal full-thickness local excision was performed after a median of 54 days (range, 31–90) from chemoradiotherapy completion. Ten patients received post-operative chemotherapy.
Results: Pathologically complete responses occurred in eight patients, ypT1 in two and ypT2 in one. The pathologic tumor size for three ypT1–2 tumors was 0.9, 1.1 and 2.2 cm. The follow-up period was a median of 59 months (range, 24–85). One patient (ypT0) developed recurrence at the excision site 14 months after surgery, but was successfully salvaged with an abdominoperineal resection and adjuvant chemotherapy. Another patient (ypT2) developed bone metastasis after 8 months and died of the disease. The 5-year local recurrence-free, disease-free and overall survival rates were 90.9%, 81.8% and 88.9%, respectively. No Grade 3 or worse gastrointestinal toxicity was detected.
Conclusions: Full-thickness local excision following chemoradiotherapy may be an acceptable option for cT3 distal rectal cancer that responds well to chemoradiotherapy.

Key words: local excision – locally advanced rectal cancer – pre-operative chemoradiotherapy – downstaging

INTRODUCTION

The mainstay of surgical therapy for locally advanced rectal cancers remains low anterior resection or abdominoperineal resection. However, significant morbidity and mortality (2–6%) risks are associated with radical resection. Frequent defecation, voiding problems and sexual dysfunction are common functional consequences of radical surgery. Furthermore, the lifestyle and body image of patients who undergo abdominoperineal resection are profoundly altered (1–3).

Patients who either refuse abdominoperineal resection to preserve anal sphincter or have pre-existing medical co-morbidities have led some clinicians to advocate for local excision in selected rectal cancer cases. Local excision of rectal cancer is associated with a much lower rate of complications than low anterior resection or abdominoperineal resection and can avoid post-operative urinary/sexual dysfunction and preserve anal sphincter. However, local excision has been accepted as an adequate definitive procedure only for patients with T1 cancer with favorable histology (4–8). Adding post-operative chemoradiotherapy (CRT) after local excision for patients with T1 cancer with unfavorable histology or those with T2–3 cancer has been attempted, but produced unsatisfactory outcomes (9,10).

The introduction of pre-operative CRT, followed by radical surgery, for the management of locally advanced

rectal cancer has resulted in significant advantages in terms of toxicity, sphincter preservation, local disease control and tumor downstaging versus post-operative CRT (11). Significant tumor regression in patients undergoing neoadjuvant CRT has led to the use of local excision as an alternative treatment option in patients with downstaged tumors. Additionally, these tumors frequently exhibit significant downsizing after CRT, which facilitates excising a margin-negative specimen through a transanal approach (12,13).

This report describes the results for a series of 11 patients with cT3 distal rectal cancer who underwent pre-operative CRT, local excision and post-operative chemotherapy. The purpose of the study was to investigate the long-term efficacy of local excision following pre-operative CRT-induced downstaging in selected patients with locally advanced distal rectal cancer.

PATIENTS AND METHODS

Patients

Medical records were retrospectively reviewed for patients with locally advanced rectal cancer who underwent curative-intent surgery, following pre-operative CRT. Between January 2003 and February 2008, a total of 540 cT3–4 rectal cancer patients received pre-operative CRT and curative-intent surgery at the National Cancer Center (Goyang, Korea). Among these, 11 patients who underwent local excision were included in this study. We recommended local excision for patients who met all of the following criteria: (i) refusal of radical surgery or no acceptance of anal ablation, (ii) initial cT3 classification, (iii) clinically complete remission or minimal residual and (iv) full recognition of risks for local excision. Informed consent was obtained from patients before surgery, with an explanation regarding potential risks of increased disease recurrence and reduced survival.

Patient characteristics are summarized in Table 1. The median age was 61 years (range, 42–71). Clinical lymph node status was positive in five patients. The median tumor size and volume was 3 cm (range, 2–5) and 4.4 cm^3 (range, 1.7–39.6), respectively. The median distance of the caudal tumor edge from the anal verge was 3 cm (range, 1–4).

Table 1. Patient characteristics

Characteristic	No. (%)
Age (years)	
Median	61
Range	42–71
Gender	
Male	9 (82)
Female	2 (18)
Serum carcinoembryonic antigen (ng/ml)	
Median	1.7
Range	0.7–5.2
Distance from anal verge (cm)	
Median	3
Range	1–4
Clinical nodal classification	
N0	6 (55)
N1	5 (45)
Histologic grade	
Well	2 (18)
Moderate	8 (73)
Poor	1 (9)
Tumor size (cm)	
Median	3
Range	2–5
Tumor volume (cm^3)	
Median	4.4
Range	1.7–39.6

Evaluation

Before pre-operative CRT, all patients were evaluated by staging workups, including a digital rectal examination, complete blood counts, liver function tests, determination of carcinoembryonic antigen level, video colonoscopy, chest radiography, abdominopelvic computed tomography (CT) and magnetic resonance (MR) imaging of the pelvis. Transrectal ultrasonography was performed in eight patients. The clinical T classification was determined, based primarily on MR imaging. The same workups were repeated immediately (1–4 days) before surgery to evaluate the CRT response. The clinical and pathological stages were determined according to the American Joint Committee on Cancer TNM staging system (14). Three-dimensional region-of-interest MR volumetry was performed at each of the two workups to calculate the tumor volume reduction rate (%) (15). Positive lymph node involvement was defined as a lymph node with the smallest diameter of $\geq$0.5 cm observed on CT or MR imaging (16). After surgery, each specimen was serially sliced into 4 mm-thick sections, which were embedded in paraffin to evaluate the CRT response using the tumor regression grade system proposed by Dworak et al. (17). Tumor regression was graded as follows: Grade 0, no regression; Grade 1, minimal regression; Grade 2, moderate regression; Grade 3, near-complete regression; and Grade 4, complete regression.

Chemoradiotherapy

The radiotherapy and chemotherapy methods used in those who underwent local excision did not differ from those used

in patients who underwent radical surgery. Pre-operative radiotherapy was delivered to the whole pelvis at a dose of 45 Gy in 25 fractions, followed by a 5.4 Gy boost in three fractions within 6 weeks. All patients underwent CT simulation for three-dimensional conformal radiotherapy planning, and a three-field treatment plan used a 6 MV photon posterior–anterior field and 15 MV photon opposed lateral beams. The prescription dose was specified at the International Commission on Radiation Units and Measurements reference point (isocenter) of the planning target volume. The initial radiation field encompassed a volume that included the gross tumor, mesorectum, presacral space, the entire sacral hollow and the regional lymphatics including perirectal, internal iliac, presacral and distal common iliac lymphatics. The superior border was placed at L5/S1 and the inferior border at 3 cm or more caudal to the gross tumor. The boost field included the gross tumor volume and mesorectum, plus a minimum 2 cm margin in all directions (18).

Pre-operative concurrent chemotherapy was administered to all patients. One of the following three regimens was used: 5-fluorouracil and leucovorin [two cycles of an intravenous bolus injection of 5-fluorouracil (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) for 3 days in the first and fifth weeks of radiotherapy]; capecitabine [oral capecitabine (825 mg/m^2) twice daily during radiotherapy without weekend breaks]; or capecitabine and irinotecan [oral capecitabine (825 mg/m^2) twice daily during radiotherapy with weekend breaks, and intravenous irinotecan (40 mg/m^2/day) once weekly during radiotherapy].

Ten patients received post-operative chemotherapy, which commenced 3–6 weeks after surgery. One of the following two regimens was used: 5-fluorouracil and leucovorin [four cycles of a monthly intravenous bolus injection of 5-fluorouracil (400 mg/m^2/day, days 1–5) and leucovorin (20 mg/m^2/day, days 1–5)]; or capecitabine [six cycles of capecitabine (1250 mg/m^2 twice daily for 14 days, followed by 7 days rest in each cycle)]. One patient received only three cycles of capecitabine, due to a cardiovascular event. Another patient refused post-operative chemotherapy. The chemotherapeutic regimens, both pre-operative and post-operative, were selected for each patient according to the preferences of the attending medical oncologists.

Surgery

Surgery was recommended 4–8 weeks after CRT for patients with locally advanced rectal cancer. Transanal local excision was performed after a median of 54 days (range, 31–90) after CRT completion; the procedure was delayed in two patients (85 and 90 days) due to their personal circumstances. A full-thickness excision of the tumor or scar with negative margins was performed, including the adjacent perirectal fat (Fig. 1). The largest amount of local perirectal fat was dissected and removed to the avascular plane of the mesorectal fascia for the posterior and lateral lesions and to the prostate capsule or vaginal septum for the anterior lesions. After confirming the presence of a negative frozen section at the specimen margin, the rectal wall was closed with absorbable sutures.

Follow-up

Patient follow-up by a radiation oncologist, medical oncologist or colorectal surgeon was performed every 3 months for the first two post-operative years, and every 6 months thereafter. Follow-up evaluations included a physical examination, a digital rectal examination, complete blood counts, liver function tests and an assessment of carcinoembryonic antigen levels at each visit. Chest radiography and CT scanning of the abdomen and pelvis were conducted every 6 months after surgery. Video colonoscopy was performed every year (at 1, 3 and 5 years for patients with radical surgery). Recurrence was proven pathologically by surgical resection, biopsy or cytology, and/or radiological findings, which increased in size over time. Treatment toxicity was assessed using the Common Terminology Criteria for Adverse Events version 3.0.

Statistical Analyses

Local failure was defined as any disease recurrence within the pelvis, and any failure outside the pelvis was classified as a distant metastasis. Time to recurrence was measured from the onset of CRT to the date of recurrence. Survival was estimated using the Kaplan–Meier method, with commencement of CRT as the starting point. Statistical analysis was performed using the SPSS software (release 14.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Short-term Response

Treatment results are summarized in Table 2. The distance of the caudal tumor edge from the anal verge at post-CRT workups was a median of 3 cm (range, 1–5). It increased by

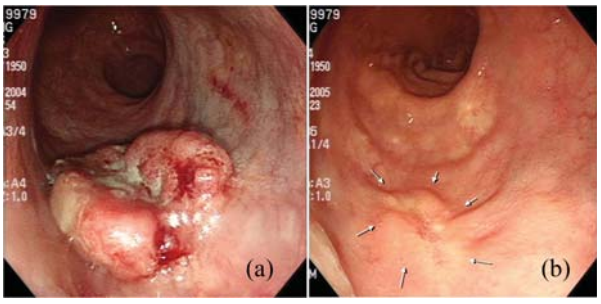

Figure 1. Video colonoscopy images of patient no. 1 in Table 2. (a) Initial ulcerofungating tumor on the rectal wall and (b) remaining scar lesion after pre-operative chemoradiotherapy.

0.5–1 cm in five patients and was unchanged in six. The tumor volume reduction rate was 100% in six patients, indicating a complete radiological response on post-CRT MR imaging. The minimum tumor volume reduction rate was 57%. A pathologically complete response (ypT0 or tumor regression grade 4) occurred in eight patients, ypT1 in two and ypT2 in one. The tumor regression grade was Grade 3 in one patient and Grade 2 in two patients. The pathologic tumor size in three patients with incomplete responses was 0.9, 1.1 and 2.2 cm.

Complications

Acute toxicities from pre-operative CRT were all Grade ≤ 2: hematologic toxicity in six patients (neutropenia in four and leukopenia in three), gastrointestinal toxicity in five (nausea in four, anorexia in two and diarrhea in two) and hand–foot syndrome in one. Post-operative complication, immediate dehiscence of suture, occurred in only one patient, and it was managed conservatively. Acute toxicities during post-operative chemotherapy were also Grade ≤ 2: hematologic toxicity in seven patients (neutropenia in four, leukopenia in three and thrombocytopenia in one), gastrointestinal toxicity in three (nausea in three and anorexia in two) and hand–foot syndrome in two. Late toxicities included Grade 3 leukopenia in one patient and Grade ≤ 2 radiation-induced proctitis in two. No case of Grade 3 or worse gastrointestinal complication (acute or late) was observed.

Long-term Outcomes

The follow-up period was a median of 59 months (range, 24–85). Two patients showed disease recurrence; local recurrence in one and distant metastasis in one. One patient (ypT0) developed recurrence at the excision site after 14 months. He was successfully salvaged with an abdominoperineal resection (rpT2N0) and adjuvant chemotherapy consisting of six cycles of 5-fluorouracil and leucovorin. Another patient (ypT2) developed bone metastasis after 8 months. He received palliative radiotherapy and chemotherapy. Further metastases to the liver and para-aortic lymph node region developed, and the patient died 21 months after the first recurrence. The remaining nine patients were alive without recurrence at the last follow-up. Five-year local recurrence-free, disease-free and overall survival rates were 90.9%, 81.8% and 88.9%, respectively.

DISCUSSION

Patients with locally advanced rectal cancer who achieve downstaging or a complete response following pre-operative CRT and radical resection show favorable long-term outcomes (19–21). The key reasoning is a correlation between the radiosensitivity and low intrinsic aggressiveness of rectal cancer (13). Early surrogate endpoints, that is, the CRT responses, allow for choosing appropriate candidates who can avoid aggressive treatments. In other words, pre-operative CRT provides an opportunity for expanding the applicability of full-thickness local excision for cT2–3 tumors. Additionally, despite the optimized surgical technique made available by total mesorectal excision, higher local recurrence rates have been reported for lower rectal tumors (22). The distal mesorectum is characterized by a circumferential decrease in healthy tissue surrounding the tumor, leading to a loss of tissue layers and

Table 2. Treatment results

Patient	cStage	HG	Pre-size (cm)	Pre-TV (cm^3)	Pre-AV (cm)	Preop CT	Post-AV (cm)	TVRR (%)	ypT (tumor size, cm)	TRG	Postop CT	Recur (site)	RFS (months)
1	T3N0	M	4.0	10.4	2	FL	2.5	100	T1 (0.9)	2	FL	N	80
2	T3N+	P	5.0	39.6	1	FL	1	94	T0	4	FL	N	85
3	T3N0	M	2.5	2.9	2	X	2.5	68	T1 (1.1)	3	FL	N	81
4	T3N0	M	3.0	2.8	3	X	3	100	T0	4	FL	Y (local)	14[a]
5	T3N+	M	3.0	4.2	4	IX	4	78	T0	4	X	N	65
6	T3N+	M	2.5	1.7	4	IX	5	100	T0	4	X	N	58
7	T3N+	W	2.0	5.2	4	IX	5	100	T0	4	X	N	58
8	T3N+	M	2.5	6.3	3.5	FL	4.5	57	T2 (2.2)	2	FL	Y (bone)	8[b]
9	T3N0	M	5.0	4.7	3	IX	3	78	T0	4	X	N	59
10	T3N0	M	2.0	3.9	3	FL	3	100	T0	4	FL	N	29
11	T3N0	W	3.0	2.6	2	FL	2	100	T0	4	None	N	24

HG, histologic grade; pre-size, pre-CRT tumor size; pre-TV, pre-CRT tumor volume; pre-AV, pre-CRT distance from anal verge; preop CT, pre-operative chemotherapy; post-AV, post-CRT distance from anal verge; TVRR, tumor volume reduction rate; TRG, tumor regression grade; postop CT, post-operative chemotherapy; RFS, recurrence-free survival; W/M/P, well/moderate/poor; FL, 5-fluorouracil and leucovorin; X, capecitabine; IX, irinotecan and capecitabine.
[a]No evidence of disease at 72 months.
[b]Dead with disease at 29 months.

a restricted field of view. This constitutes another basis on which pre-operative CRT, followed by local excision, may represent a viable alternative to rectal extirpation in patients with cT2–3 lower rectal cancer. The present study analyzed 11 patients with cT3 distal rectal cancer who received local excision following a favorable response to pre-operative CRT and yielded a 5-year local recurrence-free survival rate of 90.9%.

Several studies have reported the feasibility of performing local excision for cT2–3 rectal cancer following pre-operative CRT (13,23). These studies had limitations in a variety of selection criteria, including small patient numbers, long accrual periods and non-cancer-related deaths by selecting patients with medical co-morbidities. Nonetheless, they generally showed favorable long-term outcomes for selected cT2–3 rectal cancer, which was downstaged to ypT0–1 post-CRT. Guerrieri et al. (24) reported on patients who underwent pre-operative radiotherapy/CRT and transanal endoscopic microsurgery for 145 cT2–3N0 rectal cancer. The ypT classification was ypT0–1 in 55 patients and ypT2–3 in 90. Disease recurrence (local or distant, $n = 10$) occurred only in ypT2–3 patients, after a median follow-up of 81 months. Both Kim et al. (25) and Bonnen et al. (26) analyzed 26 cT2–3 rectal cancer patients who underwent local excision. They categorized the pre-operative CRT pathologic tumor response as complete or incomplete, and none of the complete responders developed disease recurrences in the former study or local recurrences in the latter. In a prospective randomized study by Lezoche et al. (27), which reported similar recurrence and survival between transanal microscopic excision and laparoscopic total mesorectal excision for cT2N0 rectal cancer following pre-operative CRT, all recurrences occurred in ypT2 patients. The small patient number in the present study made a comparative analysis difficult; however, we observed two recurrences in one ypT2 and one ypT0 patient, yielding a crude overall recurrence rate of 100% (1/1) for ypT2 and 10% (1/10) for ypT0–1.

Local excision does not surgically address the lymphatic tissue at risk within the mesorectum. Thus, tumors at high risk for lymphatic spread or clinically obvious nodal involvement would not be readily amenable to this approach. For this reason, indications for local excision alone have been highly restricted to tumors without factors associated with mesorectal lymph node metastasis, such as cT2–3, high grade, lymphovascular/perineural invasion, >3–4 cm in size, or >40% of the rectal wall circumference (4–8). However, pre-operative CRT induces downstaging of tumors and ypN status has been reported to be significantly associated with ypT classification. Read et al. (28) analyzed 644 patients receiving pre-operative radiotherapy/CRT and a proctectomy. The ypN+ rate was 2% in ypT0, 4% in ypT1, 23% in ypT2, 47% in ypT3 and 48% in ypT4. The authors suggested that it was reasonable to select ypT0–1 for local excision and to reserve a proctectomy for patients demonstrated to have residual ypT2–4 disease. We previously reported that the ypT classification was the most reliable predictor of ypN status in a multivariate analysis including 282 rectal cancer patients (29). The ypN+ rate was 3.4% in ypT0–1, 16.9% in ypT2 and 49.3% in ypT3. Perez et al. (12) reported a ypN+ rate of 19% in 88 ypT2 patients among 289 patients managed with radical surgery following pre-operative CRT. After simulation, in which patients with ypT2 would have been treated by local excision, additional recurrences would have recurred as a result of positive lymph nodes left behind, and 5-year local recurrence rates were significantly worse than in patients managed by radical surgery after pre-operative CRT (33% versus 14%, $P = 0.009$). In several studies, the conversion criteria for immediate radical surgery after performing local excision was ypT2 or a positive resection margin (30,31). In the present study, five (45.5%) patients including a patient with ypT2 showed initially as cN+, but did not develop a local recurrence. We strongly recommended immediate radical surgery for a patient with ypT2, but he refused and died of disease recurrence. However, recurrence occurred only in a distant organ, so our results indicated that suspected disease in mesorectal lymph nodes was controlled by CRT, and local excision did not increase local recurrence, which could occur due to positive unresected lymph nodes.

One local recurrence occurred at the excision site in a patient with a pathologically complete response. A few reports have suggested tattooing the tumor border before CRT, because CRT reduces the tumor mass and healthy mucosa regenerates, rendering it difficult to safely recognize the entire area of the initial tumor (24,27,32). The absence of neoplastic tissue in the surgical margins might not indicate that the excision included the dispersed microscopic residual tumor cells completely. Another patient with ypT2 developed a distant metastasis without local recurrence. Pre-operative concurrent chemotherapy, which was responsible for less tumor downstaging by insufficient radiosensitizing efficacy, might be ineffective, like post-operative chemotherapy, for eradicating micrometastases that could exist from the initial disease presentation. Novel regimens incorporating oxaliplatin, irinotecan, cetuximab or bevacizumab may help to improve CRT response and lower the recurrence risk (33). It remains controversial as to who should receive post-operative chemotherapy following pre-operative CRT (34); however, we routinely recommend it for locally advanced rectal cancer patients, according to the National Comprehensive Cancer Network guidelines, regardless of their CRT response.

Local excision has been selectively attempted mostly for patients who are medically unfit for or who refuse radical surgery. However, if a CRT response can be reliably assessed pre-operatively, indications for local excision can be expanded. MR imaging or transrectal ultrasonography has limitations in accurately predicting pathologic CRT responses. Thickening of the rectal wall by marked fibrosis, and peritumoral infiltration of inflammatory cells and

vascular proliferation induced by CRT decrease the accuracy (35,36). Novel methods for assessing CRT response have included positron emission tomography-CT (37) and biologic molecular markers (38,39). Additionally, we reported that tumor volume reduction rate was significantly associated with downstaging or a pathologic complete response (15). The usual colorectal tumor is an irregular configuration, so three-dimensional region-of-interest tumor volumetry using MR imaging could provide data more closely reflecting actual tumor volume changes than traditional diameter-based estimations. In the present study, the lowest two tumor volume reduction rates, 57% and 68%, occurred in ypT2 and ypT1 patients, respectively. Tumor regression grade was significantly correlated with ypN status, regardless of ypT classification (29,40). Although no relationship with recurrence was apparent in this study, a combined analysis of tumor regression grade and ypT classification might assist in predicting ypN status and the decision for those who need an immediate conversion to radical surgery.

In conclusion, although the follow-up period may have been insufficient to detect recurrence in some patients, long-term oncologic outcomes for patients with cT3 distal rectal cancer were favorable when using pre-operative CRT and local excision. Full-thickness local excision following CRT may be an acceptable option for cT3 distal rectal cancer that responds well to CRT. Further studies are needed to accurately evaluate CRT responses pre-operatively, and randomized prospective trials are needed to refine the selection criteria for those who can avoid radical surgery-associated morbidities without compromising long-term outcomes.

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Conflict of interest statement

None declared.

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