Neoadjuvant Concurrent Chemoradiotherapy in Treating Locally Advanced Rectal Cancer

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Background: Colorectal cancer is a common cancer and a major cause of morbidity and mortality worldwide. Middle to lower rectal cancer, a challenge for surgeons, is problematic. Neoadjuvant concurrent chemoradiotherapy (CCRT), introduced in the last decade, leads the local control of advanced rectal cancer to a high percentage of R0 resection (margin negative under microscopic examination) and a low recurrence rate.

Methods: From January 2005 to June 2007, 46 patients with locally advanced rectal cancer who received neoadjuvant CCRT were included. Factors including disease-free survival time, overall survival time, local recurrence, metastasis, and postoperative complications were evaluated retrospectively. Response was defined according to Mandard's classification, in which TRG1 is no residual tumor and TRG2–3 is 50–100% tumor shrinkage.

Results: In this series, 3 patients who did not receive post-CCRT curative resection were excluded. The remaining 43 patients (22 males, 21 females) had received curative surgery and were included. Thirty-four patients had tumor shrinkage, and the response rate was 79% (Mandard's classification: TRG1–TRG3). The median follow-up time was longer than 1.5 years. Patients who responded to CCRT had lower local recurrence rates (5.9% *vs.* 55.6%; $p = 0.002$) and a greater curative resection rate (97.1% *vs.* 66.7%; $p = 0.024$). The complication rates of both groups were similar.

Conclusion: Neoadjuvant CCRT gives locally advanced rectal cancer patients a more favorable result, with acceptable toxicity. [*J Chin Med Assoc* 2009;72(4):179–182]

Key Words: locally advanced rectal cancer, neoadjuvant concurrent chemoradiotherapy, R0 resection

Introduction

Colorectal cancer is a common cancer and a major cause of morbidity and mortality worldwide. Middle to lower rectal cancer, a challenge for surgeons, is problematic. Surgical therapy for rectal cancer has evolved since Ernest Miles first described the abdominoperineal resection in 1908.[1] By the 1920s, he had reduced the recurrence rate from almost 100% to approximately 30%,[2] thus ensuring that this technique was the gold standard at that time while advocating extensive aggressive cancer therapy. In retrospect, it is perplexing that such extreme surgery was standard, given its considerable local failure rate and its potential to result in urinary, sexual, and gastrointestinal dysfunction. Several modifications were proposed to promote locoregional control and survival, with little success.[3,4] Better suture material, as well as devices enabling lower anastomosis, led to a shift toward sphincter-saving approaches with respect to cancer of the rectum. Anterior resection replaced abdominoperineal resection as the mainstay of therapy, although adequate consideration of circumferential margins and lymph node harvests were often neglected in early reports in the 1950s. Not surprisingly, there was concern that sphincter-saving surgery might increase local recurrence. It was in this setting that total mesorectal excision (TME) was first described in 1982 by Heald and colleagues;[5] TME reduced recurrence rates to less than 10%.[6] Neoadjuvant concurrent chemoradiotherapy (CCRT), introduced in the last decade, has led to local control for advanced rectal cancer to a higher percentage of R0 resection (margin clear under microscopic examination) and a lower recurrence rate.[7]

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Methods

From January 2005 to June 2007, 46 patients with locally advanced (fixed tumor by digital rectal exam or T3–4 tumor by computed tomography [CT]/sonography) rectal cancer who received CCRT were retrospectively reviewed. The neoadjuvant CCRT for locally advanced rectal cancer in our hospital was 5-fluorouracil 400 mg/m^2 plus leucovorin 20 mg/m^2 intravenously for 1 hour, on days 1–4 and 29–32, concurrent with radiotherapy (200 cGy/day, Monday–Friday, for 5 weeks).

Three of the patients, who achieved confirmed clinical complete response by CT scan and physical examination, and who received only local excision, were excluded, leaving 43 patients included in our study. Based on post-CCRT CT and digital rectal examination, we defined the clinical response. Five (12%) patients had complete response and 29 (67%) had partial response; the overall response rate was 79%. Several parameters, including local recurrence, curative resection (R0 resection), and postoperative complications, were evaluated. The method of statistical analysis for disease-free survival time and overall survival time was Kaplan-Meier survival analysis, whereas that for postoperative complications, metastasis, curative resection rate and Duke's stage was Fisher's exact test.

Results

Patients' characteristics are shown in Table 1. Most of them received TME, and almost all had protective ileostomy. Curative resection rate (R0 resection rate) was higher in the responding group (97%) than in the non-responding group (66.7%), with statistical significance ($p=0.024$). As shown in Table 2, the local recurrence rate was low in the responding group (5.9%) compared with the non-responding group ($p=0.002$). Disease-free survival was also higher in the responding group, with marginal statistical significance ($p=0.06$). Otherwise, there was no significant difference between groups in overall survival time. The anastomotic leakage rate was high, up to 25% in both groups. Mean hospital stay was 11.5 days, with no significant difference between groups. As can be seen in Table 3, the risk factors for local recurrence were high Duke grade and incomplete resection (R1 [microscopic margin positive] and R2 [gross margin positive] resection). Incomplete resection rate was higher in the non-responding group. During the period of CCRT, there was only 1 patient who developed grade III neutropenia, and no distant metastatic lesions occurred.

Table 1. Patient characteristics*

Age (yr)	55.57 ± 13.10
Interval (d)	41.28 ± 27.11
Sex	
Male	22 (51.2)
Female	21 (48.8)
Diabetes mellitus	
+	5 (11.6)
−	38 (88.4)
Liver/lung/kidney	
+	10 (23.3)
−	33 (76.7)
Cardiovascular	
+	10 (23.3)
−	33 (76.7)
Schedule	
Others	11 (25.6)
TME + loop ileostomy	32 (74.4)
Laparoscopy/open	
Laparoscopy	25 (58.1)
Open	18 (41.9)

**Data presented as mean ± standard deviation or n (%). TME = total mesorectal excision.*

Discussion

Incomplete resection of rectal cancer eventually results in local recurrence and death. To improve this, Miles[1] introduced abdominoperineal resection in the early 1900s. With evolving instruments, a sphincter-saving procedure was performed in rectal cancer. Heald et al[5] developed TME in 1982, which decreased the local recurrence rate to less than 10%. In locally advanced rectal cancer, it remained a challenge until the early 1990s. Neoadjuvant CCRT[8,9] offered the possibility of tumor-shrinking, hence making curative resection possible. In our series, 43 patients received neoadjuvant CCRT, with a mean follow-up time of 1.5 years. The overall recurrence rate was 16.3%, including 5.9% in the responding group and 55.6% in the non-responding group, respectively ($p=0.002$). The curative resection rates were 97.1% in the responding group and 66.7% in the non-responding group, respectively ($p=0.024$). It is well known that by inducing tumor shrinkage and hence leading to further curative resection, CCRT improved the local control rate. It could have caused other problems if we had saved the sphincter in the non-responding group. The anastomotic leakage rate was 27.8%, similar in both groups. As most of our patients had received protective ileostomy, the problem was solved and the mean hospital stay was only 11.5 days.

Table 2. Response*

RR	Complete + partial response	No response	*p*
Anal verge (cm)	5 (3–13)	5 (4–8)	0.861†
DFT (mo)	16 (4–36)	13 (4–34)	0.060‡
OST (mo)	17.5 (5–36)	25 (14–34)	0.206‡
Stay (d)	9.5 (6–28)	14 (8–26)	0.705†
U/M/L			1.000§
L	26 (76.5)	8 (88.9)	
M	6 (17.6)	1 (11.1)	
U	2 (5.9)	0 (0.0)	
Complications			0.225§
+	2 (8.7)	2 (28.6)	
–	21 (91.3)	5 (71.4)	
Leak			1.000§
+	8 (28.6)	2 (25.0)	
–	20 (71.4)	6 (75.0)	
Pelvic abscess			0.188§
+	2 (5.9)	2 (22.2)	
–	32 (94.1)	7 (77.8)	
Local recurrence			0.002§
+	2 (5.9)	5 (55.6)	
–	32 (94.1)	4 (44.4)	
Metastasis			0.026§
+	3 (8.8)	4 (44.4)	
–	31 (91.2)	5 (55.6)	
Stage (Duke)			0.001‖
0	5 (14.7)	0 (0.0)	
A + B	21 (61.8)	1 (11.1)	
B2	0 (0.0)	2 (22.2)	
C	8 (23.5)	6 (66.7)	
CRM			0.024§
R0	33 (97.1)	6 (66.7)	
R1 + R2	1 (2.9)	3 (33.3)	
Poorly/A-V-N			0.238§
+	10 (29.4)	5 (55.6)	
–	24 (70.6)	4 (44.4)	
Node			0.040§
+	8 (23.5)	6 (66.7)	
–	26 (76.5)	3 (33.3)	
Schedule			1.000§
Others	9 (26.5)	2 (22.2)	
TME + loop	25 (73.5)	7 (77.8)	
Laparoscopy/open			0.455§
Laparoscopy	21 (61.8)	4 (44.4)	
Open	13 (38.2)	5 (55.6)	

**Data presented as median (range) or n (%); †Mann-Whitney U test; ‡Kaplan-Meier survival analysis; §Fisher's exact test; ‖Pearson's χ^2 test. DFT = disease-free survival time; OST = overall survival time; U = upper rectum; M = middle rectum; L = lower rectum; CRM = circumferential radial margin; A-V-N = cancer invasion to artery, vein or nerve; TME = total mesorectal excision.*

Table 3. Local recurrence*

LR	Complete + partial response	No response	*p*
Stage (Duke)			0.025†
0	0 (0)	5 (13.9)	
A + B	2 (28.6)	20 (55.6)	
B2	2 (28.6)	0 (0)	
C	3 (42.9)	11 (30.6)	
CRM			0.010†
R0	4 (57.1)	35 (97.2)	
R1 + R2	3 (42.9)	1 (2.8)	
Poorly/A-V-N			0.215†
+	4 (57.1)	11 (30.6)	
–	3 (42.9)	25 (69.4)	

**Data presented as n (%); †Pearson's χ^2 test; ‡Fisher's exact test. LR = local recurrence; CRM = circumferential radial margin; A-V-N = cancer invasion to artery, vein or nerve.*

In our study, major complications were acceptable: <10%, similar to other series.[10] Thirty-two patients received sphincter-saving surgery, and 5 of them (15.6%) converted to permanent stoma. In our series, the toxicity related to CCRT was mild, as in other reports. There were 20–30% of patients who developed grade I–II nausea/vomiting and grade I–II neutropenia, and only 1 patient developed grade III neutropenia. No metastatic lesions occurred during the period of CCRT.

In conclusion, neoadjuvant CCRT gives a high chance of tumor shrinkage, and hence improves the curative resection and local control rates. Patients who responded to CCRT had a better local control rate with tolerable adverse effects.

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