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Sphincter-preserving surgery after preoperative radiochemotherapy for T3 low rectal cancers

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Abstract. The aim of this study was to evaluate the feasibility and the effectiveness of preoperative radiochemotherapy followed by total mesorectal excision (TME) and sphincter-preserving procedures for T3 low rectal cancer. Patients with rectal cancer and T3 tumors located within 1-6 cm of the dentate line received preoperative radiochemotherapy. Concurrent 5-fluorouracil-based radiochemotherapy was used. Radical resection with TME and sphincter-preserving procedures were performed during the six to eight weeks following radiotherapy. Survival was analyzed using the Kaplan-Meier method. The anal function was evaluated using the Wexner score. The clinical response rate was 83.5%, overall downstaging of T classification was 75.3% and pathological complete response was 15.3%. The anastomotic fistula rate was 4.7%. A median follow-up of 30 months showed the local recurrence rate to be 4.7% and the distant metastasis rate to be 5.9%. The three-year overall survival rate was 87%. The degree of anal incontinence as measured using the Wexner score decreased over time, and the anal sphincter function in the majority of patients gradually improved. Preoperative radiochemotherapy was found to improve tumor downstaging, reduces local recurrence, increase the sphincter preservation rate, and is therefore of benefit to patients with T3 low rectal cancer.

Introduction

The surgical and multimodal management of rectal cancer has evolved significantly over the past decades. In terms of surgical technology, total mesorectal excision (TME) is now the standard approach for rectal cancer (1,2). The introduction of TME in rectal cancer surgery may lead to a reduction in local recurrence rates to below 10% (3,4). However, prevention of local recurrenceremains one of the key problems in resectable rectal cancer (5,6). Findings of randomized trials showed that neoadjuvant therapy improves local control (7,8). Preoperative radiochemotherapy combined with TME has led to significant improvements in local control in patients with locally advanced rectal cancer and a reduction in the local recurrence rate (9,10). Preoperative radiochemotherapy combined with TME not only improves local control and oncological cure, but provides support and a greater probability of sphincter preservation in patients with low-middle rectal cancer (11,12). However, the role of preoperative radiochemotherapy in enhancing sphincter-preserving surgery for rectal cancer is controversial (13). In the present study, preoperative radiochemotherapy was administered followed by TME and sphincter-preserving procedures in patients with low rectal cancer with T3 tumor. The aim was to observe and verify the effects of preoperative radiochemotherapy in controlling local recurrence and to improve sphincter-preserving surgery in patients with advancing low rectal cancer.

Patients and methods

Patients. In total, 85 patients with biopsy-proven rectal adenocarcinomas were identified between March 2006 and May 2009, including 48 men and 37 women, median age 51 years, range 25 to 68 years. The local tumor staging was assessed with endorectal ultrasound (EUS) and MRI or CT scan in all patients. T3 staging of the 85 patients was based on the TNM classification system. The distal margin of rectal cancers was located within 1-6 cm of the dentate line, and there was no clinical evidence of distant metastasis. The study was approved by the ethics committee of The Military General Hospital of Beijing PLA, and informed consent was obtained from each patient.

Preoperative radiochemotherapy

Radiotherapy. All 85 patients received preoperative pelvic radiotherapy with concurrent 5-fluorouracil (5-FU)-based radiochemotherapy. Radiotherapy was performed using a three or four-field technique. The targeted volume included the rectum, the whole mesorectum and the draining lymph node chains. A fraction dose of 2.0 Gy was administered 5 times a week. The total dose was 50 Gy in 25 fractions over 5 weeks.

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Chemotherapy. The preoperative concomitant chemotherapy was administered with 5-FU at 350 mg/m^2/d, and leucovorin at 200 mg/m^2/d for five days during radiotherapy in weeks one and five. Following radiotherapy, the regimen was administered as 5-FU at 350 mg/m^2/d and leucovorin at 200 mg/m^2/d for five consecutive days for two cycles.

Radical rectum resection. Radical resection for rectal cancer was performed following the principles of TME during the six to eight weeks following radiotherapy. To ensure that the surgery was en bloc resection of the rectal cancer with complete pararectal mesorectum, the rectum was mobilized in an anterior and posterior manner with sharp dissection through Denonvilliers' and Waldeyer's fascia. Lateral dissection of the rectum was performed in order not to breach the fascia propria of the rectum, remaining outside the margins of the mesorectum. The surgery achieved complete resection of the rectal cancer with adequate radial and circumferential margins.

Sphincter preservation. Rectal mobilization was carried out using the TME technique. Since our patients had mid and low rectal cancers, we extended the dissection of mesorectum to the levators. An assessment was made as to whether a double stapling anastomosis or a transanal coloanal anastomosis was to be performed. With double stapling anastomosis, the rectum was transected at the level of the pelvic floor with a transverse stapler. A circular stapler of a suitable size was applied to perform the double stapling anastomosis.

A transanal anastomosis was constructed when the rectal cancer was low and the transverse stapler could not be applied. Following full mobilization of the rectum, the transection was completed transanally at 0.5 to 1.0 cm above the dentate line. The hand-sewn low anterior resection with coloanal anastomosis was performed. For the extremely low lesions, we applied intersphincter protectomy with coloanal anastomosis to obtain an adequate margin. The proximal end of the colon was introduced into the sheath of the pelvic floor and the superior anal canal, and the coloanal anastomosis was completed.

Preventive transverse colostomy was selectively created according to the bowel preparation, anastomosis, leakage test and incomplete doughnuts.

Follow-up protocol. Following surgery, patients were followed up at intervals of three months during the first two years and six months from year three onwards. The follow-up included clinical, physical examination, blood test, serum carcinoembryonic antigen, chest radiography and abdominal ultrasound. Colonoscopy was performed once a year during the first three years following surgery. The Wexner score was used in evaluating anal function following sphincter-preserving surgery and in judging the impact of anal incontinence on the quality of life of patients.

Statistical analysis. Comparison of categorical variables was performed using the χ^2 test. Quantitative variables were compared with analysis of variance and the Q test. Survival was analyzed using the Kaplan-Meier method and the factors were compared with the log-rank test. $P<0.05$ was considered statistically significant.

Table I. Patient characteristics.

Characteristics	No. of patients
Age (years)	
Median	51
Range	25-68
Gender	
Male	48 (56.5%)
Female	37 (43.5%)
Distance from the dentate line (cm)	
Median	3
Range	1-6
Histology	
Adenocarcinoma	85
Well-differentiated	52 (61.2%)
Poorly differentiated	33 (38.8%)
Lymph nodes sampled	
Median	9
Range	5-21
pN0	53 (62.4%)
pN1	21 (24.7%)
pN2	11 (12.9%)

Results

Patient characteristics. In total, 85 patients (Table I) with rectal cancer located at a median distance of 3 cm from the dentate line were evaluated and all tumors were easily felt on digital rectal examination. Preoperative radiochemotherapy was well-tolerated and all of the patients received the planned dose of chemotherapy and completed the course of radiotherapy. The median interval between the end of preoperative radiochemotherapy to surgery was 6.5 weeks (range, 6-8 weeks). The median follow-up period was 30 months (range, 10-56 months).

Clinical and pathological response. The clinical responses in terms of tumor downsizing were evaluated four weeks following the end of preoperative radiochemotherapy prior to surgery. Digital rectal examination and rigid proctoscopy were used for the evaluation. The maximum tumor diameter and the perpendicular diameter were measured and an objective response was recorded according to the percentage of reduction in the product of the two perpendicular diameters of the primary tumor. The clinical response rate was 83.5%. Complete regression of the rectal tumor was observed in 12 patients (14.1%). Twenty-four patients (28.2%) had a reduction of >50% and 35 patients (41.2%) had a reduction of >30%. No tumor progression was found.

To evaluate pathological response, surgical specimens without microscopic disease were obtained with TME and margin-free resection for all 85 patients. Pathological response was estimated according to the replacement of neoplastic

Table II. Wexner score for anal incontinence in 85 patients after preoperative radiochemotherapy and sphincter-preserving surgery.

Time (months)	Mean score	No. of patients		
		<5	5-9	≥10
6	8.78±4.83	14	41	30
12	7.75±4.48	30	37	18
18	4.65±4.11	60	16	9

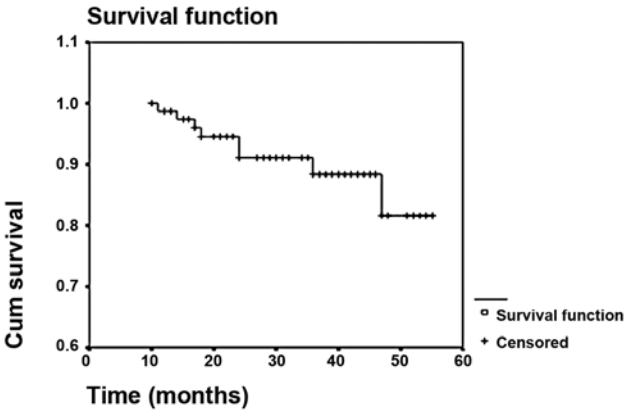

Figure 1. Kaplan-Meier curve of recurrence and metastasis-free survival. Four patients developed recurrent disease, and four metastases. The 3-year recurrence and metastasis-free survival was 87.7%. The median follow-up period was 30 months.

glands with loosely fibrous tissue and scattered chronic inflammatory cells. Overall downstaging of the T classification was achieved in 64 patients (75.3%). Pathological complete response was found in 13 patients (15.3%). T1 disease was observed in 18 patients (21.2%) and T2 in 33 patients (38.8%). Twenty-one patients (24.7%) remained T3 pathologically.

Postoperative complications. Radical excision with TME and the sphincter preservation procedure was performed for all 85 patients. Low anterior resection was carried out for 49 patients, while abdominal-anal resection was carried out for 36 patients. A protective diverting colostomy was performed for five patients, two that underwent anterior resection, and 3 for abdominal-anal resection. A gross resection of rectal tumor with negative distal resection margin and circumferential resection margin was obtained in all cases. There was no procedure-related mortality. Anastomotic fistula was present in four patients (4.7%); two underwent repeat-surgery with temporary transverse colostomy, and two were treated with conservative therapy.

Local recurrence and metastasis. A median follow-up of 30 months (range, 10-56 months) for 85 patients showed the local recurrence rate to be 4.7% (4 of 85). Four patients, two with T3N1 tumors at 3.0 and 2.0 cm from the dentate line, and two with T3N2 tumor at 4.0 cm from the dentate line, presented with extramural pelvic recurrence without involvement of the coloanal anastomosis. The 4 patients were treated by re-excision; three with abdominoperineal resection and one with curative pelvic exenteration. Distant metastasis was found in five patients (5.9%), four with metachronous liver metastasis and one with lung metastasis; subsequently, palliative chemotherapy was performed. The three-year overall survival rate was 87% in 85 patients (Fig. 1) and the cancer-specific survival rates were noted (Table II).

Quality of life. The degree of anal incontinence was measured using the Wexner score from 0 to 20. A Wexner score of ≥5 was considered to define anal incontinence, and a score of ≥10 severe anal incontinence (Table II). For the 85 patients, in the initial six months post-surgery, the Wexner score was 8.78±4.83: <5 for 16.5% of the patients, from 5 to 10 for 48.2%, and ≥10 for 32.3% of the patients. Twelve months subsequent to surgery, the mean score was 7.75±4.48: <5 for 35.3% of the patients, from 5 to 10 for 43.5% and ≥10 for 21.2% of the patients. The Wexner score decreased to 4.65±4.11 one and half years post-surgery: <5 for 70.6% of patients, from 5 to 10 for 18.8% and ≥10 for 10.6% of the patients. At the end of follow up, lifestyle was altered for 12.9% of the patients.

Discussion

The strategy of treatment for rectal cancer markedly changed with the advance of surgical techniques, instruments, radiotherapy, chemotherapy and molecular-targeted therapy. Improving survival and quality of life are equally crucial and are the main goals for the treatment of rectal cancer. The age of onset of rectal cancer in the Chinese population is younger than that in Western population groups (14) and low rectal cancer constitutes a high proportion clinically. Previously, abdominoperineal resection was the main option for treatment of patients in China, particularly for low rectal cancers with T3 tumors. The sphincter preservation rate was low in order to obtain a complete resection to prevent local recurrence. Postoperative radiochemotherapy followed. The conventional treatments were established for local control and disease-free interval following surgical resection (15,16), but improving sphincter preservation constituted a challenge. Colostomy caused serious inconvenience to the patients and limited their quality of life. Reducing local recurrence and improving sphincter preservation continue to be the challenges in the treatment of rectal cancer.

Ideal surgery for rectal cancer should not only obtain adequate radial and circumferential margins, but also preserve normal sphincter function. The strategy of conventional surgery and postoperational radiochemotherapy for the

treatment of low rectal cancer of T3 tumors signified the loss of sphincter-preserving opportunities for the patients during curative surgical procedures. Sphincter preservation also signified facing the risk of local recurrence. However, balancing radical resection and sphincter preservation for the treatment of low rectal cancer has always been problematic.

The advent of preoperative radiochemotherapy was beneficial in the treatment of local advancing rectal cancer (17,18). It was better tolerated by the patients and more effective for local control and downstaging compared to postoperative therapy (19-21). Due to the response and downstaging with preoperative radiochemotherapy, the lengthened distance between the anorectal ring and lower edge of rectal tumor facilitated radical excision and sphincter-preserving procedures (11,22). This reduced the risk of local recurrence and maximized sphincter preservation. Preoperative radiochemotherapy followed by radical resection with total mesorectal excision resulted in abdominoperineal resection surgery being reduced and sphincter-saving surgery being increased significantly.

The current study presents similar results compared with other literature reports. In our 85 cases, 85% of the patients demonstrated clinical and pathological response and 14.3% achieved complete pathological response. For those patients, curative resection and sphincter preservation procedures were completed, which are difficult to achieve with the conventional strategy. The results proved that preoperative radiochemotherapy was extremely effective in downstaging advanced rectal cancer and facilitated radical surgery with sphincter preservation.

Local recurrence is a major issue in rectal cancer following a surgical resection. Although local recurrence rates vary according to hospital and the skill of the surgeon, T stage of the primary tumor is a crucial factor (23-25). With regards to TME procedure, the standard technique is performed in radical surgery of rectal cancer, and the local recurrence is controlled (26,27). Concerning preoperative radiochemotherapy, downstaging of the tumor was demonstrated, providing another safeguard against local recurrence (28,29). As such, our cases of T3 tumors had a local recurrence rate of 3.5%, similar to that of T2 tumors.

Surgical and postoperative complications were not increased in our patients. Abdominal adhesions were commonly encountered during surgery following preoperative radiochemotherapy, but increased difficulty for radical excision was limited. Since preoperative radiation induced thickening of the presacral fascia, the TME procedure could be performed safely with no significant increase in bleeding. Postoperative complications, especially anastomotic fistula, were not increased. Based on our findings, downstaging of the rectal tumor with preoperative radiochemotherapy provided lengthened distance, ensured a safe anastomosis and guaranteed that the sphincter-preserving procedure could be completed smoothly.

Impairment of the anal sphincter with preoperative radiochemotherapy has been an issue of concern (30). In low rectal cancer, sphincter-preserving surgery itself has some impact on anal function. The effects of irradiation on anorectal function are dose-dependent. In their study, Ammann *et al* reported that neoadjuvant radiochemotherapy resulted in disordered anal sphincter function in patients with midrectal cancer. Low and rectoanal anastomosis appeared to obtain a better anal sphincter function than higher anastomosis in neoadjuvant radiochemotherapy patients (31). Results obtained using the Wexner score indicated that our patients had different degrees of anal incontinence following surgery. This discrepancy occurred due to the combined impact of preoperative radiochemotherapy and surgery on the anal sphincter function. The follow-up results revealed that the Wexner score changed from high to low in our patients and, over time, the anal sphincter function in the majority of patients gradually improved. Although preoperative radiochemotherapy has an adverse impact on anal sphincter function, it should not be abandoned as a treatment option. Overall, patients with T3 low rectal cancer could benefit from preoperative radiochemotherapy and sphincter-preserving surgery and obtain a better quality of life.

In conclusion, preoperative radiochemotherapy significantly improves tumor downstaging, decreases local recurrence for patients with T3 low rectal cancers, and increases the sphincter preservation rate. Preoperative radiochemotherapy followed by TME and sphincter-preserving procedures was associated with low complication rates, minor impairment of the anal sphincter and the anal function were satisfactory in most patients. For T3 low rectal cancer, preoperative radiochemotherapy is a sensible choice for reducing the local recurrence rate and increasing the sphincter preservation rate.

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