

Routine defunctioning stoma after chemoradiation and total mesorectal excision: A single-surgeon experience

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Abstract

AIM: To investigate the 10-year results of treating low rectal cancer by a single surgeon in one institution.

METHODS: From Oct 1998 to Feb 2009, we prospectively followed a total of 62 patients with cT2-4 low rectal cancer with lower tumor margins measuring at 3 to 6 cm above the anal verge. All patients received neo-

adjuvant chemoradiation (CRT) for 6 wk. Among them, 85% of the patients received 225 mg/m²/d 5-fluorouracil using a portable infusion pump. The whole pelvis received a total dose of 45 Gy of irradiation in 25 fractions over 5 wk. The interval from CRT completion to surgical intervention was planned to be approximately 6-8 wk. Total mesorectal excision (TME) and routine defunctioning stoma construction were performed by one surgeon. The distal resection margin, circumferential resection margin, tumor regression grade (TRG) and other parameters were recorded. We used TRG to evaluate the tumor response after neoadjuvant CRT. We evaluated anal function outcomes using the Memorial Sloan-Kettering Cancer Center anal function scores after closure of the defunctioning stoma.

RESULTS: The median distance from the lower margin of rectal cancer to the anal verge was 5 cm: 6 cm in 9 patients, 5 cm in 32 patients, 4 cm in 10 patients, and 3 cm in 11 patients. Before receiving neoadjuvant CRT, 45 patients (72.6%) had a cT3-4 tumor, and 21 (33.9%) patients had a cN1-2 lymph node status. After CRT, 30 patients (48.4%) had a greater than 50% clinical reduction in tumor size. The final pathology reports revealed that 33 patients (53.2%) had a ypT3-4 tumor and 12 (19.4%) patients had ypN1-2 lymph node involvement. All patients completed the entire course of neoadjuvant CRT. Most patients developed only Grade 1-2 toxicities during CRT. Thirteen patients (21%) achieved a pathologic complete response. Few post-operative complications occurred. Nearly 90% of the defunctioning stomas were closed within 6 mo. The local recurrence rate was 3.2%. Pathologic lymph node involvement was the only prognostic factor predicting disease recurrence (36.5% vs 76.5%, $P = 0.006$). Nearly 90% of patients recovered sphincter function within 2 year after closure of the defunctioning stoma.

CONCLUSION: Neoadjuvant CRT followed by TME,

combined with routine defunctioning stoma construction and high-volume surgeon experience, can provide excellent surgical quality and good local disease control.

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Key words: Rectal cancer; Neoadjuvant chemoradiation; Total mesorectal excision; Pathologic complete response; Defunctioning stoma

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INTRODUCTION

Since total mesorectal excision (TME) was first described by Heald in 1982, low rectal cancer treatment has experienced a revolutionary advancement. The traditional abdominoperineal resection procedure has gradually been replaced by TME and coloanal anastomosis for resectable rectal cancers. Improved overall survival and decreased local recurrence rates have been achieved with the combined progression of knowledge about surgical anatomy and technique, new chemotherapy regimens and radiotherapy technology. For locally advanced rectal cancers, randomized controlled trials have shown that neoadjuvant chemoradiation therapy (CRT) leads to a decrease in tumor size and enhances the possibilities of tumor resectability and sphincter preservation^[1,2]. Furthermore, with new chemotherapy regimens developing at a rapid pace, every new clinical trial has attempted to incorporate these new drugs into their protocols to gain better oncologic results. However, the complications related to CRT overuse can be devastating, including treatment toxicity, anastomotic leakage, or any type of postoperative complications, such as persistent fistula^[3] and subsequent permanent colostomy. These complications can adversely affect patient quality of life and even make patients abandon the treatment course before the scheduled operation. In addition, many large series have reported that chemotherapy regimens can differ between series and surgeon experience can be variable between the institutions, making a uniform comparison difficult. To avoid these problems, our team has adopted a less toxic chemotherapy regimen and routine defunctioning stoma construction after TME surgery since the initiation of the treatment protocol 10 year ago. Because surgical resection remains the only curative treatment for locally advanced rectal cancer, we believe patients will have better chance of cure if they can benefit from neoadjuvant CRT without associated complications and

proceed to surgical operations in good physical condition. The aim of this report is to present our recent 10 years' experience of 62 consecutive low rectal cancer patients undergoing neoadjuvant CRT and TME surgery at National Cheng Kung University Hospital where all operations were performed in a standard fashion by a single surgeon.

MATERIALS AND METHODS

From Oct 1998 to Feb 2009, we prospectively followed patients with locally advanced low rectal cancer who underwent a radical operation by a single surgeon, Jenq-Chang Lee. Patients with clinical tumor category cT2-4 or clinical node category cN1-2 low rectal cancer and a lower tumor margin within 3-6 cm of the anal verge were offered the choice of receiving neoadjuvant CRT and were included in the study. The exclusion criteria included other synchronous malignancies, previous chemotherapy or radiotherapy to the pelvis, contraindications to CRT and unwillingness to receive neoadjuvant CRT. All patients had a confirmed pathological diagnosis before undergoing any treatment. Among a total of 302 rectal cancers operated by Dr. Lee during this time period, 63 consecutive patients were included according to the above criteria. All but one patient received neoadjuvant CRT and then underwent a radical operation. All operations achieved R0 resection. One patient was excluded because she refused the radical operation after CRT. In the end, a total of 62 patients were included for retrospective data analysis. All of them were followed for more than 3 year.

A clinical staging evaluation was performed before neoadjuvant CRT with a digital examination and computed tomography. Magnetic resonance imaging, endorectal ultrasonography and positron emission tomography were used selectively. All patients were well informed before treatment initiation. All patients received neoadjuvant CRT for 6 wk. Among them, 85% of the patients received 225 mg/m²/d 5-fluorouracil (5-FU) using a portable infusion pump. The whole pelvis received a total dose of 45 Gy of irradiation in 25 fractions over 5 wk. The duration from CRT completion to surgical intervention was planned to be approximately 6-8 wk. The clinical staging was re-evaluated just before the operation. Each rectal cancer was reviewed and staged according to the American Joint Committee on Cancer Staging Manual^[4]. The distal resection margin (DRM), circumferential resection margin (CRM), tumor regression grade (TRG) and other parameters were recorded. We used the TRG to evaluate the tumor response to neoadjuvant CRT^[5]. The follow-up protocol was based on the National Comprehensive Cancer Network (NCCN) guidelines^[6]. We evaluated anal function outcomes using the Memorial Sloan-Kettering Cancer Center anal function scores (MSK-AF)^[7] after closure of the defunctioning stoma.

Table 1 Clinical demographics (*n* = 62) *n* (%)

Variable	
Age (yr) (mean ± SD)	58.7 ± 12.8
Gender (male/female)	40/22 (64.5/35.5)
Distance of tumor from anal verge (cm) (median, range)	5 (3-6)
Pre-treatment stage	
cT2/T3/T4	17/42/3 (27.4/67.7/4.8)
cN0/cN1/N2	41/16/5 (66.1/25.8/8.1)
Tumor response to CRT (tumor size reduction) ¹	
100% response	8 (12.9)
50%-99%	22 (35.5)
< 50%	32 (51.6)
Toxicity of neoadjuvant CRT	
Skin ²	1 (1.6)
Nausea/vomiting ²	7 (11.3)
Diarrhea ³ (Grade II/Grade III)	20/1 (32.3/1.6)
Hematological toxicity	0
Adjuvant chemotherapy	57 (91.9)

¹Evaluated by digital examination and computed tomography; ²Grade I - II;³Grade I - III. CRT: Chemoradiation therapy.

Surgical technique

Total mesorectal excision (TME) was performed in every patient. The methods of TME^[8,9] have previously been described in detail. Low anterior resection with the double-stapling technique and straight coloanal anastomosis was attempted in every patient if feasible. If double-stapling anastomosis could not be performed for low-lying rectal cancer, intersphincteric resection was performed for patients with adequate oncological margins. Abdominoperineal resection (APR) was chosen for patients with inadequate oncological margins or by patients themselves. All patients who underwent sphincter-saving procedures underwent the routine construction of a defunctioning loop colostomy or ileostomy. The defunctioning loop colostomy construction was performed by simply pulling the transverse colon out through the right upper quadrant abdominal wall incision and was matured immediately without placing a fixation suture between the colonic serosa and abdominal wall peritoneum or fascia layer.

Post-operative adjuvant chemotherapy

Postoperative adjuvant chemotherapy was proposed to every patient. A total of five patients (8.1%) refused adjuvant chemotherapy. Forty-one patients (71.9%) received a short-term infusion of 5-FU/leucovorin. Fourteen patients (24.6%) received either the FOLFOX or FOLFIRI regimen. Two patients (3.5%) received oral capecitabine. Two patients (3.5%) did not complete adjuvant chemotherapy due to personal reasons.

Statistical analysis

The survival rates were assessed by Kaplan-Meier analysis, and survival curves were compared by the log-rank test. The analysis was performed using Prism 4 software. A *P* value < 0.05 (two tailed) was regarded as statistically significant.

Table 2 Peri-operative and pathological characteristics (*n* = 62) *n* (%)

Variable	
Interval between CRT and TME (d) (median, range)	49 (28-101)
Types of surgical procedure	
TME + straight coloanal anastomosis with	
Double stapling	44 (71.0)
Intersphincteric resection	12 (19.4)
APR	6 (9.7)
DRM (cm) (median, range)	2.5 (2.0-4.5)
Positive CRM	2 (3.2)
Retrieved lymph node number (median, range)	8 (1-20)
Pathologic TNM stage	
ypCR	13 (21.0)
ypT0/ypT1/ypT2/ypT3/ypT4	2/5/9/32/1 (3.2/8.1/14.5/51.6/1.6)
ypN0/ypN1/ypN2	37/8/4 (59.7/12.9/6.5)
TRG ¹	
1	13 (21.0)
2-3	41 (66.1)
4-5	8 (12.9)

¹Tumor regression grade (TRG): Grade 1, no residual tumor; Grade 2, rare residual cancer; Grade 3, fibrosis outgrowing residual cancer; Grade 4, residual cancer outgrowing fibrosis; Grade 5, absence of regressive change. DRM: Distal resection margin; CRM: Circumferential resection margin; APR: Abdominoperineal resection; TME: Total mesorectal excision.

RESULTS

Patient demographics

The patient demographics are summarized in Table 1. The median distance from the lower margin of the rectal cancer to the anal verge was 5 cm: 6 cm in 9 patients, 5 cm in 32 patients, 4 cm in 10 patients, and 3 cm in 11 patients. Before neoadjuvant CRT, 45 patients (72.6%) had a cT3-4 tumor and 21 (33.9%) patients had a cN1-2 lymph node status. After CRT, 30 patients (48.4%) had a greater than 50% clinical reduction in tumor size. The final pathology reports revealed that 33 patients (53.2%) had a ypT3-4 tumor and 12 (19.4%) patients had ypN1-2 lymph node involvement. All patients completed the entire course of neoadjuvant CRT.

Toxicity associated with chemoradiation

The toxicity profiles are summarized in Table 1. Twenty-seven patients (43.5%) experienced Grade 1-2 toxicity. No Grade 4-5 toxicity was reported. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria^[10].

Surgical and pathological characteristics

The peri-operative characteristics are summarized in Table 2. All patients who underwent sphincter-preserving surgery also underwent temporary defunctioning stoma construction. Among them, fifty-four patients (96.4%) underwent a loop transverse colostomy, and two patients underwent a loop ileostomy.

Table 3 Post-operative morbidity and mortality (*n* = 62) *n* (%)

	Case number
Mortality	0 (0)
Early complication	
Anastomotic leakage	1 (1.6)
Wound infection	2 (3.2)
Delayed perineal wound healing	1 (1.6)
Pelvic abscess	0 (0)
Rebleeding	0 (0)
Adhesion ileus	1 (1.6)
Central venous port infection	1 (1.6)
Pneumonia	0 (0)
Deep vein thrombosis	0 (0)
Urinary tract infection	1 (1.6)
Late complication	
Anastomotic stenosis	1 (1.6)
Fistula formation	0 (0)
Incisional hernia	1 (1.6)
Anal bleeding	2 (3.2)

Operative morbidity and mortality

The post-operative morbidity and mortality are summarized in Table 3. One patient had subclinical Grade A anastomotic leakage by the definition of the International Study Group of Rectal Cancer^[11]. No patient developed Grade B or C anastomotic leakage. One patient developed post-operative adhesion ileus and recovered after conservative treatment. Late post-operative complications occurred in three patients, including incisional hernia, anastomotic stenosis, and occasional anal bleeding related to irradiation proctitis, which were all managed uneventfully and without the necessity of creating a permanent defunctioning stoma.

Anal function outcome

Six patients received APR. Among the 56 patients who underwent a sphincter-saving procedure, 49 patients also underwent defunctioning stoma closure, and their post-operative anal functions are summarized in Table 4. We performed the defunctioning stoma closure 5-6 mo after the sphincter-saving procedure and the completion of adjuvant chemotherapy. Among the seven patients who did not undergo stoma closure, four patients had early disease recurrence and one patient had a major co-morbidity. The other two patients died from noncancerous causes. The MSK-AF scores revealed that 32 patients (65.3%) had fair or poor anal function one month immediately after stoma closure. However, the proportion of patients with fair or poor anal function decreased at 12 (24.5%) and 24 (12.2%) mo. At 12 and 24 mo after defunctioning stoma closure, the proportion of patients with excellent or good anal function improved from 75.5% to 87.8%, meaning that most patients had recovered anal function within 1 to 2 year after stoma closure.

Recurrence and survival

The median follow-up period of our patients was 58 mo. All patients were followed up for more than 3 year. One

Table 4 Post-operative anal function (*n* = 49) *n* (%)

MSK-AF ¹ (mo)	1 ²	12 ²	24 ²
Excellent/good	8/9 (16.3/18.4)	23/14 (46.9/28.6)	23/20 (46.9/40.8)
Fair/poor	12/20 (24.5/40.8)	10/2 (20.4/4.1)	4/2 (8.2/4.1)

¹Memorial Sloan-Kettering Cancer Center anal function score (MSK-AF): Excellent: 1-2 bowel movements/d and no soilage; Good: 3-4 bowel movement/d or mild soilage; Fair: More than 4 bowel movements/d or moderate soilage; Poor: More than 6 bowel movement/d or significant leakage or enema dependent; ²Periods after stoma closure.

patient (1.6%) had only local recurrence. One patient (1.6%) had both local recurrence and distant metastasis, and another thirteen patients (21%) had distant metastases. For patients with distant metastasis, the lungs were the most frequent site of metastasis (12/14, 85.7%). Seven patients with isolated lung metastasis underwent pulmonary metastasectomy, and four are still alive. For these four patients, lung metastasis occurred at 16, 17, 34 and 46 mo, respectively, after TME, and they have lived for an additional 21, 63, 41 and 20 mo, respectively, to date. Among the thirteen patients with a PCR, twelve patients (92.3%) remain disease free and one patient who refused adjuvant chemotherapy developed lung metastasis 18 mo after surgery.

Six patients (10%) died of disease recurrence. Four patients died from noncancerous causes. Nine patients (14.5%) had disease recurrence or distant metastasis but are still alive. The five-year overall survival and disease-free survival rates were 83.6% and 69.3%, respectively (Figure 1A). Our data show that, if patients achieved a pathologic complete response (PCR), a favorable disease-free survival trend could be observed in the TRG1 group, although no statistical significance was reached (Figure 1B, *P* = 0.07). Our data also demonstrate that persistent pathologic lymph node involvement after neoadjuvant CRT increases the risk of subsequent disease recurrence (Figure 1C, *P* = 0.006). However, neither TRG nor pathologic lymph node status affects overall survival.

DISCUSSION

This study investigated the treatment results of neoadjuvant CRT with protracted venous infusion of 5-FU followed by TME and routine defunctioning stoma construction in locally advanced low rectal cancer patients by a single surgeon at one institution. Beginning in 1998, we treated our locally advanced low rectal cancer patients with neoadjuvant CRT followed by TME surgery. In accordance with the NCCN guidelines, we have prescribed protracted venous infusion of 5-FU as a neoadjuvant radio-sensitizer for most patients with concurrent radiotherapy, which has resulted in less treatment toxicity and made all patients more likely to complete the entire

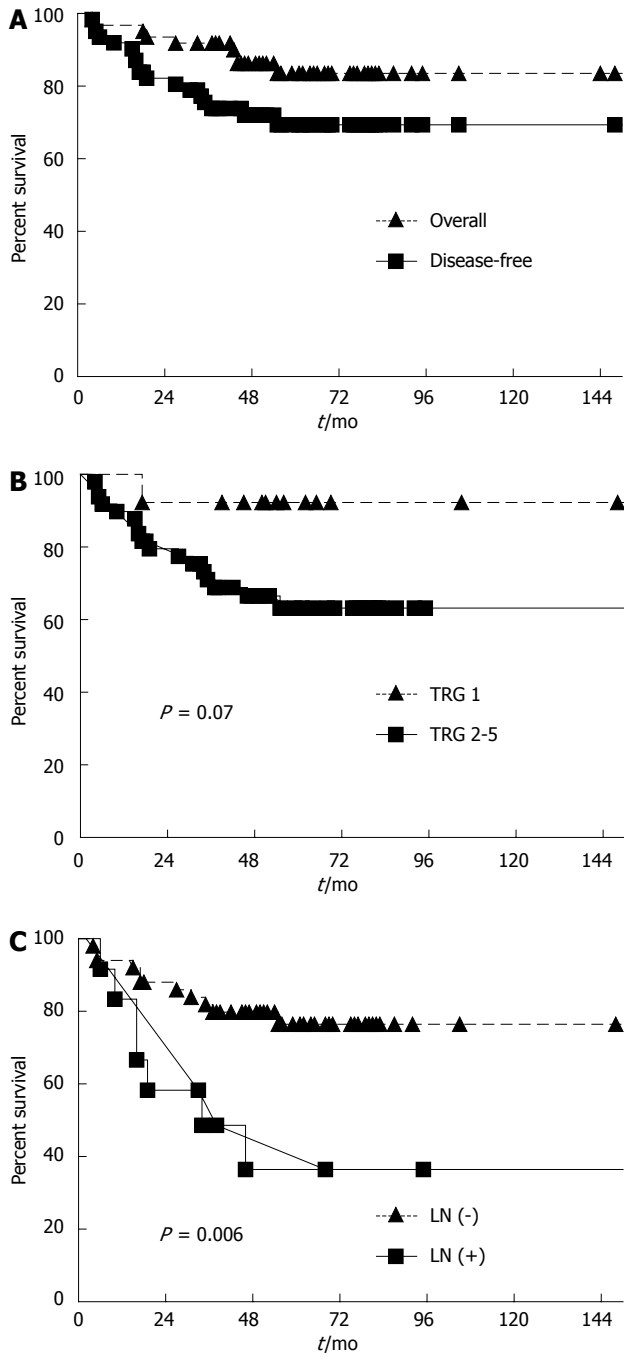


Figure 1 Five-year survival rate of the low rectal cancer patients treated with neoadjuvant chemoradiation and total mesorectal excision. A: The 5-year overall and disease-free Kaplan-Meier survival curves; B: The 5-year disease-free survival rates of patients with tumor regression grade (TRG) 1 and TRG 2-5 are 92.3% and 63.2%, respectively; C: The 5-year disease-free survival rates of patients with positive and negative lymph node (LN) involvement are 36.5% and 76.5%, respectively.

course of CRT and subsequent radical surgery after a 6-8 wk interval. Our protocol is identical to that of the Cleveland Clinic and has achieved very similar PCR and completion rates to theirs^[12]. With this neoadjuvant CRT protocol, we achieved a PCR rate of 21%, a nearly 50% decrease in preoperative tumor size, and only 1.6% associated Grade 3 toxicity, with a 100% CRT completion

rate. Long-term follow-up also demonstrated a five-year overall survival rate of 83.6%, a five-year disease-free survival rate of 69.3%, and a local recurrence rate of approximately 3%. These outcomes were comparable to other prospective trials using different neoadjuvant CRT regimens, including short-term 5-FU/leucovorin infusion and 5-FU plus oxaliplatin, cetuximab, or bevacizumab^[13]. Most of these trials reported PCR rates of 8%-20%. Very few reports using stronger regimens achieved more than 30% PCR rates^[14,15], but these also incurred more serious treatment toxicities, which could possibly make patients abandon the entire treatment protocol. Clearly, our protocol achieved lower treatment toxicity without compromising the desirable treatment effects of neoadjuvant CRT.

The DRM has been identified as one of the prognostic factors affecting local recurrence. In our series, the median DRM was 2.5 cm. All our patients achieved a DRM of more than 2 cm. However, in some studies, 1 cm was postulated to be a sufficient DRM in low rectal cancer patients receiving neoadjuvant CRT^[16]. The CRM is another important prognostic factor^[17]. Tumor involvement over the CRM has a negative impact on the five-year local recurrence, distant metastasis, and overall survival rates in patients with low rectal cancer^[18,19]. In our series, two patients (3.2%) acquired positive CRMs and developed local and distant metastases, corresponding to the negative impact on survival. In addition, recent studies have shown that a PCR is associated with favorable outcomes with regard to local control, disease-free survival and overall survival^[20-22]. In our series, we also achieved the same favorable trend.

Frequently, fewer than 12 lymph nodes can be harvested despite maintaining vigorous surgical standards in low rectal cancer patients if neoadjuvant CRT was performed^[23,24]. However, the persistence of lymph node metastasis after neoadjuvant radiotherapy is known to be associated with poorer prognosis and survival and may serve as a marker for more aggressive tumor behavior^[25]. In our series, the median number of retrieved lymph nodes was 8, which is the same as the median number of retrieved lymph nodes published in EORTC trial 22 921^[26]. Our result confirms that the persistence of lymph node metastasis after neoadjuvant CRT is a poor prognostic factor and a possible predictor of future recurrence.

Routine temporary defunctioning stoma construction after TME was, at one time, a controversial issue^[27]. However, current opinions have gradually shifted to support the routine construction of defunctioning stoma to decrease post-operative complications^[28-30]. A recent meta-analysis has also demonstrated that anastomotic leakage can have a negative impact on local recurrence and cancer-specific survival in colorectal cancers^[31]. In our series, a defunctioning loop stoma was created for every low rectal cancer patient treated with neoadjuvant CRT and a sphincter-saving procedure, achieving very

low rates of early and late surgical complications. Only one patient who underwent a sphincter-saving procedure suffered from sub-clinical anastomotic leakage. We believe that our good result was the consequence of stool diversion by the defunctioning stoma. In addition, we did not encounter major complications associated with the colostomy takedown procedure because we only trimmed the colocolic junction and closed the colonic wall directly, instead of routinely performing segmental resection. No sutures were used to attach the colon serosa to the abdominal wall fascia or peritoneum during the colostomy construction stage, and we therefore did not need to perform segmental resection of the colon at the colostomy reversal stage. Our method of colostomy construction and reversal was proven to be safe and feasible by other authors as well^[32]. Only patients dying shortly after the procedure due to early recurrence or noncancerous causes did not have their stomas closed. Based on our experience, we believe that routine defunctioning stoma construction prevents significant postoperative complications, including fistula formation due to anastomotic leakage and subsequent permanent colostomy, and guarantees a smooth and safe treatment course.

For patients undergoing TME and coloanal anastomosis, post-operative anal function recovery is crucial, and sphincter preservation without adequate function can be troublesome or even meaningless to patient quality of life. In addition, neoadjuvant radiotherapy has been reported to delay postoperative anorectal function recovery^[33]. In our series, one month after closure of the defunctioning stoma, only one third of the patients reported good to excellent sphincter function, but most recovered to good to excellent sphincter function within 2 year. Only 6 patients (12.2%) reported fair or poor anal sphincter function 2 year after closure of the defunctioning stoma. Our result was consistent with other reports noting that patients could achieve equal anal sphincter function two year after a straight coloanal anastomosis procedure to those who underwent J-Pouch coloanal anastomosis or T-colooplasty^[34].

TME is the integral part of low rectal cancer treatment in which surgeon experience plays the most critical role. However, current large series, both prospective and retrospective in nature, have to enroll a large numbers of patients and involve many surgeons with different training backgrounds and techniques. In this situation, surgeon experience is arbitrarily unified, and complications related to personal skill become difficult to evaluate. There is a paucity of evidence in the literature regarding the volume-outcome relationship in the field of rectal surgery. Two systemic reviews and a meta-analysis reveal that surgeons with more experience are associated with decreased mortality, decreased local recurrence, better overall survival, lower permanent stoma, and lower APR rates^[35,36]. The important surgical quality parameters of our team, including the DRM, CRM, retrieved lymph

node number, anastomotic leakage rate, and local recurrence rate, are in line with the current standards throughout the world. Our results can be largely attributed to the experience of the surgeon.

In conclusion, our experience demonstrates that neoadjuvant CRT with protracted venous infusion of 5-FU can minimize associated morbidities and achieve a comparable pathologic response for patients with locally advanced low rectal cancer. TME at 6-8 wk after CRT and routine defunctioning stoma construction can achieve excellent local control and better quality of life. The whole process can be safely executed in a standard fashion by experienced surgeons.

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COMMENTS

Background

Rectal cancer incidence has increased steadily year by year. Although surgical resection remains the only chance of cure, low rectal cancer surgery is still relatively difficult because the lesion is located in a confined pelvic space and is near the anal sphincters.

Research frontiers

The procedure of total mesorectal excision (TME) and pre-operative chemoradiation have gradually become a standard procedure for low rectal cancer. Clinical trials have successfully demonstrated that this procedure can decrease local recurrence rates and make tumor shrink before surgery, achieving better chance of anal sphincter preservation.

Innovations and breakthroughs

Although the procedure is popular in the western society, this is still not a common practice in the eastern society. The authors' ten-year single-surgeon experience demonstrates that this procedure can be safely performed with continuous infusion chemotherapy, routine defunctioning stoma construction and sufficient surgeon experience.

Terminology

TME is a surgical procedure involving resection of all perirectal soft tissue, which contains rectal lymphatic drainage and is the origin of local recurrence. Defunctioning stoma is a surgical procedure involving pulling out a part of bowel segment for stool diversion to protect the distal bowel anastomosis site.

Peer review

This is a paper addressing a single-surgeon's experiences regarding treatment for patients with mid-low rectal cancer. The authors emphasized the importance of routine defunctioning stoma after chemoradiation and TME. It is a reasonable paper although there are no novel points reported compared to pertinent literatures.

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