

Original Article

Chemo-radiotherapy Followed by Full-thickness Local Excision with Transanal Endoscopic Microsurgery for Rectal Cancer: Long-term Survival and Outcome Analysis

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Key Words

Transanal endoscopic microsurgery;
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Purpose. Compared with traditional radical surgery for rectal cancer, patients who underwent chemo-radiotherapy followed by transanal endoscopic microsurgery (TEM) have less risk of complications and neither a temporary nor a permanent enterostomy. This study aimed to analyze the long-term oncological prognosis and survival of selected patient with rectal cancer undergoing TEM after neoadjuvant chemo-radiotherapy.

Methods. From September 2013 to March 2015, there were 18 patients with rectal cancer who received neoadjuvant chemo-radiotherapy followed by TEM. Data of survival rate, local recurrence rate, and tumor characteristics were collected and analyzed.

Results. In 18 patients with rectal cancer undergoing TEM, there were only two patients who developed local recurrence/distant metastasis during regular follow-up after surgery. The 3-year survival rate was 100%, local recurrence rate was 5.6%, and disease-free survival rate was 88.9%. Four patients (22.2%) had complications at the surgical site (including infection, leakage, poor healing, and dehiscence), one of them had a temporary transverse colon colostomy because of severe ischio-rectal abscess.

Conclusions. Although TEM is not a traditional radical surgery for rectal cancer, it has the advantage of preserving the anus in low and ultra-low rectal malignancies. Furthermore, the outcome is not inferior to that of traditional radical surgery.

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Until now, the incidence of colorectal cancer in Taiwan is the highest among all malignant neoplasms (approximately 9% are colon cancers, and 5% are rectal cancers), and the death related to colorectal cancers ranks third according to the statistics from the Taiwan cancer registry.¹

Though there are treatment guidelines developed by experts from different organizations, it is still chal-

lenging in the management of rectal cancers due to the possibility of failed anus preservation, fecal incontinence, sexual dysfunction, and other surgical difficulties and associated morbidities that may potentially compromise the quality of life of patients.

The standard treatment for middle to low rectal cancers is concurrent chemo-radiotherapy (CCRT) and total mesorectal excision (TME). There is increasing

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literature addressing the superior outcome of preoperative CCRT because of lower local recurrence rate and the possibility of complete remission of cancer cells (ypT0). Recent studies showed a complete remission rate of 15-27% of locally advanced rectal cancers after concurrent chemo-radiotherapy.² However, the watch and wait approach may result in increased local recurrence rate (nearly 20% versus < 10% after TME). Thus, setting a compromised but also effective treatment modality is necessary for selected patients.³

Comparing simple local excision to total mesorectal excision for rectal cancers, an increased local recurrence rate and distant metastasis rate in the local excision group are undoubtful because of inadequate depth of resection under limited visualization. Somehow this disadvantage had been eliminated with the introduction of TEM. By using delicate endoscopic instruments and clear imaging system, full-thickness excision could be done safely and even harvest part of the mesorectum and/or adjacent organs.

This study aimed to collect oncological outcome and survival data of patients with rectal cancer who had undergone preoperative CCRT followed by full-thickness local excision with TEM.

Materials and Methods

From April 2013 to March 2015, there were 167 patients being diagnosed of middle or low rectal cancers at Kaohsiung Chang-Gung Memorial Hospital and met the criteria for preoperative CCRT (including clinical stage T3/T4, or low rectum with stage T2, or any T stage with positive lymph node metastasis). All patients with obvious distant metastasis or positive nodes after CCRT were excluded. There were 18 patients who were found to have clinically complete remission or apparent tumor shrinkage after CCRT, who chose to undergo full-thickness local excision with TEM.

The initial diagnostic tools include complete blood cell count, biochemistry, and chest radiography. We use colonoscopy, abdominal computed tomography (CT), and pelvis magnetic resonance imaging (MRI) for clinical staging, as well as the evaluation tools after CCRT.

The treatment modality is divided into three parts: preoperative CCRT, full-thickness local excision with TEM, and postoperative follow-up.

Preoperative CCRT includes chemotherapy with 5-FU intravenous infusion using Roswell-Park's formula (5-FU 500 mg/m² IV bolus after starting leucovorin, leucovorin 100 mg/m² IV over 2 h, every week × 17-18 cycles) or oral capecitabine 2000 mg/m² daily, taken for 2 weeks with rest of 1 week × 15-18 weeks (total 5-6 cycles). Radiation dose is 180/fraction for 28 fractions, with a total of 5040 cGy. The interval between CCRT and preoperative evaluation is about 9-10 weeks, and the interval between CCRT and surgery is 10-12 weeks in average.

All patients in this study had undergone full-thickness local excision with TEM. Under the assistance of endoscopic camera and instruments, a full-thickness excision was made with a safe margin of at least 1 cm. After excision, the defect was closed using absorbable multifilament stitches. The postoperative follow-up strategy is out-patient department appointment and blood test of serum CEA level every three months. Colonoscopy, CT, and chest radiograph are obtained every year for the evaluation of local recurrence and distant metastasis. In case of local recurrence or lesions more advance than ypT2, a salvage radical surgery with lower anterior resection (LAR) or abdomino-perineal resection (APR) will be suggested for a better outcome. The follow-up period ended on December 31, 2017. The patients' characteristics and survival data were then analyzed.

The survival curves were presented using the Kaplan-Meier method, with the comparison of two subgroups (ypT0 and ypT(+)). The Kaplan-Meier curves were plotted using SPSS version 20.0. The statistical significance was set at *p*-value < 0.05.

Results

There were 18 patients enrolled in this study, including 16 men and 2 women, with an average age of 65 years. Ten patients were proved to have ypT0 after surgery (9 men and one woman), and 8 patients were diagnosed with ypT(+) (7 men and one woman). The

median follow-up time was 48 months (ranging from 33 to 51 months). Tumor locations consisted of middle rectal tumors in 5 patients and lower rectal tumors in 13 patients (one middle rectal tumor and 9 lower rectal tumors in the ypT0 subgroup, and 4 middle rectal tumors and 4 lower rectal tumors in the ypT(+) subgroup). The mean distance to anal verge was 3.00 ± 2.94 cm and 4.75 ± 3.67 cm in ypT0 and ypT(+) subgroup. The average RT to surgery interval was 100.7 ± 22.66 days and 96 ± 16.16 days in the ypT0 and ypT(+) subgroup (Table 1).

Local recurrence occurred in one patient in the ypT(+) subgroup (5.6%), and distant metastasis occurred in 2 patients (one in the ypT0 subgroup and another in the ypT(+) subgroup, 11.2%). There were 4 patients who developed postoperative complications. Two of them had infection (including one leakage-associated ischio-rectal abscess, which required debridement surgery and a temporary transverse colon colostomy), one had dehiscence, and one had poor healing. The 3-year survival rate was 100%, and disease-free survival rate was 88.9%.

Evaluating all specimens with residual tumor harvested by TEM, the mean tumor size was 4.9 ± 3.5 mm (range, 0.1-10.8 mm). The mean safe margin was 5.1 ± 3.7 mm (range, 1-11 mm). Mean operation time was 144.38 ± 56.06 min (range, 73-241 min).

One patient in the ypT0 subgroup had developed distant metastasis to the paraaortic lymph node 32 months after TEM. He had undergone radiotherapy (3300 cGy) and chemotherapy with the formula of

mFOLFOX-6. The enlarged paraaortic lymph node had complete remission after treatment.

One patient in the ypT(+) subgroup had developed local recurrence 24 months after TEM. She had undergone LAR subsequently. A temporary transverse colon colostomy was created due to anastomotic leakage. However, multiple lung metastasis was found 12 months after LAR. She refused to receive any aggressive treatment including chemotherapy due to personal reasons (Fig. 1).

Local recurrence-free survival and distant metastasis-free survival were plotted with the SPSS version 20.0 (Fig. 2a and 2b).

Discussion

According to recent data, the treatment modality of preoperative CCRT followed by TME led to significantly enhanced tumor control, with local recurrence rates of less than 10%. In ypT0 cases, 10-year disease-free survival rates were greater than 80%.⁴ However, radical surgeries carry a significant risk of morbidity and mortality. Furthermore, the quality of life in patients who underwent radical surgeries is also affected by fecal/urine incontinence, sexual dysfunction, and other anterior resection symptoms. In some

Table 1.

	ypT0	ypT(+)	p value
Age (years)	61.60 ± 11.51	68.88 ± 7.87	0.1696
Male/female	9/1	7/1	0.8763
Rectum middle/low	1/9	4/4	0.0651
Initial stage			
T3, T4	2	4	0.2011
Any T, N(+)	4	3	0.9201
Low rectal T2	6	1	0.0417
From anal verge (cm)	3.00 ± 2.94	4.75 ± 3.67	0.2320
RT to OP interval (days)	100.7 ± 22.66	96 ± 16.16	0.5020
CEA level >5 (ng/ml)	0	3 (37.5%)	0.0346
Local recurrence	0	1	0.2764
Distant metastasis	1	1	0.8763

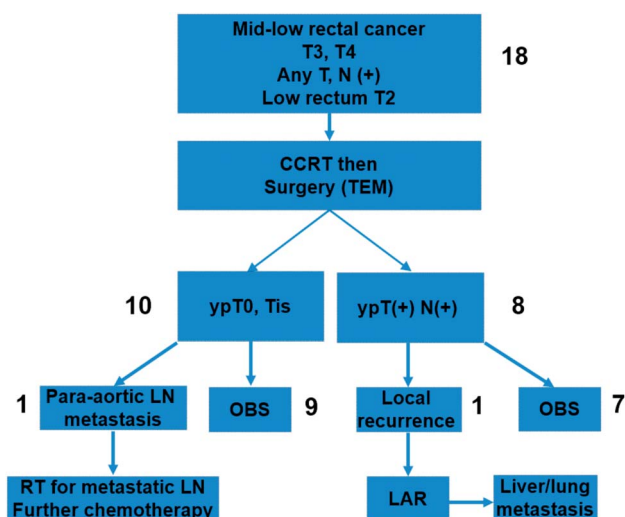


Fig. 1. There were two patients found post-op local recurrence/distal metastasis. The former was managed by salvage LAR, and the later was treated by RT for the affected LN.

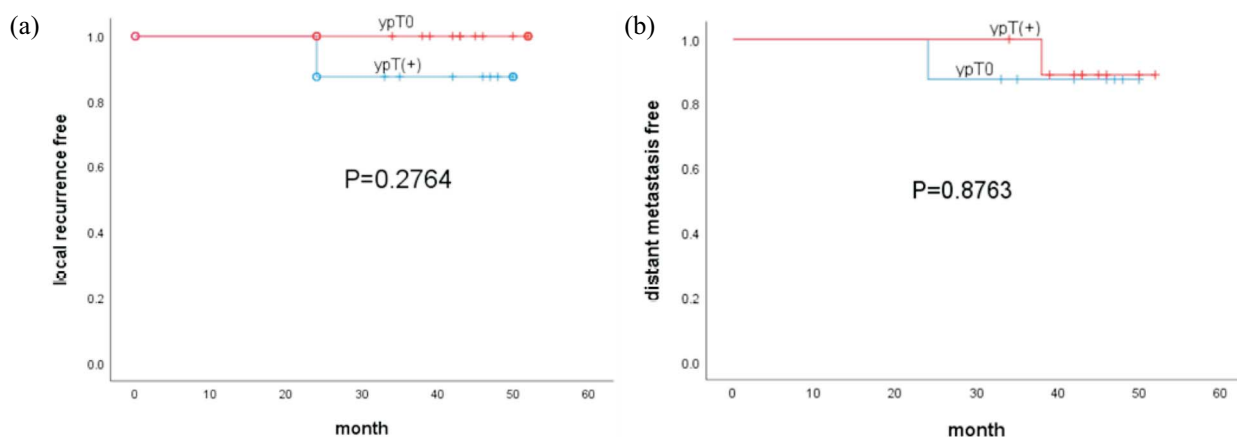


Fig. 2. The local recurrence free survival rate and distal metastasis free survival rate are both greater than 80% in the follow-up period up to 5y.

cases, a temporary or permanent stoma or the inability to preserve anus would deeply influence the remaining life of the patients. Considering the relatively high morbidity and mortality rate of TME, some choose to undergo local excision instead. This implies that a treatment modality that carries lower morbidity/mortality rate without a statistically inferior outcome is needed in selected cases.

Local excision is never a new idea for surgeons; however, in rectal cancers, statistics showed very high local recurrence rate (up to 28.8%) in simple transrectal excisions.⁵ Analyzing the factors of local recurrence after local excision, an inadequate resection margin is possibly the main reason of unacceptable high local recurrence rate.

Compared to transrectal local excision, TEM has the advantage of better visualization and delicate operating system including laparoscopic instruments, which allows surgeons to perform more adequate full-thickness excision (including the mesorectum and even harvest lymph nodes and/or resection of a part of the adjacent organ, including the prostatic capsule or vaginal wall). At the same time, TEM shares the same benefits of less blood loss, shorter operation time, lower morbidity/mortality, and quicker bowel recovery.^{6,7}

At the introduction of TEM in the 1980s, it was performed for benign rectal lesions and early rectal cancers.⁸⁻¹⁰ As the improvement of public health policy in cancer screening and non-surgical treatment for

rectal cancers, there is an increase in early stage cancers due to early detection and successful down-staging after neoadjuvant therapy. Thus, a less aggressive treatment modality with a similar outcome is needed in our aging society because of significant higher morbidity and mortality rate in the elderly population after conventional radical surgery.

In our study, there were 4 patients who developed postoperative complications, and all complications were about the surgical site. This may be related to chronic inflammation of the pelvic tissue caused by preoperative CCRT. Three of them were treated medically, and one of them was treated surgically (debridement of the ischio-rectal abscess and creation of a temporary colostomy). None of our patients developed incontinence, sexual dysfunction, or anterior resection syndrome.

In literature, there is a complete remission rate of up to 27% of locally advanced rectal cancers after concurrent chemo-radiotherapy. Though it is controversial whether the watch and wait approach is adequate in a clinical completely remised rectal cancer after CCRT, a reported high local recurrence rate of nearly 20% is unacceptable. Regarding an individual's clinical condition and the will to avoid severe complications after radical surgeries, TEM may probably offer some help in resolving the dilemma.

The selection criteria for TEM are different for each specialist and lack a consensus. There is evidence indicating that T1 rectal cancer with a diameter larger

than 3 cm with submucosal invasion depth is a significant predictive factor for locoregional failure after TEM. Moreover, there is also literature showing a local recurrence rate of 8% with TME compared with 6% with TEM in pathological T2 rectal cancers after neoadjuvant CCRT. However, some reported higher local recurrence rate of ypT2 lesions.¹¹⁻¹⁶

Our patients fulfilled all the criteria of neoadjuvant CCRT, and all had apparent clinical response to CCRT. To obtain precise initial clinical stage of rectal cancers, we use pelvic MRI to evaluate the T stage and abdominal CT to survey for lymph node and distant metastasis before and after CCRT. Colonoscopy was also performed in all patients to compare treatment effectiveness. We do not offer TEM for all patients who had apparent tumor shrinkage and negative nodal/distant metastasis; however, the 18 enrolled patients are those who denied radical surgery or had advanced age/higher American Society of Anesthesiologists (ASA) level or the will to preserve the anus whatever it takes.

Limitation of the study

The limitations of the study are its retrospective nature and small number of patients enrolled. However, most of the literatures about TEM had a small sample size. Furthermore, not all enrolled patients had undergone chest CT before surgery to exclude pulmonary metastasis.

Conclusions

In the revolution of the treatment modality for rectal cancer, TEM plays a role because of its quicker recovery and lesser complication rate. Our study had shown that chemo-radiotherapy followed by TEM is also an alternative to conventional surgery in not only early but also selected locally advanced rectal cancers.

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原 著

直腸癌經放射治療及化學治療後，行局部廣泛切除之長期存活率分析

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目的 與傳統根治性手術比較，直腸癌病患經放射治療及化學治療後，接受經肛門內視鏡顯微手術 (TEM) 有助於降低手術相關併發症發生之機會，並大幅降低暫時性或永久性腸造口之可能性。此篇研究將分析特定直腸癌病患經放射治療及化學治療後，接受 TEM 做全層局部廣泛切除手術後，長期的預後及存活率。

方法 從 2013 年 9 月至 2015 年 3 月，共有 18 位直腸癌病患經放射治療及化學治療後，接受 TEM 做全層局部廣泛切除手術。病患的存活率、局部及遠端復發率及併發症發生率在文章中將做分析及討論。

結果 18 位病人中，有 2 位於術後發生局部復發或遠端轉移。三年存活率為 100%，局部復發率 5.6%，無疾病存活率 88.9%。4 位病患於手術部位有局部併發症 (感染、滲漏、癒合不佳等)，併發症發生率 22.2%；其中 1 位因局部感染引發坐骨直腸膿瘍，而須做暫時性腸造口。

結論 雖然肛門內視鏡顯微手術 (TEM) 並非傳統根治性手術，但對於中低位直腸惡性腫瘤，經放化療後如有顯著臨床反應，接受全層局部廣泛切除手術可降低併發症發生機率，且病患預後亦佳。

關鍵詞 直腸癌、放射治療、局部切除。