

Adjuvant Chemoradiotherapy Versus Radical Surgery After Transanal Endoscopic Microsurgery for Intermediate Pathological Risk Early Rectal Cancer: a Single Center Experience With Long-term Surveillance

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Research

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Abstract

Background

The choice of subsequent treatment for intermediate risk rectal tumors after Transanal endoscopic microsurgery (TEM) between adjuvant chemoradiotherapy and total mesorectal excision (TME) is controversial. The present study aimed to compare survival and functional outcome between these two strategies.

Methods

This retrospective study included intermediate risk early rectal cancer patients after TEM in our center between 2010 and 2017. Patients were divided into adjuvant treatment and TME groups. Intermediate risk was defined as pT1 with lymphovascular invasion, poor differentiation or large diameter (3-5 cm) or pT2 with small diameter (less than 3cm). The study was based on follow-up data on survival and results from distributed validated scales for functional outcome.

Results

Postoperative overall survival (OS) and disease-free survival (DFS) were comparable between groups ($p = 0.619$ and $p = 0.712$ respectively). Pathological T stage was an independent risk factor for DFS (HR 3.09, 95% CI 1.66 - 4.18, $p = 0.044$). Anorectal symptoms, such as buttock pain, was significantly prevalent in the TME group ($p = 0.030$). TME group presented with poorer bowel function, including stool urgency ($p < 0.001$), bowel frequency ($p = 0.016$), severity of LARS ($p = 0.039$) and total LARS score ($p = 0.040$). Except for a lower score of vaginal lubrication in TME group than the adjuvant treatment group, sexual function was similar between the groups.

Conclusion

Like TME, adjuvant chemoradiotherapy is an alternative option for intermediate risk early rectal cancer after TEM and is associated with similar survival outcomes and better bowel function.

Background

Because of the widespread popularization of colonoscopy and other screening methods, the overall incidence of rectal cancer has exhibited a dramatic increase in recent years [1, 2–4]. Total mesorectal excision (TME) has remained the gold-standard for the treatment of rectal cancer without metastases since it was proposed by professor Heald in 1982 [5]. Radical TME surgery, primarily including low anterior resection (LAR) and abdominoperineal resection (APR), was adopted for over 30 years [6]. Investigations of oncologists validated that early stage rectal cancer, especially T1 rectal cancer without risk factors for recurrence and metastases (i.e., low differentiated and lymphatic or vascular invasion) may be treated via local excision with the absence of radical TME [7–9]. Transanal endoscopic microsurgery (TEM), which was invented by Dr. Buess in 1983, was put into constant use for the

treatment of rectal carcinoma over years of practice [8–10]. The full-thickness resection makes it an advisable approach for low-risk early rectal cancer, according to several guidelines [9, 11–14]. Despite of the advantages, the deficiency of resecting lymph nodes in TEM resection remains highly controversial. Patients with poor histological characteristics hinder its application in clinical practice. Patients with pT1 or pT2 stage rectal cancer with high risk factors after TEM are highly recommended to undergo radical resection to lower the recurrence risk and improve survival outcome [15–16]. However, patients with intermediate risk of local recurrence and lymph node metastases after TEM occupy over half of locally resectable rectal cancer patients, which create a dilemma for treatment options between adjuvant chemoradiotherapy (CRT) and radical surgery [17]. TME may include lymph node dissection, but it is accompanied with a higher morbidity rate. CRT is beneficial for health-related quality of life (HRQoL) because of organ preservation, but it is inferior to radical surgery because of the absence of lymph node dissection. An increasing number of studies reported high morbidity and HRQoL problems caused by radical surgeries [16, 18–20].

The present study primarily compared oncological and functional outcomes between TME and adjuvant CRT in patients who were diagnosed with early rectal cancer with intermediate risk after primary TEM resection at our hospital.

Methods

Patients and study design

A retrospective study was performed based on the constructed database at Peking Union Medical College Hospital (PUMCH), Department of General Surgery. TEM has been adopted for treating early rectal cancer for one decade in PUMCH. Surgeons in our unit have accumulated abundant clinical experience, and patients' intact pathological and clinical information were available in the specific database created in our clinical center.

The present study involved patients who underwent TEM in our clinical center and were diagnosed with intermediate risk early rectal cancer via pathological examination, in accordance with relevant guidelines, between January 2010 and December 2017. Intermediate risk early rectal cancer was defined as a patient with one of the following properties: (1) pT1: Diameter range from 3 to 5 cm or < 3 cm but accompanied with at least one risk factor, including lymphatic and/or venous invasion and/or neural invasion and/or poor differentiation; or (2) pT2: Diameter less than 3 cm with the absence of any risk factors. For large benign lesions with small invasive component, tumor size was considered to be the maximum diameter of malignant tissue during pathological examination. Before the TEM procedure, all patients underwent pelvic MRI to exclude nodal metastases and preoperative colonoscopy to obtain biopsy results to satisfy the indications for surgery. Patients who met the following criteria were excluded from the study: (1) unable to give consent due to dementia; (2) barrier in comprehension of the questionnaire provided; (3) failed to return questionnaires by the cutoff date; and (4) diagnosed with malignant rectal neoplasms other than adenocarcinomas. All patients in our clinical center diagnosed with intermediate risk pT1 or

pT2 rectal cancer were recommended to receive the following treatment, including adjuvant CRT or radical surgery. Patients bearing intermediate risk rectal cancer who underwent adjuvant therapy after TEM were in a follow-up that included more intense postoperative examinations.

Patients meeting the selection criteria were grouped into the TME group (including LAR and APR) or adjuvant treatment group. Oncological outcome was acquired from telephone interviews and outpatient follow-up records. Functional outcome was primarily obtained from distributed paper questionnaires, online fillings and telephone follow-up. The European Organization for Research and Treatment of Cancer Quality of Life colorectal cancer specific module (EORTC-QLQ-CR29) was used to obtain an overall impression of a patient's HRQoL. Low anterior resection syndrome (LARS) score and Wexner score were used as scales to assess patients' defecatory or anorectal function. The Female Sexual Function Index (FSFI) and five items version of the International Index of Erectile Function (IIEF-5) were used to evaluate female and male postoperative sexual function, respectively. To avoid bias from potential confounding variables, we used the Propensity Score match (PSM) method (match tolerance = 0.05). Enrolled patients had an average 42.63 months of follow-up (range 12 – 73 months).

Radical surgery

Specimens resected during TEM were reviewed by experienced pathologists and diagnosed as intermediate risk pT1 or pT2 rectal cancer. Patients underwent radical surgeries 4 - 8 weeks after primary TEM. The choice of surgical technique between LAR and APR were primarily determined by the distance from the anal verge. All patients were informed of the possibility and inconvenience created by a permanent stoma. The anastomosis method involved stapling and hand sewing. Surgeons assessed the suitable time for diverse stoma if it was suitable. Patients received a contrast enema and abdominal CT scan before the reversal to certify the continuity and liquidity of the distal digestive tract and exclude probable distant metastasis. Patients who had lymph node metastasis on pathological examination after TME were recommended for subsequent adjuvant therapy.

Adjuvant treatment

Postoperative CRT included concurrent chemoradiotherapy (CCRT) and radiotherapy alone. Patients who received CCRT had a long course of radiotherapy with the chemotherapeutics. Chemotherapy regimen primarily included single-agent capecitabine, oxaliplatin plus intravenous 5-Fu/LV (FOLFOX) or oxaliplatin combined with capecitabine (XELOX). The choice of regimen was determined based on the oncologist's judgment.

Oncological outcome

Patients' oncological prognoses were assessed using overall survival (OS) and disease-free survival (DFS). The interval of OS was the time between the primary surgery and the date of death. The DFS interval was calculated as the interval between the primary surgery and recurrence date. Recurrence was

primarily confirmed via biopsy during follow-up colonoscopy, and death information was certified via telephone interviews.

Functional outcomes

The following questionnaires were distributed after radical surgery or the eventual course of adjuvant treatment. For patients who received LAR with diverting ileostomy, the questionnaires were distributed after the reversal of stoma. For patients who underwent APR or LAR without diverting ileostomy, the questionnaires were sent after primary radical surgeries. Since patients in the adjuvant therapy group did not have stoma, the items related to stoma care was not listed in the distributed modules.

EORTC QLQ-CR29

EORTC QLQ-CR29 is a specific module of conventional EORTC QLQ-C30 for colorectal cancer patients, and it consists roughly of 4 main scales and 18 diverse single items [21]. All items are divided into functioning scales and symptom scales. Answers were graded as the extent of severity from 1 (not at all) to 4 (very much) and from 1 (very poor) to 7 (excellent) for items about HRQoL. The initially calculated scores were transformed into scales of 0 – 100 according to a previously reported standard procedure [22].

LARS score and Wexner score

These two scales were used primarily to evaluate defecation problems. The LARS score has 5 questions on bowel movement-related disability, such as control of flatus, feces and liquid stool. The total LARS score ranges from 0 to 42. Patient scores of 0 to 20, 21 to 29 and 30 to 42 were categorized as no LARS, minor LARS and major LARS, respectively [23]. The Wexner score includes 5 questions on the frequency of solid and liquid stool, gas incontinence and the frequency of using a pad due to fecal incontinence. The overall Wexner score ranged from 0 to 20, and a higher score indicates greater severity of fecal incontinence [24].

FSFI and IIEF-5

HRQoL problems related to sexual dysfunction were evaluated using the FSFI for female patients and the IIEF-5 for male patients. FSFI is a self-report scale that includes 6 domains (desire, arousal, lubrication, orgasm, satisfaction and pain). The separate scores for each domain are calculated as a total score [25]. IIEF-5 consists of 5 questions about male erectile function. The severity of erectile dysfunction (ED) was categorized as severe (5 to 7), moderate (8 to 11), mild to moderate (12 to 16), mild (17 to 21) and no dysfunction [26].

Statistical analysis

Continuous variables are presented as the means (range) or proportions as necessary. Differences in continuous variables, such as median LARS score, were examined using the Mann-Whitney U test.

Categorical variables in this study were assessed using Pearson's chi-squared test or Fisher's exact test (if applicable). Criteria for significant differences was a *p value* < 0.050. A *p value* < 0.001 was defined as an extremely distinct difference. The Kaplan-Meier method was used to compare OS and DFS. The log-rank test was used to distinguish differences in oncological outcome. Statistical analyses were performed using SPSS version 24.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patients' Characteristics

Of the 153 patients who met the inclusive criteria, 10 patients in the adjuvant treatment group and 13 patients in the TME group were excluded due to various factors, including barrier in the comprehension of the scales provided (n = 12), dementia or other diseases prevented consent (n = 3), and functional outcome scales feedback missing (n = 8). The remaining 130 patients were enrolled and matched one-to-one using the nearest neighbor method. Tumor diameter, tumor height, cT classification, pT classification and age were considered. The proper math tolerance was calculated as 0.05 in propensity score matching, which resulted in 110 patients included in the study (n = 55 for each group). The entire inclusion and exclusion flow chart is shown in Figure 1. Patients' demographic, tumor characteristics and treatment details are listed in Table 1.

Oncological outcome

Of the 110 enrolled patients, 12 patients (10.91%) developed recurrence after initial TEM surgery, including 8 patients (7.27%) of local recurrence and 4 patients (3.64%) of distant recurrence (Table 2). The local recurrence rate of patients undergoing adjuvant treatment was higher than patients who underwent TME (9.09% vs. 5.45%), but this difference was not significant ($p = 0.463$). Four patients suffered distant metastases, with 2 patients in each group. The average interval from primary TEM surgery was 34.25 (24 - 79) months. The distant metastasis sites primarily included liver, lung, bone and distant lymph nodes. The Kaplan-Meier survival curve showed no significant differences in 5-year OS and DFS between the two treatments after primary TEM for intermediate risk early rectal cancer patients (Figure 2a and 2b).

The univariable analysis revealed that pT2, large tumor diameter, positive lymphovascular invasion and poor differentiation were the risk factors predicting recurrence (Table 3). The subsequent multivariable analysis indicated that only pT2 was an independent risk factor for DFS (HR 3.09, 95% CI 1.66-4.18, $p = 0.044$) (Figure 2c).

Functional outcomes

The study reclaimed 105 effective questionnaires (excluding patients lost to follow up and death), including 52 (94.5%) from the adjuvant treatment group and 53 (96.4%) from the TME group.

EORTC QLQ-CR29

Compared with patients in the adjuvant treatment group, patients who underwent TME suffered from buttock pain more seriously (17.99 vs. 4.67, $p = 0.030$). The adjuvant treatment group complained more about taste problems (7.91 vs. 1.73, $p < 0.001$). Other functional and symptoms scales, including body image and sexual interest, were similar between the two groups without significant differences (Table 4).

LARS score and Wexner score

Patients' LARS and Wexner scores are shown in Table 5. The anorectal function in both groups was comparable before TEM. The TME group had a higher frequency of bowel urgency ($p < 0.001$). Categorization of the severity of LARS in the two groups and median total LARS scores also showed significant differences ($p = 0.039$ and 0.040 , respectively). However, there was no significant difference between the 4 other domains of the LARS score related to flatus or liquid stool control between the two groups ($p > 0.05$). The results of Wexner scores between the two groups were not significantly different either ($p = 0.173$).

FSFI and IIEF-5

Based on the preoperative data, the sexual function of all enrolled patients was not different between the two groups. Lubrication disorder of the vaginal canal was significantly severe in female patients who underwent TME surgery (7.52 vs. 2.03, $p < 0.001$), but other indexes of FSFI and total FSFI score were comparable to the adjuvant treatment group patients (Figure 3). Postoperative erectile function evaluation revealed that males in the radical TME group experienced a higher proportion of moderate and severe ED (20.69% vs. 11.76%), but without a significant difference. Patients in both groups had a similar overall IIEF-5 score, which reflected parallel erectile function (Table 6).

Discussion

According to previous reports, approximately 75% of the patients who suffered recurrence after local excision of rectal cancer were intermediate risk pT1 or pT2 stage [27–28]. The choice between postoperative radical surgery and adjuvant treatment was always a barrier for surgeons and oncologists to implement the most appropriate treatment option. TEM is a relatively novel local excision surgical method to perform en-bloc resection through a specific working tunnel [10, 12, 14]. We performed this study to compare the oncological and functional outcomes in a series of intermediate-risk early rectal cancer patients who received adjuvant treatment or TME after TEM. Overall, each option had its pros and cons in different aspects.

Nearly 11% of the enrolled patients developed local or distant recurrence after initial TEM resection. The overall recurrence rate was consistent with previous reports [29]. The present study found no significant differences in 5-year OS and DFS between the different post-TEM treatment methods. Pathological T stage was a predisposing factor for recurrence. The present study found that although several pathological characteristics, such as tumor diameter and lymphovascular invasion, were high risk factors for a low DFS rate, only pT stage was an independent predicting factor for low DFS rate in multivariable

analysis. This result suggests that patients who were diagnosed as pT2 after TEM should be in a closer out-patient follow-up regardless of post-TEM therapy. The results were in great accordance with a systematic review done by Cutting et al., which maintained that local excision plus adjuvant therapy should not be recommended for pT2 patients [30].

We clearly observed that patients who underwent TME suffered from a greater proportion of buttock pain, which is consistent with some related work on comparisons of local excision and TME. Taste complaint was more obvious in the adjuvant treatment group patients, but this finding may be somewhat explained by the chemotherapy module bias after TEM. No other symptom or functional scales showed significant differences. There is no denying that adjuvant treatment may produce a series of side effects, such as perforation, diarrhea or proctitis, especially in patients who choose radiotherapy [31–32]. Borstlap et al. and Smart et al. reported the complication rate ranged from approximately 6–52% [17, 31]. The 2 patients who underwent CCRT in our study reported no radiotherapy-related side effects. However, this result may not represent the low risk of side effects of adjuvant treatment due to the small sample size.

TEM is an advisable method for the treatment of early rectal cancer partially because of its unique transanal working pattern. Several studies demonstrated that TEM had little effect on patients' HRQoL after surgery. Biviano et al. enrolled 66 rectal cancer patients and concluded that TEM had no significant effect on anal function [33]. Perioperative damage to the anal sphincter caused by TME is consistently a concern for surgeons and patients. Anorectal function was evaluated using 2 validated questionnaires, and great disparity occurred between the groups. Patients in the TME group demonstrated worse bowel function, particularly bowel urgency and stool control. More patients in the TME group reported major LARS, which indicates a higher level of bowel dysfunction. These results corroborate the findings of many previous works. Chen et al. found that nearly half of the patients who underwent TME suffered from major LARS [34]. Bohlok et al. (2019) also showed that a large proportion (72.1%) of patients after TME complained of LARS to different extents [35]. A meta-analysis done by Kidane et al. also proposed the viewpoint that TEM could be adopted as a reliable device which provides similar oncological control but lower mortality rate [36]. One unexpected finding was the extent to which the overall Wexner score between the 2 groups was not significantly different. This result may be partially due to the nonspecificity of the Wexner scale and distortion of the included questions, especially after filling out the LARS questionnaire. Cheong et al. performed a prospective observational study and revealed severe bowel dysfunction caused by anterior resection for rectal cancer. The dysfunction partially originated from the procedure of coloanal anastomosis [37]. Sclafani et al. concluded that CRT did not increase the significant detrimental effect on HRQoL and bowel function in rectal cancer patients [38]. Therefore, the potential benefit of adjuvant therapy in the lower rate of LARS should not be underestimated. The follow-up time was another vital factor for postoperative LARS based on some published reports. Therefore, our data should be interpreted with caution because the follow-up months for each patient were diverse [33, 39].

Latent damage to the pelvic nerve during TME is a controversial side-effect of postoperative sexual function preservation. Published reports on the differences in sexual function between adjuvant CRT and

radical surgery were limited [40]. We employed different gender-specific scales for patients' sexual functions and clearly found no obvious differences between the treatment of options. Except for a higher score of vaginal lubrication in the adjuvant treatment group, no other scales in the FSFI were different between the two groups. Male patients' erectile function is a big concern for surgeons, but there was no significant difference on median overall IIEF-5 score between the treatments. The ratio of moderate and severe ED patients was higher in the TME group than the adjuvant treatment group (20.69% vs. 11.76%), but no significant difference was found. These results may be biased to some extent due to the self-reported nature of the scales and the small number of patients who underwent adjuvant therapy when diagnosed with N2 stage after TME.

Our study has several limitations, such as its retrospective design and relatively short following-up period. Except for these points, the self-reported questionnaires we used in this study were more or less subjective. Some examinations, such as anal manometry, should be used to increase the objective evidence of bowel function. The same surgeon performed most of the TEM in our unit after standard training. However, the learning curve may also cause bias of the pathological results for the earliest cases.

Conclusion

All in all, compared with TME, adjuvant therapy poses a similar oncological outcome with no inferiority in postoperative overall or disease-free survival for intermediate risk early rectal cancer patients after primary TEM resection. Pathological T stage may be an independent risk factor for recurrence regardless of treatment. TEM with adjuvant therapy has less impact on patients' HRQoL with better bowel function and similar levels of sexual function.

List Of Abbreviations

Transanal endoscopic microsurgery (TEM); Total mesorectal excision (TME); Overall survival (OS); Disease-free survival (DFS); Low anterior resection (LAR); Abdominoperineal resection (APR); Chemoradiotherapy (CRT); Health-related quality of life (HRQoL); European Organization for Research and Treatment of Cancer Quality of Life colorectal cancer specific module (EORTC-QLQ-CR29); Female Sexual Function Index (FSFI); Five items version of the International Index of Erectile Function (IIEF-5); Concurrent chemoradiotherapy (CCRT); Erectile dysfunction (ED) Low anterior resection syndrome (LARS).

Declarations

Ethics approval and consent to participate:

Our protocol has been approved and got ethics approval and consent from the IRB of Peking Union Medical College Hospital (S-K1237).

Consent for publication:

This article doesn't include any individual person's data.

Availability of data and materials:

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to their containing information such as sex function that could compromise the privacy of research participants.

Competing interests:

All the authors declare that they have no conflict of interest.

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Authors' contributions:

Yunhao Li.: Data curation, Writing- Original draft preparation. Xiaoyuan Qiu: Software, Validation. Weikun Shi: Writing, Reviewing and Editing. Guole Lin: Visualization, Investigation.

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Tables

Table 1a Patients characteristics

Items	Adjuvant treatment (n = 55)	TME (n = 55)	<i>p</i> value
Age, mean ± SD	60.27±3.125	62.39±4.442	0.531
BMI , mean ± SD (kg/m ²)	25.67±4.679	20.32±1.213	0.147
CEA level (ng/mL)	2.78±0.797	2.92±1.013	0.351
Gender			0.175
Male	29	36	
Female	26	19	
Tumor height, mean ± SD (cm)	6.59±0.639	7.13±1.254	0.256
Tumor diameter, mean ± SD (cm)	2.57±0.263	2.64±1.002	0.198
ASA classification			0.278
I	21	27	
II	32	24	
III	2	4	
cT classification (pre-TEM)			0.249
Tis	21	27	
T1	34	28	
pT classification (post-TEM)			0.634
T1	45	43	
T2	10	12	
Resection margin			0.271
R0	53	49	
R1	2	6	
Distal margin, mean ± SD (cm)	1.11±0.375	1.26±0.654	0.885
Lymphovascular invasion†	3	7	0.320
Differentiation†			0.744
Well	4	6	
Moderate	28	25	
Poor	23	24	

TME, total mesorectal excision; *BMI*, body mass index; *ASA*, American Society of Anesthesiologists score; TEM, Transanal Endoscopic Microsurgery.

† Evaluated by resected specimens after TEM

Table 1b Post-TEM treatment data

Items	Adjuvant treatment (n = 55)	TME (n = 55)	p value
TME categorizations, n (%)			-
LAR	-	50(90.9)	
APR	-	5(9.1)	
Type of anastomosis, n (%)			-
Handsewn	-	4(8)	
Stapled	-	46(92)	
Anastomotic height, mean ± SD (cm)	-	4.02±1.127	-
Type of approach, n (%)			-
Open	-	6(10.9)	
Laparoscopy	-	49(89.1)	
Diversion stoma, n (%)		43(78.2)	-
Grading of TME specimen, n (%)			-
Complete	-	51(92.7)	
Nearly complete	-	3(5.5)	
Incomplete	-	1(1.8)	
CRM involvement, n (%)		1(1.8)	-
Pathologic N classification (post-TME)	-		-
N0	-	50	
N1	-	3	
N2	-	1	
Adjuvant therapy			<0.001
CCRT(Single-agent capecitabin)	26	0	
CCRT(FOLFOX4)	9	1	
CCRT(XELOX)	20	1	
Radiotherapy alone	0	2	

TME, total mesorectal excision; TEM, Transanal Endoscopic Microsurgery. Abdominoperineal resection; LAR, Low anterior resection; APR, Abdominoperineal resection; CRM, Circumferential Resection Margin; FOLFOX4, Oxaliplatin + 5-FU + LV; XELOX,

Oxaliplatin + Capecitabine; CCRT, concurrent chemoradiation therapy.

Table 2 Recurrence data after post-TEM treatment

Items	Total (n = 110)	Adjuvant treatment (n = 55)	TME (n = 55)	<i>p</i> value
Overall rate of recurrence, n (%)	12 (10.91)	7 (12.73)	5 (9.09)	0.541
Time interval from primary TEM (months)	28.32±6.220	25.67±4.281	32.33±5.597	0.623
Local recurrence, n (%)	8 (7.27)	5 (9.09)	3 (5.45)	0.463
Time interval from primary TEM (months)	27.66±4.975	23.52±3.227	30.18±5.421	0.318
Distant recurrence, n (%)	4 (3.64)	2 (3.64)	2 (3.64)	1.000
Liver	1	0	1	
Lung	1	1	0	
Bone	1	1	0	
Distant Lymph node	1	0	1	
Time interval from primary TEM (months)	34.25±2.573	31.79±1.223	37.23±2.982	0.213

TME, total mesorectal excision; TEM, Transanal Endoscopic Microsurgery

Table 3 Univariable and multivariable Cox regression analysis for disease-free survival

	Univariable analysis		Multivariable analysis†	
	HR(95%CI)	<i>p</i> value	HR(95%CI)	<i>p</i> value
Age(years)‡	1.05(0.99-1.13)	0.482		
Gender				
Male	1.00(reference)			
Female	1.32(0.84-1.93)	0.250		
pT classification				
pT1	1.00(reference)		1.00(reference)	
pT2	3.09(1.73-4.26)	<0.001	3.05(1.66-4.18)	0.044
Tumor diameter‡	2.29(1.13-3.06)	0.049	1.02(0.63-2.19)	0.264
Lymphovascular invasion				
Negative	1.00(reference)			
Positive	3.32(1.68-5.42)	<0.001	1.27(0.73-1.98)	0.063
Differentiation				
Well	1.00(reference)			
Moderate	1.07(0.51-2.44)	0.752		
Poor	2.55(1.72-3.78)	<0.001	2.43(0.96-4.27)	0.062
Post-TEM treatment				
Adjuvant treatment	1.00(reference)			
TME	1.35(0.43-4.18)	0.712		

TME, total mesorectal excision; *TEM*, Transanal Endoscopic Microsurgery.

†.Variables were entered the multivariable analysis if a *p* value less than 0.1 in the univariable analysis

‡.Continuous variable, β coefficient (age) = +0.014, β coefficient (tumor diameter) = +0.020

Table 4 Comparison of EORTC QLQ-CR29 score

Items	Adjuvant treatment	TME	<i>p</i> value
	Mean (<i>n</i>)	Mean (<i>n</i>)	
Functional scales†			
Anxiety	78.23(52)	77.64(53)	0.770
Body image	87.35(52)	88.97(53)	0.607
Weight	86.44(52)	89.42(53)	0.179
Sexual interest(female)§	25.03(23)	19.84(19)	0.066
Sexual interest(male)§	44.68(29)	45.29(34)	0.921
Symptom scales‡			
Urinary incontinence	9.01(52)	6.79(53)	0.374
Urinary frequency	18.12(52)	19.34(53)	0.576
Stool frequency	25.85(52)	19.73(53)	0.096
Taste	7.91(52)	1.73(53)	<0.001
Faecal incontinence	24.82(52)	15.54(53)	0.054
Sore skin	19.77(52)	16.90(53)	0.776
Embarrassment	18.24(52)	13.31(53)	0.138
Buttock pain	4.67(52)	17.99(53)	0.030
Bloating	22.21(52)	13.98(53)	0.126
Dry mouth	10.23(52)	12.24(53)	0.753
Hair loss	4.22(52)	2.97(53)	0.076
Embarrassment	18.25(52)	13.37(53)	0.552
Flatulence	42.45(52)	47.97(53)	0.814
Blood and mucus in stool	4.41(52)	3.24(53)	0.575
Dyspareunia(female)§	7.15(23)	10.65(19)	0.532
Impotence(male)§	40.23(29)	33.67(34)	0.096

EORTC QLQ-CR29, European Organization for Research and Treatment of Cancer Quality of Life of the colorectal cancer specific module (primary data has been transformed into score ranging from 0-100)

†Higher score for functional items represents better function

‡ Higher score for functional items represents more serious symptoms

§ Gender specified

Table 5 Comparison of LARS and Wexner score

Items	Adjuvant treatment (n = 52)	TME (n = 53)	<i>p</i> value
Incontinence of liquid stools			0.062
≥Once per week	12	23	
<Once per week	20	12	
Never	20	18	
Incontinence of flatus			0.532
≥Once per week	10	12	
<Once per week	10	14	
Never	32	27	
Clustering of stools			0.092
≥Once per week	13	24	
<Once per week	17	12	
Never	22	17	
Urgency			<0.001
≥Once per week	3	30	
<Once per week	18	10	
Never	31	13	
Bowel frequency			0.016
> 7 times per day	3	7	
4-7 times per day	6	12	
1-3 times per day	20	25	
< 1 time per day	23	9	
Severity of LARS†, n (%)			0.039
No	32 (57.69)	23 (43.40)	
Minor	11 (25.00)	10 (18.87)	
Major	9 (17.31)	20(37.74)	
Total LARS score	21.67±4.232	32.35±5.675	0.040
Total Wexner score	2.21±0.215	3.73±0.464	0.173

LARS, low anterior syndrome; Scores 0 to 20 (no LARS), 21 to 29 (minor LARS), 30 to 42 (major LARS)

Table 6 Comparison the results of International Index of Erectile Function (IIEF-5) score for male patients.

Items	Adjuvant treatment	TME	<i>p</i> value
	(n = 29)	(n = 34)	
Preoperative IIEF-5 score [†]	23.1±3.265	21.9±2.975	0.458
Total IIEF-5 score [†]	21.6±2.312	18.7±1.379	0.317
Grade of ED, n (%) [‡]			0.240
No	14(48.28)	12(35.29)	
Mild	5(17.24)	6(17.65)	
Mild to Moderate	4(13.79)	12(35.29)	
Moderate	5(17.24)	2(5.88)	
Severe	1(3.45)	2(5.88)	

Values in parentheses are percentages except for extra indications. *TME*, total mesorectal excision. *ED*, Erectile Dysfunction.

Scores 5 to 7 (Severe), 8 to 11 (moderate), 12 to 16 (mild to moderate), 17 to 21 (mild) and less than 5 (No dysfunction).

†. Mann-Whitney U test;

‡. χ^2 test.

Figures

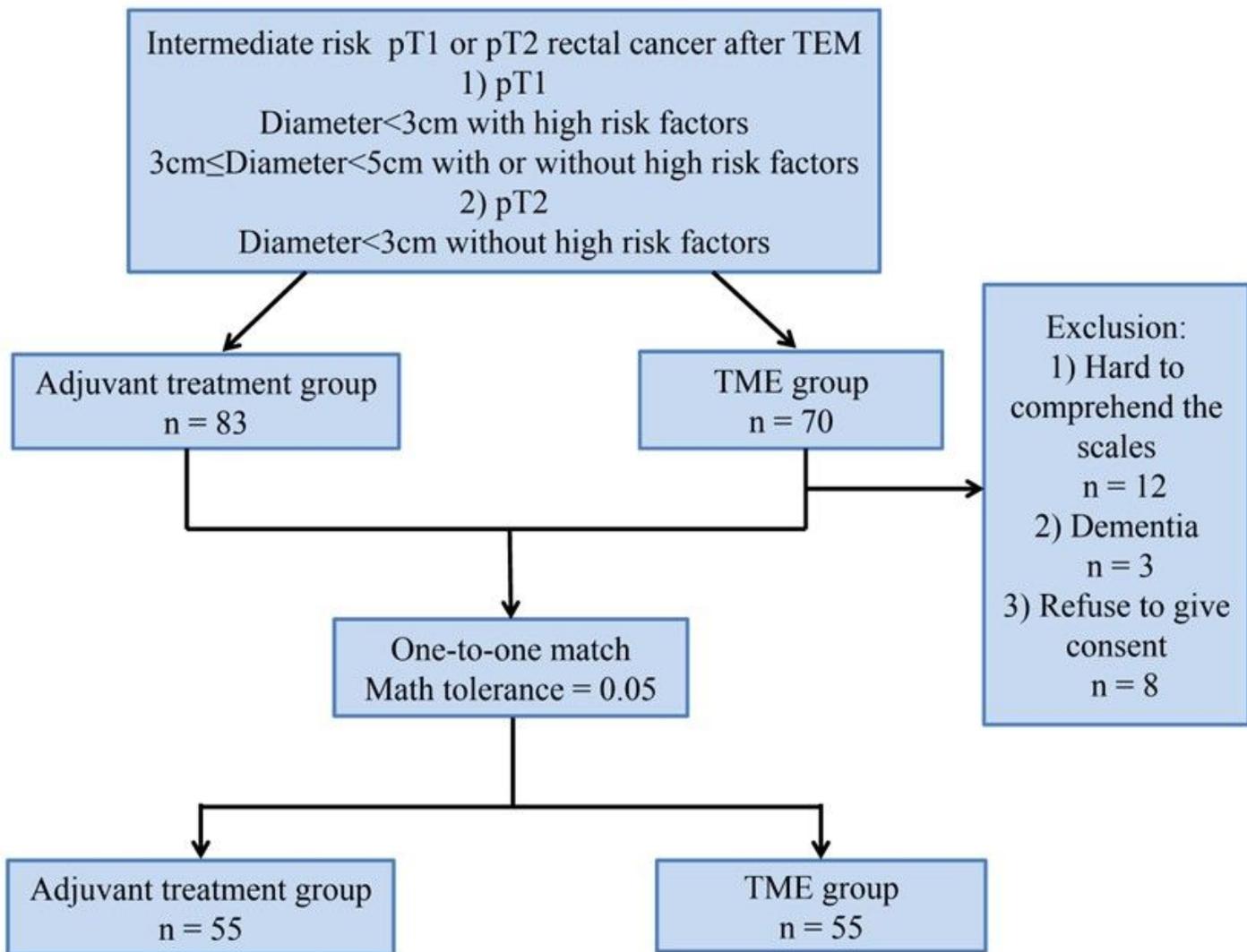


Figure 1

Inclusion flow chart of enrolled patients. 110 intermediate pathologically risk patients (55 patients each group) were enrolled in this study using one-to-one matching method (Math tolerance = 0.05). 23 patients were excluded from the study due to unsatisfied comprehension of scales, dementia and refusal consent respectively.

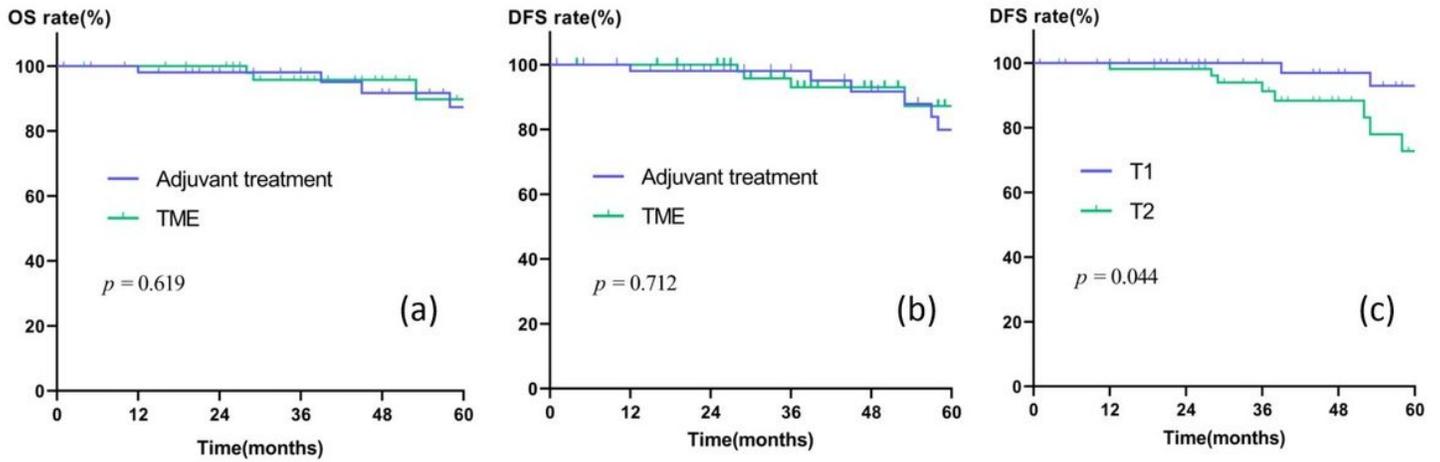


Figure 2

Survival analyses on enrolled patients. Overall survival (OS) rate comparison between the two groups (Figure2a). No significant difference was obtained between the groups ($p = 0.619$). Disease-free survival (DFS) rate comparison between the two groups (Figure2b). No significant difference was obtained between the groups ($p = 0.712$). Pathologically stage T2 was the independent risk factors for 5-year DFS ($p = 0.044$). Survival analyses on patients (OS and DFS). (a) OS comparison adjuvant treatment vs. TME. (b) DFS comparison adjuvant treatment vs. TME. (c) DFS comparison pT1 vs. pT2.

Median FSFI score (95% CI)

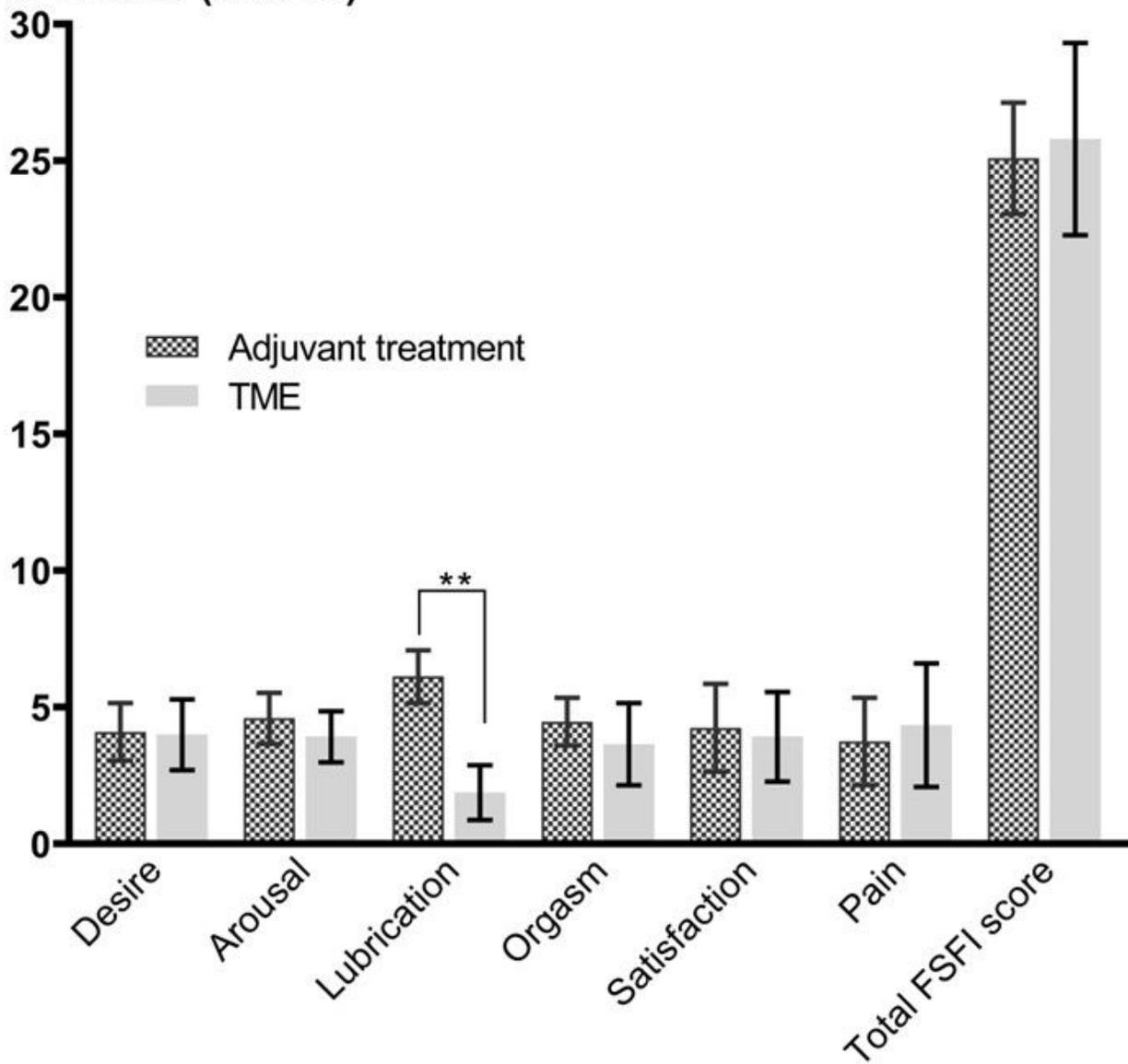


Figure 3

FSFI score comparison between two groups Adjuvant treatment group showed a better feedback on the domain of vaginal lubrication with significant difference ($p < 0.001$). Other aspects in FSFI questionnaires were in the absence of significant difference. Comparison of FSFI score and domains (**. $p < 0.001$)