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Functional outcomes after TEM in patients with complete clinical response after neoadjuvant chemoradiotherapy

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Abstract

Background In patients who exhibit a complete clinical response after radio-chemotherapy for rectal cancer, the standard surgical approach might constitute overtreatment. The aim of this study is to analyse the outcomes of anorectal function and quality of life after transanal endoscopic microsurgery (TEM) in irradiated patients with complete clinical response.

Patients and methods Between 2007 and 2014, 84 patients who were diagnosed with stage T2–T3–T4 N0 rectal cancer before chemoradiotherapy showed a complete clinical response to neoadjuvant therapy and underwent TEM. All patients were evaluated before and 1 year after TEM using the Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS) questionnaire to determine the impact of this surgical technique on the degree of faecal continence. To assess the quality of life of patients after surgery, we administered the Fecal Incontinence Quality of Life Scale.

Results Twenty-three patients exhibited a worse incontinence status after surgical intervention (27.4; 95% CI 18.2–38.2). These patients experienced a median positive absolute variation in the CCF-FIS of four points (95% CI 3.5–4.5; $p < 0.001$). Female sex and age showed a significant correlation with the worsening of continence status. Scores on the Fecal Incontinence Quality of Life Index Scale did not show a significant difference before and after TEM.

Conclusions TEM may be an alternative treatment for patients with rectal cancer who exhibit a complete clinical response to neoadjuvant chemoradiotherapy because it offers the possibility to achieve a full thickness excision of the rectal wall. TEM also allows the identification of any residual disease and provides optimal quality of life and functional results.

Keywords Transanal endoscopic microsurgery · Neoadjuvant radiotherapy · Rectal cancer · Anorectal function

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Currently, anterior resection (AR) with total mesorectal excision or abdominal perineal resection (APR) after chemoradiotherapy (CRT) still represents the standard of care for rectal cancer.

However, these approaches are associated with a number of adverse events, in particular, anorectal, urinary and sexual dysfunction, which sometimes require a permanent colostomy.

Preoperative CRT may lead to significant tumour downstaging and downsizing, and a complete clinical response (cCR) is obtained in 15–20% of patients [1, 2].

For this reason, AR and APR in patients with complete response might constitute overtreatment.

These findings have led surgeons to consider alternative organ-preserving strategies for patients with suspected cCR. In this setting, the watch and wait (W&W) approach has been considered [3].

This type of close surveillance without surgery may be insufficient due to the risk of not recognizing patients with residual tumour [4, 5].

Another possibility would be to perform transanal endoscopic microsurgery (TEM), which allows a full thickness excision of the residual tumour [6].

However, the transanal introduction of a 4-cm rectoscope with consequent anal dilation, which is required for this procedure, is concerning because of its impact on anorectal function.

This study was designed to analyse anorectal function and quality of life after TEM in patients with cCR after neoadjuvant CRT.

Materials and methods

From 2007 to 2014, all patients with rectal cancer were accurately staged prior to surgery. All staging was based on a clinical examination (digital rectal exploration), laboratory tests including those for tumour markers (e.g. CEA and CA 19-9), colonoscopy with macrobiopsies, transanal endoscopic ultrasound (EUS), and thoracic abdominal and pelvic computerized tomography (CT) or magnetic resonance imaging (MRI).

A total of 480 patients with locally advanced rectal cancer, staged as T3 or T4 according to the TNM classification, underwent neoadjuvant CRT according to a standardized protocol.

Patients with cT2N0 also underwent neoadjuvant CRT if the primary surgical alternative was an abdominal perineal resection.

Restaging was performed 30 days after RT, and EUS and/or MRI were repeated.

Standard surgical treatment was anterior resection or abdominal peritoneal resection with TME, which was performed 8 weeks after the completion of neoadjuvant therapy.

Ninety-one (18.9%) patients showed complete clinical response to CRT and underwent TEM.

Complete clinical response was determined based on the absence of residual disease upon physical examination, endoscopy and radiological imaging.

Patients who exhibited a nearly complete response or who underwent TEM for palliative purposes were excluded from this study. Another exclusion criterion was the presence of post-operative residual cancer at pathological examination after TEM.

All patients gave their informed consent to surgery.

The patients were placed on the operating table, and a modified rectoscope 4 cm in diameter (Wolf Tuttlingen, Germany) was introduced after a gentle digital divulsion of the sphincter and was fixed to the operating table.

A full thickness excision of the residual scar, including perirectal fat, was performed, and the rectal wall defect was closed by a running suture.

Tumour response was evaluated according to Mandard's tumour regression grading system [7].

Histopathological examination confirmed a pCR (ypT0 and TRG1) in 84 (92.3%) patients and revealed the presence of residual cancer in seven patients (7.7%), who were then excluded from the study.

Eighty-four patients with pCR were evaluated before and 1 year after TEM according to the Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS) questionnaire in order to determine the impact of this surgical technique on the degree of faecal continence [8, 9].

The Wexner Continence Grading Scale allows us to analyse the frequency of five different continence parameters. Each degree of the scale corresponds to a score that varies from 0 to 4, and the overall continence score varies from 0 (perfect continence) to 20 points (total incontinence). To assess the quality of life of patients after surgery, we administered the CCF-FIS questionnaire to them.

Quality of life was evaluated using the Fecal Incontinence Quality of Life Index Scale, which is composed of four different scales (lifestyle, coping/behaviour, depression/self-perception), for a total of 29 items [10].

Moreover, this questionnaire was administered before and 1 year after TEM. Scores are expressed as the mean value for all items within each scale.

Statistical analysis

Incontinence status before (S_0) and after (S_1) surgery was evaluated for each recruited patient by means of the Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS). The absolute difference $S_1 - S_0$ was calculated, and the patients were considered to have a worse condition if the difference was a positive value.

A descriptive analysis was performed to characterize the patients based on the worsening of incontinence as it related to the surgery. Qualitative variables were summarized by absolute and percent frequencies, whereas the median, 1st and 3rd quartiles were used for quantitative variables. Comparisons between patients who experienced a worsened condition and those who did not were performed using the Fisher's exact test and the Wilcoxon rank sum test.

The binomial distribution was used to evaluate 95% confidence intervals (95% CI) for the estimate of the proportion of patients with a worsened condition. The median difference $S_1 - S_0$ in patients with worsened disease was estimated by 95% CI, graphically represented by a boxplot and evaluated by Wilcoxon signed-rank test.

Logistic regression analysis was performed to estimate the effects of the patient and tumour characteristics that are associated with the worsening of incontinence after surgical intervention. Gender, age (dichotomized at 65 years), distance from the anal verge (dichotomized at 5 cm), tumour dimensions and surgical time were considered independent factors. The goodness of fit of the models was evaluated by the likelihood ratio (LR) test and the Hosmer–Lemeshow test. The results were expressed as point and 95% confidence interval (95% CI) estimations of the odds ratios.

The comparison of the results of the Fecal Incontinence Quality of Life Index Scale was performed using the Mann–Whitney nonparametric test.

All the analyses were performed using R statistical package, and statistical significance was assessed using a level of probability of 5%.

Results

The population studied was composed of 59 males (64.8%) and 32 females (35.16%). The mean age was 69.7 years (range 49–86 years), and the median operative time was 40 min (range 30–80 min).

We found only seven (9.5%) minor complications according to the Clavien–Dindo classification. These complications consisted of five cases of rectal bleeding, one case of suture dehiscence and one case of urinary retention. The cases of rectal bleeding did not require a blood transfusion and were treated conservatively. The problem of leaking sutures was resolved by the administration of antibiotics. A temporary urinary catheter was placed to solve the problem of urinary retention.

Post-operative pain, which was evaluated according to the Numeric Rating Scale (NRS), was minimal and appeased with mild analgesics. We did not observe any intraoperative or post-operative mortality. The median length of hospital stay was 3 days (range 2–7).

In this series, no patients experienced tumour recurrence at a median follow-up of 48 months (range 84–12 months) (Table 1).

Scores on the Fecal Incontinence Quality of Life Index Scale did not show a significant difference for patients before and after TEM (Table 2).

Overall, 62 patients were found to be continent before and after surgery. Eight patients were found to be incontinent before and after surgery, with a median CCF-FIS of 6 (1st–3rd quartiles: 4–8). Fourteen patients were continent before surgery and became incontinent after intervention (Table 3).

According to the Cleveland Clinic Florida Fecal Incontinence Score (CCF-FIS), 23 patients experienced a

Table 1 Characteristics of the studied population

Variables	Values
Male [n (%)]	59 (64.8%)
Age [years, mean (range)]	69.7 (49–86)
Median operative time [min, mean (range)]	40 (30–80)
Median hospital stay [days, mean (range)]	3 (2–7)
Post-operative complications [n (%)]	7 (9.5)
pCR [n (%)]	84 (87.9)
Recurrence [n (%)]	0

worsened incontinence status after surgical intervention (27.4; 95% CI 18.2–38.2). Patients with a worsened incontinence status experienced a median positive absolute variation in the CCF-FIS of four points (95% CI 3.5–4.5; $p < 0.001$) (Figs. 1, 2).

People with a worsened status were significantly more likely to be female and older; no significant difference was found in terms of tumour distance from the anal verge, tumour dimensions or surgical time (Table 4).

The variables included in the model contributed significantly to the total deviance (LR test = 19.5, $df = 5$, $p = 0.002$), and the Hosmer–Lemeshow test indicated that the model fit the observed data well ($\chi^2 = 8.29$, $df = 8$, $p = 0.406$) (Table 5).

Sixteen patients (19%) experienced referred symptomatic radiation proctitis, which caused diarrhoea, nausea, cramps, tenesmus and bleeding during the treatment period. However, almost all patients complained of milder symptoms at the time of surgery. Five of them experienced referred bleeding and altered bowel habits 1 year after surgery (5.9%). Recto-sigmoidoscopy in these patients revealed the persistence of bleeding of the frail mucosa, and histopathological examination revealed a nonspecific inflammatory tissue status. A significant portion of these events occurred in the patients who experienced a worsening of their continence status after surgery (4 vs. 1, $p = 0.001$).

We also performed endoanal ultrasound in patients with a worsened continence status 1 year after surgery.

The examination revealed scarring of the anal sphincters in 11 patients (47.2%). Seven of the women with a worsened status had a previous history of difficult labour and minimal obstetric sphincter damage documented by imaging (50%).

Discussion

Preoperative CRT for rectal cancer markedly improved local disease control, and the downstaging of tumours after CRT may be relevant to the determination of a complete clinical response (cCR) in 10–20% of cases [1, 2].

Table 2 Fecal Incontinence Quality of Life Scales

Fecal Incontinence Quality of Life Scales	Before TEM	1 year after TEM	p
Lifestyle	3.56	3.25	0.2
Coping/behaviour	2.91	2.85	0.15
Depression/self-perception	3.47	3.40	0.37
Embarrassment	2.56	2.55	0.2

Table 3 Number of incontinent patients before and after surgery and distribution of type of incontinence

| Type of incontinence	n	Before surgery					After surgery					p
		Tot.	1	2	3	4	Tot	1	2	3	4	
Continent patients before and after surgery	62											
Incontinent patients before and after surgery	9											
Solid		1	1				2	2				0.222
Liquid		4	2	2			4		3		1	0.444
Gas		3	1	2			3		1	2		0.004
Wears a pad		0	0				0					
Lifestyle alteration		0					0					
Continent patients before but incontinent after surgery	14											
Solid							0					
Liquid							6	3	3			
Gas							7	2	4	1		
Wears a pad							0					
Lifestyle alteration							1		1			

p values refer to Fisher's exact test
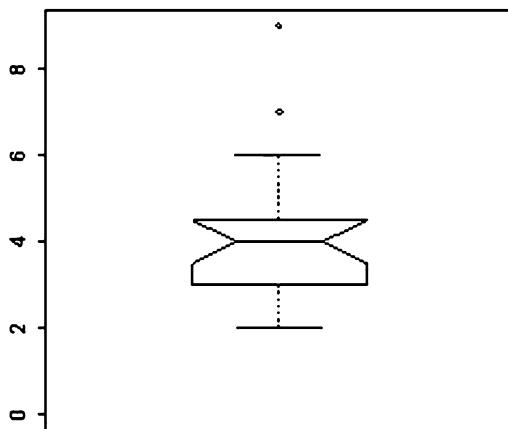
Fig. 1 CCF-FIS absolute variation in worsening patients after surgical intervention (n = 23) (p refers to Wilcoxon signed-rank test, notches indicate 95% CI of median value)

Fig. 2 Fecal incontinence severity index (FISI) scores in worsened patients (*Patients with preoperative FISI score equal to zero)

However, the management of patients who achieve a cCr is controversial.

A simple follow-up without surgery after cCR was proposed by Habr-Gama et al. [4, 9, 11–14], but the most important drawback of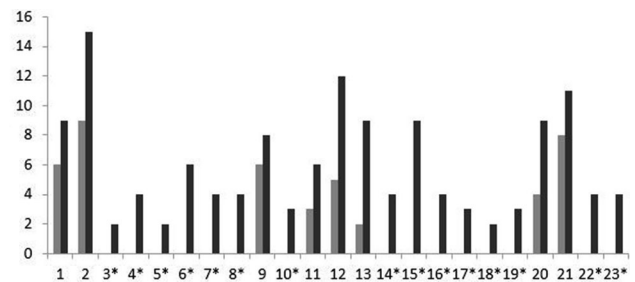 this approach is the discrepancy between cCR and pCR, which has been unanimously recognized. As Habr-Gama and colleagues have observed, endoscopic biopsy, although it is the easiest way to obtain tissue for a histopathological examination, has shown an accuracy of <25% in the prediction of a complete pathological response after neoadjuvant treatment because it may result in the failure to notice islets of cancer cells within fibrotic tissue [14].

On the contrary, since its introduction in 1982, AR has been routinely adopted and has significantly reduced the rate of local recurrences [15].

Table 4 Patients' characteristics according to worsening in incontinence status after surgery, according to CCF-FIS

Patients' characteristics	Worsening		p
	No (n = 61)	Yes (n = 23)	
Male [n (%)]	44 (72.1)	9 (39.1)	0.011
Age [years, median (1st–3rd quartiles)]	69 (58–77)	75 (68.5–81)	0.020*
Distance from anal verge [>5 cm, n (%)]	41 (67.2)	17 (73.9)	0.743
Tumour dimension [cm, median (1st–3rd quartiles)]	3 (2–4)	3 (2–4)	0.954*
Surgical time [cm, median (1st–3rd quartiles)]	45 (35–55)	50 (44.5–60)	0.089*

Chi-square test

* Wilcoxon rank sum test

Table 5 Factors associated with the risk of incontinence worsening after surgery, according to CCF-FIS. Results of the logistic regression analysis

	OR	95% CI	p
Gender (male vs female)	0.23	0.06–0.74	0.017
Age (years)	1.08	1.02–1.16	0.011
Distance from anal verge [>5 cm vs. ≤5 cm]	2.63	0.73–11.18	0.159
Tumour dimension (cm)	0.84	0.51–1.32	0.477
Surgical time (min)	1.03	1.00–1.07	0.059

Hosmer and Lemeshow goodness of fit test: Chi-square with 8 df: 8.29, $p = 0.406$

LR test: Chi-square with 5 df: 19.5, $p = 0.002$

OR odds ratio

However, this type of surgery is burdened by significant morbidity, mortality and stoma construction rates and may be excessive in the case of a cCR.

In up to 71% of patients who undergo AR, a set of evacuative dysfunctions commonly known as "anterior resection syndrome" is frequently experienced. These dysfunctions include gas and faecal incontinence, urgency, a sensation of incomplete rectal emptying, inability to defer defecation and clustering of bowel movements [16, 17].

In the current study, urinary dysfunction was seen in 5–32% of patients, while sexual impairment was seen in 13–45% of cases.

Conservative surgery such as local excision by TEM may be the optimal choice for these patients.

TEM is a minimally invasive technique that gained popularity as a valid therapeutic and diagnostic tool in the case of rectal lesions. It is a validated therapeutic approach for large rectal adenomas and T1 rectal cancer without the high-risk features [18].

In the case of irradiated locally advanced rectal cancer that is described preoperatively in patients with a complete response, it is possible to obtain a full thickness excision of the residual scar.

Local excision provides more information about the presence or absence of residual tumour than the watch and wait policy.

In our experience, definitive histology revealed tumour cells in seven patients (7.7%).

The major criticism of this approach is the impossibility of the radical removal of the mesorectum, and consequently, the inability to obtain direct pathological information regarding mesorectal lymph-node status.

Nevertheless, the results from several reports show a clear correlation between the pathological T-stage after neoadjuvant therapy and the risk of involved pelvic lymph nodes, with a very low risk (<5%) for patients with pCR [19–21].

We did not observe tumour recurrences in this series.

Short-term post-operative complications after TEM, which include suture line dehiscence, bleeding and urinary retention, are rare (9.5%).

Since TEM requires a transanal introduction of a 4-cm rectoscope, anorectal functional impairment may be a concern. However, several studies have demonstrated that TEM does not significantly affect the continence status.

In the series studied by Cataldo and colleagues, all patients were administered the FISI and FIQL questionnaires before and 6 weeks after surgery. No significant differences were noted in the measured parameters, and sometimes patients experienced an improvement in faecal incontinence and in quality of life [22].

Similarly, Doornebosch and colleagues noted significant improvements in post-operative FISI scores (10 vs. 7, $p = 0.01$) and in the mean quality of life score ($p = 0.02$) when this questionnaire was administered preoperatively and 6 months after surgery [23].

Allaix and colleagues did not find any significant differences in comparison with the preoperative and postoperative data in terms of maximum anal resting pressure, rectal sensitivity threshold during intrarectal balloon distension, MTV and the urge to defecate. They also noted that the two factors that may affect sphincter function in terms of anal resting pressure are the duration of the procedure and the size of the lesion [24].

To our knowledge, only one other study has investigated functional outcomes after TEM performed in irradiated patients. Coco and colleagues did not observe any significant difference between irradiated and non-irradiated patients in terms of the mean evacuation scores (24.72 ± 2.79 vs. 25.6 ± 2.24) [21].

Our study showed a mild worsening of anorectal function in 23 patients (27.4%) compared with preoperative data and demonstrated that this worsening did not significantly correlate with a worse quality of life.

Two demographic factors significantly correlated with the worsening of continence status: female sex ($p = 0.011$) and old age ($p = 0.02$). Operative time showed a trend towards significance, but this factor did not reach statistical significance.

It has been widely described that pelvic irradiation alone negatively affects anorectal function and that anorectal function is even more affected when the anorectum is the main target of radiotherapy [25, 26].

Based on these observations, we can affirm that the worsening in continence status observed in our patients might also be more attributable to the negative effects of radiation therapy than to those of TEM, since we demonstrated that the development of severe radiation proctitis contributed to the development of changes in of the continence status.

We did not observe a worsening of the quality of life after surgery although we did observe slight negative changes in the FISI scores. An accurate assessment of the tumour response could potentially allow for the selection of patients who require less aggressive treatment strategies after CRT.

After neoadjuvant treatment, both watchful waiting and local excision are possible alternatives to radical surgery. Both of these approaches enable us to avoid the disadvantages of surgery for pT0 rectal cancer. Local excision is an increasingly appealing alternative due to the good local control offered by high-dose radiation. In addition, TEM offers the possibility to achieve a full thickness excision of the rectal wall and the identification of any residual disease and provides optimal quality of life and functional results.

The limits of this study are primarily due to its retrospective nature.

A prospective randomized clinical trial would better reveal the impact of TEM and RT on anal function.

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