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

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(Article begins on next page)

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Surgical Endoscopy

Functional outcomes after TEM in patients with complete clinical response after neoadjuvant chemo-radiotherapy.

--Manuscript Draft--

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Full Title:	Functional outcomes after TEM in patients with complete clinical response after neoadjuvant chemo-radiotherapy.
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Response to Reviewers:	Ancona, 23th October 2016 Dear Editor Dear Reviewers, Thank you very much for your mail, we are grateful for your comments of appreciation of our manuscript. First of all, we had the text revised by a native English speaker expert in this field, as suggested by two reviewers. You can find below the answers to your questions. Reviewer #1 -we provided, as he suggested, the description of the CRT protocol and added three references in the text (Marks G, Mohiuddin M, Masoni L. The reality of radical sphincter preservation surgery for cancer of the distal 3 cm of rectum following high-dose radiation. Int J Radiat Oncol Biol Phys 1993; 27: 779–783- Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006; 24: 4620–25.-Bosset JF, Calais G, Mineur L, et al, and the EORTC Radiation Oncology Group. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014; 15: 184–90) -we decided not to use anorectal manometry because its efficacy to determine anorectal function after TEM is controversial. Some studies did not find a significant difference between pre and post operative manometric values. Other studies found

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that does not exist a correlation between manometric value and clinical outcomes (Mora López L, Serra Aracil X, Hermoso Bosch J et al, Study of anorectal function after transanal endoscopic surgery. Int J Surg. 2015 Jan;13:142-7, -Barendse RM, Oors JM, de Graaf EJ, et al, The effect of endoscopic mucosal resection and transanal endoscopic microsurgery on anorectalfunction. Colorectal Dis. 2013 Sep;15(9):e534-41.-

-we believe a free margin of 1 cm is enough
-we agree with the comment of the reviewer and moved the sentence in the Materials section as he suggested
-we cut off the penultimate sentence of Material and Methods because it was unnecessary
Results
-we moved the sentence suggested on hystopatological examination in the Materials section
Reviewer#2
Major issues
1.As he recommended we expanded table 3

2.We appreciated the comment of the reviewer. We administered the Wexner questionnaire before any treatment to avoid any alteration due to the radiotherapy to affect our results. Different studies discuss the detrimental effects of radiotherapy alone on anorectal function (Jorge JMN, Habr-Gama A and Bustamante-Lopez LA. Effects of Radiation Therapy for Rectal Cancer on Anorectal Function. In Eli D. Ehrenpreis et al. (eds.), Radiation Therapy for Pelvic Malignancy and its Consequences, New York Springer Science+Business Media; 2015: 143-151.- Sedgwick DM, Howard GC, Ferguson A. Pathogenesis of acute radiation injury to the rectum. A prospective study in patients. Int J Colorectal Dis. 1994 Apr;9(1):23-30.)
At page 14 of the discussion we explained about this aspect.

3.The total percentage of patients with clinical CR was reported in the manuscript in the Materials section in the sixth paragraph. We included our definition of complete response in the Materials section in the seventh paragraph.

4.Looking at urinary and sexual disfunction is a very good suggestion. It would be the topic of further studies; in this one we wanted to concentrate our attention on the anorectal function.

5.This is the way we move in our department if a complete clinical response is diagnosed, since the results we observed are good, as we stated in previous studies, we continued in this line. In our opinion the watch and wait approach is a very interesting alternative to surgery but still, nowadays there are not sufficient data to justify these kind of approach.

Minor issues

1.In this study we excluded patients with incomplete response because we wanted to focus only on the functional aspect. We better specified it in the Materials and Methods session. The study of difference among patients with complete and incomplete response is an optimal hint for another study and we thank him for this.

2.The chemo-radiation therapy was standardized, we specified the used protocol in the Materials and Methods section as he requested

3.We collected our scores with physical visit both preoperatively and postoperatively

4.In our twenty years experience of TEM, we always closed the mucosal defects. Our database is composed by up to 1300 patients. To our opinion the tip to avoid suture dehiscence rate is to make big hold of tissue at both the edge of the defect while suturing. Suture dehiscence was confirmed by clinical visit and proctoscopy. We

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	routinely perform the first proctoscopy at two weeks from surgery. Reviewer#3 We have to thank the reviewer for his positive comments. As reported at the beginning a native English speaker revised the test. We send to you our best regards. Monica Ortenzi, MD Università Politecnica delle Marche Clinica Chirurgica Ancona, Italy Mario Guerrieri, Università Politecnica delle Marche Chief of the Department of Clinica Chirurgica Ancona, Italy
Funding Information:	Università Politecnica delle Marche — Prof Roberto Ghiselli
Abstract:	Background In patients with complete clinical response after radio chemotherapy for rectal cancer the standard surgical approach could be an overtreatment. The aim of this study is to analyze the results 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, eighty-four patients with rectal cancer staged as T2-T3-T4 N0 pre chemoradiotherapy showed complete clinical response to neoadjuvant therapy and underwent TEM. All patients were evaluated before and 1 year after TEM with the Cleveland Clinic Florida Fecal Incontinence (CCF-FIS) questionnaire to determine the impact of this surgical technique on the degree of fecal continence. In order to assess patients' quality of life after surgery, we administered the Fecal Incontinence Quality of Life Scales (FIQL). Results Twenty-three patients got worse in their incontinence status after surgical intervention (27.4%; 95%CI: 18.2-38.2). Worsened patients experienced a median positive absolute variation in CCF-FIS of 4 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 scale did not show a significant difference before and after TEM. Conclusions TEM can be an alternative for treating rectal cancer with a complete clinical response to neoadjuvant chemoradiotherapy because it offers the possibility to achieve a full thickness excision of the rectal wall while identifying any residual disease and providing optimal quality of life and functional results.

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8 **ORIGINAL ARTICLE**
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12 **chemo-radiotherapy.**
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14 **A single-centre experience**
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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.

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Patients and methods

Between 2007 and 2014, eighty-four 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.

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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 (FIQL) 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 4 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.

Introduction

Currently, anterior resection (AR) with total mesorectal excision or abdominal perineal resection (APR) after chemo radiotherapy (CRT) still represent 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 to 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).

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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.

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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 7 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 [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.

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Quality of life was evaluated using the Fecal Incontinence Quality of Life Index Scale, which is composed of 4 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 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 non-parametric 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 minutes (range=30-80 minutes).

We found only 7 (9.5%) minor complications according to the Clavien-Dindo classification. These complications consisted of 5 cases of rectal bleeding, 1 case of suture dehiscence and 1 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, sixty-two 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), twenty-three patients experienced a 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 4 points (95%CI: 3.5-4.5; $p<0.001$) (*Figure 1, Figure 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-square=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 one 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 one 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%).

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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 to 20% of cases [1, 2].

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

A simple follow-up without surgery after cCR was proposed by Habr-Gama and colleagues [4,9,14], 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].

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 7 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 v. 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].

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Allaix and colleagues did not find any significant differences in the comparison of the preoperative and post-operative 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.

Acknowledgements

Roberto Ghiselli contributed substantially to the conception and design of the study. Monica Ortenzi organized the data collection process, developed and led the project, and prepared the manuscript. Maria Luca Cardinali contributed to the acquisition and analysis of the data. Rosaria Gesuita and Edlire Skramy participated in the interpretation of the data for the study and provided advice on statistics. Mario Guerrieri drafted the manuscript, revised it critically for important intellectual content, and gave final approval of the version to be published. All the authors deny any conflict of interest.

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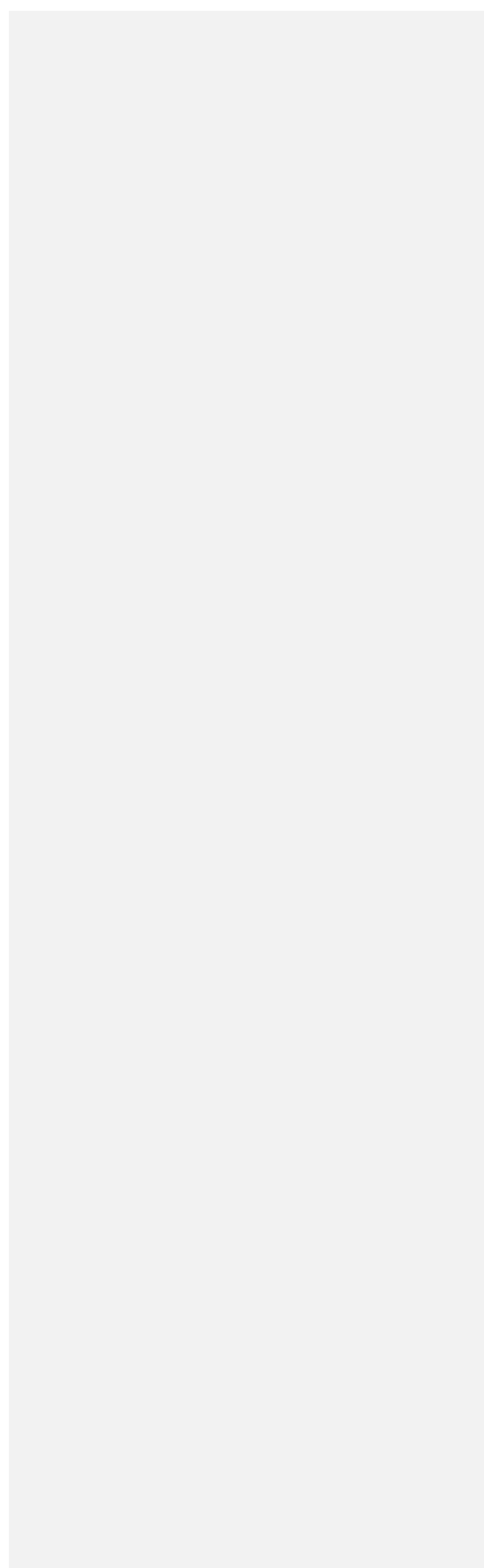

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Variables	**Values**
Male [n(%)]	59(64.8%)
Age [years, mean(range)]	69.7(49-86)
Median operative time [min, mean(range)]	40 (30-80)
Median hospital stay[days, mean(range)]	3(2-7)
Post-operative complications[n(%)]	7(9.5)
pCR[n(%)]	84(87.9)
Recurrence[n(%)]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

Table 1 Characteristics of the studied population

Fecal Incontinence Quality of Life Scales	Before TEM	1 year after TEM	p
Lyfestyle	3.56	3.25	0.2
Coping/Beahavior	2.91	2.85	0.15
Depression/Self perception	3.47	3.40	0.37
Embarassment	2.56	2.55	0.2

Table 1 Fecal Incontinence Quality of Life Scales

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

			Before Surgery					After Surgery					p
	Type of incontinence	n	**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 refere to Fisher Exact test

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

Patients' characteristics	Worsening No (n=61)	Worsening Yes (n=23)	p
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 [>5cm, n (%)]	41 (67.2)	17 (73.9)	0.743
Tumor 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 Click here to download Table Table 5.doc

Table 5. Factors associated to 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
Tumor Dimension (cm)]	0.84	0.51 -1.32	0.477
Surgical time (min)	1.03	1.00 -1.07	0.059

OR: Odds ratio
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

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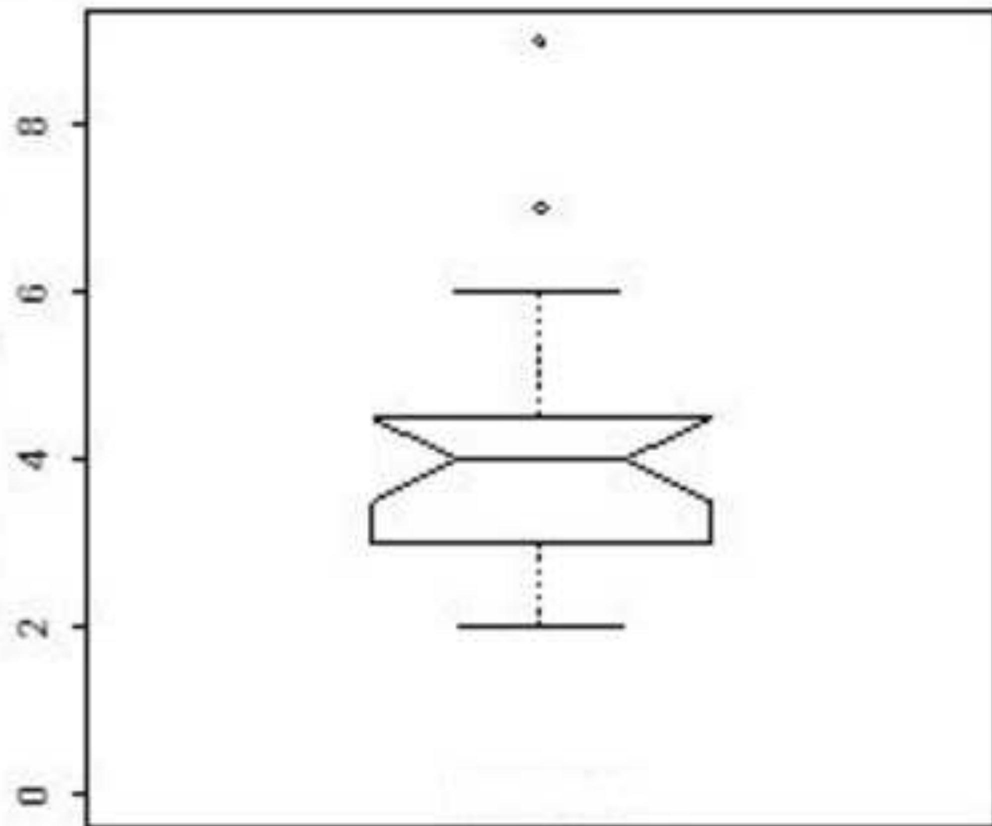

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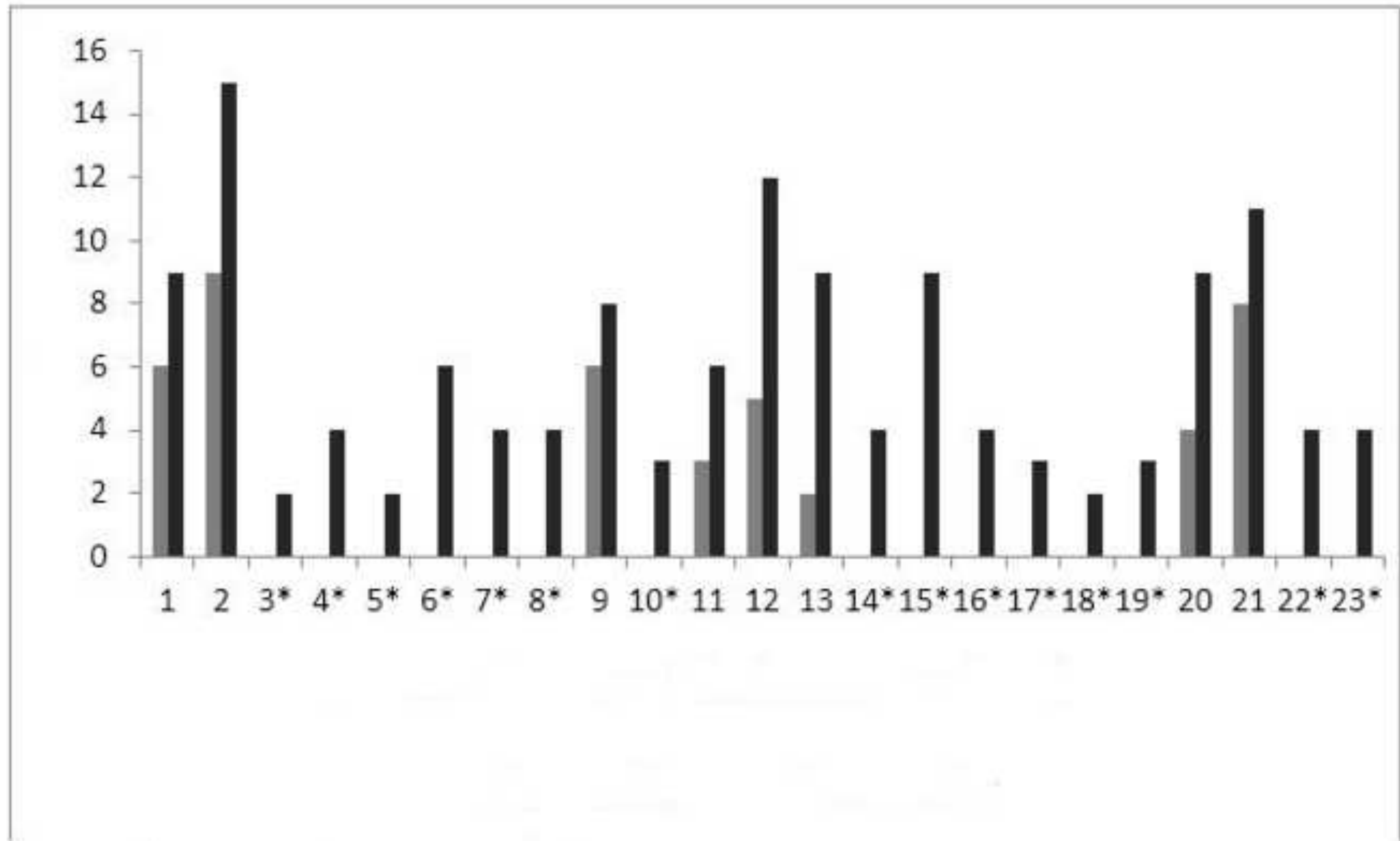

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