Controversies in local excision for stage I rectal cancer

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ABSTRACT

Introduction: The standard treatment for rectal cancer is total mesorectal excision and neoadjuvant treatment in Stage II and III. However, it results in undesirable functional consequences. In T1 and T2 tumors without lymph node involvement, studies have demonstrated that organ-preserving treatment is possible, with similar outcome to radical treatment.
Aim: To present the results of a series of Stage I rectal cancer patients treated by local excision (LE).
Material and methods: Thirteen Stage I rectal cancer patients treated with LE between 2012 and 2021.
Results: Gender: 7 women, mean age: 63.1 years. Mean height of the lesions was 4.07 (range 2-8) cm from the anal verge. Posterior 6, anterior 4, anterolateral 2 and posterolateral 1. Three patients with T2 tumors received neoadjuvant treatment, and the histopathological report after LE was ypT1 in 2 and complete pathological response in 1. In the remaining 10 patients, histopathology result was T2: 3, T1 Sm1: 3 and T1 Sm3: 4. Lymphovascular invasion was negative in 8 patients. Complications occurred in 2 (15.4%) patients.
Two patients were re-operated, one due to insufficient margins and another due to adverse histological features. With a mean follow-up of 54.5 (range 12-120) months, 12 patients are free of local and distant recurrence. One patient died at 8 months due to carcinomatosis.
Conclusion: The strategies currently used in the conservative treatment of rectal cancer are promising, so they should be offered to patients in the setting of a clinical trial with rigorous and safe registration. The quality of evidence to date is insufficient to replace the current standard of care.
Key words: *transanal endoscopic microsurgery, TAMIS, transanal minimally invasive surgery, stage I rectal cancer*

INTRODUCTION

The standard treatment for rectal cancer is resection with total mesorectal excision (TME), accompanied by neoadjuvant treatment in stages II and III. However, although long-term oncologic results have improved, this treatment is associated with functional disorders, which in patients who develop a modern social life generate a significant degree of dissatisfaction. For this reason, doctors and patients are looking for new alternatives to avoid these undesirable consequences.
Tumors that are limited to the muscularis propria, without involving lymph nodes, have generated enthusiasm in the surgical and oncological community with some studies showing encouraging results through conservative treatment. However, there are various controversies regarding the strategy to use.
The objective of this study is to present the results of a series of patients with stage I rectal cancer treated by local excision (LE).

MATERIAL AND METHODS

Thirteen patients with stage I rectal cancer located up to 8 cm from the anal verge, who were treated by LE between June 2012 and November 2021, were retrospectively selected from a prospective database.

All patients, except those who initially presented as a villous tumor, were staged locally preoperatively by physical examination, rectosigmoidoscopy, colonoscopy, high-resolution MRI, and/or endorectal ultrasound and interpreted by a specialist with extensive rectal experience. CT scans of the chest, abdomen and pelvis, routine laboratory tests and tumor biomarkers were also performed. The height and location of the tumor was established by digital examination and/or rectosigmoidoscopy.
All patients were explained how the attempted organ-preserving surgery would proceed and the possible variants; as well as the need to extend the resection if histological risk features for an adverse outcome were found in the definitive pathological study.
Those who refused radical resection were included in this series. Initially, patients with tumors preoperatively classified as T2 were prescribed neoadjuvant therapy and LE. Starting in 2015, it was modified to LE and adjuvant treatment if the pathological result showed risk features and the patient rejected radical surgery. Otherwise, resection with TME was performed within 30 days after the first intervention.
Neoadjuvant treatment was long course chemoradiotherapy (CRT). Radiotherapy was performed with a total dose of 5040 cGy for a period of 5 weeks, divided into doses of 2 Gy per day. Chemotherapy was performed with 5-Fluoracil (225 mg/m²/day) plus Leucovorin. Adjuvant treatment with 5-Fluoracil was performed for a period of 4 months, starting 4 to 12 weeks after surgery.
Surgery was performed between 8 and 12 weeks after completing treatment. The technique was transanal endoscopic microsurgery (TEM) and the platform used was Endorec® in the first period and Gel Point® later. The patients were operated on in the jackknife, gynecological, right or left lateral position, depending on the location of the lesion, so that it was located below the position of the instruments and the operator's eye. The laparoscopy equipment used was Stryker®, composed of a high-resolution LED camera and display, a 40lt high-flow insufflator and an X8000.1 xenon light source.[1]
In cases with doubtful or incomplete margins, a new LE was indicated in T1, and resection with TME in T2. Those patients in whom the specimen was fragmented were discarded.
All surgical specimens were studied by one of the authors (JPS), who evaluated the macroscopy by measuring the surgical specimen, describing the appearance, consistency, color and size of the tumors, and the distance to the lateral and deep margins. Microscopy evaluated the degree of differentiation, lymphovascular invasion, resection margin, depth of invasion, and dedifferentiation/budding) (Figs. 1 y 2). To determine the presence or absence of lymphovascular invasion, immunostaining was used to demonstrate vascular endothelium (CD34, CD31, and/or D2-40) (Fig. 3). Differentiation, lymphovascular invasion, deep invasion and budding were considered risk features.

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All patients were followed up by an interdisciplinary team. Postoperative control was performed by physical examination, high-resolution MRI, computed tomography, and tumor markers every 3 months. Colonoscopy was performed one year after surgery.

RESULTS

Of the 13 patients, 6 were men and 7 women, the average age was 63.1 (range 42-81) years. Lesions were located between 2 and 8 (mean 4.07) cm from the anal verge. The location was posterior: 6, anterior: 4, anterolateral: 2 and posterolateral: 1.

Preoperative staging was performed in 7 patients, 4 were T2N0 and 3 were T1N0. After the histopathological study, a false negative was confirmed (T1 Sm3, in which two positive nodes were found in the surgical specimen after radical resection).

In 6 patients with initial biopsy of villous adenoma, the final pathological result was: T2N0 in 2, T1 sm3 in 1 and T1 sm1 in 3.

In 3 patients staged T2, neoadjuvant treatment was performed, and the definitive pathological result was: yptT1 in 2 and complete pathological response in 1. In the remaining 10 patients who did not receive preoperative treatment, the pathological result was: T2 in 3 (in 1 of them with positive margins, an extended LE was performed), T1 Sm1 in 3 and T1 Sm3 in 4 (1 with lymph node invasion, N1 final). In relation to lymphovascular invasion, the remaining 8 were negative. (Figs, 1, 2 and 3)

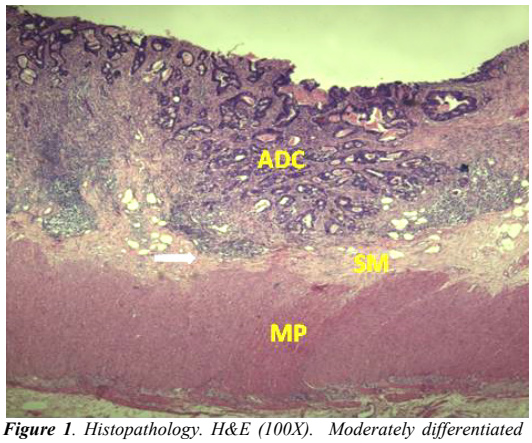

***Figure 1**. Histopathology. H&E (100X). Moderately differentiated adenocarcinoma (ADC) with deep invasion of the submucosa (SM) Sm3 (arrow). MP (muscularis propria).*

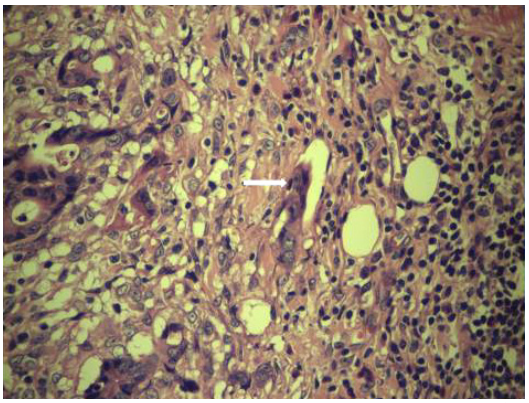

***Figure 2.** Histopathology. H&E (400X). Neoplastic invasion of a lymphatic vessel (arrow).*

One patient had complications intraoperatively, with perforation of the cul-de-sac of Douglas, and two (15.4%) in the postoperative period, with urethral perforation, and uncontrollable sacral pain.

After LE, TME was performed in two patients; one initially had a villous adenoma that turned out to be a T2 adenocarcinoma with involved margins, (finally T2 N0). He underwent radical resection 20 days after LE, and died 8 months later due to pelvic carcinomatosis. Another patient had a T1 tumor with risk factors, (lymphovascular invasion and foci of intermediate dedifferentiation), and the final pathological report was T1N1 (Fig.4). This patient received adyuvant treatment with FOLFOX.

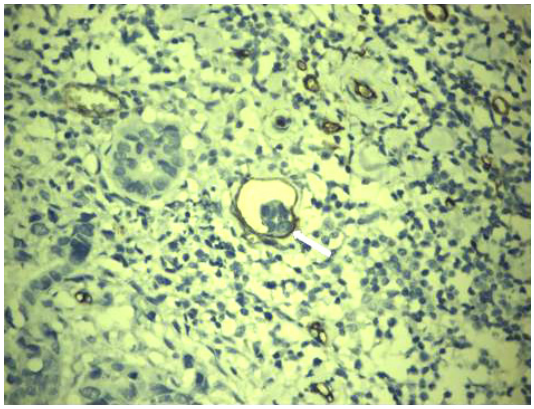

***Figure 3.** Histopathology (400X). Immunohistochemistry for CD34 to label endothelium. Neoplastic vascular invasion is observed.*

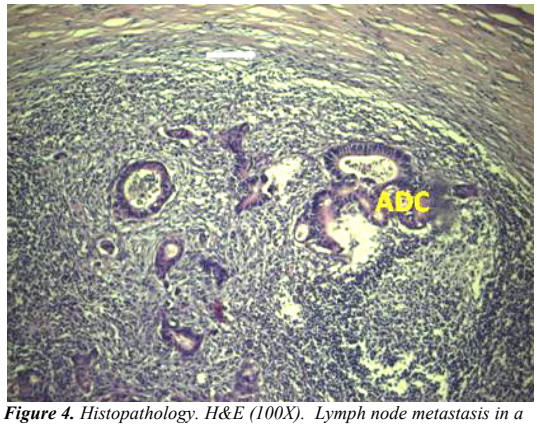

***Figure 4.** Histopathology. H&E (100X). Lymph node metastasis in a T1 Sm3 adenocarcinoma (ADC), with dedifferentiation and lymphovascular invasion. Intranodal neoplasia without capsular rupture (arrow) can be seen. Preoperative staging by MRI and endorectal ultrasound had been T1N0.*

The remaining 12 patients have no evidence of local or distant disease with an average follow-up of 54.5 (range 12-120) months (Fig. 5).

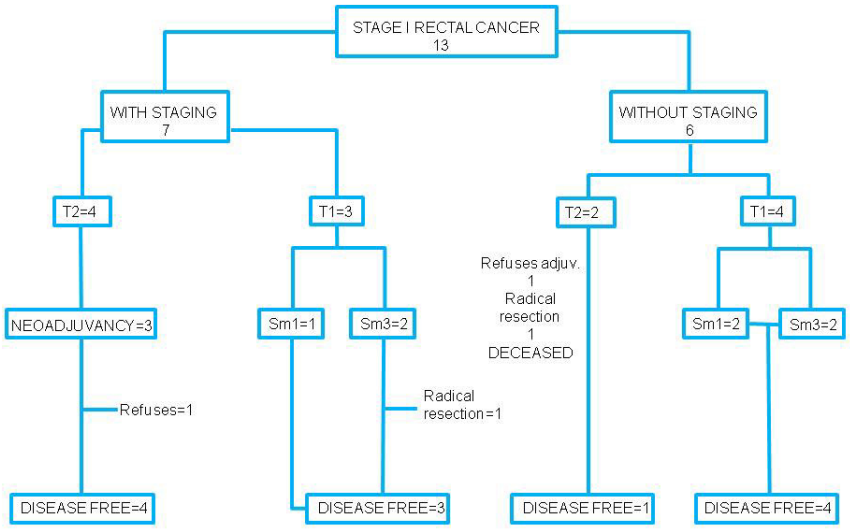

Figure 5. *Long-term outcome.*

DISCUSSION

The treatment of low rectal cancer is very well established and includes TME and the addition of neoadjuvant treatment in stages II and III. Although oncological results in terms of local recurrence and survival have improved, the impact of this treatment in quality of life is still high.[2]

The classic LE described by Sir Alan Parks has shown that it is possible to treat tumors confined to the mucosa and submucosa with good results when they present favorable histological factors. However, it is a technically-demanding procedure and, consequently, the specimens resected are frequently fractionated or with incomplete or doubtful margins.[3,4]

The development of TEM, as a variant approach, has revealed better results with a lower rate of recurrence and complications.[4,5]

The good results of local resection in T1 tumors and the notable response to radio and chemotherapy in advanced tumors have led to the proposal of organ-preserving treatment in lesions with muscular propria invasion.[6,7]

Local resection in T2 tumors has shown local recurrence rates of around 20% when no treatment is added. The use of neoadjuvant therapy reduces these rates to around 5% to 12%, with a pathological complete response of 20% to 40% and disease-free and overall survival rates comparable to patients treated with TME.[8-10]

When neoadjuvant therapy is used, staging notably loses certainty, since the effect of CRT significantly distorts the initial histological structure, regarding parietal invasion and lymph nodes.[11] The accuracy of preoperative staging of stage I rectal cancer has not been as high as desired. Endorectal ultrasound and high-resolution magnetic resonance imaging (MRI) are commonly used alone or in combination. The main difficulties encountered are that both procedures are highly dependent on the operator and when it comes to submucosal invasion close to the muscularis propria, controversial interpretations are generated given the tenuous changes that occur. Regarding the presence of pathologic lymph nodes close to the tumor, MRI with or without diffusion is presented as the best option based on the anatomical, structural and diffusion changes. None of these characteristics alone or in combination is a guarantee of neoplastic involvement.[12] For these reasons, the results mentioned in relation to T have a sensitivity and specificity of 87 and 75%, respectively, while for the involved lymph nodes it is 77 and 71%.[13-16]

After neoadjuvant treatment, all nodes decrease in size and approximately 44% disappear. MRI with the addition of diffusion may improve outcomes. However, even in highly trained hands the margin of error is 11%.[7]

Most research regarding local resection in T2 tumors has been developed with the use of neoadjuvant therapy. Some series include conventional LE, TEM, and combined resections.[18-20] If initial imaging staging is not accurate and neoadjuvant treatment radically changes the pathologic findings, then oncologic outcomes relative to the true initial staging will be affected by these distortions.

The advantage of initially performing the resection is obtaining a virgin specimen that can be accurately staged by histopathology which enables more precise decision-making (adjuvant treatment, radical resection) in the presence of risk factors.

Nodal invasion in rectal cancer has been widely studied. Global analyzes indicate that when there is submucosal or muscular involvement, the risk of metastasis is 12 and 23%, respectively. In recent years, various authors have dedicated themselves to investigate in detail the risk factors for lymph node involvement.

Initially, Kikuchi et al.,[21] in 1995 described the importance of the depth of submucosal invasion for lymph node metastases in T1 carcinoma. The authors subcategorized according to the depth of the submucosal invasion, into upper, middle and lower third (Sm1, Sm2 and Sm3) invasion. The series of 182 patients, operated on between 1982 and 1989 with a 5-year follow-up, included local, endoscopic or surgical excision of the colon and rectum. Intestinal resections were performed in 108, and lymphatic metastases were found in 13 (14.4%), 4 in Sm2, and 9 in Sm3. Of these, 9 had lymphatic invasion and 4 had vascular invasion. During follow-up, 2 developed distant metastases.

Recently Ushigome et al.,[22] from the International Cancer Institute of Osaka, published a study that investigated the risk factors for lymph node metastasis in T2 rectal tumors located below 10 cm from the anal verge, with radical resections without prior treatment. Over a period of 10 years (2008-2018), 95 patients were analyzed and lymphatic

invasion was confirmed in 26 (27%), including 2 (2%) with lateral pelvic invasion. Univariate analysis indicated that lymphovascular invasion (p=0.008), tumor budding (p=0.012), and dedifferentiation (p=0.08) were associated with lymph node invasion. Multivariate analysis revealed that lymphovascular invasion (p=0.03) was the only independent risk factor. No lymph node metastases were found in 8 cases that did not present any histological risk factor. Invasion of the muscular layer ≥2 mm was not a risk factor (p=0.854). They conclude that lymphovascular invasion, budding and histological type may be risk factors for lymph node invasion in low T2 rectal tumors.

Similar results were found by Rasheed et al.,[23] in a study of 55 T1 and 248 T2 patients. The incidence of involved lymph nodes was 12.7 and 19%, respectively. There was no significant difference in the number of patients with involved nodes according to the depth of tumor invasion Sm1-3, or T2. In the multivariate analysis, the presence of extramural vascular invasion (odds ratio = 10) and degree of tumor differentiation (odds ratio for poorly vs. well differentiated = 11.7) were independent predictors of lymph node metastasis. In this short series, 8 patients without lymphatic or vascular invasion, regardless of the depth of tumor invasion, did not receive neoadjuvant treatment and were free of local recurrence during follow-up.

Regarding the strategy to use in the presence of risk factors, the debate that arises is whether to use adjuvant therapy (chemotherapy, radiotherapy or both), adjuvant therapy and surgery, or add total excision of the mesorectum only.

After LE, radical surgery performed in a short period of time does not seem to affect the final outcome. This has been demonstrated by Hahnloser et al.[24] After comparing 3 groups: 1) 52 patients treated with LE and TME within 30 days due to risk factors, 2) 78 patients who underwent primary radical surgery, and 3) 77 patients treated only with LE, they found no differences in survival and local recurrence at 5 or more years.

In our series, a patient with a T1 tumor with risk factors (dedifferentiation and lymphovascular invasion) underwent radical resection within 40 days and two 4-mm positive lymph nodes were found in the surgical specimen. Chemotherapy was added and there was no evidence of local or distant recurrence at 4 years of follow-up.

When, after LE, there are histological risk features, the addition of adjuvant treatment is a valid alternative, with long-term outcome similar to radical resection.[24]

Sasaki et al.,[25] in 2017 reported the long-term results of a multi-institutional phase II study in 53 patients with low T1 and T2 rectal cancers with adverse histological features that underwent adjuvant treatment after LE. Follow-up at an average of 7.3 years showed a 5-year disease-free survival and overall survival of 94% and 75%, respectively.

In 2020, Kang Xu et al.[26] published a study comparing the results of 62 patients with high-risk T1 or T2 tumors treated by TEM with and without adjuvant treatment (20 and 42, respectively). Follow-up was 52.5 months and showed a 3-year overall survival of 93.3% for those treated with adjuvant treatment vs. 66.6% for those treated with LE alone (p=0.022). Local recurrence was 5 and 31%, respectively (p=0.025). In the multivariate analysis, the only independent prognostic factor was adjuvant treatment.

CONCLUSIONS

Local resection in stage I rectal cancer is feasible. The study of the surgical specimen allows an exact pathological staging, defining the risk factors with certainty.

Subsequent treatment will depend on the histopathology of the tumor and the surgical risk compared to a major resection.

The final decision must be agreed upon with the patient after a deep and thoughtful understanding of the treatment proposal.

When radical surgery is waived, follow-up at frequent intervals that includes clinical monitoring, endoscopy, and imaging studies is recommended.

The strategies currently used in the conservative treatment of rectal cancer are promising, so they should be offered to patients within the framework of a clinical trial with rigorous and safe registration.

The quality of evidence to date is insufficient to replace the current standard of care.

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