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Multidisciplinary approach to the treatment of rectal cancer: the benefits of neoadjuvant therapy

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ABSTRACT

Objective: the aim of this study was to assess the impact of neoadjuvant treatment on rectal cancer following involvement of a multidisciplinary team (MDT).

Materials and methods: between January 2000 and December 2005, 90 patients with rectal adenocarcinoma were evaluated by a MDT and operated on after receiving neoadjuvant treatment with radiochemotherapy (RTCT) –67% were men and 33% were women, with a mean age of 65.04 years (21-83 years). Surgery was low anterior resection in 50% and abdominoperineal amputation in 42.2%.

Results: the rate of complications associated with neoadjuvant treatment was 54.4%, with gastrointestinal complications being most frequent. However, this toxicity was tolerated by most patients. It was severe in two cases (2.2%), leading to chemotherapy discontinuation. A histological analysis of specimens showed a complete pathologic response in 10 cases (11.1%) and a partial response (downstaging of T) in 32 cases (35.6%), hence overall response to neoadjuvant treatment was 46.6%. Postoperative complications included anastomotic leakage in 8.3%, perineal wound complications in 34.2%, and urinary disease in 12.2%. The surgical mortality rate was 0%. Local recurrence occurred in 4.4%, and distant metastases were found in 22.2%. Both overall and disease-free survivals were 80 and 64%, respectively.

Conclusions: neoadjuvant treatment results in low local recurrence rates and optimal survival rates, with no increase in morbidity or mortality. A systematic evaluation by a MDT in the context of a clinical protocol offers better cure rates.

Key words: Rectal cancer. Neoadjuvant therapy. Radiotherapy. Chemotherapy. Survival. Recurrence. Pathological response. Multimodality approach.

RESUMEN

Objetivo: evaluar el papel de la terapia neoadyuvante en el tratamiento del cáncer de recto en nuestro hospital, tras la implantación de un grupo multidisciplinar de trabajo (MDT).

Material y métodos: desde enero de 2000 hasta diciembre de 2005 se ha evaluado en sesión clínica por el grupo MDT un total de 90 pacientes diagnosticados de adenocarcinoma de recto e intervenidos quirúrgicamente tras recibir tratamiento neoadyuvante con radioquimioterapia (QMRT). La edad media fue de 65,04 años (21-83 años), siendo un 67% varones y un 33% mujeres. Los procedimientos quirúrgicos realizados fueron fundamentalmente resección anterior baja en un 50% y amputación abdominoperineal en un 42,2%.

Resultados: la tasa de complicaciones asociada al uso del tratamiento neoadyuvante fue del 54,44%, siendo más frecuentes las gastrointestinales. Sin embargo, esta toxicidad fue bien tolerada en la mayor parte de los casos, siendo grave y acarreando la suspensión del tratamiento quimioterápico en 2 pacientes (2,2%). El análisis anatomopatológico de las piezas resecadas demostró una respuesta completa en 10 casos (11,1%) y una respuesta parcial (disminución del parámetro T de la clasificación TNM) en 32 casos (35,6%), con lo que la respuesta global del tratamiento neoadyuvante fue del 46,6%. Entre las complicaciones postoperatorias se produjeron un 8,3% de dehiscencias anastomóticas, un 34,2% de complicaciones de la herida perineal y un 12,2% de complicaciones urinarias. La mortalidad quirúrgica fue del 0%. La tasa de recidiva pélvica fue del 4,4% y la sistémica del 22,2%. La supervivencia actuarial global y libre de enfermedad a los 5 años fue del 80 y 64% respectivamente.

Conclusión: el tratamiento QMRT neoadyuvante proporciona una cifras bajas de recidiva pélvica junto con buenas tasas de supervivencia, no añadiendo una morbimortalidad importante al acto quirúrgico. La evaluación sistemática por un grupo MDT en el contexto de un protocolo clínico parece ofrecer al paciente mejores oportunidades de curación.

Palabras clave: Cáncer de recto. Neoadyuvancia. Radioterapia. Quimioterapia. Supervivencia. Recidiva. Respuesta patológica. Abordaje multidisciplinar.

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INTRODUCTION

Despite the fact that surgery still is the elective treatment of rectal cancer(1), the management of this disease should be performed by a multidisciplinary team (MDT) with contributions by surgeons, oncologists, pathologists, medical and radiation radiologists, and gastroenterologists (2,3).

The objective of treatment is to decrease rate of recurrence (which is the most frequent cause of mortality in these patients) and to increase the survival (4).

In the last decades many papers have been published (5,6) showing the importance of neoadjuvant treatment, with chemoradiotherapy (CRT) decreasing not only the rate of local recurrence but also in some cases increasing survival (7-9).

Simultaneously, improved radiotherapic techniques and new chemotherapy agents have brought about a decrease in the toxicity of neoadjuvant treatment, and have increased pathology downstaging rate, so it is now accepted that neoadjuvant treatment with subsequent surgery is the treatment of choice for rectal cancer in stages II-III.

The aim of the study was to evaluate the efficacy of preoperative CRT in the treatment of rectal cancer in terms of pathology downstaging rate, local recurrence, survival, and the possibility of radical surgery with sphincter preservation since the implantation of a multidisciplinary group for colorectal cancer in our hospital.

MATERIAL AND METHODS

Since January 2000 to December 2005 104 patients with a diagnosis of rectal adenocarcinoma surgically treated after neoadjuvant treatment with CRT were evaluated prospectively.

We excluded 14 patients due to the presence of metastatic disease or irresectable tumor at the moment of the preoperative diagnosis, so the study finally included 90 patients.

All patients were discussed in a meeting session by the MDT, who coordinated diagnostic and therapeutic interventions in all cases. This group is formed by surgeons, oncologists, pathologists, medical and radiation radiologists, and gastroenterologists.

Preoperative evaluation of a patient with rectal cancer

Basic preoperative workup

In addition to history taking and a complete physical examination (digital rectal examination included) all patients underwent chest X-rays (to exclude pulmonary metastases), an electrocardiogram, and a blood test including carcinoembryonic antigen levels (CEA).

Colonoscopy

A complete colonoscopy should be performed before surgical resection as it not only allows tumor visualization but also biopsy sample collection for a histological study of the tumor. In cases in which a complete colonoscopy could not be performed, in obstructive tumors or in patients with poor tolerance to the test, we performed a barium enema to exclude the presence of a colonic synchronic lesion (5% of the cases)(10).

Endorectal ultrasound (ERUS)

All patients underwent ERUS by the authors and were preoperatively studied (uTuN) in relation to depth of invasion and presence or absence of mesorectal lymph-node metastasis.

A 360º, 10-Mhz transducer was used. Rectal cancer appears like a hypoechoic image originating in the mucosa and extending through the rectal wall into perirectal fat. Based on the TNM classification, a uT1 lesion denotes a tumor confined to the mucosa and submucosa, a uT2 lesion implies the penetration of the muscularis propia but confinement to the rectal wall, a uT3 lesion indicates invasion into perirectal fat, and uT4 denotes adjacent organ spread. In our experience this test has an accuracy for T staging of about 80%, and of 60% in predicting lymph-node metastases.

Abdominopelvic CT scan

We systematically performed a CT scan to all patients not only to exclude the presence of liver metastases, but also to determine the relation of the tumor to adjacent pelvic structures.

Neoadjuvant treatment

In relation to the management of rectal cancer in our hospital, neoadjuvant treatment is used in patients with stage T3-4 or N1, or in cases of big, circumferential or fixed tumors during digital rectal examination. We used long-term preoperative radiotherapy (45 Gy in 180 cGy/day for 5 weeks) combined with chemotherapy (2 courses of 5-fluorouracil and leucovorin).

Surgical treatment

Surgery was at 4-6 weeks after RT. Surgical treatment consisted basically of low anterior or abdominoperineal resection, leading to rectum dissection following the plane between the endopelvic and visceral fascia of the rectum.

A statistical analysis was carried out using SPSS (14.0 version); qualitative variables were analyzed with the Chi-square test, and the Kaplan Meyer test was used for survival. A result is considered to be statistically meaningful when $p < 0.05$.

RESULTS

Of the 90 patients included in the study, 60 were men and 30 women, with a mean age of 65.04 years (range 21-83 years).

The tumor was found in the superior third (11-15 cm) in 12 cases, in the middle third (6-10 cm) in 44, and in the inferior third (0-5 cm) in 34.

The histological characteristics of tumors are described in table I.

Table I. Histological tumor characteristics

	Number of patients
Dukes' classification	
A	18
B	44
C (N positive)	19
Grade of differentiation	
High	73
Moderate	5
Poor	1
Number of nodes in the surgical specimen	596 (6.62 nodes for patients)
Number of positive nodes in the surgical specimen	49
Mucinous component	
Yes > 50%	11
Yes < 50%	3
No	66
Lymphatic, venous and perineural infiltration	21 (23.3%)

The rate of complications associated with neoadjuvant treatment was 54.4% (49 cases). Most frequent side effects included gastrointestinal (43 cases), skin (8 cases), neurologic (4 cases), genitourinary (4 cases), and hematological (3 cases) conditions. However, this toxicity was tolerated in most cases. Only two cases (2.2%) were severe, and led to chemotherapy discontinuation.

One patient had a convulsive status secondary to cerebral thrombosis, and another patient had a pulmonary embolism with thrombosis in the catheter.

Surgery was low anterior resection (LAR) for 45 patients (50%) and abdominoperineal amputation (APR) for 38 patients (42.2%).

Other procedures included: temporary proximal diverting colostomy in 2 patients (after this initial surgery and after receiving CRT with disease regression, we performed a second intervention to completely remove the tumor, in one case with a posterior pelvic exanteration and in another case by a APR), posterior pelvic exanteration (1), Hartmann's procedure (1), left hemicolectomy (1), proctectomy (1), and proctocolectomy (1). All interventions were performed using an open approach. There was no laparoscopic procedure.

Mean operating time was 193.68 minutes (80-340 minutes), and mean postoperative hospital stay was 19.51 days (4-127 days).

Among all 48 patients undergoing resection and colic anastomosis we performed ileostomy for 31 cases (64.6%). All cases were again operated to reconstruct intestinal transit.

The rate of postoperative complications was 52.2% (47 in 90 patients), with anastomotic leakage (8.3%; 4 of 48 patients), perineal wound complications (34.2%; 13 of 38 patients), and urinary complications (12.2%; 11 of 90: urinary infections areflexic bladder, obstructive uropathy, incontinence, erectile disfunction, fistula…) being most relevant.

The rate of postoperative mortality was 0%. Six patients (6.6%) were reoperated during their stay in hospital.

Fifty five patients (61.1%) received adjuvant treatment after surgery, this being chemotherapy in 47 cases, chemo- and radiotherapy in 5 cases, and isolated radiotherapy in 1 case.

The histological analysis of specimens showed a complete pathological response (absence of tumor in the specimen, pT0N0M0) in 10 cases (11.1%), and a partial response (downstaging of T) in 32 cases (35.6%), so the overall response rate to neoadjuvant treatment was 46.6% (Table II).

Table II. Anatomopathological analysis ot resected pieces

	T0	*T1*	*T2*	*T3*	*T4*	*Total*
Preoperative staging	0	1	6	80	3	90
Postoperative staging	10	6	28	43	3	90

We noticed no circumferential margin involvement in any of the patients, and margins were above 1 mm in all cases.

When analyzing for differences in response to neoadjuvant treatment, we observes no statistical differences in any of the parameters analyzed, but noticed a higher absolute survival rate for patients with a complete pathological response versus patients with a partial response o no response to treatment ($p = 0.82$) (Fig. 1).

During postoperative follow-up (mean 33.4 months. Range 12-82 months), 4 local recurrences (4.4%) and 20 systemic metastases (22.2%) were detected. Of all 4 patients with local recurrence, only one case (25%) could be reoperated (perineal recurrence after APR).

There were only two parameters with statistical differences in survival: venous, lymphatic and perineural infiltration was associated with higher recurrence rates versus no infiltration (43% *vs*. 22% p: 0.031), and patients with positive nodes in the specimen had a greater percentage of recurrences when compared to patients with negative nodes after neoadjuvant treatment (N+:36.8% *vs*. N-: 0% p: 0.022).

Overall and disease-free survival at 5 years was 80% and 64%, respectively, with mean overall survival being 33.4 months (range 4-82 months) and mean disease-free survival being 27.8 months (range 1-80 months) (Figs. 2 and 3).

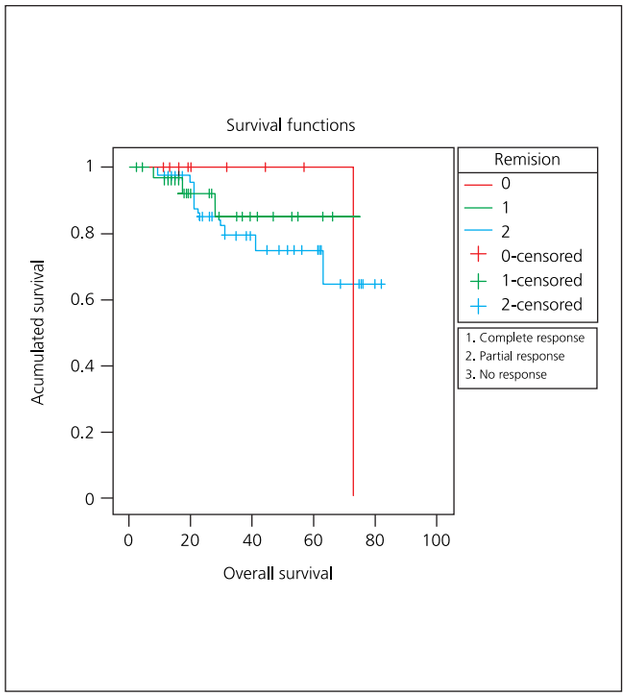

Fig. 1. Relation between survival and treatments response.

When we analyzed whether there were any differences in survival in relation to the different parameters, the only factor with statistical significance was recurrence, with survival being higher in patients with no recurrence (p = 0.0018) (Fig. 4).

Despite neoadjuvant treatment administration in patients with tumors in the lower rectum, an APR was performed for 73.5% of cases (Table III).

DISCUSSION

Despite the fact that surgery continues being the treatment of choice for rectal cancer(1), the management of this disease should be performed by a multidisciplinary team (MDT), with contributions by surgeons, oncologists, pathologists, medical and radiation radiologists, and gastroenterologists (2,3).

Although there is no evidence to support the key role of MDT in improving treatment outcomes and to reduce cost-effectiveness, it is difficult to understand how quality of care could be improved otherwise, since so many different specialists are involved in cancer care(3).

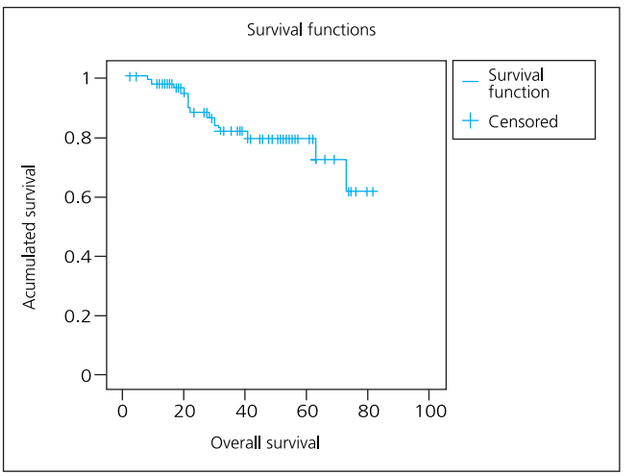

Fig. 2. Overall survival.

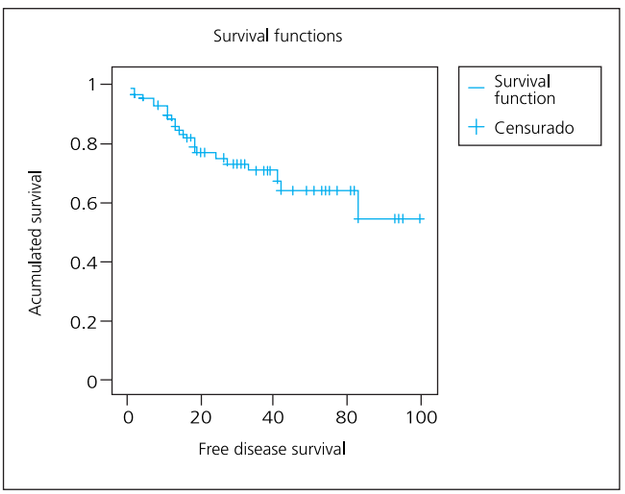

Fig. 3. Free disease survival.

Moreover, all our patients were discussed individually in conference by the MDT, which coordinated diagnostic and therapeutical interventions in all cases according to the protocol for the management of rectal cancer in our hospital.

Preoperative rectal cancer staging still is controversial. The problem is avoiding patient understaging because this results in disease undertreatment. In definitive, to avoid this problem we tend to overstage and overtreat patients. The objective of staging is identifying patients who may benefit from combined treatment, excluding those in whom benefits do not outweigh adverse effects (1).

Our group supports the use of endorectal ultrasound (ERUS) in the preoperative staging of all patients because, while less useful in predicting lymph node metastases, with an accuracy of 60-80%, it is very useful in the diag-

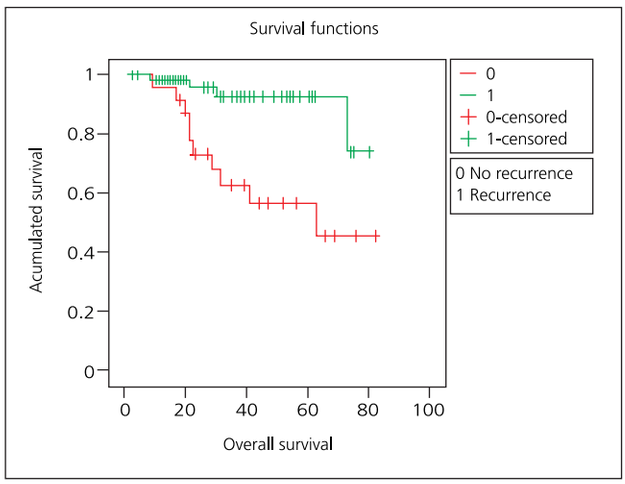

Fig. 4. Relationship between survival and recurrence.

Table III. Relationship between neoadjuvant treatment and sphincter preservation surgery

	RAB	*AAP*	*Otras*
Sup rectum (11-15 cm)	10	1	1
Med rectum (6-10 cm)	28	12	4
Inf Rectum (0-5 cm)	7 (20.58%)	25 (73.53%)	2

nosis of tumor invasion depth in the rectal wall (with an accuracy of 80-90%) (11,12).

While ERUS has proven superior to CT in the preoperative diagnosis of rectal cancer because of a higher accuracy in the staging of T and N, CT has shown its utility for local advanced tumors, and to evaluate the liver, so we consider it a good complementary test in the preoperative staging of patients.

We had no magnetic resonance imaging (MRI) available to preoperatively assess these patients.

Different authors have claimed that MRI visualizes not only the intestinal wall but also the surrounding pelvic anatomy. The crucial advantage of MRI is not its bringing accuracy to T-staging but its precise evaluation of the topographic relationship of tumors and lymph nodes to the mesorectum and the mesorectal fascia, which may predict the relation of the tumor to a circumferential resection margin (CRM).

Some studies by Bisset et al. (13) and Brown et al. (14) showed a 92-95% weighted agreement between MRI and pathology assessment, and predicted circumferential resection margin involvement with 80-92% agreement, respectively (11,15). The authors who supported routine MRI claimed that the better identification of CRM may identify more precisely those patients where neoadjuvant treatment is going to be more clinically effective and less cost-effective versus digital rectal examination and ERUS (16).

Kim et al.(11) compared the accuracy and clinical usefulness of ERUS, CT, and MRI for preoperative staging, and observed that the accuracy of ERUS and MRI in the staging of depth of invasion was similar (around 81%) and superior to CT (65%), while the accuracy of all three in predicting lymph node metastases was poor in the three modalities (64, 57, and 63% to ERUS, CT and MRI).

If ERUS may be superior to CT and MRI in the evaluation of T, the other techniques were superior to ERUS mainly in locally advanced tumors. For this reason we consider ERUS, CT, and MRI as complementary rather than excluding techniques.

The controversy about the use of pre- or postoperative RT seems inclined in favor of the former technique, which not only has shown less recurrence and complication rates, but also a higher rate of survival and response to treatment (17-19). However, the use of short- or long-term RT, or its combination with chemotherapy remains controversial (8,20).

In our experience, the use of long-term preoperative CRT does not result in a high rate of complications, and has not increased morbidity or mortality from surgery.

As I have previously reported, most of these have been gastrointestinal (diarrhea, vomiting…) complications that subsided with symptomatic treatment. If we compare these complications with those found in other studies (7,8,21,22) we see a slightly superior rate in our series, but this may be related to long-term RT with 45 Gy for 5 weeks, as the other authors used short-term RT with 25 Gy for 1 week. In the latter studies most patients were operated on one week after RT, so adverse effects had no time to develop. Moreover, in our series only in 2.2% of patients had treatment to be interrupted due to major complications; hence, given the huge overall benefit that neoadjuvant treatment entails in our experience, we did not reduce its use.

Recently, Swedish and Dutch studies (23,24) have reported on the late side effects of short-course preoperative RT, suggesting that irradiated patients report increased rates of intestinal dysfunction (incontinence, anal blood and mucus, pad wearing), but their quality of life is good and without significant differences as compared to the non-radiated group. The conclusion was that although preoperative short-term radiotherapy for rectal cancer resulted in increased local control, potential late complications may lead to establish patient selection strategies RT in the future, e.g., patients at high risk for local recurrence. The shorter follow-up in our patients allowed no late complications to be assessed.

In relation to recurrence after curative surgery, after a follow-up period of 33.4 months, we obtained a low rate of pelvic recurrence (4.4%). Because approximately 80% of recurrences happened within 24 months, we deem our results very real. These results are very good when compared to other studies in the literature, of 3-30% (8,20, 25). This point has likely been influenced not only by the effects of RT but also the better specialization of the surgical team. An analysis of the different factors has basi-

cally found an increased rate of recurrence in patients with venous, lymphatic and perineural infiltration, and in patients with positive nodes in the specimen (Dukes C).

Regarding the response to neoadjuvant treatment, it is known that after receiving long-term RT a downstaging/disappearance of the tumor may occur, with complete pathological response being around 5-50%. In our series, overall response to neoadjuvant treatment is around 47%, with a complete pathological response rate of 11%, which is similar to the literature (2,26-33); however, we have found this rate increased versus the results obtained in our hospital between the years 1995 and 2002 (4.7%). This could be not only due to higher experience but also improved radiotherapy equipments and facilities as implemented during the last few years, and the use of new chemotherapy agents. If we compare our results with those of other authors (26-33) we see that some of them report better response rates after neoadjuvant treatment. However, this may be due to different ways of analyzing response to neoadjuvant treatment. In our series, we have exclusively considered a response to treatment when a downstaging of the T parameter occurred after that treatment. In this way, it is possible that even if a tumor decreased in volume after treatment, the presence of tumor cells in the perirectal fat led us to consider it a failure.

The rates of overall and disease-free survival at 5 years, around 80% and 64%, respectively, are very interesting when compared to other groups (5,8,9,20).

The only factor that influenced survival, as expected, was the presence of recurrence, for this is the most frequent cause of mortality in these patients. We found no differences in survival according to sex, tumor location, preoperative Dukes' stage, histological characteristics, type of operation, and response after neoadjuvant treatment.

Finally, the possibility of sphincter preservation in the surgical treatment of rectal cancer after neoadjuvant treatment is also controversial, with differing results in the literature. The rate of sphincter preservation is 23-89%, with a mean of 63% (33-35). Even though the design and aim of the study was not to solve this problem (because the indication of APR or the preserving sphincters procedure was performed prior to the administration of neoadjuvant treatment and was not modified by response), based on our results we think that neoadjuvant treatment is not going to increase the rate of sphincter preservation, as APR was performed in our series for 73.5% of lower rectal cancers. In our experience, the rate of sphincter preservation is therefore 58%. However, we think that the decision to perform a sphincter preservation technique is not based on surgical team experience or neoadjuvant treatment effects, but patient characteristics. Many patients had problems of continence before surgery; if we perform an ultra low rectal resection with sphincter preservation we will probably cure the disease at the expense of severely impairing quality of life. For this reason we think that this procedure should not be used systematically in all patients, and indication must depend on other factors.

One of the critics of the study is that, if we want to get more conclusive results with a greater statistical significance, we have to include more patients with a longer follow-up. However, despite these two factors, we think that our results are similar to other described in the literature. In the future we should improve preoperative staging tests to avoid overstaging, and therefore overtreatment, and to advance in the molecular study of tumors with the objective of selecting those patients in whom the benefit of treatment will outweigh adverse effects (1). It would be also interesting to know the long-term results obtained by a Brazilian group (2), as these could revolutionize the therapeutic management of rectal cancer.

Finally, and to conclude, neoadjuvant treatment with CRT provides low rates of pelvic recurrence with good survival rates in our experience, and entails no additional morbidity or mortality.

The rate of complete pathological responses after neoadjuvance is similar to that described in the literature, and in our experience in low rectal cancers neoadjuvance does not improve sphincter preservation rates.

A systematic evaluation by a MDT in the context of a clinical protocol offers the patient better cure rates.

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