Evaluation of the Response Rate to Neoadjuvant Chemoradiotherapy in Patients with Rectal Adenocarcinoma: A Retrospective Long-term Study in Two Terciary Reference Centers

Juliana Lima Toledo Rossoni[1] Marley Ribeiro Feitosa[2] Caio Vinícius Souza Tosetti[3] Omar Feres[4] José Joaquim Ribeiro da Rocha[2]

[1] Department of Surgery & Anatomy, University of São Paulo, Hospital das Clínicas, Faculty of Medicine of Ribeirão Preto, Ribeirão Preto, São Paulo, SP, Brazil
[2] Department of Surgery & Anatomy, Division of Coloproctology, University of São Paulo, Faculty of Medicine of Ribeirão Preto, São Paulo, SP, Brazil
[3] Department of Surgery & Anatomy, University of São Paulo, Hospital das Clínicas, Faculty of Medicine of Ribeirão Preto, São Paulo, SP, Brazil
[4] Department of Surgery & Anatomy, Division of Coloproctology, University of São Paulo, Hospital das Clínicas, Faculty of Medicine in Ribeirão Preto, São Paulo, SP, Brazil

Address for correspondence Juliana Lima Toledo Rossoni, MD, University of São Paulo, Hospital das Clínicas, Faculty of Medicine in Ribeirão Preto, Ribeirão Preto, São Paulo, Brazil (e-mail: julianalimatoledo@gmail.com).

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Abstract

Objectives To evaluate the complete response (CR) rate and surgeries performed in patients with rectal adenocarcinoma who underwent neoadjuvant therapy (NT) at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo and at Hospital São Paulo, in Ribeirão Preto, from January 2007 to December 2017.

Methods We evaluated 166 medical records of patients with locally advanced rectal adenocarcinoma (T3, T4 or N+) who underwent NT. The regimen consisted of performing conventional (2D) or conformational (three-dimensional-3D/ radiotherapy with modulated intensity – IMRT) at a dose of 45-50.4Gy associated with capecitabine 1650mg/m^2 or 5-fluorouracil (5FU) and leucovorin (LV). The following variables were analyzed: gender, age, pretreatment stage, radiotherapy, CR index, local and distant recurrence rates. Surgical treatment and complications were also evaluated.

Results The CR index was 28.3%. Patients treated with 3D/IMRT radiotherapy had a higher rate of CR (36.3% x 4.8%; $p < 0.001$), higher rates of clinical follow-up (21% x 0%; $p < 0.001$), lower surgery rates (79% x 100%; $p < 0.001$), higher rates of transanal resection (37.1% x 9.5%; $p = 0.001$), lower rates of abdominal rectosigmoidectomy (25.8% x 50%; $p = 0.007$) and lower rates of abdominoperineal resection of the rectum (16.1% x 40.5%; $p = 0.002$), when compared to patients treated with 2D radiotherapy.

Keywords
- rectal cancer
- neoadjuvant therapy
- radiotherapy

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Conclusion Modern radiotherapy techniques such as 3D conformal and IMRT, by offering greater adequacy and precision of treatment, could result in better local control and less toxicity in organs at risk, enabling organ preservation strategies and less invasive approaches in selected cases.

Introduction

Colorectal cancer (CRC) is the second most common neoplasm among men and women in Brazil, excluding non-melanoma skin tumors, being responsible for high morbidity and mortality rates. According to the *Instituto Nacional do Câncer* it is estimated, for each year of the 2023-2025 period, 45,630 cases of colon and rectal cancer in Brazil.[1]

During the last decades we have observed a considerable change of concepts in the treatment of rectal cancer (RC), resulting from the increasing adoption of the multidisciplinary approach. In the 1980s, the surgical treatment of RC underwent a real revolution with the standardization of total mesorectal excision (TME) advocated by Heald et al. The proposed resection involved en bloc removal not only of the rectum, but also of the mesorectal fat, containing the lymphovascular structures, all enveloped by the mesorectal fascia. With the systematization of this technique, it was possible to drastically reduce the rate of local recurrence of CR by removing possible tumor foci disseminated along the mesorectum.[2]

After the standardization of the TME surgical technique proposed by Heald, another important improvement in the locoregional control of CR was the introduction of NT.[3]

NT consists of performing preoperative chemoradiotherapy in patients with locally advanced low and medium rectal tumors. Its use was able to further reduce the local recurrence rate when compared with postoperative radiotherapy, which has been demonstrated by several prospective randomized clinical studies.[4]

Preoperative chemoradiotherapy is capable of reducing local recurrence rates, reducing the dimensions of the primary lesion, increasing the distance from the tumor to the mesorectal fascia, increasing the sphincter preservation rate and, in some cases, even allowing organ preservation, although it has not demonstrated a significant impact on the overall survival of patients.[5] NT followed by TME is considered the standard treatment of locally advanced rectal adenocarcinoma (T3, T4 or N+).[6]

Conventional or 2D external radiotherapy was the first modality of external radiotherapy used for the treatment of CR. It uses bone anatomy through radiographs as a method of simulation and treatment planning. This modality or radiotherapy is less precise than the most modern techniques, and because of it, the radiation dose directed to the target area is limited due to the high toxicity in relation to neighboring tissues.[7]

Three-dimensional (3D) conformational radiotherapy uses images acquired by tomography, magnetic resonance or positron emission tomography that are transferred to the planning computer to create a three-dimensional image of the tumor, allowing multiple beams of radiation to be conformed to the contour of the target area of treatment, with established safety margins. This technology provides good control during treatment and guarantees patients adequate doses of radiation to the tumor, with less exposure of surrounding healthy tissues.[7] Intensity modulated radiotherapy (IMRT) is another highly precise conformational external radiotherapy modality that allows, in a very efficient way, the administration of high doses of radiation in the target volume, minimizing the dose in the adjacent normal tissues. The radiation dose is designed to reach the tumor three-dimensionally by modulating the intensity of the segments of each radiation beam, thus enabling an increase in treatment accuracy.[8]

With the improvement of preoperative chemoradiotherapy techniques, a progressive improvement in results has been observed over the years, with a consistent rate of pathological complete response (PCR) between 15-35% being achieved.[9]

As a result of the considerable rates of PCR, observed in several studies, some centers began to question the possibly unnecessary exposure to surgical procedures with a great impact on the quality of life of patients, especially Habr-Gama et al., who suggest the validity of a non-operative treatment in selected cases of apparent complete clinical response (CCR) – absence of a clinically, endoscopically, and radiologically identifiable tumor on NT.[10]

National data available in the literature on oncological outcomes of patients undergoing NT are limited, which motivated the present study.

Methods

We performed a retrospective study through the analysis of physical and electronic medical records of patients with locally advanced rectal adenocarcinoma (cT3-4 or cN+) who underwent NT, from January 2007 to December 2017, with the approval of the Ethics Committee from *Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto-Universidade de São Paulo*.

We selected 393 medical records. Of these, 227 records were excluded, as follows: 46 with incomplete or inconsistent data; 90 patients with misdiagnosis; 74 patients with metastatic disease and 17 patients under palliative care, as shown in **figure 1**.

After diagnosis, all patients underwent full colonoscopy to exclude synchronous tumours, chest, abdomen and pelvis tomography or pelvis magnetic resonance and carcinoembryonic antigen (CEA) serum level.

Patients were treated with preoperative chemoradiotherapy that was performed with 25-28 radiotherapy sessions of

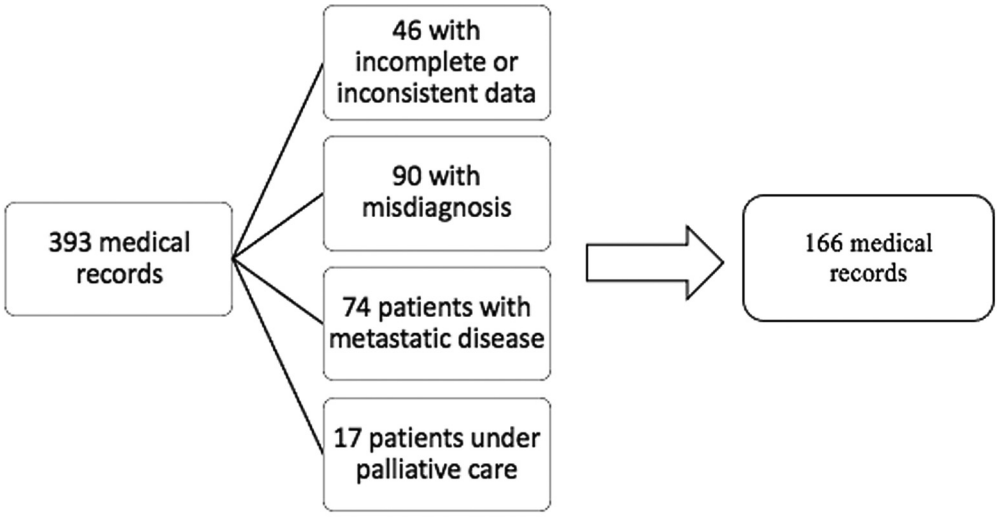

Fig. 1 Patient selection

180cGy each, totaling 45 or 50.4 Gy and concurrent fluoropyrimidine-based chemotherapy (capecitabine or infusional fluorouracil and leucovorin), for 5 weeks.

After 8-16 weeks interval after the end of NT, all the patients underwent physical evaluation with digital rectal examination, rectoscopy, magnetic resonance imaging or tomography of the pelvis and CEA serum level.

We classified the NT response as complete response (CR), which corresponds the patients with clinical complete response (CCR) and pathological complete response (PCR), incomplete response and no response. Patients with CCR are those who did not have evidence of active neoplastic disease after NT. Patients with PCR are those who underwent surgical treatment, either by local resection or with TME and no viable tumor cells were identified in the surgical specimen. Patients with incomplete response are those who had a partial response to neoadjuvant therapy, underwent surgical treatment and had tumor downstaging and/or downsizing, that was shown in parietal invasion degree reduction, lymph node involvement or tumor size. Patients with no response to NT are those who had disease progression, or no change was identified after treatment.

The following variables were analyzed: sex, age, pretreatment and posttreatment clinical stage, radiotherapy technique used during treatment, NT response, type of surgery performed after treatment (when performed), perioperative complications, need for intestinal stomas, local and/or distant recurrence, mortality.

Statistical analysis was performed using the IBM® SPSS® Statistics 20 program (IBM SPSS, Costa Mesa, CA). Categorical variables were expressed as frequencies/percentages and continuous variables as means ± standard deviations, when appropriate. The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. The ANOVA test was used to compare continuous variables. Categorical variables were submitted to univariate analysis using Fisher's exact test or $\chi 2$. Variables with a positive association were submitted to logistic regression using the Wald backward method to identify risk factors for response to radiotherapy (complete, partial, or absent). A significance level of 5% was established as a statistical limit for the entire analysis. The patients selected in this period totaled 312. The sample calculation, the selection of 166 cases, gave us an analysis with a confidence level of 95% and a margin of error of 5.12%.

Results

In total, 166 patients were included in the study. Most were male n = 104 (62.7%), with a mean age of 59.2 ± 12.5 years. The lower rectum was the most frequent tumor site (n = 106, 63.9%) followed by the middle rectum (n = 60; 36.1%).

The main chemotherapy regimens were isolated capecitabine (n = 120; 72.3%), 5FU + LV (n = 36; 21.7%) and isolated 5FU (n = 10; 6.0%). Regarding radiotherapy, the conformacional techniques (3D/IMRT) was most used (n = 124; 74.7%), followed by conventional or 2D technique (n = 42; 25.3%).

Regarding the clinical stage at diagnosis, stage 3 was the most common (n = 102; 61.4%), followed by stage 2 (n = 47; 28.3%) and 1 (n = 17; 10.2%). Still regarding the TNM classification at diagnosis, the degree of T3 tumor invasion (n = 109; 65.7%) and N1 lymph node involvement (n = 68; 41.0%) were the most frequently diagnosed.

Overall, after NT, most patients had a partial response (n = 79; 47.6%). The CR rate was 28.3% (n = 47). In 40 cases (24.1%), there was no response to NT.

The CR rate was higher in patients undergoing 3D/IMRT radiotherapy compared to those undergoing 2D (36.3% x 4.8%; $p < 0.001$) and in those who used capecitabine in chemotherapy (34.2% x 13.0%, $p = 0.007$) (►**Figure 2**). Both variables were submitted to logistic regression and radiotherapy with the 3D/IMRT technique was the only independent predictor of complete response to NT (36.3% x 4.8%; $p = 0.001$; OR: 11.3; 95%CI %: 2.6-49.3).

The non-response rate was higher in patients submitted to the 2D radiotherapy technique, compared to those submitted to 3D/IMRT (47.6% x 16.1%; $p < 0.001$) and in those who used QT with 5FU ± LV (39 .1% x 18.3%, $p = 0.007$).Both

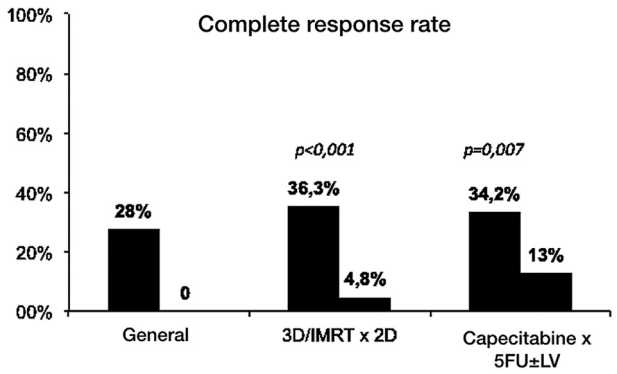

Fig. 2 Complete response rate (overall and according to the type of radiotherapy technique and chemotherapy used).

variables underwent logistic regression and radiotherapy with the 2D regimen, which was the only independent predictor of non-response to NT (47.6% x 16.1%; $p < 0.001$; OR: 4.7; 95%CI %: 2.1-10.2).

A decrease in the percentage of T3 (from 65.7% to 34.3%) and T4 (from 17.5% to 2.4%) tumors was observed after NT. There was a decrease in the degree of lymph node invasion N1 (from 41.0% to 16.9%) and N2 (from 20.4% to 6.0%). In general, NT promoted a reduction in the percentage of tumors with stage E2 (from 28.3% to 20.5%) and E3 (from 61.4% to 22.9%).

After NT, 140 (84.3%) patients were referred for surgery and 26 (15.7%) for clinical follow-up, according to the organizational chart shown in ►**Figure 3**.

When compared to the conventional group, patients submitted to the 3D/IMRT radiotherapy technique had higher rates of clinical follow-up (21% x 0%; $p < 0.001$), lower rates of surgery (79% x 100%; $p < 0.001$), higher rates of transanal resection (37.1% x 9.5%; $p = 0.001$), lower rates of abdominal rectosigmoidectomy (25.8% x 50%; $p = 0.007$) and lower rates of abdominoperineal rectum amputation (16, 1% x 40.5%; $p = 0.002$) (►**Table 1**).

Of the patients undergoing surgical treatment, the rate of intestinal stoma was 62.1% ($n = 87$). Patients submitted to transanal resection had lower rates of intestinal stoma (10% x 91.1%, $p < 0.001$) when compared to surgeries with TME.

Table 1 Post-neoadjuvant treatment according to radiotherapy technique

Treatment	2D n (%)	3D/IMRT n (%)	P*
Watch and wait	0	26 (21,0%)	<0,001
Surgery	42 (100%)	98 (79,0%)	<0,001
TR	4 (9,5%)	46 (37,1%)	0,001
ARS	21 (50,0%)	32 (25,8%)	0,007
APR	17 (40,5%)	20 (16,1%)	0,002

*p-value calculated by Fisher's exact test. 2D, conventional radiotherapy. 3D/IRMT, three-dimensional intensity-modulated radiotherapy.

The median OS of patients was 109 months (1-208 months). The overall rate of cancer recurrence in the follow-up period was 28.9% (48 patients). Distant recurrence occurred in 25 (52.1%) patients and local recurrence in 15 (31.3%) cases. In 8 (16.5%) patients, both local and distant recurrence were diagnosed. The recurrence rate was higher in patients undergoing abdominoperineal resection (43.2% x 24.8%; $p = 0.039$) and in those with lymph node involvement (52.6% x 21.9%; $p < 0.001$). The overall mortality rate was 16.3% (27 patients). Deaths occurred mostly due to disease progression ($n = 15$; 55.6%), followed by non-oncological causes ($n = 11$; 40.7%) and 1 (3.4%) due to surgical complications.

Discussion

Regarding the response to NT, we observed a CR rate of 28.3%, a result compatible with the interval described in the literature. In a systematic review and meta-analysis, Min Chen et al. (2019) evaluated 13 randomized controlled trials totaling 3772 patients and compared different chemotherapy regimens within NT for the treatment of locally advanced CR. Chemotherapy regimens varied between 5-FU, LV,

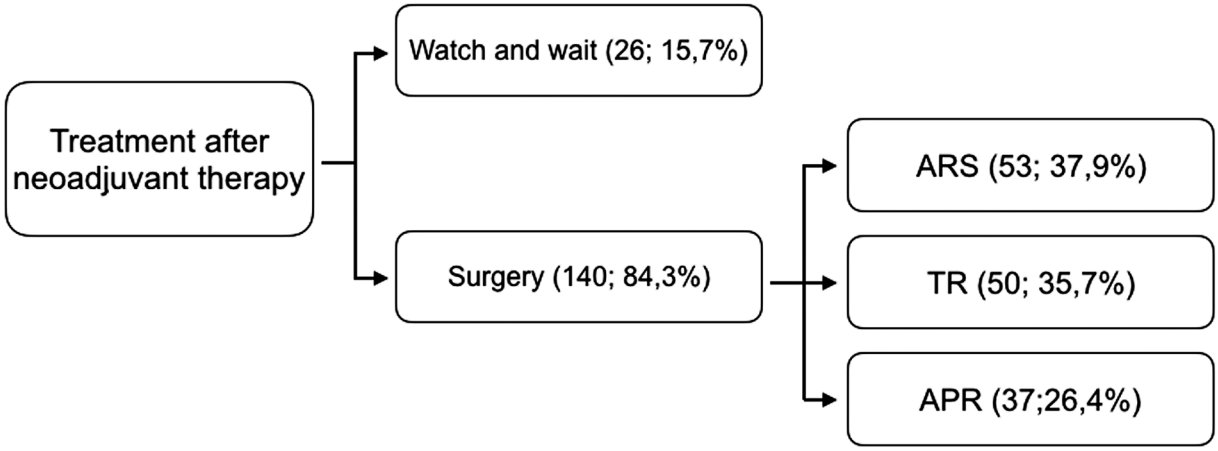

Fig. 3 Organogram of treatment after neoadjuvant chemoradiotherapy. TR, transanal resection. ARS, abdominal rectosigmoidectomy. APR, abdominoperineal resection.

oxaliplatin and capecitabine, irinotecan, in combinations and/or alone. Radiotherapy doses varied between 45-50Gy. The PCR rate ranged from 13.9-44%.[11]

In another review, Yi Li et al (2016) evaluated 6 randomized studies published between 2004 and 2009, which compared preoperative chemoradiotherapy with preoperative radiotherapy alone or postoperative chemoradiotherapy. The PCR rate in the groups that received preoperative chemoradiotherapy ranged from 14-16%.[12]

In a German study, Sauer et al. (2004) compared neoadjuvant versus adjuvant treatments in patients with high-risk rectal tumors (CE II and III). The regimen consisted of radiotherapy with 50.4Gy in 28 fractions directed at the tumor and pelvic lymph nodes, concomitantly with infusional 5-FU and LV for 5 consecutive days, with this protocol being performed in the first and fifth week of the radiotherapy period. All patients received adjuvant chemotherapy with 4 cycles of 5-FU at a dose of 500mg/m2 in a daily bolus for 5 days, repeated every 4 weeks. About 10.4% of patients achieved PCR with neoadjuvant therapy.[3]

Park et al (2011) in a randomized phase III study made the same comparison between neoadjuvant and adjuvant therapy with capecitabine-based chemotherapy and achieved a PCR index of 17%, with a higher rate of sphincter preservation in lower rectal tumors, in the group of neoadjuvance.[13]

In another cohort study published in 2016, Angelita Habr Gama et al. compared standard preoperative chemoradiotherapy with extended chemoradiotherapy or consolidation chemotherapy. 99 patients undergoing standard neoadjuvant chemoradiotherapy registered in a previous prospective study of the same group were compared with 12 patients undergoing preoperative chemoradiotherapy with extended or consolidation chemotherapy. The standard regimen consisted of performing 3D conformational radiotherapy at a total dose of 54Gy with 2 cycles of 5FU with LV, at the beginning and end of radiotherapy. The regimen with extended or consolidation chemotherapy consisted of performing 3D conformational radiotherapy at a total dose of 54Gy with 6 cycles of QT with 5FU (450mg/m2) and 50mg of LV on 3 consecutive days, 3 cycles during radiotherapy treatment and 3 cycles after. The CCR index of the group submitted to the standard regimen was 23% against 66% of the group submitted to the regimen with consolidation chemotherapy.[14]

In the present study, we observed a higher CR rate in patients who underwent radiotherapy with conformational techniques 3D/IMRT, when compared to those who underwent conventional 2D planning (36.3% x 4.8%; $p < 0.001$). The conformational techniques were the only independent predictor of complete response to NT, among the other variables analyzed. 2D radiotherapy uses radiographs of bony pelvic structures for treatment planning, which results in large-volume irradiation of normal tissue. The introduction of tomography-based treatment planning allowed the direct identification and delineation of relevant target volumes in 3D, enabling the delivery of highly accurate treatment plans. Modern conformational radiotherapy techniques, through this advance in imaging, provide high accuracy in the application of treatment, with less exposure of healthy tissues, maximizing therapeutic effects. In CR, this development provides for the individualization of treatment strategies, especially in terms of choice of radiotherapy dose.[15]

A retrospective cohort study conducted by Corner C et al (2011) compared preoperative chemoradiotherapy treatment plans with conventional 2D and conformational techniques for locally advanced RC. 50 consecutive patients undergoing chemoradiotherapy had dual planning using conventional 2D orthogonal and 3D conformational techniques. Patients underwent radiotherapy according to a total dose of 45 Gy divided into 25 daily fractions (1.8 Gy per day) with concomitant capecitabine 850 mg m2 twice daily on each day of radiotherapy. The same patients were then retrospectively planned conventionally. The planned target volume defined by conformational planning was not achieved by conventional planning in 58% of patients. The median planned target volume coverage was higher in the conformational design (99.2% versus 94.2% $p < 0.05$). Furthermore, conformational design resulted in a significantly lower median dose to the small intestine compared to conventional plans.[8]

Although few comparative data between conventional and conformational radiotherapy techniques is available in the literature, these findings suggest that conformational planning is superior to conventional simulation in planning locally advanced RC, in terms of better planned target volume coverage and reduction in mean organ volume surrounding areas at risk, which could reflect on the response to preoperative chemoradiotherapy, as observed in the present study with the finding of a higher CR index in patients undergoing treatment with conformational techniques.

In the present study, 15.7% of patients undergoing NT achieved CCR and were referred to clinical follow-up (watch and wait). When we evaluated the CCR index in patients who underwent conformational radiotherapy planning, this index reached 21%, results compatible with other centers that used the same dose of radiotherapy (45-50Gy).[16]

We also observed lower surgery rates (79% x 100%; $p < 0.001$), higher local resection rates (37.1% x 9.5%; $p = 0.001$), and lower rates of major surgeries such as abdominal rectosigmoidectomy (25.8% x 50%; $p = 0.007$) and abdominoperineal resection of the rectum (16.1% x 40.5%; $p = 0.002$) in the group submitted to the conformational radiotherapy regimen when compared to the 2D radiotherapy group. These findings demonstrate the radiotherapy importance in NT for CR treatment. Evidence is limited, but more modern radiotherapy techniques such as 3D conformal radiotherapy and IMRT, by offering greater adequacy and precision of treatment, could result in better local control and less toxicity in organs at risk, enabling organ preservation strategies in selected cases.

In the present study, 50 patients (35.7%) underwent local resection by transanal endoscopic technique using equipment called proctoscope or “Ribeiroscope”, developed at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo and shown in ►**Figure 4**. Less invasive therapeutic alternative than transabdominal surgeries, as effective as conventional transanal excisions, with a lower

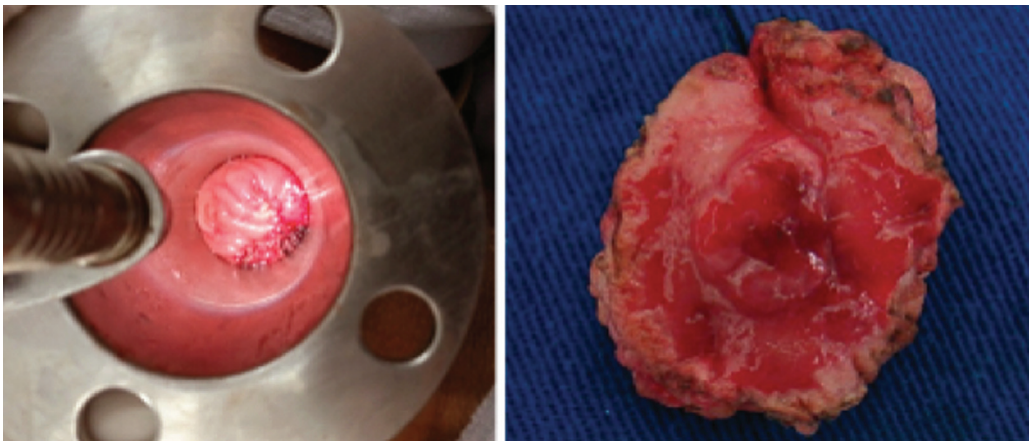

Fig. 4 Transanal resection using the "Riberoscope" and surgical specimen

risk of complications, with low-cost and easy-to-use surgical equipment.[17,18] Of these 50 patients who underwent local resection, 46 (92%) underwent conformational 3D/IMRT radiotherapy, suggesting that the use of modern radiotherapy techniques may reflect better local control, enabling less invasive resections after neoadjuvant therapy.

Conclusion

The CR rate to NT (28.3%) observed in the present study, was compatible with the range described in the literature for similar regimens of preoperative chemoradiotherapy. When we evaluated only patients undergoing radiotherapy with conformational techniques (3D/IMRT), this rate reached 36.3%, which is the only independent predictor of complete response to NT, among the other variables analyzed.

Transabdominal surgeries with TME are associated with significant morbidity and mortality rates. The lower rates of transabdominal surgeries, such as abdominal rectosigmoidectomy and abdominoperineal resection of the rectum, and higher rates of clinical follow-up (watch and wait) and local resection observed in the group which underwent conformational radiotherapy, when compared to the conventional radiotherapy group, demonstrate the radiotherapy importance in the NT for CR treatment.

Evidence is limited, however, modern radiotherapy techniques such as 3D conformal radiotherapy and IMRT, by offering greater adequacy and precision of treatment, could result in better local control and less toxicity in organs at risk, enabling organ preservation strategies and approaches less invasive in selected cases.

Conflict of Interest
None declared.

Acknowledgements
Not applicable

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