

Transanal endoscopic operation for rectal cancer after neoadjuvant therapy¹

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ABSTRACT

PURPOSE: In this paper we report the oncological outcomes from clinical series of patients with rectal cancer submitted to local excision after neoadjuvant therapy and discuss the indications for local excision in partial clinical responders.

METHODS: We analysed a prospective database of 39 patients submitted to a transanal endoscopic operation for rectal cancer after neoadjuvant chemoradiation between 2006 and 2015, comparing clinical and pathological variables, perioperative complications, recurrence rate and overall survival.

RESULTS: We obtained 15.4% ypT0, 17.9% ypT1, 35.9% ypT2 and 28.2% ypT3. After a median follow-up of 24 months, tumoral recurrence was observed in 4 patients, one of them with isolated pulmonary metastasis. R0 resection was achieved in 79.5%, and postoperative complications were observed in 30.2% patients and no perioperative mortality occur. Compromise surgical margins do not affect recurrence rate, and 94.9% of patients are alive nowadays.

CONCLUSION: Local excision could be associated with low recurrence rate and good overall survival. Short hospitalization time and low level of serious complications observed could be an interesting option for patients who would not tolerate a radical procedure or for those who declined a total mesorectal excision. A strict long-term follow-up must be warranted to detect early tumoral recurrence.

Key words: Rectal Neoplasms. Rectum. Neoadjuvant Therapy. Natural Orifice Endoscopic Surgery. Neoplasm Recurrence.-

Introduction

Worldwide, colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women, with more than 1 million cases yearly¹. In Brazil, almost 32600 new cases are expected in 2015².

Neoadjuvant Chemoradiation (NCR) followed by rectosigmoidectomy with total mesorectal excision (TME) is the cornerstone of rectal cancer treatment and significantly reduced local recurrence from 8.2% to 2.4% compared with surgery alone^{3,4}. However, a significant functional impact is associated with radical resection, like urinary retention or incontinence, sexual dysfunction and changes in bowel habit⁵. Moreover, no difference has been observed in overall survival⁶.

In some cases, local excision (LE) of early rectal adenocarcinomas has been performed to reduce morbimortality. The indications of LE are usually limited to patients with well-differentiated, small (< 4cm), T1 rectal adenocarcinomas that exhibit no lymphovascular and perineural invasion, located within 15 cm of the anal verge⁷. Nevertheless, patients with T2 and T3 lesions who are reluctant to undergo radical resection could benefit from LE⁸. In patients with elevated surgical risk, LE showed lower recurrence rates, fewer post-operative complications and less anorectal, urinary and sexual dysfunctions compared to conventional procedures^{9,10}.

Choosing the appropriate treatment requires weighing of some factors: overall survival optimization, local recurrence reduction and prevention of genitourinary and intestinal dysfunctions. Attention must be paid in the elderly patients, with higher operation risks¹¹, and in the economically active younger patients¹².

In the past 10 years, there has been a 21% increase in the number people older than 65 years old, with a consequent increase in the number of surgical procedures in the elderly^{13,14}. A significant portion of geriatric patients, show a complex and not completely understood syndrome of frailty. This vulnerability to a stressful event has been suggested as a risk predictor and is associated with substantial morbidity and mortality¹⁵⁻¹⁷.

There is limited information regarding LE after NCR in our country. The main objective of the present study is to present the oncological results from a group of patients with rectal cancer submitted to transanal endoscopic operation (TEO) after NCR.

Methods

Patient selection

A prospective database of patients submitted to TEO for rectal adenocarcinoma after neoadjuvant chemoradiation between 2006 and 2015 was analyzed after approval from the Institutional Review Board. The patients were selected according to the previously mentioned indications for local excision⁷. We also included patients with T1 lesions exhibiting lymphovascular invasion and those with T2 or T3 tumors who refused or could not tolerate radical surgery due to frailty. Patients submitted to palliative surgery were not considered candidates.

Treatment and follow-up

Surgical resection was carried out 8-12 weeks after the end of NCR. The same surgeon performed operations, with a previously described proctoscope¹⁸. Patients were positioned on the operation table according to the tumor location. Posterior tumors required a lithotomy position while anterior lesions required a prone jack-knife position. The resection was considered as R0 if surgical margins higher than 1 mm were achieved. Follow-up protocol included clinical examination every 3 months with serum CEA during the first 2 years and then annually. A control endoscopic procedure was performed 3 months after TEO, and then every year. Surveillance image exams (thoracic, abdominal and pelvic computed tomography) were repeated annually. Other exams (such as pelvic magnetic resonance imaging, positron emission tomography) were recommended based on the discretion of the treating physician. Patients who developed local recurrence were offered a salvage surgery. Those who refused any major procedure were submitted to a second TEO.

Analysis

Clinicopathological variables were obtained from medical records. Overall and disease-specific survival after TEO was the primary outcome of the study. Statistical analysis of all continuous variables was expressed as mean \pm *standard deviation* (SD). Categorical variables were compared with χ^2 tests. A $p < 0.05$ was considered significant. Survival curves were plotted using the Kaplan-Meier method.

Results

The study included 39 patients. Mean age was 65.5±14.4 years. The main characteristics of subjects are summarized in Table 1.

TABLE 1 - Main characteristics of subjects

| | |
|----------------------------------|------------|
| Sex | |
| Male | 27 (69.2%) |
| Female | 12 (30.8%) |
| Tumor size | |
| (mean ± SD) | 3.1±1.1 cm |
| Tumor distance* | |
| (mean ± SD) | 4.3±2.5 cm |
| Pathological analysis | |
| Adenocarcinoma | 30 (76.9%) |
| Poorly differentiated malignancy | 1 (2.6%) |
| No malignancy | 6 (15.4%) |
| Not evaluated | 2 (5.1%) |
| Staging^a | |
| ypT0 | 6 (15.4%) |
| ypT1 | 7 (17.9%) |
| ypT2 | 14 (35.9%) |
| ypT3 | 11 (28.2%) |
| Not evaluated | 1 (2.6%) |

* Distance from anal verge

^aPathological staging after neoadjuvant therapy

SD = standard deviation

The average duration of hospital stay was 2 days (1-6 days). Surgery data is summarized in Table 2.

TABLE 2 - Main characteristics of surgical procedures

| | |
|-------------------------------------|-------------------|
| Surgery duration (mean ± SD) | 67.2±27.6 minutes |
| Suture of rectal defect | |
| Manual | N=34 (87.2%) |
| Stapled | N=5 (12.8%) |
| Pattern of resection | |
| R0 | 31 (79.5%) |
| R1 | 7 (17.9%) |
| Not evaluated | 1 (2.6%) |
| Complications | |
| None | 27 (69.2%) |
| Rectal ulcer | 9 (23.1%) |
| Rectal stenosis | 2 (5.1%) |
| Rectal dehiscence | 1 (2.6%) |
| Urethral lesion | 1 (2.6%) |
| Fecal incontinence | 1 (2.6%) |

R0 = Free microscopic margins. R1 = Compromised microscopic margins

Mean follow-up of subjects was 24 months (1-110 months). Loss to follow-up rate was 38.5% (n=15). Observed

recurrence rate was 10.3% (n=4). Three subjects (75%) developed isolated local recurrence and one subject (25%) was diagnosed with distant metastasis (pulmonary). Patients with local recurrence were submitted to a new TEO in 2 cases (refused radical surgery) and abdominoperineal excision of the rectum in 1 case. The patient with pulmonary metastasis underwent pulmonary segmentectomy. No deaths were observed in the recurrence group. Twelve subjects (30.8%) underwent adjuvant chemotherapy. There was no perioperative mortality, and 5.1% mortality rate observed during follow-up were not cancer-specific. A survival analysis is illustrated in figure 1.

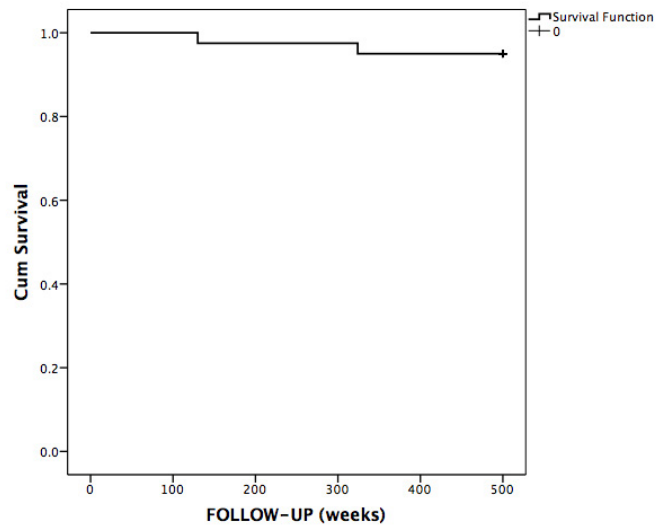


FIGURE 1 - Kaplan-Meier survival function

A univariate analysis was conducted, and no association was found between recurrence and compromised microscope surgical margins, staging, and presence of complications. Table 3 summarizes the univariate analysis results.

TABLE 3 - Univariate analysis for recurrence

| Variable | Recurrence N (%) | P* |
|------------------------------------|------------------|-------|
| Microscope margin | | |
| Free | 2 (9.5) | 0.253 |
| Compromised | 2 (28.6) | |
| Staging (ypT) | | |
| T0+T1 | 2 (15.4) | 1.0 |
| T2+T3 | 3 (11.5) | |
| Postoperative complications | | |
| Yes | 1 (7.7) | 1.0 |
| No | 4 (14.8) | |

*Fisher's exact test

ypT = Pathological T staging after neoadjuvant therapy

Discussion

TME is associated with significant morbidity (10-49%) and mortality (0-9%) rates¹⁹. Moreover, the possibility of permanent or temporary stomas is often associated with unfavorable aesthetic and functional results^{20,21}. The relevant morbimortality rates related to the procedure have led to an interest in less invasive procedures.

Tumors located 10 cm from the anal verge are usually amenable to TEO. Full-thickness excision of around mesorectal fat and clear margins are the goal of the procedure. Hemostasis and transverse closure of the resulting rectal defect are also important steps to avoid complications. A clear orientation of the margins is very important to pathological evaluation²². Postoperative pain is usually well managed with oral analgesics and non-steroidal anti-inflammatory drugs. Recovery and return to daily activities are fast²³. Postoperative complications include, rectal bleeding (6%), rectal stenosis (5.5%), urinary retention (1.5%), fecal incontinence (0.5%), and rectovaginal / rectourethral fistulas (<1%) .

TEO is characterized by less surgical stress, short hospital stay, and lower complications. It may be considered as an alternative in older and frail cancer patients²⁴. Younger and active patients concerned with higher complication rates of a radical resection may also be candidates as long as they understand and accept the risks of higher local recurrence.

The rate of R1 resection in the present study was 17.9%, and an elevated rate of tumor fragmentation and compromised tumor margins are related to a poorer surgical outcome in LE. However, compared LE and TEM, no difference in recurrence rates (21% vs. 33%) or overall survival (80% vs. 66%) was found²³.

Adjuvant chemotherapy could reduce the recurrence rates from 19-47% to 5-26%²⁵. For tumors treated by local excision following neoadjuvant therapy, a significant reduction in local recurrence rates from 12% to 4% was achieved²⁶. The high number of ypT2 and ypT3 operated tumors could explain the 10.3% recurrence rate observed in the present study. Higher recurrence rates in stage II and III patients have previously been observed^{27,28}. Both surgeon and patients should be aware this risk when contemplating any local excision procedure. Moreover, some authors have noted higher rates of unsalvageable recurrence after LE^{29,30}.

Conclusion

TEO was characterized by short hospitalization time and was performed with a low level of serious complications. LE

could be an option for patients who would not tolerate a radical procedure or for those who declined a low anterior resection or an abdominoperineal excision of the rectum. A strict long-term follow-up must be warranted in all cases since the procedure is related to a higher risk local recurrence.

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