

Prognostic factors after surgical treatment for locally recurrent distal rectal cancer

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ABSTRACT

Objectives. Local recurrence after distal rectal cancer surgery is a major complication with an increased morbidity and mortality. The therapeutic strategy consists in a complex association of radiochemotherapy with surgical approach that may improve prognosis and quality of life. It is necessary to identify the risk factors for local recurrence and to have a highly-selected patients for oncological radical treatment.

Materials and methods. The study included the analysis of 79 patients with middle and lower rectal cancer who were diagnosed and operated at Coltea Clinic Surgical Clinic Hospital, Bucharest, for a period of 4 years. Male patients were more frequent (64.4%). The average age was 65 years old. The surgical strategy included 33 patients (41.8%) who underwent abdominoperineal resection, 36 patients (45.6%) who underwent low anterior resection with stapled colorectal anastomosis and 10 patients (12.75) who underwent ultralow anterior resection.

Results. Local recurrence rate was 12.7%. The mean time from surgery until the time of discovery of local recurrence was 14.5 months. Local recurrence was associated with advanced tumor stages T3 (10.1%) and T4 (2.5%). It was also associated with histopathological features related to serous infiltration (100%) and tumor invasion of the radial margins (3.8%). The surgical treatment strategy consisted of abdominoperineal resection, permanent colostoma and R2 resections.

Discussion. The radical surgical resection is the most significant prognostic factor. There are a number of other patient-related factors and tumor-related factors that can significantly influence the evolution and overall survival. Periodic clinical, imaging scans and colonoscopy follow-ups are able to early detect the tumor recurrence and to allow a curative cancer treatment.

Conclusions. Local recurrence after mid and lower rectal cancer surgery is a major complication with direct impact on morbidity, mortality, prognosis and quality of life of these patients. The treatment strategy must be established by a multidisciplinary team in order to identify carefully-selected patients to undergo the optimal oncological therapy.

Keywords: rectal cancer, local recurrence, risk factors

INTRODUCTION

Locally recurrent rectal cancer is a major complication that occurs following primary resection of distal rectal cancer with increased morbidity and mortality rates. The prognosis and the quality of life of these patients are also

affected. According to some studies, 33% of patients with rectal cancer will develop locoregional recurrence (1).

Despite the technological advances in double stapling technique (DST) (2) and the surgical standard of the total mesorectal excision (TME), the incidence of the local recurrence after the

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initial treatment of the mid and low rectal cancer is still 4 to 33 percent (3-9). The presence of LR causes severely symptoms that are difficult to treat and have a negative outcome.

The basic principle in rectal cancer surgery is the “en-bloc” resection of the rectum surrounded by the intact mesorectum and perirectal fascia, following the embryological “Holy Plane” discovered by R. J. Heald in 1982 (3,10). He had introduced the concept of sharp-dissection in well lighted field, using optimal retractors to open the deep pelvis and following an avascular plane that will resect a cylindrical shape specimen containing the intact rectum and mesorectum. An oncological resection may be obtained either by abdominoperineal resection or by sphincter-sparing surgery (low and ultralow anterior resection with colorectal or coloanal anastomosis). The neoadjuvant radiochemotherapy may have a clinical response by tumor “downstaging” and allows the patients who benefit of preoperative chemoradiation to undergo anal sphincter preservation surgery with a major impact on the quality of life (11).

The association of the oncological radical resection and neoadjuvant therapy has greatly reduced the LR incidence allowing a better outcome and an improved long-term survival (5,6,11,12).

MATERIAL AND METHODS

The study includes a group of 79 patients with mid and lower rectal cancer surgically

treated at Department of General Surgery, Coltea Clinical Hospital, Bucharest. The patients were prospectively analysed for a period of 4 years. The patients with low and middle rectal cancers underwent sphincter-sparing surgery and abdominoperineal resections. The diagnosis was confirmed by pathological exams.

All patients were evaluated by digital rectal examination, a complete blood count, carcinoembryonic antigen (CEA) level, cancer antigen 19-9 (CA 19-9) level, chest X-ray, abdominal ultrasound, highly imaging scans like computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomino-pelvis.

Patient characteristics are shown in Table 1.

RESULTS

The local recurrence (LR) rate was 12.7% (10 patients). Anastomotic LR rate was higher (8.9%) than the pelvic wall LR rate (3.8%).

The median follow-up of all the patients in this study was 26.7 months. The recurrence-free interval from the initial treatment of the primary tumor to locoregional relapse was from 3 to 36 months (median 14.5 months).

Seven patients (8.9%) were male and three patients (3.8%) were female. The median age of the patients with LR was 61 years.

The average distance from anal verge of the tumor relapse was 4 cm (8 tumors developed at the distance of 1 to 5 cm from the anoperineal line). In case of 7 patients (8.9%), the LR occurred

TABLE 1. Patient demographics

Demographics		N (%)
Age	Median	65 years
Sex	Female	28 (35.4%)
	Male	51 (64.6%)
Location	Inferior	47 (59.5%)
	Middle	32 (40.5%)
TNM stage	T1	4 (5.1%)
	T2	26 (32.9%)
	T3	42 (53.2%)
	T4	7 (8.9%)
Preoperative	Radiotherapy	70 (88.6%)
	Chemotherapy	44 (55.7%)
Cancer biomarkers	CA 19-9	47 (59.2%)
	CEA	26 (32.9%)
Adenocarcinoma	Well-differentiated	47 (59.5%)
	Moderate-differentiated	28 (35.4%)
	Poor-differentiated	4 (5.1%)
Surgery	Abdominoperineal resection (APR)	33 (41.8%)
	Low anterior resection (LAR)	36 (45.6%)
	Ultralow anterior resection (ULAR)	10 (12.7%)

on the distal third of the rectum. For the other 3 patients (3.8%), the initial site was the middle third of the rectum.

According to the UICC clasification (13), the clinical TNM stages included 8 local recurrence (10.1%) in case of T3 stage tumors and 2 cases (2.5%) of local recurrence for T4 stage tumors ($p=0.058$). The LR rate is highly associated with locally agresive cancers. According to AJCC (American Joint Committee on Cancer) (14) tumor stage classification, 6 patients (7.6%) with LR occurred after stage T3N0M0 cancers, 1 case (1.3%) of LR occurred after stage T3N2M0 cancer, 2 cases (2.5%) of LR developed for T4N1M0 stage cancers and 1 case (1.3%) of LR occurred after stage T3N2M1 cancer. Nine patients (11.4%) have benefited of neoadjuvant radiotherapy and 6 patients (7.6%) have associated preoperative chemotherapy. Symptoms related to local recurrence were perianal region pain in 8 patients (10.1%), bowel disfunctions in all 10 patients and rectal bleeding in 5 patients (6.3%). The tumor markers CA 19-9 level increased in 8 cases (10.1%) and CEA level was higher than normal in 5 cases (6.3%).

Of these 10 patients, 7 patients (8.9 %) developed a local recurrence after sphincter-sparing surgery (5 patients following low rectal resection with stapled colorectal anastomosis and 2 patients following ultralow anterior resection) and 3 patients (3.8%) presented tumor relapse following abdominoperineal resection (Fig. 1).



FIGURE 1. Local recurrence after APR

The pathological exams revealed that 8 patients (10.1%) had well-differentiated adenocarcinoma and 2 patients (2.5%) had moderate-differentiated adenocarcinoma (Fig. 2). All 10 cases were associated with serous infiltration ($p=0.002$). Lymphovascular or perineural invasion was not encountered in any case. There were three (3.8%) cases with radial margins tumor invasion ($p=0.048$) which were associated with locally aggressive disease. The median number of the invaded lymph nodes was eight (minimum 0, maximum 10). The excised specimens had a median number of 12 lymph nodes removed.

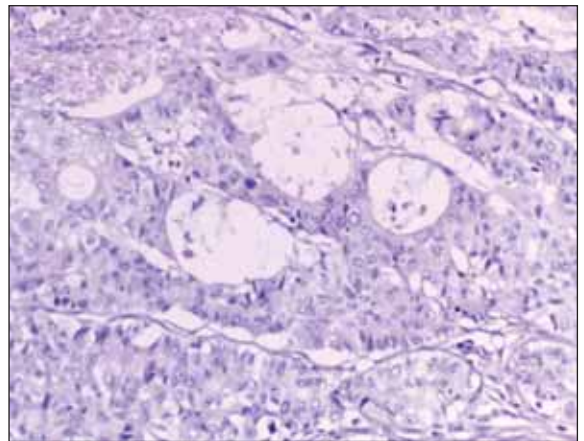


FIGURE 2. Moderate-differentiated adenocarcinoma, 20x, col HE

Nine of the 10 patients (11.4%) with LR followed postoperative chemotherapy and only one patient underwent radiotherapy for locally advanced tumor T4 stage.

Following the diagnosis of the local recurrence, the patients medical informations were reviewed by a multidisciplinary team (MDT) wich included a surgeon, a medical oncologist, a radiotherapy specialist, an imagist. The following treatment was decided based on the size of the relapsed tumor, the locoregional invasion, the comorbidities, the age of the patients. The goal of the MDT was to determine the most suitable tratment for each patient.

The surgical strategy for LR consisted in abdominoperineal resection in 3 cases (2 initial ULAR and 1 initial LAR), 1 permanent colostoma for 1 case with initial LAR, 3 R2 resections after initial APR and 2 cases underwent palliative treatment.

The patients with LR had a poor quality of life with multiple referrals to the hospital, with intensive need of adjuvant treatment for tumor relapse-related symptoms.

DISCUSSIONS

By definition, local recurrence (LR) is the tumor relapse that is identified by clinical evaluation (digital rectal examination or direct visualization) or paraclinical evaluation (flexible colonoscopy, rigid sigmoidoscopy, pelvic ultrasound, endorectal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET-CT), elevated carcinoembryonic antigen (CEA) level markers, cancer antigen 19-9 (CA 19-9) levels markers and it is confirmed by histopathological examination.

The most usual location for LR is at the anastomotic site (after rectal resection with colorectal or coloanal anastomosis) or at the pelvic wall site (the sacrum), with the invasion of local organs like genital organs, bladder, but also iliac vessels, iliac nerves and obturator fat, pelvic ureters, ischioanal fossa. LR can occur also in the loop colostomy site (after Hartmann resection) or the perineal wall (after abdominoperineal resection).

The local recurrence rate can be lowered by curative surgical treatment (3,4,6,15,16). Recurrences of distal rectal cancers are at the site of the anastomosis or on the pelvic walls. A local relapse in the lesser pelvis has the worst outcome. It can lead to major surgery, such as pelvic exenteration, with extended combined organ resection followed by permanent stoma. It increases the surgical and anesthesiological trauma, the risks and the complications leading to higher morbidity and mortality than after the initial surgery. The oncological clearance is difficult to obtain and in most cases is unlikely to reach R0 resection.

The therapeutic strategy consists in adjuvant chemoradiotherapy in order to achieve the downsizing of the tumor and to allow an R0 resection (12). The total mesorectal excision (TME) introduced by Heald is the gold-standard in rectal cancer surgery. It consists in removing the entire intact rectum with the mesorectum, following an avascular "Holy Plane". Following this embryological route, the recurrence risk is theoretically null (3,10). However, some cancers relapse. Therefore, the key for distal rectal cancer treatment is to identify the risk factors for LR in case of every patient and to discover the local relapse in a stage that can be optimally oncologically resected. Radical rectal resection is the most significant prognostic factor. The association of perioperative radiochemotherapy is

demonstrated to decrease the LR rate (5-7). Intraoperative radiation therapy (IORT) or high-dose rate brachytherapy (HDR-IORT) may be an option for more efficient therapeutic effect and it may rise the survival rate up to 43% (17,18).

There are three categories of prognostic factors for LR: patient-related factors, tumor-related factors and initial treatment-related factors (19,20):

1. Male patients and age higher than 50 years old are associated with higher comorbid conditions, like hypertension, cardiac failure, aortic atheroma, diabetes, smoke, prostate adenoma, anatomical narrow-pelvis and obesity. Therefore, they are considered risk factors for LR (21,22);

2. The tumor-related factors are related with pathological aggressive characteristics (tumor differentiation, perineural invasion, vascular invasion, lymphatic invasion). The LR rate is associated with locally advanced tumor stages. Circumferential margin invasion represents a decisive factor for tumor recurrence (23,24). The aggressive intraoperative rectal tumor handling can lead to perforation and microscopic tumor implantation in the pelvis, significantly increasing the rate of local recurrence, especially in case of patients who did not receive preoperative radiotherapy (12).

Some studies have shown that monitoring the level of preoperative and postoperative CEA (carcinoembryonic antigen) is considered the only prognostic factor for LR in rectal cancers. (25-27);

3. Initial radical treatment significantly decreases local recurrence rate in the absence of other risk factors. It is extremely important that these patients with distal rectal cancer are treated in highly-specialized in colorectal surgery centers after a correct and complete selection of cases by a multidisciplinary team (1). Cases with abdominoperineal resection may have a higher rate of local recurrence due to the initial aggressive tumor stage. The presence of permanent stoma has a significant impact on quality of life (1).

According to some authors, patients with local recurrence have also distant metastases (6,9,28,29). Therefore, the high-quality imaging scans can accurately identify tumor extension, location and size. Of these, MRI provides more detailed data compared to CT scans and it can differentiate fibrosis from tumor tissue. PET-CT provides data on peritoneal tumor recurrence and lymphatic invasion in particular (24,30).

Relapses located above the pelvis can be resected and followed by restauration of the digestive tract. The transanal tumor resections may be feasible for small tumors without deep wall invasion and in absence of other dissemination (34,35). Local recurrences involving the pelvic wall, the sacrum or the iliac vessels and nerves can be considered contraindications for local excision alone. In this case, extensive surgery is recommended and consists of abdominoperineal amputation, total or partial pelvicectomy (31,32). There are cases where only the palliative management is feasible, and even though the morbidity and mortality rate is highly increased, it provides a satisfactory quality of life (33). In these cases, radiotherapy may be acceptable.

The recurrent rectal cancer is a potentially curable disease for a highly-selected group of patients (32). The increased morbidity rate has a major impact on quality of life and overall mortality. The follow-up period needs to be extended in order to obtain an early relapse detection (28,29).

CONCLUSION

Local recurrence after distal rectal cancer is an important complication with a great impact on morbidity, mortality and quality of life.

The higher rate of locally recurrent distal rectal cancer is associated with more aggressive tumors and locally advanced stages.

The therapeutical management should be personalized for each patient according to tumor-related, patient-related and initial surgery-related characteristics. The strategy should consist in a selection of the most efficient and radical treatment.

The radical R0 resection is the goal for curative surgical treatment. The multimodal treatment can be performed by an experienced team in highly-specialised colorectal cancer centers and can result in more frequent follow-up referrals for the high-risk selected patients, so the local recurrence can be early detected.

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