Therapy of Stenosing Rectal Cancer

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Rezumat

Atitudinea terapeutică în cancerul de rect stenozant

Elaborarea unui management al cancerului de rect urmărește stabilirea unui algoritm de diagnostic, strategia aplicării tratamentului chirurgical, strategia și răspunsul tratamentului neoadjuvant și adjuvant și metodele optime de evaluare a răspunsului la tratamentul specific. În încercarea de a urmări acest management, am studiat aspectele enumerate mai sus și am efectuat un studiu clinic retrospectiv, descriptiv și a cuprins analiza datelor obținute pe un lot selectat de 90 pacienți diagnosticați cu cancer de rect stenozant, în intervalul ianuarie 2008 - decembrie 2012, tratați în cadrul Clinicii Chirurgie Generală I Institutului Oncologic București “Prof. Dr. Al. Trestioreanu” și în cadrul Clinicii Chirurgie Generală a Spitalului Clinic Colentina și a avut ca scop analiza atitudinii terapeutice în cancerul de rect stenozant. Alegerea actului operator, dar mai ales momentul aplicării radioterapiei pre-operator și postoperator, asociată sau nu cu chimioterapia concomitentă, a ținut cont de prezența stenozei (obstrucție completă sau incompletă) și de stadiul evolutiv loco-regional și la distanță al bolii.

Cuvinte cheie: cancer rect, complicație, strategie terapeutică

Abstract

Develop a rectal cancer management aims to establish an algorithm diagnostic, surgical treatment strategy implementation, strategy and neoadjuvant and adjuvant treatment response and optimal methods for assessing response to specific treatment. In trying to track this management, we studied the issues listed above, we conducted a retrospective clinical study, descriptive and included the analysis of data obtained on a sample selected 90 patients diagnosed with stenosing rectal cancer between January 2008 and December 2012 treated on the General Surgery Clinic I of "Prof. Dr. Al. Trestioreanu" Oncology Institute and on the General Surgery Clinic of Colentina Clinical Hospital, in Bucharest and aimed at analyzing the therapeutic attitudes of stenosing rectal cancer. Choosing the surgery, especially when applying preoperative and postoperative radiotherapy, with or without concomitant chemotherapy, it took into account the presence of stenosis (obstruction complete or incomplete) and the evolutionary stage locally and remotely disease.

Key words: rectal cancer, complications, therapeutic strategy

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Introduction

In most cases, rectal cancer diagnosis is established in advanced disease, both locally and remotely, sometimes only during complications. In terms of treatment, this neoplasia requires a well thought therapeutic conduct, developed by a multidisciplinary team, which monitors the evolving strategy locally and remotely, and presence of complications.

Material and method

Clinical study include retrospective analysis of data from a selected group of 90 patients diagnosed with stenosing rectal cancer between January 2008 - December 2012 treated on General Surgery Clinic I of "Prof. Dr. Al. Trestioreanu " Oncology Institute and on the General Surgery Clinic of Colentina Clinical Hospital, in Bucharest.

Conducting the clinical trial involved the following steps:

1. Stage of diagnosis and initial evaluation of the condition of the actual extension
2. Stage of surgical treatment
3. Stage of oncology treatment (neoadjuvant and adjuvant)
4. Stage of monitoring, which included postoperative complications, local recurrence for operations performed with curative visa, remote metastasis for patients who have metastases at diagnosis.

Diagnostic phase began from the time of admission the patient, which included a detailed clinical examination associated with a number of biological laboratory investigations: blood count, erythrocyte sedimentation rate, blood group and Rh, direct and total bilirubin, transaminases - TGP, TGO, GGT, LDH, alkaline phosphatase, glucose, blood urea nitrogen, serum creatinine, total protein, total fat, total cholesterol, triglycerides, serum ionogram examination, urine analysis, ECG, revealing data about vital functions. These investigations were related to exploration clinical target: X-ray thoracic pleural pulmonary, abdominal X-ray, abdominal-pelvic ultrasound, computer tomography of the thorax, abdomen and pelvis (CT), pelvic magnetic resonance (IRM), colonoscopy, cardiology specialist exam and echocardiography. Serum tumor markers were determined at diagnosis (CEA and CA 19-9) in all patients included in the study. To confirm the diagnosis of histo-pathological examination was made necessary by transanal biopsy, recto-sigmoidoscopy and colonoscopy with biopsy or intraoperative biopsy.

Stage of surgical treatment. For patients with occlusion of rectal cancer that required surgical intervention in the emergency, was performed left iliac colostomy (contiguous or terminal), with the sampling biopsy, depending on the stage of evolution of the disease, the extent to which the overall condition of the patient, and its associated diseases allowed, priority is solving complication - ensuring digestive transit, for the patient to receive radiation therapy with or without chemotherapy. For patients with stenosing cancer, but with incomplete obstruction of the rectal lumen, depending on the stage of evolution of the disease, they were performed following surgery: for stage I, in which obstruction of the lumen was incomplete, were performed anterior resection of the rectum type Dixon with end-to-end or side-to-end colo-rectal anastomosis performed manually or mechanically, with or without cecostomy protection, rectal amputation and surgery type Hartmann and then patients may benefit from adjuvant cancer treatment. Adjuvant therapeutic approach is nuanced by histopathology and staging pTNM. For locally advanced disease without distant metastases (includes stages T3N0 or T4N0 or any T N1-2 and / or unresectable or medically

inoperable local tumor) with incomplete obstruction lumens, left iliac colostomy was performed in continuity or terminal with sampling biopsy, because patients may benefit from treatment or radiotherapy, simultaneously radio-chemotherapy, tumor operability subsequent reevaluation. In patients who gave the down-grading of the tumor and the tumor has been resected within safe oncology limits, was practiced surgery with curative visa, depending on the location of the tumor in the rectum, followed by further therapy. In patients in which no tumor regression was obtained, it was charged chemo-radiotherapy further treatment. Patients who had resectable rectal tumors, but with unresectable distant metastasis, radical surgery of the tumor was practiced, followed by radio-chemotherapy. For rectal tumors and the presence of unresectable distant metastases was performed left iliac colostomy in continuity with biopsy, to prevent complete obstruction of the luminal rectal application of palliative oncologic therapy. (1,2)

Stage of oncology treatment. Patients diagnosed in stage I, which was practiced surgery with curative visa, followed adjuvant radiotherapy with or without chemotherapy, depending on the outcome histopathology. Starting radiotherapy treatment was at least 5 weeks after surgery, radiotherapy applied to the long-term, using doses of 45-50 Gy in 25-28 sessions. The association of chemotherapy was under international therapeutic protocols (3). Patients diagnosed with locally advanced stenosing rectal tumor without the presence of distant metastases (includes stages T3N0 or T4 or any T N1-2 and / or locally unresectable or medically inoperable), who underwent surgery as a first gesture the left iliac colostomy (in continuity or terminal) to ensure continuity and avoiding digestive transit occlusion during oncology treatment application, chemo-radiotherapy were treated concurrently. Patients diagnosed with resectable rectal tumors, but with unresectable distant metastases, which was practiced tumor radical surgery, adjuvant therapy was long-term radiotherapy concomitant chemotherapy. Patients diagnosed with unresectable rectal tumors and the presence of distant metastases unresectable, who underwent left iliac colostomy in continuity with the biopsy to prevent luminal rectal complete obstruction benefited from oncological palliative therapy, according to international protocols for locally advanced disease and illness metastatic.

Stage of monitoring

In this stage were evaluated patients immediately after surgery to identify and resolve immediate complications, post-operative deaths length of stay depending on the stage of disease and type of surgery practiced, aimed to tumor regression after applying radiotherapy and conducting investigations for recognition early recurrent disease, both local recurrence and metastasis away.

Results

In the study group, predominate cases diagnosed in the sixth and seventh decade of life (32.22% and 26.67% respectively), with an average age of 64, while the proportion drops to patients aged over 80 and under 50 years. Only 5 patients were

diagnosed under age of 40 and 9 aged over 80 years. The vast majority of patients were male (62.22%), while the female was represented in proportion of 37.78%. At the time of diagnosis for patients with rectal cancer stenosis was observed predominance of the urban environment of origin of 65.55% compared with 34.45% rural areas. Regarding signs and symptoms that led the presentation of the patient to the doctor, it was found that the most common were rectoragy (72.46%) and transit disorders (66.66%), pain and weight loss with a lower frequency, 52.71% and 44.92% respectively. These data are consistent with the literature (4,5,6).

A proportion of 78.89% of patients had increased carcino-embryonic antigen and 58.89% at the time of diagnosis have increased the tumor marker CA19-9. (7,8,9,10)

6.66% of the total study group required emergency surgery to restore bowel.

Regarding the location of tumor formation in the rectum for patients in the study group found that the highest frequency is the location of the upper rectum and recto-sigmoid junction (44.44%), followed by tumor located in the lower rectum (37.77%), whereas tumors located in the medium rectum is a ratio of 17.77%. Were found in 7 cases with the presence of synchronous tumor at diagnosis, the most common site is the sigmoid colon. Most cases having rectal tumors ranging in size from 1 cm to 5 cm, which were followed by cases of rectal tumor sizes ranging from 5-10 cm.

Regarding the distribution of patients with stenosing rectal cancer studied by clinical stage TNM according AJCC (11) have predominat cases diagnosed in stage IV, which shows that from the time of diagnosis the patients had advanced loco-regional and distance disease. The proportion of patients with liver metastases at diagnosis was higher in patients with localized tumor in the superior rectum to those locations situated in the medium or lower rectum (test result $\chi^2 = 5.43$, gl = 1, $p < 0.05$) (Table 1).

46.66% of the preoperative radiotherapy followed. Radiation therapy was long-lasting, using doses of 45-50 Gy in 25-28 sessions (3).

Depending on the target curative or palliative surgery practiced, 52.23% had curative visa and 47.77% were palliative visa.

Before applying preoperative radiotherapy treatment, according to clinical TNM stage, most surgeries were carried out in the left iliac anus continuity (33.33%), to provide the patient with radiotherapy administered during digestive transit. Anterior resection of the rectum kind Dixon was performed at 18.89% of patients, followed by operation type Hartmann rate of 15.56% and rectal amputation was applied at 13.33% of

patients. Iliac terminal colostomy performed preradiotherapy was applied to 10% of patients and colostomy at break in the transverse colon was performed in 1 patient (1.11%). In all these, postsurgical chemoradiation was performed.

Preoperative radiotherapy after treatment, depending on the clinical stage of cancer of the rectum stenosis of the study group, most surgeries were performed: rectal amputations (57.14%), followed by operations Hartmann (21.43%), Dixon resections (17.86%) and laparoscopic rectal amputation surgery (3.57%). Isolated preoperative radiotherapy treatment was performed in 27.78% of the patients, the preoperative concurrent chemoradiation was applied to 3.33% of patients and isolated preoperative chemotherapy was performed in 4.44% of patients.

In the study group, before administration of preoperative radiotherapy treatment, at 7.77% stenosing rectal cancer patients was not necessarily perform any surgical act, as unobtrusive stenosis and tumors were not endangered maintaining digestive transit during application radiotherapy. Thus, after long radiotherapy treatment according to tumor location in the rectum, to 4.44% of these patients rectal amputation was performed, at 2.22% patients prior to resection of the rectum Dixon type and at 1.11% patient Hartmann operation was performed.

Downstaging's getting radiation recall tumor was 23.33% of patients who received radiotherapy prior to its treatment of the left iliac colostomy or terminal continuity, because of the obstructive stenosing neoplasia. After completing radiotherapy treatment, these patients were unable to perform resection, as follows: rectal amputation was performed in 14.44% of patients, Hartmann procedure in 5.56% of patients, Dixon resection in 3.33% of patients. In 20% of all patients with rectal cancer was not obtained stenosing tumor downstaging.

24.44% of patients in the study group was performed side-to-end or end-to-end colon or rectum anastomosis, 17.78% of them were done manually and mechanically 6.66% and 16.67% in patients was performed cecostomy protection.

Of the study group, only 6.66% of patients had suppurated tumors when surgery.

Histopathological examinations found that neoplasia type was adenocarcinoma, and the degree of differentiation was frequently G2 - moderately differentiated 47.77%.

It investigated whether age differences in the degree of differentiation. The test result ($F = 0.98$, gl = (2, 3), $p > 0.05$) leads us to infer that there were no statistically significant differences in terms of age relative to the degree of differentiation of the tumor.

Table 1. Influence of tumor localization on the presence / absence of distant metastases at diagnosis, according to the portal venous territory and systemic venous territory

Port Venous Metastases Proportion Territory	Systemic Venous Metastases Proportion Territory	Statistics χ^2	Degrees of Freedom	P-Value	Difference (CI95%)
0.475	0.240	5.43	1	0.0197	0.235 0.04 to 0.42

Depending on the clinical stage and histo-pathological result, the most common chemotherapy protocols applied were CapeOx (25.56%) and Fol-Fox (17.78%) (3).

Regarding the total number of days of hospitalization between patients who underwent different types of surgery were no statistically significant differences (test result $z = 3.39$, $p < 0.01$), so patients with palliative interventions spend an average of 4 days less surgical oncology ward to those interventions with curative intent. The same correlation was observed for the number of days of hospitalization (test result $z = 3.39$, $p < 0.01$).

They died during hospitalization 3.33% patients due to associated heart disease.

75.55% of the operated patients became apparent early postoperative any complications. In patients who developed early postoperative complications (24.44%) it was found that the most common complication was perineal suppuration in wounds (6.66%) treated with topical and systemic antibiotics according to antibiogram. The same therapeutic conduct was adopted at abdominal postoperative wound complications, which totaled 3.33%. Prolapsed colostomy was performed at a rate of 3.33% and required repositioning with recovered colostomy. Postoperative ileus dynamic (3.33%) were resolved by conservative treatment. Of the 22 anastomosis performed, only 2 patients had anastomotic fistula at the anastomosis handmade and were treated conservatively. Postoperative complications that required surgical treatment were 2 cases of peritonitis, 1 case of bowel obstruction occurred on adherents clamp and 1 case of incomplete evisceration. Urethral fistula (1.11%) occurred after laparoscopic surgery rectal amputation and urethral plasty recovery required by repositioning the probe tract.

Evolving, 6 patients (12.76%) of 47 cases in which surgery was performed with curative visa tumor had developed local recurrence.

Of patients at diagnosis had no distant metastases (59 cases) and developed metastases evolving, 6 patients (10.16%) had metastases with liver location. Of patients at diagnosis had no distant metastases (59 cases) and developed metastases evolving in 7 patients (11.86%) had metastases with pulmonary location. Greater frequency of pulmonary metastases localization (11.86%) compared to the localized liver (10.16%) in the evolution of patients with stenosing rectal cancer was correlated with literature studies showing higher frequency of metastasis at lung cancer of the rectum (12,13,14,15).

Discussions

Surgeries practiced emergency could not be preceded by training local septic bowel contents. Emergency have been corrected fluid and electrolyte imbalances, hepatic and renal function improvement, the administrations of antibiotics with broad spectrum and deep venous thrombosis prophylaxis.

For elective surgery, patients could benefit the preoperative general preparation, which consisted in evaluating and improving the functions of cardio-respiratory, liver and kidney, correct anemia and fluid and electrolyte imbalances, anti-

infective prophylaxis by administration of antibiotics with broad spectrum, prevention of deep venous thrombosis, but also training local intestinal lavage using antiseptic solutions, ensuring emptiness colon.

Surgical treatment was applied at an interval of 5-12 weeks after completion of neoadjuvant therapy.

For surgery who underwent anterior resection of the rectum kind Dixon with mechanic colo-rectal anastomosis, were used linear staplers cutting the proximal end colonic (TA 45 mm or 60 mm or GIA 60 mm) and for cutting the distal end, 2 cm below the tumor, was used TA 30 mm linear stapler. To perform the colo-rectal anastomosis, both end-to-end, and side-to-end, circular staplers have been used EEA 28, 31, 33 mm. To achieve rectal dissection and total excision of mesorectum we used Ligasure forceps clotting and tissue sectioning. (Fig. 1, 2, 3) Cecostomy protection using the Pezzer probe was performed in 2/3 of patients who had undergone colo-rectal anastomosis, with its removal at about 10-14 days after the operation, and its spontaneous closure at about 1-3 months after surgery.

During the surgical procedure was considered observance of the safety oncology: outskirts resection proximal to be situated at least 5 cm of formation tumor, distal resection margins to be located at least 2 cm below the tumor, edge safety distance mesorectum to 4 cm below the caudal pole tumor. (16,17, 18,19)

Figure 1. Avascular posterior dissection plan of the rectum with pulling the rectum above, with the Ligasure forceps (personal archive)

Figure 2. Posterior rectal plan dissected (personal archive)

Figure 3. Stapler anvil fixed to the end of remaining rectal for side-to-end colo-rectal anastomosis (personal archive)

For low anastomosis was kept a minimum of 4 cm rectal stump to reduce the risk of local complications - urinary disorders, defecation disorders, ejaculation disorders. (20)

During surgery, the ends of the colon and rectum outstanding that followed to be anastomosed were disinfected with antiseptic solutions or tumoricidal and we have ensured proper vascularization of both ends before performing anastomosis without voltage, having contact entire circumference.

Starting neoadjuvant therapy was at least 5 weeks after surgery, practiced reevaluation tumor operability after concomitant and chemotherapy. In patients who achieved tumor regression, was charged surgery with curative visa, performed 5-12 weeks after completion of neoadjuvant therapy. Resection in patients who could not be performed, was completed chemotherapy treatment according to international protocols for metastatic cases. The total duration of perioperative oncology treatment did not exceed 6 months. (3)

It was found that no statistically significant differences between the average age of diagnosis in males (65.44) and the average age of diagnosis in women (61.67), nor between the average age at diagnosis for the urban environment of origin (62.72) and background areas (66.48).

In the group of patients studied, the pain was a common symptom in most patients (52.71%), which suggests that a large proportion of patients were presented in an advanced stage of disease, pain occurs because when there are reached or nerve plexus invasion and bone can be the first symptom installation occlusive syndrome. Regarding rectoragy - visible bleeding, reduced quantitatively with fresh blood, red, feces on the surface or mixed with it, they brought patients to the doctor in the proportion of 72.46%. Transit disorders characterized by the alternation of constipation with diarrhea, and constipation predominance but with low volume, thin feces were present in a proportion of 66.66% in patients with stenosing rectal cancer studied. These disorders transit points stenosing character of the disease and its advanced stage. Occult bleeding visible in order to alarm the patient to the doctor and not clinically detectable, then produce a hematologic response, with the installation of iron deficiency anemia in time, certified patient's blood counts. Thus, 48.83% of the rectal cancer patients with stenosing study were diagnosed with iron

Table 2. Comparison between tumor size and location of the tumor in the rectum

Comparison	p-value bootstrap procedure
HRvsMR	0.2173
HR vs LR	0.0095
MR vs LR	0.4046

Legend: HR - higher rectum; MR - medium rectum, LR- lower rectum, vs - versus.

deficiency anemia in biological samples, while 51.17% of the patients had anemia. Weight loss is a general sign of neoplastic impregnation, and when it became present is a bad sign, being associated with an advanced stage of neoplasia. In patients with stenosing rectal cancer in the study group, 44.92% had weight loss, and at 55.08% was not present. (4,5,21,22).

There were statistically significant differences in terms of the size of the tumors between the location at the recto-sigmoid junction and higher rectum (mean = 4.00 cm) and at the lower rectum (median = 6.50 cm) ($p < 0.01$) (Table 2).

Conclusions

1. Stenosing rectal cancer was more common in male patients diagnosed in the sixth and seventh decade of life, urban and with an average age of 64 years.
2. The most common sign that prompted patients presenting to the doctor was rectoragy, followed by disorders of transit. All rectoragy requires urgent recto-colonic endoscopic exploration. 60% of patients have been to the doctor in the first 6 months of first appearance and 21.11% of patients experienced symptoms of approx. 6-12 months. From the group of 90 patients with stenosing rectal cancer, only 6 patients were presented in an emergency, requiring emergency surgery for intestinal transit insurance.
3. The highest frequency of rectal tumor localization was upper rectum and recto-sigmoid junction (44.44%), followed by the location of the lower rectum (37.77%) and medium rectum (17.77%). Synchronous tumors were present in only 7.77% of patients, most of them located in the sigmoid colon.
4. Distribution of the stage was: stage I (11.11%), stage IIA (7.77%), stage IIIA (1.11%), stage IIIB (5.55%), stage IIIC (3.33%), stage IV (34.44%) N / A (36.66%). At the time of diagnosis in patients with stenosing rectal cancer study, we observed the presence of distant metastases in 34.44% of patients. In the evolution of the patients, there was a higher frequency of pulmonary metastases localization (11.86%) compared to the localized liver (10.16%), the data being related to studies in the literature showing higher frequency of metastasis to lung cancer of the rectum. The proportion of patients with liver metastases at diagnosis was higher in patients with localized tumor in the superior rectum to those locations situated at medium or lower rectum. The most frequent tumor differentiation grade was G2 - moderately

Table 3. Analysis of risk factors for early postoperative complications

Variable	β	S.E	p-value	Exp (β) Odds Ratio	IC95% for Exp (β)
Age	-0.00378	0.0189	0.841	0.997	0.96 la 1.02
Sex M vs F	0.1041	0.5092	0.83795	1.105	0.41 la 3.09
R vs U Environment	-0.4164	0.5073	0.4118	0.663	0.24 la 1.80
Tumor size	-0.0231	0.0882	0.7935	0.980	0.79 la 1.13
T stage	-0.5836	0.5586	0.296	0.559	0.17 la 1.59
N stage	-0.4306	0.6868	0.5307	0.650	0.13 la 2.27
Curative surgery	REF	-	-	-	-
Palliative surgery	-2.2136	0.6698	0.000951	0.109	0.02 la 0.36
Grade Differentiation	-0.0785	0.5607	0.889	0.932	0.30 la 2.80

Legend: M - male, F - female, U - urban, R - rural, T - tumor, N - lymph node, vs - versus.

differentiated (47.77%), followed by grades G3 - poorly differentiated (10%) and G1-well differentiated (8.89%).

- Locally-advanced stages (T3N0M0, TN1-2M0, T4N0M0 and/or local tumor unresectable or medically inoperable patients) and stage TNM1 received preoperative radio-chemotherapy, as follows: 27.78% of the patients received radiotherapy applied isolated, concomitant chemoradiation preoperative 3.33% was applied to the patients, and the isolated pre-operative chemotherapy was performed in 4.44% of patients.
- Priority in rectal cancer was to ensure bowel stenosis and then, depending on the stage, the possibility of radical extirpation. Thus, 52.23% of patients had operations with curative visa and 47.77% of operations had palliative visa.
- Before applying radiotherapy treatment, according to the TNM clinical stage, surgical interventions were performed: left iliac colostomy in continuity (33.33%), Dixon resections (18.89%), Hartmann operations (15, 56%), rectal amputations (13.33%), left iliac terminal colostomy (10%) and colostomy in the transverse colon (1.11%).
- After application of radiotherapy treatment, depending on the clinical stage of stenosis rectal cancer group studied, performed surgeries were rectal amputations (57.14%), Hartmann operations (21.43%), Dixon resections (17.86%) and laparoscopic rectal amputation (3.57%). At 7.78% of patients did not need perform any surgical act as unobtrusive stenosis and tumors were not endangered maintaining digestive transit during radio-therapy application.
- Getting downstaging's tumor radiation recall was 23.33% of patients who received radiotherapy prior to its treatment of the left iliac colostomy in continuity or terminal, because of the obstructive stenosing neoplasia. After completing radiotherapy treatment, these patients were unable to perform resection, as follows: rectal amputations was performed in 14.44% of patients, Hartmann operations to 5.56% of patients and Dixon resections to 3.33% patients. In 20% of all patients with rectal cancer was not obtained stenosing tumor downstaging.
- The most common chemotherapeutic protocols were

applied CapeOx (25.56%) and Fol-Fox (17.78%).

- The analysis found that the true parameter that influences the risk for early postoperative complications is the type of operation, so operations with curative intent is a risk of postoperative complications were about 10 times higher than the palliative (Table 3).
- 12.76% of the cases where surgical intervention was developed with permanent curative local tumor recurrence and 16.94% of patients developed distant metastasis in progress.
- There were statistically significant differences in terms of both total days of hospitalization and number of days of hospitalization between patients who underwent different types of surgery. Thus, patients with palliative interventions spend on average 4 days less in surgical oncology ward to those interventions with curative intent, the average hospital stay is 20 days.

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