"WATCH AND WAIT" APPROACH IN RECTAL CANCER TREATMENT

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ABSTRACT

Introduction: The colorectal carcinoma is the most common gastrointestinal neoplasm worldwide and in Bulgaria. The choice of surgical treatment is often difficult, and organ-preserving surgery is not feasible. In borderline situations, when choosing a surgical approach is difficult, the neoadjuvant chemoradiotherapy may downsize the tumor and provide better results and more surgical options. If the treatment response is partial or complete, the possibility of sphincter-sparing surgery is increased. The aim of the study is to present a clinical case of a patient with rectal carcinoma, submitted to multimodal treatment.

Case report: The presented patient is a 65-year old female, with disturbing symptoms and diagnosed rectal adenocarcinoma. The patient underwent preoperative neoadjuvant treatment. After a full course of treatment, the tumor was resized and was reported an almost complete clinical response to the therapy. After the recommended period had ended, she underwent an anterior resection of the rectum. This case is an example of the potential possibilities of a multidisciplinary team in surgical oncology.

Conclusions: There are certain criteria, regarding the “Watch and wait” approach in rectal carcinoma, and it subjected to a set of indications in the case of a complete or near complete response to the treatment. The current case is not the brightest example of applying this approach, but still is a case of performing a sphincter-sparing surgery, which may lead to higher quality of life of the target patient group. The ESMO guidelines for the neoadjuvant treatment of rectal adenocarcinoma are applicable in Bulgaria.

KEYWORDS rectal carcinoma, neoadjuvant treatment, waiting approach, chemoradiotherapy

Copyright © 2016 by the Bulgarian Association of Young Surgeons
DOI:10.5455/ijsm.20150819025133
First Received: June 28, 2015
Accepted: August 19, 2015
Manuscript Associate Editor: George Baytchev (BG)
Editor-in-Chief: Ivan Inkov (BG)
Reviewers: Jean Gerard (FR); Stavros Panidis (GR)

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surgery is impossible. In borderline situations, choosing a surgical approach is difficult, and neoadjuvant chemoradiotherapy should be considered. The aim of neoadjuvant treatment is to decrease the stage of the disease, tumor size and if the response to the therapy is partial or complete, to make the performing of sphincter-preserving surgery possible [5]. These situations are examples of the potential possibilities of multimodal treatment for rectal carcinomas and represent its effect, regarding the optimal treatment, leading to the best long-term and functional results [6]. The aim of the current case report is to present a patient with rectal adenocarcinoma, administered to a multimodal treatment by a multidisciplinary team, applying the “watch and wait” approach and a surgical treatment, following the near complete response to the therapy.

Case Report

The presented patient is a 65-year old female, admitted to the gastroenterological department, due to constipation, requiring laxatives, blood in stools, often observed after taking medications. The symptoms have been presented for about a year. The patient suffers from well-controlled stage II arterial hypertension. The objective local status shows a woman in well general condition, soft abdomen with pain along the course of the colon and physiological peristalsis. There are no palpable tumor formations, during the digital rectal examination. Standard chest x-ray imaging and laboratory tests show referent value results. Due to technical difficulties, only the descending colon was reached during the performed colonoscopy. Based on the tests and gastroenterological report, a polypoid tumor formation is presented, 12 cm away from the anal verge. The distal part of the tumor located in the middle third of the rectum - 8-9 cm away from the dentate line. The formation is covering the rectal lumen almost 2/3 circumferential and has zones of necrosis and contact bleeding. During the examination, internal and external hemorrhoids stage II-III found. Also, multiple diverticulas with different size were found, located in the sigmoid colon and one of them - in the descending colon. During the examination were taken multiple biopsies for pathological examination. The pathological report confirmed the diagnosis “moderately differentiated adenocarcinoma.” The patient referred to surgical treatment. It conducted a preoperative clinical stage ycT3N+M0 of the disease, based on AJCC TNM staging protocols. Due to the results, we performed several clinical and laboratory studies (standard X-Ray tests, abdominal echography, CT scan, serum tumor markers - CEA, CA 19-9). We also performed an EndoRectal Ultrasound (ERU) for an exact clinical stage. The current diagnosis is a locally advanced rectal neoplastic process, with suspicious metastatic lymph nodes from ERU & CT, and lack of evidence for any distant metastases. Figures 1 and 2 show images of the clinical staging results.

Based on the clinical discussion and the ESMO rectal carcinoma guidelines, it was made a decision to undergo a combined preoperative multimodal therapy. The patient referred to a specialized center where radio- (total dose of 50.40 Gy) and chemotherapy with Capecitabine administered, for the period from 23.07.2014 to 09.10.2014. Two months after neoadjuvant treatment - the tumor size, staging and clinical response to therapy were revalued by a sigmoidoscopy. Clinically, the answer to the therapy was complete, and surgical treatment performed on the 02.12.2014. The operation included an anterior rectal resection with total mesorectal excision and reattachment of the gastrointestinal tract, via end to end anastomosis. Figure 3 shows an almost complete clinical response (tumor ulcer) to the therapy, after surgery in resected specimen.

The specimen sent to the pathology department immediately after surgery. We did not find any palpable lesion and because we could not be sure the distal resection margin was clear we opened it after surgery. The patient discharged from our department at 11.12.2014 without any postoperative complications. Histology reported a surgical specimen, about 18 cm length. At the 5th cm away from the distal margin, a thickened area with superficial ulceration was found and preceded by a histological examination. Microscopic findings consisted extensive mural fibrosis, angiectasias, acellular PAS-positive mucous lakes, reaching perirectal fatty tissue, and a focus of preserved tumor glands within the desmoplastic-inflammatory stroma, with clear distal and circumferential resection margins - ypT3N2M0 R0 G2.
The effect of neoadjuvant therapy was assessed, using tumor regression grade (TRG) scale, proposed by Dworak et al. as Grade 2. The rating was done as follows: Grade 0: No regression Grade 1: Dominant tumor mass with obvious fibrosis and vasculopathy Grade 2: Dominantly fibrotic changes, with few tumor cells or groups (easy to find) Grade 3: Very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance Grade 4: No tumor cells, only fibrotic mass (total regression or response)

ESMO and NCCN protocols have monitored patient for rectal carcinoma.

Discussion

The reported case is an example of how a multidisciplinary team works in oncology, regarding the rectal carcinoma. The presence of alarming symptoms is well-presented in reported case. Their importance is widely discussed and advocated in the recommendations of the National Board for rectal cancer treatment - MOPE 2011 [7]. Standard clinical and laboratory examinations are part of a standard procedure for diagnosis and staging of rectal adenocarcinoma. The choice of treatment in rectal surgical oncology is not always straightforward. Often borderline cases are complicated, due to the difficult choice of suitable surgical approach. Clinically, the optimal treatment for rectal adenocarcinoma is anterior resection with total mesorectal excision [8]. When organ sparing operation is not feasible, an alternative is the preoperative multimodal treatment, that may provide the algorithm for treatment.

The indications of such behavior are a subject to multiple discussions [9]. The CONTRE study reported that 13, out of 38 patients underwent radical resection after neoadjuvant therapy, when primary radical surgical treatment is impossible [10]. D. Medich et al. report a complete clinical response to the preoperative therapy in 28% of the cases, and complete histological response in 8% [11]. An American clinical study, registered in the national database, by the number NCT00682786, reported that the percent of downstage participant is 64% [CI 95%: 43.7%-78.9%]. Moreover, the complete therapy response is between 18.9%-41.9%. The rest of the patients included in the group of the patients with partial response to the preoperative therapy [12]. According to different analyzed, the percentage of patients without response varies between 58.1% and 81.1% [13]. Regarding the long-term survival and remission period, M. Maas reports better long-term results in patients with a positive response, compared to patients who have not undergone neoadjuvant therapy [14]. Post-treatment results are evaluated clinically via imaging re-staging, re-size and pathologically by grading the therapy response, using different scales. The effect of neoadjuvant therapy was assessed, using tumor regression grade (TRG) scale, proposed by Dworak et al. [15].

Other therapy grading response systems, according to Mandard, Becker, Rödel, and Ryan, are also commonly used. All of them based on the extent of fibrosis and the amount of residual tumor mass. All of the gradings above systems have their limitations. They are affected by the time interval, between the neoadjuvant therapy and the surgery, the quantity of examined material, the interobserver variability and subjectivity, and the impossibility to differ therapy-induced fibro-inflammatory changes from stromal reaction in primal tumor. The evaluation of tumor regression after neoadjuvant therapy has proven its significance in several studies, given its correlation with disease-free survival (DFS) [16]. Nevertheless, TRG should always be
interpreted in correspondence to tumor and lymph node downstage as other crucial prognostic factors.

Some questions in clinical context arise: will the patient respond to the therapy and if he/she is not a responder, is this not an unnecessary delay to the radical treatment? Because of these questions the routine application of the behavior guidelines is needed - it helps us to adjust and personalize the operative behavior, according to every single patient.

More questions arise, regarding the guidelines – which one should be used and which one would be better applicable. The most popular and applied guidelines are the American National Comprehensive Cancer Network (NCCN) guideline and the guideline of the European Society of Medical Oncology (ESMO). They recommend different indications, regarding the neoadjuvant treatment of rectal carcinoma. ESMO suggests applying preoperative therapy in advanced adenocarcinomas T3-T4 and patients with middle risk low rectal carcinomas - T2-3/ N1, 2. The specific approach, based on tumor localization in the rectum is extremely beneficial for risk assessment and choice of surgical treatment. That is why ESMO specifies, that applying neoadjuvant treatment in T2 carcinomas is acceptable, only if the rectal localization is tiny. The proposed therapy fractionated radiotherapy 45-50.4 Gy (1.8 Gy per fraction), combined with 5-Fluorouracil or Capecitabine orally. A better response to the treatment is achieved by adding Oxaplatin or Irinotecan at the expense of higher frequency of toxic effects. The surgery should be performed 6 to 8 weeks after the therapy [17]. On the other hand, NCCN recommends applying the neoadjuvant treatment in cases T3/ N0, every T/ N1-2, T4 and every case assessed, as suffering from a primary non-operative disease. In the NCCN guideline, the localization of the process is not taken into consideration, but the nodal status favored instead. Regarding the therapy itself, a choice between chemotherapy as monotherapy as part of combined radiochemotherapy is offered. The recommendations, regarding the combined therapy, are identical to the ones by ESMO, yet the monotherapy is much more aggressive. FOLFOX, CapeOx, 5-Fu/Leucovorin or Capecitabine are with the significantly higher level of toxic effects, determined by the Cancer Therapy Evaluation Program (CTEP), using standardized protocols [18].

The correlation between localization, choice of surgical approach and better selection of criteria are the factors, which our team took into consideration before choosing to follow the ESMO guidelines. This choice based on lack of clinical nodal stage superiority, the low overall toxic effect of therapy and tumor localization as criteria in the guideline. The current case is a good example, how the multidisciplinary team in oncology works. There are some limitations to this approach, such as the need of re-staging every patient. Performing another colonoscopy, waiting for the biopsy results, another abdominal and pelvic imaging and other predictive factors increase financial expenses. On the other hand, they help us to define the current status of the disease, as well as the extent of the response and help us to predict the possible direction, in which the disease will develop. It is a possibility that can allow us to delay the radical operative treatment for an indefinite amount of time when a complete response to the therapy detected. Then the neoadjuvant therapy will turn into a definite method of treatment, as it is in some other oncological localizations.

Another negative side of the waiting approach is the increasing risk, due to the delay of the treatment, when no response presented. The key is the right selection, which helps to achieve excellent results, both regarding the processing of the disease, and the accomplished final quality of life [19, 20]. The expenses related to the re-hospitalization and the required maintenance of the stoma of patients with abdominoperineal extirpation are better than those, regarding the sphincter preserving surgery [21].

Conclusion
The presented case report demonstrates criteria about the “watch and waits” approach, in the treatment of rectal carcinoma. The positive response to the neoadjuvant therapy facilitates the application of organ-preserving surgery. The long-term results will show the adequacy of this approach. From the patient’s point of view, the period of the unaffected quality of life is maximally extended. The “watch and wait” approach is an example of applying a multidisciplinary team, during the treatment of cancer patients. The ESMO guidelines for the neoadjuvant treatment of rectal adenocarcinoma are applicable in Bulgaria and preferred by our team due to its exceptionally practical nature and its distinct connection to the choice of surgical treatment.

Competing Interests
The authors declare no conflict of interest.

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