

## The Effect of Neoadjuvant Radiotherapy on the Pathological Response in Patients with Rectal Cancer

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### Rezumat

#### *Efectul terapiei neoadjuvante asupra răspunsului patologic la pacienții cu cancer rectal*

*Scop:* Studiul retrospectiv are ca obiectiv descrierea rezultatelor pe termen lung și a ratei de supraviețuire la pacienții diagnosticați cu cancer rectal care au fost tratați cu radiochimioterapie neoadjuvantă.

*Metode:* Studiul retrospectiv a fost desfășurat pe secția de chirurgie a unui spital clinic cu profil oncologic. Studiul a evaluat datele pacienților tratați pentru cancer rectal între ianuarie 2014 și decembrie 2018.

*Rezultate:* Din 126 de pacienți, 13 pacienți cu vârsta medie de 58.3 ani au avut răspuns patologic complet și au fost tratați cu radiochimioterapie neoadjuvantă. 10 pacienți (76.9%) au fost tratați cu 45 Gy. Un pacient a fost tratat cu 51 Gy, unul cu 49.3 Gy și 12 pacienți au fost supuși tratamentului cu 1.8 Gy zilnic. Un singur pacient (7,7%) a beneficiat de 25 Gy cure scurte (5 zile a câte 5 Gy). Pacienții diagnosticați și tratați în 2016 au avut o rată de supraviețuire de 54 până la 57 de luni, pentru cei din 2017 rata de supraviețuire a fost de la 42 la 48 de luni, iar cei din 2018 au avut o rată de supraviețuire de la 29 până la 34 de luni. La doi dintre pacienții incluși în analiză cu răspuns patologic final complet, s-a administrat tratamentul adjuvant și s-a aplicat strategia WS. Ambii pacienți au fost de sex feminin, cu vârste de 51 și 66 ani (vârsta medie 58.5 ani).

*Concluzii:* Frecvența răspunsului patologic complet a fost similară cu frecvența acestuia identificată în alte studii în literatură. Rata de supraviețuire a pacienților incluși în studiu a fost ridicată, decesul fiind identificat la două cazuri, unul dintre cazuri fiind pacientul cel mai în vârstă. În concluzie, controlul

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oncologic pe termen lung este excelent pentru pacienții care au primit terapie neoadjuvantă, conducând la îmbunătățirea ratei de supraviețuire, îmbunătățirea calității vieții și reducerea riscului de recidivă.

Cuvinte cheie: cancer rectal, radiochimioterapie neoadjuvantă, rată de supraviețuire

## Abstract

*Objective:* The aim of this retrospective study was to describe the long-term outcomes and the survival rate in patients who underwent neoadjuvant therapy for rectal cancer.

*Methods:* This is a retrospective study undertaken in a surgery department of an oncological clinical hospital. The study evaluated the data of all patients treated for rectal cancer between January 2014 and December 2018.

*Results:* Of 126 patients, thirteen patients with mean age of 58.3 years had a pathological complete response and were treated with neoadjuvant chemoradiotherapy. Ten patients (76.9%) underwent treatment with 45 Gy. One patient was treated with 51 Gy, one with 49.3 Gy, and 12 patients were treated daily with 1.8 Gy. One patient underwent a short course of 5 days with 5 Gy. Patients diagnosed and treated in 2016 had a survival rate of 54 to 57 months, in 2017 – 42 to 48 months and in 2018 – 29 to 34 months. For two patients with final pCR, the adjuvant treatment was given and the wait and watch policy was applied. Both patients were females, aged 51 and 66 years (mean age 58.5 years).

*Conclusion:* The frequency of pCR was similar to that in other published studies. The survival rate in our cohort was high, death occurring in two cases, one being the oldest patient in the study. We concluded that the long-term oncological control is excellent in patients who receive neoadjuvant treatment leading to improved OS, improved quality of life, and decreasing the recurrence rates.

Key words: rectal cancer, neoadjuvant chemoradiotherapy, survival rate

## Introduction

The treatment of rectal cancers continues to be a challenge for healthcare professionals, despite the considerable progress that has been made so far with the use of neoadjuvant therapy. Although currently, the gold standard of multi-modal management of inferior localized rectal neoplasia is concomitant neoadjuvant chemoradiation followed by radical surgery with total excision of the mesorectum, the current interest is moving towards a conservative vision of this with the need to balance the quality of life with the curative therapy. Surgery has evolved from less radical approaches to obtaining superior oncological radicalism by total excision of the

mesorectum, but at the same time, the functional surgery techniques which include the preservation of the pelvic nerve structures and anal sphincters have improved (1). Furthermore, the combined therapy has become widely accepted as a standard therapy for tumors with local evolution above T2 stage, except the early stages of resectable rectal cancer. Most patients with stage II or III rectal cancer are now treated with preoperative chemotherapy and short-term radiation therapy before total mesorectum excision (TME) (2,3,4).

Based on recent data (GLOBOCAN 2018), colorectal cancer is the fourth most frequent cancer in the world, with an annual incidence over 70,000 cases and with the third biggest rate of mortality (1). In patients with

advanced local rectal cancer, the most recommended treatment in terms of efficacy and toxicity is the long-term neoadjuvant chemoradiation followed by mesorectum excision (2). In recent decades, intensification of treatment has been the dominant paradigm for the management of rectal cancer.

According to the National Comprehensive Cancer Network (NCCN) guidelines, if concomitant neoadjuvant chemoradiation (50.4 Gy/ 25 and capecitabine) is provided, surgery should be scheduled within 8-12 weeks of completion of treatment. Following neoadjuvant treatment, the tumor may show dimensional regression and may even completely disappear after this therapy (1). Approximately 10-20% patients can get a complete response (2). The strict definition of the complete clinical response in the neoadjuvant therapy of rectal cancer was proposed by Maas in 2016 and contained five diagnostic criteria (3). The proposed diagnostic criteria were no residual tumor and white scar on endoscopy, negative biopsies from post-radiation scars, no palpable detectable tumor on digital rectal examination, no suspicious lymph node on MRI, and no residual tumor or residual fibrosis on MRI. The purpose of this retrospective study was to describe the long-term outcomes and the survival rate in patients who underwent neoadjuvant therapy for rectal cancer.

## Methods

Between 1 January 2014 and 31 December 2018, a retrospective study was conducted on 126 patients admitted to the surgery department of Coltea Clinical Hospital. Inclusion criteria included the following: (1) age 18 to 90 years, (2) a pathological diagnosis of rectal cancer, (3) tumors located <12 cm from the anal verge based on flexible or rigid endoscopy, (4) middle, lower rectal cancer.

The exclusion criteria were: (1) incomplete clinical or pathological data, (2) age under 18 years, (3) second malignancies, (4) diagnosis was not confirmed histologically, (5) surgery was not performed in the surgery department of the Coltea Clinical Hospital, (6) there is no

evidence of the postoperative outcomes and for the therapeutic strategy, (7) patients with limited resections performed.

Patients were staged according to the TNM classification, the 8<sup>th</sup> edition of the American Joint Commission on Cancer (AJCC) Tumor Node Metastasis (TNM) classification system, based on clinical examination, endoscopy, and imaging (thoracic CT and contrast-enhanced abdominal MRI/CT). The cancer stage was defined. The cancer stage was pathological staging (ypTNM). All patients underwent abdominal CT and chest radiography or chest CT to exclude distant metastasis. The patients were asked for symptoms 2 days before the surgery. All patients underwent neoadjuvant therapy which consisted of a long-course chemoradiotherapy (45–50.4 Gy in 28 fractions over 5.5 weeks) or a short-course radiotherapy (5 × 5 Gray) with concomitant chemotherapy regimens: capecitabine 825 mg/m<sup>2</sup> taken twice daily throughout the radiotherapy session.

The pathological complete response (pCR) was investigated in all patients. A pCR was defined according to recognized criteria, as the absence of any palpable tumor or irregularity on clinical examination, no visible lesion on flexible sigmoidoscopy except for flat scarring, telangiectasia or whitening of the mucosa, and the absence of any disease on cross-sectional imaging at the site of the tumor or in the mesorectum.

All patients who had long-course chemoradiotherapy were restaged 12 weeks after the end of neoadjuvant therapy. Patients were restaged with a computed tomography scan of the chest, abdomen and pelvis, magnetic resonance imaging (MRI) of the pelvis, and flexible sigmoidoscopy.

Patients with a pCR following chemoradiotherapy were offered either surgical resection (TME) or wait and watch. The study protocol was approved by the institutional review board of the participating hospital. All patients provided written informed consent.

## Results

The study included 126 patients admitted for

rectal cancer to the surgery department of Coltea Clinical Hospital. Of all patients included, 13 cases (10.3%) received a complete response to neoadjuvant therapy. Only two patients were included in the follow-up protocol for monitoring, and 11 patients underwent radical resection and were diagnosed post-operatively as having a complete local histopathological response. Thirteen of the 126 included patients were treated with neoadjuvant chemoradiotherapy. The mean age of the patients was 58.3 years (range 33 – 77 years), half of them being over the age of 65.9 years (69.2%) were females and 4 (30.8%) males, and 10 were from the urban area (77%). The most reported symptoms were hematochezia (69.2% patients), intestinal motility disorder by 3 patients (23.1%), diarrhea, constipation, abdominal pain, and skin pallor by one patient. The patients were divided into two groups by the localization of the tumor: group 1 with 7 patients (53.8%) with the tumor located in the lower third of the rectum, group 2 with 5 patients (39.5%) with the tumor located in the middle third of the rectum. One case (7.7%) had tumor located on the anal canal. Regarding the histopathological form, 8 patients were defined histopathologically before the neoadjuvant therapy without tumor and of the remaining 5 patients, every patient had a different adenocarcinoma: well-differentiated mucinous adenocarcinoma, well-differentiated adenocarcinoma, moderately differentiated adenocarcinoma, squamous cell carcinoma, and tubular adenoma.

Of the 13 patients included, 4 patients (30.8%) had T2, 4 (30.8%) patients had T3 rectal tumor stage, 2 patients (15.4%) had T1 stage, and 3 patients (23%) had T4 stage. On the pre-operative imaging staging, the N0 stage was identified in 7 patients (53.8%), the N1-2 stage was seen in 2 patients (15.4%), and N2 stage was observed in 3 patients (23.1%). One case (7.7%) had N3 stage. All the patients in the study cohort had indications for radiotherapy after tumor staging and were treated according to standard protocols. The patients were informed of the postponement of the surgery which was to be scheduled over 8-12

weeks after the neoadjuvant treatment.

Ten patients (76.9%) underwent treatment with 45 Gy. One patient was treated with 51 Gy, one with 49.3 Gy, and 12 patients were treated daily with 1.8 Gy. One patient underwent a short course of 5 days with 5 Gy. The surgical intervention was performed between weeks 8-12 after chemotherapy. Of all the patients in the study group, for 6 patients (46.2%) the surgical intervention consisted of anterior resection of the rectum with TME, 5 patients (38.5) underwent rectum amputation, and for 2 patients no surgical intervention was performed. Postoperative complications were neutropenia and hematoma in two patients. The patients were restaged. All the patients mentioned above were also provided concomitant Capecitabine. On the histopathological examination, all patients were staged T0M0. Regarding the number of nearby lymph nodes that have cancer (N stage), one patient had N1 stage, even if the final clinical response after the neoadjuvant therapy was ypT0M0. The number of resected lymph nodes ranged from 1 to 31, and, on average, more than 11 were removed.

The survival rate for the patient with ypT0N1M0 was 21 months. Death was due to the condition of the rectal neoplasm. The oldest patient who was 77 years old at the time of the intervention had a survival rate of 41 months post-operatively. Both cases were females. In 11 patients (84.6%) no death has been reported to date. Therefore, patients diagnosed and treated in 2016 had a survival rate of 54-57 months, in 2017 – 42 to 48 months, and in 2018 – 29 to 34 months. For two patients with final pCR the adjuvant treatment was given and the “Wait and watch” (WW) policy was applied. Both patients were females, aged 51 and 66 years (mean age 58.5 years). This decision was taken by the patient together with the therapist after discussing the risks and benefits of this method, including the emotional state, type, and duration of the subsequent medical examinations. The final decision regarding the WW strategy belonged exclusively to the patient. The final answer was provided to the doctor after several days

of thinking. The patients had a permanent contact with the therapist.

The *Figs. 1-7* are from one of the cases in the study group showing histological and imaging results.

## Discussions

Several studies have described the results of treatment with neoadjuvant chemoradiotherapy in patients with rectal cancer in relation to pCR and survival.

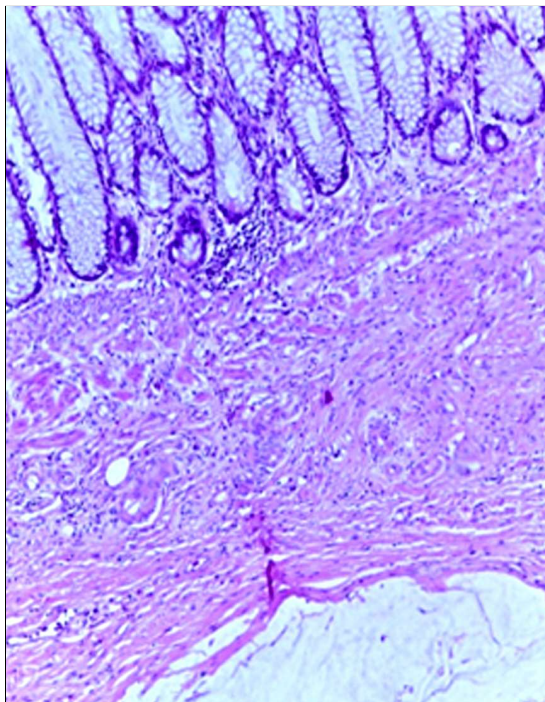
In the present study, our patients have sociodemographic characteristics very similar to those presented in other studies regarding age with a mean age of 58 years, but different when talking about sex predominance. In our study, female sex was predominant and in the other studies cited here it was found a predominance of male sex (6-9).

The frequency of pCR in our study was 10.3%, which concurs with that published in other studies. In the study by Banurra et al (10), where patients were followed for 13

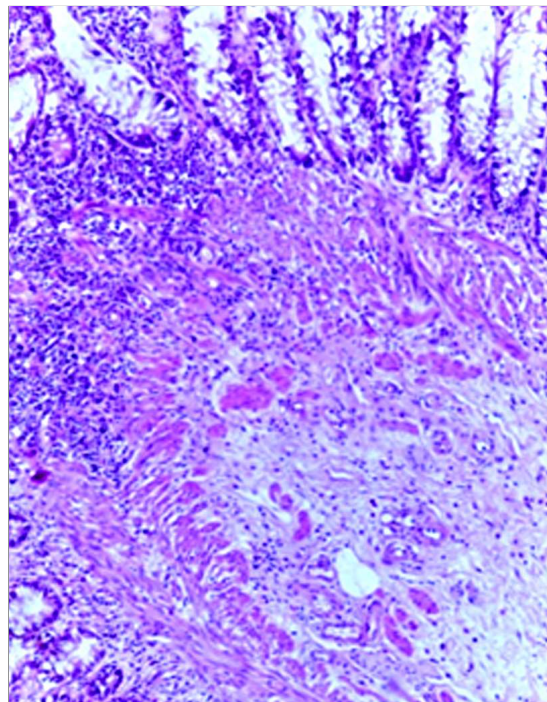
years, pCR was 12.5%. In another study on 500 patients with follow-up, currently the largest cohort reported, Cienfuegos et al (6) reported a pCR of 12%. Two studies with cohorts of 119 and 202 patients reported a pCR in Omejec and Potisek (9), 15.1%, and 14.8% of the patients, respectively. Our final pCR was 15.38%.

The survival rate in patients with pCR in our study was 84.6% and in patients with final pCR was 100%, but this cannot be extrapolated since our cohort has a small number of patients. In a meta-analysis (11), the 5-year overall survival (OS) rate was proved to be 90.2% for the patients with pCR. Those patients had a 3.3 times higher OS advantage, compared with the patients that did not have complete response. Other studies (7,8,10) described a 100% 5-year OS rate.

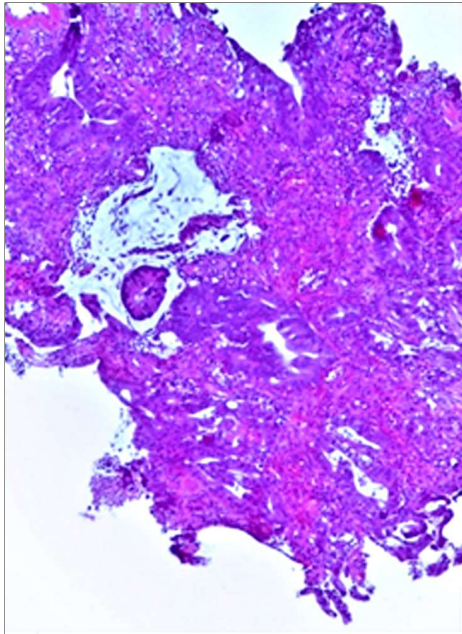
In our study, we applied the wait and watch (WW) strategy to two patients. As resulted from the scientific literature, the long-term outcomes in patients managed with the wait and watch strategy are excellent, with 5-year



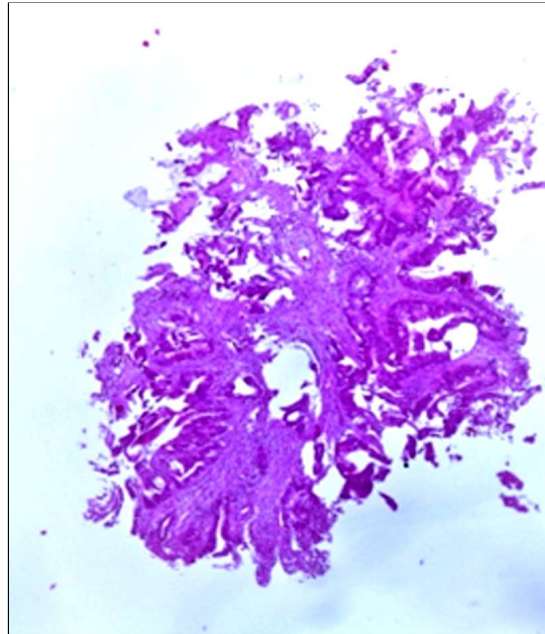
**Figure 1.** Rectal wall with post-fibrosis areas (without tumor islands remaining – complete tumor response to irradiation) x 20



**Figure 2.** Rectal wall with areas of chronic inflammatory infiltrates (lack of tumor islands - complete pathological response to irradiation) x 20



**Figure 3.** Biopsy – rectal tumoral mass (neoplastic glandular proliferation with disorganized architecture) x 4



**Figure 4.** Biopsy – rectal tumoral mass (mucus discharge with numerous malignant glands) x 10

OS rates ranging from 91% to 96%, as follows: Habr-Gama et al (5) (91%), Martens et al (12) (97%), Appelt et al (13) (100% at 2 years), and Renehan et al (14) (96%).

Most local recurrences develop in the first 2 years of surveillance; however, follow-up at risk-adjusted intervals should be performed over a period of 5 years. Therefore, we recom-

mend endoscopes at 2 months and MRI in the first 2 years at 2 months, 4 months in the third year, and 6 months in years 4 and 5 (14).

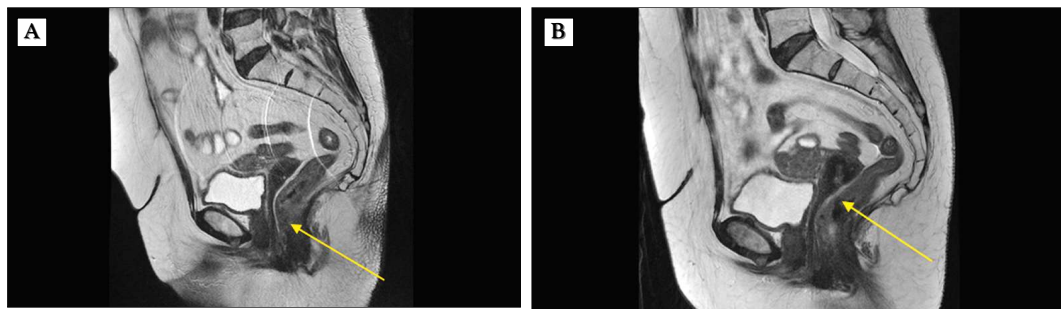
The study has several limitations given the reduced number of patients, the follow-up period, and due to the fact that it was performed in a single cancer center. Despite these limitations, the patients from our study had



**Figure 5.** Image of the tumor on colonoscopy



**Figure 6.** Image post neoadjuvant treatment



**Figure 7.** (A) MRI – sagittal T2 segment – pre-therapy. (B) MRI – sagittal T2 segment – post-therapy

results that were similar to those of other studies published in the scientific literature (15,-20). Therefore, the conclusion of this study is that the oncologic control for a long period is needed in patients that receive neoadjuvant treatment with chemoradiotherapy and achieve pCR, resulting in improvement of overall survival rate and in quality of life.

## Conclusions

Data from multicenter studies are needed to confirm the non-inferiority of the wait and watch approach to standard treatment before this strategy can be addressed on a larger scale. We conclude that the long-term oncological control is excellent in patients who receive neoadjuvant treatment leading to improved OS, improved quality of life and reducing recurrence rates.

## Conflict of Interests

The authors declare no conflicts of interests.

## Ethical Statement

All procedures performed were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments.

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