

# Complete Clinical Response following Neoadjuvant Treatment of Stage II Rectal Cancer: Observation of Surgery

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## Abstract

Complete clinical response after neoadjuvant therapy for locally advanced rectal cancer has been considered sufficient for implementation of a non-surgical approach of observation and monitoring by some authors. Standard management of this condition is radical resection of the primary tumor six to ten weeks after completion of neoadjuvant therapy. In this review the pros and cons of each proposal are presented, and implications and recommendations for each alternative are described.

## Keywords

Rectal cancer, complete medical response, nonsurgical management, neoadjuvant therapy

## INTRODUCTION

Colorectal cancer is the third most common cancer in the world and the second most common in the USA and Europe (1). In Colombia it ranks fifth in overall cancer mortality, with a rate of 5.3 per 100,000 people with an average annual increase in incidence of 1.9% to 2.2% (2). In 2010, the Instituto Nacional de Cancerología (National Cancer Institute) in Bogotá reported an incidence of 3% in men and 2.1% in women. Of these, 73% of the cases had classic adenocarcinoma histology, 5.2% were mucinous, and 4.5 % were squamous (3).

Management is then determined by strict and precise staging according to the Classification of Malignant Tumours (TNM - 7th edition of the American Joint Commission on Cancer) (4). For locally advanced rectal cancer located in the right middle or lower (within the first 12 cm from the anal margin), the treatment comprises a series of steps necessary for integral management of this condition. The process requires neoadjuvant chemotherapy and radiation therapy, surgical resection of the lesion (abdominoperineal rectal resection or low anterior resection with protective

or permanent stoma) and adjuvant treatment with chemotherapy (4, 5).

After completion of chemotherapy and radiation therapy, between weeks six and ten, the cancer is again staged and a multidisciplinary board determines whether surgery is required, and – if it is – the precise procedure to be performed. Subsequently, the necessity of adjuvant treatment and the treatment protocol are determined on the basis of pathologic findings from the surgical specimen, evidence of involvement of mesorectal lymph nodes, the degree of tumor regression, evidence of lymphovascular or perineural invasion and neutralization of resection margins (4, 7, 8).

Neoadjuvant administration of radiation therapy is preferred because the toxicity is lower than when administered after surgery. In addition, it should sterilize mesorectal tissues which in theory will ensure better quality oncological surgery (10).

## OBSERVATION AND MONITORING

From 26% to 30% of locally advanced rectal tumors present complete clinical response after chemo therapy and radia-

tion (11, 12). The first group to report these events was led by Dr. Angelita Habr-Gama. They proposed a strategy for monitoring and observation of these patients to avoid surgical treatment of this pathology (12). Nevertheless, there are still those who oppose this management option, so we have set out the pros and cons of each strategy below (13).

Complete clinical response is defined as an absence of clinical, endoscopic or imaging evidence of a rectal tumor during the restaging of a patient with locally advanced rectal cancer after neoadjuvant therapy. Complete pathological response (yT0N0M0) is the absence of evidence of a tumor in the histological study of the surgical specimen that is taken during radical oncologic resection.

## IN FAVOR

Dr. Habr-Gama and her group in the Division of Colorectal Surgery at the School of Medicine in the Universidad de Sao Paulo in Brazil were the first to describe patients with locally advanced rectal cancer who had complete clinical responses after neoadjuvant chemo therapy and radiation therapy, and they were the first to propose a non-surgical management strategy (14, 15).

Their first series describes 265 patients who had adenocarcinoma of the distal rectum (0-7 cm from the anal margin) that were considered resectable between 1991 and 2002 (15). Of this group, 71 patients (26.8%) had complete clinical responses at their assessment eight weeks after finishing chemotherapy and radiation therapy. They were incorporated into a plan for monitoring and observation. The remaining 194 patients had incomplete responses and underwent radical oncological management. Of the latter group, 22 patients had complete pathological responses and were compared with the observational group. The initial size of the tumor, patients' genders and ages, histological differentiation and initial clinical stage of the tumors had no statistically significance differences between the two groups. Two patients in the observation group had local recurrences: one at 56 months and the other at 64 months after completion of neoadjuvant therapy. They were managed by local resection and brachytherapy. There were no mortalities reported during the study period. Three cases of systemic relapse occurred: one at 18 months of follow-up, another at 48 months, and the third at 90 months. They were managed with systemic chemotherapy. The overall recurrence rate was 7% (5 patients). In the surgical group with complete pathological responses there were three systemic relapses (13.6%) before completion of two years of follow-up. Two of these patients died.

In their next series of 360 patients, Dr. Habr-Gama and her team confirmed the incidence of perioperative complications and the benefits of observational management (16).

Points to consider in implementation of this management strategy are:

- Lower morbidity rates for neoadjuvant radiation therapy than for radiation therapy administered following any surgical procedure (17).
- Radical cancer surgery of the distal third of the colon is a mutilating procedure which requires permanent ostomy and which has significant risk of mortality and morbidity.
- The morbidity of the procedure ranges from 26% to 45%.
- Anastomotic leakage occurs in 10% to 25% of cases who undergo low anterior resection of the rectum for tumors in the middle third and tumors in the lower rectum.
- Colonic-anal anastomosis can lead to fecal incontinence rates of 20% and higher in patients who have previously undergone radiation therapy.
- Sexual and urinary dysfunctions are common complications of the surgical procedure which occur in up to 50% of cases even when there has been meticulous preservation procedures for pelvic innervation in highly specialized medical centers (18).
- Slow healing of perianal region following abdominal-perineal resection in patients who have undergone pelvic radiation therapy results in significant local morbidity (17).
- Mortality rates from surgical management of rectal cancer range from 5 to 10%.
- Stoma complications (hernia, infection, prolapse) develop in two to seven percent of cases.
- Surgical management shows no benefits in rates of disease-free or overall patient survival compared with observational management.
- The anxiety of the surgeon and patient in the standard oncological management is decreased by the implementation of the monitoring strategy.

Weisser and his group reported that local recurrence after observational management occurs between weeks 12 and 18 and may still be susceptible to surgical management. They also determined that 85% to 90% of surgically treated patients survive without disease if concomitant to complete clinical response there is also a complete pathological response (11).

Initial clinical staging was not related to recurrence of disease, and patients with systemic relapses had significantly less radiological evidence of nodal metastases suggesting that systemic relapses were the result of spread through the blood more than spread through the lymphatic system (18). In addition, such relapses occur earlier than endoluminal relapses, so several groups have suggested that the addition of adjuvant chemotherapy or induction after complete clinical response to limit such relapses (19).

In 2010, Dr. Habr-Gama described the clinical and endoscopic patterns of complete clinical responses after chemo-

therapy and radiation therapy for locally advanced rectal cancer (20). Diagnosis of complete response requires the following:

- Clearance of the mucus in the compromised area of the rectal wall.
- Telangiectasias or discrete vascularization of the rectal mucosa previously affected by the tumor.
- Loss of elasticity of the rectal wall with the sensation of rigidity or a discrete local lesion. This must be distinguished from a stenosis or nodularity of the mucosa which would correspond to an incomplete clinical response.
- No visual or palpable sign of a tumor in rectal area in which there had previously been a mass.

In addition, there must be no residual disease. In other words, there must be no evidence of mucosal ulceration, no obvious irregularities, no palpable lumps or masses, no stenoses, and no local friability. Biopsies of lesions or scars at the site of a previous tumor cannot rule out residual disease. Samples should be taken at the discretion of the attending physician during consideration of the possibility of local radical surgical resection or when there are doubts or suspicions that the response may not have been complete (21, 22).

It has been determined that best chance of achieving a complete clinical response occurs when post neoadjuvant staging is done after the sixth week which allows for greater consideration of the observacional management strategy (23).

Transanal endoscopic microsurgery (TEM) should be restricted to patients with tumors confined to the rectal wall and who have no adverse pathological patterns (YpT1, complete tumor regression) after chemotherapy and radiation therapy (24).

In conclusion, although there is a risk of local relapse in the first 12 months of monitoring, the regularity and frequency of relapses allows for rapid lifesaving treatment. If thorough and strict monitoring of patients who have complete post neoadjuvant clinical responses is carried out, radical surgical procedures as well as morbidity and mortality can be avoided (25).

## AGAINST

A “wait and see” strategy is contrary to the principles of traditional surgical management of rectal cancer in which radical oncological resection of the primary tumor is done following neoadjuvant therapy.

A meta-analysis by Bonnetain and his group compared chemotherapy combined with radiation therapy with radiation therapy alone based on data from 1,011 patient in EORTC (European Organisation for Research and Treatment of Cancer) trial 22921 and 756 patients in FFCD

(Fédération Francophone de Cancérologie Digestive) trial 9203. Both trials are randomized phase III studies of neoadjuvant treatment of locally advanced rectal cancer. The meta-analysis shows that the concomitant combination of 5-fluorouracil (5-FU) with preoperative radiation therapy increases the rates of complete clinical and pathological responses, optimizes local regional control, optimizes sterilization of mesorectal deposits and decreases tumor volume. There was no evidence of increased overall or disease-free survival (26).

Glynne-Jones and his group, in a review of 218 Phase I and Phase II studies and Phase III studies and 28 Phase III studies, ratified the effectiveness and rationality of a “wait and see” policy but found that for some patients this management strategy is not convenient (3). The following points should be considered before making a decision:

- There is no uniformity in the definition of complete clinical response nor in the definition of by which means it must be depicted (diagnostic images, digital rectal examination, clinical examination, endoscopy, biopsy, or all of the above).
- None of the studies have used Response Evaluation Criteria In Solid Tumors (RECIST criteria for evaluating tumor size or regional compromise).
- It has been found that 15% to 25% of patients with complete pathological responses (ypT0) also have positive lymph nodes. Is it sufficient to consider that these lymph nodes are outside of the irradiation area and simply make an adjustment to achieve greater regional control? Does morbidity of radiation therapy justify this behavior?
- The true clinical significance of these microscopic residual foci of disease and whether or not these cells can become viable tumors in the medium or long term is one of the risks that is avoided with radical oncological management.
- Recurrence of rectal cancer after initial treatment with radiation therapy presents in diffuse fashion throughout the pelvic region and contains an inherent risk of distant relapse especially hepatic. This means that surgical solutions for relapse are more aggressive but sometimes are not viable.
- The intrinsic radiosensitivity, or relationship of dosages of radiation required to treat rectal cancer, is significantly high while the response radiation is lower in T3, T4 tumors that are fixed to deep planes.
- The data published by Dr. Habr-Gama have not been duplicated in any other unit and are not entirely consistent considering the above cases of T2N0 tumors in their series.
- Current imaging and staging techniques can lead to initial clinical overestimation of early tumors and result in

the appearance of clinical complete response after neoadjuvant treatment (27).

- In addition, current imaging techniques are unreliable for post-neoadjuvant tumor staging given the poor correlation between the prediction of disease status and the current evaluation of the surgical specimen (28).
- All patients with local recurrences after chemotherapy and radiation therapy died within three years following. There may be arguments for wait and see management of early T1 and T2 tumors and for elderly patients who have comorbidities (29, 31).
- The available evidence is insufficient to adopt such a policy in a young patient who has no comorbidities and whose surgical risk is low for comprehensive management of this pathology (32-35).

Rullier and his group have developed a surgical staging system for rectal cancer in the distal third of the colon which suggests that sphincter-sparing surgery does not compromise morbidity, local pelvic control or survival. This surgery is justified for maintaining a patient's body image, genital function and quality of life, without sacrificing radical oncological management of this pathology (36, 37).

We conclude that a cautious reserved towards the observational strategy should be maintained. This strategy involves a decision to delay or avoid performance of radical curative resection but does not have reliable data or prospectively defined protocols available to support it (38, 40).

## IMPLICATIONS OF ALTERNATIVES AND RECOMMENDATIONS

It can be inferred that a patient's response to neoadjuvant chemotherapy and radiation therapy is only one prognostic factor that helps us differentiate whether a patient has high and low risk of recurrence in order to determine who can be cured with local resection and who requires radical surgery.

For elderly patients with early T1 or T2 tumors of the distal rectum who have no possibilities for local resection, who face high risks from surgery, and/or who have serious comorbidities that contraindicate radical oncologic resection, the strategy of watchful waiting is a viable option.

This requires that the gastroenterologist, colorectal surgeon or gastrointestinal surgeon who is leading the monitoring of the patient have not only a clear understanding of the implications of each regular physical examination, but also of its components.

Monitoring requires a thorough physical examination, digital rectal examination, and a colonoscopy or sigmoidoscopy every one to three months depending on institutional protocols or the attending physician's discretion. If there is a lesion, ulcer, nodule or mass, biopsies are recommended.

While they do not rule out malignancy, biopsies provide useful documentation of relapse if it occurs.

Diagnostic imaging is recommended every 6 months. A pelvic MRI should be done to evaluate the mesorectal region, pelvic lymph nodes, and any compromise of the rectal wall and infiltration to adjacent structures. A CT scan of the chest and abdomen can rule out systemic disease. Rectal ultrasound is not considered for this type of monitoring because of alterations of the echoic layers of the rectal wall caused by radiation therapy. None of the studies routinely recommend taking a PET scan.

Blood tests are recommended every time the patient visits the doctor or has a physical examination. Tests should include a liver profile, a test for carcinoembryonic antigen and a test for CA 19-9.

The patient should clearly understand that there is a risk of recurrence of the disease, especially endoluminal but recurrence can be regional (mesorectal, lymph node or peritoneal) or systemic (lung, liver, bone). The patient must sign an informed consent form for this management strategy, and the above considerations should be entered into that consent form.

The patient should also know that surgical and oncologic management is possible for each relapse: local resection if it is endoluminal cancer or radical resection including abdominal-peri-anal resection with a permanent ostomy, low anterior resection of the rectum with a temporary ostomy, or only an ostomy if it is unresectable. As appropriate, adjuvant chemotherapy or biologic drugs may be needed.

If performance of transanal local resection or radical oncologic resection is decided upon, the patient should understand the possible complications, benefits and considerations of each alternative. This should include the possibility or requirement of a permanent ostomy and/or adjuvant chemotherapy (depending on the final pathology report) and an understanding that monitoring is a key part of treatment.

In conclusion, communication and understanding of the implications of the type of management chosen by the medical staff, whether it is observational or surgical, and patient adherence generates confidence from both sides for proper clinical, endoscopic and imaging monitoring. This will enable early diagnosis and treatment of any recurrence of the disease and also allow these patients to be prospectively evaluated in order to conduct clinical studies to provide the answers to questions that may arise in the future.

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