

LOS ANGELES

# COLON AND RECTAL SURGICAL ASSOCIATES

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## RECTAL CANCER TREATMENT. WATCH AND WAIT? A DEFINITE MAYBE.

### MANAGING THE COMPLETE CLINICAL RESPONSE.

There are over 43,000 new cases of rectal cancer diagnosed every year in the United States. Following preoperative treatment with chemotherapy and radiation, also known as neoadjuvant therapy, radical surgical resection has been the next therapeutic step. Not uncommonly, a temporary or permanent ostomy is necessary. But what if there is a complete clinical response to neoadjuvant therapy and there is no longer any visible sign of tumor? Is surgery still necessary? Until relatively recently, the resounding answer has been: YES! Surgical extirpation has been the mandatory next step in treatment.

But now, the answer is: MAYBE!

Welcome to the complete clinical response dilemma.

### HOW COMMON IS A COMPLETE CLINICAL RESPONSE?

It has been observed that 16-27% of patients treated with chemotherapy and radiation will have a complete pathologic response in stage 2 or 3 rectal cancers. After operation, no residual tumor is seen in the operative specimen.

Was it possible that these patients did not require surgery after the pre-operative chemoradiation? Maybe. However, mistaking this complete clinical response for a cure, and then foregoing surgical treatment might have fatal consequences.

In 2002, two studies noted these complete clinical responses but questioned the non-operative approach to managing

rectal cancer. In 2013, these retrospective studies were repeated and demonstrated the feasibility of pre-operative chemoradiation followed only by watchful waiting.

### HOW DO WE ASSESS THE CLINICAL RESPONSE?

Tumor depth can be evaluated with MRI or endorectal ultrasound with an accuracy of greater than 90%. However, these modalities are not as reliable for assessing lymph nodes and can miss malignant lymph nodes. It is not enough to simply note that no visible tumor remains after treatment. The regional lymph nodes must be tumor-free as well. The lack of visible tumor in response to chemoradiation may not correlate with the lymph node status. Even patients with a complete tumor response may harbor residual lymph node disease. Lymph node status is extremely important in determining prognosis and further treatment. Our challenge is to accurately assess potential disease spread.

The surefire accurate way to assess a tumor's response to neoadjuvant therapy is to operatively remove the area and examine the resected specimen. However, low anterior and ultra-low anterior resections as well as abdominoperineal resections have inherent risks, and carry the possibility of requiring a permanent stoma. Studies have evaluated MRI, CT, PET/CT, and trans-rectal ultrasound as useful modalities in the search for metastatic disease, but none have proved sufficiently accurate in identifying a complete responder. Limitations of these studies include the difficulty in distinguishing between fibrosis or scar tissue, from residual tumor.

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*"... sooner or later 'watch and wait' will become an important part of the new primary treatment modality for rectal cancer."*

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## WHY NOT “WATCH AND WAIT”?

### Norman Nigro and Anal Cancer.

The new “watch and wait” approach in the treatment of rectal cancer draws parallels to the treatment of anal cancer. Prior to the early 1970’s, the mainstay of treatment of anal cancer was surgical, with an abdominoperineal resection and permanent colostomy. A 1974 seminal paper published by **Dr. Norman Nigro** showed that treating three anal cancer patients with 30 Gy of external beam radiation combined with a five-day 5-fluorouracil infusion and a single dose of Mitomycin C effectively destroyed all evidence of the anal cancer. The two patients who underwent surgery had no tumor remaining in the specimens and the third patient who refused surgery was disease free at 14 months. Dr. Nigro’s combination radiation and chemotherapy became known as the “Nigro Protocol” and, after further study, it became the new standard of care in the treatment of anal cancer. Surgery was no longer the primary treatment, and instead was reserved for recurrent disease, for disease palliation or for use in those patients who refused surgery or were too sick to undergo surgical extirpation. Over time, refinement of the protocol occurred, and it ushered in a sea change in the treatment of anal cancer. Might this protocol work in rectal cancer patients? Can a new treatment protocol for rectal cancer equal or exceed the good results achieved with anal cancer treatment?

## WHY NOT “WATCH AND WAIT”?

### Angelita Habr-Gama and Rectal Cancer.

**Dr. Angelita Habr-Gama** from Brazil first proposed the “watch and wait” approach for rectal cancer in 2004. She published her landmark paper that same year. The paper was titled “Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results”. Her study noted there was a complete clinical response in 27% of patients after pre-operative chemoradiation. Five-year overall survival and disease-free survival were 100% and 92% respectively in the “watch and wait” group. This led her to the conclusion that surgical resection in the group of complete responders might not be superior to close, non-operative observation. She elaborated that the “watch and wait” approach might avoid the surgical complications of fecal incontinence, sexual and urinary dysfunction, permanent stoma, and other unnecessary morbidities.

The “watch and wait” protocol proposed by Habr-Gama included radiation of 54 Gy, combined with 5-fluorouracil and leucovorin. The combination chemotherapy was continued for 3 cycles beyond the neoadjuvant radiation for a total of nine weeks. After that, patients were evaluated with an initial assessment at week 10 with a digital rectal exam (DRE), flexible sigmoidoscopy, and MRI to assess for a complete clinical response. Rigorous continuing surveillance included DRE, carcinoembryonic antigen (CEA) levels, and endoscopy every 1-2 months for the first year, every 3 months in the second year, and every 6 months after 3 years. If the MRI was normal with the first assessment, then the MRI was repeated every 6 months. Habr-Gama’s results were reported in 2013. Of 70 patients, 68% had a complete clinical response with a 3-year survival of 90% and disease-free survival of 72%. Other studies from the Netherlands, the U.S., and the U.K. have displayed concordance with Habr-Gama’s study in terms of similarity in survival and disease-free rates in the “watch and wait” group versus the conventional group of neoadjuvant therapy followed by surgery.

## FAVORABLE STATISTICS. FAVORABLE PATIENTS?

Statistics, anecdotes and retrospective reviews are all important in the

advancement of our experience. They serve to push the limits of our knowledge and move us forward.

But, in clinical practice involving the care of each patient, the decision making becomes more personal and certainly more frightening for the patient, and more challenging for the surgeon.

There are several small prospective studies that may help in the decision-making process. Overall, in those patients with no demonstrable signs of tumor after initial neoadjuvant therapy, followed by “watch and wait”, there seems to be a 91% three-year survival overall. This compares well with those patients who underwent the more traditional operative treatment after neoadjuvant therapy. Of the “watch and wait” group, 25% required an operation due to tumor regrowth. Seven percent of the “watch and wait” group developed distant metastases. This is still comparable to the operative group. The three year survival in patients who recurred and underwent an operation was 87%.

These preliminary numbers appear quite encouraging.

Large, collaborative institutional prospective randomized studies are in the early stages and are ongoing.

Looming on the horizon, is the work being done at the laboratory bench level, whereby researchers are looking for genetic markers which might inform the patient and clinician as to which tumors are amenable to a “watch and wait” approach. However, this work is in its infancy.

## WHAT IS THE STANDARD OF CARE? WHO CAN WATCH AND WAIT?

Clearly and obviously, avoiding radical extirpative operative intervention is a logical goal. At a minimum, a “watch and wait” approach, if successful, would avoid the potential need for a temporary or permanent ostomy, as well as helping to avoid the urinary and sexual problems that not uncommonly follow surgery. The psychological benefits are many and certainly, patient anxiety is lessened, although the anxiety of an operation might be replaced with the anxiety of watchful waiting using this new, more conservative approach.

One of the main criticisms of the “watch and wait” approach is the uncertainty in ascertaining lymph node status. Under-staging due to limitations of imaging studies could lead to withholding radical surgery in patients who might benefit from a surgical approach. So far, there are no known factors nor identified characteristics that would predict which patients might respond with a complete response.

Presently a non-operative “watch and wait” approach can be offered to patients who refuse surgery, who are too ill with medical comorbidities, or to those who have considered the data, have had informed discussions with their physicians and then decide to use the “watch and wait” approach.

Neoadjuvant therapy followed by surgery remains the accepted cornerstone of therapy for rectal cancer. The “watch and wait” approach is not widely accepted, although more centers are considering it as an option. Large, well-designed prospective randomized trials are needed to validate the “watch and wait” approach.

## AS DAY FOLLOWS NIGHT

As researchers continue to advance our understanding of tumor biology, sooner or later “watch and wait” will become an important part of the new primary treatment modality for rectal cancer. It is not a matter of when, but of how soon?