

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Nonoperative Management of Distal Rectal Cancer After Chemoradiation: Experience with the “Watch & Wait” Protocol

Angelita Habr-Gama¹, Rodrigo Oliva Perez^{1,2}, Patricio B. Lynn¹,
Arceu Scanavini Neto^{1,2} and Joaquim Gama-Rodrigues¹

¹Angelita & Joaquim Gama institute, São Paulo,

²Department of Gastroenterology - Colorectal Surgery Division,
University of São Paulo,
School of Medicine, São Paulo,
Brazil

1. Introduction

Surgical treatment alone for locally advanced rectal cancer (T3/T4 or N1 tumors) has been associated with considerably high local recurrence rates. Even with appropriate total mesorectal excision (TME), radical surgery leads to excellent local disease control only in highly selected cases.(Simunovic et al. 2003) In this setting, the need for additional or complementary treatment strategies was highly warranted.

In the late 80's and early 90's it was observed that the addition of adjuvant radiotherapy with or without chemotherapy significantly improved disease control as well as survival rates in this group of patients.(Krook et al. 1991)

Later on, results from randomized controlled trials suggested that the neoadjuvant approach was superior for local disease control, even when appropriate surgical technique (total mesorectal excision) was performed when compared to adjuvant treatment. (Sauer et al. 2004) Apart from the theoretical advantage of exposing unscarred tissue with optimal oxygen delivery to chemoradiation (CRT), further benefits including reduced toxicity rates, significant tumor downstaging and downsizing, greater rates of sphincter preservation, and better functional results have been reported after neoadjuvant CRT. (Habr-Gama et al. 2004; Sauer et al. 2004)

Tumor downstaging in some patients may be so significant, that no residual cancer was detected during final pathological assessment. Still, radical surgery was associated with considerably immediate postoperative mortality and morbidity rates. In addition to usual postoperative complications, total mesorectal excision may lead to significant sexual and urinary dysfunctions. Also, even when abdominal perineal excision (and a permanent stoma) could be avoided, temporary loop ileostomies are mandatory in order to avoid potential septic consequences of anastomotic leaks in these patients. (Peter Matthiessen et al. 2007)

Therefore, in the setting of a complete tumor regression after neoadjuvant CRT, surgeons have searched for alternative management of patients in order to avoid the potential consequences of TME with or without abdominal perineal resection.

2. Factors associated with tumor response after CRT

Tumor response to neoadjuvant chemoradiation is not uniform and seems to be related to many factors such as specific treatment regimen, timing after CRT completion, tumor/patient characteristics and tumor biology.

2.1 Chemoradiation regimen

Fractionated long course chemoradiation followed by surgery after 6-8 weeks or pelvic short-course irradiation with 25Gy in five fractions followed by immediate surgery (short-course) have been the two most frequent regimens used in the preoperative treatment of patients with resectable T3-4 rectal cancer.

Even though the benefits in local disease control seem to be equivalent between short-course RT and long-course chemoradiation therapy, (Bujko et al. 2006) there are significant differences in terms of tumor downstaging between patients undergoing these two regimens. In patients undergoing short-course RT, the rates of pCR are significantly lower when compared with patients undergoing long-course neoadjuvant chemoradiation. Two aspects should be considered; first, the long-course regimen includes chemotherapy, second, cancer cells damaged after radiotherapy need time to undergo necrosis and usually in patients undergoing short-course RT, surgery is performed within 1 week after RT completion whereas long-course CRT is followed by radical surgery after at least 6-8 weeks. The addition of chemotherapy to radiation in the neoadjuvant setting has resulted not only in improvements in local disease control (ie, lower recurrence rates) but also in tumor downstaging. (Jose G Guillem et al. 2008) In a randomized trial of patients undergoing RT with or without 5-FU- based chemotherapy, patients in the CRT group more frequently had a complete pathologic responses less lymph node metastases as well as vascular invasion. Additionally, patients treated by CRT had fewer overall lymph nodes recovered in the resected specimens and decreased tumor size. (Bosset 2005)

A review of phase II and III studies using different neoadjuvant CRT regimens for rectal cancer identified several predictive factors for complete pathologic response, including the dose of radiation therapy delivered, the method of 5-FU infusion, and the use of additional drugs to standard 5-FU based regimens. After reviewing 71 studies with over 4,000 patients treated with different regimens, complete pathologic response ranged from 0% to 42% and was significantly associated with the delivery of radiation doses higher than 45-Gy, 5-FU regimens with continuous infusion, and the use of a second drug, most frequently oxaliplatin. (Sanghera et al. 2008)

Despite the suggestion that the use of additional drugs (other than 5-FU) could enhance tumor response to CRT, recently reported results from a prospective randomized trial showed that the addition of oxaliplatin to a 5-FU- based CRT regimen was not associated with significantly higher rates of pCR. In turn, patients treated with oxaliplatin experienced significantly more treatment-related toxicities. (Gérard et al. 2010)

Also, the observation of significant activity of targeted biological drugs, such as bevacizumab and cetuximab, led to its utilization in phase I and phase II trials in the neoadjuvant setting. However, the expected increase in pCR rates among patients

undergoing this 'triple' therapy (5-FU, oxaliplatin, and cetuximab) was not observed in any of the trials. A review of these trials also suggested a subadditive interaction between capecitabine, oxaliplatin, and cetuximab as reflected by decreased rates of pCR (9 vs. 16%) and significant decrease in tumor regression grades (more than 50% of tumor regression) among surgical specimens from these patients when compared with patients undergoing treatment with capecitabine and oxaliplatin alone. (Weiss et al. 2010) It is not clear whether the inclusion of patients according to the K-ras status could have any influence in response to neoadjuvant CRT with this triple approach. (Glynne-Jones et al 2010)

Considering that 5FU is actually relevant for the development of complete tumor regression and that other drugs have been unsuccessful in improving rates without increasing toxicity, the use of additional cycles of 5FU in the neoadjuvant regimen has also been suggested. With the use of additional cycles of 5FU and leucovorin delivered during RT and during the interval period between CRT and tumor response assessment (also known previously as the "resting period"), increased rates of complete tumor regression without increased toxicity has been reported. (Habr-Gama et al. 2009)

2.2 Timing of assessment of tumor response

Assessment of response after CRT is crucial, and remains a real challenge even for the most experienced colorectal surgeon. The issues of when and how tumor response assessment should be performed are still under debate.

Since publication of the Lyon Trial in 1999, optimal surgical timing after neoadjuvant CRT has been accepted to be 6 weeks. In this study 201 patients with distal rectal cancer T2-3Nx were randomized before radiotherapy (39 Gy in 13 fractions) into two groups. The short interval group had surgery performed within 2 weeks after completion of radiation therapy compared to 6 weeks in the long interval group. After a median follow-up of 33 months, no differences in local relapse, morbidity and short-term survival between the two groups could be observed. On the other hand, improved clinical tumor responses ($p = .007$) and pathologic downstaging (10.3% v 26% $P = .005$) were observed in the long interval group. (Francois et al. 1999) These results provided the only prospective evidence to support a interval period of at least 6 weeks from CRT completion before surgery was performed in order to obtain maximal or optimal tumor downstaging.

Even though there was a suggestion from clinical practice that 8 weeks could probably improve the effects of CRT on tumor downstaging, only recent retrospective studies were able to provide further support that longer periods after CRT completion could be associated with higher rates of tumor downstaging. These studies have shown that patients managed by radical surgery 7 to 8 weeks after CRT completion had increased rates of complete pathological responses. (Moore et al. 2004; Tulchinsky et al. 2008;) In another retrospective review of patients managed by neoadjuvant CRT, a steep increase in complete pathological response rates was observed when surgery was performed 7 weeks after CRT completion. Even more interesting, these rates of complete response seem to stabilize after 12 weeks, perhaps suggesting no additional benefit in terms of tumor downstaging after this period. (Kalady et al. 2009) Recently, a study compared patients with rectal cancer undergoing neoadjuvant CRT followed by radical surgery after 8 or 12 weeks from CRT. Even though this study was not randomized and the longer interval group (12 weeks) had significantly more advanced disease at baseline, there was a higher rate of pCR rate in this latter but without statistical significance. Noteworthy, the authors showed no increase in

postoperative surgical complications among the longer interval group (12 weeks). (Garcia-Aguilar et al. 2011)

On the other hand, the risk of leaving the tumor in situ for prolonged periods of time, with potential metastatic dissemination of tumor cells during this period has been used as an argument for performing surgery shortly (<8 weeks) after CRT completion. However, tumor cell death seems to be related to a process induced by ionizing radiation. It is thought that after exposure to a dose of 44 Gy, metastatic potential of these tumors might decrease significantly because of the potential decrease in the overall number of surviving tumor cells. (Withers and Haustermans 2004) In recent studies it was found that prolonged intervals (>8 weeks) from CRT to surgery may not have any associated oncologic compromise. In addition, these patients were associated to less postoperative morbidity, further supporting the safety of assessing tumor response at prolonged intervals. (Kerr, Norton, and R Glynn-Jones 2008) (Habr-Gama et al. 2008a)

2.3 Tumor features and biology

Several aspects of the primary rectal cancer have been considered to be predictors of tumor response or complete pathological response to neoadjuvant CRT such as initial disease staging, tumor height and extension. Even though very few studies have included patients with cT2N0 rectal treated by neoadjuvant CRT, so far there has been no data to support that these tumors would develop pCR more frequently. Still, as experience increases with these earlier tumors being treated with CRT, there is still a chance that baseline stage is indeed a predictor of response to CRT.

On the other hand, tumor extension has been shown in one retrospective study of over 500 patients to be an independent predictor of pCR after neoadjuvant CRT. In one study, circumferential tumor extent of <60% was a significant predictor of pCR. Even though tumor distance from the anal verge was not a predictor of pCR, tumors located in the distal 5cm of the rectum were more likely to develop greater tumor downstaging. (Das et al. 2007)

Finally, there is still hope that molecular biology will provide additional information regarding tumor response to neoadjuvant CRT. Few studies have addressed the role of gene expression in predicting response to CRT. (Ghadimi et al. 2005; I.-J. Kim et al. 2007; Rimkus et al. 2008) However, these studies did not seem to agree on what a “good response” was and while some of them considered only patients with pCR, others grouped together patients with significantly different ypTNM stage classification as long as less than 10% of tumor cells were present (based on tumor regression grading systems). The end-result is that all three studies suggested a set of genes capable of predicting a “good response” without a single gene in common between them. (Perez 2011) In this setting, perhaps further studies using more advanced technologies in gene expression analysis may provide more definitive and useful information.

3. Rationale for pursuing a non-operative approach

Radical surgery (with total mesorectal excision) is still considered fundamental in the treatment of distal rectal cancer, considered by many necessary regardless of tumor response to neoadjuvant CRT. However, it is associated with significant immediate morbidity and mortality. Anastomotic leak is probably the most important complication and is reported in up to 12% of cases. (Sauer et al. 2004; Chessin et al. 2005) Perioperative mortality may reach 3% and is significantly higher, reaching up to 13% when an

anastomotic leak is present among patients who do not undergo temporary diversion. (P Matthiessen et al. 2004; Eriksen et al. 2005) Considering the fact that temporary stoma is almost always required, additional morbidity or even mortality related to stoma creation and take-down should be considered in the cumulative morbidity of rectal cancer management. (Perez et al. 2006). Also, even though nerve-preserving technique is now standard, the rates of urinary and sexual dysfunctions are quite significant. Finally, even though sphincteric function and quality of life among patients undergoing ultra-low anterior resections are acceptable, results are far from perfect (Denost et al 2011). Therefore, alternative treatment strategies to TME are warranted.

Considering that final disease stage (after CRT) is the most significant prognostic factor in patients with rectal cancer and that pCR is associated with improved oncological outcomes, these patients would be ideal candidates for alternative procedures avoiding TME. Unfortunately, confirmation of absence of residual microscopic disease is only possible after TME.

After all, is it justified to make our patients undergo a morbid and sometimes mutilating procedure when not even a single cancer cell is collected? In this setting, identification of patients with complete tumor regression determined by clinical, endoscopic and radiological assessment has been proposed in order to avoid immediate TME in a significant proportion of cases. Rather than providing a radical shift in the management of rectal cancer, this approach suggests close surveillance of a select group of patients with a high suspicion of complete tumor response without immediate radical surgery. Therefore, patients with no residual cancer may have a chance to be spared from a major surgical procedure while patients with residual disease and suspected for complete response may have surgery postponed or delayed without oncological compromise

4. Assessment of tumor response

Once an alternative approach to patients with rectal based on response to CRT is considered, the next step is to establish an efficient and accurate assessment of tumor response. Even though there is no perfect tool for such purpose, combination of different modalities may provide sufficient information for identification of appropriate candidates to non-immediate surgical resection. Patients with no evidence of residual disease by such assessment are considered as complete clinical responders (cCR's). Considering timing is crucial for tumor regression after CRT as discussed earlier, assessment of tumor response should be performed at least after 8 weeks from CRT and perhaps in some patients after 12 weeks from CRT.

4.1 Clinical assessment

Although clinical symptoms do subside in patients with complete clinical response, a significant proportion of patients also present with some degree of symptoms relief despite the presence of residual cancer. Therefore, the absence of clinical symptoms should not be considered as an absolute marker of complete response to CRT.

On the other hand, clinical assessment using digital rectal examination and (rigid or flexible) proctoscopy are the mainstay of clinical response assessment after CRT. Accuracy of clinical assessment of patients with rectal cancer after neoadjuvant CRT has been studied with disappointing results regarding sensitivity and specificity by others. Still,

these studies were performed using 6-week intervals between CRT completion and response assessment and therefore could have detected residual disease in patients with ongoing tumor regression. In addition, the inclusion of different examiners could have biased results. (Hiotis et al. 2002)

4.2 Radiological studies

The use of radiological studies during assessment of tumor response in patients with rectal cancer after CRT completion is still a matter of controversy. Staging of primary tumor depth of penetration and distance from the circumferential margin seems to be adequately provided by endorectal ultrasound and magnetic resonance imaging.

However, after neoadjuvant CRT, distinguishing between residual cancer and transmural fibrosis may be significantly compromised by both imaging methods because these tools basically rely on morphologic features. (Mezzi et al. 2009; Suppiah et al. 2009)

For this reason CT, and endorectal ultrasound (ERUS) are probably best suited for the diagnosis of any residual extrarectal disease, such as a mesorectal enlarged nodes or masses. Thickening of the rectal wall, densification of the perirectal fat, or the presence of small perirectal nodes (less than 5 mm) should not precipitate any specific or immediate surgical attention, particular if other studies such as endoscopic and clinical assessment are normal. These findings are commonly seen in patients with cCR.

Previous studies addressed the value of rectal tumor volumetry on standard T2-weighted MR images for the assessment of response after CRT but showed conflicting results. One report did not find difference in tumor volume reduction rates between patients with pCR and those with residual disease. (Y.H. Kim et al. 2005) On the other hand a more recent report found a significant association with pCR for patients with a tumor volume reduction rate of more than 75%. (Kang et al. 2010)

With the introduction of diffusion-weighted (DW) MRI, significant amount of interest has been focused on this particular study. In a recent multicentric study, three trained radiologist reviewed 120 patients, comparing standard MRI with DW MRI and all them found improvement in sensitivity and specificity rates using DW MRI. (Lambregts et al. 2011) Another recent report showed that post-CRT volumetry on DW-MR images were significantly more accurate than on T2-weighted MR images to assess a CR after CRT. (Curvo-Semedo et al. 2011) Still further studies are needed before these tools are definitively incorporated into clinical practice.

The incorporation of positron emission tomography (PET/CT) imaging into the staging work-up provided significant additional information by overlaying metabolic activity data to standard radiological morphology. Also, PET imaging may provide an objective estimate of the metabolic activity of a specific area as represented by the standard uptake value measured at various phases of the study.

One study of 25 patients with rectal cancer compared the results of baseline PET-CT with a second PET-CT performed after 6 weeks from CRT completion. All patients included in the study experienced a decrease in maximum standard uptake values (SUVmax) between baseline and 6-week PET-CT scans. Also, the final SUVmax obtained at 6 weeks was significantly associated with primary tumor downstaging (patients with tumor downstaging exhibited significantly lower SUVmax). (Calvo et al. 2004) In another study including 15 patients undergoing baseline PET followed by a second PET 6 weeks after CRT completion, the visual response score was shown to provide superior prediction of tumor downstaging in addition of the extent of pathologic response to CRT compared to standard CT. (Guillem

et al. 2000) This same group of patients was prospectively followed and outcome analysis showed that patients with greater percentual decrease between baseline and 6-week PET SUVmax values were associated with improved survival. A cutoff of a 62.5% decrease/difference between baseline and 6-week PET SUVmax values was a significant predictor of disease-free survival.(Guillem et al. 2004)

However, these results should be considered carefully, since they included only a small number of patients and none of them considered that increased interval periods between CRT and tumor response assessment might have influenced results.

In another study, 30 patients with locally advanced rectal cancer treated with CRT and surgery were assessed by pre and post-CRT PET-CT for tumor response after 7 weeks from CRT. PET/CT correctly identified six of eight patients (specificity 75 percent) with complete pathologic response. However, the sensitivity and accuracy of positron emission tomography/computer tomography was only 45 percent and 53 percent respectively. The positive and negative predictive values were 83 and 33 percent, respectively. Authors concluded that PET/CT performed was not able to predict the pathological response in locally advanced rectal cancer. (Kristiansen et al. 2008)

A prospective study with the use of PET/CT for the assessment of tumor response to CRT is currently underway in our Institution analyzing nearly 100 patients with cT2-3NxM0 after neoadjuvant CRT. The results of this study may provide significant additional information to the role of PET/CT in the assessment of tumor response.

4.3 Endoscopic biopsies after CRT

Surgeons and endoscopists are frequently faced with the issue of performing post-CRT biopsies in residual lesions within the rectal wall after neoadjuvant CRT. Even though it may sound obvious that a positive biopsy may accurately identify incomplete responses, it could also be suggested that negative biopsies could possibly help in identifying complete pathological responses despite the presence of clinically detectable disease. In fact, there is not much evidence regarding the utility of forceps' biopsies for tumor response assessment. In one retrospective review of patients undergoing post-CRT biopsies, the negative predictive value was as low as 36%.(Meterissian et al. 1994) However, it must be noted that these were unselected patients being assessed significantly earlier than 8 weeks from CRT completion.

In a retrospective review of patients undergoing neoadjuvant CRT restricted to patients with significant tumor downsizing, and therefore who were most likely to have developed pCR, post-CRT biopsies resulted in a negative predictive value of 21%.(Perez et al. 2011) In this setting, a negative biopsy of a clinically detectable lesion, even after significant tumor downsizing is not capable of ruling out residual disease and should not prevent surgeons from performing radical surgery. Alternatively, select cases may be appropriate for a excisional biopsy (through a full-thickness local excision) either as a diagnostic or therapeutic procedure.

4.4 Is there a role for CEA?

In addition to clinical, radiological and endoscopic assessment of tumor response, determination of CEA levels before and after CRT may also be useful. In a study with more than 500 patients with rectal cancer managed by neoadjuvant CRT, low CEA before treatment was a predictor of ypCR after radical surgery in univariate analysis. (Das et. al.

2007) Similar findings have been reported in a retrospective analysis of patients undergoing variable neoadjuvant CRT regimens for very low (<2.5 ng/dL) pretreatment CEA levels. (Moreno García et al. 2009)

An increase in CEA levels or persistence of at least 70% from baseline levels has also been suggested as a significant predictor of worse outcome patients with CEA levels >6 ng/ml at baseline. (C.W. Kim et al. 2011) Also, different cutoff values have been considered for patients undergoing CRT when compared to standard colorectal cancer patients. A retrospective analysis of 109 patients undergoing neoadjuvant therapy, identified a cutoff value for CEA <2.7 ng/ml at 4 weeks from RT completion to be a statistically significant marker of tumor regression. (Jang et al. 2011)

The author's own experience with pre and post-CRT CEA levels suggests that only post-CRT CEA after at least 8 weeks from CRT completion was associated with the development of complete clinical response and improved disease-free survival. Both pre-treatment CEA and variation between pre and post treatment CEA levels were unpredictable of response and oncological outcomes. (Perez et al. 2009)

5. A Main concern: Lymph node assessment

In patients undergoing neoadjuvant CRT for rectal cancer, there seems to be tumor regression within the primary and perirectal nodes. This observation has been suggested by the decreased risk for the presence of lymph node metastases among patients undergoing neoadjuvant CRT when compared to patients managed by immediate radical surgery.

The presence of viable lymph node metastases within the mesorectum despite complete primary tumor regression is probably one of the most significant concerns regarding the safety of a non-immediate operative approach. The risk of residual nodal disease (N1) in patients with complete primary tumor regression (ypT0) may vary between 0% and 7%. (Stipa et al. 2004; Zmora et al. 2004; Perez et al. 2005; Pucciarelli et al. 2005) Again, these rates might reflect differences in doses of radiation therapy and timing of surgery after RT completion. Noteworthy, the higher rates of ypT0N1 are associated with patients undergoing surgery no longer than 6 weeks after CRT completion and could represent lymph node metastases that were still in the process of developing radiation-induced cell death. Additionally, the clinical relevance of microscopic residual lymph node metastases is still poorly understood. In a parallel to colorectal cancer, the presence of lymph node micrometastases has not been completely accepted as a clinically relevant finding. (Fleming et al. 2007) Even in the worst-case scenario, the risk of residual microscopic lymph node metastases after ypT0 is still less than the risk of residual microscopic lymph node metastases in patients with pT1 rectal cancer, which is around 12-13%. (Nascimbeni et al. 2002)

Still, the concept of nodal sterilization secondary to neoadjuvant CRT remains highly controversial. The finding of mucin deposits within lymph nodes that have no residual cancer cells in patients with rectal cancer who have received neoadjuvant CRT provides indirect evidence of such sterilization. (Perez et al. 2008) Recent data suggests that the presence of acellular mucin is present in up to 27% of specimens with ypCR and 19% of them also showed acellular mucin within the nodes recovered after radical resection. Surprisingly, this finding had no negative influence on the outcomes of these patients, possibly representing evidence of tumor sterilization both within the rectum and the lymph nodes. (Smith et al. 2010)

Interestingly, the effects of RT or CRT may also be observed in the number of recovered nodes after radical surgery. Data obtained from the Surveillance, Epidemiology and End Results

(SEER) database indicates that patients undergoing neoadjuvant radiation therapy had significantly fewer retrieved nodes from the surgical specimen compared to patients undergoing surgery alone after a multivariate analysis. The number of retrieved lymph nodes was significantly higher in patients with N1 disease. (Baxter et al. 2005) This observation of an overall reduction in the number of lymph nodes among patients undergoing neoadjuvant therapy seems to be influenced by the time elapsed between radiation completion and surgical resection. One study showed that the number of recovered lymph nodes was significantly affected by the interval between CRT completion and surgery, but not by total radiation doses delivered. Exposure to longer interval periods led to recovery of fewer lymph nodes in surgical specimens. Two implications could be deduced from this: first, the critical number of lymph nodes required for proper staging of rectal cancer may not be the same for patients undergoing neoadjuvant CRT as for patients who go straight to surgery; second, the effects of radiation on lymph nodes seem to be time dependent, similarly to what has been observed for primary tumor regression. (Sermier et al. 2006)

Lymph node recovery may be further influenced by technical issues, including the use of fat-clearing solutions. In this setting, even though fat cleansing solutions were once considered too labor-intensive and potentially toxic, this technique may ultimately result in improvement in rectal cancer staging in patients undergoing neoadjuvant CRT. (Wang et al. 2009)

In a retrospective review of patients with incomplete clinical response after neoadjuvant CRT managed by radical surgery, outcomes of patients with no recovered nodes in the radical surgery specimen were slightly better than those of patients with node-negative disease, and significantly better than patients with node-positive disease. These findings suggest that patients with the absence of nodes in the resected specimen may represent a subset of patients with particularly increased sensitivity to CRT. (Habr-Gama et al. 2008b)

6. What is a complete clinical response?

One of the main limitations for the widespread use of this alternative approach without immediate surgery is the lack of a definitive or standardized definition of a complete clinical response. In this setting, clinical and endoscopic findings have been suggested as clinically useful in defining what is a complete clinical response. (Habr-Gama et al. 2010)

6.1 Clinical and endoscopic findings in cCR

Considering endoscopic assessment is performed after 8 weeks from CRT completion, a few considerations may be relevant to the decision between a complete and incomplete response:

1. Whitening of the mucosa in an area of the rectal wall may be frequently observed in patients with cCR. (Fig. 1)
2. Teleangiectasia (small derogative blood vessels seen on the rectal mucosa at the area previously harboring the primary cancer) is also frequently observed in complete clinical responders, even in long-term follow-up.
3. A subtle loss of pliability of the rectal wall harboring the scar; usually observed during manual insufflations at proctoscopy with light stiffness of the wall. In the context of no additional positive findings of residual cancer, this may also be considered as a feature of cCR
4. Whenever a tumor cannot be felt or seen, patients should be considered as complete clinical responders.

6.2 Clinical and endoscopic findings of incomplete response

Some endoscopic findings should be considered to be at great risk for the presence of residual cancer. In any of these situations, a surgical action is probably warranted, at least for diagnostic purposes. In this setting, a non-surgical approach may be quite worrisome:

1. Any residual deep ulceration with or without a necrotic center.
2. Any superficial ulcer, irregularity, even in the presence of only mucosal ulceration. (Fig. 2)
3. Any palpable nodule, easily defined by digital rectal examination, even in the presence of mucosal complete integrity.

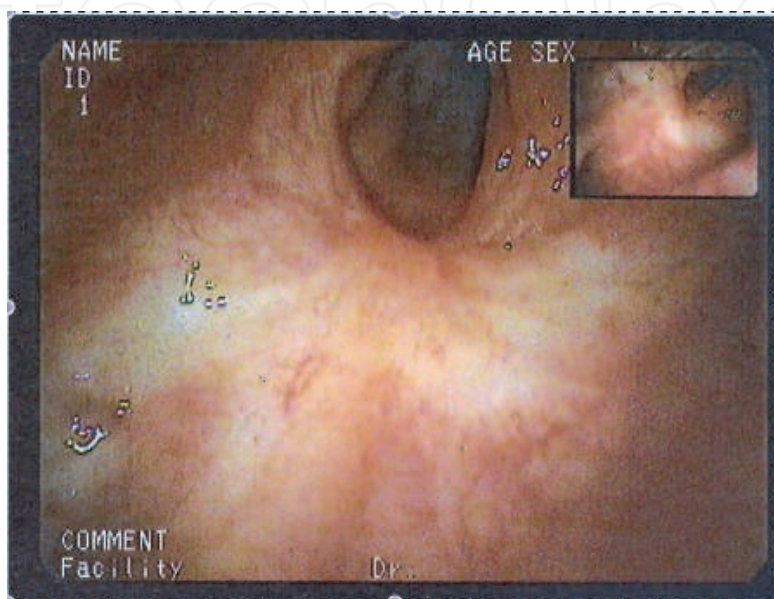


Fig. 1. Endoscopic finding in a patient with Complete Clinical response.

7. The watch-and-wait protocol algorithm

Patients with complete clinical response, either after clinical assessment or after transanal local excision (ypT0), are enrolled in a strict follow-up program (Fig. 3). Adherence to the program is critical because distinguishing between complete and near-complete responses may sometimes be difficult and final decision may only be possible after a few follow-up visits. This is why an empirical 12 month probation period has been suggested where only patients that sustain a complete clinical response are considered as cCR's (Habr-Gama et al. 1998) (Habr-Gama Ann Surg 2004).

This algorithm includes monthly follow-up visits with digital rectal examination and rigid proctoscopy in every visit for the first 3 months and every two to three months during the rest of the first year. CEA levels are determined every 2 months. As discussed previously, PET-CT is currently being investigated for its usefulness in tumor response assessment in a prospective study. Other radiological studies, including pelvic CT scans or magnetic resonance imaging, are performed at the time of initial tumor response assessment, and then every 6 months if there are no signs of tumor recurrence. Again, the main objective of these radiological studies is to rule out any sign of residual extrarectal disease, such as residual nodal disease that would require further investigation or even radical resection.

Patients are fully informed that complete clinical regression of their primary tumor may be temporary and disease recurrence or tumor regrowth may occur at any time during follow-up. In the case of obvious recurrence or tumor regrowth, radical surgery is strongly

recommended. Small nodules or scars may develop over time and can be managed by full-thickness transanal excision (either standard or Transanal Endoscopic Microsurgery), primarily as a diagnostic approach.

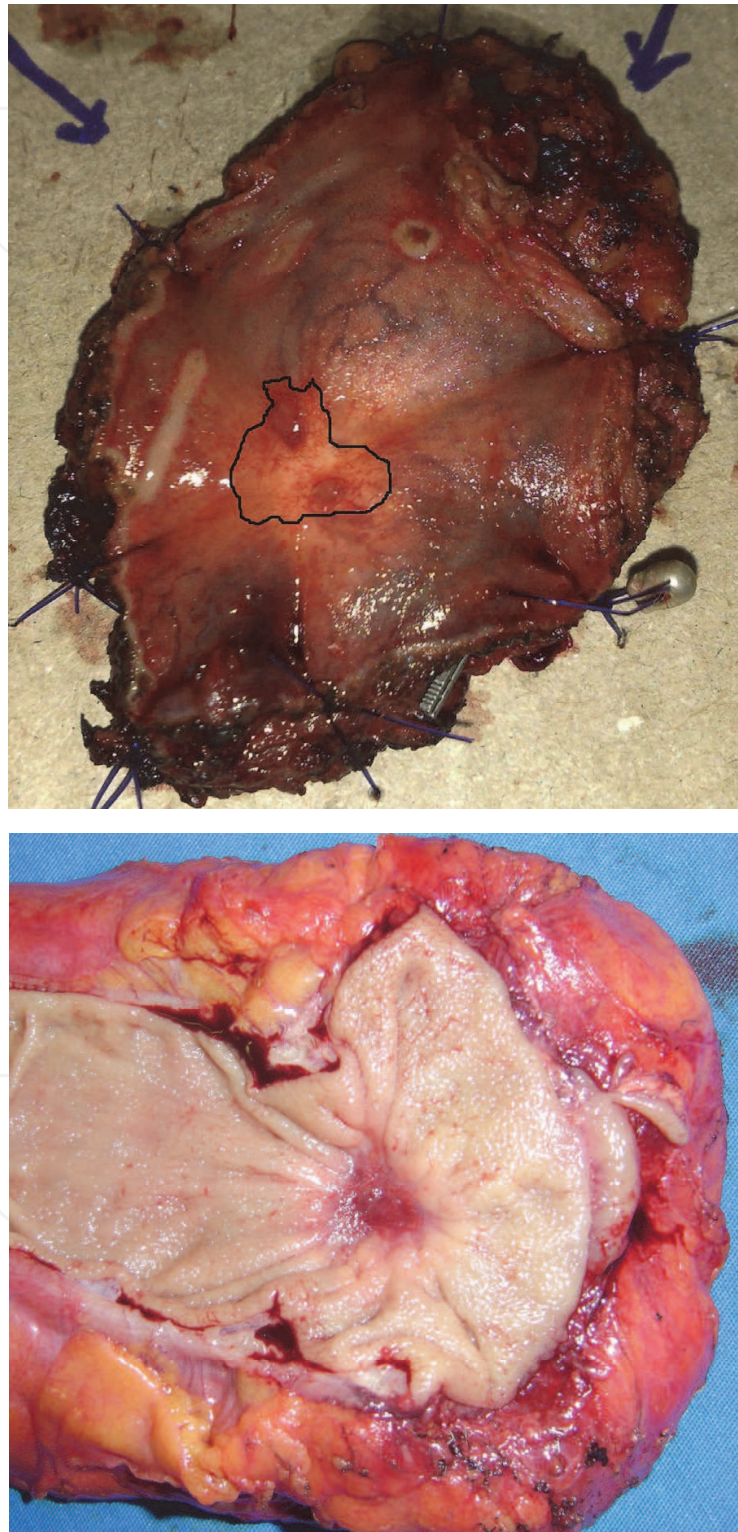


Fig. 2. Surgical specimens of rectal adenocarcinoma patients with incomplete responses to neoadjuvant chemoradiation therapy.

After 1 year of sustained, complete clinical response, patients are recommended for follow-up visits every 3 months, using the same clinical assessment tools used at initial patient assessment.

This treatment strategy evolved since the beginning of our experience in 1991. Our accuracy in clinical assessment of tumor response has probably improved significantly with growing experience. At the begining, patients were more frequently followed without immediate surgery when a near-complete clinical response was considered with the hope that time would lead to a complete clinical response. More recently, these patients have been more readily assessed using full-thickness local excision as a diagnostic procedure, and according to the pathologic report they are then either managed by strict observation or referred to immediate radical surgery. Availability of surgical techniques such as Transanal Endoscopic Microsurgery has also lowered the trigger for a excisional biopsy (Full Thickness Transanal Local Excision) in the presence of questionable residual lesions.

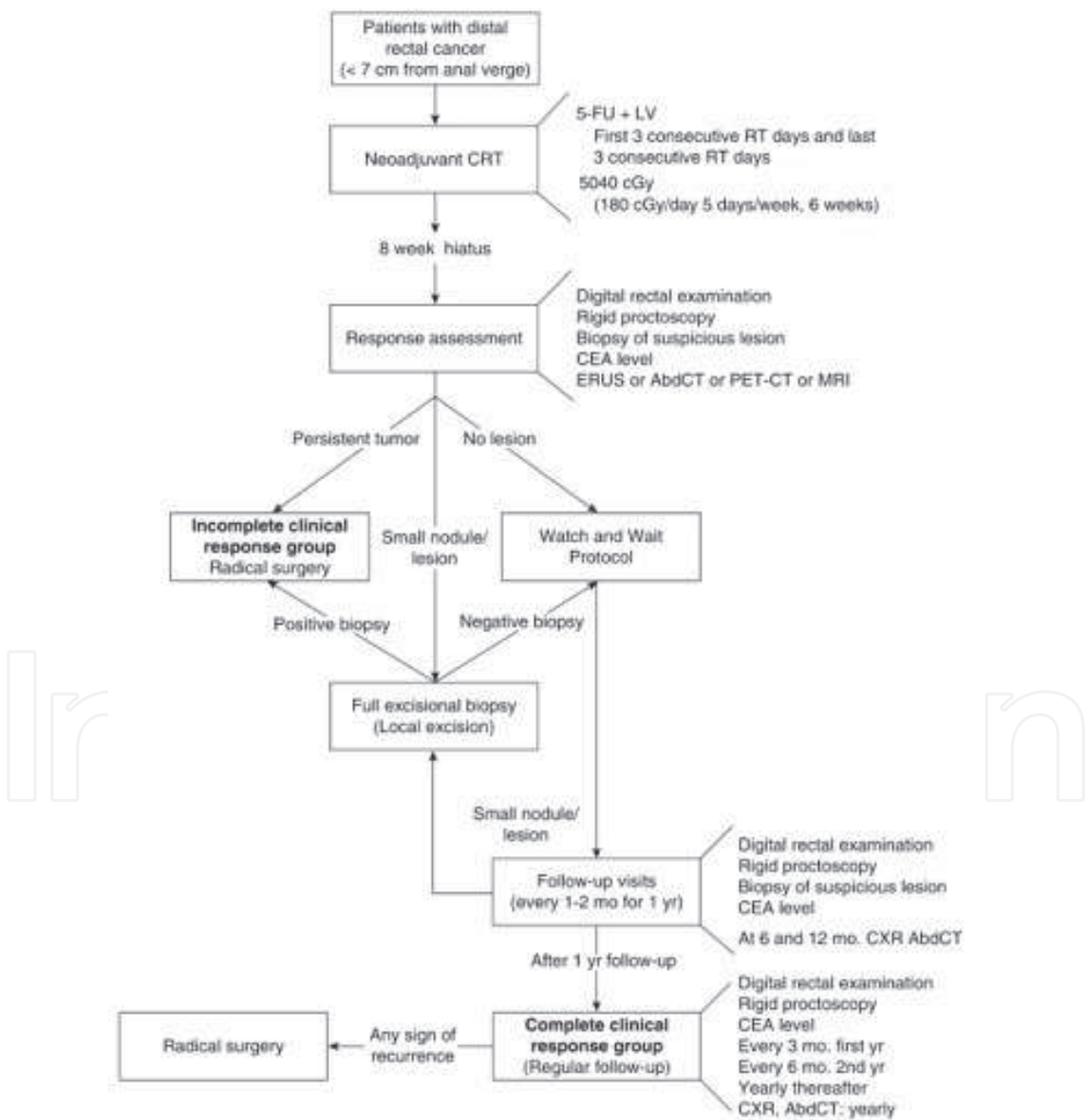


Fig. 3. Watch & Wait Algorithm

8. The extended chemoradiotherapy regimen

An interesting strategy to increase the rates of tumor response is the delivery of chemotherapy during the waiting or resting period between radiation completion and tumor response assessment. Since February 2005, this approach has been adopted at our Institution. Radiation therapy consists of 45 Gy of radiation delivered by a three-field approach with daily doses of 1.8 Gy on weekdays to the pelvis, followed by a 9-Gy boost to the primary tumor and perirectal tissue (54 Gy total). Concomitantly, patients receive three cycles of bolus 5FU (450 mg/m²) and a fixed dose of 50 mg of leucovorin for three consecutive days every three weeks. After completion of radiation, patients received three additional identical cycles of chemotherapy every three weeks (21 days) during nine weeks. Tumor response assessment is performed immediately at 10 weeks from radiation completion. (Fig 4)

In a preliminar report of our series including T2/T3 distal rectal cancers, the sustained complete clinical response rate (>12 months) was 65% with no significant increase in chemotherapy-related toxicity rates. After a recent update of this same cohort of patients, complete clinical response rate seems to be sustained after a median follow-up of more than 36 months at 65%.(Habr-Gama et al. 2009)

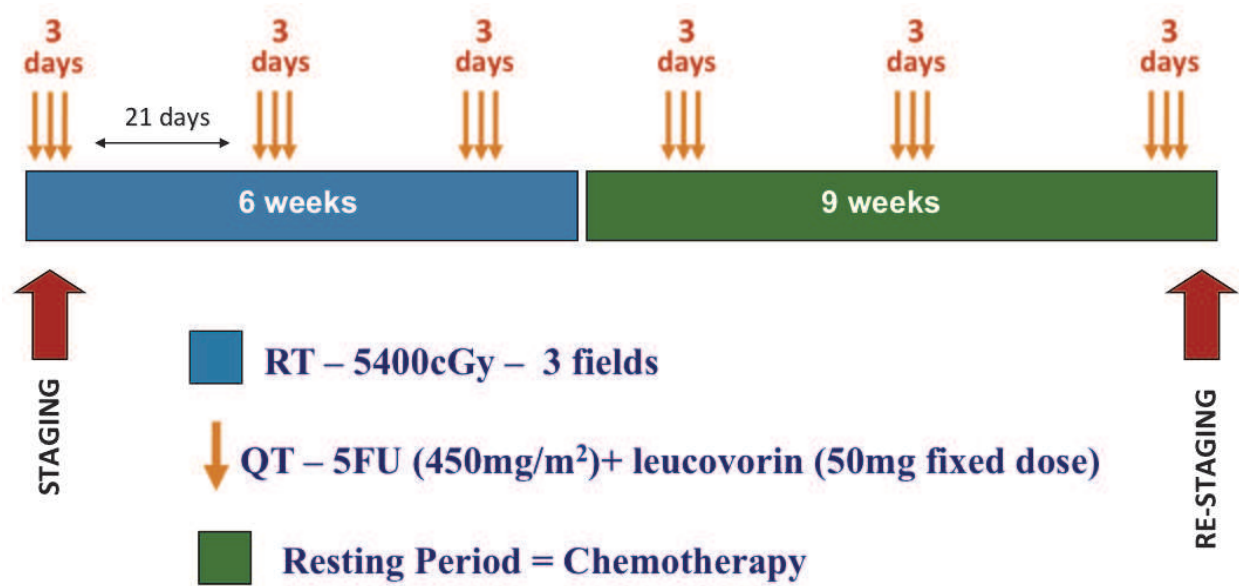


Fig. 4. The extended Chemoradiation regimen

9. Long-term results

At the beginning of our experience several patients were managed by radical surgery since residual cancer could not be confirmed or ruled out. This included patients with residual scars that were not candidates for local excision and those with partial narrowing of the rectum. In this context, many patients were operated and found to have ypT0 (absence of residual tumor). More recently, incorporation of TEM (Transanal Endoscopic Microsurgery) for diagnostic or staging purposes may lead to a significant decrease in the rates of pCR after radical TME.

In an attempt to understand the potential benefits of oncological surgery in terms of survival and local disease control, we performed a retrospective study where patients with complete

pathological response (pCR) were compared to patients with cCR managed non-operatively. (Habr-Gama et al. 2004)

Patients managed by observation alone had similar outcomes to those managed by radical surgery in terms of long term survival. On the other hand, local recurrences were higher on the observation group, but noteworthy, all recurrences were within the rectal wall and amenable to surgical salvage. No pelvic relapses without endorectal component was observed.

Five-year overall and disease-free survival rates were associated to disease stage (clinical or pathological) and were 88% and 83%, respectively, in pCR group and 100% and 92% in cCR group respectively. These excellent survival rates in patients stage pCR and cCR were significantly better than those observed in patients ypII and ypIII. Curiously patients with stage ypI had intermediate results (Habr-Gama A, Perez RO, Nadalin W, et al. Long-term results of preoperative chemoradiation for distal rectal cancer correlation between final stage and survival. *J Gastrointest Surg* 2005;9:90-9; discussion 9-101.).

10. Survival and recurrences

Final TNM classification after neoadjuvant CRT remains the best predictor of survival in patients with rectal cancer. In a study of patients with similar baseline stages, final pathological classification distinguished those with worse and better outcomes.

Still, there is no prospective evidence favoring neoadjuvant RT over adjuvant CRT in terms of survival benefits. One explanation for this observation could be the detrimental effect of neoadjuvant CRT on host immunologic response against rectal cancer such as the potential blockade of peritumoral inflammatory as immunologic response. (Perez et al. 2007)

It has been suggested that adjuvant chemotherapy can improve survival only in highly selected patients with substantial tumor downstaging (ypT0-2). (Collette et al. 2007) These results may lead to a dramatical change in management of these patients who used to be considered for adjuvant treatment according to pretreatment staging.

An interesting observation is that in our series, systemic recurrences in cCR patients occurred considerably earlier than local recurrences. Besides intrinsic tumor behavior, this could be partly explained by the staging inaccuracy of the different available imaging modalities, which were probably not capable of detecting microscopic foci or metastatic disease at initial presentation. Also, local recurrences were observed in 10% of patients managed nonoperatively after a cCR. Interestingly, there were no extrarectal pelvic recurrences. Even though some recurrences may develop from the outer layers of the rectal wall, in all cases there was some luminal evidence of recurrence that could be detected by digital and rectoscopic examination.

Again, local recurrences developed considerably later during follow-up. This has also been observed in other series, where more than one third of patients who develop local recurrences after neoadjuvant CRT and radical surgery did so after 5 years of follow-up. In contrast, 75% of patients who develop local recurrences after radical surgery alone do so within 2 years of follow-up. This information may have implications when considering follow-up and surveillance strategies. (Habr-Gama et al. 2008a)

11. Salvage therapy

It has to be highlighted that up to now, all local recurrences in patients with cCR after neoadjuvant CRT were amenable to salvage therapy. These recurrences and their salvage

procedures were performed at considerably long intervals after CRT completion (mean >50 months). In almost half of the cases an abdominoperineal resection (APR) was performed. Also, almost one third of these patients presented with low and superficial recurrences, amenable to full thickness transanal excision. (Habr-Gama et al. 2006)

A significant subgroup of patients, presented early tumor regrowth (within 12 months from CRT completion). These patients were most commonly misdiagnosed as cCR and had their definitive surgical treatment postponed for a variable period of time. This raised the issue whether these patients could have been harmed from an oncologic standpoint, by delaying definitive surgical resection. However, long-term data revealed that they fared no worse than patients with incomplete clinical response and managed by radical surgery after 8 weeks from CRT completion. Noteworthy, final pathology in this group revealed significant tumor downstaging and even lower rates of lymph node metastases, further supporting the idea that downstaging is a time-dependent phenomenon. The fact that these patients were more frequently managed by APR, could reflect the motivation (by the surgeon and the patient) to delay final decision on radical resection, knowing that tumor regression could be still going on. (Habr-Gama et al. 2008a)

12. Perspectives

Several aspects in the management of complete clinical response after neoadjuvant CRT remain unresolved and should be a focus of future clinical and basic science research.

Novel radiation therapy regimens including alternative radiation doses, delivery methods, and technical variants to maximize radiation-related tumor cell death and minimize side effects is an area of special interest. In addition, improved chemotherapy regimens might lead to an increase in the rate of complete clinical response and, possibly, improve survival rates. Some investigators have suggested the use of aggressive induction chemotherapy before the delivery of radiation to provide immediate treatment of undetected microscopic foci of metastatic tumor cells in addition to the primary tumor. These regimens are currently under investigation in controlled trials to provide data on safety and long-term benefits. (Chua et al. 2010)

Another interesting and relevant topic in rectal cancer management is the optimal interval between CRT completion and assessment of tumor response, as already said. Ongoing prospective randomized trials comparing different intervals may provide additional information regarding this particular issue in rectal cancer management. Also, perhaps data from PET/CT imaging at different intervals from CRT completion may also indicate kinetics of tumor metabolism as function of time in these patients.

Finally, development of next generation sequencing technology may allow further understanding of molecular genetic events relevant to sensitivity or resistance to neoadjuvant CRT. Perhaps identification of gene signatures will allow improvement of patient selection leading to true individualized management decisions. There is hope that studies using RNAseq technology may provide more definitive information in the near future.

13. References

- Baxter NN, Morris AM, Rothenberger DA, et al. Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. *Int J Radiat Oncol Biol Phys* 2005;61(2):426–31.

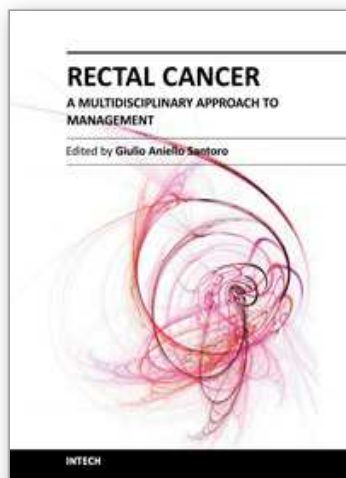
- Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. 2006. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 93:1215–1223.
- Calvo FA, Domper M, Matute R, Martínez-Lázaro R, Arranz JA, Desco M, Alvarez E, Carreras JL. 2004. 18F-FDG positron emission tomography staging and restaging in rectal cancer treated with preoperative chemoradiation. *Int. J. Radiat. Oncol. Biol. Phys.* 58:528–535.
- Chessin DB, Enker W, Cohen AM, Paty PB, Weiser MR, Saltz L, Minsky BD, Wong WD, Guillem JG. 2005. Complications after preoperative combined modality therapy and radical resection of locally advanced rectal cancer: a 14-year experience from a specialty service. *J. Am. Coll. Surg.* 200:876–82; discussion 882–4.
- Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A, Tait D, Massey A, Tebbutt NC, Chau I. 2010. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. *Lancet Oncol* 11:241–248.
- Collette L, Bosset J-F, Dulk den M, Nguyen F, Mineur L, Maingon P, Radosevic-Jelic L, Piérart M, Calais G, European Organisation for Research and Treatment of Cancer Radiation Oncology Group. 2007. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. *J. Clin. Oncol.* 25:4379–4386.
- Curvo-Semedo L, Lambregts DMJ, Maas M, Thywissen T, Mehsen RT, Lammering G, Beets GL, Caseiro-Alves F, Beets-Tan RGH. 2011. Rectal Cancer: Assessment of Complete Response to Preoperative Combined Radiation Therapy with Chemotherapy--Conventional MR Volumetry versus Diffusion-weighted MR Imaging. *Radiology*.
- Denost Q, Laurent C, Capdepon M, Zerbib F, Rullier E. Risk factors for fecal incontinence after intersphincteric resection for rectal cancer. *Dis Colon Rectum*. 2011 Aug;54(8):963-8
- Das P, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Wolff RA, Eng C, Krishnan S, Janjan NA, Crane CH. 2007. Predictors of tumor response and downstaging in patients who receive preoperative chemoradiation for rectal cancer. *Cancer* 109:1750–1755.
- Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN, Norwegian Rectal Cancer Group. 2005. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. *Colorectal Dis* 7:51–57.
- Fleming FJ, Hayanga AJ, Glynn F, Thakore H, Kay E, Gillen P. 2007. Incidence and prognostic influence of lymph node micrometastases in rectal cancer. *Eur J Surg Oncol* 33:998–1002.
- Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C, Souquet JC, Adeleine P, Gerard JP. 1999. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J. Clin. Oncol.* 17:2396.
- Garcia-Aguilar J, Shi Q, Thomas CR, Chan E, Cataldo P, Marcet J, Medich D, Pigazzi A, Oommen S, Posner MC. 2011. A Phase II Trial of Neoadjuvant Chemoradiation and Local Excision for T2N0 Rectal Cancer: Preliminary Results of the ACOSOG Z6041 Trial. *Ann. Surg. Oncol.*

- Gérard J-P, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne P-L, Vendrely V, François E, La Roche de G, Bouché O, et al 2010. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-ProDIGE 2. *J. Clin. Oncol.* 28:1638-1644.
- Ghadimi BM, Grade M, Difilippantonio MJ, Varma S, Simon R, Montagna C, Füzesi L, Langer C, Becker H, Liersch T, et al 2005. Effectiveness of gene expression profiling for response prediction of rectal adenocarcinomas to preoperative chemoradiotherapy. *J. Clin. Oncol.* 23:1826-1838.
- Glynne-Jones Rob, Mawdsley S, Harrison M. 2010. Cetuximab and chemoradiation for rectal cancer--is the water getting muddy? *Acta Oncol* 49:278-286.
- Guillem J G, Puig-La Calle J, Akhurst T, Tickoo S, Ruo L, Minsky BD, Gollub MJ, Klimstra DS, Mazumdar M, Paty PB, et al 2000. Prospective assessment of primary rectal cancer response to preoperative radiation and chemotherapy using 18-fluorodeoxyglucose positron emission tomography. *Dis. Colon Rectum* 43:18-24.
- Guillem Jose G, Moore HG, Akhurst T, Klimstra DS, Ruo L, Mazumdar M, Minsky BD, Saltz L, Wong WD, Larson S. 2004. Sequential preoperative fluorodeoxyglucose-positron emission tomography assessment of response to preoperative chemoradiation: a means for determining longterm outcomes of rectal cancer. *J. Am. Coll. Surg.* 199:1-7.
- Guillem Jose G, Díaz-González JA, Minsky BD, Valentini V, Jeong S-Y, Rodriguez-Bigas MA, Coco C, Leon R, Hernandez-Lizoain JL, Aristu JJ, et al 2008. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. *J. Clin. Oncol.* 26:368-373.
- Habr-Gama A, de Souza PM, Ribeiro U, Nadalin W, Gansl R, Sousa AH, Campos FG, Gama-Rodrigues J. 1998. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. *Dis. Colon Rectum* 41:1087-1096.
- Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Silva e Sousa AH, Campos FG, Kiss DR, Gama-Rodrigues J. 2004. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann. Surg.* 240:711-7; discussion 717-8.
- Habr-Gama A, Perez RO, Nadalin W, et al. Long-term results of preoperative chemoradiation for distal rectal cancer correlation between final stage and survival. *J Gastrointest Surg* 2005;9:90-9; discussion 9-101.
- Habr-Gama A, Perez RO, Proscurshim I, Campos FG, Nadalin W, Kiss D, Gama-Rodrigues J. 2006. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J. Gastrointest. Surg.* 10:1319-28; discussion 1328-9.
- Habr-Gama A, Perez Rodrigo Oliva, Proscurshim I, Nunes Dos Santos RM, Kiss D, Gama-Rodrigues J, Cecconello I. 2008a. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? *Int. J. Radiat. Oncol. Biol. Phys.* 71:1181-1188.
- Habr-Gama A, Perez Rodrigo O, Proscurshim I, Rawet V, Pereira DD, Sousa AHS, Kiss D, Cecconello I. 2008b. Absence of lymph nodes in the resected specimen after radical surgery for distal rectal cancer and neoadjuvant chemoradiation therapy: what does it mean? *Dis. Colon Rectum* 51:277-283.
- Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, São Julião GP, Gama-Rodrigues J. 2009. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for

- distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. *Dis. Colon Rectum* 52:1927–1934.
- Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. 2010. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. *Dis. Colon Rectum* 53:1692–1698.
- Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, Wagman R, Saltz LB, Wong WD. 2002. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. *J. Am. Coll. Surg.* 194:131–5; discussion 135–6.
- Jang NY, Kang S-B, Kim D-W, Kim JH, Lee K-W, Kim IA, Kim J-S. 2011. The role of carcinoembryonic antigen after neoadjuvant chemoradiotherapy in patients with rectal cancer. *Dis. Colon Rectum* 54:245–252.
- Kalady MF, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC, Fazio VW. 2009. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann. Surg.* 250:582–589.
- Kang JH, Kim YC, Kim H, Kim YW, Hur H, Kim JS, Min BS, Kim H, Lim JS, Seong J, et al 2010. Tumor volume changes assessed by three-dimensional magnetic resonance volumetry in rectal cancer patients after preoperative chemoradiation: the impact of the volume reduction ratio on the prediction of pathologic complete response. *Int. J. Radiat. Oncol. Biol. Phys.* 76:1018–1025.
- Kerr SF, Norton S, Glynne-Jones R. 2008. Delaying surgery after neoadjuvant chemoradiotherapy for rectal cancer may reduce postoperative morbidity without compromising prognosis. *Br J Surg* 95:1534–1540.
- Kim CW, Yu CS, Yang S-S, Kim KH, Yoon YS, Yoon SN, Lim S-B, Kim JC. 2011. Clinical Significance of Pre- to Post-Chemoradiotherapy s-CEA Reduction Ratio in Rectal Cancer Patients Treated with Preoperative Chemoradiotherapy and Curative Resection. *Ann. Surg. Oncol.*
- Kim I-J, Lim S-B, Kang HC, Chang HJ, Ahn S-A, Park H-W, Jang S-G, Park J-H, Kim DY, Jung KH, et al 2007. Microarray gene expression profiling for predicting complete response to preoperative chemoradiotherapy in patients with advanced rectal cancer. *Dis. Colon Rectum* 50:1342–1353.
- Kim YH, Kim DY, Kim TH, Jung KH, Chang HJ, Jeong S-Y, Sohn DK, Choi HS, Ahn JB, Kim DH, et al 2005. Usefulness of magnetic resonance volumetric evaluation in predicting response to preoperative concurrent chemoradiotherapy in patients with resectable rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 62:761–768.
- Kristiansen C, Loft A, Berthelsen AK, Graff J, Lindebjerg J, Bisgaard C, Jakobsen A. 2008. PET/CT and histopathologic response to preoperative chemoradiation therapy in locally advanced rectal cancer. *Dis. Colon Rectum* 51:21–25.
- Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, Kubista TP, Poon MA, Meyers WC, Mailliard JA. 1991. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N. Engl. J. Med.* 324:709–715.
- Lambregts DMJ, Vandecaveye V, Barbaro B, Bakers FCH, Lambrecht M, Maas M, Haustermans K, Valentini V, Beets GL, Beets-Tan RGH. 2011. Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. *Ann. Surg. Oncol.* 18:2224–2231.
- Matthiessen P, Hallböök O, Andersson M, Rutegård J, Sjö Dahl R. 2004. Risk factors for anastomotic leakage after anterior resection of the rectum. *Colorectal Dis* 6:462–469.

- Matthiessen Peter, Hallböök O, Rutegård J, Simert G, Sjödahl R. 2007. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. *Ann. Surg.* 246:207–214.
- Meterissian S, Skibber J, Rich T, Roubein L, Ajani J, Cleary K, Ota DM. 1994. Patterns of residual disease after preoperative chemoradiation in ultrasound T3 rectal carcinoma. *Ann. Surg. Oncol.* 1:111–116.
- Mezzi G, Arcidiacono PG, Carrara S, Perri F, Petrone MC, De Cobelli F, Gusmini S, Staudacher C, Del Maschio A, Testoni PA. 2009. Endoscopic ultrasound and magnetic resonance imaging for re-staging rectal cancer after radiotherapy. *World J. Gastroenterol.* 15:5563–5567.
- Moore HG, Gittleman AE, Minsky BD, Wong D, Paty PB, Weiser M, Temple L, Saltz L, Shia J, Guillem JG. 2004. Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. *Dis. Colon Rectum* 47:279–286.
- Moreno García V, Cejas P, Blanco Codesido M, Feliu Batlle J, de Castro Carpeño J, Belda-Iniesta C, Barriuso J, Sánchez JJ, Larrauri J, González-Barón M, et al 2009. Prognostic value of carcinoembryonic antigen level in rectal cancer treated with neoadjuvant chemoradiotherapy. *Int J Colorectal Dis* 24:741–748.
- Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. 2002. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis. Colon Rectum* 45:200–206.
- Perez OR, Habr-Gama A, Nishida Arazawa ST, Rawet V, Coelho Siqueira SA, Kiss DR, Gama-Rodrigues JJ. 2005. Lymph node micrometastasis in stage II distal rectal cancer following neoadjuvant chemoradiation therapy. *Int J Colorectal Dis* 20:434–439.
- Perez OR, Habr-Gama A, Seid V, Proscurshim I, Sousa Jr. AH, Kiss DR, Linhares M., Sapucahy M, Gama-Rodrigues J. 2006. Loop Ileostomy Morbidity: Timing of Closure Matters. *Dis. Colon Rectum.* 2006; 49: 1539–1545
- Perez OR, Habr-Gama A, Santos dos RMN, Proscurshim I, Campos FG, Rawet V, Kiss D, Cecconello I. 2007. Peritumoral inflammatory infiltrate is not a prognostic factor in distal rectal cancer following neoadjuvant chemoradiation therapy. *J. Gastrointest. Surg.* 11:1534–1540.
- Perez OR, Bresciani BH, Bresciani C, Proscurshim I, Kiss D, Gama-Rodrigues J, Pereira DD, Rawet V, Cecconello I, Habr-Gama A. 2008. Mucinous colorectal adenocarcinoma: influence of mucin expression (Muc1, 2 and 5) on clinico-pathological features and prognosis. *Int J Colorectal Dis* 23:757–765.
- Perez OR, São Julião GP, Habr-Gama A, Kiss D, Proscurshim I, Campos FG, Gama-Rodrigues JJ, Cecconello I. 2009. The role of carcinoembryogenic antigen in predicting response and survival to neoadjuvant chemoradiotherapy for distal rectal cancer. *Dis. Colon Rectum* 52:1137–1143.
- Perez OR 2011. Predicting response to neoadjuvant treatment for rectal cancer: a step toward individualized medicine. *Dis. Colon Rectum* 54:1057–1058.
- Perez OR, Habr-Gama A, Vallejos Pereyra G, Lynn PB, Praskurshim I, Arruda Alves P, Viviane R, Joaquim José G-R. The Role for Biopsies in Residual Rectal Cancer following Neoadjuvant Chemoradiation after significant downsizing - Are they reliable to rule out residual cancer? *Colorectal Disease.* 2011 (in press).
- Petersen S, Hellmich G, Mildenstein von K, Porse G, Ludwig K. 2006. Is surgery-only the adequate treatment approach for T2N0 rectal cancer? *J Surg Oncol* 93:350–354.
- Pucciarelli S, Capirci C, Emanuele U, Toppan P, Friso ML, Pennelli GM, Crepaldi G, Pasetto L, Nitti D, Lise M. 2005. Relationship between pathologic T-stage and nodal

- metastasis after preoperative chemoradiotherapy for locally advanced rectal cancer. *Ann. Surg. Oncol.* 12:111–116.
- Rimkus C, Friederichs J, Boulesteix A-L, Theisen J, Mages J, Becker K, Nekarda H, Rosenberg R, Janssen K-P, Siewert JR. 2008. Microarray-based prediction of tumor response to neoadjuvant radiochemotherapy of patients with locally advanced rectal cancer. *Clin. Gastroenterol. Hepatol.* 6:53–61.
- Sanghera P, Wong DWY, McConkey CC, Geh JI, Hartley A. 2008. Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. *Clin Oncol (R Coll Radiol)* 20:176–183.
- Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, et al 2004. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N. Engl. J. Med.* 351:1731–1740.
- Sermier A, Gervaz P, Egger JF, Dao M, Allal AS, Bonet M, Morel P. 2006. Lymph node retrieval in abdominoperineal surgical specimen is radiation time-dependent. *World J Surg Oncol* 4:29.
- Simunovic M, Sexton R, Rempel E, Moran BJ, Heald RJ. 2003. Optimal preoperative assessment and surgery for rectal cancer may greatly limit the need for radiotherapy. *Br J Surg* 90:999–1003.
- Smith KD, Tan D, Das P, Chang GJ, Kattepogu K, Feig BW, Skibber JM, Rodriguez-Bigas MA. 2010. Clinical significance of acellular mucin in rectal adenocarcinoma patients with a pathologic complete response to preoperative chemoradiation. *Ann. Surg.* 251:261–264.
- Stipa F, Zerneck A, Moore HG, Minsky BD, Wong WD, Weiser M, Paty PB, Shia J, Guillem JG. 2004. Residual mesorectal lymph node involvement following neoadjuvant combined-modality therapy: rationale for radical resection? *Ann. Surg. Oncol.* 11:187–191.
- Suppiah A, Hunter IA, Cowley J, Garimella V, Cast J, Hartley JE, Monson JRT. 2009. Magnetic resonance imaging accuracy in assessing tumour down-staging following chemoradiation in rectal cancer. *Colorectal Dis* 11:249–253.
- Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. 2008. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann. Surg. Oncol.* 15:2661–2667.
- Wang H, Safar B, Wexner SD, Denoya P, Berho M. 2009. The clinical significance of fat clearance lymph node harvest for invasive rectal adenocarcinoma following neoadjuvant therapy. *Dis. Colon Rectum* 52:1767–1773.
- Weiss C, Arnold D, Dellas K, Liersch T, Hipp M, Fietkau R, Sauer R, Hinke A, Rödel C. 2010. Preoperative radiotherapy of advanced rectal cancer with capecitabine and oxaliplatin with or without cetuximab: A pooled analysis of three prospective phase I-II trials. *Int. J. Radiat. Oncol. Biol. Phys.* 78:472–478.
- Withers HR, Haustermans K. 2004. Where next with preoperative radiation therapy for rectal cancer? *Int. J. Radiat. Oncol. Biol. Phys.* 58:597–602.
- Zmora O, Dasilva GM, Gurland B, Pfeffer R, Koller M, Nogueras JJ, Wexner SD. 2004. Does rectal wall tumor eradication with preoperative chemoradiation permit a change in the operative strategy? *Dis. Colon Rectum* 47:1607–1612.



Rectal Cancer - A Multidisciplinary Approach to Management

Edited by Dr. Giulio A. Santoro

ISBN 978-953-307-758-1

Hard cover, 410 pages

Publisher InTech

Published online 10, October, 2011

Published in print edition October, 2011

Dramatic improvements in medicine over the last few years have resulted in more reliable and accessible diagnostics and treatment of rectal cancer. Given the complex physiopathology of this tumor, the approach should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. The subtitle of this book "A Multidisciplinary Approach to Management" encompasses this concept. We have endeavored, with the help of an international group of contributors, to provide an up-to-date and authoritative account of the management of rectal tumor.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Angelita Habr-Gama, Rodrigo Oliva Perez, Patricio B. Lynn, Arceu Scanavini Neto and Joaquim Gama-Rodrigues (2011). Nonoperative Management of Distal Rectal Cancer After Chemoradiation: Experience with the "Watch & Wait" Protocol, Rectal Cancer - A Multidisciplinary Approach to Management, Dr. Giulio A. Santoro (Ed.), ISBN: 978-953-307-758-1, InTech, Available from: <http://www.intechopen.com/books/rectal-cancer-a-multidisciplinary-approach-to-management/nonoperative-management-of-distal-rectal-cancer-after-chemoradiation-experience-with-the-watch-wait->

INTeCH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen