Provisional chapter

Recent Advances in the Management of Rectal Cancer

Jeffrey Meyer, Jie J. Yao and Sergio Huerta

Additional information is available at the end of the chapter

1. Introduction

Rectal cancer continues to affect many patients in the United States and world-wide. For instance, in 2012, rectal cancer affected 40,290 Americans [1]. Patients affected with rectal cancer who have a clinical stage II (T3-T4, NO, MO) or III (Any T, N1-N3, M0) tumor are treated with pre-operative chemoradiation (CRT) followed by surgical intervention [total mesorectal excision (TME)]. In up to 40% of patients treated with CRT, the tumor becomes clinically undetectable (cCR) [2]. Clearly, this is a desirable outcome in oncology. Adding novel radiosanitizing agents, prolonging the period from CRT to TME, increasing the radiation dose, adding chemotherapy before CRT are few modalities that have been investigated to increase the number of patients achieving a complete response. The following chapter reviews current strategies in recent attempts at maximizing the ratio of patients who achieve a cCR. Current margins are resection following TME in the era of CRT are also reviewed.

2. Recent status of pre-operative biomarkers to determine a response to neoadjuvant chemoradiation

Neoadjuvant chemoradiation for the management of patients with stage II and III rectal cancer results in a clinical complete response (cCR), the absence of detectable rectal tumor with diagnostic modalities [i.e. endorectal ultrasound (EUS), magnetic resonance imaging (MRI), digital rectal exam (DRE), or proctoscopy], in 10-40% of patients [2].

The fundamental pre-clinical and clinical question is to determine whether there are markers that can detect tumors that will respond well to neoadjuvant treatment such that these patients could be potential candidates for observation without operative intervention. Conversely, if a patient is not likely to respond to neoadjuvant chemoradiation, they should submit to surgical intervention sooner. Therefore, a myriad of pathways and molecules ranging from DNA-repair molecules to molecules that mediate cell cycle dynamics to apoptotic mediators as well as hypoxic mechanisms have been investigated with a wide range of results, which are summarized by Ramzan et al [3]. Currently, there is no unifying pathway that can reliably predict responses to chemoradiation in patients with rectal cancer.

2.1. DNA repair molecules

One of three pathways is responsible for the repair of DNA double-strand breaks (DSB) induced by ionizing radiation: homologous recombination (HR), non-homologous end-joining (NHEJ) pathway, or an alternate NHEJ pathway [3]. Of these, the non-homologous end-joining (NHEJ) pathway is fundamental for DSB repair. The catalytic subunit of DNA-dependent protein kinase (DNA-PKcs) is an integral part of the NHEJ pathway. This mechanism can be broadly classified into three steps: (1) Ku 70/80 heterodimer identifies DSB and stick to DNA broken ends, facilitates the activation and recruitment of DNA-PKcs; (2) enzymatic processing of the DNA ends; and (3) ligation by DNA ligase IV. Ku 70/80 proteins play a fundamental role as they recruit DNA-PKcs which then set the cascade of DNA repair. Recent data demonstrate that DNA-PKcs and Ku proteins may have a central role in radiation induced cell death and might predict the response to radiation. However this is an area that is still under investigation.

2.2. Apoptosis

In the central mediators of apoptosis pathway in response to ionizing radiation, the initial response begins with an up-regulation of p53 (Figure 1). p53 then directly activates the cyclin dependent kinase inhibitors (such as p21). Cell cycle progression stops until the cell repairs the damage induced by ionizing radiation. If the cell is unable to repair itself, it undergoes apoptosis. The anti-apoptotic Bcl-2 inhibits p53, while p53 inhibits the inhibitor of apoptosis (survivin). All of these molecules have been investigated to determine if their up-regulation or down-regulation could predict a response to ionizing radiation. Mutations and manner of detection have to be considered in these studies. Additionally, contrary to expectations, p21 or Bax deficient cells lead to a more radiosensitive rather than a more radioresistant phenotype [4]. Thus, analyses of these molecules in predicting a response to ionizing radiation have been largely unyielding [5].

A recent systematic review analyzing the role of p53 as a predictor of a response to ionizing radiation included 30 studies of which 25 used p53 protein status, 7 used gene analysis detection and two used both. The results revealed that patients that demonstrated a p53 wild-type (and/or low expression) had a good response risk of 1.3 [CI=1.14 to 1.49], complete response RR was 1.65 [CI=1.19 to 2.30] and poor response RR 0.85 [CI = 0.75 to 0.96] [6].

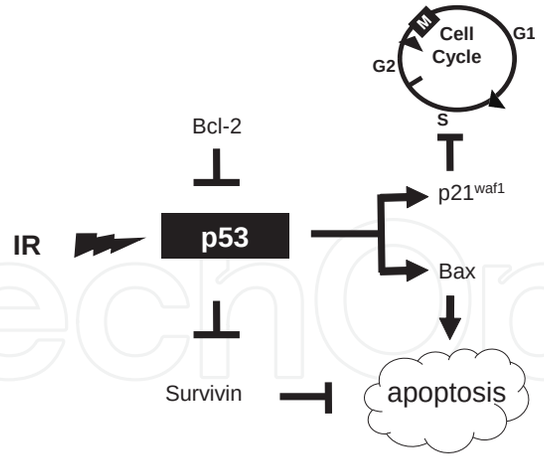

Figure 1. Central mediators of apoptosis. Ionizing radiation (IR) leads to an increase of p53, which in turn activates p21 and causes cell cycle arrest. P53 also activates Bax, which results in apoptosis

2.3. Gene modifications and polymorphisms

It is possible that with standardized techniques, we might be able to utilize other molecules in the apoptotic pathway alone or in combination to better predict neoadjuvant chemotherapeutic responses in patient affected with rectal cancer. Another area that is gaining momentum is that of epigenetic changes. For instance methylation of the retinoic acid receptor gene (RARB) and the checkpoint with forkhead and ring finger gene (CHFR) discriminated between TI-2 *vs.* T2-3 un-irradiated tumors. RARB methylation was also associated with nodal metastasis and lymphovascular invasion (LVI). Methylation of other genes have also predicted nodal metastasis [7]. Thus, methylation can predict aggressiveness and in combination with the mutation status of other molecules, a predictive panel of a response to ionizing radiation can then be constructed. In a separate study, DNA analysis of biopsies of patients prior to radiation demonstrated a gene mutation and two gene polymorphisims to be associated with resistance to radiation as measured by pCR [8].

3. Novel strategies in neoadjuvant therapy for locally advanced rectal cancer

The trimodal approach of neoadjuvant chemoradiotherapy and surgery is generally associated with high rates of local-regional control for patients with locally advanced rectal cancer [9]. However, there is room for improvement in the oncologic outcomes of the most locally advanced tumors, and also great interest in increasing the rate of complete pathologic responses to chemoradiotherapy, which may allow for increased utilization of non-operative management.

A variety of chemotherapy and targeted agents have been studied as part of novel neoadjuvant regimens in an attempt to improve on results obtained with fluoropyrimidine-based chemoradiation. Although early-phase studies have shown modest improvements in tumor responses; this has often been at the expense of increased toxicity.

3.1. Oxaliplatin

There has been much interest in particular in the use of oxaliplatin concurrent with radiation. The ACCORD 12/0405 PRODIGE 1 study randomized patients with locally advanced rectal cancer to preoperative treatment with radiation (45 Gy in 25 fractions) plus capecitabine or radiation (50 Gy in 25 fractions) plus capecitabine and oxaliplatin [10;11]. High-grade toxicity rates were higher in the oxaliplatin-treated patients (25 versus 11%), and there were no significant differences between the two arms with respect to rates of pCR, local control, and overall survival. In the STAR-01 trial, over 700 patients with locally advanced rectal cancer were randomized to neoadjuvant treatment with radiation (50.4 Gy total dose) plus infusional 5-FU with or without weekly oxaliplatin, followed by surgery [12]. The addition of oxaliplatin increased the rate of high grade toxicity (24% versus 8%) but did not improve the pathologic complete response rate (equal in the two arms at 16%). In the PETACC-6 trial, 1094 patients with locally advanced rectal cancer were randomized to preoperative radiation plus capecitabine followed by surgery and adjuvant chemotherapy versus the same regimen with oxaliplatin delivered during the chemoradiation course as well as the adjuvant course [13]. The use of oxaliplatin again increased toxicity rates, with no disease-free survival benefit.

The NSABP R-04 trial is a four-arm study that compared infusional 5-FU and capecitabine, with and without the use of oxaliplatin, during neoadjuvant chemoradiotherapy for rectal cancer [14]. Capecitabine in place of 5-FU yielded a different toxicity profile with similar rates of pCR, local-regional control, and overall survival. Patients treated with oxaliplatin had higher rates of high-grade toxicity without significant improvements in local-regional control or overall survival. Finally, in the CAO/ARO/AIO-04 trial, patients with locally advanced rectal cancer were randomized to treatment with radiation with concurrent 5-FU, surgery, and adjuvant bolus 5-FU versus radiation plus 5-FU, oxaliplatin, surgery, and adjuvant mFOLFOX6 [15]. There were no substantial differences in rates of pathologic complete response or margin-negative surgery. However, 3-year disease-free survival was higher in the oxaliplatin group (75.9% versus 71.2%). The independent contribution of the oxaliplatin delivered in the neoadjuvant setting is unclear.

3.2. Targeted therapies

Incorporation of novel targeted drug agents into trimodality regimens is also an area of dynamic clinical investigation. Bevacizumab is an anti-VEGF antibody. Willett et al. reported on 32 patients who underwent one cycle of bevacizumab followed by radiation, infusional 5-FU, further bevacizumab and subsequent surgery [16]. Local control was 100% at 5 years; disease-free survival was 75% at 5 years. Landry et al. reported on the phase 2 ECOG 3204 study, which combined capecitabine, oxaliplatin, and bevacizumab for patients with operable T3 and T4 rectal cancer [17]. Of the 49 patients who proceeded to surgery, 17% had a pathologic complete response. Surgical complications were common and may have been related to the addition of bevacizumab. Bevacizumab has also been associated with delayed wound healing in other studies [18;19].

Work is also underway evaluating combinations of the anti-EGFR agents panitumumab and cetuximab with chemoradiation. When combining such agents with conventional chemother-

apy and radiation therapy, appropriate sequencing of these treatments may be of critical importance to optimize oncologic efficacy [17;20].

3.3. Novel scheduling modalities

A more recent area of clinical study has been to incorporate systemic therapy prior to chemoradiation or to eliminate radiation as a component of neoadjuvant therapy for selected patients with locally advanced disease (Figure 2). Chua et al. reported, on a phase 2 study, incorporating induction chemotherapy prior to neoadjuvant chemoradiotherapy [21]. Patients had locally advanced rectal cancers that were considered high-risk by MRI criteria (including tumors with threatened mesorectal resection margin, extensive mesorectal fat involvement, and T4 and/or N2 tumors). Patients were treated with 12 weeks of capecitabine and oxaliplatin. This was followed by radiation (total dose of 54 Gy) and concurrent capecitabine for six weeks and finally total mesorectal excision (Figure 2 B). One hundred and five patients were enrolled. Twenty percent of the patients had a pathological complete response, and 3-year progression-free and overall survival were 68% and 83% respectively. In a similar approach, a recent randomized phase II trial incorporating induction capecitabine and oxaliplatin showed no difference in histopathologic downstaging compared to patients treated with chemoradiation alone [22]. The authors of these studies suggest that more data is needed before approaching induction chemotherapy as a standard of care for high risk patients.

Schrag et al. recently reported on 32 patients with stage II or III rectal cancer treated with 6 cycles of FOLFOX, with bevacizumab delivered during cycles 1-4, without planned radiation therapy (Figure 2 C) [23]. Thirty of the 32 patients proceeded to surgery without undergoing preoperative irradiation. Of the 32 patients, 25% had a pathologic complete response. The 4-year local recurrence rate was 0% and the 4-year disease-free survival rate was 84%. This strategy of neoadjuvant chemotherapy without planned use of radiation therapy (without use of bevacizumab) is under further study in the randomized N1048 study. However, these studies are in the initial stages of assessment at this time.

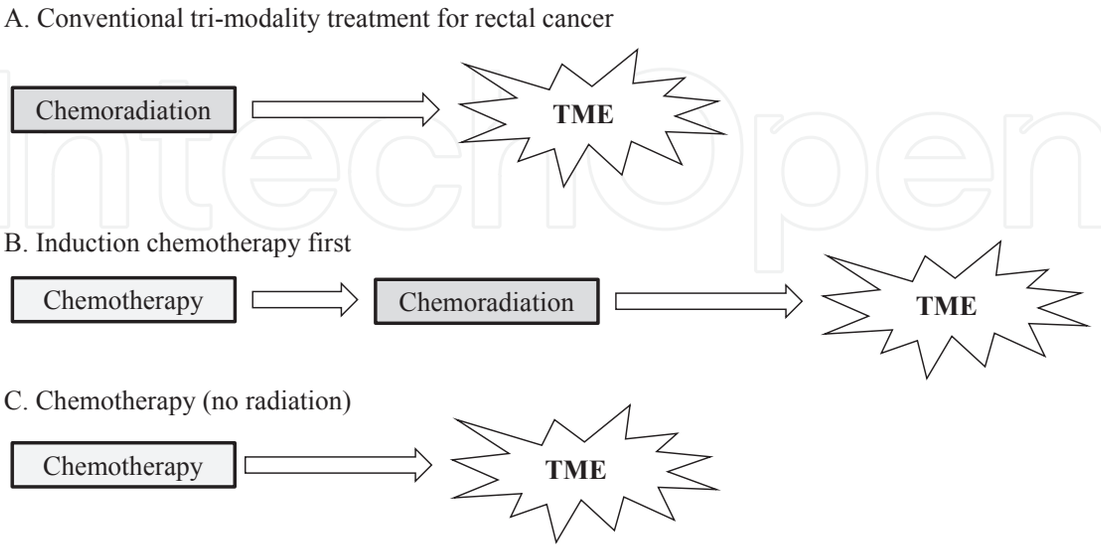

Figure 2. Novel strategies in neoadjuvat therapy for local advanced rectal cancer. Conventional treatment (A). Induction chemotherapy followed by chemoradiation (B). Elimination of radiation (C).

4. What is the appropriate length of the "waiting period" between completion of neoadjuvant chemoradiation and surgery?

Initially, the waiting period following CRT was based on sufficient time to allow the acute radiation reaction to subside. Thus, an interval between 3-5 weeks was selected based on empirical experience. Favorable outcomes in patients who achieve a pCR and the desire to obtain a cCR have led to an increase of the radiation dose to the tumor center, increased intervals between CRT and TME, addition of chemotherapy during the waiting time, or starting with induction chemotherapy [24].

Allowing for a "waiting period" without active treatment of many weeks between the completion of neoadjuvant long-course therapy and surgery is common in the management of rectal cancer. Delaying surgery may allow for continued volume reduction of the treated tumor, potentially increasing the ultimate likelihood of a sphincter-preserving surgery for low-lying tumors and facilitating ease of the operation. However, too long of a delay in proceeding to surgery, especially in patients with poor response to neoadjuvant treatment, may allow for growth of the primary tumor with an increased risk of margin-positive surgery and increased risk of distant dissemination of cancer [25]. Further, there is a perception that waiting too long after the end of CRT (> 12 weeks) might lead to radiation fibrosis, making surgical intervention more difficult. However, this has not been substantiated in the literature [24].

The Lyon R90-01 trial randomized patients with T2-3 (N-any) rectal carcinoma to treatment with preoperative radiation (39 Gy in 13 fractions, without concurrent chemotherapy) followed by either a "short interval" to surgery (surgery performed within 2 weeks of completion of radiation) or a "long interval" to surgery (surgery performed within 6-8 weeks of completion of radiation) [26]. Tumors had to be low enough in the rectum to be palpable on digital examination. The primary endpoint of the study was the rate of sphincter-preserving surgery. The decision regarding the type of surgery was made by the surgeon at the time of the operation. Of the enrolled patients, 201 were assessable. Patients in the long-interval group had improved clinical and pathologic responses compared to the short-interval group. Twenty-six percent of the patients in the long-interval group had either a complete or near-complete pathologic response compared to 10.3% in the short-interval group, likely a reflection of the increased amount of time for lethally injured tumor cells to manifest their injury as death. Ultimately, however, 75.5% of the patients in the long-interval group as opposed to 67.7% in the short-interval group underwent a sphincter-preserving operation, a difference that was not statistically significant. There were no differences in the post-operative toxicity and mortality rates between the two groups. There were also no differences in overall survival or local control rates to a median follow-up of 33 months.

Integrating systemic therapy during the waiting period may have potential benefits for patients with rectal cancer, including improved downstaging of the primary tumor as well as potentially more effective treatment (relative to delayed postoperative treatment) of distant micrometastatic disease, a major cause of the poor disease-free survival rates seen in patients with locally advanced rectal cancer. Garcia-Aguilar and colleagues performed a phased II non-randomized trial investigating the use of chemotherapy with modified FOLFOX-6 delivered

during the waiting period following standard long-course chemoradiotherapy, with successively more administrations of chemotherapy (and thus longer overall waiting periods) [27]. In a preliminary analysis of patients treated with two cycles of mFOLFOX-6 during the waiting period, with a mean time of 11 weeks from completion of neoadjuvant therapy to surgery, the pathologic complete response was 25%. In a comparison group of patients treated with neoadjuvant chemoradiation and no intervening systemic therapy, with a mean time to surgery of 6 weeks, the pCR was 18%. There was no substantial difference between the two arms with respect to postoperative complication rates.

In the large Dutch Surgical Colorectal Audit study including 1593 patients, patients were divided into three groups in terms of interval from the start of CRT to TME: < 13, 13-14, and 15-16 weeks. The largest pCR (18%) was observed in patients in the 15-16 week group (median time at the end of CRT = 9-10 weeks) [28].

A meta-analysis was conducted that compared two groups of patients: (1) less or equal to the conventional 6-8 week period from CRT to surgery and (2) longer than 6-8 weeks. pCR was the primary end point and was increased from 13.7 to 19.5% in the more than 8 week group [29]. This study included 13 trials inclusive of 3584 patients. Secondary end points (OS, DFS, R0 resection rates, sphincter preservation, and complication rates) were similar in both groups [29]. However, in patients who had a short interval (< 1 week), the rate of perineal wound complication and anastomotic leak was higher [29].

The question of appropriate waiting time periods has also emerged in the context of short course radiation therapy (5 Gy X 5 fractions without concurrent chemotherapy). In the original clinical trials of short-course neoadjuvant therapy, surgery was mandated to be performed within one week of completion of radiation [30]. This regimen has been associated with lower pCR rates relative to long-course neoadjuvant treatment, possibly as a result of the decreased interval between radiation and surgery. In the more recent Stockholm III trial, patients were randomized to one of three arms: short-course radiation followed by surgery within 1 week, short-course radiation followed by surgery at 4-8 weeks, or long-course radiation (2 Gy X 25 fractions, without concurrent chemotherapy) followed by surgery at 4-8 weeks [31]. Interestingly, pCR rates were highest in the short-course radiation group with the extended interval to surgery (12.5%, versus 0.8% in the short interval group and 5% in the long-course radiation group). Patients treated with short-course radiation and delayed surgery had postoperative complication rates that were similar to the two other groups. In an analysis of actual time to surgery, patients treated with short-course radiation followed by surgery at an interval of 11-17 days had the highest rates of postoperative complications.

Many questions remain regarding the appropriate duration of the waiting period in patients undergoing neoadjuvant therapy. Most of the data regarding CRT-TME gap emanate from retrospective studies. Thus, the recommendations of the length of time are largely observational and empirically-driven. However, cCR and pCR has been observed in three randomized controlled trials when the gap is about 8-12 weeks [26;31;32]. Surgery within 3-4 weeks in the long CRT modality should not be performed secondary to radiation reaction. There is currently limited experience in waiting over 12 weeks.

Integration of systemic therapy both during this time period as well as during the induction phase (prior to chemoradiation) remain active areas of clinical interest. In addition, determining which patients are made candidates for sphincter-preserving surgery also remains an imprecise practice. Improvements in imaging technologies and possible use of pre-treatment biomarkers may improve on patient selection for low anterior resection.

5. Current status of the role of non-operative management in rectal cancer for patients with a complete clinical response

Neoadjuvant chemoradiation for the management of patients with stage II and III rectal cancer results in a clinical complete response (cCR), which is defined as the absence of detectable rectal tumor with diagnostic modalities [i.e. endorectal ultrasound (EUS), magnetic resonance imaging (MRI), digital rectal exam (DRE), or proctoscopy] in 10-40% of patients [33]. Can these patients be followed non-operatively?

There have been three sentinel papers that have addressed this issue: one in 2004 published by Habr-Gama's group [34], the second was a reproduction of these results by a Dutch group in 2011 [35], which was followed by a systematic review by Glynne-Jones in 2012 [2]. An editorial summarizes the main aspects of these seminal events [36].

The first manuscript to document a possible approach in observing patients that achieve a cCR was published by Harb-Gama's group in 2004. In this study, 71 patients who had a cCR were compared to 22 patients that had an initial incomplete response, but after surgery, they were found to have no microscopic evidence of tumor in the resected specimen (pCR). Patients who underwent surgery had a 5-year overall survival of 88% compared to the cCR group, which was 100%. Disease free survival was 83% in the surgery group and 92% in the cCR group [34].

Mass et al. documented similar observations in 2011 [34]. This study compared 21 patients who had a cCR and compared them to 20 patients from another observational study that had documented pCR. Only one patient developed a recurrence at a 2-year follow up and they were all alive at this point in time. Comparatively, the 2-year disease free survival for patients in the surgery group was 93% with an overall survival of 91%.

A number of small institutional studies have documented similar observations in small cohort of patients such as in the United States [37] and in the United Kingdom [38] in 2012. A few other papers that demonstrated similar findings was summarized by a systematic review by Glynne-Jones in 2012 [2].

In this systematic review, 30 papers were included that met the primary end point of cCR with secondary end points of local recurrence, overall survival and disease free survival. This analysis demonstrated that 361 patients (56%) were from a single group (Habr-Gama) and the rest (n=289) were from eight different groups. cCR ranged from 11% - 39%. Results of secondary outcomes showed low local recurrence in Habr-Gama studies (~5%), but higher in all other series 33.8% (range 23%-83%). Habr-Gama reported salvage surgery to be possible in most cases, whereas only one quarter of patients could be salvaged surgically in all other groups.

Long-term outcomes (DFS, and OS) in other groups were similar to Habr-Gama's and suggested that patients who achieve cCR have similar outcomes to patients who undergo surgery and are found to have pCR.

The authors of the meta-analysis suggested that there is not enough evidence at this time to support observation in patients who have a cCR [2]. The inability to propose non-operative management for patients with a cCR primarily emanates from an inability to clearly define cCR. However, it is likely that a group of patients with a cCR can be observed without surgery; who those patients are and how we can monitor them closely is a difficult issue in the management of rectal cancer.

6. Appropriate distal margins of resection in the era of neoadjuvant therapy

Following resection of the rectum, current standard procedure is examination of the distal edge to ensure that the cells at this distal margin are free of any tumor characteristics. A positive distal margin is an unequivocal indication for additional treatment as it signifies that the resection has not been adequate.

This length from the tumor to the distal edge is of even greater importance when considering those cancers occurring in the distal or lower portions of the rectum (close to the anal sphincters). In treating patients with lower rectal tumors, a balance of performing an oncologically free operation versus obtaining proper anal sphincter function must be maintained. There is no question that when it comes to patient's preference, an LAR is always preferred to an APR [39-41].

Prior to the era of CRT, substantially large margins of resections were thought to be necessary. A 5 cm margin was widely used, which emanated from studies showing this to result in acceptable outcomes compared to those with greater than 5 cm distal margins [4-10]. In an attempt to perform sphincter preservation operations, this number was rapidly challenged and reduced to the point in which margins less than 5 cm became acceptable [42-47].

With the current tri-modality management of rectal cancer, a 2 centimeter margin has been adopted with excellent oncologic outcomes [48-52]. In 2004, Habr-Gama published results of observing patient who achieved a clinical complete response (cCR) following neoadjuvant CRT [34]. This concept, in a way, challenged the need to obtain a large margin in patients with low rectal tumors who have responded well to pre-operative treatment. Studies have emerged that indicate that even a 1 cm distal margin is oncologically safe [40;48;49;52-58]. This has been considered oncologically acceptable in the literature. The vast majority of work that has examined the question of 1 cm margins has indicated that there is no statistically significant difference in regards to survival or recurrence between groups of patients with margins greater than 1 cm than those with margins less than or equal to 1 cm [40;48;49;52;54-58] Table 1.

More recently, the 1 cm margin has been challenged to be further reduced. Some surgeons have suggested that sub-centimeter margins as small as 2 mm or 5 mm margins are also safe [54].

Paper	% Patients with Neoadjuvant Chemoradiotherapy	Number of local recurrences/total patients by margin (%)		P	% Survival		Years of Follow Up	P
		≤ 1 cm	> 1 cm		≤ 1 cm	> 1 cm		
Andreola et al *(2001)*	61	4/31 (12.9)	3/45 (6.6)	0.4407[a]				
Huh et al *(2008)*	100	1/18 (6)	0/25 (0)	0.058	71.3	81.3	5 years	0.27
Kim et al *(2009)*	71.2	7/167 (4.2)	31/747 (4.1)	0.98				
Kiran et al *(2011)*	40	7/198 (3.5)	19/586 (3.2)	0.821[a]	67.4	66.5	5 years	0.77
Kuvshinoff et al *(2001)*	100	1/16 (6)	0/12 (0)		53	85	4 years	0.06
Moore et al *(2003)*	100	2/17 (12)	7/77 (9)	0.93	82	85	3 years	0.88
Pricolo et al *(2010)*	100	0/10 (0)	0/23 (0)					
Rutkowski et al *(2008)*	100	4/42 (9.5)	17/122 (13.9)	0.597	65.6	68.7	5 years	0.66
Total		22/464 (4.7)	72/1589 (4.5)	0.8995[a]				

A meta-analysis indicated a higher rate of anastomotic recurrence by only 1.6% in the <1cm margin groups, but this small observed difference was not statistically significant. A systematic review of the literature on sub-1 cm distal margins of resection found in only two papers a possible adverse outcome associated with this smaller margin [54]. However, in these two papers, the percentage of patients submitting to neoadjuvant CRT was less than 5% [59;60].

Distal margins of 8 mm or 5 mm have also been proposed [40;54;56;61], but there is currently not enough data to draw definitive conclusions at this time. The results so far seem to point to these margins also being oncologically safe. Published data on possible adverse oncologic outcomes with 8 mm margins has been documented, but this has occurred in the absence of neoadjuvant CRT [62]. In this case, margins below the 8 mm cutoff point were found to correlate with a significantly higher rate of recurrence and lower rate of long-term survival. However, when the same length of distal margin is evaluated within the context of neoadjuvant CRT, 8 mm margins have not been found to have adverse oncologic outcomes compared to patients having more than 8 mm margins. In this study, the authors did find a higher rate of mucosal recurrence in patients with less than 8 mm margins. They concluded that the probable cause of a higher rate of mucosal recurrence was tumor shedding into the anastomosis [40].

Another study evaluated patients who had received neoadjuvant therapy with margins less than or equal to 5 mm in regards to 5 year outcome and local recurrence [61]. There was no difference in local recurrence 5 years after surgical intervention. This finding was echoed by a number of similar studies [48;53;54;56] (Table 2). Additionally, a meta-analysis demonstrated a small non-significant rate of anastomotic recurrence by 1.7% in the 5mm group, but again this also was not statistically significant [54].

Paper	Number of recurrences/total patients by margin (%)		P
	≤ 0.5 cm	> 0.5 cm	
Kuvshinoff et al *(2001)*	1/9 (11)	0/19 (0)	
Kiran et al *(2011)*	2/25 (8)	9/164 (5.5)	0.41
Rutkowski et al *(2010)*	3/29 (10.3)	10/231 (4.3)	0.166
Total	6/63 (9.5)	19/414 (4.6)	0.123

It is important to keep in mind that in all of these retrospective studies, there is a clear aspect of selection bias. Typically, patients that are selected for smaller margins are those that have tumors that are expected to have more favorable outcomes. Low tumors, which have less favorable predicted outcomes are usually treated with an abdominoperineal resection (APR), a procedure that renders the question of margins moot [54]. This makes it difficult to properly match patient populations being compared in these studies. It is also important to emphasize that there is a lack of consistent methodology of measuring the distal margin across all studies. Measurement of the distal margin is done in a variety of circumstances: pinned, unpinned, fixed, immediately after sectioning, etc [54;63;64]. A lack of standardization is disadvantageous to drawing a unified conclusion; however, the broad consensus that exists regardless of this wide range of measurement techniques suggests that the conclusion is nonetheless valid.

Furthermore, while the surgical donuts are oftentimes assessed for tumor cells, they are not included in measurement of the distal margin of resection and therefore the true margin is usually slightly larger than the distal margin of resection. Therefore, a margin reported and measured as 5 mm may in fact be significantly larger, which helps explain why some patients with low margins approaching 0 mm still seem to have acceptable oncologic outcomes.

In conclusion, in the era of neoadjuvant CRT, smaller distal margins are acceptable so long as the overall status of the patient is considered as well as the possible behavior of the tumor. Patients with well differentiated tumors who have achieved an excellent response to neoadjuvant CRT might only need negative margins. However, patients who have poorly differentiated tumors and no response to pre-operative CRT might need greater margins (greater or equal to 1 cm). The distal margin is one of the few that the surgeon can correct and monitor intra-operatively [40;64] and therefore ought to be a constant consideration for all surgeons when performing a rectal resection. This must be done by balancing the desire for sphincter preservation with the need to maintain an oncologically safe and thorough procedure.

Author details

Jeffrey Meyer, Jie J. Yao and Sergio Huerta*

*Address all correspondence to: sergio.huerta@utsouthwestern.edu

University of Texas Southwestern Medical Center, Departments of Radiation Oncology and Surgery, USA

References

[1] Huerta S, Murray B, Olson C, Patel P, Anthony T. Current evidence-based opinions in the management of adenocarcionoma of the rectum. Indian Journal of Surgery 2009; 71(6):356-362.

[2] Glynne-Jones R, Hughes R. Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. Br J Surg 2012; 99(7): 897-909.

[3] Ramzan Z, Nassri AB, Huerta S. Genotypic characteristics of resistant tumors to preoperative ionizing radiation in rectal cancer. World journal of gastrointestinal oncology 2014; 6(7):194.

[4] Huerta S, Gao X, Dineen S, Kapur P, Saha D, Meyer J. Role of p53, Bax, p21, and DNA-PKcs in radiation sensitivity of HCT-116 cells and xenografts. Surgery 2013; 154(2):143-151.

[5] Huerta S, Gao X, Saha D. Mechanisms of resistance to ionizing radiation in rectal cancer. Expert Rev Mol Diagn 2009; 9(5):469-480.

[6] Chen MB, Wu XY, Yu R, Li C, Wang LQ, Shen W et al. P53 status as a predictive biomarker for patients receiving neoadjuvant radiation-based treatment: a meta-analysis in rectal cancer. PLoS One 2012; 7(9):e45388.

[7] Leong KJ, Beggs A, James J, Morton DG, Matthews GM, Bach SP. Biomarker-based treatment selection in early-stage rectal cancer to promote organ preservation. Br J Surg 2014; 101(10):1299-1309.

[8] Garcia-Aguilar J, Chen Z, Smith DD, Li W, Madoff RD, Cataldo P et al. Identification of a biomarker profile associated with resistance to neoadjuvant chemoradiation therapy in rectal cancer. Ann Surg 2011; 254(3):486-492.

[9] Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 2012; 30(16):1926-1933.

[10] Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL et al. 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 2010; 28(10):1638-1644.

[11] Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Lafay I, Hennequin C, Etienne PL et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012; 30(36):4558-4565.

[12] Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011; 29(20):2773-2780.

[13] Schomoll HJ, Haustermans K, Jay T. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in

locally advanced rectal cancer: First results of the PETACC-6 randomized phase III trial. J.Clin.Oncol. 31, 3531. 2013. Ref Type: Abstract

[14] Allegra CJ, Yothers G, O'Connell M, Roh MS. Final results from NSABP protocol R-04: Neoadjuvant chemoradiation (RT) comparing continuous infusion (CIV) 5-FU with capecitabine (Cape) with or without oxaliplatin (Ox) in patients with stage II and III rectal cancer. J.Clin.Oncol. 32, 5s. 2014. Ref Type: Abstract

[15] Rodel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012; 13(7): 679-687.

[16] Willett CG, Duda DG, di TE, Boucher Y, Ancukiewicz M, Sahani DV et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. J Clin Oncol 2009; 27(18): 3020-3026.

[17] Landry JC, Feng Y, Cohen SJ, Staley CA, III, Whittington R, Sigurdson ER et al. Phase 2 study of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: ECOG 3204. Cancer 2013; 119(8):1521-1527.

[18] Heinzerling JH, Huerta S. Bowel perforation from bevacizumab for the treatment of metastatic colon cancer: incidence, etiology, and management. Current surgery 2006; 63(5):334-337.

[19] Huerta S, Li HC. Bevacizumab-associated hypertension: etiology, incidence, and management. Anti-cancer drugs 2009; 20:S22-S24.

[20] Glynne-Jones R, Mawdsley S, Harrison M. Cetuximab and chemoradiation for rectal cancer--is the water getting muddy? Acta Oncol 2010; 49(3):278-286.

[21] Chua YJ, Barbachano Y, Cunningham D, Oates JR, Brown G, Wotherspoon A et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 2010; 11(3):241-248.

[22] Fernandez-Martos C, Pericay C, Aparicio J, Salud A, Safont M, Massuti B et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010; 28(5):859-865.

[23] Schrag D, Weiser MR, Goodman KA, Gonen M, Hollywood E, Cercek A et al. Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 2014; 32(6):513-518.

[24] Glimelius B. Optimal Time Intervals between Pre-Operative Radiotherapy or Chemoradiotherapy and Surgery in Rectal Cancer? Front Oncol 2014; 4:50.

[25] Kaminsky-Forrett MC, Conroy T, Luporsi E, Peiffert D, Lapeyre M, Boissel P et al. Prognostic implications of downstaging following preoperative radiation therapy for operable T3-T4 rectal cancer. Int J Radiat Oncol Biol Phys 1998; 42(5):935-941.

[26] Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C et al. 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 1999; 17(8):2396.

[27] Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 2011; 254(1): 97-102.

[28] Sloothaak DA, Geijsen DE, van Leersum NJ, Punt CJ, Buskens CJ, Bemelman WA et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 2013; 100(7):933-939.

[29] Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer: A Meta-Analysis of Published Studies. Ann Surg 2013.

[30] Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997; 336(14):980-987.

[31] Pettersson D, Cedermark B, Holm T, Radu C, Pahlman L, Glimelius B et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 2010; 97(4):580-587.

[32] Pach R, Kulig J, Richter P, Gach T, Szura M, Kowalska T. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer--treatment results at 5-year follow-up. Langenbecks Arch Surg 2012; 397(5):801-807.

[33] Huerta S, Hrom J, Gao X, Saha D, Anthony T, Reinhart H et al. Tissue microarray constructs to predict a response to chemoradiation in rectal cancer. Dig Liver Dis 2010; 42(10):679-684.

[34] Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Jr., Silva e Sousa AH Jr et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004; 240(4):711-717.

[35] Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011; 29(35):4633-4640.

[36] Huerta S. Current views on clinical complete response in patients with rectal cancer following neoadjuvant chemoradiation. Colorectal Cancer 2014; 3(2):117-120.

[37] Smith JD, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 2012; 256(6):965-972.

[38] Dalton RS, Velineni R, Osborne ME, Thomas R, Harries S, Gee AS et al. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? Colorectal Dis 2012; 14(5):567-571.

[39] Camilleri-Brennan J, Steele RJ. Objective assessment of morbidity and quality of life after surgery for low rectal cancer. Colorectal Dis 2002; 4(1):61-66.

[40] Nash GM, Weiss A, Dasgupta R, Gonen M, Guillem JG, Wong WD. Close distal margin and rectal cancer recurrence after sphincter-preserving rectal resection. Dis Colon Rectum 2010; 53(10):1365-1373.

[41] Zolciak A, Bujko K, Kepka L, Oledzki J, Rutkowski A, Nowacki MP. Abdominoperineal resection or anterior resection for rectal cancer: patient preferences before and after treatment. Colorectal Dis 2006; 8(7):575-580.

[42] Kameda K, Furusawa M, Mori M, Sugimachi K. Proposed distal margin for resection of rectal cancer. Jpn J Cancer Res 1990; 81(1):100-104.

[43] Komori K, Kanemitsu Y, Ishiguro S, Shimizu Y, Sano T, Ito S et al. Adequate length of the surgical distal resection margin in rectal cancer: from the viewpoint of pathological findings. Am J Surg 2012; 204(4):474-480.

[44] Madsen PM, Christiansen J. Distal intramural spread of rectal carcinomas. Dis Colon Rectum 1986; 29(4):279-282.

[45] Shirouzu K, Isomoto H, Kakegawa T. Distal spread of rectal cancer and optimal distal margin of resection for sphincter-preserving surgery. Cancer 1995; 76(3):388-392.

[46] Ueno H, Mochizuki H, Hashiguchi Y, Ishikawa K, Fujimoto H, Shinto E et al. Preoperative parameters expanding the indication of sphincter preserving surgery in patients with advanced low rectal cancer. Ann Surg 2004; 239(1):34-42.

[47] Watanabe T, Kazama S, Nagawa H. A 1cm distal bowel margin is safe for rectal cancer after preoperative radiotherapy. Hepatogastroenterology 2012; 59(116):1068-1074.

[48] Kuvshinoff B, Maghfoor I, Miedema B, Bryer M, Westgate S, Wilkes J et al. Distal margin requirements after preoperative chemoradiotherapy for distal rectal carcinomas: are < or = 1 cm distal margins sufficient? Ann Surg Oncol 2001; 8(2):163-169.

[49] Moore HG, Riedel E, Minsky BD, Saltz L, Paty P, Wong D et al. Adequacy of 1-cm distal margin after restorative rectal cancer resection with sharp mesorectal excision and preoperative combined-modality therapy. Ann Surg Oncol 2003; 10(1):80-85.

[50] Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001; 93(8):583-596.

[51] Nishioka M, Shimada M, Kurita N, Iwata T, Morimoto S, Yoshikawa K et al. Clinicopathological analysis of distal margin for rectal cancer after preoperative chemoradiation therapy. Hepatogastroenterology 2012; 59(119):2142-2146.

[52] Pricolo VE, Abodeely A, Resnick M. Distal margins in radical resections for rectal cancer after chemoradiation therapy: how short is long enough? Dig Surg 2010; 27(3): 185-189.

[53] Andreola S, Leo E, Belli F, Bonfanti G, Sirizzotti G, Greco P et al. Adenocarcinoma of the lower third of the rectum surgically treated with a <10-MM distal clearance: preliminary results in 35 N0 patients. Ann Surg Oncol 2001; 8(7):611-615.

[54] Bujko K, Rutkowski A, Chang GJ, Michalski W, Chmielik E, Kusnierz J. Is the 1-cm rule of distal bowel resection margin in rectal cancer based on clinical evidence? A systematic review. Ann Surg Oncol 2012; 19(3):801-808.

[55] Kim YW, Kim NK, Min BS, Huh H, Kim JS, Kim JY et al. Factors associated with anastomotic recurrence after total mesorectal excision in rectal cancer patients. J Surg Oncol 2009; 99(1):58-64.

[56] Kiran RP, Lian L, Lavery IC. Does a subcentimeter distal resection margin adversely influence oncologic outcomes in patients with rectal cancer undergoing restorative proctectomy? Dis Colon Rectum 2011; 54(2):157-163.

[57] Mezhir JJ, Shia J, Riedel E, Temple LK, Nash GM, Weiser MR et al. Whole-mount pathologic analysis of rectal cancer following neoadjuvant therapy: implications of margin status on long-term oncologic outcome. Ann Surg 2012; 256(2):274-279.

[58] Tsutsumi S, Tabe Y, Fujii T, Yamaguchi S, Suto T, Yajima R et al. Tumor response and negative distal resection margins of rectal cancer after hyperthermochemoradiation therapy. Anticancer Res 2011; 31(11):3963-3967.

[59] Bokey EL, Ojerskog B, Chapuis PH, Dent OF, Newland RC, Sinclair G. Local recurrence after curative excision of the rectum for cancer without adjuvant therapy: role of total anatomical dissection. Br J Surg 1999; 86(9):1164-1170.

[60] Law WL, Chu KW. Local recurrence following total mesorectal excision with double-stapling anastomosis for rectal cancers: analysis of risk factors. World J Surg 2002; 26(10):1272-1276.

[61] Rutkowski A, Nowacki MP, Chwalinski M, Oledzki J, Bednarczyk M, Liszka-Dalecki P et al. Acceptance of a 5-mm distal bowel resection margin for rectal cancer: is it safe? Colorectal Dis 2012; 14(1):71-78.

[62] Vernava AM, III, Moran M, Rothenberger DA, Wong WD. A prospective evaluation of distal margins in carcinoma of the rectum. Surg Gynecol Obstet 1992; 175(4): 333-336.

[63] Sondenaa K, Kjellevold KH. A prospective study of the length of the distal margin after low anterior resection for rectal cancer. Int J Colorectal Dis 1990; 5(2):103-105.

[64] Tiret E. Assessment of surgical distal margin after rectal resection for cancer. Dis Colon Rectum 2010; 53(10):1353-1354.

IntechOpen