Evolving paradigms in locally advanced rectal cancer: review of the non-operative approach and future directions

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The standard treatment of locally advanced rectal cancer in the United States is neoadjuvant chemoradiation, surgical resection with total mesorectal excision, and adjuvant chemotherapy. In recent years, a non-operative approach has been suggested for patients achieving a complete clinical response with chemoradiation alone to avoid the morbidity that accompanies radical excision. This approach is justified by the observation that a significant proportion of patients (15-40%) have achieved a pathological complete response by the time of surgery. We review the most recent literature to determine if the oncologic outcomes are comparable. We also discuss future directions in management, including the consolidation of chemotherapy with neoadjuvant chemoradiation. Currently, distant recurrence rates exceed those of local recurrence and adjuvant chemotherapy is often delayed pending postoperative recovery. Offering chemotherapy up-front would simultaneously treat both the primary tumor and any micrometastatic disease without delay. A trial is currently underway at our center evaluating these treatment modalities.

Key Words: Rectal cancer; Non-operative management; Locally advanced rectal cancer

INTRODUCTION

The standard management of locally advanced rectal cancer (LARC) consists of preoperative chemoradiation, rectal resection with total mesorectal excision (TME), and adjuvant chemotherapy. Neoadjuvant chemoradiation therapy (CRT) provides excellent rates of local control, with up to 15-40% of patients exhibiting a pathological complete response (pCR) at the time of surgery such that no residual viable tumor cells are found on pathologic examination of the surgical specimen. Those patients with a pCR have improved oncologic outcomes with local recurrence rates of less than 1% and a 5-year survival rate of over 95%, suggesting that there is a possible subset of patients for whom a non-operative management (NOM) paradigm could be considered. In patients who have achieved a pCR with CRT alone, the benefit of an operation that does not remove any gross or microscopic tumor may not balance the risk of complications, which can be as high as 20%. Patients could thus avoid, temporarily or altogether, the significant risks of radical surgery, which include bleeding complications, wound infection, anastomotic leak, creation of a temporary or permanent stoma, impaired bowel function, and nerve damage leading to sexual or urinary dysfunction. In other words, curing the cancer without removing the rectum could potentially decrease long-term functional problems as above, and preserve QoL. The proportion of LARC patients who have a pathologic complete response (pCR) after CRT have lower rates of tumor recurrence, and improved survival, compared to those who do not. This leads us to question whether there is any benefit to removing the rectum in patients with a pCR.

The challenge currently lies in accurately predicting which patients will go on to have a pCR and thus may be eligible for NOM. The “watch-and-wait” approach was first defined, and has been subsequently described, in a series of retrospective studies by Habr-Gama in Brazil. Upon completion of CRT, rather than proceeding directly to surgery, selected patients with a complete clinical response (cCR) were instead closely followed. Salvage surgery was recommended at the first sign of local recurrence. Similar outcomes were noted between those patients initially managed non-operatively and those who went on to radical surgery with a confirmed pCR. This was a compelling observation that challenged a historical paradigm for LARC patients, and to date, an increasing
number of reports have yielded similar results. These will be reviewed in this article to balance the evidence.

Additionally, the idea of consolidating CRT and systemic chemotherapy prior to any surgical consideration would allow micrometastatic disease to be addressed preoperatively. It would also improve treatment compliance by avoiding delay and/or withholding of adjuvant chemotherapy due to complications of surgery. Specifically, more than one-third of eligible patients never start adjuvant therapeutic regimens because they develop post-operative complications, are too debilitated after surgery, or simply refuse treatment; unfortunately, less than half of eligible patients receive the full course of FOLFOX.

Current Literature

The seminal paper by Habr-Gama retrospectively reviewed records (1991-2002) of 265 patients with distal, resectable rectal tumors treated with preoperative CRT. Radiation (50.4 Gy) was delivered in 1.8 Gy fractions for 6 weeks, with concomitant fluorouracil or folinic acid on the first and last 3 days of radiotherapy. Patients were re-evaluated 8 weeks after completion of CRT, and those with evidence of residual tumor underwent an operation. cCR was defined as the absence of residual ulceration, mass, or mucosal irregularity on clinical and endoscopic assessment, with whitening of the mucosa and the presence of telangiectasias considered acceptable. Radiological imaging showing no evidence of distant disease was also required.

Seventy-one (27%) patients achieved an initial complete clinical and radiologic response at the 8-week mark and were treated without initial radical surgery. Surveillance in this group included monthly follow-up visits for the first year, and every 2 and 6 months during the second and third years, respectively, for digital rectal exam, proctoscopy, and CEA levels. Radiologic imaging (CT, MRI, and/or ERUS) was performed after 6 months and yearly thereafter. Adjuvant chemotherapy was not offered to either group in the absence of recurrent disease.

Of 194 patients with an incomplete clinical response who underwent resection, 22 had a pCR and served as the comparison group. Median follow-up was 5 years. Local recurrence (LR) rates were 3% and 0% in the observation and resection groups, respectively; distant recurrence (DR) rates were 4.2% and 13.6%. There was no significant difference between recurrence and mortality rates between groups. Five-year overall survival (OS) and disease-free survival (DFS) was 100% and 92% in the observation group and 88% and 83% in the resection group. Ten-year OS and DFS was 100% and 86% in the observation group. There was a small but significantly higher 5-year survival rate in the observation group, according to Kaplan-Meier estimates (p = 0.01). The series was updated in 2006 to include 360 patients, with an additional 28 having a cCR. LR occurred in an additional 3 patients, and all were amenable to salvage surgery with no further recurrence. These data indicate that an initial non-operative approach offered to carefully selected patients yields similar mortality and recurrence rates as those who undergo surgery and are found to have a pCR. The experience also suggests that those patients who undergo NOM and do have a LR are amenable to salvage surgery.

Habr-Gama et al. later further updated and summarized data from one of their two original hospitals. Out of 183 patients who underwent CRT between 1991 and 2011, 90 (49%) had initial cCR and were managed non-operatively. Of these, a total of 28 local or pelvic recurrences (31%) were documented, with 71% occurring within 18 months and the latest at 64 months. Salvage therapy was possible in 26 (93%). Of the two that were not amenable to salvage therapy, one experienced concomitant systemic recurrence and the other had significant medical comorbidities. Four patients experienced further recurrence after salvage therapy, and were subsequently managed in a palliative manner. Systemic recurrence occurred in a total of 13 (14%) patients. Overall, under the watch-and-wait protocol, 5-year OS and DFS were 91% and 68%. In this updated series, OS was similar to the rates initially reported; however, DFS was lower. Of note, most recurrences were identified relatively early, over half within the first 12 months, and the salvage rate was high at 93%. Interestingly, in the previous two reports early re-growths (within 12 months of CRT) were considered incomplete responses, as complete responders were only designated as such if they had a sustained response for 12 months. In the updated series, early
Re-growths were considered as local recurrences rather than incomplete responders, accounting for the increased rate of cCR (Table 1).

Maas et al. at Maastricht University describe data from 192 patients treated with CRT between 2004-2010, of which 21 (11%) had a cCR determined at a mean of 6.5 weeks post-CRT. This was defined as no residual tumor at endoscopy or only a small residual erythematous ulcer or scar, negative biopsies from the scar, ulcer, or former tumor location, no palpable tumor after initially palpable, and no suspicious lymph nodes on MRI. Adjuvant chemotherapy was given to those with positive nodal status at primary staging. Twenty (10%) patients were found to have a pCR and functioned as the comparison group. Notably, 5 of these also had a suspected cCR. Two-year OS and DFS was 100% and 89%, respectively, in the observation group, with no significant difference between that and the resection group (Figure 1). There was 1 LR in the observation group, managed with transanal excision. There were no LRs in the resection group, but there were 2 deaths: one related to surgical complications associated with colostomy closure, and the other due to metastatic disease. This report demonstrates a lower rate of cCR than the Habr-Gama series after CRT, but similar rates of surgical patients with a pCR. The rate of LR was lower than that summarized in the Habr-Gama data; this may be related to the shorter follow-up period and/or the lower rate of patients selected for NOM. Regardless, these data similarly demonstrate comparable OS and DFS between patients selected for NOM and those patients who had a pCR, as well as the feasibility of successful salvage surgery.

At Memorial Sloan Kettering Cancer Center (MSKCC), there have been an increasing number of patients managed under the “watch-and-wait” strategy. We began implementing the “watch-and-wait” treatment paradigm in 2006. Recent analysis from 2006 to 2010 identified 32 patients who had attained a cCR after CRT and were managed non-operatively. These patients received radiation doses between 4500-5600 cGy, and adjuvant chemotherapy was given to 17 (53%). Patients were examined at 4-10 weeks post-CRT; cCR was defined as no palpable tumor on digital rectal exam, and endoscopy showing no visible pathology other than a flat scar. The comparison group consisted of 57 patients who achieved a pCR after neoadjuvant CRT and rectal resection, with adjuvant chemotherapy given to 50 (88%). At baseline, those who were managed non-operatively were older, had lower clinical stage, and had tumors closer to the anal verge. Overall, there was a higher rate of LR in the observation group than in the resection group (21% and 0%, respectively) but similar 2-year rates of DR (8% and 2%, respectively), DFS (88% and 98%, respectively), and OS (97% and 100%, respectively). The median time to LR was 11 months, and all were controlled with salvage resection and TME, with no further LR at median follow-up of 17 months. These data indicated to us that a “watch-and-wait’ treatment paradigm could be carried out in a safe fashion and that, although there was a higher rate of LR in the NOM group, salvage rates and survival outcomes were similar to those treated with conventional CRT and surgery.

### Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>No of cCR (%)</th>
<th>Mean interval to LR(N)</th>
<th>Overall survival NOM</th>
<th>Disease-free survival NOM</th>
<th>Operative arm NOM</th>
<th>OPERATIVE ARM NOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habr-Gama, et al. 2004</td>
<td>71 (27%)</td>
<td>60 months (2)</td>
<td>5-year: 100%</td>
<td>5-year: 88%</td>
<td>5-year: 92%</td>
<td>5-year: 83%</td>
</tr>
<tr>
<td>Habr-Gama et al. 2006</td>
<td>99 (28%)</td>
<td>52 months (5)</td>
<td>5-year: 93%</td>
<td>N/A</td>
<td>5-year: 85%</td>
<td>N/A</td>
</tr>
<tr>
<td>Habr-Gama et al. 2014</td>
<td>90 (49%)</td>
<td>17 months (28)</td>
<td>5-year: 91%</td>
<td>N/A</td>
<td>5-year: 68%</td>
<td>N/A</td>
</tr>
<tr>
<td>Maas et al 2011</td>
<td>21 (11%)</td>
<td>22 months (1)</td>
<td>2-year: 100%</td>
<td>2-year: 91%</td>
<td>2-year: 89%</td>
<td>2-year: 93%</td>
</tr>
<tr>
<td>Smith et al 2012</td>
<td>32 (N/A)</td>
<td>11 months (6)</td>
<td>2-year: 97%</td>
<td>2-year: 88%</td>
<td>2-year: 100%</td>
<td>2-year: 98%</td>
</tr>
<tr>
<td>Dalton et al 2012</td>
<td>6 (12%)</td>
<td>N/A</td>
<td>Mean 25.5 month follow up: 100%</td>
<td>Mean 25.5 month follow up: 100%</td>
<td>Mean 39.3 month follow up&gt; 100%</td>
<td>Mean 39.3 month follow up: 100%</td>
</tr>
</tbody>
</table>
A smaller retrospective study published in 2013 from a tertiary cancer center in India analyzed two groups of patients with a cCR after CRT. The first group consisted of 23 patients with a cCR who did not undergo surgery, and the second group consisted of 10 patients with a cCR who underwent elective surgery. Seven (30%) patients in the observation group developed LR, compared to none in the surgical group. Median DFS and OS were 36 and 66 months in the observation group, and 36 and 37 months in the surgical group. This study demonstrates that while LR rates were higher with NOM, there was no detriment in terms of DFS or OS compared to patients managed operatively. However, this study does differ from the others in that those in the surgical comparison group were also deemed to have a cCR and made a voluntary choice to undergo surgery.

In England, another small retrospective study (2004-2009) identified patients with a cCR after CRT. At 6 weeks post CRT, a repeat MRI was performed to assess tumor response. If little evidence of residual disease was noted, an examination under anesthesia was undertaken, with biopsies of residual scar tissue. Any residual mucosal ulcers were considered to be tumor, even if the biopsies were benign. Patients who still showed no evidence of tumor underwent FDG-PET scanning, and if negative were designated as cCR. Of 49 patients who underwent CRT during this time, 6 had a cCR and are disease-free to date, after a mean follow-up of 25.5 months. With no local recurrences, this study demonstrates the best outcomes to date for NOM of LARC. Notably, this study examined a smaller number of patients, with shorter mean follow-up than the original Habr-Gama series. The selection criteria were also more stringent than those used in many of the other studies, utilizing both post-CRT MRI as well as biopsy to define a cCR, and defining all mucosal ulcers as tumor.

In summary, these studies demonstrate that a “watch-and-wait” or non-operative approach can be carried out safely with careful selection of patients, by the clinician, in a prospective fashion. The patients who elect to undergo NOM must be counseled carefully, as this is non-standard practice outside of a clinical trial and carries risks that should be carefully weighed. Review of these data does implicate a number of small, retrospective institutional case series with variable patient selection and treatment plans. Also, there is some variability in surveillance, follow-up, determination of cCR, and use of imaging modalities, as well as clinical examination, to identify re-growth or failure of non-operative management.

DISCUSSION

While the most recent literature is promising, and appears to indicate that an initial non-operative approach for select patients provides oncologic outcomes that are at least similar to those with a pCR treated by radical resection (Table 1), a longer-term prospective study is clearly warranted. A randomized trial would prove difficult, as many patients may object to randomization to the operative arm of such a study when a non-operative approach is feasible. In Habr-Gama’s series, none of the patients with a cCR who underwent the watch-and-wait approach were treated with an adjuvant chemoradiation therapy. The current published studies are relatively small, retrospective, and variable with respect to definition of cCR, chemoradiation regimens, use of adjuvant chemotherapy, and follow-up protocol. A larger prospective study may also be beneficial by providing biopsied specimens to further analyze the molecular profiles of tumor responders versus non-responders.

Given our experience with NOM and induction chemotherapy, our group is undertaking a multi-institutional, phase II randomized controlled trial evaluating 3-year DFS in patients with LARC. All patients will be treated preoperatively with both FOLFOX and long-course chemoradiotherapy (e.g., total neoadjuvant therapy). By random assignment, half will receive induction FOLFOX (8 cycles) followed by chemoradiation; the other half will receive chemoradiation followed by consolidation FOLFOX (8 cycles). The rates of clinical CR will be determined by endoscopic examination and MR scanning, and compared for the two neoadjuvant arms. Patients who achieve cCR will be given the option of NOM. In addition to evaluating success in organ preservation, the study is also designed to test the hypothesis that patients treated with total neoadjuvant therapy and surgery or non-operative management will have improved 3-year DFS compared to historical controls treated with chemoradiotherapy, surgery and adjuvant chemotherapy. Retrospective analyses to date lend support to this approach, but we feel that a prospective study will provide the data to further support or refute the benefit of total neoadjuvant therapy.

When offering a watch-and-wait approach, careful selection of patients predicted to be pathologic complete responders is of the utmost importance. The presence of pCRs in the operative group of the Habr-Gama series and the study by Maas et al., suggests that the selection criteria used to identify cCRs at those institutions may slightly underestimate the number of pCRs. Poor correlation between cCR and pCR has been reported by Hiotis et al. In that study, tumors were resected within 6 weeks of chemoradiation, and thus may not have had adequate time to respond. The subtleties of digital rectal examination alone could underestimate the number of pCRs, as a result of local inflammation and fibrosis interpreted as tumor remnant. The question of whether cCR can accurately predict pCR and the development of standardized guidelines to optimally identify such patients should be the goal of future studies.

At our institution, a two-stage assessment is used to identify potential candidates for non-operative management. Patients are evaluated with digital rectal examination and endoscopic visualization at 6-7 weeks post-CRT after initial baseline clinical assessment. Surgery is recommended for those patients with a suboptimal tumor response. Patients with a convincing cCR, noted as involution of the tumor to a pale, flat scar with allowable
telangiectasias, may proceed to adjuvant chemotherapy or surveillance. Those with minimal areas of induration, nodularity, or ulceration are reassessed at 10-12 weeks, allowing more time for regression. We have developed a matrix to better assess response in a standard way, and will report on these findings in the coming year, adding MR imaging to better define cCR in this setting.

Other tools may assist in the identification of cCR. For example, a post-CRT CEA level <5 is a significant predictor of cCR and improved OS and DFS, independent of initial CEA level. The use of imaging may also serve as a promising tool to more stringently select cCRs. Maas et al. and Dalton et al. both utilized post-CRT MRI as part of the selection criteria for a cCR, with excellent results.

Maas et al. noted only 1 LR out of 21 patients. All 6 patients from Dalton et al. who were managed non-operatively have been disease-free. Other imaging modalities do not seem as promising. For example, the predictive value of endorectal ultrasound (EUS) re-staging is only 47% in assessment of complete response. The weakness of EUS lies in limited detection of small tumor residing within fibrotic tissue, and in over-staging secondary to misinterpretation of fibrosis. FDG-PET and helical CT scanning are similarly inadequate in differentiating complete and incomplete responses to chemoradiation.

As part of the multimodality treatment approach to rectal cancers, the role and timing of chemotherapy is also under evaluation in both the operative and non-operative setting. Historically, distant recurrence rates have exceeded those of local recurrence in LARC. The rate of nodal metastases in patients with a complete tumor response to CRT varies from 0-7%. New distant metastatic disease at the time of operation with a pCR has been observed, and DR is also known to occur in patients with an initial pCR. At MSKCC, several patients have been treated with up-front chemotherapy, with the idea of simultaneously treating the primary tumor and any micrometastatic disease. This eliminates the delay that often accompanies initiation of chemotherapy after surgery, thus closing the window of time in which distant micrometastases may grow. Furthermore, by altering the sequence of treatment in this way, the delivery of systemic chemotherapy to the primary tumor is optimized because the vasculature is unaltered by post-radiation or surgical changes. A retrospective review of the patients treated in this manner have demonstrated excellent results. R0 resections were achieved in 100% of patients who underwent surgery, pCR was 27%, and 47% achieved greater than 90% response. Treatment was well-tolerated, with no grade 4 toxicities, and all patients were able to complete the combined CRT.

The clinical trial currently underway at MSKCC will assess some of these questions regarding optimization of oncologic outcomes and quality of life in patients with LARC. This Phase II trial will evaluate disease-free events in patients with locally advanced rectal cancer treated with CRT plus induction or consolidation chemotherapy, followed by either TME or non-operative management. The trial will evaluate the efficacy and safety of non-operative management in the context of modern chemotherapy regimens designed to address the micrometastatic niche, while the patient can better tolerate the treatment. In summary, these data indicate that a “watch-and-wait” paradigm may be safe, yield similar salvage and survival benefits, and prevent considerable morbidity and quality of life difficulties for many patients with LARC.

SUMMARY

RAZVOJNE PARADIGME LOKALNO UZNAPREDOVALOG KARCINOMA REKTUMA

Standardni način lečenja uznepredovalog karcinoma rektuma u SAD je neoadjuvantna hemoradioterapija, totalna mezorektalna ekscizija i adjuvantna hemoterapija. Da bi se izbjegao morbiditet koji prati radikalnu eksciziju, poslednjih godina se sugerira ne-operativni pristup kod bolesnika koji su pokazali podpun klinički odgovor posle samo hemoradioterapije. Ovaj stav je potvrđen zapažanjem da je značajan broj bolesnika (15-40%) postigao podpuni histopatološki odgovor u vreme operacije.

Prikazali smo najnoviju literaturu da bismo ustanovili uporedivost onkoloških rezultata. Takođe, razmatramo buduće pravce u lečenju, uključujući konsolidaciju hemoterapije i neoadjuvantne hemoradioterapije.

Još uvek stupa udaljenih recidiva prevazilazi stopu lokalnih recidiva a adjuvantna hemoterapija je često odložena u očekivanju postoperativnog oporavka.

Direktna hemoterapija, bez odlaganja, treba istovremeno da tretira primarni tumor i eventualne mikrometastaze.

U našem centru je preduzeto istraživanje ovih terapijskih modaliteta.

Ključne reči: karcinom rektuma, neoperativni pristup, lokalno uznepredovali karcinom rektuma

REFERENCES


Abbreviations:
cCR = Clinical complete response,
CRT = Chemoradiation therapy,
DFS = Disease-free survival,
DR = Distant recurrence,
LARC = Locally advanced rectal cancer,
LR = Local recurrence,
NOM = Non-operative management,
OS = Overall survival,
pCR = Pathologic complete response,
TME = Total mesorectal excision