



BMH Med. J. 2019;6(2):65-70. **Review Article**

Neoadjuvant Treatment In Locally Advanced Rectal Cancer: Evolving Treatment Paradigms

Durga Prasan

Baby Memorial Hospital, Kozhikode, Kerala, India

Address for Correspondence: Dr. Durga Prasan, MBBS, MD, DNB (Medical Oncology), Consultant Medical Oncologist, Department of Medical Oncology, Baby Memorial Hospital, Kozhikode, Kerala, India, PIN 673017. Email: durgaprasan@gmail.com

Abstract

Rectal cancer is a common cause of public health burden worldwide. In India, majority of rectal cancers continue to present in locoregionally advanced stage, needing multidisciplinary management in comprehensive cancer centres. Treatment of locoregionally advanced rectal cancers has shifted from surgery based management to neoadjuvant chemoradiation followed by surgery and adjuvant therapy. Newer approaches in management include integrating neoadjuvant chemotherapy into the treatment algorithm in order to maximise long term survival outcomes, and exploring non surgical and organ conserving approaches in rectal cancer.

Keywords: rectal cancer, neoadjuvant treatment

Introduction

Colorectal cancer is the third leading cause of cancer and fourth leading cause of cancer deaths worldwide [1]. In India, colon and rectal cancer incidence are 4.4 and 4.1 per 100000 population, making it among the leading cause of cancer related public health burden [2]. Due to various sociocultural factors, which include lack of awareness, lack of access to specialist care, popularity of alternative systems of medicine and lack of community based screening programs, close to 90% of patients present in locally advanced stage [3].

Management of locally advanced rectal cancer is distinct from treatment of colon cancer. Multidisciplinary care is essential in ensuring optimal treatment outcomes for patients with locally advanced rectal cancer. Treatments involve a combination of surgery, radiation therapy and systemic therapy in complex algorithms. Optimization of treatment protocols is a work in progress.

Initial evaluation of rectal cancers involve locoregional and distal metastatic staging. Colonoscopy allows for direct visualization of the tumor, assessment of feasibility of sphincter preservation, obtaining biopsy, assessment of potential intestinal obstruction and ruling out synchronous polyps and colonic cancers. Endoscopic ultrasound is an accurate mode of evaluation of T and N stage,

though high resolution MRI has supplanted it due to better characterization of nodal involvement, extramural vascular involvement, tumor stage and circumferential resection margin (CRM), information that is crucial in decision making process in rectal cancer management [4]. Early rectal cancers include cTis, T1 and T2, without nodal involvement. The management is surgical, with choice of surgery based on likelihood of sphincter preservation. Total Mesorectal Excision (TME), which involves en bloc complete excision of visceral mesorectal tissue to the levators usually with sharp dissection, is considered to be the standard of care [5]. In pioneering work, Dr. Heald and colleagues showed that rates of locoregional failure can be reduced from 30% [5] to approximately 8% at 10 years [6]. Clinical stage T3 and above, and node positive tumors are treated with multimodality treatment. Addition of radiation and chemotherapy to surgery has resulted in improvement in disease free survival (DFS) and overall survival (OS) compared to surgery alone.

Radiation and chemotherapy can either be done after surgery (adjuvant) or before definitive surgery (neoadjuvant). Although both the strategies have been equally successful in terms of improving both DFS and OS, neoadjuvant treatment is the preferred approach because of significantly lesser short term and long term morbidity, as well as higher sphincter preservation [7].

Neoadjuvant chemoradiation

Neoadjuvant chemoradiation involves delivering radiation and concurrent chemotherapy before Total Mesorectal Excision (TME) in order to reduce the locoregional recurrence post surgery, as well as to improve overall survival. This is unique to rectal cancers unlike other subsites of colon cancer, where initial surgical management followed by adjuvant chemotherapy is the standard of care in operable cancers. Apart from the improvement in locoregional control and distant metastasis, neoadjuvant chemoradiation allows sphincter preservation in cases where upfront surgical approach may have not succeeded in sphincter preservation [7].

The role of neoadjuvant radiation in preventing locoregional relapses after TME was established by German Rectal Cancer Study [7]. More than 800 patients with locally advanced rectal cancer were randomized to receive either long course preoperative chemoradiation followed by TME or TME followed by adjuvant chemoradiation. Both arms included adjuvant chemotherapy. Radiation therapy involved delivering 5040cGy in 28 fractions using 6MV photons, with concurrent infusional 5FU on week 1 and week 5 for 120 hours. In post op chemoradiation arm, an additional boost of 540cGy was delivered to the tumour bed. Although 5 year overall survival remained similar in both groups, the preoperative group had fewer local relapses (6% vs 13%, $p=0.006$) and lower acute and chronic Grade 3 and 4 adverse events [7].

The role of chemotherapy in concurrent chemoradiation for locally advanced rectal cancer was investigated by the EORTC 22921 study. More than 1000 patients were randomized into 4 groups, with one group receiving only preoperative radiation, second group with preoperative chemoradiation, third group with preoperative radiation and post operative chemotherapy, and fourth group with preoperative chemoradiation and post operative chemotherapy. Chemotherapy regimen was bolus 5FU and leucovorin for 5 days every 4 weekly. The radiotherapy alone arm had significantly inferior local recurrence rate compared to the other three arms containing chemotherapy, thereby confirming the role of systemic chemotherapy in improving locoregional control. The lack of overall survival benefit also shows the lack of effect of chemotherapy on distant metastasis control [8]. Similar results were obtained in the French FFCD 9203 trial involving 700 patients comparing preoperative radiation versus chemoradiation. Addition of chemotherapy improved local disease control but had no effect on overall survival [9].

Short course preoperative radiation 1 week prior to planned surgery has also been effective in improving local disease free survival rates. The Dutch Colorectal Cancer Group TME trial randomized 1800 patients to either preoperative short course radiation in dose of 25Gy in 5 fractions, followed within 1 week by Total Mesorectal Excision (TME), or to TME alone. The study did not

allow for chemotherapy and hence provided a clear understanding of the role of preoperative radiation. This approach is distinct from long course chemoradiation because the surgery is done within a week of completing hypofractionated radiation schedule. Unlike long course chemoradiation, pathological complete response with short course radiation followed by surgery has been consistently low compared to long course chemoradiation. However, the radiation significantly reduced locoregional recurrence without impacting overall survival [10].

Long versus short debate

Long course chemoradiation and short course radiation have both proven to be feasible and effective in preventing local recurrences as preoperative treatment strategies. Randomised trials comparing long course versus short course preoperative treatments have not found any significant difference in locoregional control, overall survival and long term morbidity. The only significant differences observed has been a slightly improved local control with long course chemoradiation in distal tumors (<5cm from anal verge) and the significantly higher pathological complete response rates with long course chemoradiation in the surgical specimens [11,12].

Pathological complete response has been associated with improved disease free survival [13]. However, despite the fact that short course preoperative radiation followed by immediate surgery produces lower pathological complete response than long course chemoradiation, long term survival data remains similar. This is perhaps because radiotherapy to surgery interval (RSI) influences pathological complete response rates. In a large retrospective cohort of Italian patients treated with preoperative long course chemoradiation, pathological complete response rates were assessed based on radiotherapy surgery interval (RSI) stratified into three groups: TME within 6 weeks, between 7-12 weeks, and > 13 weeks post radiation [14]. Pathological complete response rates were significantly higher in patients with RSI of > 13 weeks, and least in RSI of < 6 weeks. Similar conclusions have been achieved in Stockholm III trial which compared short course radiation without delay (RSI <1 week) with short course radiation with delay (RSI 4-8 weeks). The pathological complete response rates were significantly higher in the delayed arm compared to immediate surgery arm although radiation treatment remained the same (15). All the three modes of preoperative radiation are considered standard of care.

Chemotherapy in preoperative treatment

Despite achieving significant local control with preoperative treatment, distant metastasis free survival and overall survival have not been improved. This could partly be due to fluorouracil based systemic chemotherapy. Efforts have been made to improve survival outcomes by intensifying chemotherapy regimens in preoperative and adjuvant treatment protocols. The German CAO/ARO/AIO-04 study evaluated addition of oxaliplatin to both preoperative long course chemoradiation as well as adjuvant chemotherapy compared to the standard arm of 5FU in both preoperative and adjuvant treatment. Addition of oxaliplatin significantly improved disease free survival [16]. However, the PETACC 6 study, published in abstract form, failed to show any benefit of adding oxaliplatin to capecitabine in neoadjuvant and adjuvant regimens [17].

Total Neoadjuvant therapy

The standard of care for locally advanced rectal cancer management involves preoperative radiation or chemoradiation, followed by total mesorectal excision, followed by adjuvant systemic therapy. One of the challenges in adjuvant systemic treatment is that only about 60% of patients complete 6 months of adjuvant chemotherapy due to toxicity. Recent studies suggest that shorter chemotherapy regimens are equally effective compared to 6 months of adjuvant treatment in colorectal cancer [18]. With more not necessarily being better, treatment philosophy is undergoing an evolutionary

churning with interest in using systemic treatment in neoadjuvant setting either before or after neoadjuvant concurrent chemoradiation. This approach, also called total neoadjuvant therapy (TNT), has several theoretical advantages. It allows optimal utilization of an effective treatment as chemotherapy in a relatively healthy patient, allowing more patients to complete their treatment with less morbidity. It also addresses micrometastasis early, though it is too early to comment on effect on survival. Earlier completion of chemotherapy and late surgery allows earlier closure of stoma, positively influencing quality of life. Patients who achieve clinical complete response can be kept on "watchful waiting" strategy for non surgical organ conserving approach to rectal cancer.

Total Neoadjuvant therapy can be delivered in two ways, either induction chemotherapy followed by chemoradiation followed by surgery, or chemoradiation followed by chemotherapy followed by surgery. Initial chemoradiation followed by consolidation chemotherapy was studied by Garcia-Aguilar et al in a Phase 2 non randomized patient population [19]. Primary end point was proportion of patients achieving pathological complete response. Addition of mFOLFOX6 based chemotherapy significantly improved pCR rates, with higher number of chemotherapy cycles achieving higher proportional pCR rates. The Polish II trial [20] studied an interesting idea. Locally advanced rectal cancer patients were randomized to two distinct arms. Both arms had oxaliplatin fluoropyrimidine based chemotherapy, and both arms kept radiotherapy to surgery interval constant at 12 weeks. While one arm had long course chemoradiation with concurrent bolus 5FU/Leucovorin/Oxaliplatin based chemotherapy, the other arm had short course radiation followed by FOLFOX4 based consolidation chemotherapy. Patients with short course radiation followed by consolidation chemotherapy surprisingly had significantly improved disease free and overall survival, though the locoregional control and distant failure rate was same in both arms. Clearly, further studies are needed to validate this schedule of treatment.

In contrast, studies looking at Neoadjuvant chemotherapy followed by chemoradiation followed by TME schedule have not been as promising, particularly with respect to pCR rates or survival outcomes. Hence, this approach is considered experimental. Larger randomized phase 3 studies are needed to further refine the role of neoadjuvant chemotherapy in addition to chemoradiation.

Addition of targeted therapy with chemotherapy has been studied in Total Neoadjuvant Treatment strategy. EXPERT-C trial studied role of cetuximab when added to neoadjuvant chemotherapy and chemoradiation in locally advanced rectal cancers, 60% of patient population being KRAS/BRAF wild type. Although the study did not meet its primary objective of improved complete response rate, there was a significant difference in overall survival and response rate [21]. Results have been similarly disappointing with panitumumab in KRAS wild type tumors with most studies failing to achieve their primary objective. Studies involving other targeted agents such as bevacizumab have been similarly disappointing and have not added significantly to standard treatment regimens.

Managing rectal cancer without surgery

An interesting outcome of high pathological complete response rates after neoadjuvant chemoradiation is the advent of non surgical "watchful waiting" strategy. Patients who achieve complete clinical response and are endoscopic biopsy negative for residual disease after neoadjuvant treatment are subjected to intensive surveillance instead of surgery. Patients who develop locoregional recurrence are offered TME surgery at the time of recurrence. In a recent review and meta analysis of 23 studies including more than 800 patients, patients managed with watchful waiting and salvage treatments during regrowth had similar survival to patients treated with surgical approaches [22]. This approach results in almost 85% chance of sphincter sparing and organ conservation. Although large randomized data are currently lacking, there is widespread interest and move towards a conservative approach in patients attaining clinical complete response. Clearly, there appears to be a need to optimize neoadjuvant treatment strategies to improve clinical and pathological complete response rates for organ conservation in rectal cancer.

Future directions

Rectal cancer management has evolved from surgery based treatments into combined modality treatments with emphasis on achieving excellent locoregional control along with organ conservation. Distant metastasis free survival has become the most important determinant of overall survival and quality of life. Systemic therapy in locoregionally advanced rectal cancer has remained its main Achilles heel, with inconsistent results with targeted therapy and immune checkpoint inhibitor therapy. Better characterization of tumor biology with molecular biology tools such as NextGen Sequencing and other techniques is likely to help clinicians optimize treatments in order to improve overall survival significantly from the plateau we have now reached. Improvement and wider acceptance of high end radiation techniques such as stereotactic radiosurgery are further likely to have a significant impact on treatment outcomes.

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