Review Article

Tumor Board can save Sphincter, A Review of Contemporary Multidisciplinary Management of Rectal Cancer

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Abstract: Colorectal cancer ranks third amongst various malignancies worldwide out of which a major proportion is of rectal carcinoma. With increasing incidence of rectal cancer amongst younger population in past two decades various advancements towards organ preservation approach have been devised. Total Neo-adjuvant approach (TNT) is current standard of care in various clinical scenarios involving rectal malignancy. In this review article role of Radiation in neo adjuvant setting and various landmark trials leading to it are discussed in detail.

Keywords: Rectal Cancer, Multidisciplinary Treatment, Cancer, Radiotherapy, Chemotherapy, Tumor Board.

INTRODUCTION

Colorectal cancer ranks third amongst malignancies worldwide, out of which one-third are rectal cancers [1]. Overall, there is a decrement in rectal cancer cases in older patients, but within the past 25 years an increased incidence of rectal cancer among younger population has been observed in Europe and USA [2, 3]. Highest incidence witnessed amongst 40 to 44-year age group, with an annual increase of 2.29% per year [4]. Anatomically rectal cancer can be defined as carcinoma arising within 15cm from anal verge delineated using a rigid sigmoidoscope [5]. Histologically majority of rectal cancers are adenocarcinoma with mucinous type adenocarcinoma comprising 10% and signet cell variant comprising 1-2% of rectal cancers [6]. As per a multi-variant analysis signet cell variant of rectal adenocarcinoma holds worse prognosis compared to other histologies [7]. Other variants include medullary, serrated, etc. [8].

This article summarizes rectal cancer management, highlighting recent advancements and the role of multidisciplinary teams in ensuring the best oncological and functional outcomes for our patients.

CLINICAL PRESENTATION

Most of the patients experience mild to no symptoms at all, stressing upon the need for adequate screening programs. Symptomatic patients might present with changes in bowel habit, abdominal pain, melena, rectal bleeding, alternating diarrhea and constipation, generalized body weakness, iron deficiency anemia and unexplained weight loss [9]. Less common symptoms include abdominal distension, severe abdominal pain, nausea, vomiting and absolute constipation, signifying tumor related bowel obstruction.

GENETICS

20% of colorectal cancers are associated with a genetic component with first-degree relative affected the most [10]. Hereditary diseases putting at risk to colorectal cancer include FAP (Familial Adenomatous Polyposis) and MUTYH associated polyposis [11]. Majority of genetic and some sporadic form of rectal cancer harbors MSI (micro satellite instability) with such instability occurring in genes involved with DNA repair mechanism [12]. Lynch syndrome being the most frequent form of genetic disease, making up to 2% to 4% of all colorectal cancer resulting from a mutation in DNA repair mechanism (MMR) genes. It has been recommended to opt for MMR and MSI genetic mutation analysis in all rectal cancer patients diagnosed before 50 years of age as there are chances of genetic syndrome in this age group [11].

SCREENING

American Cancer Society recommends to screen at 45 years of age in average risk group. This can be done through fecal occult blood testing, flexible sigmoidoscopy (3-5 yearly, if negative repeat after 10 years), colonoscopy every 5 years.
For patients aged 76-85, decision regarding screening must be individualized depending upon life expectancy, comorbidity, risk and preferences. Screening is not indorsed after 85 years. In high-risk patient it is recommended to screen patients 10 years before first diagnosed first degree relative and repeat colonoscopy every 5 years thereafter.

DIAGNOSTIC EVALUATION

Diagnostic evaluation begins with pertinent history and physical examination, with literature supporting up to 80% of rectal

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masses picked up on digital rectal examination [13]. Endorectal ultrasound is a modality of choice to detect the T stage of rectal mass with accuracy varying from 62 to 92% [14]. MRI is gold standard in both initial and advanced stage rectal cancers with Phased array MRI considered 100% accurate in assessing presurgical status of CRM (circumferential Resection margin) [15]. Followed by pathological confirmation of Adenocarcinoma via tissue biopsy. Staging workup constitutes CT chest and abdomen, CEA levels and comprehensive metabolic profile.

STAGING

Rectal cancers are staged as per TNM staging 8th edition of AJCC cancer staging manual which defines 'T' stage as per extent of involvement, 'N' stage depending upon the involvement of regional draining nodal involvement and M stage as per distant metastasis. When the tumor involves submucosal layer its designated as T1, involvement of muscularis propria makes it T2, if the tumor invades into peri colorectal tissue it is designated as T3 and T4 is when tumor invades through the peritoneal lining [16].

MANAGEMENT

Applied clinical anatomy of rectum signifies that it is located within the pelvis and other vital structures are located within its vicinity creating a therapeutic challenges when considering surgical and adjuvant options for management. A multitude of progress has been achieved pertinent to rectal cancer management in recent era. The increasingly complex treatment algorithms mandate the involvement of a multidisciplinary team for improved oncological outcomes [17, 18].

EVOLUTION IN SURGICAL MANAGEMENT

Formerly rectal cancers were managed with non-consistent forms of surgery, rendering local recurrence rate up to 30-45% [19]. However, surgical approaches have progressed over the past 100 years, in earlier twentieth century, perineal proctectomy was intervention of choice but it displayed poor oncological consequences (recurrence rate almost 100%) and high patient morbidity [20]. In the 1980s it became established that most common site of recurrence after surgery was mesorectum which was termed "zone of upper spread" therefore APR (Abdominoperineal resection) was coined, reducing rate of local recurrence to 30% hence laying foundation towards surgical techniques involving sharp dissection of entire mesorectum [20, 21]. Current standard oncological surgery for rectal cancer is TME (Total Mesorectal Excision) via Trans abdominal approach with clear resection margin in a package form, while preserving autonomic nerves [22]. Tumor involving the upper or middle third of the rectum can be treated via TME (sphincter preservation approach). Tumors involving lower third of rectum undergo abdominoperineal resection which is a morbid procedure associated with lifelong colostomy bag placement and genitourinary dysfunction, to improve local control for rectal cancer patients and enhance their quality-of-life radiotherapy and chemotherapy in neo adjuvant setting has been incorporated which is an effective step towards organ preservation approach [23]. Hence the current gold standard in surgical management is TME with adequate clear resection margins [22].

MANAGEMENT SCENARIOS

For selected patients with localized lesions away from sphincter (lesion within submucosa cT1, N0; <3cm in diameter, >3mm clear margins) en bloc removal through trans anal excision or transabdominal excision to be considered. As per ESMO guidelines, cT1 tumors with sub mucosal involvement <1000 micrometers should be only locally excised as they have less rate of nodal involvement, approximately 0-1.8% [23, 24]. Stage I (cT1, T2) tumors have higher chances of nodal involvement, 10% or more. Therefore, NCCN guidelines and ESMO guidelines recommend transabdominal approach for TME (Trans Mesorectal Excision) as the favorable approach [25, 26].

For management of Stage II-III non metastatic rectal carcinoma (cT3, T4/N+) multidisciplinary approach is to be adopted which includes neoadjuvant/ total neoadjuvant chemotherapy and radiation therapy (short course vs long course) followed by response evaluation and then surgery [23, 24].

ROLE OF RADIOTHERAPY

The first randomized trial discussing the effect of radiation in the treatment of rectal cancer was published in 1959, signifying added benefit of radiation therapy [27]. Foremost, indication to incorporate adjuvant radiation therapy is to decrease the incidence of disease recurring locally even after TME with adequate clear resection margins (CRM). Second indication is to downstage locally advance tumor via preoperative radiotherapy to achieve improved local control and optimal surgical outcomes and ensure sphincter preservation [28].

There are two approaches towards rectal cancer management via radiation therapy. German rectal cancer study showed favorable outcomes of long course CCRT in pre surgical setting for the management of locally advanced rectal cancer. They compared LCRT (radiation delivered over a longer period of time) in neoadjuvant versus adjuvant setting. Neoadjuvant therapy involved 50.4 Gy/28 fractions concurrent with Fluorouracil (5-FU) infusions given intravenously at first and fifth week, followed by surgery after 6 weeks. This showed an improved 5 year local control for the treatment group that received CCRT prior to surgery (13% vs 6%) arm

[29]. Whereas, the Swedish Rectal Cancer Trial group compared the effects of short course pre-operative RT followed by surgery, to surgery alone arm and it was concluded that pre-operative RT minimized local recurrence from 27 to 11% at 5year follow up and OS improved from 48% to 58% [30].

Literature proves that the incorporation of Multidisciplinary tumor board discussion (MDT) has an impact on treatment outcomes. Du *et al*; concluded that MDT recommendations altered treatment strategy in 58 percent of cases achieving greater five-year OS in MDT directed arm then control arm by adding neo adjuvant therapy (chemotherapy and radiation therapy) and surgery in non-metastatic T3,T4, Rectal carcinoma [31].

Further two studies compared LCRT and SCRT approaches. First the Polish trial was published in 2006, randomized locally cT3, T4 rectal cancer patients in to two treatment groups, first experimental group received pre-operative short radiation (25Gy/5Fr) followed by surgery within 7 days and second experimental group received 50.4Gy/28Fr along with 5-FU preceded later by surgery (6 weeks later). Patients were followed up to 4 years with sphincter preservation possible in approximately 61% of patients with short course radiotherapy, while 58% in long course radiotherapy. However, greater pathological complete response and lower rate of positive radial margins was observed in long course radiotherapy arm (up to 16% vs 1% in short course arm) and (4% vs 13% in short course arm). This study was then concluded with no significant difference in local recurrence rate, 4 years overall survival and disease-free survival rate. Moreover, Long course radiation was associated with greater acute toxicity (18.2% vs. 3.2%, $p < 0.001$). Severe late toxicity was not significantly different (10% vs. 7%, $p = 0.36$) [32].

The other study published in 2012 known as TROG 01.04 compared short course RT along with chemotherapy followed by surgery within 1 week to long course RT followed by surgery within 4-6 weeks. Patients' follow up was maintained for a total of 5.9 years and study recruited T3, T4 rectal carcinoma patients with disease within 12cm of anal verge. Long Course Chemotherapy and radiation resulted in significant down staging of tumor with local control rate up to 45% and increased pathological response rate up to 15%. In conclusion this trial demonstrated significant improvement in local control and higher rate of negative circumferential resection margin in long course CCRT as compared to short course CCRT [33]. As per the side effect profile, acute toxicity was reported more in long course arm vs short course arm with grade 3 or 4 toxicity reported 28% in long arm vs 2% in short arm. Reported rate of disease recurrence at primary site within 3 years was 7.5% in short course arm vs 4.4% in long course arm [33]. Table **1** comparing characteristics of TROG and POLISH trial.

Cost effectiveness of both regimens have been compared between two treatment courses with significant cost effectiveness reported in short course RT than long course RT overall, however long course RT has been proven more cost effective in distally located locally advanced rectal cancers because of higher rate of sphincter preservation and decreased cost of permanent colostomies [34].

TOTAL NEOADJUVANT THERAPY (TNT) APPROACH

German Rectal Study Group equated preoperative chemo radiation with post-operative chemo radiation therapy (CRT) in prospective randomized clinical trial among locally advanced rectal cancer with heavy nodal burden disease. Rate of local recurrence was reduced up to 6% in pre-operative CRT arm as compared to 13% in post-operative CRT arm along with increased rate of sphincter preservation approach in pre-operative CRT arm, hence strengthening the organ preservation approach in locally advanced rectal cancer [30].

A newer advancement has become standard of care for locally advanced rectal cancer patients that is TNT which comprises delivering radiation and combination chemotherapy before surgery to get the maximum local and distant disease control before surgery. There are two ways for TNT approach, i.e., Chemotherapy before (Induction) or after (Consolidation) CRT /RT.

To study the effect of SCRT in TNT approach, Polish II trial published in the year 2019 compared SCRT preceded by consolidative chemotherapy to long course concurrent chemoradiation arm in clinically T4 or fixed cT3 rectal cancers followed by Trans Mesorectal excision, the main aim of this trial was to assess the rate of negative resection margin and secondary endpoint being severity of toxicity associated with both the regimens, with patients being followed for a duration of 7 years.515 patients were analyzed 261 in short course arm and 254 in long course arm with no significant difference in overall survival between both treatment groups however, significant difference in overall survival at 3 years was observed in short course arm73% vs 65% in long course CCRT arm. Long course CCRT had reported greater acute toxicity i.e., 83%. Hence Polish trial concludes an increased 3-year overall survival with lower toxicity profile in short course CCRT arm, however there was no significant difference in overall survival or toxicity profile at 8 years follow up of patients [32].

A multicenter randomized phase III trial published in 2021 weighed up SCRT with consolidative chemotherapy regimen 4 cycles (CAPOX) to LCRT with concurrent capecitabine. Patients in both groups underwent surgery (TME) and received CAPOX post operatively. There rate of clear margin

resection was comparable in both groups however relatively more patients randomized to short course arm received pathological complete response (26.2% vs 5.3%). Rate of treatment completion was higher for short course RT arm vs long course RT arm (76.5% vs 49%) [33].

Recently, multicenter phase III randomized open label trial , RAPIDO trial published in January 2021, included patients with cT4 disease with N1-N2 involvement compared two groups, Experimental group comprised short course radiotherapy (5Gy/5Fractions) along with chemotherapy (6 cycles of CAPOX and 9 cycles of FOLFOX4) followed by standard surgery, standard treatment group included long course radiotherapy, 50.4Gy/28Fractions with concurrent capecitabine followed by surgery and adjuvant chemotherapy with 8 cycles of CAPOX. Patients were followed for a duration of 4.6 years, at 3 years disease related treatment failure was approximately 23% in experimental group vs 30% in standard group pathological complete response was observed in 28% of patients in experimental treatment group vs 14% in standard treatment group [24].

Another approach of TNT i.e., Induction approach with long course RT was studied in PRODIGE 23 trial. This is phase III, multicenter, randomized trial which has been conducted in France. This trial recruited patients with T3, T4 disease. They compared two groups, the experimental group comprised neoadjuvant chemotherapy with FOLFIRINOX for 6 cycles followed by chemo radiotherapy (50 Gy/25 fractions with concurrent oral capecitabine) and standard surgery (TME). Adjuvant chemotherapy (3 months of modified FOLFOX6 for six cycles was administered to patients. The standard group received chemo radiotherapy, TME, and adjuvant chemotherapy (for 6 months).Patients were followed for a period of 45 months, 76% of the patients were disease free in the neoadjuvant chemotherapy group and 69% in the standard-of-care

Table 1. Comparing LCRT vs SCRT.

Study	Description	Year	Inclusion Criteria	Patients	Dose and Fractionation	TME	LAR	APR	Local Recurrence	Overall Survival	pCR	G3.4 Toxicity acute	Late G3 G4 Toxicity
Polish Trial	Pre Op SCRT vs LCRT	2004	T3-T4 Palpable on DRE	316	25Gy/5Fr vs 50.4 Gy/28Fr	Yes	61% vs 58%	32% vs 36%	At 4 years 9% vs 14.2%	At 4 years 67.2% vs 66.2%	0.7% vs 16.1 %	3% vs 18%	7.1% vs 10.1
TROG Trial	Pre Op SCRT vs LCRT	2012	T3,No. 2, M0<12cm from anal verge	326	25Gy/5Fr vs 50.4 Gy/28Fr	Yes	63% vs 69%	37% vs 31%	At 3 years 7.5 % vs 4.4%	At 5 years 74% vs 70%	1% vs 15%	0% vs 5.6%	5.8% vs 8.2%

Table 2. Summary of Landmark Trials.

Trial	Randomization arms: Experimental arm vs standard arm	Primary/ secondary end point	Results	p-value
PRODIGE-23 Trial	Randomization arms: Experimental arm vs standard arm Standard arm: Long course CRT followed by TME and adjuvant CT Experimental arm: neo adjuvant CT followed by long course RT followed by surgery and adjuvant CT	Primary aim: DFS Secondary end point: OS, pathological complete response (pCR)	3-year: 75.7% vs 68.5% 3-year MFS: 78.7% vs 71.7% Resection status ypT0 N0 27.8 vs 12.1	0.034 0.017 <0.001
RAPIDO Trial	Experimental group: short course RT followed by CT followed by TME standard group: Long course CRT followed by TME followed by CT	Primary aim: 3-year disease related treatment failure Secondary aim: pathological complete response (pCR)	3-year disease related treatment failure: 23.7% vs 30.4% 3- year OS: 89% vs 88% pCR: 28% vs 14%	0.019 0.59 <0.0001
Stellar Trial	Experimental group: SCRT+ CT followed by surgery Standard group: LCRT+CT followed by surgery	Primary aim: pCR	pCR: 26.2% vs 5.3%	0.011
POLISH-2	Experimental group: SCRT followed by CT followed by TME Standard group: LCCRT followed by surgery	Primary aim: R0 resection rate Secondary aim: overall survival	R0 resection rate: 77% vs 71% overall survival: 73% vs 65%	0.081 0.046

group. Along with improved DFS, they reported pathological complete response 27.8% in experimental arm as compared to 12.1% in conventional arm. So, the results proves that instillation of chemotherapy before preoperative chemo radiotherapy has resulted in improved disease control outcomes in comparison to solely concurrent chemo radiotherapy in patients with cT3 or cT4 [35].

It is always a matter of debate that for how long we can await surgery after neoadjuvant short course radiation. In Stockholm III trial which is a randomized phase III trial, patients were randomized in two arms, one arm receiving preoperative radiotherapy (short course and long course) followed by surgery within 1 week, second arm received short course radiotherapy followed by surgery within 4-8 weeks it was concluded that rate of postoperative complications were lower in patients whose surgery was delayed after short course radiotherapy along with that 11.8% pathological complete response was observed on short course RT with greater interval to surgery vs 1.7% for lesser duration to surgery and the local control was not significantly different between the two group [36]. Hence it has proved that the surgery can be delayed after SCRT for 4-8 weeks without compromising the local control. Table **2** providing concise summary of all the landmark trials.

NON-SURGICAL MANAGEMENT (WAIT AND WATCH APPROACH)

It refers to non-operative management of T3, T4 rectal cancer. Different treatment approaches i.e. intensification of chemotherapy in neoadjuvant setting and dose escalation of radiation therapy has been adapted by the researchers to increase the clinical complete response and spare the organ from surgery. Total neo adjuvant therapy (TNT) in the newest approach to get the pathological complete response, both the RAPIDO and PRODIGE 23 trial, has shown encouraging results for treatment response [24, 35].

With the advancements of TNT approach and increased incidence of pathological complete response after chemo radiation therapy the watch and wait strategy has emerged as one of the acceptable management options. OPRA trial signifies the importance of this strategy which can be defined as replacing surgery with active surveillance in T3, T4 rectal adenocarcinoma who have attained complete response pathologically after two different set of TNT approaches. In this trial patients with locally advanced rectal cancer who achieved complete response or near complete response on TNT were recruited. Primary aim of this trial is free from disease for a total of 3-years, a total of 324 patients are currently recruited in this trial and 307 are currently under evaluation, with an available follow up of approximately 2 years, patients being followed with sigmoidoscopy and MRI. 52 disease free survival events were observed [37]. However robust clinical evidence is still lacking before adopting wait and watch approach outside a clinical trial strategy due to lack of long-term clinical outcome data available supporting this approach.

Patients on wait and watch approach were followed with serial sigmoidoscopy 3 monthly in first year and 6 monthly in second year along with MRI pelvis 3 monthly in year one and 6 monthly thereafter. Over all 16% of patients developed local recurrence within 2 years of follow up, 94% were located within lumen and 88% of them were visible on sigmoidoscopy, this suggests that patients should be closely followed within 2 years of TNT as most of local disease recurrences occurring in 2 years duration after treatment completion. Longer interval in first two years will cause delay in diagnosis. After 2 years increasing time period from 6 to 12 months for sigmoidoscopy will not cause delays in diagnosing local recurrence [38].

SURVEILLANCE

As per NCCN guidelines, patients need to be evaluated every 3 – 6 monthly in the first two years and then at 6 monthly intervals thereafter for a total duration of 3 years. Follow up of patients involves assessing CEA levels, colonoscopy annually and, if unremarkable, can be subsequently done on 3 years and 5th year of follow up. CT scan to evaluate primary site and distant sites to be done at a frequency of 6 to 12 monthly for up to 5 years [39].

SIDE EFFECTS OF RADIATION TOXICITY

Radiation induced toxicity in rectal cancer can be categorized into acute and chronic. Acute toxicity ranges from mild abdominal discomfort to pain, diarrhea, burning micturition, skin irritation and radiation induced proctitis. Late side effects of radiation may include diarrhea, ovarian dysfunction, vaginal stenosis, or infertility. In a systemic review on long term radiation induced toxicities signified the presence of diarrhea in up to 35% of patients, fecal incontinence in 22%, bleeding per rectum 9%, rectal pain 13% and obstruction in 7.4% of patients. One of the studies reported diarrhea being the commonest side effect in patients receiving pelvic radiotherapy, reported in 64.6% of patients [40, 41].

METASTATIC RECTAL CANCER

Metastatic rectal carcinoma has propensity to involve lungs followed by liver, in patients with synchronous metastasis evaluation for surgical resection has to be done. One of the approaches to manage oligo metastatic disease is to administer short course RT followed by chemotherapy followed by surgical removal of metastatic site and primary site. No single

sequence of modalities in management of metastatic site with primary site has been devised so far, hence multidisciplinary consensus is of prime importance. For patients with unresectable synchronous metastatic disease and symptomatic primary disease, palliative surgery at primary site has to be done to relief impending bowel obstruction or perforation and then systemic chemotherapy to be initiated and in asymptomatic cases systemic chemotherapy has to be started [42].

CONCLUSION

To conclude our discussion, a new standard approach towards treating rectal carcinoma is multidisciplinary TNT approach, utilizing radiation and intensified chemotherapy before surgery to get the maximum results. Site specific MDT tumor board discussion is of prime importance in managing rectal carcinoma patients. Moreover, role of screening cannot be denied in this cancer considering an increased trend towards younger age at onset.

CONFLICT OF INTEREST

Declared none.

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