Current evidence-based opinions in the management of adenocarcinoma of the rectum

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Abstract The management of rectal cancer has drastically evolved over the past two decades as a result of implementation of circular stapling devices and the introduction of neoadjuvant chemoradiation. In spite of current aggressive multimodality treatments, the recurrence rate remains unacceptably high and the expected 5-year survival in patients who develop recurrent disease is dismal. The management of rectal cancer must involve a multidisciplinary approach. An understanding of the biology of rectal tumours may allow for selection of patients who may have an aggressive phenotype allowing for alterations in the operative and neoadjuvant planning. Efforts to improve local control and survival in rectal cancer are the focus of multiple current clinical and preclinical research efforts. Preoperative chemoradiation for and surgical management of rectal cancer, including the laparoscopic approach are areas of dynamic progression. In the present report, we review the current evidence in the new strategies pertaining to the multimodality approach in the management of rectal cancer.

Keywords Induction chemotherapy · Laparoscopic LAR · Endorectal ultrasound · Preoperative staging · Rectum

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Introduction

It is projected that rectal cancer will affect 40,870 individuals in the United States alone, which when combined with colon cancer will lead to a mortality of 49,920 Americans during the same year [1]. While many similarities exist between the colon and the rectum in terms of their biology, histology, and genetic alterations leading to carcinogenesis; rectal cancer differs substantially in terms of preoperative management and surgical intervention. The pelvic location of the rectum and its close proximity of sympathetic, parasympathetic nerves as well as to the anal sphincter creates a “Ying-Yang” effect between performing an adequate oncologic operation while minimising sexual, bladder, and/or anal dysfunction. The management of rectal cancer has drastically evolved over the past 20 years as a result of implementation of circular stapling devices and the introduction of neoadjuvant modalities. As a result, a substantial shift has occurred for the operative management of rectal cancer from an abdominoperineal resection (APR) to an anterior protosigmoidectomy with a primary colorectal anastomosis low anterior resection (LAR). The lymphatic drainage of the lower rectum is contained within the mesorectum between the investing fascia of the rectum and the presacral fascia. An adequate oncologic operation involves removal of the tumour along with the entire mesorectum [total mesorectal excision (TME)]. The pelvic location of the rectum allows for the administration of ionizing radiation (IR) in doses that would be poorly tolerated by the colon due to the presence of the small bowel. In the present report, we discuss the current evidence of preoperative staging modalities, neoadjuvant treatment, surgical intervention as well as postoperative management for rectal cancer. A preoperative definition of the rectum is a pertinent good start.

Definition of the rectum

The end of the colon is demarcated by the collation of the taenia coli. The rectum then begins below the peritoneal reflection. This anatomical definition, however, is clinically impractical. Intraoperative rigid proctoscopy has demonstrated that the distance from the anal verge in 46 subjects (50% men, BMI ~23.0) to be 9, 11 and 14 cm to the anterior, lateral and posterior peritoneal reflection, respectively. The distance from the anal verge to the sacral promontory was 16 cm and it was 18 cm to the end of the taenia coli. In this study, there were no differences between men and women and the only correlation was the height of the subject [2]. An earlier study reported similar findings for the distances and there was no correlation with height, but a correlation was found with BMI in men [3]. The importance of an accurate determination of the rectum emanates from the ability to perform transanal excision for small (T1) tumours, but more importantly for selecting patients to receive neoadjuvant chemoradiation. In a Cochrane Review reported by Wong et al. [4] investigating 19 trials comparing preoperative radiotherapy versus surgery alone, the rectum was defined below the sacral promontory in three studies, below the pelvic brim in one study, and by the distance from the anal verge in several studies: 12 cm (one study), 13 cm (one study), 14 cm (one study), 15 cm (five studies) and 16 cm (one study).

In a study reported by Kapiteijn, the authors showed that rectal cancers located ≤ 5 cm from the anal verge had a hazard ratio (HR) for recurrence of 2.78 ($p = 0.02$). The HR for tumour 5.1–10 cm was 2.13 ($p = 0.02$). However, those tumours located >10.1 cm from the anal verge demonstrated no advantage in local recurrence between the group treated with radiotherapy and surgery compared to surgery alone. An earlier study also demonstrated that the rate of recurrence in cancers 12 cm distal from the anal verge had a recurrence rate of 9.6% versus $>30\%$ for lower rectal cancers [5]. Practice guidelines in the United States provided by the National Comprehensive Cancer Network (NCCN) [6] and the NCI [7] recommend a definition of the rectum 12 cm from the anal verge by rigid proctoscopy (preferably in the left lateral decubitus position) for the purposes of neoadjuvant chemoradiation. Once the definition of the rectum is determined for purpose of induction chemotherapy, it is important to establish the patient population that might benefit from this modality in terms of tumour node metastasis (TNM) stage.

Indications for induction chemotherapy

The natural history of rectal cancer after TME without chemoradiation was reported by Rodell et al. [8]. In this cohort, 776 patients underwent surgical intervention without preoperative or adjuvant irradiation. This analysis

demonstrated that the average rate of recurrence for patients with T1 and T2 (stage-I) tumours was 4.1%. For T3 tumours, the rate of recurrence was dependent on the level of perirectal tumour invasion. For T3 with depth <1 –5 mm, the 5-year local failure was 4.4%, but increased to 14.8% with when tumour invasion was 5.0–15.0 mm deep, and to 18.0% when it was >15.0 mm. The 5-year failure rate for patients with T4 tumours was 10.6%. Nodal involvement led to recurrence rates of 18.3% and 32.3% for N1 and N2 disease, respectively. The relatively low rate of recurrence for stage-I cancers does not justify neoadjuvant chemoradiation. However, T4 tumours and tumours with nodal involvement are likely to benefit from neoadjuvant chemoradiation. Patients with T3 tumours with no nodal involvement and perirectal tumour invasion ≤ 1 –5 mm, are likely to be over-treated. However, accurate perirectal involvement is difficult to determine preoperatively. Thus, neoadjuvant chemoradiation has emerged as the standard form of treatment for most patients with stage-II (T3–T4) and stage-III (nodal involvement) tumours [6]. This practice is further supported by Kapietijn's study in which univariate subgroup analysis demonstrated no advantage in the 2-year rate of local recurrence in patients treated with neoadjuvant radiation and surgery compared to surgery alone for patients with stage-I and stage-IV cancer.

Currently, the most accepted practice in providing preoperative ionizing radiation is to reduce tumour load and to prevent locoregional recurrence. In addition, it may allow for sphincter preservation, or permit the performance of a low anterior resection compared with a APR [8] in patients with stage-II and III tumours. Adequate preoperative staging is, therefore, essential for determining treatment options.

Preoperative staging

Preoperative workup for staging directs subsequent therapy and is, therefore, an integral part of the treatment of rectal cancer. A myriad of studies have been performed to assess the accuracy of CT, MRI and endorectal ultrasound (EUS) for preoperative staging of rectal cancer. The findings of these studies can be summarised by the results of two meta-analyses on the subject. One analysis, evaluating 90 studies assessing the accuracy of EUS, MRI and CT in preoperatively staging rectal cancer, showed that EUS and MRI were similar in terms of sensitivity (Sn) with regards to tumour depth into the muscularis propria (94%). EUS, however, was superior in determining muscularis propria invasion with a specificity (Sp) of 86% compared to MRI (Sp = 69%). EUS also emerged as a more sensitive strategy (Sn = 90%) for perirectal tumour invasion compared to MRI (Sn = 82%), and CT (Sn = 79%) [all p 's < 0.05] [9]. With regards to organ or lymph node involvement all modalities were similar [9]. A second meta-analysis evaluated 84 studies indicated that there was no difference in these modalities in evaluated

N-staging [10]. In this study, the authors also found in seven studies that MRI was a superior strategy in evaluating involved circumferential margins [10]. In summarising the contrasting conclusion of these two meta-analyses, it seems that for T-staging MRI or EUS are similar. For N-staging a few independent studies suggest that EUS might be slightly superior to CT and MRI [11]. EUS is the preferred modality at our institution. This practice, however, might be different from hospital-to-hospital as the accuracy of these modalities is highly operator dependent.

Preoperative chemoradiation

Preoperative radiation therapy, alone or in combination with chemotherapy, results in a tremendously wide range of clinical response. Pathological complete response (pCR) is the total obliteration of tumour load such that only a scar (if any) can be appreciated at laparotomy. This is a desirable property of induction chemotherapy and is an objective measurement to assess the efficacy of radiochemo-therapeutic interventions in the neoadjuvant setting. However, in patients with rectal cancer, this rate is highly unpredictable. From one side of the spectrum, 9–37% of patients are able to achieve a pCR following preoperative chemoradiation. Yet, at the other side of this wide range, up to 9% of patients do not respond to the same modality treatment [4]. In fact, in some cases the tumour continues to grow in spite of neoadjuvant treatment. Habr-Gama [12] observed a cohort of patients who achieved pCR without surgical intervention. No relapse or metastasis occurred at a long-term follow up. This study, however, included patients with T2 tumours of the distal rectum. No adjuvant therapy was provided to any patients. At 57 months follow up, the patients that achieved a pCR ($n = 71$) had a disease free survival (5-year DFS) in 92% of the cases and none of them had died from their disease (100% overall 5-year survival [OS]). However, these findings have not been replicated; thus, the current recommendation for the management of rectal cancers is surgical resection for all tumours irrespective of pCR.

Historically, preoperative therapy consisted of radiation therapy alone. Two meta-analyses addressed the benefit of preoperative radiation therapy [13, 14]. Though both trials confirmed decreased rate of local recurrence (46% in patients receiving preoperative radiation versus 53% in the control patients), data on overall survival was contradictory. However, given the increased morbidity of local recurrence, the benefit of preoperative radiotherapy, despite the questionable survival advantage, is evident.

Having established the benefit of preoperative radiation therapy, the addition of chemotherapy would possibly augment the benefit of preoperative therapy. Results from a recent randomised phase II trial assessing combined chemoradiation for rectal cancer showed 28% of patients with complete pathological response and 78% with tumour

down staging [15]. Chemotherapy serves as a radiosensitiser and to decrease local burden, thus increasing number of patients in the pCR group as well as decreasing the rate of local recurrence. Multiple trials have compared preoperative radiation therapy to chemoradiotherapy. EORTC 22921 showed an increased rate of pCR in patients who underwent chemoradiotherapy (13.7%) when compared to patients who received radiation therapy alone (5.3%). In a European trial with 762 patients receiving preoperative chemoradiation versus radiation alone, the pCR rate was 11.4% versus 3.6%, respectively.

Presensitising agents have classically included 5-fluorouracil (5-FU) to be given in combination with ionizing radiation. However, recent strategies have evaluated most of the chemotherapeutic agents currently utilised for the management of colon cancer, which include: irinotecan [16], oxaliplatin [17], capecitabine [17], and bevacizumab [18] and cetuximab [19]. With such strategies, there is still a wide response to ionizing radiation.

In Europe, small fractions of ionizing radiation 5.0 Gy $\times$ 5.0, for a total of 25.0 Gy are employed. With this strategy, the Swedish Rectal Cancer Trial also found an improved rate of survival at 5 years with preoperative radiation [20]. In the United States, the typical IR dose is 45.0–50.4 Gy in combination with 5-FU in divided doses for 5–6 weeks. However, multiple studies are assessing the presensitising efficacy of other radiosensitising agents. Neoadjuvant treatment is typically followed by surgery 6–10 weeks later.

Surgery and margins of resection

Preoperative evaluation for rectal cancer includes appropriate preoperative staging and a full colonoscopy to evaluate for synchronous lesions (present in up to 5% of colorectal cancers), rigid proctoscopy (to define the level of the tumour), abdominal CT and chest X-ray, or CT to evaluate for metastases, and baseline serum carcinoembryonic antigen (CEA) level. Following adequate preoperative evaluation and chemoradiation (for stage-II/III rectal cancer), surgical intervention must be carefully planned by reviewing all the available diagnostic data as well as timing and type of chemoradiation. An operation should be planned within 6–10 weeks after the last dose of chemoradiation. Although a longer window between neoadjuvant chemoradiation and operative intervention has been associated with higher rates of pCR, this must be assessed with regards to the risk of operating in a pelvis with markedly increased adhesions. While APR and LAR are the typical operations for most stage-II/III tumours, for small rectal cancers with a good histology and for a patient with a prohibitive risk of surgical intervention, a transanal approach is an appropriate alternative.

Transanal excision

Small (≤ 3 cm) stage-I tumours located within 8 cm from the anal verge that occupy $<30\%$ of the circumference of the bowel with good histological features can be treated via a transanal approach. With this approach, the risk of operative intervention versus the incidence of local recurrence must be considered with each individual patient. Local rates of recurrence with the transanal approach might be as high as 13.2% compared to 2.7% in similarly staged tumours treated with a more radical resection [21]. This study found that 20% of patient with T1 tumours who underwent radical resection had lymph node metastases [21]. A literature review of 41 studies in patients with rectal cancer treated exclusively by local resection demonstrated that the rate of local recurrence was 9.7% for T1, 25% for T2 and 38% for T3 cancers [22]. The rate of recurrence was lower in patients receiving systemic adjuvant chemotherapy: 9.5% for T1, 13.6% for T2 and 13.8% for T3 cancers [22].

LAR and APR

Historically, the treatment for rectal cancer involved a radical proctectomy with an end colostomy. The APR, originally described in 1908 by Miles, which sometimes bears his name, has been in a drastic decline over the past 20 years. This technique involves the removal of the distal rectum and perineum with clear tumour radial margins laterally to the pelvic sidewalls. In addition to the necessity of a permanent colostomy with this procedure, it was associated with a high rate of perineal wound infections [23]. Not only does an APR lead to reduced quality-of-life resulting from a permanent colostomy, but patients receiving an APR seem to have worse local control and decrease cancer-specific survival and were less likely to have negative circumferential radial margins (CRM) compared to patients treated with an LAR [24]. These observations might have selection bias, but the substantial effects on quality-of-life and postoperative complications have been clearly demonstrated with an LAR. The analysis by Den et al. [24] also suggests an oncologic advantage. Whenever possible an LAR should be performed.

TME

Total mesorectal excision (TME) involves a complete dissection of the integral mesentery of the hind gut that circumscribes the mid rectum yielding enbloc the rectum and its associated vascular and lymphatic structures, fatty tissue and mesorectal fascia. This area is typically confined between the investing fascia of the rectum and the presacral fascia. Superiorly the mesorectum is typically defined at the level of the sacral promontory or the division

of the right and left superior haemorrhoidal arteries. The mesorectum extends distally and reduces posteriorly at the level of the investing fascia of the levators (Waldeyer's fascia). MacFarlane compared TME against reported local recurrence rates following traditional resection and radiation. The TME group had a local recurrence rate of 5.0%, versus a reported local recurrence rate of 25.0% (prior to introduction of TME) [25]. This study found that patients with CRM <2 mm had increased local recurrence (16% versus 5.8%) and higher rate of metastasis (37.6 versus 12.7%) compared with patients whose margins were more than 2 mm at a median follow up of 35 months in 656 patients. This initial observation underscores the importance of radial margins in rectal surgery.

Analysis of 17,500 patients with rectal cancer demonstrated the CRM is a superior predictor of local recurrence, distant metastasis, and overall survival in patients receiving induction chemoradiation versus patients treated exclusively with surgical intervention [26]. Thus, pathological evaluation of the resected rectal tumour must include the distance to the tumour and to the closest CRM. This will serve in providing prognostic information and further management in patients with rectal cancer.

Proximal margin and level of arterial ligation

The proximal margin of resection has typically posed less concern as this is readily obtainable. There are no studies that assess the length of the proximal margin and rates of pelvic recurrence. A proximal margin of 5 cm has been suggested by NCI guidelines for colon and rectal cancer surgery [7].

The level of arterial ligation has been typically at the level of the inferior mesenteric artery (high ligation), as this was suggested to provide a superior oncologic outcome. However, this practice is associated with a decrease in innervation and perfusion to the proximal limb of the anastomosis. Additionally, there is no evidence-basis that suggests this provides superior oncologic benefits. Thus, ligation at the level of the superior rectal artery (low ligation) has emerged as a preferred strategy [27].

Distal margin of resection

Ideally, a distal margin of ≥ 2 cm is desirable. This emanates from studies that have shown that metastatic spread is rare with distal margins of 1 cm. For low rectal cancers, a 2 cm free margin, might be impossible and 1 cm is an acceptable option. A small retrospective study in patients with rectal cancer treated for cure, a distal margin of <1.0 cm was not associated with local recurrence [28]. Thus, the main objective of rectal cancer surgery is to achieve a resection free distal margin, especially in the era of neoadjuvant/adjuvant chemoradiation.

Laparoscopic surgery for rectal cancer

Advances in minimally invasive surgery have made laparoscopic resection of rectal cancer possible; however its use remains controversial. Currently, the NCCN declares the procedure investigational [6]. Questions of oncologic efficacy, complication rates, conversion rates, patient benefit, and cost-effectiveness abound.

Initial concerns regarding laparoscopic proctectomy related to the technical feasibility of the procedure. The confines of the bony pelvis did not seem suitable for a minimally invasive approach. Initially, minimally invasive rectal cancer resections were undertaken using hybrid hand assisted techniques. Clinical trials comparing these techniques to 'pure' laparoscopic surgery have shown no difference in short-term outcomes [29]. However, as technology and techniques have advanced, particularly the development of articulating endoscopic staplers, multiple case series reporting laparoscopic TME have documented technical feasibility with satisfactory short-term outcomes [30]. Case reports also document the possibility of robotic proctectomy [31] and natural orifice extraction of laparoscopic proctectomy specimens [32]. However, at the present time, the safety and reproducibility of these techniques has not been documented in any large series.

While large, multicentre randomised controlled trials such as the COST, COLOR and CLASICC trials firmly established the oncologic efficacy of laparoscopy in the treatment of colon cancer, currently only the CLASICC trial has specifically addressed rectal cancer. Short-term results of the CLASICC trial showed similar complication rates and short-term outcomes between laparoscopic and open surgery for rectal cancer. However, there was a trend towards a higher rate of positive CRM in the laparoscopic (12%) versus the open (6%) approach ($p = 0.19$) [33]. While this did not translate into an increase in local recurrence at 3-year follow-up, the lack of statistical significance might be a reflection of the small sample size (type II error). A trend towards an improvement in survival has also been observed in the laparoscopic compared to the open approach [34].

Several single institution case series [35, 36] and a randomised controlled trial [37] examining long-term oncologic results following laparoscopic TME suggest that they are similar to the open procedure. Several multi-institutional randomised controlled trials are underway to address this question. Both the COLOR II study group based in Europe [38], and the American College of Surgeons Oncology Group trial Z6051 will shed more light into the oncologic feasibility of the laparoscopic compared to the open approach upon completion.

Complication rates, especially long-term functional outcomes, of laparoscopic proctectomy are not well established. Injury to hypogastric and pelvic splanchnic

nerves can lead to sexual and urinary dysfunction. Alteration of rectal anatomy can lead to anal dysfunction, including urgency, incontinence and tenesmus. The CLASICC trial examined quality-of-life, sexual enjoyment, micturition, and defecation dysfunction and found no significant differences between the laparoscopic and open surgical approach [34]. However, there was a trend towards worse male sexual function following laparoscopic TME (41%) compared to the open approach (23%). Unfortunately, many case series reporting oncologic results failed to address long-term functional outcomes. An additional series of 50 males undergoing laparoscopic TME found acceptable rates of sexual dysfunction, with 27% of patients experiencing impotence [39]. These authors maintain that a 'pure' laparoscopic approach, with complete laparoscopic TME and division of the rectum, as opposed to dissection or division of the rectum through a limited incision, results in less damage to the autonomic pelvic nerves.

The rate of conversion from the laparoscopic to the open approach is another area of concern. While large single institution series of laparoscopic proctectomy report low conversion rates of 5–15% [30, 35], the rate in the CLASICC trial was 57% [33]. A Japanese series found high BMI, low tumour distance from the anal verge, high tumour T stage, and pelvic outlet factors were independent predictors of an increase in operative time and conversion rates for laparoscopic TME [40]. In considering the results of these studies, selection bias must be addressed as more difficult cases are likely to be started open. In addition, case series are usually performed by an individual or small group of highly experienced laparoscopic surgeons.

Patient benefit and cost-effectiveness of laparoscopic TME are also two areas with a dearth of information. The CLASICC trial showed no difference in length of hospital stay [33], while a single institution randomised trial found a trend towards shorter hospital stay in patients undergoing laparoscopic TME (8.2 days) versus the open approach (9.9 days) [37]. Cost is another factor to consider as the considerably longer operative times [135 minutes (open) versus 180 minutes (laparoscopic) in the CLASICC Trial] and expensive equipment involved in laparoscopic TME may be difficult to justify, especially given the current lack of a defined benefit.

In all, available data confirm the short-term safety of a laparoscopic approach to rectal cancer. However, experience and patient selection play a large role in success. Long-term data regarding oncologic outcome and functional status remain at large, as do data demonstrating patient benefit and cost-effectiveness. Until these data become available following the COLOR II and Z6051 results, laparoscopic resection of rectal cancer is best approached on an investigational status.

Complications

Complications from rectal surgery, primarily as a result of the location of the rectum in the pelvis, are substantial and are typically associated with bladder and sexual dysfunction, particularly in men, whose pelvis is narrower compared to women. A review of 11 studies ($n = 698$) where TME was performed for the management of rectal cancer demonstrated the following rates of complications: bladder dysfunction 17.8%, loss of erection of 27.7%, and lack of ejaculation of 33.9% [39]. Up to 30% of patients with attempted curative surgical intervention will eventually develop regional (pelvic) recurrence [8]. Treatment failure is largely dependent on the cohort of patients studied and ranges between 15% and 70%. Up to 70% of these patients have local recurrence as well as distant metastasis.

Conclusions

In spite of current aggressive multimodality treatments, the recurrence rate is unacceptably high (5–15%) and the expected 5-year survival in patients who develop recurrent disease is a dismal 9%. Nevertheless, this is a drastic improvement compared to two decades ago. The management of rectal cancer must involve a multidisciplinary approach. An understanding of the biology of rectal tumours may allow for selection of patients who may have an aggressive phenotype allowing for alterations in the operative and neoadjuvant planning. Efforts to improve local control and survival in rectal cancer are the focus of multiple current clinical and preclinical research efforts. Molecular predictors of a response to chemoradiation in patients with rectal cancer are urgently needed.

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