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Review Article

Current trends in the treatment of rectal cancer

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Abstract: Rectal cancer continues to be a leading cause of cancer mortality despite constant improvements in early detection and treatment. The patient tailored multidisciplinary approach using radiotherapy, chemotherapy and surgery has been the traditional therapeutic algorithm for locally advanced rectal cancer. Short or long course neoadjuvant radiotherapy improves long-term local control but has no effect on overall survival. In a similar fashion, preoperative chemotherapy also reduces local recurrence rates with no survival benefit. The addition of oxaliplatin or immunotherapy to the neoadjuvant regimen is still controversial and is not supported by the clinical practice guidelines. The timely initiation of adjuvant chemotherapy decreases local recurrence and improves overall survival. Total mesorectal excision remains the ultimate surgical therapy for patients with rectal cancer and can be safely performed via a laparoscopic or open approach. Despite the promising results of robotic surgery, there are still no data to suggest superior short- or long-term outcomes when compared to laparoscopy. Further studies are required to better understand the different treatment alternatives that could be used in the surgical and medical therapy for rectal cancer.

Keywords: Rectal cancer, treatment modalities, neoadjuvant therapy, adjuvant therapy, robotic surgery

Introduction

Colorectal cancer is the third most common cancer in both men and women accounting for more than 50,000 new deaths per year. From 2006 to 2010 the mortality rates have declined 2.5% per year for men and 3% per year for women among adults 50 years of age or older as a reflection of constant improvements in early detection and treatment. However, adults younger than age 50 are generally not included in the screening guidelines and have reported an annual mortality increase of 1.8%.

According to the American Cancer Society about 40,000 new cases of rectal cancer are expected to be diagnosed in 2014 [1]. A multidisciplinary approach (surgery, chemotherapy and radiotherapy) has substantially improved the overall outcome and survival of patients with rectal cancer [1]. Despite the current advances in treatment of rectal cancer, both local and distant recurrences remain major challenges in the therapeutic strategy of this potentially devastating disease [2, 3].

This review article describes the current trends in the oncological treatment of rectal cancer based on evidence-based literature and national and international guidelines. We also highlight several key areas of improvement in the evaluation and management of the disease.

Neoadjuvant vs. adjuvant chemo-radiotherapy (CRT)

Within the last decade the standard of care in the treatment of Stage II and Stage III rectal cancer combines neoadjuvant chemotherapy followed by surgical excision utilizing the total mesorectal excision (TME) technique. Ten years ago the paradigm shifted from the widely accepted postoperative chemoradiotherapy (CRT) to neoadjuvant therapy. This change in management was influenced in a large extent by the German Rectal Cancer Study published

Table 1. Selected randomized trials investigating multimodality therapy for rectal cancer

Study	Regimen	n	Stage	TME	pCR%	SPR%	5 y LR%	5 y OS%
Swedish [10]	SCRT + Sx vs. Sx alone	1168	Dukes' A-C	no	NR	NR	11 vs. 27 (p<0.001)	58 vs. 48 (p=0.004)
German [4]	CRT + Sx Pre vs. Post	823	T3, T4 or N+	yes	8	39 vs. 19† (p=0.004)	6 vs. 13 (p=0.006)	76 vs. 74 (p=0.80)
Dutch [12]	SCRT + Sx vs. Sx alone	1861	TNM 0-IV	yes	NR	NR	6 vs. 11 (p<0.001)	64 vs. 64 (p=0.902)
NSABP- R03 [6]	CRT + Sx Pre vs. Post	267	T3, T4 or N+	some	15	34 vs. 24 (p=0.13)	11 vs. 11 (p=0.693)	75 vs. 66 (p=0.065)
TTROG 01.04 [17]	SCRT vs. CRT	326	T3, N0 or N+	NR	1 vs. 15 (p<0.001)	NR	3 yr 8 vs. 4 (p=0.24)	70 vs. 74 (p=0.62)
MRC [14]	SCRT vs. selective Post CRT	1350	TNM I-IV	some	NR	NR	5 vs. 11 (p<0.0001)	70 vs. 68 (p=0.40)

n, number of patients in study; pCR%, percent of patients with pathological complete response; SPR%, percent of patients with sphincter preservation; 5 y LR%, reported 5-year local recurrence rate; 5 y OS%, reported 5-year overall survival rate; SCRT, short course radiotherapy 25 Gy in 5 fractions; Sx, surgery; CRT, long course chemoradiotherapy; Pre, preoperative; Post, postoperative; NR, not recorded; TME, Total Mesorectal Excision. †Rate derived from subset of patients with low lying tumors.

in the New England Journal of Medicine in 2004 (**Table 1**) [4]. The authors randomized 823 patients with clinical stage T3, T4 or node-positive disease to receive either preoperative or postoperative CRT. The preoperative treatment group (n=421) received a total of 5040 cGy radiotherapy divided in 28 fractions of 180 cGy, 5 days per week in combination with continuous fluorouracil (5-FU) infusion (1000 mg/m^2/d) during the first and fifth week of radiotherapy. TME was performed 6 weeks after the completion of CRT. Four cycles of bolus fluorouracil (500 mg/m^2/d, five times per week every four weeks) were started four weeks after surgery (preoperative treatment group) or four weeks after CRT (in the postoperative-treatment group). The postoperative treatment group received an additional 540 cGy boost of radiation to the postoperative tumor bed, for a total dose of 5400 cGy.

At year 5 the authors demonstrated a significant difference in the local recurrence rate among the groups: 6% in the neoadjuvant treatment group vs. 13% in the adjuvant treatment group, p=0.006. In addition to improved local control neoadjuvant therapy was also associated with reduced toxic effects related to the treatment. Specifically, the preoperative regimen resulted in a statistically significant reduction in anastomotic stricture and Grade 3 and 4 diarrhea. Importantly, preoperative chemoradiation did not result in an increase in postoperative morbidity including anastomotic leakage, delayed sacral-wound healing, bleeding or ileus. Finally, in the subgroup of patients who were deemed by the surgeon to require abdominoperineal excision at the time of randomization, there was a higher rate of sphincter preservation rate with neoadjuvant therapy (39% vs. 19%, p=0.004). Despite improvements in local control and treatment morbidity with preoperative therapy, there was no difference in the rates of distant metastases, disease free survival or five-year overall survival (76% vs. 74%, p=0.80). At year 11 there was still a significant improvement in local control in the preversus postoperative CRT [5]. Similar to the initial study published in 2004, there was no effect on overall survival. Although the chemotherapy used in that regimen is different from the standard treatment today, the neoadjuvant approach with 5-FU modulated chemotherapy has been widely adopted.

The results of the German Rectal Cancer Study were further supported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial (**Table 1**) [6]. The authors randomized 267 patients with clinical T3 or T4 or node positive rectal cancer in a preoperative and postoperative CRT group. The chemotherapy again was delivered during the first and fifth weeks of radiation and consisted of 5-FU (325 mg/m^2/d) and leucovorin (20 mg/m^2/d). The radiation dose was 4500 cGy in 25 fractions with a 540-cGy boost to gross tumor or the postoperative tumor bed for preoperative and postoperative treatment groups, respectively. In the preoperative group surgery was performed within 8 weeks of completion of the radiotherapy. In the postoperative group, chemotherapy began no later than 4 weeks after surgery. The 5-year disease free survival was significantly better for the neoadjuvant group than the adjuvant group (64.7% vs. 53.4%, p=0.011) and there was a trend toward improved overall survival (74.5% vs. 65.6%, p=0.065).

The advantages of preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue [7]. Reducing tumor burden facilitates resection and is associated with increased rates of sphincter preservation [7, 8]. In addition, preoperative radiation can decrease the risk of radiation enteritis, which is more likely when small bowel loops are trapped in the pelvis due to postoperative adhesions. Finally, all structures that are being irradiated will be safely removed during the TME allowing a healthy colon anastomosis to be created without the negative effects of radiation on wound healing. It is reasonable to question that neoadjuvant radiation will occasionally over-treat early stage tumors [8, 10]. However, preoperative testing with endorectal ultrasound and magnetic resonance imaging is performed to reduce the rate of inaccurate upstaging.

Based on those data the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology included neoadjuvant ionizing radiation therapy to the pelvis in combination with 5-FU infusion, followed by TME and an adjuvant course of chemotherapy as the official standard of care for locally advanced resectable rectal cancer (Stage II and Stage III) [59].

Short-course or long course neoadjuvant and adjuvant radiotherapies

The current body of literature does support the use of neoadjuvant radiotherapy. However there is still a lack of consensus among large international centers regarding the length of therapy: short versus long.

In Europe, it is common to deliver the radiation within a week (5 Gy x 5 daily treatments) followed by surgery a week later, which differs from the long-course CRT approach currently used in the United States. The idea of short-course radiation (SC-RT) was described almost two decades ago in the Swedish Rectal Cancer Trial (**Table 1**) [11]. The authors randomized a total of 1168 patients with resectable rectal cancer (T1-3) into two groups: one underwent preoperative irradiation (25 Gy delivered in five fractions in one week) followed by surgery within a week after completion of the radiation and a control group that received surgery alone. At year five the SC-RT not only reduced the rates of local recurrence (11% vs. 27%, $p<0.001$) but also improved the overall survival (58% vs. 48%, $p=0.004$). After a median follow up of 13 years, the beneficial effects of the SC-RT persisted [10]. The overall survival (38% vs. 30%, $p=0.008$) and the local recurrence rate (9% vs. 26%, $p<0.001$) were significantly improved in the neoadjuvantly-radiated group. This is the only study, to date, that demonstrated a survival difference with preoperative radiation.

Similar results were reported by the Dutch TME trial (**Table 1**) [12]. The authors randomized 1862 patients with resectable rectal cancer to be treated with or without SC-RT followed by TME. Although the trial did not show any effect on overall survival, the five-year local recurrence risk of patients undergoing macroscopically complete local resection after preoperative radiotherapy was 5.6% compared with 10.9% in patients undergoing TME alone ($p<0.001$). Also in this study, after a 12-year follow up the effect of SC-RT on local recurrence persisted [13].

The results of those studies were supported by a large multicenter randomized controlled trial led by the Medical Research Council in the United Kingdom and the National Cancer Institute of Canada (**Table 1**) [14]. Eighty centers in four different countries included 1350 patients with adenocarcinoma of the rectum. The patients were randomly assigned to SC-RT (25 Gy in five fractions) followed by surgery or to initial surgery with selective postoperative CRT (45 Gy in 25 fractions with concurrent 5-FU). Only patients with involvement of the circumferential resection margin were eligible for adjuvant CRT. After a median follow up time of 4 years the local recurrence rate was 4.4% in the preoperative SC-RT group versus 10.6% in the selective postoperative group ($p<0.0001$). The disease-free survival was also improved (77.5% vs. 71.5%, $p=0.013$), however no overall survival benefit was observed. This study suggests that in locally advanced rectal cancer it is advantageous to treat preoperatively with radiation, compared to waiting and selecting for CRT in patients who had the poor prognostic factor of a positive margin. Ongoing studies are required to properly select a group of locally advanced patients who would not benefit from adjuvant radiation.

In a randomized controlled trial (RCT) Bujko et al were the first to compare both short- and long-term neoadjuvant approaches [15, 16]. The study included a total of 312 patients with resectable rectal cancer (clinical stage T3 or T4). The patients were randomized to receive both preoperative irradiation (25 Gy in five fractions of 5 Gy) and surgery within 7 days or CRT (50.4 Gy in 28 fractions of 1.8 Gy, bolus 5-FU and leucovorin) and surgery 4-6 weeks later. Postoperative chemotherapy was allowed but not mandatory. After a 4-year follow up the authors reported no statistically significant difference in sphincter preservation, local recurrence or survival [17]. Although the acute-toxicity frequency was higher in the long course CRT group (18% vs. 3%, $p<0.001$), no difference was observed in the late-toxicity or severe late-toxicity frequencies.

More recently the Trans-Tasman Radiation Oncology Group randomized 326 patients with T3N0-2M0 low-lying rectal adenocarcinoma to receive either preoperative SC-RT (25 Gy in 5 fractions) followed by surgery within a week or CRT (50.4 Gy in 28 fractions with concurrent 5 FU) followed by surgery within 4-6 weeks (**Table 1**) [18]. All patients received adjuvant chemotherapy (six cycles for the SC-RT and four cycles for CRT). The study detected no significant difference in local recurrence rates (though the

recurrence rate was lower in patients treated with CRT), distant recurrence, relapse-free survival, overall survival or late radiation toxicity.

The interim analysis of the Stockholm III trial was published several years ago [19]. This study was carried out to assess whether increasing the interval between short-course radiation and surgery was beneficial. The authors randomized the patients into 3 distinct groups: SC-RT (5 x 5 Gy) and surgery within one week, SC-RT and surgery within 4-8 weeks and long course radiotherapy (LC-RT, 25 x 2 Gy) and surgery after 4-8 weeks. There was no significant difference in the postoperative complications between the groups (46.6% vs. 40.0% vs. 32%, p=0.164). Significantly more complications were observed in the patients who underwent surgery 11-17 days after the start of the RT when compared with the patients who underwent surgery less than 11 days after the start of the RT (65% vs. 39%, p=0.04).

The long-term consequences of a SC-RT and LC-RT were also compared in the Polish randomized trial involving 316 patients [20]. No significant difference was found in quality of life, anorectal or sexual dysfunction between the groups. However, cautions should be taken because of the relatively small sample-size.

To date, there are no data to suggest significant differences in survival, local control or sphincter preservation between the two neoadjuvant approaches. Advantages of short-course radiation include lower cost, patient convenience, and equivalent patient outcomes. Advantages of long course treatment include an ability to give concurrent chemotherapy, slightly improved local control, and perhaps a lower surgical complication rate. New short course regimens that combine short course radiation with systemic chemotherapy, with a longer time interval to surgery, may improve patient outcomes. Larger randomized controlled trials are needed to optimize the advantages of both SC-RT and CRT treatment modalities.

Use of chemotherapy in the neoadjuvant setting

As mentioned above several studies confirmed the benefits of neoadjuvant radiotherapy in the treatment of resectable rectal cancer. The effects of adding chemotherapy to the preoperative regimen have been extensively investigated for more than a decade. In a large randomized trial including 733 patients with T3-4, Nx, Mo rectal cancer, the authors stratified the subjects into two groups: the experimental group received preoperative radiotherapy with 4500 cGy in 25 fractions during 5 weeks in addition to combined chemotherapy of 5-FU and leucovorin and the control group received only preoperative radiotherapy [21]. In addition, both groups underwent adjuvant chemotherapy with the same 5-FU and leucovorin regimen as the experimental group. The authors did not find any difference in sphincter preservation or in the overall survival at 5 years. However, despite a moderate increase in acute toxicity (14.6 vs. 2.7, p<0.05) preoperative chemotherapy significantly improved the rate of local recurrence (8.1% vs. 16.5%, p<0.05).

Another large phase III trial with more than 1000 patients compared the addition of chemotherapy to preoperative radiotherapy in patients with T3-T4 resectable rectal cancer [22]. The preliminary results of the study showed that neoadjuvant 5-FU and leucovorin clearly enhanced the tumoricidal effects of radiation and resulted in a significant reduction in tumor size, pT and pN stage. More mature results of this trial showed that despite significant benefit with respect to local control there was no difference in the 5-year overall survival [17].

The conclusions of those trials have been supported by a recent Cochrane Database meta-analysis [23]. The meta-analysis included four RCT and showed that addition of preoperative chemotherapy to preoperative radiotherapy significantly increased grade III and grade IV acute toxicity (OR 1.68-10, p=0.002) while no difference was observed in the postoperative morbidity and mortality. Compared to preoperative RT alone, preoperative CRT significantly increased the rate of complete pathological response (OR 2.52-5.27, p<0.001) and also decreased the incidence of local recurrence at five years (OR 0.39-0.72, p<0.001). Despite those promising results, there was no benefit in disease free or overall survival.

A more recent Cochrane review including 6 randomized controlled trials reinforced the same results: the addition of preoperative chemotherapy improves the local recurrence rate but has no effect on overall survival [24].

In an ongoing randomized trial supported by the National Cancer Institute, investigators are comparing the neoadjuvant FOLFOX regimen with selective use of CRT versus preoperative combined modality CRT for locally advanced rectal cancer patients undergoing a low anterior resection with TME [60]. Although radiation therapy to the pelvis has been a standard and important part of the treatment for rectal cancer and has been shown to decrease the risk of cancer recurrence, the authors hypothesize that the current advances in surgery and chemotherapy might be able to provide an equivalent outcome (local recurrence, R0 resection, overall survival, pathologic complete response etc.) while avoiding the adverse effects of radiotherapy. The study is expected to include more than 1000 patients and is to be completed by July 2017.

Optimal chemotherapy in the neoadjuvant treatment of rectal cancer

The optimal choice of what chemotherapy to use during neoadjuvant radiation has also been the subject of several recent trials. Based on earlier studies and the activity of oxaliplatin as an effective agent in the adjuvant and metastatic settings, the use of oxaliplatin (despite the absence of any randomized Phase III data) had become part of the most commonly used regimens. This was based on the results of several Phase II trials, showing that there was an improvement in pathological response in patients who received oxaliplatin + 5-FU. The NSABP R04 trial randomized patients in a 2x2 factorial design to either the oral fluoropyrimidine capecitabine or infusional 5-FU with or without the addition of oxaliplatin [58]. In this trial, treatment was given concurrent with preoperative RT (45 Gy in 25 fractions over five weeks followed by a boost) in 1608 patients undergoing preoperative chemoradiotherapy for clinical stage II or III rectal cancer. Concurrent chemotherapy consisted of continuous infusion 5-FU (225 mg/m^2 daily, five days per week) with or without oxaliplatin (50 mg/m^2 weekly), or capecitabine (825 mg/m^2 twice daily five days per week) with or without oxaliplatin (50 mg/m^2 weekly). Compared with infusional 5-FU, patients receiving capecitabine had comparable rates of downstaging surgery and sphincter preservation, similar pathologic complete response rates (21 versus 18 percent for capecitabine and infusional 5-FU), and the primary endpoint (three-year incidence of any locoregional event 12 versus 11 percent), and comparable overall survival (81 versus 80 percent) [61].

Similar results were reported in a German trial that also compared capecitabine to infusional 5-FU. In this trial, the patients receiving capecitabine had significantly more hand foot syndrome, fatigue, and proctitis, but less neutropenia. At a median follow-up of 52 months, the local recurrence rate was similar (6 versus 7 percent with infusional 5-FU), but the distant metastasis rate was lower with capecitabine (19 versus 28 percent). Capecitabine was not inferior to 5-FU for five-year overall survival, the primary endpoint (75 versus 67 percent, p = 0.0004) [62].

Collectively, on the basis of several trials, oxaliplatin in the neoadjuvant setting with radiation is now no longer recommended. However, because these trials did show equivalence between oral and intravenous versions of 5-FU and because of the ease of administration and tolerability, capecitabine with radiation is now considered a reasonable standard.

Targeted therapy for rectal cancer (cetuximab and panitumumab)

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor that is being used in the treatment of metastatic colorectal cancer, metastatic non-small cell lung cancer and head and neck cancer. It is a chimeric (mouse/human) monoclonal antibody that is intravenously administered. In a multicenter phase II trial, patients with resectable KRAS/BRAF wild-type rectal cancer were randomized to receive weekly cetuximab in addition to conventional neoadjuvant CRT, surgery and adjuvant chemotherapy [25]. The addition of cetuximab improved the radiologic response (51% vs. 71%, p=0.038 after chemotherapy and 75% vs. 93% p=0.0.28 after chemoradiation) and the overall survival (HR, 0.27, p=0.034).

Panitumumab is a fully humanized monoclonal antibody specific to the epidermal growth factor receptor that is also approved for the treatment of patients with metastatic KRAS Wild Type colorectal cancer [26]. In another large multicenter phase II trial, panitumumab was

added to the neoadjuvant regimen in patients with wild-type KRAS locally advanced cancer. The addition of the EGFR monoclonal antibody resulted in high near-complete or complete tumor response (53% vs. 32%) but also increased the toxicity of the therapeutic regimen.

A multicenter clinical trial from Switzerland and Hungary enrolled a total of 94 patients with locally advanced KRAS mutated rectal cancer, who underwent treatment with capecitabine and sorafenib in addition to neoadjuvant radiotherapy [63]. The authors reported sphincter preservation in 89.5%, R0 resection in 94.7% and down staging in 81.6% of the patients.

However, at this point, randomized Phase III studies are still ongoing.

Induction chemotherapy

As mentioned above standard treatment for locally advanced rectal cancer includes preoperative combination of chemotherapy and radiotherapy followed by total mesorectal excision (TME). For the last two decades those treatment modalities became more sophisticated and resulted in a decreased local recurrence rate at 5 years. Unfortunately, despite the benefit with respect to local control there is no significant effect on long-term survival [17].

Induction chemotherapy is a relatively new approach that recently emerged in the hope of improving the overall outcome in cancer patients. The potential benefit of this treatment modality before concomitant CRT in locally advanced rectal cancer has been raised in recent studies [27]. In a randomized multicenter phase II study, patients with T2-T4/N+ rectal adenocarcinoma were assigned to induction chemotherapy with oxaliplatin, folinic acid and 5-FU followed by CRT and surgery. The study was closed prematurely due to lack of locoregional impact on standard therapy.

In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive capecitabine and oxaliplatin before neoadjuvant chemoradiotherapy or after surgery [64]. The authors reported more favorable compliance and toxicity profiles in the induction chemotherapy group, however no significant difference in the R0 resection rates was observed.

Garcia-Aguilar et al recently reported the effects of adding cycles of mFOLFOX-6 after neoadjuvant CRT in patients with locally advanced rectal cancer [65]. In four sequential prospective phase II trials a total of 291 patients with Stage II and III locally advanced rectal cancer received initially neoadjuvant 5-FU based CRT followed by 0, 2, 4 or 6 cycles mFOLFOX-6 and TME. The results of the study did not show a significant difference in the rates of R0 resection, sphincter sparing resection or the rate of surgical complications. However, adding increasing number of cycles of mFOLFOX6 after CRT and delaying surgery increased the probability of achieving a pathologic complete response.

Induction chemotherapy remains an area of current investigation and is not yet endorsed by the NCCN panel for routine care. Hence, caution must be used when adopting this practice.

Surgical approaches in rectal cancer

Node-negative T1 lesions

Node-negative T1 lesions can be treated either with transabdominal resection or transanal excision as appropriate. Those patients do not require neoadjuvant radio- or chemotherapy. However, a transabdominal resection should be considered if the surgically obtained pathologic specimen after a local excision reveals poorly differentiated histology, if the resection margins are positive (R1 resection), if there is a clear invasion into the lower third of the submucosa or if the tumor is restaged to T2.

In a large retrospective study including more than 7000 patients, Nascimbeni et al. showed a lymph node metastasis rate of 13% of T1 lesions [28]. Significant predictors of lymph node metastasis were penetration of the lower third of the submucosa (p=0.001), lymphovascular invasion (p=0.005) and lesions in the lower third of the rectum (p=0.007). Other authors also reported similar results [29].

In patients not considered surgical candidates, systemic therapy is indicated based on the so-called “sandwich regimen” where 5-FU based chemotherapy is administered before and after pelvic irradiation [30-32].

Node-negative T2 lesions

The patients with node-negative T2 lesions may best be treated with a formal transabdominal resection due to the high incidence of local recurrence rates observed following local excision. Overall survival may be compromised when compared with radical surgery [33]. Despite the improved 30 day mortality (0.5% vs. 2.4%, p=0.008) and 30 day morbidity (4.4% vs. 12.7%, p<0.001) when compared to radical resection [34], several studies reporting on the long-term results of transanal excision showed higher rate of local recurrence when compared with radical resection [33]. Garcia-Aguilar et al reported local recurrence rates as high as 18% for T1 tumors and 37% for T2 tumors at 54 months follow up [35]. Those results were supported by larger studies [36].

However, in a highly selected group of patients local excision might give results comparable to transabbdominal excision [37]. Patients with negative resection margins, no signs of venous/lymph vessel involvement and well or moderately differentiated cancers show similar recurrence free survival (87% vs. 91%) and local control (96% vs. 91%) to the patients undergoing abdominoperineal resection.

The ACOSOG (American College of Surgeons Oncology Group) Z6041 trial is a prospective, multicenter single arm, phase II trial that was initially designed to evaluate the efficacy and the safety of neoadjuvant chemoradiation and local excision (LE) for T2N0 rectal cancer [38]. The preliminary results of the study showed that CRT before local excision of T2N0 tumors results in high pathologic complete response and negative resection margins. However, the incidence of associated complications was relatively high (39%). The long-term oncologic outcomes of the study included a total of 76 patients with a mean follow up of 4.2 years [66]. The trial showed a local recurrence rate of 3%. The patients who developed local recurrence were salvaged with an R0 abdominoperineal excision with subsequent recurrence observed in one of the subjects. Five patients (7%) developed distant metastasis (lung 3, liver 1, uterus 1) and the 3-year disease free survival was calculated to be 0.87 (0.79-0.95, 95% CI).

For patients staged as pT1N0M0 or pT2N0M0, there are no data to date to support the need for additional adjuvant chemo or chemoradiotherapy. However, if the surgical pathology reveals higher stage disease (pT3) or node positive disease (pN1) the so-called "sandwich regimen" may be indicated [39]: a combination of adjuvant 5-FU ± Leucovorin or FOLFOX or capecitabine ± oxaliplatin is followed by 5-FU and radiotherapy or capecitabine and radiotherapy followed by 5-FU ± Leucovorin or FOLFOX or capecitabine ± oxaliplatin.

Novel surgical approaches

As the field of colorectal surgery evolved a variety of surgical approaches were developed based on the location and the extent of the disease. The following section will focus on the newly emerging robotic approach for treatment of rectal diseases.

More than two decades ago as Jacobs et al described laparoscopic colorectal surgery for the first time in the literature [40], it has progressively expanded and was recognized as a safe and effective alternative to open surgery [41]. Multiple studies were published supporting the use of laparoscopy for benign and malignant colonic diseases based on less postoperative pain, reduced postoperative morbidity, shorter length of stay and earlier return to normal activities [42, 43].

Despite the recent advances, the laparoscopic approach in colorectal practice remains a challenging task for many surgeons. The reduced range of motion especially inside the pelvis makes TME a technically demanding procedure with reported high conversion rates and involvement of circumferential resection margins [44].

The Da Vinci robotic surgical system (Intuitive Surgical Inc., Sunnyvale, California, United States) is a specially designed robotic-assisted approach that is believed to be able to overcome some of the technical challenges of conventional laparoscopic rectal surgery. Use of a surgeon-operated three-dimensional, high definition, 10-fold magnification camera, along with endoscopic instruments with 180-degree articulation and 540-degree rotation has been proven to reduce physiologic tremors, provide superior dexterity and far greater ergonomic comfort [45]. Those characteristics make robotic systems a great tool for surgeries where a high level of precision is demanded, especially if the anatomical field is limited as it is in the

pelvis. Several case series and multicenter studies have already demonstrated that robotic surgery is feasible, effective and provides a sufficient level of safety when used for minimally invasive TME. However, controversy exists regarding the role of robotics when compared with laparoscopic surgery.

In a recent systematic review, the authors identified 32 studies including a total of more than 1700 patients with rectal cancer who underwent minimally invasive robotic treatment [46]. When compared to the laparoscopic approach, no significant difference in morbidity (0%-41.3% vs. 5.5%-29.3%) and anastomotic complications (0-13.5% vs. 0%-11.1%) were found. In addition, no differences were found in the immediate oncologic outcomes: positive circumferential margins varied from 0%-7.5% for robotics and 0%-8.8% for laparoscopic surgery. Robotic rectal surgery was associated with higher costs and operating time, however, no significant superiority of robotics over laparoscopic surgery in terms of immediate and short-term outcomes was shown. Two other recent meta-analysis concluded that robotic assisted surgery decreases conversion rate when compared to conventional laparoscopy and is also associated with decreased intraoperative blood loss [47, 48].

There are several limitations that might impact the use of robotic surgery such as: very high cost to acquire and maintain the console, need for specific training not only for the surgeon but also for the entire nursing staff involved in the procedure. Another factor is the relatively slow penetrance in the practice of already well-established laparoscopic and colorectal surgeons. In order to be able to justify those limitations, well proven advantages in the use of robotic surgery are required.

However, to date there is no compelling evidence to suggest better results in either laparoscopic or robotic approach. Currently, two large multicenter randomized controlled trials comparing robotic versus laparoscopic surgery for rectal cancer are being conducted: the ROLARR and the ACOSOG-Z6051 trial. Hopefully, those studies will be able to give us further insights in the oncologic value and functional results of robotic assisted surgery. Currently, there are no guidelines recommending (or endorsing) the use of robotic surgery in the treatment of rectal cancer.

Adjuvant therapy

Following neoadjuvant CRT and surgical resection for stage II and III rectal cancer, the NCCN guidelines recommend the administration of adjuvant chemotherapy regardless of the surgical pathology results [59]. Surprisingly only few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer. Historically, the standard treatment has been in the form of 4 cycles of the Mayo clinic 5-FU/leucovorin regimen or 2-3 cycles of the Roswell Park 5-FU/leucovorin regimen. Most of the support to use FOLFOX or capecitabine as an adjuvant treatment modality is an extrapolation from the data available for colon cancer [49, 50].

In order to quantitatively summarize the available evidence regarding the impact of adjuvant chemotherapy in patients with resectable rectal cancer, a Cochrane Database Systematic review identified 21 eligible RCT for the time period between 1975 until 2011 [51]. The results of the meta-analysis showed a significant reduction in the risk of death (17%) among patients undergoing adjuvant 5-FU chemotherapy as compared to those undergoing observation (HR-0.83, CI: 0.76-0.91). In addition, there was a reduction in the risk of disease recurrence (25%) among patients undergoing postoperative CT as compared to those undergoing observation (HR=0.75, CI: 0.68-0.83).

Although currently FOLFOX (continuous-infusion 5-FU, leucovorin and oxaliplatin) has become a favored adjuvant regimen, the exact duration of the treatment has not been well determined [52, 53]. In the MOSAIC trial, patients with stage II/III colon cancer received the FOLFOX regimen for a total of 6 months after the surgery [54]. The use of a shorter course of adjuvant FOLFOX (i.e., 4 months) could be justified if preoperative radio-chemotherapy has been performed.

In addition to the length of adjuvant chemotherapy, the decision of when to initiate treatment after surgery has been shown to have an important effect on overall prognosis. In a systematic review Biagi et all identified 10 studies involving 15410 patients with colorectal cancer [55]. The meta-analysis demonstrated that a 4-week increase in the time to initiation of adjuvant chemotherapy was associated with significant

decrease in both overall survival (HR, 1.14; 95% confidence interval [CI], 1.10-1.17) and disease free survival (HR, 1.14; 95% CI, 1.10-1.18). Therefore, the time to initiating adjuvant chemotherapy should be kept as short as possible.

The role of chemotherapy after neoadjuvant chemoradiation

Most of the evidence used to support the adjuvant treatment of rectal cancer after neoadjuvant chemoradiation is an extrapolation of the proven benefit of postoperative adjuvant therapy with radiation therapy (RT) and chemotherapy that was the standard of care in the era before preoperative combined modality therapy. A Cochrane review of adjuvant chemotherapy in resectable rectal cancer concluded that 5-fluorouracil (5-FU)-based chemotherapy significantly reduced the risk of death (hazard ratio [HR] 0.83, 95% CI 0.76-0.91) and disease recurrence (HR 0.75, 95% CI 0.68-0.83).

In addition, the optimal choice of adjuvant treatment for patients who undergo neoadjuvant chemoradation is still not well defined. There are few randomized phase III trials comparing different postoperative regimens after neoadjuvant chemoradiotherapy, and no consensus on the best approach. Common approaches include four months of LV-modulated 5-FU or capecitabine alone, extrapolating from experience in adjuvant treatment of colon cancer. In addition, recent trials have shown mixed results with some studies suggesting that adding oxaliplatin is less meaningful and has not yet been defined by adequately powered phase III trials.

Therefore, reasonable options for postoperative chemotherapy include LV-modulated 5-FU, fluoropyrimidine monotherapy, FOLFOX, or capecitbine plus oxaliplatin. The role of newer regimens containing oxaliplatin or capecitabine plus oxaliplatin has not yet been defined by adequately powered phase III trials. However, some direct evidence supporting the benefit of adjuvant oxaliplatin in patients with resected rectal cancer after the same neoadjuvant chemoradiotherapy was provided by the randomized phase II ADORE trial, in which 321 patients with curatively resected rectal cancer after neoadjuvant fluoropyrimidine-based chemoradiotherapy and a pathologic ypII (ypT3-4ypN0) or III (ypAny, ypN1-2) stage disease were randomly assigned to four months of monthly bolus 5-FU/LV (5-FU 380 mg/m^2 plus LV 20 mg/m^2, daily on days 1 to 5, every 28 days) or FOLFOX [67]. At a median follow-up of 38.2 months, adjuvant FOLFOX was associated with a significantly improved three-year DFS (71.6 versus 62.9 percent, HR 0.66, 95% CI 0.43 to 0.99). As expected, patients receiving FOLFOX had significantly higher rates of all-grade fatigue, nausea, and sensory neuropathy, although rates of grade 3 or 4 toxicity were not higher. In an exploratory subgroup analysis, patients with ypN1b/N2 stage III disease and those with minimally regressed tumors derived the most benefit from FOLFOX, while there was no significant DFS benefit in those with ypII or ypN1a disease. Therefore, some clinicians routinely utilize an oxaliplatin-based regimen for all patients who have received neoadjuvant chemoradiotherapy regardless of yp status. However, use of a risk-adapted treatment strategy (ie, selecting an oxaliplatin-containing regimen preferentially for those patients with lesser degrees of tumor downstaging after preoperative chemoradiotherapy [i.e., ypT3-4 or node-positive disease]) is also reasonable. NCCN guidelines suggest that LV-modulated 5-FU, FOLFOX, or capecitabine with or without oxaliplatin are all appropriate alternatives for adjuvant therapy after neoadjuvant chemoradiotherapy.

ESMO (european society for medical oncology) guidelines

Similarly to the NCCN guidelines, in Europe and Asia practice guidelines are being constantly revised and published. Treatment algorithms were published in the Annals of Oncology in 2013 [56].

Conclusions

The outcomes in rectal cancer have steadily improved as many patients are diagnosed earlier in the disease process, mostly due to timely detection and treatment. Neoadjuvant chemoradiotherapy followed by total mesorectal excision and adjuvant chemotherapy represents the current standard of care for locally advanced rectal cancer. In addition to improved surgical techniques, the incorporation of sophisticated preoperative and postoperative CRT regimens resulted in improved local con-

trol, morbidity and mortality. However, better-refined studies are needed to understand the disease process to allow further improvements in the current treatment paradigm to improve patient survival.

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