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Multimodal approaches to the treatment of rectal cancer.

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Introduction

Colorectal cancer is the most common noncutaneous malignancy in Europe and the second most frequent cause of cancer-related deaths, with 436,000 cases (13.6% of the total) diagnosed in 2008, accounting for 212,000 deaths (12.3% of all cancer-related deaths)[1]. United States is the only country in the world where incidence rates from colorectal cancer are reported to be decreasing significantly,[2] while mortality rates have been in a gradual decline in developed countries[3]. Adenocarcinoma of the rectum, defined as disease occurring in the distal 12–15 cm of the large bowel, accounts for approximately 30% of all colorectal malignancies[4]. The extraperitoneal rectum is placed within the narrow and bony confines of the pelvis, making surgical resection more difficult. Additionally, the absence of serosa below the peritoneal reflection facilitates deeper tumor growth in the perirectal fat and may contribute to higher rates of locoregional failure[5].

The mainstay of treatment for patients who have rectal cancer has been curative surgical resection. Significant improvements in local control and overall survival have been seen in patients who have resectable rectal cancer[6-11]. Standardized surgical techniques, specifically total mesorectal excision (TME), have reduced local recurrence rates in rectal cancer from 39% to 10% and increased 5-year-survival rates to 71%[12] TME is one of the most influential factors in rectal cancer outcomes and is now considered the standard of care for clinical practice[13]. A better understanding of the natural history of the disease, patterns of recurrence, and more precise histopathologic reporting have helped to define patients who have a higher risk for local recurrence and disease progression after curative resection. This knowledge has prompted a progression in the multidisciplinary approach to treatment, with the integration of expertise from additional disciplines such as pathology, medical and radiation oncology, gastroenterology and radiology[14]. Particularly, modern imaging techniques (transrectal and endoscopic ultrasound and pelvic-rectal MRI) allow physicians to more precisely determine tumor characteristics and prognostic factors in the preoperative setting[15-17] This knowledge has been used to improve cancer stage specific treatments.[14] The combination of anatomic and biologic factors contributes to the complex and often challenging nature of treating rectal cancers. Optimal management and outcomes of patients depend greatly on the successful communication and collaboration of a multidisciplinary treatment team.[18]

Pre-operative treatment

Before 1980, surgery alone was the standard treatment for all stages of rectal cancer. The observation that high rates of locoregional recurrence were associated with locally advanced rectal cancer[19] led to the development of randomized trials, exploring the possible benefit of perioperative chemotherapy and radiotherapy, selecting a subset of high-risk patients.[18]

The advantages of neoadjuvant therapy utilizing radiation are thought to be due to improved responsiveness of tissue without hypoxia induced by previous surgery. Theoretically, ionizing radiations are more effective in presence of virgin tissue because of the increased oxygen tension in this tissue. Therefore, preoperative radiation and chemotherapy are more effective in producing tumor necrosis when delivered to an area where the blood supply has not been compromised by surgery. Other advantages of neoadjuvant therapy include less radiation-induced small bowel injury in the pelvis, which

has not been fixed by previous surgery; moreover the ability to excise the irradiated rectal segment and perform an anastomosis using a healthy, non-irradiated colon, results in improved postoperative function compared to those patients who receive postoperative radiation.[20] In addition, studies have shown chemoradiation therapy, in the preoperative setting, results in less acute grades 3 and 4 toxic side effects (P<0.001) and long-term toxic effects (P<0.01) compared to giving it postoperatively.[21] Not surprisingly, there is less patient's compliance to chemotherapy regimens provided in the postoperative period compared with the preoperative one.[21, 22]

Pre-operative radiation therapy

In the late 1990s, neoadjuvant radiation therapy was extensively studied in locally advanced rectal cancer. In this period two randomized studies - the Swedish Rectal Cancer Trial[23] and the Dutch Rectal Cancer Study Group Trial[24] - compared neoadjuvant radiation therapy and surgery to surgical therapy, showing a decrease in the local recurrence rates in the group of patients treated preoperatively. Both the studies showed a statistically significant difference in the local recurrence rate between the group receiving radiotherapy prior to surgery and the group treated with surgery alone (respectively 11% v.s. 27% in the Swedish study, P<0.001[23] and 2,4% v.s. 8.2% in the Dutch trial, p<0.001[24]), while the Swedish trial found a difference in the 5-year overall survival (58% in the radiation therapy plus surgery group compared to 48% in the surgery-alone group, P<0.004).[23] No significative difference in overall survival was observed in the Dutch trial, even if a difference in follow-up length (2 years in the Dutch study and 5 years in the Swedish one) may explain this difference.

Conventionally fractionated chemoradiation (45 Gy given in 5-6 weeks of treatment) with delayed surgery (after 6-8 weeks) or short-course irradiation (25 Gy in five fractions) with immediate surgery are probably the most frequent regimens in the preoperative treatment of patients with resectable rectal cancer. The only study currently available comparing these two regimens is considered not conclusive.[25]

In the following years, more than 20 randomized controlled trials (RCTs) comparing preoperative radiation therapy and surgery to surgical therapy alone was published, with heterogeneous results, mostly due to differences in treatment algorithms, i.e., dosage and duration of irradiation, timing of surgery, stage of cancer, quality of resection, and duration of follow-up.

Attempting to better understand inconsistencies between these trials, three meta-analyses have been conducted[26-28]; all reported a significant decrease in the local recurrence rate of stage II and III rectal cancers treated with radiation prior to resection, and, in two of the three studies, an improvement in overall survival. Generally, the association of pelvic radiation therapy with decreased local recurrence and a high likelihood of improved survival, holds for radiation delivered either before or after resection.[27]

In the same years Heald and colleagues developed the TME technique, which in itself resulted in a dramatic reduction in local recurrence compared with historical rates.[29] Subsequently, the TME technique was incorporated into the Dutch CKVO 95-04 trial[24] that confirmed the local control benefit of preoperative radiation even in the setting of optimal surgery, with an overall 5-year rate of local recurrence of 12% for TME alone compared with 6% for radiation plus TME (P<0.001).

Pre-operative chemo-radiation therapy

At the turn of the century, the clinical advantages of radiotherapy in locally advanced rectal cancer, combined with evidence that adjuvant chemotherapy also improves survival, provided rationale to study the combination of these therapies. This approach was attractive because of several theoretic benefits, such as enhanced radiosensitivity, increased sphincter preservation rates, improved likelihood of resection, and less acute and late toxicity[30-32](table 1).

The German Rectal Cancer Study Group[21] randomized to preoperative versus postoperative chemoradiotherapy patients who had stage II and III rectal cancer. No difference in 5-yearsurvival rates were found between these two groups (76% and 74%, P=0.80)[4]. The study found a significant decrease in local recurrence rate in the preoperative treatment arm compared to the arm receiving chemoradiation in the postoperative treatment period (6% vs. 13%) (P=0.006). Other noteworthy results were noted: a) the evidence of tumor downstaging, appreciated as earlier TNM stages in the group receiving preoperative chemoradiation

(P<0.001), with the 8% of complete pathologic response; b) a similar rates of sphincter preservation and morbidity and mortality between these groups despite a larger number of distal tumors in the preoperative group (39 vs. 30 at <5 cm; P=0.008); c) an improved treatment compliance in the preoperative group (92% vs. 50%) stated by less acute grade 3 and 4 toxic side effects (P=0.001) and long-term toxic effects (P=0.01) in the preoperative treatment group.

Two more recent clinical trials have found similar results in their evaluation of preoperative radiotherapy and chemotherapy in locally advanced rectal cancer. In the FFCD 9203 trial[33] 733 patients with resectable T3 or T4, Nx, M0 rectal adenocarcinoma were randomly assigned to preoperative radiotherapy alone or preoperative radiation therapy plus concurrent chemotherapy. The adjunction of chemotherapy resulted in increasing complete pathologic response rates (11.4% vs. 3.6%, P<0.05) and decreasing rates of local recurrence (8.1% vs. 16.5%, P<0.05). No difference in 5-year-survival was observed. The EORTC 22921 trial[22] randomized 1,011 patients with T3 or T4 resectable rectal cancer into four arms - preoperative radiotherapy, preoperative chemoradiation, preoperative radiotherapy with postoperative chemotherapy, and preoperative chemoradiation with postoperative chemotherapy. No difference in overall survival was found between the four groups. Patients who received chemotherapy – either preoperative or postoperative - both were found to have significantly lower local recurrence rates compared to the group who received radiotherapy alone (8–10% vs. 17%). Additionally, preoperative chemotherapy resulted in significantly smaller tumors, with less nodal involvement, less advanced pathological tumor stages, and less frequent lymphatic, venous, and perineural invasion compared to preoperative radiotherapy alone.

Even if several randomized trials have been unable to demonstrate a survival benefit with chemoradiation therapy compared to radiation therapy alone, a consistently lower local recurrence rate with the addition of chemotherapy is noted, regardless the preoperative or postoperative setting.

The analysis of secondary outcomes of these trials have found an increased rate of tumor downstaging, and a significantly higher complete pathologic response rate; furthermore an improved treatment compliance rate in groups who received chemotherapy and radiation preoperatively was detected[21,22,33]. Because of the above mentioned results, the combination of neoadjuvant chemotherapy and radiation therapy is now considered the gold standard in the care of preoperatively staged greater than T3 or node-positive rectal cancer. Usually, doses of 45 Gy are delivered to the whole pelvis in fractions of 1.8 Gy, in conjunction with FU-based chemotherapy[34]. An additional intraoperative radiotherapy (IORT)[35-37], which involves direct exposure of tumors to RT during surgery, should be considered for patients with T4 tumors or recurrent cancers.

More recently studies have been conducted on the association of radiotherapy with new drugs targeted against the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor (VEGF); these immunohistochemical proteins are currently considered the most important predictor markers of the pathologic response, the prognosis and the recurrence-free survival in rectal cancer following neoadjuvant therapy[38,39]. Particularly Bevacizumab (Avastin®; Genentech Pharmaceuticals, South San Francisco, CA), a humanized monoclonal antibody directed against VEGF, when combined with capecitabine, oxaliplatin, and radiation therapy, seems to improve the results of the preoperative treatment[40]. These encouraging results will lead to further investigations aimed to define the most effective drug combination.

Response to pre-operative therapy

Currently, preoperative combined modality therapy regimens are associated with a pathologic complete response rate (pCR) ranging from 4% to 33%[41-45]. A pathologic complete response is defined by no evidence of viable tumor cells on pathologic analysis, whereas tumors that display any evidence of residual cancer cells in the resection specimen are defined as having a partial pathologic response (pPR)[41,44,46] Vecchio and colleagues[47] showed a 5-year relapse-free survival of 96% for patients experiencing a pCR compared to only 56% in the group showing a low degree of pathologic downstaging (P<.001), with an improvement in the 5-year overall survival (51% versus 63%; P=.016). Chan and colleagues[48] reported similar data from Canada for 128 patients undergoing preoperative combined modality therapy for locally advanced rectal cancer. On multivariate analysis, tumor stage after the preoperative therapy was the most statistically

significant independent predictor of survival (P = .003) and relapse-free survival (P<.001).

In a landmark study, Habr-Gama and colleagues[49] presented long-term results of avoidance of surgery for selected patients with radiological and clinical evidence of complete response after neoadjuvant CRT. Even if preliminary results seem to confirm the safety of the "organ sparing" approach, to date this treatment should be offered to patients only in the setting of clinical trials, until more knowledge accumulates on the biology of tumor response and on the accuracy of its clinical evaluation.

In summary, communication between surgeons and pathologists is essential to optimize both the surgical treatment and pathologic evaluation of rectal cancer specimens. Mutual feedback can enhance quality of care provided by both disciplines, with the goal of improving patient outcomes.

Trial	Year	n	Phase	CT	RT, Gy	pCR rate (%)
Stockholm I[50]	1995	849	3	None	25	N/R
Stockholm II[51]	1996	557	3	None	25	N/R
Swedish Rectal Cancer Trial[23]	1997	1168	3	None	25	N/R
Dutch TME Trial[24]	2001	1861	3	None	25	N/R
German Trial[21]	2004	799	3	Induction vs post-op FU	Induction vs post-op 50.4	8
Polish Trial[52]	2004	312	3	FU+Leucovorine vs none	50.4 vs 5x5	16 vs 1
SOCRATES[53]	2005	94	2	CAPOX	N/R	18
EXPERT[54]	2006	77	2	CAPEOX	50.4-54	24
RTOG 0012[55]	2006	106	2R	FU vs FU+Iri	55.2-60 vs 50.4-54	28
EORTC 22921[22]	2006	1011	3	FU	45	5.3 (RT alone) vs 13.7 (RT+CT)
FFCD 9203[33]	2006	733	3	FU	45	3.7 (RT alone) vs 11.7 (RT+CT)
CORE[56]	2006	85	2	CAPEOX	45	13
CALBG 89901[57]	2006	32	2	FOLFOX	50.4	25
Rodel et al[58]	2008	48	2	CAPEOX+ Cetuximab	50.4	9
RTOG 0247[59]	2008	96	2R	CAPIRI vs CAPEOX	50.4	10 vs 21
Jakobsen et al[60]	2008	35	2	Uracil-Tegafur+ Celecoxib	60	21
Crane et al[61]	2008	25	2	Capecitabine+ Bevacizumab	50.5	32
Valentini et al[62]	2008	33	2	FU+Iressa	50.4	30
ACCORD[63]	2009	747	3	Capecitabine vs CAPEOX	45 vs 50	14 vs 19
STAR[64]	2009	586	3	FU vs FOLFOX	50.3 vs 50.4	15 vs 15
Willett et al[65]	2009	32	2	CAPEOX+ bevacizumab	50.4	16
GCR-3[66]	2009	108	2R	Induction vs post-op CAPEOX	50.4	14 vs 13
Carlomagno et al[67]	2009	46	2	CAPOX	50.4	21
MARGIT[68]	2009	50	2	FU+Cetuximab	50.4	8

CT=Chemotherapy. RT=adiotherapy. CAPEOX=Capecitabine+Oxaliplatin. RTOG=Radiation Therapy Oncology Group. FU=Fluorouracil. Iri=Irinotecan. EORTC=European Organisation for Research and Treatment of Cancer. FFCD= Fédération Francophone de la Cancérologie Digestive. CORE= Capecitabine, oxaliplatin, radiotherapy, and excision. FOLFOX=Oxaliplatin+Fluorouracil. CALBG=Cancer and Leukemia Group B. R=Randomized. CAPIRI=Capecitabine+Irinotecan

Table 1: Selected trials of preoperative treatments.

Principles of surgery

Local excision is generally accepted as an option for the treatment of T1 adenocarcinomas of the rectum with favorable features and is associated with low rates of recurrence and surgical morbidity[69,70]. Transanal endoscopic microsurgery (TEM) can facilitate excision of small tumors through the anus that are located higher up in the rectum. Both transanal excision and TEM involve a full thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (> 3 mm) deep and mucosal margins are required and tumor fragmentation should be avoided[71,72]. If pathologic examination reveals adverse features such as high grade malignancy, positive margins, lymphovascular invasion (LVI) or perineural invasion, a more radical resection is recommended. Local excision for more advanced lesions (T2 and T3) has been reported to have unacceptably high rates of recurrence (17%–62%), even with the use of adjuvant chemoradiation strategies[44,73-75] Therefore, enthusiasm for local excision for T2 and T3 lesions has waned significantly. However, when it was evident that radiotherapy can determine a complete regression of the tumor in up to 30% of patients, renewed interest has been shown in the application of local excision for select situations. In well selected patients, long-term outcome does not differ significantly from transabdominal techniques and no difference between conventional and endoscopic technique has been never evidenced. However, local excision has not been yet well accepted by the surgical community. Main scepticisms in using this technique derive from the lacking of mesorectal lymphectomy and the undefined lymphnodal staging. In theory, local excision should be performed only in case of clinical complete regression without signs of nodal involvement, but clinical and pathologic response sometimes do not match. Radiotherapy can determine a progressive fibrosis of the tumor, but neoplastic tissue can residuate, and this could happen both in primary tumor and in mesorectal lymphnodes. As the modality of tumor regression grade has been clarified, it is evident that clinical regression of the tumor can also hide an incomplete histological regression. Many clinical and radiological data have been investigated as predictors of complete pathological response in the lymphnodes, with conflicting results[76,77].

At least half of the patients with local recurrence after local excision and radiation therapy can still achieve the cure with a salvage transabdominal resection[78-82]. Local excision is also an option for palliation in patients with locally advanced rectal cancer or stage IV patients who are unsuitable for or refuse radical surgery.

Patients with rectal cancer who do not meet requirements for local surgery should be treated with a transabdominal resection. Abdominoperineal resection (APR) was first established in the early 20th century as the gold standard procedure for rectal cancer, leading to decreased local recurrence rates from almost 100% to 30% at that time[83,84]. Sphincter-sparing anterior resection was the next step forward, but there was concern for increased local failure with this less radical procedure. This led to the development of the concept of total mesorectal excision (TME). The concept of TME takes into account the predilection for locoregional recurrence in this disease and also allows for an adequate circumferential resection margin. The procedure involves resection of the tumor and mesorectum en bloc. Total mesorectal excision is limited by the fact that more operative time is required, and the procedure is associated with increased risk of anastomotic dehiscence and higher rates of gastrointestinal, sexual, and urinary dysfunction. However, the locoregional failure rate is consistently lower in published series of TME compared with historical and contemporary controls, with 5-year failure rates as low as 4% in the initial series reported by Heald[85,86].

Post-operative treatments

Despite improvements in rates of local recurrence associated with preoperative chemoRT in patients with operable rectal cancer, metastases' rate remains high in this population (ie, 30%-35%)[87]. Adjuvant chemotherapy of approximately 4 months duration is recommended for all patients with stage II/III rectal cancer following neoadjuvant chemoRT/surgery regardless of the surgical pathology results (ie, 6 months total duration of pre- and post-operative chemotherapy);[88] however, few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer and its role is not well defined, being most of the studies conducted on both colon and rectal malignances.

Postoperative radiotherapy is an option still largely diffused in North America. Its main advantage is the better selection of the patients, based on the final pathological staging. However, it's burdened by an higher toxicity rate, due to the presence of the small bowel in the radiation field, an higher radioresitency of the tissues and the negative effects of the irradiation to the perineal wound in case of APR resection.

The efficacy of postoperative 5-FU–based chemoradiation therapy for stage II and III rectal cancer was established by a series of prospective, randomized clinical trials[89-91]. These studies demonstrated an increase both in disease-free interval and in overall survival compared to surgery alone or surgery plus postoperative RT alone. Following the publication of these trials, the National Cancer Institute (NCI) concluded at a Consensus Development Conference in 1990 that combined modality therapy is the recommended postoperative adjuvant treatment for patients with stage II and III rectal carcinoma[92]. To further improve survival for these patients, subsequent studies have sought to optimize 5-FU administration, as well as employing new agents. The optimal schedule and duration of 5-FU–based chemotherapy in the adjuvant setting has been addressed in the current Intergroup 0144 trial. Patients were randomized to the following three arms: arm I bolus 5-FU - RT plus 5 + FU – bolus 5-FU; arm II prolonged venous infusion (PVI) 5-FU – PVI 5-FU + RT – PVI 5-U; arm III bolus 5-FU+LE+LEV – bolus 5-FU+LE+LEV+RT - bolus 5-FU+LE+LEV. Preliminary results demonstrated that the relapse-free survival and overall survival were similar in all arms, with the lower toxicity rate observed in arm II.[93] Therefore the postoperative therapy with continuous infusion 5-FU + RT was considered the standard treatment for patients with stage II or III rectal cancer.

Although combined-modality therapy has been associated with decreased rates of local recurrence of rectal cancer, considering the potential toxic side effects of these treatments, it has been suggested that low risk patients (eg with proximal rectal cancer T3/N0) may obtain an adequate local treatment with the sole TME (at least 12 lymph nodes examined). In this sitting, a potential benefit of 4-5% in local control could not justify the risks, especially in young fertile women[94-96].

Several RCTs have addressed this issue whether radiotherapy should be given preoperatively or postoperatively.[97,98] These trials used conventional doses and techniques of radiotherapy plus concurrent 5-fluorouracil (5-FU)-based chemotherapy. Low accrual resulted in the early closure of two of the trials, the National Surgical Adjuvant Breast and Bowel Project Protocol (NSABP) R-03 trial and the INT 0147 trial[99,100]. However, the German trial CAO/ARO/AIO-94 has been conducted successfully, with the planned accrual of more than 800 patients.[101] In this prospective randomized phase-III trial patients with locally advanced resectable rectal cancer were randomly assigned to a preoperative or a postoperative chemoradiotherapy group. The chemoradiotherapy regimens and the intervals between chemoradiotherapy and surgery – 4–6 weeks – were identical in both groups. The postoperative complication rates were similar in both groups. The results showed that preoperative radiotherapy significantly improved local control and the sphincter preservation rate in patients with low-lying tumors in comparison with postoperative radiotherapy.

Conclusions

There have been significant improvements in the treatment of rectal cancer during the past few years. The combination of chemotherapy with preoperative radiotherapy has been reported to improve the outcome after curative resection for rectal cancer. Currently, the gold standard of care for patients with locally advanced disease is neoadjuvant combined chemoradiation with a continuous infusion of 5-FU, followed by TME surgery, and then adjuvant 5-FU-based chemotherapy. The addition of oxaliplatin, capecitabine, irinotecan, cetuximab, and bevacizumab to neoadjuvant strategies in rectal cancer is being studied. Even if there does not appear to be a benefit in overall survival with preoperative chemoradiation, these regimens appear to improve the local control of the disease, nearing the point of complete tumor eradication. However, at this time there is insufficient evidence to support the ‘‘wait and see’’ strategies without surgical resection of rectal cancer. Future studies will need to assess markers or indicators of complete response to non-surgical treatments (either clinical or pathological), and the most effective chemo-radiation regimens to maximize rectal cancer patients'outcome.

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