Management of Locally Advanced Primary and Recurrent Rectal Cancer

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ABSTRACT

Treatment for patients with locally advanced and recurrent rectal cancer differs significantly from patients with rectal cancer restricted to the mesorectum. Adequate preoperative imaging of the pelvis is therefore important to identify those patients who are candidates for multimodality treatment, including preoperative chemoradiation protocols, intraoperative radiotherapy, and extended surgical resections. Much effort should be made to select patients with these advanced tumors for treatment in specialized referral centers. This has been shown to reduce morbidity and mortality and improve long-term survival rates. In this article, we review the best treatment options for patients with locally advanced and recurrent rectal cancer. We also emphasize the necessity of a multidisciplinary team, including a radiologist, radiation oncologist, urologist, surgical oncologist, plastic surgeon, and gynecologist in the diagnosis and treatment of patients with these pelvic tumors.

KEYWORDS: Primary locally advanced rectal cancer, recurrent rectal cancer, surgery, radiotherapy

Objectives: On completion of this article, the reader should be able to summarize the treatment options and outcome of primary locally advanced and recurrent rectal cancer.

The majority of patients with primary rectal cancer present with a tumor located within the mesorectal fascia, which is generally treated with total mesorectal excision (TME). Results of TME surgery are excellent with a significant reduction in local recurrences when preoperative short-term radiotherapy (5 x 5 Gy) is delivered one week prior to surgery.[1] In ~10% of all rectal cancer patients the tumor extends into or beyond the enveloping fascia propria of the mesorectal compartment. Often these tumors infiltrate adjacent structures and therefore have a higher risk to develop a local recurrence.[2]

Patients with these primary locally advanced or recurrent rectal cancer are historically difficult to treat with surgery alone, but outcome has significantly improved using multimodality treatment. Although preoperative and adjuvant therapy is important in these patients, the mainstay of treatment in rectal cancer is complete surgical removal of the tumor. In both locally advanced and recurrent rectal cancers, this involves not only the removal of the total mesorectum, but en bloc resection of involved structures is often needed. In this review, the therapeutic approach for locally advanced primary and recurrent rectal cancer is discussed with a focus on multimodality treatment protocols to downstage and downsize tumors and extended resections to enable complete removal of all tumor tissue.

IMAGING AND STAGING

Based on clinical information it is difficult to distinguish patients with locally advanced tumors, although certain patient complaints such as pneumaturia, hematuria, and vaginal bleeding suggest involvement of other organs. In addition, digital rectal examination can provide useful information such as large bulky lesions or lesions that are tethered or fixed to the pelvic wall.[3] However, accurate and detailed anatomic information of the tumor extent is essential to select locally advanced rectal tumors for neoadjuvant treatment modalities and planning of the optimal surgical procedure. Few studies have addressed the problems of predicting rectal tumor infiltration into adjacent organs.[4] The computed tomography (CT) scan has long been used to evaluate the local tumor extent because of initial optimistic results and the advantage of a single investigation to combine local, regional, and systemic staging.[5]

At present, magnetic resonance imaging (MRI) is demonstrated to be superior to CT for prediction of tumor invasion in surrounding pelvic structures, which is important in locally advanced and recurrent rectal cancer.[6–11] Although the large difference in outcome between MRI and CT in the comparative studies could be partially attributed to the fact that a state-of-the-art MRI technique was compared with a conventional CT technique. In theory, new-generation multidetector row spiral CT scanners, with superior contrast and spatial resolution and capability for reconstructions in multiple planes, are expected to provide better performances. Results of further studies are awaited to determine if new-generation CT can compete with MRI. Probably the most important factor is using adequate imaging in combination with preoperative multidisciplinary team discussions to decrease the number of positive resection margins as has been demonstrated by Burton et al.[12]

PREOPERATIVE TREATMENT

Although postoperative chemoradiotherapy (CRT) has long been recommended for locally advanced and node-positive rectal cancer patients, preoperative treatment is now widely used worldwide. A recent German trial has demonstrated the benefits of preoperative CRT with improved compliance, reduced toxicity, and increased local control.[13] In many European centers, radiotherapy only was used as neoadjuvant treatment for locally advanced rectal cancer,[14] but the addition of chemotherapy has recently been demonstrated to improve local control in two large randomized trials.[15,16] Addition of 5-FU and leucovorin to preoperative radiation slightly increased the amount of acute toxicity in T3 to T4 resectable rectal cancer patients.[17] However, it increased the number of complete responses and decreased the local recurrence rate after 5 years. It is important is to note that overall survival did not differ in these studies

and that sphincter preservation was not increased. New chemoradiation strategies are now published in numerous phase II trials including the use of oral 5-FU[18,19] and the addition of irinotecan[20,21] and oxaliplatin[22] to 5-FU-based regimens. A recent British trial has demonstrated high response rates in nonresectable rectal cancer patients after induction systemic chemotherapy followed by chemoradiation.[23] Although this was accompanied with considerable toxicity complete response rates were promising. Not only new chemotherapeutic drugs, but also a vascular endothelial cell growth factor- (VEGF-) specific monoclonal antibody in combination with chemoradiation was recently reported by Willet et al[24] to lead to considerable downstaging of the tumor. Other modalities such as the use of intensity-modulated radiotherapy (IMRT), which has the potential of more accurate delivery of higher radiotherapy dosages, thus avoiding the damage of critical structures surrounding the tumor, are being tested in rectal cancer. Higher radiation dosages could result in more radiation-induced necrosis and eventually in the possibility of further tumor downstaging.[25] These and other phase II and III trials are ongoing, but until randomized phase III trials demonstrate improved results, 5-FU based chemoradiation therapy is the golden standard for locally advanced and recurrent rectal cancer patients.[26]

SURGERY

Primary Locally Advanced Rectal Cancer

Some studies do not discriminate between primary locally advanced and recurrent rectal cancer; results are described as one group.[27] It is important to differentiate between these two because 5-year overall survival of patients treated for recurrent rectal cancer is generally reported between 15 to 55%[2,28,29] compared with a much higher 40 to 75% in primary locally advanced rectal cancer.[14–16,30–34] A similar difference in local control in favor of locally advanced rectal cancer has been described.[2,28,29]

Primary locally advanced rectal cancer is sometimes defined as stage III rectal cancer, which also represents resectable tumors with clinically suspicious lymph nodal involvement. Although these patients are treated in many centers with aggressive chemoradiation protocols, surgery can be performed with standard TME surgery[30] and after short-course radiotherapy (5 x 5 Gy) local recurrence rates and survival were demonstrated to be excellent.[1] Locally advanced rectal cancer is here characterized as tumors invading or extending close to the mesorectal fascia.

A complete excision of the tumor is of significant beneficial influence on local control and survival, especially in patients with locally advanced tumors.[14,35,36] During surgery, distinction between benign adherence

and malignant invasion is difficult to make, especially after neoadjuvant therapy. Because of this difficulty, the surgeon must resect en bloc the adjacent structures depending on the location and depth of invasion.[3] In case of clear lateral lymph node involvement, dissection of these nodes or parts of the pelvic wall sometimes including autonomic nerves is inevitable, but in these cases prognosis is generally poor.[37] Elective lateral lymphadenectomy has been extensively studied by Japanese surgeons and standard dissection yields generally a 10 to 15% involvement. In low rectal cancer and T3 to T4 tumors, the frequency is even reported to be higher and an improved locoregional control for this extensive surgery is claimed.[38–44] On the other hand, low positive lateral lymph node yields, questionable prognostic significance, and high morbidity (urinary and sexual dysfunction) are main reasons against this procedure. Due to major improvements in preoperative chemoradiation protocols and surgical technique (TME), only a few patients may profit from lateral lymph node dissection. In western centers, this technique is not in routine use.[45–47] In fact, lateral pelvic lymph node metastases were in very few cases the cause of a local recurrence in a large Swedish database study.[45] Therefore, dissection of the lateral lymph nodes should only be restricted to patients with enlarged suspicious nodes. Direct invasion in the iliac vessels and the obturator space is even more uncommon; resection of these structures might be indicated only in selected cases.[48]

In case of dorsal invasion, abdominosacral resections can be performed,[27,49] but this is a demanding procedure not often necessary in primary rectal cancer. Ventral invasion in a female patient usually requires resection of the uterus and/or part of the vaginal wall. In men, partial removal of the prostate is possible in case of ventral invasion, but a total pelvic exenteration is more commonly performed in patients with involvement of the prostate or bladder, which is discussed later in this review.

In the literature, completeness of resection, negative lymph node status, extent of resection, fixation of the tumor and presentation of pain are reported as prognostic factors for survival and local control.[14,29,50–53]

Distant metastases were traditionally contraindications for surgical treatment of patients with locally advanced rectal cancer. Recent improvements in systemic chemotherapy and a more aggressive surgical approach have made patients with resectable distant metastatic disease candidates for curative surgery.[54] Especially in patients with isolated liver metastases, complete resection of the metastases can lead to long-term survival and cure. In case of synchronous metastases, logistic issues play an important part in the treatment of patients. Locally advanced rectal cancer patients are treated with preoperative chemoradiation in a course of 5 weeks, followed by surgery 6 to 10 weeks later. Sometimes, small liver metastases can be removed in combination with a surgical procedure of the rectal cancer. If morbidity of combined surgery is considered to be high, staged resection could be considered. Treatment of the synchronous metastatic liver disease that is decisive for survival may be postponed for over 3 to 6 months after diagnoses when the rectum is treated first. For these reason, the proposed reversed approach by Mentha et al[55] is an attractive option for these patients. In this approach, patients are first treated with systemic chemotherapy, followed by liver surgery in those patients who respond. Because liver surgery is generally associated with minimal morbidity, chemoradiation treatment of the primary rectal cancer can commence shortly after discharge from the hospital. After finishing the chemoradiation treatment, surgery of the rectal cancer can be performed after the usual 6 to 10 weeks. In our hospital, we treated 11 patients with locally advanced rectal cancer and multiple synchronous liver metastases according to this approach.[56] One patient was progressive on oxaliplatin-based chemotherapy and 10 patients underwent a subsequent liver resection and received after the liver resection (chemo)radiotherapy for the rectal tumor. After radiotherapy, imaging demonstrated new extensive pulmonary and/or hepatic metastases in 3 patients and they were subsequently treated with palliative chemotherapy. Seven patients underwent radical rectal surgery and are alive without evidence of disease after a median follow-up of 23 months (range = 6 to 39 months). Long-term data from Mentha et al and other series are needed to find the optimal strategy for these patients, who are difficult to treat.

Recurrent Rectal Cancer

Despite improvements in the treatment of primary rectal cancer, recurrences occur in ~5 to 15% of the patients. The development of a local recurrence depends on various factors such as surgical technique,[57] lymph node involvement,[1] resection margins,[36] and location of the tumor.[1,58] Locally recurrent rectal cancer is often associated with severe symptomatic disease, especially pain.[29] For most patients, especially patients with extraluminal tumor mass involving other organs, the treatment used to be strictly palliative. Radiotherapy as a palliative treatment option effects the tumor mass for a period of 6 to 11 months, without the possibility of prolonging overall survival.[59–62] Due to neoadjuvant treatment modalities, a selective group of patients with recurrent disease can be operated on with curative intent.[29,49] Curative treatment can be successful in selected patients with true anastomotic recurrence, or in patients without pelvic sidewall involvement and early detection of the tumor.[63] In the past, resections of recurrent rectal cancer, which resulted in complete removal of all tumor were scarce with reported

R0-resections around 20%. Recent studies show that the current multimodality treatment provides possibility for curative resection in 40 to 80%.[29,60,64–69] This lower rate of complete resections is reflected in a lower local control and overall survival of patients with recurrent rectal cancer compared with primary rectal cancer.[2,28,29,53,64,70–73]

Symptomatic disease indicates a more advanced character of tumor growth, which will result in a higher rate of incomplete resections and an associated lower local control and survival.[29,65,74] Symptoms such as pain or hydronephrosis[75] are therefore considered to be a relative contraindication for resection of recurrent rectal cancer due to poor outcome. Tumor infiltration in bony structures is not uncommon in recurrent rectal cancer and used to be another contraindication for these patients. Some studies have reported long-term survivors after sacrectomy or composite resections; for highly motivated and carefully selected patients this procedure may be indicated.[76]

Because most patients are now treated with radiotherapy for their primary rectal cancer, most recurrences occur in a previously irradiated pelvis. In a Dutch multicenter study, the majority of patients who presented with a local recurrence after previous radiotherapy had simultaneous distant metastases. All patients who developed a localized recurrence died within 3 years despite multimodality treatment in some of these patients.[77] The authors conclude that the clinical nature and prognosis of those patients who do develop locally recurrent rectal cancer has been changed, and that meticulous imaging for distant metastases should be performed before aggressive treatments for local recurrence are administered. Some patients can be re-irradiated, although this has long been discouraged because it is thought to be associated with high incidence of late normal tissue complications. An Italian multicenter study reported promising results after hyperfractionated chemoradiation in previously irradiated patients with an overall survival of 39% in all patients. Survival was exceptionally good in 21 patients were a R0 resection was performed with a 67% 5-year survival rate.[78] Further studies are needed to identify those patients with recurrent rectal cancer that are candidates for multimodality treatment protocols and extensive surgery.[29]

Total Pelvic Exenteration

Total pelvic exenteration (TPE) is a widely used technique for resection of locally advanced or recurrent rectal tumors invading the bladder and/or prostate.[79] Long-term survival with excellent local control is possible after TPE for primary locally advanced rectal cancer (Table 1).[70,72,80–87] The majority of resections in primary cancer are without microscopic or macroscopic residual tumor mass, which clearly justifies the use of TPE in selected patients with primary disease. Although current guidelines for colorectal cancer surgery advocate TPE, only one third of the patients in a recent study based on SEER (survival, epidemiology, and end results) data underwent the appropriate surgical resection. These patients had a clinically significant overall survival benefit with no increase in short-term mortality compared with similar patients who did not receive a multivisceral resection.[80]

In recurrent rectal cancer, the visceral fascia surrounding the rectum has been resected in previous surgery, which makes a complete resection of all recurrent disease more difficult.[71,72,81,82,88,89] Successful complete resection of recurrent disease is often restricted to selected patients, for example, with an early-detected tumor or an anastomosis-limited recurrence after previous sphincter-sparing surgery.[66] Nonresectable distant metastases, poor physical condition, and/or irresectable local tumor are all contraindications for this type of surgery. Symptomatic pain or leg edema in patients who underwent TPE for primary and recurrent rectal cancer is related with an inferior outcome of both local control and survival.[90]

Table 1 Selected Series of Total Pelvic Exenteration for Rectal Cancer from 2001 – 2006

Author	N	Morbidity (%)	Mortality (%)	5-Year Survival (Primary) (%)	5-Year Survival (Recurrent) (%)
Chen and Sheen-Chen[86]	50	37	2	49	–
Wiig et al[82]	47	38	4	36	18
Yamada et al[71]	64	50	2	60	23
Jiminez et al[115]	55	78	5	77	28
Kecmanovic et al[72]	28	43	10	32	17
Ike et al[85]	71	66	4	54	–
Ike et al[88]	45	77	13	–	14
Lopez and Luna-Perez[97]	19	67	0	–	44*
Kakuda et al[87]	22	68	5	–	12
Moriya et al[98]	57	58	4	–	36*
Vermaas et al[81]	35	70	3	52	16

*Composite exenteration.

Morbidity is generally high after TPE with morbidity rates between 37 to 78%. The complications related to the urinary conduit are frequent causes for reintervention, which was demonstrated to occur especially in patients who previously received radiotherapy.[81,91] Although refinements in radiation therapy (3D-planning and exclusion of small-bowel from the irradiated field) may have resulted in a decreased toxicity, radiotherapy is still considered as one of the reasons for a high complication rate.[66,92] In recent years, mortality after TPE has decreased from rates up to 33% down to rates varying from 0 to 10%.[70,72,91,93]

In selected cases, patients have large tumors attached or infiltrating the bony structures of the dorsal pelvis. Some of these patients are candidates who undergo a sacropelvic resection or composite resection as developed and described by Wanebo et al and others.[49,94–97] This procedure is even more demanding than a total pelvic exenteration; it has a high morbidity rate and a mortality rate of ∼10%.[97,98] Because most of these patients develop a second recurrence and die of distant metastases, future studies have to focus on more adequate treatment of systemic disease in this group of patients. Each patient should carefully be judged preoperatively by a multidisciplinary team including a surgeon, urologist, gynecologist, radiotherapist, medical oncologist, radiologist, and an anesthetist before surgery.

Pelvic Reconstruction

Reconstruction of the pelvis after an extended resection is another challenge. Postoperative morbidity is high and late complications include perineal hernia, evisceration, or fistulae between the perineum and the gastrointestinal or genitourinary tract. When a low rectal anastomosis is possible after an extended resection it should be performed when conditions permit. This gives the patients not only the opportunity for a restored continence, but also fills the pelvis with vital tissue. When an abdominoperineal resection is performed, an omentoplasty might reduce the incidence of the perineal dehiscence and the need for secondary opening of the perineal wound,[99,100] although there is no direct evidence that this promotes primary healing.[101] If the omentum is not available, transposition of a myocutaneous flap can offer a solution to obliterate the pelvic space. Many flaps have been described, but the inferior-based rectus abdominis flaps, the inferior gluteal thigh fasciocutaneous flaps, and the gracilis muscle and myocutaneous flaps have emerged as the most reliable for use in the pelvis.[102–106] The gracilis muscle lies outside the external radiation field and can be mobilized relatively simply without major complications; the transposition will not result in functional disability but will have in a high percentage of wound closure. However, the gracilis muscle is not voluminous and not usable for large pelvic defects. The vertical rectus abdominis muscle is especially safe. It can used in the reconstruction of the vagina or in pelvic reconstruction; it should routinely be used after extensive resections.[76]

INTRAOPERATIVE RADIOTHERAPY

Local control in rectal cancer patients is related to the dose of irradiation, but because of toxicity to radiosensitive organs such as small bowels, the external radiation dose should not exceed 60 Gy. A combination of external radiation and intraoperative radiation therapy (IORT) allows the safe delivery of higher effective doses of irradiation than can be delivered with external-beam-only techniques. IORT is used when resection margins are narrow or involved with tumor cells and can be applied very specifically to an area at risk, under direct visual control, and with the ability to shield the surrounding structures from radiation. The biological effectiveness of single-dose IORT is considered to be as effective as 2 to 3 times the equivalent dose of fractionated radiotherapy.[89,107] IORT can be delivered using intraoperative electron beam radiotherapy (IOERT) or high-dose-rate brachytherapy (HDR-IORT). The advantages of IOERT are the treatment depth of > 1 cm with a choice of electron energies and quick delivery of the radiation. The flexible template in HDR-IORT can treat all surfaces with the highest dose at the area at risk, however, treatment time is longer.[108] Different centers worldwide use one of these techniques. Although no randomized trials concerning IORT have been performed, several studies have reported that IORT was feasible, safe, and improved both local control and overall survival; however, patient numbers are often small in these series.[32,33,35,50–52,73,108–111] In the analysis of our complete database of patients with both recurrent and locally advanced rectal cancer, patients who received IORT for narrow or microscopically incompletely resected tumors had a local control rate comparable to patients with wide R0 resection margins.[2,14] Because there is a good rationale for dose escalation in locally advanced and recurrent rectal cancer, IORT is one of those promising techniques for further improving local control and overall survival.

CONCLUSIONS

Treatment for patients with locally advanced and recurrent rectal cancer differs significantly from patients with rectal cancer with tumors restricted to the mesorectum. Therefore, preoperative imaging using MRI of the pelvis is important to identify those patients who are candidates for multimodality treatment including preoperative chemoradiation protocols, intraoperative radiotherapy, and extended surgical resections. Because only a third of the patients with locally advanced rectal

tumors are treated with the appropriate resection,[80] much effort should be made to select these patients for treatment in specialized referral centers. This has been shown to reduce morbidity and mortality, but also improved long-term survival rates.[112–114] Not only volume, but also a multidisciplinary team, including a radiation oncologist, urologist, surgical oncologist, plastic surgeon and gynecologist is of importance in these surgical procedures.

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