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review

Locally recurrent rectal cancer: treatment options

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Background. *Although the preoperative radiochemotherapy and the optimised surgical technique have improved the outcome in patients with rectal cancer, the local recurrence still remains a therapeutic problem. In up to 50% of patients the local recurrence appears without simultaneous distant metastases. This review highlights current treatment options of locally recurrent rectal cancer.*

Conclusions. *The optimal management of the isolated local recurrence remains a difficult and controversial issue. The radical surgical resection is the mainstay of the curative treatment, but an extended surgery can be associated with significant morbidity and impaired quality of life. The preoperative chemoradiation for turnout down staging increases the chance of resectability and the addition of intraoperative radiotherapy may further improve the local control and survival. Re-irradiation is feasible in patients who already received irradiation as part of the primary rectal cancer treatment.*

Key words: locally recurrent - rectal cancer; multi-modality therapy

Introduction

The local recurrence (LR) of rectal cancer occurs in up to 30% of patients who had undergone only the radical resection. The introduction of total mesorectal excision (TME) has reduced the rate of LR to <10%[1,2] and to ≤6% when TME has been combined with the preoperative radiotherapy alone or combined with chemotherapy.[3,4] Seventy-five percent of LR are detected within two years from diagnosing primary tumor.[5] From 20% to 50% of patients with LR have isolated the local recurrence without distant metastasis. LR may be accompained with pain, bleeding or constipation, depending on the type of the previous surgery. The management of the isolated locoregional recurrence is difficult and treatment options may be limited in patients who have already received a local radiation therapy for the primary rectal cancer. In the absence of the surgical intervention, the 5-year survival of these patients is less than 4% and the median survival of 8 months.[6,7]

The choice of therapy depends upon disease location, extent and prior treatment. Predictors for the outcome in patients who received radiotherapy for locally recurrent rectal cancer were performance status, stage, chemotherapy, surgery, extent of resection, histologic grading, and like in other

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localization haemoglobin levels both before and during radiotherapy.[8,9] Radical surgery (R0) remains the mainstay of the treatment for achieving the longterm local control and survival for locally recurrent rectal cancer (LRRC), but many times an aggressive multimodality approach is required to accomplish negative margins and a chance of cure.

Predictors of local recurrence

Many factors affect the risk of the local recurrence. The risk increases with the advanced stage[10] and adverse pathological features of primary tumour, including perineural and vascular invasion and grade.[11] LR is more likely associated with tumours located in distal rectum, the presence of obstruction or perforation and tumour fixation to adjacent structures.[12] The significance of the involvement of lateral or circumferential resection margin (CRM) as an independent prognostic factor for LR and the survival has been confirmed in a prospective randomised study on 190 patients who underwent the curative resection of rectal cancer. The rate of CRM involvement was 25%; among those with clear margins, 90% remained free of pelvic recurrence at 5 years, whereas only 23% of those with the lateral margin involvement were without LR.[13]

Recently published data from Davis *et al.* showed that there was no difference in the incidence of LR after sphincter-saving resections compared to the abdominoperineal excision, as long as the appropriate technique was used, the distal margin of clearance was at least 1 cm and CRM margins were free of tumour. By avoiding continuing the TME dissection into the pelvic floor and removing low lying tumours en block with the surrounding levator, the rate of involved CRM was reported to be 0% and the LR rate only 5%.[14] As LR after both surgical procedures most commonly arise from residual extramucosal disease, the incomplete removal of the potentially tumour-bearing mesorectum is the main cause of LR.[15] There is a different level of training and experience performing »total mesorectal excision« (TME) among surgeons, resulting in wide range of LR in published reports. A study comparing local recurrence rates after the rectal cancer resection in a group of Canadian surgeons showed that patients of surgeons who had additional training or expertise in colorectal surgery had a local relapse rate of 13%, compared with 34% in general surgeons' group whose practice included fewer of these operations.[16] Finally, the rate of LR in patents receiving preoperative or postoperative radiotherapy, either alone or combined with chemotherapy, is reduced comparing with patients treated with surgery alone. More favourable local control rates were reported in series using the preoperative approach.[14,15]

Surgery

The only chance for the curative treatment of isolated LR is provided by the radical re-resection.[17] Several studies have analyzed factors which could help to select patients with LRRC for surgery *i.e.* that might predict resectability and, consequently, prognosis. Results are controversial. However, factors most often associated with the increased chance of the radical resection were younger age, female gender, prior local excision or restorative surgery that was performed at another institution. The poorer outcome was related to the presence of pain (as a symptom of LR), lateral tumour extension, increasing number of sites of the recurrent tumour fixation in the pelvis and elevated CEA level before the re-resection.[18]

Surgical procedures available in LRRC are low anterior resection, abdominoperineal resection, pelvic exenteration and ab-

Table 1. Locally recurrent rectal cancer - external beam radiation without or with intraoperative radiation

Author	Year	Patients (n)	Therapy	Survival (%)	Local relapse (%)	Distant relapse (%)
Gunderson *et al.*[30]	1996	123	EBRT/CT→surg→IORT	5y, 20	5y, 37	5y, 72
Lowy *et al.*[31]	1996	43	EBRT/CT→surg→IOHDR	2y, 58	2y, 36	-
Farouk *et al.*[32]	1997	116	EBRT→surg	5y, 7	3y, 93	3y, 54
		64	EBRT→surg→IORT	5y, 18	5y, 27	5y, 75
Wong *et al.*[29]	1998	519	EBRT	5y, 5	5y, 93	-
Mannaerts *et al.*[33]	2001	94	EBRT	3y, 14	3y, 90	-
		19	EBRT→surg	3y, 11	3y, 86	-
		33	EBRT→surg→IORT	3y, 60	3y, 27	-
Wiig *et al.*[34]	2002	48	EBRT/CT→surg	5y, 30	5y, 70	-
		59	EBRT/CT→surg→IORT	5y, 30	5y, 50	-
Rades *et al.*[35]	2008	84	EBRT+/- CT→surg	3y, 36	3y, 67	41

Abbreviations: EBRT - external beam radiotherapy; CT - chemotherapy; IORT - intraoperative radiation.

dominosacral composite resection, and the decisions on the most appropriate one depends upon the site and extend of LR. The anastomotic recurrence without fixation to surrounding structures may be cured by the surgical resection alone in as many as 50% of cases.[19] In more extensive cases, sacrectomy with pelvic reconstruction is required to achieve a complete resection and 5-year survival rates in the range of 20-35% have been reported.[19,20] The resection with negative microscopical margins can be achieved in approximately 45% of cases (range 10-67%).[21-23] Results of surgical resection alone with positive margins left behind are poor, with less than 10% of those patients surviving 3 years and no 5-year survivors.[24] Because of the significant perioperative morbidity and the poor survival outcome extended surgery is not very popular.[25] On the other hand, untreated LR significantly reduces the quality of life which became more and more important in the treatment of oncological patients.[26,27] Furthermore, Miller *et al.* argued that the aggressive surgical treatment of LR improved survival, favourably affected quality of life and represented a cost-effective use of resources.[28]

Combined modality treatment in patients with LR undergoing curative surgery for primary rectal cancer

Despite the radical resection of LRRC, in 25% to 61% of patients another recurrence developed locally or disease progressed systemically.[25] In addition, external beam radiotherapy (EBRT) alone (*i.e.* not being accompanied with surgery) or in combination with 5- fluorouracil (5-FU) chemotherapy has only a palliative effect and offers no hope for cure. It allows a temporary symptomatic improvement in majority of patients, but the median duration of symptom relief is only a few months and the 5-year survival is usually less than 5%.[29] Because of the generally poor results achieved with the surgical resection or EBRT alone, the logical approach for LRRC seemed to be the combination of both modalities.

The effect of the preoperative chemoradiation (45-55 Gy in 5-6 weeks) with 5-fluorouracil (5-FU) chemotherapy in previously nonirradiated patients is supported by data from retrospective series (Table 1). To further increase the response rate and consequently to reduce the need for extensive surgery, improve resectability, local control and survival, other

chemotherapy agents (CPT-11, oxaliplatin, capecitabine) and targeted agents may be of benefit in the future.

According to above mentioned reports, the EBRT doses to the whole pelvis usually should not exceed 50 Gy because small bowel toxicity restricts delivery of higher dose. However, this dose is insufficient to sterilize gross residual disease after the surgery.[36] With the use of intraoperative irradiation (IORT) or high-dose rate brachytherapy (IOHDR), a boost of ionizing radiation can be given directly to the parts of tumour resection bed that are most prone for recurrence, yet avoiding irradiation of surrounding normal structures. IORT can achieve the biologic equivalent dose of 2 to 3 times that of the same dose delivered using conventionally fractionated EBRT.[30] The combination with IORT allows the reduction of the EBRT dose which – together with the physical removal of healthy normal structures from IORT field – reduces toxicity of this modality and potentially improve the therapeutic ratio. IORT has generally been delivered by accelerator-generated electron beam or high-dose rate (HDR) brachytherapy using gamma rays or beta rays emitted by the encapsulated radioactive sources inserted during the surgery, to a total dose in a range of 10–30 Gy. The treatment with IORT requires a dedicated operating suite or transfer of the anesthetized patient from the operating room to the radiotherapy suite. For the mobile HDR-IORT machine, a shielded facility is necessary. Recently, mobile IORT machines were constructed which can be used in conventional hospitals on a daily basis and shared between several operating rooms.

As the IORT facilities are available only in a very limited number of radiotherapy centres, treatment results in the literature are rare and conflicting. While Wiig *et al.*[34] showed that IORT did not modify the outcome after the surgery, regardless of the volume of residual disease, reports from some centres suggest that improved the local control and the survival can be achieved in selected patients when the combination of preoperative chemoradiotherapy, radical surgery and IORT is implemented. Five-year survival rates of 18% to 30% and local control rates of 50% to 73% were reported (Table 1).[30-35] Recently, a comparison of various treatment combinations revealed significantly improved survival, disease-free survival, and local control rates at 3 years of 60%, 43%, and 73%, respectively, when the combination of EBRT, surgery, and IORT was used.[33] The most frequently observed IORT-related toxicities were ureteral stenosis (6%) and peripheral neuropathy (16%-34%).[30,33] Similarly, a relationship between IORT dose and the incidence of Grade 2 or 3 neuropathy was also demonstrated by Gunderson *et al*., although not reaching the level of statistical significance ($\leq$ 12.5 Gy *vs.* $\geq$ 15 Gy, 7% vs. 19%; $p = 0.12$).[30]

Multimodality treatment in patients with LR who have received previous external beam radiation therapy

The anatomic location of local failure after the ''optimized'' rectal cancer surgery was studied by Syk *et al*.[37] All recurrences were found within the irradiated volume in the low pelvis, anatomically below the S1-S2 interspace, if the patients had undergone preoperative radiotherapy or if they had not.[37] Similar results were reported by Yu *et al*. with only a limited number of marginal and out-of-field failures, indicating that standard pelvic radiotherapy fields are appropriate for most rectal cancer patients. Of the in-field recurrences, nearly 80% occurred in the low pelvic and presacral regions.[38]

As a majority of patients with LR have already received the local radiation therapy in neoadjuvant or adjuvant setting during the primary rectal cancer treatment and because of fear of a high probability of severe late toxicity related to the Re-RT, patients are usually

Table 2. Locally recurrent rectal cancer - treatment of previously irradiated patients

First author	Patients (n)	Year	Therapy	Survival (%)	Local relapse (%)	Distant relapse (%)
Alektiar *et al.*[44]	74	2000	surg→ IOHDR±EBRT±CT	5y, 23	61	38
Haddock *et al.*[41]	51	2001	EBRT±CT +surg+IORT	5y, 12	5y, 66	5y, 76
Lindel *et al.*[45]	69	2001	EBRT/CT→surg→IORT	27	65	-
Mohiuddin *et al.*[46]	103	2002	EBRT/CT→surg	19	-	-
Valentini *et al.*[47]	59	2003	EBRT/CT→surg	5y, 39	5y, 47	5y, 30
Das *et al.*[48]	50	2007	EBRT/CT→surg	48	3y, 64	

Abbreviations: EBRT - external beam radiotherapy; CT - chemotherapy; IORT - intraoperative radiation; surg - surgery.

treated with the best supportive care.[39,40] This is most probably the reason why the prognosis for patients with LRRC is on average worse in previously irradiated patients than in those without prior irradiation. Two Mayo Clinic studies demonstrated a better local control and survival when the palliative resection of LR was followed by IORT; however, in previously irradiated patients both outcome measures were lower than in patients not receiving prior EBRT: at 5-years, 34% *vs* 63% and 12% *vs* 20%, respectively.[30,41] In the randomized Stockholm trial comparing the preoperative irradiation to the surgical resection alone, 15% of irradiated patients suffered a local recurrence. They were treated with a variety of combinations of surgery, RT, and chemotherapy that resulted in a median survival of 11 months and no 5-yr survivors compared to 15 months in patients from surgery only group ($p = 0.0002$).[42]

Recent data suggest that limited doses of 30 Gy external beam Re-RT are likely to be safe, even when combined with concomitantly administered chemotherapy, if the small bowel can be excluded from the irradiation field, and an additional booster dose of up to 10 Gy can be used for limited volumes.[43] Subsequent toxicity in re-irradiated patients is accaptable and resulted tumor shrinkage could be followed by surgical salvage and long-term survival in selected patients (Table 2).[41,44-48] The irradiated volume usually encompasses recurrent tumor with a 2-4 cm margin. As the late intestinal toxicity strongly depends on the fractionation pattern used, hyperfractionation RT schedules with small fraction doses are preferred.

Conclusions

Despite the improved local control in rectal cancer achieved by preoperative chemoradiotherapy and TME surgery, a substantial proportion of patients will experience the local recurrence. A complete resection is crutial for achieving a long-term local control and survival. The addition of local high-dose radiation delivered in the form of IOERT or IO-HDR brachytherapy appears to have the potential to improve the treatment outcome after the extended surgery. However, in patients with gross residual disease after the surgical procedure, the local tumour control is inadequate despite aggressive treatment combinations. For a more accurate administration of higher radiation doses, advanced EBRT techniques such as 3D-conformal RT, intensity modulated radiotherapy (IMRT) and proton beam therapy are to be employed, whereas for the precise localisation of the disease, the integration of different imaging modalities is essential. To a further increase response rate, the evaluation of new radiation sensitizing drugs or biologic modifiers during EBRT is warranted. Because of the high probability of distant metastases, chemo-

therapy should be an essential component of these aggressive treatment approaches. As LR is more common in patients with locally advanced tumours, who have already received 5-FU-based chemotherapy in the context of the primary treatment, a systemic therapy employing more effective novel agents is indicated.

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