THE ROLE OF RADIOTHERAPY IN THE CONTEMPORARY MULTIMODALITY MANAGEMENT OF RECTAL CANCER

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ABSTRACT

During the last 20 years the results of a significant number of trials concerning the multimodality management of rectal cancer have been published. This led to improvement of rectal cancer treatment. Radiotherapy (RT) is part of the standard multimodality treatment of rectal cancer and results in 50% local control improvement. The findings of the trials have answered some questions like the modalities sequencing, the combination of RT and chemotherapy, the RT fractionation regimens and the required total dose in addition to surgery either local or radical, the application of contact RT in early rectal cancer and intraoperative radiotherapy (IORT) in locally advanced and recurrent rectal cancer. Neoadjuvant chemoradiation (CRT) followed by total mesorectal excision (TME) is the current standard treatment of patients with locally advanced rectal cancer with improved local control over postoperative CRT. In spite of the improved locoregional control, controversies exists and other opportunities for improvement are being investigated. In the present paper, the evidence behind the current standard of RT and the controversies in the treatment of patients with rectal cancer are reviewed.

Key words: *rectal cancer, multimodality management, radiotherapy, neoadjuvant chemoradiation, intraoperative radiotherapy, total mesorectal excision*

INTRODUCTION

The treatment modalities and treatment results of early and advanced rectal cancer have significantly improved during the last two decades. Although surgery is the leading treatment modality for rectal cancer, the multidisciplinary management has shown to achieve best clinical results (44).

The introduction of total mesorectal excision (TME) is the most significant treatment improvement reducing the local recurrence (LR) rate to less than 10%, compared with 30% with older surgical techniques. The advances in both pathology and imaging additionally have improved the multidisciplinary management (44).

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The role of adjuvant radiotherapy (RT) for rectal cancer has been well established in multiple clinical trials (39,48). RT either alone or with chemotherapy is applied mostly for locally advanced disease, before or after surgery. Chemoradiation (CRT) is often used before surgery. Preoperative RT (at biologically effective doses ≥30 Gy) and postoperative RT reduce the risk of LR from rectal cancer by 50% (8).

In this article, we review findings from the multiple clinical trials addressing the application of RT in the multimodality management of rectal cancer and defining the current standard of RT and the unanswered questions in the treatment of patients with rectal cancer.

Trial evidence

Preoperative RT or surgery alone

When preoperative RT for resectable tumours is applied before surgery, improved local control (LC) over surgery alone is reported.

Swedish Rectal Cancer Trial (12,30) included 1,168 patients with resectable rectal cancer

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randomized to preoperative RT (5/25 Gy) and surgery versus surgery alone (non-TME surgery). The RT arm showed improved 5-year LR (11% versus 27%) and 5-year overall survival (OS) (58% versus 48%). The continuous follow-up showed thirteen-year OS 38% for RT arm versus 30% with increased risk of postoperative hospitalization for gastrointestinal (GI) complication in the RT arm.

Dutch Colorectal Cancer Group (TME trial) (24,31) randomized 1,861 patients with resectable rectal cancer to preoperative RT (25 Gy in 5 fractions) and surgery versus surgery alone (TME surgery). An improved 2-year LR (2% versus 8%), 5-year LR (6% versus 12%) and 10-year LR (5% versus 10%) with no difference in survival were reported in the RT arm. The gastrtointestinal toxicity at 5 years was higher in RT arm. A 12-year-long follow-up showed significantly improved 10-year survival in stage III patients with negative circumferential resection margins (CRM) when RT was applied before surgery to surgery alone (50% versus 40%; p=0,032) (45). The rate of secondary malignancy and the non-cancer-related dead was higher in RT arm (14% versus 9%).

After standardization of TME, no OS benefit in a preoperative randomized trial was found. However, the long follow-up demonstrated a survival benefit (45).

Preoperative chemoradiation or preoperative RT

Preoperative RT aims to lower the LR, to improve the resectability with higher R0-resections when mesorectal fascia (MRF) involvement is suspected or T4 disease, and to increase the sphincter preservation. There are two different preoperative RT approaches.

The preoperative RT is either short-course RT, or long-course CRT. The short-course RT (5x5 Gy) followed by surgery one week later on is applied mostly in Scandinavia. The long-course RT includes 50,4 Gy in 28 fractions with concurrent chemotherapy and the surgery is performed 4-8 weeks later on. When needed boost to a 55,4 Gy total dose could be applied. Intraoperative radiotherapy (IORT) or brachytherapy could be used for boost but they are not applied routinely. The short-course RT disadvantages are the lack of sphincter preservation, the inability to safely combine it with adequate doses of chemotherapy, and the toxicity (42). The ongoing Stockholm III trial tests if delayed surgery from 4 to 8 weeks after short-course RT could obtain downsizing with sphincter preservation (32). Its advantage is the short treatment time interval compared to CRT. The advantage of CRT is the higher rate of downsizing and downstaging with higher pathological complete response (pCR), improved CRM, sphincter preservation, and lower rate of LR.

French FFCD 9203 (15) study included 733 resectable rectal cancer patients with T3/4N0 randomized to preoperative RT (1,8/45 Gy) versus preoperative CRT (bolus 5FU-LV). Four more cycles of 5-FU-LV were added. pCR (4% versus 11%) and LC (83% versus 92%) were improved with preoperative RT, but 3-4 grade toxicity was higher (3% versus 15%). There was no difference in OS (67%) and sphincter preservation (52%).

EORTC 22921 (4) trial included 1,011 patients with resectable rectal cancer randomized to preoperative RT, preoperative CRT, preoperative RT and postoperative chemotherapy, or preoperative chemotherapy and postoperative CRT. RT of 45 Gy and 5-FU-LV chemotherapy were used (2 plus 4 cycles). No significant difference in 5-year OS between preoperative and postoperative chemo-groups (64,8% versus 65,8%). For CRT groups, 5-year LR rate was improved (by 8,7%; 9,6% and 7,6%) compared to RT alone group (17,1%)(p=0,002). CRT increased the pCR rate (5% versus 14%). Disease free survival (DFS) and OS differed significantly between the T0-2 and the T3-4 patients (p=0,009): only the T0-2 patients seemed to benefit from adjuvant chemotherapy (p=0,011) (7).

Polish Colorectal Study Group (5) investigated 312 patients with T3/4 resectable rectal cancer randomized to preoperative short-course RT (5/25 Gy) and surgery versus preoperative CRT (50,4 Gy with bolus 5-FU-LV) and surgery. In the CRT group, higher acute toxicity (18,2% versus 3,2%) but no increased OS, LC, or late toxicity were observed compared to short-course RT alone. Only downstaging was higher with CRT.

Trans-Tasman Radiation Oncology Group trial 01.04 (28) included 326 patients with T3 rectal cancer randomized to preoperative short-course RT (5/25 Gy) and surgery versus preoperative CRT (50,4

Gy with 5-FU continuous infusion) and surgery. Three-year LR rates between short-course RT and CRT were not statistically significantly different. No differences in rates of distant recurrence, DFS, OS, or late toxicity were detected.

Preoperative CRT according to these studies increases the pCR (by 5% versus 15%) and LC (by 80-85% versus 90%), but does not lead to sphincter preservation (50%) or increased OS (65%) compared with preoperative RT alone.

Short-course RT appears to give the reasonable LC and the same OS like CRT and could be applied in resectable rectal cancer patients where downsizing is not necessary and MRF is not involved. However, short-course RT is much easier and more cost effective. Locally advanced tumours (i. e. involved MRF or *c*T4) require CRT.

Preoperative or postoperative CRT

German Rectal Cancer Study Group (38) investigated 823 rectal cancer patients with stage T3/4 or positive lymph nodes randomized to preoperative versus postoperative CRT. All the patients received 50,4 Gy with 5-FU and in the postoperative arm a 5,4 Gy boost was applied. Preoperative CRT improved 5-year LR rate (6% versus 13%), increased sphincter preservation surgery rate (39% versus 19%) and decreased the early and late toxicity. No difference in survival was revealed.

MRC CR07/NCIC-CTG C016 (40) was a Phase III trial and included 1,350 patients with resectable rectal cancer randomized to preoperative short-course RT (5 /25Gy) and surgery compared to surgery and selective postoperative CRT (45 Gy and 5-FU) given only to patients with involved CRM. Lower LR rate was observed in the preoperative RT arm versus the selective postoperative CRT arm (4,4% versus 10,6%) with no improved OS. Preoperative CRT achieved better LC with less morbidity compared to postoperative CRT.

CRT with different regimens

CRT should be given with fluoropyrimidine chemotherapy. The standard preoperative CRT includes 5-FU administered as continuous infusion (better than bolus) or oral 5-FU prodrugs (capecitabine or UFT).

Since the NSABP R-04 trial and an AIO trial have proved that 5-FU and capecitabine are equivalent (22,37), capecitabine becomes the preferred drug. It is applied in a dose of 825 mg/m^2 twice a day.

The combination of 5-FU and oxaliplatin or irinotecan plus irradiation were evaluated in II and III phase trials for response rate and acute toxicity. Despite the expectation in the STAR-01, ACCORD 12/0405-Prodige 2, and NSABP R-04 trials (2,16,37) no increase in the complete pCR was observed when 5-FU/oxaliplatin or capecitabine/oxaliplatin regimens were used compared to 5-FU alone. One trial only, CAO/ARO/AIO-04, showed a significant increase of pCR by 4,5% (34) Because of the increased acute toxicity and not improved pCR, oxaliplatin is not included in the standard preoperative CRT regimens. Survival and LC rates in the above mentioned and the ongoing PETACC 6 trials are expected to evaluate the benefit of combined regimens.

Targeted agents such as bevacizumab and cetuximab were investigated within preoperative CRT regimens, too (9,46). The results are interesting but conflicting and their use out of clinical trial is not recommended.

Organ preservation and 'wait and watch' approach in rectal cancer

Approximately 15-20% of the patients will achieve CR after preoperative CRT for advanced rectal cancer. Patients with ypT0 after CRT show only 5% positive nodes and a low recurrence rate (26). The need of radical surgery in case of complete clinical response (shown on biopsy) for distal rectal cancer was analyzed (19). The study included patients with *c*T1-3 disease and 'watch and wait' policy was applied in case of clinical CR to CRT. Surgery was performed after a recurrence occurred. A 5-year OS and DFS were 96% and 72%, respectively, but no reproducibility of the results was achieved by other authors. The pCR after CRT for *c*T3 stage could be evaluated only by radical surgery since no imaging modality is sufficient (11,14,17). Two other trials interested in optimal timing of surgery are recruiting patients in the United Kingdom now (1,41).

The use of local excision after preoperative CRT is rising. The following LR rates were achieved, respectively: 2% in ypT1 and 6%-20% in ypT2 (3).

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In non-responders, LR rate of 43% in ypT3 tumours was observed. In another study (26) including 320 patients with T2-4N0-1 rectal cancer, 14 patients with ypT0 disease received local excision only. In a mean of 48 months following-up period, no LR or distant failure were observed. The ACOSOG Z6031 trial investigated full-thickness local excision in patients with uT2N0 disease after an oxaliplatin-capecitabine CRT (13). Patients with stage ypT0-2 disease and negative margins after local excision were observed only. The patients with stage ypT3 and/or positive margins received radical surgery. A pCR rate of 43% was observed in a total of 77 patients. LR and survival data were expected. A similar French trial GRECCAR 2 is ongoing. Although preliminary results suggest that local excision may be an option in ypT0 patients, long-term follow-up is required and more accurate non-invasive diagnostic predicting ypT0 disease is necessary (6).

IORT

IORT is delivered during surgery. There are two IORT modalities - intraoperative electron beam radiotherapy (IOERT) and high-dose rate brachytherapy. IORT is usually combined with external beam radiotherapy (EBRT) with or without chemotherapy and surgical resection. National Comprehensive Cancer Network (NCCN) USA guidelines recommend the use of IORT in case of very close or positive margins after resection as an additional boost, especially for patients with T4 or recurrent cancers.

IORT in locally advanced rectal cancer

For patients with rectal cancer, IORT improves the LC. Adjuvant IORT could improve the response rates with no serious toxicities and the survival as well in locally advanced colorectal cancer (21,33). Thus, the positive impact of IORT on LC of CRC cancer justifies the inclusion of this therapeutic modality.

IORT in locally recurrent rectal cancer

Despite the significant advances in the treatment of primary rectal cancer with the introduction of TME and preoperative CRT, the observed LR rate is around 5-15% (31,38). The mean survival following locoregional relapse after resection is 11 to 15 months (25,27), and 5-year OS is 5% (18,47). In 50% of the patients, no metastatic disease is present (29) but the morbidity remains high (20) and local treatment options should be offered including surgery. In most cases, the radical surgery is not possible due to altered anatomy and tumour growth (10). Because of previous EBRT in most of the patients there is a limited room for external beam reirradiation in terms of normal tissue tolerance. In these cases, IORT application in addition to surgery is reasonable. IORT advantages are that the radiation field could be defined very simply with removing the healthy tissue out of the treatment field (35).

In the German study, 97 patients with locally recurrent rectal cancer received IOERT (36). In the patients without any previous irradiation, 10-15 Gy IOERT was combined with EBRT. Patients who had been previously irradiated received 15-20 Gy IOERT alone. The mean survival was 39 months with a 5-year OS rate of 30% and a 5-year LC rate of 41%. In patients with R0 resection, 5-year OS and LC rates were 63% and 68%, respectively. In patients with R1 and R2 resection, the observed 5-year OS and LC rates were worst (11% and 19%, respectively).

In a large trial (20) including 607 patients, 5-year OS of 30% and LC rate of 72% were reported. A similar 5-year OS of 31,5% was achieved in another study (10) while 5-year LC rate was 50%.

Brachytherapy boost

High dose rate (HDR) brachytherapy is used in case of advanced tumours (>3 cm T1/T2/T3a N1 M0). After initial downstaging with EBRT and concurrent chemotherapy, HDR brachytherapy could be applied when there is a visible or palpable persistent tumour. By this way, the deeper residual tumour receives a higher radiation dose. Transanal endoscopic microsurgery (TEMS) is an option when minimal residual disease <2 cm is present (43). A phase 3 randomized Danish trial compared HDR rectal boost following CRT with CRT alone. HDR boost improved the pCR rates and R0 resection ones in T3 rectal tumours (23).

CONCLUSION

Although the surgery is the mainstay in the treatment of rectal cancer, its multimodality management is recommended based on the evidence available. In this rapidly developing field, RT applied either as neoadjuvant or adjuvant treatment plays an important role in the management of local advanced disease or in case of limited surgical intervention.

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