Neoadjuvant and adjuvant radio- and radio-chemotherapy of rectal carcinomas

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Abstract The objectives in treating rectal cancer are to achieve locoregional tumor control and to prolong overall survival. With surgery alone the reported local failure rates in recent decades have been unacceptably high, and this is associated with substantial morbidity and mortality. Perioperative radiotherapy with or without concomitant chemotherapy has been used extensively to reduce the high frequency of local recurrence. Adjuvant radiotherapy reduces the local recurrence rate dramatically if the dose is high enough and is administered preoperatively. Although a higher dose has been used in most postoperative radiotherapy trials, the reduction has not proven particularly pronounced. If the reduction were as great as that with preoperative radiotherapy, it would also have a positive effect on survival, which as yet has not been achieved with postoperative radiotherapy. However, postoperative irradiation combined with chemotherapy yields a survival benefit of the same magnitude as preoperative irradiation. Modern radiation techniques allow preoperative radiotherapy to be delivered without interfering substantially in the postoperative healing process; it does not increase mortality or morbidity and entails a low rate of late toxicity if the radiation technique is optimal. A major question today is whether radiotherapy is necessary if surgery is optimal. Control trials report an average local recurrence rate of 29% with standard surgery. With optimal surgery the figure reported from institutional series is about 10%. Other questions to be answered include whether to use superfractionation or standard fractionation in radiotherapy, and how chemotherapy should be given, concomitantly to radiotherapy or in the classical method of postoperative intravenous treatment.

Keywords Rectal cancer · Radiotherapy · Chemotherapy · Adjuvant

Introduction

The role of surgery remains important in the primary treatment of rectal cancer. Overall 5-year survival figures have improved slowly in recent decades, and about one-half of patients with a rectal cancer survive today [1, 2]. Some 10–20% of newly diagnosed patients with a rectal cancer already have distant metastases or a locally inoperable tumor. The two major causes of fatal outcome in patients receiving curative surgery are occult distant metastases not found at surgery and local recurrence, the rate of which remains unacceptably high. The average local recurrence rate reported from all control trials worldwide is 29%. The majority of local recurrences are probably due to inappropriate surgery. Recent data have demonstrated that a positive margin, i.e., microscopic tumor foci left behind, is a very important prognostic marker not only of survival but also of good surgery [3, 4]. Even if surgery is performed correctly and assuming total mesorectal excision (TME), some areas with
microscopic tumor foci are not resected. It has been recommended to use a more aggressive surgical strategy in resecting these areas [5], but this would probably lead to an increase in postoperative morbidity [6]. On the other hand, such deposits are small enough to be eradicated by radiotherapy. The potential benefit of combining surgery and radiotherapy is therefore obvious since surgery eradicates the tumor bulk while radiotherapy eradicates tumor cells in the periphery.

This review focuses on the correct use of radiotherapy and chemo-radiotherapy for achieving local control and for improving survival. We also discuss adverse effects, both acute and late, and the rational for using radiotherapy in combination with optimal surgery. It is important that the treatment of rectal cancer depend upon the initial tumor stage. It is of the utmost importance to determine whether the tumor is resectable (T1–T3) or non-resectable (T4). Radiotherapy is of questionable value in patients with a T1–T3 tumor and can therefore be considered adjuvant treatment, but it is essential in those with a T4 tumor and must be part of the treatment schedule.

**Radiotherapy in resectable rectal cancer: adjuvant treatment**

The high local recurrence rate reported in numerous series worldwide led to the combining of radiotherapy and surgery. The reported recurrence rates range from less than 10% to more than 50% [7–11]. This substantial variation in the incidence of local failure is difficult to explain, but probable factors include patient selection, definition of local radical surgery, definition of a local recurrence, follow-up routines, and skill of the surgeon. Recurrence rates after standard surgery are found in the surgery-alone arm in controlled randomized trials using adjuvant pre or postoperative radiotherapy, and these range from 23% to 46% [12–28] (Table 1). The average recurrence rate of 29% is very high but probably reflects the real figure, since randomized trials report all patients with resected cancer (R0, R1, and R2 resections). Studies reporting excellent results often include only patients with an R0 resection [7, 8, 10, 29].

**Local recurrence rate**

The trials summarized in Table 1 demonstrate a clear dose-response relationship in the local recurrence rate. Lower rates are seen particularly in trials that include preoperative radiotherapy. Dose levels vary more widely in trials using preoperative radiotherapy, and these show that a higher dose reduces the local recurrence rate. They also demonstrate that with the same dose level the local failure rate is much lower using preoperative than postoperative radiotherapy. Only one randomized trial has focused on this question, comparing patients randomly allocated to preoperative or postoperative radiotherapy [30, 31], and this found preoperative superior to postoperative irradiation in reducing local recurrence rates. The reasons for the greater effect of preoperative than of postoperative radiotherapy are not clear, and the difference is difficult to explain. Two factors seem in particular to be important here. First, radiotherapy requires oxygen to work, and the tissue is well oxygenated in a preoperative setting. Second, the period between surgery and postoperative radiotherapy is generally longer than 4 weeks, and most patients in fact begin radiotherapy only after 6 weeks [30]. This delay probably enhances the re-population of tumor cells and creates a tumor burden that is too great to eradicate [32–33].

**Survival**

Radiotherapy to the pelvic region can hardly have any impact on occult distant metastases, but the local recurrence is often the first instance among patients operated upon for rectal cancer. Achieving a survival effect would therefore be possible if the local failure rate could be reduced as much as possible with additional radiotherapy. The hypothesis that survival is improved by better local control is supported by a study demonstrating that surgeons with low local recurrence rates have better survival [34]. A survival benefit would be possible to achieve if the subsequent recurrence rate could be reduced by adjuvant radiotherapy. No trial with postoperative radiotherapy alone has shown an effect on survival, probably because the reduction in local recurrence is not sufficiently great. After preoperative radiotherapy, on the other hand, an effect on cancer-specific survival has been shown in several trials using high-dose radiotherapy [18, 19, 35, 36]. The largest trial with preoperative radiotherapy, the Swedish Rectal Cancer Trial (SRCT), observed an effect on both cancer-specific and overall survival [36]. This trial reported a relative reduction in the local recurrence rate of 60% and a 5-year survival rate of 48% in patients receiving surgery alone, compared to 58% in those receiving preoperative radiotherapy followed by surgery the next week.

Although postoperative radiotherapy alone does not have a demonstrable impact on survival, the combination of radiotherapy and chemotherapy in the postoperative setting shows a survival benefit of almost the same magnitude as that of preoperative radiotherapy alone [25, 37–39]. If these data could be extrapolated to the preoperative treatment concept, an even better effect on survival could be achieved. However, whether preoperative chemo-radiotherapy would improve results has still not been confirmed despite its theoretical advantages [40, 41] since no trial has used radiotherapy and chemotherapy in an adjuvant preoperative setting. This is now being