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Review

# Could preoperative short-course radiotherapy be the treatment of choice for localized advanced rectal carcinoma?

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ABSTRACT

Short-course preoperative radiotherapy (RT) is widely used in northern Europe for locally advanced resectable rectal cancer, but its role in the era of advanced imaging techniques is uncertain. Here, we reviewed articles and abstracts on SCRT published from 1974 through 2013 with the goal of identifying patients who might be best suited for short-course RT. We included relevant articles comparing surgery with or without preoperative radiation published before and after the advent of total mesorectal excision. We also analyzed two randomized trials directly comparing short-course RT with conventionally fractionated chemoradiation (the Polish Colorectal Study Group and the Trans-Tasman Radiation Oncology Group) that compared short-course RT with conventional chemoradiotherapy. We conclude from our review that short-course RT can be generally applied for operable rectal cancer and produces high rates of pelvic control with acceptable toxicity; it reduces local recurrence rates but does not increase overall survival. SCRT seems to be best used for tumors considered "low risk," i.e., those that are >5 cm from the anal margin, without circumferential margin involvement, and involvement of fewer than 4 lymph nodes. Whether sequential chemotherapy can further improve outcomes remains to be seen, as does the best time for surgery (immediately or 6–8 weeks after RT). We further recommend that selection of patients for short-course RT should be based on findings from magnetic resonance imaging or transrectal ultrasonography.



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## 1. Background

The optimal treatment for rectal cancer that presents as non-metastatic locally advanced disease remains a topic of debate.[1] Although the value of neoadjuvant treatment that could render initially unresectable disease resectable is clear, whether that treatment should be radiation therapy (RT) alone or concurrent chemoradiation therapy remains controversial.[2,3] The 2013 guidelines of the U.S. National Comprehensive Cancer Network for the treatment of rectal cancer (available at www.nncn.org) recommend preoperative therapy consisting of RT with fluorouracil or capecitabine chemotherapy for patients with clinical $T_3$ $N_0$ or any-T, $N_{1-2}$ disease. The other form of preoperative therapy, short-course RT, has been validated by some European studies but is not recommended in the NCCN guidelines. The European Society for Medical Oncology (ESMO)[4] describes two options for preoperative RT for rectal cancer: (1) a standard dose of 45–50.4 Gy, given in 1.8- to 2-Gy fractions, with concomitant use of fluoropyrimidines followed 6–8 weeks later by radical surgery, which is more commonly used in the United States and parts of Europe; and (2) short-course RT to a total dose of 25 Gy in five 5-Gy fractions over 1 week followed immediately by surgery (<10 days from the first radiation fraction); this regimen is more common in northern Europe.[5,6]

We sought here to review and update the literature on the use of short-course RT for the treatment of rectal cancer and to clarify which procedure is the most appropriate when disease staging is based on findings from newer imaging techniques, such as magnetic resonance imaging (MRI).[7,8]

## 2. Comparisons of surgery versus neoadjuvant RT plus surgery

### 2.1. *Radiation dose*

The dose and schedule of neoadjuvant RT, and the nature of the surgery itself, for rectal cancer have evolved since its earliest use in the 1970s. The first randomized comparison of radiation alone versus radiation followed by surgery, published by Stearns in 1974,[9] used an RT dosage of 20 Gy given in 10 fractions of 2 Gy each. In that study, the addition of radiation before surgery did not increase overall survival but did reduce the rate of local recurrence. In 1975, the first results of a trial by the Veterans Administration Surgical Oncology Group[10] suggested that preoperative RT to a dose of 20–25 Gy given in 10 fractions given over a 12-day period seemed to reduce both local recurrence (LR) and distant metastasis compared with surgery alone; however, those results could not be reproduced in a second study by the same group.[11] Similarly, a contemporaneous report of a large trial by the British Medical Research Council found that preoperative RT given as a single 5-Gy dose or as ten 2-Gy fractions did not affect LR, distant recurrence, or overall survival (OS) relative to surgery alone,[12] suggesting that if preoperative RT is to be effective, the dose should be at least 20 Gy. Indeed, a phase III study by the European Organization for Research and Treatment on Cancer (EORTC) reported by Gérard et al.[13,14] showed that preoperative RT to a dose of 34.5 Gy, given in 15 fractions over 19 days, did not significantly improve OS, but it did led to marked reductions in LR. The toxicity of this regimen was deemed acceptable, except when it was given to elderly patients (age ≥ 70 years) or to patients with pre-existing cardiovascular disease. The results of these studies suggest that the RT dose to be given as preoperative therapy should be at least 20 Gy.

### 2.2. *Randomized comparisons of radiation schedules*

A 1990 report of a large multicenter trial conducted by the Stockholm Rectal Cancer Study Group comparing an RT regimen of 25 Gy to be given over 5–7 days ("short-course" RT) versus surgery alone showed that at a median follow-up time of 53 months, preoperative short-course RT led to lower LR regardless of the stage of the tumor.[15] However, again no difference was found among groups in distant control or OS. Postoperative morbidity was noted to be higher in the preoperative RT group, as was postoperative mortality (8% RT vs. 2% no-RT, $P < 0.01$) (Tables 1 and 2).

Another report that same year from Uppsala University[16] compared preoperative short-course RT (25.5 Gy given over a 1-week period) with conventionally fractionated *postoperative* RT (60 Gy over 6–8 weeks) for rectal cancer. The LR rate was lower for the group receiving preoperative RT (12% vs. 21%, $P = 0.02$), but at a mean 6 years of follow-up, the OS rate was no different between groups (42% vs. 38%, $P = 0.5$).

A subsequent study by the Stockholm Rectal Cancer Study Group[17–19] compared LR and OS for patients given surgery alone versus short-course RT followed by surgery 7 days later. The addition of preoperative RT led to a lower LR rate (12% vs. 27%, $P < 0.001$) and an improved 5-year OS rate (58% vs. 48%, $P = 0.004$). However, this study has been criticized for imbalances between groups (more patients with Dukes stage A and B in the RT + surgery group, which the authors attributed to downstaging after RT and for the "unacceptably high" LR rate for Dukes stage A tumors in the surgery group).[20] Indeed, pathologic review of findings from another trial conducted in the Netherlands (the Dutch TME + RT trial) revealed that short-course RT did not result in tumor downstaging.[21] To date, few, if any, studies have replicated the finding of improved OS after preoperative RT.[22,23]

### 2.3. *Randomized studies of radiation schedules after the standardization of total mesorectal excision*

The recognition that involvement of the circumferential resection margin (CRM) by tumor cells is important in LR has led to the general use of total mesorectal excision (TME), in which the entire mesorectum is enveloped and resected by precise, sharp dissection. In the time since TME became the recommended surgical technique for extirpation of rectal cancer,[24–26] the question has been raised as to whether RT is necessary when this technique is used. To address this question, the Dutch Colorectal Cancer Group began a study in 1996 to compare surgery (TME) only with short-course preoperative RT (5 Gy given over 5 days) followed by TME.[22] A total of 1805 eligible patients were randomly assigned to one of the two treatment groups; among the 1748 patients who underwent a macroscopically complete local resection, the LR rate