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Preoperative Treatment of Locally Advanced Rectal Cancer: Assets and Drawbacks of Short Course and Long Course in Clinical Practice

Samuel Y. Ngan, MBBS, FRCSEd, FRANZCR

Preoperative short-course radiotherapy and preoperative long-course chemoradiotherapy are the standards of care for high-risk rectal cancer in different parts of the world. Both treatments are effective in local control and carry a low morbidity. The advantage of short course is its simplicity, whereas long course has the advantage of downsizing tumors thus increasing the chance of sphincter preservation. Although 2 randomized trials comparing short course and long course have been performed, the better form of preoperative treatment remains a subject of discussion. This article reviews the evidence supporting each approach, and it discusses their relative merits and future directions.
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Introduction

Preoperative radiotherapy has become the standard of care for patients with high-risk rectal cancer. Treatment is usually delivered in 1 of the following 2 ways: a shorter course of radiotherapy, and a longer course of radiotherapy with concomitant chemotherapy. "Short course" refers to 25 Gy in 5 Gy per fractions delivered over 1 week, followed by surgery within a week. "Long course" is 50.4 Gy in 1.8 Gy per fraction, delivered over 5.5 weeks with concomitant 5-fluorouracil (5-FU) chemotherapy, followed by surgery in 4-8 weeks and often adjuvant chemotherapy. Both treatments are delivered before surgery and are similar in radiation target volume, but they differ in total radiation dose, fraction size, duration of radiation, concomitant chemotherapy, timing of surgery, and adjuvant chemotherapy.

Short-course radiotherapy and long-course chemoradiotherapy have been developed in parallel. Both forms of preoperative radiotherapy have been accepted as the standard of care in different cancer centers around the world; short course is more accepted in northern Europe, whereas long course enjoys more support in North America and in the rest of Europe. Both practices are based on strong evidence from multiple clinical trials, and 2 randomized trials comparing short course and long course have been performed. In spite of this, the better form of preoperative radiotherapy remains a point of debate.

Long-Course Chemoradiotherapy

Long-course preoperative chemoradiotherapy evolved from postoperative chemoradiotherapy.[1] Although postoperative chemoradiotherapy is effective in reducing local recurrence and improving overall survival in patients with stage II and III rectal cancer, treatment-related toxicity remains a concern. Preoperative chemoradiotherapy reduces radiation toxicity and potentially increases the chance of sphincter-saving procedure for low rectal cancer.

German CAO/ARO/AIO-94 Trial

The German CAO/ARO/AIO-94 trial randomized patients with clinical T3 or T4 or node-positive rectal cancer to either preoperative chemoradiotherapy or postoperative chemoradiotherapy.[2] In total, 421 patients were randomly assigned to

Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.
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Address reprint requests to Samuel Ngan, MBBS, FRCSEd, FRANZCR, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria 3000, Australia. E-mail: Sam.Ngan@petermac.org

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receive preoperative chemoradiotherapy, and 402 patients were assigned to receive postoperative chemoradiotherapy. The rate of local recurrence at 5 years was lower in the preoperative chemoradiotherapy group than in the group that received chemoradiotherapy postoperatively (6% vs 13%, $P = 0.006$). Overall survival rates were similar. The preoperative chemoradiotherapy group had significantly lower acute toxicity. No significant differences were observed in terms of postoperative complications, anastomotic leakage, or long-term toxicity rates. It was noted that preoperative chemoradiotherapy increased the chance of sphincter preservation. Among the 194 patients with tumors that were determined by the surgeons before randomization to require abdominoperineal resection, there was a statistically significant difference in sphincter preservation rates in favor of the preoperative chemoradiotherapy group.

After a median follow-up of 11 years, the local recurrence rate remained significantly lower for preoperative chemoradiotherapy group.[3] There were no differences in distant metastasis, disease-free survival, or overall survival between the preoperative chemoradiotherapy group and the postoperative chemoradiotherapy group. Overall, 12% of local recurrences and 7.6% of distant metastases occurred beyond 5 years of follow-up.

NSABP R-03 Trial

NSABP R-03 (National Surgical Adjuvant Breast and Bowel Project R-03) trial compared the preoperative chemoradiotherapy with the postoperative chemoradiotherapy in patients with clinical T3 or T4 or node-positive rectal cancer.[4] The study was terminated after 6 years because of slower recruitment than anticipated recruitment, falling short of the initial goal of 900 patients. Analysis of 267 patients accrued showed a significant difference in 5-year disease-free survival favoring preoperative chemoradiotherapy but the differences were not significant for local recurrence or overall survival.

Long-Course Radiotherapy or Radiochemotherapy

Although chemoradiotherapy became the standard adjuvant treatment in North America after the Gastrointestinal Tract Study Group trial in the 80s, radiotherapy alone with conventional fractionation continued to be the standard preoperative treatment for T3-T4 disease in France and other European countries. The Fédération Francophone de Cancérologie Digestive (FFCD) 9203 trial compared preoperative radiotherapy with chemoradiotherapy.[5] Eligible patients were those with resectable T3-T4, Nx, and M0 rectal adenocarcinoma accessible to digital rectal examination. Preoperative radiotherapy with 45 Gy in 25 fractions during 5 weeks was delivered. Patients in the chemoradiotherapy group received 5-FU and leucovorin during the first and fifth week of radiotherapy. Surgery was planned for 3-10 weeks after the end of radiotherapy and both the groups received adjuvant chemotherapy. In total, 733 patients were eligible for analysis. The 5-year local recurrence was lower with chemoradiotherapy, but overall 5-year survivals in the 2 groups were similar.

The European Organisation for Research and Treatment of Cancer (EORTC) 22921 trial randomly assigned 1011 patients with clinical T3 or T4 resectable rectal cancer to 1 of the following 4 treatment arms: preoperative radiotherapy, preoperative chemoradiotherapy, preoperative radiotherapy and postoperative chemotherapy, or preoperative chemoradiotherapy and postoperative chemotherapy.[6] Radiotherapy consisted of 45 Gy in 1.8 Gy per fraction. One course of chemotherapy consisted of 5-FU 350 mg/m^2/d and leucovorin 20 mg/m^2/d for 5 days. During chemoradiotherapy, 2 courses of chemotherapy were given. A total of 4 courses of chemotherapy were given in groups receiving postoperative chemotherapy. After a median follow-up of 10.4 years, there were no statistically significant differences in 10-year overall survival rates or disease-free survival among treatment groups.[7] The local recurrence rate for the radiotherapy alone group was significantly higher than for the other 3 groups. There were no differences in the rates of distant metastases.

Short-Course Radiotherapy

Swedish Rectal Cancer Trial

The Swedish Rectal Cancer Trial established 5 × 5 Gy as the standard short-course preoperative radiotherapy.[8] In total, 1168 patients with resectable rectal cancer were randomly assigned to undergo preoperative irradiation (25 Gy delivered in 5 fractions in 1 week) followed by surgery within 1 week or to have surgery alone. This radiation schedule was designed to correspond approximately to a dose of 45 Gy given with conventional fractionation (ie, 2 Gy daily 5 days a week). Tumor stages of the nonirradiated group and irradiated group were Dukes' A 28% and 33%, Dukes' B 31% and 35%, and Dukes' C 41% and 32%, respectively.

After 5 years of follow-up, the rate of local recurrence was 11% in the irradiated group and 27% in the nonirradiated group ($P < 0.001$). This difference was found in all subgroups defined according to Dukes' stage. Improvement in overall survival was also seen in the irradiated group. There were significant differences favoring the irradiated group in overall survival and disease-free survival at 5 years. In-hospital mortality rates were similar for both irradiated and nonirradiated groups. However, patients irradiated with a two-beam technique had considerably higher in-hospital mortality.

After median follow-up time of 13 years, analysis showed that short-course preoperative radiotherapy retained the advantage over surgery alone on overall and cancer-specific survival and on local recurrence rates.[9] The local recurrence rates in the irradiated group and nonirradiated group were 9% and 26%, respectively ($P < 0.001$). The reduction of local recurrence rates was observed at all tumor heights, although it was not statistically significant for tumors greater than 10 cm from the anal verge. Local recurrences were found up to 12 years after surgery. Improvement in overall survival with short course was observed and was likely because of a significant decrease in local recurrence.