Preoperative chemoradiation for rectal cancer: kudos and a caution

Wayne S. Kendal, MD, PhD; Hartley S. Stern, MD

With the first results of the German rectal cancer trial (CAO/ARO/AIO-94) now made public, we have a prospective randomized study that has confirmed what those treating rectal cancer have long suspected: preoperative chemoradiation provides a significant advantage over postoperative therapy in terms of pelvic control and sphincter preservation. Full-course radiation therapy with 5-fluorouracil-based chemotherapy, similar to that employed in the German trial, provides clinical complete response (clinical CR) rates of 19%-38% and pathologic CR rates of 8%-30% (Table 1). Such therapy, as distinct from the short-course preoperative radiotherapy that came into wide use after the Swedish rectal cancer trial, can provide for significant downstaging of bulky and non-resectable rectal cancers. With full-course therapy, 60%-90% of clinically nonresectable tumours can be made resectable.

The apparent success of preoperative chemoradiation has led some to ask whether surgery is necessary after a CR. For example, Rossi and colleagues reported on a prospective trial of 16 patients with low-infiltrative rectal cancers who were treated with preoperative chemoradiation. The 6 patients who achieved clinical CR were followed without surgery by monthly proctoscopy. After 34 months of follow-up only 1 patient remained free of disease; the other 5 developed a local recurrence after periods of 1-10 months. The authors concluded that surgery was necessary in view of the temporary nature of most clinical CRs.

Nakagawa and associates provided data from a series of 104 patients with mid- or low-rectal adenocarcinomas who were treated with full-course chemoradiation. The 10 patients who sustained clinical CR (confirmed by proctoscopic biopsy) were followed by clinical and proctoscopic examinations every 3 months. Of these patients, 8 (80%) developed recurrent cancer within a median follow-up period of 6 months, of whom 4 were salvaged by surgical intervention. Only 2 patients sustained CRs and remained disease-free at 37.5 and 58 months. These authors likewise concluded that patients with CRs should not go without prompt surgery.

Interestingly, a similar study led Habr-Gama and colleagues to a very different conclusion. They reported on 38 patients with low rectal cancers who sustained an initial clinical CR (confirmed by physical exam, biopsy, transrectal ultrasound and pelvic CT) with preoperative chemoradiation without immediate surgery. Of these patients, 8 (21%) required resection for recurrent disease within 3-14 months of chemoradiation. Nonetheless, 30 patients remained disease-free after a median follow-up of 36 months. These authors concluded that it was acceptable to delay surgical management of patients with CRs. They further suggested that salvage surgery could be done at the time of local recurrence without detriment to the patients.

Habr-Gama and colleagues’ study raises a number of issues, such as the accuracy of clinical staging. This par-

Table 1

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Ref = reference citation; ? = data unavailable.
ticular question has been examined extensively. For example, when Kahn and coauthors\textsuperscript{16} evaluated postradiation neoadjuvant chemoradiation for 25 patients with rectal cancer who sustained pathologic CRs they observed significant limitations with preoperative staging. Computed tomography could accurately stage only 23% of cases, and endorectal ultrasound only 17%. Digital examination had a negative predictive value of 24%. They concluded that current staging methods could not reliably distinguish between residual cancer and postirradiation fibrosis. Furthermore, they were unable to reliably predict which patients with clinical CR did not require definitive surgery.\textsuperscript{16}

Another issue raised was the potential salvage rate for recurrent cancer after an initial clinical CR and nonsurgical follow-up. The best available data are necessarily drawn from studies of recurrent rectal cancer after curative surgery. Garcia-Aguilar and coworkers\textsuperscript{17} reported one such study of 87 patients. At the time of recurrence, fewer than one-half of their patients were suitable for curative salvage surgery; of those resected with curative intent, the 5-year survival was 35%. Clearly, for patients treated with transition surgery and followed up in the community, recurrent rectal cancer is a serious problem. It would be reasonable to expect a similar concern for patients treated with chemoradiation alone.

Beyond these two issues there remains a fundamental difference between surgical treatment and chemoradiation. With surgery, one can be certain that any cancer tissue removed will never contribute to recurrence; the limitation to surgery stems from the cancerous tissue that can not be removed. The effectiveness of surgery is well illustrated by the technique of total mesorectal excision (TME). In the Dutch CKVO 95-04 study,\textsuperscript{18,19} the 5-year local failure rate with TME alone was about 12%\textsuperscript{20} — an excellent achievement.

The effects of chemoradiation are not as clear-cut as for surgery. Typically administered as 25–33 daily treatments over a period of several weeks, each treatment affects only a fixed fraction of the tumour cells within the treatment field. On a semi-logarithmic plot the dose–response curve approximates the form shown in Fig. 1: a straight line. A typical rectal tumour might initially consist of $10^{10}–10^{11}$ cells; several orders of magnitude of reduction would be required to attain a clinical CR, leaving an aggregated tumour cell volume of $1 \text{ mm}^3$, say. To achieve a pathologic CR, possibly a further order of magnitude of volume reduction would be necessary. To approach the effectiveness of TME, a further reduction in tumour volume of 5–6 orders of magnitude would be needed. Essentially, then, about twice as much chemoradiation would be required to achieve the equivalent surgical response as would be required for a pathologic CR.

Each treatment modality has its advantages and disadvantages. When disease is extensive or a patient has microscopic residual disease, the usefulness of surgical management is limited. Chemoradiation is limited by the tolerances of normal tissue and the intrinsic resistance of tumour cells, but it can sterilize microscopic disease in regions that either cannot be resected or ought to be spared. It is through the combination of these 2 modalities that current treatment of rectal cancer can be best optimized. In the German rectal cancer trial\textsuperscript{14} preoperative chemoradiation reduced the 5-year local recurrence rate from 11% to 7% — figures in keeping with those from the Swedish rectal-cancer trial,\textsuperscript{15} but with accompanying downstaging of the tumour sufficient to permit sphincter preservation.

FIG. 1. Dose–response curve for neoadjuvant chemoradiation. Chemoradiation is typically administered as multiple daily fractions over a period of 4–6 weeks. With each fraction a fixed proportion of tumour cells would be inactivated, so that on a semi-logarithmic plot the dose–response relationship would approximate a straight line. Here the number of remaining viable tumour cells (together with their aggregated volume) is plotted against the total accumulated dose. A clinical complete response (CR) might be attained with only a million cells remaining; a pathologic CR might be attained with perhaps a further 10-fold reduction. The probability of tumour control can be estimated on the basis of Poisson statistics, as shown on the right-hand ordinate axis. A 90% chance of local pelvic control (comparable to that achievable with total mesorectal excision alone) could be expected with chemoradiation, but only with about twice the dose needed to achieve a pathologic CR.
Preoperative chemoradiation is now established as an important component in the management of rectal cancer. In its current form, chemoradiation alone should be considered only for patients who refuse operative management or are considered unfit for definitive surgery.

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**References**


