Preoperative chemoradiation for rectal cancer: kudos and a caution

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With the first results of the German rectal cancer trial (CAO/ARO/AIO-94)[1] 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,[1] provides clinical complete response (clinical CR) rates of 19%–38% and pathologic CR rates of 8%–30% (Table 1).[1–14] Such therapy, as distinct from the short-course preoperative radiotherapy that came into wide use after the Swedish rectal cancer trial,[15] can provide for significant downstaging of bulky and nonresectable rectal cancers.[2,4,9] With full-course therapy, 60%–90% of clinically nonresectable tumours can be made resectable.[2,4]

The apparent success of preoperative chemoradiation has led some to ask whether surgery is necessary after a CR. For example, Rossi and colleagues[6] 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[13] 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 coworkers[7] 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.[7]

Habr-Gama and colleagues' study[7] raises a number of issues, such as the accuracy of clinical staging. This par-

Table 1

Clinical (CCR) and Pathologic (PCR) Complete Response Rates (%) for Chemoradiation of Rectal Cancer

Ref.	Study author(s)	Year	CCR	PCR
1	Sauer	2003	?	8
2	Minsky et al	1992	?	20
3	Grann et al	1997	22	13
4	Videtic et al	1998	?	13
5	Berger et al	1998	?	27
6	Rossi et al	1998	38	?
7	Habr-Gama et al	1998	31	?
8	Pucciarelli et al	2000	?	16
9	Mohiuddin et al	2000	?	30
10	Chan et al	2000	?	25
11	Onaitis et al	2001	21	14
12	Hiotis et al	2002	19	10
13	Nakagawa et al	2002	19	?
14	Garcia-Aguilar et al	2003	?	13

Ref = reference citation; ? = data unavailable.

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ticular question has been examined extensively. For example, when Kahn and coauthors[16] evaluated postradiation preoperative staging in 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.[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[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 initial 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,[18,19] the 5-year local failure rate with TME alone was about 12%[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 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[1] preoperative chemoradiation reduced the 5-year local recurrence rate from 11% to 7% — figures in keeping with those from the Swedish rectal-cancer trial,[15] but with accompanying downstaging of the tumour sufficient to permit sphincter preservation.

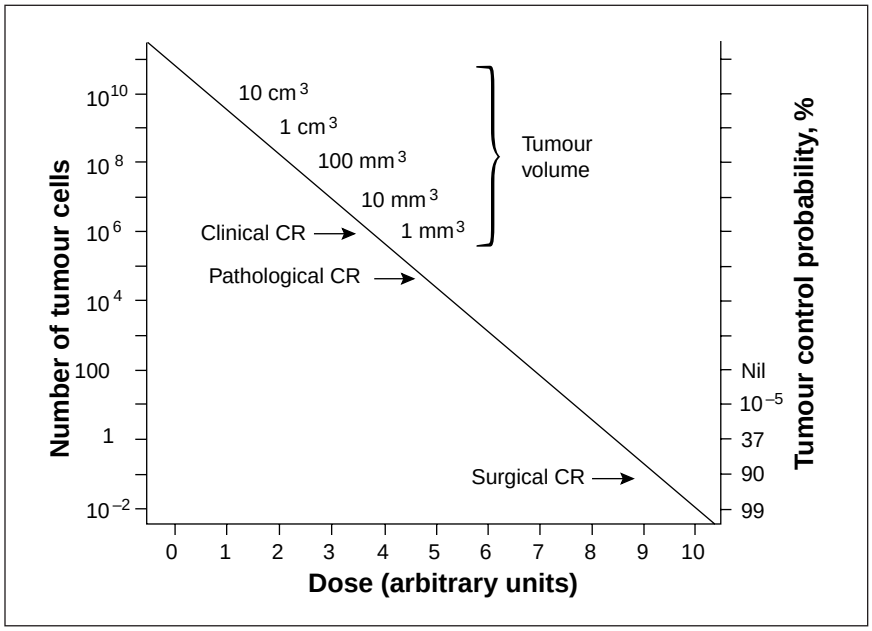

FIG. 1. Dose–response curve for neoadjuvant chemoradiation. Chemoradiation is typically administered as multiple daily fractions over a period of 4–6 weeks. With each fraction a fixed proportion of tumour cells would be inactivated, so that on a semi-logarithmic plot the dose–response relationship would 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

1. Sauer R. Adjuvant versus neoadjuvant combined modality treatment for locally advanced rectal cancer: first results of the German rectal cancer study (CAO/ARO/AIO-94). *Int J Radiat Oncol Biol Phys* 2003;57:S124-5.

2. Minsky BD, Cohen AM, Kemeny N, Enker WE, Kelsen DP, Reichman B, et al. Enhancement of radiation-induced downstaging of rectal cancer by fluorouracil and high-dose leucovorin chemotherapy. *J Clin Oncol* 1992;10:79-84.

3. Grann A, Minsky BD, Cohen AM, Saltz L, Guillem JG, Paty PB, et al. Preliminary results of preoperative 5-fluorouracil, low-dose leucovorin, and concurrent radiation therapy for clinically resectable T3 rectal cancer. *Dis Colon Rectum* 1997;40:515-20.

4. Videtic GM, Fisher BJ, Perera FE, Bauman GS, Kocha WI, Taylor M, et al. Preoperative radiation with concurrent 5-fluorouracil continuous infusion for locally advanced unresectable rectal cancer. *Int J Radiat Oncol Biol Phys* 1998;42:319-24.

5. Berger C, Kirscher S, Félix-Faure C, Cuavet B, Vincent P, Brewer Y, et al. Radiochimiothérapie concomitante préopératoire pour cancer du rectum. *Cancer Radiother* 1998; 2:260-5.

6. Rossi BM, Nakagawa WT, Novaes PE, Filho WD, Lopes A. Radiation and chemotherapy instead of surgery for low infiltrative rectal adenocarcinoma: a prospective trial. *Ann Surg Oncol* 1998;5:113-8.

7. Habr-Gama A, de Souza PM, Ribeiro U Jr, Nadalin W, Gansl R, Sousa AH Jr, et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. *Dis Colon Rectum* 1998;41:1087-96.

8. Pucciarelli S, Friso ML, Toppan P, Fornasiero A, Carnio S, Marchiori E, et al. Preoperative combined radiotherapy and chemotherapy for middle and lower rectal cancer: preliminary results. *Ann Surg Oncol* 2000;7:38-44.

9. Mohiuddin M, Regine WF, John WJ, Hagihara PF, McGrath PD, Kenady DE, et al. Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. *Int J Radiat Oncol Biol Phys* 2000;46:883-8.

10. Chan AK, Wong AO, Langevin J, Jenken D, Heine J, Buie D, et al. Preoperative chemotherapy and pelvic radiation for tethered or fixed rectal cancer: a phase II dose escalation study. *Int J Radiat Biol Phys* 2000;48:843-56.

11. Onaitis MW, Noone RB, Fields R, Hurwitz H, Morse M, Jowell P, et al. Complete resonse to neoadjuvant chemoradiation for rectal cancer does not influence survival. *Ann Surg Oncol* 2001;8:801-6.

12. Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, et al. Assessing the predictive value of complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. *J Am Coll Surg* 2002;194:131-5.

13. Nakagawa WT, Rossi BM, de O Ferreira F, Ferrigno R, David Filho WJ, Nishimoto IN, et al. Chemoradiation instead of surgery to treat mid to low rectal tumors: Is it safe? *Ann Surg Oncol* 2002;9:568-73.

14. Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P, Lee SH, Madoff RD, Rothenberger DA. A pathological complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. *Dis Colon Rectum* 2003;46:298-304.

15. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;336:980-7.

16. Kahn H, Alexander A, Rakinic J, Nagle D, Fry R. Preoperative staging of irradiated rectal cancers using digital rectal examination, computed tomography, endorectal ultrasound and magnetic resonance imaging does not accurately predict T0,N0 pathology. *Dis Colon Retum* 1997;40: 140-4.

17. Garcia-Aguilar J, Cromwell JW, Marra C, Lee SH, Madoff RD, Rothenberger DA. Treatment of locally recurrent rectal cancer. *Dis Colon Rectum* 2001;44:1743-8.

18. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638-46.

19. Richard CS, Phang PT, McLeod RS, Canadian Association of General Surgeons Evidence Based Reviews in Surgery Group. CAGS-EBRS 5: Need for preoperative radiation in rectal cancer. *Can J Surg* 2003; 46:54-6.

20. van de Velde CJH. Preoperative radiotherapy and TME-surgery for rectal cancer: detailed analysis in relation to quality control in a randomized trial [abstract]. *Proc Am Soc Clin Oncol* 2002;21:127a.