# Long-course chemoradiation versus short-course radiation for rectal cancer and overall comparison

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Sir,

There are two broad approaches to preoperative pelvic radiation therapy for resectable rectal cancer: short-course radiation and long course chemo radiotherapy. Although the radiation techniques are similar, the fractionation and timing of surgery differ. In general, short-course radiation delivers 25 Gy (5 Gy in five fractions) of radiation followed by surgery 1 week later. Long-course chemo radiotherapy delivers 50.4 Gy (1.8 Gy in 28 fractions) of radiation concurrently with chemotherapy, followed by surgery 4 to 8 weeks later. These competing approaches evolved in parallel; short-course radiation developed in northern Europe and Scandinavia and long-course chemoradiotherapy in the United States and selected European countries. Advocates for each approach base their unwavering enthusiasm on the results of three large randomized trials that were published during the last 15 years. Two landmark trials support the use of short-course preoperative radiation. The Swedish Rectal Cancer Trial randomly assigned patients with cT1-3 disease to short-course radiation versus surgery alone.[1,2] This was the first (and only) trial that revealed a significant improvement in survival with preoperative radiation. However, the high local recurrence rate in the preoperative arm (46%) prompted the Dutch group to perform the Commissie Klinisch Vergel ijkend Onderzoek (CKVO) 95-04 trial, which used the same design but mandated the use of total mesorectal excision (TME). Both the initial[3] and long-term reports[4] revealed a significant improvement in local control with preoperative radiation, although no difference in overall survival was observed. Three years later, the results of the German Rectal Cancer trial were reported. Both the initial[5] and long-term follow-up reports[6] confirmed significant improvements in local control, acute and long-term toxicity, and sphincter preservation with preoperative chemoradiotherapy. However, there was no difference in overall survival. This trial changed the standard of care for patients with cT3-4 and/or node-positive disease to preoperative long course chemoradiotherapy. There is an ongoing and at times heated controversy as to the ideal preoperative approach.

The first randomized trial comparing these two approaches in patients with resectablecT3 disease was reported by Bujko et al.[7,8] TME was performed for distal tumors only, postoperative chemotherapy was optional, and there was no central radiation review. Although the long-course chemo radiotherapy arm had a lower incidence of positive radial margins (4%v13%; P.017), there were no significant differences in crude local recurrence or4-year survival. Advocates of short-course radiation have quoted patient convenience and lower cost. Supporters of long-course chemo radiotherapy have emphasized the lower surgical morbidity, increased sphincter preservation, and the ability to safely combine radiation with concurrent systemic chemotherapy. Cross-trial comparisons were not helpful. Phase III trials of short-course radiation versus surgery alone included patients with cT1-3Nx disease, whereas trials of long-course chemoradiotherapy were limited to patients with cT3 and/or no depositive disease. The lines were drawn, alliances formed, and we sat at different dinner tables at the American Society of Clinical Oncology GI Cancers Symposium. Then our brave friends in Australia and New Zealand challenged us and successfully completed a randomized trial. In the article that accompanies this editorial, the Trans-Tasman Radiation Oncology Group (TROG) report the results of their well designed, carefully performed, multicenter randomized trial.[9] In brief, patients with ultrasound- or magnetic resonance imaging–staged cT3Nany adeno carcinoma located in the lower two thirds of the rectum were randomly assigned to short-course radiation versus long course chemo radiotherapy. Patients in both arms received 6 months of postoperative adjuvant chemotherapy. The primary end point was 3-year local recurrence. Compared with short-course radiation, patients who received long-course chemo radiotherapy had a 3% lower cumulative local recurrence rate at 3 years (4.4% v 7.5%) and a 2% lower cumulative local recurrence rate at 5 years (5.7% v 7.5%). Neither were statistically significant. Likewise, there were no significant differences in distant failure, overall survival, or late radiation toxicity. A subset analysis of the 79 patients with distal tumors revealed a cumulative incidence of local recurrence of 12.5% for short-course radiation and 0% for long course

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chemoradiotherapy. There are two shortcomings of the trial. Firstis the relatively small number of patients (n326) who were randomly assigned. The trial was not powered to show equivalence. It was designed to have an 80% power to detect a difference in the projected 3-year local recurrence rate of 15% for short-course radiation compared with 5% for long course chemoradiotherapy. If it was powered for a smaller difference (or ideally, equivalent local recurrence), the statistics would have been more robust. This point is illustrated by the limitations of the CIs. Although the 3% lower incidence of local recurrence with long-course chemoradiotherapy versus short-course radiation did not reach statistical significance (P.24), the 95% CI for the difference included an 8% difference in favour of long course (ie, 10% v 2%). The authors appropriately conclude that "the data are consistent with either no difference or an important clinical difference in favor of LC [longcourse]; it's unlikely that there is an important difference favoring SC [short course]." [9] Clearly, the patient numbers limit the interpretation. In my view, the data suggest a small local control advantage for long course chemoradiotherapy, especially for distal tumors. A second criticism is the relatively short follow-up. As the authors emphasize in the discussion section, although the median potential follow-up time is 5.9 years, late local recurrences can occur. This was seen in the Dutch trial, in which the incidence increased from 3% at a 3.5-year median follow-up to 6% at a 6-year median follow-up.10 Likewise, the German trial reported 5% at 5 years, increasing to 7% at 10 years.[6]

These data underscore the importance of long-term follow-up in rectal cancer adjuvant trials, regardless of which preoperative approach is used. Since the TROG 01.04 trial began accrual in 2001, a new generation of short-course radiation trials has been developed. Historically, the reasons for not using short-course radiation were the lack of sphincter preservation, the inability to safely combine short-course radiation with adequate doses of systemic chemotherapy, and the higher surgical complications. However, these shortcomings may be mitigated by increasing the interval between the completion of radiation and surgery and delivering chemotherapy either neoadjuvantly (before) or sequentially (after) preoperative radiation. Increasing the interval between radiation and surgery is being prospectively tested in the ongoing Stockholm III trial.[11] This three arm phase III trial will determine if increasing the interval between short-course radiation and surgery from 1 week to 4 to 8 weeks improves sphincter preservation and reduces toxicity. The third arm includes long-course radiation (without chemotherapy) followed by surgery 4 weeks later. Because short-course radiation cannot be safely combined with systemic chemotherapy, alternative sequencing approaches have been examined. The Dutch Colorectal Group treated 50 patients presenting with primary rectal cancer and synchronous resectable metastasis on a phase II trial of short-course radiation followed by six cycles of capecitabine plus oxaliplatin plus bevacizumab (restaging after two cycles), with resection of the primary and resection and/or ablation of themetastasis.[12] They reported no toxicity during radiation. Of the 41 patients who underwent surgery, 44% achieved a tumor regression grade of 0 to 2. This approach is being now being tested in the phase III setting. The Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial randomly assigns patients with locally advanced but non metastatic disease to preoperative short-course radiation followed by six cycles of capecitabine plusoxaliplatin and TME versus preoperative long-course chemoradiotherapy and TME. The Polish Colorectal Cancer Study Group is performing a similar phase III trial. Patients are randomly assigned to preoperative short-course radiation followed by three cycles of infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus long-course chemoradiotherapy. The primary end point is R0 resection. Few centers in the United States have used short-course radiation. Myerson et al[13] have reported preliminary results of preoperative short-course radiation followed by sequential mFOLFOX6. After surgery, 75% of patients had ypT0-2 disease, including 30% with ypT0 and 32% with ypN0 disease. Is the new standard of care preoperative short-course radiation? The short answer is no. As presently designed long-course chemoradiotherapy still has a local control advantage (albeit small), especially for distal tumors. However, the TROG 01.04 trial challenges us to look harder. The results of new randomized trials that are testing neo adjuvant and/or sequential chemotherapy combined with short-course radiation as well as extending the interval between radiation and surgery are anxiously awaited.

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