Short-Course Versus Standard Chemoradiation in T3 Rectal Cancer

Section Editor's note: Locally advanced rectal cancer, in contrast to colon cancer, has a substantial risk for local recurrence. Two approaches of neoadjuvant therapy have been formally tested in multiple randomized trials. Short-course radiation therapy uses 1 week of radiation without chemotherapy (5 Gy $\times$ 5) followed by surgery the next week. In contrast, standard chemoradiation uses 45–50.4 Gy in 25–28 fractions with concurrent 5-FU chemotherapy followed by 4–8 weeks of rest before surgery. Short-course radiation therapy is not frequently used in the U.S. The pros and cons of short-course radiation therapy and standard chemoradiation are presented herein.

PRESENTATION OF THE CASE

A 68-year-old woman with no past medical history presents with rectal bleeding. Colonoscopy reveals a mass in the midrectum at approximately 8 cm. Biopsy shows adenocarcinoma. On physical exam, the tip of the mass is barely palpable. A magnetic resonance imaging (MRI) scan of the pelvis demonstrates a tumor with invasion through the muscularis in the midrectum (Fig. 1). There is at least 2 cm between the tip of the mass and the mesorectum. A single 8-mm lymph node is seen in the perirectal space. A medical oncologist, surgical oncologist, and radiation oncologist see the patient and they recommend that the patient receive 6 weeks of infusional 5-fluorouracil (5-FU) and external beam radiation to a dose of 50.4 Gy. After chemoradiation, the oncologists expect the patient to undergo a low anterior resection and, upon recovery, 4 months of 5-FU-based adjuvant chemotherapy. The oncology fellow asks the attending physicians whether short-course radiation therapy is appropriate for this patient. *The Oncologist* 2011;16:717–721

Figure 1. An adenocarcinoma of the rectum showing invasion through the muscularis propria for a cT3 stage on a T2-weighted magnetic resonance imaging scan. The arrow shows the penetration of the tumor through the thick black line of the muscularis propria.

PRO

By Theodore S. Hong
Massachusetts General Hospital

Short-course radiation therapy has a long history of evaluation, yet a limited history of use in the U.S. In spite of consistent reports of efficacy in multiple randomized trials [1–3], en-

Theodore S. Hong, M.D.

CON

By Harvey Mamon
Dana-Farber Cancer Institute and
Brigham and Women's Hospital

We are entering an era of personalized medicine. One manifestation of this phenomenon is genetic characterization of tumors leading to specific

Harvey Mamon, M.D., Ph.D.

thusiasm has been tempered by early reports of both short-term and long-term toxicity [1, 4]. Additionally, the superior toxicity profile reported in the preoperative chemoradiation arm of the German Rectal Study, compared with the historical U.S. standard of postoperative chemoradiation, provided even further incentive to lean away from short-course radiation [5].

However, recent trials evaluating the use of short-course radiation have shed new light on the toxicity of this regimen. As a field, radiation oncologists believe that our newer technologies allow for greater normal tissue sparing, and that this lower dose to critical organs will likewise lead to fewer long-term complications. Although this has been widely accepted for many other diseases, there remains, on the part of American radiation oncologists, skepticism that improvement in technology may be the reason for the lower toxicity. Clearly, there are some patients for whom short-course radiation is inappropriate (concern for a positive margin, borderline candidate for sphincter preservation), as Dr. Mamon also states. Yet, in this specific patient presented, short-course radiation is a reasonable, data-driven option. It is unequivocally shorter for the patient, as well as less costly for society.

Table 1. Select short-course radiation therapy trials

Study/treatment	Local recurrence (%)	DFS (%)	OS (%)
Swedish I [1]			
Short course	9 (13 yr)	72 (13 yr)	38 (13 yr)
Observation	26	62	30
<i>p</i> -value	<.001	.04	.008
Dutch [2]			
Short course	5.6 (6 yr)	75.4 (6 yr)	64.2 (6 yr)
Observation	10.9	72.4	63.5
<i>p</i> -value	<.001	.013	NS
Medical Research Council CR07 [3]			
Short course	4.4 (3 yr)	77.5 (3 yr)	80.3 (3 yr)
Selective postoperative chemoradiation	10.6	71.5	78.6
<i>p</i> -value	NS	.013	NS
Polish [6]			
Short course	15.6 (4 yr)	58.4 (4 yr)	67.2 (4 yr)
Chemoradiation	10.6	55.6	66.2
<i>p</i> -value	NS	NS	NS
TROG [7]			
Short course	7.5 (3 yr)	NR	74 (5 yr)
Chemoradiation	4.4	NR	70
<i>p</i> -value	NS	NR	NS

Abbreviations: DFS, disease-free survival; NR, not reported; NS, not significant; OS, overall survival; Trans-Tasman Radiation Oncology Group.

treatment decisions, such as limiting the use of cetuximab to colorectal cancer patients whose tumors have a wild-type *K-Ras* gene, or basing the recommendation for adjuvant chemotherapy in breast cancer patients on the Oncotype DX® (Genomic Health, Inc., Redwood City, CA) score. Personalized medicine can also describe our ability to choose among valid treatment options, such as short-course versus long-course preoperative radiation therapy for rectal cancer, based on the specific constellation of clinical features and risk factors in an individual patient.

For the patient described above, either the long- or short-course approach would be valid, though I suspect that in the future, more patients such as this one will be offered short-course radiation. My esteemed colleague, Dr. Hong, describes the data that support short-course radiation. A recent comprehensive review of short- versus long-course therapy was published by Mohiuddin et al. [1]. Here, I briefly describe some reasons to consider standard long-course chemoradiation, and the selection of patients for whom this choice may be most appropriate.

THE OPPORTUNITY TO BENEFIT FROM THE SYNERGY OF CHEMOTHERAPY AND RADIATION EARLIER IN THE TREATMENT COURSE

5-FU has long been recognized as a radiosensitizer. Clinical data from multiple solid malignancies such as lung cancer and cervical cancer have shown that the combination of concurrent chemotherapy and radiation produces better outcomes than either treatment alone. In the case of rectal cancer, a pivotal study was the four-arm Gastrointestinal Tumor Study Group GI-7175 trial [2, 3]. In that study, there was a trend toward longer survival when either adjuvant chemotherapy or radiation was added to surgery, but it was only when combined chemoradiation was administered that a statistically significant survival benefit was observed. In another classic trial, which established the use of infusional rather than bolus 5-FU in rectal cancer treatment, and, by extension, in other gastrointestinal malignancies, early administration of infusional 5-FU led to significantly better outcomes [4]. In that trial, 660 patients who had undergone curative surgery for rectal cancer were randomized to receive postoperative radiation with either 3 days of bolus 5-FU given during the first and last weeks of radiation or infusional 5-FU given throughout the course of radiation. The latter treatment was associated with a significantly lower overall tumor relapse rate, 37% versus 47%, a significantly lower distant metastasis rate, 31% versus 40%, and a significantly greater overall survival rate, 70% versus 60%, at 4 years. In the modern era of FOLFOX, we tend to discount the value of single-agent infusional 5-FU, but this study demonstrated clearly superior rates of distant metas-

SHORT-COURSE RADIATION WORKS

Short-course radiation has been tested in multiple trials (Table 1). The Swedish Rectal Cancer Trial randomized patients with “clinically resectable rectal cancer” to preoperative short-course radiation followed by surgery versus surgery alone. The patients receiving short-course radiation had better local control as well as a longer overall survival duration [1]. The Dutch Colorectal Cancer Group Study similarly demonstrated better local control with the addition of radiation to the more oncologic total mesorectal excision (TME) [2]. More recently, the Medical Research Council CR07 trial randomized 1,350 patients to short-course preoperative radiation therapy versus selective postoperative chemoradiation therapy in margin-positive patients [3]. All patients had centrally reviewed TME. Patients receiving short-course radiation demonstrated significantly better local control and disease-free survival.

When compared with standard chemoradiation, short-course radiotherapy shows similar efficacy. Bujko et al. [6] recently compared neoadjuvant short-course radiotherapy with concurrent chemoradiation using a more protracted radiation course (50.4 Gy in 28 fractions) in a randomized trial. There was no benefit from the protracted radiation in terms of sphincter preservation, local control, or survival, though the local control trend actually favored short-course radiation. Because none of the previously mentioned studies had standardized adjuvant chemotherapy recommendations and all lacked formal tumor staging, a more recent study from the Trans-Tasman group sought to eliminate these confounding factors and compared short-course radiotherapy with standard chemoradiation in patients with ultrasound- or MRI-defined T3 rectal cancer [7]. All patients were required to receive cycles of 5-FU plus leucovorin (Mayo Clinic schedule). In the 326 patients randomized, there was no difference in local control or overall survival.

SHORT-COURSE RADIATION HAS NOT BEEN SHOWN TO LEAD TO MORE LATE EFFECTS THAN STANDARD CHEMORADIATION

As Dr. Mamon notes, large fractions have been associated with greater long-term late effects. However, when one performs a radiobiological effect correction, the short-course regimen actually predicts a *lower* equivalent dose. Indeed, the original report of toxicity showed that radiation therapy was associated with a higher risk for in-field fractures, thromboembolic events, and small bowel obstruction, and a higher postoperative mortality rate [1, 4]. However, the Swedish Rectal Study used extraordinarily large fields (the upper border including lumbar [L]1 and L2) and only two portals (anteroposterior/posteroanterior), and did not mandate blocking [4]. This field design is as different from modern field design as old kitchen-wall rotary phones are

taxis and overall survival in patients receiving this chemotherapy concurrently with pelvic radiation. Although these are both adjuvant rather than neoadjuvant studies, the results are almost certainly applicable in the neoadjuvant setting as well.

SHORT-COURSE RADIATION, WITH SURGERY SHORTLY THEREAFTER, DOES NOT RESULT IN DOWNSTAGING

Among the considerations that led investigators to change from adjuvant to neoadjuvant chemoradiation is the ability to shrink bulky tumors, facilitating R0 resections and negative circumferential margins, and increasing the rate of sphincter preservation. Long-course chemoradiation results in a pathologic complete response in approximately 10%–30% of patients, with a much higher percentage demonstrating significant downstaging. In contrast, a Dutch trial, which demonstrated significantly better local control when short-course radiation was given up to 10 days prior to TME, showed no downstaging in radiated patients [5]. Similarly, in a Polish randomized study, pathologic complete responses were seen in 1% of patients receiving short-course radiation, versus 16% of patients receiving combined chemoradiation [6]. For patients with distal tumors, in whom the surgeon felt an abdominoperineal resection would be needed, Sauer et al. [7] demonstrated that preoperative chemoradiation led to a doubled sphincter-preservation rate, 39% versus 20%. Although some have questioned this result, another recent randomized trial of pre-versus postoperative chemoradiation for rectal cancer also showed a statistically significant higher sphincter-preservation rate following preoperative long-course chemoradiation therapy [8]. Short-course radiation has not been demonstrated to produce a higher sphincter-preservation rate, and given the lack of pathologic response with this approach, short-course radiation is not anticipated to allow a change in the surgical procedure. Another concern with the lack of pathologic downstaging is the importance of achieving a negative circumferential margin, which is one of the major determinants of the risk for local recurrence [9–11]. Imaging by MRI is increasingly successful in identifying patients at risk for a positive circumferential margin [12–14], and these patients likely represent another group that would benefit from the downstaging achievable with neoadjuvant chemoradiation [15].

THE RADIOBIOLOGY OF LARGE FRACTIONS REMAINS A CONCERN

Even accounting for calculations of radiobiological equivalence, 500 cGy in five fractions is a lower dose than 180 cGy in 28 fractions. However, it is a basic principle of radiobiology that a large fraction size carries a higher risk for late toxicities. Although it is somewhat reassuring that late

from iPhones. In the two above-mentioned randomized trials, the late toxicities appear to be comparable, supporting the assertion that, if reasonable field design is used, there should be no substantial difference in toxicity [6, 7].

OVERTREATMENT AND THE ROLE OF CHEMOTHERAPY

In rectal cancer, our recommendations are only as good as our staging. Whereas there is increasing interest in selectively using radiation therapy, there has been little discussion regarding the amount of overtreatment with adjuvant chemotherapy. In the German Rectal Study, 20% of patients were actually found to have stage I disease in the postoperative arm [5]. However, because of the significant amount of downstaging with chemoradiation, adjuvant chemotherapy, specifically 5-FU, leucovorin, and oxaliplatin (FOLFOX), is recommended. Currently, this means that 20% of patients are being exposed to FOLFOX who absolutely don't need it. In the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colorectal Cancer study, 24.1% and 15.4% of patients continued to have peripheral neuropathy at 18 and 48 months, respectively [8]. Furthermore, it is not clear whether all stage II rectal cancer patients really need chemotherapy. The lack of downstaging with short-course radiation [9] allows for the 20% of overstaged patients to avoid adjuvant chemotherapy and potentially allows for the judicious use of adjuvant chemotherapy in those patients with stage II rectal cancer.

DISCLOSURES

Theodore S. Hong: *Research funding/contracted research:* Novartis.

REFERENCES

- 1 Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997;336:980–987.
- 2 Kapiteijn E, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638–646.
- 3 Sebag-Montefiore D, Stephens RJ, Steele R et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): A multicentre, randomised trial. *Lancet* 2009;373:811–820.
- 4 Birgisson H, Pahlman L, Gunnarson U et al. Adverse effects of preoperative radiation therapy for rectal cancer: Long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol* 2005;23:8697–8705.
- 5 Sauer R, Becker H, Hohenberger W et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731–1740.
- 6 Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;93:1215–1223.

toxicities appeared comparable in the two randomized trials of short- versus long-course therapy [6, 16], the late effects reported in a Swedish trial, including higher incidences of bowel obstruction, abdominal pain, and nausea, remain of some concern [17].

PATIENT SELECTION

The Dutch and Swedish trials, of short-course preoperative radiation versus surgery alone, and the more recent Polish and TROG studies, of short-course radiation versus long-course chemoradiation, all demonstrated that short-course radiation is a valid treatment option. However, the lack of downstaging with this approach suggests that it may not be the preferred treatment for patients with bulky tumors, those who may be borderline candidates for sphincter preservation, and those with MRI evidence of a threatened circumferential margin. In addition, the clear benefit for combined chemoradiation demonstrated in the early adjuvant rectal trials raises the concern that patients treated with short-course radiation alone, followed by surgery and a recovery period before receiving systemic therapy, may be missing the opportunity to benefit from early exposure to chemotherapy. For all of these reasons, the current U.S. standard of neoadjuvant combined chemoradiation therapy in patients with locally advanced rectal cancer remains a valid option.

DISCLOSURES

Harvey Mamon: None.

REFERENCES

- 1 Mohiuddin M, Marks J, Marks G. Management of rectal cancer: Short- vs. long-course preoperative radiation. *Int J Radiat Oncol Biol Phys* 2008;72:636–643.
- 2 Prolongation of the disease-free interval in surgically treated rectal carcinoma. Gastrointestinal Tumor Study Group. *N Engl J Med* 1985;312:1465–1472.
- 3 Thomas PR, Lindblad AS. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: A review of the Gastrointestinal Tumor Study Group experience. *Radiother Oncol* 1988;13:245–252.
- 4 O'Connell MJ, Martenson JA, Wieand HS et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994;331:502–507.
- 5 Marijnen CA, Nagtegaal ID, Klein Kranenbarg E et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001;19:1976–1984.
- 6 Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;93:1215–1223.
- 7 Sauer R, Fietkau R, Wittekind C et al. Adjuvant versus neoadjuvant radiochemotherapy for locally advanced rectal cancer. A progress report of a phase-III randomized trial (protocol CAO/ARO/AIO-94). *Strahlenther Onkol* 2001;177:173–181.

- 7 Ngan S, Fisher R, Goldstein D et al. A randomized trial comparing local recurrence (LR) rates between short-course (SC) and long-course (LC) preoperative radiotherapy (RT) for clinical T3 rectal cancer: An intergroup trial (TROG, AGITG, CSSANZ, RACS). *J Clin Oncol* 2010;28(15 suppl): Abstract 3509.
- 8 André T, Boni C, Navarro M et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;27:3109–3116.
- 9 Marijnen CA, Nagtegaal ID, Klein Kranenbarg E et al. No downstaging after short-term preoperative radiotherapy in rectal cancer patients. *J Clin Oncol* 2001;19:1976–1984.
- 10 Park JH, Yoon SM, Yu CS et al. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. *Cancer* 2011 Feb 15. doi: 10.1002/cncr.25943. [Epub ahead of print].
- 11 Nagtegaal ID, Marijnen CA, Kranenbarg EK et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: Not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002;26:350–357.
- 12 Mawdsley S, Glynne-Jones R, Grainger J et al. Can histopathologic assessment of circumferential margin after preoperative pelvic chemoradiotherapy for T3–T4 rectal cancer predict for 3-year disease-free survival? *Int J Radiat Oncol Biol Phys* 2005;63:745–752.
- 13 Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 2008;26:303–312.
- 14 MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: Prospective observational study. *BMJ* 2006;333:779.
- 15 Brown G, Radcliffe AG, Newcombe RG et al. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. *Br J Surg* 2003;90:355–364.
- 16 Salerno GV, Daniels IR, Moran BJ et al. Magnetic resonance imaging prediction of an involved surgical resection margin in low rectal cancer. *Dis Colon Rectum* 2009;52:632–639.
- 17 Kelly SB, Mills SJ, Bradburn DM et al. Effect of the circumferential resection margin on survival following rectal cancer surgery. *Br J Surg* 2011 Jan 25. doi: 10.1002/bjs.7372. [Epub ahead of print].
- 18 Ngan S, Fisher R, Goldstein D et al. A randomized trial comparing local recurrence (LR) rates between short-course (SC) and long-course (LC) preoperative radiotherapy (RT) for clinical T3 rectal cancer: An intergroup trial (TROG, AGITG, CSSANZ, RACS). *J Clin Oncol* 2010;28(15 suppl): Abstract 3509.
- 19 Birgisson H, Pahlman L, Gunnarsson U et al. Adverse effects of preoperative radiation therapy for rectal cancer: Long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol* 2005;23:8697–8705.

To join the conversation, please visit:

www.ChallengingCases.TheOncologist.com