Evolving Role of Radiotherapy in the Management of Rectal Carcinoma

Clayton A. Smith, MD, PhD[a,*], Lisa A. Kachnic, MD[b]

KEYWORDS

• Rectal • Cancer • Radiotherapy • Radiation • Neoadjuvant
• Intensity-modulated radiation therapy

KEY POINTS

- Neoadjuvant radiation improves local control of rectal cancer and reduces acute and late toxicity compared with adjuvant treatment.
- Neoadjuvant radiation combined with chemotherapy improves pathologic complete response rates.
- Alternative treatment strategies either omitting radiotherapy or omitting surgery may be feasible in select populations and are under evaluation in prospective trials.
- Intensity-modulated radiation therapy may reduce toxicity and treatment delays compared with traditional 3-dimensional conformal radiation therapy.

INTRODUCTION

The incidence of rectal cancer is estimated to be 39,220 in the United States in 2016, with an estimated 49,190 deaths from combined colon and rectal cancer.[1] Although surgery remains the primary definitive treatment of colorectal cancers, additional local treatment with radiotherapy is indicated in many patients because of the anatomy of the rectum and pelvis. The limited space within the pelvis can make complete surgical resection more difficult for rectal tumors while at the same time providing a fixed target for radiation treatments. The role of radiotherapy as adjunct to surgery has evolved over the decades with changes in the timing (preoperative vs postoperative), length (short course vs long course), intent (neoadjuvant vs definitive), and delivery (3-dimensional conformal radiation therapy [3D-CRT] vs intensity-modulated radiation therapy

Disclosure Statement: The authors have nothing to disclose.
[a] Division of Radiation Oncology, University of South Alabama Mitchell Cancer Institute, 1660 Spring Hill Avenue, Mobile, AL 36604, USA; [b] Department of Radiation Oncology, Vanderbilt University Medical Center, 2220 Pierce Avenue, Preston Research Building B-1003, Nashville, TN 37232, USA
* Corresponding author.
E-mail address: Claytonsmith@health.southalabama.edu

Surg Oncol Clin N Am 26 (2017) 455–466
http://dx.doi.org/10.1016/j.soc.2017.01.011
surgonc.theclinics.com

[IMRT]), significantly improving the outcomes of patients. This review summarizes the evolution in radiation therapy (RT) for the management of rectal cancer and addresses some of the current questions regarding its role in the future.

FROM SURGERY ALONE TO COMBINED MODALITY THERAPY

Historically, the primary management of rectal carcinoma was surgical resection, with rates of local failure of 25% or higher with older surgical techniques.[2] It was also observed that positive resection margin resulted in significantly worse local failure rates.[3] The advent of total mesorectal excision (TME), which uses sharp dissection of mesorectal contents, further reduced the rate of local recurrence to as low as 8%.[4] For patients with higher risk disease (such as T3/T4 disease and node positivity), the risk of local and distant failure remained elevated, so adjuvant therapies including radiation and chemotherapy were administered in an attempt to reduce rates of local and distant failure. Multiple studies examined this adjuvant role of pelvic radiation and collectively found that adjuvant radiation alone decreased the risk of local recurrence but did not significantly improve overall survival.[5] The addition of adjuvant chemotherapy was noted to reduce the rates of distant metastases while improving disease-free survival.[6,7] Since that time, more modern trials have examined the appropriate sequencing of therapies (surgery, radiation, chemotherapy) and assessed which patients may be candidates for omission of certain modalities to reduce the late effects of treatment.

PREOPERATIVE RADIATION THERAPY REGIMENS

In the 1980s and 1990s, the standard management of rectal cancer was surgical resection with low anterior resection (LAR) or abdomino-perineal resection for proximal and distal tumors, respectively, followed by adjuvant radiation (with or without chemotherapy) and further chemotherapy. For some patients, it was difficult to complete the entire postoperative course of adjuvant treatment, which led to the emergence of several trials to address the question of whether neoadjuvant radiation therapy (RT) with or without chemotherapy could be safely administered without sacrificing disease control. The German Rectal Cancer Study CAO/ARO/AIO-94 randomly assigned more than 800 patients to treatment with either neoadjuvant RT to 5040 cGy with continuous infusion 5-fluorouracil (5-FU) or adjuvant RT to 5580 cGy with 5-FU.[8] Both groups underwent TME resection and 4 cycles of adjuvant 5-FU. With the long-term update, neoadjuvant chemoradiation (chemo-RT) was found to decrease local recurrence (7.1% vs 10.1%; $P = .048$); however, there were no differences in overall survival [OS] rate (59.6% vs 59.9%; $P = .85$) or distant metastases (29.8% vs 29.6%; $P = .9$).[9] Pathologic complete response (pCR) rate in the preoperative group was 9% as of the long-term update. In the initial publication, acute grade 3 or higher toxicity, an important endpoint, was significantly less in the preoperative group (27% vs 40%; $P = .001$), and late grade 3 or higher toxicity was also decreased with preoperative therapy (14% vs 24%; $P = .01$).

Two additional trials, the European Organisation for Research and Treatment of Cancer (EORTC) 22,921 and the Federation Francophone de Cancerologie (FFCD) 9203, examined the effect of neoadjuvant chemo-RT over RT alone (with or without adjuvant chemotherapy) on outcomes for patients with cT3-4 resectable disease.[10–12] Pooled analysis of the data found that chemo-RT significantly improved 3-year local control (92.3% vs 84.7%; $P<.0001$) and pCR rates (11.2% vs 3.7%; $P<.0001$).[13] However, there were no differences in 5-year OS (66.3% vs 65.9%; $P = .66$) or 3-year distant progression-free rates (71.3% vs 70.7%; $P = .5$). Based on the totality of the