Rectal Cancer

Ann Raldow and Jennifer Wo

Contents

Abstract

Radiation therapy has a well-established role in the treatment of locally advanced, clinically node-positive rectal cancer. Radiation therapy has been demonstrated in numerous randomized trials to decrease the rates of local failure. There are two radiation treatment schemas which have been proven to be effective, including standard fractionated chemoradiation and short-course radiation therapy. More recent studies are evaluating the potential impact of omission of radiation therapy and surgical resection, respectively, for favorable-risk locally advanced tumors.

1 Introduction

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in both men and women in the United States (Siegel et al. 2014). In 2014, there were 136,830 new cases of colorectal cancer in the United States; of these, 28% was cancer of the rectum (Siegel et al. 2014). Surgery is at the cornerstone of curative therapy for patients with resectable rectal cancer. Most patients present with tumors that are mobile and invasive into or beyond the rectal wall, requiring surgical resection with either a low anterior resection (LAR) or abdominoperineal resection (APR), depending on the size, location, and extent of the cancer. A small percentage of

A. Raldow, M.D., M.P.H.
University of California, Los Angeles,
Los Angeles, CA, USA

J. Wo, M.D. (✉)
Massachusetts General Hospital, Boston, MA, USA
e-mail: JWO@mgh.harvard.edu

Med Radiol Radiat Oncol (2018)
DOI 10.1007/174_2018_175, © Springer International Publishing AG
Published Online: 05 April 2018

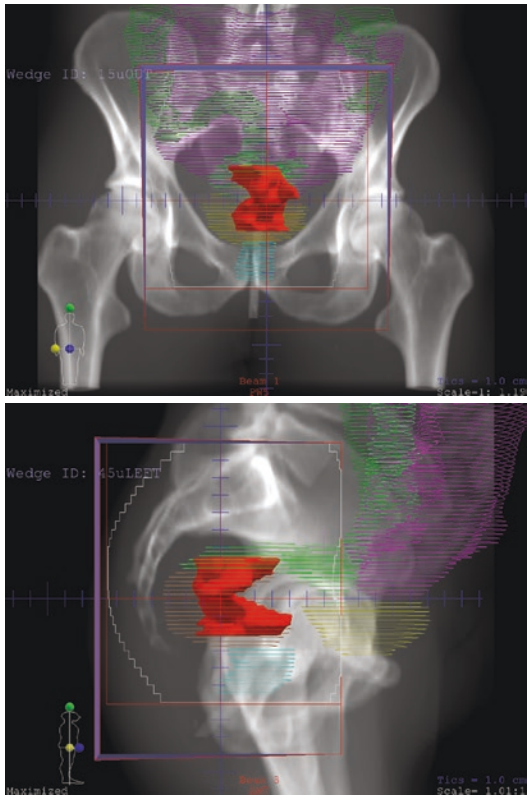

Fig. 1 Standard radiation fields for rectal cancer (courtesy of Theodore Hong)

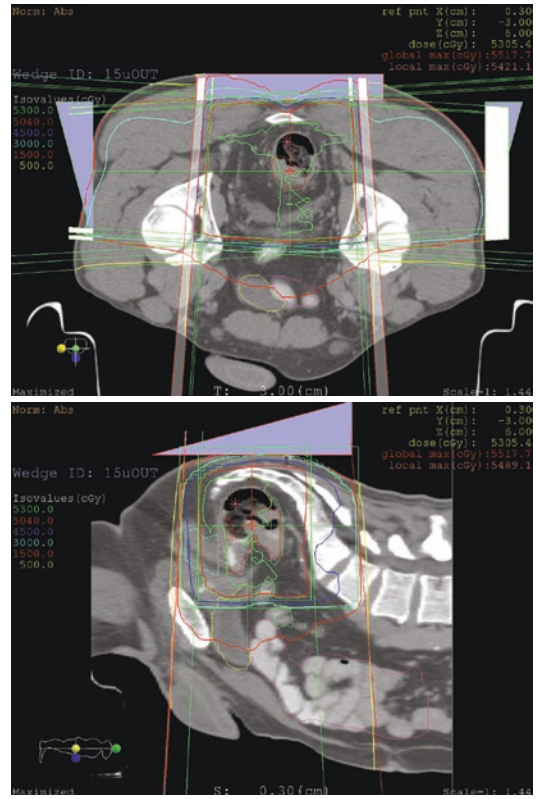

Fig. 2 Standard three-field radiation plan for rectal cancer (courtesy of Theodore Hong)

patients present with locally advanced, unresectable tumors that are adherent or fixed to adjoining structures such as the sacrum, pelvic sidewalls, prostate, or bladder.

Although patients with resected stage I disease have excellent prognoses with surgery alone, locoregional failure after surgery alone in patients with transmural or node-positive tumors is unacceptably high. Several randomized trials were designed to improve the results of surgery alone through the addition of radiation therapy, and these reported significant reductions in local recurrence (Folkesson et al. 2005; Peeters et al. 2007; Gastrointestinal Tumor Study Group 1985). Early trials of multimodality therapy in rectal cancer evaluated postoperative radiation with or without chemotherapy, but the role and sequencing of these therapies have changed over time (Fisher et al. 1988). More recently, neoadjuvant treatment is more common as it results in better local control, increased likelihood of sphincter preservation, and a lower risk of chronic anastomotic stricture. Figures 1 and 2 represent standard radiation treatment fields for rectal cancer.

There are two strategies to preoperative therapy for patients with T3-4 or node-positive rectal cancer: short-course radiation and long-course chemoradiation (CMT). While the radiation techniques are comparable, the radiation schedule and timing of resection differ. Typically, short-course radiation consists of 25 Gy in five fractions followed by surgery 1 week later. Long-course CMT consists of 50.4 Gy in 28 fractions with concurrent fluoropyrimidine chemotherapy, followed by surgery in 4–8 weeks. Although short-course radiation therapy is used in northern European countries and Scandinavia where it was developed, it is not favored in North America and several other European countries because it cannot be com-

bined with concurrent chemotherapy. Proponents of each of these approaches base their treatment decisions on the results of several recently published randomized trials.

2 Short-Course Radiotherapy

Two key trials support the use of short-course preoperative radiation versus surgery alone for resectable rectal cancer. The Swedish Rectal Cancer Trial randomized 908 patients with stage I–III disease to short-course radiation followed by surgery or surgery alone (Folkesson et al. 2005; Birgisson et al. 2005; Swedish Rectal Cancer Trial et al. 1997). With a median follow-up of 13 years, preoperative radiation significantly decreased the rate of local recurrence (9% vs. 26%, $p < 0.001$) and increased the rates of overall survival (38% vs. 30%, $p = 0.008$). Of note, this was the first and only trial that revealed a significant improvement in survival with short-course preoperative radiation. However, the study did not require total mesorectal excisions (TME) and disease stage was not balanced between the two arms.

The high local recurrence rate in the preoperative arm of the Swedish Rectal Cancer Trial motivated the Dutch to perform the CKVO 95-04 trial, which used the same design to randomize 1861 patients, but required total mesorectal excisions (Peeters et al. 2007; Kapiteijn et al. 2001; Van Gijn et al. 2011). With a median follow-up of 5 years, preoperative radiation significantly decreased the rate of local recurrence (5.6% vs. 10.9% at 5 years); however, there was no significant difference in cancer-specific or overall survival.

3 Long-Course/Standard Fractionation Radiotherapy

Advocates of long-course CMT quote the results of two important randomized trials: the German Rectal Trial and NSABP R-03. In fact, only 3 years after the CKVO 95-04 trial was published, the results of the German Rectal Cancer trial were reported. The German Rectal Trial randomized 823 patients to either preoperative long-course CMT with concurrent CI 5-FU or the same treatment in the postoperative setting with an added 5.4 Gy boost (Sauer et al. 2004, 2012). The patients were required to undergo TME and four cycles of adjuvant 5-FU chemotherapy were planned. Both the initial and long-term follow-up publications showed significant decreases in local failure (5-year local failure rate of 6% vs. 13%), acute and long-term toxicity, and sphincter preservation with preoperative CMT. However, there was no difference in overall survival. Of note, a large minority (18%) of patients in the postoperative treatment arm were found to have stage I disease at surgery. This trial established preoperative long-course CMT as the standard of care for patients with cT3–4 and/or node-positive rectal cancer.

In the United States, the results of the German Rectal Trial were confirmed with the NSABP R-03 study, where 256 patients were assigned to either preoperative long-course CMT with concurrent 5-FU or the same treatment in the postoperative setting (Fisher et al. 1988). Patients received an additional three cycles of adjuvant 5-FU chemotherapy, but TME was not required. Although the study was closed early due to poor accrual, patients in the preoperative CMT arm had a significantly improved 5-year DFS (74.5% vs. 65.6%) and a nonsignificant trend towards improved 5-year OS (74.5% vs. 65.6%, $p = 0.065$). There was no difference in locoregional recurrence (11% in both arms). Patients in the preoperative CMT arm had a significant reduction of pathologic lymph node involvement and a pCR of 15%. Together, the German Rectal Trial and the NSABP R-03 study show improved LC and superior rates of sphincter preservation in patients undergoing preoperative long-course CMT as compared to postoperative therapy.

4 Randomized Trials of Short-Course Versus Long-Course CMT

The first randomized trial comparing preoperative short-course radiation therapy with long-course CMT with 5-FU/LV in patients with

resectable cT3 disease was the Polish Rectal Study (Bujko et al. 2004, 2006). Although the long-course CMT arm had a lower incidence of positive radial margins (4% vs. 13%, $p = 0.017$), there was no difference with respect to local recurrence, sphincter preservation, or survival. However, the study has several limitations that deserve consideration. In the study, TME was performed for distal tumors only, postoperative chemotherapy was optional, there was no consistency in pre-therapy staging evaluation, and there was no radiation quality-control review. In addition, there was surgeon subjectivity with respect to whether patients underwent sphincter preservation (5/18 patients underwent an APR after a clinical complete response following preoperative CMT) and the study was underpowered to detect differences in local control and survival.

Ngan et al. published a similar trial from Australia (TROG 01-04), where 326 patients with T3 rectal cancer (56% were N0) were randomized to short-course radiation versus long-course CMT with 5-FU, followed by surgery (Ngan et al. 2012). In contrast to the Polish Rectal Study, patients were scheduled to receive 6 months of postoperative chemotherapy. There were no significant differences in 3-year local recurrence (7.5% vs. 4.4%), 5-year distant recurrence (27% vs. 30%), or 5-year overall survival (74% vs. 70%) between the short-course and long-course arms, respectively. Likewise, there were no significant differences in late radiation toxicity. However, the study included a relatively small number of patients and was not powered to show equivalence. In addition, there was short follow-up and late local recurrences and toxicities can occur. Another key result that has not been presented is sphincter function.

5 Controversies Regarding the Preoperative Treatment

There is controversy as to the ideal preoperative treatment approach for patients with T3-4 or node-positive rectal cancer: short-course radiation and long-course CMT. These competing strategies have been proven effective in randomized trials and evolved in parallel. While short-course radiation was established in northern Europe and Scandinavia, long-course CMT evolved in the United States and several other European countries. Unfortunately, intertrial comparisons of the two different approaches were not feasible because the eligibility criteria varied; recent trials comparing the two approaches have significant limitations.

Proponents of short-course radiation point to patient convenience, lower cost, as well as lack of pathologic downstaging. Because the pathologic findings at the time of surgery are more likely to represent pretreatment staging, more appropriate adjuvant chemotherapy recommendations can be made. Sparing selected patients from adjuvant FOLFOX could potentially reduce treatment-related toxicity (e.g., long-term peripheral neuropathy) without compromising oncologic outcomes. Nonetheless, short-course radiation is not regularly recommended in the United States for patients with locally advanced rectal cancer because it cannot be safely combined with adequate doses of chemotherapy and does not increase sphincter preservation. In addition, there was some concern over long-term toxicity associated with the short-course regimen. Long-term toxicity data from these trials and quality-of-life comparison studies will be crucial in determining toxicity profiles for the two treatment strategies.

However, some of these limitations may be diminished by lengthening the time period between the completion of short-course radiation and surgery and giving chemotherapy either neoadjuvantly or after preoperative radiation. The Stockholm III trial is evaluating the consequences of increasing the interval between radiation and surgery (Pettersson et al. 2010). In this phase III trial, 303 patients were randomized to one of the three arms: short-course radiation and surgery within 1 week, short-course radiation and surgery after 4–8 weeks, and long-course radiation (50 Gy in 25 fractions) and surgery after 4–8 weeks. This trial will establish whether increasing the time interval between short-course radiation and surgery improves sphincter preservation and reduces toxicity.

In addition, there has been recent interest in defining the potential role of neoadjuvant chemotherapy without the use of routine radiation therapy for locally advanced rectal cancer. Schrag et al. recently evaluated the use of preoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX)-bevacizumab with selective use of radiation therapy prior to surgery in clinically staged II/III patients (Schrag et al. 2014). After chemotherapy, patients with stable or progressive disease were to have preoperative radiation, whereas responders were to proceed immediately to TME. In addition, postoperative radiation was planned if there was not a R0 resection. Administration of six cycles of adjuvant FOLFOX was recommended. Of the 30 patients who completed preoperative chemotherapy, all had tumor regression and proceeded to immediate TME without preoperative radiation therapy. The pathologic complete response rate with chemotherapy alone was 25% (95% CI, 11–43%) and the 4-year local recurrence rate was 0% (95% CI, 0–11%). These results suggest that neoadjuvant chemotherapy with selective radiation does not compromise outcomes. A phase III trial (PROSPECT) to validate this study is currently under way.

The ideal treatment management for patients with locally advanced rectal cancer is debatable. While short-course radiation and long-course CMT are established treatment paradigms, the role and sequencing of radiation, chemotherapy, and surgery continue to change with time. The results from trials evaluating additional treatment approaches will be revealing. To ultimately assume the optimal treatment approach, it is crucial that we better do preoperative radiographic assessment of postoperative high-risk pathologic features. In addition, we need to improve our evaluation of the molecular profile of rectal cancers, which holds the potential of proper identification of patients at high risk of recurrence and, therefore, suitable for the receipt of adjuvant treatment. In the meantime, at our institution, we treat locally advanced rectal cancer patients with long-course CMT using concurrent 5-FU followed by TME 4–6 weeks later, as well as 4–6 months of adjuvant 5-FU-based chemotherapy.

6 Future Directions: Minimizing Therapy with the Wait-and-See Approach

Although the standard of care for patients with locally advanced rectal cancer is chemoradiation followed by TME and adjuvant chemotherapy, there has recently been increasing interest in treatment de-escalation. Preoperative chemoradiation produces pathologic complete response in approximately 10–20% of patients; therefore, a subgroup of rectal cancer patients may not need surgery after chemoradiation. Although it is challenging to determine which patients will have a pathologic complete response after chemoradiation, there are several analyses that have studied the feasibility of a watch-and-wait approach in patients with a clinical complete response to chemoradiation (Maas et al. 2011; Habr-Gama et al. 2004, 2006; Hughes et al. 2010; Smith et al. 2012).

Mass et al. performed one such study, in which they prospectively evaluated 21 patients with localized rectal cancer treated with chemoradiation (Maas et al. 2011). Patients were eligible for the study after confirmation of clinical complete response with magnetic resonance imaging (MRI), endoscopy, and biopsies. They were subsequently followed every 3–6 months with MRI, endoscopy, and computed tomography scans, so that local recurrences could be detected early. After a mean follow-up of 25 months, one patient developed a local recurrence and underwent salvage surgery. The remaining 20 patients survived without evidence of disease.

Although Mass et al. provide evidence in support of a watch-and-wait approach to the treatment of rectal cancer, there are challenges to this approach. For instance, present-day approaches to measuring tumor response are limited, and a clinical complete response does not necessarily denote a pathologic complete response. Careful patient selection, rigorous methods of evaluating clinical response, and close follow-up will be crucial to the success of this strategy. In the future, we hope that the wait-and-see approach will be evaluated in a randomized clinical trial.

Conclusion

For locally advanced, node-positive rectal cancer, neoadjuvant radiation therapy, either prescribed as neoadjuvant chemoradiation or short-course RT, is an effective treatment to achieve tumor downstaging and local control. Given concern for distant disease spread, more recent studies have looked at front-loading neoadjuvant chemotherapy and have even suggested a potential role for omission of RT in good responders. Additionally, for patients with a clinically complete response after definitive chemoradiation, an increasing number of studies are looking to evaluate the feasibility of a wait-and-wait nonoperative approach. For all of these approaches, careful patient selection and rigorous and close monitoring are necessary.

References

Birgisson H, Påhlman L, Gunnarsson U, Glimelius B, Swedish Rectal Cancer Trial Group (2005) Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. J Clin Oncol 23:8697–8705

Bujko K et al (2004) Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol J Eur Soc Ther Radiol Oncol 72:15–24

Bujko K et al (2006) Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 93:1215–1223

Fisher B et al (1988) Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst 80:21–29

Folkesson J et al (2005) Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 23:5644–5650

Gastrointestinal Tumor Study Group (1985) Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med 312:1465–1472

Habr-Gama A et al (2004) Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 240:711–717; discussion 717–718

Habr-Gama A et al (2006) Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. J Gastrointest Surg 10:1319–1328; discussion 1328–1329

Hughes R, Harrison M, Glynne-Jones R (2010) Could a wait and see policy be justified in T3/4 rectal cancers after chemo-radiotherapy? Acta Oncol 49:378–381

Kapiteijn E et al (2001) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 345:638–646

Maas M et al (2011) Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 29:4633–4640

Ngan SY et al (2012) Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 30:3827–3833

Peeters KCMJ et al (2007) The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 246:693–701

Pettersson D et al (2010) Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 97:580–587

Sauer R et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740

Sauer R et al (2012) Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol 30:1926–1933

Schrag D et al (2014) Neoadjuvant chemotherapy without routine use of radiation therapy for patients with locally advanced rectal cancer: a pilot trial. J Clin Oncol 32:513–518

Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics, 2014. CA Cancer J Clin 64:9–29

Smith JD et al (2012) Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 256:965–972

Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, Glimelius B, Påhlman L, Rutqvist LE, Wilking N (1997) Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 336:980–987

Van Gijn W et al (2011) Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 12:575–582