Short-Course Radiation Versus Long-Course Chemoradiation for Rectal Cancer

Bruce D. Minsky, MD[a]; Claus Rödel, MD[b]; and Vincenzo Valentini, MD[c]

Abstract

The 2 broad approaches to preoperative therapy for rectal cancer are chemoradiation and short-course radiation. The outcomes of these 2 approaches reported in nonrandomized trials are not comparable because patients selected for treatment with short-course radiotherapy included those with cT1–3 disease, whereas patients selected for chemoradiation included those with T3 and/or N+ disease. However, more recent trials of short-course radiation have included patients with cT3 and/or N+ disease who also underwent sequential or postoperative chemotherapy, allowing a more relevant comparison with chemoradiation. This article compares the 2 preoperative approaches and addresses their emerging roles. (*JNCCN* 2012;10:1223–1231)

The 2 broad approaches to preoperative therapy for rectal cancer are chemoradiation and short-course radiation. The evolution to preoperative therapy is based on data from 2 randomized trials in which patients received preoperative therapy followed by a total mesorectal excision (TME). The German Rectal Cancer Trial compared preoperative and postoperative chemoradiation (45–50.4 Gy in 25–28 fractions plus concurrent chemotherapy).[1,2] Compared with postoperative chemoradiation, preoperative chemoradiation significantly decreased acute and late toxicity, and increased local control and sphincter preservation. The Dutch CKVO trial compared short-course radiation (25 Gy in 5 fractions) with surgery alone.[3,4] Compared with surgery alone, preoperative short-course radiation significantly increased local control. The outcomes of these 2 trials are not comparable because the patients selected for treatment with short-course radiotherapy included those with stages cT1–3, whereas 95% of the patients in the German trial had stages T3 and/or N+. More recent trials of short-course radiation have included patients with stages cT3 and/or N+ disease who also underwent sequential or postoperative chemotherapy, allowing a more relevant comparison with chemoradiation.

From the [a]Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas; [b]Department of Radiotherapy and Oncology, Johann Wolfgang Goethe-Universität, Frankfurt, Germany; and [c]Department of Radiotherapy, Università Cattolica del Sacro Cuore, Policlinico A. Gemelli, Rome, Italy.

Submitted April 25, 2012; accepted for publication July 16, 2012.

Dr. Minsky has disclosed that he has an advisory role or serves as a consultant for Roche and Bayer AG Pharmaceuticals, Inc. Drs. Rödel and Valentini have disclosed no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in this article or their competitors.

Correspondence: Bruce D. Minsky, MD, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 97, Room B2.4562, Houston, TX 77030. E-mail: bminsky@mdanderson.org

Preoperative Chemoradiation

The standard treatment for T3–4 and/or N+ rectal cancer is preoperative chemoradiation. Braendengen et al[5] randomized 207 patients with cT4 or recurrent rectal cancer to 50 Gy of radiation with or without concurrent 5-FU/leucovorin. Patients who received chemoradiation had higher rates of R0 resection (84% vs. 68%; $P = .009$), pathologic complete response (pCR; 16% vs. 7%), 5-year local control (82% vs. 67%; $P = .03$), time to treatment failure (63% vs. 44%; $P = .003$), cancer-specific survival (72% vs. 55%; $P = .02$), and overall survival (66% vs. 53%; $P = .09$). As would be expected, these improvements were associated with an increase in acute grade 3 to 4 toxicity (29% vs. 6%; $P = .001$) and an increase in long-term toxicity. Compared with radiation alone, patients who received chemoradiation had a lower chance of being stoma-free and having good anal function (11% vs. 30%; $P = .046$).[6]

The clinical utility of intensity-modulated radiation therapy (IMRT) in treatment planning and delivery is being investigated.[7,8] Phase I/II trials of IMRT suggest

that this modality reduces the volume of radiation to the small bowel in the treatment area[9] and decreases acute gastrointestinal toxicity.[8] However, the clinical benefit of IMRT compared with 3-dimensional or conventional treatment delivery remains to be determined.[10]

Recent trials have examined the role of different chemoradiation regimens. The NSABP R-04 trial reported equivalent rates of pCR (22% vs. 19%), sphincter-sparing surgery (63% vs. 61%), and grade 3+ diarrhea (11%) with continuous-infusion 5-FU and capecitabine-based chemoradiation.[11] The noninferiority trial from Hofheinz et al[12] confirmed the equivalence of 5-FU and capecitabine-based chemoradiation.

Four randomized trials examined the effects of adding oxaliplatin to 5-FU or capecitabine-based preoperative chemoradiation.[11,13–16] Three of these (NSABP R-04,[11] STAR-01,[13] and ACCORD 12[14]) reported no significant improvement in the pCR rate and a corresponding increase in acute toxicity. In contrast, the German CAO/ARO/AIO-04 trial revealed a significant improvement in pCR with no corresponding increase in acute grade 3+ toxicity.[16] Preliminary data from the ACCORD 12 trial revealed no improvement with the addition of oxaliplatin in 3-year local control (4% vs. 5%) or survival (88% vs. 85%).[15] A fifth trial (PETACC-6) is investigating a similar question and results are pending.

The benefit of adding targeted biologic agents, such as bevacizumab and cetuximab, is being tested. Initial phase I/II trials of bevacizumab plus preoperative 5-FU or capecitabine-based chemoradiation revealed pCR rates of 18% to 24%.[17,18] However, more recent trials report increased acute toxicity and have subsequently been closed.[19,20] Furthermore, given bevacizumab's lack of a survival benefit in the NSABP C-08 adjuvant colon cancer trial, its ultimate role in the adjuvant management of rectal cancer remains unclear.[21]

Patient selection based on *KRAS* expression is useful for those treated in the metastatic setting.[22] In the adjuvant setting, preliminary results from the phase II EXPERT-C trial (50.4 Gy/CAPOX/cetuximab) suggest a survival benefit in patients whose tumors are *KRAS* wild-type versus mutant.[23] However, the NCCTG Intergroup trial N0147 showed that the addition of cetuximab to mFOLFOX6 (modified continuous-infusion 5-FU, leucovorin, and oxaliplatin) in patients with resected stage III colon cancer and mutated *KRAS* resulted in an impaired disease-free survival and a trend toward impaired overall survival.[24]

Therefore, the standard preoperative chemoradiation regimen remains 50.4 Gy plus either concurrent continuous-infusion 5-FU or capecitabine.

The improvements in systemic chemotherapy may allow preoperative radiation to be used more selectively. In a prospective trial reported in abstract form, Schrag et al[25] treated 32 selected patients who had uT2,N1 or uT3,N0–1 rectal cancer with neoadjuvant FOLFOX (5-FU, leucovorin, and oxaliplatin) plus bevacizumab. Patients who required an abdominoperineal resection were excluded. Pelvic radiation was reserved for patients who experienced preoperative progression or, after surgery, had either pT4, pN2, or positive margins. Among the 30 patients who underwent surgery, none required radiation, the pCR rate was 27%, and 2 required postoperative radiation. This approach remains investigational and is being prospectively tested in the phase II/III Alliance N1048 trial.

Preoperative Short-Course Radiation

Twelve modern randomized trials of preoperative short-course radiation have been reported.[26] Fractionation varied from 5 Gy in 1 fraction to the more standard 25 Gy administered over 5 fractions (5 Gy × 5). Most of the trials revealed a decrease in local recurrence, and in 5 this difference reached statistical significance. Some trials revealed a significant improvement in survival in selected subsets. Only the Swedish Rectal Cancer Trial reported a survival advantage for the total treatment group.[27] Two meta-analyses reported conflicting results with one another, although both revealed a decrease in local recurrence; Camma et al[28] reported a survival advantage, whereas the analysis by the Colorectal Cancer Collaborative Group[29] did not.

In the Swedish Rectal Cancer Trial, patients with cT1–3 rectal cancer were randomized to 25 Gy over 5 fractions followed by surgery 1 week later versus surgery alone.[27] With 13-year follow-up, survival is still significantly improved (38% vs. 30%; $P = .008$).[30] The local recurrence rate in lymph node–positive patients who underwent surgery alone was 46%, illustrating the inferior results of surgery before the adoption of TME. This trial, and the other 10

that preceded it, did not mandate TME. Although interesting from a historical perspective, these trials are not discussed further.

The Dutch CKVO 95-04 trial randomized 1805 patients with cT1–3 disease to either TME alone or 25 Gy of preoperative radiation administered over 5 fractions followed by TME.[3] Preoperative radiation significantly decreased local recurrence (8% vs. 2%), but no difference was seen in 2-year survival (82%). With a 12-year median follow-up, the 5-year local failure rate was higher with TME alone (11%) but was significantly decreased to 5% with preoperative radiation.[31] The acute toxicities seen in the Dutch CKVO 95-04 trial were substantial, and included neurotoxicity (10%), perineal wound complications (29%), and postoperative leaks (12%).[4] Notably, of the patients who developed postoperative leaks, 80% required surgery, resulting in 11% mortality. In contrast to the earlier randomized trials of short-course radiation, multiple-field radiation techniques were used. Whether the increases in morbidity and mortality were caused by the learning curve associated with TME, the 1-week interval between the completion of radiation and surgery, or both is unknown.

What is the Preferred Preoperative Therapy?

Historically, the primary reasons for not using short-course radiation are the lack of sphincter preservation, the inability to safely combine the radiation with adequate doses of systemic chemotherapy, and the acute toxicity.[32] However, these shortcomings may be mitigated by increasing the interval between preoperative radiation therapy and surgery and by delivering chemotherapy sequentially (after radiation) as opposed to concurrently (Table 1).

Increasing the Interval Between Short-Course Radiation and Surgery

Increasing the interval between radiation and surgery is being prospectively tested in the Stockholm III trial. This phase III trial will determine whether increasing the interval between short-course radiation and surgery from 1 week to 4 to 8 weeks improves sphincter preservation and reduces toxicity. Patients are being randomized to 5 Gy × 5 followed by surgery 1 week later, 5 Gy × 5 followed by surgery 4 to 8 weeks later, or 2 Gy × 25 (50 Gy total) followed by surgery 4 to 8 weeks later.

Short-Course Radiation and Sequential Chemotherapy

Because short-course radiation cannot be safely combined with systemic chemotherapy, sequential treatment has been examined. This approach is based on the positive results of chemoradiation trials of induction and sequential chemotherapy.

Rationale of Induction Chemotherapy: The Spanish GCR-3 randomized phase II trial compared induction chemotherapy with conventional preoperative chemoradiation followed by surgery and postoperative chemotherapy.[33] A total of 108 patients received preoperative 50.4 Gy plus CAPOX (capecitabine and oxaliplatin) and were randomized to receive 4 months of CAPOX either through induction or adjuvant (postoperative) therapy. With the induction approach, no detriment was seen in the pCR rate (14% vs. 13%), grade 3+ toxicity was lower (17% vs. 51%; $P = .00004$), and the ability to receive all 4 chemotherapy cycles was higher (93% vs. 51%; $P = .0001$).

Garcia-Aguilar et al[34] tested a similar approach. In their randomized phase II trial, 144 patients with cN+ rectal cancer received preoperative chemoradiation (50.4 Gy of radiation + continuous-infusion 5-FU) followed by surgery 6 weeks later versus

Table 1 Short-Course Radiation Versus Chemoradiation

Variable	Short-Course Radiation	Chemoradiation
Combine with chemotherapy	Sequential	Concurrent
Increased sphincter preservation and pCR	No, but Stockholm III trial results pending	Yes, confirmed by the German CAO/ARO/AIO 94 trial[16]
3D or IMRT possible	Yes	Yes
Time to radiation completion	5 d	28 d
Clinical stages entered on trials	cT1–3	cT3 and/or N+

Abbreviations: IMRT, intensity-modulated radiation therapy; pCR, pathologic complete response.

chemoradiation and, if they experienced a clinical response, mFOLFOX6 followed by surgery 11 weeks later. The pCR rate was nonsignificantly higher in the mFOLFOX arm (25% vs. 18%), with no increase in postoperative complications (40% in each arm). The preliminary data suggest that delaying surgery in patients who have a response to preoperative therapy and delivering additional chemotherapy are not detrimental to the tumor response or surgical complication rates.

In a series from the Dutch Colorectal Cancer Group, 50 patients with primary rectal cancer and synchronous resectable metastasis in 1 or 2 organs (liver, 42; lung, 5; both, 3) were enrolled in a phase II trial of short-course radiation followed by 6 cycles of CAPOX plus bevacizumab (restaging after 2 cycles) and resection of the primary and resection and/or ablation of the metastasis.[35] The median time between the completion of radiation and chemotherapy was 11 days (3–44 days). The investigators reported "no toxicity" during radiation. Of the 41 patients brought to surgery, 44% achieved a tumor regression grade of 0 to 2.

This approach is being now being tested in the neoadjuvant setting. The RAPIDO (Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation) phase III trial randomizes patients with locally advanced but nonmetastatic disease to short-course radiation followed by CAPOX × 6 and TME versus chemoradiation followed by TME.

The Polish Colorectal Cancer Study Group is performing a similar phase III trial in patients with primary cT4 or locally recurrent rectal cancer without distant metastases. Patients are randomized to preoperative short-course radiation (5 Gy × 5) followed by FOLFOX4 × 3 versus chemoradiation (50.4 Gy in 28 fractions + concurrent 5-FU/leucovorin/oxaliplatin). The primary end point is R0 resection.

Myerson et al[36] reported preliminary results of short-course radiation followed by sequential chemotherapy. A total of 60 patients with cT3–4, any N, any M rectal cancer were entered and 44 were evaluable at the time of analysis. Clinical stages of the evaluable patients included cT4 in 4 patients, cT3 in 40, cN+ in 32, and cM1 in 4. Preoperative radiation treatment was given in 5 fractions (25 Gy to the involved mesorectum and 20 Gy to the pelvic nodes) followed by 4 cycles of mFOLFOX6. Postoperative chemotherapy was given at the discretion of the medical oncologist. After surgery, 33 (75%) had ypT0–2 disease, including 13 (30%) who were ypT0 and 14 (32%) who were ypN0.

Nonrandomized Trials of Chemoradiation Versus Short-Course Radiation

MRC C07

The UK Medical Research Council Trial MRC C07 randomized 1350 patients with clinical stage I–III rectal cancer to 5 Gy × 5 or selective postoperative chemoradiation (45 Gy with concurrent 5-FU), which was delivered only to patients with a histologic circumferential radial margin (CRM) less than 1 mm (12% of all patients with immediate surgery).[37] This trial did not compare, in a randomized fashion, short-course radiation with chemoradiation, because only patients with close/positive CRM were selected to receive postoperative treatment. With a median follow-up of 4 years, patients who received preoperative compared with selective postoperative treatment had significantly lower 3-year local recurrence rates (4.4% vs. 10.6%; $P < .0001$) and higher 3-year disease-free survival rates (77.5% vs. 71.5%; $P = .013$).

SCRIPTS

Short-course radiation is 1 of the 2 preoperative treatment options in the ongoing SCRIPTS (Simply Capecitabine in Rectal Cancer After Irradiation Plus TME Surgery) trial from the Dutch Colorectal Group (CKTO 2003-16) that opened in 2007. Patients with clinical stage II (T3–T4, N0) or III (any T, N+) rectal adenocarcinoma (below the level of S1/S2 or with the inferior margin within 15 cm of the anal verge) can receive either preoperative 5 Gy × 5 or chemoradiation (45 Gy + 5-FU–based chemotherapy) followed by TME. Patients are then randomized postoperatively to either capecitabine or observation. Although not randomized, this trial will provide additional data comparing these preoperative approaches.

Randomized Trials of Short-Course Radiation Versus Chemoradiation

Two randomized trials of short-course radiation versus chemoradiation have been reported: the Polish trial reported by Bujko et al[38,39] and the Intergroup trial (TROG, AGITG, CSSANZ, RACS) reported by Ngan et al[40] (Table 2).

Table 2 Randomized Trials of Preoperative Chemoradiation Versus Short-Course Radiation

Characteristics	Bujko et al[38,39]		Ngan et al[40]	
Patients, N	316		326	
Clinical stage	T3–4		T3, any N (56% N0)	
Chemoradiation	50.4 + 5-FU/LV		50.4 Gy + CI 5-FU	
Short-course radiation	5 Gy × 5		5 Gy × 5	
Postoperative chemotherapy	Not required		5-FU/LV (4–6 cycles)	
Outcome	**Chemoradiation (%)**	**Radiation (%)**	**Chemoradiation (%)**	**Radiation (%)**
pCR	16	1[a]		
SP	58	61		
CRM+	4	13[a]		
Compliance	69	98		
Local failure	14	9 (4-y)	4	8 (3-y)
Survival	66	67 (4-y)	70	74 (3-y)
Grade 3–4 late toxicity			9	8

Abbreviations: CI, continuous infusion; CRM+, positive circumferential radial margin; LV, leucovorin; pCR, pathologic complete response; SP, sphincter preservation.
[a]Statistically significant.

Polish Trial

Bujko et al[38,39] randomized 316 patients with cT3 rectal cancer. All tumors were above the anorectal ring; TME was performed for distal tumors only. Postoperative chemotherapy was at the discretion of the investigator. No radiation quality control review occurred and TME was performed only for distal tumors. Compared with patients who received short-course radiation, those who received chemoradiation had a higher pCR rate (16% vs. 1%) and a lower incidence of CRM+ (4% vs. 13%; $P = .017$). However, no significant differences were seen in sphincter preservation (58% vs. 61%), crude local recurrence (14% vs. 9%), disease-free survival (56% vs. 58%), and 4-year survival rates (66% vs. 67%). Although acute toxicity was significantly higher with chemoradiation (18% vs. 3%; $P < .001$), no difference was seen in postoperative complications.

TROG, AGITG, CSSANZ, RACS Intergroup Trial

Ngan et al[40] reported on a similar trial from Australia and New Zealand in abstract form. In this intergroup trial, a total of 326 patients with ultrasound or MRI staged T3, any N rectal cancer of the distal two-thirds of the rectum were randomized to short-course radiation versus chemoradiation (50.4 Gy plus continuous-infusion 5-FU). In contrast to the trial from Bujko et al,[38,39] patients in both arms received postoperative 5-FU/leucovorin adjuvant chemotherapy. The median follow-up was 5.9 years. Comparing short-course radiation with chemoradiation, no significant differences were seen in 3-year local recurrence (8% vs. 4%), 5-year distant recurrence-free (72% vs. 69%), 5-year survival (74% vs. 70%), and RTOG grade 3 to 4 late toxicity rates (8% vs. 9%).

Although the trial had more robust quality control than the Polish trial, it did have some criticisms, including the small number of patients randomized and that it was not powered to show equivalence. Lastly, the potential median follow-up was only 5.9 years and, as discussed later, may not be adequate to identify local recurrences (the final manuscript is pending).

These trials have challenged the role of long-course chemoradiation in selected patients. However, the results must be examined in perspective. Neither trial was limited to patients with N+ disease and both require longer follow-up.

The Need for Long-Term Follow-up

Local recurrences can occur after 5 years in patients with rectal cancer. In contrast to the results reported in the trials of adjuvant treatment of colon cancer, in which 3-year and possibly 2-year disease-free survival predicts for 5-year survival,[41] the INT 0114 postoperative rectal adjuvant trial confirmed that local control and survival continue to decrease beyond 5

years.[42] At 7 years, the local recurrence rate was 17% and the survival was 56% compared with 14% and 64%, respectively, at 5 years.

Limiting the analysis to trials in which all patients underwent a TME, a similar detriment in outcomes was seen with long-term follow-up. In the German CAO/ARO/AIO 94 trial, patients who received preoperative chemoradiation had an increase in local recurrence rates (7% vs. 5%) and a decrease in survival rates (60% vs. 74%) at 10 versus 5 years, respectively.[2] The incidence of local recurrence for all patients in the short-course radiation arm of the Dutch CKVO trial of 5 Gy × 5 increased from 3% at a median follow-up of 3.5 years to 6% at a median follow-up of 6 years.[43] These data underscore the importance of long-term follow-up, regardless of which preoperative approach is used.

Does Preoperative Treatment Impact the Need for Postoperative Adjuvant Chemotherapy?

Two randomized trials address whether postoperative chemotherapy is beneficial after preoperative therapy. Neither the EORTC 22921[44] or the FFCD 9203[45] revealed a survival advantage. A pooled analysis of the 2 trials with a median follow-up of 5.6 years confirmed that patients who received preoperative chemoradiation compared with radiation had a significant decrease in local recurrence (11% vs. 15%; $P = .0001$); however, no difference was seen in 5-year overall survival (66%).[46]

These results must be examined in perspective. Given that most patients did not receive adequate doses of postoperative chemotherapy in the EORTC trial, and the FFCD trial tested the impact of only 6 weeks of chemotherapy concurrent with preoperative radiation, the standard practice in many centers remains preoperative chemoradiation followed by surgery and 4 months of postoperative adjuvant chemotherapy. A recent analysis revealed that among 810 patients who received preoperative chemoradiation at 8 NCCN Member Institutions, 20% did not receive postoperative adjuvant chemotherapy. The most frequent reason for physician refusal was comorbid illness (54%), and the most frequent reason chemotherapy was not received when it was recommended by the medical oncologist was patient refusal (73%).[47] Whether the ability to deliver postoperative chemotherapy is more successful in patients who receive short-course radiation compared with chemoradiation is unknown.

Beets et al[48] performed a pooled analysis of 2724 patients who received preoperative chemoradiation. Overall, 41% received postoperative chemotherapy and no benefit in disease-free survival was seen in the subsets of patients with ypT0,N0 or ypT3–4, any N disease. Patients with ypT1–2,N0 disease had the greatest benefit, although the hazard ratio was 0.45 (95% CI, 0.27–0.75).

Nomograms may also be helpful in decision-making. Valentini et al[49] pooled data from 5 major European clinical trials for rectal cancer and developed multivariate nomograms based on Cox regression analysis. The nomograms were able to predict events with a c-index for external validation of local recurrence, distant metastases, and overall survival. These may be used as decision support tools by using the 3 defined risk groups to select patients for postoperative chemotherapy versus close follow-up.

Most investigators feel it is reasonable to use the same adjuvant chemotherapy for colon and rectal cancer. For patients selected to receive postoperative adjuvant chemotherapy, 4 months (8 cycles) of mFOLFOX6 is recommended. However, its benefit remains controversial.[50]

Does the Distance From the Anal Verge Impact the Treatment Approach?

The limited data on how distance from the anal verge affects local recurrence come from subset analyses not stratified by distance; no prospective randomized data are available. Furthermore, additional variables may have contributed to differences in local recurrence. For example, TME was standard in the Dutch CVKO and German trials and not in the Swedish trial. All 3 trials included patients with tumors greater than 12 cm from the anal verge in the "upper or high" category. Because the peritoneal reflection varies from 12 to 16 cm, some patients with tumors above the peritoneal reflection (colon cancer) were included in the 3 trials. Most investigators now limit preoperative treatment to tumors 12 cm or less from the anal verge.[51] Lastly, distance measurements using a flexible proctoscope are less accurate than those with a straight proctoscope. Flexible scopes were

used in the Dutch CKVO trial, whereas the German trial used a straight scope. In the Swedish trial, proctoscopic information was not mentioned and eligibility was limited to tumors "below the promontory as identified by barium enema." The Polish trial is not included because all tumors were within reach on digital examination.[39]

Tumors identified as "high" in the Dutch CKVO and Swedish trials (defined as > 10.1 and 11 cm, respectively) had a lower incidence of local recurrence compared with mid and lower tumors. Short-course radiation did not significantly decrease local recurrence. On multivariate analysis, tumor location was an independent prognostic variable in the Dutch CKVO trial. In the 12-year update, the impact of preoperative radiation significantly increased as the distance from the anal verge increased (P = .03). However, excluding patients with CRM+, the relationship between distance from the anal verge and the impact of radiation became nonsignificant (P = .62). Interestingly, radiation significantly decreased local recurrence for mid-tumors in both trials, whereas it was helpful for lower tumors in the Swedish trial.

In contrast, no significant difference was seen in local recurrence between mid and upper tumors in the German trial.[52] In a retrospective analysis of 627 patients with stage I–IV rectal cancer treated with either surgery alone or chemoradiation, Nash et al[53] reported that the pelvic recurrence rate was lower for tumors 7 to 12 cm, compared with 0 to 6 cm, from the anal verge (3% vs. 7%, respectively; P = .009). However, mucosal, distant, and overall recurrences were not significantly different.

Given the conflicting data, combined with the report from Guillem et al[51] confirming that the incidence of positive nodes is the same in patients whose tumors are 0 to 12 cm from the anal verge, treatment decisions should not be made based on the current definitions of low versus mid versus high regardless of whether the patient receives preoperative chemoradiation or short-course radiation.

Summary

The conventional treatment for T3 and/or N+ rectal cancer is preoperative chemoradiation. Emerging data are challenging the chemoradiation approach. Randomized trials comparing chemoradiation with short-course radiation are encouraging, but longer follow-up is needed. The addition of sequential chemotherapy after short-course radiation is feasible and is being tested prospectively. The effect on outcome, acute and chronic toxicity, and sphincter preservation must be determined.

References

1. Sauer R, Becker H, Hohenberger P, et al. Preoperative chemoradiotherapy as compared with postoperative chemoradiotherapy for locally advanced rectal cancer. N Engl J Med 2004;351:11–20.
2. Sauer R, Liersch T, Merkel S, et al. 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 2012;30:1926–1933.
3. 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.
4. Marijnen CA, Kapiteijn E, van de Velde CJ, et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002;20:817–825.
5. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 2008;22:3687–3694.
6. Braendengen M, Tveit KM, Bruheim K, et al. Late patient-reported toxicity after preoperative radiotherapy or chemoradiotherapy in nonresectable rectal cancer: results from a randomized phase III study. Int J Radiat Oncol Biol Phys 2012;81:1017–1024.
7. Arbea L, Martinez-Monge R, Diaz-Gonzalez J, et al. Four-week neoadjuvant intensity-modulated radiation therapy with concurrent capecitabine and oxaliplatin in locally advanced rectal cancer patients: a validation phase II trial. Int J Radiat Oncol Biol Phys 2012;83:587–593.
8. Samuelian JM, Callister MD, Ashman JB, et al. Reduced acute bowel toxicity in patients treated with intensity modulated radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:1981–1987.
9. Callister MD, Ezzell GA, Gunderson LL. IMRT reduces the dose to small bowel and other pelvic organs in the preoperative treatment of rectal cancer [abstract]. Int J Radiat Oncol Biol Phys 2006;66(Suppl):Abstract s290.
10. Aristu JJ, Arbea L, Rodriguez J, et al. Phase I-II trial of concurrent capecitabine and oxaliplatin with preoperative intensity modulated radiotherapy in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2008;71:748–755.
11. Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04 [abstract]. J Clin Oncol 2011;29(Suppl):Abstract 221s.
12. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitibine versus fluorouracil for locally advanced rectal cancer: a randomized, multicentre, non-inferiority phase III trial. Lancet Oncol 2012;13:579–588.
13. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response

to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29:2773–2780.

14. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III ACCORD 12/0405 PRODIGE 2. J Clin Oncol 2010;28:1638–1644.
15. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Clinical results at 3 years of the ACCORD 12 randomized trial in rectal cancer [abstract]. J Clin Oncol 2012;30(Suppl):Abstract 389.
16. Roedel C, Becker H, Fietkau R, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with 5-fluorouracil and oxaliplatin versus 5-fluorouracil alone in locally advanced rectal cancer: first results of the German CAO/ARO/AIO-04 randomized phase III trial [abstract]. J Clin Oncol 2011;29(Supp):Abstract 222s.
17. Willett CG, Duda D, di Tomaso E, et al. Efficacy, safety, and biomarkers of neoadjuvant bevacizumab, radiation therapy, and fluorouracil in rectal cancer: a multidisciplinary phase II study. J Clin Oncol 2009;27:3020–3026.
18. Crane CH, Eng C, Feig BW, et al. Phase II trial of neoadjuvant bevacizumab, capecitabine, and radiotherapy for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2008;76:824–830.
19. Dipetrillo T, Pricolo V, Lagares-Garcia J, et al. Neoadjuvant bevacizumab, oxaliplatin, 5-fluorouracil, and radiation for rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:124–129.
20. Resch G, DeVries A, Ofner D, et al. Preoperative treatment with capecitabine, bevacizumab and radiotherapy for primary locally advanced rectal cancer - a two stage phase II clinical trial. Radiother Oncol 2012;102:10–13.
21. Allegra CJ, Yothers G, O'Connel MJ, et al. Phase III trial assessing Bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 2011;29:11–16.
22. van Cutsem E, Lang I, D'haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTA experience [abstract]. J Clin Oncol 2008;26(Suppl):Abstract 1006s.
23. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). J Clin Oncol 2012;30:1620–1627.
24. Goldberg RM, Sargent DJ, Thibodeau SN, et al. Adjuvant mFOLFOX6 plus or minus cetuximab (Cmab) in patients (pts) with KRAS mutant (m) resected stage III colon cancer (CC): NCCTG Intergroup phase III trial N0147 [abstract]. J Clin Oncol 2012;28(Suppl):Abstract 3508.
25. Schrag D, Weiser MR, Goodman KA, et al. Neoadjuvant FOLFOX-bev, without radiation, for locally advanced rectal cancer [abstract]. J Clin Oncol 2010;28(Suppl):Abstract 3551.
26. Skibber JM, Hoff PM, Minsky BD. Cancer of the rectum. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology, 6th ed. Philadelphia, PA: Lippincott Williams and Wilkeins; 2001:1271–1318.
27. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980–987.
28. Camma C, Giunta M, Fiorica F, et al. Preoperative radiotherapy for resectable rectal cancer. A meta-analysis. JAMA 2000;284:1008–1015.
29. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 22 randomised trials involving 8507 patients. Lancet 2001;358:1291–1304.
30. Birgisson H, Pahlman L, Glimelius B. 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.
31. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011;12:575–582.
32. Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patient's quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. J Clin Oncol 2010;27:4233–4239.
33. Fernandez-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging–defined, locally advanced rectal cancer: Grupo Cáncer de Recto 3 Study. J Clin Oncol 2010;28:859–865.
34. Garcia-Aguilar J, Smith DD, Avila K, et al. Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. Ann Surg 2011;254:97–102.
35. van Dijk TH, Havenga K, Beukema J, et al. Short-course radiation therapy, neoadjuvant bevacizumab, capecitabine and oxaliplatin, and radical resection of primary tumor and metastasis in primary stage IV rectal cancer: a phase II multicenter study of the Dutch Colorectal Cancer Group [abstract]. J Clin Oncol 2010;28(Suppl):Abstract 295s.
36. Myerson RJ, Parikh PJ, Tan B, et al. A single institution phase II trial of five fractions of radiotherapy followed by four courses of FOLFOX chemotherapy as preoperative therapy for rectal adenocarcinoma [abstract]. J Clin Oncol 2012;30(Suppl):Abstract 553.
37. 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 multicenter, randomised trial. Lancet 2009;373:811–820.
38. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomized trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004;72:15–24.
39. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long term results of a randomized trial comparing preoperative short-course radiotherapy with preperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215–1223.
40. Ngan S, Fischer R, Goldstein D, et al. A randomized trial comparing local recurrence (LR) rates between short course (SC) and long course (LC) radiotherapy (RT) for clinical T3 rectal cancer: an Intergroup trial (TROG, AGITG, CSSANZ, RACS) [abstract]. J Clin Oncol 2010;28(Suppl):Abstract 15s.
41. Sargent D, Yothers G, van Cutsem E, et al. Use of two-year disease-free survival (DFS) as a primary endpoint in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: new data from 12,676 patients from MOSAIC, X-ACT,

PETACC-3, NSABP C-06 and C-07, and C89803 [abstract]. J Clin Oncol 2009;27(Suppl):Abstract 170s.

42. Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control—final report of Intergroup 0114. J Clin Oncol 2002;20:1744–1750.
43. Peeters KC, Marijnen CA, Nagtegaal ID, et al. 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 2007;246:693–701.
44. Bosset JF, Collette L, Bardet E, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114–1123.
45. Gerard JP, Conroy T, Bonnetain F. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;28:4620–4625.
46. Bonnetain F, Bosset JF, Gerard JP, et al. An analysis of preoperative chemoradiotherapy with 5FU/leucovorin for T3-4 rectal cancer on survival in a pooled analysis of EORTC 22921 and FFCD 9203 trials: surrogacy in question? [abstract]. J Clin Oncol 2011;29(Suppl):Abstract 222s.
47. Khrizman P, Niland JC, ter Veer A, et al. Postoperative adjuvant chemotherapy (CTX) use in patients (Pts) with stage II/III rectal cancer treated with neoadjuvant therapy: a National Comprehensive Cancer Network (NCCN) analysis [abstract]. J Clin Oncol 2011;29(Supp):Abstract 224s.
48. Beets GL, Mass M, Nelemans PJ, et al. Evaluation of response after chemoradiation for rectal cancer as a predictive factor for the benefit of adjuvant chemotherapy: a pooled analysis of 2724 individual patients [abstract]. J Clin Oncol 2011;29(Suppl 4):Abstract 139.
49. Valentini V, van Stiphout RG, Lammering G, et al. Concomitant boost radiotherapy and multidrug chemotherapy in the neoadjuvant treatment of locally advanced rectal cancer: results of a phase II study. J Clin Oncol 2011;29:3163–3172.
50. Valentini V, Aristei C, Glimelius B, et al. Multidisciplinary rectal cancer management: 2nd European Rectal Cancer Consensus Conference. Radiother Oncol 2009;92:148–163.
51. Guillem JG, Diaz-Gonzalez J, Minsky BD, et al. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. J Clin Oncol 2008;26:368–373.
52. Sauer R, Roedel C. The author's reply. N Engl J Med 2005;352:510–511.
53. Nash GM, Weiss A, Dasgupta R, et al. Close distal margin and rectal cancer recurrence after sphincter-preserving rectal resection. Dis Colon Rectum 2010;53:1365–1373.