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Several different radiation strategies improve outcomes for patients with rectal cancer.

Radiation Therapy for Rectal Cancer: Current Status and Future Directions

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Background: Treatment for rectal cancer has evolved over the past 70 years from surgery alone to the selective use of trimodality therapy for high-risk patients. Radiotherapy (RT) has improved the potential for tumor downstaging, thus enhancing sphincter preservation and local control.

Methods: This article reviews the evolution of strategies that incorporate pelvic RT, intraoperative RT, and high-dose-rate endorectal brachytherapy (HDRBT). By tracing the arc of the pendulum that has swung from postoperative RT to preoperative RT, we address the current standard of care and explore the potential of novel radiation techniques and radiosensitizing agents to improve outcomes.

Results: With randomized trial data confirming that preoperative RT in addition to chemotherapy improves local control and decreases acute and late morbidity, neoadjuvant programs have now demonstrated the prognostic significance of downstaging as well. Patients with tumors that have a good response to preoperative treatment have superior survival.

Conclusions: Future studies will determine the optimal regimen to enhance the pathologic complete or near complete response rates for locally advanced disease. Advances in radiation technology are being investigated to determine whether efficacy can be increased and toxicity decreased so that more aggressive chemotherapeutic agents can be combined. With the growing improvements in combined modality therapy, a future of better rectal cancer outcomes looms brighter than ever before.

Introduction

Colorectal cancer is the third most common malignancy in the United States.¹ Each year, over 40,000 patients are diagnosed with rectal cancer, a malignancy defined by the National Cancer Institute panel of experts as occurring in the distal large bowel 12 cm or less from

the anal verge by rigid proctoscopy.² This consensus definition has been adopted based on the fact that it is measurable and reproducible. However, considerable differences in terminology exist, with some authors reporting that the most useful landmark to discriminate sigmoid colon from rectum is the loss of taenia coli, the appendices epiploicae, and the surgical mesocolon at approximately the level of the third sacral vertebra.³

By 1940, pathologic analysis of rectal cancer resection specimens had identified penetration of the primary tumor through the bowel wall and involved lymph nodes as factors associated with worse outcomes.^{4,5} In 1954, Astler and Collier⁶ confirmed the prognostic significance of direct cancer extension outside the bowel wall. In the 1970s, areas of failure found at reoperation

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Submitted June 1, 2009; accepted August 4, 2009.

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following an initially curative resection for rectal adenocarcinoma were investigated, with results showing that survival and disease relapse rates are indeed related to the degree of bowel wall penetration and the extent of nodal disease.⁷ This early work paved the way for the identification of those patients with high-risk disease, described in the modern TNM staging system as T3/T4 and/or node-positive. This review traces the evolution of pelvic radiation therapy (RT) and brachytherapy into the treatment arsenal for these patients, with emphasis on our current and future practice.

In the era before the adoption of total mesorectal excision (TME), surgery alone for transmural or node-positive rectal adenocarcinoma was associated with local failure rates of up to 50%.⁸⁻¹⁰ This setting provided the foundation for exploration of strategies to improve outcomes following resection. The first trial was conducted by the Gastrointestinal Tumor Study Group (GITSG 7175), which randomized patients to surgery alone vs semustine and 5-fluorouracil (5-FU) vs pelvic RT alone vs chemoradiation.¹¹ The arm that combined chemotherapy and RT showed a significant improvement in local control and survival.¹² Following this trial, investigators at the Mayo Clinic/North Central Cancer Treatment Group (Mayo/NCCTG) explored the question of postoperative RT alone vs postoperative chemoradiation with semustine and 5-FU on protocol NCCTG 794751.¹³ With over 7 years of median follow-up, there was a 34% reduction in tumor recurrence ($P = .002$) and a 36% reduction in cancer-related death ($P = .007$) in favor of the chemoradiation arm. These two positive trials set a new standard for the postoperative management of high-risk rectal cancer. In 1990, the NCI issued a consensus conference statement declaring that combined-modality therapy is the new standard of care in this setting.¹⁴

Once the new standard of care was established, ongoing studies sought to determine the best regimen. To explore whether semustine was necessary, the Mayo/NCCTG group performed a subsequent trial comparing it to continuous infusion vs bolus 5-FU.¹⁵ Results showed that semustine did not improve local control or survival and was abandoned. Furthermore, the trial demonstrated that continuous infusion 5-FU was superior to bolus 5-FU when given concurrently with pelvic RT, with significantly increased time to relapse ($P = .01$) and improved survival ($P = .005$). The Intergroup Trial 0114 built upon these data and looked more closely at the optimal delivery method of 5-FU.^{16,17} The trial compared two cycles of bolus 5-FU followed by continuous infusion 5-FU and 50.4 Gy RT followed by two additional cycles of bolus 5-FU vs the same concurrent arm preceded and followed by continuous infusion 5-FU vs all arms consisting of bolus 5-FU/leucovorin and levamisole. Results showed that continuous infusion 5-FU is not beneficial during all six cycles, indicating that it is optimally delivered concurrently with pelvic RT. The regimen of choice was bolus 5-FU followed by continuous infusion 5-FU and RT followed by additional bolus 5-FU.

With postoperative adjuvant therapy showing superiority to surgical resection alone, the questions being explored by the National Surgical Adjuvant Breast and Bowel Project (NSABP) group centered on determining the true benefit conferred to the treatment program by inclusion of pelvic RT. Trials thus developed that compared arms with chemotherapy alone to RT alone to determine whether improved outcomes could be achieved in the absence of RT. Over 500 patients were randomized on the NSABP R-01 trial to one of three arms: surgery alone, postoperative RT, or postoperative chemotherapy with semustine/vincristine/5-FU.¹⁸ After 5 years of follow-up, results showed that RT alone decreased locoregional relapse as an initial site of failure compared with surgery alone (25% vs 16%, $P = .06$), but there was no statistically significant improvement in disease-free or overall survival. The next trial, NSABP R-02, compared chemotherapy alone to chemotherapy combined with RT.¹⁹ Results showed that postoperative RT resulted in no beneficial effect on disease-free survival ($P = .90$) or overall survival ($P = .89$), regardless of which chemotherapy regimen was utilized. However, pelvic RT did reduce the cumulative incidence of locoregional relapse from 13% to 8% at 5-year follow-up ($P = .02$). These trials emphasized that although the addition of RT to chemotherapy does not improve survival, it does improve the potential for local control, which avoids the significant morbidity associated with pelvic recurrence.

While optimizing the treatment regimen and rationale for postoperative adjuvant therapy, investigators were also questioning whether preoperative therapy would be even more beneficial. Many reasons were proposed to demonstrate why treatment in the preoperative setting would be more efficacious.^{20,21} First, it would be given to a well-vascularized region that would offer a better radiobiological environment than the hypoxic postoperative tumor bed. Second, the small bowel would be more mobile preoperatively and could be displaced away from the pelvic radiation field by treatment in the prone position with a bellyboard or with bladder distention techniques. This would decrease the potential for acute and late toxicity. Third, treatment would allow the potential for the tumor to be downstaged, which might allow less radical surgery and enhanced chances for sphincter preservation. Fourth, the irradiated segment of large bowel would be surgically removed and replaced with a nonirradiated segment, allowing the potential for improved bowel function.

Preoperative RT: Short Course

In the 1990s, multiple institutions began evaluating the integration of a preoperative RT approach. In Europe, investigators focused on the delivery of a short course of higher-dose RT alone followed in 1 week by resection. The Swedish Rectal Cancer Trial reported improved survival with such an approach in 1997.²² This study randomized 1,168 patients with resectable rectal cancer to surgery alone or to surgery following a 1-week course

of pelvic RT delivering 25 Gy in 5 daily fractions. Results showed that not only was the 5-year local recurrence rate significantly improved with preoperative RT (11% vs 27%, $P < .001$), but also the 5-year survival rate was significantly improved (58% vs 48%, $P = .004$). The external beam RT in this trial was delivered to the whole pelvis with the superior border at L4/5 and inferior border below the anal canal. The study did not treat solely patients with locally advanced disease as there were significant numbers of patients in both arms with Dukes A disease. In addition, the Swedish Rectal Cancer Trial was conducted in the surgical era prior to the adoption of TME, a technique in which the entire covering of the rectum containing its immediately adjacent vessels and nodes is removed en bloc, including the lateral extensions of the perirectal fat.^{23,24} Indeed, MacFarlane et al²⁵ noted that with such sharp dissection around the integral mesentery of the hindgut alone, expected local recurrence rates at 5 years would be in the 5% range.

Once surgical techniques evolved to TME resections, European investigators then asked if preoperative RT would still be beneficial. The Dutch TME trial reported in 2001 showed a higher local recurrence rate with TME alone without preoperative RT.²⁶ In this trial, 1,861 patients were randomized to TME alone or following a short course of preoperative external beam RT delivering 25 Gy in 1 week. A significant benefit was seen with preoperative RT in patients with TNM stage II and III disease, with 2-year local relapse rates decreasing from 5.7% to 1% ($P = .01$) and from 15% to 4.3% ($P < .001$), respectively. The update of the trial reported in 2007 noted a reduction in local relapse from 21% to 11% for stage III patients but no significant reduction for stage II patients, and there continued to be no difference in distant metastases or 5-year overall survival.²⁷ Subgroup analyses showed a significant reduction in local recurrence in patients with nodal involvement, with lesions between 5 and 10 cm from the anal verge, and with uninvolved circumferential margins.

Of those patients undergoing TME alone, the Dutch Colorectal Cancer Group also evaluated the effect of RT on local recurrence rates in patients with different circumferential radial margin (CRM) involvement.²⁸ The importance of measuring the distance from the site of maximal tumor penetration into the bowel wall (outer border of muscularis propria) and the line of surgical excision²⁹ has been shown clinically since lateral spread of tumor correlates with local recurrence.^{30,31} In the Dutch TME study, CRM involvement was a strong predictor of local recurrence.³² A margin of ≤ 2 mm was associated with a local recurrence risk of 16% compared with 5.8% in patients with a wider excision ($P < .0001$). Patients with a margin of ≤ 1 mm had an increased risk of distant metastases (37.6% vs 12.7%, $P < .0001$) as well as shorter survival. Those patients who received TME alone and were found to have CRM involvement of ≤ 1 mm (defined as a positive CRM)

were mandated to receive postoperative RT alone to a dose of 50.4 Gy in 28 fractions, but only 47% received treatment. There was no difference in irradiated vs non-irradiated patients (17.3% vs 15.7%, $P = .98$). Furthermore, although preoperative RT was effective in patients with a narrow CRM (1.1 mm to 2 mm; 0% vs 14.9%, $P = .02$) and a wide CRM (> 2 mm; 0.9% vs 5.8%, $P < .0001$), there was no benefit in patients with positive margins (9.3% vs 16.4%, $P = .08$).

Given the higher local failure rates with a CRM ≤ 2 mm, the question has also been addressed by investigators in the United Kingdom as to whether selective postoperative RT could improve outcomes in this setting. The Medical Research Council trial (MRC CR07) sought to answer this by randomizing 1,350 patients to TME preceded by 25 Gy in 1 week vs TME followed by chemoradiation if the CRM was positive.³³ The selective postoperative RT was a standard pelvic course of 50.4 Gy fractionated over 5.5 weeks with 5-FU chemotherapy delivered concurrently. Overall, the results showed that the rate of local recurrence at 5 years was significantly better in the preoperative RT group (5%) compared with the postoperative RT group (17%) ($P < .001$). In the subgroup analysis of those 193 patients with a positive CRM, however, the local recurrence rates were not statistically different between the two arms (16% preoperative vs 23% postoperative).

In the above two trials, the postoperative dose utilized in the setting of a close or positive CRM was 50.4 Gy at 1.8 Gy per fraction either alone, as in the Dutch TME trial, or with concurrent chemotherapy, as in the MRC trial. The results raised the question of the adequacy of the radiation dose. Allee et al³⁴ reported data from the Massachusetts General Hospital Cancer Center, noting a trend toward a dose response curve for those with microscopic disease when total doses of 60 Gy to 70 Gy could be safely given with the exclusion of small bowel. Schild et al³⁵ reported data from a Mayo Clinic series of 17 patients receiving external beam RT after subtotal resection of rectal carcinoma. Doses of up to 60 Gy were delivered; although the majority of patients experienced local failure, 24% were free of disease for greater than 5 years.

In the Swedish Rectal Cancer Trial and the Dutch TME trial, the interval from the end of pelvic RT to surgical resection was 1 week. The influence of the interval between preoperative treatment to surgery on downstaging and sphincter preservation was investigated in the Lyon R90-01 study.³⁶ In this study, 210 patients were randomized to either surgery within 2 weeks of RT completion or within 6 to 8 weeks. The radiation in this trial was delivered at 3 Gy per fraction for 13 fractions for a total dose of 39 Gy. Results showed that a longer interval between completion of RT and surgery was associated with increased tumor downstaging (26% vs 10.3%, $P = .005$) and clinical tumor response (71.7% vs 53.1%, $P = .007$). There were no significant differences in morbidity, local relapse, or sphincter preservation.

Preoperative RT: Long Course Plus Chemotherapy

Although European investigators pursued preoperative strategies that utilized high-dose pelvic RT alone without chemotherapy, such was not the case in the United States. In the 1990s, data from the Memorial Sloan-Kettering Cancer Center and the M. D. Anderson Cancer Center accumulated to support the benefits of combining a total dose of 50.4 Gy of pelvic RT fractionated over 5.5 weeks in conjunction with concurrent chemotherapy.^{37,38} Results from these small series advocated for an improvement in sphincter preservation rates. Patients with low-lying T2 lesions who would otherwise be offered abdominoperineal resection (APR) were shown to benefit from such therapy as well.³⁹

The German Rectal Cancer Study Group confirmed the efficacy of a preoperative combined modality approach over the traditional strategy of providing subsequent postoperative adjuvant therapy.⁴⁰ In this CAO/ARO/AIO-94 study, 823 patients were randomized to receive either 50.4 Gy delivered to the pelvis with continuous infusion 5-FU during week 1 and week 5 preoperatively or essentially the same regimen postoperatively with the exception of a boost to the tumor bed postoperatively for an additional 5.4 Gy. Although there was no difference in the 5-year overall survival rates between the two arms (76% in the preoperative group vs 74% in the postoperative group, $P = .80$), there was a statistically significant improvement in the 5-year local failure rates from 13% in the postoperative group to 6% in the preoperative group. Preoperative treatment not only was more effective, but also was associated with significantly lower rates of acute toxicity (27% vs 40%, $P = .001$) and late toxicity (14% vs 24%, $P = .01$). The rate of pathologic complete response (pCR) in this trial was 8%, with an improved rate of sphincter preservation in the subset of patients deemed by the surgeon upon initial examination to require an APR for surgical extirpation of disease (39% vs 19%, $P = .004$). Overall, however, there was no significant difference in sphincter preservation with a preoperative approach.

Additional trials have now shown that with longer-course preoperative RT, chemotherapy significantly improves local control, tumor downsizing, and downstaging compared with RT alone. In a study by the Fédération Francophone de Cancérologie Digestive (FFCD 9203), patients with palpable T3/4 tumors were randomized to undergo 45 Gy preoperative RT alone vs 45 Gy in conjunction with 5-FU at 350 mg/m² for 5 days with leucovorin 20 mg/m² during the first and fifth weeks.⁴¹ Both arms underwent surgery 3 to 10 weeks later followed by adjuvant chemotherapy. Of the 733 patients enrolled, the rate of grade 3 or 4 acute toxicity was more frequent with the combined modality therapy (14.6% vs 2.7%, $P < .05$), but patients had higher complete response rates (11.4% vs 3.6%, $P < .05$) and a lower 5-year incidence of local recurrence (8.1% vs 16.5%, $P < .05$). There were no significant differences in sphincter preservation or overall survival.

Similar results were reported in the EORTC 22921 trial.⁴² Over 1,000 patients were entered onto this trial, which randomized patients to the following arms: arm 1, preoperative RT to 45 Gy in 25 fractions; arm 2, preoperative RT plus two 5-day courses of chemotherapy (5-FU 350 mg/m² along with 20 mg/m² leucovorin during the first and fifth weeks); arm 3, preoperative RT plus four postoperative chemotherapy courses; and arm 4, preoperative RT and chemotherapy plus postoperative chemotherapy. After preoperative chemoradiation, tumors were smaller ($P < .0001$), had less advanced pathologic T ($P < .001$) and pathologic N stages ($P < .001$), had smaller numbers of examined nodes ($P = .046$), and less frequent lymphatic/venous/perineural invasion ($P \leq .008$). The 5-year cumulative incidence rates for local recurrences were 8.7%, 9.6%, and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive chemotherapy ($P = .002$).⁴³ For the whole group, adding 5-FU-based chemotherapy either preoperatively or postoperatively to the pelvic RT had no impact on survival. Yet, in contrast, the treatment effect differed between those patients downstaged to T0–2 vs those with residual T3–4 disease with only the T0–2 downstaged patients deriving benefit from the addition of chemotherapy ($P = .011$).⁴⁴ Subsequent analysis of data from over 800 patients on this trial who underwent surgery with no metastases at the time of resection showed that CRM involvement was associated with a higher risk of local relapse and reduced disease-free and overall survival.⁴⁵

The quality of surgery following chemoradiation thus remains an important factor in optimal rectal cancer management. In addition to the involvement of the lateral margin, the plane of surgery achieved has been shown to be an important prognostic factor for local recurrence.⁴⁶ In an analysis by Quirke et al⁴⁶ of 1,156 patients from two randomized trials, 128 patients (11%) had involvement of the CRM, and the plane of surgery achieved was classified as good (mesorectal) in 604 (52%), intermediate (intramesorectal) in 398 (34%), and poor (muscularis propria plane) in 154 (13%). The authors found that both a negative circumferential resection margin and a superior plane of surgery achieved were associated with low local recurrence rates.

Other factors that may increase a patient's risk of local recurrence include increasing body mass index (BMI).⁴⁷ In a cohort of 1,688 patients with stage II and III rectal cancer treated on the Intergroup 0114 trial, obese patients with a BMI of 30.0 kg/m² or higher were more likely to undergo an APR than normal-weight patients. Meyerhardt et al⁴⁷ analyzed the data by sex and noted that increasing adiposity in men was a strong predictor of having an APR ($P < .0001$). Obese men with rectal cancer were more likely than normal weight men to develop a local recurrence. There was no association with obesity and cancer recurrence in women, however, nor did BMI predict overall mortality in either men or women.

To enhance the possibility of long-term local control in T4 cancers, intraoperative RT can be considered

as well. This technique delivers a single high dose of RT at the time of open surgical resection, either with electrons generated by a linear accelerator or with photons generated by a high-dose-rate gamma-emitting radioisotope. This procedure requires close cooperation between the radiation oncologist and the surgeon to ensure maximal irradiation of the designated tumor bed and minimal irradiation of the adjacent normal tissues. Hu and Harrison⁴⁸ note that intraoperative RT does appear to improve outcomes for patients with primary locally advanced and recurrent rectal cancer.

Prospective data comparing the short-course RT alone strategy with the longer-course RT combined with a chemotherapy strategy are pending from the Berlin Cancer Society.⁴⁹ This trial will compare 25 Gy in 5 fractions followed in 5 days by TME vs 50.4 Gy along with continuous infusion 5-FU plus TME 4 to 6 weeks later. Given that similar local control and survival data have been reported for each approach, the data from this trial will help to determine whether one approach may, in fact, be superior.

Prognostic Impact of Downstaging

With the current standard of care thus being to offer preoperative therapy to T3-4 and/or node-positive patients, the effect of downstaging becomes increasingly important. Analysis of data from patients treated preoperatively on the German Rectal Cancer Study has shown that the most important independent prognostic factors on multivariate analysis for disease-free survival are pathologic T category and nodal status after chemoradiation.⁵⁰ On this trial, there was a prospective assessment of tumor response to neoadjuvant treatment using a standardized 5-point tumor regression grading (TRG) as initially described by Dworak et al.⁵¹ TRG was determined by the amount of viable tumor vs fibrosis. TRG 0 was defined as complete absence of fibrosis, whereas TRG 4 showed no viable tumor cells. TRG 1 was defined as a morphologically unaltered tumor mass, with TRG 2 showing regression < 50% and TRG 3 showing regression > 50% with fibrosis outgrowing the mass. Results showed that the 5-year disease-free survival rate after treatment was 86% for TRG 4, 75% for grouped TRG 2+3, and 63% for grouped TRG 0+1 ($P = .006$).

Further analysis was done on data from 40 patients treated neoadjuvantly on the German trial to evaluate the prognostic impact of molecular biomarkers.⁵² Intratumoral levels of thymidylate synthetase (TS), thymidylate phosphorylase (TP), and dihydropyrimidine dehydrogenase (DPD) were assessed and correlated with outcome. Results showed that disease-free and overall survival were significantly increased in patients with downstaging ($P < .001$ and $P = .003$, respectively). All patients who developed cancer recurrence had persistent positive lymph node involvement posttreatment ($P < .001$) or significantly higher TS gene expression ($P = .35$).

In the setting of upfront resection, the current guidelines state that a minimum of 12 lymph nodes is necessary to accurately delineate patients with stage II

colorectal cancers.⁵³ There is considerable variation in the literature because many studies combine patients with colon or rectal cancer together. Tepper et al⁵⁴ reported data from over 1,600 isolated high-risk rectal cancer patients treated on a national intergroup adjuvant therapy trial and indicated that the number of nodes examined was significantly associated with time to relapse and survival among node-negative patients, noting that 14 nodes would need to be evaluated to correctly define nodal status. After preoperative combined modality therapy, the number of retrievable lymph nodes is decreased.⁵⁵ Thus, the number of nodes needed to accurately stage neoadjuvantly treated patients is not currently known. However, recent data suggest that in the neoadjuvant setting, it is not just number of residual nodes that may be prognostic but also their location.⁵⁶ Leibold et al⁵⁶ noted that proximal lymph node involvement is associated with a high risk of metastatic disease at the time of resection. These authors have indicated that the pathologic TNM staging system should incorporate distribution as well as the number of lymph node metastases after preoperative therapy.

The clinical data supporting the importance of the pathologic response to preoperative therapy is abundant. In an evaluation of data from Memorial Sloan-Kettering Cancer Center (MSKCC), Stipa et al⁵⁷ studied outcomes from the prospectively collected institutional database comparing the group of locally advanced rectal cancer patients who achieved a pCR (no viable tumor) with those with no downstaging (no difference between the pre-CMT endoscopic rectal ultrasound stage and the pathologic stage). Results showed a 5-year recurrence-free survival rate of 96% for patients achieving a pCR vs 54% in the no-downstaging group ($P < .00001$). Sphincter preservation rates were higher in the pCR group as well ($P = .01$). Further data from MSKCC has combined pathologic analysis using a regression grading system from 0% to 100%.⁵⁸ Quah et al⁵⁸ reviewed data on 342 consecutive patients and reported a predictive model for disease-free survival that stratified patients by final pathologic T and N classification, with a concordance index of 0.75. Chan et al⁵⁹ reported similar data in the setting of tethered or fixed rectal carcinoma. In this series of 128 patients, survival correlated with pathologic TNM stage. The 5-year relapse-free survival rate was 97% for pCR stage 0, 80% for pCR stage I, 72% for pCR stage II, 42% for pCR stage III, and 0% for pCR stage IV ($P < .000001$). The 5-year local control rate was 98% for pCR T0-2, 89% for pCR T3, and 65% for pCR T4 disease ($P = .00044$). On multivariate analysis, the pCR TNM stage was the most statistically significant predictor of survival ($P = .003$) and relapse-free survival ($P < .001$).

Current Status of Postoperative Therapy and Implications for Preoperative Therapy

After the 1990 National Institutes of Health Consensus Statement, patients with T3, T4, or node-positive disease were categorized as “high risk” and were offered post-

operative adjuvant therapy.¹⁴ More recent analysis has further elucidated risk classification that has important implications for radiation oncology recommendations. Data from two pooled analyses of adjuvant therapy in rectal cancer are instructive in this regard.^{60,61} Results show the independent prognostic significance of N substage within the T classification and of T substage within the N classification. Those patients with the best survival are those with low-risk disease, either T1 or T2N0, who share a 5-year overall survival rate of 90% with a distant relapse rate of 10% and a local relapse rate of $\leq 5\%$. Intermediate-risk categories are essentially those patients who have one high-risk feature: T1N1, T2N1, or T3N0 disease. The 5-year survival rate for this group ranges from 75% to 80%. Within this risk category, further refinements may be possible. Especially low-risk T1–2N1 lesions may be those upper rectal cancers with only one or two nodes involved. For lower-risk T3N0 lesions, data suggest that tumors that are well or moderately well differentiated have invasion of ≤ 2 mm into fat, and no lymphatic or venous vessel invasion may achieve this designation. Those patients with moderately high-risk disease (T4N0, T1N2, T2N2, or T3N1) have 5-year survival rates in the range of 60% to 70%, local relapse rates of 8% to 15%, and distant relapse rates in the range of 26% to 34%. Finally, those patients with truly high-risk disease (T3N2, T4N1, T4N2) have poor outcomes, with 5-year overall survival rates of 30% to 50%, local recurrence rates of 15% to 22%, and distant metastasis rates of 39% to 50%.

These data raise the question whether all patients seen preoperatively with T3N0 or T1–2N1 rectal cancers located in the upper rectum should routinely receive preoperative combined-modality therapy. In the German Rectal Cancer CAO/ARO/AIO-94 trial, 18% of patients on the postoperative arm clinically staged by endoscopic rectal ultrasound (ERUS) as having T3 or N+ cancer were found to have pathologic T1–2N0 disease.⁴⁰ Guillem et al⁶² evaluated 188 patients with ERUS stage T3N0 disease within 12 cm of the anal verge treated at MSKCC with preoperative 5-FU-based combined-modality therapy. The authors reported that despite preoperative therapy, 22% of patients had undetected mesorectal lymph node involvement, concluding that potential overtreatment in this population is still warranted. Kachnic et al⁶³ suggested that patients with ERUS stage T3N0 disease be considered for short-course preoperative RT so that the local control benefit is maintained; if those patients are found to have occult positive nodes, they can still receive postoperative chemotherapy.

Novel Approaches: Integrating New Agents and Techniques

In the setting of better pathologic response to neoadjuvant therapy correlating with improved outcomes, the search to find more active combined modality therapy regimens to be delivered preoperatively has become more important than ever before. With the integration of advanced radiation technologies into clin-

ical practice, strategies to minimize toxicity are being actively pursued. One such technique has been the omission of whole pelvic RT in favor of high-dose short-course internal RT delivered to the tumor and mesorectum only, since whole pelvic RT has been associated with worse functional anorectal outcome and sexual function compared with surgery alone (Figs 1 and 2).^{64,65} Investigators from McGill University have championed the incorporation of high-dose-rate brachytherapy (HDRBT) to deliver a focal dose of 26 Gy in 4 outpatient fractions with a flexible endorectal applicator.⁶⁶⁻⁶⁸ In their phase I/II study, 47 patients with newly diagnosed invasive rectal cancer (stages T2–early T4) were treated with this regimen followed by resection 4 to 8 weeks later.⁶⁹ Results showed a complete clinical response in 68% of patients, with 32% pathologically staged T0N0–1 and 36% with only residual microfoci of carcinoma. Surgical complication rates were not higher following HDRBT. Acute toxicity was limited to a moderate RTOG grade 2 proctitis and 2 patients with tumors extending into the anal canal experiencing grade 3 dermatitis. A multicenter trial randomizing patients between HDRBT and 5-FU-based chemoradiation is planned.

Other strategies have explored ways to integrate additional chemotherapeutic agents. With data showing that the orally active prodrug of 5-FU, capecitabine, is equally efficacious to conventional 5-FU in randomized studies, investigators have incorporated this agent into preoperative schema.^{70,71} The randomized phase II RTOG 0247 trial sought to combine standard pelvic RT

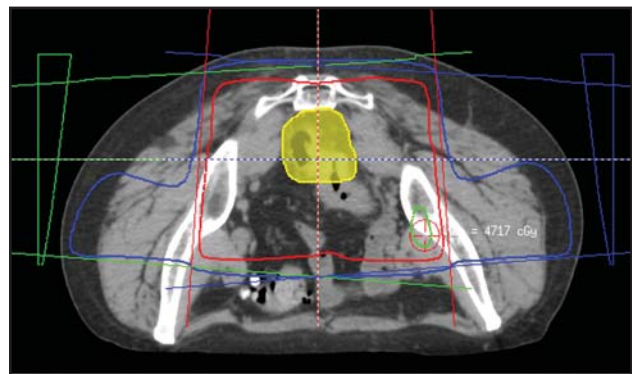


Fig 1. — Standard preoperative RT: posteroanterior and laterals in prone position.



Fig 2. — Endorectal brachytherapy with fiducial markers (arrows) placed endoscopically to delineate the extent of tumor.

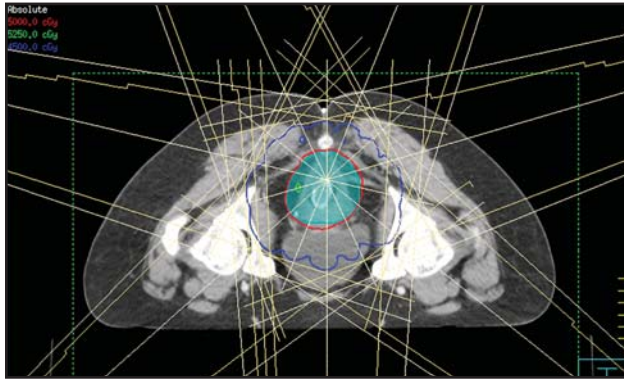


Fig 3. — Axial image displaying seven-beam intensity-modulated RT plan for postoperative patient to spare small bowel and femoral heads.

with capecitabine and either irinotecan or oxaliplatin. In this trial, however, the investigators noted unexpectedly high rates of grade 3–4 nonhematologic toxicity in both arms that was mostly gastrointestinal in nature. This temporarily suspended accrual to the trial, reopening only when the doses of capecitabine and oxaliplatin were lowered. The small bowel is considered to have a 5% risk of complications at 5 years with 45 to 50 Gy.^{72,73} Radiation oncologists have thus sought ways to lower the amount of small bowel irradiated. Gallagher et al⁷⁴ have shown that the absolute volume of small bowel receiving 45 Gy or higher is predictive of late toxicity. Baglan et al⁷⁵ have shown that the volume of small bowel receiving 15 Gy or greater is also an important constraint and is related to development of grade 3+ acute small bowel toxicity. Intensity-modulated RT (IMRT) is a potential solution; in this technique, the radiation beam is subdivided into individual beamlets so that the delivered dose can be maximized to target regions and minimized in nontarget regions (Fig 3). Guerrero Urbano et al⁷⁶ have shown reduction in the volume of small bowel receiving 45 Gy by 64% compared with 3D conformal RT alone.⁷⁶ This work has paved the way for the RTOG to proceed with their

current phase II trial (RTOG 0822) that combines capecitabine (825 mg/m² b.i.d. on RT days), oxaliplatin (50 mg/m² weekly), and RT delivered with IMRT for the first 45 Gy and then a 3D conformal boost to 50.4 Gy. Surgery will be performed 4 to 8 weeks later followed by adjuvant FOLFOX chemotherapy. The RTOG has developed clinical target volumes for radiation planning with an atlas for the purpose of reproducibly generating treatment volumes.⁷⁷

The question of whether radiation can be safely intensified with IMRT has been explored. Freedman et al⁷⁸ reported phase I data evaluating T3–4 and/or N1–2 patients treated with capecitabine 825 mg/m² 7 days a week along with IMRT delivering a simultaneous integrated boost. With this advanced technique, commonly referred to as dose painting (Fig 4),⁷⁹ the whole pelvic elective targets are comprehensively irradiated to a lower dose while the gross disease target receives a higher daily dose. In this study, the whole pelvis received 45 Gy in 25 fractions while the gross tumor volume plus 2 cm would receive 55 Gy with planned escalation in 5 Gy increments. This study was discontinued because of a 38% rate of grade 3 toxicity. Of the patients who were treated, none had a complete response. However, De Ridder et al⁸⁰ reported no excessive toxicity in a phase II study utilizing a helical tomotherapy technique alone without chemotherapy with a similar simultaneous integrated boost to a total of 55.2 Gy that was given to patients with a CRM < 2 mm on MRI. With the TomoTherapy Hi-Art System (Tomotherapy, Inc, Madison, WI), patients are positioned using image-guided RT so that prior to each treatment, a megavoltage CT is generated on the treatment unit and shifted accordingly. In this study of 24 patients, only 1 developed grade 3 enteritis, and the metabolic response rate was 77% in the boost group. A metabolic response was defined as a decrease in the standardized uptake value (SUV) max > 36% since this has been shown to correlate with histopathologic response (Fig 5).⁸¹

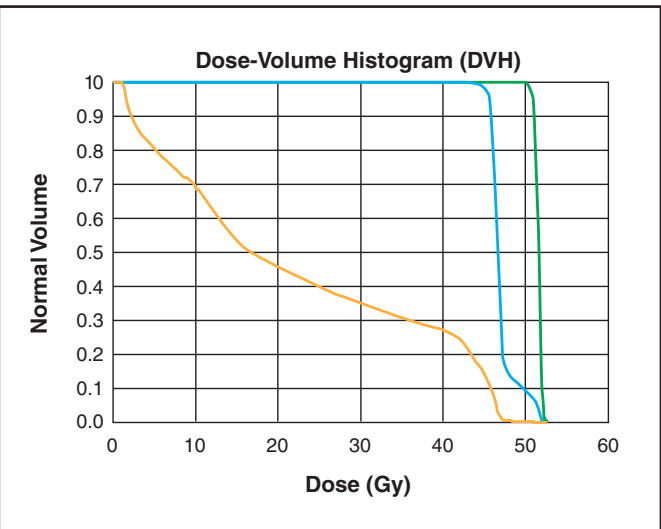
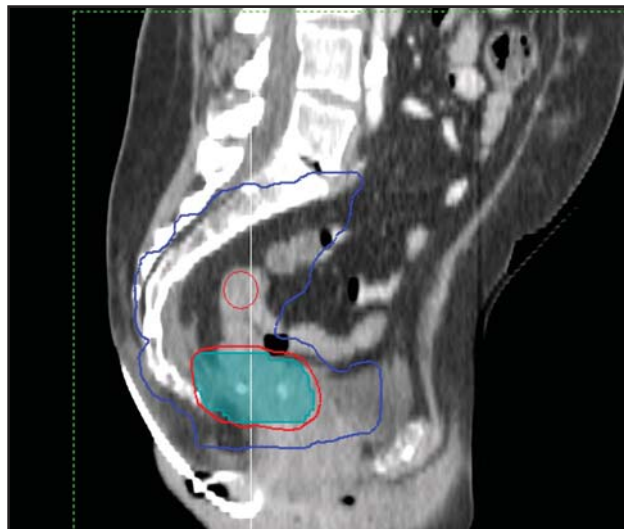


Fig 4. — Sagittal image displaying dose painting with tumor bed receiving 50 Gy (red) while surrounding region at risk receives 45 Gy (blue). Note on the dose-volume histogram that small bowel dose (orange) decreases while targets (blue, green) receive full dose.

Additional strategies have been developed to incorporate other novel agents such as bevacizumab. Willett et al⁸² recently reported results of a multidisciplinary phase II study in patients with locally advanced rectal cancer and evaluated potential biomarkers for response. In this trial, 32 patients were treated with four cycles of therapy: (1) bevacizumab infusion on day 1 of each cycle, (2) 5-FU infusion 225 mg/m²/24 hours during cycles 2–4, (3) external beam RT consisting of 50.4 Gy over 5.5 weeks, and (4) surgery 7 to 10 weeks later. In all patients, pathologic examination revealed either no cancer or varying numbers of scattered cancer cells in a bed of fibrosis at the primary site. The actuarial 5-year local control and survival rates were 100%, with an actuarial 5-year disease-free survival rate of 75% (5 patients developed metastases postsurgery). There were no grade 4 or 5 toxicities with this regimen. Plasma vascular endothelial growth factor receptor (VEGF), placenta-derived growth factor (PlGF), plasma vascular endothelial growth factor 1 (VEGFR1), and interleukin-6 (IL-6) as well as circulating endothelial cells showed correlation with outcome and were believed to be candidate biomarkers for this regimen.

Conclusions

Preoperative 5-FU-based combined modality therapy remains the standard of care in the United States. Outcomes are clearly improved for those patients who experience favorable downstaging of their disease. Future strategies center on increasing the pathologic response rate by combining advanced radiation strategies with novel radiosensitizers. Hopefully these strategies will cul-

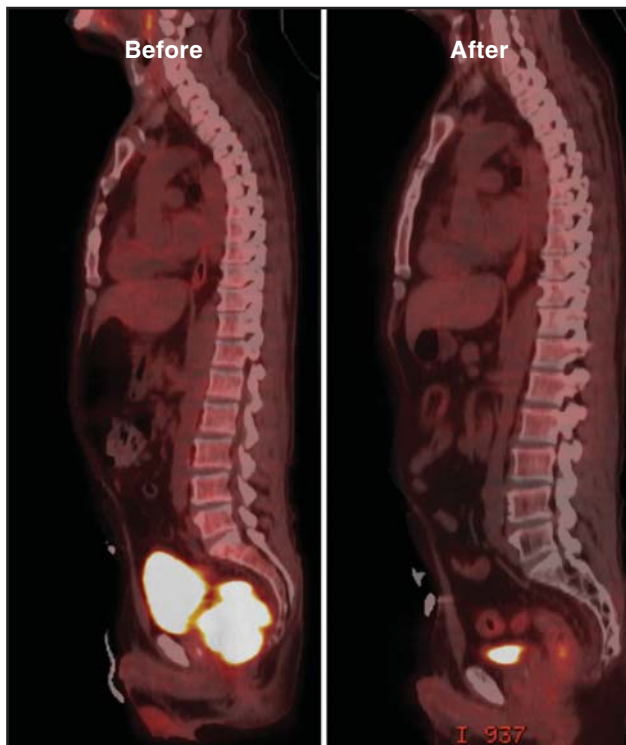


Fig 5. — PET CT showing excellent response to preoperative chemoradiation with near complete resolution of uptake of tumor posterior to the bladder.

minate in better cure rates with reduced short- and long-term toxicity. Omission of the traditional whole pelvic RT field and treatment of the rectum/mesorectum alone in the neoadjuvant setting warrants further investigation.

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