Adjuvant Therapy for Rectal Cancer

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ABSTRACT

Patients with stage II and III rectal cancer benefit from a multidisciplinary approach to treatment. Studies of postoperative adjuvant therapy consistently demonstrate decreases in locoregional recurrence with the use of radiation therapy. The use of postoperative chemotherapy results in improved disease-free survival and overall survival in certain studies. Preoperative radiation therapy decreases locoregional recurrence and in one study demonstrated an improvement in survival. The addition of chemotherapy to preoperative radiation results in improved locoregional control, but not survival. Preoperative chemoradiation is the standard of care for patients with clinical stage II and III rectal cancer in the United States due to improved local recurrence, acute and late toxicity, and sphincter preservation compared with postoperative chemoradiation. Promising approaches include the incorporation of new chemotherapeutic and biologic agents into chemoradiation and adjuvant chemotherapy regimens; new radiation techniques, such as the use of intraoperative radiation therapy and an accelerated concomitant radiation boost; and gene and protein expression profiling, to better predict response to treatment and prognosis.

KEYWORDS: Rectal cancer, radiation, chemotherapy, adjuvant, review

Objectives: Upon completion of this article, the reader should be able to: (1) summarize the role of preoperative radiotherapy in oncological outcomes and sphincter preservation in rectal cancer; (2) discuss the benefits of preoperative chemoradiation compared with postoperative chemoradiation; and (3) describe a predictive assay for response to preoperative chemoradiotherapy.

In 2007, an estimated 41,420 new cases of rectal cancer will be diagnosed.¹ Although biologically similar to colon cancer, rectal cancer poses unique challenges due to its location within the pelvis and proximity to the anal sphincter, which limit the extent of surgical resection. Total mesorectal excision (TME) results in low rates of local recurrence of less than 10% for patients with stage II and III rectal cancers.^{2,3} Minimizing the risk of local recurrence is especially important in rectal cancer due to the morbidity that can result from a local recurrence, such as pain, bleeding, and obstruction. Even with expert TME, the rate of distant recurrence was 18% in stage II patients and 37% in stage III patients in one

large series.³ Adjuvant chemotherapy and radiation therapy have demonstrated improvement in disease-free survival (DFS) and overall survival (OS) of patients with stage II and III rectal cancer, which will be the focus of this article.

POSTOPERATIVE THERAPY

In 1975, a Gastrointestinal Tumor Study Group trial randomly assigned patients with Dukes B and C rectal cancer who had undergone curative surgery to one of four arms: observation, postoperative chemotherapy with 5-fluorouracil (5-FU) and semustine for 18 months,

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postoperative radiotherapy (4500 to 4800 rad), or postoperative chemoradiation followed by chemotherapy (4000 to 4400 rad; 5-FU during the first and last 3 days of radiation, then 5-FU and semustine as in the chemotherapy-alone arm).⁴ Recurrence rates were 55% with observation, 46% with chemotherapy, 48% with radiation therapy, and 33% with combined modality treatment. A proportional hazards analysis revealed a statistically significant difference between the arms ($p=0.04$), which was greatest between the control patients and patients assigned to combined modality treatment ($p=0.009$). At the time of analysis, 64% of patients in the control arm had died, as compared with 54% of patients treated with chemotherapy, 54% of patients treated with radiation therapy, and 44% of patients treated with combined modality treatment. The differences in survival were not statistically significant, but the study had only 30% power to detect a 50% improvement in survival.

The North Central Cancer Treatment Group's (NCCTG) protocol 79-47-51 was designed to evaluate a shorter chemotherapy regimen in combination with a higher dose of radiation in comparison to the same higher-dose radiation regimen.⁵ The NCCTG study randomly assigned 204 patients to receive postoperative radiation therapy or postoperative radiation therapy combined with semustine and 5-FU chemotherapy. This study used a radiation dose of 45 Gy plus a 5.4 Gy boost. Patients assigned to chemotherapy plus radiation began treatment with two cycles of chemotherapy followed by radiation therapy, beginning on day 64, followed by two more cycles of chemotherapy. Radiation therapy was given in the same manner and dose as for patients treated with radiation alone. After a median follow-up time of over 7 years, the estimated 5-year recurrence rate in the radiation arm was 62.7% compared with 41.5% in the combination therapy arm. The time to recurrence was significantly increased by combination therapy ($p=0.0025$). The addition of chemotherapy to radiation therapy resulted in a relative reduction in local recurrence by 46% and also a relative reduction in distant metastases by 37%. Survival was also significantly improved by the addition of chemotherapy to radiation therapy ($p=0.025$ using a proportional hazards model). The death rate was reduced by 29% in the combination therapy arm (95% confidence interval = 7 to 45%). Combination therapy was more toxic than radiation alone and resulted in an increased incidence of nausea, vomiting, diarrhea, stomatitis, leukopenia, and thrombocytopenia. There was no significant increase in delayed toxicity with the addition of chemotherapy to radiation therapy.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 study randomly assigned 574 patients who had undergone curative resection of Dukes B and C rectal cancer to (1) no further treatment;

(2) postoperative radiation therapy; and (3) postoperative chemotherapy consisting of semustine, vincristine, and 5-FU (MOF).⁶ Chemotherapy was administered every 10 weeks for eight cycles or until disease progression. Radiation therapy was administered at a dose of 46 to 47 Gy or 51 to 53 Gy for patients receiving a perineal boost. Postoperative chemotherapy resulted in improved DFS ($p=0.006$) with the cumulative odds at 5 years comparing the disease-free interval in the chemotherapy group with the disease-free interval in the control group being 1.50 (95% confidence interval = 1.13, 1.99). There was an improvement in OS of borderline significance ($p=0.05$) with the cumulative odds at 5 years comparing survival times in the chemotherapy group to those of the control group being 1.30 (95% confidence interval = 0.95, 1.79). Of note is that the benefit of chemotherapy in prolonging DFS and OS was limited to men. Women had no improvement in DFS with chemotherapy and experienced worse OS with chemotherapy (cumulative odds of survival = 0.64 with chemotherapy) despite there being no deaths associated with the chemotherapy administered. Postoperative radiation therapy resulted in decreased local regional failure of 16 versus 25% in the control group and 21% in the chemotherapy group ($p=0.06$ for the comparison with the control group). There was no significant benefit of radiation on DFS or OS.

These studies led to a consensus statement that was issued by the National Institutes of Health in 1990 that concluded that postoperative chemotherapy and radiation improved local control and survival in patients with stage II and III rectal cancer.⁷ The NSABP R-02 study sought to determine if the addition of radiation to chemotherapy was superior to chemotherapy alone as adjuvant therapy of Dukes B and C rectal cancer.⁸ Male patients were randomly assigned to one of four postoperative treatment groups: (1) 5-FU plus leucovorin (LV), (2) 5-FU plus LV plus radiation, (3) MOF chemotherapy, and (4) MOF chemotherapy plus radiation. Female patients were randomly assigned to 5-FU plus LV or 5-FU plus LV plus radiation. The MOF chemotherapy was given for five cycles instead of the eight cycles prescribed in NSABP R-01. Patients assigned to treatment with 5-FU and LV were to receive six cycles of therapy, each consisting of 6 weekly intravenous doses of 5-FU and LV followed by 2 weeks with no treatment. The chemotherapy during radiation therapy for both combined modality arms consisted of bolus infusions of 5-FU during the first 3 and last 3 days of radiation therapy. The total radiation dose was 45 Gy plus a 5.4 Gy boost. The addition of radiation therapy to chemotherapy reduced the cumulative incidence of locoregional recurrence, with a relative risk of 0.57 (95% confidence interval = 0.36 to 0.92), and the absolute risk of locoregional recurrence was reduced by 5%. Radiation therapy was not

associated with improved relapse-free survival (RFS), DFS, or OS when added to chemotherapy. Men treated with 5-FU plus LV compared with MOF experienced significantly better RFS (61% compared with 55% at 5 years) and DFS (55% compared with 47% at 5 years), but not OS (65% compared with 62% at 5 years). On each regimen, nearly 40% of patients experienced a severe toxicity. The efficacy results of NSABP R-02 supported the results of the earlier NSABP R-01 study, in which postoperative radiation therapy resulted in decreased locoregional recurrence, but not in improved DFS or OS.

PREOPERATIVE VERSUS POSTOPERATIVE ADJUVANT THERAPY IN RECTAL CANCER

Interest in preoperative therapy developed because of several potential advantages of preoperative therapy over postoperative approaches. First, preoperative therapy permits better identification of the tumor resulting in less radiation administered to normal tissues. Second, tissue oxygenation has been shown to be impaired in the postoperative tumor bed and tissue hypoxia, at least in part, is thought to result in relative radioresistance.^{9,10} Third, the response to preoperative therapy can be assessed pathologically, which may guide postoperative adjuvant therapy. Fourth, downstaging following preoperative therapy may increase the rate of sphincter preservation and complete resection. Postoperative therapy has an advantage in that pathological stage can be used to avoid unnecessary treatment of stage I patients, which might occur with preoperative therapy even with the use of endorectal ultrasound and magnetic resonance imaging (MRI).

Several clinical trials established the effectiveness of preoperative radiotherapy for rectal cancer.^{11–18} These studies consistently showed decreased local failure with preoperative radiotherapy using various radiation dose fractionation regimens, as compared with surgery alone. Adding preoperative radiotherapy resulted in a ~50% reduction of local failure. A seminal trial, the Swedish Rectal Cancer Trial, was specifically designed to examine OS in addition to local control, and showed improved OS using preoperative radiotherapy compared with surgery alone.^{19,20} During the same time (1980s to 1990s), a recognition of distal cancer spread in the mesorectum guided surgeons to perform TME.²¹ A review of 51 surgical series showed that TME reduced the median local recurrence rate from 18.5 to 7.1%.²² Based on the hypothesis that preoperative radiotherapy further decreases local failure in patients treated with TME, the Dutch Colorectal Cancer Group conducted a randomized trial of this hypothesis during the 1990s.² This trial demonstrated the efficacy of preoperative radiotherapy on local control combined with TME, but it did not improve 2-year OS.

A direct comparison of pre- and postoperative radiotherapy was first performed without concurrent chemotherapy.²³ Preoperative accelerated radiotherapy of 25.5 Gy/5 fractions showed better local control than conventional fractionated postoperative radiotherapy of 60 Gy.

Two randomized studies in the United States sought to compare preoperative chemoradiation with postoperative chemoradiation for the treatment of clinical stage II and III rectal cancer. The Intergroup 0147 study closed early due to poor accrual. The NSABP R-03 study also closed early due to poor accrual, but results have been presented with a median 7.8 years of follow-up.²⁴ Patients assigned to preoperative therapy received one cycle of 5-FU and LV administered weekly for 6 weeks followed by 2 weeks with no treatment. Radiation therapy was administered after cycle 1 and included 5 days of daily 5-FU and LV during the first and fifth weeks of radiation. After radiation, patients underwent surgery followed by four more cycles of chemotherapy were administered as per cycle 1. Patients assigned to postoperative chemoradiation received the same schedule and dose of therapy as per the preoperative group. There was a trend toward improved DFS with preoperative therapy compared with postoperative therapy (64% compared with 52%, $p = 0.08$). There was also a trend toward improved OS with preoperative therapy (74% compared with 66%, $p = 0.14$).

The best comparison of preoperative and postoperative chemoradiation comes from the German Rectal Cancer Study Group trial (CAO/ARO/AIO-94).²⁵ Patients with resectable histologically confirmed adenocarcinoma located within 16 cm of the anal verge that clinically appeared to be stage II or III were randomly assigned to preoperative or postoperative chemoradiation. All patients received postoperative chemotherapy. This study utilized endorectal ultrasound and computed tomography (CT) scanning to stage patients clinically. Surgeons were asked to state whether sphincter preservation was considered possible or not before randomization. The study mandated that a TME be performed according to standardized technique. Chemoradiation consisted of 50.4 Gy delivered in 28 fractions with 5-FU administered as a 120-hour infusion during weeks 1 and 5 of radiation. Patients receiving postoperative radiation therapy also received a 5.4 Gy boost to the tumor bed. Four cycles of bolus 5-FU administered daily for 5 days every 28 days began 5 weeks after surgery in the preoperative group or 4 weeks after chemoradiation in the postoperative group. Eighteen percent of patients in the postoperative group were found to have pathologic stage I disease, raising the concern that a similar percentage of patients in the preoperative group may have received chemoradiation inappropriately. Preoperative chemoradiation was associated with a decreased rate of local recurrence of 6% compared with 13% in patients

treated with postoperative chemoradiation ($p=0.006$). Among the 194 patients with tumors deemed before randomization to require an abdominoperineal resection, 39% of those treated with preoperative chemoradiation underwent sphincter-preserving surgery compared with 19% of those treated with postoperative radiation therapy ($p=0.004$). Grade 3 and 4 (severe) toxicities occurred at a significantly lower rate in patients treated with preoperative chemoradiation compared with patients treated with postoperative chemoradiation. Only 54% and 50% of patients assigned to postoperative therapy received the full dose of radiation and chemotherapy, respectively, compared with 92% and 89% of patients assigned to preoperative therapy. There was no difference in DFS or OS in the comparison of preoperative with postoperative chemoradiation. Findings from this study have led to preoperative chemoradiation becoming the new standard of care for patients with clinical stage II and III rectal cancer in the United States.

CHEMOTHERAPY IN COMBINATION WITH PREOPERATIVE RADIATION

In 1993, the European Organization for Research and Treatment of Cancer (EORTC) initiated a trial to evaluate whether preoperative chemoradiation would improve survival compared with preoperative radiation therapy and whether postoperative chemotherapy would improve survival compared with no postoperative chemotherapy.²⁶ Eligible patients had clinical T3 or T4 tumors without evidence of metastases. Patients were randomly assigned to one of four treatment arms: (1) preoperative radiation (standard group), (2) preoperative chemoradiation, (3) preoperative radiation and postoperative chemotherapy, and (4) preoperative chemoradiation and postoperative chemotherapy. Total mesorectal excision was recommended beginning in 1999. Radiotherapy consisted of 45 Gy delivered in 25 fractions over 5 weeks. Preoperative chemotherapy consisted of bolus 5-FU and LV given daily for 5 days during the first and fifth weeks of radiation. Postoperative chemotherapy using the same regimen and doses was administered every 3 weeks for four courses beginning 3 to 10 weeks after surgery. There was no difference in 5-year OS between the two groups treated with preoperative radiation therapy and the two groups treated with preoperative chemoradiation therapy. The 5-year OS was 63.2% in the two groups assigned to no postoperative chemotherapy and 67.2% in the two groups assigned to postoperative chemotherapy ($p=0.12$). The HR for death in the postoperative chemotherapy groups was 0.85 (95% CI=0.68 to 1.04). The 5-year DFS did not differ between the two groups treated with preoperative radiation therapy and the two groups treated with preoperative chemoradiation. The two groups treated with postoperative chemotherapy had a 5-year DFS rate of

58.2% compared with the 52.2% DFS in the two groups that were not assigned to postoperative chemotherapy. Local recurrences were 17.1% in the preoperative radiation alone group, 8.7% in the preoperative chemoradiation group, 9.6% in the preoperative radiation plus postoperative chemotherapy group, and 7.6% in the preoperative chemoradiation plus postoperative chemotherapy group ($p=0.002$ for the preoperative radiation therapy group compared with the other groups). The pathologic tumor stage and nodal status was significantly improved with the addition of preoperative chemotherapy, but preoperative chemotherapy did not significantly increase the rate of sphincter-sparing surgery. Although this study did not demonstrate a survival advantage for the use of preoperative or postoperative chemotherapy, longer follow-up than the median 5.4 years is necessary, as the survival curves diverged after 4 years. The study was not powered to detect an improvement in survival of < 10%. Over 25% of patients assigned to receive postoperative chemotherapy did not receive any postoperative treatment, suggesting a potential role for preoperative chemotherapy.

The Federation Francophone de Cancerologie Digestive 9203 study was a randomized trial of preoperative radiation (45 Gy) with or without concomitant bolus 5-FU/LV chemotherapy followed by resection and then four cycles of 5-FU/LV chemotherapy.²⁷ The addition of chemotherapy to radiation significantly increased the rate of severe acute toxicity from 3 to 15% ($p<0.05$), but also increased the pathologic complete response (pCR) rate from 3.7 to 11.7% ($p<0.05$). Similar to the EORTC trial discussed above, the local recurrence rate was decreased with chemotherapy from 16.5 to 8%. There was no improvement in sphincter-sparing surgery.

A Polish randomized trial compared short-course preoperative radiation (25 Gy in 5 fractions) to chemoradiation with a 50.4 Gy dose and two concomitant courses of bolus 5-FU/LV chemotherapy, both followed by TME.^{28,29} Significant downstaging of the primary tumor and nodal disease was observed, but there was no difference in sphincter-sparing surgery, local recurrence, or survival. Early toxicity was significantly increased with the addition of chemotherapy to radiation.

SPHINCTER PRESERVATION AS AN ENDPOINT OF PREOPERATIVE TREATMENT IN RECTAL CANCER

Based on the hypothesis that a longer interval between radiotherapy and surgery results in more downstaging and an improved sphincter preservation rate, French investigators conducted the Lyon R90-01 trial, which used accelerated hypofractionation 39 Gy administered in 13 fractions. They then randomized patients to a < 2 weeks (SI) or a 6 to 8 weeks (LI) interval between the

end of radiotherapy and surgery. There was a non-significant trend toward greater sphincteric preservation with the LI arm, but no difference in adverse normal tissue effects nor oncologic outcomes.^{30,31} Stein et al³² further examined the effect of a longer interval (10 to 14 weeks) compared with a shorter (4 to 8 weeks) interval between preoperative treatment and surgery. No improvement was, however, found in tumor response rates with the longer interval.

The Lyon 96-02 trial tested the role of a brachytherapy boost dose using a contact X-ray unit prior to surgery to assess any impact on local control and sphincter preservation.³³ This randomized study compared 39 Gy administered in 13 fractions of external beam radiotherapy with or without a contact X-ray boost to 85 Gy administered in 3 fractions. The brachytherapy boost improved the complete clinical response rate (24 versus 2%; $p < 0.05$) and sphincter preservation rate (76 versus 44%; $p = 0.004$).

In the studies discussed previously, preoperative chemoradiation improved the rate of sphincter-sparing surgery compared with postoperative chemoradiation, but the addition of chemotherapy to preoperative radiation did not improve the rate of sphincter-sparing surgery.²⁵⁻²⁹ In general, standard preoperative treatment over 5 to 6 weeks has been shown to result in greater tumor responses and tumor downstaging compared with short-course preoperative treatment (1 to 2 weeks) followed by immediate surgery, although this has not resulted in an increased rate of sphincter preservation.^{34,35} In patients with low clinical stage II and III rectal cancer, standard preoperative combined modality therapy with an appropriate interval (4 to 5 weeks) before surgery may increase the chance of sphincter preservation.

ESTABLISHING THE OPTIMAL PREOPERATIVE RADIATION REGIMEN: RADIATION DOSE ESCALATION/ALTERED FRACTIONATION REGIMEN

By analyzing the various radiation dose regimens used in randomized trials testing pre- or postoperative radiotherapy, Glimelius et al³⁶ demonstrated a clear dose-response effect on improving local tumor control. To further improve tumor response and local control, multiple phase II studies and retrospective analyses were conducted using alternative dose escalation and intensification schedules. Mohiuddin et al³⁷ compared the pCR rates in patients receiving low-dose (≤ 50 Gy) versus high dose (≥ 55 Gy) preoperative radiotherapy as well as bolus infusion versus continuous infusion (CI) 5-FU. Overall, a pCR was observed in 2 of 21 (10%) patients treated with bolus 5-FU as compared with 8 of 12 (67%) for patients treated with CI ($p = 0.002$). A pCR was observed in 8 of 18 (44%)

patients receiving a radiation dose > 55 Gy as compared with 2 of 15 (13%) patients treated to a dose < 50 Gy ($p = 0.05$). In this nonrandomized series, the authors concluded that dose intensity of 5-FU and radiation dose correlate significantly with the likelihood of achieving a pCR. However, because all patients in the low-dose radiation group received bolus 5-FU and 12 of 18 patients in the high-dose radiation group received CI 5-FU, it is difficult to know which contributed to the favorable result—the mode of 5-FU administration or radiation dose. One small phase II trial tested a hyperfractionated boost following 45 Gy of conventional fractionation radiotherapy to the pelvis with CI 5-FU.³⁸ The hyperfractionated boost consisted of 1.2 Gy given twice daily for 7 days at the total dose of 61.8 Gy. Ten of 20 (50%) patients with T4 or large T3 had evidence of clinical downstaging and 5 patients (25%) had $\geq 90\%$ fibrosis in the resected specimen. In this small series, the 4-year OS, DFS, and local control rates were 64%, 62%, and 84%, respectively.

Accelerated hyperfractionated radiotherapy shortens overall treatment time and has theoretical radiobiological benefits against rapid tumor repopulation during treatments. Clinical benefit from accelerated hyperfractionation has been demonstrated in head and neck cancer as well as small cell lung cancer. Coucke et al³⁹ conducted a small phase II trial of accelerated hyperfractionated radiotherapy alone in patients with UICC stages II and III rectal cancer. The patients were treated to a total dose of 41.6 Gy, delivered in 2.5 weeks at 1.6 Gy per fraction twice daily with a 6-hour interfraction interval. Surgery was performed within 1 week after the end of irradiation. Theoretical calculations using a linear quadratic model yielded a potential benefit of 13 to 29% in tumor cell kill compared with conventional fractionated radiotherapy. The 5-year local control, freedom from relapse, and OS rates were 91.7%, 71.5%, and 59.6%, respectively. Downstaging was observed in 38% of the tumors. This approach may also have another potential advantage with respect to reduced late complications over an accelerated hypofractionated regimen (5 Gy $\times$ 5 fractions), where significant long-term side effects were reported compared with surgery alone.^{40,41} An accelerated concomitant radiation boost was also tested to intensify a standard preoperative combined modality regimen by investigators at M.D. Anderson Cancer Center in Houston, Texas. Concomitant boost 7.5 Gy in 5 fractions was given with a 6-hour interval on the last week of pelvic radiotherapy (45 Gy/25 fractions/5 weeks) with CI 5-FU chemotherapy.⁴² Compared with a historical control with their conventional preoperative combined modality regimen, improvements were seen in the sphincter preservation rate (79 versus 59%; $p = 0.02$), and downstaging (86 versus 62%; $p = 0.003$).

Intraoperative radiotherapy (IORT) has been mainly utilized for locally recurrent rectal cancers in previously irradiated patients where it appears to be of benefit when combined with surgery for these poor prognosis patients.⁴³ Reports of IORT as a part of the initial combined modality therapy are rare. Calvo et al⁴⁴ reported the outcome of 100 locally advanced rectal cancer patients who were treated with IORT (10 to 15 Gy) following preoperative chemoradiotherapy (40 to 50 Gy). Three patients developed pelvic recurrence as the only site of initial failure, and distant metastasis was observed in 14 patients. The 4-year local control, DFS, and OS rates were 94, 75, and 65%, respectively. Ferenschild et al⁴⁵ used intraoperative high-dose-rate brachytherapy for patients with < 2 mm circumferential margin on frozen sections. Preoperative chemoradiotherapy was given to 123 patients, of which 27 patients received IORT due to close/positive margin. Intraoperative radiotherapy improved rates of 5-year local control (58 versus 0%, $p = 0.016$) and OS (38 versus 0%, $p = 0.026$) for patients with R1/2 resections. However, IORT did not change the local control and survival outcome in patients with R0 resections with close margin (< 2 mm). A large single dose of IORT might have a potential advantage in tumors resistant to conventional radiotherapy. Clearly, further studies are still needed to confirm this hypothesis.

ESTABLISHING THE OPTIMAL CHEMOTHERAPY FOR CHEMORADIATION

Intergroup study 864751 was initiated in 1986 to evaluate whether infusional 5-fluorouracil would be superior to bolus 5-fluorouracil during radiation therapy.⁴⁶ In vitro data had demonstrated maximal cytotoxicity when tumor cells were exposed to 5-fluorouracil for 24 to 48 hours after irradiation.⁴⁷ Given the short half-life of 5-fluorouracil, an infusional regimen compared with a bolus regimen would lead to prolonged exposure of tumor cells to 5-fluorouracil. This study randomly assigned patients with completely resected stage II or III rectal cancer to one of four treatment arms: (1) chemotherapy with fluorouracil and semustine, plus radiation therapy with concurrent bolus 5-FU; (2) chemotherapy with 5-FU and semustine, plus radiation therapy and CI 5-FU; (3) chemotherapy with 5-FU plus radiation therapy with concurrent bolus injection of 5-FU; and (4) chemotherapy with 5-FU, plus radiation therapy with concurrent CI 5-FU. After 445 eligible patients had been entered on study, an interim analysis found no improvement in DFS or OS with the addition of semustine, and the last 215 patients were randomized to the 5-FU-only treatment arms. Patients who received CI 5-FU experienced a significant decrease in overall tumor relapse (37% compared with 47%, $p = 0.01$), distant metastases (31% compared with 40%, $p = 0.03$),

but not local tumor recurrence ($p = 0.11$). The decrease in distant metastases observed suggested that administration of 5-FU by continuous infusion is more effective against micrometastases. Time-to-relapse ($p = 0.01$) and survival ($p = 0.005$) were also improved for patients receiving CI 5-FU compared with bolus 5-FU. These improvements in time-to-relapse and survival may have been due to the prolonged exposure of tumor cells to 5-FU with a continuous infusion or may reflect the higher dose of 5-FU that could be administered as a continuous infusion compared with bolus injection (6546 mg/m² compared with 2499 mg/m²). Diarrhea was significantly increased with CI 5-FU, whereas severe leukopenia was significantly increased by bolus administration of 5-FU. Results from this study led to the use of CI 5-FU concurrently with radiation as a standard of care for adjuvant therapy of rectal cancer.

Studies in advanced colorectal cancer and adjuvant therapy for colon cancer had demonstrated enhanced efficacy of bolus 5-FU when administered with LV. LV stabilizes the binding of 5-FU with thymidylate synthase, thus inhibiting the formation of thymidylate, which is necessary for DNA synthesis.⁴⁸⁻⁵¹ Studies of adjuvant therapy of colon cancer had also demonstrated the efficacy of 5-FU and levamisole, an anthelmintic considered to have immunomodulatory properties.⁵²⁻⁵⁴ Based on these findings, but before the results of its earlier trial comparing bolus 5-FU with CI 5-FU were available, the Intergroup conducted a prospective, randomized trial of postoperative radiation therapy combined with either bolus 5-FU, bolus 5-FU plus levamisole, bolus 5-FU plus leucovorin, or bolus 5-FU plus LV and levamisole in patients with stage II and III rectal cancer, who had undergone potentially curative resections.⁵⁵ In all arms, systemic chemotherapy was administered for two 28-day cycles, followed by radiation therapy (50.4 to 54 Gy) with chemotherapy administered during weeks 1 and 5, followed by two more 28-day cycles of systemic chemotherapy. There was no statistically significant difference in DFS or OS between any of the four treatment arms. The local failure rate was 11% for the entire patient population. The LV-containing arms resulted in statistically significantly increased diarrhea and anorexia, $p < 0.002$, whereas the 5-FU alone arm resulted in statistically significantly increased granulocytopenia ($p < 0.01$). The most toxic arm was the combination of 5-FU, LV, and levamisole, leading the authors to conclude that there was no role for this therapy outside of a clinical trial. Of note is that the DFS at 3 years in the 5-FU and LV arm was 68%, similar to the 4-year DFS of 63% noted in the Intergroup study comparing bolus to CI 5-FU.⁵⁶

The Intergroup 0144 study was a randomized, phase III trial of 5-FU-based chemotherapy regimens plus radiotherapy as postoperative treatment of rectal cancer.⁵⁷ Patients with completely resected rectal cancer

were assigned to one of three treatment arms: (1) Two cycles of bolus 5-FU for 5 days every 28 days before and after radiation therapy (50.4 to 54 Gy), plus 5-FU as a continuous infusion during radiation; (2) CI 5-FU for 42 days before and 56 days after identical radiation plus CI 5-FU as in arm 1; (3) bolus 5-FU and LV for 5 days every 28 days for two cycles before and after radiation plus bolus 5-FU and LV given on days 1 through 4 of weeks 1 and 5 of radiation. Relapse-free survival and OS were similar in all three arms. Arms 1 and 3 (containing bolus 5-FU) had more grade 4 (severe) hematologic toxicity than arm 2. All three regimens were considered acceptable for use in clinical practice.

Retrospective comparisons of capecitabine and 5-FU with radiation therapy have found equivalent efficacy.^{58,59} The NSABP R-04 study was designed as a randomized trial, in patients with clinical stage II or III rectal cancer, of capecitabine concurrent with preoperative radiation versus CI 5-FU concurrent with preoperative radiation. The capecitabine dose used in this study of 825 mg/m² administered twice daily was based on the maximum tolerated dose identified in earlier smaller studies of capecitabine and radiation therapy.^{60,61} The R-04 study should definitively answer the question of whether oral capecitabine has equivalent efficacy and toxicity compared with CI 5-FU. For patients who cannot be treated on the R-04 protocol, the authors consider capecitabine to be an acceptable fluoropyrimidine to use in conjunction with radiation, based upon the efficacy demonstrated by studies of capecitabine in the adjuvant and metastatic settings.⁶²⁻⁶⁴

Several published phase I and II trials have evaluated irinotecan and oxaliplatin, two chemotherapeutic agents with activity in colorectal cancer, in combination with 5-FU or capecitabine with radiation therapy for rectal cancer. Pathologic complete response rates in the range of 14 to 26% have been reported with irinotecan and fluoropyrimidine-based chemoradiation.⁶⁵⁻⁶⁹ Of note is one randomized phase II study that demonstrated no improvement in the pathologic complete response rate with the addition of irinotecan.⁶⁸ Both treatment arms in that study demonstrated a relatively high pathologic CR rate of 26%. Studies incorporating oxaliplatin into the chemoradiation regimen have reported pCR rates of 7 to 28%.⁷⁰⁻⁷⁷ The NSABP R-04 study has been modified to include a second randomization to oxaliplatin or no oxaliplatin administered along with the fluoropyrimidine and radiation therapy. The Radiation Therapy Oncology Group (RTOG) is conducting a randomized phase II study of two preoperative chemoradiation regimens for patients with clinical stage T3 and T4 rectal cancers. Patients treated in Arm I will undergo chemoradiation using capecitabine Monday through Friday and irinotecan on days 1, 8, 22, and 29. Patients in arm II will undergo chemoradiation with capecitabine as in arm I and ox-

aliplatin on days 1, 8, 15, 22, and 29. All patients will undergo surgical resection and patients with completely resected disease and negative surgical margins will receive nine cycles of FOLFOX-type (oxaliplatin, 5-FU, LV) adjuvant chemotherapy.

TARGETED THERAPY FOR CHEMORADIATION

Cetuximab (Erbix; ImClone Systems, Inc., New York, NY) is an antibody directed against the epidermal growth factor receptor (EGFR). Cetuximab has single-agent activity in metastatic colorectal cancer with an ~10% response rate.⁷⁸⁻⁸⁰ When used in combination with irinotecan chemotherapy, cetuximab can reverse resistance to irinotecan in ~20% of patients.⁸⁰ Preclinical studies demonstrated enhanced antitumor activity with the addition of cetuximab to radiation therapy.^{81,82} Studies have demonstrated that full-dose cetuximab can safely be used in combination with 5-FU or capecitabine and radiation therapy as preoperative treatment of rectal cancer.^{83,84} Two other studies of cetuximab with preoperative chemoradiation are described below in the section, "Induction Chemotherapy before Preoperative Chemoradiation."

Bevacizumab (Avastin; Genentech, South San Francisco, CA), is an antivascular endothelial growth factor (VEGF) antibody. Preliminary results from a phase I study of bevacizumab, 5-FU, and radiation therapy administered preoperatively to patients with rectal cancer demonstrated decreases in perfusion, microvessel density and interstitial pressures in tumors just 12 days after the initial dose of bevacizumab, which was administered 2 weeks before the start of chemoradiation.⁸⁵ Several trials are ongoing evaluating the use of bevacizumab with chemoradiation, such as Eastern Cooperative Oncology Group (ECOG) study E3204, a phase II study for patients with T3 or T4 rectal tumors. In study E3204, patients receive preoperative chemoradiation consisting of 50.4 Gy in 1.8 Gy fractions with concomitant capecitabine twice daily Monday through Friday, oxaliplatin weekly for 5 weeks and bevacizumab on days 1, 15, and 29. Six to 8 weeks after the completion of chemoradiation, patients undergo resection and then begin adjuvant chemotherapy 4 to 8 weeks after surgery. Adjuvant chemotherapy in ECOG 3204 consists of 12 cycles of FOLFOX-type chemotherapy with oxaliplatin omitted from the last 3 cycles (to reduce the incidence of peripheral neuropathy), plus bevacizumab at every 2 weeks.

IMPACT OF CHEMORADIATION UPON SURGERY

A study of clinical T3 rectal cancer patients at M.D. Anderson Cancer Center who underwent full-thickness

local excision of their rectal cancer after completing chemoradiation had unexpected findings.⁸⁶ Most of these patients had refused abdominoperineal resection. Fifty-four percent of the patients who underwent local excision had a pCR to chemoradiation. At a median follow-up of 46 months, the rate of intrapelvic recurrence in the local excision group was 6%, which was equivalent to the intrapelvic recurrence rate among patients who had a clinical complete response to chemoradiation and underwent TME. Actuarial 5-year OS was also equivalent (86 and 85%) among patients treated with local excision and patients with a pCR to chemoradiation who underwent TME.

In a bold study design, investigators in Brazil closely monitored patients who had a complete clinical response following chemoradiation with 50.4 Gy, 5-FU, and LV instead of referring patients for surgery.⁸⁷ Of 361 patients treated, 122 (33.7%) achieved a complete clinical response. Of these 122 patients, 99 had sustained tumor regression for at least 12 months and were the subjects of the study. With a median follow-up of almost 60 months, only 13.1% of the 99 patients with sustained clinical response experienced a recurrence. Overall survival and DFS at 5 years were 93 and 85%. These studies imply added significance for the attainment of a pCR and suggest a role for more aggressive preoperative chemoradiation. The option of local excision or no surgery for patients who achieve a complete clinical response is worthy of further study.

INDUCTION CHEMOTHERAPY BEFORE PREOPERATIVE CHEMORADIATION

A different treatment paradigm using prolonged systemic chemotherapy before preoperative chemoradiation was utilized in two studies at the Royal Marsden Hospital in London.^{88,89} The later study limited enrollment to patients considered to be of poor risk based on high-resolution MRI of the pelvis. Poor risk was defined as tumor extending to within 1 mm of or beyond the mesorectal fascia, T3 low-lying tumor at or below the levators, tumor extending 5 mm or more into perirectal fat, or tumor invading surrounding structures or the peritoneum. Twelve weeks of neoadjuvant chemotherapy were administered, consisting of oxaliplatin every 3 weeks and capecitabine administered twice daily for 14 days every 21 days. Chemoradiation began after the 12 weeks of chemotherapy were completed. The radiation therapy consisted of 45 Gy administered in 25 fractions to the tumor and pelvic lymph nodes plus another 9 Gy administered in 5 fractions to the tumor plus a 2-cm margin in all directions. Capecitabine was administered twice daily continuously during radiation. Patients underwent TME 6 weeks after the completion of chemoradiation. Postoperative chemotherapy consisted of 4 cycles of capecitabine administered twice

daily for 14 days every 21 days. Interestingly, the tumor response rate by imaging after neoadjuvant chemotherapy was 88%, and this increased to 97% after chemoradiation. Considering that response rates reported in metastatic colorectal cancer with capecitabine and oxaliplatin have been in the range of 36 to 55%, these data suggest that primary rectal tumors may respond better to chemotherapy than colorectal metastases.^{62,90-92} No patient had disease progression during neoadjuvant chemotherapy or chemoradiation. The median time to complete resolution of symptoms was 32 days. Pathologic complete response, the primary endpoint of the study, was achieved in 16 of 77 patients (24%) on an intent-to-treat basis. This pCR rate is especially noteworthy considering the poor-risk patient population in this study.

The Royal Marsden Hospital is now leading a randomized phase II study in patients with high-risk rectal cancer as defined by MRI. In this study, patients receive neoadjuvant chemotherapy consisting of oxaliplatin and capecitabine followed by chemoradiation with capecitabine, followed by TME, followed by adjuvant oxaliplatin and capecitabine for four cycles versus the same regimen plus weekly cetuximab during neoadjuvant chemotherapy, chemoradiation, and adjuvant chemotherapy.

The use of induction chemotherapy may be gaining popularity in the United States. The University of Pennsylvania in Philadelphia is conducting a phase II study of induction capecitabine, oxaliplatin, and cetuximab followed by chemoradiation using capecitabine, oxaliplatin, and cetuximab, followed by surgery, followed by adjuvant capecitabine, oxaliplatin, and cetuximab for patients with clinical T3 and T4 rectal cancer. The Hoosier Oncology Group is conducting a phase II study of preoperative capecitabine plus irinotecan for two cycles, followed by chemoradiation using capecitabine, followed by surgery, and then adjuvant chemotherapy at the investigator's discretion. The primary endpoint of this study is to determine the pathologic response rate of this regimen.

ADJUVANT POSTOPERATIVE CHEMOTHERAPY: TYPE AND DURATION

The MOSAIC trial demonstrated an improvement in DFS at 3 years by 5% with 12 cycles of FOLFOX chemotherapy compared with 12 cycles of 5-FU and LV as adjuvant therapy of stage II and III colon cancer, at a cost of increased neuropathy, myelosuppression, nausea, vomiting, and diarrhea.⁹³ This is in contrast to three randomized trials of irinotecan-based adjuvant therapy that demonstrated no benefit compared with 5-FU and LV as adjuvant treatment of stage III colon cancer.⁹⁴⁻⁹⁶ Bevacizumab improves survival of patients with metastatic colorectal cancer when administered

with chemotherapy in the first- and second-line settings.^{97,98} Building upon the above data, the ECOG E5204 study randomly assigns patients who have undergone chemoradiation followed by resection of clinically stage II or III rectal cancer to FOLFOX for 12 cycles (with oxaliplatin omitted for the last three cycles to reduce the incidence of neuropathy) with or without bevacizumab. Safety data presented from the ECOG E3201 study comparing postoperative 5-FU/LV, FOLFIRI (irinotecan, infusional 5-FU, and LV), and FOLFOX suggests that adjuvant FOLFOX can be safely administered to rectal cancer patients after chemoradiation and surgery.⁹⁹ Extrapolating from the data in colon cancer, many oncologists use a FOLFOX regimen for postoperative chemotherapy. The optimal number of cycles of such treatment has not been determined.

IS ADJUVANT CHEMOTHERAPY NECESSARY?

Several studies have demonstrated an improvement in DFS and OS for patients who achieve a pCR following preoperative chemoradiation for rectal cancer.^{100–104} However, as many of these patients received postoperative chemotherapy, a complete pathologic response cannot be used at present to identify patients who do not benefit from adjuvant chemotherapy.

In the United Kingdom, the CHRONICLE trial is enrolling patients with locally advanced rectal cancer to treatment with preoperative chemoradiation using a minimum of 45 Gy radiation and fluoropyrimidine-based chemotherapy. Patients who are able to have an R0 resection are randomly assigned to capecitabine and oxaliplatin for six cycles versus follow-up only. Patients are permitted to receive up to 6 weeks of neoadjuvant chemotherapy before enrolling.

NEWER PREDICTIVE ASSAY OF TUMOR RESPONSE TO PREOPERATIVE ADJUVANT THERAPY

Although the pathological response rate to preoperative chemoradiation is reasonably high, tumors are genetically heterogeneous and behave variously in response to preoperative therapy. Development of a predictive assay is important because patients with nonresponsive tumors could either be spared from possible side effects of chemotherapy and radiotherapy or be offered an alternative treatment regimen. Such predictive assays will become more crucial as molecularly targeted therapies are incorporated in standard preoperative treatment regimens and the number of targeted treatment options increase. Many investigators have attempted to correlate expression levels of candidate genes, proteins, or both in response to different chemotherapeutic agents, radiation, and their combinations, although routine use of a

predictive assay is not commonly performed in clinical trials to date (Table 1).

Thymidylate synthase (TS) and other 5-FU-associated enzymes, such as thymidylate phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD), are among the most extensively investigated molecular targets with respect to determining response to chemotherapy and chemoradiotherapy. Experimental data clearly indicate that TS is a key enzyme targeted by 5-FU-based chemotherapy.^{105,106} Low levels of TS- and TP-gene expression were shown to be associated with a greater tumor response and better survival with preoperative 5-FU-based chemoradiation.^{107–109} Although many researchers also have focused on p53 as a predictor for preoperative radio(chemo)therapy, both negative and positive associations with tumor response have been reported in rectal cancer patients.^{110–114} Predictive values of other molecular markers, relating to cell death, cell survival/proliferation, cell cycle, and DNA repair, etc., were also tested (Table 1).^{115–128} Of those molecules, EGFR is particularly promising for response prediction as well as for a potential treatment target with radiotherapy. It was reported that the overall response rate was 34% in EGFR-positive patients versus 62% in those who were EGFR-negative ($p = 0.07$). Only 1 of the 7 patients with a pCR was EGFR-positive ($p = 0.003$).¹²⁹ Kim et al¹³⁰ also examined the association of EGFR overexpression and pathological response in 183 patients, of which tumor downstaging occurred in 97 patients (53%) and a pCR was obtained in 27 patients (15%). Epidermal growth factor receptor expression levels were low in 113 patients (62%) and high in 70 patients (38%). Using logistic regression analysis, the authors found a significant predictive value for increased tumor downstaging by a low level of EGFR expression. Recently, a polymorphism in the Sp1 recognition site of the EGFR promoter region was identified. A significant correlation was found between EGFR Sp1 -216 G/T polymorphism and treatment response to chemoradiation in locally advanced rectal cancer.¹³¹

Multiple molecular pathways are likely responsible for determining a response to chemotherapy and radiotherapy. In addition, a molecule may have multiple functions that appear to contradict each other, such as p53, which has a crucial role in DNA repair as well as in determining apoptosis. A result of a deletion or a mutation of p53 depends on the multiple genetic or epigenetic alterations within a cancer cell. Therefore, single or a few markers are unlikely to be sufficient for predicting tumor response in patients treated with combined modality therapy. Gene expression profiling based on a DNA microarray is a promising technology and has been tested in experimental model systems. As an attempt to translate these data into a clinical setting, DNA microarray analysis was performed in a subset of patients in the CAO/ARO/AIO-94, German Rectal

Table 1 Summary of Selected Articles Using Predictive Assays for Tumor Response to Preoperative Adjuvant Therapy in Rectal Cancer

Authors	N	Markers		Treatment	Technique
		Positive Result	Negative Result		
Jacob et al ¹⁰⁷	40	TS, TP	DPD	50.4 Gy/28 fx 5-FU	RT-PCR
Saw et al ¹⁰⁸	60	TS	p53, DCC	45–50.4 Gy/25–28 fx 5-FU	IHC PCR-SSCP (p53)
Okonkwo et al ¹²³	25	TS	p53, bcl-2		IHC
Luna-Perez et al ¹¹⁰	28	p53		45 Gy/25 fx 5-FU	IHC
Adell et al ¹¹⁴	163	p53		25 Gy/5 fx	IHC
Spitz et al ¹²⁴	42	mut-p53		45 Gy/25 fx 5-FU	IHC
Komuro et al ¹¹¹	96	p53, p21, p16, Ku70, Ku86			IHC
Kandioler et al ¹¹³	64	mut-p53	p53	25 Gy/5 fx	IHC gene sequencing
Lopez-Crapez et al ¹¹²	70		p53 mut-p53	45Gy/25fx ± 15 Gy 5-FU + leucovorin	IHC gene sequencing
Elsaleh et al ¹²⁶	48		p53, mut-p53	45Gy/25fx 5-FU	IHC PCR-SSCP
Rau et al ¹¹⁶	66	p21, Ki67	p53, mut-p53, BAX	45 Gy/25 fx 5-FU + leucovorin	IHC PCR-SSCP (p53)
Charara et al ¹¹⁹	57	p21, Ki67, bcl-2, p27	p53, MSI	45–54 Gy/25–30 fx 5-FU + CPT-11	IHC
Nehls et al ¹²⁸	92	BAX	p53	30 Gy/15 fx	IHC
Chang et al ¹²⁷	130	BAX	p53, p21, bcl-2, Ki67, HDAC1, mGluR4	50.4 Gy/28 fx 5-FU/capecitabine + leucovorin	IHC
Rodel et al ¹²⁵	44	Spontaneous AI	Ki67, p53, bcl-2	50.4 Gy/28 fx 5-FU	IHC
Rodel et al ¹²¹	54	Surviving	p53, bcl-2	50.4–55.8 Gy/28–31 fx 5-FU + / – oxaliplatin	IHC
Komuro et al ¹¹¹	96	Telomerase-rt			IHC
Willet et al ¹¹⁷	90	PCNA, MI			IHC
Lammering et al ¹¹⁸	84	S-phase fraction		30 Gy/15 fx	FC
Debucquoy et al ¹¹⁵	30		COX2, IL-6, osteopontin, Ki67	45 Gy/25 fx 5-FU ± celecoxib	IHC
Zlobec et al ¹²²	59	VEGF		26 Gy/4 fx	IHC
Giralt et al ¹²⁹	45	EGFR		50.4 Gy/28 fx 5-FU + leucovorin	IHC
Kim et al ¹³⁰	183	EGFR		50.4 Gy/28 fx, 5-FU/capecitabine + leucovorin	IHC
Spindler et al ¹³¹	63	EGFR-SNP	EGFR	65 Gy Uftoral + leucovorin	SNP IHC
Ghadimi et al ¹³²	30	54 Discriminating gene set		50.4 Gy/28 fx 5-FU	DNA microarray
Watanabe et al ¹³³	52	33 Discriminating gene set		50.4 Gy/28 fx	DNA microarray

RT-PCR, real-time polymerase chain reaction; DCC, deleted in colorectal cancer gene; IHC, immunohistochemistry; PCR-SSCP, polymerase chain reaction single strand conformation polymorphism; mut-p53, p53 mutation; HDAC1, histone deacetylase inhibitor-1; mGluR4, metabotropic glutamate receptor 4; AI, apoptotic index; telomerase-rt, telomerase reverse transcriptase; MI, mitotic index; FC, flow cytometry; SNP, single nucleotide polymorphism.

Cancer Trial.¹³² The authors analyzed global gene expression profiles in preoperative diagnostic biopsies from 30 patients with locally advanced rectal carcinoma. Class-comparison statistics were used to correlate the expression results with tumor downsizing after preoperative chemoradiotherapy as well as with tumor regression grade. Responders and nonresponders showed significantly different expression levels for 54 genes ($P=0.001$). Tumor behavior was correctly predicted in

83% of patients ($p=0.02$). Sensitivity (correct prediction of response) was 78%, and specificity (correct prediction of nonresponse) was 86%, with a positive and negative predictive value of 78 and 86%, respectively. Response prediction to radiotherapy alone was analyzed in another study using global gene expression profiles.¹³³ In this study, 33 novel discriminating genes between responders and nonresponders were identified in rectal cancer specimens from patients receiving preoperative radiotherapy.

The positive predictive value of the new model using the discriminating genes was 82.4%. The 33 discriminating genes included growth factor, apoptosis, cell proliferation, signal transduction, or cell adhesion-related genes. Apoptosis inducers (lumican, thrombospondin 2, and galectin-1) showed higher expression in responders, whereas apoptosis inhibitors (cyclophilin 40 and glutathione peroxidase) showed higher expression in non-responders. Although a large-scale confirmatory study is necessary, these data suggest that the use of the genomics is a promising approach for a tumor response prediction. The Southwest Oncology Group conducted a study S0304 in patients with T3 and T4 rectal cancer in which patients were assigned to induction chemotherapy based upon expression levels of TS, dihydropyrimidine dehydrogenase (predictors of response to 5-FU), and the ERCC-1 (predictor of response to oxaliplatin) genes in their tumors, followed by chemoradiation, with results pending.

CONCLUSION

Patients with stage II and III rectal cancer benefit from a multidisciplinary approach to treatment. Studies of postoperative adjuvant therapy consistently demonstrate decreases in locoregional recurrence with the use of radiation therapy. Postoperative chemotherapy results in improved DFS and OS in certain studies.⁴⁻⁸ Preoperative radiation therapy decreases locoregional recurrence and has demonstrated an improvement in survival.^{11-13,16-19} The addition of chemotherapy to preoperative radiation results in improved locoregional control, but not survival.²⁶⁻²⁹ Preoperative chemoradiation is the standard of care for patients with clinical stage II and III rectal cancer in the United States due to improved local recurrence, acute and late toxicity, and sphincter preservation compared with postoperative chemoradiation.²⁵ Even with preoperative chemotherapy, standard TME, and postoperative chemotherapy, the 75% 5-year survival rate of patients with clinical stage II and III rectal cancer in the German Rectal Cancer Study Group trial leaves room for improvement.²⁵ Promising approaches include the incorporation of new chemotherapeutic and biologic agents into chemoradiation regimens and adjuvant chemotherapy regimens; new radiation techniques such as the use of IORT and an accelerated concomitant radiation boost; and gene and protein expression profiling to better predict response to treatment and prognosis.

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