THE GOAL IN THE TREATMENT OF RECTAL CANCER IS COMPLETE ERADICATION OF DISEASE, BUT FREQUENTLY THIS CANNOT BE ACHIEVED BY SURGICAL RESECTION ALONE. RESIDUAL MICROSCOPIC DISEASE MAY REMAIN AT THE SURGICAL MARGINS OR AT DISTAL SITES. ADJUVANT THERAPY TREATS THIS MICROSCOPIC DISEASE, DECREASES RECURRENCE, AND IMPROVES SURVIVAL. HIGHER-RISK PATIENTS BENEFIT THE MOST FROM ADJUVANT THERAPY. THE AVERAGE 5-YEAR POSTOPERATIVE SURVIVAL RATE WITHOUT ADJUVANT THERAPY FOR STAGE II RECTAL CANCER IS 70% WITH STAGE III PATIENTS HAVING A 40% 5-YEAR SURVIVAL RATE. STAGE II AND III PATIENTS ARE FREQUENTLY CONSIDERED FOR ADJUVANT THERAPY. WE REVIEW THE RECENT DEVELOPMENTS, APPLICATIONS, AND OUTCOMES OF NEOADJUVANT CHEMORADIATION THERAPY IN PATIENTS WITH RECTAL CANCER.

INITIAL USE OF RADIATION THERAPY ALONE

Many early studies established that radiation therapy lowered local recurrence rates but did not improve survival. In the Veterans Administration Surgical Oncology Group trial, 20 Gy of preoperative radiation therapy was used over 2 weeks to irradiate patients who subsequently underwent abdominoperineal resection. These patients had a higher 5-year survival rate than their nonirradiated counterparts (47% vs 34%), but this was not considered statistically significant. Irradiated patients also had fewer positive lymph nodes in the surgical specimen and a lower incidence of pelvic recurrence on postmortem examination. The Stockholm Rectal Cancer Study Group demonstrated that patients receiving 25 Gy over 5 to 7 days preoperatively had fewer pelvic recurrences, but again no improvement in overall survival was observed. Postoperative morbidity was significantly higher in the irradiated patients with a significantly higher postoperative mortality rate compared with those in the surgery alone group (8% vs 2%).

Improvement in survival has only been reported in studies using higher dosages of radiation. The Swedish Rectal Cancer Trial found that high-dose preoperative radiotherapy (5-Gy doses 5 times followed by surgery within a week) decreased local recurrence (11% vs 27%) with an improvement in the overall survival rate after radiation therapy and surgery compared with patients who underwent surgery alone (58% vs 48%). The Dutch Colorectal Cancer Group showed that preoperative radiation therapy (25 Gy over 5 days)
decreased the local recurrence rate in patients who underwent total mesorectal excision but had no effect on survival at 2-year follow-up.6

TIMING OF RADIATION THERAPY: PREOPERATIVE VS POSTOPERATIVE

Many studies have focused on the timing of treatment. Rectal cancers appear to be more responsive to preoperative as opposed to postoperative irradiation. Radiation enteritis is more prevalent when the bowel is more mobile preoperatively. In addition, a distended bladder during treatment can displace bowel out of the radiation field. However, more accurate staging is possible if patients are irradiated postoperatively. Radiation therapy also can be limited to the areas of interest, limiting irradiation of bystander tissue. Frykholm et al6 compared 2 groups of patients, one receiving a total of 25.5 Gy delivered preoperatively in 5 fractions over 5 to 7 days and the other group receiving 60 Gy postoperatively over 6 weeks with a 1- to 2-week break after administration of a dose of 40 Gy. The preoperative group had a local recurrence rate of 13% compared with 22% in the postoperative group. The postoperative group also had a higher incidence of late small-bowel obstruction, urinary tract symptoms including radiation cystitis, and chronic skin fibrosis. In summary, preoperative radiation therapy was more effective and had fewer adverse effects than postoperative radiation therapy.

DURATION OF TREATMENT

The length of radiation therapy varies widely based on a patient’s geographic location. Radiation therapy can be administered over 5 to 6 weeks, as is common in the United States, or over 5 to 7 days, a modality frequently found in Europe. A short course of radiation therapy is obviously more convenient to patients and more economical. The possible complications of short-course radiation therapy can be significant. Early complications include wound infections, wound dehiscence, and anastomotic leak.1 Late effects, observed after 3 months, include higher rates of severe gastrointestinal, urologic, musculoskeletal, and thromboembolic toxic side effects.7

Several studies have examined postoperative complications and survival rates with preoperative short-course radiation therapy. A British Columbia study examined 63 patients receiving 25 Gy in 5 fractions over 1 week: 11 patients (17%) had postoperative complications, which included anastomotic leak (n = 3), perineal wound breakdown (n = 3), fecal incontinence (n = 2), rectovaginal fistula (n = 1), bowel obstruction (n = 1), and anastomotic stricture (n = 1). Local recurrence occurred in 3 patients (5%).8 The 5-year recurrence-free survival rate was 83% for stage I, 75% for stage II, and 62% for stage III. Read et al8 evaluated 260 preoperatively irradiated patients with rectal cancer and compared the outcome in patients receiving either short-course irradiation (20 Gy in 5 fractions), long-course irradiation (45 Gy in 25 fractions), or long-course irradiation with concomitant chemotherapy. A complete response (eg, no evidence of residual tumor) was found in 5% of patients receiving short-course irradiation, in 4% of patients receiving long-course irradiation, and in 8% of the combined chemoradiation group. Tumor down-staging occurred in 42% of patients receiving short-course irradiation compared with 45% of long-course patients and 48% of the combined chemoradiation group. Although the complication rates were similar in all groups, chemoradiation patients had the highest rates of toxic side effects (25%) and short-course irradiation patients the lowest (0%). Short-course irradiation appears to have similar clinical efficacy and is associated with fewer adverse effects than long-course irradiation.

CHEMORADIATION: RADIATION AND CONCOMITANT CHEMOTHERAPY

Many studies have demonstrated improved survival and decreased local recurrence with combined chemotherapy and radiation therapy. The Gastrointestinal Tumor Study Group showed that patients with stage II and III rectal cancer receiving pelvic irradiation (40-44 Gy), methyl lomustine (methyl-CCNU), and 5-fluorouracil (5-FU) after surgical resection had an improved survival rate and improved local tumor control.10,11 Local recurrence was 24% in patients receiving no adjuvant therapy, 27% in patients receiving chemoradiation alone, 20% in patients receiving radiation therapy alone, and 11% in patients receiving both adjuvant therapies. The North Central Cancer Treatment Group reported similar results.12

Better functional results have been reported with preoperative as compared with postoperative chemoradiation. Saito et al13 evaluated the postoperative genitourinary function of 167 patients undergoing nerve-sparing resections. Sixty of these 167 patients were treated with tegafur (a 5-FU produg) suppositories and preoperative irradiation (total dose of 42.6 Gy over 4 weeks), and 107 had nerve-sparing resection alone. The patients receiving chemoradiation plus nerve-sparing resection had no significant difference in postoperative urinary function. Kollmorgen et al14 assessed long-term bowel function in patients receiving postoperative chemoradiation. These patients were more likely to have clustering of bowel movements and more bowel movements per day on average than the surgery-only patients. Only 44% of the chemoradiation patients had normal continence as opposed to 93% of surgery-only patients. Most of the chemoradiation patients (93%) reported bowel function significantly different from preoperative function compared with 61% of the surgery-only group. Postoperative chemoradiation had significant detrimental effects on bowel function.

Perhaps one of the largest studies comparing preoperative vs postoperative chemoradiation was recently published by the German Rectal Cancer Study Group.15 Patients with clinical T3 or T4 and node-positive disease were randomly assigned to receive either preoperative (n = 421) or postoperative (n = 402) chemoradiation. The overall 5-year survival rates were 76% and 74%; the local recurrence rates, 6% and 13%; acute toxic effects, 27% and 40%; and long-term toxic effects, 14% and 24%, respectively. Importantly, there were no differences in postoperative morbidity and mortality between groups.
One of the most intriguing aspects of preoperative chemoradiation is the concept of “NO” disease or “complete pathologic response” without any evidence of residual malignant disease (Table 1). In one very unique and somewhat controversial study, Habr-Gama et al25 compared the disease and clinical courses of 71 patients with rectal cancer (27%) who were observed after complete clinical response following chemoradiation with 22 patients (8%) who had incomplete clinical response after chemoradiation and who subsequently underwent surgical resection and were found to have complete pathologic response in the resected specimen. No difference was seen in the rate of local or systemic recurrences between the 2 patient groups. The overall and disease-free 10-year survival rates in these 2 groups were 98% and 84%, respectively.

NEoadjuvant Therapy And Operative Technique

Neoadjuvant chemoradiation may often result in pathologic down-staging of the tumor and a decrease in tumor bulk.26 This in turn allows for a higher likelihood of sphincter preservation.25 Traditionally, abdominoperineal resections have been performed in patients with cancers of the lower third of the rectum within 5 cm of the dentate line (Table 2). The anal sphincter, rectum, and distal sigmoid are removed and an end-diverting colostomy is created in this procedure. Currently, the only absolute indications for abdominoperineal resection have become involvement of the anal sphincter with cancer and inability to obtain a cancer-free margin. Patients with an incompetent anal sphincter or morbidly obese patients with a narrow pelvis may still require an abdominoperineal resection.27

Preoperative chemoradiation may permit avoidance of abdominoperineal resection by reducing tumor bulk. Shumate et al28 demonstrated that sphincter-sparing procedures were performed more frequently in patients receiving preoperative irradiation. In another study, sphincter-sparing procedures were performed in patients with T3 tumors an average of 4.5 cm from the anal verge 6 weeks following chemoradiation. Distal and radial margins were negative in 98% of patients, and down-staging occurred in 42%. The survival and disease-free rate was 85% at 3 years.21

Sphincter preservation is further enhanced by obtaining narrower distal margins following chemoradiation. Moore et al24 demonstrated no significant difference in local recurrence or disease-free survival in patients with 2-cm distal margins vs 1-cm margins. Kuvshinoff et al29 reported that patients undergoing preoperative chemoradiation and sphincter-sparing surgery with distal margins of 1 cm or less had similar disease-free survival rates compared with patients who underwent abdominoperineal resection.

Improvement in the sphincter-sparing technique has also reduced tumor recurrence. Inadequate lateral margins have been identified as an important cause of local recurrence.30 Total mesorectal excision (TME) involves sharp dissection along the avascular plane of the endopelvic fascia to excise the entire mesorectum intact.31 Mesorectum, rectum, and pelvic lymph nodes are removed en masse, leaving clear margins and limiting possible seeding of the tumor. With TME, local recurrence rates as low as 4% have been reported.32 Total mesorectal excision confers further benefit when combined with neoadjuvant therapy. Kapiteijn et al3 reported on 1861 pa-

<p>| Table 1. Preoperative Chemoradiation and Pathologic Complete Response Rate |
|-----------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Patients, No.</th>
<th>Radiation Dose, Gy</th>
<th>Radiation Duration, wk</th>
<th>Chemotherapeutic</th>
<th>Time to Operation After XRT, wk</th>
<th>Complete Response, %</th>
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<tr>
<td>Chen et al31</td>
<td>1994</td>
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<tr>
<td>Rich et al22</td>
<td>1995</td>
<td>77</td>
<td>45.0</td>
<td>5</td>
<td>5-FU</td>
<td>6</td>
<td>29</td>
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<tr>
<td>Grann et al21</td>
<td>1997</td>
<td>32</td>
<td>50.4</td>
<td>5</td>
<td>5-FU, leucovorin</td>
<td>4-5</td>
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<tr>
<td>Willett et al30</td>
<td>1998</td>
<td>103</td>
<td>45.0-50.0</td>
<td>5</td>
<td>5-FU</td>
<td>4-6</td>
<td>12</td>
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<tr>
<td>Onaitis et al21</td>
<td>2001</td>
<td>141</td>
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<td>50.0</td>
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<td>6</td>
<td>9</td>
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<td>Dunst et al21</td>
<td>2002</td>
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<td>Stein et al21</td>
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<td>Irinotecan,5-FU</td>
<td>2 Groups: 4-8 and ≤2</td>
<td>21 and 14</td>
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<tr>
<td>Moore et al24</td>
<td>2003</td>
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<td>50.4</td>
<td>5</td>
<td>5-FU, leucovorin</td>
<td>4-7</td>
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</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; NA, not available; XRT, radiation therapy.

| Table 2. Surgical Options in Patients With Rectal Cancer |
|-----------------------------|-----------------|-----------------|-----------------|
| Cancer Location Within Rectum | Surgical Procedure |
| Upper third                  | Anterior resection and colorectal anastomosis |
|                               | Local excision using TEM |
| Middle third                 | Low anterior resection and colorectal anastomosis |
|                               | Low anterior resection and colopouch-rectal anastomosis |
|                               | Low anterior resection and coloplasty-rectal anastomosis |
|                               | Local excision with or without TEM |
|                               | Abdominoperineal resection if sphincter incompetent |
| Lower third                  | Ultra-low anterior resection and colorectal anastomosis with or without colonic J-pouch |
|                               | Local excision with or without TEM |
|                               | Coloanal anastomosis with or without colonic J-pouch |
|                               | Coloplasty anal anastomosis |
|                               | Abdominoperineal resection if sphincter incompetent or inadequate distal margin |

Abbreviation: TEM, transanal endoscopic microsurgery.
tients who were randomly assigned to either TME and preoperative radiotherapy (5 Gy in 5 fractions) or surgery alone. The 2-year survival rate in each of these groups was nearly equivalent (82% with combined therapy vs 81.8%). The 2-year rate of local recurrence in the combined therapy group was 2.4% compared with 8.2% in the surgery-alone group. Despite the decrease in local recurrence from TME alone, preoperative radiation therapy continues to confer benefit.

Controversy remains as to whether TME should be used in all rectal cancers. The same is true for radiation therapy. Some advocate that TME be applied to tumors of the middle and lower rectum and not to the upper rectum. Lopez-Kostner et al investigated the treatment of 229 patients with tumors in the upper rectum (10-15 cm from the anal verge), 437 in the lower rectum, and 275 in the sigmoid colon. Total mesorectal excision was used in lower rectal tumors but not for sigmoid or upper rectal tumors. The rate of combined local and distant recurrence was 3.9% and 4.7% for sigmoid and upper rectal tumors, respectively. This is compared with lower rectal tumors, which had a recurrence rate of 12.9%. Patients with upper rectal and sigmoid cancers had similar mortality rates, which were also less than the mortality rates in patients with lower rectal tumors.

Choice of Operation

Whether or not TME is used, surgeons employing sphincter-sparing procedures have several options for reconstruction following resection (Table 1).

Coloanal/Colopouch Anal Anastomosis

Coloanal anastomosis (Figure 1A) can be performed to bring the proximal colon back into continuity with the anus. Patients with “straight” coloanal anastomosis often complain of high stool frequency, urgency, and incontinence. To avoid these problems, a colonic J-pouch (Figure 1B) or coloplast (Figure 1C) can be created. Both involve constructing neorectal reservoirs for stool. In coloplasty, a longitudinal colotomy is made 10 cm proximal to the distal end of colon and then closed transversely. A colonic J-pouch with 5- to 7-cm limbs is created similarly to an ileal J-pouch. The functional results of coloplasty and colonic J-pouch have been compared with respect to postoperative manometry, compliance, and stool frequency and have been found to be similar. Patients with a colonic J-pouch who underwent preoperative irradiation were, however, more likely to have nocturnal defecation (36% vs 15%) and diarrhea (39% vs 13%). Sphincter-sparing procedures may require a diverting ileostomy if patients have risk factors for impeded healing such as irradiation, immunosuppression, and/or malnutrition.

Local Excision

Local excision can be used in patients who are not likely to tolerate general anesthetic or long procedures. Posterior approaches, such as the transsphincteric (Mason) and transsacral (Kraske) procedures, are largely unused. The transanal approach causes less morbidity and allows faster recovery. This was formerly restricted to tumors within the reach of the surgeon’s finger. The development of transanal endoscopic microsurgery, however, allows local excision of tumors in the upper middle third and upper rectal cancers. Lev-Chelouche et al describe transanal endoscopic microsurgery excision of tumors located 3 to 18 cm from the dentate line. Ideal patients for local excision have mobile, exophytic, and well-differentiated tumors with no lymphovascular invasion. Frequently, endorectal ultrasound (Figure 2) is used to evaluate the depth of invasion and any possible lymphovascular involvement. Chemoradiation is often used in patients with T2 or T3 lesions. In patients with com-
One hundred two patients underwent surgery with a 10- to 14-week interval between radiation and surgery does not increase down-staging compared to shorter 4- to 8-week interval. However, this study may not have had the statistical power to note subtle differences. More study in this area is clearly warranted.

MODE OF ADMINISTRATION AND TYPE OF ADJUVANT CHEMOTHERAPY

5-Fluorouracil is the primary chemotherapeutic agent used in neoadjuvant chemoradiation. This pyrimidine antagonist resembles uracil. It inhibits thymidylate synthetase and decreases de novo DNA synthesis and repair. When 5-FU is incorporated into DNA, DNA strands are more likely to break. The effects of 5-FU are further potentiated by radiation therapy. Randomized trials have shown that 5-FU and radiation therapy improve local control of tumor compared with either irradiation or chemotherapy alone.

5-Fluorouracil is often administered intravenously because it has variable oral bioavailability. In the Gastrointestinal Tumor Study Group trial and North Central Cancer Treatment Group trials evaluating chemoradiation, 5-FU was administered by intravenous bolus. The improvement in survival rates reported in these trials resulted in the recommendation of postoperative chemoradiation by the National Institutes of Health in 1990. The drawback of 5-FU bolus therapy is the wide range in plasma concentration of the drug because it is a bolus and subsequently quickly metabolized. Attention then turned to administration of 5-FU as a continuous infusion to maintain a steady state plasma concentration. O’Connell et al demonstrated that continuous intravenous infusion of 5-FU was associated with an increased time of relapse and survival rates as compared with bolus injections. The toxic effects from the modalities of 5-FU administration (diarrhea, stomatitis, nausea, vomiting, leukopenia, thrombocytopenia, dermatitis) were evaluated as well. Severe diarrhea was more frequently found with continuous infusion of 5-FU, and severe leukopenia was more common with bolus injection. Parenteral administration of 5-FU is inconvenient and expensive because an infusion pump and intravenous access are needed. For this reason, strides have been made toward the development of oral fluoropyrimidine combinations such as uracil/tegafur. 5-Fluorouracil itself is a poor candidate for oral administration because it is inconsistently metabolized by dihydropyrimidine dehydrogenase. A recent randomized, multicenter, phase 3 study compared oral uracil/tegafur with oral leucovorin to intravenous bolus 5-FU and leucovorin in the treatment of metastatic colorectal cancer. The survival and overall response rates were similar. Uracil/tegafur with leucovorin had fewer adverse effects along with a decreased incidence of diarrhea; nausea/vomiting; stomatitis; mucositis; and most importantly, myelosuppression. Capecitabine (Xeloda; Hoffman-La Roche Inc, Nutley, NJ) is the first oral fluoropyrimidine available in the United States, and it dif-

Figure 2. Endorectal ultrasound illustrating rectal cancer invading beyond the rectal wall into perirectal fat. This patient was treated with preoperative radiation and chemotherapy and subsequently underwent colopouch anal anastomosis. At the time of surgery, no residual tumor was present in the resected specimen.
fers from 5-FU with respect to tumor selectivity with a more than 3-fold higher concentration within tumor than within normal tissues. The conversion of capecitabine to 5-FU occurs within tumor cells. Several phase 3 trials have compared capecitabine with bolus 5-FU plus leucovorin in previously untreated metastatic colorectal cancer and demonstrated an equivalent overall survival rate and time to disease progression. Hand-foot syndrome was found in patients treated with capecitabine; however, a lower incidence of neutropenia and stomatitis were also observed. The use of such oral agents in conjunction with radiation could have a major economic and quality-of-life advantage for patients if shown to be as effective as intravenous administration in terms of tumor response and down-staging. Suppository administration of 5-FU is another interesting mode of administration. Although this has been used clinically, it has not become popular in this country, but it has advantages in terms of achieving high local concentrations and not requiring intravenous access. 48,49

**PREDICTING RESPONSE TO NEOADJUVANT CHEMOTHERAPY**

Many studies are focusing on thymidylate synthase (TS), an enzyme essential for DNA synthesis, as a prognostic factor to determining tumor response to chemotherapy. Patients with high TS expression treated with 5-FU had longer disease-free survival compared with patients with low TS expression. In metastatic disease, however, TS expression in primary tumors seemed to have no predictive value in outcome or response to 5-FU. 51 The TS gene promoter has tandemly repeated sequences in the enhancer region. These tandemly repeated sequences vary in length, depending on a person’s ethnicity. These polymorphisms in the tandemly repeated sequence affect TS expression. Villafranca et al reported on 65 patients with rectal cancer receiving preoperative 5-FU-based chemoradiation. The pathologic down-staging of the surgical specimen and patients’ TS polymorphism were evaluated. Patients who were homozygous or heterozygous for TS double tandem repeats had a higher probability of tumor down-staging and showed a trend toward an improved 3-year disease-free survival rate. In another study, Ki-67 immunostaining used as a marker of a tumor’s proliferative index was higher in patients who were complete or partial responders following chemoradiation for rectal cancer than in patients who were nonresponders.

Although chemotherapeutic agents such as 5-FU radiosensitize tumors, they also radiosensitize normal tissue and subsequently cause toxic effects with radiation therapy. The discovery of radioprotectant agents that protect normal tissue from radiation hold promise for improved chemoradiation therapy with fewer toxic effects. Agents such as amifostine (Ethyl; MedImmune Inc, Gaithersburg, Md) appear to decrease toxic side effects for cancers of the head and neck as well as lung cancer. A study is being conducted on combining amifostine and 5-FU to minimize the effects of radiation therapy. 53 A limitation of such studies is clearly the desire to minimize affecting the tumoricidal effects of chemoradiation while maximizing the protective effect on normal tissue.

The development of intensity modulated radiation therapy (IMRT) may further decrease radiation toxicity. With this technology, radiation is delivered more precisely to the tumor with greater sparing of surrounding normal tissues than with conventional external beam radiation. Computers are used to optimize treatment fields and conform radiation exposure to the location of the tumor. In many cases, IMRT is delivered by conventional linear accelerators equipped with multileaf collimators. 55 Intensity modulated radiation therapy has been used to treat central nervous system, head and neck, and prostate cancers. Advantages of IMRT include the ability to treat multiple targets simultaneously and the avoidance of radiating normal areas. More than 40 studies are currently being conducted on the efficacy of neoadjuvant IMRT and chemotherapy. A helical machine offers a more sophisticated delivery that is less time-intensive than conventional IMRT. The tomotherapy unit is mounted on a spiral computed tomographic ring gantry and combines IMRT with computed tomographic imaging capability. 56

Many strides have been made in the treatment of advanced rectal cancer. Enhanced disease-free survival with decreased local recurrence is clearly demonstrated with preoperative chemoradiation. Recent developments in both radiation and chemotherapy have reduced the toxic effects of treatment. Further developments in the field will continue to optimize tumor response and minimize toxic effects and will perhaps allow us to better predict which patients will benefit most from treatment.

**REFERENCES**