

Induction Chemoradiation for Rectal Cancer

Nancy Han, MD; Susan Galandiuk, MD

Objective: To review the application, outcome, and recent developments of neoadjuvant chemoradiation therapy with respect to rectal cancer.

Data Sources and Study Selection: Articles written in English after 1980 selected from MEDLINE and PubMed from the National Library of Medicine. Case reports were excluded. There were no other criteria for exclusion of published information pertaining to this topic.

Data Extraction and Synthesis: Articles were ob-

tained and organized from MEDLINE and PubMed as well as the reference lists of pertinent literature.

Conclusions: Published reports have demonstrated that neoadjuvant chemoradiation improves survival and decreases local recurrence in patients with stage II and III rectal cancers. It is anticipated that advances and technical developments in both chemotherapy and radiation therapy will lead to improved oncologic results with decreased toxic side effects.

Arch Surg. 2006;141:1246-1252

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.¹ 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.² 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

See Invited Critique at end of article

had fewer pelvic recurrences, but again no improvement in overall survival was observed.³ 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%).⁴ The Dutch Colorectal Cancer Group showed that preoperative radiation therapy (25 Gy over 5 days)

Author Affiliations: Section of Colon and Rectal Surgery, Department of Surgery, University of Louisville School of Medicine, Louisville, Ky.

decreased the local recurrence rate in patients who underwent total mesorectal excision but had no effect on survival at 2-year follow-up.⁵

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 preventable 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.³ 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 al⁹ 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 re-

ceiving 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 chemotherapy 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 prodrug) 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 or 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.

Table 1. Preoperative Chemoradiation and Pathologic Complete Response Rate

Source	Year	Patients, No.	Radiation Dose, Gy	Radiation Duration, wk	Chemotherapeutic	Time to Operation After XRT, wk	Complete Response, %
Chen et al ¹⁶	1994	31	55.8	NA	5-FU	6-8	10
Rich et al ¹⁷	1995	77	45.0	5	5-FU	6	29
Grann et al ¹⁸	1997	32	50.4	5	5-FU, leucovorin	4-5	9
Willett et al ¹⁹	1998	103	45.0-50.0	5	5-FU	4-6	12
Onaitis et al ²⁰	2001	141	45.0-50.4	5	5-FU, cisplatin	4-8	24
Rullier et al ²¹	2001	43	50.0	4.5	5-FU	6	9
Dunst et al ²²	2002	10	50.4	6	Capecitabine	NA	10
Stein et al ²³	2003	33	45.0-54.0	5	Irinotecan, 5-FU	2 Groups: 4-8 and ≤2	21 and 14
Moore et al ²⁴	2003	94	50.4	5	5-FU, leucovorin	4-7	9

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.

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.¹⁵ 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 al⁵ reported on 1861 pa-

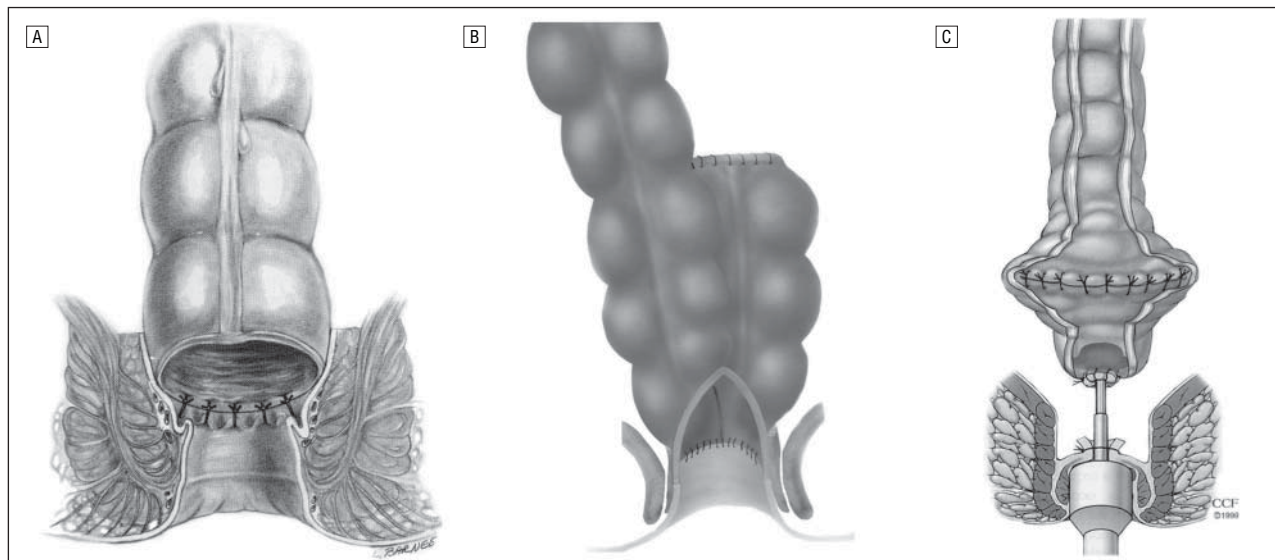


Figure 1. Schematic representations of “straight” coloanal anastomosis (A) (with permission from Corman ML, ed. *Colon and Rectal Surgery*, 4th ed. St Louis, Mo: Lippincott Williams & Wilkins, 1998); colopouch rectal anastomosis (B); and coloplasty-anal anastomosis (C) (with permission from Cleveland Clinic Foundation, ©CCF 1999).

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 al³³ 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 in-

continence. To avoid these problems, a colonic J-pouch (**Figure 1B**) or coloplast (**Figure 1C**) can be created.³⁴⁻³⁶ 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.^{37,38} 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 al³⁹ 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-

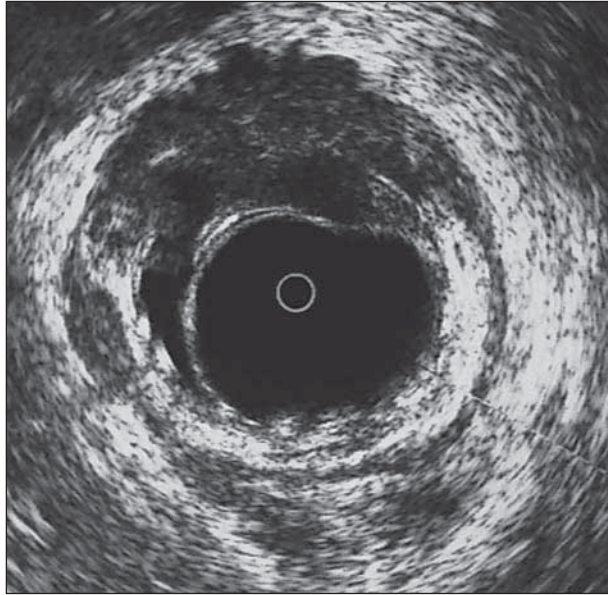


Figure 2. Endorectal ultrasound illustrating rectal cancer invading beyond the rectal wall into perirectal fat. This patient was treated with preoperative radiation and chemotherapy and subsequently underwent colopouch anal anastomosis. At the time of surgery, no residual tumor was present in the resected specimen.

plete pathologic response to chemoradiation, local excision may be an effective surgical option.²⁷ Garcia-Aguilar and colleagues⁴⁰ reported an 18% local recurrence rate in T1 lesions and a 37% recurrence rate in T2 lesions, which has dampened enthusiasm for local excision, particularly as subsequent salvage surgery is often noncurative. Paty et al⁴¹ reported similar results with 10-year local recurrence and survival rates of 17% and 74% in T1 lesions and 26% and 72% in T2 lesions, respectively. Patients receiving chemoradiation had similar outcomes, but selection bias may exist.

TIMING OF SURGERY

The optimal timing between radiation therapy and surgery has yet to be determined. In the Lyon R90-01 randomized trial, 201 patients with stage T2 to T3 tumors received preoperative radiation of 39 Gy in 13 fractions.⁴² One hundred two patients underwent surgery within 2 weeks of completing radiation, whereas 99 patients had surgery 6 to 8 weeks after radiation therapy. Long-interval patients had better clinical tumor responses as compared with short-interval patients (71.7% vs 53.1%) and greater pathologic down-staging (26% vs 10.3%). No differences in survival, recurrence, or morbidity rates were observed over the 33-month follow up. Sphincter-preserving surgery was performed more frequently in the long-interval group (76% vs 68%). In a more recent study, 40 patients with rectal cancer received preoperative radiation (45-54 Gy) with concomitant 5-FU and irinotecan.²³ Patients were divided into 2 groups. One group underwent surgery 4 to 8 weeks after completion of radiation therapy, and the other group underwent surgery 10 to 14 weeks after completion of radiation therapy. Tumor down-staging was reported in 58% of the short-interval group compared with 43% in

the long-interval group. Nodal down-staging was similarly found more frequently in the short interval group (78% vs 67%). Although these differences did not reach statistical significance, these results suggest that a longer 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.⁴³

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.¹⁰⁻¹² The improvement in survival rates reported in these trials resulted in the recommendation of postoperative chemoradiation by the National Institutes of Health in 1990.⁴⁴ 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 al⁴⁵ 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.^{43,46} 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.⁴⁷ 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-

fers from 5-FU with respect to tumor selectivity with a more than 3-fold higher concentration within tumor than within normal tissues.⁴⁶ 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.⁵⁰ 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 al⁵² 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.⁵³

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 (Ethyol; 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.⁵⁴ 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.⁵⁵ 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.

Accepted for Publication: October 13, 2005.

Correspondence: Susan Galandiuk, MD, Department of Surgery, University of Louisville, Louisville, KY 40292 (susan.galandiuk@louisville.edu).

Author Contributions: Study concept and design: Han and Galandiuk. Acquisition of data: Han. Analysis and interpretation of data: Han and Galandiuk. Drafting of the manuscript: Han and Galandiuk. Critical revision of the manuscript for important intellectual content: Han and Galandiuk. Administrative, technical, and material support: Galandiuk. Study supervision: Galandiuk.

Financial Disclosure: None reported.

REFERENCES

1. Bleday R, Wong WD. Recent advances in surgery for colon and rectal cancer. *Curr Probl Cancer*. 1993;17:1-68.
2. Higgins GA Jr, Conn JH, Jordan PH Jr, Humphrey EW, Roswit B, Keehn RJ. Preoperative radiotherapy for colorectal cancer. *Ann Surg*. 1975;181:624-631.
3. Stockholm Rectal Cancer Study Group. Preoperative short-term radiation therapy in operable rectal carcinoma. *Cancer*. 1990;66:49-56.
4. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med*. 1997;336:980-987.
5. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345:638-646.
6. Frykholm GJ, Glimelius B, Pahman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum*. 1993;36:564-572.
7. King M, Tolan S, Giridharan S, McConkey C, Hartley A, Geh JI. Late toxicity after short course preoperative radiotherapy and total mesorectal excision for resectable rectal cancer. *Clin Oncol (R Coll Radiol)*. 2003;15:233-236.
8. Tanel K, Hay J, Ma R, Toy E, Larsson S, MacFarlane J. Short-course preoperative radiation therapy for operable rectal cancer. *Am J Surg*. 2002;183:509-511.

9. Read TE, McNeven MS, Gross EK, et al. Neoadjuvant therapy for adenocarcinoma of the rectum: tumor response and acute toxicity. *Dis Colon Rectum*. 2001; 44:513-522.
10. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med*. 1985;312:1465-1472.
11. Douglass HO Jr, Moertel CG, Mayer RJ, et al. Survival after postoperative combination treatment of rectal cancer. *N Engl J Med*. 1986;315:1294-1295.
12. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med*. 1991;324:709-715.
13. Saito N, Sarashina H, Nunomura M, et al. Clinical evaluation of nerve-sparing surgery combined with preoperative radiotherapy in advanced rectal cancer patients. *Am J Surg*. 1998;175:277-282.
14. Kollmorgen CF, Meagher AP, Wolff BG, Pemberton JH, Martenson JA, Illstrup DM. The long-term effect of adjuvant postoperative chemoradiotherapy for rectal carcinoma on bowel function. *Ann Surg*. 1994;220:676-682.
15. Sauer R, Becker H, Hohenberger W, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351:1731-1740.
16. Chen ET, Mohiuddin M, Brodovsky H, Fishbein G, Marks G. Downstaging of advanced rectal cancer following combined preoperative chemotherapy and high dose radiation. *Int J Radiat Oncol Biol Phys*. 1994;30:169-175.
17. Rich TA, Skibber JM, Ajani JA, et al. Preoperative infusional chemoradiation therapy for stage T3 rectal cancer. *Int J Radiat Oncol Biol Phys*. 1995;32:1025-1029.
18. Grann A, Minsky BD, Cohen AM, et al. Preliminary results of preoperative 5-fluorouracil, low-dose leucovorin, and concurrent radiation therapy for clinically resectable T3 rectal cancer. *Dis Colon Rectum*. 1997;40:515-522.
19. Willett CG, Hagan M, Daley W, Warland G, Shellito PC, Compton CC. Changes in tumor proliferation of rectal cancer induced by preoperative 5-fluorouracil and irradiation. *Dis Colon Rectum*. 1998;41:62-67.
20. Onaitis MW, Noone RB, Fields R, et al. Complete response to neoadjuvant chemoradiation for rectal cancer does not influence survival. *Ann Surg Oncol*. 2001; 8:801-806.
21. Rullier E, Goffre B, Bonnel C, Zerbib F, Caudry M, Saric J. Preoperative radiochemotherapy and sphincter-saving resection for T3 carcinomas of the lower third of the rectum. *Ann Surg*. 2001;234:633-640.
22. Dunst J, Reese T, Sutter T, et al. Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer. *J Clin Oncol*. 2002; 20:3983-3991.
23. Stein DE, Mahmoud NN, Anne PR, et al. Longer time interval between completion of neoadjuvant chemoradiation and surgical resection does not improve downstaging of rectal carcinoma. *Dis Colon Rectum*. 2003;46:448-453.
24. Moore HG, Riedel E, Minsky BD, et al. Adequacy of 1-cm distal margin after restorative rectal cancer resection with sharp mesorectal excision and preoperative combined-modality therapy. *Ann Surg Oncol*. 2003;10:80-85.
25. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg*. 2004;240:711-717.
26. Fleshman JW, Kodner IJ, Fry RD, et al. Results of radiotherapy and resection, endocavitary irradiation, local excision and preoperative clinical staging. *Dis Colon Rectum*. 1985;28:810-815.
27. Kim CJ, Yeatman TJ, Coppola D, et al. Local excision of T2 and T3 rectal cancers after downstaging chemoradiation. *Ann Surg*. 2001;234:352-359.
28. Shumate CR, Rich TA, Skibber JM, Ajani JA, Ota DM. Preoperative chemotherapy and radiation therapy for locally advanced primary and recurrent rectal carcinoma: a report of surgical morbidity. *Cancer*. 1993;71:3690-3696.
29. Kuvshinov B, Maghfoor I, Miedema B, et al. Distal margin requirements after preoperative chemoradiotherapy for distal rectal carcinomas: are < or = 1 cm distal margins sufficient? *Ann Surg Oncol*. 2001;8:163-169.
30. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection: histopathological study of lateral tumour spread and surgical excision. *Lancet*. 1986;2:996-999.
31. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet*. 1993;341:457-460.
32. Stocchi L, Wolff BG. Operative techniques for radical surgery for rectal carcinoma: can surgeons improve outcomes? *Surg Oncol Clin N Am*. 2000;9:785-798.
33. Lopez-Kostner F, Lavery I, Hool GR, et al. Total mesorectal excision is not necessary for cancers of the upper rectum. *Surgery*. 1998;124:612-617.
34. Z'graggen K, Maurer CA, Birrer S, Giachino D, Kern B, Buchler MW. A new surgical concept for rectal replacement after low anterior resection: the transverse coloplasty pouch. *Ann Surg*. 2001;234:780-785.
35. Lazorthes F, Chiotasso P, Gamagami RA, Istvan G, Chevreau P. Late clinical outcome in a randomized prospective comparison of colonic J pouch and straight coloanal anastomosis. *Br J Surg*. 1997;84:1449-1451.
36. Berger A, Tiret E, Parc R, et al. Excision of the rectum with colonic J pouch-anal anastomosis for adenocarcinoma of the low and mid rectum. *World J Surg*. 1992; 16:470-477.
37. Mantyh CR, Hull TL, Fazio VW. Coloplasty in low colorectal anastomosis: manometric and functional comparison with straight and colonic J-pouch anastomosis. *Dis Colon Rectum*. 2001;44:37-42.
38. Dehni N, McNamara DA, Schlegel RD, Guiguet M, Tiret E, Parc R. Clinical effects of preoperative radiation therapy on anorectal function after proctectomy and colonic J-pouch-anal anastomosis. *Dis Colon Rectum*. 2002;45:1635-1640.
39. Lev-Chelouche D, Margel D, Goldman G, Rabau MJ. Transanal endoscopic microsurgery: experience with 75 rectal neoplasms. *Dis Colon Rectum*. 2000; 43:662-667.
40. Garcia-Aguilar J, Mellgren A, Sirivongs P, Buie D, Madoff RD, Rothenberger DA. Local excision of rectal cancer without adjuvant therapy: a word of caution. *Ann Surg*. 2000;231:345-351.
41. Paty PB, Nash GM, Baron P, et al. Long-term results of local excision for rectal cancer. *Ann Surg*. 2002;236:522-529.
42. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol*. 1999;17:2396-2402.
43. Blanke CD, Teng M, Choy H. The role of UFT in combined modality therapy. *Oncology*. 1999;13:47-54.
44. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA*. 1990;264:1444-1450.
45. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med*. 1994;331:502-507.
46. Rich TA, Shepard RC, Mosley ST. Four decades of continuing innovation with fluorouracil: current and future approaches to fluorouracil chemoradiation therapy. *J Clin Oncol*. 2004;22:2214-2232.
47. Douillard JY, Hoff PM, Skillings JR, et al. Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*. 2002;20:3605-3616.
48. Galandiuk S, Wrightson W, Marr L, Myers S, LaRocca RV. Suppository delivery of 5-fluorouracil in rectal cancer. *Ann Surg Oncol*. 1996;3:270-276.
49. Takahashi T, Mizusawa H, Kato T, Yamaguchi T. Preoperative irradiation and 5-fluorouracil suppository for carcinoma of the rectum. *Am J Surg*. 1988;156: 58-62.
50. Edler D, Glimelius B, Hallstrom M, et al. Thymidylate synthase expression in colorectal cancer: a prognostic and predictive marker of benefit from adjuvant fluorouracil-based chemotherapy. *J Clin Oncol*. 2002;20:1721-1728.
51. Johnston PG, Benson AB III, Catalano P, Rao MS, O'Dwyer PJ, Allegra CJ. Thymidylate synthase protein expression in primary colorectal cancer: lack of correlation with outcome and response to fluorouracil in metastatic disease sites. *J Clin Oncol*. 2003;21:815-819.
52. Villafranca E, Okruzhnov Y, Dominguez MA, et al. Polymorphisms of the repeated sequences in the enhancer region of the thymidylate synthase gene promoter may predict downstaging after preoperative chemoradiation in rectal cancer. *J Clin Oncol*. 2001;19:1779-1786.
53. Kim NK, Park JK, Kee KY, et al. p53, BCL-2 and Ki-67 expression after concurrent chemoradiation for advanced rectal cancer. *Ann Surg Oncol*. 2001;8:418-424.
54. Curran WJ. Reports from the Kimmel Cancer Center Symposium: The First Investigators' Congress on Radioprotection. *Oncol News Int*. 2001;10:1-20.
55. Teh BS, Woo SY, Butler EB. Intensity modulated radiation therapy (IMRT): a new promising technology in radiation oncology. *Oncologist*. 1999;4:433-442.
56. Beavis AW. Is tomotherapy the future of IMRT? *Br J Radiol*. 2004;77:285-295.