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Preoperative Radiation and Chemotherapy in the Treatment of Adenocarcinoma of the Rectum

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Objective

In this study, the impact of preoperative chemotherapy and radiation on the histopathology of a subgroup of patients with rectal adenocarcinoma was examined. As well, survival, disease-free survival and pelvic recurrence rates were examined, and compared with a concurrent control group.

Summary Background Data

The optimal treatment of large rectal carcinomas remains controversial; current therapy usually involves abdominoperineal resection plus postoperative chemoradiation; the combination can be associated with significant postoperative morbidity. In spite of these measures, local recurrences and distant metastases continue as serious problems.

Methods

Fluorouracil, cisplatin, and 4500 cGy were administered preoperatively over a 5-week period, before definitive surgical resection in 43 patients. In this group of patients, all 43 had biopsy-proven lesions >3 cm (median diameter), involving the entire rectal wall (as determined by sigmoidoscopy and computed tomography scan), with no evidence of extrapelvic disease. The patients ranged from 31 to 81 years of age (median 61 years), with a male:female ratio of 3:1. A concurrent control group consisting of 56 patients (median: 62 years, male:female ration of 3:2) with T2 and T3 lesions was used to compare survival, disease-free survival, and pelvic recurrence rates.

Results

The preoperative chemoradiation therapy was well tolerated, with no major complications. All patients underwent repeat sigmoidoscopy before surgery; none of the lesions progressed while patients underwent therapy, and 22 (51%) were determined to have complete clinical response. At the time of resection, 21 patients (49%) had gross disease, 9 (22%) patients had only residual microscopic disease, and 11 (27%) had sterile specimens. Of the 30 patients with evidence of residual disease, 4 had positive lymph nodes. In follow-up, 39 of the 43 remain alive (median follow-up = 25 months), and only 1 of the 11 patients with complete histologic response developed recurrent disease. Six of the 32 patients with residual disease (2 with positive nodes) have developed metastatic disease in follow-up (median time to diagnosis 10 months, range 3–15 months). Three of these patients with metastases have died (median survival after diagnosis of

metastases = 36 months). Local recurrence was seen in only 2 of 43 patients (<5%). Cox-Mantel analysis of Kaplan-Meier distributions demonstrated increased survival ($p = 0.017$), increased disease-free survival ($p = 0.046$), and decreased pelvic recurrence ($p = 0.031$) for protocol *versus* control patients.

Conclusions

This therapeutic regimen has provided enhanced local control and decreased metastases. Furthermore, the marked degree of tumor downstaging, as seen by a 27% incidence of sterile pathologic specimens and a low rate of positive lymph nodes in this group with initially advanced lesions, strongly suggest that less radical surgery and sphincter preservation may be used with increasing frequency.

Rectal carcinoma remains a common malignant disease in the United States, with an estimated 42,000 new cases being diagnosed, which lead to approximately 7000 deaths in 1994.[1] This tumor frequently is diagnosed at a stage when complete resection is possible, and traditionally, rectal carcinoma limited to the pelvis has been treated by abdominal perineal resection after diagnosis. Although surgical resection often is curative for small lesions that do not extend through the bowel wall, the risk of relapse and death is increased if the carcinoma has penetrated through the rectal wall (TNM stage II) or has spread to the regional lymph nodes (TNM stage III). Only half of these patients who undergo surgery will be cured[2] and 30% of patients who have undergone curative resection of primary rectal cancer will have pelvic recurrences.[3]

In most reported surgical series, treatment failures have ranged from 15% to 70%, with overall survival ranging from 60% to 80% (stage II) and 30% to 50% (stage III) at 5 years.[4] Analysis of patterns of treatment failures has demonstrated that 20% to 30% of patients fail with distant metastases alone, whereas 70% to 80% of patients fail with either local recurrence alone or local recurrence and distant metastases, the two categories being about evenly divided.[5] The principal reason for local recurrence in resected rectal cancer appears to be related to the anatomic constraints in obtaining wide radical margins, even though proximal and distal margins are adequate.[6] Local recurrences are associated with significant morbidity and are ineffectively palliated by local (surgery or radiation therapy) or systemic chemotherapy at the time of recurrence. Collectively, these observations suggest that even though the primary surgical treatment may have been classified as curative, patients with stage II and stage III tumors must be considered as having occult disease and therefore, are candidates for adjuvant therapy to improve local control and perhaps improve survival as well.

Over the past 15 to 20 years, the use of adjuvant therapy to improve results of surgical resection of rectal carcinoma has been evaluated in both preoperative and postoperative settings. Interpretation of data from early randomized trials assessing the impact of preoperative radiation therapy is hampered by relatively low doses with variable fraction size and duration.[7] Accordingly, no clear-cut local control or survival benefit has been demonstrated. Two more recent European studies using doses greater than 45 cGy have both demonstrated a reduction in local recurrence, but show inconsistent results with respect to survival.[8,9] Similarly, reports of postoperative radiation therapy alone have failed to demonstrate local control or survival benefit.[7]

Interestingly, the combination of chemotherapy plus radiation does appear to improve local control and survival.[10] Most studies investigating combined chemoradiation therapy have been in the setting of postoperative adjuvant therapy so that the exact stage of rectal cancer is known. Results from studies conducted by the Gastrointestinal Tumor Study Group,[10,11] and the North Central Cancer Treatment Group,[12] led a 1990 National Institutes of Health Consensus Development Conference to conclude that the combination of postoperative chemotherapy and radiation improved local tumor control and survival in stage I and II rectal cancer; it was recommended that this approach be followed in clinical practice.[6]

Demonstration recently in prospective randomized trials that preoperative radiation therapy led to improved local regional control as compared with postoperative radiation therapy,[8,9] combined with improved imaging modalities to allow more accurate preoperative staging, pushed this institution to investigate preoperative chemoradiation for patients with advanced rectal cancer. Few studies have investigated the role of preoperative combination chemoradiation therapy. Recently, Minsky et al.[13] and Meterissian et al.[14] have demonstrated that the addition of fluorouracil (5-FU) alone or

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5-FU and leucovorin to preoperative external-beam radiotherapy increases the resectability and downstaging rates compared with preoperative external-beam radiotherapy alone. Neither of these studies examined the impact of preoperative chemoradiation on survival and local recurrence. The current study was initiated to determine histopathologically the response rate of preoperative chemoradiation in patients with rectal carcinoma, and evaluate the impact of this therapy on local relapse, disease-free survival, and overall survival.

MATERIALS AND METHODS

Patients

The patient population for this study was derived from two groups. Informed consent was obtained from all patients in the study group (n = 43) before enrollment in a Duke University Institutional Review Board-approved prospective trial, aimed at evaluating the efficacy of preoperative chemoradiation in the treatment rectal cancer. All had biopsy proven adenocarcinoma of the rectum, with no evidence of extrapelvic disease. All patients were evaluated before initiation of treatment by history, physical examination, and chest roentgenograms, as well as flexible sigmoidoscopy to 25 cm with biopsy. Barium enema or colonoscopy was obtained to rule out synchronous lesions. Abdominal and pelvic computed tomography scans, along with liver function tests were obtained to ascertain extrapelvic disease. Patients with preoperative extrapelvic disease were excluded from the study. All rectal lesions were evaluated by computed tomography scan and sigmoidoscopy and determined to involve the entire rectal wall. No patient had previous abdominal surgical therapy other than rectal biopsy, and no previous radiation or chemotherapy. All patients had a Karnofsky status of >70, and a serum creatinine level of <2.0 mg/dL, white blood cell count of >4000/mm^3, and platelet count of >100,000/mm^3. All lesions had a median diameter of >3.0 cm. All patients began chemotherapy within 5 days of the initiation of radiation therapy, after informed consent was obtained. None of the patients received additional postoperative therapy.

The control group of patients was obtained retrospectively, and consisted of patients with rectal carcinoma treated surgically at Duke University Medical Center from 1987 to 1993, who were not enrolled in the protocol (n = 56). No patient had previous surgical therapy other than biopsy, and no patient had previous radiation or chemotherapy. All patients had a Karnofsky status of >70, and a serum creatinine level of <2.0 mg/dL, white blood cell count of > 4000/mm^3, and platelet count of >100,000/mm^3. None of the patients had evidence of preoperative or operative extrapelvic disease. Only patients with T2 or T3 rectal lesions, as determined by postoperative pathology, were included. Postoperative management with chemotherapy or external beam radiation therapy was performed at a level commensurate with acceptable standards of care in the treatment of rectal carcinoma.

Preoperative Radiation Therapy and Chemotherapy

Radiation therapy was delivered by photon radiation generated by a 6-mV or greater linear accelerator. Isoentric technique with a source axis distance of 100 cm was used. The three-field or four-field technique was used, with all fields initially localized on a simulator. All patients were simulated with small bowel contrast, and attempts made to exclude small bowel from the fields were made using either an external bladder compression device or bladder distension. The superior field of the AP and anterior-posterior fields was the top of the L5 vertebral body whereas the inferior border was the inferior aspect of the ischial tuberosities or 2 cm inferior to the most inferior aspect of the tumor, whichever was greater. The lateral borders of the anterior-posterior/posterior-anterior fields were 1.5 cm lateral to the pelvic brim. The lateral fields maintained the same superior-inferior borders as the anterior-posterior/posterior-anterior. The anterior border was at the posterior edge of the pubic symphysis, unless there was evidence of invasion of a structure draining to the external iliac nodes; in these cases, the anterior border was extended to the front of the pubic symphysis. The posterior border was 1.5 cm. behind the flat of the sacrum. Treatment was administered five times per week with a daily fraction of 180 cGy. Twenty-five treatments were delivered with a total pelvic dose of 45 Gy.

Chemotherapy consisted of 5-FU and cisplatin, and was begun within 5 days of the first radiation treatment. The dose of 5-FU was 500 mg/m^2 per day, administered as a rapid infusion on 5 consecutive days, followed by a ½ hour infusion of cisplatin (20 mg/m^2 per day). The same chemotherapy was repeated during the last week of radiotherapy. Five hundred milliliters of normal saline were given with each weekly dose of chemotherapy. Premedication with prochlorperazine (10 mg by mouth), dexamethasone (10 mg intravenously), diphenhydramine (50 mg by mouth) and metoclopramide (2 mg/kg by mouth) was used.

Toxicities were graded according to the National Cancer Institute common toxicities criteria, and frequency of toxicity occurrence was tabulated by type and grade. Patients were seen weekly to assess tolerance, weight, and complete blood counts. Radiotherapy and chemotherapy was interrupted for cystitis greater than grade 3, di-

arrhea greater than grade 3, or for moist skin desquamation. Moderate diarrhea and grade 2 cystitis were treated with 20% reduction of 5-FU. Cisplatin was withheld for serum creatinine levels >2.0 mg/dL, until the creatinine decreased below 2.0 mg/dL. Patients with a hemoglobin level of <8.0 were transfused. The dose of 5-FU was reduced by 20% for white blood cell counts <2000/mm^3 but >1000/mm^3 or platelet counts of <75,000/mm^3 but >25,000/mm^3 on the day of treatment. Flouruoracil and cisplatin were withheld for white blood cell counts <1000/mm^3 or platelets count of <25,000/mm^3.

Surgery

Clinical response to chemoradiation was assessed with sigmoidoscopy 2 to 4 weeks after the completion of therapy. Patients with no demonstrable evidence of tumor by examination or biopsy were judged to have complete response; patients judged to have experienced greater than 50% tumor regression were judged to have partial response. Surgery was performed 3 to 4 weeks after completion of chemotherapy. Operative options included abdominoperineal resection, low anterior resection, and transanal excision.

Statistics

Separate analyses were performed on the following three response variables: the time to disease recurrence (with censoring of all patients who remained free of local or distant metastases), the time to pelvic recurrence (with censoring of all patients who remained free of pelvic recurrence), and the survival (with censoring of all patients who remained alive without regard to disease status). Survival distributions were estimated according to the product-limit method of Kaplan-Meier.[15] Distribution comparisons were made with the Cox-Mantel test. A p value of <0.05 was considered significant. Additionally, the protocol group was subdivided into three groups based on final pathologic diagnosis—sterile, microscopic disease only, and residual gross disease. Kaplan-Meier distributions for these three subgroups compared with the control group also were examined.

RESULTS

Patient-Study Group

Forty-three patients with a mean age of 59.2 years (median 61 years, range 31–81 years) were enrolled in the study between January 1987 to December 1993. There were 31 men and 12 women. By sigmoidoscopy, all tumors were >3.0 cm before therapy, and by computed tomography scan, all tumors were shown to involve the entire rectal wall. There were 56 patients in the control group, with a mean age of 61.5 years (median 62 years, range 29–89 years); 35 were men and 21 were women.

Table 1. NONHEMATOLOGICAL TOXICITIES REQUIRING PROTOCOL ALTERATION

Toxicity	Number of Patients (%)
Moderate diarrhea*	5 (12)
Severe diarrhea†	2 (5)
Intractable diarrhea‡	1 (2)
Severe cystitis§	1 (2)

* Required 20% dose reduction in 5-FU.
† Required interruption of protocol for 2 weeks.
‡ Required termination of the protocol after 3 weeks.
§ Required interruption of the protocol for 1 week.

Response to Therapy

The nonhematologic toxicities associated with chemoradiation are shown in Table 1. The protocol was well tolerated without event in most patients. Diarrhea was the most common side effect, seen in 42 (97%) patients. Five patients suffered moderate diarrhea requiring dose reduction of 5-FU, 2 had the chemoradiation interrupted for 2 weeks because of severe diarrhea, and 1 patient failed to complete the preoperative protocol after 3 weeks because of intractable diarrhea. One patient had severe cystitis requiring suspension of chemoradiation for 1 week. One additional patient suffered from radiation-induced neuritis after the course of radiation therapy, and required prolonged rehabilitation after surgery. Hematologic toxicity was seen in six patients, necessitating transfusion for anemia; preoperative therapy was not interrupted.

All patients had reduction in the size of the tumor as determined by sigmoidoscopic evaluation postchemoradiation. Twenty-two patients were assessed with clinical complete response. The clinical response, however, did not impact on surgical therapy. All patients underwent operations deemed appropriate for the original tumor, not the postchemoradiation tumor.

Surgery

In the protocol group, 34 patients underwent abdominoperineal resection. Five patients underwent low anterior resection with primary reanastomosis whereas two had transanal wide-local excision after their chemoradiation therapy. Two patients refused definitive surgery when they were informed that their chemotherapy and

Table 2. POSTOPERATIVE COMPLICATIONS

Complication	Preoperative Chemoradiation (n = 41)	Control Group (n = 56)
Perineal drainage	20 (49)	5 (9)
Perineal dehiscence	4 (10)	0 (0)
Small bowel obstruction	3 (7)	2 (4)
Operative management	2 (5)	0 (0)
Abdominal wound infection	6 (15)	5 (9)
Abscess—operative drainage	2 (5)	0 (0)

radiation therapy had resulted in apparently complete response. Pathologic examination of the surgical specimens revealed that 11 of the 41 (27%) were microscopically free of tumor and had negative lymph nodes. Thus, 11 of the 20 patients (55%) determined to have complete clinical response actually had sterile operative specimens; 9 had microscopic disease alone. Twenty-one specimens had residual gross disease, and 35 of 39 (90%) specimens evaluated for nodal metastases were negative. Four patients had node-positive disease (range of 1–10 nodes positive).

There was no operative mortality from the protocol group. The morbidity of the combined modality treatment is outlined in Table 2. Twenty patients (49%) had prolonged perineal drainage, and four (10%) had perineal wound dehiscence and healed by secondary intention. Three patients had postoperative small bowel obstructions, and two of these patients required operative management. Six patients had delayed wound healing of the abdominal wound, and two others had abscesses requiring operative drainage.

In the control group, 35 patients underwent abdominoperineal resection, 16 underwent lower anterior resection, 2 had Kraske procedures performed, and 3 had transanal removal of tumor. Twenty-five lesions were pathologically graded T2, and 29 were T3. Nodes were positive in 14 of 51 patients (27%), with number of positive nodes ranging from 1 to 14. Postoperative complications are outlined in Table 2.

Survival

Of the patients in the protocol, 39 of the 43 remain alive (median follow-up = 25 months), and 1 of the 11 patients with complete response has suffered local recurrence and lung metastases. Six of the 32 (19%) patients with residual disease at the time of operation (2 with positive nodes) had metastases (median time to metastases 10 months, range 3–15 months). Three patients had metastases to the lung, two had metastases to the liver, and

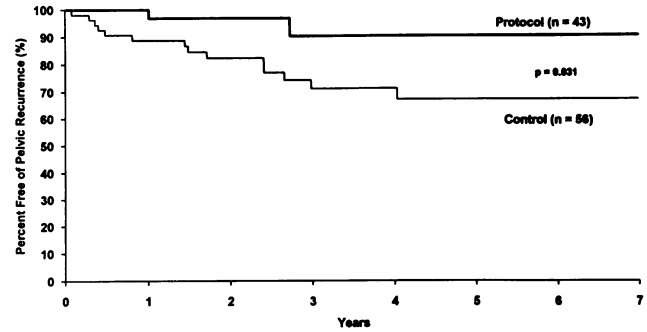

Figure 1. Kaplan-Meier survival distribution, according to treatment. Distibution comparisons were made with the Cox-Mantel test. p of <0.05 was considered significant.

one had metastases to the base of the skull. Three patients with metastases have died (median survival after diagnosis of metastases 36 months). Local recurrences were seen in 2 of 43 patients (<5%) in the protocol.

In the control group, there were pelvic recurrences in 13 (23%) patients, with a median time to recurrence of 13 months (range 1–54 months). Twelve patients (21%) suffered metastatic recurrence of disease (8 liver, 3 lung, and 1 brain). Twenty-two patients (1 with T2, 21 with T3) underwent postoperative chemoradiation (5-FU and 45–55 Gy), and five other patients with T3 lesions, not treated with postoperative chemoradiation, underwent postrecurrence chemotherapy (5-FU) and 45 to 50 Gy radiation therapy. One patient with lower anterior resection suture-line recurrence underwent abdominoperineal resection, and one patient with isolated liver metastases underwent hepatic resection. Of the 14 patients with positive nodes, 10 have developed metastatic disease, and 8 have died. Median survival with node-positive disease was 19 months. Median follow-up in the control group is 36 months, and the overall mortality is 38% (21 of 56).

Figures 1, 2, and 3 depict pelvic recurrence-free survival, disease-free survival, and overall survival of the

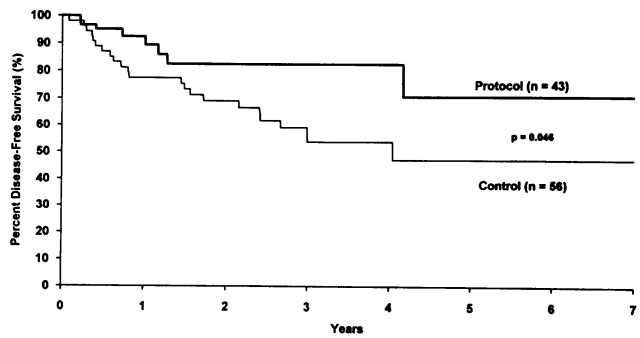

Figure 2. Kaplan-Meier survival distribution for time to pelvic recurrence, according to treatment. Distibution comparisons were made with the Cox-Mantel test. p of <0.05 was considered significant.

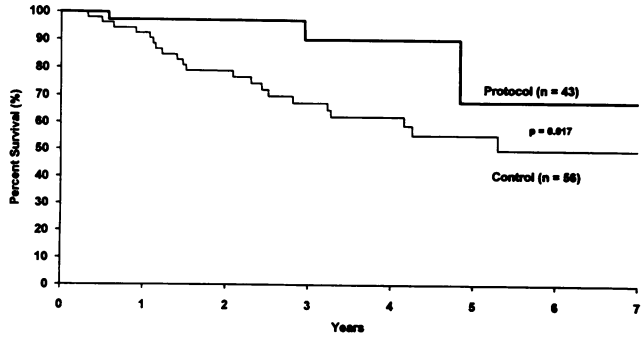

Figure 3. Kaplan-Meier distribution for disease-free survival, according to treatment. Distibution comparisons were made with the Cox-Mantel test. p of <0.05 was considered significant.

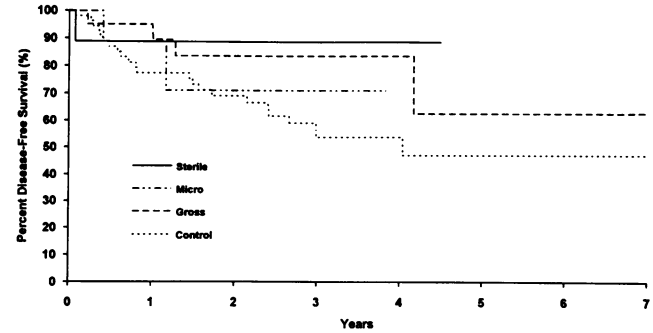

Figure 5. Kaplan-Meier survival distribution for time to pelvic recurrence, according to pathologic subgrouping of patients in protocol.

protocol group compared with the control group. There is a statistically significant increase in overall (p = 0.017) and disease-free survival (p = 0.046), as well as a decrease in pelvic recurrence (p = 0.031) for patients undergoing this protocol compared with conventional management. Distributions for local recurrence, disease-free survival, and overall survival of the protocol subgroups (based on final pathology) are shown compared with the control group, in Figures 4, 5, and 6.

DISCUSSION

Traditionally, therapy for large rectal carcinomas using radical surgery alone has been accompanied by poor survival and high local recurrence rates. The use of chemotherapy and radiation therapy in the adjuvant management of rectal carcinoma has been found to increase disease-free survival and decrease local recurrences. This report details the use of neoadjuvant chemotherapy and radiation therapy in a series of patients with large (>3.0 cm diameter) rectal carcinomas involving the entire rectal wall.

Preoperative radiotherapy has been examined in a number of trials. Theoretically, there are several potential advantages of delivering radiotherapy preoperatively: 1) the radiation is delivered to well-vascularized and well-oxygenated tumor; 2) the implantation of viable tumor cells, either locally or through vascular channels as the tumor is manipulated during surgery, can be minimized; and 3) radiation injury to the small bowel decreased because the small bowel is free and not adhered to the pelvis. Preoperative radiotherapy has been explored in a number of retrospective and prospective trials.[16–18] All of these studies demonstrated considerable improvement in both survival and local control when compared with historic controls. Seven randomized prospective trials also have been reported.[7] Unfortunately, five of the seven delivered a dose of radiotherapy, which is quite low by modern standards. Accordingly, all five were negative studies. However, two more recent studies from Europe[8,9] were performed with more appropriate doses of radiotherapy. The European Organization for Research in the Treatment of Cancer randomized 466 patients with rectal cancer to receive either surgery alone or preoperative therapy plus surgery.[8] When considering only the 341 patients found to have localized disease at the time of surgery, the local recurrence rates in the radiated group was 15% compared with 30% in the control group (p = 0.003). Survival was improved from 60% to

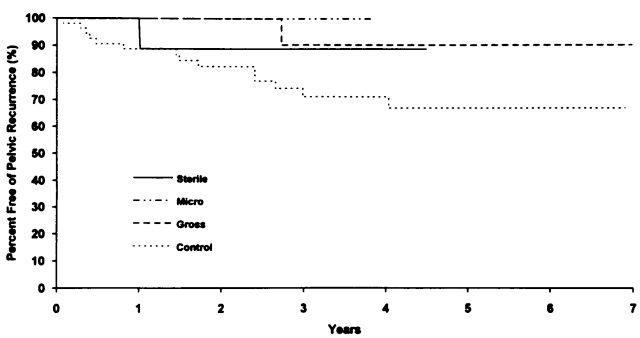

Figure 4. Kaplan-Meier survival distribution according to pathologic subgrouping of patients in protocol.

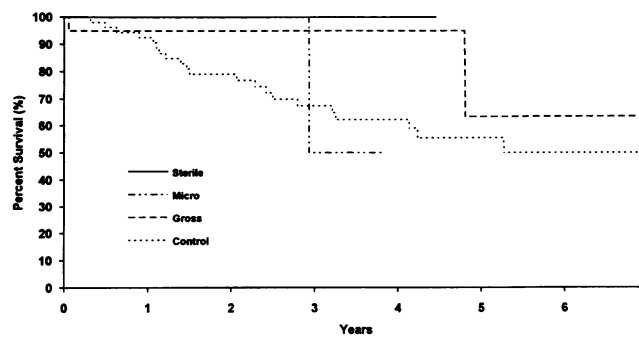

Figure 6. Kaplan-Meier distribution for disease-free survival, according to pathologic subgrouping of patients in protocol.

70% for patients receiving preoperative therapy (p = 0.08). The Stockholm study[9] randomized 849 patients and examined results in 679 without metastatic disease. There was a significant reduction in radiated patients in both local recurrence and death due to rectal cancer. In both of these studies, stage A and B_1 disease were included in the analyses, and it is conceivable that the results would have been better if these were excluded. In a recent Swedish report, preoperative radiation therapy was compared with postoperative radiotherapy in a randomized multicenter trial.[19] Although the dose of preoperative group was lower than that given to postoperative group (25.5 Gy *vs.* 60 Gy, respectively), the local control rate was significantly better in the preoperative group compared with the postoperative group (12% local failure *vs.* 21% in those with curative resection; p = 0.02). There was no difference in survival between the groups. To date, no randomized series has concluded that preoperative radiation therapy as a single adjuvant has a significant survival benefit.

In an attempt to improve local control and increase systemic control, several different chemotherapeutic agents have been used in conjunction with radiotherapy. Cisplatin was first described to enhance radiation cytotoxicity by Zak and Drobni.[20] Although the exact mechanism of cisplatin radiation sensitization are unclear, it has been shown to enhance radiation both before and after radiation.[21-23] *In vitro* and *in vivo* laboratory data indicate the enhancement is greatest in cells that are intrinsically sensitive to cisplatin. Moreover, there is indication that the radiation sensitization is dose dependent,[24] and that doses in the range of 100 mg/m^2 lead to tissue concentrations that should provide radiation enhancement. Similarly, 5-FU is known to have radiation sensitization effects. Shortly after its original description, 5-FU was shown to be a radiation sensitizer[25,26]; recent *in vitro* and *in vivo* experiments have supplemented this, although the exact mechanism has yet to be elucidated.[27,28]

Surprisingly, there have been few studies examining the effect of preoperative radiotherapy and chemotherapy. In preoperative radiotherapy for rectal carcinoma, Minsky et al.[13] and Meterissian et al.[14] have demonstrated the radiation enhancement of 5-FU with or without leucovorin. The results from our preliminary report demonstrate that preoperative 5-FU/cisplatin and radiation treatment resulted in histopathologically confirmed tumor response, which translated into local-relapse, disease-free survival and overall survival benefits. Only one patient with a sterile operative specimen suffered local recurrence, and overall, only two patients had local recurrences. Cox-Mantel comparison of Kaplan-Meier distributions demonstrates a statistically significant improvement in local recurrence (p = 0.031) and disease-free survival (p = 0.046). Overall, only 3 (7%) protocol patients have died, compared with 21 (37.5%) in the control group (p = 0.017).

The combination of radiotherapy and chemotherapy was well tolerated by most patients, with diarrhea not requiring alteration of the protocol noted in 77%. Hematologic toxicity was seen only in six patients, and preoperative therapy was not interrupted. The toxicities compare well with data reported by Minsky[13] and Meterissian.[14] In these series, incidence of diarrhea were 100% and 73%, respectively. In postoperative protocols using combined chemoradiation therapy, the incidence of diarrhea has been reported at a rate of 80%.[10] In our study, diarrhea was most frequently mild and easily controlled with antimotility agents. Postoperative complications in the protocol group occurred more frequently than in the control group. The most common occurrence was delayed wound healing with prolonged wound (perineal) drainage. In the Stockholm report, preoperative radiation therapy was associated with a higher incidence of wound infection, compared with the surgery-alone group.[9] The same observation was made in our study. Two previous reports of preoperative chemoradiation therapy in the treatment of rectal carcinoma did not report data on their postoperative complication type and frequency.[13,14]

In this series, 11 of 41 (27%) patients had no evidence of tumor in their resected specimens, and overall, 10% (4 of 39) of the patients had positive lymph nodes. The percentage exceeds the rates quoted in studies using preoperative radiation therapy alone.[11,29-31] Minsky reported a slightly lower rate of 20% sterile specimens after preoperative 5-FU and leucovorin, with 30% having positive nodes. The lower rate of sterile specimen may reflect the fact that the group receiving combined therapy represented more advanced disease; alternatively, it could reflect fact that the dose of 5-FU used in their series was not optimal.[32] In our series, all of the tumors appeared to have decreased in size after the course of therapy; this was based on pretherapy computed tomography, physical examination, and biopsy compared with post-therapy sigmoidoscopy and biopsy. Beynon et al. have shown that endoscopic rectal ultrasound is more accurate than computed tomography in predicting depth of invasion.[33] It is possible that preoperative staging methods used in our series allowed the inclusion of less advanced disease; this may have accounted for a higher rate of sterile specimens. To reduce this possibility, endoscopic ultrasound is now included in our protocol as a more accurate means to stage rectal carcinoma preoperatively.[34] Pre- and post-therapy staging with endoscopic ultrasound was examined by Meterissian et al. In their series, there was a 30% complete response after 5-FU and radiation therapy, which compared favorably to our series. Importantly, they note that with regards to post-therapy staging after chemoradiation, the pathologic pre-

sentation of rectal cancer may be altered, implying that surgical resection is imperative to confirm complete clinical remission[14] as 64% of patients with negative proctoscopic biopsy post-treatment had residual tumor on final pathology. In our series, the percentage with negative post-treatment proctoscopic examination who actually had residual minor was lower, at 45%.

Seventy-seven percent (34/43) of patients received abdominoperineal resection, 12% received (5 of 43) lower anterior resection, and 5% (2) had wide local excision. As mentioned previously, there was no attempt in this preliminary study to reduce the magnitude of the operative procedure. The operation performed was selected based on the tumor size and location before the administration of the neoadjuvant protocol. The high rate of tumor downstaging (27% sterile specimens) however, suggests that less radical surgery may be possible. In a recent retrospective review, Paty et al. examined the treatment of rectal cancer by low anterior resection with coloanal anastomosis.[35] This study determined that pelvic recurrence was not associated with short distal margin, but rather correlated with T stage (T3 *vs.* T1–2), positive microscopic margins, perineural and blood vessel invasion, tumor grade, and mesenteric implants; pelvic recurrence was independent of tumor size and N stage. Thus, the ability to perform sphincter-sparing surgery depends primarily on control of the tumor. The ability to downstage tumors, as our protocol has demonstrated, suggests that less radical surgery could be performed without compromising local control. We currently are investigating the role of sphincter-preserving surgery in selected patients after chemoradiation downstaging.

This therapeutic regimen has provided enhanced local control, decreased metastases and increased survival, and supports the continued investigation of preoperative chemotherapy and radiation therapy for the management of advance rectal cancers. The data, however, should be interpreted with caution, because a prospective randomized trial is needed to determine the ultimate impact of complete response and decreased pelvic node involvement on local control, survival, and the ability to perform sphincter-sparing surgery. Furthermore, optimization of preoperative chemotherapeutic regimes may enhance sterile specimen rates. Already, a 27% incidence of sterile pathologic specimens and a low rate of positive lymph nodes in a group with advanced lesions strongly suggest that significant tumor downstaging is occurring with neoadjuvant therapy; this may allow less radical surgery, and hopefully, will lead to increased rate of sphincter preservation in the future.

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Discussion

DR. EDWARD M. COPELAND III (Gainesville, Florida): At the University of Florida, our group has used preoperative radiation therapy for the past 14 years, and Dr. Kirby Bland presented the results of this treatment before the Southern Surgical Association in 1991. Like Seigler's group, we compared our results to a nonrandomized control group with similar preoperative staging. Most patients were downstaged, and both survival and local control were significantly improved by preoperative radiation therapy.

We had fewer treatment complications in our patients, probably because we did not use concomitant chemotherapy. Currently, we are using continuous infusion of 5-fluorouracil in combination with preoperative radiation therapy, and our toxicity remains minimal.

Unlike Dr. Seigler's group, for some time now, we have tailored the operation to the status of the post-treatment lesion. If significant tumor regression occurs, we transanally excise the remaining lesion and ensure complete excision by frozen section control of the resected margins. For gross residual disease, an abdominoperineal resection, low anterior resection, or coloanal procedure has been done with satisfactory healing. I have several questions for Dr. Seigler:

I was surprised by your operative complication rate. The cisplatinum may be contributing to poor wound healing, is it necessary?

Now that you are beginning to tailor your operation to post-treatment staging, what are your criteria for transanal local excision?

Several control patients underwent postoperative chemoradiation. If you compare preoperative *versus* postoperative chemoradiation therapy, is there a benefit for giving the chemoradiation therapy preoperatively?

What has happened to the two patients who had a complete response and refused a surgical procedure?

Thank you for allowing me to discuss this paper.

DR. MARSHALL M. URIST (Birmingham, Alabama): Dr. Chari and Dr. Seigler are to be congratulated for this very clear summary of a group of patients that has been treated under very strict conditions so that we can compare them to other results. I enjoyed reading this manuscript very much and certainly enjoyed receiving it 1 month before the meeting. My questions are very similar to Dr. Copeland's:

First of all, why were the patients who were treated with this protocol chosen for this, and what were the differences in the other patient population? Specifically, were the operations the same?

How many surgeons are involved with the control patient population? I suspect that they were all treated by a single surgeon in the neoadjuvant treatment group. Were the procedures for the other patients as carefully done?

In regard to the control population, the patients in this group were treated according to the standard therapy of that particular time. The question is, did all those patients receive postoperative radiation therapy, and did they also receive chemotherapy?

Also, if they were treated postoperatively, then there was a specimen available. And how many of those specimens had positive lateral margins? Because we know that you really cannot compare positive lateral margin patients with those who had preoperative radiation therapy and then read something into the local recurrence rate.

Finally, these results are very impressive. You have seen statistically significant long-term survivals in these patients and significant decreases in local recurrence. Does this mean that this form of therapy is now the new standard of treatment? Do we now require a randomized trial? Where should we go from here?

DR. RAVI S. CHARI (Closing Discussion): Dr. McDonald, Members, I'd like to thank the discussants for their questions and their kind comments regarding the manuscript.

Dr. Copeland asked the first question about significant tumor regression and what type of operation should be performed. In our manuscript, we did allude to the fact that we are entertaining the thought of sphincter-preserving type of surgery. Right now, all these procedures were performed based on the initial pathology. The difficulty right now is that even though we saw 20 patients preoperatively by biopsy and sigmoidoscopy to have complete clinical response, only 11 of those 20, or 55%, actually had a sterile specimen. And that is a similar result to that reported from the Anderson trial, where they actually saw a lower number, only 36%, having actual sterile specimen. That segment which is going to be amenable to limited procedure still has to be determined.