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The Impact of 5-Fluorouracil and Intraoperative Electron Beam Radiation Therapy on the Outcome of Patients With Locally Advanced Primary Rectal and Rectosigmoid Cancer

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Objective

To analyze the effects of 5-fluorouracil (5-FU) chemotherapy combined with preoperative irradiation and the role of intraoperative electron beam irradiation (IOERT) on the outcome of patients with primary locally advanced rectal or rectosigmoid cancer.

Methods

From 1978 to 1996, 145 patients with locally advanced rectal cancer underwent moderate- to high-dose preoperative irradiation followed by surgical resection. Ninety-three patients received 5-FU as a bolus for 3 days during the first and last weeks of radiation therapy (84 patients) or as a continuous infusion throughout irradiation (9 patients). At surgery, IOERT was administered to the surgical bed of 73 patients with persistent tumor adherence or residual disease in the pelvis.

Results

No differences in sphincter preservation, pathologic downstaging, or resectability rates were observed by 5-FU use. However, there were statistically significant improvements in 5-year actuarial local control and disease-specific survival in patients receiving 5-FU during irradiation compared with patients undergoing irradiation without 5-FU. For the 73 patients selected to receive IOERT, local control and disease-specific survival correlated with resection extent. For the 45 patients undergoing complete resection and IOERT, the 5-year actuarial local control and disease-specific survival were 89% and 63%, respectively. These figures were 65% and 32%, respectively, for the 28 patients undergoing IOERT for residual disease. The overall 5-year actuarial complication rate was 11%.

Conclusions

Treatment strategies using 5-FU during irradiation and IOERT for patients with locally advanced rectal cancer are beneficial and well tolerated.

Carcinoma of the rectum is a heterogeneous disease. At one end of the clinical spectrum, a few patients with superficially invasive cancers are well served by limited procedures such as transanal local excision. The majority of patients with rectal cancer, however, have mobile but more deeply invasive tumors that require low anterior or abdominoperineal resection. At the less favorable end of the clinical spectrum are patients with locally advanced tumors that are adherent to adjoining structures such as the sacrum, pelvic sidewalls, prostate, or bladder. Because these patients do poorly with surgery alone, moderate- to high-dose preoperative irradiation has been used to promote tumor regression and thus facilitate a curative resection.[1,2] Although many of these tumors can become resectable by preoperative irradiation, local control remains a problem, because at least a third of such patients suffer a local recurrence even after complete resection.[1,2] Local recurrence is ominous: first, most of these patients are incurable, and second, locally recurrent cancer eventually causes appreciable pelvic complications.

During the past 20 years, innovative treatment strategies

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have evolved to improve local control beyond external beam irradiation alone. These have included the administration of 5-fluorouracil (5-FU)-based chemotherapy during preoperative external beam irradiation, and the application of intraoperative electron beam radiation therapy (IOERT) to the tumor bed at the time of resection. This study analyzes the impact of these two treatment modalities on the outcome of patients with locally advanced rectal cancer.

MATERIALS AND METHODS

From June 1978 to May 1996, 160 patients underwent preoperative radiation therapy for locally advanced carcinoma of the rectum or rectosigmoid. Fifteen patients were subsequently found to have metastases (liver, paraaortic nodes, or peritoneal implants) at surgery and were excluded from analysis, resulting in 145 evaluable patients. Of these 145 patients, 98 patients were men and 47 patients were women, with a median age of 65 years (range 26 to 85 years). All tumors were biopsy-proven invasive adenocarcinomas and were classified as unresectable either surgically (42 patients) or clinically or radiographically (103 patients).

Presurgical radiation therapy was delivered by a four-field technique to the pelvis to a total dose of 45 Gy in 25 fractions over 5 weeks.[3,4] With reduced fields, additional irradiation to the primary tumor was usually given to a total dose of 50.4 Gy. During the early period of this study (1978 to 1985), patients did not routinely receive 5-FU during the course of external beam irradiation (52 patients). Beginning in 1986, patients received 5-FU (500 mg/m^2 per day) for 3 consecutive days during the first and last weeks of irradiation (84 patients), usually the first 3 and last 3 days. More recently, the administration of 5-FU has changed. Since 1994, patients received 5-FU as a protracted venous infusion (225 mg/m^2 per 24 hours) throughout the 5- to 6-week course of preoperative radiation therapy (nine patients). Because of small patient numbers, the clinical data of the 9 patients receiving the protracted venous infusion of 5-FU were pooled with the results of the 84 patients receiving bolus 5-FU, for a total of 93 patients receiving 5-FU. This information was compared with that for the 52 patients treated with external beam irradiation without chemotherapy.

Four to 6 weeks after completion of radiation therapy, patients underwent laparotomy. At surgery, the abdomen was examined, and patients found to have metastases underwent diversion or resection alone (15 patients). These patients were excluded from analysis. Patients without metastases underwent an abdominoperineal resection, low anterior resection, or exenteration. In most patients, gross removal of tumor was carried out. In the remainder, subtotal resection was carried out, leaving as little residual cancer at the points of adherence as feasible. Three patients had completely unresectable tumors. Close attention was paid to sites of tumor adherence during the resection. For patients undergoing gross total resection of their tumor, the specimen was taken to the frozen-section pathology laboratory, where the tumor was grossly and microscopically examined for margin status. Patients found to have no tumor adherence and negative margins did not receive IOERT. Patients with residual tumor or patients with positive or close (<5 mm) margins were then evaluated for IOERT.

The technique of IOERT at the Massachusetts General Hospital has previously been described.[3] The area at highest risk was defined jointly by the surgeon and the radiation oncologist, with the most common site being the pelvic sidewall or the sacrum. From our library of cones with various angles and sizes, an appropriate cone was selected to direct the electron beam to the tumor bed in the pelvis. The incision was then temporarily closed with the patient still anesthetized, and the patient was sterilely draped and transported to the radiation therapy department for treatment. Once in the IOERT treatment room, the patient was redraped, the abdomen (or less frequently the perineum) was reopened, and the cone was repositioned in the pelvis and then attached to the head of the linear accelerator. By a 9- to 15-MeV electron beam, a dose of 10 to 20 Gy was delivered to the tumor bed. The lower doses were given for minimal residual disease and the higher doses for gross residual cancer after resection.

Postsurgical external beam radiation therapy was given to 24 patients (19 patients with completely resected tumors and 5 patients with subtotally resected tumors) who did not receive IOERT but who were judged to be at increased risk for local recurrence by surgical and pathologic findings. In these patients, metallic clips were placed at surgery to define the high-risk region, and the small bowel was separated from the pelvis by an omentoplasty or mesh sling. After obtaining a small bowel x-ray to confirm the absence of small bowel within the radiation field, an additional 9 to 18 Gy was given to the demarcated region through carefully designed fields.

Patients were seen 6 to 8 weeks after surgery, and then at 3- to 6-month intervals. Follow-up included physical examination and blood studies (liver enzymes, complete blood count, and carcinoembryonic antigen). Abdominal and pelvic computed tomography scans were usually performed yearly or as needed. The mean follow-up and the median follow-up were 53 and 41 months, respectively. Local control (LC) and disease-specific survival (DSS) rates were calculated at 5 years using the actuarial method of Kaplan–Meier.[5] Local failure and distant metastases were scored until death.

RESULTS

Effect of 5-FU

After preoperative irradiation, no differences were observed in procedure type (low anterior resection *vs.* abdominoperineal resection or exenteration) or extent of surgical

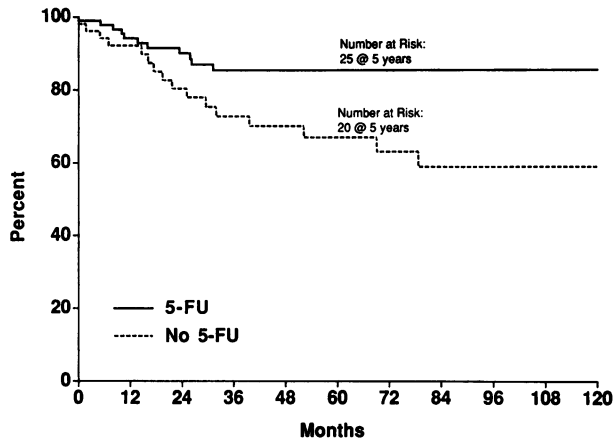

Figure 1. Local control by pre-op 5-FU. Five-year actuarial LC rate with 5-FU administration.

resection (complete *vs.* partial), according to whether or not 5-FU was administered. For patients undergoing preoperative irradiation with 5-FU, the rates for sphincter-preserving procedures and complete resections were 29% and 80%, respectively, *versus* 27% and 71% for patients receiving irradiation only. Similarly, no differences were observed in pathologic downstaging rates by 5-FU administration. A complete pathologic response, or tumor confined to the rectal wall, was seen in 8% and 12%, respectively, of the surgical specimens of patients receiving irradiation and 5-FU. These downstaging rates were 8% and 13% for patients receiving irradiation only.

Analysis of 5-year actuarial LC and DSS rates according to 5-FU use demonstrated an improved outcome for patients receiving 5-FU during irradiation *versus* patients receiving irradiation only (Figs. 1 and 2 and Table 1). The 5-year actuarial LC and DSS rates of the 93 patients receiving 5-FU and irradiation were 85% and 67%, respectively. These figures were 68% and 54% for patients receiving preoperative irradiation only. Subset analysis by extent of resection showed improved LC and DSS rates for patients

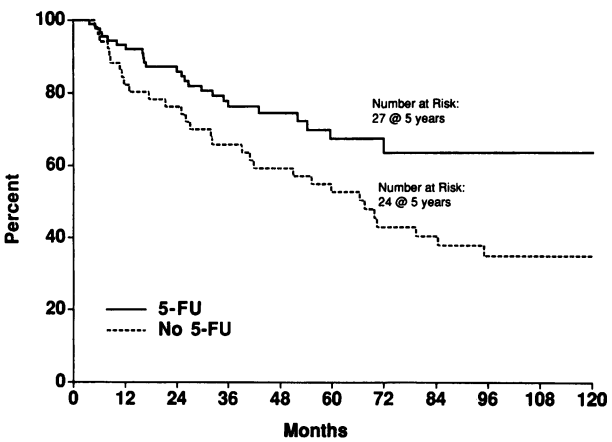

Figure 2. Disease specific survival by pre-op 5-FU. Five-year actuarial DSS rate with 5-FU administration.

undergoing complete resection and partial resection with microscopic residual receiving 5-FU *versus* patients not receiving 5-FU.

Correlation of LC and DSS rates to pathologic stage and 5-FU use was also observed (Table 2). For patients with no residual tumor or tumor confined to the rectal wall, the 5-year actuarial LC and DSS rates of 18 patients receiving 5-FU were both 100%, whereas these results were not as good for the 11 patients not receiving 5-FU. Similar benefits in LC and DSS rates by 5-FU administration were seen for patients with tumors with transmural invasion.

Effect of IOERT

Although IOERT administration was planned for all 145 patients, only 73 patients (50%) actually received IOERT to the tumor bed. The most common reason for IOERT not being given was the perception at surgery of an excellent response of the tumor to preoperative irradiation (absence of tumor adherence to pelvic structures, and satisfactory margins by frozen-section analysis); treatment was judged to be unnecessary (Table 3). This selection bias of IOERT use in patients with more advanced disease is reflected by noting the rates of complete resection and the pathologic stage of the tumors of patients receiving and not receiving IOERT (Tables 4 and 5). Of the 73 patients receiving an IOERT boost, only 45 (62%) underwent complete resection, whereas 66 of 72 patients (92%) not receiving IOERT had a complete resection. This difference was statistically significant by a chi square test ($p = 0.0002$) In patients receiving IOERT, only 9% of the tumors exhibited significant downstaging (no residual tumor or tumor confined to the rectal wall without lymph node metastases). In contrast, 30% of the tumors in patients not receiving IOERT demonstrated no residual tumor or tumor limited to the rectal wall without lymph node metastases. This difference was also statistically significant by a chi square test ($p = 0.002$)

The 5-year actuarial LC and DSS rates for 45 patients undergoing complete resection with IOERT were 89% and 63%, respectively (Figs. 3 and 4 and Table 6). For patients undergoing partial resection, LC and DSS rates correlated with the extent of residual cancer: 68% and 40%, respectively, for microscopic residual disease and 57% and 14% for gross residual disease. The outcome of the 72 patients undergoing resection without IOERT is also summarized in Table 6. Of the 66 patients undergoing complete resection, 47 did not receive additional postsurgical radiation therapy. These patients had 5-year actuarial LC and DSS rates of 76% and 77%, respectively. Although the number of patients at risk is small and the follow-up short, the outcome of the 19 patients receiving postsurgical irradiation after complete resection was excellent, with 95% LC and 88% DSS at 5 years. Five patients with residual disease received postsurgical irradiation; the DSS rate was 0%.

LC and DSS rates with and without IOERT are correlated with pathologic findings of the completely resected tumors

Table 1. FIVE-YEAR ACTUARIAL LOCAL CONTROL AND DISEASE-SPECIFIC SURVIVAL BY RESECTION EXTENT AND 5-FU ADMINISTRATION

Extent of Resection	5-FU # Pts	5-FU LC (%)	5-FU DSS (%)	No 5-FU # Pt	No 5-FU LC (%)	No 5-FU DSS (%)
Complete resection	74	90	77	37	77	68
Microscopic residual	15	83	48	8	25	14
Macroscopic residual	4	25	0	7	43	14
Total	93	85	67	52	68	54

LC = Local Control; DSS = Disease Specific Survival.
Difference in LC and DSS by 5-FU administration for completely resected and microscopic patients as well as total patients is statistically significant ($p < 0.05$).

in Table 7. Although there was a trend toward improved LC and DSS rates for patients with transmural tumors or node-positive tumor receiving IOERT compared with similarly staged patients not receiving IOERT, these differences were not statistically significant.

Complications

For the entire group of 145 patients, the 5-year actuarial risk of complications was 11% (Table 8). The risk of complications for patients receiving or not receiving IOERT was 15% and 7%, respectively ($p = 0.08$). No deaths were seen as a consequence of these complications. The use of chemotherapy did not increase the incidence of complications: at 5 years, the rate was 10% for patients treated with 5-FU.

DISCUSSION

The treatment of locally advanced or clinical stage T4 rectal cancer has evolved during the past 20 years. In the 1980s, treatment programs using moderate- to high-dose preoperative irradiation followed by surgery were carried out at several centers in the United States. These studies showed that a complete resection was possible in one half to two thirds of patients with locally advanced rectal cancer after full-dose preoperative irradiation.[1,2] Despite irradiation and complete resection, local failure occurred in at least one third of these patients. Recent efforts to improve local control have included the administration of concurrent chemotherapy with preoperative irradiation and the use of IOERT at resection.

Because of the efficacy of postsurgical irradiation and 5-FU in the adjuvant treatment of rectal cancer,[6] there has been interest in investigating this approach neoadjuvantly. These investigations have studied combinations of moderate- to full-dose preoperative irradiation (45 to 50.4 Gy) with 5-FU-based chemotherapy. The endpoints of these studies have included not only resectability, local control, and survival but also pathologic downstaging and sphincter preservation rates. One such report recently came from the M.D. Anderson Hospital.[7] Patients with locally advanced rectal cancer who received 45 Gy of preoperative irradiation with continuous-infusion chemotherapy of 5-FU or cisplatin and surgery had 3-year survival and local recurrence rates of 82% and 3%, respectively. These results were in contrast to figures of 62% and 33% for 36 similarly staged patients undergoing preoperative irradiation without chemotherapy. Although there was a higher rate of sphincter-preserving

Table 2. FIVE-YEAR ACTUARIAL LOCAL CONTROL AND DISEASE-SPECIFIC SURVIVAL BY POSTIRRADIATION STAGE AND 5-FU ADMINISTRATION

Postirradiation Pathologic Stage	5-FU (93 pts) # Pts	5-FU (93 pts) LC (%)	5-FU (93 pts) DSS (%)	No 5-FU (52 pts) # Pts	No 5-FU (52 pts) LC (%)	No 5-FU (52 pts) DSS (%)
No residual tumor	7	100	100	4	67	75
Tumor limited to bowel wall	11	100	100	7	69	86
Tumor through wall	53	84	67	24	71	54
Lymph node metastases	22	73	38	17	50	35

LC = Local Control; DSS = Disease Specific Survival.
No significant differences in LC and DSS by 5-FU administration.

Table 3. REASONS IOERT IS NOT UTILIZED

Reason	# Patients
No obvious site of adherence	49
Technically not possible	13
Unresectable disease	3
Other causes	7
Total	72

IOERT = intraoperative electron beam irradiation.

procedures in patients receiving chemoirradiation *versus* patients undergoing irradiation only (35% *vs.* 7%), there were no differences in resectability rates or pathologic downstaging. Other investigations, however, have reported higher pathologic response and resectability rates with the use of preoperative chemoirradiation.[6–10] Studies from the Memorial Sloan-Kettering Cancer Center and Emory University have reported complete pathologic response rates of 20% after preoperative chemoirradiation for locally advanced rectal cancer.[8,9] A Swedish study reported an enhanced resectability rate in patients with initially unresectable rectal cancer who received preoperative irradiation, 5-FU, methotrexate, and leucovorin rescue compared with patients who received radiation alone (71% *vs.* 34%).[10]

In the present study, the addition of chemotherapy to preoperative irradiation did not increase the frequency of sphincter-preserving procedures, pathologic downstaging, or resectability rates for patients with locally advanced rectal cancer. Sphincter-sparing procedures were performed in 29% of the patients receiving chemotherapy *versus* 27% of those not receiving chemotherapy. The rate of complete pathologic response was 8% in patients receiving chemoirradiation *versus* 8% in patients not receiving chemoirradiation. Complete resections were obtained in 80% of patients receiving chemoirradiation *versus* 71% of patients treated with irradiation only. Although no differences were seen in these endpoints, there were statistically significant improvements in LC and DSS rates in patients receiving 5-FU during external beam irradiation compared with patients receiving preoperative irradiation without 5-FU. The 5-year actuarial LC and DSS rates of the 93 patients receiving 5-FU and irradiation were 85% and 67%, respectively, *versus* 68% and 54% for patients receiving preoperative irradiation only. Although these data are based on a retrospective analysis, it is nevertheless encouraging to see an improved outcome by a simple treatment modification.

IOERT has been used in combination with preoperative irradiation (with and without 5-FU) and surgical resection when there is gross residual cancer, positive

Table 4. TYPE AND EXTENT OF RESECTION BY IOERT ADMINISTRATION

	IOERT (73 Pts) (%)	No IOERT (72 Pts) (%)
Type of resection		
LAR	16 (22)	25 (35)
APR/exenteration/other	57 (78)	47 (65)
Extent of resection		
Complete resection	45 (62)	66 (92)
Partial resection (Micro/macro residual)	28 (38)	6 (8)

IOERT = intraoperative electron beam irradiation; LAR = low anterior resection; APR = abdominoperineal resection.
Difference in frequency of low anterior resection between IOERT and no IOERT patients was borderline statistically significant (p = 0.09).
Difference in rates of extent of resection between IOERT and No IOERT patients was statistically significant (p = 0.0002).

Table 5. POSTIRRADIATION PATHOLOGIC STAGE IOERT ADMINISTRATION

PostIrradiation Tumor Stage	IOERT (73 Pts) (%)	No IOERT (72 Pts) (%)
1. No residual tumor	3 (4)	8 (11)
2. Tumor limited to bowel wall	4 (5)	14 (19)
3. Tumor through bowel wall	40 (55)	37 (51)
4. Lymph node metastases	26 (36)	13 (18)

IOERT = intraoperative electron beam irradiation.
Statistically significant difference (p = 0.002) in rates of pathologic downstaging between IOERT and no IOERT patients.

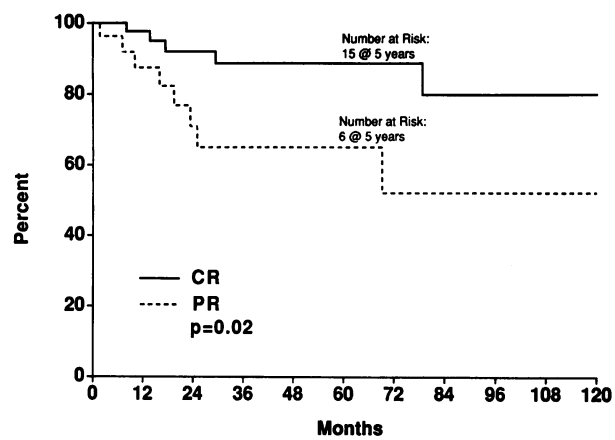

Figure 3. Local control: IOERT CR *vs.* PR. Five-year actuarial LC rate in patients receiving IOERT by extent of resection.

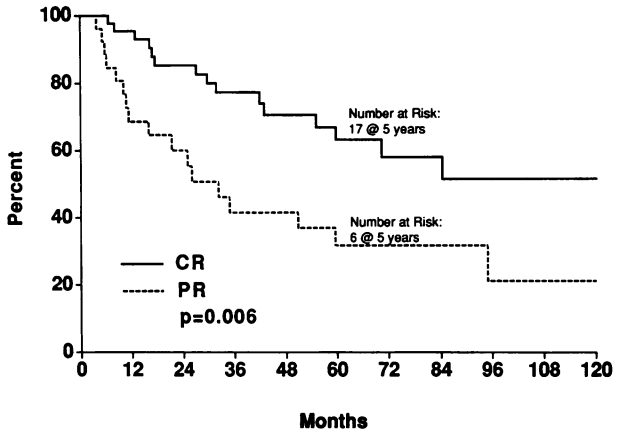

Figure 4. Disease specific survival: IOERT CR *vs.* PR. Five-year actuarial DSS rate in patients receiving IOERT by extent of resection.

microscopic resection margins, or simply tumor adherence. For patients undergoing complete resection followed by IOERT to defined areas of tumor adherence in the pelvis, the 5-year actuarial LC and DSS rates were 89% and 63%, respectively. These results are especially encouraging in view of the advanced stage of disease in the patients receiving IOERT. Similar observations were reported in an analysis of patients treated with preoperative chemoirradiation therapy with or without IOERT at the M.D. Anderson Cancer Center.[7] In that report, of the 11 patients treated with IOERT, no local failures were observed, even though all patients had tumors with full-thickness bowel wall penetration at pathologic examination. In a study from the Mayo Clinic, a local failure developed in only 2 of 39 high-risk patients receiving pelvic irradiation, resection, and IOERT.[11] Researchers at the Memorial Sloan-Kettering Cancer Center reported

Table 6. FIVE-YEAR ACTUARIAL LOCAL CONTROL AND DISEASE-SPECIFIC SURVIVAL BY IOERT ADMINISTRATION

	#Pts	LC (%)	DSS (%)
IOERT			
Complete resection	45	89	63
Partial resection	28	65	32
Microscopic	21	68	40
Macroscopic	7	57	14
No IOERT			
Complete resection	66	82	80
No postop EBRT	47	76	77
Postop EBRT	19	95	88
Partial resection	6	17	0
No postop EBRT	1	0	0
Postop EBRT	5	20	0

IOERT = intraoperative electron beam irradiation; EBRT = external beam radiation therapy; LC = local control; DSS = disease specific survival.

Table 7. FIVE-YEAR ACTUARIAL LOCAL CONTROL AND DISEASE-SPECIFIC SURVIVAL OF COMPLETELY RESECTED PATIENTS BY PATHOLOGIC STAGE

	# Pts	LC (%)	DSS (%)
IOERT			
1. No tumor or intramural tumor only	7	100	63
2. Transmural, and/or lymph node positive	38	86	64
Total	45	89	63
No IOERT			
1. No tumor or intramural tumor only	20	87	90
2. Transmural and/or lymph node positive	27	68	58
3. Postoperative EBRT	19	95	88
Total	66	82	80

IOERT = intraoperative electron beam irradiation; LC = local control; DSS = disease specific survival; EBRT = external beam radiation therapy.

the results of preoperative 5-FU and high-dose leucovorin chemotherapy with sequential radiation therapy for patients with unresectable rectal cancers[12] and noted a 3-year actuarial local failure rate of 29%. Nevertheless, when a high-dose brachytherapy implant was given, the local failure rate dropped to 17%. These data offer compelling evidence that the use of IOERT or brachytherapy in combination with external beam irradiation and surgery improves local control in this high-risk group of patients.

Nineteen of our patients who underwent complete resection and who were considered to be at risk for local failure but did not receive IOERT received postsurgical radiation therapy with encouraging results. Although the numbers are too small and follow-up is too short to draw meaningful conclusions, additional postsurgical irradiation may be of benefit if IOERT (or brachytherapy) is not available. Careful treatment planning must be used to exclude the small bowel from the treatment field. The use

Table 8. COMPLICATIONS

Description	No.
Pelvic abscess	3
Anastomotic leak (temporary colostomy)	1
Sepsis (from central line)	1
Wound dehiscence	1
Small bowel obstruction (required surgery)	2
Small bowel fistula (required surgery)	5
Delayed perineal wound healing	2
Sacral osteoradionecrosis	2
Sacral stress fracture (healed)	1
Ureteral obstruction	2
Urethral fistula (healed)	1
Decubitus ulcer (healed)	1
Total	22

of pelvic omentoplasty or a polyglycolic mesh is often effective in minimizing the amount of small bowel in the postsurgical pelvis.

Residual disease is a therapeutic challenge. Treatment results are inferior to those in patients who undergo complete resection. The patients treated for microscopic residual disease had 5-year actuarial LC and DSS rates of 68% and 40%, respectively, *versus* 57% and 14% for patients with macroscopic disease. Efforts to intensify the neoadjuvant treatment with continuous infusion of 5-FU or leucovorin and 5-FU with external beam irradiation to enhance resectability are being investigated.

The treatment-related toxicity of high-dose preoperative radiation therapy with or without IOERT was acceptable. The 5-year actuarial incidence of complications for the entire group of patients was 11%: 15% for patients receiving IOERT and 5% for patients not receiving IOERT. Case selection may have contributed to the higher complication rate because patients with more advanced disease underwent more extensive surgery and also received IOERT. With continued experience and the lower doses of IOERT currently used (10 to 12.5 Gy for complete resection with negative margins; 12.5 to 15 Gy for subtotal resection with microscopic positive margins; 15 to 20 Gy for subtotal residual with gross residual), the incidence of severe complications should be further reduced.

In conclusion, treatment strategies using 5-FU during external beam irradiation and IOERT for patients with locally advanced rectal cancer are beneficial and well tolerated. Current efforts at improving the outcome in this group of patients with rectal cancer are directed at intensification of the 5-FU chemotherapy regimen during irradiation and the use of maintenance chemotherapy after surgery.

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