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Curative Potential of Multimodality Therapy for Locally Recurrent Rectal Cancer

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Objective
To assess the results of multimodality therapy for patients with recurrent rectal cancer and to analyze factors predictive of curative resection and prognostic for overall survival.

Summary Background Data
Locally recurrent rectal cancer is a difficult clinical problem, and radical treatment options with curative intent are not generally accepted.

Methods
A total of 394 patients underwent surgical exploration for recurrent rectal cancer. Ninety were found to have unresectable local or extrapelvic disease and 304 underwent resection of the recurrence. The latter patients were prospectively followed to determine long-term survival and factors influencing survival.

Results
Overall 5-year survival was 25%. Curative, negative resection margins were obtained in 45% of patients; in these patients a 5-year survival of 37% was achieved, compared to 16% ($P < .001$) in patients with either microscopic or gross residual disease. In a logistic regression analysis, initial surgery with end-colostomy and symptomatic pain (both univariate) and increasing number of sites of the recurrent tumor fixation in the pelvis (multivariate) were associated with palliative surgery. Overall survival was significantly decreased for symptomatic pain ($P < .001$) and more than one fixation ($P = .029$). Survival following extended resection of adjacent organs was not different from limited resection (28% vs. 21%, $P = .11$). Patient demographics and factors related to the initial rectal cancer did not affect outcome. Perioperative mortality was only 0.3%, but significant morbidity occurred in 26% of patients, with pelvic abscess being the most common complication.

Conclusions
This study demonstrates that many patients with locally recurrent rectal cancer can be resected with negative margins. Long-term survival can be achieved, especially for patients with no symptoms and minimal fixation of the recurrence in the pelvis, provided no gross residual disease remains.

In contrast to the acceptance of hepatic and pulmonary resection for isolated colorectal cancer metastasis, there is not general acceptance for the same radical approach for isolated locally recurrent rectal cancer. Rates of local recurrence following "primary" surgery for rectal cancer vary from 5% to 50%.[1,2] Without treatment, mean survival is approximately 8 months[3] and is associated with severe symptomatic disease, especially pain. Radiotherapy alone or in combination with chemotherapy achieves temporary symptomatic improvement in the majority of patients, but 5-year survival is usually less than 5%.[4–6] Complete surgical removal of the recurrent disease remains the best chance of cure after a local recurrence. Palliative surgery alone will prolong survival to a mean of 11 months.[3] Administration of intraoperative radiotherapy (IORT) can achieve the biologic equivalence of two to three times that of the equivalent dose of fractionated external beam radiotherapy.[7] In addition, IORT has the advantage of accurate delivery to the area of maximum concern, while adjacent normal structures are displaced from the irradiation field. In previous studies, the combination of preoperative chemoradiotherapy with delivery of an additional boost of irradiation intraoperatively has been performed in selected patients and has been suggested to improve both local control and survival.[3,8–13] However,

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these studies of multimodality therapy (preoperative chemoradiotherapy, surgery, and IORT) have been limited by small number of patients and short follow-up. While the benefits of such treatment must be also weighed against the potential for significant morbidity associated with multimodality therapy, the morbidity of treatment must be weighed against the morbidity of uncontrolled cancer.[14,15]

The aim of this study was therefore to assess the 5-year results of aggressive multimodality therapy for patients with recurrent rectal cancer, and in particular to identify subgroups of patients who may benefit much from such intervention.

METHODS

Between January 1981 and July 1996, 429 patients were diagnosed as having locally recurrent rectal cancer and, following the initial staging studies, were considered suitable for operative intervention at the Mayo Medical Center (Rochester, MN). All had previously undergone resection of a primary rectal tumor within 15 cm of the dentate line. The patients who received full-dose preoperative chemoradiotherapy (45–54 Gy in 1.8-Gy fractions) were restaged 3 to 5 weeks after completing treatment before proceeding to resection. Thirty-five patients had new evidence of extrapelvic disease and were considered unsuitable for surgery. Surgical exploration was performed in the remaining 394 patients with the intent of performing a gross total resection. Of the 394 patients, 90 were found at the time of surgery to have unresectable local or extrapelvic disease. The remaining 304 patients underwent resection of their recurrent tumor and are the subject of this report. Sixty-three percent of these 304 patients were male and the mean age for all patients at time of reoperation was 60.8 years (range 25–82).

Data were collected by means of chart review, tumor registry information, and a prospectively collected database of all patients who received IORT. Follow-up was available for 96% of patients and was complete for 5 years or until death occurred in 95%.

Stage and Treatment of Primary Tumors

Initial tumor stage according to the modified Astler-Coller criteria was A in 15 patients (5%), B1 in 54 (18%), B2 in 76 (25%), B3 in 15 (5%), C1 in 19 (6%), C2 in 72 (24%), C3 in 15 (5%), and unknown in 38 patients (12%). Primary cancers had been operated on by transanal resection (10%), low anterior resection (56%), abdominoperineal resection (29%), or Hartmann's procedure (5%).

Recurrent Tumors

The interval between resection of the primary cancer and presentation with locally recurrent disease varied between 2 months and 14.6 years (mean 33 months). The interval was less than 1 year in 19%, between 1 and 2 years in 26%, and greater than 2 years in 55% of patients. Recurrence was asymptomatic (SO) in 23% of patients, symptomatic without pain (S1) in 23%, and symptomatic with pain (S2) in 54%. Staging of all patients included chest radiography, CT or MRI of abdomen and pelvis, endoscopic screening of the remainder of the colon, and histologic confirmation of recurrence. The number of sites of fixation to surrounding structures in the pelvis was determined preoperatively by cross-sectional imaging and again at the time of surgery. Recurrent tumors were classified as not fixed (F0, 31%), fixed at one site (F1, 28%), fixed at two sites (F2, 22%), or fixed at three or more sites (F3, 16%).[13] Two patients underwent surgery for para-aortic nodal recurrence (1%).

Surgical and Intraoperative Irradiation Procedure

A reoperation was defined as *curative* if the area where resection was performed was grossly and microscopically free of residual cancer. Resections were considered *palliative* if either gross or microscopic cancer remained at the end of the procedure. Following the administration of anesthesia, patients underwent ureteric stenting and urethral catheterization and were placed in the Lloyd-Davies position. A thorough abdominal exploration was carried out to rule out extrapelvic disease after adhesions were divided. Ureters and iliac vessels were identified and dissected free of the operative field as required unless involved by tumor. Recurrent tumor was resected, along with any adjacent structures involved. Frozen-section analysis was performed of the resected specimen and of the closest margins. On detection of any positive margins, further tissue was resected until negative margins were achieved or until it was not possible to resect further. Duration of the surgical procedure varied from 55 to 1,000 minutes (mean 470). Resection was considered *limited* (n = 174) if no adjacent organ was excised or *extended* (n = 130) if at least one of the involved surrounding organs was removed (i.e., bladder, ureter, vagina, uterus, prostate, sacrum, coccyx, small bowel, omentum and portions of the pelvic wall). Of these 130 patients, 37 (28%) had multiple resections.

Following maximal resection of the recurrent tumor, the radiation oncologist joined the surgeon in the operating room to determine whether patients with suspected or confirmed gross or microscopic residual disease should receive IORT with an electron beam. Lucite applicators of variable diameters were placed in the pelvis, directed at the tumor bed or residual cancer, and fixed to the operating table with a modified Buchwalter retractor. For patients with macroscopic residual disease, IORT was preferably not given unless all residual disease could be included within the selected Lucite applicator. In most instances, the residual disease could be encompassed. The patient was then moved to the linear accelerator in the dedicated operating suite (available since April 1989) and IORT was administered.

Before April 1989, delivery of IORT with electrons required a second operative procedure, usually done within 1 to 7 days in the outpatient radiation oncology suite. The dose of IORT was dependent on the amount of residual tumor and the dose of external irradiation that had been preoperatively delivered. Following IORT the abdominal cavity was closed and the perineum reconstructed.

Patients who presented with central pelvic relapse (anastomotic, other) in whom curative or gross total resection appeared feasible based on CT imaging may have proceeded directly to surgical resection in a routine operating room, having received no preoperative irradiation. The latter patients received postoperative external beam radiotherapy, as indicated, and rarely would have had a second operative procedure to deliver IORT with electrons.

Adjuvant Therapy

Techniques and inclusion criteria of external beam radiotherapy, IORT, and brachytherapy have been described previously.[13] External beam radiotherapy was delivered perioperatively as part of a planned sequence (within 2 months of reoperation) in 244 patients (80%). IORT was delivered in 131 patients (43%). Perioperative chemotherapy for the locally recurrent tumor, usually 5-fluorouracil-based, was given to 166 patients (54%), most frequently concomitant during external beam radiotherapy.

Statistics

Survival curves were generated by the Kaplan-Meier method, and univariate survival comparisons were performed using the log-rank test. Multivariate survival analyses were performed using a Cox proportional hazards model. Univariate and multivariate analyses of factors influencing curative versus palliative resection were performed using logistic regression. A backward stepwise regression technique was used to identify multivariately significant prognostic factors, with variables being eliminated according to likelihood ratio statistics. This process terminated when all maximum likelihood estimate statistics were significant at the 0.05 level. All probability values reported are two-sided, with $P < .05$ used to denote statistical significance.

RESULTS

Surgical Procedures, Morbidity and Mortality

Although all patients went to the operating room with the intention of a curative resection, only 138 patients underwent a histologically confirmed curative resection. The remaining 166 patients had a palliative operation because of either gross (n = 139) or microscopic (n = 27) residual cancer in the pelvic area. Low anterior resection with restoration of intestinal continuity was possible in only 5% of patients with recurrence. The remainder underwent abdominoperineal resection (41%), Hartmann's procedure (7%), or wide local resection of the pelvic recurrence (25%). A further 9% required radical surgery (i.e., sacrectomy, pelvic exenteration, cystectomy with ileal conduit) due to the advanced nature of the tumor. Fourteen patients (5%) had no detectable tumor cells in the resected specimen despite histologic confirmation of recurrent tumor before preoperative chemoradiotherapy. Perioperative mortality was 0.3% (one patient with uncontrollable hemorrhage). Complications required extended hospitalization in 96 patients (32%) and readmission and/or an additional surgical procedure in 78 patients (26%, Table 1). Higher complication rates were observed in those undergoing extended resections (32% vs. 21%, $P = .04$) and in patients whose recurrence was fixed in more than two sites in the pelvis (20% no or one fixation vs. 35% two fixations vs. 32% three or more fixations, $P = .05$). Complications occurred with similar frequency in curative and palliative surgery and had no influence on overall survival. Mean length of hospital stay was similar in patients with curative (15.7 days) and palliative reoperation (16.4 days). Variables associated with palliative versus curative surgery in both the univariate and multivariate analysis are shown in Table 2.

Table 1. COMPLICATIONS

Pelvic abscess	20 (6.6%)
Bowel obstruction	16 (5.3%)
Fistula	13 (4.3%)
Perineal wound	14 (4.6%)
Cardiovascular	3 (0.9)
Others	30 (9.8%)
Total number of complications	96
Total number of patients with complications	78 (26%)

Values are no. (% of 304 patients).

Survival and Influencing Factors

One-year, 3-year, and 5-year survivals and median survival of 304 patients were 84%, 43%, 25%, and 31 months, respectively (Table 3). Five-year survival was greater after curative than after palliative surgery (37% vs. 16%, $P < .001$). Patients with microscopic residual disease tended to have increased survival compared to those with gross residual disease (22% vs. 14% $P = .10$, Fig. 1). Survival for patients with extended resection was not significantly different from those with limited resection (21% vs. 28%, $P = .11$). The number of sites of fixation of the recurrence in the pelvis was significantly associated with poor survival (Fig. 2), as was symptomatic pain. Adjuvant radiotherapy was not indicated in 32 patients after a curative resection and was not used in 18 patients with residual disease (mainly because patients refused further therapy). Five-year survivals for those groups were 56% and 0%, respectively. IORT with

Table 2. FACTORS ASSOCIATED WITH PALLIATIVE VERSUS CURATIVE SURGERY

	Univariate (Frequency)			Multivariate (Logistic)		
Variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Gender						
Male vs. female	0.8	0.5–1.3	.32	—	—	—
Age						
<60 years vs. >=60	1.0	0.7–1.6	.88	—	—	—
Primary operation						
Sphincter-preserving vs. stoma	1.7	1.1–2.0	.02	0.5	0.2–0.9	.06
Recurrent cancer						
No vs. 1 fixation	5.8	3.1–10.9	.001	8.3	3.9–17.4	.001
No vs. 2 fixations	12.9	6.5–25.9	.001	16.2	7.0–37.6	.001
No vs. 3 or more fixations	48.8	19.9–118.9	.001	57.2	17.2 –189.5	.001
Presence of symptoms						
Asymptomatic vs. symptomatic, no pain	0.9	0.5–1.9	.97	—	—	—
Asymptomatic vs. symptomatic + pain	3.2	1.8–5.7	.001	1.4	0.67–3.0	.35

OR, odds ratio; 95% CI, 95% confidence interval.

or without external beam radiotherapy was performed in 52% of patients with palliative surgery; these patients achieved an overall 5-year survival of 21%. Survival for the main prognostic factors within that group were 43%, 24%, 20%, and 0% for nonfixed (F0), F1, F2, and F3 recurrent tumors and 41%, 20%, and 15% for S0, S1, and S2 symptomatic patients, respectively. In the curative surgery group, IORT was used selectively in only 33% of patients and resulted in 26%, 40%, and 0% long-term survival in F0+1, F2, and F3 fixed tumors and 37%, 0%, and 33% in S0, S1, and S2 symptomatic patients, respectively.

DISCUSSION

Published series of surgery for locally recurrent rectal cancer have to date been hampered by small numbers, selected groups, and heterogeneous patient populations. With 304 patients reported and a minimum observation of 5 years for all surviving patients, this is to our knowledge the largest study with the most mature follow-up on surgical resection and multimodality therapy for recurrent rectal cancer. Our results demonstrate that this regimen can be undertaken with acceptable morbidity and low mortality. Multidisciplinary team involvement, rigid management protocols, and a dedicated intraoperative radiation surgical suite are all factors that may have contributed to the low rate of complications.

The goals of treatment for locally recurrent rectal cancer are palliation of symptoms, a good quality of life, and, if possible, cure. Five-year survival rates between 21% and 34% have been reported in several studies and are shown to be influenced by different variables related to the patient demographics, the primary cancer, or the recurrent rectal cancer.[10,11,14,16–19]

Demographics and Primary Cancer

In two recent studies, significant factors for curative reoperative surgery included female gender[17,20] and previous transanal local excision of the primary tumor.[17] In this study, neither patient demographics nor factors associated with the primary rectal cancer or with treatment of the primary cancer appeared to have any influence on survival following resection of the recurrence. These factors included the tumor stage, the type of original resection, use of adjuvant radiotherapy for the primary cancer, and the interval between the primary resection and the presentation with local recurrence, none of which had an impact on survival (unpublished data). Although 33 patients had previously been treated with a transanal excision, a fair number, we also analyzed them combined with other sphincter-saving procedures to see if we could identify significant trends as shown by others.[17] None was found even for this group of 200 patients treated with sphincter-preserving surgery. It was anticipated that these patients would tend to do better based on early detection of recurrence and the increased likelihood of achieving negative margins. Early diagnosis of local recurrence after sphincter-preserving operation is facilitated by surveillance digital rectal examination, sigmoidoscopy, and symptoms of bleeding or changes in bowel habit, whereas the majority of local recurrences after abdominoperineal resections are diagnosed after detection of elevated CEA levels or pelvic pain.[18] When the rectum is surgically absent, recurrent pelvic tumors are quick to invade neighboring structures such as the sacrum or the ureters. This is not so common when the rectum has been reconstructed and should be less so when the native rectum is preserved after local excision.

Table 3. ASSOCIATION BETWEEN POTENTIAL PROGNOSTIC FACTORS AND OVERALL SURVIVAL

	At Risk	Median (yr)	3-yr (%)	5-yr (%)	Log-Rank (univariate) *P* Value
Patient demographics					
Male	192	2.7	45.5	26.2	.80
Female	112	2.2	38.2	23.1	
<60 y	122	2.8	48.0	25.2	.59
>=60 y	182	2.5	39.4	24.9	
Primary operation					
Sphincter-preserving procedure	200	2.8	46.0	28.5	.07
Stoma	104	2.2	36.5	18.5	
Recurrent cancer					
No fixation (F0)*	103	3.1	52.2	37.4	<.001
1 fixation (F1)*	84	3.3	54.2	30.8	
2 fixation (F2)*	66	2.4	37.7	17.2	
>=3 fixations (F3)*	51	1.4	10.6	0	
Asymptomatic (S0)†	71	3.3	53.8	39.4	.001
Symptomatic, no pain (S1)†	69	2.6	49.3	28.4	
Symptomatic, pain (S2)†	164	2.1	35.4	17.6	
Treatment modalities					
Curative	138	3.7	55.5	36.7	<.001
Palliative	166	2.0	32.4	15.5	
Microscopic residual	27	2.5	37.0	22.2	.10
Gross residual	139	1.9	31.5	14.1	
APR	133	2.9	48.3	26.6	.06
LAR	12	4.5	66.7	48.6	
Hartmann	18	1.4	33.3	22.2	
Local resection	100	2.0	33.7	17.6	
Radical resection	27	2.6	40.2	28.1	
No resection	14	4.2	53.8	43.1	
Limited resection	174	2.8	45.1	27.5	.10
Extended resection	130	2.2	39.8	21.2	
Surgery alone‡	50	2.6	46.8	37.3	.39
+ EBRT only‡					
Residual disease	63	1.58	24.5	11.7	
No residual disease	60	3.73	59.9	34.8	
+ IORT ± EBRT‡					
Residual disease	85	2.55	42.4	20.8	
No residual disease	46	2.65	43.3	27.0	
Complications					
Yes	78	2.2	39.1	21.6	0.16
No	226	2.6	44.1	26.3	

APR, abdominoperineal resection; LAR, low anterior resection; radical resection, sacrectomy and/or pelvic exenteration; IORT, intraoperative radiotherapy; EBRT, external beam radiotherapy.

* F0 vs. F1 + F2 + F3: $P < .001$, F0 vs. F1: $P = .06$, F1 vs. F2: $P = .03$, F2 vs. F3: $P < .001$.

† S0 vs. S1: $P = .26$, S0 vs. S2: $P < .001$, S1 vs. S2: $P = .007$.

‡ Regardless of adjuvant chemotherapy.

Local Recurrent Cancer

Variables associated with the presentation of the local recurrence and the amount of residual disease following maximal surgical resection had an important impact on long-term survival in this study. Surgical margin following resection of recurrence was confirmed as having the most significant influence on long-term survival. Negative resection margins were achieved in almost half of the patients in our series and were associated with a 5-year survival of 37%. Patients with microscopically positive margins following maximal surgical resection, even with IORT, had a 5-year survival that was still significantly poorer than from those with negative resection margins, but was slightly better than survival in patients with gross residual disease. Residual gross disease remained the most significant predicting factor for local and systemic failure, despite the use of IORT.[21]

Apart from the margins of resection, the degree of fixa-

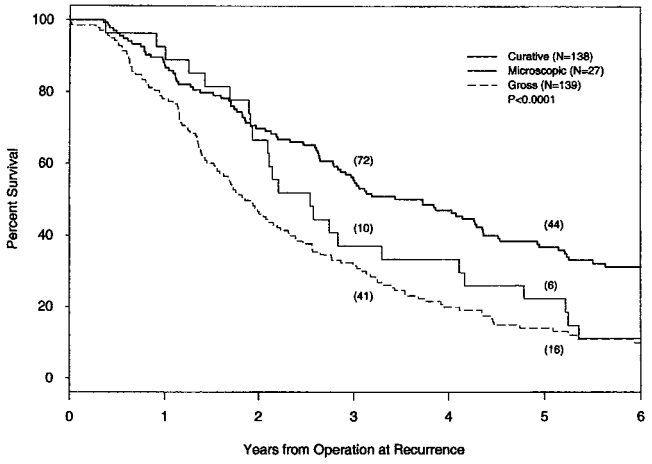

Figure 1. Kaplan-Meier survival curve comparing curative resection to palliative resection (microscopic residual and gross residual disease). The numbers in brackets on each curve indicate the number of patients alive at 3 and 5 years, respectively.

tion of the local recurrence in the pelvis was the most significant prognostic indicator for palliative surgery and for overall survival. Two or more sites of fixation were associated with a significantly worse outcome compared with mobile tumors or those with only one site of fixation. Increasing number of sites of fixation was indicative of a more advanced local tumor recurrence, made surgery difficult, and created technical difficulties in delivery of IORT. Previous reports, with the exception of a recently published study from Japan,[22] have failed to show a significant correlation between local fixation of recurrent rectal cancer and survival, perhaps due to small numbers. This study, however, clearly shows that an increased number of sites of fixation of the recurrent tumor in the pelvis is associated with a significantly inferior outcome with respect to local failure and long-term survival.

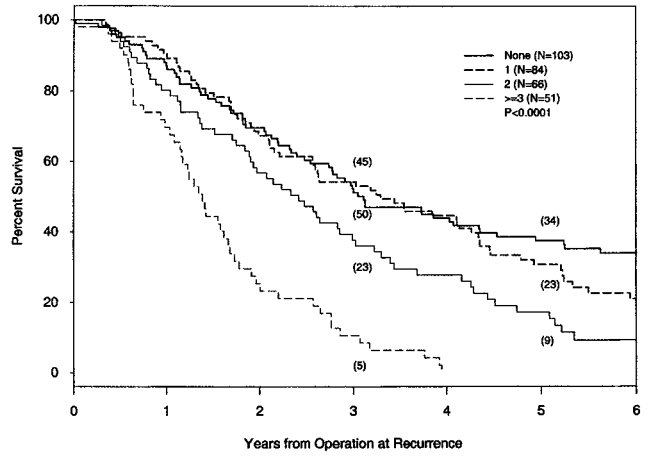

Figure 2. Kaplan-Meier survival curve comparing the number of fixations of the locally recurrent rectal cancer to the pelvis. The numbers in brackets on each curve indicate the number of patients alive at 3 and 5 years, respectively.

Symptomatic pain, another variable associated with the presentation of local recurrence, was also significantly predictive for inferior long-term survival in the current study, but not for curative or palliative resection. The impact of symptomatic stage on overall outcome has been demonstrated in another recent study.[11] Both pain and increased number of fixations in the pelvis indicate an advanced stage of local recurrence, and extended radical resections were more frequently performed in this group of patients.

In addition to examining patient and tumor variables, we considered whether extent of surgery or the use of IORT might influence outcome. Interestingly, extended radical surgery (i.e., complete pelvic exenteration, with or without sacrectomy) was not associated with significantly worse survival at 5 years in this series when compared with more limited or en bloc resection. Without surgery, this group of patients face a grim future, with sacral or trigone invasion. Quality of life following such procedures, therefore, becomes a primary issue in this group of patients. While we did not, in this study, examine quality of life following such radical procedures, a previous study from this institution,[23] which followed 16 patients after sacrectomy for recurrent rectal cancer, found that eight of nine patients remaining alive reported a reduction in pain and an improved quality of life, with 67% of patients returning to gainful employment postoperatively.

As regards the use of IORT, applied as a boost to the area of risk for residual tumor, it theoretically offers the ability to overcome the dose limitation of external beam radiotherapy. IORT can be applied to a specific target field to increase the dose of radiation delivered while at the same time limiting the exposure of normal tissue. Previous studies have demonstrated that IORT achieves excellent local control in primary advanced and recurrent rectal cancers (local control rates of 73%).[7,9] However, no studies to date have been performed in a controlled manner to document a survival advantage for patients treated with IORT in addition to external beam radiotherapy and surgery.[24,25] In our study, IORT was applied selectively in 52% and 33% of patients with palliative or curative surgery and achieved good 5-year survivals (21% and 27%, respectively). The possibility of selection bias precludes the ability to draw definitive conclusions about the independent contribution of the IORT treatment effects for these data. Based on the overall results of the multimodality approach and the specific results of local control with IORT, it seems reasonable to continue this practice of combined therapies.

A small group of patients (5%) had no detectable tumor in the resected specimen despite pathologic confirmation of recurrent cancer before preoperative chemoradiotherapy. These patients behaved identically in terms of long-term survival to those with negative resection margins. This would appear to confirm resection of the area in question. Interestingly, long-term survival was not superior to those patients with recurrent tumor confirmed histologically in the resected specimen who had clear resection margins. Previ-

ous studies of chemoradiotherapy regimens as the only treatment for patients with recurrent rectal cancer have shown 0% to 5% 5-year survivals. This suggests that resection following chemoradiotherapy is preferable, when feasible, in an attempt to improve long-term survival, even when complete tumor eradication apparently has been achieved.

Our resection criteria over the 16 years during which we have performed this type of surgery have become less rigid, as experience grows and facilities improve. All patients with locally recurrent rectal cancer are now accepted for surgical resection following preoperative chemoradiation, with the exception of those with unresectable extrapelvic disease, bilateral ureteric obstruction, or circumferential involvement of the pelvic wall. Long-term survival can be achieved, especially in patients who present with no symptoms and minimal fixation of the recurrence in the pelvis, provided no gross residual disease remains. For patients who present with pain or gross residual disease after maximal resection, overall 5-year survivals of 15% and 21% were achieved in this analysis in patients who had both IORT and external beam radiotherapy. Preferably, patients should receive 5-fluorouracil-based chemotherapy concomitant with external beam radiotherapy preoperatively and four to six cycles of maintenance chemotherapy after resection and IORT in an attempt to maximize disease control (local and systemic) and survival.

References

1. McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. *Int J Colorectal Dis.* 1995;10: 126–132.
2. Carlsson U, Lasson A, Ekelund G. Recurrence rates after curative surgery for rectal carcinoma, with special reference to their accuracy. *Dis Colon Rectum.* 1987;30:431–434.
3. Kramer T, Share R, Kiel K, et al. Intraoperative radiation therapy of colorectal cancer. In: Abe M, ed. *Intraoperative radiation therapy.* New York: Pergamon Press, 1991:308–310.
4. Cummings BJ, Rider WD, Harwood AR, et al. Radical external beam radiation therapy for adenocarcinoma of the rectum. *Dis Colon Rectum.* 1983;26:30–36.
5. Danjoux CE, Gelber RD, Catton GE, et al. Combination chemoradiotherapy for residual, recurrent or inoperable carcinoma of the rectum: ECOG study (EST 3276). *Int J Radiat Oncol Biol Phys.* 1985;11:765–771.
6. Rhomberg W, Eiter H, Hergan K, et al. Inoperable recurrent rectal cancer: results of a prospective trial with radiation therapy and razoxane. *Int J Radiat Oncol Biol Phys.* 1994;30:419–425.
7. Gunderson LL, Martin JK, Beart RW, et al. Intraoperative and external beam irradiation for locally advanced colorectal cancer. *Ann Surg.* 1988;207:52–60.
8. Gunderson LL, Nelson H, Martenson JA, et al. Intraoperative electron and external beam irradiation with or without 5-fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. *Dis Colon Rectum.* 1996;39:1379–1395.
9. Mannaerts GH, Rutten HJ, Martijn H, et al. Comparison of intraoperative radiation therapy-containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer. *Dis Colon Rectum.* 2001;44:1749–1758.
10. Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. *Dis Colon Rectum.* 2002;45:585–592.
11. Hashiguchi Y, Sekine T, Sakamoto H, et al. Intraoperative irradiation after surgery for locally recurrent rectal cancer. *Dis Colon Rectum.* 1999;42:886–893.
12. Lanciano R, Calkins A, Wolkov H, et al. A phase I, II study of intraoperative radiotherapy in advanced unresectable or recurrent carcinoma of the rectum: an RTOG study. In: Abe M, ed. *Intraoperative radiation therapy.* New York: Pergamon, 1991:308–310.
13. Suzuki K, Gunderson LL, Devine RM, et al. Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. *Cancer.* 1995;75:939–952.
14. Willett CG, Shellito PC, Tepper JE, et al. Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. *J Clin Oncol.* 1991;9:843–849.
15. Shaw EG, Gunderson LL, Martin JK, et al. Peripheral nerve and ureteral tolerance to intraoperative radiation therapy: clinical and dose-response analysis. *Radiother Oncol.* 1990;18:247–255.
16. Garcia-Aguilar J, Cromwell JW, Marra C, et al. Treatment of locally recurrent rectal cancer. *Dis Colon Rectum.* 2001;44:1743–1748.
17. Lopez-Kostner F, Fazio VW, Vignali A, et al. Locally recurrent rectal cancer: predictors and success of salvage surgery. *Dis Colon Rectum.* 2001;44:173–178.
18. Salo JC, Paty PB, Guillem J, et al. Surgical salvage of recurrent rectal carcinoma after curative resection: a 10-year experience. *Ann Surg Oncol.* 1999;6:171–177.
19. Suzuki K, Dozois RR, Devine RM, et al. Curative reoperations for locally recurrent rectal cancer. *Dis Colon Rectum.* 1996;39:730–736.
20. Law WL, Chu KW. Resection of local recurrence of rectal cancer: results. *World J Surg.* 2000;24:486–490.
21. Kim HK, Jessup JM, Beard CJ, et al. Locally advanced rectal carcinoma: pelvic control and morbidity following preoperative radiation therapy, resection, and intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys.* 1997;38:777–783.
22. Yamada K, Ishizawa T, Niwa K, et al. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. *Br J Surg.* 2001;88:988–993.
23. Magrini S, Nelson H, Gunderson LL, et al. Sacropelvic resection and intraoperative electron irradiation in the management of recurrent anorectal cancer. *Dis Colon Rectum.* 1996;39:1–9.
24. Wiig JN, Poulsen JP, Tveit KM, et al. Intra-operative irradiation (IORT) for primary advanced and recurrent rectal cancer. A need for randomised studies. *Eur J Cancer.* 2000;36:868–874.
25. Wiig JN, Tveit KM, Poulsen JP, et al. Preoperative irradiation and surgery for recurrent rectal cancer. Will intraoperative radiotherapy (IORT) be of additional benefit? A prospective study. *Radiother Oncol.* 2002;62:207–213.