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ORIGINAL ARTICLE

Preoperative Radiotherapy for Resectable Adenocarcinoma of the Rectum

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ABSTRACT

Objective: *To evaluate recurrence and survival rates in patients with resectable rectal adenocarcinoma treated with preoperative radiotherapy.*

Patients and Methods: *Two hundred and ten patients with resectable rectal adenocarcinoma treated with preoperative radiotherapy and surgery were seen for a minimum 5 years of follow-up. No patient received adjuvant chemotherapy.*

Results: *Local control was 94% at 5 years and 90% at 10 years. Absolute and cause-specific survival rates were 62% and 72% at 5 years, and 40% and 63% at 10 years, respectively. Delayed wound healing and postoperative infections were the most common acute treatment-related side effects, each occurring in 17% of cases. Small bowel obstruction occurred in 4% of patients. Anastomotic leak occurred in 3 (12%) of the 25 patients in whom low anterior resection was performed.*

Conclusion: *This data demonstrates that moderate-dose preoperative radiotherapy increases the likelihood of local control for resectable rectal adenocarcinomas and may thus improve survival. The risk of significant treatment-related complications with this approach is low.*

Key Words: *Radiotherapy, Rectal neoplasms, Surgery*

INTRODUCTION

The risk of local recurrence after surgery alone for rectal adenocarcinoma varies from approximately 20% to 30%.[1-6] The likelihood of salvage after local recurrence has developed is poor.[7-11] Various combinations of adjuvant radiotherapy (RT) and/or chemotherapy, administered either preoperatively or postoperatively, have been used to reduce the risk of local recurrence and improve survival rates. Preoperative RT may also be used to convert patients requiring an abdominoperineal resection (APR) to a sphincter-sparing operation, such as a low anterior resection (LAR). Optimal adjuvant therapy remains to be defined. In particular, debate continues as to whether preoperative or postoperative adjuvant treatment regimens are superior. Preoperative RT has a lower risk of acute treatment side effects compared with postoperative RT, particularly for patients in whom the surgical procedure is an APR.[12] A concern raised by advocates of postoperative adjuvant therapy has been that preoperative RT may unnecessarily 'overtreat' patients who have tumours limited to the muscularis propria with negative nodes, or those with unresectable distant metastases discovered at laparotomy. There is general agreement that a fluorouracil-based chemotherapy regimen is indicated for patients with transmural invasion and/or positive nodes, if adjuvant therapy is administered postoperatively. The role of adjuvant chemotherapy is unclear in patients treated with preoperative RT. The preferred method of administering preoperative RT in the United States is to use a conventionally fractionated course, often combined with adjuvant chemotherapy, based on data extrapolated from the postoperative setting.[13-15] In contrast, the preferred approach in Europe is often a short course of hypofractionated RT alone.[16] The aim of

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this paper is to present our experience with preoperative RT alone in the management of resectable rectal cancer.

PATIENTS AND METHODS

Between 1975 and 1990, 210 patients were treated at the University of Florida with preoperative external beam RT for clinically resectable, previously untreated adenocarcinoma of the rectum. All patients were treated with curative intent. Rectal cancers were defined as clinically resectable if they were freely mobile, 'tethered' (reduced mobility but not fixed), or not palpable on digital rectal examination. Patients usually had clinical and/or radiographic evidence of transmural invasion and/or positive regional lymph nodes (clinical B2–C disease). Patients with disease clinically limited to the muscularis propria were treated with surgery initially unless an abdominoperineal resection would have been required, in which case preoperative RT was given in an attempt to convert the operation to a sphincter-sparing procedure.[17] Cancers involving structures which could be readily removed in conjunction with an APR or LAR, such as the vagina or uterus, were defined as clinically resectable. Patients with tumours defined as clinically unresectable (completely fixed to pelvic structures, i.e. sacrum, side wall, prostate, or bladder) were excluded.[18]

Preoperative evaluation included biopsy of the primary tumour to confirm pathologic diagnosis and digital rectal examination to determine tumour length and configuration, distance from the anal verge, circumferential (annular) involvement, and degree of clinical fixation (freely mobile versus tethered). Additional preoperative tests included a complete blood count, liver function tests, carcinoembryonic antigen (CEA) level, barium enema, colonoscopy, chest radiography, and CT scans of the abdomen and pelvis. All patients also underwent a transrectal ultrasound to assess depth of invasion and to evaluate perirectal lymph nodes. Pretreatment tumour characteristics are shown in Table 1, along with the radiation dose schedules.

All patients were treated with once-daily, continuous–course RT. No patient received adjuvant chemotherapy. Two hundred and nine patients were treated with a four-field box technique; one patient was treated with sacral-perineal wedged fields. The anterior-posterior fields were usually 10 to 12 cm high and 12 to 14 cm wide; the lateral fields were usually 10 to 12 cm in the anterior-posterior dimension. Details of the radiation treatment techniques have been previously published.[2]

Patients were treated with three different dose-fractionation protocols. Beginning in 1975, 32 patients

Table 1. Tumour characteristics (n=210).

Tumour characteristics	Radiation dose			
	30 Gy in 10 fractions (n=73)	31 to 35 Gy* (n=32)	>35 Gy* (n=105)	Total (n=210)
Distance from anal verge				
0–6 cm	47 (64%)	15 (47%)	59 (56%)	121 (58%)
7–12 cm	26 (36%)	14 (44%)	42 (40%)	82 (39%)
13–18 cm	0 (0%)	3 (9%)	3 (3%)	6 (3%)
No data	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
Length of primary tumour				
0–4 cm	40 (55%)	17 (53%)	47 (45%)	104 (49%)
5–8 cm	26 (36%)	15 (47%)	47 (45%)	88 (42%)
≥9 cm	0 (0%)	0 (0%)	2 (2%)	2 (1%)
No data	7 (9%)	0 (0%)	9 (8%)	16 (8%)
Histologic grade				
Well differentiated	5 (7%)	4 (12%)	19 (18%)	28 (13%)
Moderately differentiated	56 (77%)	22 (69%)	70 (67%)	148 (71%)
Poorly differentiated	7 (9%)	6 (19%)	14 (13%)	27 (13%)
No grade	5 (7%)	0 (0%)	2 (2%)	7 (3%)
Fixation				
Mobile	44 (60%)	27 (84%)	60 (57%)	131 (62%)
Tethered	26 (36%)	5 (16%)	38 (36%)	69 (33%)
No data	3 (4%)	0 (0%)	7 (7%)	10 (5%)
Circumferential involvement				
Annular	14 (19%)	8 (25%)	23 (22%)	45 (21%)
Not annular	58 (80%)	20 (63%)	79 (75%)	157 (75%)
Unknown	1 (1%)	4 (12%)	3 (3%)	8 (4%)

* 1.8 Gy per fraction.

Table 2. Operative procedures utilised (n=210).

Operation	Radiotherapy			
	30 Gy in 10 fractions (n=73)	31 to 35 Gy* (n=32)	>35 Gy* (n=105)	Total (n=210)
Abdominoperineal resection	68 (93%)	25 (78%)	82 (78%)	175 (83%)
Low anterior resection	4 (6%)	4 (13%)	17 (16%)	25 (12%)
Abdominal trans-sacral resection	0 (0%)	1 (3%)	1 (1%)	2 (1%)
Total proctocolectomy	0 (0%)	1 (3%)	2 (2%)	3 (1.5%)
Other	0 (0%)	1 (3%)	1 (1%)	2 (1%)
Declined surgery	1 (1%)	0 (0%)	2 (2%)	3 (1.5%)

* 1.8 Gy per fraction.

were treated with doses of 30 to 35 Gy at 1.8 Gy per fraction. Thereafter, the dose was increased to 40 to 50 Gy at 1.8 Gy per fraction for 105 patients. In November 1983, a new treatment protocol was initiated with the objective of reducing the time required for preoperative RT from approximately 5 to 2 weeks. Based on the recommendations of Papillon,[19] a dose of 30 Gy in 10 fractions was delivered to 73 patients who were scheduled for APR surgery. Patients who were expected to undergo an LAR continued to receive 45 to 50 Gy in 25 to 28 fractions.

Surgery was performed for 207 patients; three patients declined resection (Table 2). Surgery occurred an average of 4.5 weeks from the completion of RT (range, 2 to 12 weeks). Sixty eight percent of patients (141 of 207) underwent surgery between 2 and 4 weeks after RT. APR was performed for 175 patients (83%), LAR for 25 patients (12%), abdominal transsacral resection for 2 patients, total colectomy for 3 patients, and exploratory surgery only for 2 patients. A temporary protective colostomy was not routinely performed in patients undergoing sphincter-sparing surgery. After surgery, pathologic staging was completed according to the Astler-Coller modification of the Dukes' staging system.[20,21]

Acute complications secondary to RT were defined as minimal to transient and managed with conservative measures; moderate to persistent and requiring aggressive management but not requiring a break in treatment; and severe, that is, requiring an unplanned interruption in the course of RT.[2,22] Postoperative complications were scored as follows: requiring a second extra-abdominal operation; requiring a second intra-abdominal operation; or fatal.[2] Late complications were defined as those occurring after discharge from hospital and recovery from surgery.

Local recurrence was defined as recurrence within the true pelvis and the perineum. Recurrence in the inguinal lymph nodes and/or peritoneal seeding in the upper abdomen was defined as distant metastasis. All known sites of disease recurrence are included in the analysis of patterns of failure, not only the first site of recurrence.

Patients had a minimum 5-year follow-up period. Four patients were lost to follow-up at 50, 65, 76, and 111 months, respectively; all were without evidence of disease at last contact. Local control, freedom from distant metastasis, absolute survival, and cause-specific survival rates were calculated using the Kaplan-Meier product-limit method.[23,24] Significance of the differences between curves was calculated using the log-rank test.[18,19] Multivariate analysis was performed using the stepwise sequence of chi-squares for the log rank test.[24,26] The following tumour- and treatment-related variables were tested in each multivariate analysis: length of tumour, distance from the anal verge, tumour fixation, annularity of the lesion, external-beam RT dose, operation performed, Dukes' pathologic stage, and tumour histology.

RESULTS

Acute Effects of Treatment

Radiotherapy (210 patients)

The acute side effects of RT were almost always minimal to moderate, regardless of the RT dose protocol used. All patients treated with 30 Gy in 10 fractions or 31 to 35 Gy at 1.8 Gy per fraction experienced either minimal or no acute effects. In those who were given 40 to 50 Gy at 1.8 Gy per fraction, no acute effects were observed in 67 patients, and minimal and moderate acute effects in 34 and 3 patients respectively. A severe acute effect of marked moist desquamation of the perineum developed in one patient during treatment with a sacral-perineal wedged field technique, requiring an unplanned treatment interruption.

Surgery (207 patients)

Acute postoperative complications are presented in Table 3. Of 25 patients who underwent an LAR, 3 (12%)

Table 3. Postoperative complications (207 patients*).

Complication	No. (%)
Bleeding	5 (2)
Infection	36 (17)
Delayed healing	36 (17)
Bowel obstruction	8 (4)
Anastomotic leak	3 (12†)
Embolism	2 (1)
Incontinence	15 (7)
Fistula	7 (3)
Ostomy necrosis	4 (2)
Other	19 (9)

* Three patients declined surgery.
† Percent incidence of anastomotic leak occurrence is based on the 25 patients who underwent a low anterior resection.

experienced an anastomotic leak. No difference was detected in the likelihood of anastomotic leak between patients with a stapled anastomosis and those with a hand-sewn anastomosis. Complications in the 'other' category were minor, contributing to delays in discharge. There were no second operations required and no fatalities due to postoperative complications.

The incidence of postoperative complications necessitating a second operation, stratified by the RT dose-fractionation protocol, is presented in Table 4. No significant difference was seen between the three RT treatment groups. Additionally, no other treatment or tumour variables were significantly predictive for severe complications, including the use of LAR versus the use of APR. Small bowel obstruction was the indication for a second intra-abdominal operative procedure in 7 of the 14 patients (50%). Fistula formation and ostomy failure were the two other most common causes for secondary operative procedures. Two postoperative deaths occurred less than 30 days after surgery, one caused by bleeding and the other secondary to femoral arterial thrombosis.

Findings at Surgical Resection (207 Patients)

Gross total resection of tumour was performed in 190 (90%) of the 210 patients. Pathologic stage, stratified by preoperative dose-fractionation protocol, is presented in Table 5 for the 207 patients who underwent a surgical procedure. A complete pathologic response to preoperative RT, with no identifiable residual tumour, occurred in 17 (8%) of 207 patients. Positive nodes (pathologic stage C1 or C2) were seen in only 38 (18%) of 207 patients, presumably reflecting down-staging as a result of the preoperative RT.

Incomplete resection was due to distant metastasis in 16 patients, and inadequate margins of resection in one patient. Three patients also declined to undergo resection, with clinical signs and symptoms of local tumour progression eventually developing. Of the 16 patients with known distant metastases after surgery, local recurrence developed in three patients (19%). In one patient with a pathologic stage C2 tumour, the operating surgeon indicated that adequate margins of resection were not achieved because an unresectable structure was in close proximity. Early symptoms of local recurrence developed in this patient, who died with no evidence of distant metastases. These 20 patients were excluded from further outcome analysis because the planned treatment could not be completed.

Table 4. Postoperative complications necessitating surgery versus fractionation schedule (207 patients*).

	Radiation dose			
Second operative procedure performed	30 Gy in 10 fractions (n=72)	31–35 Gy† (n=32)	>35 Gy† (n=103)	Total (n=207)
Intra-abdominal	4 (6%)	2 (6%)	8 (8%)	14 (7%)
Other	3 (4%)	1 (3%)	6 (6%)	10 (5%)

* Three patients excluded who declined surgery.
† 1.8 Gy per fraction.

Table 5. Dukes' pathologic stage versus fractionation schedule (207 patients*).

	Radiotherapy			
Stage	30 Gy in 10 fractions (n=72)	31–35 Gy† (n=32)	>35 Gy† (n=103)	Total (n=207)
O	7 (10%)	2 (6%)	8 (8%)	17 (8%)
A	3 (4%)	2 (6%)	7 (7%)	12 (6%)
B1	20 (27%)	8 (25%)	31 (30%)	59 (29%)
B2	24 (33%)	11 (35%)	30 (29%)	65 (31%)
C1	2 (3%)	1 (3%)	5 (5%)	8 (4%)
C2	12 (17%)	2 (6%)	16 (15%)	30 (14%)
D	4 (6%)	6 (19%)	6 (6%)	16 (8%)

* Three patients declined surgery.
† 1.8 Gy per fraction.

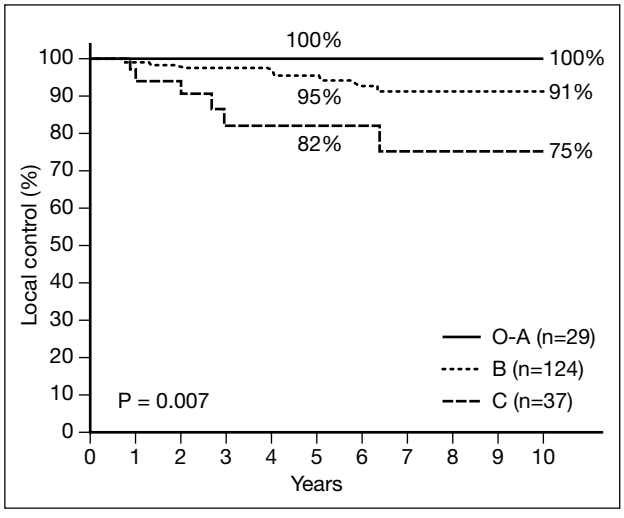

Figure 1. Local tumour control following treatment according to Dukes' pathologic stage (n=190).

Local Control (190 Patients)

The local control rate was 94% at 5 years and 90% at 10 years and was related to pathologic stage (Figure 1). Local recurrence developed in 14 (7%) of the 190 patients who underwent an apparent complete resection, nine of whom also developed distant metastasis. Patterns of tumour recurrence according to pathologic stage are presented in Table 6. No patient who had a local recurrence was successfully retreated. On univariate analysis, the pathologic stage was significantly predictive of local control whether stratified as 0-A vs B vs C (p = 0.007; Figure 1) or 0-A vs B1-C1 vs B2-C2 (p = 0.02).

At 5 and 10 years, local control rates according to surgical procedure performed were as follows: APR, 95% and 91%; LAR, 91% and 91%; other procedures, 80% and 53% (p = 0.02). No significant difference was found in local control rates for patients who had LAR compared to those who had APR (p = 0.7). On multivariate analysis, the variables prognostic for local control were Dukes' pathologic stage (p = 0.0004) and surgical procedure performed (p = 0.01).

Distant Metastasis (190 Patients)

Distant metastasis was the most common form of recurrence, occurring in 55 of 190 patients in the analysis group (as well as 16 patients found to have Stage D disease at surgery and excluded from analysis). In 46 patients who underwent an apparent complete resection, distant metastasis was the only 'failure' noted. The distant metastasis rate was 29% at 5 years and 33% at 10 years. On univariate analysis, local recurrence was a significant predictor of distant metastasis (p = 0.0001). On multivariate analysis, the only variable predictive for distant metastasis was Dukes' pathologic stage (p = 0.0002).

Survival

The absolute survival rate was 78% at 3 years, 62% at 5 years, and 40% at 10 years (Figure 2). The cause-specific survival rate was 84% at 3 years, 72% at 5 years, and 63% at 10 years (Figure 2). On univariate analysis, local recurrence was a significant prognostic factor for both absolute survival (p = 0.007) and cause-specific survival (p = 0.0001). On multivariate analysis, variables that were prognostic for absolute survival were Dukes' pathologic stage (p = 0.0004) and length of the primary tumour (p = 0.04); for cause-specific survival, Dukes' pathologic stage was the only significant prognostic factor (p = 0.0001; Figure 3).

Late Complications of Therapy (210 Patients)

Late complications included one death 50 months after initial treatment. This resulted from a late small bowel obstruction treated surgically, with subsequent anastomotic breakdown leading to fatal peritonitis. Eight (4%) patients experienced small bowel obstruction 2 to 50 months after completion of all treatment — 7 of the patients had undergone APR and 1 patient an LAR.

DISCUSSION

The incidence of local recurrence after surgery alone for rectal adenocarcinoma varies from approximately 20% to 30%.[2,3] The likelihood of successful salvage is

Table 6. Site of recurrence* versus Dukes' stage (190 patients†).

Stage	No. patients	Local recurrence alone	Local recurrence and distant metastasis	Distant metastasis alone
O	17	0	0	3
A	12	0	0	0
B1	59	0	1	9
B2	65	2	5	22
C1	8	1	1	0
C2	29	2	2	12

* Includes all sites of recurrent disease, not simply the first site of failure.
† Twenty patients excluded who did not have complete resection of tumour.

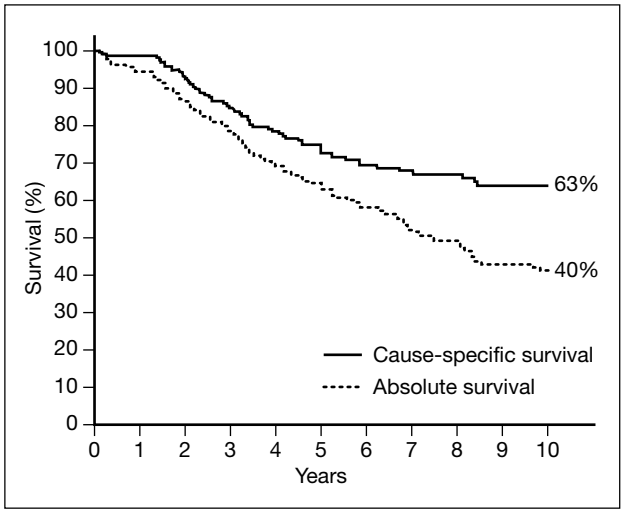

Figure 2. Absolute survival and cause-specific survival rates (n=190).

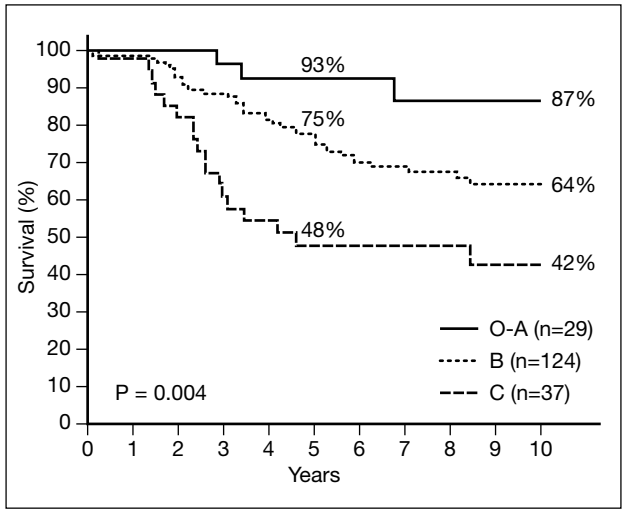

Figure 3. Cause-specific survival according to Dukes' pathologic stage (n=190).

less than 5%, and approximately half of the patients with local recurrence die without obvious evidence of distant metastases. Local recurrences are often associated with severe pain that is difficult to palliate effectively. Thus, preventing local recurrence improves patients' quality of life and may increase the likelihood of cure.

The initial experience with preoperative RT for resectable rectal adenocarcinoma was with low-dose RT.[27,28] The reports published by the Memorial Sloan-Kettering Cancer Center group[28] and the Veterans Administration Surgical Adjuvant Group [29] stimulated considerable interest in preoperative RT because low-dose RT appeared to be safe and to improve survival rates in some subsets of patients. In an effort to enhance the efficacy of preoperative RT, some investigators increased the dose to a level shown to be highly effective for destroying subclinical disease in breast cancer and head and neck cancer (i.e. 45 to 50 Gy over 5 to 5.5 weeks or its radiobiological equivalent).[30-34]

The results of several important randomised trials were published in the 1980s and significantly influenced the management of rectal cancer in the United States. The Gastrointestinal Tumor Study Group[13] reported a trial in which patients with B2-C rectal adenocarcinoma were assigned to one of four treatment groups: surgery alone, surgery plus postoperative RT, surgery plus postoperative chemotherapy, and surgery plus postoperative chemotherapy and RT (chemoradiation). Adjuvant chemotherapy consisted of fluorouracil and semustine. Patients who received chemoradiation had a significantly lower risk of local recurrence and a significantly improved survival rate compared with patients who had surgery alone. The National Surgical Adjuvant Breast and Bowel Project (NSABP)[14] subsequently reported the results of the R-01 protocol, in which patients with B2-C rectal cancer received surgery alone; surgery followed by postoperative RT; or surgery followed by fluorouracil, semustine, and vincristine. Patients who received adjuvant chemotherapy had significantly improved survival and disease-free survival rates compared with the surgery-alone group. However, although patients who had adjuvant RT had a lower local recurrence rate than those who received surgery alone or surgery plus chemotherapy, there was no improvement in survival in the RT arm. Finally, the Mayo-North Central Cancer Treatment Group[15] reported a trial in which patients with B2-C tumours received either surgery followed by RT, or surgery followed by RT combined with fluorouracil and semustine. Patients who received chemoradiation had significantly higher rates of disease-free survival and overall survival. These studies led the National Institutes of Health Consensus Conference[35] to recommend adjuvant postoperative RT and fluorouracil-based chemotherapy for patients with B2-C rectal adenocarcinoma. Although semustine is not commercially available because of its leukaemogenic potential, fluorouracil–based adjuvant chemotherapy is generally thought to be efficacious, and the search continues for the optimal drug combination.[36,37]

While the postoperative adjuvant trials were being conducted, several studies were completed evaluating preoperative RT. Gerard et al[16] reported findings of the European Organization for Research and Treatment of Cancer randomised trial in which patients with UICC T2-T4, NX rectal cancer received surgery alone

or preoperative RT (34.5 Gy in 15 fractions) followed by surgery. Three hundred and forty-one patients had an apparent complete resection. The 5-year survival and local recurrence rates after preoperative RT and surgery compared with surgery alone were 69% versus 59% (p = 0.08) and 15% versus 30% (p = 0.003), respectively. Reis-Neto et al[38] reported a small Brazilian randomised trial in which 68 patients received either 40 Gy in 4 weeks followed by surgery, or surgery alone. Patients in the RT group had a significantly lower local recurrence rate (15% vs 47%) and improved 5-year survival (70% vs 29%) compared with those treated with surgery alone. Marsh et al[39] recently reported a randomised trial conducted by the Northwest Region Rectal Cancer Group (Manchester, UK) in which 284 patients with tethered or fixed rectal adenocarcinomas received either surgery alone, or RT (20 Gy in 4 fractions) plus surgery. Patients were seen for follow-up for a minimum of 8 years. Survival rates were significantly improved in those patients who underwent a potentially curative resection and received preoperative RT compared with those who had surgery alone. Local recurrences were significantly fewer after preoperative RT and surgery for the overall group, as well as for the subset of patients who underwent an apparent complete resection.

Cedermark et al[40] reported the results of the Stockholm I randomised trial in which 849 patients received either surgery alone, or RT (25 Gy in 5 fractions over 5 to 7 days) followed by surgery. Preoperative RT significantly reduced the risk of local recurrence and improved disease-free survival rates in the overall group of patients and the subset of patients who underwent an apparent complete resection. Overall survival was not improved, possibly because of the increased postoperative mortality rate in the irradiated patients. This may have been related to the large size of the RT fields and the anterior-posterior two-field arrangement used. The Stockholm II trial employed the same RT dose-fractionation schedule but with smaller fields and a four-field box technique.[41] Patients were randomly assigned to receive preoperative RT (n=272) or surgery alone (n=285); surgery was thought to be curative in 479 patients. Median follow-up was 50 months. Patients in the preoperative RT group had a significantly lower rate of local failure and improved overall survival rates compared with patients treated with surgery alone. The Swedish Rectal Cancer Trial included 1168 patients randomly assigned between 1987 and 1990 to surgery, or preoperative RT (25 Gy in 5 fractions over 1 week) followed by surgery.[42] Patients were seen for follow-up for 5 to 8 years. The 5-year rates of local recurrence, survival, and cause-specific survival were significantly better for patients irradiated preoperatively compared with those treated with surgery alone: 11% versus 27% (p < 0.001); 58% versus 48% (p = 0.004); and 74% versus 65% (p = 0.002). There was no increased postoperative mortality associated with RT.

Our data similarly support the hypothesis that preoperative RT alone significantly reduces the risk of local recurrence and may improve survival. The abbreviated short course of 30 Gy in 10 fractions over 2 weeks was as effective as 45 to 50 Gy at 1.8 Gy per fraction over 5 to 5.5 weeks. The toxicity associated with these treatment schedules was minimal. Frykholm et al[43] reported a randomised study in which 471 patients with B2-C disease received either preoperative RT (25.5 Gy in 5 fractions) plus surgery, or resection followed by postoperative RT (60 Gy in 30 fractions, using a split-course technique). Patients were seen for follow-up for a minimum of 5 years. Although the risk of local recurrence was significantly lower in the preoperatively irradiated patients (13% vs 22%; p = 0.02), there was no difference in overall survival. The incidence of small bowel obstruction with treatment was 5% after preoperative RT compared with 11% after postoperative RT.

Interest in preoperative RT has persisted, despite the promising adjuvant postoperative studies, because of several potential advantages with this approach:

(1) preoperative RT may be more effective in reducing the risk of local recurrence;
(2) preoperative RT may be associated with less morbidity, both in terms of acute effects and the risk of late small bowel obstruction;
(3) preoperative RT may increase the likelihood of sphincter preservation; and
(4) the likelihood of patients' completing treatment as planned is possibly higher.

In two prospective randomised trials in the United States, preoperative chemoradiation was compared with postoperative chemoradiation. The Intergroup trial assigned patients with resectable rectal adenocarcinoma with evidence of transmural invasion to receive either preoperative RT and two cycles of concomitant fluorouracil and leucovorin followed by surgery plus postoperative chemotherapy, or surgery followed by postoperative chemoradiation.

The NSABP R-03 study also assigned patients with resectable rectal adenocarcinoma to receive either preoperative RT and adjuvant fluorouracil plus leucovorin or surgery followed by postoperative chemoradiation.[44] The dose of RT in both arms was 50.4 Gy in 28 fractions, with concomitant chemotherapy during the first and fifth weeks of treatment. A significant difference between the preoperative arms of the Intergroup and the NSABP trials was that the former began with RT and concomitant chemotherapy, whereas the latter began with 8 weeks of chemotherapy. It is possible that the subset of tumours resistant to chemotherapy might have progressed during this 8-week period, thus biasing the results against the preoperative group in comparison with the postoperative group, in which the initial treatment was surgery. Regrettably, both trials recently closed because of poor accrual.

The role of adjuvant RT and/or chemotherapy must also be evaluated in light of the total mesorectal excision.[45] Several authors have reported local recurrence rates of less than 10% after 'curative' total mesorectal excision alone for patients with transmural invasion and/or positive nodes.[45,46] It is unclear whether this surgical technique can or will be widely applied in private practice, where most rectal cancer surgery is performed, with the same degree of success.[47,48] Preliminary data from a multicenter prospective trial in the Netherlands, in which total mesorectal excision alone was compared with total mesorectal excision combined with preoperative RT, showed a significant decrease in the risk of local recurrence at 2 years for those patients who underwent RT but no short-term survival advantages.[45]

Currently, patients evaluated at the University of Florida with rectal adenocarcinomas that are locally advanced — based on tethering, annularity, and/or transmural invasion on radiographic studies, such as computed tomography, magnetic resonance imaging, or transrectal ultrasound — are treated with preoperative RT and concomitant chemotherapy. The dose-fractionation schedule used is 45 Gy in 25 fractions over 5 weeks using a four-field box technique, followed by a reduction and additional boost of 5.4 Gy in 3 fractions. Patients with localised, clinically unresectable rectal cancer, based on definite fixation to adjacent structures such as the sacrum or pelvic side wall, are treated with 55.8 Gy in 31 fractions with concomitant continuous infusion fluorouracil. Chemotherapy consists of a continuous fluorouracil infusion administered with a portable, programmable pump.[49] The variable dose rate pump delivers 250 to 300 mg/m^2 per day. Additionally, patients who are borderline candidates for low anterior resection versus APR are irradiated preoperatively using the same treatment protocol. Although 30 Gy in 10 fractions has proven to be effective, we have not used this schedule with concomitant chemotherapy in order to increase the amount of chemotherapy delivered preoperatively and to avoid combining it with high-dose-per-fraction RT.

At present, there are two reasons for considering preoperative chemoradiation:
(1) the superior efficacy of postoperative chemoradiation compared with postoperative RT alone; and
(2) the improved down-staging observed after preoperative chemoradiation compared with preoperative RT.

Whether the addition of chemotherapy to preoperative RT results in improved local-regional control and survival is as yet unclear.

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