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ORIGINAL ARTICLE

Bolus Versus Continuous Infusion of Fluorouracil Plus Radiotherapy for Preoperative Treatment of Rectal Cancer

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ABSTRACT

Objective: *To evaluate preoperative bolus versus continuous infusion chemoradiation.*

Patients and Methods: *Sixty eight patients received either bolus fluorouracil or continuous infusion fluorouracil combined with radiotherapy.*

Results: *The pathologic stages for bolus fluorouracil, continuous infusion fluorouracil, and overall were pT0, 18%, 31%, and 25% of patients, respectively; pT1-2, 39%, 28%, and 33%, respectively; and pT3-4, 43%, 41%, and 42%, respectively. Nodal downstaging for the 3 groups was N0, 96%, 85%, and 90%, respectively. Sphincter preservation was possible for 51% of patients. Sphincter preservation surgery was performed for 38% of patients receiving bolus fluorouracil compared with 62% of those receiving continuous infusion fluorouracil (p = 0.053). Five-year local control, absolute, and cause-specific survival rates were 88%, 73%, and 76%, respectively. The 5-year outcomes for continuous infusion fluorouracil versus bolus fluorouracil were: local control, 97% versus 76% (p = 0.1944); absolute survival, 80% versus 65% (p = 0.2867); and cause-specific survival, 83% versus 68% (p = 0.425). Nineteen percent of patients did not finish chemotherapy because of European Cooperative Oncology Group grade 3 or greater toxicity.*

Conclusion: *Both chemotherapy regimens produced high rates of pathologic downstaging and were well tolerated. There was a trend toward higher rates of downstaging, local control, survival, and sphincter preservation with continuous infusion fluorouracil compared with bolus fluorouracil, but at the expense of greater acute toxicity.*

Key Words: *Adenocarcinoma, Combined-modality therapy, Radiotherapy, Rectal neoplasms, Surgery*

INTRODUCTION

The optimal management of patients with locally advanced adenocarcinoma of the rectum has been in transition during the past decade and remains controversial. Although surgery remains the mainstay of treatment, the role of adjuvant chemotherapy and/or radiation therapy is the focus of continued debate. Adjuvant postoperative radiation therapy has been used to reduce the high likelihood of local-regional recurrence after resection for tumours with transmural invasion and/or positive lymph nodes. Several series have shown that concomitant chemotherapy improves the efficacy of postoperative irradiation, leading investigators to postulate that combined modality treatment in a preoperative setting might be more effective than preoperative irradiation alone.[1-3] Preoperative radiotherapy is used to downstage the lesion to increase the likelihood of complete surgical resection.[4-8] Relatively high rates of local recurrence have been observed for advanced lesions even when treated with high dose preoperative radiotherapy (16% to 43%).[9,10]

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At the University of Florida, the authors have attempted to treat all locally advanced or fixed adenocarcinomas of the rectum with combined modality treatment since 1991. To date, there have been no completed randomised trials comparing the administration methods of fluorouracil (FU) during preoperative combined modality therapy. This retrospective study was undertaken to ascertain the effectiveness of continuous infusional and bolus injection administration of FU at the University of Florida, and to assess any differences in potential benefits and/or side effects and complications between the 2 regimens.

PATIENTS AND METHODS

The use of preoperative radiotherapy for patients with locally advanced rectal cancer began at the University of Florida in 1975. Concomitant FU-based chemotherapy was added to the treatment regimen in 1991.[11] Initially, patients were given 2 x 5-day courses of FU by daily bolus fluorouracil injection (BTX regimen) during the first and fifth weeks of radiation therapy at a dose of 500 mg/m^2 per day.

Beginning in 1992, patients received continuous infusion or chronobiologically-infused fluorouracil (CTX regimen) at a dose of 225 to 300 mg/m^2 per day throughout the entire course of radiation therapy.[2] Patients who were not candidates for continuous infusion FU, primarily because of patient preference or infusion pump unavailability, continued to receive 2 x 5-day cycles of FU. Surgery was performed 3 to 6 weeks after preoperative treatment. All of the patients who received BTX were male compared with 79% of those who received CTX. Otherwise, the groups were comparable in terms of age and performance status.

Rectal cancers are defined as those originating below the peritoneal reflection, which is approximately 11 cm from the anal verge. Only those patients with clinically fixed or tethered lesions treated between January 1991 and January 2000 were analysed in this report. Pretreatment evaluation included a chest X-ray (CXR), computed tomography (CT) of the abdomen and pelvis, colonoscopy, complete blood count, and carcinoembryonic antigen (CEA) level. A subset of patients underwent a transrectal ultrasound (US). Patients with distant metastases at the time of diagnosis were excluded. A minimum 1-year follow-up was required, leaving a total of 68 patients for the analysis. The median follow-up was 37.8 months (range, 3.0 to 101.4 months).

Patients ages ranged from 31 to 84 years (mean, 62 years) and they were predominately Caucasian (7:1) and male (8:1). Patients were clinically staged according to the 1997 American Joint Committee on Cancer staging system.[12] Forty three percent of patients received BTX and 57% received CTX. Concomitant irradiation was delivered with a minimum tumour dose of 45 Gy in 25 fractions to the whole pelvis, with or without a boost to the tumour. Patients with tethered lesions were treated to 45 Gy using a 4-field box technique. In the mid 1990s, a change in institutional policy occurred, and the dose was escalated to 50.4 Gy with a 3-field boost after 45.0 Gy. Fixed lesions were treated to 45.0 Gy and then with a boost to 55.8 Gy with the 3-field technique. The median tumour dose was 50.4 Gy (range, 45.0 to 59.4 Gy). Twenty one of 39 CTX patients (54%) received more than 45 Gy compared with 19 of 29 BTX patients (66%). Radiation therapy was delivered using linear accelerators and high-energy photons, typically 18 to 20 MV from the anterior and lateral fields and 6 MV from the posterior field. The typical daily dose was 1.8 Gy; no patients were treated twice daily. Patient demographics are shown in Table 1.

Patients proceeded to surgical resection 3 to 6 weeks after completion of chemoradiation, based on the operating surgeon's evaluation of clinical tumour regression and resolution of acute side effects. The surgical resections performed were low anterior resection (32 patients; 47%), abdominoperineal resection (27 patients; 40%), and transrectal excision, other, or none (9 patients; 13%). Two patients with positive lymph nodes received postoperative FU-based chemotherapy.[11] Thirteen of 29 patients (45%) treated prior to 1996 underwent an abdominal resection compared with 13 of 39 patients (33%) treated between 1996 and 2000.

Follow-up evaluation included periodic physical examinations and CEA determinations. CXRs were obtained annually. Patients who underwent an anterior resection had a follow-up sigmoidoscopy annually for 5 years.

Table 1. Chemoradiation treatments (n = 68).

Treatment	No. of patients (%)
Fluorouracil chemotherapy	
Bolus weeks 1 and 5	29 (43)
Circadian rhythm	33 (48)
Continuous infusion	6 (9)
Radiation therapy dose	
45 Gy	30 (44)
50.4 Gy	23 (34)
>50.4 Gy	15 (22)

Follow-up colonoscopies were performed every 3 to 5 years. CT scans of the abdomen and pelvis were not routinely obtained unless indicated based on physical findings or a rising CEA level.

RESULTS

A high degree of downstaging was observed in both treatment groups. The pathologic tumour (pT) stages and rates of lymph node positivity for the BTX group, CTX group, and overall, are shown in Table 2. Sphincter preservation was observed in 51% of patients overall. Patients treated with CTX were more likely to undergo sphincter-sparing surgery compared with those treated with BTX (62% versus 38%, p = 0.053). Of 10 patients (15%) with the tumour located less than 4 cm from the anal verge, none retained sphincter function, compared with 51% of those with tumours 4 to 9 cm from the anal verge and 100% of those with tumours greater than 10 cm from the anal verge (Table 3). Ninety one percent of patients who underwent sphincter preservation surgery had excellent to good control of bowel movements as graded on the Memorial Sloan-Kettering Cancer Center anal function criteria.[13] Local-regional control and absolute and cause-specific survival rates at 5 years were 88%, 73% and 76%, respectively (Figures 1, 2, and 3). There were higher

Table 2. Pathologic staging (n = 67).

	Total* No. (%)	Bolus fluorouracil No. (%)	Continuous or chronobiologically infused fluorouracil No. (%)
Primary tumour			
T0	17 (25)	5 (18)	12 (31)
T1-2	22 (33)	11 (39)	11 (28)
T3-4	28 (42)	12 (43)	16 (41)
Total	67	28	39
Nodes			
N0	60 (90)	27 (96)	33 (85)
N+	7 (10)	1 (4)	6 (15)
Total	67	28	39

* One patient had no pathologic staging; no operation was performed due to development of distant metastases.

Table 3. Sphincter preservation (n = 68).

Parameter	No. with sphincter preservation/ no. of patients in group (%)
All patients	35/68 (51)
Resectability	
Unresectable	6/19 (32)
Resectable	29/49 (59)
Distance from anal verge	
<4 cm	0/10 (0)
4-9 cm	24/47 (51)
≥10 cm	11/11 (100)

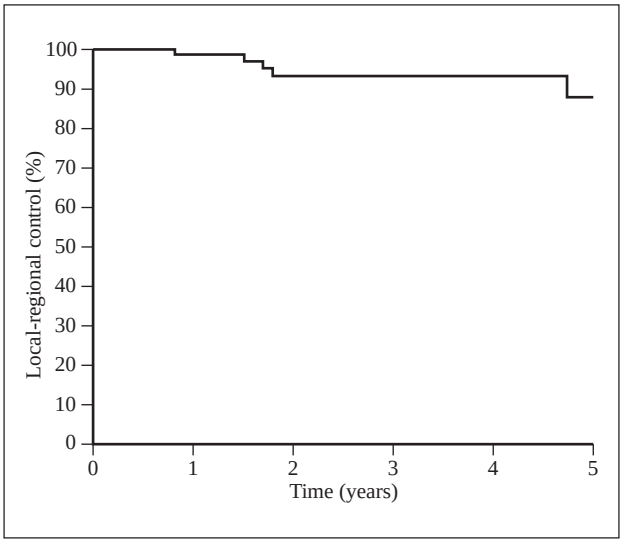

Figure 1. Local-regional control of disease (n = 68).

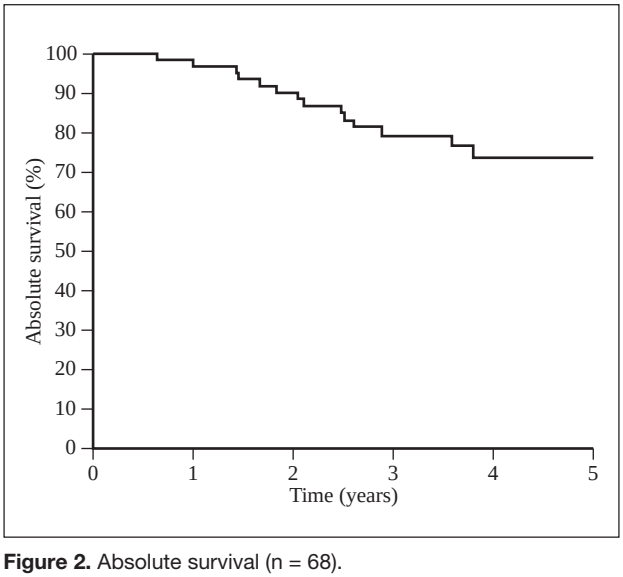

Figure 2. Absolute survival (n = 68).

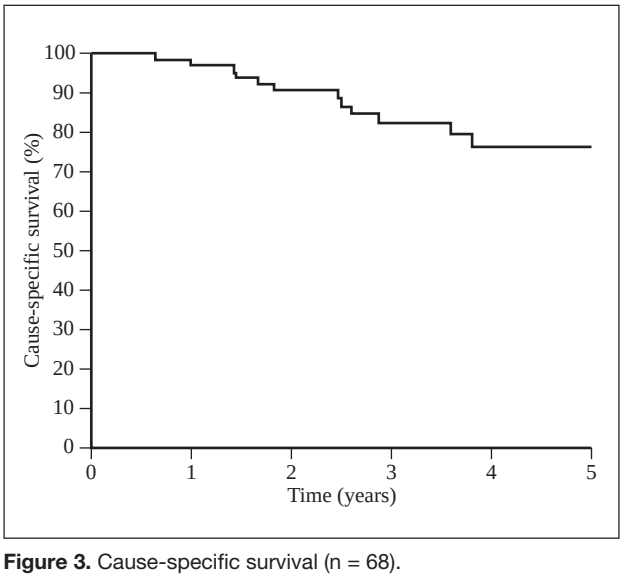

Figure 3. Cause-specific survival (n = 68).

Table 4. Local-regional recurrence according to treatment (direct methods; 1 year minimum to unlimited follow-up).

Treatment (n = 68)	No. with local-regional recurrence/no. in group (%)
Surgery	
Abdominoperineal resection	3/27 (11)
Low anterior resection	2/32 (6)
Transrectal excision, other operation, or none	1/9 (11)
Radiation therapy dose	
45.0 Gy	4/30 (13)
50.4 Gy	0/23 (0)
>50.4 Gy	2/15 (13)
Chemoradiation	
Bolus fluorouracil	4/29 (14)
Continuous or chronobiologically infused fluorouracil	2/39 (5)

Table 5. European Cooperative Oncology Group grade 3 or greater toxicities after chemoradiation, according to treatment group.

Side effect	Bolus fluorouracil (n = 29) No. (%)	Continuous or chronobiologically infused fluorouracil (n = 39) No. (%)
Proctitis	3 (10)	7 (18)
Hand/foot/mouth	2 (7)	4 (10)
Weight loss	3 (10)	2 (5)
Diarrhoea	1 (3)	7 (18)
Dehydration	0 (0)	1 (3)
Nausea	0 (0)	1 (3)
Mucositis	0 (0)	3 (8)
Dermatitis	0 (0)	1 (3)

5-year rates of local control and absolute and cause-specific survival for CTX compared with BTX, but the differences were not significant (97% versus 76%, 80% versus 65%, and 83% versus 68%, respectively). No local failures occurred in patients with tethered lesions who received a dose of 50.4 Gy (Table 4).

Both treatment regimens were well tolerated. There were no treatment breaks from radiotherapy. Only 1 patient did not undergo surgical resection — liver metastases were discovered at the time of surgery. Nineteen percent of patients did not finish chemotherapy because of European Cooperative Oncology Group (ECOG) grade 3 or greater toxicity (Table 5). No instances of severe leukopenia, anaemia, thrombocytopenia, colitis, or fever were observed. Postoperative complications as a function of treatment group are depicted in Table 6. No occurrences of colostomy necrosis, pulmonary embolus, or postoperative death were noted in this series.

DISCUSSION

Since publication of the results of the European Organization for Research and Treatment of Cancer and Swedish Rectal Cancer Trials, use of preoperative radiotherapy for the treatment of patients with advanced rectal cancers has increased.[14,15] Goals of treatment are to downstage the tumour, improve local control rates, and allow for less radical surgery to be performed in the hope of preserving the anal sphincter and improving the patient's quality of life. In an effort to enhance overall outcome, chemotherapy has been added to the treatment. Several studies have shown that combined-modality treatment is well tolerated and also improves the efficacy of radiotherapy.[1-3,11] This study was performed to compare the efficacy of 2 common forms of chemotherapy administration. Although the study is a retrospective analysis and patients were not randomised, important data can be gleaned from this series. Overall, both chemotherapy regimens were well tolerated, and there were few severe (ECOG grade 3 or greater) side effects. There appeared to be a trend toward greater efficacy with continuous infusion chemotherapy but at the cost of increased side effects. Also, dose escalation to 50.4 Gy was well tolerated and associated with improved local control rates with no increase in late or acute complications when compared with 45 Gy. Tumour downstaging was consistent with, or higher than, that reported in the literature.[1,16]

The overall sphincter-preservation rate in this series was modest at 51%. Although some surgeons may perform sphincter-preserving surgery for patients with tumours as close to the anal verge as 3 cm, the authors were

Table 6. Postoperative complications by radiation dose and chemotherapy regimen.

Complication	No. with postoperative complications/no. in group (%)				
	Dose			Regimen	
	45.0 Gy (n = 30)	50.4 Gy (n = 23)	>50.4 Gy (n = 15)	Bolus fluorouracil (n = 29)	Continuous chronobiologically infused fluorouracil (n = 39)
Infection	5 (17)	3 (13)	2 (13)	4 (14)	6 (15)
Wound healing	4 (13)	2 (9)	1 (7)	2 (7)	5 (13)
Anastomotic leak	2 (7)	2 (9)	0 (0)	2 (7)	2 (5)
Bleeding	2 (7)	0 (0)	1 (7)	2 (7)	1 (3)
Obstruction	0 (0)	1 (4)	1 (7)	1 (3)	1 (3)
Incontinence	1 (3)	1 (4)	0 (0)	0 (0)	2 (5)

unable to perform sphincter-preserving surgery for patients with tumours less than 4 cm from the anal verge. The use of CTX treatment did, however, improve the chance of sphincter preservation. Due to the non-randomised nature of this study, it is impossible to discern if sphincter-preserving surgery may have been an option, but because of fear of local recurrence with low-lying lesions, a more radical surgical approach was taken. Of interest is that of the patients who underwent sphincter-preserving therapy, the function of the sphincter was excellent or good for the vast majority, leading to a much better quality of life.

In conclusion, there appears to be no clear-cut answer to the question of which chemotherapy regimen to administer. The author's preference is to administer continuous-infusion FU because of the trend toward better outcomes. Further prospective trials will be needed to fully answer this question. In addition, rates of tumour downstaging and overall survival continue to be improved when compared with rates after surgery alone. In regard to sphincter preservation, further work is needed to better define the subset of patients suitable for conservative surgery.

REFERENCES

1. Janjan NA, Khoo VS, Abbruzzese J, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the MD Anderson Cancer Center experience. Int J Radiat Oncol Biol Phys 1999;44:1027-1038.
2. Marsh RDW, Chu NM, Vauthey JN, et al. Preoperative treatment of patients with locally advanced unresectable rectal adenocarcinoma utilizing continuous chronobiologically shaped 5-fluorouracil infusion and radiation therapy. Cancer 1996;78: 217-225.
3. Minsky BD. Adjuvant therapy for rectal cancer: results and controversies. Oncology (Huntingt) 1998;12:1129-1139.
4. Mendenhall WM, Million RR, Pfaff WW. Patterns of recurrence in adenocarcinoma of the rectum and rectosigmoid treated with surgery alone: implications in treatment planning with adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 1983;9:977-985.
5. Mendenhall WM, Million RR, Bland KI, Pfaff WW, Copeland EM III. Preoperative radiation therapy for clinically resectable adenocarcinoma of the rectum. Ann Surg 1985;202:215-222.
6. Mendenhall WM, Bland KI, Pfaff WW, Million RR, Copeland EM III. Initially unresectable rectal adenocarcinoma treated with preoperative irradiation and surgery. Ann Surg 1987;205: 41-44.
7. Mendenhall WM, Bland KI, Rout WR, Pfaff WW, Million RR, Copeland EM III. Clinically resectable adenocarcinoma of the rectum treated with preoperative irradiation and surgery. Dis Colon Rectum 1988;31:287-290.
8. Mendenhall WM, Bland KI, Souba WW, Sombeck MD, Copeland EM, III, Million RR. Preoperative irradiation for clinically resectable rectal adenocarcinoma. Semin Radiat Oncol 1993;3:48-54.
9. Pilepich MV, Munzenrider JE, Tak WK, Miller HH. Preoperative irradiation of primarily unresectable colorectal carcinoma. Cancer 1978;42:1077-1081.
10. Tobin RL, Mohiuddin M, Marks G. Preoperative irradiation for cancer of the rectum with extrarectal fixation. Int J Radiat Oncol Biol Phys 1991;21:1127-1132.
11. Vauthey JN, Marsh RW, Zlotecki RA, et al. Recent advances in the treatment and outcome of locally advanced rectal cancer. Ann Surg 1999;229:745-752.
12. American Joint Committee on Cancer. In: Greene Fl, Page DL, Fleming ID, et al, editors. AJCC cancer staging manual. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 1997.
13. Minsky BD, Cohen AM, Enker WE, Paty P. Sphincter preservation with preoperative radiation therapy and coloanal anastomosis. Int J Radiat Oncol Biol Phys 1995;31:553-559.
14. Gerard A, Buyse M, Nordlinger B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg 1988;208:606-614.
15. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997; 336:980-987.
16. Mohiuddin M, Hayne M, Regine WF, et al. Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancers. Int J Radiat Oncol Biol Phys 2000;48:1075-1080.