Preoperative Treatment of Patients with Locally Advanced Unresectable Rectal Adenocarcinoma Utilizing Continuous Chronobiologically Shaped 5-Fluorouracil Infusion and Radiation Therapy

Robert de W. Marsh, M.D.[1]
Nei-Min Chu, M.D.[1]
Jean-Nicholas Vauthey, M.D.[2]
William M. Mendenhall, M.D.[3]
Gregory Y. Lauwers, M.D.[4]
Carol Bewsher, R.N.[1]
Edward M. Copeland, M.D.[2]

[1] Division of Hematology/Oncology, College of Medicine, University of Florida, Gainesville, Florida.

[2] Department of Surgery, College of Medicine, University of Florida, Gainesville, Florida.

[3] Department of Radiation Therapy, College of Medicine, University of Florida, Gainesville, Florida.

[4] Department of Pathology, College of Medicine, University of Florida, Gainesville, Florida.

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Address for reprints: Robert de W. Marsh, M.D., F.A.C.P., P.O. Box 100277, College of Medicine, University of Florida, Gainesville, FL 32610-0277.

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BACKGROUND. This study was designed to determine the efficacy and maximally tolerated dose of 5-fluorouracil when administered by chronobiologically shaped prolonged infusion in combination with radiation therapy in patients with both locally advanced and unresectable rectal carcinoma.

METHODS. Eighteen sequential patients determined clinically to have either locally advanced or unresectable rectal carcinoma were treated by 4500 centigray (cGy) or 5580 cGy, respectively, combined with continuous chronobiologically modulated 5-FU infusion starting at 250 mg/m^2/day, with the dose escalating in each cohort of 5 patients if no Grade 3 or higher toxicity was observed in each cohort. Imaging studies were obtained prior to and after completion of treatment.

RESULTS. All 18 patients completed the full course of radiation therapy and all were subsequently resectable for potential cure. The maximum tolerated dose of 5-FU was 275/m^2/day for 5 weeks. Seven patients had a sphincter-sparing procedure, and ten patients underwent an abdominoperineal resection, all with clear margins. Five complete pathologic responses (28%) were obtained. The average follow-up time was 12 months with a range of 6 to 37 months. With the exception of two patients, one of whom declined surgery and one of whom died of widespread disease, all of the patients have remained free of disease.

CONCLUSIONS. The combination of radiation therapy and continuous chronobiologically shaped 5-FU infusion at a dose of up to 275/m^2/day is well tolerated and appears to be more effective in downsizing and possibly downstaging locally advanced and unresectable rectal carcinoma than radiation therapy alone. Longer follow-up will determine whether ultimate disease free and overall survival are improved by this method. *Cancer* **1996; 78:217–25.** © *1996 American Cancer Society.*

KEYWORDS: chronobiology, circadian, rectal carcinoma, chemotherapy, radiotherapy, preoperative.

In 1995, 38,200 new cases of rectal carcinoma will be diagnosed in the United States.[1] Many of these will be either unresectable or locally advanced and not readily amenable to immediate curative surgery. In this situation, preoperative radiation therapy has an established role in increasing the likelihood of complete resection and subsequent cure.[2–5]

This is certainly an advance over palliative surgery alone, but a number of tumors do not adequately respond, and either remain unresectable or have positive resection margins. In addition, patients with low to midrectal carcinomas often require an abdominoperineal resection with a permanent colostomy.

In an attempt to improve on these results, adjuvant chemotherapy has been combined with preoperative radiation therapy. This is based on the known synergy between radiation and 5-fluorouracil (5-FU) (the chemotherapy agent used almost exclusively),[6-8] the favorable results of postoperative combined therapy in resectable disease,[9-11] and the belief that early initiation of chemotherapy has many theoretic advantages, including undisturbed pelvic vasculature with good drug penetrance and tissue oxygenation, lowest potential metastatic tumor burden with less likelihood of drug resistance,[12] and abrogation of the increased proliferation of possible distant metastases initiated by treatment of the primary tumor.[13,14]

To this end, a number of trials have been performed. The majority of these have used 5-FU given by bolus injection or short course infusion with or without other agents,[15-18] and a small number have used prolonged continuous infusion 5-FU, with or without other agents.[19-21] The current consensus is that resectability is increased by this approach, but that it is too early to reliably judge the effects on disease free survival and overall survival. In addition, toxicity in many of these trials has not been inconsequential, with subsequent delays in therapy and modification of treatment protocols due to patient intolerance.

In the study by Shumate et al.,[21] which used 4500 centigrays (cGy) of radiation combined with 5-FU (250 mg/m^2/day) and cisplatin (4 mg/m^2/day) for 5 days per week, 14% of patients had Grade 3 toxicity requiring treatment interruption and dose modification. Twenty percent of these patients experienced major postoperative complications. Minsky et al.[15] used 5040 cGy of radiation together with leucovorin (200 mg/m^2) and 5-FU (escalating from 200 mg/m^2 to 300 mg/m^2/day) by bolus for 5 days, 1 week before radiation therapy, and a second cycle during the 4th week of radiation therapy. Grade 3 diarrhea, tenesmus, and dysuria were seen in 10%, 11%, and 5% of patients, respectively. In a subsequent study using low dose leucovorin (20 mg/m^2) with 5-FU (at 325 mg/m^2 escalating to 375 mg/m^2/day) for 5 days times 2 cycles with 5040 cGy of radiation, there was 18% overall Grade 3 toxicity.[18]

In an attempt to minimize toxicity while maintaining or improving on the current results, we performed a trial of preoperative prolonged continuous infusion 5-FU plus radiation therapy in patients with locally advanced and unresectable tumors. However, rather than a flat, continuous infusion, we utilized a chronobiologically determined, circadian-shaped infusion, which we and others have studied in a variety of settings and found to be advantageous with respect to both achievable dose intensity and toxicity, owing to the circadian nature of both 5-FU pharmacodynamics and pharmacotherapeutics, and the circadian cycle of gut mucosal cell proliferation.[22-25] By escalating the dose intensity of the daily infusions of 5-FU, we determined both the maximum tolerated dose of continuous infusion, circadian-based 5-FU that could be administered in combination with a predetermined dose of radiation therapy, and the resectability and pathologic response of tumors so treated.

PATIENTS AND METHODS

All patients with previously untreated adenocarcinoma of the rectum were presented and discussed in a multidisciplinary gastrointestinal tumor conference at the University of Florida Shands Cancer Center. If deemed an appropriate candidate, the patient signed an informed consent approved by the University of Florida's Shands Hospital Institutional Review Board and subsequently underwent pretherapy staging to evaluate the extent of disease. This included history and physical examination, pelvic magnetic resonance imaging scan, transrectal ultrasound, endoscopy with biopsy, serum chemistries, carcinoembryonic antigen, complete blood cell count, and chest X-ray. Locally advanced disease was defined as a tumor likely to extend through the muscularis propria, and/or to regional lymph nodes based on either tethering (reduced mobility), annularity, and/or findings consistent with Astler-Coller Stage IIB/C disease on transrectal ultrasound. Unresectable disease was defined as disease fixed to either the sacrum, pelvic sidewalls, bladder trigone, and/or prostate gland. All patients were required to have a Karnofsky performance status of $>$ 60, a serum bilirubin of $<$ 1.5 mg/dL, and a serum creatinine of $<$ 1.5 mg/dL. All patients with prior nonrectal carcinomas (excluding nonmelanomatous skin cancers and noninvasive cervical cancers) and all those who had received prior pelvic radiation therapy or 5-FU were excluded. Pregnant patients were also excluded. This full evaluation was repeated after chemo/radiation therapy had been completed and the appropriate surgical procedure was determined. Responses and toxicities were assessed by published Eastern Cooperative Oncology Group guidelines. The pathology material of the 17 patients who underwent surgery was reviewed by one of us (G.Y.L.). In each case, the pathologic staging was assessed according to the American Joint Committee on Cancer (AJCC).[26] The lymph node status was also recorded and a tumor regression grade (TRG) established. The tumor regression grading system used was modified from the criteria published elsewhere.[27] A five-tiered system was designed as follows:

- Grade 1: no residual tumor observed.

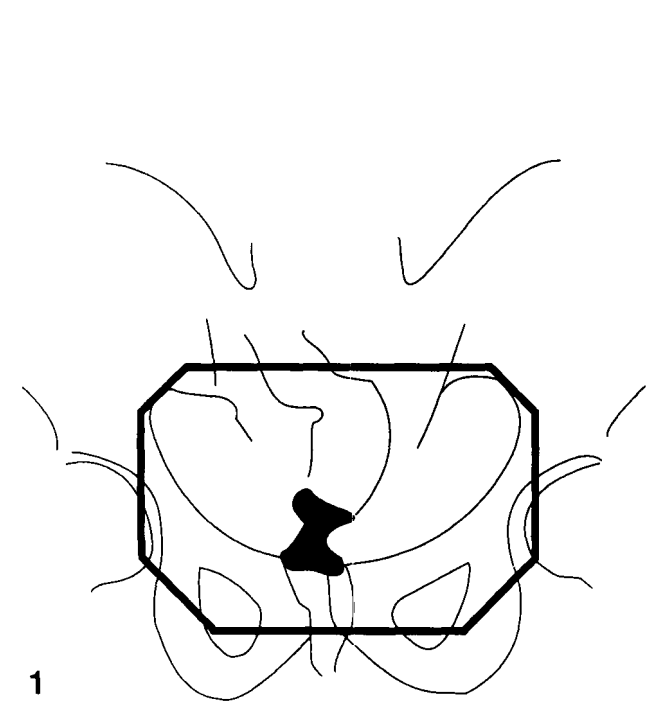

FIGURE 1, 2, AND 3. Isodose distribution for the 4-field box technique using 18-megaelectron volt photons.

- Grade 2: rare residual single cells or small aggregates of tumor.
- Grade 3: extensive regressive changes (fibrosis/necrosis) with residual large aggregates of tumor.
- Grade 4: abundant residual tumor with regressive changes.
- Grade 5: tumor without regressive changes.

Radiotherapy

Patients were stratified to receive at least 4500 cGy in locally advanced tumors (13 patients) (boosted to 5040 cGy in 2 patients), or 5580 cGy in unresectable lesions (3 patients), at 180 cGy/fraction, 5 fractions per week, continuous course. A four-field box technique was used. The anterior and posterior portals were 10–11 cm in height and 13–14 cm in width and corner blocks were added to decrease the amount of small bowel treated. The fields were arranged to irradiate the tumors with a 2–4 cm distal and proximal margin and to include the lateral pelvic wall lymph nodes. The lateral portals were approximately 10 cm × 10 cm or 10 cm × 11 cm and were arranged to include the tumor, the posterior aspect of the bladder, and the presacral space. The entire thickness of the sacrum/coccyx was included in the lateral portal to achieve an adequate posterior border. The isodose distribution for the 4-field box technique using 18-megaelectron volt (MeV) photons is shown in Figures 1, 2, and 3. The tumor dose is specified at the point at which the 4 treatment fields intersect (i.e., the maximum dose), so that if 4500 cGy is delivered to that point, the anterior abdominal wall receives approximately 3000 cGy, the small intestine dose varies from 3000 to 4500 cGy, and the pelvis receives approximately 2500 cGy. The minimum dose to the primary bowel lesion would be approximately 4300 cGy and the maximum dose, 4500 cGy. The inguinal lymph nodes receive approximately 60% of the specified tumor dose, so that to irradiate these lymph nodes electively to a total dose of 4500 cGy, it is necessary to add 1550–2000 cGy with 10 MeV

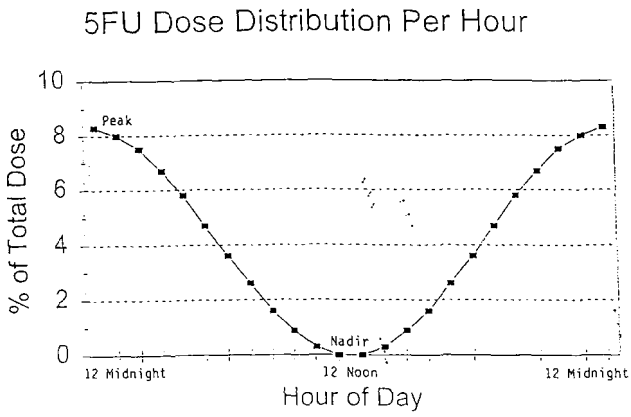

FIGURE 4. Nomogram represented by curve, approximating a true circadian sinewave infusion pattern.

to 12 MeV electrons. Elective inguinal lymph node irradiation is employed when the distal margin of the tumor is within 2–3 cm of the anal verge. By using this technique, radiation fields conform more to the true pelvis than the whole pelvis, thereby limiting toxicity.

Patients were simulated for the initiation of radiation therapy by transrectal placement of a stainless steel pin into the inferior margin of the tumor using a spinal needle. Roentgenograms were obtained to ascertain the location of the pin in relation to the bony pelvis. Barium was placed into the rectum to outline the remainder of the tumor and iothalamate meglumine (CYSTO-CONRAY-2®, Mallinckrodt Inc., Paris, NY) was placed into the bladder to outline that structure, after which roentgenograms were obtained.

Chemotherapy

A venous access device (Infusaport®, Infusaid, Norwood, MA) was placed surgically and 5-FU was initiated at 250 mg/m^2/day. The 5-FU was administered using a VIVUS-4000®, I-Flow (Irvine, CA), portable, programmable infusion pump. The total dose for the day was divided into 24 1-hour segments with the patient receiving a percentage of the total dose each hour according to a nomogram represented by the curve in Figure 4, approximating a true circadian sinewave infusion pattern. If no Grade 3 or higher toxicity was experienced by any of the 5 patients at the dose intensity of 250 mg/m^2/day, then the next 5 patients received 275 mg/m^2/day, the following 5 patients 300 mg/m^2/day, and the final cohort of 5 patients 325 mg/m^2/day. If Grade 3 or higher toxicity was observed in any patient, the intention was to treat an additional three patients at that dose level. If ≥50% of patients at that dose level experienced Grade 3 or higher toxicity, the maximum tolerated dose was determined and the preceding (lower dose) was defined as the optimal dose for a Phase II study. No dose escalation was permitted for individual patients and the study was designed to close temporarily after each five-patient stratum had completed therapy to evaluate toxicity and results.

TABLE 1
Patient Population

Median age (yrs)	62
Range	32–78
Sex (M/F)	11/7
Tumor characteristics	
Fixed	3
Locally advanced	15
Distance from anal verge	
1–5 cm	8
6–10 cm	8
11–15 cm	2

M: male; F: female.

RESULTS

Eighteen patients (11 males and 7 females) completed the full course of combined therapy. The patient characteristics are summarized in Table 1. The treatment parameters and toxicity profiles are summarized in Table 2. The mean age was 62 years (range, 32 to 78 years). All patients received chronobiologically based, continuous infusion 5-FU for an average of 5 weeks, concomitant with the course of preoperative radiation therapy. Five patients received 5-FU in the initial stratum at a dose of 250 mg/m^2/day. Six patients received 275 mg/m^2/day in the 2nd stratum, 6 patients received 300 mg/m^2/day in the 3rd stratum (an additional patient was included in each stratum for adequate toxicity analysis), and 1 patient received 325 mg/m^2/day in the 4th stratum. There were no treatment-related complications requiring hospitalization and there also were no pump-related problems that interrupted therapy. All patients were able to receive the complete course of planned radiation therapy. Four patients required early discontinuation of chemotherapy because of Grade 2 and 3 diarrhea (1, 2, 4, and 21 days early, respectively). There patients complained of rectal pain and three patients had Grade 2 stomatitis, but there were no other serious complications, such as neutropenic fever. No patients receiving 275 mg/m^2/day or less of 5-FU experienced Grade 3 toxicity of any kind. With one exception, all patients underwent final definitive surgery. Mesorectal excision as described by Heald et al.[28] was used in all patients to optimize results and standardize technique.

TABLE 2
Treatment Parameters and Toxicity

5-FU dose schedule	Patient's sex	Patient's age (yrs)	Radiotherapy dose	Surgery	Toxicity
250 mg/m^2/day × 5 weeks	4 M	76, 78, 40, 77	4500 cGy × 5	1 APR 3 LAR	2 Diarrhea: Grade 1
	1 F	67		1 Coloanal pull-through	
275 mg/m^2/day × 4–5 weeks	4 M	68, 63 32, 49	4500 cGy × 3 5040 cGy × 1	3 APR 2 LAR	3 Diarrhea: Grade 2
	2 F	49, 74	5580 cGy × 2	1 APR after AR	
300 mg/m^2/day × 4–5 weeks	2 M 4 F	71, 63 74, 50, 62, 65	4500 cGy × 4 5040 cGy × 1 5580 cGy × 1	5 APR 1 Patient refused surgery	4 Diarrhea; Grade 2 Grade 3 1 hand-foot syndrome 1 Port-related DVT 2 Stomatitis Grade 2 Grade 3
325 mg/m^2/d × 4–5 weeks	1 M	58	4500 cGy	LAR	1 Diarrhea: Grade 3 1 Stomatitis: Grade 2

5-FU: 5-fluorouracil; M: male; F: female; cGy: centigray; APR: abdominoperineal resection; LAR: low anterior resection; DVT: deep venous thrombosis.

TABLE 3
Comparison of Surgical Procedure, AJCC Pathologic Staging, and Tumor Regression Grade

	Final pathology		
Surgery	pT	LN	TRG
LAR	1	–	2
APR	3	None	4
APR	0	–	1
APR	3	–	4
APR	3	–	4
LAR with colostomy	0	–	1
LAR with coloanal anastomosis	3	–	3
APR	0	None	1
APR	3	–	2
LAR	2	–	2
LAR	3	None	4
LAR	2	+	4
LAR	0	None	1
LAR → APR	2	None	3
APR	0	None	1
APR	3	–	3
Deferred	No surgery after RT		
APR	3	None	4

AJCC: American Joint Committee on Cancer; APR: abdominoperineal resection; LAR: low anterior resection; pT: pathologic tumor stage; TRG: tumor regression grade; LN: lymph nodes; –: not involved by tumor; +: involved by tumor.

Pathologic evaluation (Table 3) determined that in 5 patients (28%) there was no residual tumor (pT0). One patient had a pT1 tumor, three patients had pT2 tumors, and eight patients had pT3 residual tumors. In terms of TRG, obviously all pT0 tumors had a TRG of 1. Among the TRG 2, one tumor was a pT1, one tumor was a pT2 tumor, and one tumor was a pT3 tumor. Finally, the two TRG 3 and all but one TRG 4 tumors were pT3. In comparison, the ratio of pathologically negative specimens after preoperative radiotherapy alone at our institution was 14 of 132 patients (11%) with clinically resectable lesions and 0 of 42 patients (0%) with clinically unresectable lesions.[2,5] A sphincter-sparing procedure (low anterior resection) was performed in seven patients; the remaining ten patients (one patient declined surgery) were all able to successfully undergo abdominoperineal resection of the tumor with clear margins. Those patients who required abdominoperineal resection either had involvement of the dentate line and/or fixation to adjacent tissue. In one paraplegic patient, initially fecally incontinent, the surgeons elected to perform a colostomy for control, although sphincter-sparing surgery was possible.

The average follow-up time as of this article was 12 months, ranging from 6 to 37 months. Two patients were noted to have positive lymph nodes on final pathology. One had disease recurrence in the periaortic lymph nodes together with brain metastases 10 months after surgery and died 3 months later. All patients with either positive lymph nodes or residual tumor in the specimen at the time of surgery (12 patients) were offered postoperative adjuvant chemotherapy with 5-FU and leucovorin for an intended period of 6 months; only 2 patients accepted. Fifteen patients were deemed locally advanced and received at least 4500 cGy as intended, with 2 patients boosted to 5040 cGy. Three patients were deemed clinically unresectable and received 5580 cGy.

DISCUSSION

We believe that the findings of this study are valuable for a number of reasons. First, the excellent response of the primary tumor to the combination of circadian-based continuous infusion 5-FU and radiation therapy (allowing 100% of patients to undergo potentially curative surgery with 28% pathologic complete response, and an additional 22% clinical complete remissions for a total of 50% of patients with minimal or no residual tumor and no evidence of peripheral fat invasion or positive lymph nodes) confirms the value of a combined approach in this disease. Although we are as yet unable to comment on ultimate disease free and overall survival, improved local (and distant) control is, of necessity, a precursor to improvement in these two important endpoints. Although the number of patients treated in our series is relatively small, the results are encouraging, and clinical complete remission appears to be as good as or better than other reported studies; Chen et al.[20] had 49% clinical complete remissions, Minsky et al.[18] had 30%, and Picciocchi et al.[17] had 24%. It is unclear as yet whether the TRG provides additional or improved data regarding the ultimate prognosis as compared with AJCC staging, allowing more precise stratification of patients into risk categories (as in esophageal carcinoma), but further follow-up will permit analysis of this question.

Perhaps more important, these results have been achieved without major toxicity and/or interruption of treatment. In 4 patients, early cessation of chemotherapy was necessitated by significant diarrhea, but in 3 of the 4 patients this occurred within 2–3 days of the intended completion of therapy and the subsequent morbidity was minimal, with no patient requiring hospitalization. The 4th patient was in the final stratum of 325 mg/m^2/day of 5-FU and had coexistent diabetes mellitus with gastrointestinal motility problems, which may have increased the likelihood of treatment toxicity. No patient experienced Grade 3 toxicity of any kind at the recommended dose level of 275 mg/m^2/day.

This appears to be an improvement over regimens using bolus doses of 5-FU and leucovorin, in which significant toxicity is frequent and even potentially life-threatening.[15–18] It also appears to be less problematic than the limited studies with flat infusions of 5-FU, such as that reported by Chen et al.[20] In this trial, which combined preoperative radiotherapy with flat, continuous infusion of 5-FU, 73% of patients developed some degree of diarrhea, 41% developed stomatitis, 36% developed leukopenia, 14% developed thrombo-cytopenia, and 23% developed anemia. The exact doses administered to the patients in this trial are unclear (200–300 mg/m^2/day were reported), with 26% of patients requiring dose interruption for 1–2 weeks and 33% of patients requiring early discontinuation of therapy.[20] This is considerably more toxicity than noted in the current study using doses of up to 300 mg/m^2/day.

There are two important questions that may ultimately determine the optimum mode of chemotherapy administration. The first is whether there is schedule dependency with respect to timing of chemotherapy relative to radiation, and the second whether a continuous dose-response effect in the potentiation of radiation therapy by 5-FU exists, or whether there is a threshold dose intensity, beyond which no therapeutic gains will be realized but toxicity will increase.

With respect to the first question, infusional programs would seem to offer distinct theoretic advantages. 5-FU has an extremely short serum half-life (11 minutes)[29] and within approximately 6 hours of administration, plasma concentrations are less than 1 μM, which appears to be the threshold for exerting a cytotoxic effect in tissue culture. Although the active metabolites of 5-FU, such as 5-deoxyuridine monophosphate (dUMP) and fluorouridine triphosphate (FUTP), have prolonged intracellular half-lives, uptake of 5-FU into susceptible cells may only occur at times of cellular proliferation.[30] Pulse thymidine labeling studies in colon carcinoma demonstrate uptake of 5-FU in only 3% of tumor cells after bolus treatment.[31] Thus, because most gastrointestinal tumors have a fairly low proliferative index, and because radiotherapy potentiating effects appear to be optimized if the drug is present simultaneously and shortly after radiotherapy, prolonged continuous infusion becomes an attractive approach for both maximal drug exposure and optimal interaction with radiation.[6–8]

As to the second issue of dose intensity, the limited patient numbers in this study do not permit a definitive conclusion but, at face value, there does not appear to be a difference in initial therapeutic response dependent on dose intensity of 5-FU within the given range, with excellent responses, including complete remissions, in all strata. It seems probable that a threshold dose may exist (at least for potentiation of radiotherapy) and that this may require a relatively low dose intensity of 5-FU when given by continuous infusion.

Conversely, the optimal treatment of micrometastatic disease needs to be addressed. Because a significant proportion of patients historically fail at distant sites, it is clear that improved results will require more effective treatment strategies for this phenomenon. To this end, a number of approaches have been developed to potentiate the efficacy of 5-FU. Other agents may be added to modify the pharmacologic actions of

intracellular 5-FU. These include leucovorin (which supplies tetrahydrofolate, a cofactor for inhibition of thymidylate synthase),[32] PALA (an inhibitor of aspartate transcarbamoylase used in de novo pyrimidine biosynthesis to produce uridine triphosphate [UTP],[33] and α-interferon (uncertain mechanism involving the increased conversion of 5-FU to 5-dUMP and direct inhibition of thymidylate synthase).[34]

Prolonged continuous infusion of 5-FU has been equally successful when compared with simple bolus dose administration.[35] This may be related to the pharmacokinetics as alluded to before, or may simply be a result of the increased total deliverable dose of drug. The recent report by Milano et al.,[36] which analyzes the relationship between 5-FU systemic exposure, tumor response, and survival in patients with head and neck cancers, suggests that the area under the curve achieved in each individual is of great importance in determining ultimate survival. The relative merits of the enhanced 5-FU or infusional schedules have been difficult to determine. Ongoing cooperative group trials will assist in this analysis. Of great interest has been the important study by O'Connell et al.,[11] which found that continuous infusion of 5-FU administered with radiation therapy potentiated the efficacy of this combination when used postoperatively in patients with resectable rectal adenocarcinomas. More comprehensive use of continuous infusion 5-FU is now to be tested in the postsurgical setting.

The determination by this trial that 5-FU at a dose of 275 mg/m^2/day can be administered safely and with minimal toxicity together with concomitant radiation therapy when a chronobiologic approach is used is valuable. This is a significantly higher dose intensity than the 225–250 mg/m^2/day most often utilized in combined therapy. As Hryniuk et al. have demonstrated, namely a steep dose intensity/response relationship for fluoropyrimidines,[37] a method such as this can be used to safely achieve increased dose intensities that may be highly desirable. The cellular biology, pharmacodynamics, and pharmacokinetics responsible for this phenomenon are still incompletely understood, but it has been observed that the cellular proliferation of the gastrointestinal mucosa is time-dependent, with increased proliferation occurring during the early waking hours and decreased cellular turnover taking place later.[38,39] In addition, rat liver and human mononuclear cell concentration of dihydropyrimidine dehydrogenase (DPD), which is one of the primary enzymes in the degradation of 5-FU, also shows a definite circadian variation with peak levels in humans close to the midsleep cycle.[40,41] Interestingly, measurement of a random level of DPD activity in peripheral lymphocytes has been found to correlate with 5-FU clearance.[42] Many other enzymes are involved in 5-FU metabolism, but only a small fraction of potentially relevant pathways has been explored for chronobiologic data. Timing the infusion according to the known data, i.e., 5-FU infusion should peak during the late hours of sleep and be minimal during the period of maximal activity, appears to lessen the toxicity while maintaining efficacy.

This approach can therefore facilitate increased achievable dose intensity whenever continuous infusion 5-FU or FUDR is used and appears to be equally applicable to other chemotherapy drugs and biologic agents. The argument is often made that the complexity of such a program places this type of therapy out of the reach of the practicing oncologist. However, we have determined that it is a simple matter to obtain, program, and use these pumps with a low complication rate and excellent reliability. If chronomodulated infusions become more widely used, it will be a straightforward process for any oncologist to adapt.

In summary, we believe that this trial has demonstrated the low toxicity, efficacy, and safety of combined radiation therapy and chronomodulated 5-FU infusion in patients with locally advanced and unresectable rectal carcinoma. A dose intensity of 275 mg/m^2/day of 5-FU is readily achievable for the duration of the radiation therapy (at minimum 4500 cGy and very probably up to 5580 cGy over 5–6 weeks) but the impact of this dose intensity on micrometastatic disease is as yet unknown and will require longer follow-up. The majority of, if not all, patients will become potentially resectable for cure, and a number of these individuals will have rectal sparing and/or a complete pathologic remission. Newer chronobiologic regimens that incorporate both 5-FU and leucovorin given by circadian continuous infusion appear to be even more active than 5-FU alone.[24] This will be evaluated in the next generation of trials. In addition, optimal postsurgical therapy (if any) is yet to be determined. A minimalist approach to radiologic studies is probably sensible, with either a pretherapy transrectal ultrasound or magnetic resonance imaging being sufficient to determine the stage of the disease.[43,44]

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