RAPID PUBLICATION

Randomized Comparison of Fluorouracil Plus Cisplatin Versus Hydroxyurea as an Adjunct to Radiation Therapy in Stage IIB-IVA Carcinoma of the Cervix With Negative Para-Aortic Lymph Nodes: A Gynecologic Oncology Group and Southwest Oncology Group Study

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Purpose: **In 1986, a protocol comparing primary radiation therapy (RT) plus hydroxyurea (HU) to irradiation plus fluorouracil (5-FU) and cisplatin (CF) was activated by the Gynecologic Oncology Group (GOG) for the treatment of patients with locally advanced cervical carcinoma. The goals were to determine the superior chemoradiation regimen and to quantitate the relative toxicities.**

Methods: **All patients had biopsy-proven invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix. Patients underwent standard clinical staging studies and their tumors were found to be International Federation of Gynaecology and Obstetrics stages IIB, III, or IVA. Negative cytologic washings and para-aortic lymph nodes were required for entry. Patients were randomized to receive either standard whole pelvic RT with concurrent 5-FU infusion and bolus CF or the same RT plus oral HU.**

Results: **Of 388 randomized patients, 368 were eligible; 177 were randomized to CF and 191 to HU. Adverse effects were predominantly hematologic or gastrointestinal in both regimens. Severe or life-threatening leukopenia was more common in the HU group (24%) than in the CF group (4%). The difference in progression-free survival (PFS) was statistically significant in favor of the CF group ($P = .033$). The sites of progression in the two treatment groups were not substantially different. Survival was significantly better for the patients randomized to CF ($P = .018$).**

Conclusion: **This study demonstrates that for patients with locally advanced carcinoma of the cervix, the combination of 5-FU and CF with RT offers patients better PFS and overall survival than HU, and with manageable toxicity.**

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AS PRIMARY TREATMENT for locally advanced invasive carcinoma of the cervix, radiotherapy alone fails in a substantial number of patients so treated.[1,2] The radiotherapy failure rate for patients with stage IIB disease is 20% to 50%; for patients with more extensive stage III disease, the rate ranges from 50% to as high as 75%.[3,4] Such treatment failure may be due to unrecognized metastatic disease at the time of original diagnosis. The more common and consequential component of treatment failure is the inability of primary radiotherapy alone to completely eradicate all pelvic disease.[5] It is estimated that 2,700 additional lives could be saved annually if perfect local control of pelvic tumor were possible.[6] Local control may be increased by escalating the radiation doses but at the cost of increased toxicity. Altered fractionation schedules have yet to show significantly increased local control or survival. Hyperbaric oxygen, particle therapy, and hyperthermia are not widely accessible and have shown only marginal improvements.

Theoretically, the concomitant administration of chemotherapy with radiotherapy could increase local control and survival.[7] The concept has proven helpful in a variety of tumor sites, including the head and neck,[8] lung,[9] esophagus,[10] bladder,[11] and anus.[12] The concept is particularly appropriate for locally advanced cervical carcinoma. For nearly its entire 25-year history, the Gynecologic Oncology Group (GOG) has evaluated the concept of chemoradiation for patients with locally advanced cervical carcinoma. The GOG reported a significant improvement in survival for patients treated with hydroxyurea (HU) and radiation therapy

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compared with those treated solely with radiotherapy.[13] The GOG has reported a significant improvement in pelvic control, progression-free interval, and, most importantly, survival for patients treated with HU and radiation therapy compared with patients treated solely with radiotherapy.[13-16] Therefore, on this basis, the GOG has used chemoradiation with HU as its standard treatment of patients with locally advanced cervical carcinoma.

Other cytotoxic agents have been used, singly and in combination, concurrently with radiation therapy, including mitomycin, fluorouracil (5-FU), cisplatin (CF), carboplatin, vincristine, etoposide, bleomycin, and paclitaxel. The combination of 5-FU and CF demonstrates synergy when given concurrently with radiation therapy in animal models.[17] The combination has been well tolerated when added to standard pelvic radiotherapy.[18-22] On the basis of these encouraging theoretical and early clinical results, the GOG activated a protocol (GOG Protocol #85) with the collaboration of the Southwest Oncology Group (SWOG 8695). The trial compared primary irradiation with either concomitant 5-FU/CF or HU as initial treatment of patients with locally advanced carcinoma of the cervix. The goals were to compare the efficacy as measured by progression-free interval and survival and to quantitate the relative toxicities.

PATIENTS AND METHODS

All patients had biopsy-proven invasive squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the uterine cervix. All patients' tumors were staged by criteria of the International Federation of Gynecology and Oncology and had stage IIB, III, or IVA disease. Normal renal, hepatic, and bone marrow function were required for entry. Eligible patients had to be free of clinically significant infection, have no prior exposure to pelvic irradiation or cytotoxic chemotherapy, be without medical contraindications to surgery, and have a GOG performance grade of 3 or lower. Patients with previous or concomitant other cancers, other than skin cancer but excluding melanoma, were not eligible for inclusion in this study. Written informed consent conforming to all federal, state, and local regulations was obtained from each participant before institution of protocol therapy.

All patients underwent standard clinical staging studies, including chest x-ray, intravenous pyelogram or computerized axial tomography with intravenous contrast, and examination under anesthesia. After this, all patients underwent para-aortic lymphadenectomy via a retroperitoneal approach. Lymph node tissue was removed from the level of the inferior mesenteric artery to the mid–common iliac arteries bilaterally. This was followed by intraperitoneal exploration, with inspection of all intraperitoneal organs and cytologic washings from the pelvis. Any suspicious area required biopsy. Pelvic lymphadenectomy was not required of patients and was left to the discretion of the investigator. Patients with metastasis to the para-aortic lymph nodes or intra-abdominal contents and those whose cytologic washings were positive for carcinoma were not included in this trial.

The experimental regimen used standard fractionation of external-beam whole-pelvis radiotherapy with concurrent 5-FU infusion and bolus CF. The control regimen was the same radiotherapy and oral HU. Randomization with equal probability of assignment to each treatment regimen was carried out by a block arrangement balancing the treatment assignment within the three major categories of clinical stage and institution.

Within 6 weeks of surgery, patients began radiation therapy with standard fractionation. Patients whose tumors were staged as IIB were to receive 40.8-Gy external-beam therapy delivered homogeneously to the whole pelvis in 24 fractions. After completion of external-beam therapy, 40 Gy was to be delivered to point A via one or two intracavitary applications (tandem and colpostats) of radium or its equivalent. If necessary, a parametrial boost was given to bring the point-B dose to 55 Gy. Those patients whose tumors were staged as III or IVA were to receive 51 Gy in 30 fractions if an intracavitary implant was not possible. Point A received 30 Gy from one or two intracavitary implants. Point B received 60 Gy from both sources with or without a parametrial boost. Those patients treated solely with external-beam therapy were to receive 61.2 Gy. The total elapsed time for external and intracavitary therapy could not exceed 10 weeks.

The patients were treated with either anteroposterior and posteroanterior parallel ports or a four-field box technique. External-beam radiation treatment was delivered using either cobalt-60 irradiators or a linear accelerator with a minimum photon-beam energy of 4 MeV at a target or skin source distance of 80 cm. Intracavitary radiation was delivered by standard radium, cesium, or cobalt sources. The irradiated volume was to include the whole uterus, the paracervical, parametrial and uterosacral regions, as well as the external iliac, hypogastric, and obturator lymph nodes. Minimum margins were the upper margin of L-5 (superiorly), the midportion of the obturator foramen or the lowest extension of the disease (inferiorly), and 1 cm beyond the lateral margins of the bony pelvis and its widest plane (laterally). For the lateral fields, the anterior margin was the anterior edge of the symphysis or 3 cm in front of the sacral promontory. The posterior margin was the S2-S3 interspace. Beam verification films and orthogonal dosimetry films were reviewed by the Radiologic Physics Center of the American Association of Physicists in Medicine for proper dosimetry.

Representative stained microscopic slides of the primary site and any site of metastatic disease were reviewed by the Pathology Committee of the GOG. This confirmed the primary site, histologic type, grade, depth, and location of invasion. Eligibility was confirmed by the Gynecologic Oncology Committee of the GOG by review of all records, forms, and operative reports. Protocol treatment violations were determined by the study chair (C.W.W.).

Patients randomized to the CF regimen received, 4 hours before the first dose of external-beam radiotherapy, intravenous CF (50 mg/m^2) infused at a rate of 1 mg/min with standard hydration. The same infusion schedule was repeated on day 29, again, 4 hours before a dose of external-beam irradiation. On days 2, 3, 4, 5, 30, 31, 32, and 33, 5-FU was intravenously infused at a dose of 1,000 mg/m^2/d (4,000 mg/m^2 total dose, each course). Patients on the HU regimen received HU orally at a dose of 80 mg/kg body weight every Monday and Thursday or Tuesday and Friday each week of external-beam therapy. No single dose was to exceed 6,000 mg. Chemotherapy was withheld until the WBC count was greater than 3,000 cells/mm^3 and the platelet count was greater than 100,000 cells/mm^3. Radiotherapy was withheld for grade 3 or 4 hematologic toxicity.

Adverse effects were recorded and graded according to the GOG adverse effects criteria. Any grade 4 (life-threatening) adverse effect or unusual adverse reaction was to be reported immediately to the GOG administrative office and the study chair.

The accrual goal was set at 340 eligible patients. The follow-up, as of this report, shows that 96% of patients have died or have been followed at least 5 years. A total of 187 deaths have been observed, which provides detection of a 31% reduction (relative risk [RR] of 0.69) in the death hazard rate with a statistical power of 80% (type I error of 5%, one tail).[23]

Progression was defined as a substantial increase in the primary tumor from a previous examination, physical or radiographic evidence of extension of the primary disease, or the appearance of any new lesion.[24] Progression-free survival (PFS) was defined as the time from study entry to disease progression or death, whichever came first, or to the date the patient was last seen alive. Similarly, survival time was defined from entry to death, or date last seen. Life tables and medians were computed using the method of Kaplan and Meier.[25] The ''intent-to-treat'' principle of eligible patients was used in the analysis. Differences in PFS and survival by treatment were evaluated using the log-rank test.[26] The comparisons of PFS and survival by treatment, while adjusting for prognostic factors, were accomplished using the Cox model.[27] Correlations between the grading of adverse effects and treatment were evaluated using the Mann-Whitney test.[28]

A variety of methods were used to evaluate the potential effect of the patients who were lost to follow-up (lost) on the survival analysis. Computer simulation was used to generate the follow-up for these lost patients. The risk of death was generated using the Gompertz model, with parameters estimated from fitting the survival time of the entire study population. The prognosis of each lost patient was incorporated by multiplying the initial hazard parameter from the Gompertz model by the RR estimate determined from the Cox modeling of survival. The simulated follow-up included no differential benefit for those on the CF regimen (null hypothesis). This method was introduced by Lan et al[29] for the purpose of interpreting interim results. Their method involved simulating the survival time from the present follow-up into the future ''final analysis'' point in time. Our application of this statistical method is somewhat different in that it simulates the survival time from the past follow-up of the lost patients to the present time. The method yields an estimate of the conditional probability of the type I error that is used to calculate an upper bound of the type I error. The results of these simulations indicated that the upper bound for the type I error was only negligibly increased above the .05 level.

An ad hoc method focused on the excess six lost patients in the CF regimen. The method eliminated all patients registered by small contributing GOG institutions with a lost patient. This was considered an unbiased way of evaluating the treatment difference because the randomization scheme for this trial was blocked on GOG institutions. The lost patients from large contributing GOG institutions were recorded as dead as a way of evaluating the impact of the worst possible implication of being lost on the survival analysis results. No matter which GOG institutions were included as small contributors, the survival difference was statistically significant. Therefore, we conclude that the influence of this imbalanced number of lost cases on the results of this trial was negligible.

RESULTS

Between August 1986 and December 1990, 388 patients were entered onto this study. Of these, 188 were randomized to a regimen of radiotherapy with concurrent 5-FU and CF and 200 to radiotherapy with concurrent HU. Fourteen patients were ineligible—nine on the CF regimen (wrong stage [n = 2], inadequate surgery [n = 3], positive nodes [n = 3], and active tuberculosis [n = 1]) and five on the HU regimen (wrong stage [n = 1], inadequate surgery [n = 2], positive nodes [n = 1], and wrong primary [n = 1]). Six patients were unassessable because of inadequate data submission (two patients on the CF regimen and four patients on the HU regimen). The remaining patients—177 in the CF regimen and 191 in the HU regimen—are the basis of this report.

Prognostic variables of stage, age, performance status, and positive pelvic lymph nodes were nearly equally distributed between the two treatment regimens (Table 1). The factor with the greatest distributional difference between treatment regimens was cell type. Twenty-one patients (12%) assigned to CF had adenocarcinoma or adenosquamous carcinoma compared with 12 patients (6%) on the HU regimen. More patients on the HU regimen had the more

Table 1. Patient Characteristics

Characteristic	Treatment Regimen			
	5-FU + CF		HU	
	No.	%	No.	%
Total	177	100.0	191	100.0
Age, years				
≤ 30	10	5.6	11	5.8
31-40	35	19.8	45	23.6
41-50	57	32.2	65	34.0
51-60	45	25.4	37	19.4
61-70	26	14.7	26	13.6
≥ 71	4	2.3	7	3.7
Cell type				
Squamous	156	88.1	179	93.7
Adenocarcinoma	8	4.5	6	3.1
Adenosquamous	13	7.3	6	3.1
Stage				
IIB	108	61.0	120	62.8
IIIA	4	2.3	6	3.1
IIIB	60	33.9	58	30.4
IVA	5	2.8	7	3.7
GOG performance status				
0	119	67.2	119	62.3
1	54	30.5	64	33.5
2	4	2.3	7	3.7
3	0	0.0	1	0.5
Pelvic lymph node status				
Not dose	48	27.1	75	39.3
Positive	28	15.8	24	12.6
Negative	101	57.1	92	48.2
Tumor size, cm				
≤ 4.0	40	22.6	33	17.3
5.1-7.0	58	32.8	68	35.6
7.1-8.0	54	30.5	57	29.8
8.1+	25	14.1	33	17.3
Parametrial involvement				
None	1	0.6	1	0.5
Unilateral	120	67.8	137	71.7
Bilateral	56	31.6	53	27.7

favorable pure squamous cell histology (94% *v* 88%). The clinical stage distribution was quite similar for the two regimens. Of the entire study population, 62% had stage IIB disease, 35% had stage III, and 3% had stage IVA. The median age of the patients on the CF regimen was 48 years (range, 26 to 81 years) and for patients on the HU regimen, 47 years (range, 22 to 81 years). The majority of patients (65%) had a GOG performance status of 0 (Karnofsky scale, 90 to 100). Pelvic lymph nodes were sampled more often among those on the CF regimen (73% *v* 61%). This patient population was comparable to the patient population of previous GOG studies.

Three patients in the CF regimen (all had stage IIB disease) and in the HU regimen (all had stage III disease) refused all radiotherapy. One patient randomized to the HU regimen died of a pulmonary embolus 25 days after registration and had received no protocol therapy. Of the 363 patients who received external-beam radiotherapy, 40 (11%) had no intracavitary therapy (18 patients on CF and 22 on HU). Of these 40 patients, 10 had stage IIB disease.

All eligible patients were included in the statistics quantifying the protocol therapy received. Twenty-one patients (12%) on the CF regimen and 23 (12%) on the HU regimen did not receive brachytherapy. The point A dose was within 15% of the prescribed dose for 92% of patients assigned to CF versus 86% for those assigned to HU. The point B dose was within 15% of the prescribed dose for 87% of patients on the CF regimen versus 88% on the HU regimen (Table 2). The median total treatment time was 9.1 weeks (10th and 90th percentiles, 7.0 and 12.2 weeks; range, 0.0 to 19.3 weeks) for the CF regimen and 9.1 weeks (10th and 90th percentiles, 7.1 and 11.6 weeks; range, 0 to 28.6 weeks) for the HU regimen. The number of brachytherapy implants and the stage of disease influenced the radiotherapy treatment time as well as the unplanned events that forced modification and discontinuation of radiotherapy. To account for this variation, the delay time was calculated by taking the actual elapsed days during radiotherapy and subtracting the anticipated elapsed days for the prescribed radiotherapy (defined as 7 days for every 5 treatment days prescribed plus 10 days for each implant). The analysis of delay time included only patients who received doses within 15% of the prescribed dose to both points A and B. The median delay time was 12 days (10th and 90th percentiles, 1 and 32.8 days; range, −13 to 72 days) for the CF patients and 13 days (10th and 90th percentiles, 2.1 and 28 days; range, −5 to 150 days) for the HU patients. In all cases, tumor geometry precluded placement of the intracavitary source.

Table 2. Percent and Fraction of Patients Who Received Within 15% of Prescribed Radiation Therapy Dose to Point A and Point B (prescribed dose was a function of stage and the use of brachytherapy)

Stage / Brachytherapy Status	Prescribed Dose (Gy)	5-FU / CF		HU	
		%	Fraction	%	Fraction
Point A					
IIB with / without brachytherapy or III / IVA with brachytherapy	8,100	94.4	153/162	86.8	151/174
III / IVA without brachytherapy	6,100	64.3	9/14	76.5	13/17
Entire study group*	—	90.9	160/176†	86.4	165/191
Point B					
IIB	5,500	84.1	90/107	87.5	105/120
III / IVA	6,000	91.3	63/69	90.1	64/71
Entire study group‡	—	86.9	153/176†	88.5	169/191

*Thirteen (7.4%) and 10 patients (5.2%) received less than 85% of the prescribed dose in the 5-FU / CF and HU regimens, respectively.

†One patient; the doses of radiotherapy were not available.

‡Twelve (6.8%) and 18 patients (9.4%) received less than 85% of the prescribed dose in the 5-FU / CF and HU regimens, respectively.

Thirty-three patients received less than 85% of the prescribed dose to either point A or point B (15 patients on the CF and 18 on the HU regimen). Five of these patients received no radiotherapy (referred to above). Discontinuation of radiotherapy was medically indicated for eight patients: two patients had a severe adverse effect, five had progression of disease, and one patient required a hysterectomy for a medical condition. Nine patients were noncompliant with the radiotherapy schedule, and the remaining 11 received low doses because of technical problems (dosimetry errors and an inability to place intracavitary source).

A total of 161 patients (91%) randomized to CF received both drug courses. Seven patients (4%) did not receive any drug, eight (5%) received one course, and one (1%) received three courses. Of those assigned to HU, 163 (85%) received at least 4 weeks of drug. Three patients (2%) did not receive any HU, three (2%) received 1 week, eight (4%) received 2 weeks, and 14 (7.3%) received 3 weeks of HU. All patients receiving 5-FU/CF were hospitalized for drug administration, whereas no patients receiving HU required hospital admission for drug administration.

Adverse effects were evaluated for patients who received radiotherapy and had at least one course/week of drug (Table 3). Adverse effects were predominately hematologic or gastrointestinal in both treatment groups. Decreases in the WBC count were more common and more severe on the HU regimen ($P < .00001$). Severe (grade 3) or life-threatening (grade 4) leukopenia occurred in only six CF patients (4%) compared with 46 HU patients (24%). All patients' WBC counts recovered to normal levels.

Grade 3 or 4 gastrointestinal toxicity was slightly more common (not statistically significant) for patients randomized to CF (8%) than for the HU group (4%). Adverse effects prevented one patient from each regimen from completing

Table 3. Adverse Effects

	5-FU/CF (n = 169)										HU (n = 188)									
	Grade										Grade									
	0		1		2		3		4		0		1		2		3		4	
Adverse Effect	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
WBCs	93	55.0	39	23.1	31	18.3	4	2.4	2	1.2	32	17.0	34	18.1	76	40.4	41	21.8	5	2.7
Platelets	163	96.4	4	2.4	2	1.2	0	0.0	0	0.0	178	94.7	7	3.7	2	1.1	0	0.0	1	0.5
Other hematologic	124	73.4	24	14.2	16	9.5	4	2.4	1	0.6	141	75.0	11	5.9	25	13.3	9	4.8	2	1.1
Gastrointestinal	53	31.4	38	22.5	65	38.5	9	5.3	4	2.4	77	41.0	35	18.6	68	36.2	6	3.2	2	1.1
Genitourinary	125	74.0	30	17.8	12	7.1	2	1.2	0	0.0	145	77.1	31	16.5	9	4.8	0	0.0	3	1.6
Neurologic	162	95.9	5	3.0	2	1.2	0	0.0	0	0.0	179	95.2	4	2.1	5	2.7	0	0.0	0	0.0
Pulmonary	167	98.8	0	0.0	1	0.6	1	0.6	0	0.0	187	99.5	0	0.0	0	0.0	0	0.0	1	0.5
Cutaneous	131	77.5	25	14.8	9	5.3	4	2.4	0	0.0	165	87.8	14	7.4	6	3.2	3	1.6	0	0.0
Cardiovascular	167	98.8	0	0.0	1	0.6	1	0.6	0	0.0	185	98.4	0	0.0	3	1.6	0	0.0	0	0.0
Fever	162	95.9	3	1.8	2	1.2	2	1.2	0	0.0	183	97.3	1	0.5	2	1.1	2	1.1	0	0.0
Other	168	99.4	1	0.6	0	0.0	0	0.0	0	0.0	185	98.4	2	1.1	0	0.0	1*	0.5	0	0.0

*Acute vulvitis.

the protocol therapy, one because of small bowel obstruction (CF regimen) and the other because of severe nausea and vomiting (HU regimen). No patient in either group developed grade 4 fever or evidence of overwhelming sepsis. There was no grade 4 nephrotoxicity in the CF group. The remaining categories for adverse effects had a low frequency ($< 2\%$) of grade 3 or 4 toxicity, and no substantial imbalances between the two regimens were present. A life table analysis was applied to the late-complications data to account for patients who were not at risk of late complications because of either death or loss to follow-up. The late major complication rate (grades 3 and 4) was 16.2% at 3 years for the CF group and 16.5% at 3 years for the HU group.

There were no patient deaths solely attributed to the concurrent cytotoxic drug therapy. The one treatment-related death was in the HU group. This patient with stage IVA disease developed a vesicovaginal fistula during radiotherapy. She died of a pulmonary embolus after undergoing a urinary diversion.

The median follow-up time among those patients who are alive is 8.7 years. Seventy-six (43%) of 177 patients in the CF group had disease progression, whereas 101 (53%) of 191 in the HU group suffered the same outcome. PFS was statistically significant favoring the CF regimen (Fig 1, $P = .033$, one-tailed). The RR of progression/death of the CF group to the HU group was 0.79 (90% confidence interval, 0.62 to 0.99). Multiple regression analysis was performed using the following prognostic variables, identified by Stehman et al[2] in a previous GOG publication: clinical stage, pelvic lymph node status, age at diagnosis, and performance status. Using the Cox Model and adjusting for these factors, the results were essentially the same as those for the univariate analysis presented above.

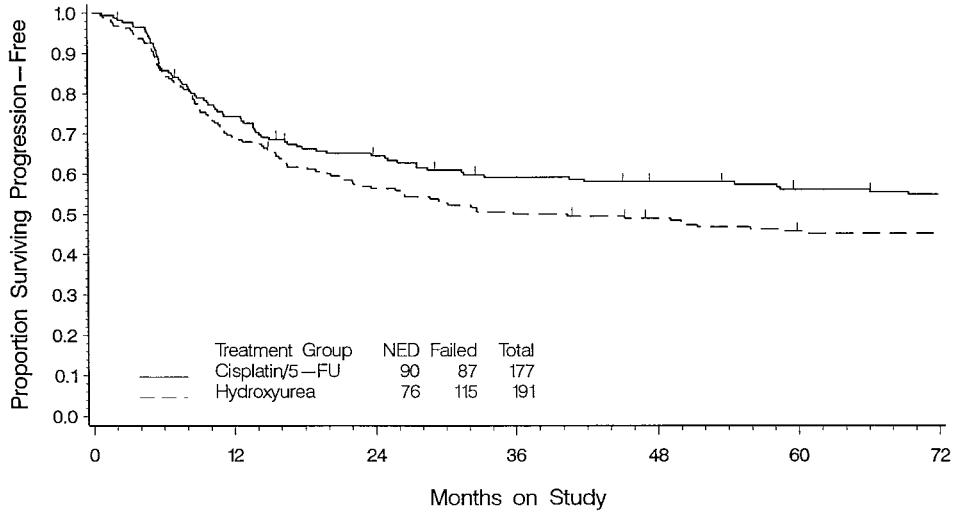

Fig 1. PFS by treatment group.

Seventy-nine patients (45%) from the CF regimen have died, compared with 108 (57%) from the HU regimen. The survival rate is statistically significant ($P = .018$, log-rank test, one-tailed; Fig 2). The relative mortality rate of the CF group to the HU group was 0.74 (90% confidence interval, 0.58 to 0.95). The median survival time for the CF group could not be estimated (last death occurred at 115.5 months and reflected a survival rate of 50.4%), whereas for the HU group, the median was 59.8 months. The results of the multiple regression analysis of survival nearly equaled those of the univariate analysis.

The two outcomes of interest, progression and death, were contrasted. Fifteen patients had disease progression but were still alive as of the date of last contact, and 25 patients died without progression. For the former group, the median follow-up since the date of progression was 80.0 months (range, 0 to 117 months). The patient with the shortest follow-up time since progression failed in the cervix just recently at 9.4 years on study. The latter group included 12 patients who died of unknown causes, 12 who died of intercurrent disease, and one patient who died of treatment-related causes (referred to above).

Table 4 compares the reported sites of first progression. A small difference occurred between CF and HU regimens in the percentage of pelvic progressions (CF, 25%; HU, 30%). Pulmonary progressions were slightly more common in the HU regimen (9% *v* 6%). The frequency of distant sites of progression (ie, outside the pelvic region), excluding the lung, were similar.

Table 4. Site of Progression

Site	5-FU + CF		HU	
	No.	%	No.	%
Pelvis only*	44	24.9	58	30.4
Lung with/without other sites	11	6.2	17	8.9
Distant† (except lung) with/without pelvis	20	11.3	23	12.0
Unknown site	1	0.6	3	1.6
No evidence of disease	101	57.1	90	47.1
Total	177	100.0	191	100.0

*Includes vagina.
†Includes inguinal lymph nodes and bone.

DISCUSSION

There is no curative surgical option for patients with locally advanced invasive carcinoma of the uterine cervix. Primary radiotherapy to the pelvis cures many, but not all, of these patients.[1,2] This treatment failure may be due to unrecognized metastatic disease at diagnosis. Surgical staging and extended-field radiation have yet to have a significant impact on this problem. The more common and consequential component of treatment failure occurs within the field of pelvic radiation.[5] The radiotherapy failure rate for patients with stage IIB disease is 20% to 50%; for patients with more extensive stage III disease, the failure rate ranges from 50% to as high as 75%.[3,4] Neither adjuvant surgery nor increasing doses of radiotherapy alone are likely to increase the rate of pelvic control in patients without the consequence of increased early and late complications. Altered fractionation schedules have yet to offer significant improvement, may increase complications, and are not convenient for patients. Technical equipment and cost limitations have constrained the widespread use of particle beams, hyperbaric oxygen, and hyperthermia; in any event, they are not readily accessible.

Chemotherapeutic agents delivered concomitantly with radiotherapy are used in an attempt to improve local control and, it is hoped, the survival of patients with locally advanced cervical carcinoma.[7] Concomitant chemotherapy

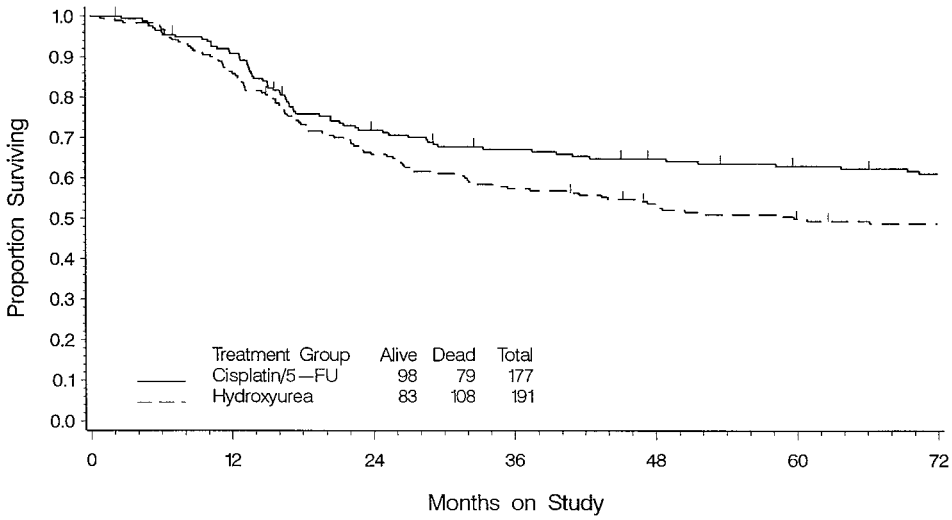

Fig 2. Survival by treatment group.

has the advantage of limited technical requirements and, if systemically active agents are chosen, has the potential to have a favorable impact on distant micrometastatic disease. This is particularly true if the currently most active agent, CF, is used. A variety of agents, which have been identified in vitro as potential radiation sensitizers, have been studied in an attempt to exploit the theoretical advantages of combination therapy. These advantages include the inhibition of repair of sublethal radiation-induced damage for HU,[30] 5-FU[31] and CF,[32] the induction of cell synchrony for agents such as HU,[33,34] and inherent cytotoxic effects of CF.[35] Sensitization of hypoxic cells to the cytotoxic effects of radiation occurs with misonidazole[36] and CF.[32]

Chemoradiation has proven to be of value for patients with head and neck carcinoma,[8] lung carcinoma,[9] esophageal cancer,[10] and cancers of the bladder[11] and anus.[12] Many are interested in the combined modality concept for the treatment of locally advanced cervical carcinoma. Phase II studies of single-agent chemoradiation for cervical carcinoma have used CF[37-41] and, less commonly, 5-FU,[42] carboplatin,[43] or paclitaxel[44] as the sensitizer. Some studies include ''bulky stage IB'' lesions, as well as, stage IIB, III, and IVA lesions, and some also include patients with stage IVB disease. All use external-beam therapy and brachytherapy, as in two studies that included para-aortic lymph node irradiation.[39,40] Response rates, pelvic control rates, and survival in these uncontrolled studies are higher than would be expected from radiation alone.

A larger number of trials have explored the use of combination chemotherapy with radiotherapy. The most commonly reported combinations include 5-FU/mitomycin[43-51] and 5-FU/CF.[18-22,52] Others have used CF/mitomycin,[53] CF/vincristine/bleomycin,[54] CF/etoposide/bleomycin/5-FU,[55] and ornidazole.[58] Some of these trials include patients with bulky stage IB disease, and one included patients with stage IVB disease. Reported complete response rates vary from 62% to 98%. Pelvic control rates are quoted from 55% to 85% and are generally higher than historical controls. Survival rates are reported at various time intervals in only a few of the available studies, but some studies quote survival rates as high as 97%.[55] Despite the small numbers in each individual study, over 700 patients' experience with chemoradiation has been reported. The response, pelvic control, and survival rates are encouraging. Toxicity was reported as manageable in all studies.

Randomized studies, although fewer in number, are congruent in favoring radiation plus chemotherapy over radiation alone.[57-60] The GOG has extensively studied one such agent, HU. The precise mechanism of action is unclear. In vitro studies suggest that HU induces cell synchrony at the radiation sensitive G_1/S interface[34] and inhibits the repair of sublethal radiation-induced cellular damage.[32] Hreschyshyn et al,[13] for the GOG, reported the results of a placebo-controlled study of HU and radiation therapy. There were 104 assessable patients with stage IIIB and IVA disease. The radiation therapy dose delivered was the same for both the placebo and the HU groups. As expected, there was significantly more hematologic depression for patients taking HU. The placebo group achieved only a 48.8% complete response rate, compared with a 68.1% complete response rate for the adjuvant HU group ($P = .05$). The progression-free interval and survival were likewise better for the patients taking HU. At subsequent follow-up, the increased complete response rate, progression-free interval, and survival were all maintained.[16] This study and confirmatory studies by Piver et al[57,58] led the GOG to adopt chemoradiation with HU as its standard treatment for locally advanced cervical carcinoma.

A second GOG study (Protocol #56), reported by Stehman et al,[14] compared HU to the hypoxic cell sensitizer, misonidazole. Patients with stage IIB to IVA disease and negative para-aortic lymph nodes were eligible. Again, the radiation therapy prescription was the same for both treatment arms. Grade 3 or 4 leukopenia occurred in 16.8% of patients receiving HU. Misonidazole was found to be inferior to HU. Pelvic control of tumor was better for patients receiving HU. This study validated the concept of chemoradiation for cervical carcinoma and maintained HU as the sensitizer of choice. The Radiation Therapy Oncology Group closed their randomized trial of misonidazole early because of the lack of any evidence of efficacy.[61]

CF has been studied as a single agent in a randomized setting. CF remains the single most active agent for recurrent and metastatic carcinoma of the cervix.[35] CF inhibits the repair of radiation-induced cellular damage and may also act as a hypoxic cell sensitizer.[23,62] CF is easily administered with radiation. Choo et al[63] reported a 55% complete response rate for 20 patients treated with weekly CF and radiotherapy. This was in contrast to a 20% rate in the radiation-only group. Unfortunately, on longer follow-up, this randomized trial failed to demonstrate any improvement in long-term survival as compared with radiation alone.[59]

5-FU has activity in cervical carcinoma.[64] It selectively inhibits cells in the S phase of the cell cycle and is effective in inhibiting the repair of radiation-induced cellular damage.[42] This agent has been used alone as an adjunct to irradiation but is more frequently used as a component of combination therapy.[18-22,45-51] 5-FU is active as a sensitizer,[31] is relatively easy to administer with radiation, and does not greatly increase toxicity. A randomized study by Christie et al[65] confirmed that the addition of 5-FU to

radiotherapy increased survival and local control. The addition of mitomycin increased complications.

The combination of 5-FU and CF is active in recurrent or metastatic cervical carcinoma.[66] Each agent is an effective radiation sensitizer. The combination is also more effective in a mouse model than either agent alone when given concomitantly with radiotherapy.[17] These data, and encouraging results for other primary tumor sites, have stimulated interest in using 5-FU and CF with radiation therapy for patients suffering from locally invasive cervical carcinoma. Continuous-infusion 5-FU has the potential to be more potent than bolus 5-FU.[67,68] CF is more effective when given before radiation,[62] although the optimal dose and schedule have not been determined.

Our study is a phase III comparison of the GOG standard chemoradiation (HU) to the promising 5-FU/CF combination. The treatment groups randomly formed were balanced on the known prognostic variables of patient age, performance status, tumor cell stage, clinical tumor size, and positive pelvic lymph nodes. Although treatment time is long, by current practice, there is no difference in the overall treatment time (median time of 9.1 weeks for each regimen). The point A and point B doses are also not different in the treatment arms. These doses are currently considered by some to be too low but are consistent with the radiotherapy practices of the 1980s, when the current study was designed. The inability to deliver intracavitary therapy in 10% of patients in each treatment arm is consistent with that report in other studies of chemoradiation conducted in the same time frame.[69] None of the radiotherapy variables are different between the treatment arms. Therefore, the observed increased survival for patients treated with the concomitant 5-FU/CF combination must be attributed to something other than differences in the radiotherapy delivered. Hematologic toxicity was more common and much more severe in the HU group, but this did not increase total treatment time. Other severe and life-threatening toxicities were not significantly different, and both regimens are well tolerated.

PFS was significantly different in favor of the 5-FU/CF regimen, with a risk reduction of 21% (RR, 0.79). Patients in the 5-FU/CF group suffered fewer pelvic progressions (25% *v* 30%). There were slightly fewer pulmonary progressions in the 5-FU/CF group (6% *v* 9%), although the frequency of other sites of progression outside the radiation therapy treatment field was similar. Most importantly, a 26% reduction in the risk of death (RR, 0.74) for patients with locally advanced cervical carcinoma treated with 5-FU and CF concomitant with pelvic radiation therapy is demonstrated in this randomized prospective trial. The median survival time for the study group has not yet been reached, whereas the median survival time for the control group was only 59.8 months.

The GOG has long had an interest in chemoradiation for the treatment of locally advanced carcinoma of the uterine cervix. In this article, we report the results of a large randomized clinical trial of chemoradiation, using the most active agent in the treatment of cervical cancer, CF. When this drug combined with 5-FU and radiation, patients can expect increased survival.

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The Radiological Physics Center (RPC), through its comprehensive quality assurance program, enssured that the radiation doses delivered to all patients in this study were clinically comparable. The RPC reviewed all technical aspects of the treatment, verified the reported doses, and participated in the clinical evaluation of all patients. In addition, the RPC monitored the calibration of the therapy units using mailed dosimeters at all participating institutions and conducted on-site evaluations of selected institutions as needed.

APPENDIX
Participating Institutions

The following institutions participated in this study (National Cancer Institute grant numbers are given in parentheses):

University of Alabama at Birmingham (CA 12484), Oregon Health Sciences Center (unfunded), Duke University Medical Center (CA 12534), Temple University Health Science Center Hospital (CA 27816), University of Rochester Medical Center (CA 12482), Walter Reed Army Medical Center (CA 23501), University of Southern California Medical Center at Los Angeles (CA 37535), University of Mississippi Medical Center (CA 13633), Colorado Foundation for Medical Care (CA 15975), University of California Medical Center at Los Angeles (CA 13630), University of Miami School of Medicine (CA 37234), The Milton S. Hershey School of Medicine of the Pennsylvania State University (CA 16386), Georgetown University Hospital (CA 16938), University of Cincinnati College of Medicine (unfunded), University of North Carolina School of Medicine (CA 23073), University of Iowa Hospitals and Clinics (CA 19502), University of Texas Health Science Center at Dallas (CA 28160), Indiana University Medical Center (CA 21720), Bowman Gray School of Medicine of Wake Forest University (CA 21946), State University of New York at Syracuse (unfunded), The Albany Medical College of Union University (CA 27469), University of California Medical Center at Irvine (CA 23765), Tufts New England Medical Center (CA 37569), Illinois Cancer Council (CA 27806), St Louis University Medical Center (CA 35571), Stanford University Medical Center (CA 35640), State University of New York Downstate Medical Center (CA 34477), Latter Day Saints Hospital (unfunded), Eastern Virginia Medical School (CA 40296), The Johns Hopkins Oncology Center (unfunded), State University of New York at Stony Brook (unfunded), Pennsylvania Hospital (unfunded), Southwest Oncology Group (CA 32101), Cooper Hospital University Medical Center (unfunded), and Columbus Cancer Council (unfunded).

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