RAPID PUBLICATION

Concurrent Chemotherapy and Pelvic Radiation Therapy Compared With Pelvic Radiation Therapy Alone as Adjuvant Therapy After Radical Surgery in High-Risk Early-Stage Cancer of the Cervix

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Purpose: **To determine whether the addition of cisplatin-based chemotherapy (CT) to pelvic radiation therapy (RT) will improve the survival of early-stage, high-risk patients with cervical carcinoma.**

Patients and Methods: **Patients with clinical stage IA_2, IB, and IIA carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium were eligible for this study. Patients were randomized to receive RT or RT + CT. Patients in each group received 49.3 GY RT in 29 fractions to a standard pelvic field. Chemotherapy consisted of bolus cisplatin 70 mg/m² and a 96-hour infusion of fluorouracil 1,000 mg/m²/d every 3 weeks for four cycles, with the first and second cycles given concurrent to RT.**

Results: **Between 1991 and 1996, 268 patients were entered onto the study. Two hundred forty-three patients were assessable (127 RT + CT patients and 116 RT patients). Progression-free and overall survival are significantly improved in the patients receiving CT. The hazard ratios for progression-free survival and overall survival in the RT only arm versus the RT + CT arm are 2.01 (P = .003) and 1.96 (P = .007), respectively. The projected progression-free survivals at 4 years is 63% with RT and 80% with RT + CT. The projected overall survival rate at 4 years is 71% with RT and 81% with RT + CT. Grades 3 and 4 hematologic and gastrointestinal toxicity were more frequent in the RT + CT group.**

Conclusion: **The addition of concurrent cisplatin-based CT to RT significantly improves progression-free and overall survival for high-risk, early-stage patients who undergo radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.**

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BOTH RADICAL HYSTERECTOMY with pelvic lymphadenectomy and radical radiation therapy (RT) are used as primary therapy for early-stage carcinoma of the cervix. Comparison studies suggest that the overall 5-year survival rates are similar and, for patients with stage IB lesions, are in the 80% to 90% range.[1-3] According to a patterns-of-care study performed by the American College of Surgeons, surgery is increasingly being used in the United States as the primary mode of treatment.[4,5] Patients with stage IA2 and IIA are treated in a similar fashion to patients with stage IB lesions.

Recurrences are much more frequent in patients with lymph node involvement and involvement of the parametrium or surgical margins and in patients with large or deeply invasive lesions.[1,2,6-14] When one or more of these factors is found, the 5-year survival drops to the 50% to 70% range.

After radical hysterectomy, adjuvant RT has commonly been used for patients at high risk for recurrence. Retrospective comparisons of patients with positive pelvic lymph nodes treated with postoperative RT have generally shown a decrease in the local recurrence rate but no improvement in long-term survival.[15,16] Several small phase II studies have suggested a potential benefit for adjuvant chemotherapy (CT) in high-risk patients, with the combination of cisplatin and fluorouracil (5-FU) demonstrating activity in patients with advanced or metastatic cervical cancer.[17-19] Both cisplatin and 5-FU are radiation sensitizers and their concurrent use seems to be synergistic.[20] The concurrent

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use of cisplatin (with or without 5-FU) and pelvic irradiation in patients with advanced disease seemed to improve local control and overall survival in phase II trials, as well as four recently reported phase III trials.[21-25] The current study was designed to see if the addition of CT to standard pelvic RT could improve the progression-free survival and overall survival in patients at high risk for relapse after primary radical hysterectomy.

PATIENTS AND METHODS

Eligibility Criteria

Patients in this trial had undergone a type 3 radical hysterectomy with pelvic lymphadenectomy for a clinical stage IA_2, IB, or IIA carcinoma of the cervix.[26] Patients were eligible if they had a squamous carcinoma, adenocarcinoma, or an adenosquamous carcinoma and had histologically confirmed positive pelvic lymph nodes, positive parametrial involvement, or a positive surgical margin. Registration was required within 6 weeks of surgery, with RT to begin within 5 working days of registration. Patients randomized to the CT arm began CT on the same day that they began the RT. Patients were required to have a Southwest Oncology Group (SWOG) performance status of 0 to 2, a WBC count $\geq 3{,}000/\mu L$, platelets $\geq 100{,}000/\mu L$, and normal creatinine and bilirubin.

All institutions participating in the protocol obtained the approval of their human investigation committee in accordance with local, state, and federal regulations, and all patients were entered onto the study after obtaining proper informed consent.

Treatment Plan

Patients were randomized to either pelvic RT or pelvic RT with four cycles of CT. The RT consisted of 1.7 Gy per day on days 1 to 5 of each week, for a total of 29 fractions (49.3 Gy). Pelvic RT was given to a standard four-field box. Patients with positive high common iliac lymph nodes also received treatment to a paraaortic field with a dose of 1.5 Gy per day on days 1 to 5 of each week, for a total of 30 fractions (45 Gy). The radiation source for treatment was 4 MeV or more. The radiation fields were reviewed by the Radiation Physics Center of M.D. Anderson Cancer Center (Houston, TX). It is important to note that brachytherapy was not permitted.

For patients randomized to CT, treatment was begun on day 1 of their RT. One cycle of CT consisted of cisplatin 70 mg/m^2 by 2-hour intravenous infusion given on day 1 and 5-FU at a dose of 1,000 mg/m^2 per day for 4 days given as a 96-hour continuous infusion on days 1 to 4. The second cycle of CT began on day 22. The third and fourth cycles of CT were scheduled after completion of RT, to begin on days 43 and 64. Toxicity was defined by standard SWOG criteria.[27]

Treatment Modifications

Chemotherapy was repeated every 3 weeks, providing the patient's total WBC count recovered to $\geq 2{,}500/\mu L$ and platelets were $\geq 100{,}000/\mu L$. The 5-FU doses were reduced by 25% for grade 3 stomatitis and by 50% for grade 4 stomatitis. If the patient had a nadir platelet count of $< 50{,}000/\mu L$ or a nadir WBC of $< 2000/\mu L$, the 5-FU dose was reduced by 25%. Treatment was held if the calculated creatinine clearance decreased to < 50 mL/min. When the calculated creatinine clearance became ≥ 50 mL/min, treatment was resumed with the cisplatin dose reduced to 50 mg/m^2. Cisplatin was discontinued for grade 3 or 4 peripheral neuropathy.

During those weeks in which the patient did not receive CT, RT was continued as long as the WBC count was $\geq 2000/\mu L$ and the platelet count was $\geq 50{,}000/\mu L$. RT was interrupted for a period of no greater than 1 week for grade 3 or 4 diarrhea.

This intergroup study was open to patients from SWOG, the Gynecologic Oncology Group (GOG), and the Radiation Therapy Oncology Group (RTOG). Pertinent histopathologic sections from the biopsies and radical hysterectomies were submitted to the responsible study member (R.J.S.) of the Pathology Committee of GOG for review. The final histopathologic diagnostic categories were squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. Lesion size was recorded as the greatest tumor diameter on histologic section. The diagnoses were based solely on hematoxylin and eosin–stained material.

Statistical Analysis

Based on previous data, the 5-year survival rate for the RT only arm was assumed to be 60%. Two hundred forty eligible patients were targeted over a 5.5-year enrollment period. With an additional 4 years of follow-up before the final analysis and the assumptions of uniform patient entry, exponential survival distributions, a one-sided log-rank test at 0.05 significance level, and a death hazard ratio of 1.78 between the RT only arm and the CT + RT arm (corresponding to 5-year survival rates of 60% and 75%, respectively); the power to detect a difference is approximately 0.85. For progression-free and overall survival, Cox regression analyses would be performed. The models would primarily take into account the randomization stratification factors: clinical stage, nodal involvement, and cooperative group. Other prognostic factors taken into account were age, race, lesion size, microscopic parametrial involvement, positive surgical margins, and histologic cell type.

Interim analyses were planned when approximately one quarter, one half, and three quarters of the anticipated deaths had occurred. Under standard SWOG guidelines, the decision for early termination or reporting of the study would be made by the SWOG Data and Safety Monitoring Committee, if warranted.[28] The statistical guideline for initiating such considerations is if either the null hypothesis of no CT benefit or the alternative hypothesis of a 1.5 RT alone versus RT + CT hazard ratio is rejected at a 0.005 significance level for progression-free and/or overall survival. The actual decision would take into account other factors such as toxicities, complications, and data from other sources.

RESULTS

Between 1991 and 1996, 268 patients were entered onto this trial (19 patients from SWOG, 226 from GOG, and 23 from RTOG). Twenty-five patients were ineligible, leaving 243 assessable patients (127 patients in the CT + RT arm and 116 in the RT alone arm). After patient accrual was completed and the second interim analysis was performed for the study, results of several randomized trials in cervical cancer (GOG 85, 120, and 123) became available. The Data and Safety Monitoring Committee called for a special interim analysis and decided in April 1998 to release the results of the current study. The statistical boundaries for rejecting the null hypothesis of no CT benefits were crossed

when the decision was made to early release the study results.

Among the 25 ineligible patients, two patients were ineligible based on surgical review, four patients were ineligible on pathology review, and 19 patients had insufficient information or lack of submission of pathology material.

In the CT + RT group, one patient was not treated because of a surgical complication, five patients refused CT, and four patients refused both the CT and RT. In the RT only arm, three patients refused RT and a fourth patient was never treated because of physician discretion. The nine patients (five CT + RT patients and four RT only patients) receiving no protocol treatment were not included in toxicity analysis. All 243 patients are included in survival analysis according to the intent-to-treat principle. The patient characteristics in the two arms are depicted in Table 1 and include age, race, clinical stage, primary lesion size, presence of positive pelvic lymph nodes, positive high common iliac lymph nodes, positive margins, parametrial involvement, and cell type. There are no statistically significant differences in any of the patient characteristics between the two arms.

Table 2 summarizes the completeness of the RT in the two treatment arms. Eighty-nine percent of the patients (113 of 127) randomized to CT + RT and 94% (109 of 116) randomized to RT alone received more than 45 Gy. These rates are not statistically different (Fisher's exact test, $P = .12$). The details of time to RT completion for those who received more than 45 Gy are displayed in Table 3. Of those receiving more than 45 Gy, the median time to RT completion was 43 days (range, 35 to 79 days) for the CT + RT arm and 41 days (range, 38 to 65 days) for the RT only arm. This difference is statistically significant (Wilcoxon rank sum, $P = .01$).

Table 4 is a summary of the number of cycles of CT for patients randomized to CT + RT. Overall, 71% of patients received at least three cycles of CT. Of 27 patients who received only one or two cycles of CT, six patients were taken off of CT because of toxicity and one because of disease progression. The other 20 patients refused further therapy.

Survival Analysis

At the time of this report, the median follow-up time is 42 months. Figure 1 is a Kaplan-Meier depiction of progression-free survival by treatment arm. Patients receiving CT + RT had a statistically significant improvement in progression-free survival. The estimated 4-year progression-free survival for patients receiving CT + RT was 80%, versus 63% for patients receiving RT alone. Figure 2 shows overall survival by treatment group. The estimated 4-year survivals were 81% for CT + RT and 71% for RT only. When adjusted for stratification factors (clinical stage, nodal involvement, and cooperative group), Cox model analysis projected an RT only versus RT + CT hazard ratio of 2.01 ($P = .003$) for progression-free survival and 1.96 ($P =$

Table 1. Patient Characteristics

Characteristic	Patients Treated With CT + RT (n = 127) No.	%	Patients Treated With RT (n = 116) No.	%
Age				
Median	41.0		38.0	
Range	20-74		20-77	
Race				
White (non-Hispanic)	82	65	76	66
Black (non-Hispanic)	22	17	19	16
Hispanic	18	14	11	9
Other	4	3	7	6
Stage				
IA2	0	0	0	0
IB	119	94	110	95
IIA	8	6	6	5
Cell type				
Squamous	97	76	96	83
Adenocarcinoma	18	14	13	11
Adenosquamous	12	9	7	6
Lesion size, cm				
Median	2.2		2.1	
Range	0.6-5.2		0.2-4.0	
Positive pelvic nodes				
Yes	110	87	97	84
No	17	13	19	16
Positive common iliac nodes				
Yes	4	3	6	5
No	123	97	110	95
Positive margins				
Yes	5	4	7	6
No	122	96	109	94
Parametrial involvement				
Yes	42	33	41	35
No	85	67	75	65

Table 2. Total Pelvic Radiation Dose by Treatment Arm

Radiation Dose Received	No. of Patients CT + RT	RT
0 (refused)	5	4
≤ 20.00 Gy	1	2
20.01-30.00 Gy	2	0
30.01-35.00 Gy	1	0
35.01-40.00 Gy	4	0
40.01-45.00 Gy	1	1
> 45.00 Gy	113	109
Total	127	116

Table 3. Time to RT Completion by Treatment Arm for Patients Receiving > 45 Gy

Time to Completion (days)	Patients on CT + RT Arm		Patients on RT Arm	
	No.	%	No.	%
≤ 42	54	48	79	72
43-49	40	35	24	22
50-56	12	11	2	2
57-63	1	1	3	3
≥ 64	6	5	1	1
Total who completed	113		109	

.007) for overall survival. The results were unchanged when age, race, parametrial involvement, positive surgical margins, and cell type were added to the Cox models. Of the variables included in the multivariate analyses, lesion size was the only statistically significant prognostic factor for progression-free survival ($P = .05$) and overall survival ($P = .03$).

Both pelvic and extrapelvic recurrences were less frequent in those patients receiving CT (Table 5). There is no statistically significant differences in the pattern of recurrence between the two treatment arms (χ^2 test, $P = .20$).

Fig 3 is a comparison of the Kaplan-Meier progression-free survival curves in patients randomized to RT alone by cell type. Patients with adenocarcinoma or adenosquamous carcinoma have a worse prognosis. As shown in Fig 4, this difference in prognosis for nonsquamous tumors disappears in patients who receive CT. When a treatment versus cell type (adenocarcinoma or adenosquamous carcinoma *v* squamous carcinoma) interaction was introduced to the Cox model, this difference in response to the addition of CT by cell type did not reach statistical significance ($P = .12$ for progression-free survival and $P = .19$ for overall survival).

Analyses were performed to explore potential associations between the number of courses of therapy received and survival. To avoid the bias introduced by short-term survivors' inherent inability to receive higher numbers of treatment courses, survival was measured from 91 days after study registration, which was chosen because it was the median time to CT completion for those who received the entire four courses of therapy.[29] Patients who died or for whom the disease recurred before 91 days were excluded from the relevant analyses. The resulting numbers of eligible patients were 124 for progression-free survival (three exclusions) and 125 for overall survival (two exclusions). Higher numbers of CT courses were favorably associated with both progression-free survival and overall survival (Cox model, $P = .03$ for both progression-free and overall survival) (Fig 5).

Table 4. Number of Cycles of Chemotherapy for Patients Randomized to CT + RT Arm

No. of Cycles Received	Patients (n = 127)	
	No.	%
0 (refused)	10	8
1	8	6
2	19	15
3	14	11
4	76	60

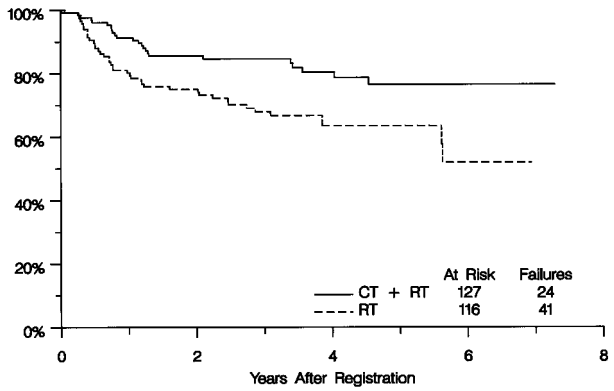

Fig 1. Progression-free survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

Toxicity

Among the 122 patients assessable for toxicity in the CT + RT arm, there were 27 episodes of grade 4 toxicity in 21 patients (Table 6), most of which were hematologic. Among 112 patients randomized to RT alone and assessable for toxicity, four patients had grade 4 toxicity.

There was one late death in the series that may have been treatment-related. The patient was randomized to receive

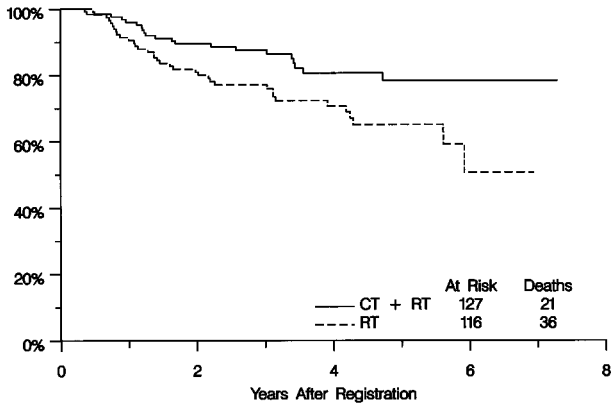

Fig 2. Overall survival for 127 patients randomized to receive CT + RT and for 116 patients randomized to receive RT alone.

Table 5. Site of First Recurrence

Site	No. of Patients CT + RT (n = 127)	RT (n = 116)
Local	7	20
Distant	9	13
Local and distant	4	5
Unknown	0	1
Total with first recurrence	20	39

CT + RT but refused the CT and was treated with RT alone. Seventeen months after RT, she developed bilateral ureteral obstructions with fibrosis and renal failure, which was managed with chronic ureteral stents. She had a history of prior coronary artery disease and had a sudden unexplained death 39 months after completing RT.

DISCUSSION

Both radical RT and radical surgery have been considered appropriate for patients with stage IA_2, IB, and IIA carcinoma of the cervix.[1,2] A choice between these two modalities is frequently influenced by the availability of specialists, the age of the patient, and perceived toxicities. Since the establishment of subspecialty training in gynecologic oncology, radical surgery has been increasingly used in the United States as first-line therapy.[4,5]

It has long been recognized that survival after radical hysterectomy was impacted by lymph node status.[1,2,8,10] Other high-risk factors have included margin status and parametrial involvement.[6,11,14] More recent analyses of large series of radical hysterectomies have shown that depth of cervical stromal invasion, clinical lesion size, and patient age are also independent prognostic factors.[2,9,10,13] The presence of tumor in lymph-vascular channels has been an independent factor in some analyses,[8-10] whereas other analyses have not found this to be an independent risk factor.[13] This trial was planned before the most recent clinical pathologic studies and does not include all patients who would currently be considered high risk.

Postoperative pelvic RT has frequently been used for patients with positive pelvic lymph nodes. Although a few series have reported a survival benefit associated with postoperative irradiation, the preponderance of studies have only shown a decrease in the local failure rate and no improvement in survival.[15,16] A recently completed study (GOG 92) compared RT after surgery with surgery alone in an intermediate-risk group.[30] There was a reduction in the recurrence rate from 28% to 15% with the addition of RT. Because GOG 92 excluded patients with positive lymph nodes, it cannot be directly compared with the current study, but it does suggest that RT has a role in adjuvant therapy.

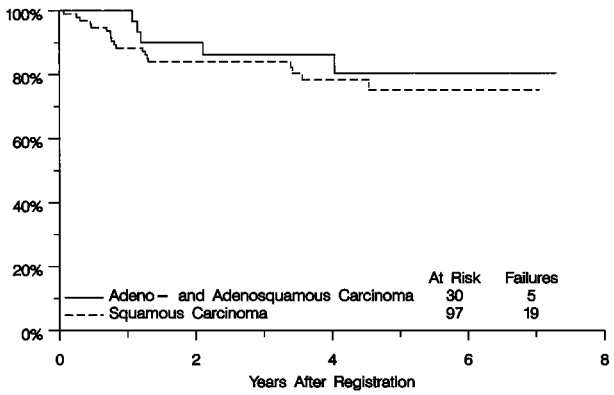

Fig 4. Progression-free survival for 98 patients with squamous carcinoma and 29 patients with adenocarcinoma or adenosquamous carcinoma in the CT + RT arm.

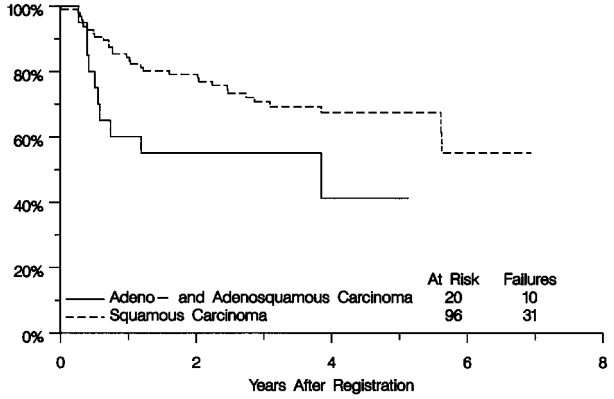

Fig 3. Progression-free survival for 93 patients with squamous carcinoma and 23 patients with adenocarcinoma or adenosquamous carcinoma in the RT only arm.

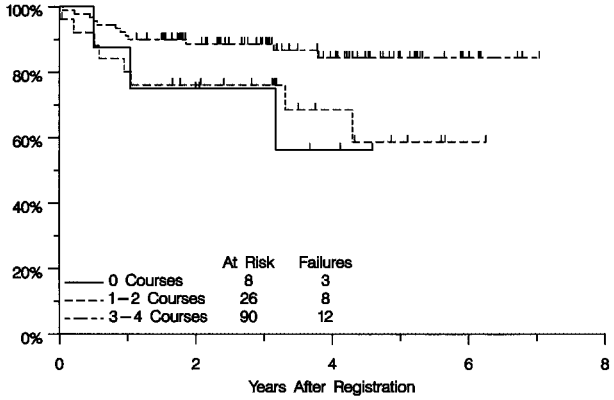

Fig 5. Progression-free survival by number of cycles of CT for patients randomized to the CT + RT arm.

Table 6. Major Toxicities

	CT + RT (n = 122)						RT (n =112)					
	No. of Patients With Toxicity Grade						No. of Patients With Toxicity Grade					
Toxicity	0	1	2	3	4	5	0	1	2	3	4	5
Abdominal pain	111	7	0	4	0	0	99	9	2	2	0	0
Anemia	63	28	27	3	1	0	87	12	13	0	0	0
Cardiac dysrhythmia	120	0	1	0	1	0	112	0	0	0	0	0
Diarrhea	54	22	34	8	4	0	50	41	13	6	1	0
Dyspnea	119	0	2	0	1	0	111	0	0	0	1	0
Granulocytopenia	44	18	25	24	11	0	101	7	1	2	1	0
Hearing	113	2	6	1	0	0	112	0	0	0	0	0
Infection	116	3	2	1	0	0	110	1	0	0	1	0
Leukopenia	15	17	47	40	3	0	47	48	16	1	0	0
Local/desquamation in RT field	115	2	2	3	0	0	109	2	1	0	0	0
Malaise/fatigue/lethargy	100	18	3	1	0	0	94	14	3	1	0	0
Nausea	34	31	40	17	0	0	79	24	7	2	0	0
Renal failure	121	0	0	0	0	1	112	0	0	0	0	0
Skin rash/urticaria	116	4	1	1	0	0	109	2	1	0	0	0
Small bowel obstruction	119	0	1	0	2	0	110	0	1	1	0	0
Stomatitis	96	16	7	2	1	0	112	0	0	0	0	0
Thrombocytopenia	92	27	2	1	0	0	103	9	0	0	0	0
Vomiting	46	23	38	12	3	0	98	8	4	2	0	0
Weakness	114	5	2	1	0	0	110	2	0	0	0	0

For high-risk postsurgical patients, several retrospective studies have suggested a benefit to cisplatin-based CT either given alone or before RT.[31-36] In a small randomized trial, Curtin et al[37] compared CT with CT + RT and showed the same relapse rate in a high-risk patient group. In another small randomized trial for node position patients, Tattersall et al[38] compared RT with CT followed by RT and found no difference in disease-free or overall survival. Concomitant CT with RT has been shown to improve survival and reduce relapses in select groups of cervical cancer patients when compared with RT alone. In a randomized three-arm study performed by the GOG comparing the efficacy of hydroxyurea versus 5-FU infusion, hydroxyurea, and bolus cisplatin versus weekly bolus cisplatin as concomitant chemoradiation in advanced cervical cancer (stages IIB, III, and IVA), both platinum regimens were superior to hydroxyurea alone in reducing the risk of progression and death.[22] For bulky stage IB cervical cancer, the GOG found improvement in the recurrence-free interval and survival for patients treated with weekly cisplatin during irradiation compared with RT alone. In this trial, both groups completed treatment with adjuvant hysterectomy.[23] The RTOG has compared extended-field RT with pelvic RT + CT (concurrent cisplatin and 5-FU) for patients with stages IIB to IVA or bulky stages IB or IIA disease and found a significant survival advantage in the CT + RT group.[24] In patients with stage IIB to IVA disease who were surgically staged and had negative paraaortic lymph nodes, a GOG/SWOG intergroup study compared pelvic RT plus hydroxyurea with pelvic RT plus concurrent cisplatin and 5-FU. There was an improvement in relapse-free and overall survival in the cisplatin plus 5-FU group.[25] These large, randomized, prospective studies, when combined with the data from the present report, reveal a remarkably consistent advantage for chemoradiation over RT alone in patients with cervical cancer, including a wide range of stages, cell types, and other prognostic factors. Despite the patients refusing all CT and the substantial number of patients who did not complete all four cycles of CT, we saw a profound decrease in recurrence and an improvement in progression-free and overall survival with the addition of CT to pelvic RT. Despite a slightly longer total treatment time, the percentage of patients receiving $\geq$ 45 Gy was almost identical. Many of the treatment delays and some of the reductions in CT cycles could potentially have been eliminated with the use of biologic modifiers not in use at the time this study was conceived. All of the recently completed trials, including this one, have shown greater hematologic toxicity in the RT + CT arm, and this must be considered in the decision to use CT + RT.

It is not possible to determine from our analysis whether the effect of the CT was as a radiation sensitizer or as systemic CT with elimination of micrometastasis or both. The favorable survival seen in patients receiving the third and fourth cycles of CT after completion of RT would suggest that the CT was having an effect independent of the RT. However, such a

conclusion can only be established from future randomized studies and not from the current data because of the possibility that patients with a poorer tolerance of CT have an inherently inferior prognosis independent of the total number of cycles. Regardless of the mechanism of action, we conclude that the addition of CT to RT significantly improves progression-free and overall survival for high-risk early-stage patients who undergo a radical hysterectomy and pelvic lymphadenectomy for carcinoma of the cervix.

It has been suggested that adenocarcinomas and adenosquamous carcinomas have a more ominous prognosis than squamous carcinomas, particularly if there is extracervical extension of the tumor.[39] In this trial, adenocarcinomas and adenosquamous carcinomas had a poorer prognosis in patients with at least one other poor prognostic factor. Importantly, the addition of chemotherapy seems to improve disease-free survival in this subgroup of poor-prognosis patients.

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