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PELVIC RADIATION WITH CONCURRENT CHEMOTHERAPY COMPARED WITH PELVIC AND PARA-AORTIC RADIATION FOR HIGH-RISK CERVICAL CANCER

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ABSTRACT

Background and Methods We compared the effect of radiotherapy to a pelvic and para-aortic field with that of pelvic radiation and concurrent chemotherapy with fluorouracil and cisplatin in women with advanced cervical cancer. Between 1990 and 1997, 403 women with advanced cervical cancer confined to the pelvis (stages IIB through IVA or stage IB or IIA with a tumor diameter of at least 5 cm or involvement of pelvic lymph nodes) were randomly assigned to receive either 45 Gy of radiation to the pelvis and para-aortic lymph nodes or 45 Gy of radiation to the pelvis alone plus two cycles of fluorouracil and cisplatin (days 1 through 5 and days 22 through 26 of radiation). Patients were then to receive one or two applications of low-dose-rate intracavitary radiation, with a third cycle of chemotherapy planned for the second intracavitary procedure in the combined-therapy group.

Results Of the 403 eligible patients, 193 in each group could be evaluated. The median duration of follow-up was 43 months. Estimated cumulative rates of survival at five years were 73 percent among patients treated with radiotherapy and chemotherapy and 58 percent among patients treated with radiotherapy alone ($P=0.004$). Cumulative rates of disease-free survival at five years were 67 percent among patients in the combined-therapy group and 40 percent among patients in the radiotherapy group ($P<0.001$). The rates of both distant metastases ($P<0.001$) and locoregional recurrences ($P<0.001$) were significantly higher among patients treated with radiotherapy alone. The seriousness of side effects was similar in the two groups, with a higher rate of reversible hematologic effects in the combined-therapy group.

Conclusions The addition of chemotherapy with fluorouracil and cisplatin to treatment with external-beam and intracavitary radiation significantly improved survival among women with locally advanced cervical cancer. (N Engl J Med 1999;340:1137-43.)

OF the estimated 13,700 women in the United States in whom invasive cervical cancer was diagnosed in 1998,[1] nearly 5000 will ultimately die of the disease because of the inadequacies of current treatment. In the United States, cervical cancer disproportionately affects women who are members of minority groups and women of low socioeconomic status, partly because such women tend to have insufficient access to and knowledge of screening programs for cervical cancer. The nationwide use of such screening programs has greatly reduced the incidence of invasive cervical cancer.

Women with early cervical cancer can be successfully treated with radical surgery. Those with a large cervical lesion at presentation or with spread to the pelvic lymph nodes or other pelvic tissues are usually treated with a combination of external-beam and intracavitary radiation.[2-6] A previous study reported improved survival among women with locally advanced cervical cancer who received prophylactic radiation to the para-aortic nodes.[7]

To eradicate micrometastases and sensitize tumor cells to radiation, several studies have explored the use of radiotherapy with concomitant chemotherapy.[8-11] The results of these studies are inconclusive and have been criticized because they lacked a comparison group treated with radiation alone and be-

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cause the radiation therapy used may have been deficient according to current standards. In 1990, the Radiation Therapy Oncology Group (RTOG) began a randomized clinical trial to compare the effects on survival of treatment with extended-field radiation and treatment with pelvic radiotherapy and concurrent chemotherapy in patients with cervical cancer. We report the first results of this study.

METHODS

Patients

We enrolled women of all ages who had stages IIB through IVA squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix according to the staging system of the International Federation of Gynecology and Obstetrics (Table 1) or stage IB or IIA of one of these cancers with a tumor diameter of at least 5 cm or biopsy-proved metastasis to pelvic lymph nodes. Women with a Karnofsky performance score of at least 60 and blood counts and serum levels of blood urea nitrogen, creatinine, and bilirubin that were within normal ranges were eligible for the study. Women were excluded from the study if they met any of the following criteria: disease outside the pelvic area or spread to para-aortic lymph nodes; a prior cancer other than cutaneous basal-cell carcinoma; medical contraindications to chemotherapy; a rare histologic subtype; and prior hysterectomy or transperitoneal staging procedure for cervical cancer, pelvic radiotherapy, or systemic chemotherapy.

A medical history taking and clinical examination were required before enrollment. The initial evaluation also included chest radiography, cystoscopy, proctoscopy, a complete blood count, and measurement of liver and renal function. The renal-collecting system of each patient was assessed by intravenous pyelography or contrast computed tomography. Para-aortic lymph nodes were evaluated by bipedal lymphangiography or retroperitoneal surgical exploration.

The surveillance committees of the National Cancer Institute and participating institutions approved this trial. Patients were required to understand the trial and provide written informed consent.

Patients who completed the pretreatment evaluation and met all eligibility criteria were randomly assigned to receive extended-field radiotherapy or radiotherapy to the pelvic region with concurrent treatment with cisplatin and fluorouracil. The patients in each treatment group were stratified according to the tumor stage (IB, IIA, or IIB vs. III or IVA) and the staging method used for para-aortic lymph nodes (clinical vs. surgical).

TABLE 1. STAGING OF CARCINOMA OF THE CERVIX.*

STAGE	DEFINITION
I	Invasive cancer is confined to the cervix.
IA1, IA2	Invasive cancer is identified microscopically, with a maximal depth of 5 mm and a maximal width of 7 mm.
IB1	Clinically apparent lesions are no greater than 4 cm in diameter.
IB2	Clinically apparent lesions exceed 4 cm in diameter.
II	The tumor extends beyond the cervix but not to the pelvic wall or distal vagina.
IIA	Up to two thirds of the vagina is involved, with no obvious parametrial involvement.
IIB	There is obvious parametrial involvement.
III	The tumor extends to the pelvic wall or involves the lowest third of the vagina.†
IIIA	The lowest third of the vagina is involved but not the pelvic wall.
IIIB	The pelvic wall is involved, or hydronephrosis or a nonfunctioning kidney is present.
IV	The tumor extends beyond the pelvis or involves the bladder or rectum.
IVA	Rectal or bladder mucosa is involved.
IVB	There is spread to distant organs.

*Data were adapted from the International Federation of Gynecology and Obstetrics.[12]

†This category includes all cases in which hydronephrosis is present, unless it is known to be due to another cause.

Treatment

External-beam radiation was delivered with anteroposterior and posteroanterior opposed beams of at least 15-MV photons or the use of four fields (anteroposterior, posteroanterior, and two lateral fields) of at least 4-MV photons. For patients who were assigned to receive radiotherapy and chemotherapy, the treatment field extended from the space between L4 and L5 to the midpubis or to a line 4 cm below the most distal vaginal or cervical site of disease. Lateral fields were designed to encompass S3 posteriorly, with a margin of at least 3 cm from the primary cervical tumor. Custom shielding was designed to treat the pelvic lymph nodes, with a margin of at least 1 to 1.5 cm. For patients who were assigned to receive radiotherapy alone, the pelvic and para-aortic areas were treated as a continuous area, with a superior-field border at the space between L1 and L2. The radiation dose was keyed to the central ray at the patient's midplane (for anteroposterior–posteroanterior fields) or to the isocenter of the beams. The total dose to be delivered to pelvic lymph nodes as well as to para-aortic nodes was 45 Gy, given at a dose of 1.8 Gy per fraction of radiation.

The radioisotopes used for low-dose-rate intracavitary radiotherapy were cesium-137 or radium-226 in 392 of 402 patients (98 percent). The first intracavitary treatment was performed before or during external-beam radiotherapy, and additional external-beam therapy was delivered with a midline block. Interstitial brachytherapy was used only if necessary to increase the dose directed at distal vaginal sites of disease. Brachytherapy was performed within two weeks (preferably less than one week) after the completion of pelvic radiation, with the goal of keeping the total duration of treatment under eight weeks when possible.

The protocol specified that all patients receive a total cumulative dose to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) of at least 85 Gy. The suggested maximal doses to the bladder, the rectum, and the lateral surface of the vagina were 75, 70, and 130 Gy, respectively.

Within 16 hours after the first radiation fraction was administered, patients in the combination-therapy group received the first cycle of chemotherapy, which consisted of an intravenous infusion of 75 mg of cisplatin per square meter of body-surface area over a 4-hour period followed by an intravenous infusion of 4000 mg of fluorouracil per square meter over a 96-hour period. This timing corresponded to days 1 through 5 of radiation therapy. Two additional cycles of chemotherapy were scheduled at three-week intervals. One of these was administered at the time of the second intracavitary insertion. To avoid treatment delays, intracavitary insertions were performed without chemotherapy if a patient had a granulocyte count of less than 1500 per cubic millimeter and a platelet count of less than 100,000 per cubic millimeter.

Follow-up

During treatment, patients were evaluated weekly by clinical assessments, a complete blood count with differential and platelet counts, and a pelvic examination. Before each cycle of chemotherapy, serum levels of creatinine, urea nitrogen, alanine aminotransferase, alkaline phosphatase, and bilirubin were measured. Patients had a pelvic examination under anesthesia at the time of each intracavitary treatment.

Once treatment ended, patients were evaluated every three

months for the first two years, every four months during the third year, every six months during the fourth and fifth years, and then annually. Disease status and the degree of treatment-related toxic effects were assessed by history taking, physical examination, and appropriate laboratory and radiologic tests. Suspected cases of persistent or recurrent disease were confirmed by a biopsy whenever possible.

Toxicity was assessed at the time of each evaluation with use of the Cooperative Group Common Toxicity Criteria, the Acute Radiation Morbidity Scoring Criteria, and the Late Radiation Morbidity Scoring Scheme of the RTOG and the European Organization for Research and Treatment of Cancer.

Quality Control

All chemotherapy records were reviewed by a gynecologic oncologist to assess compliance with the protocol. Radiotherapy records, including data concerning external-beam fields, intracavitary placement, doses of radiation to tumor and normal tissues, and other treatment variables, were reviewed by a radiation oncologist. Variations were scored as minor, major but acceptable, or major and unacceptable, if they differed by more than 5, 10, or 20 percent, respectively, from the specified dose of radiation or duration of treatment. Each institution's equipment was calibrated by employees of the Radiological Physics Center in Houston.

Statistical Analysis

Overall survival was the primary end point for the comparison of the two treatments and was calculated from the date of study entry until the date of death or the date of the last follow-up visit. Death from any cause was considered a failure in the analysis. Disease-free survival was also compared in the two groups and was calculated from the date of study entry to the date of the first occurrence of disease progression, a second diagnosis of cancer, or death from any cause, or if none of these events occurred, to the date of the last follow-up visit.

The Kaplan–Meier method was used to calculate both survival rates.[13] Log-rank tests were used to compare treatments.[14] All patients who could be assessed were included in the intention-to-treat analysis. Five-year rates of secondary end points such as locoregional recurrence, para-aortic recurrence, and distant metastasis were estimated with the use of cumulative-incidence methods,[15] and treatment effects were tested with use of the Gray algorithm.[16] The Cox proportional-hazards model was used to estimate the hazard ratios.[17] The statistical significance of associations between treatment assignments and characteristics of the patients was assessed by chi-square analysis. Acute side effects of treatment were defined as those that occurred within 60 days after the completion of radiotherapy, and late effects were defined as those occurring or persisting more than 60 days after radiotherapy.

The study was initially designed to be able to detect a reduction of 33 percent in the annual death rate, with a statistical power of 80 percent and a two-sided significance level of 0.05. On the basis of the results of two earlier RTOG trials,[7,11] we predicted that the five-year survival rate for the control group (radiotherapy alone) would be 65 percent for patients with stage IB or II disease and 40 percent for patients with stage III or IVA disease. We estimated that 40 to 70 percent of the patients would have stage IB or II disease. A 33 percent reduction in the death rate as a result of chemotherapy would yield an absolute improvement of approximately 10 percent in the five-year survival rate. To detect such a difference, we predicted that we would need to enroll 400 women in the study over a four-year period and then follow them for an additional four years. We estimated that 199 women would have died by the time of the initial analysis of treatment.

Interim analyses were scheduled to occur when 50 percent of the patients had been enrolled and when the enrollment goal was met. Early reporting of results was permitted if a significant difference was observed between the two treatment groups. The nominal significance level required for early reporting was originally set at $P=0.005$, but we subsequently adopted a more conservative approach,[18] because it allowed the number of deaths observed to determine the nominal level required for early reporting. The results of the interim analyses, in which patients' treatment assignments were masked, were presented to the data-monitoring committee. At the interim analysis conducted in July 1998 after the enrollment goal was met, the difference between the two groups was determined to have met the requirements for early reporting. For this early report, we updated the results using all information received and entered at study headquarters by November 11, 1998.

RESULTS

Characteristics of the Patients

A total of 403 patients were enrolled in the study between September 1990 and November 1997: 201 were randomly assigned to receive radiotherapy and concurrent chemotherapy, and 202 were assigned to receive radiotherapy alone. Fifteen patients (4 per-

TABLE 2. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	RADIOTHERAPY AND CHEMOTHERAPY (N=195)	RADIOTHERAPY ALONE (N=193)
Median age — yr	47	47
Race or ethnic group — no. (%)		
White	99 (51)	86 (45)
Black	46 (24)	56 (29)
Hispanic	39 (20)	43 (22)
Other or unknown	11 (6)	8 (4)
Karnofsky performance score, <90 — no. (%)	29 (15)	38 (20)
Histologic diagnosis — no. (%)		
Squamous-cell carcinoma	176 (90)	174 (90)
Adenocarcinoma	11 (6)	13 (7)
Adenosquamous carcinoma	8 (4)	6 (3)
Extent of differentiation of tumor cells — no. (%)		
Well	12 (6)	18 (9)
Moderate	71 (36)	75 (39)
Poor	74 (38)	73 (38)
Unknown	38 (19)	27 (14)
FIGO stage — no. (%)†		
IB	54 (28)	52 (27)
IIA	11 (6)	13 (7)
IIB	71 (36)	69 (36)
III	53 (27)	57 (30)
IVA	6 (3)	2 (1)
Staging method for para-aortic lymph nodes — no. (%)		
Lymphangiography	145 (74)	141 (73)
Lymph-node dissection	36 (18)	35 (18)
Both	14 (7)	17 (9)
Pelvic lymph nodes — no. (%)		
All negative	147 (75)	130 (67)
External iliac nodes positive, common iliac nodes negative	30 (15)	43 (22)
Common iliac nodes positive	17 (9)	19 (10)
Unknown	1 (1)	1 (1)
Tumor diameter‡		
<5 cm — no. (%)	4 (6)	9 (14)
≥5 cm — no. (%)	61 (94)	56 (86)
Median — cm	6	6

*Because of rounding, not all percentages total 100.

†FIGO denotes International Federation of Gynecology and Obstetrics.

‡Only stage IB and IIA tumors were included.

TABLE 3. WORST SIDE EFFECTS REPORTED DURING TREATMENT OR WITHIN 60 DAYS AFTER THE COMPLETION OF TREATMENT.*

SIDE EFFECT	RADIOTHERAPY AND CHEMOTHERAPY (N=195)			RADIOTHERAPY ALONE (N=193)		
	GRADE 3	GRADE 4	GRADE 5	GRADE 3	GRADE 4	GRADE 5
	number of patients (percent)					
Skin abnormalities	4	1	0	0	1	0
Nausea and vomiting	14	3	0	2	0	0
Bowel or rectal abnormalities	12	5	0	1	0	0
Bladder abnormalities	2	0	0	0	0	0
Hematologic effects	57	16	0	2	0	0
Other	8	3	1	0	0	0
Maximal grade of toxicity	65 (33)	22 (11)	1 (1)	5 (3)	1 (1)	0
Maximal grade of nonhematologic toxicity	15 (8)	4 (2)	1 (1)	3 (2)	1 (1)	0

*A grade of 3 indicates a moderate effect, a grade of 4 a severe effect, and a grade of 5 a fatal effect.

cent) — six in the combined-therapy group and nine in the radiotherapy group — were subsequently disqualified because of failure to undergo the required evaluation of para-aortic lymph nodes (eight patients), the presence of extrapelvic cancer (two), the presence of a rare histologic subtype (one), the presence of a stage IB1 tumor with no involvement of pelvic nodes (one), the absence of pretreatment data (two), and receipt of chemotherapy before radiotherapy (one). The 388 remaining patients (195 in the combined-therapy group and 193 in the radiotherapy group) form the basis of this analysis.

The characteristics of the two treatment groups are summarized in Table 2. There were no significant differences in these characteristics between the groups.

TABLE 4. WORST SIDE EFFECTS OF TREATMENT OCCURRING OR PERSISTING MORE THAN 60 DAYS AFTER THE COMPLETION OF TREATMENT.*

SITE OF SIDE EFFECT	RADIOTHERAPY AND CHEMOTHERAPY (N=193)†		RADIOTHERAPY ALONE (N=193)	
	GRADE 3	GRADE 4	GRADE 3	GRADE 4
	number of patients (percent)			
Skin or subcutaneous tissue	1	0	0	1
Small bowel	1	4	0	7
Large bowel or rectum	4	13	2	17
Bladder	4	1	1	2
Ureters	1	2	0	2
Other	2	1	1	3
Maximal grade of toxicity	8 (4)	16 (8)	2 (1)	20 (10)

*A grade of 3 indicates a moderate effect, and a grade of 4 a severe effect.

†No follow-up data were available for two patients.

Treatment and Compliance

Radiotherapy was delivered according to the protocol or with minor deviations in 83 percent of the patients in the combined-therapy group and 84 percent of those in the radiotherapy group. Major but acceptable treatment deviations occurred in another 11 percent and 9 percent of these groups, respectively. Eleven patients (3 percent) did not undergo brachytherapy: three patients refused, and eight patients did not undergo it for other reasons. In all, 26 patients did not complete treatment. The median total duration of radiation was 58 days, with a mean dose of 89 Gy delivered to point A in each group.

Of the 195 patients in the combination-therapy group, 159 (81 percent) completed at least two cycles of chemotherapy, and 133 (68 percent) completed three cycles. Chemotherapy was discontinued because of toxic effects in 9 patients, refusal to continue in the case of 17 patients, diminished performance status in 4 patients, and other reasons in 4 patients. Four patients refused or were unable to receive any chemotherapy but were included in the analysis according to the intention to treat.

Side Effects

Although moderate (grade 3) and severe (grade 4) side effects occurred more frequently during or within 60 days after the completion of treatment with combined therapy than with radiotherapy alone, these effects were usually self-limited or resolved with medical management (Table 3). Hematologic effects were generally moderate.

The late complications of treatment are summarized in Table 4. There were no significant differences in the seriousness of late effects between the treatment groups.

TABLE 5. ESTIMATED OVERALL SURVIVAL RATES AT FIVE YEARS, ACCORDING TO STRATIFICATION VARIABLES.*

VARIABLE	RADIOTHERAPY AND CHEMOTHERAPY (N=193)†		RADIOTHERAPY ALONE (N=193)		P VALUE
	NO. OF DEATHS/ TOTAL NO. OF PATIENTS	5-YR SURVIVAL RATE (95% CI)	NO. OF DEATHS/ TOTAL NO. OF PATIENTS	5-YR SURVIVAL RATE (95% CI)	
		percent		percent	
All patients	46/193	73 (65.7–80.3)	71/193	58 (49.8–66.2)	0.004
FIGO stage					
IB, IIA, or IIB	26/135	77 (68.4–85.6)	46/134	58 (48.2–67.8)	0.002
III or IVA	20/58	63 (49.7–76.3)	25/59	57 (42.7–71.3)	0.44
Method of evaluating para-aortic lymph nodes					
Lymphangiography only	34/143	74 (66.2–81.8)	50/141	60 (50.4–69.6)	0.02
Lymph-node dissection alone or with lymphangiography	12/50	70 (53.1–86.9)	21/52	54 (39.1–68.9)	0.07

*CI denotes confidence interval, and FIGO International Federation of Gynecology and Obstetrics.

†No follow-up data were available for two patients.

Outcome

The median duration of follow-up was 43 months. Follow-up data were available for 193 of the 195 patients in the combined-therapy group and for all 193 patients in the radiotherapy group. Of these, 147 patients in the combined-therapy group (76 percent) and 122 patients in the radiotherapy group (63 percent) were alive at the time of the last analysis. In addition, 13 patients in the combined-therapy group and 32 patients in the radiotherapy group were alive but had recurrent cervical cancer. Kaplan–Meier analysis revealed that overall survival rates were significantly better among patients treated with radiotherapy and chemotherapy than among those treated with radiotherapy alone (73 percent vs. 58 percent, P=0.004) (Table 5 and Fig. 1). Disease-free survival at five years was 67 percent in the combined-therapy group and 40 percent in the radiotherapy group, according to Kaplan–Meier analysis (P<0.001) (Fig. 2). The relative likelihood of disease-free survival in

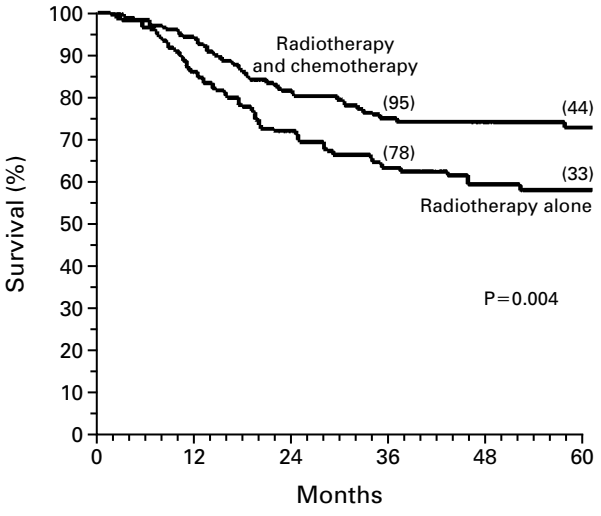

Figure 1. Kaplan–Meier Estimates of Survival among Patients Assigned to Receive Radiotherapy and Concurrent Chemotherapy and Those Assigned to Receive Radiotherapy Alone.

Numbers in parentheses are the numbers of patients alive and included in a follow-up assessment at three and five years.

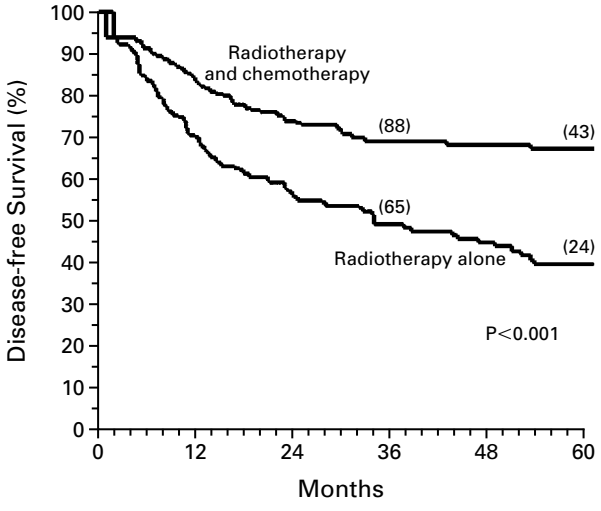

Figure 2. Kaplan–Meier Estimates of Disease-free Survival among Patients Assigned to Receive Radiotherapy and Concurrent Chemotherapy and Those Assigned to Receive Radiotherapy Alone.

Numbers in parentheses are the numbers of patients at risk at three and five years.

the combined-therapy group, as compared with the radiotherapy group, was 0.48 (95 percent confidence interval, 0.35 to 0.66). The rates of distant relapse were 14 percent in the combined-therapy group and 33 percent in the radiotherapy group ($P<0.001$), with a relative risk of relapse of 0.39 (95 percent confidence interval, 0.24 to 0.63) in the combined-therapy group. The rate of locoregional recurrences was 19 percent in the combined-therapy group and 35 percent in the radiotherapy group ($P<0.001$), with a relative risk of locoregional recurrences of 0.47 (95 percent confidence interval, 0.31 to 0.71) in the combined-therapy group.

The estimated five-year survival rates according to various stratification variables are summarized in Table 5. Approximately 70 percent of the patients assigned to each group had stage IB, IIA, or IIB disease. For these patients, overall survival was significantly better if they were treated with radiotherapy and chemotherapy. There was no significant difference in overall survival between treatment groups among patients who had stage III or IVA disease, although the study was not designed to have a sufficient number of patients in these subgroups to test for a statistically significant difference. For patients with stage III or IVA disease, the five-year disease-free survival rates were 58 percent in the combined-therapy group and 38 percent in the radiotherapy group ($P=0.13$).

DISCUSSION

We found that the combination of pelvic radiation and concomitant chemotherapy with cisplatin and fluorouracil was more effective for locally advanced cervical cancer than pelvic and para-aortic radiation alone. The inclusion of chemotherapy substantially reduced both local and distant recurrences of cervical cancer, leading to higher overall and disease-free survival rates. Although chemotherapy increased the hematologic toxicity, this effect was reversible and the incidence of late side effects was similar in the two treatment groups.

We are not the first to investigate the role of concomitant chemotherapy in the treatment of locally advanced cervical cancer. The Gynecologic Oncology Group has also studied the effect of radiotherapy in combination with either hydroxyurea or placebo in women with stage IIIB or IVA disease.[19] Although the group reported significant improvements in overall and disease-free survival with the addition of hydroxyurea therapy, the study has been criticized for the use of a low dose of radiation and the poor survival rates in both groups and because more than half of the 190 patients who were enrolled could not be evaluated. Despite these criticisms, the results of that study and those of trials assessing concurrent chemotherapy and radiotherapy for other tumors stimulated studies of the effects of radiotherapy and various combinations of fluorouracil, cisplatin, mitomycin, carboplatin, and paclitaxel as treatments for locally advanced cervical cancer.[8,9,20-23] The results of these trials have been encouraging, but most clinicians have not found them sufficiently convincing to justify the inclusion of chemotherapy in the routine treatment of locally advanced cervical cancer.

Our treatment regimen differed from previous regimens in several ways. Our protocol emphasized the importance of delivering a radiation dose of at least 85 Gy to point A within eight weeks whenever possible. As a result, the median dose was higher and the median duration of treatment was shorter than those reported in other studies. The results of the Patterns of Care studies and large retrospective analyses suggest that these features correlate with survival rates and rates of local control of cervical cancer.[24,25] We also used a somewhat more aggressive regimen of chemotherapy than have other groups. We used a higher dose of cisplatin (75 mg per square meter) than that used with fluorouracil in the Gynecologic Oncology Group studies, and we also included a third cycle of chemotherapy during one of the intracavitary procedures. The importance of this third cycle is uncertain, but because close to 25 percent of the total paracentral dose of radiation is delivered with each intracavitary procedure, the addition of concurrent chemotherapy during this time may be important.

Reports by Rose et al.[26] and Keys et al.[27] in this issue of the *Journal* strengthen the body of evidence supporting the use of combined therapy in women with advanced cervical cancer. Future studies will continue to evaluate cisplatin and fluorouracil as well as other drugs to determine the most effective doses and routes of administration. Weekly or daily infusions of cisplatin are well tolerated.[28,29] For patients who were receiving postoperative radiation for rectal cancer, a prolonged, continuous infusion of fluorouracil with pelvic radiation was found to be more effective than short infusions.[30] We do not know whether the combination of fluorouracil and cisplatin is more effective than either drug alone.

The role of prophylactic extended-field radiation has always been controversial. In our study, the benefit of para-aortic radiation may have been less than that observed in an earlier RTOG trial,[7] because our trial required more rigorous staging of para-aortic lymph nodes and included patients with more advanced pelvic disease. However, no radiographic test is currently capable of detecting microscopic para-aortic disease, and selected patients may still benefit from prophylactic para-aortic radiation. For patients with known metastases to the para-aortic lymph nodes, para-aortic radiation is probably necessary. Another RTOG study[31] tested the feasibility of combining hyperfractionated extended-field radiation with

the same regimen of cisplatin and fluorouracil that we used. The acute side effects were severe, possibly because of the addition of chemotherapy or the altered regimen of fractionation.

We believe there is now sufficient evidence to recommend that women with locally advanced cervical cancer confined to the pelvis receive pelvic radiation concomitantly with treatment with cisplatin and fluorouracil. Future studies are needed to define the optimal regimen for these agents and to evaluate other combinations. The role of extended-field radiation with chemotherapy must also be defined.

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