CISPLATIN, RADIATION, AND ADJUVANT HYSTERECTOMY COMPARED WITH RADIATION AND ADJUVANT HYSTERECTOMY FOR BULKY STAGE IB CERVICAL CARCINOMA

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ABSTRACT

Background Bulky stage IB cervical cancers have a poorer prognosis than smaller stage I cervical cancers. For the Gynecologic Oncology Group, we conducted a trial to determine whether weekly infusions of cisplatin during radiotherapy improve progression-free and overall survival among patients with bulky stage IB cervical cancer.

Methods Women with bulky stage IB cervical cancers (tumor, ⩾4 cm in diameter) were randomly assigned to receive radiotherapy alone or in combination with cisplatin (40 mg per square meter of body-surface area once a week for up to six doses; maximal weekly dose, 70 mg), followed in all patients by adjuvant hysterectomy. Women with evidence of lymphadenopathy on computed tomographic scanning or lymphangiography were ineligible unless histologic analysis showed that there was no lymph-node involvement. The cumulative dose of external pelvic and intracavitary radiation was 75 Gy to point A (cervical parametrium) and 55 Gy to point B (pelvic wall). Cisplatin was given during external radiotherapy, and adjuvant hysterectomy was performed three to six weeks later.

Results The relative risks of progression of disease and death among the 183 women assigned to receive radiotherapy and chemotherapy with cisplatin, as compared with the 186 women assigned to receive radiotherapy alone, were 0.51 (95 percent confidence interval, 0.34 to 0.75) and 0.54 (95 percent confidence interval, 0.34 to 0.86), respectively. The rates of both progression-free survival ($P<0.001$) and overall survival ($P=0.008$) were significantly higher in the combined-therapy group at four years. In the combined-therapy group there were higher frequencies of transient grade 3 (moderate) and grade 4 (severe) adverse hematologic effects (21 percent, vs. 2 percent in the radiotherapy group) and adverse gastrointestinal effects (14 percent vs. 5 percent).

Conclusions Adding weekly infusions of cisplatin to pelvic radiotherapy followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers. (N Engl J Med 1999;340:1154-61.)

THE American Joint Committee on Cancer[1] and the International Federation of Gynecology and Obstetrics define stage IB cervical cancer as invasive cancer that is confined to the cervix, with a depth of more than 5 mm and a width of more than 7 mm. In patients with large stage IB cervical cancers, local control and survival are poorer than in patients with smaller stage I cancers, whether treated by surgery or irradiation.[2-4] The optimal treatment of large stage IB cervical cancer has been a source of controversy since the late 1960s.[5-9]

In a previous randomized trial of combined external and intracavitary irradiation alone or followed by extrafascial hysterectomy, the Gynecologic Oncology Group found that hysterectomy did not improve survival, but it did significantly reduce the rate of relapse in the pelvic region (unpublished data). Several phase 2 studies have reported that concomitant treatment with cisplatin during radiotherapy results in faster and more complete responses and better survival than expected with radiotherapy alone.[10-17] We elected to test this combination in a phase 3 trial to determine whether concurrent weekly treatment with cisplatin during radiotherapy would improve progression-free survival and survival in women with large "bulky," or barrel-shaped, stage IB cervical cancers.

METHODS

Patients

Women of any age with biopsy-proved primary squamous-cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix of stage IB (exophytic or expansile barrel-shaped tumors

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with a minimal diameter of 4 cm) were eligible for the study. In addition, patients could have no radiographic evidence of lymphadenopathy on computed tomographic scanning or lymphangiography, and in those with enlarged or suspicious-appearing lymph nodes, no evidence of cancer on fine-needle aspiration or histologic evaluation.

Extraperitoneal surgical staging of lymph nodes was optional. Patients with histologic evidence of lymph-node involvement were not eligible, nor were those who had previously received radiotherapy or chemotherapy or those with a history of cancer other than nonmelanoma skin cancer.

All patients were required to have a Gynecologic Oncology Group performance status of 0, 1, 2, or 3 (equivalent to Karnofsky performance scores of 90 or 100, 70 or 80, 50 or 60, and 30 or 40, respectively) and adequate bone marrow, renal function, and hepatic function. Patients were excluded from the study if they were thought to be unable to complete the planned course of therapy or the follow-up evaluations. In addition, patients had to be medically suitable for hysterectomy.

The institutions that participated in the study are listed in the Appendix. Written informed consent was obtained before entry into the study, fulfilling all institutional, state, and federal regulations.

Radiotherapy

All patients were scheduled to undergo external irradiation, intracavitary brachytherapy, and extrafascial hysterectomy, with half the patients randomly assigned to receive weekly intravenous infusions of cisplatin during the period of radiotherapy.

The prescribed regimen of radiotherapy was identical in both groups. Pelvic radiation was delivered with the four-field technique with x-ray accelerators of at least 4-MV photons at a distance of at least 100 cm. The treatment field was set to extend 3 cm beyond the known extent of disease and to encompass iliac and lower common iliac lymph nodes. Fractions of 1.8 to 2.0 Gy were delivered 5 days a week over a period of 4½ to 5 weeks, for a total dose of 45 Gy. External irradiation was withheld if the white-cell count fell below 1000 per cubic millimeter and was resumed once the count rose above that level.

Low-dose brachytherapy was performed in one or two intracavitary applications after the completion of pelvic radiotherapy. Standard Fletcher–Suit or Henschke applicators were used. The dose to point A (a reference location 2 cm lateral and 2 cm superior to the cervical os) was 30 Gy, for a cumulative dose of 75 Gy, and the cumulative dose to point B (the pelvic wall) was 55 Gy.

Chemotherapy

Cisplatin was given intravenously once a week at a dose of 40 mg per square meter of body-surface area, with the total dose not to exceed 70 mg per week. A maximum of six doses of cisplatin was given. The final dose could be given during a patient's hospitalization for intracavitary brachytherapy.

Treatment with cisplatin was withheld if the total white-cell count fell below 3000 per cubic millimeter or if creatinine clearance fell below 50 ml per minute.

Hysterectomy

Extrafascial hysterectomy was performed three to six weeks after the completion of radiotherapy. The corpus and cervix were removed but not contiguous parametrial tissue. The uterine vessels were transected at the uterine wall medial to the ureters, which were not unroofed. No vaginal cuff was removed.

Quality Control and Follow-up

Patients' medical records, films, and pathology slides were reviewed by the appropriate Gynecologic Oncology Group committees. The Radiological Physics Center in Houston coordinated the reviews of radiotherapy.

Patients were evaluated every three months for the first two years and then semiannually for three additional years. Adverse effects were reported in accordance with the Gynecologic Oncology Group criteria.[18]

Outcome

The primary end points were progression-free survival and survival. Progression-free survival was calculated from the date of entry into the study to the date of disease recurrence, death, or the last follow-up visit. Survival was calculated from the date of entry into the study to the date of death or the last follow-up visit. Recurrences were classified as local if they were detected in the pelvis, cervix, or vagina and as distant if they were detected in extrapelvic locations. The hysterectomy specimens were evaluated for evidence of cancer.

Statistical Analysis

We estimated that 173 patients were needed in each treatment group in order to be able to detect a 40 percent decrease in the recurrence rate in the group given radiotherapy and chemotherapy. The design called for a final analysis when 56 events (recurrences or deaths) had occurred in patients receiving the control regimen (radiotherapy alone) and provided the study with a statistical power of 80 percent with use of the log-rank test and a one-sided significance level of 0.05.[19] At the time of this analysis, 69 patients in the group receiving the control regimen had had a recurrence of disease and 49 had died — 88 percent of the number of deaths needed for a final analysis of survival. Therefore, because of the large difference in outcome between the two groups and the similarity in the rates of progression-free survival and survival within each group, this analysis is the final analysis of survival.

Randomization was carried out by a block arrangement; the treatment assignments were stratified according to center and to whether para-aortic lymph nodes were evaluated surgically, with approximately equal numbers of patients assigned to each group. Life-table estimates were calculated according to the method of Kaplan and Meier.[20] The difference between groups in survival and progression-free survival was evaluated with use of the log-rank test[21] according to the intention-to-treat principle. The Cox model was used to evaluate the difference between treatment regimens, adjust for prognostic factors,[22] and estimate the relative likelihood (and 95 percent confidence intervals) of survival and progression-free survival. Differences between groups in the severity of adverse effects and the frequency of hysterectomy specimens that were negative for cancer were evaluated with use of Pearson's chi-square test.[23] All reported P values are two-tailed.

Two scheduled interim analyses were conducted during the enrollment phase of the trial: the first was conducted after 29 recurrences had been reported, and the second after 47 recurrences had been reported. The first stopping rule was chosen to reject the null hypothesis at the 1 percent level, whereas the second was chosen so that the level of rejection for both interim tests was 2 percent. This interim testing increased the value of the type I error from the conventional 5 percent to 6 percent. To simplify presentation, the P values were not adjusted for the results of the two interim analyses.

RESULTS

Characteristics of the Patients

From February 1992 to April 1997, a total of 374 women were enrolled in the study at 48 Gynecologic Oncology Group institutions. Four were subsequently excluded after a central review by the pathology committee found that the specimen was inadequate for evaluation in the case of one patient, the primary lesion had been misidentified in the case of one patient, the cell type had been misidentified

in the case of one patient, and the stage of the tumor had been overestimated in the case of one patient. An additional patient was also excluded because she had received radiotherapy before entry. Three of these patients had been randomly assigned to receive radiotherapy alone, and two had been assigned to receive radiotherapy and concomitant treatment with cisplatin. Thus, a total of 369 patients were evaluated, 186 in the radiotherapy group and 183 in the combined-therapy group.

Pretreatment surgical evaluation of para-aortic lymph nodes was optional and was performed in 13 patients (7 percent) assigned to radiotherapy alone and 14 patients (8 percent) assigned to radiotherapy and cisplatin. There were no significant differences in demographic or tumor characteristics between the two groups (Table 1). All patients had primary cervical cancers that were at least 4 cm in diameter, and the distribution of the tumors according to size was similar in the two groups. There was a slightly higher percentage of patients with grade 3 tumors in the combined-therapy group (38 percent, vs. 31 percent in the radiotherapy group).

Four patients assigned to the cisplatin regimen (2 percent) received no cisplatin. A total of 164 patients (90 percent) received four or more courses of cisplatin. The median weekly dose of cisplatin was 39.0 mg per square meter (10th and 90th percentiles, 32.3 and 40.3, respectively; range, 0 to 49.7).

One patient assigned to receive radiotherapy alone and two patients assigned to receive radiotherapy and cisplatin refused to undergo radiotherapy. Otherwise, compliance with radiotherapy with respect to the dose, the volume, and the total treatment was good and was similar between the two groups (Table 2). The median total treatment time was 50 days in both groups (Table 2).

Extrafascial hysterectomy was performed after radiotherapy in 168 patients (90 percent) in the group given radiotherapy alone and 175 patients (96 percent) in the group given radiotherapy and cisplatin. More patients in the group given radiotherapy alone refused to undergo the operation (nine, vs. five in the combined-therapy group), and more patients in this group also had an early recurrence (eight vs. two). There were significantly more hysterectomy specimens without detectable cancer in the combined-therapy group than in the group given radiotherapy alone (52 percent vs. 41 percent, $P=0.04$).

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	RADIOTHERAPY ALONE (N=186)	RADIOTHERAPY AND CISPLATIN (N=183)
	no. of patients (%)	
Histologic diagnosis		
Squamous-cell carcinoma	152 (82)	147 (80)
Adenocarcinoma, not specified	14 (8)	9 (5)
Adenosquamous carcinoma	10 (5)	17 (9)
Other	10 (5)	10 (5)
Tumor grade†		
1	10 (5)	15 (8)
2	118 (63)	98 (54)
3	58 (31)	69 (38)
Not graded	0	1 (1)
Age (yr)		
≤30	23 (12)	15 (8)
31–60	151 (81)	152 (83)
61–70	8 (4)	10 (5)
71–80	4 (2)	5 (3)
81–90	0	1 (1)
Karnofsky performance score		
90 or 100	157 (84)	156 (85)
70 or 80	26 (14)	26 (14)
50 or 60	3 (2)	1 (1)
Race or ethnic group		
White	108 (58)	110 (60)
Black	46 (25)	40 (22)
Hispanic	23 (12)	23 (13)
Other	9 (5)	10 (5)
Tumor type		
Not barrel-shaped	110 (59)	96 (52)
Barrel-shaped	76 (41)	84 (46)
Unknown	0	3 (2)
Tumor size (cm)‡		
4	14 (8)	15 (8)
5	37 (20)	55 (30)
6	69 (37)	53 (29)
7	39 (21)	29 (16)
≥8	26 (14)	31 (17)
Unknown	1 (1)	0

*Because of rounding, not all percentages total 100.

†A grade of 1 indicates that 75 percent of cells were well differentiated, a grade of 2 that 50 percent of cells were well differentiated, and a grade of 3 that less than 25 percent of cells were well differentiated.

‡Tumor size is the largest diameter of the tumor or, if the tumor was barrel-shaped, the largest diameter of the cervix.

Adverse Effects

There were no treatment-related deaths, but 64 patients (35 percent) in the combined-therapy group had grade 3 (moderate) or grade 4 (severe) adverse effects, as compared with 25 patients (13 percent) in the group given radiotherapy alone. These reactions consisted almost exclusively of transient hematologic effects (39 and 3 patients in the respective groups) and gastrointestinal effects (26 and 9 patients) (Table 3). Grade 3 hematologic toxicity was defined as a total white-cell count of less than 2000 per cubic millimeter, and grade 4 as a total white-cell count of less than 1000 per cubic millimeter. Grade 3 gastrointestinal toxicity was defined as intractable vomiting despite treatment with antiemetic drugs that ultimately required hospitalization, and grade 4 as dehydration, gastrointestinal bleeding, or both. Very few patients required surgical intervention for obstruction or formation of a fistula, and these patients were equally divided between the two groups. The frequency of grade 1 (minimal) and grade 2 (mild) genitourinary and neurologic adverse effects was higher in the combined-therapy group.

TABLE 2. CHARACTERISTICS OF RADIOTHERAPY.

CHARACTERISTIC	RADIOTHERAPY ALONE (N=186)	RADIOTHERAPY AND CISPLATIN (N=183)
Total dose to point A (Gy)		
Median	74.6	74.6
Range	0–94.3	0–93.7
10th and 90th percentiles	71.5, 76.1	72.2, 76.5
Total dose to point B (Gy)		
Median	53.1	53.3
Range	0–67.3	0–69.6
10th and 90th percentiles	51.0, 56.4	51.4, 55.2
Duration of radiotherapy (days)*		
Median	50	50
Range	23–95	21–93
10th and 90th percentiles	41, 66	41, 65

*One patient in the radiotherapy group and two patients in the combined-therapy group declined to receive radiotherapy and are not included in the analysis.

Progression-free Survival

The disease recurred in 69 patients in the group given radiotherapy alone (37 percent) and 38 patients given radiotherapy and cisplatin (21 percent) (Table 4). This difference predominantly reflects the fact that there were fewer local recurrences in the combined-therapy group (16, vs. 39 in the radiotherapy group). At the time of this analysis, the rate of progression-free survival was significantly higher among patients in the combined-therapy group ($P<0.001$ by the log-rank test) (Fig. 1). The relative risk of recurrence in the combined-therapy group as compared with the group given radiotherapy alone was 0.51 (95 percent confidence interval, 0.34 to 0.75).

Survival

The median duration of follow-up was 36 months. Forty-nine of the patients in the group given radiotherapy alone died of cervical cancer (26 percent), as compared with 27 of the patients in the group given radiotherapy and cisplatin (15 percent) (Table 4). One patient who received cisplatin died after an automobile accident; she had no evidence of cancer at her last examination. The relative risk of death in the combined-therapy group as compared with the group given radiotherapy alone was 0.54 (95 percent confidence interval, 0.34 to 0.86). The three-year survival rates were 74 percent in the group given radiotherapy alone and 83 percent in the combined-therapy group ($P=0.008$ by the log-rank test) (Fig. 2). The numbers of patients who were alive at the time of this analysis but in whom disease had recurred were 20 and 11, respectively.

Prognostic Factors

Cox multiple regression analysis showed that the size of the tumor as assessed by physical examination and the histologic grade of the tumor were both significant prognostic factors. Adjustment for these factors had no significant effect on the differences between the groups in survival and progression-free survival.

DISCUSSION

The treatment of women with bulky stage IB cervical cancers has historically been only partially satisfactory, with survival rates of 70 to 75 percent, substantially below the rates of 88 to 92 percent expected with smaller stage IB cancers. The recognition, in some centers, that patients with bulky stage

TABLE 3. ADVERSE EFFECTS.*

ADVERSE EFFECT	RADIOTHERAPY ALONE (N=186)					RADIOTHERAPY AND CISPLATIN (N=183)				
	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	number of patients									
Hematologic	149	18	16	3	0	42	36	66	33	6
Gastrointestinal	114	36	27	4	5	51	57	49	17	9
Genitourinary	145	24	11	5	1	123	43	14	1	2
Cutaneous	165	10	7	3	1	158	18	7	0	0
Neurologic	184	0	1	1	0	167	6	8	2	0
Other	163	7	11	4	1	137	24	10	9	3

*Some patients had more than one adverse effect. Adverse effects were assessed with use of the National Cancer Institute Common Toxicity Criteria. A grade of 0 indicates the absence of an adverse effect, a grade of 1 a minimal effect, a grade of 2 a mild effect, a grade of 3 a moderate effect, and a grade of 4 a severe effect. Other grade 3 and grade 4 adverse effects in the group given radiotherapy alone were as follows: grade 3 pelvic abscess (one patient), grade 3 vaginal bleeding (one), grade 4 radiotherapy-induced necrosis (one), and grade 3 fever (two). Other grade 3 and grade 4 adverse effects in the group given radiotherapy and cisplatin were as follows: grade 3 depression (two patients), grade 3 anorexia (one), grade 3 perianal excoriation (one), grade 3 hyperglycemia (one), grade 3 or 4 radiotherapy-induced necrosis (two), grade 4 hypocalcemia (one), grade 3 fatigue (one), grade 3 or 4 cardiovascular effects (two), and grade 3 pulmonary abnormalities (one).

TABLE 4. RATES OF DISEASE PROGRESSION AND DEATH.*

OUTCOME	RADIOTHERAPY ALONE (N=186)	RADIOTHERAPY AND CISPLATIN (N=183)
	no. of patients (%)	
Progression status		
Recurrence†		
Local	39 (21)	16 (9)
Distant	25 (13)	19 (10)
Combined	5 (3)	3 (2)
No evidence of disease	117 (63)	145 (79)
Vital status		
Died of disease	49 (26)	27 (15)
Died of other causes	0	1 (1)
Alive	137 (74)	155 (85)

*Because of rounding, not all percentages total 100.

†Recurrences were classified as local if they were first detected in the pelvis, cervix, or vagina; as distant if they were first detected outside the pelvis; and as combined if they were first detected at sites within and outside the pelvis.

IB cancers had higher rates of recurrent disease within the cervical area led to the inclusion of adjuvant extrafascial hysterectomy in the treatment regimen for these women.[5,6] This approach was, however, associated with considerable morbidity.[24]

The use of extrafascial hysterectomy after radiotherapy has gradually been abandoned,[25] but there has continued to be disagreement about the value of the operation.[7,8] This controversy stimulated an earlier Gynecologic Oncology Group trial in which patients were randomly assigned to undergo either hysterectomy after radiotherapy or radiotherapy alone (unpublished data). In 1992, when the current study was initiated, complete data on survival in the earlier trial were not available, but an early analysis showed a significantly lower rate of relapses in the pelvic region among women who underwent hysterectomy. Therefore, we chose to test the value of concurrent treatment with cisplatin during radiotherapy followed by hysterectomy as compared with that of radiotherapy alone followed by hysterectomy.

Like others,[9,26] we found that the size of the tumor was an important prognostic factor. All our patients had cervical cancers of at least 4 cm in diameter, and the distribution of the tumors according to size was similar in the two treatment groups.

The role of chemotherapy in the treatment of locally advanced cervical cancers has been uncertain. Various drugs have been used in clinical trials and increasingly in clinical practice in the past 15 years.[10-27] The possibility that these drugs may have additive effects, regardless of the mechanism, when given concurrently with radiotherapy has been the subject of study. Cisplatin potentiates the sublethal damage induced by radiation[28] and inhibits the repair of potentially lethal radiation-induced damage.[29]

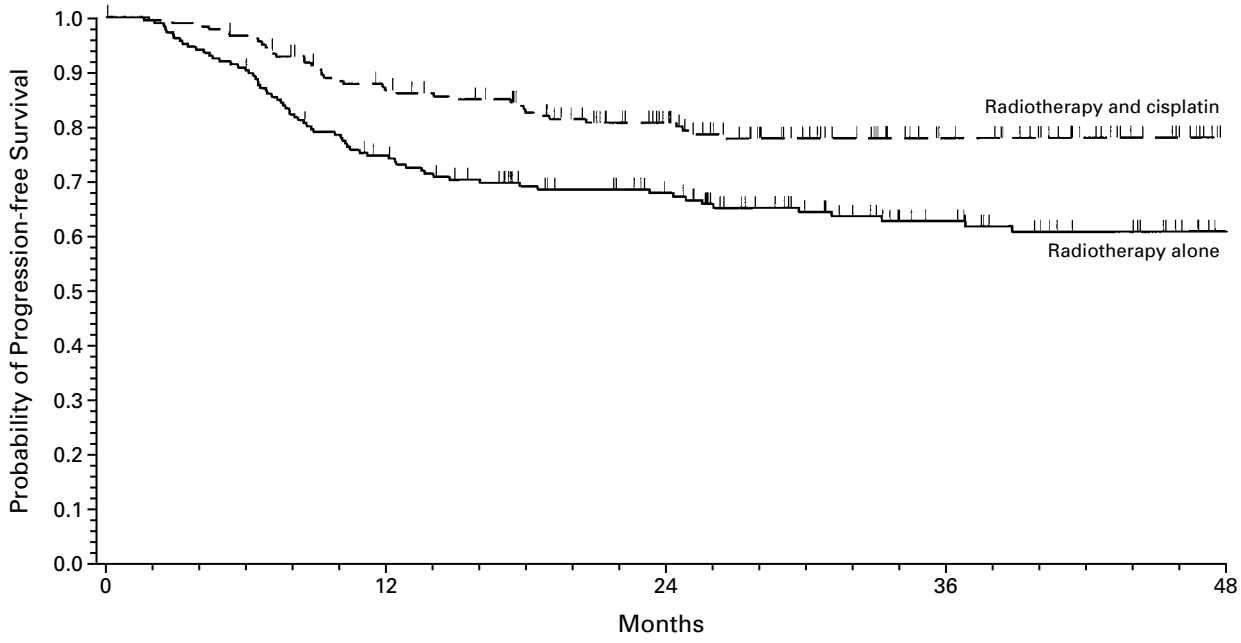

Figure 1. Kaplan–Meier Estimates of Progression-free Survival in Patients with Cervical Cancer Given Radiotherapy and Cisplatin or Radiotherapy Alone.

The rate of progression-free survival was significantly higher among patients in the combined-therapy group ($P<0.001$). Tick marks indicate patients with progression of disease.

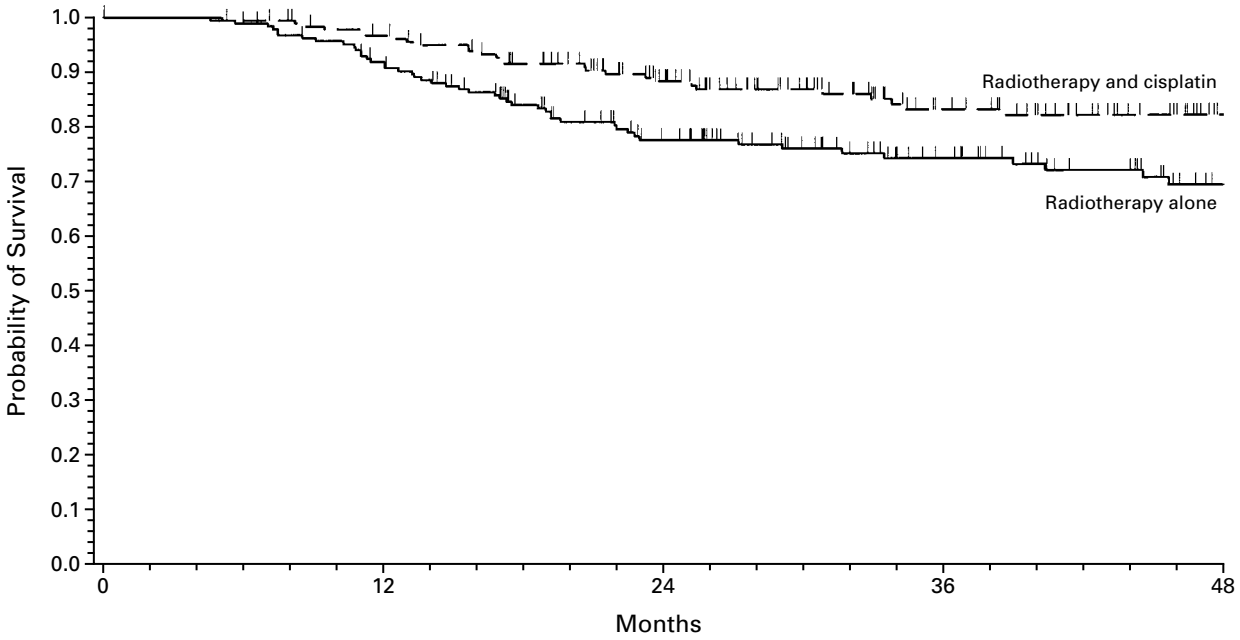

Figure 2. Kaplan–Meier Estimates of Overall Survival in Patients with Cervical Cancer Given Radiotherapy and Cisplatin or Radiotherapy Alone.

The rate of survival was significantly higher among patients in the combined-therapy group (P=0.008). Tick marks indicate patients who died.

Weekly treatment with cisplatin during radiotherapy has been assessed in several phase 2 studies.[11-15] The promising results of these studies as well as the fact that this combination is well tolerated and easy to administer on an outpatient basis led us to evaluate it in this trial.

Both cisplatin and fluorouracil are active against cancer of the cervix in patients with recurrent disease.[30,31] The effect of these two drugs in combination with radiotherapy was compared with the effect of hydroxyurea and radiotherapy in a randomized phase 3 trial by the Gynecologic Oncology Group involving patients with cervical cancer of stages IIB through IVA (unpublished data). In that study, the combination of concurrent radiotherapy and cisplatin-containing chemotherapy was superior to treatment with hydroxyurea and radiotherapy. The results of a subsequent trial involving similar patients are reported by Rose et al.[32] in this issue of the *Journal*. They compared treatment with radiation and hydroxyurea, treatment with radiation and weekly cisplatin, and treatment with radiation and hydroxyurea, cisplatin, and fluorouracil and found that the rate of relapse-free survival was significantly higher in both regimens containing cisplatin.

In addition to these three trials, two other randomized trials have also found that combining radiotherapy and cisplatin-containing chemotherapy improves survival and disease-free survival.[32] The Radiation Therapy Oncology Group study, whose results appear elsewhere in this issue of the *Journal*,[33] compared pelvic and para-aortic radiotherapy with pelvic radiotherapy in combination with cisplatin and fluorouracil in patients with clinical stage IB through IVA cervical cancer. The Southwest Oncology Group study compared pelvic radiotherapy alone with pelvic radiotherapy in combination with fluorouracil and cisplatin in high-risk patients with involvement of lymph nodes or surgical margins who had undergone radical hysterectomy for cervical cancer stage IA2, IB, or IIA (unpublished data). Both studies found that survival was increased by the use of radiotherapy in combination with cisplatin-containing chemotherapy.

In our trial the only difference in the protocols for the two groups was the use of weekly infusions of cisplatin during radiotherapy for bulky stage IB cervical cancers. The risk of recurrence and death was significantly reduced by concurrent treatment with cisplatin and radiotherapy. This difference appeared to be due to the lower rate of relapses in the pelvic region in the combined-therapy group. Although this regimen was also associated with higher rates of adverse effects, these effects consisted predominantly of transient hematologic and gastrointestinal effects, with no evidence of an increase in other serious effects. There was no evidence of a difference in the frequencies of late adverse effects between the groups.

Of the 369 eligible patients in our study who were scheduled to undergo hysterectomy after the completion of radiotherapy, 93 percent did undergo the surgery. We believe that the value of hysterectomy in these patients is doubtful. In the earlier Gynecologic Oncology Group study that assessed the value of extrafascial hysterectomy after radiotherapy, surgery was associated with a significant reduction in the rate of relapses in the pelvic region, but the overall risk of recurrence was not significantly reduced (relative risk, 0.76; 95 percent confidence interval, 0.52 to 1.12) and there was no significant difference in survival (relative risk of death, 0.91). It is reasonable to conclude on the basis of these results and our results that the elimination of hysterectomy from both regimens would not have affected the increase in survival associated with the use of cisplatin. Therefore, radiotherapy in combination with treatment with cisplatin should be adequate for patients with bulky stage IB cervical cancer.

The five randomized trials of cervical cancer that we have discussed involve different stages of cervical cancer and combinations of treatment, but they share a common result: all five studies found that concomitant treatment with cisplatin and radiotherapy led to better outcomes than radiotherapy alone or in combination with treatments that did not include cisplatin. This remarkable consistency offers a compelling reason to consider cisplatin therapy in combination with radiotherapy as a new standard of care for patients with bulky stage IB, stage IIB through IVA, and high-risk cervical cancers.

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APPENDIX

The following Gynecologic Oncology Group institutions participated in the study: University of Alabama, Oregon Health Sciences University, Duke University Medical Center, Abington Memorial Hospital, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, University of Southern California, University of Mississippi, Colorado Gynecologic Oncology Group, University of California at Los Angeles, University of Washington, University of Miami School of Medicine, Milton S. Hershey Medical Center, Georgetown University Hospital, University of Cincinnati Medical Center, University of North Carolina, University of Iowa Hospitals and Clinics, Indiana University Medical Center, Bowman Gray School of Medicine, State University of New York–Syracuse, Albany Medical College, University of California Medical Center at Irvine, Tufts–New England Medical Center, Rush–Presbyterian–St. Luke's Medical Center, Stanford University Medical Center, State University of New York at Brooklyn, University of Kentucky, Eastern Virginia Medical School, Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Eastern Pennsylvania Gynecology–Oncology Center, Cooper Hospital, University Medical Center, Columbus Cancer Council–Ohio State, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, University of Chicago, Tacoma General Hospital, Thomas Jefferson University Hospital, Case Western Reserve University, Tampa Bay Cancer Consortium, and New York Hospital–Cornell Medical Center.

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