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Pelvic Irradiation With Concurrent Chemotherapy Versus Pelvic and Para-Aortic Irradiation for High-Risk Cervical Cancer: An Update of Radiation Therapy Oncology Group Trial (RTOG) 90-01

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To report mature results of a randomized trial that compared extended-field radiotherapy (EFRT) versus pelvic radiotherapy with concomitant fluorouracil and cisplatin (CTRT) in women with locoregionally advanced carcinomas of the uterine cervix.

Patients and Methods
Four hundred three women with cervical cancer were randomly assigned to receive either EFRT or CTRT. Patients were eligible if they had stage IIB to IVA disease, stage IB to IIA disease with a tumor diameter ≥ 5 cm, or positive pelvic lymph nodes. Patients were stratified by stage and by method of lymph node evaluation.

Results
The median follow-up time for 228 surviving patients was 6.6 years. The overall survival rate for patients treated with CTRT was significantly greater than that for patients treated with EFRT (67% *v* 41% at 8 years; $P < .0001$). There was an overall reduction in the risk of disease recurrence of 51% (95% CI, 36% to 66%) for patients who received CTRT. Patients with stage IB to IIB disease who received CTRT had better overall and disease-free survival than those treated with EFRT ($P < .0001$); 116 patients with stage III to IVA disease had better disease-free survival ($P = .05$) and a trend toward better overall survival ($P = .07$) if they were randomly assigned to CTRT. The rate of serious late complications of treatment was similar for the two treatment arms.

Conclusion
Mature analysis confirms that the addition of fluorouracil and cisplatin to radiotherapy significantly improved the survival rate of women with locally advanced cervical cancer without increasing the rate of late treatment-related side effects.

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INTRODUCTION

Between September 1990 and November 1997, the Radiation Therapy Oncology Group (RTOG) conducted a prospective randomized trial (RTOG 90-01) designed to test the hypothesis that concurrent administration of cisplatin and fluorouracil would improve the outcome of patients treated with radiotherapy for locoregionally advanced carcinoma of the cervix. Because an earlier trial (RTOG 79-20) [1] had demonstrated an improvement in survival when prophylactic para-aortic radiotherapy was added to pelvic radiotherapy, patients in the control arm of RTOG 90-01 were treated with extended radiotherapy fields. Because a phase II trial of combined chemotherapy and extended-field radiotherapy had shown unacceptable toxicity with this approach [2], the experimental arm consisted of pelvic radiotherapy combined with chemotherapy.

In July 1998, 9 months after accrual to RTOG 90-01 had been completed, the RTOG data monitoring committee re-

viewed the results of a scheduled preliminary analysis of the trial. A highly significant difference between the two arms of the study was revealed. Because this difference met requirements for early release of the results, the preliminary data were published in April 1999 [3]. These results, combined with consistent findings from four other trials that completed accrual at about the same time [4-7], led to issuance of a clinical alert by the National Institutes of Health [8] and stimulated a dramatic change in the standard of care for many patients with carcinoma of the cervix.

These compelling results have justifiably led clinicians to offer concurrent cisplatin-based chemotherapy to most of their patients with locoregionally advanced cervical cancer. However, three of the five trials that were reported in 1999 and 2000 were immature at the time of publication, having completed accrual within 2 years of publication. Most of the studies had insufficient follow-up to permit meaningful analysis of the influence of concurrent chemotherapy on late radiation effects, and the influence of many of the relapse events on survival had not yet been registered. The purpose of this analysis was to update the results of RTOG 90-01 with an additional 3 years of follow-up.

PATIENTS AND METHODS

Details regarding selection criteria, treatment, follow-up, quality assurance, and statistical analysis for RTOG 90-01 have been published previously [3]. The most important details will be reviewed briefly here.

The study was open to women of all ages with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix who had disease classified as International Federation of Obstetrics and Gynecology (FIGO) stage IIB to IVA; disease classified as FIGO stage IB or IIA with a tumor diameter of at least 5 cm; or biopsy-proven metastasis to pelvic lymph nodes. To be eligible, women were required to have a Karnofsky performance score of at least 60 and blood cell counts and serum levels of blood urea nitrogen, creatinine, and bilirubin within normal ranges. Women were excluded from the study if they met any of the following criteria: involvement of the para-aortic lymph nodes; other disease outside the pelvic area; a prior cancer other than cutaneous basal-cell carcinoma; medical contraindications to chemotherapy; a rare histologic subtype; transperitoneal staging procedure for cervical cancer; or prior hysterectomy, pelvic radiotherapy, or systemic chemotherapy.

A medical history was recorded and clinical examination was performed before enrollment. The initial evaluation also included chest radiography, cystoscopy, proctoscopy, a complete blood cell count, and measurement of liver and renal function. The renal-collecting system of each patient was assessed with intravenous (IV) pyelography or contrast computed tomography. Para-aortic lymph nodes were evaluated with 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 *v* III or IVA) and the staging method used for para-aortic lymph nodes (clinical *v* surgical).

Treatment

External-beam radiotherapy was delivered with anteroposterior-posteroanterior opposed beams of at least 15-MV photons or with 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 calculated at the patient's midplane in the central ray of the field (for anteroposterior-posteroanterior fields) or to the isocenter of the beams. The total dose to be delivered to the pelvic and para-aortic lymph nodes was 45 Gy, given at a dose of 1.8 Gy per fraction.

Three hundred seventy-seven of 388 patients with available information were treated with a combination of external-beam and intracavitary therapy. In 315 patients, the first intracavitary treatment was delivered after 45 Gy of external radiotherapy had been delivered to pelvic or pelvic and para-aortic nodes. In 72 patients, the first intracavitary treatment was performed after 20 to 30 Gy of pelvic 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 2 weeks (preferably within 1 week) after the completion of pelvic radiotherapy, with the goal of keeping the total duration of treatment less than 8 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. It was recommended that the total course of treatment be completed in less than 56 days.

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 IV infusion of cisplatin 75 mg/m^2 of body-surface area over a 4-hour period followed by an IV infusion of fluorouracil 4,000 mg/m^2 over a 96-hour period. Thus, chemotherapy was administered during days 1 through 5 of radiotherapy. Two additional cycles of chemotherapy were scheduled at 3-week intervals. One of these was administered at the time of the second intracavitary insertion. Patients who developed a WBC count less than 1,500/μL, an absolute granulocyte count less than 1,000/μL, a platelet count less than 75,000, or grade 4 nausea or diarrhea had treatment interrupted for up to 1 week followed by a 50% reduction in the dose of fluorouracil. If these side effects persisted for more than 1 week, no additional fluorouracil was given.

Follow-Up

During treatment, patients were evaluated weekly with clinical assessments and a complete blood cell count with differential and platelet counts. Before each cycle of chemotherapy, serum levels of creatinine, urea nitrogen, ALT, alkaline phosphatase, and bilirubin and serum electrolyte levels were measured. Patients had a pelvic examination under anesthesia at the time of each intracavitary treatment. Once treatment ended, patients were evaluated every 3 months for the first 2 years, every 4 months during the third year, every 6 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 persistent or recurrent disease was confirmed with a biopsy whenever possible. Toxicity was assessed at the time of each evaluation according to 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 regarding external-beam fields, intracavitary placement, doses of radiation to tumor and normal tissues, and other treatment variables, were reviewed by a radiation oncologist. Variations from the specified dose of radiation or the specified duration of treatment were scored as follows: difference of more than 5% but not more than 10%, minor; difference of more than 10% but not more than 20%, major but acceptable; and difference of more than 20%, unacceptable. Each institution's equipment was calibrated by employees of the Radiological Physics Center (Houston, TX).

Statistical Methods

Overall survival was the primary end point for treatment comparison, with death as a result of any cause considered a treatment failure. The secondary end points evaluated were disease-free survival, locoregional recurrence, para-aortic node recurrence, distant metastasis, cause-specific failure, time to late side effects grade 3 or higher, and time to late side effects grade 4 or higher. For calculation of disease-free survival, treatment failure was defined as locoregional recurrence, para-aortic recurrence, distant progression, second cancer diagnosis, or death as a result of any cause. Cause-specific failure was defined as death attributed to the treated cancer, complications of the protocol treatment, or unknown causes. All times were calculated from the date of study entry until the date of treatment failure or last date of follow-up.

All assessable patients were included in the intent-to-treat analysis. Overall and disease-free survival rates were estimated using the Kaplan-Meier method [9], and treatments were compared using log-rank tests [10]. Locoregional recurrence, para-aortic recurrence, distant metastasis, cause-specific failure, time to late side effects grade 3 or higher, and time to late side effects grade 4 or higher were estimated using cumulative incidence methods, [11] and treatment effects were tested using the Gray test [12]. Five- and 8-year rates were estimated for all end points. The significance of associations between treatment assignment and patient characteristics was assessed by χ^2 analysis. Side effects of treatment that occurred within 90 days of the start of radiotherapy were considered acute effects, and those occurring or persisting more than 90 days after the start of radiotherapy were considered late effects.

For this updated report, the results are based on all information received and entered at RTOG headquarters by September 4, 2002. For all patients, the minimum potential follow-up time was 4 years.

RESULTS

Of the 403 patients who were enrolled onto the trial, 13 were subsequently disqualified because they did not meet the eligibility requirements [3]. Follow-up data were not submitted on one eligible patient. This patient is included in the analysis of pretreatment characteristics but is excluded from the outcome analyses. The remaining 389 patients (194 in the combined-therapy group and 195 in the radiotherapy group) are included in this analysis. The median follow-up time for all patients was 4.6 years. The median follow-up time for the 228 surviving patients was 6.6 years (range, 0.2 to 11.4 years; interquartile range, 6.3 to 8.1 years).

Patient and Tumor Characteristics

A detailed comparison demonstrated no significant differences in the characteristics of patients in the two patient groups [3]. The median patient age was 47 years in both groups; 83% of the patients enrolled had Karnofsky performance scores of 90 or 100. Tumor characteristics for the two patient groups are listed in Table 1. Of the 130 patients with stage IB to IIA disease, 84 patients (65%) had tumors that measured 6 cm or more in diameter. Of the 112 patients with stage IIIB to IVA disease, 51 patients (46%) had hydronephrosis.

Outcomes

Status at the time of last follow-up for all patients in the study is listed in Table 2. At the time of last follow-up, 132 of 194 patients treated with chemoradiotherapy and 85 of 195 patients treated with extended-field radiotherapy were alive without evidence of disease. Eleven patients were alive with disease at last follow-up; of these, four patients were alive with disease in 2002, and seven patients (two who received chemoradiotherapy and five who received radiation alone) had been lost to follow-up after recurrence. Fifty-nine patients treated with chemoradiotherapy and 102 patients treated with extended-field radiotherapy had died; their causes of death are listed in Table 2. The nine patients who died as a result of unknown causes were assumed to have died of cancer.

The overall survival rate of patients who were treated with chemoradiotherapy was significantly greater than that of patients treated with radiation alone (73% *v* 52% at 5 years; $P < .0001$; Table 3; Fig 1). Patients who were treated with chemoradiotherapy also had a significantly higher disease-free survival rate and lower rates of locoregional, dis-

Table 1. Pretreatment Tumor Characteristics

Characteristic	Pelvic RT + Chemotherapy (n = 195)*	Pelvic + Para-Aortic RT (n = 195)
Squamous carcinoma	176	176
Adenosquamous carcinoma or adenocarcinoma	19	19
FIGO stage IB to IIA, cm	65	65
< 5	4	9
5-5.9	16	17
6-6.9	26	18
7	19	21
FIGO stage IIB	71	71
FIGO stage IIIA	4	2
FIGO stage IIIB	49	55
FIGO stage IVA	6	2
Hydronephrosis	26	25
Pelvic lymph node status		
All negative	147	132
Only distal nodes positive	30	43
Common iliac nodes positive	17	19
Method of detection of positive nodes		
Biopsy confirmation	24	37
Lymphangiography only	23	25
Para-aortic nodal staging method		
Lymphangiography only	145	142
Surgery with or without lymphangiography	50	53

Abbreviations: RT, radiotherapy; FIGO, International Federation of Gynecology and Obstetrics.
*Includes the patient who was eligible but had no follow-up data reported. This patient was included in the analysis of pretreatment characteristics but not in outcome analyses.

Table 2. Status at Time of Last Follow-Up

Characteristic	Pelvic RT + Chemotherapy (n = 194)	Pelvic + Para-Aortic RT (n = 195)
Alive with no evidence of disease	132	85
Alive with disease	3	8
Dead	59	102
Cancer	45	80
Complications of protocol treatment	2	3
Complications of nonprotocol treatment	1	0
Second primary cancer	3	3
Unrelated or other*	7	8
Information not available	1	8

Abbreviation: RT, radiotherapy.
*Pelvic RT + chemotherapy: heart disease, three patients; stroke, two patients; pulmonary embolus, one patient; renal failure, one patient. Pelvic + para-aortic RT: heart disease, four patients; pulmonary embolus, one patient; pneumonia, one patient; septicemia, one patient; murdered, one patient.

tant metastatic, and cause-specific failure. Overall, there were 68 pelvic recurrences in patients who were treated with radiation alone versus only 33 pelvic recurrences in patients treated with chemoradiotherapy (Table 4; Fig 2). At 5 years, the cumulative incidence of para-aortic failure was 7% for patients treated with pelvic radiotherapy and chemotherapy versus 4% for those treated with extended fields ($P = .15$; Table 3). There was an overall reduction in the risk of death or recurrence of 51% (95% CI, 34% to 64%) and a reduction in the risk of locoregional recurrence of 58% (95% CI, 36% to 72%) for patients who were randomly assigned to receive concurrent chemotherapy. The risk of death in these patients was reduced by 52% (95% CI, 34% to 64%).

To maintain a balance of risk factors between the randomization groups, patients were stratified according to stage (IB and II *v* III and IVA). The study was not designed to detect differences in outcome within the subgroups; in particular, the relatively small number of patients with stages III and IVA disease (n = 116) contributed to broad CIs for outcome in this subgroup. However, among patients with FIGO stage IB or II disease, those who were randomly assigned to receive chemoradiotherapy had significantly higher rates of survival, disease-free survival, and locoregional control than patients treated with radiation only for cancers of similar stage (Table 5; Fig 3). Among patients with stage III or IVA disease, those who were treated with chemoradiotherapy had a significantly better disease-free survival rate than those treated with radiation only. There was also a trend toward improved survival and locoregional control for patients with stages III and IVA disease who received chemoradiotherapy.

The patients in our study were not stratified according to the presence or absence of lymph node involvement, and the number of patients with lymph node metastasis was somewhat higher in the group that received extended-field radiation therapy (Table 1). To rule out the possibility that this imbalance explained the difference in outcome between the groups, patients with or without lymph node involvement were analyzed separately. The 147 patients with negative lymph nodes who received concurrent chemotherapy had significantly better overall survival ($P = .002$), disease-free survival ($P = .0003$), and locoregional control ($P = .01$) than 132 patients who had negative nodes treated with radiation alone. Patients who had positive lymph nodes also had significantly better outcomes if they were treated with concurrent chemotherapy ($P < .01$ for all three end points). Although the results of staging were not used to stratify patients in our study, they were stratified according to the type of lymph node staging. The 50 patients who received concurrent chemotherapy after retroperitoneal lymph node staging had a significantly better overall survival than 53 patients who had radiation only after surgical staging ($P = .026$); patients who received concurrent chemotherapy after clinical staging also had a significantly better survival than clinically staged patients who received radiation only ($P < .0001$).

Table 3. Survival and Recurrence Rates

Outcome	Pelvic RT + Chemotherapy (n = 194) %	Pelvic RT + Chemotherapy (n = 194) 95% CI	Pelvic + Para-Aortic RT (n = 195) %	Pelvic + Para-Aortic RT (n = 195) 95% CI	Relative Risk* Valve	Relative Risk* 95% CI	P
Overall survival					0.48	0.35 to 0.67	< .0001
5 years	73	67% to 80%	52	45% to 59%			
8 years	67	60% to 75%	41	33% to 49%			
No. of patients at risk beyond 8 years	48		26				
Disease-free survival					0.49	0.36 to 0.66	< .0001
5 years	68	62% to 75%	43	36% to 50%			
8 years	61	53% to 68%	36	29% to 44%			
Patients at risk beyond 8 years	44		22				
Locoregional failure					0.42	0.28 to 0.64	< .0001
5 years	18	12% to 23%	34	28% to 41%			
8 years	18	12% to 23%	35	28% to 42%			
Para-aortic failure					1.65	0.70 to 3.90	.15
5 years	7	3% to 11%	4	1% to 7%			
8 years	9	4% to 13%	4	1% to 7%			
Distant metastasis (excluding para-aortic failure)					0.48	0.32 to 0.73	.0013
5 years	18	13% to 24%	31	25% to 38%			
8 years	20	14% to 26%	35	28% to 42%			
Cause-specific failure†					0.45	0.32 to 0.64	.00012
5 years	24	17% to 29%	41	34% to 48%			
8 years	26	19% to 32%	47	39% to 55%			

Abbreviation: RT, radiotherapy.
*A value less than 1 indicates an advantage for pelvic RT and chemotherapy.
†Failure is death as a result of treated cancer, complications of protocol treatment, or unknown causes.

Treatment Tolerance

The details of treatment, including its acute side effects, are summarized in an earlier report of the trial [3]. A total of 362 of 388 patients completed the planned course of radiotherapy (information was incomplete for one patient). The median duration of treatment for the study population overall was 58 days (interquartile range, 52 to 64 days); the median duration of treatment was 56 days for patients treated with radiation alone and 59 days for patients treated with chemoradiotherapy ($P = .62$). The median total dose of radiation that was delivered to point A was 87.0 Gy in both arms. This figure is lower than that quoted in the earlier report of this study [3] because an error was found in the calculated doses from one facility just after publication.

The late complications of treatment are summarized in Table 6. Twenty-four (13%) of 191 patients treated with chemoradiotherapy and 23 (12%) of 194 patients treated with extended-field radiotherapy had grade 3 or 4 late complications of treatment. At 5 years, the cumulative inci-

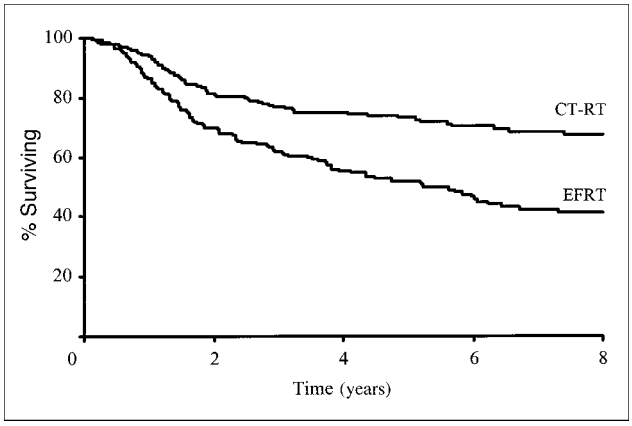

Fig 1. Kaplan-Meier estimates of overall survival for patients who received extended-field radiotherapy (EFRT) or concurrent chemotherapy and radiotherapy (CT-RT; $P < .0001$).

Table 4. Disease Failure Pattern and Survival Status

Failure Pattern	Pelvic RT + Chemotherapy (n = 194)	Pelvic + Para-Aortic RT (n = 195)
No evidence of disease		
Alive	123	78
Dead	7	15
Locoregional failure only	20	36*
Distant failure only†	22	30
Locoregional and distant failure	13	32*
Second primary tumor	9	4

Abbreviation: RT, radiotherapy.
*Including one patient who also developed a second primary cancer.
†Including para-aortic nodes.

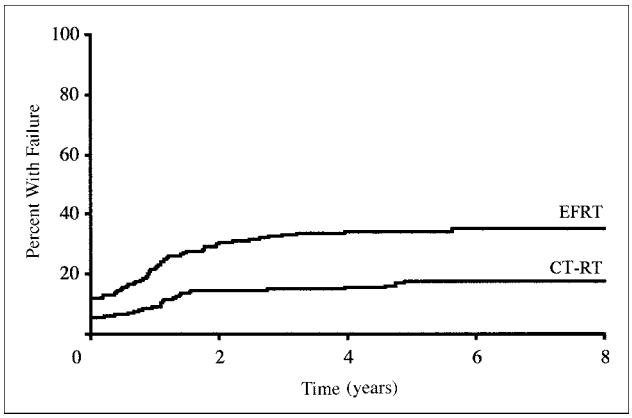

Fig 2. Kaplan-Meier estimates of locoregional recurrence for patients who received extended-field radiotherapy (EFRT) or concurrent chemotherapy and radiotherapy (CT-RT; $P < .0001$).

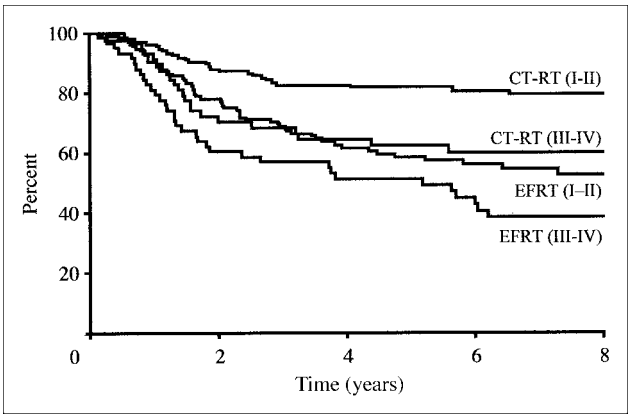

Fig 3. Kaplan-Meier estimates of overall survival for patients who received extended-field radiotherapy (EFRT) or concurrent chemotherapy and radiotherapy (CT-RT) in subgroups stratified by International Federation of Gynecology and Obstetrics stage ($P < .0001$).

dences of grade 3 or higher late complications for the chemoradiotherapy and extended-field radiotherapy groups were 14% (95% CI, 9% to 19%) and 14% (95% CI, 8% to 20%), respectively. There were three late treatment-related deaths in the extended-field radiotherapy arm. The cumulative incidence of grade 3 or higher late complications was 14% (95% CI, 9% to 19%) for patients who had surgical staging and 14% (95% CI, 8% to 20%) for those who had only clinical staging ($P = .50$).

DISCUSSION

These data confirm our earlier findings that concurrent administration of cisplatin and fluorouracil with radiation significantly improves the rates of local and distant disease control for patients with locoregionally advanced cervical cancer [3]. In our trial, concurrent administration of chemotherapy resulted in a 51% reduction in the risk of recurrence and a 52% reduction in the risk of death. This improvement was accomplished without any increase in the rate of serious late effects of radiation. Although our study was not designed to have sufficient power to detect or rule out important differences in the outcomes of patients within the stratified subsets, this update did demonstrate a significantly improved outcome for patients with stages III to IVA disease as well as for those with earlier-stage cancers.

In our study, locoregional recurrence rates were reduced by 58% with administration of concurrent chemotherapy. These data suggest that concurrent delivery of cisplatin and fluorouracil dramatically enhances the tumoricidal effect of radiation, acting as a potent radiation sensitizer. It is more difficult to be confident that chemotherapy had a direct effect on micrometastatic disease. The dramatic reduction in distant metastases seen with concurrent chemotherapy reflected, in large part, the much smaller number of patients who had combined distant and local treatment failures (13 *v* 32 patients). In these patients, the

Table 5. Estimated 5-Year Survival and Local Recurrence Rates in Stratified Stage Groups

Outcome	Pelvic RT + Chemotherapy (n = 194)		Pelvic + Para-Aortic RT (n = 195)		Relative Risk*		
	%	95% CI	%	95% CI	Value	95% CI	*P*
Overall survival							
FIGO stage IB or II	79	72% to 86%	55	46% to 64%	0.41	0.27 to 0.63	< .0001
FIGO stage III or IVA	59	46% to 72%	45	32% to 59%	0.63	0.39 to 1.04	.07
Disease-free survival†							
FIGO stage IB or II	74	67% to 82%	46	37% to 55%	0.43	0.29 to 0.63	< .0001
FIGO stage III or IVA	54	41% to 67%	37	24% to 49%	0.62	0.39 to 0.99	.05
Locoregional failure							
FIGO stage IB or II	13	7% to 19%	31	23% to 39%	0.35	0.20 to 0.62	.0002
FIGO stage III or IVA	29	16% to 41%	44	29% to 55%	0.55	0.30 to 1.03	.065

Abbreviations: RT, radiotherapy; FIGO, International Federation of Gynecology and obstetrics.
*A value less than 1 indicates an advantage for pelvic RT and chemotherapy.
†Failure is death as a result of treated cancer, complications of protocol treatment, or unknown causes.

Table 6. Late Complications Reported During or After the Second Follow-Up Visit

	Maximum Grade of Late Complications					
	Pelvic RT + Chemotherapy (n = 191)			Pelvic + Para-Aortic RT (n = 194)		
Site*	3	4	5	3	4	5
Skin	0	0	0	0	0	0
Subcutaneous tissue	0	0	0	0	0	0
Vaginal mucosa†	1	0	0	0	0	0
Small bowel	1	6	0	0	9	0
Large bowel or rectum	3	14	0	1	14	3
Bladder	4	2	0	2	3	0
Bone	0	0	0	0	0	0
Renal	2	3	0	0	2	0
Hematologic	0	0	0	0	0	0
Nausea and vomiting	0	0	0	0	0	0
Ototoxicity	0	0	0	0	0	0
Stomatitis	0	0	0	0	0	0
Other	1	1	0	1	1	0
Maximum toxicity per patient	7	17	0	2	18	3
%	4	9	—	1	9	2

Abbreviation: RT, radiotherapy.
*Some patients had complications involving more than one site.
†Twenty cases of fistula involving the vagina and small bowel (one patient in the chemoradiation group, two patients in the radiotherapy-only group), and/or rectum (eight patients in the chemoradiation group, 10 patients in the radiotherapy-only group), and/or bladder (one patient in the chemoradiation group, two patients in the radiotherapy-only group) are listed as complications involving those structures.

distant metastases may have represented secondary spread from uncontrolled pelvic disease. It is also important to note that chemotherapy did not eliminate the risk of para-aortic recurrence: the rate of para-aortic recurrence in patients treated with chemoradiotherapy was 7% at 5 years.

The results of RTOG 90-01 are consistent with those of other studies of cisplatin-based chemoradiotherapy (Fig 4). In two studies of patients with stage IIB to IVA cervical cancer (Gynecologic Oncology Group [GOG]-85 and GOG-120) [5,7], the GOG compared three different schedules of cisplatin-based chemotherapy and concurrent radiation with their then-standard regimen of concurrent radiation and hydroxyurea. All three cisplatin-based regimens were superior to the combination of radiation and hydroxyurea. In a third trial (GOG-123) [4], patients who had stage IB tumors that measured 4 cm or more in diameter were treated either with radiation, concurrent weekly cisplatin, and adjuvant hysterectomy or with radiation and hysterectomy alone; again, the relative risks of disease progression and death were significantly lower in the patients who received concurrent chemotherapy. Another trial, published by the Southwest Oncology Group, evaluated the addition of concurrent and adjuvant cisplatin and fluorouracil to postoperative pelvic radiotherapy in patients who had high-risk tumor features after radical hysterectomy for cervical cancer. This study also demonstrated that patients who received concurrent chemotherapy had better rates of progression-free survival and overall survival than those treated only with adjuvant radiotherapy.

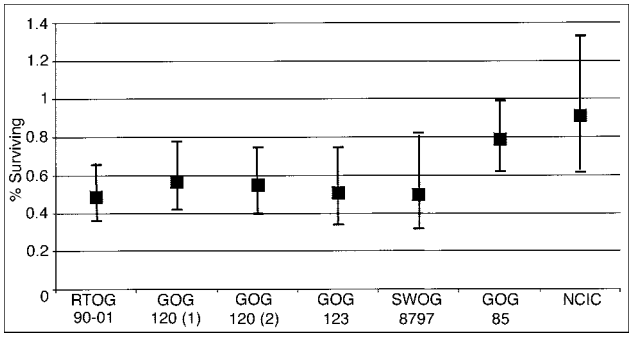

Fig 4. Relative risks of disease recurrence for the seven cisplatin-containing arms of six recent randomized clinical trials in patients with locally advanced cervical carcinoma (RTOG, Radiation Therapy Oncology Group; GOG, Gynecologic Oncology Group; SWOG, Southwest Oncology Group; NCIC, National Institute of Cancer Canada).

Only one large trial has failed to demonstrate an advantage from the addition of concurrent cisplatin to radiotherapy in patients with high-risk cervical cancer. In 2002, Pearcey et al [13] published results of a randomized trial that was conducted by the National Cancer Institute of Canada (NCIC) during the same period as the RTOG, GOG, and Southwest Oncology Group trials. The NCIC trial compared pelvic radiotherapy with a combination of pelvic radiotherapy and concurrent weekly cisplatin; the eligibility requirements were similar to those of RTOG 90-01, and the chemotherapy regimen of weekly cisplatin was similar to that used in GOG-123 and GOG-120. However, the NCIC trial failed to demonstrate a significant difference

in progression-free survival or overall survival between the two arms of the trial. The NCIC used an external-beam radiotherapy schedule similar to that used by the other groups but used a brachytherapy schedule more compact than that used by the other groups; this contributed to a shorter median duration of radiotherapy (48 to 50 days) in the NCIC trial than in GOG-85 (64 days), GOG-120 (62 days), or RTOG 90-01 (58 days). The NCIC also required higher hemoglobin levels for patients entering their trial than did the other the other groups (11 *v* 10 g/dL). Pearcey et al [13] suggest that their patients' more compact treatment and higher hemoglobin levels may have provided less opportunity for improvement with chemotherapy; they also found that their patients who received chemotherapy had lower minimum hemoglobin levels during radiotherapy, and the authors argued that this may have countered any benefit from the concurrent cisplatin.

We are not convinced that these differences are sufficient to explain the inconsistent result of the NCIC trial. Examination of the control arms of the RTOG and NCIC trials suggests that the margins for improvement should have been similar. The 5-year survival rates were 52% and 58% for patients treated with radiotherapy only in the RTOG and NCIC trials, respectively; the crude rates of pelvic recurrence were 33% and 35%, respectively, and the pelvic disease recurrence rates were 22% at 1 year for patients in the control arms of both trials [14]. However, other differences could have been important. The NCIC trial is the smallest of the randomized trials, with only 253 eligible patients analyzed; this contributed to relatively large CIs for this trial (Fig 4), suggesting that the result may have been due to statistical variance. In addition, the NCIC trial required only computed tomography for abdominal staging; this method may have permitted the inclusion of more patients with undetected para-aortic metastases than RTOG and GOG trials that required lymphangiography or retroperitoneal surgical staging, further reducing the benefit of effective locoregional treatment.

It is not possible from available data to determine whether the inclusion of fluorouracil in the RTOG regimen contributed importantly to the benefit of this regimen. The GOG recently completed a trial comparing concurrent radiotherapy and weekly cisplatin versus radiotherapy and continuous-infusion fluorouracil; an interim analysis of this trial reportedly, "showed no reasonable possibility of a superior outcome in the fluorouracil treatment group" [15]. However, the possibility of a synergistic effect between cisplatin and fluorouracil has never been tested. Combinations of cisplatin and fluorouracil with radiation have consistently yielded significant reductions in the risk of recurrence when compared with radiation alone or radiation plus hydroxyurea [3,5-7], suggesting that the combination is highly effective. However, GOG-120 demonstrated a benefit of similar magnitude using weekly cisplatin alone, although the NCIC trial [13] failed to demonstrate an advantage with weekly cisplatin. Because of differences in patient eligibility, control treatments, and other elements of the various trials, it is impossible to use these experiences to compare the relative benefits of cisplatin-based regimens; only a large prospective randomized trial comparing cisplatin alone with the combination of cisplatin and fluorouracil could answer this important question.

Although attention in North America has focused on the use of cisplatin alone or in combination with fluorouracil, other drug combinations have shown efficacy in international trials. A large multicenter trial from Thailand [16] recently demonstrated significantly improved survival, disease-free survival, and locoregional control rates when concurrent mitomycin and fluorouracil were added to radiotherapy in patients with stage IIB to IVA disease. The addition of postradiotherapy chemotherapy to radiotherapy alone or to concurrent chemotherapy and radiotherapy did not improve survival. In an earlier prospective trial from Southeast Asia, Tattersall et al [17] reported improved survival when a combination of epirubicin and cisplatin was given during and after radiotherapy for locally advanced cervical cancers. Although these trials indicate that other drugs may be beneficial, the dramatic results of North American trials now have made it difficult to study combinations that do not include cisplatin.

In our study the risk of serious late treatment-related complications was similar for patients who received concurrent chemotherapy or radiation alone. Although this finding is encouraging, the difference in the volume of tissue irradiated in the two arms complicates this comparison. In our study, the overall cumulative incidence of major complications in patients who received concurrent chemotherapy and pelvic radiation was somewhat higher than has been reported in patients treated with pelvic radiation alone in the earlier RTOG trial 79-20 [1]; however, the cumulative incidence of grade 4 to 5 toxicity in our study (10% at 5 years) was similar to that reported for patients who received extended field irradiation in RTOG 79-20 (8% at 5 years) [1].

In 1999, many clinicians believed that the results of prospective studies, although preliminary, justified a move to routine use of chemoradiotherapy to treat most patients with locoregionally advanced cervical cancer. The updated results of RTOG 90-01 validate that decision, confirming that radiotherapy with concurrent cisplatin-based chemotherapy should be considered standard treatment for this group of patients. Current randomized trials are investigating possible ways to improve further the effectiveness of cisplatin-based chemoradiotherapy regimens without increasing treatment-related morbidity. In an ongoing GOG trial, investigators are trying to improve tumor oxygenation by administering erythropoietin to anemic patients receiving chemoradiotherapy. Other groups are using biologic response

modifiers such as celecoxib in an effort to improve radiation response. These concepts are promising, although improved outcomes achieved with current standard regimens mean that large numbers of patients may be required if future trials are intended to detect additional improvements in outcome. The success of RTOG 90-01 and other recent trials should serve as an inspiration to clinicians and patients to continue their commitment to the clinical research that makes such advances possible.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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