

# Randomized Trial of Epirubicin and Cisplatin Chemotherapy Followed by Pelvic Radiation in Locally Advanced Cervical Cancer

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**Purpose:** Pelvic radiation is standard treatment for women with stage IIb to IVa cervical cancer, but treatment results are disappointing, particularly for women with bulky tumors. We investigated the role of primary chemotherapy followed by pelvic radiotherapy in a randomized trial.

**Patients and Methods:** Two hundred sixty patients with stage IIb and IVa cervical cancer received either standard pelvic radiotherapy or primary chemotherapy with cisplatin 60 mg/m<sup>2</sup> and epirubicin 110 mg/m<sup>2</sup> administered at 3-week intervals for three cycles, followed by pelvic radiotherapy.

**Results:** Ninety-nine patients have relapsed with a median follow-up duration of 1.3 years; in 62 patients, the first site of progressive disease was the pelvis. Patients who received primary chemotherapy had a significantly higher pelvic failure rate than those who re-

ceived radiotherapy alone ( $P < .003$ ). Seventy-six patients have died, and those who received primary chemotherapy had significantly inferior survival compared with those who received radiotherapy alone ( $P = .02$ ). Tumor response following chemotherapy was observed in 63%. After radiotherapy, tumor response occurred in 72% of those who received combined modality treatment, compared with 92% of those who received radiotherapy alone.

**Conclusion:** Primary chemotherapy with epirubicin and cisplatin, although resulting in tumor response in a significant proportion of patients, is accompanied by an inferior local control rate and survival compared with standard pelvic radiotherapy alone.

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CERVICAL CANCER is the fifth most common cancer globally and the second most common cancer in women.<sup>1</sup> Screening for cervical cancer by Papanicolaou smear and treatment of women with preinvasive disease reduces cervical cancer incidence and deaths. New understanding of the possible role of papilloma virus infection in the development of cervical cancer has opened the way to possible new strategies for primary prevention, which ultimately may reduce the prevalence of preinvasive and invasive cervical cancer.

For those women diagnosed with cervical cancer, treatment approaches have not changed significantly in recent

years and treatment outcome has not improved.<sup>2</sup> Radical pelvic surgery or pelvic radiotherapy is effective treatment for many women who present with early invasive cervical cancer (stage Ib to IIa), but for women with more locally advanced disease and extension to the pelvic side wall, radiotherapy is the standard treatment. Treatment results in women with locally advanced cervical cancer (stage IIb to IVa) are unsatisfactory, particularly for those with bulky local disease, in whom failure of radiotherapy to control the disease in the pelvis and relapse in the paraaortic nodes and beyond are common.<sup>3</sup>

Chemotherapy was first evaluated in the management of patients with recurrent or metastatic cervical cancer. Tumor response rates of less than 20%, with responses usually lasting only a few weeks in most patients, were observed until the introduction of cisplatin. Over the last 10 years, cisplatin-based chemotherapy has been used extensively in patients with metastatic cervical cancer. The tumor response rate is approximately 50%, with a median duration of response of approximately 6 months.<sup>4</sup> Complete tumor regression in the range of 5% to 20% has been reported in some studies, and some of those patients have tumor responses that last for a number of years.<sup>4</sup>

A variety of studies have investigated how chemotherapy may be integrated into the management of patients with localized cervical cancer. These strategies include primary chemotherapy followed by surgery or radiotherapy,<sup>4</sup> chemotherapy given after radical surgery,<sup>5</sup> and chemotherapy given concurrently with radiotherapy<sup>6</sup> (in part

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as a radiosensitizer). Primary chemotherapy has been reported to cause tumor shrinkage in 50% of patients with locally advanced cervical cancer, and subsequent surgery has been feasible in some patients who were initially regarded as inoperable, with perhaps improved outcomes.<sup>4,7-9</sup> Pelvic radiotherapy following primary chemotherapy has not been more toxic than usual; however, evidence of an improved outcome has not been established.<sup>4,6</sup> However, these studies suggest that absence of tumor response after primary chemotherapy identifies patients whose tumors will not respond well to subsequent radiotherapy.<sup>8,10</sup> Major criticisms of most of these trials are the small number of patients included and too early presentation of the data to allow definite conclusions on treatment effects.

We now report the results of a large randomized trial of primary chemotherapy in patients with locally advanced cervical cancer conducted in several countries in South-east Asia over the last 4 years. Our results confirm that primary chemotherapy causes tumor response in a high proportion of patients with locally advanced cervical cancer, and that subsequent radiotherapy in these patients has been uncomplicated. However, our results indicate not only that patient survival is compromised by primary chemotherapy, but also that local treatment failure is more common in patients who receive chemotherapy before radiation. These results indicate that chemotherapy followed by pelvic radiotherapy in patients with locally advanced cervical cancer using standard fractionations is not an advantageous strategy. Altered chemotherapy or radiation fractionation schedules and/or radical surgery should be investigated if primary chemotherapy is to be explored further in women with locally advanced cervical cancer.

## PATIENTS AND METHODS

Eligibility criteria were a histologically confirmed diagnosis of cervical cancer stage IIb to IVa according to the International Federation of Gynecology and Obstetrics (FIGO), age between 30 and 75 years, Eastern Cooperative Oncology Group performance status of 0 to 2, total WBC count  $\geq 4 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , and hemoglobin level more than 10 g/dL or transfused to above that level. In addition, serum creatinine concentration had to be less than 1.5 mg/dL and serum bilirubin level less than 2 mg/dL. Patients had to have no history of significant cardiovascular disease, have had no prior radiotherapy or chemotherapy, and be judged suitable for radical pelvic irradiation. Before entry onto the study, patients had to give informed consent in accordance with institutional requirements.

At trial entry, patients had a standard physical examination and disease was assessed by pelvic examination, usually under anesthetic. Para-aortic nodes were not routinely assessed by imaging techniques or surgical staging. Patients who met the eligibility criteria were randomly assigned to treatment by telephone contact with the randomization center. Following treatment allocation, patients were

required to commence treatment within 2 days. In those who were receiving chemotherapy, pelvic radiotherapy commenced within 3 weeks of the last chemotherapy treatment. Chemotherapy consisted of epirubicin 110 mg/m<sup>2</sup> administered as an intravenous push over 10 minutes and cisplatin 60 mg/m<sup>2</sup> administered as a 2-hour intravenous infusion with fluid loading before and after cisplatin. Antiemetics were given to minimize nausea and vomiting, but no specific anti-emetic treatment was recommended. Chemotherapy was administered at 3-week intervals for a total of three cycles, provided the WBC and platelet counts had reached  $4 \times 10^9/L$  and  $100 \times 10^9/L$ , respectively. If on the twenty-second day after treatment, the WBC count was less than  $3 \times 10^9/L$  or platelet count less than  $70 \times 10^9/L$ , treatment was delayed until these levels had been reached. If these levels had not been reached after a delay of 14 days, chemotherapy was abandoned and pelvic radiotherapy started. Doses of epirubicin were reduced to 50% if the serum bilirubin level increased to between 2 and 3 mg/dL. No epirubicin was administered to patients whose bilirubin level increased to greater than 3 mg/dL. Cisplatin dose was reduced to 50% if the serum creatinine concentration increased to between 1.5 and 2 mg/dL, but no cisplatin was given if the serum creatinine concentration was more than 2 mg/dL.

Pelvic radiotherapy was given according to institutional policy. While there were some variations in technique among institutions, 40 to 55 Gy was given to the whole pelvis over 4 to 5 weeks, with external beam followed by intracavitary treatment of 30 to 35 Gy to point A.

Patients were assessed before each cycle of chemotherapy and during radiotherapy. In patients randomized to receive chemotherapy, if there was no evidence of tumor response or progressive disease after two cycles, chemotherapy was stopped and pelvic radiotherapy commenced immediately. If, on the other hand, there was evidence of tumor response, a third cycle of chemotherapy was given before pelvic radiotherapy was begun. The pelvic radiotherapy protocol was not varied in patients who had received chemotherapy.

Following completion of pelvic radiotherapy, all patients were monitored at 1 month, then every 3 months for 2 years, and then at 6-month intervals. If patients developed recurrent or metastatic disease, the site of first relapse was documented. The pattern of initial tumor relapse was defined as being local (within the irradiated treatment volume), systemic, or both. Patients were monitored until death or date last known to be alive.

Tumor response following chemotherapy and after completion of radiotherapy was assessed by standard World Health Organization (WHO) criteria.<sup>11</sup> Toxic effects attributable to chemotherapy and radiotherapy were recorded.

The protocol proposed to accrue 200 patients, and with a follow-up duration of 2 years, it was estimated that the trial had an 80% chance to detect a 20% improvement in median survival duration.

## RESULTS

Between October 1989 and February 1993, 260 patients with stage IIb to IVa cervical cancer were randomized from participating institutions located in Thailand, Malaysia, Singapore, Hong Kong, Philippines, Korea, Taiwan, and Indonesia. Table 1 lists the clinical and pathologic characteristics of these patients. The two randomized groups were well balanced for known prognostic factors, although more patients in the group that received chemotherapy followed by radiotherapy had stage IIb



Table 1. Patient Characteristics

Characteristic	Chemotherapy Followed by Radiation		Radiation Alone		Total
	No.	%	No.	%	
FIGO stage					
Ib	57	44	67	51	124
IIa	1	1	3	2	4
IIb	69	53	58	44	127
IVa	2	1	2	2	4
Unspecified			1		1
Total	129		131		260
Tumor histology					
Squamous	118	93	118	90	236
Adenocarcinoma	11	9	13	10	24
Age (years)					
Mean	47		52		
Range	26-75		27-78		

tumors. The vast majority of cancers were squamous in histology.

Table 2 lists tumor response results after combined chemotherapy and radiotherapy and after radiotherapy alone. Table 2 also lists responses after chemotherapy and before commencing radiotherapy in patients on the combined treatment arm. In the latter patients, tumor response was documented in 63% before commencing radiotherapy. Following completion of radiotherapy, there was a somewhat higher complete tumor response rate in patients randomized to receive radiotherapy alone compared with combined treatment. Progressive disease following completion of radiotherapy occurred in  $\leq 5\%$  of patients in both treatment groups. The duration of radiotherapy was similar between the two randomized groups.

Table 3 lists the patterns of first disease progression according to randomized treatment. Most patients have

Table 2. Tumor Response and Treatment Details

Variable	Chemotherapy Followed by Radiation				Radiation Alone	
	No.	%	No.	%	No.	%
Tumor response						
Complete response	8	6	55	43	85	65
Partial response	74	57	38	29	35	27
Stable disease	24	19	13	10	1	
Progressive disease	5	4	7	5	4	3
Unknown	18	14	16	12	6	4.5
Total	129		129		131	
No. of cycles of chemotherapy						
Mean	2.6					
Range	0-3					
Days of radiation (mean $\pm$ SD)			47 $\pm$ 14		44 $\pm$ 15	

Table 3. Pattern of First Relapse/First Disease Progression According to Randomization Group

First Site of Treatment Failure	Treatment Group Chemotherapy Followed by Radiation (N = 129)		Radiation Alone (N = 131)	
	No.	%	No.	%
Pelvis (local)	33	26	21	16
Systemic (outside pelvis)	12	9	17	13
Both	4	3	4	3
Unknown	4	3	4	3
Total	53	41	46	35

not relapsed, but treatment failure was most common in the pelvis (62 of 99 patients known to have relapsed). First relapse in the pelvis was seen more often in patients who received chemotherapy before radiotherapy compared with those who received only radiotherapy, but this difference was not statistically significant. Figures 1 and 2 present the time to disease progression or tumor recurrence among the total population and according to randomization group. In 29 patients, the first relapse was at a systemic site only. Figures 3 and 4 present the time to treatment failure in the pelvis according to randomization group and for the entire population. Patients who received primary chemotherapy had a significantly higher pelvic failure rate than patients who received radiotherapy alone ( $P < .003$ ).

Currently, 76 patients have died; Figs 5 and 6 show the survival curves of the total population and according to randomization group. Patients randomized to receive chemotherapy followed by radiotherapy had a significantly inferior survival compared with those who received pelvic radiotherapy alone ( $P = .02$ ). Currently, with a median follow-up duration of 1.3 years, 46 patients are alive with disease and 116 are known to be alive without evidence of recurrent disease.

Nausea and vomiting related to chemotherapy were common, and 14 of 129 patients refused to complete chemotherapy before commencing radiotherapy. Myelosuppression was rarely a cause of treatment delay, and only one patient developed significant myelosuppression that required interruption of treatment. Proctitis and cystitis after radiotherapy occurred equally in both treatment groups.

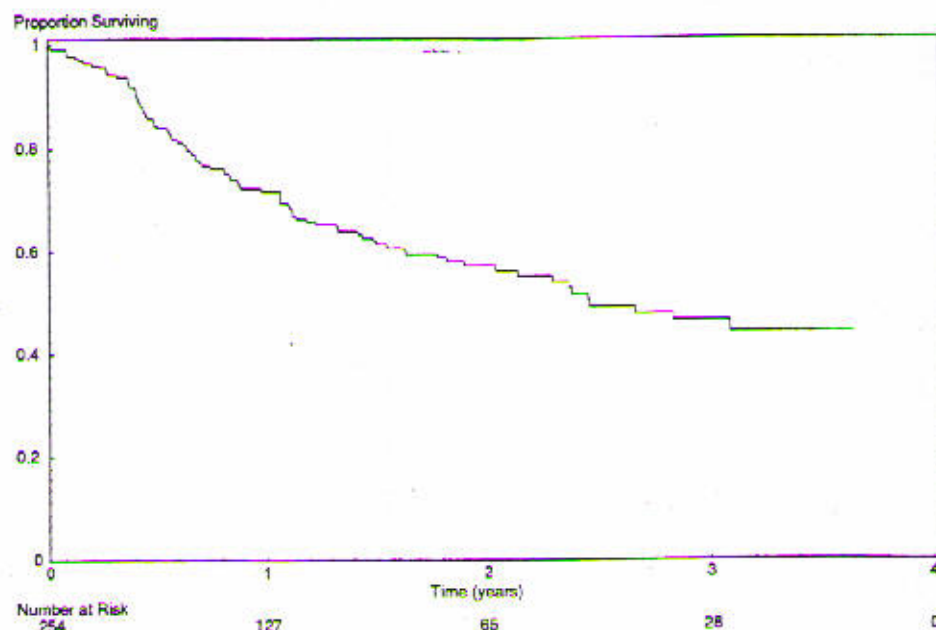
Patient follow-up data are incomplete, with 29 patients having their last known contact before 1992 and 70 before 1993. Results are presented according to patient status when last reviewed.

## DISCUSSION

Radiotherapy controls local disease in most patients with stage Ib to IIa cervical cancer, and treatment failure,



Fig 1. Time to disease progression in the total cohort of 254 patients for whom data were available.



when it occurs, is usually outside the treated volume. However, in patients with more advanced local disease (stage IIb to IVa), although radiotherapy is standard treatment, failure of disease control is common and occurs in a significant proportion of patients due to failure to control disease in the pelvis.<sup>6</sup> Cisplatin-based chemotherapy causes tumor shrinkage in approximately 50% of patients with metastatic cervical cancer.<sup>4</sup> In patients with locally advanced disease who have received primary chemother-

apy, a high rate of tumor shrinkage has also been reported, which has led to the notion that subsequent radiotherapy in these patients may be more effective and may be associated with improved local disease control and/or survival. Randomized trials that have examined the effectiveness of primary chemotherapy followed by radiotherapy versus standard pelvic radiotherapy have, for the most part, been small, and the results have been inconclusive.<sup>4,6,7,12</sup> Our trial, which included more patients

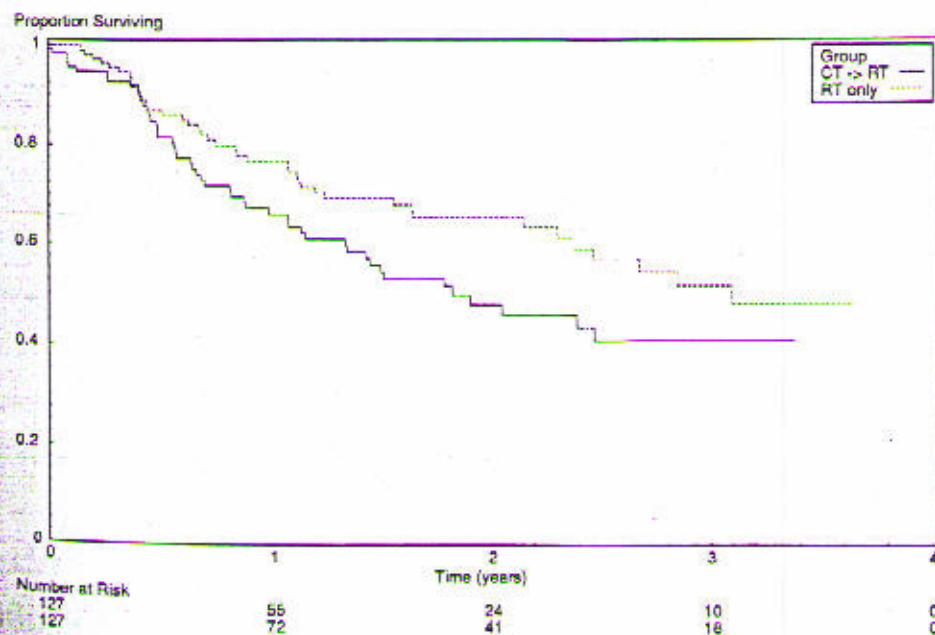


Fig 2. Time to disease progression according to randomization group.

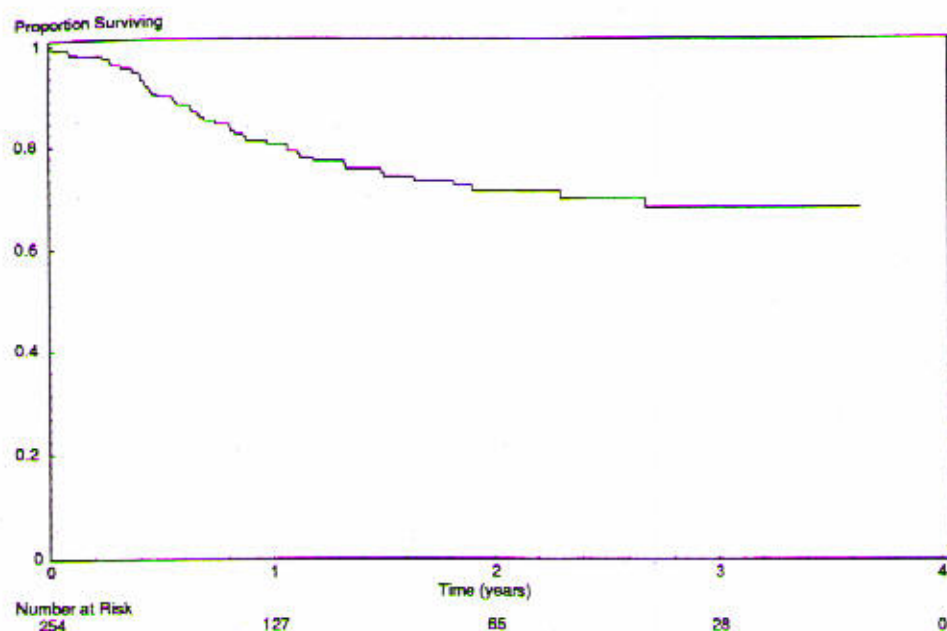


Fig 3. Time to progressive disease within the pelvis in the total group.

than most previous studies, indicates that although tumor response following chemotherapy is common, subsequent radiotherapy is less effective at controlling local disease than is radiotherapy given to patients who have not had previous chemotherapy (Fig 4 and Table 3). Delay in commencement of pelvic radiotherapy in patients who received prior chemotherapy may have contributed to the increased local recurrence rate, but the possibility that the chemotherapy may itself have changed tumor-cell kinet-

ics in the surviving population such that traditionally fractionated radiation treatment was less effective than usual requires further exploration.<sup>13</sup>

The observation that patients randomized to receive primary chemotherapy followed by pelvic radiotherapy had an inferior survival compared with patients who received radiotherapy alone is disquieting, particularly when tumor response following chemotherapy was observed in 63% of patients. These results may be partly

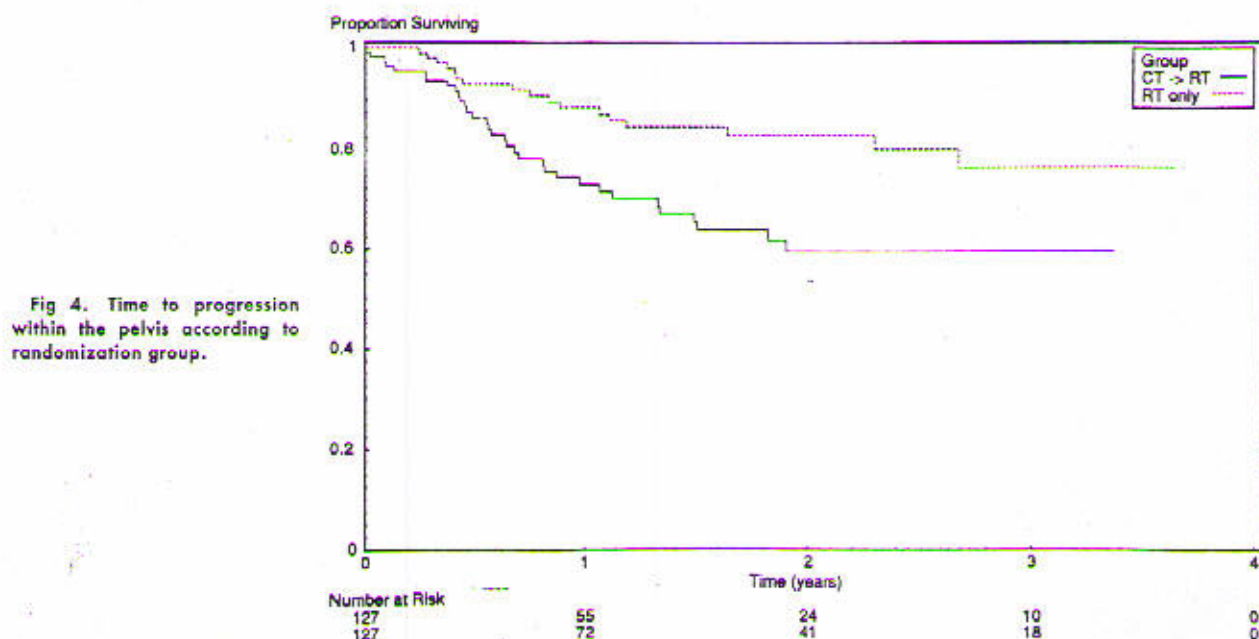
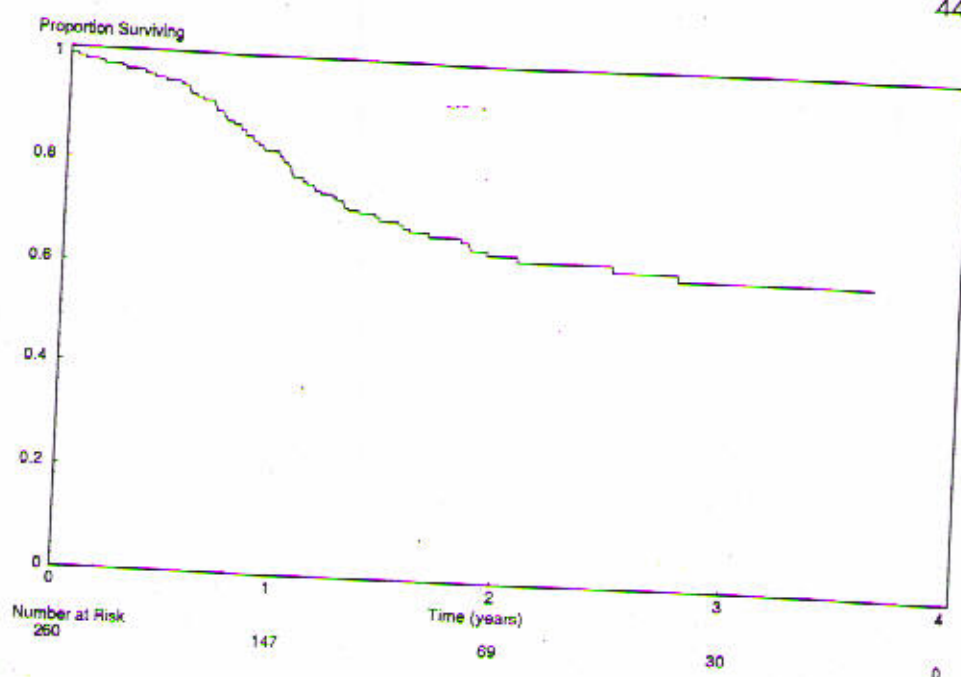


Fig 4. Time to progression within the pelvis according to randomization group.



Fig 5. Overall survival in the total group of 260 patients.



explained by the increased local treatment failures observed in the group, but the fact that first systemic failure was not reduced raises other possibilities.

Some previous reports have indicated that locally advanced cervical cancers that do not respond to chemotherapy commonly do not respond to local radiotherapy.<sup>8,10</sup> The possibility of cross-resistance between cisplatin-based chemotherapy and radiotherapy has been proposed and requires further investigation.<sup>8,10</sup> Our trial indicates

that in those patients who have stable or progressive disease following chemotherapy, subsequently applied radiotherapy is less effective at achieving a tumor response in this setting than in patients whose tumors responded to chemotherapy (Table 2). The observation of an increased local tumor failure rate in patients who received primary chemotherapy suggests that cell kinetic changes following chemotherapy may contribute to treatment failure in the irradiated volume.<sup>13</sup> Shorter-course chemotherapy and/or

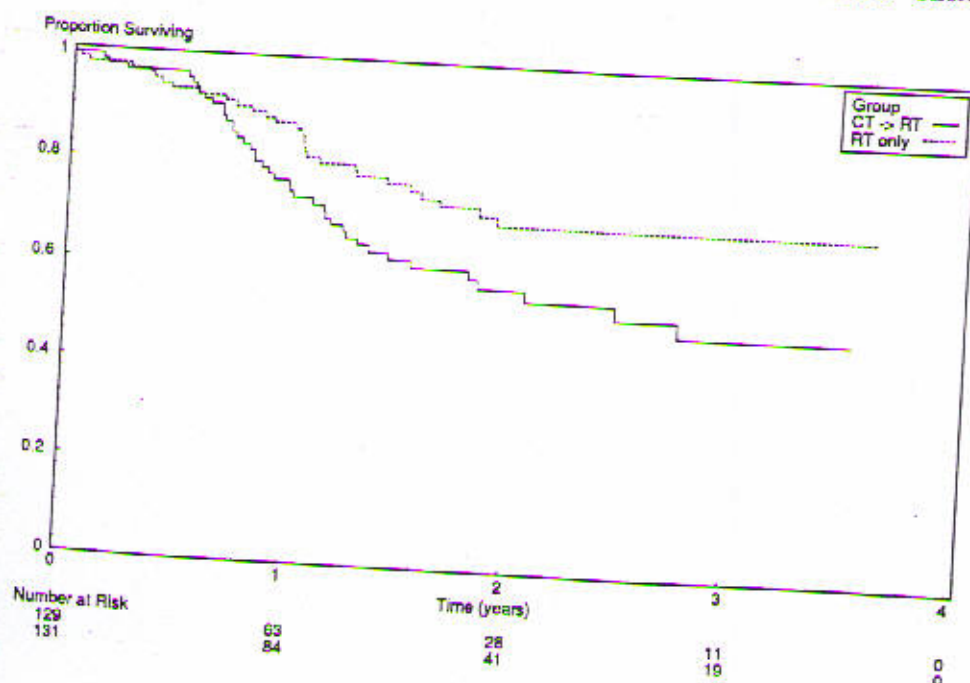


Fig 6. Overall survival according to randomization group.



simultaneous radiotherapy and chemotherapy may be more successful strategies.<sup>9,10</sup>

Previous reports of primary chemotherapy followed by surgery in patients with locally advanced cervical cancer have noted a lower than expected proportion of lymph node metastases in patients who proceed to radical pelvic surgery.<sup>8,9</sup> It is therefore disappointing that our study found no significant change in the proportion of patients who relapsed first at a systemic site compared with those who received only pelvic radiotherapy. It would appear that the problem of systemic disease control has not been solved by the use of epirubicin and cisplatin in our treatment program.

It may be argued that the drugs we chose to investigate in this trial are not the most effective in cervical cancer. Vermorken<sup>4</sup> has noted in a recent review of chemotherapy in cervical cancer that the two most active drugs are epirubicin and cisplatin.<sup>14</sup> Moreover, in a study previously undertaken in patients with advanced disease, we reported a greater than 50% response rate to epirubicin/cisplatin treatment.<sup>15</sup> This chemotherapy regimen is not substantially less effective than any of the other cisplatin-containing regimens reported in the literature to date.

Future research should investigate the use of primary chemotherapy followed by radical surgery. Such a strategy in patients with locally advanced cervical cancer appears to be associated with improved outcomes.<sup>9</sup> Certainly, removal of the primary tumor site after tumor shrinkage caused by chemotherapy may overcome cell kinetic-based changes that may contribute to pelvic radiotherapy being relatively ineffective at controlling local disease in our patient population.<sup>13</sup> Recent reports that primary chemotherapy with growth factor support may lead to increased numbers of circulating tumor cells, at least in some patient groups, raises some additional concerns about the wisdom of this strategy,<sup>16</sup> and should encourage appropriately designed and sufficiently powerful studies to explore this treatment approach.

Many studies that have combined chemotherapy and radiotherapy in cervical cancer have administered the chemotherapy as a radiosensitizer during the early and latter weeks of radiation treatment.<sup>17</sup> Trials currently examining this approach will hopefully have adequate patient numbers to confirm or refute the suggestion from early small studies that this strategy is advantageous. It may also be appropriate to continue chemotherapy after radiation treatment has been completed in the hope that microscopic metastases lying outside the treated volume may be eradicated.

The strategy of combining doxorubicin therapy and radiation therapy, at least in patients with lung cancer, has been associated with enhanced radiation reactions. Our experience that radiotherapy following three cycles of epirubicin and cisplatin was not associated with unexpected local radiation reaction may be due to the different pharmacokinetics of epirubicin compared with doxorubicin, or perhaps to the fact that the radiotherapy was not commenced until epirubicin had been completed.

We conclude that primary chemotherapy with epirubicin and cisplatin causes tumor shrinkage in a significant proportion of patients with locally advanced cervical cancer. However, patients treated with primary chemotherapy and subsequent radiotherapy have an inferior survival and somewhat lower local control rate compared with patients who are treated only by pelvic radiotherapy. We conclude that primary chemotherapy for two to three cycles at 3-week intervals followed by radiotherapy in standard fractionation is a treatment approach that can no longer be recommended in the management of patients with locally advanced cervical cancer.

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