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Adjuvant Chemotherapy versus Chemotherapy plus Pelvic Irradiation for High-Risk Cervical Cancer Patients after Radical Hysterectomy and Pelvic Lymphadenectomy (RH-PLND): A Randomized Phase III Trial[1]

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Objective: To compare the clinical efficacy of adjuvant chemotherapy alone vs chemotherapy plus whole pelvic radiation therapy (RT) on recurrence rates, patterns of recurrence, and survival of patients post-RH-PLND for cervical cancer at high risk for recurrence. Methods: Prospective multicenter randomized Phase III trial. Patients with Stage IB–IIA cervical cancer undergoing RH-PLND were eligible. Risk factors include deep cervical invasion, tumor ⩾4 cm, parametrial involvement, nonsquamous histology, and/or pelvic lymph node metastasis. Chemotherapy consisted of cisplatin and bleomycin, alone or in combination with whole pelvic RT. Survival was determined by Kaplan–Meier estimate. Results: Eighty-nine patients were entered from 1987 to 1994. Seventy-five patients had a Stage IB cancer and 14 patients had Stage IIA. Twenty-five patients had ⩾3 risk factors. Forty-four patients received chemotherapy alone vs 45 patients treated with chemotherapy and RT. Nineteen patients had recurrences and 16 patients have died. Nine of 44 (20%) patients receiving chemo alone recurred compared to 10/45 (22%) patients receiving chemo and RT (P = ns). Patterns of recurrence were statistically similar between the two treatment arms, even among the subgroup of patients with ⩾3 risk factors. Both regimens were well tolerated. Conclusion: CT + RT did not prove a superior adjuvant therapy for patients at high risk of recurrence after RH-PLND for early cervical cancer in this limited trial. Recurrence rates and patterns of recurrences (local, regional, or distant) were not influenced by the addition of RT.

The preferred treatment of women with early-stage cervical cancer (FIGO IA2–IIA) is radical hysterectomy with bilateral pelvic lymphadenectomy. The procedure is well tolerated, with minimal associated morbidity and rare mortality [1–4]. The overall prognosis for patients undergoing radical hysterectomy is good, with reported 5-year survival rates ranging from 75 to 90%. However, among patients with a clinically early cancer, there are prognostic features which identify patients at increased risk for recurrence; recurrent cervical cancer after initial radical hysterectomy and pelvic lymphadenectomy has a poor prognosis, with a reported 5-year survival rate of 5% or less [5].

The clinicopathologic factors which predict a poorer prognosis for patients with an early carcinoma of the cervix have been well established. A retrospective study of patients undergoing radical hysterectomy at Memorial Sloan–Kettering Cancer Center (MSKCC) from 1939 to 1977 identified the following risk factors: metastatic tumor to the pelvic lymph nodes, large cervical tumor, parametrial extension of disease, nonsquamous or grade 3 histology, and deep (>75%) cervical stromal invasion [6]. These factors have been shown to be associated with a high risk of recurrence in other studies, both from single institutions and from cooperative groups [4, 7].

There have been multiple studies published which have retrospectively analyzed the outcome of patients at risk for recurrence who received adjuvant therapy compared to those patients not receiving adjuvant therapy. Whole pelvic postoperative radiation therapy has been found to possibly decrease the incidence of local/regional recurrence with little or no effect on overall survival [8–11]. Chemotherapy plus pelvic radiation has been studied in our institution in a prospective Phase II trial, with an apparent improvement in survival rates when compared to historical controls [12, 13]. Preoperative neoadjuvant chemotherapy has been reported

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as another approach to management of women with early cervical cancer and high-risk features [14, 15]. Few reports have utilized adjuvant postoperative chemotherapy alone after radical surgery for invasive cervical cancer [16]. In an effort to determine whether the improved survival in the Memorial Hospital Phase II trial was due to the combination of chemotherapy plus pelvic radiation therapy or due to the effect of the chemotherapy alone, a multicenter randomized Phase III clinical trial was designed. This report summarizes the preliminary results of the trial which closed to patient accrual in June 1994.

MATERIALS AND METHODS

Patients with clinical Stage IB–IIA cancer of the uterine cervix treated by radical hysterectomy, bilateral pelvic lymphadenectomy, and aortic lymph node sampling were eligible for entry into this prospective study if they had one or more of the following risk factors: (1) metastatic disease to pelvic lymph nodes, (2) large primary tumors greater than or equal to 4 cm in diameter, (3) deeply invasive lesions with 75% or greater stromal invasion, (4) nonsquamous histology, and/or (5) occult parametrial involvement or positive surgical margins. Patients who met the entry criteria were given the opportunity to participate in this clinical trial; entry and initiation of therapy had to be within 6 weeks of the date of radical hysterectomy. Patients were assigned a stage based on International Federation of Gynecologists and Obstetricians (FIGO) criteria [17]. After signing an IRB-approved informed consent form, patients were randomized to receive one of two treatments. One arm consisted of 2 cycles of chemotherapy (given 3–4 weeks apart) utilizing bleomycin 20 U/m^2/day via continuous 24-hr infusion on Days 1–3 after an initial intravenous bolus of 20 U/m^2 followed by cisplatin 75 mg/m^2 by iv infusion on Day 4. Following recovery from the second cycle of chemotherapy, patients received a course of whole pelvic radiation therapy to a dose of 45 Gy, delivered in 20 fractions via a four-field technique; patients did not receive intravaginal therapy. Two additional cycles of cisplatin alone (75 mg/m^2) were prescribed after completion of the pelvic radiation therapy. In the second arm of the study, patients were randomized to treatment with a similar regimen of chemotherapy as described above without pelvic radiation; following the first two cycles of cisplatin and bleomycin, the patient then received the third and fourth treatment of cisplatin alone at 3- to 4-week intervals.

Four centers participated in this clinical trial. At each institution, the protocol was approved by the institutional review board prior to entry of patients; all patients signed an informed consent prior to entry. Central pathology review was not required, although at each institution the specific pathologic criteria for determining depth of invasion were carried out according to written guidelines. Randomization was performed at Memorial Sloan–Kettering Cancer Center by the Department of Biostatistics using an envelope system. Data forms were maintained in a central location, also at MSKCC.

Additional entry criteria included histologic confirmation of negative para-aortic lymph nodes, normal renal function (creatinine clearance of greater than 60 ml/min), normal liver function tests, hemoglobin of greater than 8.0 g/dl, and a normal DLCO pulmonary function test.

At the completion of treatment, patients were followed according to the individual surgeons' preference. Patients with recurrent disease were classified by the site of recurrence and the interval from the date of radical hysterectomy to the date of recurrence.

The initial accrual goal of the trial was 160 patients, with 80 patients randomized to each of the two treatment arms. The null hypothesis considered that the two treatment arms, chemotherapy alone and chemotherapy plus radiation, would both result in 5-year disease-free survival of 70%. The alternative hypothesis considered that chemotherapy alone would result in a 5-year disease-free survival of 20% less or 50% (significance level of 0.05 and a power of 0.80). The estimated duration of the trial when it opened in 1987 was 4–5 years. The trial was closed to patient entry in June 1994 due to less than optimal accrual.

Overall and disease-free survival curves were computed using the method of Kaplan–Meier [18] and the differences in survival were compared by the log-rank method [19].

RESULTS

Between 1987 and 1994, a total of 89 patients were entered into the trial; 45 patients were entered at MSKCC, 24 from

TABLE 1
Patient Characteristics (n = 89)

Mean age	45 years
Range	23–70 years
Stage	
IB	75 patients
IIA	14 patients
Histology	
Squamous	51
Adenocarcinoma	30
Pelvic lymph node metastasis	33
Number of positive-lymph nodes	
1–2	24
>2	9
Bilateral	9
Deep cervical invasion	45
Tumor size ⩾4 cm	33
Parametrial involvement	9
Positive vaginal margins	2
Risk factors	
1–2	64
3+	25

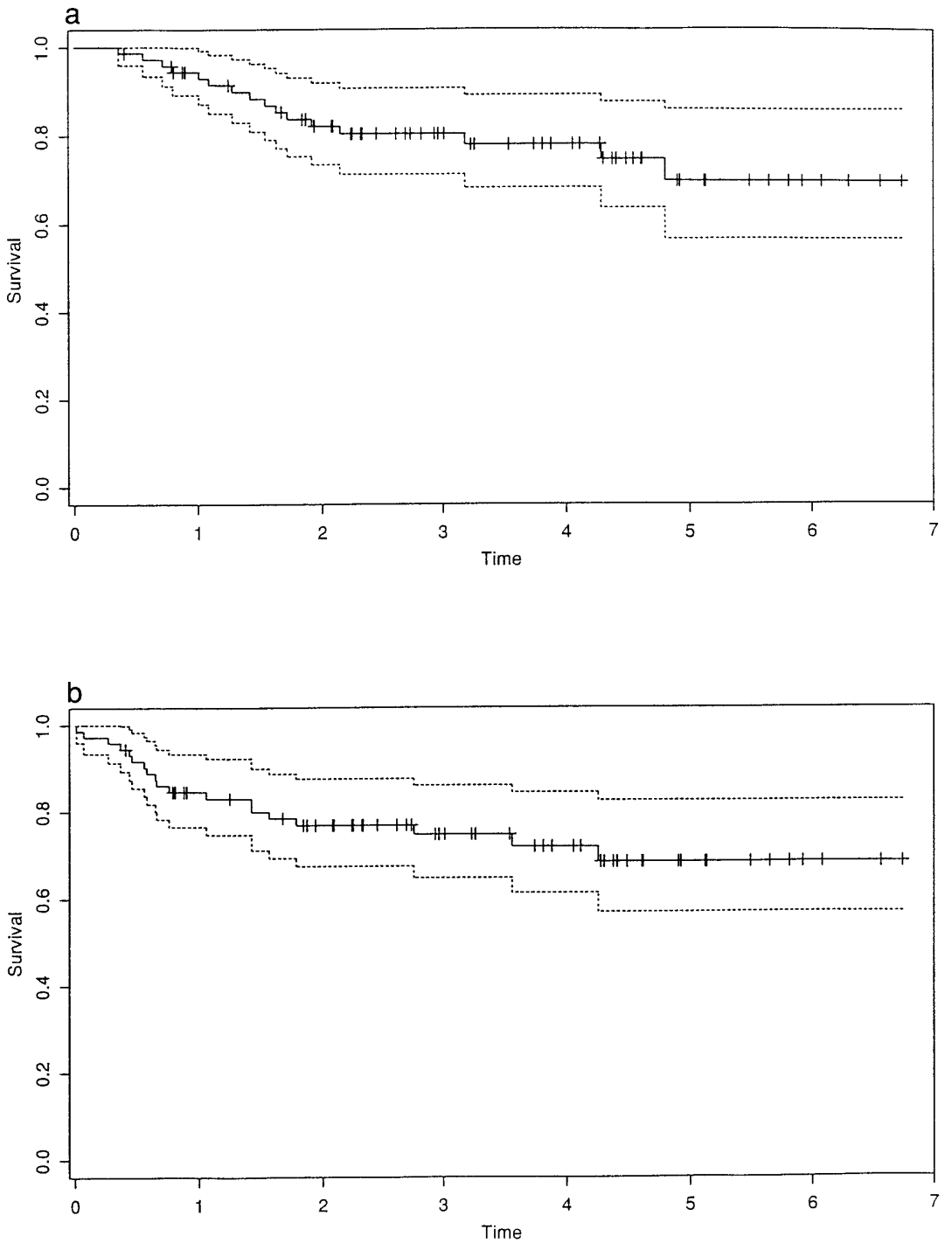

FIG. 1. Overall survival (a) and disease-free survival (b) (solid line) with 95% confidence limits (dotted lines).

the Mayo Clinic, and 10 each from the Uniform Services Health Center and the University of Miami. The average age of the patients was 45 years and patients ranged in age from 23 to 70 years. Seventy-five patients had a Stage IB cervical cancer and the remaining 14 patients had a Stage IIA cancer. All patients met the entry criteria for surgical procedures and had undergone a radical hysterectomy, bilateral pelvic lymphadenectomy, and periaortic lymph node sampling within 6 weeks of entry into the trial. Twenty-five patients had 3 or more high-risk factors and 64 had 1 to 2 risk factors; 33 of these patients had 1 risk factor. Additional histopathologic features of the patients are presented in Table 1.

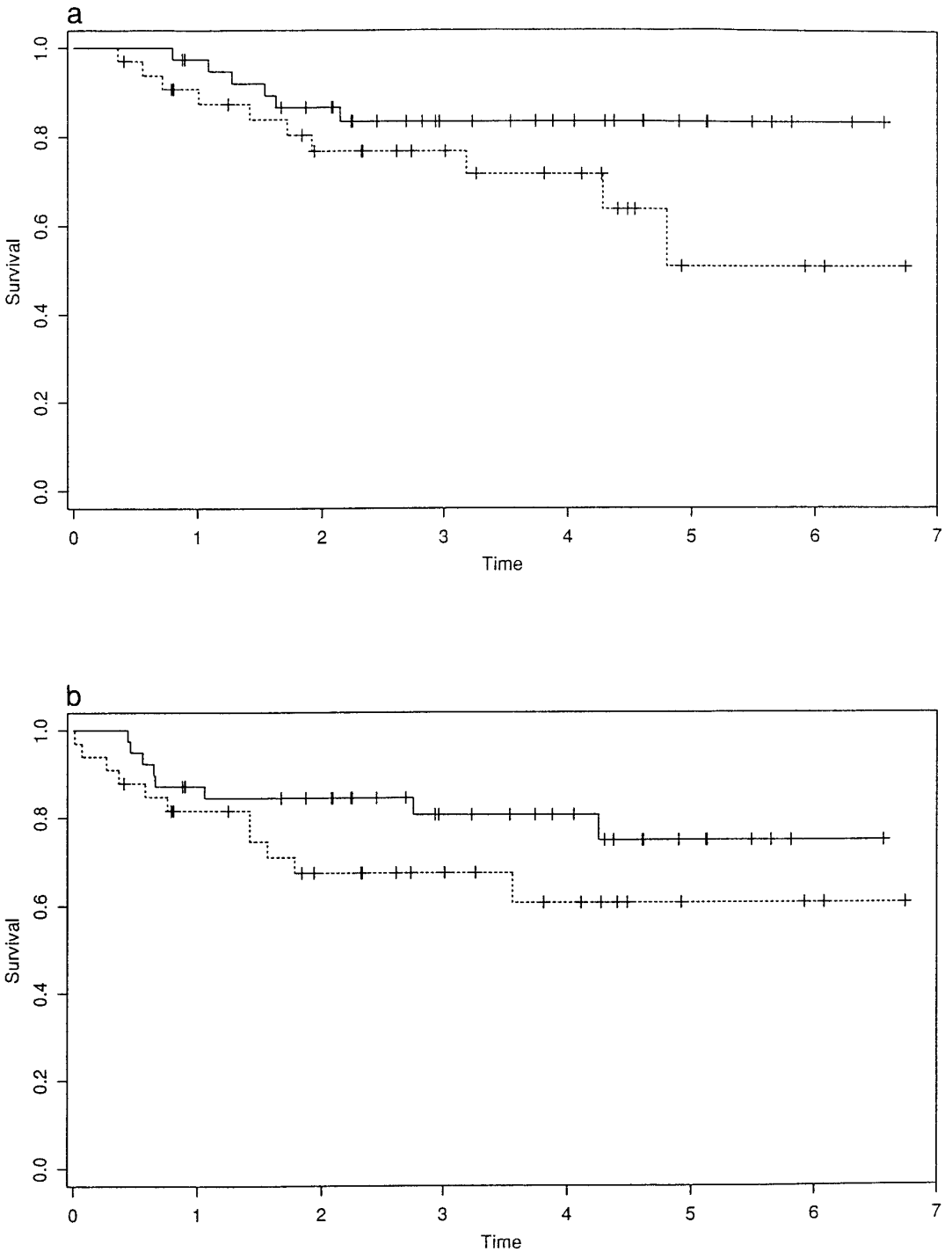

FIG. 2. Overall survival (a) and disease-free survival (b) by treatment (P = ns) (solid line, chemotherapy alone; dotted line, chemotherapy plus radiation therapy).

Forty-five patients were randomized to the chemotherapy plus radiation therapy treatment arm and 44 patients received chemotherapy alone. There were 12 major protocol violations, including 7 patients who were randomized (6 to chemotherapy plus radiation therapy and 1 patient to chemotherapy alone) and then either refused treatment (n = 6) or were withdrawn by the institutional principal investigator due to poor medical condition of the patient (n = 1). Five of 12 patients received only a portion of the proscribed treatment; one patient, randomized to chemotherapy, withdrew after experiencing an allergic bleomycin reaction during the initial infusion of bleomycin during cycle 1. Four patients random-

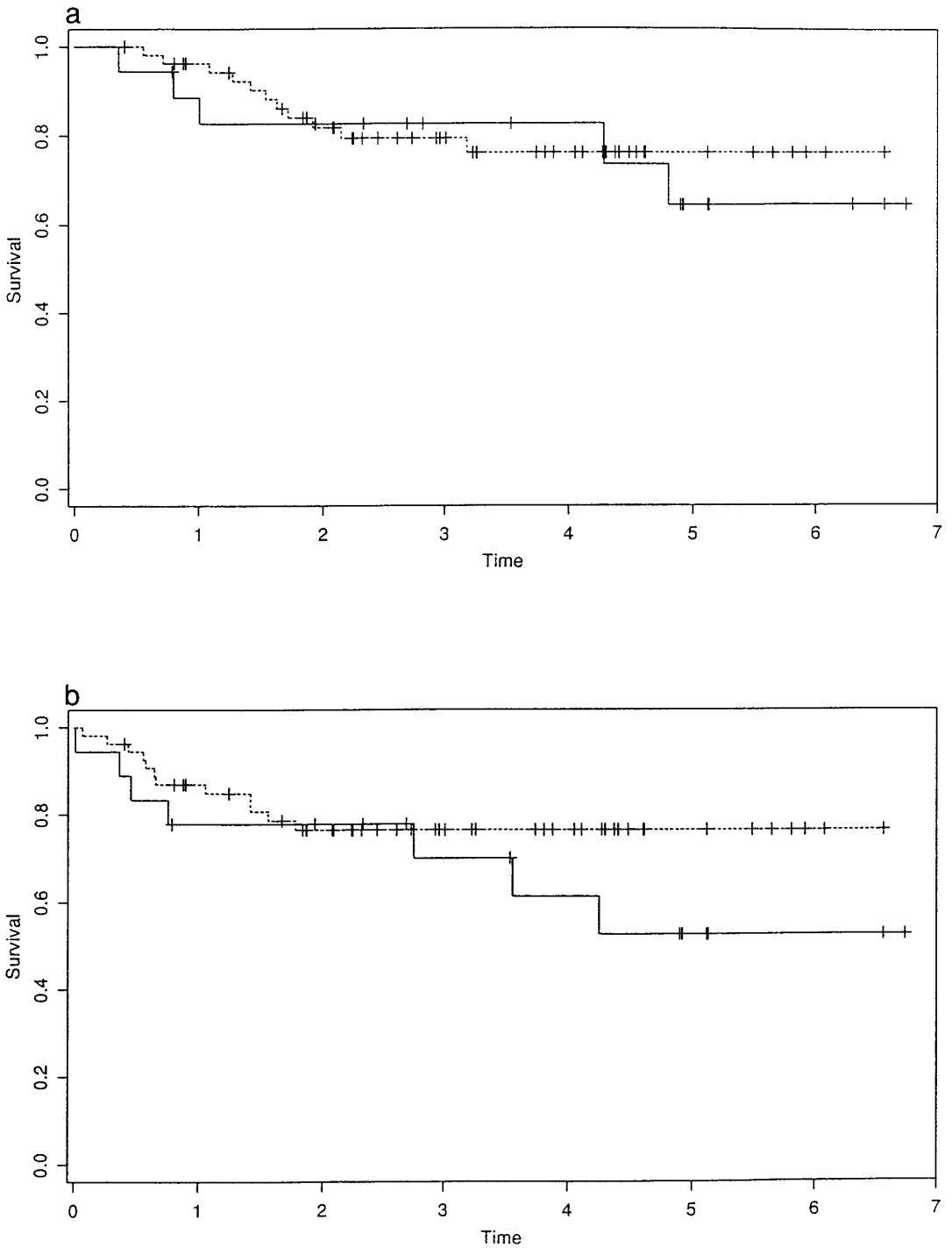

FIG. 3. Overall survival (a) and disease-free survival (b) by risk factors (P = ns) (solid line, 3 or more risk factors; dotted line, 1–2 risk factors).

ized to chemotherapy plus radiation refused either the radiation therapy ($n = 3$) or had a major violation in the radiation therapy treatment plan when intravaginal radiation therapy was administered, and she did not receive the last 2 cycles of cisplatin ($n = 1$).

Among the 77 patients evaluable for response, 5 were lost to follow-up or had no follow-up data available for analysis. Thus, there were 33 patients who received the combination of chemotherapy and pelvic radiation and 39 who received chemotherapy alone who could be evaluated for disease-free and overall survival. Overall survival and disease-free survival curves are presented in Fig. 1. At a median follow-

TABLE 2
Risk Factors and Recurrence

Number of risk factors	Risk factors	Stage	Site of recurrence	Status
	Chemotherapy only (n = 9)			
1	Depth inv	IB	Local	DOD
1	Size	IB	Local	DOD
2	Depth inv, PLN/pos (1)	IB	Local	DOD
2	Depth inv, margin pos	IIA	Local	DOD
2	Adenoca, PLN/pos (1)	IB	Local	DOD
3	PLN/pos (6), size, depth inv	IB	PSW	AWD
3	Size, depth inv, PLN/pos (2)	IB	Local and mets	DOD
3	PLN/pos (2), depth inv, pos parametria	IB	Local and distant	AWD
4	PLN/pos (1), depth inv, pos parametria, size	IB	Local	AWD[a]
	Chemo and radiation therapy (n = 11)			
1	Adenosquamous	IB	Local	AWD[b]
1	PLN/pos (1)	IB	Local	DOD
1	Size	IB	Local	DOD
1	PLN/pos (1)	IB	Distant	DOD
1	PLN/pos (2)	IB	No recurrence	Died (renal failure)
2	Depth inv, pos parametria	IIA	Local	DOD
2	PLN/pos (1), adenoca	IB	Local	DOD
3	PLN/pos (5), adenoca, depth inv	IB	Rt PSW	DOD
3	Depth inv, PLN/pos (1), size	IIA	Local	DOD
3	Depth inv, pos parmetria, size	IB	Local	DOD[c]
4	Adenoca, PLN/pos (16), depth inv, size	IB	Local and distant	DOD

Note. Abbreviations: PLN, pelvic lymph nodes; DOD, dead of disease; AWD, alive with disease; PSW, paracolic side wall; mets, metastasis
[a] Violation: Refused treatment after first cycle.
[b] Recurred prior to start of radiation therapy.
[c] Inevaluable: Recurrence within 1 week of radical hysterectomy.

up of 36 months (range 4–81 months), 19 patients have histologic documentation of recurrent cervical cancer. There has been no significant difference in disease-free survival between the two treatment groups (Fig. 2); 10 patients in the chemotherapy plus pelvic radiation therapy arm have experienced recurrences compared to 9 recurrences in the group of patients treated with chemotherapy alone. Among patients with 3 or more risk factors, there was also no difference in the disease-free survival or overall survival when compared to patients with 1–2 risk factors (Fig. 3). Patterns of recurrence did not appear to be significantly different, as presented in Table 2.

Toxicity was tolerable in the two treatment arms. Most acute toxicity was generally of a minor level related to anticipated toxicity of cisplatin and bleomycin. Major toxicity included one patient who did not receive the second cycle of bleomycin due to the onset of pulmonary symptoms and a significant decrease in pulmonary function compared to a pretreatment study. One patient had the fourth cycle of cisplatin held due to persistent grade 3 neutrophil toxicity (grade 3 = neutrophil count $<$ 1000 cells/mm^3). Two patients experienced significant toxicity secondary to the pelvic radiation therapy; 1 patient received 3780 cGy of 4500 cGy planned dose when treatment was stopped due to a severe skin reaction. One patient developed radiation proctitis requiring a colostomy after completion of the prescribed dose of pelvic radiation therapy.

DISCUSSION

The debate regarding the role of adjuvant therapy for patients at high risk for recurrence after radical hysterectomy for an early-stage cervical cancer has generally focused on whether radiation therapy alone is beneficial in reducing recurrence rates. Radiation therapy alone probably reduces the incidence of local and regional recurrences but does not affect the overall survival [8–10]. Monk and colleagues suggest that a 65% 5-year survival rate after therapy combining radical hysterectomy, pelvic lymphadenectomy, and postoperative pelvic radiotherapy for patients with pelvic lymph node metastases is an improvement compared to historical controls [11]. However, many patients who have these risk factors are at an increased risk for early, subclinical dissemination of disease which will not be affected by radiation therapy directed to the pelvis. The rationale for adding chemotherapy to the pelvic radiation is to provide systemic

cytotoxic agents active against cervical cancer with the potential to eradicate micrometastasis. In the Memorial Hospital pilot trial of the combination of chemotherapy plus pelvic radiation, there was a promising improvement in outcome when compared to historical controls who had received pelvic radiation alone [12, 13]. Killackey *et al.* reported no recurrences among 22 patients with cervical cancer at high risk after radical hysterectomy utilizing a similar treatment regimen consisting of chemotherapy plus pelvic radiation therapy [20]. Tattersall *et al.* were unable to demonstrate a difference in disease-free or overall survival in 71 patients randomized to either pelvic radiation versus chemotherapy plus pelvic radiation after radical hysterectomy for Stage IB–IIA cervical cancer [21].

The rate or recurrences among all the patients in the trial validates the selection of the entry criteria as high-risk factors. The risk factors did not appear to be additive, since the disease-free and overall survival were similar when patients with 1–2 risk factors were compared to those patients with 3 or more risk factors. Twelve of the 19 recurrences were either local recurrences only or local plus distant metastases, with no difference in the number of local occurrences between the two treatment arms. This finding is somewhat surprising since there was no apparent effect of the addition of pelvic radiation to the treatment regimen.

The closure of this clinical trial prior to completion of the accrual goal was disappointing. The initial statistical prediction was that in order to show a 20% improvement in survival of one treatment over the other, 80 patients were needed in each treatment arm. The analysis of the data from the 89 patients entered is not able to document that the two treatments are equivalent, but must be taken to suggest that the likelihood of finding a significant difference between these two treatment modalities in a full trial of 160 patients is small. The investigators hope that future cooperative group trials will consider a chemotherapy-only treatment arm in any studies addressing the role of adjuvant therapy after radical hysterectomy for patients at high risk for recurrence. The advantages of eliminating the radiation therapy component of postoperative therapy are apparent in that the duration of treatment is shorter, costs are reduced, and the long-term side effects of pelvic radiotherapy after radical pelvic surgery are eliminated. Additionally, if the patient does experience a local or regional recurrence after chemotherapy, pelvic radiation therapy still has curative potential. Investigators who design adjuvant trials for patients at high risk for recurrence after radical hysterectomy for invasive cervical cancer must balance the potential benefit to be gained by a minority of patients against the risks inherent in treating all patients.

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