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A Randomized Trial of Standard versus Partially Hyperfractionated Radiation with or without Concurrent 5-Fluorouracil in Locally Advanced Cervical Cancer

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The objective of this study was to determine whether the addition of concurrent 5-fluorouracil (5-FU) and/or a change in radiation fractionation improves pelvic control and survival or decreases complications in advanced cervical cancer, FIGO stages IB/IIA (⩾5 cm) to IVA inclusive. After stratification by pelvic disease extent, 234 of a planned 292 patients were randomized to receive one of four possible treatments: (a) standard external beam pelvic irradiation (RT) 5000 cGy in 25 fractions versus (b) RT as in arm (a) with infusional IV 5-FU 1g/m^2 daily in the first and last 4 days of RT, (c) partially hyperfractionated RT, 5280 cGy in 33 fractions, two fractions per day on the first and last 4 days of RT, or (d) arm (c) with the same FU. All were followed with a linear source of intracavitary RT to deliver 40 Gy. The median duration of follow-up for the 221 evaluable patients was 59 months. The 5-year Kaplan–Meier disease-free survival (DFS) in arm (a), (c), (d), and (b), respectively, were 45, 53, 58, and 61%. The differences in survival and pelvic control were not statistically significant. An exploratory subset analysis was performed within stratum 1 and stratum 2 to generate hypotheses for future studies. Only for the 99 patients in stratum 1 (IB/IIA or medial parametrial IIB disease) was the 5-year DFS significantly better (long rank $P = 0.05$) for standard RT and 5-FU. The DFS was 39% for arm (a), 76% for arm (b), 58% for arm (c), and 65% for arm (d). A multivariate analysis of patient, tumor, and treatment related prognostic factors identified only the use of 5-FU to account for the observed difference. The crude serious late bowel or bladder complication rate was 5.9%. Overall concurrent infusional 5-FU was not beneficial when added to standard RT in this study. The possible benefit for patients in stratum 1 requires exploration in a further randomized trial with appropriate accrual.

INTRODUCTION

Radical external beam plus intracavitary radiation continues to be the standard therapy for advanced cervical cancer to which all new therapies must be compared. While this treatment is relatively effective in small volume tumors, tumor control and survival decline as the bulk of pelvic disease and FIGO stage advance. Overall 5-year survival rates are reported for stage IIB cancers between 50 and 80% and from 25 to 50% for stage III [1–4]. No substantial improvements have been made in the treatment of advanced cervical cancer in the past two decades. An analysis of the patterns of failure after radiation therapy in locally advanced cervical cancer reveals that of those who recur over 70% have some component of pelvic failure as the first site of relapse and two-thirds develop some component of distant disease. As the bulk of pelvic disease increases, the proportion of patients with disease recurrent or persistent in the pelvis as the only site of failure increases compared to the proportion developing distant metastases. The problem of enhancing pelvic control and survival cannot be approached simply by increasing conventionally delivered radiation dose since late complications produced by radiation are at the upper limit of acceptability with currently employed doses.

Many investigations are ongoing to identify more effective treatment. These include modifications of radiation treatment volume or fractionation including extended field radiation [5, 6], hyperfractionated RT [7], strategies to overcome the negative impact of tumor hypoxia such as hyperbaric oxygen [8, 9], or hypoxic cell radiation sensitizers [10, 11]. In addition to modifications of radiation therapy multiple studies have investigated, and are investigating, strategies that combine radiation with chemotherapy either as neoadjuvant or concurrent administration [12–17]. The results reported for trials of neoadjuvant cisplatin-containing chemotherapy prior to radiation have been disappointing with six randomized trials [12–14, 16, 17], showing no advantage in local control or survival and possibly some detrimental effect.

Concurrent chemotherapy with radiation offers a number of theoretical advantages over those of the neoadjuvant strategy. These advantages include no delay in the start of definitive irradiation, no prolongation of overall treatment time (thus minimizing the theoretical risk of accelerated clonogen proliferation during the antineoplastic course), and possible interaction of the concurrently administered chemotherapy with radiation through such mechanisms as inhibition of repair of radiation damage, cell synchronization, recruitment of nonpro-

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liferating cells into cell cycle, and reduction of the hypoxic fraction [18]. Chemotherapy may also, as in the neoadjuvant strategy, have an independent, additive cytotoxic effect. Theoretical disadvantages of concurrent administration include increased acute toxicity which might limit or delay the delivery of definitive irradiation or increased late toxicity particularly if the drugs and radiation do not exhibit ''toxicity'' independence [18]. Last, it is unlikely that concurrent chemotherapy usually given as only one or two doses would significantly reduce established distant micrometastases. To date, the only reported randomized studies of concurrent therapy are those of hydroxyurea and radiation versus radiation alone [10]. While these studies suggested some benefit for patients with FIGO stage IIIB cancer, methodological problems in the study have not resulted in wide acceptance of the conclusion of benefit from concurrent hydroxyurea and its concurrent use has not entered standard practice [10, 19].

Interest in infusional 5-fluorouracil (5-FU) with or without other agents such as mitomycin C and cisplatin, developed from both laboratory data suggesting enhanced tumor cell kill over radiation alone and clinical data. The success of concurrent regimens with these agents in patients with squamous cell carcinomas of other sites such as the anal canal [20, 21] and esophagus [22] suggested that similar regimens were worthy of exploration in carcinomas of the cervix.

In vitro data suggested that the addition of infusional 5-FU to radiation therapy would enhance the radiation effect [23]. Nakajima *et al.* also had shown that enhancement could be improved by increasing the concentration of 5-FU [24]. The optimal dosing schedule for maximizing cell kill with infusional 5-FU and radiation remains undefined, but laboratory data suggested greater effects with increasing dose and prolonged exposure to 5-FU and when drug was present for intervals in excess of 48 h after radiation [23, 24].

An earlier extensive phase I/II study of radical irradiation and infusional 5-FU based on the *in vitro* information established a safe regimen with acceptable toxicity for comparison in this randomized study [25].

MATERIALS AND METHODS

Between May of 1987 and August of 1995, 234 patients predominantly from two centers, with others participating, were stratified by their extent of pelvic disease and randomized to receive one of four possible treatments. The original statistical design required 292 patients but the study was closed early due to poor accrual. Stratification was based on a retrospective analyses which defined subgroups with different prognoses based on a combination of FIGO stage and pelvic disease volume [26]. All patients were to have tumors 5 cm or greater regardless of FIGO stage (stages IB, II, IVA). Stratum 1 included those with FIGO stage IB/IIA or stage IIB with parametrial involvement limited to one or both *medial* parametria. Stratum 2 included those with FIGO stage IIB disease with any lateral parametrial involvement or stage IIIB with involvement of one pelvic sidewall. Stratum 3 included those with FIGO stage IIIB and bilateral pelvic wall involvement or stage IVA. Eligible patients were to have biopsy proven invasive carcinoma of the cervix of any pathological type excluding small cell carcinoma and to have primary radiotherapy with curative intent selected as their definitive treatment. Exclusion criteria included preexisting malignancy except basal or squamous cell carcinoma of the skin. A screening chest X-ray was to be negative for metastases and if lymphography or abdominal CT scanning was performed, there should be no apparent evidence of involvement of the para-aortic nodes. The protocol was reviewed by the ethics committees of the involved universities and hospitals and patients gave informed consent for study. Patients were randomized to receive either (a) standard external beam pelvic irradiation (EBRT) in a dose of 5000 cGy in 25 fractions defined at 100% versus, (b) RT as in arm (a) with infusional intravenous 5-FU in a dose of 1 g/m^2 daily on the first and last 4 days of RT, (c) partially hyperfractionated RT, 5280 cGy in 33 fractions, 2 fractions per day on the first and last 4 days of RT, or (d) arm (c) with the same infusional 5-FU. After EBRT all patients were planned to receive low dose rate intracavitary irradiation to deliver a dose of 40 Gy at point A.

The radiation energy to be used was 6 MeV or greater. Patients were treated prone preferably using a four-field box technique, or a parallel pair. A posterior midline attenuator of two half value layers, 3 cm in width at the midplane of the pelvis was used to reduce the dose to the bladder and rectum. The attenuator was used throughout the treatment course in those treated with a box technique and for half the fractions in those treated with a parallel pair. The partially hyperfractionated radiation fractionation schedule used equal fraction sizes of 160 cGy. Twice daily treatments on days 1 to 4 and 22 to 25 were delivered at least at 6 h apart. The superior border of the radiation treatment volume was the L5/S1 junction, the inferior, the bottom of the obdurator foramina, or 2 cm below the lowest identified extent of vaginal disease. Laterally the fields included, with a 1-cm margin, the pelvic sidewall lymph nodes visualized by lymphography. Where lymphography was not performed, the lateral margins were 2 to 2 $\frac{1}{2}$ cm wider than the bony pelvis. The anterior border of the lateral fields was in front of the symphysis pubis, while the posterior border was tailored to the clinical evaluation of the presence or absence of utero sacral disease extension. If necessary to encompass disease, the volume could include the entire rectum. Intracavitary irradiation was to be delivered as soon after external beam therapy as possible using a linear source without colpostats, usually of cesium-137. It was loaded to extend at least 2 cm above the clinically identified superior extent of disease and inferiorly to 1 cm below the cervix or 1 cm below the lowest extent of vaginal disease identified after external therapy. For rare patients with disease extension to the lower one-third of vagina, the first application to the cervix and uterus was mod-

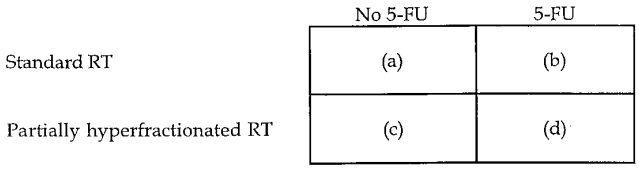

FIG. 1. Study treatment arms.

ified to deliver 30 Gy at 2 cm from the center of the sources and a second application as a line source in the vagina, was used to deliver a further 20 Gy at 0.5 cm depth from the surface of the vagina. 5-FU was given as an infusion from days 1 to 4 inclusive and on treatment days 22 to 25 inclusive. Where possible, chemotherapy infusion was given on four consecutive days without a weekend break. If a weekend break was necessary, the infusion was only given on radiotherapy treatment days. In the latter years of the study, the 5-FU infusion was given in the outpatient setting by continuous infusion pump. Appropriate guidelines for 5-FU dosage reduction or elimination were recommended for hematologic or mucosal toxicity, but RT interruptions were not.

Statistical Methods and Study Design

The outcomes of interest in this study were pelvic control, survival, and disease-free survival, as well as the serious late complication rate. Figure 1 demonstrates the study design, the four-arm study was designed to determine whether any significant differences in outcome were evident between arms (a) and (d) and to be explanatory with respect to causation. Two factors were altered in arm (d) compared to standard arm (a):

(1) the addition of 5-FU,
(2) the change in radiation fractionation scheme.

If differences were to be observed in pelvic control and survival in arm (d) versus arm (a), this could be due to a change in either or both factors. A factorial design was planned to test to what degree observed differences were attributable to either factor. Assuming that the magnitude and direction of the 5-FU effects were similar in arms (b) and (d) then the effect of the addition of 5-FU could be tested by comparing arms (b) and (d) with arms (a) and (c). The reduced fraction size in arms (c) and (d) was designed to attempt to take advantage of knowledge of the affect of fraction size on late complications and to determine whether complication rates were decreased by using decreased fraction size [27]. Additionally, the changed fractionation scheme with delivery of two fractions daily at the beginning and end of therapy was designed to maximize the potential for interaction between 5-FU and radiation and to potentially reduce complication rates [25]. The effect of the fractionation was to be tested by comparing arms (c) and (d) with arms (a) and (b) (Fig. 1). In order to detect a 20% improvement in pelvic control rate from an expected 50% for arm (a) to 70% for arm (d) assuming an alpha of 0.05 and beta of 0.20, 73 patients in each of four treatment arms would be required for a total of 292 patients. In order to detect an improvement of 15% in survival in arms (c) and (d) compared to that seen in arms (a) and (b), assuming a 40% cause-specific survival rate in arm (a) and an alpha of 0.05 and beta of 0.2, the total number of patients required was 272.

The ''Lifetest Procedure'' in SAS UNIX was used to compare survival curves. This procedure uses the Kaplan–Meier method that calculates the ranked test pooled across the strata adjusting for strata differences. Additionally, statistics testing homogeneity over strata were computed and checked. The Kaplan–Meier method was used to calculate median follow-up duration, censoring patients who died. Cox's proportional hazards model was used to examine the variables which might contribute to pelvic control or survival within stratum 1. Where information was missing for some parameters, single models were fitted for these parameters. Where the data were complete, the stepwise regression method was used to identify the relevant prognostic factors.

Because patient accrual slowed considerably in the latter years of the study due to multiple factors including a decline in eligible patients, the study was terminated prior to reaching the planned accrual goal.

Complications

Complications were considered acute and severe if occurring during or within 3 months from the end of radiation therapy and requiring hospitalization, e.g., diarrhea. Severe late or chronic bowel symptoms were those of fistula, perforation, stricture, or obstruction requiring hospitalization or surgery and bleeding requiring transfusion. Severe bladder symptoms were any condition requiring surgery, e.g., fistula, or hematuria requiring transfusion. Oral mucositis due to 5-FU was graded on a scale of 0 to 4: (1) pain without frank ulceration, (2) ulceration present but able to eat, (3) ulceration requiring a liquid diet, (4) alimentation not possible. Cytopenias were classed as grade 3 if bleeding or infection/fever occurred due to low blood counts and grade 2 if neutrophils were less than 1000 units/L or platelets less than 50,000 units/L.

RESULTS

Of the 234 patients randomized, 221 were evaluable. The reasons for exclusion were the presence of extrapelvic disease at presentation in 7, patient refusal after randomization in 4, and missing chart/information in 2. The number excluded in each stratum were 6 in stratum 1, 3 in stratum 2, and 4 in stratum 3. The median age of the patients was 48 years with a range of 23 to 85 years. For strata 1 and 2 the distribution of FIGO stage, tumor size, nodal involvement on lymphography, tumor grade, and capillary lymphatic space involvement (CLS) for each treatment are shown in Tables 1 and 2. Ninety-nine patients were in stratum 1, of which 46 were stage IB/IIA and

TABLE 1
Stratum 1

	(a) Standard RT	(b) Standard RT + FU	(c) ''Partially'' hyperfract'd	(d) ''Partially'' hyperfract'd RT + FU
Patient No.	27	27	22	23
Size %				
5–6 cm	74	56	77	69
>6 cm	26	44	23	31
FIGO Stg (%)				
IB/IIA	52	37	45	52
IIB	48	63	54	48
Nodes (%)				
Negative	74	70	59	69
Positive	26	30	41	31
CLS inv. %				
No	56	59	41	57
Yes	−15	15	9	13
N/S	29	26	50	30
Tumor Gr. (%)				
1 and 2	63	56	50	48
3	22	37	27	43
N/S	15	7	23	9

Note. Distribution (percentage) of clinical/pathological characteristics within stratum 1 by treatment assigned. N/S, not stated; CLS, capillary lymphatic space.

53 were stage IIB. One hundred and five were in stratum 2, of which 38 were stage IIB and 63 stage IIIB. Only 17 were in stratum 3. In view of the small number of patients in stratum 3, a detailed breakdown of possible tumor prognostic factors is not shown. The median duration of follow-up for the whole population is 59 months (95% confidence interval, 57 to 66 months). The median size of tumor was 6.5 cm (range 3.5 to 18 cm). The median tumor size in stratum 1 of 6 cm was large despite the relatively earlier FIGO stage compared to stratum 2. The median tumor size in stratum 2 was 7 cm.

One hundred and ninety of 221 patients received external beam radiation using the box technique, while 31 were treated with a parallel pair. Intracavitary radiation was used in all but 19 of the 221 patients. Compliance with the planned radiation schedules was good. In the ''standard arm'' (a), 53 of 54 received the prescribed tumor dose of 50 Gy in 25 fractions. In the ''partially hyperfractionated irradiation arm'' (c), two patients had radiation dose violations, one a dose of 50 Gy in 25 fractions and the other a dose of 59 Gy in 33 fractions. In the standard radiation plus 5-FU arm (b), 52 of the 53 patients received the standard dose prescription. In the ''partially hyperfractionated RT with 5-FU arm'' (d), 3 of 58 received nonprescribed doses of 46 Gy to 52 Gy in 29 to 32 fractions. Of the 23 patients who received no intracavitary radiation or doses less than 500 cGy, there was a relatively even distribution across the treatment arms with 5 in arm (a), 5 in arm (b), 3 in arm (c), and 9 in arm (d). Seven of these 23 patients received a compensatory boost of external radiation in doses of 6 to 16 Gy.

The histopathology was not centrally reviewed. One hundred and eighty-seven of 221 patients had squamous cell carcinoma, 17 adenocarcinoma, 12 adenosquamous, and the remainder clear cell or unclassified. Tumor was grade 1 in 8 of 221 (4%), grade 2 in 106 of 221 (48%), and grade 3 in 75 of the 221 (34%). Grade was not stated in 32 of 221. Capillary lymphatic space (CLS) involvement was commented on in 146 of 221 (66%). CLS involvement was found in 34 of the 146 (23%).

Compliance with planned chemotherapy administration was good. Of the patients randomized to receive standard radiation with 5-FU, four received no chemotherapy and three received less than 1 g/m^2 with each course. In patients randomized to receive hyperfractionated irradiation and 5-FU, three received no chemotherapy and three received less than 1 g/m^2 with each course.

Pelvic Control and Survival

With a median duration of follow-up of 59 months, 119 of 221 patients are alive, 111 without evidence of disease, and 8

TABLE 2
Stratum 2

	(a) Standard RT	(b) Standard RT + FU	(c) ''Partially'' hyperfract'd	(d) ''Partially'' hyperfract'd RT + FU
Patient No.	22	23	28	32
Size %				
5–6 cm	41	35	32	25
>6 cm	59	65	57	63
FIGO Stg (%)				
IIB	23	39	36	44
III	77	61	64	56
Nodes (%)				
Negative	68	74	71	75
Positive	32	26	29	25
CLS inv. %				
No	69	39	57	47
Yes	18	22	18	16
N/S	13	39	25	37
Tumor Gr. (%)				
1 and 2	59	39	57	44
3	32	48	36	34
N/S	9	13	7	22

Note. Distribution (percentage) of clinical/pathological characteristics within stratum 2 by treatment assigned. N/S, not stated; CLS, capillary lymphatic space.

TABLE 3
Overall Disease-Free Survival (DFS) and Pelvic Control and for Each Stratum

	5-Year Kaplan–Meier DFS %	5-Year Kaplan–Meier pelvic control %
Overall	55	66
Stratum 1	60	75
Stratum 2	52	61
Stratum 3	37	37

with disease present. Eighty-four have died of disease and 4 have died of other causes with disease present. For the purpose of analysis, the latter group are considered dead of disease. One patient died of complications and 13 died of causes other than disease or complications. Twelve patients are lost to follow-up, 6 with a duration of less than 2 years, 4 with less than 3 years, and 2 with less than 5 years. Table 3 shows the Kaplan–Meier estimates of 5-year disease-free survival and pelvic control for each stratum. The Kaplan–Meier plots of overall disease-free survival, disease-free survival for each stratum, and disease-free survival by treatment assigned are shown in Figs. 2, 3, and 4, respectively. There is no significant difference in the overall 5-year disease-free survival between the treatment arms. There is a trend in favor of standard radiation and 5-FU. The disease-free 5-year survival in arm (a), (c), (d), and (b), respectively, were 45, 53, 58, and 61%. The overall pelvic control by treatment assigned for arms (a), (c), (d), and (b) was 58, 65, 68, and 69%, respectively. Whereas there was once again a trend in favor of concurrent 5-FU, particularly in combination with standard radiation, the difference was not statistically significant.

The disease-free survival by treatment arm for the 99 patients in stratum 1 is shown in Fig. 5. There was a significant improvement in 5-year survival and disease-free survival for those treated with standard radiation and 5-FU compared to the other treatments (log rank test $P = 0.05$). The actuarial 5-year disease-free survival was 76% compared to 65% for hyperfractionated irradiation plus 5-FU, 58% for hyperfractionated irradiation alone, and 39% for standard radiation. Similar differences were observed in pelvic control, but the addition of 5-FU to standard radiation resulted in a greater improvement in disease-free survival than in pelvic control. Table 4. A factorial analysis of the magnitude of the impact of differences in the radiation schedule or the addition of 5-FU on the improvements in pelvic control and disease-free survival in stratum 1 was performed. In examining the effect of the addition of 5-FU on disease-free survival in stratum 1, there is a highly significant difference in favor of the use of 5-FU regardless of the radiation employed. The 5-year Kaplan–Meier disease-free survival for those irradiated without 5-FU was 48% versus 71% for those who received 5-FU (log rank $P = 0.02$) (Fig. 6). Pelvic control was 66% for those who did not receive 5-FU compared to 84% for those who did ($P = 0.07$). However, in

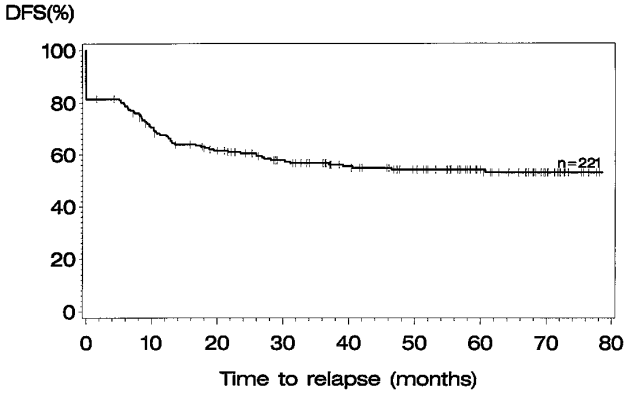

FIG. 2. Kaplan–Meier plot of overall disease-free survival (DFS).

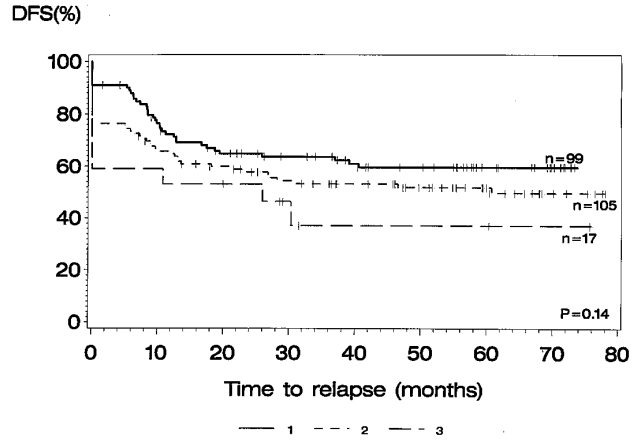

FIG. 3. Kaplan–Meier plot of disease-free survival (DFS) for each stratum.

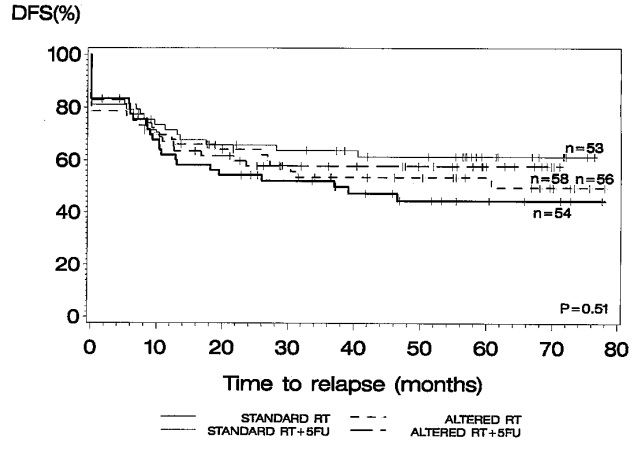

FIG. 4. Kaplan–Meier plot of overall disease-free survival (DFS) for each treatment.

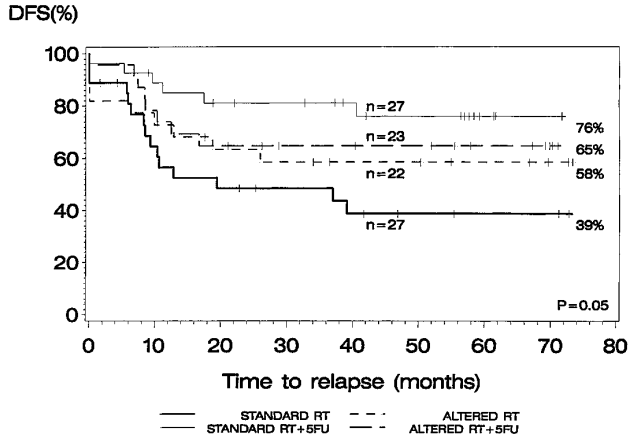

FIG. 5. Kaplan–Meier plot of disease-free survival (DFS) for each treatment in stratum 1.

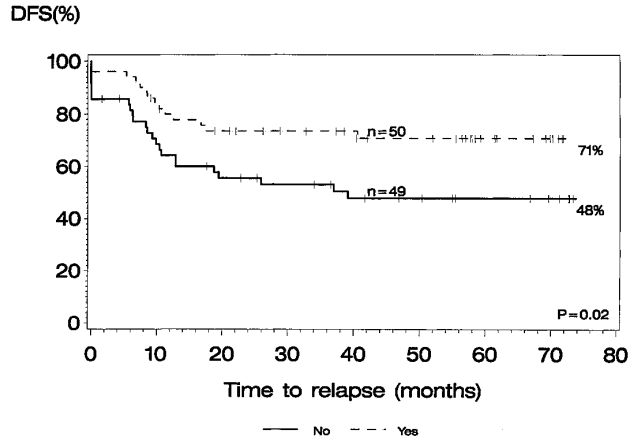

FIG. 6. Kaplan–Meier plot of disease-free survival (DFS) within stratum 1 for those treated without 5-FU (No) versus with 5-FU (Yes).

evaluating the importance of the contribution of the change in fractionation to the differences observed, there was no significant difference in the 5-year survival of those treated on standard radiation versus those treated with hyperfractionated irradiation whether or not 5-FU was used. When the radiation fraction size is reduced as in this altered fractionation scheme a compensatory increase in total dose over the same overall time is required to reach a biologically similar dose. The dose of 5280 cGy in 33 fractions is biologically similar to the standard dose of 5000 cGy in 25 fractions. It was hoped that the use of two treatments daily during the 5-FU infusion would increase any opportunity for 5-FU-radiation interaction by increasing the total amount of radiation given concurrently with 5-FU. The 5-year Kaplan–Meier survival was 62% for those treated with hyperfractionated irradiation and was not significantly different from the 58% survival of those treated with standard irradiation. The observed differences in pelvic control and survival in favor of the standard radiation and concurrent 5-FU associated with the addition of 5-FU rather than the change in radiation schedule.

Stratum 2 was examined for differences in pelvic control and survival between the treatment arms and no significant differences were observed. There were too few patients in stratum 3 to do valid statistical analyses. Since significant differences in pelvic control and survival were observed in stratum 1 which contained only 99 patients, it is important to examine whether there was an uneven distribution of other possible patient or tumor-related prognostic factors across the treatment arms to account for the differences observed. We wished to determine whether there was an accumulation of ''bad risk'' factors in the group receiving standard radiation alone or alternatively that there was an accumulation of ''good risk'' factors in patients receiving standard RT and 5-FU. For those receiving standard RT, the pelvic control rate was 60% but the disease-free survival was only 39%. Table 1 shows the distribution of identifiable possible prognostic factors by treatment assigned. There appears to be no imbalance in the distribution by FIGO stage, cell type or CLS involvement. If anything, there was a slight excess of larger tumors in those receiving standard radiation and 5-FU, the arm with the best outcomes.

TABLE 4
Stratum 1

Sites of relapse	Standard RT	''Partially'' hyperfractionated	Standard RT + FU	''Partially hyperfract'd RT + FU
Patient No.	27	22	27	23
None	12	13	21	15
Pelvis alone	3	1	3	3
Pelvis ± Dist	9	6	3	5
Dist alone	6	3	3	3
Dist ± Pelvis	12	8	3	5

Note. The sites of relapse by treatment arm within stratum 1. Hyperfract'd, hyperfractionated; Dist, extrapelvic.

The time to development of serious late complications was seven to 53 months (median 16 months). Eight occurred in those receiving standard radiation and five in those receiving altered RT. There was no apparent increase in late complications associated with the addition of 5-FU. Seven occurred in the group receiving 5-FU and six in those without 5-FU. Serious complications resolved (obstruction resolved or colostomy closed) in all but four of the patients. Given the low incidence of late complications it is not possible to establish an actuarial probability of risk with these regimens. The crude incidence of 5.9% (13 of 221) presents a good estimate of the overall risk for chronic bowel complications in survivors, since most occur in the first 3 years after radiation therapy. The median duration of follow up on this series at 59 months is sufficient to observe approximately 80% of expected events [28].

DISCUSSION

Other than the report on the use of concurrent hydroxyurea [10] this is the first published report of the results of a randomized study examining the role of concurrent chemotherapy and radiation in advanced cervical cancer. To reach the conclusion that concurrent chemotherapy truly adds benefit to results achievable with radiation alone, it is important that the radiation be delivered in an optimal manner with adequate doses at ''Point A'' (80 to 90 Gy) and limited overall treatment times [30]. The radiation scheme used in this study conforms to those guidelines, although the inability to apply intracavitary radiation in 10% of these patients with advanced disease was disappointing.

The rationale for the use of concurrent infusional 5-FU and the treatment regimens studied has been discussed in detail in a previous publication [29]. Patients were stratified into three groups in this study because pelvic control and survival outcomes are strongly influenced by the bulk of pelvic disease, declining with increasing bulk [26, 30, 31]. The specific strata selected were based on previous retrospective data [26] indicating significantly different prognoses for these specific clinical groupings of bulk of pelvic disease. The original design for this study required 292 patients with adequate power to detect a 15% difference in pelvic control and survival. Unfortunately, because accrual was protracted and declined in the latter years of the study, the study was closed prematurely with 234 patients accrued. It is therefore not surprising that significant differences in survival and pelvic control were not observed in the overall population. However, given the observation of a consistent trend in favor of standard RT plus 5-FU it was felt justified to perform an exploratory subset analysis of each stratum. It was anticipated that the magnitude of benefit might vary for each stratum. There were too few patients (17) in stratum 3 to justify further analysis. In strata 1 and 2 there were sufficient patients to perform exploratory analyses. Within stratum 2 there was an improvement in pelvic control with the use of 5-FU but the difference was not statistically significant. However, in stratum 1 constituted of patients with stage IB/IIA and those IIB tumors with medial parametrial involvement, a significant improvement in both pelvic control and disease-free survival in favor of standard radiation with concurrent 5-FU was observed (Figs. 5 and 6). The disease-free survival with standard radiation alone, however, was surprisingly low at 39%. A factorial analysis compared the outcome for all patients treated with concurrent 5-FU compared to those without 5-FU. A similar analysis compared all those treated with standard radiation to those treated with hyperfractionated irradiation. The benefits observed occurred in relation to the use of concurrent 5-FU rather than to the change in radiation fractionation. The direction of benefit in favor of 5-FU with standard radiation compared to the other treatments was the same in strata 1 and 2. Because of the small numbers in each treatment arm it was surprising to observe a significant difference. With so few randomized the possibility exists that an imbalance in prognostic factors exists between the treatment arms might account for the observed outcome differences. A number of patient- and tumor-related factors were analyzed for their impact on outcome using the Cox's proportional hazard model. The tumor- and patient-related factors examined were FIGO stage (IB versus IIA versus IIB), size of tumor (greater or less than 6 cm and greater or less than 7 cm), grade of tumor the presence or absence of capillary-like space involvement, nodal involvement, and patient age as a continuous variable. The treatment related factors examined were the use of intracavitary radiation, the use of 5-FU, and the fractionation scheme, standard versus partially hyperfractionated. Unfortunately the data are not yet available to analyze the impact of variability in overall treatment time. The only significant factor predicting for disease-free survival was the use of 5-FU. The risk ratio for recurrence and death from disease was reduced to 0.49 (95% confidence interval 0.25 to 0.97). Thus, there is no obvious explanation for the differences observed other than a treatment effect from the 5-FU. With so few patients, however, there may still be a maldistribution of some unrecognized tumor or patient-related prognostic factor which could be responsible for the differences observed.

The changed fractionation scheme, using smaller than conventional fraction sizes and a 6% increase in total dose was designed to be approximately biologically equivalent for tumor control to that of standard radiation yet lead to reduced complications. The overall incidence of serious complications was too low to detect differences between the treatment arms. The observed complication rate in any of the treatment arms appears acceptable, 7% with standard radiation whether or not 5-FU was added and 4% in the hyperfractionated radiation arms whether or not 5-FU was added.

The second rationale for use of the partially hyperfractionated radiation scheme was to attempt to maximize the dose of radiation delivered during the infusion of 5-FU. Two fractions of 160 cGy per day were delivered during the infusion at the beginning and end of treatment in arm (d). Hyperfractionated radiation and 5-FU should theoretically have offered a benefit over that of standard radiation and 5-FU if increased tumor cell kill results from any interaction between the modalities. Such a benefit was not observed in this study. Theoretical explanations for the lack of benefit may include a reduction in tumor cell kill due to the reduced radiation fraction size and/or an insufficient compensatory increase in total dose to compensate for the reduced fraction size. The mechanism by which 5-FU exerts benefit is unknown, but may be simply by additivity due to its independent cytotoxic effect rather than to an interaction with radiation.

The lack of significant benefit for 5-FU in stratum 2 may be due to the small sample size or, theoretically, that the added chemotherapy was insufficient to significantly impact on more advanced disease.

The observation that 5-FU impacted more on survival

than pelvic control in stratum 1 is difficult to explain. It was not expected that the 5-FU dosage would be sufficient to directly reduce distant micrometastases. An alternative explanation is that 5-FU contributed to pelvic control and better pelvic control decreased the frequency of distant metastases [32–34].

From the subset analysis of this trial we have generated the hypothesis that there may be a beneficial effect of adding concurrent infusional 5-FU to standard in patients with the disease characteristics of stratum 1. Since the data are not conclusive because of limited numbers, confirmation of the beneficial effects observed in this study is necessary. The number of patients is too few to recommend that concurrent infusional 5-FU with pelvic irradiation should become the standard therapy for these patients.

Other completed or ongoing randomized studies of the Gynecologic Oncology Group (protocols 85 and 120) and of the NCI Canada examine concurrent radiation and cisplatin or cisplatin combinations with 5-FU. The results of these additional studies will be influential in confirming whether the strategy of concurrent chemotherapy and radiation is beneficial for patients with advanced cervical cancer.

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