Radiotherapy and Neoadjuvant Chemotherapy for Cervical Carcinoma

A Randomized Multicenter Study of Sequential Cisplatin and 5-Fluorouracil and Radiotherapy in Advanced Cervical Carcinoma Stage 3B and 4A

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BACKGROUND. The locoregional failure rate remains high in advanced cervical carcinoma. Chemotherapy (CT) was added to radiotherapy (RT) in order to increase disease control and to improve 5-year survival.

METHODS. CT+RT included cisplatin administered 100 mg/m^2, d.1 plus 5-fluorouracil 1000 mg/m^2 D.1 to 5, ci (120 hrs), q every 3rd week for 3 cycles, followed by RT. RT included external beam irradiation 64.8 Gy in 1.8 Gy fractions, five days a week, by 4-field box technique. The median follow-up was 46 months. Ninety-four patients were evaluable for survival, 47 in the CT+RT group and 47 in the RT group. Ninety-two patients were evaluable for response. Known prognostic factors were equally distributed between the two groups.

RESULTS. Of the 43 patients evaluable before RT, 31 (72%) achieved a partial or complete response after CT alone. After RT, 52 patients attained a complete response, 25 in the CT+RT group and 27 in the RT-group. Sixty-three patients developed distant metastases or local relapse, 30 in the CT+RT group and 33 in the RT group. In the CT+RT group 6 of the 9 patients with metastases also had local progression at relapse, in the RT group, 7 of 17 patients. The survival rates for the two groups are not statistically different. Thirty-seven patients are alive, 29 have no evidence of disease. Fifty-seven have died, 29 in the CT+RT group and 28 in the RT group. Fifty-four deaths were related to cancer, and 3 to therapy.

CONCLUSIONS. Sequential CT and RT did not improve the survival, local control, or metastasis rate compared with RT alone. ***Cancer* 1996; 77:2371–8.**

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Radiotherapy (RT) has been the established treatment for locally advanced cervical carcinoma and the only curative treatment for tumors extending to the pelvic wall. Despite decades of development, the failure rate for treatment of locally advanced tumors has remained high. According to FIGO's *Annual Report*, the 5-year survival of patients with International Federation of Gynecology and Obstetrics (FIGO) Stage IIIB tumor (extending to the pelvic wall or hydronephrosis or nonfunctioning kidney) and FIGO Stage IVA tumor (clinically involved the mucosa of the bladder or rectum) together has been about 25%.[1] During the 70s and 80s new drugs and drug combinations caused high response rates in the treatment of recurrent cervical carcinoma. Among the most promising drugs documented in well-designed studies were 5-fluorouracil (5-FU) and cisplatin (CP). The response rates with CP varied between 23 and 50%.[2–5] Continuous infusion (ci) of 5-FU during several days showed an

effect on the treatment of squamous cell carcinoma in the head and neck region. Kish et al. reported that patients responding to induction chemotherapy (CT) seemed to have a longer survival than nonresponders.[6] Other studies showed the lack of cross-resistance and possible synergism between CP and 5-FU.[7-9] In a pilot study on neoadjuvant CP and 5-FU, Simonsen et al. noted clinical remission in 21 of 25 patients.[10] Kaern et al. observed high response rates in patients with recurrent cervical carcinoma treated with CP and 5-FU.[11]

Based on these results, we planned the present study. The aim was to improve 5-year survival. Secondary endpoints were to improve disease free survival by improving local control. The possibility of reducing the occurrence of distant metastases was also considered, but this aspect was not the central point in the discussions. We planned to do the analysis after a median follow-up of 4 years, because most events would have happened within the first 2 or 3 years.

PATIENTS AND METHODS

Patients with untreated, locally advanced tumors of the uterine cervix were eligible. Eligibility criteria also included histologically verified squamous cell carcinoma of the uterine cervix, measurable tumor or unmeasurable but evaluable tumor, FIGO Stage IIIB or FIGO Stage IVA tumor. For Stage IVA, tumor involvement of the mucosa of the bladder or rectum had to be histologically verified. The patients had to be younger than age 70 years with no past history of malignancy and a performance status of 60 or greater on the Karnofsky scale. Adequate hematologic values were: white blood cell count, $\geq 3 \times 10^9$/l; and platelet count, $\geq 100 \times 10^9$/l. A hemoglobine concentration of ≥ 110 g/l was accepted when necessary after blood transfusion. Serum creatinin had to be ≥ 120 μ/l. By higher values or ureter obstruction, creatinin clearance had to be >1 ml/s. Creatinin clearance ≤ 1 ml/s could be accepted if due to pressure from the tumor. Ultrasound guided percutan pyelostomy or ureter stenting were usually performed by marked ureter obstruction, and the normalization of kidney function confirmed by hippuran clearance before inclusion in the study. Patients with medical contraindications for study treatments, psychosis, or senility were not eligible. Written, informed consent was obtained from the patients. The study was examined and approved by the ethical committees concerned in each country. It followed the principles of the Declaration of Helsinki.

The staging procedure was performed according to the system adopted by FIGO. It included a complete medical history, physical examination, gynecologic examination under anesthesia, cystoscopy, chest X-ray, intravenous (i.v.) pyelograms, complete blood counts, and biochemistries. Computed tomographic (CT) scans, abdominal ultrasound scan, or magnetic resonance (MR) imaging were not included in the diagnostic procedure unless symptoms or findings in the routine examination indicated distant metastatic disease. Thus, patients with nonsymptomatic paraaortic nodes would not be revealed and not be excluded from the trial. This was according to FIGO rules.

Patients were randomized to receive either three courses of CT followed by RT, the "CT+RT" group, or RT alone, the "RT" group. CT in the CT+RT group consisted of CP 100 mg/m^2 i.v., infused over 2 hours, Day 1 with hyperhydration, and 5-FU 1000 mg/m^2 Day 1 to 5, ci (120 hours). This schedule was repeated every third week for 3 cycles. RT started D 14 in the third cycle. RT in both groups was external beam irradiation 64.8 g ray (Gy) in 1.8 Gy fractions, 5 days a week, by 4-field box technique to the small pelvis, all 4 fields being exposed in each fraction. No field reduction was employed. Brachytherapy was not employed. The energy was 6 MeV to 11 patients, 10 MeV to 5 patients, and 14 to 16 MeV to 76 patients. RT was administered using an isocentric technique via a pair of parallel opposed anterior and posterior ports combined with a pair of parallel opposed transverse ports. The superior limit of the radiation fields was the L5-S1 junction, and the lower limit was 1 centimeter below the caudal limit of the obturator foramen for all 4 fields. The lateral border of the anterio-posterior field was 1 cm lateral to the most lateral point of the pelvic walls. The anterior border of the lateral field was 1 cm posteriorly from the upper part of the symfysis, and the posterior border, 1 cm in front of the most posterior part of the sacrum. Tumor volume was supposed to be included with a margin of 2 cm. When necessary, borders were adjusted. Corners were shielded in all 4 fields to exclude tissue outside the small pelvis.

Patients were examined under anesthesia after two-thirds of the planned RT and 7 weeks after completed treatment. Thereafter clinical examination was performed every second month during the first year, every third month the second year, and every sixth month the following years. No patient was lost to follow-up. Chest X-rays were taken before the second CT course in the CT+RT group and in the sixth week of RT in the RT group, at 6 months, 1 year, and every year thereafter. Other X-ray examinations, CT scan, MR imaging, ultrasound examinations, or biopsies were performed when indicated by symptoms or by suspected relapse. Response to treatment was evaluated according to the criteria of the World Health Organization (WHO).[12] All histologic slides were reviewed in the department of pathology at the actual participating center. The inclusion of each patient was based on the primary routine diagnosis from these laboratories at the time of randomization. We disregarded later reclassification to adenosquamous carcinoma in a few patients based on special mucus-staining of addi-

tional biopsies taken for other scientific purposes. The inclusion period was between March 1989 and December 1992. All patients were followed until death or until June 1994. Follow-up information was collected from the medical records and from the Cancer Registers of Norway, Denmark, and Sweden.

STATISTICS

The 5-year survival rate with standard treatment was about 25% for tumors Stage III and IV together.[1] Assuming α = 5% (2-sided test) and β = 20%, about 150 patients would be required in each treatment arm to demonstrate a significant survival difference of 15%, i.e., a percentage change from 25 to 40%. With the number reported here, the β value is changed to 40% for the same 15% expected difference, still assuming α = 5%. Wilcoxon rank sum test, or the chi-square test when appropriate, was used for the analysis of differences between the two groups. Survival time and time to recurrence were calculated from time of study entry. The survival rates are crude survival, though all observed deaths were until now diagnosed as related to cancer or treatment. Survival probability was calculated by the method of Kaplan and Meier. Observed differences were examined by the Mantel–Haenszel log rank test. A significance level of 0.05 was used; all *P* values are 2-sided.

RESULTS

Patients

Ninety-six patients were included in this study: 62 from the Norwegian Radium Hospital, 14 from the University Hospitals in Linköping and Tromsø, 11 from the University Hospital in Trondheim, and 9 from the University Hospital in Odense. Two patients were excluded, one in each treatment group, due to violations of the inclusion criteria. The first patient had tumor Stage IVB with huge inguinal gland and upper abdominal tumor. The other had adenocarcinoma intestinal type. Thus, 47 patients were allocated to the CT+RT group, and 47 to the RT group. All 94 patients were included in the analysis of survival, response, and recurrence. Pretreatment patient characteristics are shown in Table 1. There was no imbalance in prognostic factors between the two treatment groups. The median age was 52.7 years (range: 25–70 years) in the CT+RT group, and 52.5 years (range: 26–70 years) in the RT group. The median follow-up time was 46 months (range: 18–62 months) in the CT+RT group, and 45 months (range: 18–62 months) in the RT group. The median observation time for patients alive was 39 months (range: 18–62 months) in the CT+RT group, and 39 months (range: 19–58 years) in the RT group.

TABLE 1
Patient Characteristics Pretreatment

	CT + RT	RT
No. of patients	47	47
Median age	52.7 (25–70)	52.5 (26–70)
Karnofsky index		
100	19	18
90	16	16
80	10	7
70	2	6
HB g/100 mL		
>14	10	4
12–14	20	21
10–12	16	18
<10	1	4
FIGO		
Stage 3B	44	44
Stage 4A	3	3
Histologic grade		
Highly differentiated	2	1
Moderate differentiated	23	31
Poorly differentiated	18	15
Not specified	4	0
Parametrial involvement		
Unilateral	14	14
Bilateral	32	32

CR + RT: chemotherapy + radiotherapy group; RT: radiotherapy group; FIGO: International Federation of Gynecology and Obstetrics.

Treatment

Chemotherapy

In the CT+RT group, 31 of 47 patients completed all three CT courses without dose reduction or delay. Three patients had a 1-week delay in 1 course due to leucopenia. One patient had the last day's 5-FU treatment stopped because of general weakness. Four patients had full-dose CT stopped after 1 or 2 cycles because of: stable disease after the second course (1); ototoxicity (2); and nephrotoxicity (1). Two patients refused further chemotherapy after the first course. Another 4 patients had major dose reductions through all 3 cycles because: the CP dose was reduced to 75% due to low creatinin clearance (2); the 5-FU dose was miscalculated to 57% (1); and the 5-FU infusion stopped after 3 days because of mucotoxicity and then ototoxicity, so both CP and 5-FU were reduced to 50% for the last 2 courses (1). Two patients died during CT, 1 after the first course and 1 after the second.

Radiotherapy

All patients, except two, completed RT to the prescribed dose. These 2 patients were switched to CT after they completed 40 to 52 Gy due to new symptomatic metastatic disease.

TABLE 2
Pelvic Response Rates in the Two Treatment Groups

	Before radiotherapy		Follow-up			
	CT + RT		CT + RT		RT	
CR	2	5%	25	56%	27	61%
PR	29	67%	11	24%	9	20%
SD	12	28%	—		—	
	—					
PD		—	9	20%	8	18%
Evaluable response	43	100%	45	100%	44	100%
Not evaluated	4					
Early death			2		—	
Early metastases			—		3	
Total	47		47		47	

CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; CT + RT: chemotherapy + radiotherapy group; RT: radiotherapy group.

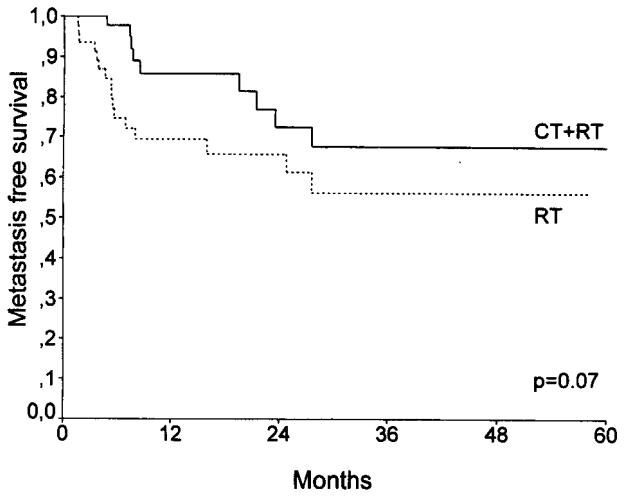

FIGURE 1. Time to disease progression presenting with metastases according to randomization group is shown.

Response

Within the CT+RT group the overall response rate before the start of RT was 72% (31/43), 2 patients had complete and 29 partial responses (Table 2). In the follow-up period, the overall response rate was 80% in the CT+RT group and 82% in the RT group. Twenty-five patients in the CT+RT group and 27 in the RT group had complete response. Partial response was recorded for 11 patients in the CT+RT group and 9 in the RT group.

Metastases

Distant metastases occurred in three patients in the RT group during treatment. At the first posttreatment visit, another five patients in the RT group had metastases compared with only one in the CT+RT group. Within the next 4 months, another 4 patients in both groups developed metastases, and during later follow-up, 4 patients in the RT group and 4 in the CT+RT-group relapsed with metastatic disease. (Fig. 1). A total of nine patients in the CT+RT group had distant metastases at relapse, six out of these patients also had locoregional progression. In the RT group, 16 patients had distant metastases at relapse, but only 6 were combined with locoregional progression (Tables 3 and 4). Only 4 of the 25 patients with metastases outside the pelvis had neither residual nor progressive disease in the irradiated area.

TABLE 3
Site of Progressive Disease at Recurrence in the Two Treatment Groups

	CT + RT[a]		RT[b]	
Pelvis	21	47%	17	34%
Pelvis + distant	6	13%	6	13%
Distant	3	6%	10	22%
Total	30	67%	33	70%

CT + RT: chemotherapy + radiotherapy group; RT = radiotherapy group.
[a] 45 evaluable patients (surviving prime treatment).
[b] 47 evaluable patients.

Pelvic Recurrence

In one patient in the RT group pelvic progression was noted when finishing RT. At the first posttreatment visit another seven patients in the RT group and nine in the CT+RT group had pelvic progression. During the next 4 months, pelvic progression occurred in another 5 patients in the RT group and in 10 in the CT+RT group. For the remainder of the observation time, pelvic recurrence occurred in 10 patients in the RT group and in 8 in the CT+RT group. (Fig. 2). A total of 27 patients in the CT+RT group had pelvic recurrence or progression, 6 of whom also had metastatic disease. In the RT group, there were 23 patients with pelvic recurrence or progression, 7 combined with metastases. Within the CT+RT group, patients with stable disease during CT had a tendency toward a higher risk for pelvic failure compared with those responding to CT, but the difference was not significant. Patients responding to CT had the same risk of pelvic failure as those responding to RT. Disease progression with metastases and/or central recurrence has occurred in 30 patients in the CT+RT group, and in 33 in the RT group. Median time to recurrence was 12 months in the CT+RT group, and 11 in the RT group.

Survival

Thirty-seven patients are alive, of whom 29 are without evidence of disease. Fifty-seven patients have died, 29 in

TABLE 4
Site of Tumor and Metastasis by Distant Failure, Time to Recurrence, and Death

		Site of recurrent disease					Time in months			
Group	Patient	Local	Inguinal vulva	Paraaortal	Lung thorax	Liver	Recurrence	Survival	Status	Stage FIGO
CT + RT	85	PD	—	—	PD	—	5	9	D	3B
CT + RT	12	PD	—	—	PD	—	7	9	D	3B
CT + RT	39	PD	PD	—	PD	—	8	17	D	4A
CT + RT	24	—	—	—	PD	—	8	19	D	3B
CT + RT	31	PD	—	PD	—	—	8	16	D	3B
CT + RT	63	—	—	PD	—	—	20	28	A	3B
CT + RT	59	PD	—	—	—	PD	21	23	D	3B
CT + RT	96	PD	—	PD	PD	—	23	28	D	3B
CT + RT	78	—	—	—	PD	—	28	31	D	3B
RT	51	PS	—	—	PD	—	2	14	D	3B
RT	17	PS	—	PD	PD	—	2	15	D	3B
RT	66	PS	—	—	PD	PD	2	7	D	3B
RT	18	PD	—	PD	—	—	3	12	D	4A
RT	60	PD	—	PD	—	—	4	10	D	3B
RT	55	PS	—	—	PD	—	4	5	D	3B
RT	3	PS	PD	—	—	—	5	15	D	3B
RT	73	PS	—	PD	PD	PD	5	9	D	3B
RT	68	PD	—	PD	—	—	5	19	D	3B
RT	36	PD	—	PD	—	—	5	14	D	4A
RT	50	PS	—	PD	—	—	6	27	D	3B
RT	88	PD	—	PD	—	—	7	20	A	3B
RT	10	PD	—	—	—	PD	8	9	D	3B
RT	8	—	—	—	PD	—	16	37	D	3B
RT	65	—	—	PD	—	—	25	32	A	3B
RT	84	—	—	PD	—	—	28	29	A	3B

PD: progressive disease/recurrent disease; PS: persistent local tumor without progression; (–): no evidence of disease; A: alive; D: dead; CT + RT: chemotherapy + radiotherapy group; RT: radiotherapy group; FIGO: International Federation of Gynecology and Obstetrics.

the CT+RT group and 28 in the RT group (Fig. 3). Median survival was 26 months in the CT+RT group and 22 months in the RT group. We could neither find statistical differences in disease free nor in crude survival between the two groups. Excluding 3 treatment-related deaths, all of the deaths were due to cancer.

Prognostic Factors

Young age was the only independent poor prognostic factor significant for recurrence or death ($P = 0.002$). Low hemoglobin at the start of treatment, tumor Grade I to II and low performance index had some impact in cited order, but did not reach significance. Unilateral versus bilateral parametrial infiltration was not prognostic for survival ($P = 0.83$).

Toxicity

Mucosal toxicity was the dominating acute toxicity during CT (Table 5). Eight patients experienced a mucosal toxicity of Grade III or IV. For one patient it was the reason for refusing further CT. During RT and the first following months, 19 patients had diarrhea Grade III or IV, 7 in the CT+RT group and 12 in the RT group. Diarrhoea Grade I or II persisted beyond 6 months in about 35% of the patients. Three patients in the CT+RT group experienced weakness or localized paresis in the upper or lower extremities after the end of therapy, but function was restored within a few months. Several patients experienced minor hearing disturbances, often as tinnitus. Nine patients had a measurable hearing loss, mainly in the higher frequencies, 6000 to 8000 Hz, and 1 patient had ototoxicity Grade III, but restored to Grade I after the end of the treatment. Late gastrointestinal toxicity Grade III as persistent diarrhea until recurrence after 8 and 10 months was experienced in 3 patients. Gastrointestinal toxicity Grade IV and V was experienced in 4 patients (Table 6). In the follow-up period, one patient in the RT group suffered from a small bowel obstruction and was cured after resection of a stenosis. One patient in the CT+RT group had a perforation in the upper part of the rectum. The site was resected. Both these patients were without evidence of recurrent cancer. One patient in the CT+RT-group had

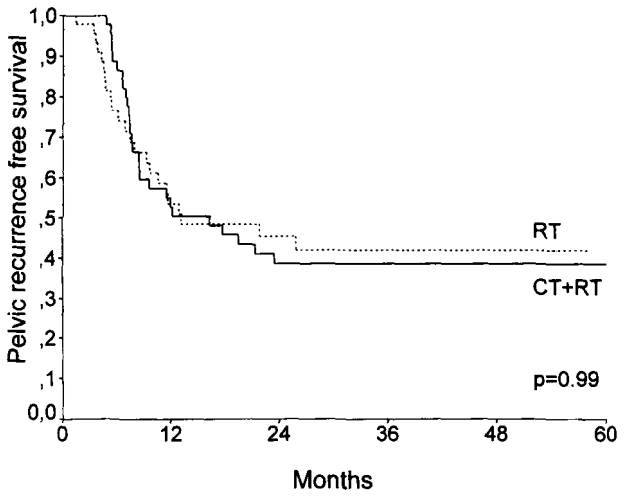

FIGURE 2. Time to disease progression within the pelvis according to randomization group is shown.

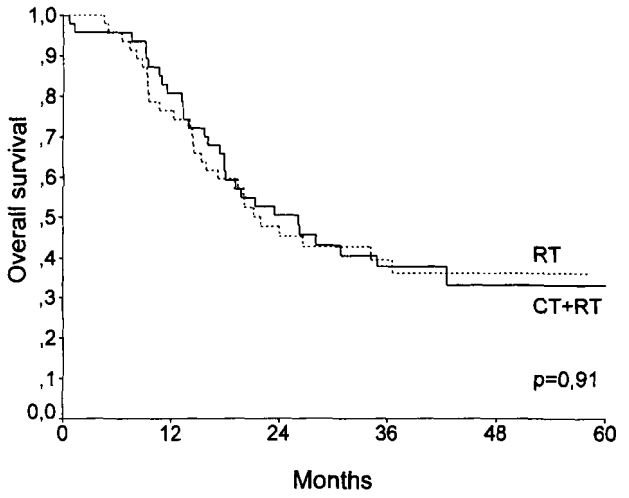

FIGURE 3. Survival (crude) according to randomization group is shown.

gastrointestinal bleeding, diarrhea, and fever. She was treated in hospital for 4 months. Three patients died due to treatment, two in the CT+RT-group, one in the RT group. The first patient was admitted to a local hospital 1 week after completion of the first course. She had a moderately elevated creatinin level of 300 to 500 μmol/L. Her condition deteriorated rapidly and she died the third day. No autopsy was done. The death was classified as due to therapy. The second patient had complete response before the second course. She weakened at the end of the second course and died after a week. The autopsy showed caval thrombosis, probably due to a central venous port. No residual tumor was found at the autopsy. The third patient belonged to the RT group. She had a central recurrence 5 months after the start of treatment. Three months later she underwent surgery for an acute perforation of the small bowel. She died of peritonitis. Only small supravaginal tumors were found at the autopsy. The death was also classified as a complication to the primary therapy.

TABLE 5
Acute Toxicity

	WHO Grade 3 and 4		
	CT + RT	RT	Total
Mucosa			
Grade 3	6	0	6
Grade 4	2	0	2
Diarrhea			
Grade 3	7	12	19
Neurotoxicity (peripheral)			
Grade 3	1	0	1
Ototoxicity			
Grade 3	1	0	1
Hair loss			
Grade 3	2	0	2
General			
Grade 5	2	0	2

CT + RT: chemotherapy + radiotherapy group; RT: radiotherapy group; WHO: World Health Organization.

TABLE 6
Late Toxicity

	WHO Grade 3 and 4		
	CT + RT	RT	Total
Diarrhea			
Grade 3	—	2	2
Rectal/intestinal			
Grade 4	2	1	3
Grade 5	—	1	1

CT + RT: chemotherapy + radiotherapy group; RT: radiotherapy group; WHO: World Health Organization.

DISCUSSION

Combination CT based on 5-FU and CP has been used in our institutions for the treatment of recurrent cervical carcinoma since 1986 with an overall response rate of 49%.[11] High response rates with CP-based regimes had been reported in treatment of advanced and recurrent squamous cell carcinoma of the uterine cervix and of the head and neck region.[3,6] Based on these results, we planned the present study. RT offers good local control in early stage cervical carcinoma, but in advanced cervical carcinoma the recurrence rate is still high. Local control

failure is the dominating problem in the treatment of advanced cervical carcinoma. Increase in radiation doses to overcome local failure is encumbered by rapidly increasing late radiotoxicity. We would combine RT with CT to increase local control in an attempt to improve 5-year survival significantly. To avoid increased radiotoxicity we chose the sequential design. This also offered the possibility of giving chemotherapeutics in systemically efficient dosages.

In the present study, primary CT caused substantial tumor shrinkage, but did not influence disease free or crude survival. This is in accordance with the reports from other randomized studies on neoadjuvant CT.[13-17] However, except from Tattersall et al., who reported inferior survival with combined treatment in the CT group, most previous studies did not come to any significant conclusions. Tattersall et al. concluded from their study that patients treated with neoadjuvant CT (CP and epirubicin) have inferior local control despite good CT response before RT. Souhami et al., who reported a marked disadvantage to the CT arm, used a CT combination with bleomycin, vincristine, mitomycin, and CP. The whole difference in their study was attributable to deaths from disease progression during CT or CT toxicity. In the patients receiving combined treatment, they reported no difference. In the present study there was a high response rate and no treatment failure in the CT arm when evaluated before the start of RT. In the follow-up period, however, there was no statistical difference in pelvic failure between the two groups. There was, however, a tendency to reduced distant metastases in the CT group ($P = 0.07$), but no improved survival was obtained.

Several mechanisms might counteract the additive effect of sequential chemo-RT. Delayed effective RT to the local disease is said to give significant disadvantage in combined treatment due to tumor regrowth; however, this will only occur during the course of CT if the treatment is actually ineffective as pointed out by Steel.[18] This applies to a nonselective delay effect. The selection and regrowth of chemoresistant and possibly radioresistant cells may occur during chemo-RT and cause early relapse. Diminished local control might also be caused by a change in tumor kinetics during treatment. The concept of accelerated regrowth may additionally increase a tumor rebound effect.[19,20] The induction of resistance may be considered, but is less likely. The high tumoricidal dose used and the few cycles given make it less likely that resistance induction might occur.

The most marked risk of therapy failure from selection and regrowth occur when there is overlap in resistance between CT and RT. A low chemo-RT cure rate in patients with stable disease during CT compared with patients responding to CT may indicate cross-resistance. The tendency toward increased pelvic failure among our patients with stable disease during CT is in accordance with the proposed cross-resistance between CP-resistance and radioresistance.[21,22] More patients with early local recurrence after treatment in the CT+RT group than in the RT group might reflect: (1) a higher frequency of radioresistant cell populations at the start of RT; (2) a larger partially radioresistant population in each patient (reflecting repopulation of a resistant fraction before RT; and (3) an accelerated repopulation of surviving cells started earlier than usual during RT. Accelerated repopulation might give earlier local recurrence, but it might also cause an increase in local failure as more marginally radiosensitive tumors might resist treatment. Increased rate of patients with radio resistant cell populations may increase the number of failure, not decrease the median time to local recurrence. Our results show minimal differences in local recurrence between the CT+RT group and the RT group, but a few more and earlier local recurrences were observed in the CT+RT group as might be expected from a selection and accelerated regrowth of resistant cells during the course of chemo-RT. Intensive chemo-RT with a shorter interval from the start of CT to RT, and surgical removal of the central heterogeneous tumor might reduce an effect of accelerated regrowth, selection, and repopulation of cross-resistant cells or resistance induction. This might be the explanation for the positive results reported from such an approach.[23,24] Eight patients in the RT group developed distant metastases rather quickly in the course of their disease, 5 with lung metastases which was not demonstrable on pretreatment X-rays. However, 4 included paraaortic disease, minor disease in this region would not be demonstrable by the diagnostic methods employed. There was no difference in the distribution of the prognostic criteria between the CT+RT and the RT groups. Thus the CT+RT group should have the same risk for developing early metastases, but had a tendency towards fewer distant, early metastases in the CT group ($P = 0.07$). The high risk of occult, early developing clinical metastases shown in the RT group, might be expected because our study includes patients with Stage IIIB and IVA only. Other studies that include many patients with Stage IIB will not have the same chance to disclose an effect on occult distant metastases. Our results might suggest a possibility to control clinically occult metastases by this CT combination, but the small number of patients in the present study is too small to provide a definite conclusion. Other chemo-RT combinations with lower CT intensity in simultaneous chemo-RT regimens might probably not be efficient against occult metastases. The conclusion is that RT remains the curative modality for advanced cervical carcinoma. The addition of neoadjuvant CT to pelvic RT has shown no impact on overall survival, local control, or distant control rates in patients with locally advanced carcinoma of the cervix.

REFERENCES

1. Petterson F. FIGO's Annual report on the results of treatment in gynecological cancer. Vol. 19. Stockholm: Radiumhemmet, 1985:27–49.
2. Malkasian GD, Decker DG, Jorgensen EP. Chemotherapy of carcinoma of ther cervix. *Gynecol Oncol* 1977;5:109–20.
3. Thigpen T, Shingleton H, Homesly H, Lagasse L, Blessing J. Cisplatinum in treatment of advanced or recurrent squamous cell carcinoma for the cervix: a phase II study of the Gynecologic Oncology Group. *Cancer* 1981;48:899–903.
4. Muscato MS, Perry MC, Yarbro JW. Chemotherapy of cervical carcinoma. *Semin Oncol* 1982;9:373–87.
5. Bonomi P, Blessing JA, Stehman FB, DiSaia PJ, Walton L, Major FJ. Randomized trial of three cisplatin dose schedules in squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. *J Clin Oncol* 1985;3:1079–85.
6. Kish JA, Ensley JF, Jacobs J, Weaver A, Cummings G, Al-Sarraff M. A randomized Trial of Cisplatin (CACP) + 5-fluorouracil (5-FU) Infusion and CACP + 5-FU Bolus for Recurrent and Advanced Squamous Cell Carcinoma of the Head and Neck. *Cancer* 1985;56:2740–4.
7. Beaupain R, Dionet C. Effects of combined treatments of cis-diamminedichloro-platinum UII), 5-fluorouracil, and x-rays on growth of human cancer nodules maintained in continuous organotypic culture. *Cancer Res* 1985;45:3150–4.
8. Schabel FM Jr, Trader MW, Laster WR Jr, Corbett TH, Griswold DP Jr. Cis-dichlorodiammineplatinum (II): combination chemotherapy and cross-resistance studies with tumors of mice. *Cancer Treat Rep* 1979;63:1459–73.
9. Teicher BA, Cucchi CA, Lee JB, Flatow JL, Rosowsky A, Frei E III. Alkylating Agents: In Vitro Studies of Cross-Resistance Patterns in Human Cell Lines. *Cancer Res* 1986;46:4379–83.
10. Simonsen E, Högberg T, Persson H, Stendahl U. Advanced primary or recurrent squamous cell carcinoma of the cervix uteri treated with chemotherapy, combination used: cisplatinum and 5-fluorouracil. In: Proceedings of the European Conference on Clinical Oncology and Cancer Nursing; 1987 Nov 1-4; Madrid Federation of European Cancer Societies, 1987;791.
11. Kaern J, Tropé C, Sundfør K, and Kristensen GB. Cisplatin/5-fluorouracil treatment of recurrent cervical carcinoma: A phase II study with long-term follow-up. *Gynecol Oncol* 1996;60:387–92.
12. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
13. Chauvergne J, Rohart J, Heron JF, Fargeot P, Berlie J, David P, et al. Randomized phase III trial of neo-adjuvant chemotherapy (CT) + radiotherapy (RT) vs. RT in stage IIB, III carcinoma of the cervix (CACX): a cooperative study of French Oncology Centers. *Proc Am Soc Clin Oncol* 1988;7:136.
14. Tobias J, Buxton EJ, Blackledge G, Mould JJ, Monaghan J, Spooner D, et al. Neoadjuvant bleomycin, ifosfamide and cisplatin in cervical cancer. *Cancer Chemother Pharmacol* 1990;26(Suppl):59–62.
15. Souhami L, Gil RA, Allan SE, Canary PCV, Araujo CCM, Pinto LHJ, et al. A randomized trial of chemotherapy followed by pelvic radiation therapy in stage IIIB carcinoma of the cervix. *J Clin Oncol* 1991;9:970–7.
16. Cárdenas J, Olguin A, Figueroa F, Pena J, Becerra F, Huizar R. Neoadjuvant chemotherapy (CT) in cervical carcinomas (CC) PEC + RT vs. RT. Preliminary results. *Proc Eur Conf Clin Oncol* 1991;6:124S.
17. Tattersall MHN, Lorvidhaya V, Vootiprux V, Cheirsilpa A, Wong F, Azhar T, et al. Randomized trial of epirubicin and cisplatin chemotherapy followed by pelvic radiation in locally advanced cervical cancer. *J Clin Oncol* 1995;13:2:444–51.
18. Steel GG. The search for therapeutic gain in the combination of radiotherapy and chemotherapy. *Radiother Oncol* 1988;11:31–53.
19. Stephens TC, Steel GG. Regeneration of tumors after cytotoxic treatment. In: Meyn RE, Withers HR, editors. Radiation biology in cancer research. New York: Raven Press, 1980:385.
20. Withers HR, Taylor JMF, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol* 1988;27:131–46.
21. Ozols RF, Masuda H, Hamilton TC. Keynote address: mechanisms of cross-resistance between radiation and antineoplastic drugs. *NCI Monogr* 1988;6:159–65.
22. Carmichael J, Hickson ID. Keynote address: mechanisms of cellular resistance to cytotoxic drugs and x-irradiation. *Int J Radiat Oncol Biol Phys* 1991;20:197–202.
23. Sardi J, Sananes C, Giarolli A, Bayo J, Rueda NG, Vighi S, et al. Results of a prospective randomized trial with neoadjuvant chemotherapy in stage 1b, bulky, squamous carcinoma of the cervix. *Gynecol Oncol* 1993;49:156–65.
24. Resbeut M, Noirclerc M, Viens P, d'Ercole C, Houvenaeghel G, Boubli L, et al. Concomitant chemotherapy and radiotherapy in the treatment of advanced cervix carcinomas. (Fr) *Bull Cancer* 1993;80:984–93.