Acta Oncologica Vol. 34, No. 6, pp. 787–795, 1995

PROGNOSTIC VALUE OF PRETREATMENT FACTORS IN PATIENTS WITH LOCALLY ADVANCED CARCINOMA OF THE UTERINE CERVIX TREATED BY RADIOTHERAPY ALONE

DORTE PEDERSEN, HELMER SØGAARD, JENS OVERGAARD and SØREN M. BENTZEN

The prognostic effect of pretreatment patient- and tumor characteristics, and the influence of radiotherapy schedule on local control, distant metastases, and crude survival were analyzed in 424 consecutive patients with FIGO stage IIB (n = 137), IIIA (n = 10), IIIB (n = 211) and IVA (n = 66) cancer of the uterine cervix. All patients were given radiotherapy alone. From 1974 and through 1977, the external and intracavitary combined radiotherapy was given continuously in 4 to 6 weeks. From 1978 and through 1983, the treatment policy was changed to split-course radiotherapy by introducing planned pauses, resulting in an overall treatment time of 10 to 12 weeks. The results were estimated by univariate actuarial- and Cox multivariate regression analyses. Multivariate analysis showed that significant adverse variables for local control were large lateral tumor diameter, young age, low hemoglobin at time of admission, many pregnancies, split-course strategy, and high FIGO stage. Risk of metastases increased with decreasing hemoglobin, increasing malignancy grade and split-course treatment. Poor survival probability were related to large lateral tumor diameter, high malignancy grade and FIGO stage, low hemoglobin, split-course therapy, and adeno/adenosquamous tumor type.

Although the incidence of uterine cervix carcinoma is decreasing in several countries, including Denmark, as a consequence of screening procedures (1), worldwide it is still one of the most common cancers with a poor prognosis in patients with locally advanced tumors. The treatment, usually consisting of different combinations of intracavitary and external radiotherapy, may imply a high risk of late morbidity as recently reported (2, 3). In the past few years, several studies have been published reporting results from multivariate analyses identifying prognostic factors in cervical cancer patients (4–16). Although the FIGO stage is generally found to be a major prognostic factor, variability of other patient and treatment characteristics may considerably influence the outcome. Furthermore, identification of patients at high risk of either distant or loco-regional failure may help in suggesting strategies for improving the treatment results.

The aim of the present retrospective study was to analyze the prognostic significance of the various available pretreatment patient and tumor characteristics and to evaluate the consequence of different radiation treatment strategies using local control, distant metastases, and survival as the endpoints.

Material and Methods

Four hundred and fifty-two patients were admitted to radiotherapy during a 10-year study period from January 1, 1974 to December 31, 1983. Ten patients were excluded either due to missing case records (7 patients) or because treatment consisted of surgery alone or in combination with radiotherapy (3 patients). Information about local control was missing in 18 patients, and these patients were

Accepted 19 June 1995.
From the Department of Oncology (D. Pedersen) and Institute of Pathology (H. Søgaard), Aarhus University Hospital, and Danish Cancer Society, Department of Experimental Clinical Oncology (J. Overgaard, S.M. Bentzen), Aarhus, Denmark.
Correspondence to: Dr Dorte Pedersen, Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Nørrebrogade 44, DK-8000 Aarhus C, Denmark.

 ISSN 0284-186X

Table 1

Patient characteristics

Characteristics	Quartiles	No. of pts	5-year actuarial estimates of: Local control	Distant control	Crude survival
Age[1]	24–49	120	49 ± 5	59 ± 5	35 ± 4
	50–59	108	66 ± 5	65 ± 6	45 ± 5
	60–67	101	67 ± 5	63 ± 6	38 ± 5
	68–88	95	57 ± 5	62 ± 7	30 ± 5
			$p = 0.64$	$p = 0.68$	$p = 0.12$
Number of pregnancies[1,2]	0–1	114	66 ± 5	64 ± 5	42 ± 5
	2–2	97	64 ± 6	56 ± 6	34 ± 5
	3–4	114	56 ± 5	65 ± 5	39 ± 5
	5–15	82	51 ± 6	62 ± 7	37 ± 5
			$p = 0.29$	$p = 0.78$	$p = 0.95$
Primary symptoms					
vaginal bleeding[1]					
yes		306	61 ± 3	62 ± 3	39 ± 3
no		118	56 ± 5	61 ± 6	32 ± 4
			$p = 0.11$	$p = 0.44$	$p = 0.01$
pain[1]					
yes		152	53 ± 4	66 ± 5	34 ± 4
no		272	63 ± 3	60 ± 4	39 ± 3
			$p = 0.02$	$p = 0.68$	$p = 0.11$
other					
yes		186	56 ± 4	59 ± 5	35 ± 4
no		238	62 ± 4	64 ± 4	39 ± 3
			$p = 0.08$	$p = 0.16$	$p = 0.16$
Delay[1] (months) from primary symptoms until hospitalization	0–2	166	61 ± 4	59 ± 5	35 ± 4
	3	75	53 ± 6	65 ± 7	35 ± 6
	4–6	104	55 ± 6	67 ± 6	38 ± 5
	7–60	79	69 ± 6	59 ± 6	41 ± 6
			$p = 0.35$	$p = 0.63$	$p = 0.98$
Hemoglobin (mmol/l)[2]					
at admission	2.0–6.8	113	43 ± 6	52 ± 6	23 ± 4
	6.9–7.6	117	63 ± 5	67 ± 6	38 ± 4
	7.7–8.2	93	60 ± 6	57 ± 5	38 ± 5
	8.3–10.6	101	73 ± 5	74 ± 5	52 ± 5
			$p < 0.0000$	$p = 0.0012$	$p = 0.0001$
before radiotherapy	5.4–7.1	109	47 ± 5	56 ± 6	24 ± 4
	7.2–7.6	100	60 ± 5	60 ± 6	36 ± 5
	7.7–8.2	109	59 ± 5	58 ± 6	38 ± 5
	8.3–10.6	106	72 ± 5	72 ± 5	51 ± 5
			$p = 0.003$	$p = 0.0465$	$p = 0.009$
during radiotherapy	4.3–6.3	112	38 ± 5	45 ± 6	16 ± 3
	6.4–7.0	109	62 ± 5	68 ± 5	45 ± 5
	7.1–7.6	96	73 ± 5	64 ± 6	44 ± 5
	7.7–9.2	103	67 ± 5	70 ± 5	44 ± 5
			$p < 0.0000$	$p < 0.0000$	$p < 0.0000$
Blood transfusion before radiotherapy[1]					
yes		73	35 ± 7	47 ± 7	22 ± 5
no		351	64 ± 3	65 ± 3	40 ± 3
			$p < 0.0000$	$p = 0.0004$	$p = 0.00004$

[1] Included in multivariate analysis.

[2] Information about number of pregnancies and hemoglobin value during radiotherapy was missing in 17 and 4 patients respectively.

therefore excluded, leaving 424 patients for analysis. There was no significant time trend in the number of patients referred per year or in the distribution of disease stage.

All patients were seen at our institution every 3 months the first two years after treatment, and thereafter every 6 to 12 months until recurrent disease or for at least 5 years. No patients were lost to follow-up during that time. No regulatory follow-up was performed after 5 years. Although vital status after that time was obtained from central personal registry, cause of death could not be specified.

Patient characteristics. Table 1 shows the patient characteristics and related outcome. The age at the time of diagnosis of the cervical cancer and at first pregnancy, number of pregnancies prior to malignant diagnosis and duration of symptoms before the patient asked for medical advice (delay in months) were recorded as continuous parameters. Information about the number of pregnancies was missing for 17 patients, while age at first pregnancy remained unknown in 120 cases. The first symptoms noticed by the patient were subdivided into bleeding, pain and other symptoms. Performance status of the patients could not be evaluated restrospectively.

The hemoglobin concentration (normal range 7.0–10.0 mmol/l; 1 mmol/l = 0.621 g%) was measured at the time of admission. Blood transfusions prior to treatment were only recorded as given or not. These variables were used in the multivariate analysis. In addition, the hemoglobin concentration before (i.e., after blood transfusion) and during radiotherapy were recorded when available in the patients' records. The latter hemoglobin value was the lowest measured. However, there was no policy for measuring the hemoglobin during radiotherapy, and in most cases only a single value was available.

Tumor characteristics. The tumor characteristics are shown in Table 2. The proportion of patients with FIGO stage IIB, IIIA, IIIB, and IVA was 32%, 2%, 50% and 16% respectively.

Table 2

Tumor characteristics and treatment strategy

Characteristics	Quartiles	No. of pts	5-year actuarial estimates of		
			Local control	Distant control	Crude survival
FIGO stage[1]					
IIB		137	74 ± 4	67 ± 4	53 ± 4
IIIA		10	78 ± 13	56 ± 16	30 ± 13
IIIB		211	57 ± 4	62 ± 4	34 ± 3
IVA		66	29 ± 8	45 ± 9	15 ± 4
			$p < 0.0000$	$p = 0.0206$	$p < 0.0000$
Histopathology[1]					
squamous cell		393	61 ± 3	63 ± 3	38 ± 2
adeno/adenosquamous		31	42 ± 10	46 ± 13	23 ± 8
			$p = 0.034$	$p = 0.16$	$p = 0.0082$
Tumor cell differentiation[1,2]					
well		68	60 ± 6	70 ± 7	43 ± 6
moderate		238	65 ± 4	64 ± 4	39 ± 3
poor		99	41 ± 6	46 ± 7	24 ± 4
anaplastic		16	73 ± 11	73 ± 11	50 ± 12
			$p = 0.18$	$p = 0.14$	$p = 0.002$
Tumor diameter (cm)[2] lateral[1] (from left to right pelvic wall)	3–6	154	83 ± 4	69 ± 4	52 ± 4
	7–8	101	56 ± 5	59 ± 6	36 ± 4
	9–10	111	46 ± 5	56 ± 6	29 ± 4
	11–15	56	39 ± 8	55 ± 9	24 ± 6
			$p < 0.0000$	$p = 0.12$	$p = < 0.0000$
Radiotherapeutic stategy[1]					
from 1973–1977, (continuous)		182	62 ± 4	65 ± 4	41 ± 4
from 1978–1983, (split-course)		242	58 ± 4	59 ± 4	34 ± 3
			$p = 0.18$	$p = 0.093$	$p = 0.16$

[1] Included in multivariate analysis.

[2] Information about lateral, tumor diameter and tumor cell differentiation was missing in 2 and 3 of the patients respectively.

All tumors were histologically verified and reviewed by one pathologist (HS) according to the international classification of diseases for oncology, WHO 1976. Tumor cell differentiation in adenocarcinomas was evaluated according to the WHO grading of endometrial tumors. Different squamous tumor types ($n = 393$) were grouped together as were adenocarcinomas ($n = 18$) and adenosquamous cell carcinomas ($n = 13$). Tumor cell differentiation was scored as well, moderate, poor, and anaplastic. In 3 patients it was not possible to evaluate the tumor cell differentiation.

Tumor extensions in three directions (lateral—from right to left pelvic wall, antero-posterior, proximal-distal) were measured by gynecological examination during general anaesthesia and clinical staging. Drawings of the tumors were performed in two orthogonal standard pelvic figures in the case records. Information about the lateral, antero-posterior and proximal-distal diameters was missing in 2, 10 and 7 of the patients respectively. The tumor volume (cm^3) was calculated as the product of these 3 orthogonal diameters.

Treatment characteristics. The strategy and schedules for radiotherapy has been described previously (17). In brief, different combinations of external and intracavitary radiotherapy were given depending on the tumor stage and size. External irradiation was given on two opposing fields, including the tumor and regional lymph nodes. A central partial shield was used for parts of the external therapy. Each field was irradiated 5 days a week on either a ^{60}Co machine or a linear accelerator. Intracavitary therapy was applied according to a modified Stockholm technique with dose prescriptions in point A as defined in the Manchester system (18).

From 1974 and through 1977, the external and intracavitary combined radiotherapy was given at a planned overall treatment time of 4 to 6 weeks and without any planned pauses (continuous treatment). From 1978 and through 1983, the treatment policy was changed to split-course radiotherapy by introducing planned pauses, resulting in a planned overall treatment time of 10 to 12 weeks. The change of treatment strategy also included a reweighting of dose contributions from the intracavitary and external radiotherapy (17). The rationale for the split-course treatment was based on the cell population kinetic model described by Cohen (19), and the therapeutic outcome of this strategy has previously been reported (17, 20). Patients diagnosed between April 1979 and January 1982 were randomized in a multicenter trial, investigating the effect of either the hypoxic cell sensitizer misonidazole or placebo combined with radiotherapy (21). The trial showed no significant difference concerning local control, disease-free survival, and survival and consequently these patients were also included in the present study.

Based on tumor size (less than 4 cm, between 4 and 8 cm, and more than 8 cm in diameter) there were 3 different treatment plans consisting of combined external and intracavitary radiotherapy in each time period. However, intracavitary radiotherapy alone was planned in 16 patients and the treatment plans were not specified before start of radiotherapy in another 27 patients. Usually these latter regimens were received by patients in a poor general condition.

Endpoints and statistics. The endpoints were local control, distant metastases, and crude survival. Local control was recorded if no recurrences occurred in the radiation field, and only positive evidence of distant metastases was recorded as distant failures. Estimates of local control and distant metastases were censored corresponding to a 5-year follow-up period.

For the univariate analyses, actuarial estimates (± 1 SE) of all endpoints were obtained by the Kaplan-Meier method. The log-rank test was used for comparison of two groups only whereas the associated test for trend was applied for testing the significance of differences between several ordered categories, for this purpose continuous variables were divided into quartiles.

Multivariate analyses were performed using the Cox proportional hazard model with time to local failure, distant metastases, and death as the endpoints. The prognostic effect of the characteristics was expressed by the relative risks (RR) with the estimated 95% confidence interval. The analyses were restricted to pretreatment characteristics as indicated in Tables 1 and 2. Some characteristics were excluded due to a high proportion of missing values. Thus 397 patients had all the required data and were included in the analysis. The FIGO stage and the degree of differentiation were scored from 1 to 4. Young patients were defined as being in the lowest quartile of the age distribution (<50 years). Relationship between the various characteristics were analyzed by Spearman's rank correlation test.

Results

Univariate analysis of prognostic factors. The univariate analyses of the prognostic importance of the various recorded patient and tumor characteristics are given in Tables 1 and 2 for each of the endpoints: local control, distant control and crude survival.

No significant trend was seen in prognosis as a function of age. However, patients in the first quartile of the age distribution, (<50 years), had a significantly poorer local control rate ($49 \pm 5\%$) than older patients ($64 \pm 3\%$), $p = 0.02$. There was no strong association between the type of primary symptom and the outcome, although patients with bleeding tended to do better, and patients with pain worse than other patients, with respect to survival and local control respectively. Duration of symptoms and number of pregnancies had no significant influence on any of the three endpoints. FIGO stage was a strong determinant of local control and survival rates but less so for distant failure.

Table 3

*Cox multivariate regression analysis of all patients**

Characteristics	Local failure			Distant metastases			Death		
	p-value	RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI
Age	0.69			0.32			0.27		
Age <50 years	0.007	1.62	(1.15–2.29)	0.35			0.76		
No. pregnancies	0.01	1.09	(1.02–1.17)	0.86			0.23		
Bleeding as symptom	0.18			0.31			0.07		
Pain as symptom	0.55			0.36			0.78		
Delay (months)	0.28			0.98			0.43		
Hb at admission (mmol/l)	0.01	0.85	(0.75–0.96)	0.003	0.79	(0.69–0.92)	0.008	0.88	(0.80–0.96)
Transfusion	0.14			0.15			0.71		
FIGO (IIb, IIIa, IIIb, IVa)	0.04	1.22	(1.00–1.47)	0.23			0.006	1.20	(1.05–1.37)
Adenocarcinoma	0.09			0.45			0.05	1.53	(1.02–2.32)
Degree of differentiation	0.11			0.01	1.35	(1.06–1.70)	0.008	1.25	(1.01–1.46)
Lateral tumor size (cm)	0.0001	1.19	(1.10–1.30)	0.09			0.02	1.07	(1.01–1.14)
Proximal-distal tumor size (cm)	0.32			0.08			0.37		
Split-course treatment	0.03	1.45	(1.03–2.04)	0.03	1.51	(1.04–2.22)	0.04	1.28	(1.01–1.61)

* Includes 397 patients in whom all characteristics are recorded.

Adeno- and adenosquamous carcinomas did significantly poorer than squamous cell carcinomas with respect to local control rate and survival. The tendency was the same but did not reach statistical significance for distant control. Most tumors were evaluated as moderately differentiated. Poorly differentiated tumors did worse with respect to all endpoints. However, these tumors were significantly correlated with FIGO stage ($p = 0.00004$, Spearman's rank correlation test), and 43% of stage IVA tumors were poorly differentiated compared to 15% and 24% of stages IIB and IIIB respectively. The few so-called anaplastic (small cell non keratinized) tumors appeared to have a relatively good prognosis.

Four different tumor sizes were investigated. All of these had a strong influence on local control and survival and a marginal influence on the risk of distant failure, except for increasing tumor volume which was also associated with an increasing risk of metastases (Table 2).

Decreasing hemoglobin levels were strongly associated with poorer prognosis whether the hemoglobin was measured at the time of admission, before, or during treatment. Patients who received blood transfusions had a significantly poorer prognosis than those who did not (Table 1). The 73 patients who received transfusion, had all a hemoglobin concentration below 6.8 mmol/l at the time of admission.

Patients treated before and after January 1978, i.e. at the time at which the continuous radiotherapy were changed into split-course schedules, showed no significant difference with respect to any of the 3 endpoints.

Multivariate analysis of prognostic factors. The multivariate analyses (Table 3) were partly in agreement with the pattern seen in the univariate analyses. High risk of local failure was strongly associated with lateral tumor extension, even after correcting for the significant effect of FIGO stage. Also young age and a high number of pregnancies had a significant negative influence on local control. Furthermore, patients treated during the period with split-course radiotherapy did significantly worse than patients treated with continuous radiotherapy.

The risk of distant metastases increased significantly with decreasing tumor cell differentiation, low hemoglobin at the time of admission, and split-course strategy. Stage had no independent prignostic value for distant metastases.

Crude survival was generally influenced by the characteristics that were significantly associated with either local control or distant metastases, however with two exceptions; number of pregnancies did not reach significance in the analysis of survival, nor did young age. The explanation for the latter finding is possibly the fact that the increased mortality from all causes with increasing age has offset the negative influence of young age.

Prognostic effect of treatment strategy and radiotherapeutic regimen. The multivariate analysis showed an increased risk of local failure, distant metastases and death (Table 3) in all patients treated according to the split-course strategy, while there was no significant prognostic effect of treatment strategy on the 3 endpoints in the univariate analysis (Table 2).

In the time periods of different treatment strategies, there was basically 3 different radiotherapeutic regimens consisting of different combinations of external and intracavitary radiotherapy depending on tumor size. Table 4 shows that in patients with tumors less than 4 cm or between 4 and 8 cm in diameter there was no significant difference between estimates of local control and crude

Table 4

Radiotherapeutic regimens

Radiotherapeutic regimens	Number of patients	5-years actuarial estimates of	
		Local control	Crude survival
Intracavitary radiotherapy alone	16	32 ± 17	25 ± 11
Combined external and intracavitary radiotherapy			
tumors less than 4 cm in diameter			
1974–1977	15	100	60 ± 13
1978–1983	18	83 ± 9	44 ± 12
		p = 0.09	p = 0.30
tumors 4–8 cm in diameter			
1974–1977	40	75 ± 7	53 ± 8
1978–1983	57	71 ± 6	47 ± 6
		p = 0.39	p = 0.43
tumors more than 8 cm in diameter			
1974–1977	101	61 ± 5	40 ± 5
1978–1983	150	49 ± 5	29 ± 4
		p = 0.03	p = 0.04
Radiotherapeutic regimen not specified before treatment start	27	34 ± 11	15 ± 7

survival in relation to treatment strategy. However, in patients with tumors larger than 8 cm the 5-year actuarial estimates of local control and crude survival were significantly higher in patients planned to receive continuous radiotherapy than in those planned to receive split-course treatment (Table 4, Figure).

The results of different treatment strategies in the periods from 1974 to 1978 and from 1978 to 1984 including all patients may be biased by differences between the radiotherapeutic regimens applied to patients with different tumor sizes. Therefore multivariate analyses, including the same characteristics as examined for all patients, were performed in the group of patients with tumors larger than 8 cm in diameter (Table 5). Almost all these patients would be classified as FIGO stage IIIB or IVA.

The almost similar results of prognostic important factors found in all patients (Table 3) and in patients with tumors larger than 8 cm (Table 5) indicate that a treatment strategy with a planned prolonged overall treatment time had a significantly adverse effect on both local control and survival in patients with large tumors.

Discussion

In the multivariate analysis, young patients ran an increased risk of local failure, whereas age <50 years showed no significant prognostic effect on development of distant metastases, as was also reported by Kapp et al. (4) and Lowrey et al. (11). As a consequence of the poorer local outcome in the younger patients, the crude survival was not significantly influenced by the patients' age, apparently because the increased risk of dying of cancer following local failure counteracted the natural age-related risk of death. A similar lack of age effect on crude survival has been reported by others (6, 13), but several studies have also described either a higher (4, 7, 9) or a lower survival in young patients (8, 10).

In contrast to our results, which showed a poor local control with increasing number of pregnancies, Kapp et al. (4) found that patients with few pregnancies had poor local control and disease-free survival. They suggested that a narrow vagina in these patients may have caused difficulties in application of the intracavitary sources leading to lower tumor doses. However, our results may be explained by cervical and uterine adhesions and scar formations in parous patients resulting in hypoxic areas in the cervix and uterus, which may lead to decreased local control due to increasing tumor hypoxia. Also, in a recent study by Höckel et al. (22) intratumoral pO_2 and FIGO stage were found to be independent prognostic factors in cervical cancer.

In the present study, the influence of hemoglobin level at the time of admission exerted a significant prognostic effect on local control, probability of developing distant meta-stases and crude survival. Several studies have examined the effect of hemoglobin and blood transfusions on the prognosis in cervical cancer (4, 11, 12, 16, 21, 23). An almost unanimous observation has been that low hemoglobin values were associated with a decreased local control probability and frequently associated with a similar reduction in disease-free or crude survival probability (4, 12, 16, 21, 23). Only the study by Lowrey et al. (11) did not observe this correlation, but they analyzed only patients in FIGO stages I and II. However, they found an

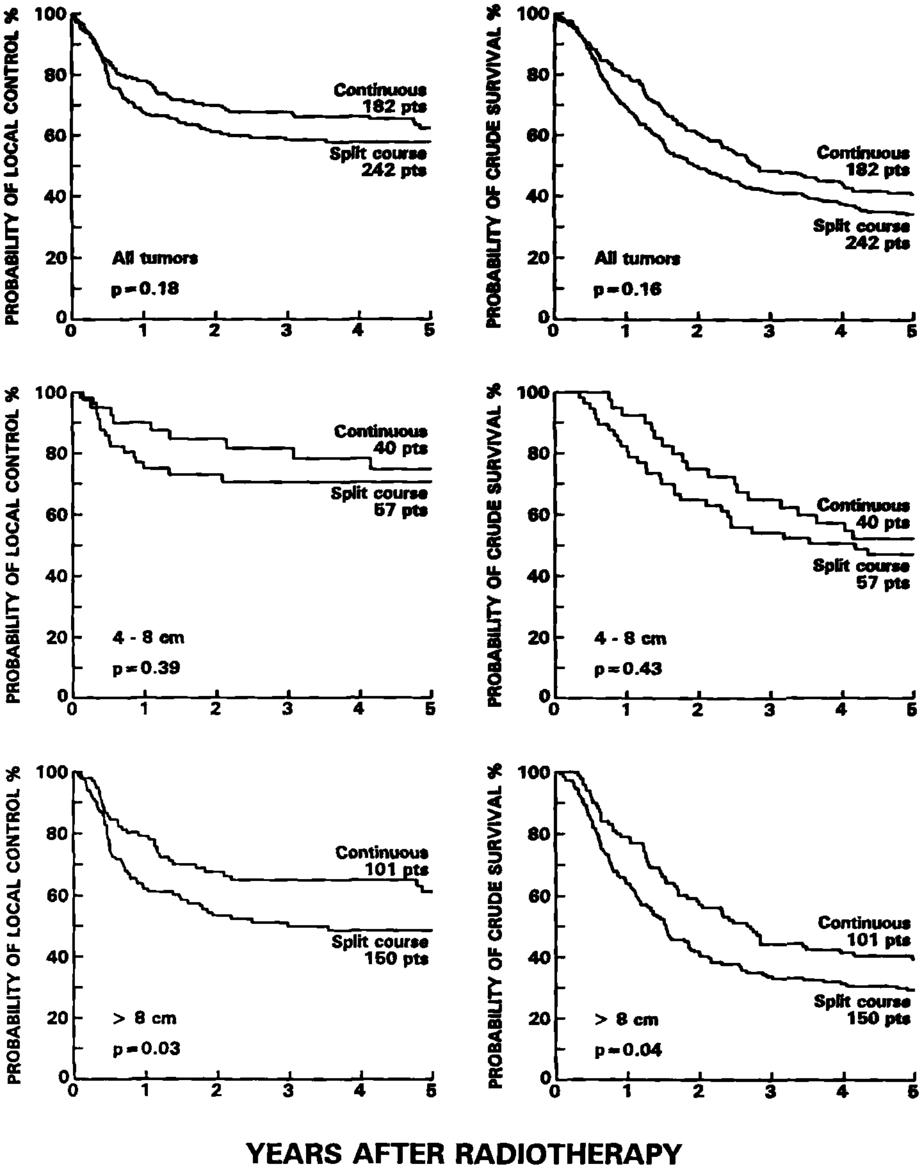

Figure. Actuarial estimates of local control and crude survival in patients with tumors of all sizes and tumors between 4 to 8 cm or more than 8 cm as a function of continuous or split-course radiotherapeutic strategy.

increased risk of distant metastases with decreasing hematocrit which is in accordance with our current, but in contrast to our previous results, (21) and to the results found in other studies (8, 16).

In our department, it was not the policy to transfuse anemic patients to a specific level of hemoglobin prior to radiotherapy, but in general patients with clinical sign of anaemia were transfused before treatment. The apparent lack of an independent prognostic effect of blood transfusion on prognosis is due to this policy, because all transfused patients belonged to the lower quartile of the hemoglobin at the time of admission. Therefore, these two factors are strongly dependent and cannot be separated. Assuming that the influence of hemoglobin on local tumor control is only caused by increased hypoxia, it should be expected that transfusion would improve prognosis in patients with low hemoglobin levels. In the present study, almost all patients with low hemoglobin values have been transfused, and it is therefore impossible to separate the two factors, which both must be considered to be associated with a poor prognosis. The strong relationship between low hemoglobin during treatment and poor prognosis found in the univariate analysis is probably partly due to the above mentioned problems. Hemoglobin during radiotherapy was neither measured frequently nor included in the multivariate analysis because it is not a pretreatment factor, but our findings are nevertheless strongly in agreement with the results by Girinsky et al. (12).

Table 5

*Cox multivariate regression analysis of patients with tumors above 8 cm**

Characteristics	Local failure			Death		
	p-value	RR	95% confidence	p-value	RR	95% confidence
Age	0.81			0.12		
Age <50 years	0.004	1.85	(1.22–2.81)	0.17		
No. pregnancies	0.007	1.12	(1.04–1.22)	0.36		
Bleeding as symptom	0.24			0.33		
Pain as symptom	0.13			0.32		
Delay (months)	0.45			0.07		
Hb at admission (mmol/l)	0.03	0.85	(0.73–0.99)	0.03	0.88	(0.80–0.96)
Transfusion	0.16			0.78		
FIGO (IIb, IIIa, IIIb, IVa)	0.13			0.004	1.20	(1.05–1.37)
Adenocarcinoma	0.23			0.03	2.56	(1.40–4.76)
Degree of differentiation	0.07			0.06		
Lateral tumor size (cm)	0.002	1.18	(1.06–1.30)	0.0003	1.12	(1.04–1.21)
Proximal-distal tumor size (cm)	0.39			0.81		
Split-course treatment	0.006	1.80	(1.17–2.79)	0.02	1.44	(1.07–1.95)

*Includes 236 patients in whom all characteristics are recorded

To our knowledge the prognostic effect of symptoms has not been examined in prior studies. In the univariate analysis, vaginal bleeding as a primary symptom exerted a significant good prognostic influence on crude survival, whereas this finding could not be confirmed by the multivariate analysis. This may be due to the fact that vaginal bleeding was found to be correlated with a low FIGO stage ($p = 0.02$, Spearman's rank correlation test). A similar correlation was also found between high FIGO stage and pain as symptom ($p = 0.008$).

The time from the first symptom noticed by the patient until diagnosis was established was short (median 3 months) and may explain why the delay was of no prognostic importance.

The independent prognostic effect of FIGO stage on local control and/or crude survival which decreased with increasing stage, has been reported in several studies (4, 6–10, 13, 16, 24), although stage has also been described to be prognostically unimportant (8, 11, 12). In patients with cervical cancer it may be difficult to know whether the influence of prognostic factors on local control is different from the effect on crude survival due to the fact that almost all patients with local failures will die from the malignant disease. However, development of distant metastases may be expected to be related to intrinsic tumor cell characteristics as e.g. histopathologic tumor type and degree of differentiation rather than FIGO stage, although metastases also may be a consequence of local failure (25).

Patients with adeno/adenosquamous cell tumors showed an increased risk of death and local failure, although the latter was only observed in the univariate analysis. A decreased survival in patients with adenocarcinomas has previously been reported (4, 7, 9, 11, 24), while some found that histopathological tumor type was unimportant to the risk of local failure and distant metastastases (8, 11, 13). In the present study, degree of tumor cell differentiation exerted independent prognostic effect on the risk of distant metastases and death, which increased by increasing malignancy grade. This is in agreement with the results of others (7, 9, 13, 26), although Stehman et al. (8) did not find a prognostic effect of grade of malignancy.

The FIGO classification does not include an evaluation of tumor size, but of tumor extension. This may explain the independent strong prognostic effect of lateral tumor diameter on local control and crude survival in the present study. It may also be assumed that large tumors are less well oxygenated and have more tumor stem cells than small ones (27). Other authors have also described a prognostic effect of tumor size on local control and survival (4–6, 8, 9, 11). In the univariate analysis, an influence of a large proximal-distal tumor diameter on the occurrence of distant metastasis was observed. This may be due to a higher probability of involved paraaortic lymph nodes in such large tumors, although this diameter was not prognostically significant in the multivariate analysis.

The split-course radiotherapeutic strategy from 1978 to 1984 implied a longer total treatment time compared with the continuous strategy from 1974 through 1977. Also, the dose contributions from the intracavitary and external radiotherapy in separate treatment regimens differed in the two time periods. The significant independent adverse effect of split-course radiotherapy on local control, probability of developing distant metastases, and crude survival analyzed in all patients may therefore be biased. However, the result was supported by the finding of a similar prognostic profile in all patients and in the subgroup with tumors larger than 8 cm (Tables 3 and 5), and at least this result could partly be explained by an increased repopulation of tumor cells during the course of radiotherapy (28, 29). This finding is in agreement with Fyles et al. (30), who observed a significant relationship between overall treatment time and response to radiotherapy in cervical carcinoma, and with the report by Lanciano et al. (14) of an increased risk of pelvic failure and survival in stage III patients as the total treatment time was prolonged.

In conclusion, the following factors exerted a significant prognostic effect on local control, distant metastases and/or crude survival: young age (<50 years), number of pregnancies, hemoglobin at the time of admission, FIGO stage, lateral tumor diameter, histopathologic tumor type, tumor cell differentiation, and treatment strategy.

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