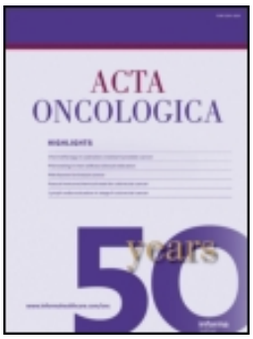

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Prognostic Significance of Pretherapeutic and Therapeutic Factors in Patients with Advanced Cancer of the Uterine Cervix Treated with Radical Radiotherapy Alone

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The prognostic importance of various pretherapeutic and therapeutic factors was analysed in a group of 413 cervical cancer patients with stage IIB (183 pts) and IIIB (230 pts) treated with radical radiotherapy, which consisted of external irradiation and intracavitary brachytherapy. Univariate analysis of pretherapeutic factors revealed the prognostic significance of patient age, history of abortion, stage, haemoglobin and hematocrit levels. Five-year overall survival rate in stage IIB patients was 51%, in stage IIIB 40% and the respective rates for local control at each stage were 61%, and 46%. Univariate analysis of therapeutic factors showed that survival and local control rates increased with the dose, but a significant difference was found only in the case of a paracentral (point A) dose. In a multivariate analysis only patient age, abortions, and clinical stage appeared to have a significant and independent impact on survival. Linear regression analysis results indicated that prolongation of treatment time between 33 and 108 days caused a loss of local control of 0.36% per day.

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Cancer of the uterine cervix is the second most common neoplasm in female patients in Poland. In 1993, 3903 new cases were registered and 2028 women died of this disease, which gives an incidence of 19.8/100000 and mortality of 10.3/100000 (1). Unfortunately, as many as 40% of patients are diagnosed with advanced disease (1–3).

Radiotherapy is the treatment of choice in patients with advanced cancer of the uterine cervix and routinely consists of a combination of external irradiation and intracavitary brachytherapy (4–10). The optimal combination of these methods has not been clearly defined.

Identification of patients with a high risk of recurrence as well as the radiotherapy parameters influencing outcome is important in the development of better treatment strategies.

The aim of our study was to analyse the prognostic importance of various pretreatment and treatment factors in patients with advanced cancer of the uterine cervix treated with radical radiotherapy.

MATERIAL AND METHODS

Between January 1970 and December 1980, 413 patients with cancer of the uterine cervix, stages IIB and IIIB according to FIGO classification, were treated at the Centre of Oncology in Cracow.

The mean age of the patients was 53.1 years (range 25–76 years), and the mean duration of symptoms was 7.5 months with a range of from 1 to 72 months. Most (62%) of the patients were postmenopausal and 38% were still menstruating.

Squamous cell cancer was diagnosed in 93% of patients, undifferentiated cancer was found in 5%, and adenocarcinoma in 2%.

Treatment techniques

All patients were treated with teleradiotherapy (TRT) and brachytherapy (BRT). In 95% of patients TRT was given first; in 5% treatment was started with BRT.

TRT techniques. Two opposing beams were used in 48% of patients, mainly between 1970 and 1975. Tumour dose

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Table 1

Doses at points A (paracentral doses) and points B (parametrial doses)

Doses at points A (Gy)	No. patients	Doses at points B (Gy)	No. patients
<40	2	<50	11
40–<60	35	50–<55	28
60–<80	124	55–<60	159
80–<100	84	60–<65	59
100–<120	159	65–<70	134
>120	9	70–<75	21
		≥75	1

calculated on the central axis at the mid-distance between fields was 40 Gy in 20 fractions over 4 weeks. Central shielding was used in the majority (93.5%) of patients. In 19.4% shielding was applied from the beginning of TRT; in 74.1% it was introduced after the dose of 20 Gy and in the remaining 6.5% of patients shielding was not used.

During the second half of the study (after 1975), 235 patients (52%) were irradiated with four beams: anterior–posterior and two lateral; the so-called 'box' technique. The tumour dose of 50.4 Gy in 24 fractions over 5 weeks was applied without shielding. TRT was performed with ^{60}Co equipment in 93% of patients, and the remaining 7% were treated with 18 MeV photons from a Betatron. External irradiation was completed according to schedule in 83% of patients; 17% did not receive a full dose because of excessive acute reactions, concurrent disease, patient refusal, and machine break-downs.

BRT techniques. BRT was performed according to a modified Paris technique and consisted of a single application of an intrauterine tube and fornix ovoids containing radioactive sources of ^{226}Ra (92% of pts) or ^{137}Cs (8% of patients).

The dose rates at points A (as defined in the Manchester system) and the rectum were calculated using our own computer program described by Szymczyk et al. (11). The calculations were based on the radiographs of the sources taken at two projections.

Between 1970 and 1975 a fixed time of BRT equal to 120 h was applied irrespective of the calculated dose rate, which resulted in doses of 44 Gy to 81 Gy to points A. Later, this approach was changed and BRT time was calculated according to individual dose rate in order to deliver to point A the dose biologically equivalent to 60 Gy in 168 h (100 TDF) using the TDF formula proposed by Elis & Sorensen (12) and Orton (13). BRT was completed according to the planned schedule in 94% of patients. In 6% it had to be terminated earlier because of acute pelvic symptoms or intercurrent medical conditions.

The total dose from TRT and BRT was calculated by analysis of individual treatment plans. This is defined as the sum of the physical doses delivered during external and intracavitary irradiation. Two doses were calculated:

1. The paracentral dose (point A) is the sum of the BRT dose at point A plus the TRT dose allowing for central shielding. The range of the paracentral dose was 44 to 131 Gy (mean 88.3 Gy). These large variations in total paracentral dose resulted from the already described change in treatment policies and techniques from the TRT alone paracentral dose varying from 0 (central shielding) for the whole TRT to 50 Gy (box technique). The variation in doses from BRT was also considerable because of large differences in dose rates at point A in individual patients and the described methods of choosing the intracavitary treatment time.
2. Peripheral dose (parametrial dose) is the sum of 30% of BRT dose to point A, plus the dose delivered by TRT. Mean peripheral dose amounted to 61.3 Gy ranging from 38 to 78.4 Gy. The distributions of the values of paracentral and peripheral dose are illustrated in Table 1.

The overall treatment time was defined as the sum of the duration of TRT, BRT, and all planned and unplanned pauses in the therapy course. Distribution of treatment duration is shown in Fig. 1. Mean treatment time was 64 days with a very wide range from 29 to 215 days. However, 75% of patients completed their treatment within 77 days.

Statistical analysis

The main endpoints in the assessment of treatment results were the 5-year rates of overall survival and local control. These rates were analysed in relation to pretreatment

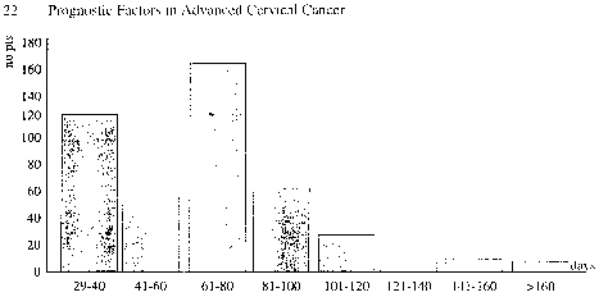

Fig. 1. Time of treatment.

Table 2

Univariate analysis of pretherapeutic factors: 413 patients, IIB and IIIB

Prognostic factor	Category	No. pts	5-years survival		5-years local control	
			%	p	%	p
Age	<45	80	27		36	
	45–49	77	43		47	
	50–54	74	42		62	
	55–59	66	56		61	
	60–64	53	58		63	
	>64	63	49	0.0088	53	0.0059
Duration of symptoms (months)	1–5	231	44		46	
	6–12	154	54		54	
	>12	28	62	N.S.	60	N.S.
Menarche	<14	87	44		45	
	14–16	168	53		52	
	>16	158	49	N.S.	51	N.S.
Still menstruating		160	43		44	
Last menstruation	≤50	163	52	N.S.	54	N.S.
	>50	90	55		56	
Parity	Nullipare	17	57		58	
	1–3	224	47		48	
	>3	172	51	N.S.	52	N.S.
Miscarriages	No	327	50		51	
	Yes	86	48	N.S.	50	N.S.
Abortions	No	311	48		57	
	Yes	102	34	0.0063	47	0.0027
Histology	Squamous cell	400	49		50	
	Other	13	52	N.S.	53	N.S.
Stage	IIB	183	51		61	
	IIIB	230	40	0.0053	46	0.0009
Hb level (mmol/l)	<10	72	34		46	
	10–12	184	43		50	
	>12	157	51	0.0148	59	0.0345
Ht level /1/1/	<36.6	141	38		47	
	36.6–40.1	130	43		52	
	>40.1	142	52	0.0075	59	0.0094
No. of white blood count	≤4 000	29	54		55	
	>4 000–10 000	334	50		51	
	>10 000	50	43	N.S.	45	N.S.

N.S. = non-significant.

variables and treatment factors. Pretreatment variables included: age, duration of symptoms, reproductive history details (age of menarche, menopausal status, number of deliveries, natural miscarriages and abortions), clinical stage, histology, levels of haemoglobin (Hb), hematocrit (Ht) and leukocyte numbers. Treatment parameters under consideration included: paracentral dose, peripheral dose and overall treatment time.

In the univariate analysis, the rates of 5-year overall and local relapse-free (local control) survival were estimated using the Kaplan–Meier method and the differences between rates were assessed with a logrank test. Subsequently, the multivariate analysis was performed with the Cox model (14). In addition, a linear regression analysis was carried out to assess the impact of overall treatment time on the probability of local control.

RESULTS

During the follow-up period 272 patients died: 232 of cervical cancer and 40 of other causes. Twenty-two patients were lost to follow-up after 9–89 months. Patients who were disease-free at the last examination and patients who died of non-cancer causes were considered as censored.

Univariate analyses of pretherapeutic and therapeutic factors

A univariate analysis of pretherapeutic factors is presented in Table 2.

Data from Table 1 show that the following factors had a deleterious effect on survival and local control: age (young vs. older patients), stage (IIIB vs. IIB), history of abortions (yes vs. no), Ht and Hb levels (low vs. normal).

Table 3 presents the univariate analysis of therapeutic factors, i.e.: paracentral dose, peripheral dose and overall treatment time. In this analysis, stage of disease is also taken into account.

Data from Table 3 show that survival and local control rates in general increased with the dose but a significant difference was found only in the case of paracentral dose for the whole group and for stage IIB patients. There was a tendency toward decreased local control rate with longer treatment time in stage IIIB patients, but this was not significant.

Multivariate analysis of pretherapeutic and therapeutic factors

The results of multivariate analysis of pretherapeutic and therapeutic factors according to the Cox model are presented in Table 4.

In multivariate analysis, only patients' ages, abortions, and clinical stage appeared to have a significant and independent impact on survival and local control.

Results of linear regression analysis of impact of overall treatment time on LRFS

This additional analysis was performed by dividing treatment time into narrow intervals. We felt that results obtained in patients treated either over a very short (less than 33 days) or a very long (over 108 days) time may be unreliable because these patients did not receive complete treatment or had unusually long intervals between TRT and BRT. After exclusion of these subgroups, the remain-

Table 3

Influence of doses and overall treatment time on survival and local control—413 patients IIB and IIIB

Prognostic factor (doses = Gy time = days)	Category	No. pts	5-year survival		5-year local control	
			%	p	%	p
Doses at points A	≤7 400	94	36		45	
IIB+IIIB	>7 400	319	47	0.0167	55	0.0203
Doses at points B	≤5 700	158	43		53	
IIB+IIIB	>5 700–6 500	99	44		44	
	≥6 500	156	46	N.S.	55	N.S.
Doses at points A	≤7 400	40	39		45	
IIB	>7 400	143	55	0.0169	65	0.0005
Doses at points B	≤5 700	77	47		59	
IIB	>5 700–6 500	48	48		54	
	≥6 500	58	56	N.S.	69	N.S.
Doses at points A	≤7 400	54	34		45	
IIIB	>7 400	176	42	N.S.	47	N.S.
Doses at points B	≤5 700	81	39		48	
IIIB	>5 700–<6 500	51	40		43	
	≥6 500	98	41	N.S.	46	N.S.
Time of treatment	≤35	91	43		55	
IIB+IIIB	>35–<65	100	47		56	
	≥65–<75	101	46		51	
	≥75	121	43	N.S.	49	N.S.
Time of treatment	≤35	47	49		65	
IIB	>35–<65	44	53		59	
	≥65–<75	45	50		59	
	≥75	47	51	N.S.	61	N.S.
Time of treatment	≤35	44	37		45	
IIIB	>35–<65	56	42		55	
	≥65–<75	56	43		45	
	≥75	74	39	N.S.	42	N.S.

N.S. = non-significant.

Table 4

Multivariate analysis (Cox model) of prognostic factors for overall and local control relapse-free survivals in the group of 413 patients with advanced cancer of the uterine cervix

Prognostic factor	Category	Overall survival		Local control	
		RR	p	RR	p
Age	145	1.00		1.00	
	<45	1.63	0.0034	1.54	0.0158
Abortion	No	1.00		1.00	
	Yes	1.31	0.0856	1.44	0.0438
Stage	IIB	1.00		1.00	
	IIIB	1.38	0.0251	1.50	0.0124

ing 365 patients were divided into 16 time interval groups—each comprising 19 to 27 patients. Mean and median treatment times for each interval were calculated as well as a probability of local control. These values were subsequently used for linear regression analysis, the results of which are presented in Fig. 2. Data from the figure showed that prolongation of treatment for between 33 and 108 days causes a small but significant loss of local control of 0.36% per day.

DISCUSSION

Pretherapeutic factors

The main cause of treatment failure in patients with advanced cancer of the uterine cervix is the inability to control local disease within the cervix and parametria. Distant metastases are of relatively minor importance particularly because their incidence appears to be strongly correlated with uncontrolled disease in the pelvis (15, 16).

Treatment results obtained in our group of patients with advanced cancer of the uterine cervix are similar to those published in the literature. According to the Annual Report on Results of Treatment in Gynaecological Cancer (17), which included data from many centres during the period 1976–1978, the 5-year overall survival rate in stage II patients was 60% and in stage III patients between 20 and 35%. Yonessi (10) summarized the published data on the results of radiotherapy of advanced cervical cancer and defined the efficacy of this method at the level of 56% 5-year survival in stage IIB and 37% in IIIB patients. Higher survival rates (76% for IIB and 50% for IIIB) were obtained in a large group of patients treated in nine French centres, as reported by Horiot et al. (4). In Table 5 our results are presented in comparison with data from several large series.

In our analysis of pretherapeutic prognostic factors, only age, clinical stage and history of abortion appeared to be significant in the multivariate analysis; in addition, Ht and Hb levels were found significant in the univariate analysis. Young age was found to be associated with poor prognosis in many other reports, although in most publications the correlation was not so strongly significant and the cut-off values were different, e.g. 35, 40, 50 years (18–22). In general, age is not considered to be the only factor influencing therapeutic decisions.

We found that clinical stage IIB vs. IIIB was of prognostic significance, which is in agreement with numerous reports from the literature (2–4, 6, 7, 9, 16, 21). FIGO classification, although simple and widely accepted, has also been criticized because it does not take into account the tumour volume and the exact anatomical extension of the disease within the vagina, uterine body, parametria and pelvic nodes (4, 16–19, 23, 24). Our observations (results not presented here) indicate that within the same FIGO stage, prognosis may be different in relation to the extent and bulk of disease, e.g. unilateral vs. bilateral parametrial involvement, fixation of the uterus, etc.

The Hb level was found to be of prognostic significance in our univariate analysis, but not confirmed by multivariate Cox analysis. Low value of pretreatment Ht or Hb was correlated with poor prognosis in many other studies (25–27). Dische (26) summarized the results of 16 retrospective studies in which the influence of anaemia on the results of radiotherapy in patients with cervical cancer was assessed. Most of these studies confirmed, although to varying degrees, the correlation between low Hb levels and decreased local control or survival.

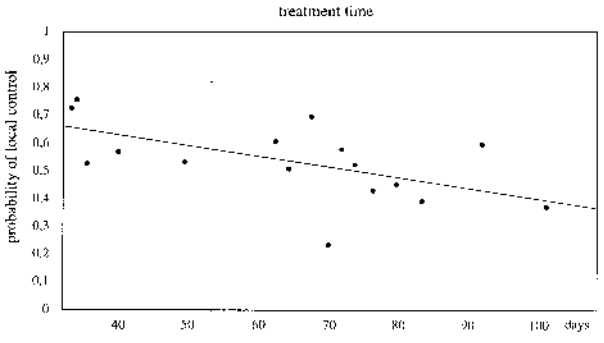

Fig. 2. Result of analysis of the influence of total radiotherapy time on local control in 365 stage IIB + IIIB patients with total treatment times of 33 to 108 days.

Table 5

Results of treatment of advanced cervical cancer

Author (ref.)	Stage	No. pts	% 5-year survival	% of 5-year pelvic relapse
Hunter (5)	III	296	39.5	43.0
Horiot (4)	IIB	314	76.0	10.0
	IIIA	266	62.0	15.0
	IIIB	216	50.0	28.0
Lanciano (6)	II	291	65.0 (4-year)	20.0 (4-year)
	III	131	48.0 (4-year)	47.0 (4-year)
Perez (44)	IIB	352	72.0	23.0
	III	293	52.0	47.0
Karolewski (this study)	IIB	183	51.0	39.0
	IIIB	230	40.0	54.0

A common explanation for this observation is the radioresistance of cancer cells due to hypoxia. Höckel et al. (28) reported a prognostic significance of the frequency of low pO_2 value and of the median pO_2 in cancer of the uterine cervix. The results of a randomized trial conducted by Bush et al. (25) demonstrated that blood transfusion may improve the results of radiotherapy in patients with low Hb before treatment. On the other hand, the degree of anaemia could correlate with a more advanced stage due to more intensive bleeding. A poorer prognosis was also observed in a patient who required blood transfusion during radiotherapy (27). Usually bleeding is diminished or stopped within 1 or 2 weeks from the beginning of irradiation. It is hypothesized that in patients who continue to bleed during treatment, the tumour does not regress, because of its radioresistance or rapid proliferation. It is therefore possible that different mechanisms contribute to a poorer prognosis in patients with low Hb levels: radioresistance as a result of hypoxia in anaemic patients, but also anaemia, may be more frequent in patients with more advanced, aggressive or inherently radioresistant cancer.

A history of abortion appeared to be an independent prognostic indicator in our analysis. In the literature we did not find any relevant publications on this subject. Furthermore, other parameters of reproductive history such as number of pregnancies and deliveries are rarely analysed.

Pedersen et al. (29) have recently reported decreased local control with increasing number of pregnancies. They sought to explain this finding as being due to formation (in parous patients) of cervical and uterine adhesions and scars which could lead to hypoxia and consequently to decreased local control.

Our observation of lower local control and survival in patients with a history of abortions is difficult to interpret and certainly needs confirmation in other studies. One might speculate that patients with a history of abortions are likely to have a more intensive sexual life, possibly with many partners, which could be connected with a higher frequency of HPV infection. This infection was found to correlate with poor prognosis in patients with cervical cancer (30).

Therapeutic factors

Schedules of radiotherapy used in various centres show considerable variations in techniques, dose specifications, treatment time, and so on. Assessment of the influence of total tumour dose on treatment results is difficult because of the combination of external and intracavitary irradiation. Dose distribution from brachytherapy is inevitably inhomogeneous, with a rapid fall in both dose and dose

Table 6

Loss of pelvic control in % per day of prolonged treatment in cancer of uterine cervix

First author (ref.)	No. pts	Stage II	Stage III	All stages
Fyles (37)	830	0.5%	0.8%	1–1.2%
Lanciano (30)	837	N.S.	0.8%	0.1–0.5%
Girinsky (38)	386			1–1.6%
Peterait (41)	209	0.3%	0.6%	0.7%
Perez (40)	1 224	0.68% (IIB)	0.45%	0.85%
Karolewski (this study)	339			0.36% (IIB + IIIB)

N.S. = non-significant.

rate. Radiobiological mechanisms of action of fractionated and continuous irradiation are different. Therefore the simple addition of physical doses from tele- and brachytherapy at selected points is probably not appropriate; nevertheless this approach is commonly used in the literature and is in agreement with the ICRU 38 Report recommendations.

We found an improvement in local control and survival rates with higher paracentral and lateral doses, but the difference was significant only in the case of paracentral dose, particularly in patients with stage IIB disease. One should stress that in our group of patients stage did not influence the technique and dose, which is in contrast to some other series in which treatment volume and dose were modified in relation to stage: for example, elective irradiation of para-aortic nodes or parametrial boost. The influence of the total physical dose on results was confirmed in several publications. Perez et al. (9) reported higher local control in patients who received above 90 Gy to point A in comparison with those treated with lower doses. Furthermore, lateral dose above 45 Gy in stage IIB and above 60 Gy in stage IIIB resulted in approximately 10% higher control rates than lower doses. Similarly, a pattern on care study (31), which includes results from many US centres, reports that the relationship between dose and local control was found at least in some subgroups of patients.

In recent years, many reports on primarily radiotherapy of head and neck cancer have demonstrated a correlation between prolonged treatment time and decreased local control and survival (32–36). The commonly accepted explanation of this relationship is repopulation of tumour cells during radiotherapy.

In the case of cancer of the uterine cervix, this correlation has also been observed (29, 30, 37–44). Mendenhall et al. (40) found that in bulky IIB cervical cancer, local control rate was significantly decreased in patients with a treatment duration of longer than 60 days (50% vs. 79%). Recently, Pedersen et al. (29) reported lower local control and survival in patients treated with split-course irradiation (overall time 10–12 weeks) in comparison with those who received continuous treatment (4–6 weeks).

So far, more detailed analyses of this relationship include five reports in which the deleterious effect of treatment prolongation was calculated in terms of loss of pelvic control or survival per day of this prolongation. These data, with the addition of our own, are presented in Table 6. In all these studies some decrease in control rate per day was found. These figures are lower than those published for head and neck cancer perhaps because in patients with cervical cancer higher total doses are applied from a combination of tele- and brachytherapy.

In their recent editorial Eifel & Thames (37) concluded that these retrospective studies 'Do not prove causative relationship between treatment protraction and local recurrence'. In their opinion there are numerous reasons why patients with a poor prognosis have relatively protracted treatment, for example more advanced stage, poor response to radiotherapy, treatment complications, and so on. All of these factors could increase the duration of treatment because, for example, a teleradiotherapy boost is used or brachytherapy is delayed to allow for tumour regression after external irradiation. These correlations may confound the analysis of the impact of treatment prolongation on local control. Nevertheless, our results and data from the literature suggest that the prolongation of overall treatment time may be harmful and that unnecessary treatment breaks should be avoided.

REFERENCES

1. Zatoński WA. Nowotwory złośliwe w Polsce. Warszawa: Centrum Onkologii, 1993.
2. Koszarowski J, Gadomska H, Wronkowski Z, Romejko M. Epidemiologia nowotworów złośliwych w Polsce w latach 1952–1982. Nowotwory 1985; 35: 93–113.
3. Tarłowska L, Kamińska G, Mielcarzewicz Z, et al. Zmiany zachodzące w składzie i wynikach leczenia chorych na raka szyjki macicy badanych i leczonych w polskich zakładach onkologicznych. Nowotwory 1979; 29: 183–99.
4. Horiot JC, Pigneux J, Pourquier H, et al. Radiotherapy alone in carcinoma of the intact uterine cervix according to G. H. Fletcher/Guidelines: a French cooperative study of 1383 cases. Int J Radiat Oncol Biol Phys 1988; 14: 605–11.
5. Hunter RD, Cowie VJ, Blair V, Cole MP. A clinical trial of two conceptually different radical radiotherapy treatments in stage III carcinoma of the cervix. Clin Radiol 1986; 37: 23–7.
6. Lanciano RM, Won M, Coia LR, Hanks GE. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 patterns of care studies. Int J Radiat Oncol Biol Phys 1991; 20: 667–76.
7. Montana GS, Fowler WC, Varia MA, Walton LA, Marck Y, Shemanski L. Carcinoma of the cervix stage III. Results of radiation therapy. Cancer 1986; 57: 148–54.
8. Perez CA, Breaux S, Madoc-Jones H, et al. Radiation therapy alone in the treatment of carcinoma of the uterine cervix. I. Analysis of tumor recurrence. Cancer 1983; 51: 1393–402.
9. Perez CA, DiSaia PJ, Knapp RC. Gynecologic tumors. In: Cancer principles and practice of oncology. 2nd ed. Philadelphia: J.B. Lipincott, 1985: 1013–41.
10. Yoonessi M. Treatment of advanced invasive cervical cancer. Changing times and trends. J Surg Oncol 1984; 26: 161–7.
11. Szymczyk W, Siuda J, Medvey W, Polak B, Polok B. Rozkład dawek w obrębie miednicy mnieszej w leczeniu raka szyjki macicy. Pol Przegl Rad I Med Nukl 1971; XXXV: 475–80.
12. Ellis F, Sorensen A. A method of estimating biological effect of combined intracavitary low dose rate radiation with external radiation in carcinoma of the cervix uteri. Radiology 1974; 110: 681–6.
13. Orton CG. Time–dose factors (TDFs) in brachytherapy. Br J Radiol 1974; 47: 603–7.
14. Cox DR. Regression models and life tables. J R Stat Soc 1972; 34: 187–220.
15. Fagundes H, Perez CA, Grigsby PW, Lockett MA. Distant metastases after irradiation alone in carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1992; 24: 197–204.

16. Fletcher GH. Squamous cell carcinoma of the uterine cervix. In: Textbook of radiotherapy. Philadelphia: Lea and Febiger, 1980: 720–73.
17. Pettersson F. Annual report on the results of treatment of gynecological cancer. International Federation of Gynecology and Obstetrics, vol. 21. Stockholm, 1993.
18. Ashby MA, Smales E. Invasive carcinoma of the cervix in young women: clinical data and prognostic features. Radiother Oncol 1987; 10: 167–74.
19. Benstead K, Cowie VJ, Blair V, Hunter RD. Stage III carcinoma of the cervix. The importance of increasing age and extent of parametrial infiltration. Radiother Oncol 1986; 5: 271–6.
20. Carmichael JA, Clarke DH, Moher D, Ohlke ID, Karchmar EJ. Cervical carcinoma in women aged 34 and younger. Am J Obstet Gynecol 1986; 2: 264–8.
21. Kapp DS, Fischer D, Gutierrez E, Kohorn EI, Schwartz PE. Pretreatment prognostic factors in carcinoma of the uterine cervix: a multivariable analysis of the effect of age, stage, histology and blood counts on survival. Int J Radiol Oncol Biol Phys 1983; 9: 445–55.
22. Spanos WJ, King A, Keeney E, Wagner R, Slater JM. Age as a prognostic factor in carcinoma of the cervix. Gynecol Oncol 1989; 35: 66–8.
23. Jampolis S, Andras EJ, Fletcher GH. Analysis of sites and causes of failures of irradiation in invasive squamous cell carcinoma of the intact uterine cervix. Radiology 1978; 115: 681–5.
24. Perez CA, Camel HM, Askin F, Breaux S. Endometrial extension of carcinoma of the uterine cervix: a prognostic factor that may modify staging. Cancer 1981; 48: 170–80.
25. Bush RS. The significance of anemia in clinical radiation therapy. Int J Radiat Oncol Biol Phys 1986; 12: 2047–50.
26. Dische S, Anderson PJ. Carcinoma of the cervix—anaemia, radiotherapy and hyperbaric oxygen. Br J Radiol 1983; 56: 251–255.
27. Girinsky T, Pejovic MH, Bourhis J, et al. Prognostic value of hemoglobin concentrations and blood transfusions in advanced carcinoma of the cervix treated by radiation therapy: results of a retrospective study of 386 patients. Int J Radiat Oncol Biol Phys 1989; 16: 37–42.
28. Höckel M, Vorndran B, Schlenger K, Baussman E, Knapstein PG. Tumor oxygenation: a new predictive parameter in locally advanced cancer of the uterine cervix. Gynecol Oncol 1993; 51: 141–149.
29. Pedersen D, Sogaard H, Overgaard J, Bentzen SM. Prognostic value of pretreatment factors in patients with locally advanced carcinoma of the uterine cervix treated by radiotherapy alone. Acta Oncol 1995; 34: 787–95.
30. Schneider A. HPV infections in women and their male partners. Contemp Obstet Gynecol 1988; 32: 131.
31. Lanciano RM, Pajak TF, Martz K, Hanks GE. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: a patterns-on-care study. Int J Radiat Oncol Biol Phys 1993; 25: 391–397.
32. Barton MB, Keane TJ, Gadalla T, Maki E. The effect of treatment time and treatment interruption on tumor control following radical radiotherapy of laryngeal cancer. Radiother Oncol 1992; 23: 137–43.
33. Bentzen S, Johansen LV, Overgaard J, Thames HD. Clinical radiobiology of squamous cell carcinoma of the oropharynx. Int J Radiat Oncol Biol Phys 1991; 20: 1197–1206.
34. Fowler JF, Tanner MA, Bataini JP, Asselain B, Bernier J, Lave C. Further analysis of the time factor in squamous cell carcinoma of the tonsillar region. Radiother Oncol 1990; 19: 237–44.
35. Keane TJ, Fyles A, O'Sullivan B, Barton M, Maki E, Simm J. The effect of treatment duration on local control of squamous carcinoma of the tonsil and carcinoma of the cervix. Semin Rad Oncol 1992; 2: 26–8.
36. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988; 27: 131–46.
37. Eifel PJ, Thames HD. Has the influence of treatment duration on local control of carcinoma of the cervix been defined? Int J Radiat Oncol Biol Phys 1995; 32: 1527–9.
38. Fyles A, Keane TJ, Barton M, Simm J. The effect of treatment duration in local control of cervix cancer. Radiother Oncol 1992; 25: 273–9.
39. Girinsky T, Rey A, Roche B, et al. Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. Int J Radiat Oncol Biol Phys 1993; 27: 1051–6.
40. Mendenhall WM, Thar TL, Bova FJ, Marcus RB, Morgan LS, Million RR. Prognostic and treatment factors affecting pelvic control of stage IB and IIA–B carcinoma of the intact uterine cervix treated with radiation therapy alone. Cancer 1984; 53: 2649–54.
41. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys 1995; 32: 1275–88.
42. Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 1995; 32: 1301–7.
43. Keys H, Gibbons SK. Optimal management of locally advanced cervical carcinoma. J Natl Cancer Inst Monogr 1996; 21: 89–92.
44. Perez CA, Grigsby PW, Nene SM, et al. Effect of tumor size on prognosis of carcinoma of the uterine cervix treated with irradiation alone. Cancer 1992; 69: 2796–806.