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Prognostic Significance of Pretreatment Serum Levels of Squamous Cell Carcinoma Antigen and CA 125 in Cervical Carcinoma

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Serum levels of squamous cell carcinoma antigen SCC, carcinoembryonic antigen CA 125, and tissue polypeptide antigen were determined in 142 patients with primary cervical carcinoma, 60 patients with precancerous lesions and in 129 healthy women. With regard to elevated tumour marker levels, specificity ranged from 94.6% to 97.7%. Sensitivity was highest (44.4%) for SCC. A stage relation was found for all tumour markers except for carcinoembryonic antigen. In stage Ib, SCC levels increased according to tumour volume. SCC, CA 125 or both markers were elevated in 7 of 8 patients with pelvic lymph node metastases compared with only 17 of 58 patients with negative nodes ($P = 0.005$). In a multivariate analysis, pretreatment serum levels of SCC and CA 125 were found to be significantly related to patient survival, in addition to stage. In cervical SCC, the risk of a fatal outcome increased 16 times with SCC levels ≥ 4.5 ng/ml, compared with SCC levels ≤ 1.3 ng/ml. We conclude that pretreatment serum levels of SCC may be of value as an adjunct to clinical staging. In addition, serum determinations of SCC and CA 125 seem to be useful in predicting the risk of pelvic lymph node metastases and as prognostic risk factors for disease outcome.
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INTRODUCTION

THE OVERALL incidence of cervical carcinoma has declined in Sweden during the last decades, constituting 2–3% of newly diagnosed cancers in women today [1]. Although many of these women present clinically in early stages of cervical carcinoma, which indicate a favourable prognosis, 10–20% of them will die of their disease [2].

The extension of disease, estimated by clinical staging according to the International Federation of Gynaecology and Obstetrics (FIGO), is usually the factor which determines the mode of treatment and the disease outcome. Several authors have suggested that the volume of the tumour is of prognostic value [3]. However, treatment is more or less identical for a given stage (especially in the early stages) despite sometimes significant variations in tumour volume.

The discrepancies between clinical and surgical staging, which

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Table 1. Clinical data concerning patients with cervical carcinoma

Group	Total *n*	Stage (FIGO) Ia (*n*)	Ib (*n*)	IIa (*n*)	IIb (*n*)	IIIa (*n*)	IIIb (*n*)	IVa (*n*)	IVb (*n*)
Cervical carcinoma	142	2	64	29	14	5	20	4	4
Squamous	117	2	50	24	12	5	17	4	3
Adenocarcinoma	16	—	9	2	2	—	3	—	—
Adenosquamous	8	—	5	2	—	—	—	—	1
Undifferentiated	1	—	—	1	—	—	—	—	—
Age: median (range)		43	(22–81)	58	(24–90)	62	(28–84)	67	(55–83)
Deceased (*n*)	45	0	5*	9	5	5	15	3	3†

*1 woman died of a squamous lung tumour which was diagnosed after a disease-free interval of 42 months. It was histopathologically impossible to determine whether the tumour was primary or a recurrence of the patient's cervical squamous cell carcinoma.
†The fourth woman had a progressive disease when she returned abroad. She was lost to follow-up.

are found in about 30% of the cases [4] suggest that clinical staging alone is inaccurate for estimating the extent of the disease. However, apart from the risk of increased morbidity and mortality due to extensive surgery, surgical staging does not exclude that viable cancer cells remain after the operation.

Additional prognostic factors are therefore needed for individualising the therapy. It is especially important to identify the high-risk patients in the early stages of cervical carcinoma to offer them further treatment. It is equally necessary to identify patients who run little risk of a fatal outcome to avoid overtreatment.

Several studies have indicated that serum determinations of squamous cell carcinoma antigen (SCC) [5], CA 125 [6], tissue polypeptide antigen (TPA) [7] and carcinoembryonic antigen (CEA) [8] may be of value in monitoring patients with cervical carcinoma.

The purpose of the present study was to investigate the prognostic significance of the tumour markers, compared with clinical, histopathological and laboratory parameters in routine practice.

PATIENTS AND METHODS

Patients

The study comprised 142 patients with invasive primary carcinoma of the uterine cervix who were referred to the Department of Gynaecological Oncology, Radiumhemmet, between February 1986 and March 1989. Approval for the study was given by the local medical ethics committee and consent was obtained from all the participants. All patients entered the study prospectively and consecutively. The files of the patients were reviewed without knowledge of the results of the analyses.

A routine review of the histological specimens at Radiumhemmet confirmed the initial diagnosis in all patients. Pretreatment blood samples were drawn on admission to Radiumhemmet and the serum was stored at −20°C until analysed.

Staging of the patients according to the classification made by FIGO [2] was routinely performed during general anaesthesia by two experienced specialists (for clinical data, see Table 1). Histological grading revealed 14 well differentiated, 70 moderately, 51 poorly and 1 undifferentiated carcinomas. A bimanual examination permitted estimation of the tumour volume into three categories, i.e. no palpable tumour (group a), enlargement of the cervix (group b) and greatly enlarged cervix (group c).

7 women had other concomitant malignant diseases (i.e. 3 with breast carcinoma and 1 each with myeloma, chronic leukaemia, malignant melanoma and laryngeal cancer) but they were in complete remission and not currently receiving treatment. 35% of the patients had a benign intercurrent disease; of these, cardiovascular disease was the commonest. 49% of the patients smoked. 67 women were postmenopausal.

In general, the patients were treated according to a standard schedule. The 2 patients in stage Ia underwent primary surgery (conisation and radical hysterectomy, respectively). Patients below 60 years of age, with a tumour in stages Ib and IIa, received two intracavitary radium applications, followed by a radical hysterectomy with pelvic node dissection ($n = 68$). Patients in the same stages but above 60 years of age received intracavitary and external radiation only. Women in the advanced stages (IIb–IVb) underwent a combination of intracavitary and external radiation therapy, with or without chemotherapy. Operated patients with positive lymph nodes received external beam irradiation postoperatively.

The last day of follow-up was May 31, 1991. 45 patients died of cervical carcinoma (verified by autopsy or histological evidence of disease prior to death in 44 patients) and 3 died of intercurrent disease. 2 patients were lost to follow-up. The median observation time of the patients who were still alive was 36.6 (range 6.9–57.9) months and of the patients who died of cervical carcinoma 13.4 (1.8–56.5) months.

Routine haematological tests prior to treatment included haemoglobin, white blood cell and platelet counts, serum levels of creatinine, bilirubin, liver enzymes, calcium and albumin. Abnormal values were found in 2–29% of the patients.

Blood samples were also collected froom 129 healthy female controls, mainly blood donors, having a median age of 45 (range 22–77) years, and from 60 women having a median age of 37 (19–80) years, with histologically confirmed precancerous lesions (mild, moderate or severe dysplasia, $n = 34$) or carcinoma *in situ* (CIS, $n = 26$) of the uterine cervix.

Methods

All serum samples were coded and the analyses were carried out blindly. SCC was measured by a recently developed micro-

particle capture enzyme immunoassay, which employs monoclonal antibodies [9] utilising a fully automated instrument, the IMx™ (Abbott Laboratories, Chicago, USA). CEA levels were determined by means of radioimmunoassay kits using polyclonal antibodies from Diagnostic Products Corporation (Oxfordshire, UK). CA 125 and TPA were determined by means of immunoradiometric assay kits from Byk-Sangtec Diagnostica (Dietzenbach, Germany) and Sangtec Medical (Bromma, Sweden), respectively.

The procedures recommended by each manufacturer were followed throughout. Intra- and interassay coefficients of variation (CV) were below 10% and 17%, respectively, for all assays. With regard to SCC, the intra-assay CV for low levels (mean 2.0 ng/ml) varied between 8% and 15%. The detection limit for the respective tumour marker assays was 0.3 ng/ml for SCC, 0.9 ng/ml for CEA, 10 U/l for TPA, and < 2 U/ml for CA 125. In the case of TPA, levels obtained below the lowest standard concentration (25 U/l) were considered as equal to this standard concentration.

Statistical analyses

The Kruskal–Wallis one-way analysis of variance and the χ^2-test were used. Comparison of tumour marker results between two groups of patients was performed with the Wilcoxon–Mann–Whitney test and the χ^2-test with Yates correction. In the bivariate and the multivariate analyses, the Cox regression model was used [10]. Among the routine blood tests, only those tests showing abnormal values in more than 10% of the patients were included in the statistical analyses. The skewed distribution of tumour marker concentrations required logarithmic transformation. 3 patients died of intercurrent disease and were considered as censored observations. Differences between life-tables were tested by the log-rank test [11, 12]. Probability values of $P < 0.05$ were considered significant.

RESULTS

95% of the 129 healthy women had SCC levels of ≤ 1.4 ng/ml, CEA levels of ≤ 5.3 ng/ml, CA 125 levels of ≤ 38 U/ml and TPA levels of ≤ 74 U/l. The mean concentration + 2 S.D. was computed to be 2.1 ng/ml for SCC, 5.4 ng/ml for CEA, 32 U/ml for CA 125, and 78 U/l for TPA. When the recommendations from the respective manufacturers were also taken into consideration, the following were defined as the cut-off levels: 2.5 ng/ml for SCC, 5.2 ng/ml for CEA, 35 U/ml for CA 125, and 95 U/l for TPA.

In the control women, specificity ranged between 94.6% (for CEA and CA 125, respectively) and 97.7% (for SCC) while the sensitivity in cervical carcinoma varied between 22.5% (for CA 125) and 44.4% (for SCC) (see Table 2). The concentrations of the tumour markers did not significantly rise with increased severity of the precancerous/CIS lesions (data not shown). Although the squamous tumour type comprised 82.4% (cf. Table 1) of the cervical carcinoma cases, the sensitivity serum SCC was not significantly increased (59/117) in patients with this cell type compared with all cervical carcinomas.

Serum SCC was the sole marker compound that was elevated in 20 patients, CEA was elevated in 8, CA 125 in 9 and TPA the sole marker elevated in 2 of the 142 patients. Of the 39 patients with raised TPA levels, 33 patients also had elevated SCC levels (cf. Table 2). The highest sensitivity (63.4%, $P = 0.002$) was found when at least one of the four markers was elevated, whereas the specificity decreased ($P < 0.001$) to 82.9% compared with the use of SCC alone (97.7%). A combination of SCC, CEA and CA 125 resulted in a sensitivity of 62% (64% in squamous cell carcinoma), while the specificity decreased ($P = 0.004$) to 87.6%, compared with 97.7% for SCC alone. In cervical carcinoma the most frequently elevated panel of two markers consisted of SCC and CA 125 (80/142), closely followed by SCC and CEA. The difference between the combination and SCC alone was almost significant ($P = 0.058$). Serum median levels of SCC and TPA were higher in patients with squamous and adenosquamous carcinomas than in those with cervical adenocarcinomas (Table 3). In adenocarcinomas, 8/16 patients had elevated serum tumour marker levels (CA 125 was increased in 6, CEA in 4, SCC in 1 and TPA in none of these patients). In the adenosquamous cell type, serum SCC and CA 125 levels were

Table 2. Serum levels of SCC, CEA, CA 125, and TPA in patients with precancerous lesions and carcinoma of the uterine cervix, as well as in control women

Analyte	Control women		P*	Precancerous lesions/CIS		P*	Cervical carcinoma	
SCC (ng/ml)								
Median (range)	0.5	(0–6.0)	< 0.001	1.0	(0.3–3.6)	< 0.001	2.1	(0.3–185.0)
No. of elevated levels	3/129	(2.3%)	ns	3/56	(5.4%)	< 0.001	63/142	(44.4%)
CEA (ng/ml)								
Median (range)	1.1	(0–8.6)	< 0.01	2.0	(0–11.3)	< 0.001	3.3	(0–83.9)
No. of elevated levels	7/129	(5.4%)	ns	4/57	(7.0%)	< 0.01	35/142	(24.6%)
CA 125 (U/ml)								
Median (range)	9	(2–52)	< 0.001	17	(0–147)	ns	21	(<25–113)
No. of elevated levels	7/129	(5.4%)	ns	5/60	(8.3%)	< 0.5	32/142	(22.5%)
TPA (U/l)								
Median (range)	30	(<25–124)	ns	25	(<25–724)	<0.001	50	(<25–724)
No. of elevated levels	6/129	(4.7%)	ns	1/60	(1.7%)	< 0.001	39/142	(27.5%)

ns = Not significant. Significant differences in tumour marker levels ($P < 0.001$) between the three groups of women were found for all tumour markers (Kruskal–Wallis and the χ^2-test).

*The significant differences in tumour marker levels were further tested by the Mann–Whitney test and the χ^2 test with Yates' correction.

Significant differences in the median concentrations and the frequency of elevated concentrations of all of the tumour markers were noted between the control women and those with cancer ($P < 0.001$).

Table 3. Relation between the pretreatment median (range) serum levels of SCC, CEA, CA 125 and TPA and the histopathological findings in patients with cervical carcinoma

Analyte	Histopathology				
	Squamous (n = 117)	P*	Adenocarcinoma (n = 16)	P*	Adenosquamous (n = 8)
SCC (ng/ml)	2.6 (0.4–185.0)	0.03	1.3 (0.8–3.8)	0.049	2.2 (0.3–4.6)
CEA (ng/ml)	3.4 (0–83.9)		2.6 (0–21.2)		2.6 (1.2–5.6)
CA 125 (U/ml)	20 (0–418)		22 (4–360)		24 (11–789)
TPA (U/l)	52 (<25–724)	< 0.001	<25 (<25–95)	0.042	67 (<25–226)

The patient with undifferentiated cervical carcinoma had the following analyte levels: SCC, 0.5 ng/ml; CEA, 2.7 ng/ml; Ca 125, 21 U/ml and TPA, 54 U/l. Significant differences between the three cell types (Kruskal–Wallis Test) were found for SCC (P = 0.046) and for TPA (P = 0.008).

*The significant differences were further tested by the Mann–Whitney test. Comparison between squamous and adenosquamous cervical carcinoma revealed no significant difference in median levels of SCC and TPA, respectively.

increased in 5/8 patients (3 patients had normal serum levels of all tumour markers). There was no significant difference in median tumour marker levels between the tumour grades (data not shown).

A stage-related difference in serum levels was found for SCC, CA 125 and TPA but not for CEA in cervical carcinoma (Table 4). Only the levels of TPA differed between stages I and II. However, in the squamous tumour type, a difference ($P < 0.05$) in SCC median values was also found between stage I (1.4 ng/ml) and stage II (2.4 ng/ml). In addition, SCC levels in stage I differed from the levels in both the control women ($P < 0.001$) and the patients with precancerous lesions (P = 0.009) (data not shown).

8 of 66 patients (12.5%) were found to have pelvic lymph node metastases at surgery. SCC and/or CA 125 levels were raised in 7 of these 8 women (i.e. in 5 of 5 patients with stage Ib and in 2 of 3 patients with stage IIa). No other combination of markers was equally sensitive. In the 58 patients with negative nodes, SCC and CA 125 were elevated in 17 (29.3%) which was significantly different from the 7 of 8 patients with positive nodes (P = 0.005). In the eighth woman all four tumour markers were negative.

The patients in stage Ib (n = 63) cervical carcinoma were divided into three groups (groups a, b and c) according to tumour volume. Significant differences were only found in the median concentrations of SCC, i.e. between groups a (1.3 ng/ml, n = 31) and c (4.7 ng/ml, n = 6, P = 0.002) and between groups b (1.7 ng/ml, n = 26) and c (P = 0.002).

Serum tumour marker levels in relation to patient survival. In the initial statistical screening, nine risk factors were found to be significant for the prediction of a fatal outcome in cervical carcinoma (Table 5). These significant factors competed subsequently in a multivariate analysis and were included in a

Table 4. Pretreatment serum levels of SCC, CEA, CA 125 and TPA, according to the stage of cervical carcinoma

Analyte	FIGO stage									
	I (n = 66)		P	II (n = 43)		P	III (n = 25)		P	IV (n = 8)	
SCC (ng/ml)											
Median (range)	1.6	(0.3–38.2)	ns	2.1	(0.4–43.3)	< 0.001	5.3	(1.2–185.0)	ns	23.3	(1.0–151.0)
No of elevated levels	16/66	(24.2%)	ns	19/43	(44.4%)	0.001	22/25	(88.0%)	ns		6/8
CEA (ng/ml)											
Median (range)	3.6	(0–23.6)		3.1	(0–43.5)		3.9	(0–83.9)		3.6	(1.0–16.7)
No. of elevated levels	11/66	(16.7%)		14/43	(32.6%)		7/25	(28.0%)			3/8
CA 125 (U/ml)											
Median (range)	15	(0–140)	ns	21	(0–360)	ns	26	(4–418)	ns	66	(6–789)
No. of elevated levels	7/66	(10.6%)	ns	11/43	(25.6%)	ns	8/25	(32.0%)	ns		6/8
TPA (U/l)											
Median (range)	32	(<25–144)	< 0.001	65	(<25–230)	0.01	108	(35–576)	ns	213	(28–724)
No. of elevated levels	5/66	(7.6%)	< 0.01	13/43	(30.2%)	ns	14/25	(56.0%)	ns		7/8

ns = Not significant. Significant differences in median levels (Kruskal–Wallis test) and frequency of elevated levels (χ^2-test) between the stages were found for SCC ($P < 0.001$), CA 125 (P = 0.003 and $P < 0.001$, respectively) and TPA ($P < 0.001$). Significant differences were further tested by comparing each stage with the nearest highest stage (Mann–Whitney test and the χ^2-test with Yates' correction).

Table 5. Cox bivariate regression analyses showing risk factors for a fatal outcome of cervical carcinoma, with time to death as the dependent variable

Factor*		Deceased†	RH‡	CI	*P* value	χ^2
Stage (I–IV)		45/142	3.6	1.4–5.0	< 0.001	64.0
Grade		43/135	1.1	0.7–1.7	0.80	0.1
Histopathology		45/142	1.0	0.6–1.7	0.93	0.0
Age (years)§		45/142	1.2	1.0–1.5	0.03	4.9
Haemoglobin (g/l)§		45/140	0.7	0.6–0.8	< 0.001	23.4
Leucocyte count (× 10^9/l)		45/140	1.1	1.1–1.2	< 0.001	16.3
Platelet count (× 10^9/l)§		45/139	1.0	1.0–1.1	< 0.001	16.0
Albumin (g/l)		45/137	0.9	0.8–0.9	< 0.001	28.0
SCC (ng/ml)	≤ 1.3	7/48	1.0	Reference		
	1.4–3.6	9/46	1.2	0.4–3.2	0.76	0.1
	≥ 3.7	29/48	4.9	2.1–11.2	< 0.001	14.1
CEA (ng/ml)	≤ 1.9	13/47	1.0	Reference		
	2.0–4.1	13/46	1.2	0.5–2.5	0.73	0.1
	≥ 4.2	19/49	1.5	0.7–3.0	0.28	1.2
CA 125 (U/ml)	≤ 12	12/46	1.0	Reference		
	13–28	10/47	1.0	0.4–2.3	0.97	0.1
	≥ 29	23/49	2.7	1.3–5.7	0.007	7.3
TPA (U/l)	≤ 34	5/47	1.0	Reference		
	35–70	13/45	3.2	1.1–8.8	0.03	4.7
	≥ 71	27/50	7.3	2.8–19.0	< 0.001	16.6

χ^2values are presented in order to facilitate the comparison of the importance of the different variables. RH = Relative hazards; CI = 95% confidence intervals.
*The limits which are shown for the respective tumour marker were calculated using the 33% cumulative frequency.
†No. of deaths from cervical carcinoma (uncensored observations) divided by the total no. of patients.
‡RH is reported for one unit increment of the respective factor unless otherwise specified.
§10 units increment.

stepwise manner according to the power of significance. Table 7a shows that, apart from stage, only CA 125 and SCC had an additional significant effect on patient survival.

The factors in Table 5 were also included in the bivariate analyses for cervical squamous cell carcinoma alone (Table 6, factors of no significance are not shown). Age was the only factor that did not correlate with a fatal outcome. With an SCC level of ≥ 4.5 ng/ml there was an approximately 16 times increased risk of a fatal outcome in cervical squamous cell carcinoma, as compared with an SCC level of ≤ 1.3 ng/ml. In the corresponding multivariate analysis (Table 7b),the importance of stage for survival decreased slightly, while the prognostic importance of CA 125 and especially of SCC increased (cf. Table 7a).

The survival curve for cervical carcinoma of the squamous tumour type (Fig. 1) illustrates the favourable prognosis for patients with SCC levels ≤ 1.3 ng/ml, yielding a 3-year survival rate of 94.4%, compared with one of 39.8% in patients with SCC levels of ≥ 4.5 ng/ml. The corresponding 3-year survival rate of patients according to clinical stages was 93.9% (n = 52) in stage I, 72.5% (n = 36) in stage II, 27.3% (n = 22) in stage III, and no patient survived for 3 years in stage 4 (n = 7).

The 3-year survival rate of patients with CA 125 > 35 U/ml was 40%, compared with one of 78% in patients with CA 125 ≤ 35 U/ml (Fig. 2). No difference in survival was found between those with cervical carcinoma and the squamous tumour type alone.

Regardless of the observation time, 14 patients in the early stages (stages Ib and IIa) of cervical carcinoma died (31% of all deaths) of their cancer (Table 1). The patients are listed in Table 8 in relation to clinical data and serum tumour marker levels. CA 125 was elevated in 1 of the 2 patients who died of their squamous carcinoma but in whom the SCC level was within normal limits. The same was also true of both women with an adenocarcinoma component in their tumour.

With respect to survival, the predictive value of an SCC level of ≤ 1.3 ng/ml (negative predictive value) was 1/23 (95.7%), among the patients in the early stages of cervical squamous cell carcinoma with an observation time of 30 months. Thus, 22 patients with SCC levels of ≤ 1.3 ng/ml survived. However, the predictive value of an SCC level of ≥ 3.7 ng/ml (positive predictive value) was only 3/12, i.e. 3 patients in early stages and with SCC levels ≥ 3.7 ng/ml died of their cervical squamous cell carcinoma.

DISCUSSION

In interpreting serum tumour marker results in cancer patients the clinician should be acquainted with the possible influence of non-tumour-related factors on serum tumour marker levels [13]. This is especially important when judging a single serum sample, although serial measurements may clarify the often transient rise seen in benign cases.

As our results are based on a single pretreatment serum sample we cannot exclude interference with intercurrent diseases [14, 15] or smoking [16] leading to a false-positive rate. The frequency of serious intercurrent diseases, however, was relatively low (i.e. 6% in renal failure and 8% with liver disorders). None of our patients suffered from a significant cutaneous disease known to cause elevated serum SCC levels [17]. In

Table 6. Cox bivariate regression analyses of cervical squamous cell carcinoma, with time to death as the dependent variable

Factor*		Deceased†	RH‡	CI	*P*	χ^2
Stage (I–IV)		38/117	1.9	1.6– 2.2	< 0.001	48.9
Age (years)§		38/117	1.2	1.0– 1.5	0.09	2.9
Haemoglobin (g/l)		38/115	1.0	0.9– 1.0	< 0.001	27.6
Leukocyte count (× 10^9/l)		38/115	1.2	1.1– 1.3	< 0.001	25.2
Platelet count (× 10^9/l)		38/115	1.1	1.0– 1.1	< 0.001	18.7
Albumin (g/l)		38/112	0.9	0.8– 0.9	< 0.001	26.9
SCC (ng/ml)	≤ 1.3	2/ 37	1.0	Reference		
	1.4–4.4	10/ 39	4.1	0.9–19.3	0.07	3.3
	≥ 4.5	26/ 41	15.8	3.7–67.0	< 0.001	14.1
CA 125 (U/ml)	≤ 12	11/ 38	1.0	Reference		
	13–27	8/ 35	0.9	0.4– 2.3	0.84	0.0
	≥ 28	19/ 44	2.3	1.0– 5.0	0.045	4.0
TPA (U/l)	≤ 38	3/ 39	1.0	Reference		
	39–84	11/ 38	4.0	1.1–14.5	0.04	4.4
	≥ 85	24/ 40	11.8	3.5–39.2	< 0.001	16.1

χ^2 values are presented in order to facilitate the comparison of the importance of the different variables. RH = Relative hazards; CI = 95% confidence intervals.
*The limits which are shown for the respective tumour marker were calculated using the 33% cumulative frequency.
†No. of deaths from cervical carcinoma (uncensored observations) divided by the total no. of patients.
‡RH is reported for one unit increment of the respective factor unless otherwise specified.
§ 10 units increment.

clinical practice it may be advisable to use two pretreatment serum samples collected on different occasions [18].

The present study shows that serum levels of SCC, CA 125 and TPA are significantly related to patient survival in cervical carcinoma (Tables 5 and 6). However, TPA showed a strong relation to the stage of disease (Table 4) and no significant additional effect on patient survival was found with serum TPA alone (Tables 7a and 7b). Thus, TPA appears to be less useful in the prognosis of cervical carcinoma.

Interestingly, the negative predictive value of an SCC level of ≤ 1.3 ng/ml was 95.7% in the early stages of cervical squamous cell carcinoma, which accords with the 3-year survival rate of 94.4% in patients with SCC ≤ 1.3 ng/ml, including stages I–IV (Fig. 1). Although based on so few patients, these data can hardly be neglected. A possible clinical application of identifying low-risk patients in the early stages of cervical carcinoma would be to use less extensive treatment.

Our results indicate that SCC levels are influenced, not only by the extent of the disease, estimated by clinical staging, but also by the tumour volume in the same stage (stage Ib). These results confirm other reports [5, 18]. Such findings may imply a clinical application of SCC levels as an adjunct to staging, especially when surgical staging is not performed.

We also found that in combining SCC with CA 125, 7 of the 8 patients with pelvic lymph node metastases showed elevated marker levels, whereas only 17 of 58 patients with a negative lymph node status had increased SCC and CA 125 levels

Table 7a. Cox multivariate regression analyses regarding risk factors for a fatal outcome from cervical carcinoma, with time to death as the dependent variable

Factor	β	RH*	CI	*P*	χ^2
Stage of disease	0.48	1.6	1.3–2.0	< 0.001	22.1
CA 125	0.40	1.5	1.1–2.0	0.007	7.4
SCC	0.40	1.5	1.1–2.1	0.027	4.9

Stepwise analysis was carried out. The total no. of patients was 136, because of six missing values, and the number of deaths was 45. RH = Relative hazards; CI = 95% confidence intervals.
The other factors (age, haemoglobin, leucocytes, platelets, albumin and TPA) which were significant in the bivariate analyses did not meet the 0.05 significance level for entry.
*RH is reported for one unit increase in the e log SCC value (ng/ml), and e log CA 125 value (U/ml).

Table 7b. Cox multivariate regression analyses regarding risk factors for a fatal outcome from cervical squamous cell carcinoma, with time to death as the dependent variable

Factor	β	RH*	CI	*P*	χ^2
Stage	0.41	1.5	1.2–1.9	< 0.001	13.2
SCC	0.63	1.9	1.3–2.8	0.002	9.9
CA 125	0.61	1.8	1.3–2.7	0.002	10.1

Stepwise analysis was carried out. The total no. of patients was 112, because of 5 missing patients, and the no. of deaths 38. RH = Relative hazards; CI = 95% confidence intervals.
The other variables (haemoglobin, leucocytes, platelets, albumin and TPA) which were significant in the bivariate analysis did not meet the 0.05 significance level for entry.
*RH is reported for one unit increase in the e log SCC value (ng/ml), and the e log CA 125 value (U/ml).

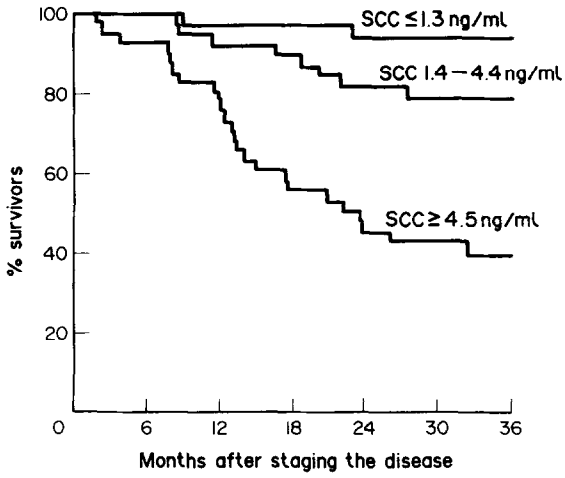

Fig. 1. Life table estimates of percentage survivors in patients with cervical squamous cell carcinoma according to various concentrations of pretreatment serum SCC. The overall *P* value was < 0.001 using the log-rank test. The number of patients still alive and under observation at entry and every 6 months thereafter were: 37, 36, 35, 35, 32, 25 and 16 patients with SCC levels ≤ 1.3 ng/ml; 39, 39, 36, 35, 32, 27 and 17 patients with SCC levels 1.4–4.4 ng/ml; and 41, 38, 32, 22, 17, 15 and 12 patients with SCC levels ≥ 4.5 ng/ml.

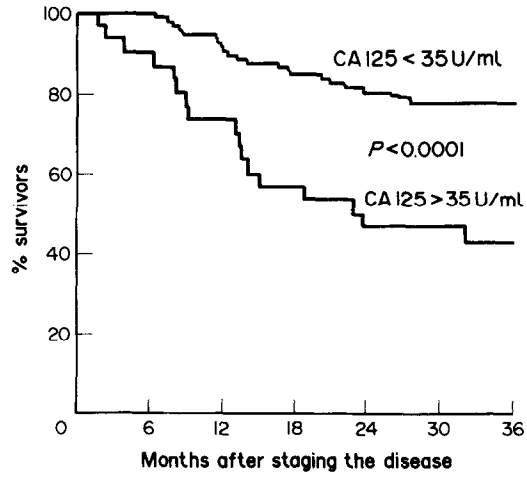

Fig. 2. Life table estimates of percentage survivors in patients with cervical carcinoma according to pretreatment serum levels of CA 125. The *P* value was calculated using the log-rank test. The numbers of patients still alive and under observation at entry and every 6 months thereafter were: 110, 110, 101, 92, 83, 68 and 44 patients with CA 125 levels ≤ 35 U/ml; and 32, 28, 22, 17, 14, 13 and 11 patients with CA 125 levels > 35 U/ml.

(P = 0.005). This is in agreement with previous reports. Thus, to assess the impact of tumour-related parameters on the serum SCC levels in cervical squamous cell carcinoma, Duk *et al.* [18] compared the tumour volume, the depth of the stromal infiltration, the tumour grade, pelvic lymph node status and vascular invasion in multivariate analyses. In stages Ib and IIa disease, depth of invasion and lymph node status were found to have a significant effect. The influence of pelvic lymph node metastases in stage Ib on SCC levels was also proposed by Patsner *et al.* [19], who found elevated SCC levels in all patients (n = 8) with bilateral pelvic lymph nodes, in 3 of 5 patients with unilateral nodes, but in none of 3 women with para-aortic lymph node metastases.

The low positive predictive value of SCC (35.7% with a fatal outcome in the early stages of cervical carcinoma) seems to limit its usefulness. However, SCC values exceeding 3.7 ng/ml or 4.5 ng/ml increased the risk of a fatal outcome by five or 16

Table 8. Clinical data and pretreatment serum tumour marker levels in patients with stage Ib (n = 5) and stage IIa (n = 9) who died of their cervical carcinoma

Patient no.	Histology	Tumour volume*	Therapy†	Positive lymph nodes	Intercurrent disease	SCC	CEA	CA 125	TPA
Stage Ib									
1	Squamous	b	S	Yes, unilateral	No	4.8	—	—	—
2‡	Squamous	a	R	—	Cardiovascular	—	—	—	—
3	Squamous	b	S	No	Gastritis	3.2	—	—	—
4	Squamous	c	S	No	No	4.7	—	—	—
5	Squamous	c	S	Yes, bilateral	Psychiatric	38.2	13.4	—	124
Stage IIa									
6	Squamous	b	R	—	No	4.0	—	—	
7	Squamous	c	R	—	No	43.3	9.0	—	155
8	Adenosquamous	b	S	No	Pulmonary	—	5.6	48	—
9	Squamous	c	S	No	Drug addict	2.7	—	—	—
10	Squamous	b	R	—	Psychiatric	3.3	—	—	—
11	Undifferentiated	c	R	—	Cardiovascular	—	—	—	—
12	Adenocarcinoma	b	R	—	Multiple	—	21.2	59	—
13	Squamous	b	R	—	Renal failure	—	—	66	221
14	Squamous	c	S	Yes, unilateral	No	3.6	—	—	138

Only the levels above the cut-off are presented: for SCC > 2.5 ng/ml, for CEA > 5.2 ng/ml, for CA 125 > 35 U/ml and for TPA > 95 U/l.

*a = No palpable tumour, b = enlargement of the cervix, c = greatly enlarged cervix.

†S = Intracavitary radiotherapy followed by radical hysterectomy and pelvic lymph node dissection. R = Irradiation only.

‡See footnote *, Table 1.

times, respectively. If SCC is combined with other prognostic indicators [3] it may be possible to identify at least some of the patients at high risk in the early stages of cervical carcinoma. The importance of such predictive information may be of particular value in the future when more efficient treatment modalities may become available.

The influence of serum CA 125 levels on patient survival was surprising because over 80% of the cervical carcinomas in our study were of the squamous tumour type [20]. An overclassification of the squamous cell type cannot be excluded as the specimens were histopathologically evaluated in routine practice using morphological assessment [21, 22]. The serum level of a tumour-associated antigen seems rather to depend upon the infiltrative growth of the tumour than on the local tissue content [23, 24], which is consistent with the prognostic value of the CA 125 levels that we found. Our results may also be caused by disseminated tumour growth mechanically involving the peritoneum [25–27].

We did not find a combination of multiple serum tumour markers which improved the sensitivity for cervical carcinoma without reducing the specificity. The use of multiple tumour markers in cervical carcinoma may still be attractive so long as they are not used for screening or diagnostic purposes. For instance, during the clinical course there may be a change in the subset of tumour-associated antigens expressed by the tumour [28].

Duk *et al.* [29] have recently suggested that the pretreatment CA 125 levels in adenocarcinoma of the cervix may be of prognostic value. Other authors have found CEA valuable as a prognostic factor [8]. Our group of adenocarcinoma patients was too small to provide confirmation of these data.

In conclusion, the present study suggests that pretreatment serum levels of SCC and CA 125 may be of value in predicting patient survival and pelvic lymph node status in cervical carcinoma. SCC levels may also serve as an adjunct in clinical staging.

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