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SCC antigen in the serum as an independent prognostic factor in operable squamous cell carcinoma of the cervix

H.-G. Strauss[a,*], C. Laban[a], C. Lautenschläger[b], J. Buchmann[c], I. Schneider[d], H. Koelbl[a]

[a]*Department of Gynecology, Martin-Luther University Halle-Wittenberg, Germany*
[b]*Institute of Medical Epidemiology, Biometry and Medical Informatics, Martin-Luther University Halle-Wittenberg, Germany*
[c]*Department of Pathology, Martin-Luther University Halle-Wittenberg, Germany*
[d]*Institut of Clinical Chemistry und Pathobiochemistry, Martin-Luther University Halle-Wittenberg, Germany*

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Abstract

The aim of this study was to retrospectively examine whether the occurrence of squamous cell carcinoma (SCC) antigen tumour marker in the serum has prognostic significance in operable SCC of the cervix at the International Federation of Gynaecology and Obstetrics (FIGO) stages IA2–IIB. A total of 129 patients who had undergone a radical hysterectomy for SCC of the uterine cervix at the Department of Gynecology of the Martin-Luther University, Halle-Wittenberg in 1991–2000 were included. SCC antigen (Ag) was measured by IMx SCC-Ag microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). To assess the prognostic value of SCC antigen in the serum, we used a step-by-step multivariate analysis based on the Cox proportional hazard regression model. Using a cut-off value of 3.0 ng/ml, we detected preoperative SCC antigen in the serum as an independent prognostic factor in SCC of the cervix, both for recurrence-free and overall survival ($P = 0.003$ and 0.0078). In this retrospective analysis the value of the SCC antigen tumour marker correlates with prognosis in operable SCC of the cervix, independent of tumour size, pelvic nodal status, cervical stroma infiltration, parametrial spread and tumour grading.

Keywords: SCC antigen; Prognostic significance; Squamous cell cancer; Cervix uteri

1. Introduction

Cervical cancer is one of the most common cancers, accounting for 6% of all malignancies in women. The prognosis for this disease is markedly affected by the progress of the disease at the time of diagnosis. Tumour size [1–6], depth of stromal invasion [2,4,6,7], parametrial spread [8] and nodal status [1,3,6,8,9] are well-established prognostic factors of cervical carcinoma in everyday clinical practice and may influence the decision to use adjuvant therapy in operable cases. Of these, only nodal status can be determined precisely prior to radical hysterectomy by means of laparoscopic or extraperitoneal surgical staging as an invasive diagnostic method.

As regards the prognostic value of other factors such as grading [4,5], lymph capillary invasion [2], blood capillary vessel density in the tumour [10], histological subtype [5,9], age [11] and S-phase rate [12], there are a number of positive, but also some negative, findings in the literature.

Detection of molecular biological prognostic factors in the tumour or serum of cervical carcinoma patients has not been established in clinical practice to date, either because analysing these factors is too expensive or because the presently available positive data from prospective studies are not sufficient to recommend evaluation as a generally applicable measure. These factors include the expression of the vascular endothelial growth factor (VEGF) [13], epidermal growth factor (EGF)-receptor [14], cyclooxygenase-2 [15], c-myc [16] or bcl-2 in tumours [17] and the detection of human papillomavirus (HPV) 16/18-mRNA in plasma [18] or of HPV 16-E7-antibodies in serum [19].

Until new therapeutic approaches are available, prognostic factors, in particular those for operable cervical carcinomas, need to be defined more precisely.

* Corresponding author. Tel.: +49-345-557-1531; fax: +49-345-557-4634.
E-mail address: hans.strauss@medizin.uni-halle.de (H.-G. Strauss).

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Squamous cell cancer (SCC) antigen is a glycoprotein with a molecular weight of approximately 45 kDa [20]. Two nearly identical structural variants—SCC A1 and SCC A2—have been observed, both of which are coded on chromosome 18q21.3 and are detectable in the cytosol of squamous epithelia [21]. These proteins are inhibitors of lysosomal serine proteinases, whose increased release into the serum is a sign of a change in the proliferation activity of these epithelial cells. In the cytosol of malignant epithelial cells, only the expression of SCC A2 mRNA is increased [22]. In routine clinical usage, however, both structural variants are detected indiscriminately by means of an enzyme immunoassay. The SCC antigen level in the serum, depending on the stage of the disease, is elevated in 37–90% of all SCCs [20]. It is unclear from the literature what the importance of a preoperatively elevated SCC antigen level is and whether it could be an independent prognostic factor in cervical carcinoma [23,24].

2. Patients and methods

Our analysis to assess the prognostic value of a pretherapeutic SCC antigen value was based on data from 129 patients who had a radical hysterectomy for SCC of the uterine cervix in the Department of Gynecology, Martin-Luther University, Halle-Wittenberg between 1991 and 2000.

96 women with the International Federation of Gynaecology and Obstetrics (FIGO) stage I (IA2: 1, IB1: 87, IB2: 8) and 33 with FIGO stage II disease (IIA: 9, IIB: 24) were included in this retrospective analysis. The mean age of our patients at diagnosis was 42.7 years (range 24–75 years).

All patients underwent a radical hysterectomy according to PIVER III. They were given postoperative adjuvant therapy if the pelvic lymph nodes were affected by the tumour or in cases with a parametrial infiltration of the tumour. Adjuvant treatment consisted of percutaneous high-voltage radiation therapy using fractions of 1.8 Gy up to a total dose of 50.4 Gy and brachytherapy based on the High Dose Rate Afterloading method (2× 5 Gy) in those cases where an infiltration of the vaginal cuff was diagnosed. Since 1999, the generally established procedure was to administer a simultaneous dose of 40 mg/m^2 cisplatin weekly × 6, as well as the radiotherapy. None of the patients had tumour-affected resected margins in the study group. The SCC antigen level in the serum was determined in all 129 patients prior to surgery. SCC antigen was measured by the IMx SCC-Ag microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA).

In our study, a cut off-value of 3.0 ng/ml was selected as this corresponded to 2 times the serum concentration of the 95 percentile that was obtained in an analysis of 885 healthy women.

We analysed retrospectively whether the preoperative SCC antigen value in the serum constituted a prognostic factor in operable cervical carcinoma of FIGO stages IA2–IIB. The median follow-up period for patients included in our study was 68 months (range 3–115 months). To examine the prognostic relevance of the SCC tumour marker, we performed a step-by-step multivariate analysis according to the Cox regression model [25], using the well-established prognostic factors of maximal tumour diameter, pelvic nodal status, cervical stroma infiltration, parametrial spread and grading. The endpoints of analysis were defined in terms of recurrence-free and overall survival. A P value <0.05 was considered to be statistically significant.

3. Results

All 129 patients with SCC of the uterine cervix who underwent surgery during the period 1991–2000 reached a 5-year survival rate of 93.0%. The patients' tumour characteristics are shown in Table 1. Overall, 15 patients recurred in the follow-up period, which corresponds to a recurrence rate of 11.6%. As expected, the recurrence rate was highest in FIGO-stage IIB patients (33.3% (8/24)).

9 of the 15 relapsed patients have since died after a median period of 12 months (range 2–13 months); the other 6 patients are still alive (median 39 months; range 2–104 months).

Table 1
Tumour characteristics of squamous cell carcinomas (SCCs) of the uterine cervix in the study population ($n=129$)

FIGO stages	Total no. of patients (n)	Pelvic nodal infiltration (n)			Grading (n)				Cervical stroma infiltration (n)		SCC value (n)	
		No	1 lymph node	>1 lymph node	G1	G2	G3	GX[a]	Inner third	>Inner third	⩽3.0 ng/ml	>3.0 ng/ml
IA2	1	1	0	0	0	0	0	1	1	0	1	0
IB1	87	76	4	7	1	29	45	12	66	21	82	5
IB2	8	6	1	1	0	1	7	0	2	6	5	3
IIA	9	5	1	3	0	2	7	0	3	6	4	5
IIB	24	10	4	10	0	6	18	0	5	19	8	16

[a] GX, grading not determined.

In 29 patients (22.5%), we observed a preoperative value of SCC antigen in the serum above the cut-off level of 3.0 ng/ml.

A preoperative SCC in the serum of >3.0 ng/ml significantly predicted a cervical stroma infiltration of more than the inner third of the cervix uteri (Relative Risk (RR) = 33.2), a maximum tumour diameter $\geqslant 4$ cm (RR = 32.6), a higher FIGO stage (RR = 45.6) and a positive pelvic nodal status (RR = 14.0), but not a higher tumour grading (RR = 1.2—see Table 2).

In an univariate analysis of all of the SCCs, the preoperative SCC antigen value both for recurrence-free and overall survival was a statistically significant prognostic factor ($P<0.00001$ and $P=0.001$, respectively). A pretherapeutic SCC antigen value of >3.0 ng/ml was associated with a significantly poorer prognosis in patients with SCC of the uterine cervix. Likewise, the preoperative SCC antigen level in the serum was also a factor of independent prognostic significance in a step-by-step multivariate analysis based on the Cox regression method, in which we included as established prognostic factors, maximal tumour diameter, cervical stroma infiltration, pelvic lymph node invasion, parametrial spread and tumour grading. This finding applied to both recurrence-free ($P=0.003$) and overall survival ($P=0.0078$; see Figs. 1 and 2). Patients with an elevated SCC value were found in a multivariate analysis to have a 25-fold RR of dying of the carcinoma during the follow-up period compared with the other patients.

Table 2
Correlation between elevated SCC serum antigen (>3.0 ng/ml) and established prognostic factors in operable squamous cell carcinoma (SCC) of the cervix

Prognostic factor	RR (SCC >3.0 ng/ml)	P value (Exact Fisher test)
FIGO stage IIB	45.6	<0.0001
Grading 3	1.2	0.377
Positive pelvic nodal status	14.0	0.001
Deep cervical stroma infiltration ($>1/3$)	33.2	<0.0001
Maximum tumour diameter $\geqslant 4$ cm	32.6	<0.0001

RR, Relative Risk.

In 13 of 15 SCC patients that recurred, which in 86.7% of the cases occurred at a disease-free period of $\leqslant 24$ months (mean 18 months; range 6–64 months), we observed an increase in the SCC antigen levels in the serum to a level of >3.0 ng/ml when a recurrence was diagnosed.

4. Discussion

Our analysis shows that the preoperative level of the SCC antigen in the serum, using a cut-off value of 3.0 ng/ml, is an independent prognostic factor in operable SCC of the uterine cervix.

A full causal explanation for this phenomenon is not available. Maruo and colleagues were able to show in 1998 that there is a positive correlation between the

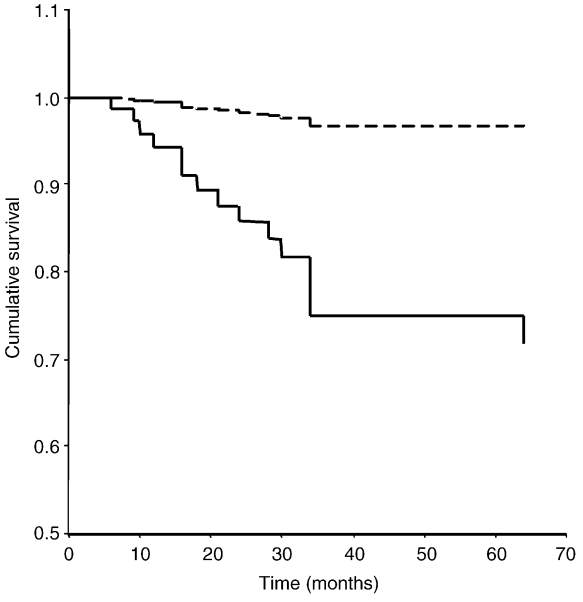

Fig. 1. Disease-free survival curves of 129 patients with squamous cell cervical cancer (SCC) according to the preoperative SCC-antigen (Ag) level—adjusted to pelvic nodal status, tumour size, depth of cervical stroma infiltration, parametrial spread and grading—results of a multivariate proportional hazard regression analysis (Cox $^{24}/P=0.003$/ Relative Risk (RR) 9.1) ___: SCC-Ag >3.0 ng/ml, _ _ _: SCC-Ag $\leqslant 3.0$ ng/ml.

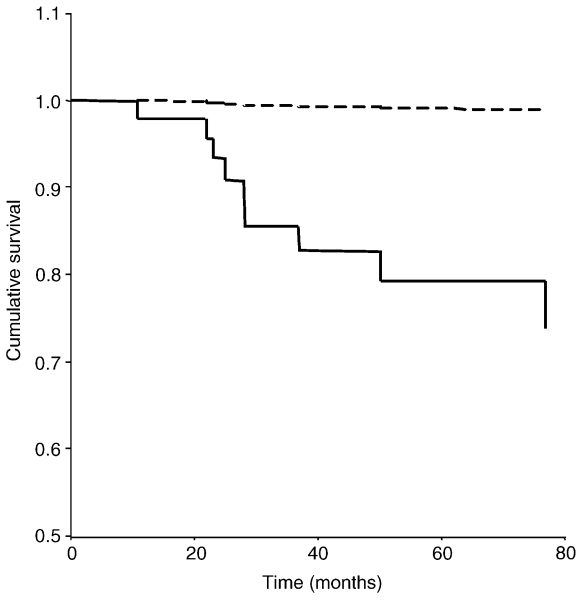

Fig. 2. Overall survival curves of 129 patients with squamous cell cervical cancer (SCC) according to preoperative SCC-antigen (Ag) level—adjusted to pelvic nodal status, tumour size, depth of cervical stroma infiltration, parametrial spread and grading—results of a multivariate proportional hazard regression analysis (Cox $^{24}/P=0.0078$/ Relative Risk (RR) 25.0) ___: SCC-Ag >3.0 ng/ml, _ _ _: SCC-Ag $\leqslant 3.0$ ng/ml.

EGF-receptor and SCC-antigen expression levels [26]. The fact that an elevated EGF-receptor expression is associated with a poor prognosis in cervical carcinoma was established in 1999 by Kersemaekers and colleagues in a multivariate analysis of 136 patients [14]. An increase in the level of SCC antigen might thus be indicative of the amount of cell proliferation occurring in cervical carcinoma.

In a step-by-step multivariate analysis, taking into account the established prognostic factors in cervical carcinoma, the preoperative SCC antigen value remained a statistically significant, independent prognostic factor for recurrence-free and overall survival. As for the factors included in the Cox regression analysis of tumour characteristics—pelvic nodal status [6], maximal tumour diameter [1], cervical stroma infiltration [2], parametrial spread [8] and tumour grading [4]—their prognostic value in cervical carcinoma is not disputed.

There are conflicting reports in the literature regarding the importance of the pretherapeutic SCC antigen level in the serum as a prognostic factor for operable cervical carcinoma. While Duk and colleagues in 653 patients [23], and Scambia and colleagues in 102 patients [27], determined the preoperative level of the SCC antigen in the serum as an independent prognostic factor for overall survival, such a conclusion was not made by other authors [28,29].

The absolute values of the SCC antigen in the serum have shown considerable fluctuation between the different studies, apparently due to differences in the laboratory tests used. In our study, a cut-off value of > 3 ng/ml was selected on the basis of an analysis that measured the serum SCC antigen levels in 885 healthy women. In these healthy women, the SCC serum antigen levels never increased > 3.0 ng/ml. 846 (95.6%) of these women showed SCC antigen levels < 1.5 ng/ml, whereas the SCC serum concentrations of 39 (4.4%) subjects ranged between 1.5 and 3.0 ng/ml.

While Scambia and colleagues in their 1994 study found an SCC antigen value of > 2.5 ng/ml in 65% of cervical cancer patients, and an SCC antigen value of > 5 ng/ml in 45% of patients with operable SCC of the cervix [27], Bolger and colleagues in 1997 were only able to detect a level of SCC antigen of > 2 ng/ml in 21.6% of their patients [28]. In our study, we found a value of SCC antigen in the serum of > 3 ng/ml in 22.5% of the patients.

Hong and colleagues in a 1998 analysis of 401 cases of SCC of the cervix of stages IB–IVA treated with primary radiation, found an SCC antigen value of > 10 ng/ml was an independent prognostic factor [30]. In their study, an SCC antigen value between 2 and 10 ng/ml was of no prognostic relevance.

In our group of 129 SCCs, there were 15 recurrences during the follow-up period. The level of SCC antigen in one patient with a diagnosis of recurrence was < 3 ng/ml, while there was no measurement in another case. In 13 patients (86.7%), an increased level of this tumour marker above the cut-off value of 3.0 ng/ml was found at the time of diagnosis of recurrent disease. In 10/13 patients, recurrent disease was diagnosed at the clinical investigation and imaging analysis. Evaluation of SCC at regular intervals was not carried out in these patients. In 3 patients, assessment of recurrent disease was initiated due to an elevated SCC antigen serum level.

The results of our study demonstrate that a preoperative increase in the SCC antigen levels in the serum in SCC of the cervix permits the selection of operable patients with a less favourable prognosis. These patients may require adjuvant therapy that may not be indicated as a result of the established indications resulting from the histopathological examination of the surgical preparation.

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