

# The Correlation Between the Serum Squamous Carcinoma Antigen and the Prognosis of Recurrent Cervical Squamous Carcinoma

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**Background:** To explore the relationship of the serum squamous cell carcinoma antigen (SCC-Ag) with the pathologic characteristics, occurrence, and prognosis of cervical squamous carcinoma. **Methods:** The enzyme-linked immunosorbent assay (ELISA) method was used to determine the serum SCC-Ag levels for the patients, which included 424 pretreatment patients and 500 cases after treatment. **Results:** (a) Pretreatment SCC-Ag levels of patients were related to clinical stages, lymphatic metastasis, and myometrial invasion, (b) within a median follow-up of 54 months, 180 recurrences (36%) and 102 disease-associated deaths (20.4%) were recorded, 161 recurrent patients showed elevated SCC-Ag levels (161/180, 89.4%), and 60 of them (37.3%) had a

significant increase in SCC-Ag serum levels before clinical manifestation of relapse. The lead time ranged between 1 and 5 months (median: 2.3 months). The total survival rates were 23.4% and 17.8% for 3-year and 5-year period, respectively, and (c) clinical stages, the site of recurrence, and SCC-Ag levels after treatment were closely related with recurrent patients' survival time ( $P < 0.01 \sim 0.005$ ). Multivariate analysis indicated that the clinical stages and SCC-Ag levels of recurrent patients were independent prognostic factors ( $P < 0.05 \sim 0.01$ ). **Conclusion:** Serum SCC-Ag level was an important predictor for the cervical squamous carcinoma recurrence and prognosis. *J. Clin. Lab. Anal.* 31:e22020, 2017. © 2016 Wiley Periodicals, Inc.

**Key words:** cervical carcinoma; prognosis; squamous cell carcinoma antigen; tumor recurrence

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## INTRODUCTION

In recent years, cervical cancer is the fourth leading cause of cancer death in women worldwide. More than 85% of cervical cancers are of the squamous cell type. Squamous cell carcinoma antigen (SCC-Ag), the serine protease inhibitor (Serpin) family of proteins, has been identified as a predictive and prognostic factor for cervical carcinoma (1–5).

According to literature reports, pretreatment SCC-Ag was closely related to FIGO stage and has been shown to be an independent indicator of treatment response in patients with cervical squamous carcinoma. In addition, an elevated pretreatment level of SCC-Ag was found to be associated with a higher rate of lymph node metastases. Also, elevated pretreatment

SCC-Ag was reported to be an independent risk factor for poor survival (1, 6). However, the SCC-Ag level might be altered by treatment. Li et al. reported that elevated posttreatment (after neoadjuvant chemotherapy) level of SCC-Ag was an independent predictive factor for both DFS and OS (7).

In this study, we detected the serum SCC-Ag levels of 424 pretreatment patients with cervical squamous carcinoma and 500 posttreatment (after completion of

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a whole treatment cycle) patients in the follow-up during 2006–2011. We investigated the serum levels of SCC-Ag of all these patients and conducted long-term follow-up of relapsing patients to assess the impact of serum SCC-Ag level on prognosis, follow-up.

## MATERIALS AND METHODS

### Patients

A total of 424 patients with cervical cancer who were treated at Shanxi Cancer Hospital, China, from January 2006 and December 2011 were enrolled in this study. Inclusion criteria were as follows: (a) patients with stage IA-III according to the Federation of Gynecology and Obstetrics (FIGO), (b) patients whose pathologic examinations showed squamous cell carcinoma of the cervix, (c) patients who did not receive prior hysterectomy, pelvic radiotherapy, or concurrent chemoradiotherapy, and (d) patients with serum SCC-Ag levels measured before and after treatment.

Concurrently we selected 500 patients from the follow-up after treatment for cervical squamous carcinoma during 2006–2011.

### Measurement of SCC-Ag Levels and Clinical Data Collection

Peripheral blood from patients was obtained at the preoperative workup and regularly during the follow-up. And the samples were collected at 8–11 am and then centrifuged for 10 min at RCF  $1435.76 \times g$ ; serum was then immediately separated for examination. Serum SCC-Ag was measured using ELISA. The level of SCC-Ag  $> 1.0$  ng/ml has being regarded as elevated status.

The analysis was conducted by the patented products from Sweden CanAg diagnosis reagent Corp and the microplate reader and the automatic plate washer were from Austria TECAN. All patients' clinical data, initial times for treatment, every SCC-Ag level, recurrent time, and ages were recorded.

Follow-up procedure was conducted for those recurrent patients with cervical squamous carcinoma and the results from the follow-up were registered. SCC-Ag was measured every 3 months for the first 2 years and twice per year thereafter; chest radiography and abdominopelvic MRI (or alternatively chest-abdominopelvic CT scan) were performed every 6 months for the first 3 years and every 12 months thereafter; additional diagnostic procedures were performed according to specific clinical suspicion. The recurrent disease was finally confirmed by histology, B-type ultrasonography, or other imageology methods.

### Statistical Analysis

SPSS 19.0 statistical software was used to perform the analyses (IBM Corp., Armonk, NY). The  $\chi^2$  test or Fisher's exact test was used to analyze the proportion of unusual SCC-Ag levels according to different clinico-pathologic factors. Logistic regression analysis was used for multivariate analysis which can affect serum SCC-Ag levels. Postrelapse survival was calculated by the Kaplan–Meier method, and the log-rank test was used to assess the statistical significance. Cox's regression model was used to perform multivariate analysis of prognostic factors.  $P < 0.05$  was considered statistically significant.

## RESULTS

Among the 424 pretreatment patients, 180 were of I, 190 were of II, and 54 were of III. A total of 64 patients underwent radical hysterectomy with pelvic + aortic lymphadenectomy, and 123 patients received chemoradiation therapy, and the other 237 received radical surgery plus chemotherapy/radiotherapy. The mean age of the patients was 50.65 years (ranged: 22–81). Among the 424 patients, 190 were less than 50 years old and 234 were over 50 years old.

### The Analysis of Pretreatment Serum SCC-Ag Levels and Clinico-Pathological Characteristics of Patients

A total of 424 patients with squamous cell carcinoma of the cervix were enrolled in this study. One hundred and eighty-seven patients showed normal levels of serum SCC-Ag before the treatment and 237 patients showed higher levels of SCC-Ag, which had a sensitivity of 55.9% (237/424). Univariate analysis indicated that the pretreatment serum SCC-Ag levels were closely related to clinical stages, lymphatic metastasis, and stromal invasion ( $P < 0.001$ ); however, they were not related to patient's age and tumor growth type ( $P > 0.05$ ). The results are summarized in Table 1.

Multiple linear regression analysis indicated that the clinical stages, cavum pelvis lymphatic metastasis, and myometrial invasion were independent prognoses factors ( $P = 0.0084$ ,  $P = 0.0156$  and  $P = 0.0171$ , respectively). The results are summarized in Table 2.

### The Association of Elevated Serum SCC-Ag and Recurrent of Disease

Of the 500 patients after treatment enrolled in our study, one refused surgery, four refused radiotherapy

**TABLE 1. The Relationship of Pretreatment SCC-Ag Levels and Clinico-Pathological Characteristics of Patients With Cervical Squamous Cell Carcinoma**

Clinico-pathological characteristics	No.	SCC-Ag level $\geq 1$ ng/ml No. (%)	<i>P</i>
Age (years)			
<50	190	108 (56.8)	>0.05
$\geq 50$	234	129 (55.2)	
Clinical stages			
I	180	70 (38.9)	<0.001
II	190	129 (67.9)	
III	54	38 (70.4)	
Stromal invasion			
No	27	7 (25.9)	<0.001
<1/2	147	59 (40.1)	
$\geq 1/2$	250	171 (68.4)	
Lymphatic metastasis			
Yes	47	37 (78.7)	0.001
No	377	200 (53.1)	

**TABLE 2. Multivariate Analyses for Pretreatment SCC-Ag Levels According to the Clinico-Pathological Characteristics**

Parameter	Regression coefficient: <i>b</i>	Sx( <i>b</i> )	<i>t</i>	<i>P</i>
Clinical stages	0.6632	0.2303	2.880	0.0084
Lymphatic metastasis	0.4023	0.1540	2.612	0.0156
Myometrial invasion	0.2870	0.1117	2.570	0.0171

after radical surgery, and seven progressed during treatment.

Among these, within a median follow-up time of 54 months (range 3–60 months), 180 recurrences (36%) and 102 disease-associated deaths (20.4%) were recorded. The recurrence was proven by histology/B-type ultrasonography/other imageology methods. For these 180 patients, a median recurrence time was 14 months and the median recurrence age was 47.5 years (average: 43.8). Of these recurrences, 161 (89.4%) had serum SCC-Ag elevated, and 60 of them (37.3%) had increase in SCC-Ag before clinical manifestation of relapse. The median leading time was 2.3 months (range: 1–5 months, with an average of 4.2 months). Except for the 20 lost cases, the rest of the 160 cases with recurrent disease had a median survival time of 27 months, with an average of 35.4 months (range, 4–60 months). The total survival rates were 23.4% and 17.8% for 3-year and 5-year period, respectively.

Most of the recurrences (60%) presented no clinical symptom during the follow-up except for elevated SCC-Ag levels. Thirty-five patients (19.4%) had edema of lower extremity or pain and 25 patients (13.9%) reported abnormal vaginal bleeding. Only 12 patients

**TABLE 3. Univariate Analyses for Postrelapse Survival**

Factor	Cases	3-year survival rate (%)	$\chi^2$	<i>P</i>
Clinical stages				
IA–IIA	58	65	10.26	<0.05
IIB–III	102	33		
Recurrent location				
Recurrence of centrality	62	61	14.65	<0.005
Pelvic and distant recurrent	98	19		
Early elevation of SCC-Ag levels				
Yes	50	26	0.89	>0.05
No	91	30		
SCCAg level at recurrence				
$\geq 5$ ng/ml	79	29	1.79	>0.05
<5 ng/ml	81	32		
SCCAg level during treatment				
Increase	58	0	8.97	<0.01
Decrease	102	35		

**TABLE 4. Multivariate Analyses for the Prognoses of Relapsing Patients With Cervical Squamous Carcinoma**

Factor	Regression coefficient	Standard deviation	$\chi^2$	<i>P</i>
Clinical stages	1.7616	0.5479	10.3372	0.0013
SCC-Ag posttreatment	0.9313	0.4445	4.3889	0.0362

(6.7%) had clavicle lymph node and groin lymph nodes enlargement and distant metastasis.

### The Factors Affecting the Prognosis of Recurrent Patients

Univariate analysis indicated that clinical stages of recurrent patients, the site of recurrence, and modification of SCC-Ag levels after treatment of recurrent disease were closely related with patients' survival time ( $P < 0.005 \sim P < 0.01$ ). There was no statistically significance in survival between recurrent patients with increased SCC-Ag level at the recurrence and without increased SCC-Ag levels ( $P > 0.05$ ). Multivariate regression analysis indicated that the clinical stages ( $P = 0.0013$ ) and SCC-Ag levels after treatment of recurrent disease ( $P = 0.0362$ ) were independent prognoses factors. The results are summarized in Tables 3 and 4.

### DISCUSSION

Squamous cell carcinoma antigen is the most useful tumor marker in cervical squamous carcinoma for the early detection and/or diagnostic of cancers, predicting

prognosis, response to specific treatment (8, 9), and disease monitoring (3, 10). It has been shown by previous studies that elevated pretreatment levels of SCC-Ag in the serum were associated with certain clinico-pathologic characteristics (1–3, 11–13), such as FIGO stages, myometrial infiltration, and lymphatic metastasis. We found comparable results in this study. Li et al. (7) revealed that elevated pretreatment level of SCC-Ag was shown to be an independent risk factor for lymph node metastases. It has been reported that SCC-Ag was able to regulate the expression of antigen-E protein associated with cell migration and invasion (14). Moreover, some studies found that elevated pretreatment level of serum SCC-Ag was correlated with cervical cancer recurrence (8, 15) and poor prognoses (16).

Furthermore, the elevated SCC-Ag level after treatment can precede the clinical diagnosis of relapse in 46–92% of cases, with a median lead time ranging from 2 to 8 months (10, 11, 17). Our study showed that serum SCC-Ag levels after treatment were important for the prediction of tumor recurrence for patients with cervical squamous carcinoma. In the recurrent patients, 37.3% of them had elevated levels of SCC-Ag before clinical manifestation of relapse. The median time between elevated SCC-Ag levels and clinical discovery was 2.3 months with an average of 4.2 months in this analysis. And the longest time range was 150 days. Forni et al. (8) found that for recurrent patients with cervical squamous carcinoma after treatment, 79.1% of them showed elevated SCC-Ag levels before the appearance of any clinical symptoms. And Micke et al. (17) found even more. Ma et al. (18) reported that 85% of the recurrent patients with cervical carcinoma showed elevated SCC-Ag levels; 32.8% cases showed significant elevation in SCC-Ag levels before any obvious clinical symptoms, which was similar to our results.

Patients with recurrent tumor generally had poor prognosis. Median survival time was 27 months with an average of 35.4 months (range, 4–60 months). The total survival rates were 17.8% for 5-year period.

These numbers were in good agreement with literature reports. It was reported that factors, including initial clinical stages, lymphatic metastasis, recurrence region, levels of SCC-Ag prior to recurrent, and the variation in SCC-Ag levels during the treatment, would affect the prognoses of recurrent patients (19, 20). Our study indicated that patients initially in poor clinical stages and with pelvic and distant recurrent and elevated posttreatment SCC-Ag levels had a low survival rate. Multivariate analysis showed that the clinical stages and posttreatment SCC-Ag levels were independent factors for the prediction of

prognosis. Interestingly enough, among the parameters associated with recurrence's prognosis, including the pattern of recurrence, the size of recurrence, SCC-Ag serum levels at recurrence, and secondary radical surgery in univariate analysis, Legge et al. (21) found that secondary radical surgery was the only one factor that retained an independent prognostic role for survival.

Because there were recurrent patients in this study and some patients did not have their SCC-Ag levels measured before the treatment, and also some pretreatment patients without complete follow-up data, we did not include the pretreatment SCC-Ag levels as a prognoses factor for the multiple factor analysis. Therefore, more studies would be conducted to determine whether the SCC-Ag level before the treatment can be used as a prognosis factor.

In summary, serum SCC-Ag levels showed clinical significance in understanding the disease conditions of patients before treatment. It is also important for the prediction of recurrence and prognosis. Identifying those patients who are at high risk of recurrence would improve their overall treatment efficacy.

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