ORIGINAL ARTICLES

# Both TPA and SCC-Ag levels are prognostic even in high-risk stage Ib-IIa cervical carcinoma as determined by a stratification analysis

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**Summary**

*Objective:* To determine the prognostic values of tissue polypeptide antigen (TPA), squamous cell carcinoma antigen (SCC-Ag), and carcinoembryonic antigen (CEA) in the sera of cervical carcinoma patients, especially in those with a poor prognosis.

*Methods:* In this retrospective study, the preoperative serum SCC-Ag, TPA, and CEA were analyzed in 779 patients with cervical squamous cell carcinoma of stage Ib-IIa who received radical hysterectomy and pelvic lymph node dissection (RAH-PLND) between 1984 and 1994.

*Results:* Due to poor predictive value and poor correlation between serum CEA and clinico-pathological factors, CEA was abandoned in this study. Elevated TPA and SCC-Ag levels, pelvic lymph node metastasis (PLNM), lymphvascular space involvement (LVSI) and deep stromal invasion (DSI) were associated with poor survival time by univariate analysis. The correlation study showed that elevated serum TPA was significantly related to PLNM, LVSI, and DSI ($p = 0.004$, 0.008, and 0.021, respectively), and SCC-Ag was related to PLNM and bulky tumor size ($p = 0.001$ and 0.02, respectively). In the multivariate analysis, only PLNM and LVSI remained independently significant indicating poor survival. Further stratification studies by PLNM and LVSI showed that elevated TPA levels could even indicate higher recurrence rates in patients with PLNM ($p = 0.045$), as well as SCC-Ag in patients with LVSI ($p = 0.038$).

*Conclusions:* The results suggest that both elevated TPA and SCC-Ag levels depicting poor prognosis in stage Ib-IIa cervical SCC, especially indicates a group of high-risk patients who may need more aggressive therapy.

*Key Words*: Squamous cell carcinoma antigen; Tissue polypeptide antigen; Stage IB-IIA cervical carcinoma.

## Introduction

Prognostic analysis has been performed in a variety of cancers to predict prognosis and to treat patients accordingly. In cervical carcinoma, most investigations have taken the following clinicopathological factors as significant by either or both univariate and multivariate analyses [1-5]. They include pelvic lymph node metastasis (PLNM), lymphvascular space involvement (LVSI), deep stromal invasion (DSI), bulky tumor size, parametrial extension, and poor differentiation, etc. Serum tumor markers such as tissue polypeptide antigen (TPA), squamous cell carcinoma antigen (SCC-Ag), and carcinoembryonic antigen (CEA) have commonly been used in the monitoring of cervical cancer and are correlated with disease status [6-8]. They have been reported as associated with stage, tumor size, recurrence or progressive diseases and survival [9-11].

Our previous data, which focused on low-risk patients who did not have any poor prognostic factors: PLNM, LVSI, DSI, bulky tumor size, parametrial extension and poor differentiation, showed that elevated TPA could indicate poor prognosis [12]. Compared with the conventional factors, especially PLNM which has been shown to be predominant in most studies [2, 13, 14], serum tumor markers seemed to have only a modest but not consistent role in prognostic analysis [6, 7, 15, 16]. Therefore, it would be interesting to know if SCC-Ag, TPA, and CEA are still valid tests, especially in the presence of PLNM and other prognostic factors. In this study, a stratification method was used including univariate and multivariate analyses, which was then correlated to conventional factors and challenged by these factors.

## Materials and Methods

From 1984 to 1994, serum samples were collected preoperatively from 779 patients with FIGO stage Ib and IIa cervical squamous cell carcinoma who received radical hysterectomy plus pelvic lymph node dissection (RAH-PLND). Serum markers were assayed preoperatively for SCC-Ag, TPA, and CEA by radioimmunoassay (RIA) with Abbott SCC RIA, Prolifigen TPA IRMA, and International CIS CEA RIA. The cut-off levels for SCC-Ag, TPA, and CEA were 1.5 ng/ml, 111 ng/ml, and 15.5 ng/ml, respectively, based on our previous report [17]. According to our previous univariate study [1, 2, 12], five prognostic factors: PLNM, DSI, LVSI, parametrial extension and bulky tumor size were included for analysis. DSI was defined as invasion more than one-half the depth of the cervical stroma. Bulky tumor size (> 4 cm) was determined by

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pathology. Finally, only 431 patients fulfilled the criteria and they had at least one of the five prognostic factors. Adjuvant therapy was given for patients with PLNM either using radiation or chemotherapy. Chemotherapy consisted of six courses of cisplatin, oncovin, and bleomycin. External irradiation consisted of 4500 ~ 5500 cGy delivered to the mid-plane of the pelvis with a six-million-volt linear accelerator for 5-6 weeks. Intracavitary irradiation with cesium was given to patients with positive cut margins at a dosage of 3000 ~ 4000 cGy and at a depth of 5 mm from the vaginal surface. The prognosis was evaluated by recurrence rate and survival time. Recurrence was defined as the disease found at any time after surgery.

Statistical methods included univariate analysis initially with the $x^2$ test and one-way analysis of variance. Differences between patient groups were analyzed using the $x^2$ test and Fisher's exact test. The univariate analysis of survival was performed using the Wilcoxin log-rank test. Multivariate analyses of recurrence and survival time were performed using the Cox regression models [18]. Significance was declared at $p < 0.05$.

## Results

The sensitivity of SCC-Ag, TPA and CEA was 65.1%, 50.6%, and 22.3%, respectively and the specificity was 93.1%, 95.1%, and 86.4%, respectively. CEA was much less ideal than SCC-Ag and TPA. The specificity of SCC-Ag and TPA was similar, but the sensitivity of SCC-Ag seemed higher. We found that preoperative serum SCC-Ag and TPA levels were significantly correlated to cumulative 5-year survival after stratification at cut-off values but preoperative serum CEA did not reach statistical significance (Figures 1, 2, 3).

Correlation studies showed that elevated TPA levels were significantly associated with PLNM, DSI and LVSI; in addition, elevated SCC-Ag levels were correlated with PLNM and tumor size, but elevated CEA levels were not correlated with any factor (Table 1). In univariate analysis, factors indicating poor survival were TPA, SCC-Ag, PLNM, LVSI, DSI (all $p = 0.0001$) and CEA ($p = 0.0018$), but not parametrial extension ($p = 0.263$) or tumor size ($p = 0.393$). In multivariate analysis only PLNM and LVSI were independently significant for survival time (Table 2). Therefore, PLNM and LVSI were enlisted as the stratification conditions to further check the prognostic value of elevated SCC-Ag levels and TPA levels on survival, while elevated CEA levels were omitted as they were much less adequate compared to elevated SCC-Ag levels and elevated TPA levels. This study disclosed that both elevated SCC-Ag and TPA levels indicated higher recurrence rates in the low-risk patients who did not have LVSI, PLNM or DSI (Tables 3 & 4). In the high-risk group, which was evident by PLNM, elevated TPA levels indicated a worse outcome than normal TPA levels, i.e., the recurrence rates increased significantly from 35.7% to 75% (Table 3). However, elevated SCC-Ag did not add any additional effect in the same test. On the other hand, elevated SCC-Ag levels led to a higher recurrence rate in the presence of LVSI (Table 4).

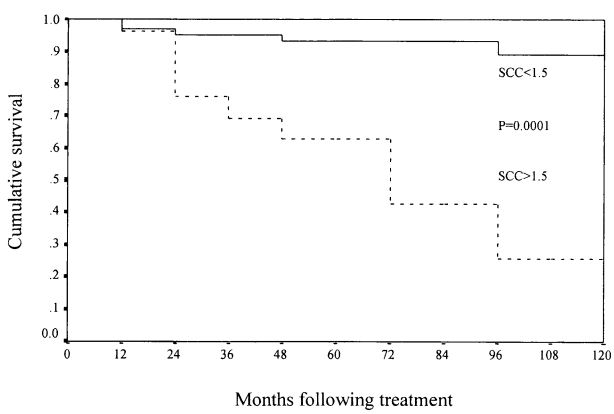


Figure 1. — Survival curve of SCC-Ag with stratification at cut-off value.

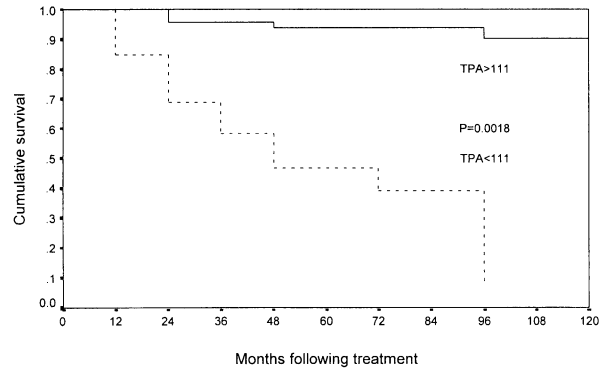


Figure 2. — Survival curve of TPA with stratification at cut-off value.

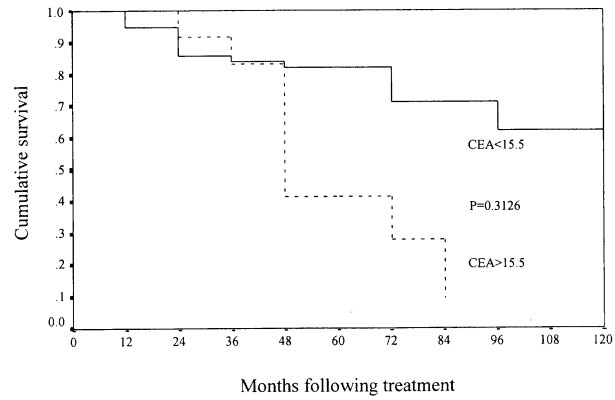


Figure 3. — Survival curve of CEA with stratification at cut-off value.

## Discussion

In a functional view, TPA, a single chain polypeptide with a mixture of epitopes from cytokeratin 8, 18 and 19, was demonstrated mostly in the proliferative cells and is synthesized during the late S and G2 phase of the cell cycle [19]. SCC-antigen is an inhibitor of several serine proteases or cysteine protease, and is capable of regulating proteolytic events, such as metastasis and tumor pro-

Table 1. — *Correlations between tumor markers and prognostic factors.*

| Markers | | PLNM | | LVSI | | DSI | | Parametrial extension | | Size ≥ 4cm | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | % | No. | % | No. | % | No. | % | No. | % | No. |
| TPA | < 111 | 17.3 | 81 | 14.4 | 83 | 13.6 | 81 | 4.2 | 71 | 26.1 | 69 |
| | ≧111 | 44.4 | 27 | 40.7 | 27 | 26.9 | 26 | 10.0 | 20 | 33.3 | 21 |
| | P | 0.004 | | 0.008 | | 0.021* | | 0.32* | | 0.52 | |
| SCCA | < 1.5 | 11.8 | 76 | 18.1 | 77 | 16.0 | 75 | 4.7 | 64 | 15.8 | 57 |
| | ≧ 1.5 | 48.8 | 80 | 30.4 | 82 | 27.9 | 79 | 6.5 | 77 | 34.5 | 55 |
| | P | 0.001 | | 0.106 | | 0.115 | | 0.73* | | 0.02 | |
| CEA | < 15.5 | 25.0 | 132 | 20.5 | 136 | 18.5 | 130 | 4.4 | 113 | 42.9 | 154 |
| | ≧ 15.5 | 15.6 | 32 | 28.1 | 32 | 15.6 | 32 | 15.4 | 13 | 23.1 | 26 |
| | P | 0.26 | | 0.491 | | 0.906 | | 0.25* | | 0.06 | |

Fisher's exact test, other: by Chi-square test
PLNM: pelvic lymph node metastasis, LVSI: lymphvascular space involvement, DSI: deep stromal invasion. No.: number of the patients.

Table 2 – *Survival analysis by Cox's proportional hazards model.*

| Risk factors | Odds ratio | 95% CI | P |
|---|---|---|---|
| CEA | 1.43 | 0.21-4.69 | 0.621 |
| TPA | 2.11 | 0.81-18.62 | 0.348 |
| SCC-Ag | 1.29 | 0.09-2.78 | 0.847 |
| LN | 4.99 | 1.56-16.98 | 0.009 |
| LVSI | 7.39 | 1.89-22.15 | 0.009 |
| DSI | 0.82 | 0.12-5.29 | 0.728 |
| Parametrium | 2.25 | 0.47-13.21 | 0.939 |
| Tumor size | 2.09 | 0.51-9.44 | 0.821 |

LN: pelvic lymph node metastasis, LVSI: lymphvascular space involvement, DSI: deep stromal invasion.

Table 3 – *Recurrence rate determined by TPA levels and clinical prognostic factors*

| | TPA<111 | | | TPA≧111 | | | |
|---|---|---|---|---|---|---|---|
| | Recurrence No. | No. | % | Recurrence No. | No. | % | P. |
| LVSI | | | | | | | |
| (–) | 11 | 59 | 18.6 | 6 | 9 | 66.7 | 0.006 |
| (+) | 6 | 12 | 50.0 | 8 | 11 | 72.7 | 0.247 |
| PLNM | | | | | | | |
| (–) | 12 | 57 | 21.1 | 5 | 8 | 62.5 | 0.024 |
| (+) | 5 | 14 | 35.7 | 9 | 12 | 75 | 0.045 |

No.: number of patients; LVSI: lymphvascular space involvement, PLNM: pelvic lymph node metastasis.

Table 4. – *Recurrence rate determined by SCC-Ag levels*

| | SCC-Ag < 1.5 | | | SCC-Ag ≧ 1.5 | | | |
|---|---|---|---|---|---|---|---|
| | Recurrence No. | No. | % | Recurrence No. | No. | % | P. |
| LVSI | | | | | | | |
| (–) | 9 | 50 | 18.0 | 23 | 52 | 44.2 | 0.004 |
| (+) | 9 | 14 | 64.3 | 19 | 25 | 76.0 | 0.038 |
| PLNM | | | | | | | |
| (–) | 10 | 55 | 18.2 | 18 | 38 | 47.4 | 0.003 |
| (+) | 5 | 9 | 55.6 | 24 | 39 | 61.5 | 0.741 |

No.: number of patients; LVSI: lymphvascular space involvement, PLNM: pelvic lymph node metastasis.

gression [20]. These characteristics make TPA and SCC-Ag very possible indicators for poor prognosis. In this study, univariate analysis confirmed the prognostic significance of TPA and SCC-Ag on survival, as well as the three conventional factors: PLNM, LVSI and DSI, which is compatible with other reports [2, 21-24]. By multivariate analysis, PLNM and LVSI were the only two independent factors while SCC-Ag and TPA were not. On the contrary, some scattered multivariate analyses still showed the independent role of these biomarkers [19, 24, 25]. Duk et al. showed that pretreatment SCC-Ag levels, bulky cervical mass, and LVSI were independent risk factors for the presence of PLNM [10] and furthermore, Avall-Lundqvist et al. showed SCC-Ag levels correlated with poor survival [25]. TPA was also found independently significant for disease-free intervals in stage Ib - IVb, but not in Ib -IIa patients [24].

The incompatible data may be explainable due to the different variables selected [2, 26, 27]. The different cut-off values for each biomarker could be the another explanation. Hong et al. found that SCC-Ag was an independent factor for survival when the cut-off level was set at 10 ng/ml in multivariate analysis, but it was not at 2-10 ng/ml in patients with cervical carcinoma treated by radiation therapy [26]. Bolger et al. showed that the positive prediction rates for lymph node metastasis were 51, 70, and 100% with cut-off values of 2, 4, and 8.6 ng/ml, respectively [27].

Although SCC-Ag and TPA were not independent factors in this study, their roles in predicting prognosis can not be ignored as the correlation study disclosed that elevated TPA was related to PLNM, LVSI and DSI while elevated SCC-Ag was related to PLNM. All these clinico-pathological factors were prognostically significant, and PLNM and LVSI were even independent factors. Biologically LVSI, DSI and PLNM represent different stages in developing invasion and metastasis. Therefore, correlations between SCC-Ag, TPA and these clinico-pathological factors fulfilled the original theory that all of these biomarkers and clinical factors are invasion/metastasis related. Furthermore, subsequent stratification studies manifested that even in the presence of

PLNM, the most important factor for prognosis from many reports [2, 21, 22], elevated TPA still had a role in indicating higher recurrence rate. However, SCC-Ag did not have a role in this regard. In a similar way, SCC-Ag still had a value in indicating higher recurrence rate in the presence of LVSI. LVSI was are independent factor with the highest odds ratio (7.39, vs. 4.99 of PLNM) in this study. Sevin et al. reported that depth of stromal invasion, LVSI, age > 40 and lymph node metastasis were the best combination of risk factors determined by the tree-structured survival analysis [28].

We concluded that pretreatment serum TPA and SCC-Ag levels had an indicative value on recurrence. Application could be either for low-risk patients who do not have any of the poor prognostic factors or for high-risk patients who even have the worst prognostic factors such as PLNM and LVSI, respectively. These higher-risk patients are candidates for more aggressive therapeutic trials.

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