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SPECIAL ARTICLE

Serum Squamous Cell Carcinoma Antigen and Its Application in Cervical Cancer Patients

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ABSTRACT

Cervical cancer is the second most common female cancer in Thailand. The treatment depends on the stages of disease. Serum squamous cell carcinoma antigen (SCC-Ag) produces through squamous formation of cervical squamous epithelium and increased during the neoplastic transformation. However, it is not organ specific. In healthy women, serum SCC-Ag is found at a concentration of less than 1.9 µg/L. The cervical cancer clinical utilities of serum SCC-Ag reported in the literatures comprised of the indicative of pelvic or paraaortic lymph node metastases at the pretreatment evaluation period, the prediction of prognosis, the monitor the treatment response and the detection of early recurrence. With the limitation in health care resources of Thailand, raising of serum SCC-Ag also reminds the physician about distant recurrence of disease. Moreover, the detection of asymptomatic recurrence may be associated with prolonged survival.

Keywords: cervical cancer, SCC-Ag

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Cervical cancer is a major world health problem for women. The global annual incidence of cervical cancer in 2012 was 528,000 cases and the death was 266,000 cases[1]. It is the fourth most common cancer in women worldwide, with 85% of cases occurring in developing countries, where cervical cancer is a leading cause of cancer death in women[2]. In Thailand, cervical cancer is the second most common of female cancer. In 2015, the age-standardized incident rate of the year 2010-2012 was reported 14.4 per 100,000 women year[3]. Squamous cell carcinoma(SCC) accounts for approximately 80% of cervical cancers and adenocarcinoma accounts for approximately 20%. In developed countries, the substantial decline in incidence and mortality of squamous cell carcinoma of the cervix is presumed to be the result of effective screening[4]. The treatment approaches which compose of surgery, concurrent chemoradiation therapy, systemic chemotherapy or multimodalities depend on the stage of disease. The international federation of gynecology and obstetrics (FIGO) staging system has been applied for standardization, comparison between the treatment

methods and the prognosis of disease. The prognosis of disease is also based on the stage of diagnosis; 5 year survival for stage I, II, III and IV was 81-96%, 65-87%, 35-50% and 15-20%, respectively. During the treatment; patients symptoms; physical and pelvic examination; imaging technique such as computerized tomography, magnetic resonance image, even positron emission tomography were utilized for monitoring the response of treatment. After complete remission, the methods previously mentioned also use for surveillance of disease.

Serum biomarkers have several roles in cancer management including early detection or diagnostic confirmation of cancers, predicting prognosis and/or response of specific treatment, and disease monitoring after primary treatment. Serum squamous cell carcinoma antigen (SCC-Ag), a neutral and acidic sub-fractions of tumor antigen 4(TA-4) firstly named by the discoverers in 1977[5], it produces through squamous formation of cervical squamous epithelium in cervical cancer and increased during the neoplastic transformation of the cervical squamous epithelium[6]. Elevated serum SCC-Ag levels have been detected in 28-88% of cervical squamous cell carcinomas[7]. Molecular cloning of the SCC genomic region has revealed the presence of 2 genes, SCC-Ag1 and SCC-Ag2, which belong to the ovalbumin-serpin/clade B family, Serpin B3 and Serpin B4, respectively. Both located on chromosome 18q21.3. SCC-Ag1 codes for the neutral isoform of SCC-Ag and SCC-Ag2 codes for the acidic isoform. The neutral isoform is detected in both normal epithelial cells and malignant tissues, whereas the acidic isoform is found only in tumor cells, especially those located at the periphery of the tumor. The acidic form may also be found in the sera of cancer patients with well-differentiated squamous cell carcinomas. It has been suggested that SCC-Ag1 and SCC-Ag2 are capable of regulating proteolytic events involved in both normal (e.g., tissue remodeling, protein processing) and pathologic processes (e.g., tumor progression). Structurally, SCC-Ag1 and SCC-Ag2 are almost identical, differing only in their reactive site loops. The 2 forms, however, may have different biological functions[8]. SCC-Ag1 and SCC-Ag2 reside in the cytosol of squamous cells and their presence in the sera of patients with advanced cervical cancer is mainly due to a passive release rather than an active secretory process into the circulation[9]. Both serum SCC-Ag1 and SCC-Ag2 were elevated in cervical cancer patients and followed the clinical course of the disease during the follow-up. In the laboratory commercial tests (ARCHITECT® SCC Kit, Abbott) can detect SCC-Ag1 but not SCC-Ag2. So the SCC-Ag mentioned in the literatures was SCC-Ag1, otherwise depended on what the authors stated.

- **SCC-Ag reference intervals**[8, 10]

In apparently healthy women, the 99th percentile of circulating SCC-Ag is found at a concentration of 1.9 µg/L. Most studies have adopted a cutoff point between 2.0 and 2.5 µg/L. SCC-Ag is not organ specific. Elevated concentrations have been found in patients with squamous cell carcinoma of the vulva, vagina, head and neck, esophagus, and lung as well as in patients with benign diseases of the skin (e.g., psoriasis, eczema), lung (e.g., sarcoidosis), liver, and kidney. Very high values (up to 18 µg/L) have been found in patients with renal failure, lung disease, and head and neck tumors. There is no cutoff point that is specific for cervical malignancy.

- **The serum SCC-Ag in cervical cancer patients**

o *Suggestive of pelvic or paraaortic lymph node metastases in pretreatment evaluation*;

Huang EY and colleagues retrospectively analyzed 188 patients with squamous cell carcinoma of the uterine cervix from 1995 to 2008. They concluded that pretreatment carcinoembryonic antigen (CEA) ≥ 10 ng/mL was a risk factor of paraaortic lymph nodes relapse following definitive concurrent chemoradiation (CCRT) in patients with pretreatment SCC-Ag levels < 10 ng/mL. They also suggested the more comprehensive examination before CCRT and intensive follow-up schedules for early detection and salvage in patients with serum SCC-Ag or CEA levels ≥ 10 ng/mL[11].

Lekskul N and colleagues reported a different

result. This study retrospectively included 232 patients from 2009 to 2014 with locally advanced cervical cancer. The SCC-Ag level was significantly correlated with paraaortic lymph node status but not with pelvic lymph node status and parametrial involvement[12].

Both of those studies might have limitation due to retrospective study design with selection bias and small sample sizes. These need further evaluation for clinical usefulness.

o *Prediction of the prognosis*;

An elevated pretreatment serum SCC-Ag has been investigated to be an independent risk factor for the poor survival outcome. Ogino I and colleagues assessed the linear correlation between disease free survival (DFS) as the treatment outcome and serum pretreatment SCC-Ag in 352 patients with FIGO stage IIB-IVA squamous cell carcinoma of cervix[13].

Reesink-Peters N and colleagues analyzed 337 surgically treated patients whether the preoperative serum SCC-Ag, at the 1.9 ng/mL cutoff level, allow better identification of patients with a low likelihood for adjuvant radiotherapy than currently used clinical parameters. The results demonstrated that preoperative serum SCC-Ag at 1.9 ng/mL was the only independent predictor for a postoperative indication for radiotherapy (odds ratio 7.1; $p < 0.001$). Moreover, in the patients with stage IB1 who did not have indication for adjuvant radiotherapy, 15% of these patients with elevated preoperative serum SCC-Ag recurred within 2 years, compared with 1.6% of patients with normalized serum SCC-Ag levels ($p < 0.02$). They conclusion that in early-stage cervical cancer, determination of serum SCC-Ag level allows more refined preoperative estimation of the likelihood for adjuvant radiotherapy than current clinical parameters, and simultaneously identifies patients at high risk for recurrence when treated with surgery only[14].

Liu SC and colleagues reported a study of 197 stage IB1 cervical cancer patients who received curative treatment with various modalities between January 2004 and December 2010. Pretreatment clinical parameters including age, serum SCC-Ag, CEA, hemoglobin (Hb) level, platelet count, histological type, and treatment modality were analyzed. Among squamous cell carcinoma histology, patients with Hb level less than 12 g/dl and serum SCC-Ag level more than 3 ng/ml had worse treatment outcomes. The 5-year DFS rates were 89.2 and 44.4% for the patients at low-risk (Hb >12 g/dl, SCC-Ag ≤ 3 ng/ml) and high-risk (Hb ≤ 12 g/dl, SCC-Ag > 3 ng/ml), respectively ($p < 0.001$)[15].

Jeong BK and colleagues retrospectively analyzed the serum SCC-Ag before and after treatment and reviewed the records of 506 cervical cancer patients between 1994 and 2010. They used serum SCC-Ag at 1.5 ng/mL for cutoff level and discovered that patients with pretreatment SCC-Ag level more than 1.5 ng/mL have worsen prognosis when compared with the patients with pretreatment SCC-Ag ≤1.5 ng/mL[16].

Kawaguchi R and colleagues assessed the prognostic factors in 128 patients with locally advanced cervical cancer treated with radiotherapy or CCRT. Of these, 116 patients who had SCC-Ag levels > 1.5 ng/mL prior to treatment were analyzed retrospectively. Multivariate analysis showed that pretreatment anemia ($p=0.041$), pelvic lymph node metastasis ($p=0.016$) and posttreatment SCC-Ag levels ($p=0.001$) were independent prognostic factors for three-year overall survival (OS). They concluded that the posttreatment serum SCC-Ag levels <1.15 ng/mL predicted better three-year OS rates[17].

o *Monitoring the response of treatment and detection of early recurrence*;

Several studies have indicated that serum SCC-Ag has been potentially useful in monitoring the cervical cancer after primary therapy. Persistently elevated and/or increasing serum SCC-Ag after treatment suggest tumor persistence or progression.

The serum SCC-Ag has been also used in the evaluation of chemotherapy response. Such as the study from Hashimoto K and colleagues. They evaluated the changes in serial serum SCC-Ag levels in chemotherapy response in 55 metastatic cervical cancer patients. They found that the serum SCC-Ag levels declined between the second and third cycles of

chemotherapy may possible for the response[18].

There were plenty of clinical researches about serum SCC-Ag and the early detection of recurrence. Although the cutoff levels were difference between studies, the similar results were demonstrated. Yoon SM and colleagues reviewed the records of 112 cervical cancer patients who treated with CCRT. They considered a single serum SCC-Ag level more than 2 ng/mL or the difference between the two consecutively serum SCC-Ag increases more than 0.95 ng/mL. They reported these values were good method of detection of recurrence of disease in their population[19].

Shimura K and colleagues have explored that the level of serum SCC-Ag at cervical cancer at recurrence can be used for deciding upon the appropriate salvage treatment. They reviewed the clinical records from 167 cervical cancer patients who developed recurrence between 1996 and 2010. They used the cutoff level of serum SCC-Ag more than 2.0 ng/mL. The serum SCC-Ag were elevated in 125 patients (75%) when the recurrence was diagnosed. These also exhibited significantly shorter postrecurrent survival than those with normal SCC-Ag levels. Multivariate analyses revealed that an elevated serum SCC-Ag level was an independent prognostic factor for poor postrecurrent survival[20].

Ryu HK and colleagues reviewed the records of 783 squamous cell cervical cancer patients who underwent primary therapy and showed complete remission between January 2000 and April 2014. The median follow-up period was 41.2 months, and 154 patients (19.7%) had recurrent disease. The median pretreatment and posttreatment SCC-Ag level was 2.6 ng/mL (range, 0.1 to 532.0 ng/mL) and 0.7 ng/mL (range, 0.0 to 46.8 ng/mL), respectively. Both pretreatment and posttreatment SCC-Ag levels were higher in the recurrence group (p=0.017 and p=0.039). Optimal cutoff value of pretreatment and posttreatment SCC-Ag for predicting recurrence was 1.86 ng/mL (area under the curve (AUC) 0.663; p=0.000), and 0.9 ng/mL (AUC 0.581; p=0.002), respectively. In the multivariate, pretreatment SCC-Ag > 1.86 ng/mL (odds ratio (OR) 2.11; 95% confidence interval(CI) 1.38, 3.22; p=0.001) and posttreatment SCC-Ag > 0.9 ng/mL (OR 1.64; 95%CI 1.18, 2.28; p=0.003) were significantly associated with poorer DFS[21].

Hirakawa M and colleagues evaluated 108 patients with FIGO stage IB2-IV4 cervical cancer treated with CCRT between 1996 and 2003. They found that serum SCC-Ag immediate after the treatment was an independent factor for distant recurrence. They stated SCC-Ag level at 1.5 ng/mL for cutoff[22].

A lead time of up to 14 months for detecting recurrent disease has been reported, with a mean or median between 2 and 6 months. Although serum SCC-Ag is suitable for monitoring and shows a strong correlation with the clinical course, it is not yet known whether earlier detection of recurrent disease influences treatment outcome and prognosis[8]. Almost all of the researches are retrospective studies that have some potential biases such as lead time bias, where the diagnostic anticipation simply extends the survival time during which the patient is aware of the disease, and length-time bias, where patients with slowly progressive disease are more suitable to be diagnosed by screening tests; in those studies, most of the patients are symptomatic at the time of the diagnosis of recurrence. The detection of asymptomatic recurrences is associated with prolonged OS and survival from time of initial detection of recurrence. It is certainly possible that a subset of asymptomatic patients may have a more indolent disease and a greater likelihood of detection within the screening intervals. This group may have a better survival because of the presence of a biologically less aggressive tumor. On the other hand, it has been suggested that the use of routine follow-up visit may in fact delay the detection of recurrence because some women delay presenting symptoms until their next routine appointment. The new available imaging techniques in combination with the use of tumor markers could change the approach to early detection of recurrent disease and may have a significant impact on survival that has yet to be demonstrated. To date, there is no evidence-based guideline exist for imaging of tumor metastasis/ recurrence from cervical cancer[23].

From reviewing of literatures, serum SCC-Ag demonstrated many aspects of clinical implement. However, the cutoff levels of serum SCC-Ag for detection of disease recurrence and prediction of the prognosis are different among studies. With the limitation in health care resources of Thailand, serum SCC-Ag might play roles in the pretreatment evaluation of disease, the monitor after treatment and detection of recurrence. The raising of serum SCC-Ag also reminds the physician about distant recurrence of disease in the concealed areas such as intraabdominal lymph nodes, lung or liver. The detection of asymptomatic recurrences is associated with prolonged survival.

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