

## RESEARCH ARTICLE

# The Level of Squamous Cell Carcinoma Antigen and Lymph Node Metastasis in Locally Advanced Cervical Cancer

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### Abstract

**Background:** This study aimed to determine the utility and a cut-off level of serum squamous cell carcinoma antigen (SCC-Ag) to predict lymph node metastasis in locally advanced cervical cancer cases. We also investigated the correlation between SCC-Ag level and lymph node status. **Materials and Methods:** From June 2009 to June 2014, 232 patients with cervical cancer stage IB2-IVA, who were treated at Ramathibodi Hospital, were recruited. Receiver operating characteristic (ROC) curves were used to identify the best cut-off point of SCC-Ag level to predict lymph node metastasis. Quantile regression was performed to evaluate the correlation between SCC-Ag levels and pelvic lymph node metastasis, paraaortic lymph node metastasis, and parametrial involvement as well as tumor size. **Results:** Pelvic lymph node metastasis and paraaortic lymph node metastasis were diagnosed in 46.6% and 20.1% of the patients, respectively. The median SCC-Ag level was 6 ng/mL (range, 0.5 to 464.6 ng/mL). The areas under ROC curves between SCC-Ag level and pelvic lymph node metastasis, paraaortic lymph node metastasis, parametrial involvements were low. SCC-Ag level was significantly correlated with paraaortic lymph node status ( $p=0.045$ ) but not with pelvic lymph node status and parametrial involvement. SCC-Ag level was also related to the tumor diameter ( $p<0.05$ ). **Conclusions:** SCC-Ag level is not a good predictor for pelvic and paraaortic lymph node metastasis. However, it is still beneficial to assess the tumor burden of squamous cell carcinoma of the cervix.

**Keywords:** Cervical cancer - squamous cell carcinoma antigen - lymph node metastasis - tumor size

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### Introduction

More than 270,000 women die from cervical cancer every year with more than 85% of these deaths in the low and middle income countries. Because of the insufficient resources, impotent health systems and limited number of trained health care providers, cervical cancer prevention and control are difficult to achieve high coverage in these countries (WHO, 2013). In Thailand, projection from the previous study revealed a declining trend since the introduction of the cervical cancer screening program in 1989 (Sriplung et al., 2014). Nevertheless, cervical cancer remains the second leading cancer among Thai women with the mortality rate as high as 55.14% (Farley et al., 2013).

Cervical cancer is clinically staged because most patients, especially in the locally advanced stages, are treated with the non surgical approaches and there was no demonstrable benefit from surgical staging in terms of both overall and progression-free survival (Brockbank et al., 2013). Although lymph node status assessment does not change staging, lymph node metastasis is the most important prognostic factor that may affect the plan

of treatment (Sakuragi et al., 1999; Shim et al., 2013; Song et al., 2013; Hacker et al., 2015). Hence, computed tomography (CT) and magnetic resonance imaging (MRI) are essential for an evaluation of lymph node metastasis with the comparable accuracy of 86% (Hacker et al., 2015). However, besides the increasing costs of such investigations, in the developing countries with limited resources, the waiting time for these imaging studies is potentially long and might result in the delayed diagnosis and treatment decision, advocating the necessity of an alternative.

Squamous cell carcinoma antigen (SCC-Ag) is a common tumor marker, widely used to monitor the response of treatment and the recurrence of disease. Previous studies suggested the potential correlation of serum SCC-Ag with clinical stage, deep cervical invasion, patient survival and lymph node metastasis (Duk et al., 1996; Porika et al., 2010; Kawaguchi et al., 2013). Thus, the main objective of this study was to define the cut-off level of serum SCC-Ag to predict lymph node metastasis. In addition, the correlations between serum SCC-Ag and lymph node metastasis in the patients with locally advanced cervical cancer were also examined.

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## Materials and Methods

After the approval from the institutional Ethical Committee, patients with cervical carcinoma treated at Ramathibodi Hospital, Bangkok, Thailand from July 2009 to June 2014 were identified from the cancer registry. The inclusion criteria were as follows: patients with pathologically confirmed squamous cell carcinoma or carcinoma with squamous cell element of the cervix, patients who were clinically diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IB2-IVA or locally advanced cervical cancer. Two hundred and thirty one patients fulfilled the criteria.

All of the patients underwent clinical staging, including physical examination, complete blood count, serum blood urea nitrogen, creatinine, liver function test, chest X-ray, cystoscopy, proctoscopy, computed tomography (CT scan) and serum squamous cell carcinoma antigen (SCC-Ag). The pelvic and paraaortic lymph nodes were assessed from CT scan and those greater than 1 cm were considered positive. (Hacker et al., 2015). The tumor size was established from the cervical tumor's largest diameter in the CT scan. Parametrial involvement was determined from the pelvic examination at the time of diagnosis.

SCC-Ag concentration was detected using ARCHITECT SCC assay which was a two-step Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of SCC-Ag in human serum on the Architect i2000SR analyzer (IMX, Abbott Diagnostics, Illinois, USA.). According to manufacturer's recommendations, the reference range for SCC-Ag was 1.5 ng/mL.

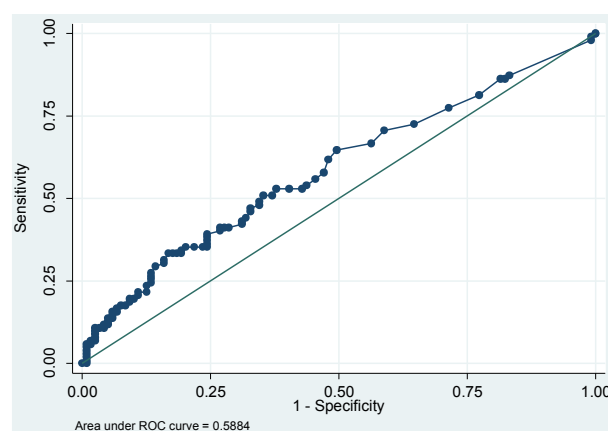
Receiver operating characteristic (ROC) curves were utilized to determine the best cut-off point of SCC-Ag level to speculate lymph node metastasis. Quantile regression was performed to evaluate the correlation between SCC-Ag levels and other variables (pelvic lymph node metastasis, paraaortic lymph node metastasis, parametrial involvement and tumor size). All analyses were conducted with Stata version 13.1 statistical software (StataCorp, College Station, Texas, USA).

## Results

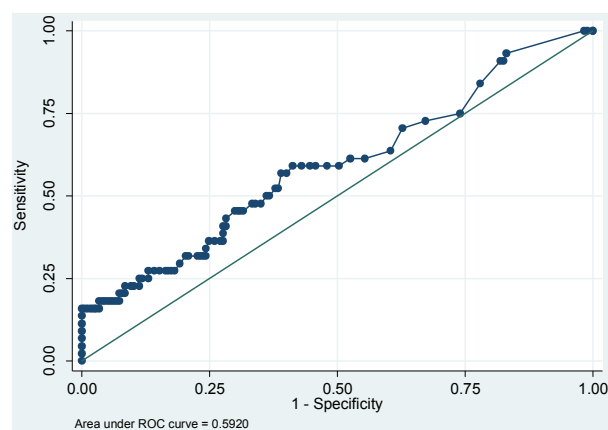
The characteristics of the enrolled patients were summarized in Table 1. Pelvic lymph node metastasis was detected in 46.6% of the patients and paraaortic lymph node involvement was diagnosed in 20.1%. The mean tumor diameter, as measured from CT scan, was 5.3 cm (standard deviation 1.89 cm). The median SCC-Ag level was 6 ng/mL (range, 0.5 to 464.6 ng/mL). We were unable to determine the cut-off value of SCC-Ag level to predict pelvic and paraaortic lymph node metastasis as well as parametrial involvement since the areas under ROC curve were all low. (Table2, Figure 1-3). Still, as demonstrated in Table 3, SCC-Ag level was significantly related to paraaortic lymph node status ( $p=0.045$ ) but not to pelvic lymph node status and parametrial involvement. Additionally, SCC-Ag level was also correlated with the tumor diameter with the coefficient of 0.23 ( $p<0.05$ ).

**Table 1. Patient Characteristics**

Characteristics	Total	N(%)
Histopathology	231	
squamous		220 (95.2)
adenosquamous		11 (4.7)
FIGO staging	231	
IB2		18 (7.7)
IIA1		3 (1.3)
IIA2		6 (2.6)
IIB		100 (43.2)
IIIA		5 (2.1)
IIIB		92 (39.8)
IVA		7 (3.0)
Parametrium	231	
Positive		200 (86.5)
Negative		31 (13.4)
Pelvic lymph node	223	
Positive		104 (46.6)
Negative		119 (53.3)
Paraortic lymph node	223	
Positive		45 (20.1)
Negative		178 (79.8)
Primary treatment	231	
RT		3 (1.2)
CCRT		223 (96.5)
Surgery		5 (2.1)
Adjuvant treatment	228	
None		146 (64.0)
Surgery		16 (7.0)
Chemotherapy		62 (27.1)
Both		4 (1.7)



**Figure 1. SCC-Ag Level in Predicting Pelvic Lymph Node Metastasis**



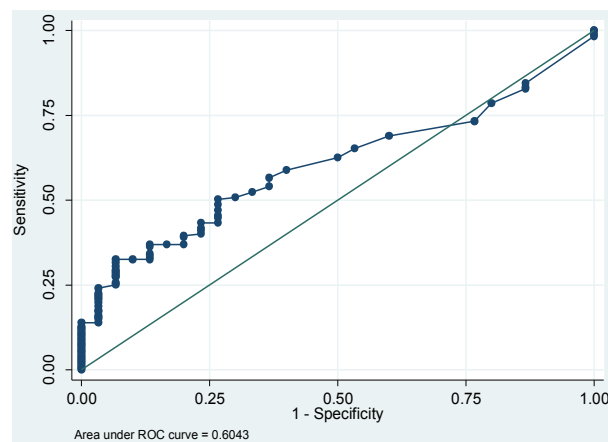
**Figure 2. SCC-Ag level in Predicting Paraortic Lymph Node**

**Table 2. Area under ROC Curve**

Parameters	Area under ROC curve	95% CI	N
Pelvic lymph node	0.59	0.51-0.66	223
Paraortic lymph node	0.59	0.49-0.69	223
Parametrium	0.6	0.51-0.69	231

**Table 3. Comparison of SCC-Ag Levels and Pelvic Lymph Node Status, Paraortic Lymph Node Status and Parametrial Involvement**

Parameter	SCC-Ag level median (range)	Coefficients	p-value
Pelvic lymph node		5	0.051
Positive	9 (0.5-351)		
Negative	4 (0.5-464.5)		
Paraortic lymph node		5.5	0.045
Positive	10 (1-464.5)		
Negative	5.5 (0.5-171)		
Parametrium		3	0.36
Positive	7 (0.5-464.5)		
Negative	4 (1-64)		

**Figure 3. SCC-Ag in Predicting Parametrial Involvement**

## Discussion

Tumor markers play important roles in the field of oncology, with the clinical applications in diagnosing and mainly treatment or recurrence monitoring. SCC-Ag is a glycoprotein which elevates in association with squamous cell carcinoma with reported increasing clinical usefulness. In this study, we tried to establish the cut-off level of pretreatment SCC-Ag to predict pelvic and paraortic lymph node metastasis. Nonetheless, the ROC curves showed that SCC-Ag was not a good predictor of lymph node status and there was also no demonstrable correlation to pelvic lymph node metastasis. Some previous studies reported SCC-Ag as a predictor for lymph node metastasis (Takeda et al., 2002) and the levels higher than 4 ng/mL (Takeshima et al., 1998) or 8 ng/mL (Lin et al., 2000) were categorized in a high-risk zone for nodal metastasis. Gaarenstroom et al. concluded that pretreatment SCC-Ag was found to be related to tumor volume but not a reliable predictor of lymph node metastasis (Gaarenstroom et al., 2000). Yoon et al. (2007) also described the association between SCC-Ag level and tumor volume. Porika et al.

(2010) reported no correlation between tumor size and SCC-Ag but SCC-Ag rose in the patients with advance disease. Our study confirmed the correlation between SCC-Ag level and tumor size, rationally explained by the fact that SCC-Ag was produced by tumor cells. Because we included the patients with cervical cancer from stage IB2 to IVA, consequently with variable tumor burden, the effects of tumor size on SCC-Ag level were unavoidable. This might interfere with the analysis of SCC-Ag level to represent lymph node status since the previous studies were performed in early stage cervical cancer (Lin et al., 2000; Takeda et al., 2002).

In cervical cancer patients with surgical treatment, pathologic characteristics, such as lymphovascular space invasion possessed prognostic values (Khunamornpong et al., 2013; Khunamornpong et al., 2013). Moreover, lymphovascular space invasion was a well-accepted risk factor for lymph node metastasis. We did not include this factor in the analysis due to the limited data of this retrospective study. There was also a proposed benefit of SCC-Ag to predict patient survival (Duk et al., 1996; Kawaguchi et al., 2013). A prospective study is needed to verify the value of SCC-Ag level to reflect these components.

In conclusion, SCC-Ag level is not a good predictor for pelvic and paraortic lymph node metastasis. There are still some potential benefits as it is correlated with paraortic lymph node metastasis and tumor size.

## References

- Brockbank E, Kokka F, Bryant A, Pomel C, Reynolds K (2013). Pre-treatment surgical paraortic lymph node assessment in locally advanced cervical cancer (Review). *Cochrane Database Syst Rev*, **3**, 8217.
- Duk JM, Groenier KH, de Bruijn HW, et al (1996). Pretreatment serum squamous cell carcinoma antigen: a newly identified prognostic factor in early-stage cervical carcinoma. *J Clin Oncol*, **14**, 111-8.
- Ferley J, Soerjomataram I, Ervik M, et al (2013). GLOBOCAN 2012 v 1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: international agency for research on cancer. [cited 2015 March 28]. Available from: <http://globocan.iarc.fr>
- Gaarenstroom KN, Kenter GG, Bonfrer JM, et al (2000). Can initial serum cyfra21-1, SCC antigen, and TPA levels in squamous cell cervical cancer predict lymph node metastases or prognosis? *Gynecol Oncol*, **77**, 164-70.
- Hacker NF, Vermorken JB (2015). Cervical cancer. In 'Berek & Hacker's Gynecologic oncology, Eds Berek JS and Hacker NF. Wolters Kluwer, Philadelphia, 326-80.
- Kawaguchi R, Furukawa N, Kobayashi H, Asakawa I (2013). Posttreatment cut-off levels of squamous cell carcinoma antigen as a prognostic factor in patients with locally advanced cervical cancer treated with radiotherapy. *J Gynecol Oncol*, **24**, 313-9.
- Khunamornpong S, Settakorn J, Sukpan K, et al (2013). Prognostic value of pathological characteristics of invasive margins in early-stage squamous cell carcinomas of the uterine cervix. *Asian Pac J Cancer Prev*, **14**, 5165-9.
- Khunamornpong S, Lekawanvijit S, Settakorn J, et al (2013). Prognostic model in patients with early-stage squamous cell carcinomas of the uterine cervix. *Asian Pac J Cancer Prev*, **14**, 6935-40.

- Lin H, ChangChien CC, Huang EY, et al (2000). The role of pretreatment squamous cell carcinoma antigen in predicting nodal metastasis in early stage cervical cancer. *Acta Obstet Gynecol Scand*, **79**, 140-4.
- Porika M, Vemunoori AK, Tippani R, et al (2010). Squamous cell carcinoma antigen and cancer antigen 125 in Southern Indian cervical cancer patients. *Asian Pac J Cancer Prev*, **11**, 1745-7.
- Sakuragi N, Satoh C, Takeda N, et al (1999). Incidence and distribution patter of pelvic and paraaortic lymph node metastasis in stages IB, IIA and IIB cervical carcinoma treated with radical hysterectomy. *Cancer*, **85**, 1547-54.
- Shim SH, Lee SW, Park JY, et al (2013). Risk assessment model for overall survival in patients with locally advanced cervical cancer treated with definitive concurrent chemoradiotherapy. *Gynecol Oncol*, **128**, 54-9.
- Song S, Kim JY, Kim YJ, et al (2013). The size of the metastatic lymph node is an independent prognostic factor for the patients with cervical cancer treated by definitive radiotherapy. *Radiother Oncol*, **108**, 168-73.
- Sriplung H, Singkham P, Iamsirithaworn S, Jiraphongsa C, Bilheem S (2014). Success of a cervical cancer screening program: Trends in incidence in Songkhla, Southern Thailand, 1989-2010, and prediction of future incidences to 2030. *Asian Pac J Cancer Prev*, **15**, 10003-8.
- Takeda M, Sakuragi N, Okamoto K, et al (2002). Preoperative serum SCC, CA125, and CA19-9 levels and lymph node status in squamous cell carcinoma of the uterine cervix. *Acta Obstet Gynecol Scand*, **81**, 451-7.
- Takeshima N, Hirai Y, Katase K, et al (1998). The value of squamous cell carcinoma antigen as a predictor of nodal metastasis in cervical cancer. *Gynecol Oncol*, **68**, 263-6.
- World Health Organization (WHO) (2013). Introduction. in 'Comprehensive cervical cancer prevention and control: a healthier future for girls and women', World Health Organization (WHO). WHO press, Geneva, 2.
- Yoon SM, Shin KH, Kim JY, et al (2007). The clinical values of squamous cell carcinoma antigen and carcinoembryonic antigen in patients with cervical cancer treated with concurrent chemoradiotherapy. *Int J Gynecol Cancer*, **17**, 872-8.