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, paraaotic 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

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 heath 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 advance 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)
Paraaortic 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)
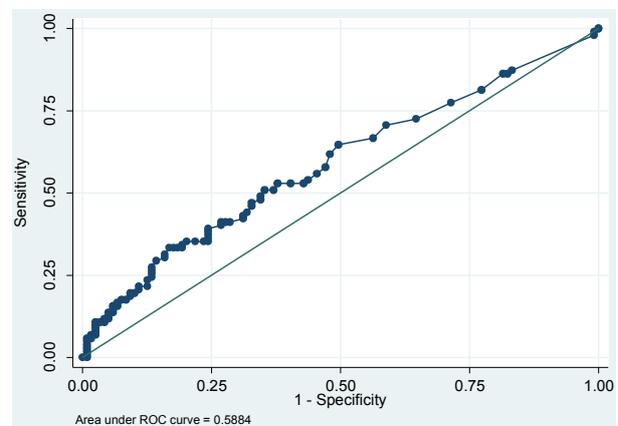
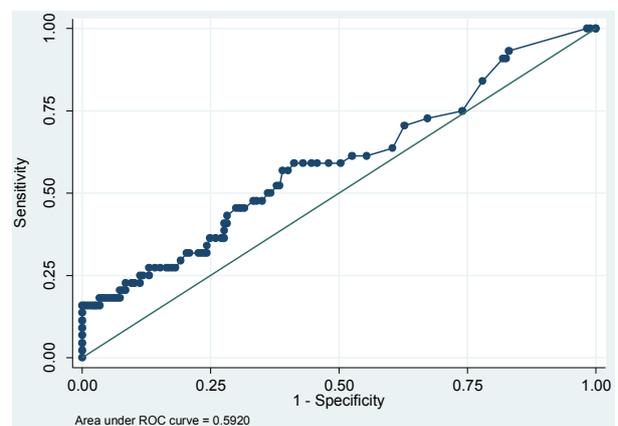**Figure 1. SCC-Ag Level in Predicting Pelvic Lymph Node Metastasis**

Figure 2. SCC-Ag level in Predicting Paraaortic 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
Paraaortic 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, Paraaortic 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)		
Paraaortic 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)		

Area under ROC curve = 0.6043
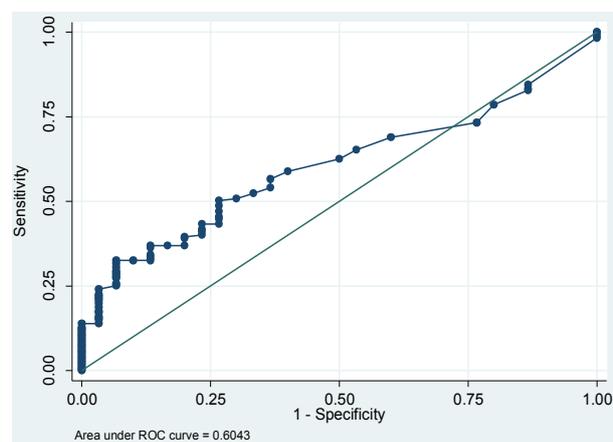
Figure 3. SCC-Ag in Predicting Parametrial Involvement

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 paraaortic 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 lymphphovascular 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; Kawagushi 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 paraaortic lymph node metastasis. There are still some potential benefits as it is correlated with paraaortic lymph node metastasis and tumor size.

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