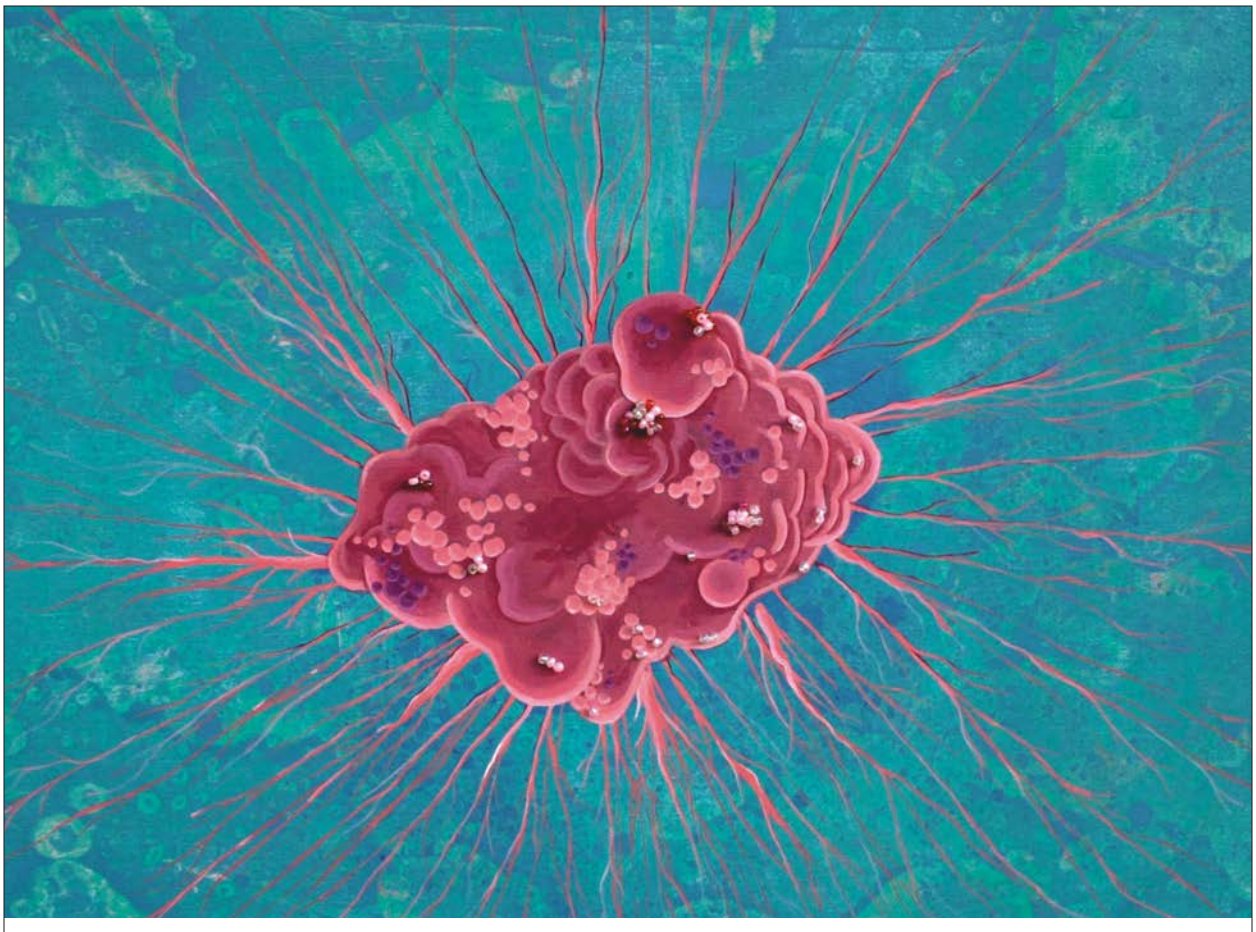

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Pretreatment Serum Squamous Cell Carcinoma Antigen Levels in Esophageal Squamous Cell Carcinoma

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Abstract: The present study tried to evaluate pretreatment SCCAg in esophageal squamous cell carcinoma patients in this region. Forty six patients with a biopsy-proven diagnosis of esophageal squamous cell carcinoma were recruited to this study. Tumors were located by endoscopy. The lesions were histologically graded and TNM staging was performed according to the radiologic, clinical and postoperative findings. Pretreatment serum SCCAg levels were measured by RIA and compared with clinicopathological aspects of tumor. The mean pre-treatment SCCAg level was 3.82 ng mL^{-1} while 21.7% of patients had elevated levels (>3 ng mL^{-1}). Tumor size was the only studied clinicopathologic factor significantly associated with SCCAg. Positive patients had greater tumor size compared to negative ones ($p = 0.031$). Although, SCCAg marker was positive in minority of the patients, but considering its relation with tumor size and probability disease stage, it is suggested to carry out survival study on more cases to find out the relation between marker positivity and cancer recurrence.

Key words: Squamous cell carcinoma antigen, esophageal cancer, squamous cell carcinoma, Iran

INTRODUCTION

Iran is a high incidence area of esophageal cancer (Ghavamzadeh *et al*., 2001). The majority of Iranian patients have been reported from the north and northeast regions of the country (Ghavamzadeh *et al*., 2001). Squamous cell carcinoma is the most common pathologic diagnoses with esophageal malignancy (Ghavamzadeh *et al*., 2001). Several potential tumor markers have been suggested for esophageal squamous cell carcinoma. Preoperative serum Squamous Cell Carcinoma Antigen (SCCAg) levels in squamous cell carcinoma of cervix and lung are usually accompanied by higher stage and poorer prognosis (Bae *et al*., 1997; Body *et al*., 1990; Hatzakis *et al*., 2002; Kornafel and Wawrzkiewicz, 1989) but its prognostic significance in esophageal carcinoma is still under investigation.

According to high prevalence of esophageal carcinoma in our region, this study aimed at evaluation of serum levels of this antigen in esophageal squamous cell carcinoma and correlation of its levels with clinicopathologic characteristics of patients. Up to now, such study has not been performed in Iran.

MATERIALS AND METHODS

Patients

Forty six patients with a biopsy-proven diagnosis of esophageal squamous cell carcinoma were recruited to this study. They consisted of 16 males and 30 females (mean age, 61.21 years; median,

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58; range, 40-90) referred to oncology departments of Ghaem and Omid hospitals of Mashhad University of Medical Sciences (Mashhad, Iran) between 2005 and 2007. All cases had not undergone radiotherapy, chemotherapy and surgery and had not any sign or symptom of primary squamous cell carcinoma in other parts of the body.

The locations of tumors were determined by endoscopy. In 39 patients, it was located 16 to 40 cm from the incisor teeth (mean, 27.06; median, 28.5) of which 30 (76.9%) and 9 (23.1%) cases had tumor in the middle and distal third of esophagus, respectively.

The lesion length of 34 patients was reportable according to the radiological view or endoscopic report with the mean of 7.25 cm (median, 7.5; range, 3-13.5).

The lesions were histologically graded. Clinical staging was based on TNM staging using a combination of radiologic, clinical and postoperative findings (Table 1).

Radioimmunoassay

Patients' samples which had been taken before treatment were assayed for SCCAg levels in reference laboratory based upon the direct sandwich RIAs using CanAg SCC EIA kit (Fujirebio Diagnostics AB, Sweden).

Samples were incubated with biotinylated Anti-SCC monoclonal antibody for 1 h. After 4 times washing, Chromogen reagent was added to each well and the enzyme reaction was allowed to progress. During the enzyme reaction a blue color developed if antigen was present. The intensity of the color was proportional to the amount of SCCAg present in the samples.

After 5 min, the enzyme reaction could be stopped by HCl solution. The color intensity was determined by spectrophotometer at 620 nm (or at 405 nm after addition of stop solution). The SCCAg concentrations of samples were then read from the standard curve (Fig. 1).

Table 1: Clinicopathologic factors of patients with esophageal squamous cell carcinoma

Factor	Value (n [%])
Histological grade	
I	13(33.3)
II	11(28.2)
III	15(38.5)
TNM stage	
I	6(13)
II	12(26)
III	18(39)
IV	10(21)

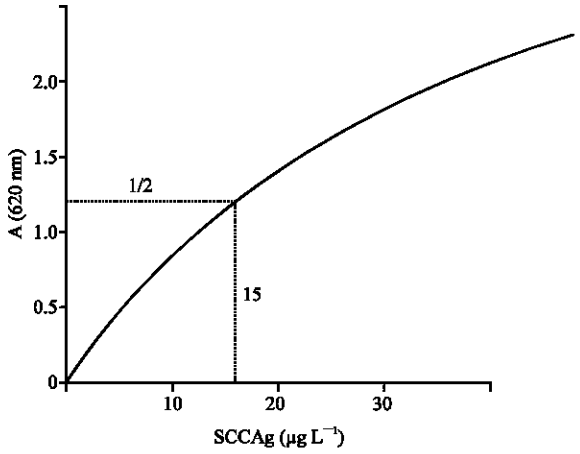

Fig. 1: The standard curve of SCCAg concentrations

According to manufacturer instruction, CanAg SCC calibrator values should be assigned regarding a set of in-house reference standards. So, in present study, SCCAg concentration of more than 3 ng mL^{-1} was considered as positive.

Statistical Analysis

Data were analyzed using descriptive indexes and analytical tests including Chi-square, t-student and Mann-Whitney.

RESULTS AND DISCUSSION

The mean pre-treatment SCCAg level was 3.82 ng mL^{-1} (median, 0.8; range 0.1-87) and just 10 patients (21.7%) had the elevated rate of SCCAg.

Two of 8 patients (25%) aged 50 years and under had positive SCCAg levels, roughly the same as 8 of 38 (21%) in those aged over 50 at diagnosis. The positive rate of SCCAg was 37.5% (6 of 16) in males and just 13.3% (4 of 30) in females (Table 2).

Three of 13 patients (23.1%) with grade I tumor had positive rates of SCCAg compared to 3 of 11 (27.3%) and 3 of 15 (20%) in those with grade II and III, respectively (Table 2).

Patients with stage IV disease had the highest percentage of SCCAg positive serum (6 of 10, 60%) while the figures in cases with stage I and II were 2 of 6 (33.3%) and 2 of 12 (16.7%), respectively. It was only 2 of 18 (11.1%) in patients with stage III.

Tumor size was the only studied clinicopathologic factor significantly associated with SCCAg. The mean tumor size for SCCAg positive patients was 8.8±1.89 cm (median, 9.5; range, 5-11) in contrast to 6.99±2.21 cm (median, 7; range, 3-14) for the SCCAg negative ones ($p = 0.031$).

In present study, 21.7% of patients with esophageal squamous cell carcinoma had positive rate of SCCAg according to the cut-off point of 3 ng mL^{-1}. But most similar studies have used lower cut-off level. With cut-off point of 2.5 ng mL^{-1}, Molina *et al*. (1990) have detected this marker in 57.7% of patients suffered from squamous cell carcinoma of various organs. Even the cut-off point has been set at 1.5 ng mL^{-1} in some studies (Kosugi *et al*., 2004; Shimada *et al*., 2005). Considering cut-off level of 2.5 ng mL^{-1} in this analysis, the positive rate will reach to 23.9% which is not significantly different from the previous state. Shimada *et al*. (2005) found that 34% of 103 patients with esophageal carcinoma had positive marker which is nearly similar to present results. In their investigation all cases had esophageal squamous cell carcinoma, but in several other studies SCCAg was assessed in

Table 2: Relationship between SCCAg levels and clinicopathologic factors in esophageal squamous cell carcinoma

	SCCAg		
Clinicopathologic factor	Positive (n [%])	Negative (n [%])	p-value
Age at diagnosis (years)			
≤50	2(25)	6(75)	0.564
>50	8(21.1)	30(78.9)	
Gender			
Male	6(37.5)	10(62.5)	0.067
Female	4(13.3)	26(86.6)	
Histological grade			
I	3(23.1)	10(76.9)	0.190
II	3(27.3)	8(72.7)	
III	3(20)	12(80)	
TNM stage			
I	2(33.3)	4(66.7)	0.223
II	2(16.7)	10(83.3)	
III	2(11.1)	16(88.9)	
IV	6(60)	4(40)	

esophageal adenocarcinoma e.g., Mroczko *et al*. (2008) reported the positive rate of 64% while 29% of their cases had esophageal adenocarcinoma and the rest had esophageal squamous cell carcinoma. In addition Sánchez De Cos *et al*. (1994) showed elevated SCCAg levels in 47.7% of lung squamous cell carcinoma and 14.3% of lung adenocarcinoma patients. Nevertheless the related measure is lower than other studies given omission of esophageal adenocarcinoma cases.

The marker positivity of present cases has no relation with the tumor grade and although it was lower in grade III carcinomas compared to low grade tumors, the difference was not statistically significant. It has been suggested by some investigations that SCCAg expression in patients with well differentiated squamous cell carcinoma of esophagus is higher than cases with poorly differentiated ones. In immunohistochemical study of SCCAg in esophagus tissue, Matsuda *et al*. (1990) found that well differentiated tumors stained with more intensity than poorly differentiated cases.

In the present study, 60% of metastatic (stage IV) patients were marker positive which was higher than other stages. However, the difference was not significant. In the study of Kosugi *et al*. (2004) SCCAg positivity considerably correlated with stage of disease. Although some investigations revealed the significant relationship between marker positivity in patients with esophageal squamous cell carcinoma with tumor size, tumor depth and lymph node involvement (Shimada *et al*., 2003, 2005), seropositivity of SCCAg and high SCCAg mRNA level were shown not to be related to stage in other studies (Honma *et al*., 2006; Mroczko *et al*., 2008).

The only clinicopathologic feature of the patients with significant correlation with SCCAg positivity was tumor size. This finding also emerged in the study of cervix cancer patients in this center.

The prognostic value of serum SCCAg level has been confirmed by some survival studies with a proper post treatment follow up. Takeuchi *et al*. (2003) have shown the prognostic role of SCCAg level in the serum of patients with lung adenocarcinoma but not in lung squamous cell carcinoma cases. In both group they interestingly found that patients with preoperative positive SCCAg who became negative after surgery had better prognosis compared to patients who remained positive postoperatively.

CONCLUSION

Although, SCCAg marker was positive in minority of the patients, but considering its relation with tumor size and probability disease stage, it is suggested to carry out survival study on more cases to find out the relation between marker positivity and cancer recurrence.

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