Pretreatment Serum CYFRA 21-1 Level Correlates Significantly with Survival of Cervical Cancer Patients: A Multivariate Analysis of 506 Cases

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- ABSTRACT -

Pretreatment Serum CYFRA 21-1 Level Correlates Significantly with Survival of Cervical Cancer Patients: A Multivariate Analysis of 506 Cases

To determine whether pretreatment CYFRA 21-1 levels can be a useful prognostic indicator in cervical cancer with reference to squamous cell carcinoma-antigen (SCC-Ag). We retrospectively analyzed data on 506 consecutive cervical cancer patients who were treated by radical hysterectomy or primary concurrent chemoradiation therapy. The pretreatment serum SCC-Ag and serum CYFRA 21-1 levels were measured in these patients. A multivariate analysis using Cox's proportional hazard model was performed to evaluate the prognostic significance of pretreatment variables. In patients who underwent radical hysterectomy, there was a significant correlation between pretreatment serum SCC-Ag/CYFRA 21-1 levels and patient age, advanced International Federation of Gynecology and Obstetrics (FIGO) stage, large tumor size, lymph node metastasis, and deep stromal invasion. In the stepwise Cox regression analysis, large tumor size > 4cm was an independent prognostic factor for disease-free survival (OR, 3.110; [95% CI, 1.588-6.093], P=0.001) and overall survival (OR, 8.497; [95% CI, 1.797-40.184], P=0.007) in patients with squamous cell carcinoma, while pretreatment CYFRA 21-1(P=0.010) serum levels had a significant independent effect on overall survival. Likewise, pretreatment CYFRA 21-1($p<0.001$ and P=0.006) serum levels were the only independent prognostic factor for

disease-free survival and overall survival in patients with non-squamous cell carcinoma. Pretreatment CYFRA 21-1 levels may be considered as a useful prognostic indicator in cervical cancer with reference to SCC-Ag.

Key words: SCC-Ag, CYFRA 21-1, Cervical cancer, Survival.

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I. INTRODUCTION

Serum tumor markers are commonly used for early detection of tumor, treatment response, and follow-up. An ideal tumor marker should have a high sensitivity and a high specificity in order to discriminate among patients with cancers, and should also provide information related to tumor burden and activity (Duffy, 2004).

There have been a number of studies on the expression and distribution of tissue markers in cervical cancer such as squamous cell carcinoma-antigen (SCC-Ag), carcino-embryonic antigen (CEA), cancer antigen 125 (CA 125), and an enzyme-immunoassay termed CYFRA 21-1 that measures serum fragments of cytokeratin-19. A large body of literature has been reported that SCC-Ag and CYERA 21-1 can be used for monitoring patients receiving therapy and for early detection of recurrence with invasive squamous cell carcinoma (SCC) (Duk et al., 1990; Scambia et al., 1991; Å vall-Lundqvist et al., 1992; Kainz et al., 1995; Tsai et al., 1995; Bonfrer et al., 1996; Ngan et al., 1996; Callet et al., 1998; Hong et al., 1998; Suzuki et al., 2000; Pras et al., 2002; Gadducci et al., 2008). In addition, good agreement has been found between CEA and CA 125 values with progression, recurrence, and lymph node (LN) metastasis of cervical adenocarcinoma (Duk et al., 1990; Montag, 1990; Farghaly, 1992). Up to now, however, the validation of tumor markers has not been fully realized in prospective studies, and it is still debated whether pretreatment tumor markers may represent a prognostic variable in cervical cancer.

The purpose of this study was to determine whether pretreatment serum CYFRA 21-1 levels can be a useful prognostic indicator in cervical cancer with reference to SCC-Ag.

II. MATERIAL AND METHODS

After receiving the approval of the Institutional Review Board for the medical records, we retrospectively analyzed data on 506 consecutive patients with invasive cervical cancer who were treated at Ajou University Hospital from June 1994 through May 2010. All of the patients were diagnosed by cervical biopsy and the serum levels of SCC-Ag and CYFRA 21-1 were also measured before initiation of treatment. Patients were treated either primary concurrent chemoradiation therapy (CCRT) or radical hysterectomy (RH) with pelvic and/or para-aortic lymphadenectomy and adjuvant radiation therapy (RT) or CCRT based on the results of postoperative histologic examination. In order to respond to the primary treatment, follow-up examination had been performed every 3 months during the second year, at 6-month intervals the second year, and then yearly.

The response to treatment was evaluated using physical examination, determination of serum SCC-Ag and CYFRA 21-1, and Papanicolaou test. Computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography-computed tomography (PET-CT) was also performed when clinically necessary. The recurrence was confirmed by the histologic examination, increased level of serum SCC-Ag and CYFRA 21-1, and a clinical suspicion of recurrent disease underwent CT, MRI, or PET-CT. In recurrence cases, chemotherapy or RT was given.

SCC-Ag was measured by the IMX SCC-Ag microparticle enzyme immunoassay (Abbott Laboratories**,** Abbott Park, IL, U.S.A.**).** CYFRA 21-1 was measured with a solid-phase sandwich-type (IRMA), using monoclonal antibodies (CIS Bio international,

Gif/Yvette, France). Data were analyzed by Student t-test, Chi-square test, or the Pearson correlation coefficient. Survival curves were computed using the Kaplan-Meyer test and analyzed by means of the log-rank test. The simultaneous effect of prognostic factors on survival was analyzed by means of Cox proportional hazard model of forward logistic regression analysis. The p-values (from two-sided tests) less than 0.05 were considered to indicate a significant difference. Data were analyzed using SPSS ver. 20.0 (IBM Co., Somers, NY, U.S.A.).

III. RESULTS

The mean duration of follow-up was 36 months. The mean age of the patients was 48.5 years (range 22-79 years), and their clinical characteristics are summarized in Table 1. Histology revealed SCC in 410 patients (81%), adenocarcinoma in 75 patients (14.8%), and adenosquamous carcinoma in 21 patients (4.2%). All patients were clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria. This study included 349 (68.9%) patients with stage I, 115 (22.8%) patients with stage II, 31 (6.1%) patients with stage III, and 11 (2.2%) patients with stage IV. Treatment consisted of RH with 341 patients (67.4%) and with CCRT in 165 patients (32.6%).

Table 2 shows the correlation between clinicopathological variables and pretreatment SCC-Ag and CYFRA 21-1 in patients who underwent RH. There were significant relationships between pretreatment serum SCC-Ag and CYFRA 21-1 levels and patient age, advanced FIGO stage, large tumor size, LN metastasis, deep stromal invasion, and lymph-vascular space invasion (LVSI).

Table 3 shows univariate and multivariate analyses of various pretreatment factors for 5-year disease-free survival (DFS) and overall survival (OS) in patients with SCC. Advanced FIGO stage (stage III and IV, P=0.020) and large tumor size (>4 cm, P=0.001) were significantly decreased 5-year DFS rates (Table 3). In the stepwise Cox regression analysis, large tumor size>4 cm (OR, 3.110; [95% CI, 1.588-6.093], P=0.001) was the only independent prognostic factor for DFS. Advanced FIGO stage (P<0.001), large tumor size (P<0.001), pretreatment serum SCC-Ag (P<0.001) and CYFRA 21-1 (P<0.001) levels were

found to be significant prognostic factors on univariate analysis for OS. On multivariate analysis, large tumor size>4 cm (OR, 8.497; [95% CI, 1.797-40.184], P=0.007) and pretreatment serum CYFRA 21-1 (P=0.010) levels were independent prognostic factors for OS (Fig. 1, Table 3).

Table 4 shows univariate and multivariate analyses of various pretreatment factors for 5-year DFS and OS in patients with non-squamous cell carcinoma (non-SCC). Advanced FIGO stage (P<0.001) and pretreatment serum SCC-Ag (P=0.002) and CYFRA 21-1 (P<0.001) levels were significantly decreased 5-year DFS rates (Fig. 1, Table 4). In the stepwise Cox regression analysis, pretreatment CYFRA 21-1 (P<0.001) levels were the only independent prognostic factor for DFS. Pretreatment SCC-Ag (P=0.019) and CYFRA 21-1 (P=0.006) levels were found to be significant prognostic factors on univariate analysis for OS. On multivariate analysis, pretreatment CYFRA 21-1 (P=0.006) levels were the only independent prognostic factor for OS.

Fig. 1 shows 5-year DFS and overall survival OS in patients with SCC (A, B) and non-SCC (C, D) according to pretreatment CYFRA 21-1. For SCC patients with CYFRA 21-1 ≤3.0 ng/mL, the 5-year DFS and OS rates were 97.4% and 90.0%, respectively. Likewise, the respective 5-year DFS and OS rates were 76.2% and 33.3% with CYFRA 21-1> 3.0 ng/mL. For non-SCC patients with CYFRA 21-1 ≤3.0 ng/mL, the 5-year DFS and OS rates were 99.6% and 93.4%, respectively. Likewise, the respective 5-year DFS and OS rates were 85.8% and 57.1% with CYFRA 21-1> 3.0 ng/mL.

Table 1. Clinical characteristics of 506 patients.

Variables	Mean (range or %)	
Mean age at diagnosis (years)	48.5 (22-79)	
Mean parity	2 (0-10)	
Histology		
Squamous cell carcinoma	410 (81)	
Adenocarcinoma	75 (14.8)	
Adenosquamous carcinoma	21 (4.2)	
Number of patients with elevated biomarkers by FIGO stage	SCC > 2.0 ng/mL	Cyfra 21-1 > 3.0 ng/mL
IB1 (n=294)	49 (16.7)	16 (5.4)
IB2 (n=55)	23 (41.8)	9 (16.4)
IIA (n=21)	11 (52.4)	6 (28.6)
IIB (n=94)	63 (67.0)	42 (44.7)
IIIA (n=5)	3 (60.0)	3 (60.0)
IIIB (n=26)	24 (92.3)	23 (88.5)
IVA (n=8)	7 (87.5)	8 (100.0)
IVB (n=3)	3 (100.0)	3 (100.0)
Clinical tumor size		
≤ 4cm	294 (8.1)	
> 4cm	212 (41.9)	
Type of primary treatment		
Surgery	205 (40.5)	
Surgery + adjuvant RT	13 (2.6)	
Surgery + adjuvant CCRT	123 (24.3)	
CCRT	165 (32.6)	
Follow-up (months)	36 (1-160)	

FIGO, International Federation of Gynecology and Obstetrics; n, number; RT, radiation therapy; CCRT, concurrent chemoradiation therapy.

Table 2. Correlation between clinicopathological variables and pretreatment SCC-Ag/CYFRA 21-1 levels in patients who underwent radical hysterectomy.

	SCC-Ag		CYFRA 21-1[a]	
	r^2	*P*	r^2	*P*
Age	0.161	<0.001	0.176	<0.001
FIGO stage III-IV	0.488	<0.001	0.551	<0.001
Lymph node metastasis	0.241	<0.001	0.227	<0.001
Tumor size > 4cm	0.273	<0.001	0.330	<0.001
Deep stromal invasion	0.290	<0.001	0.279	<0.001
Lymph-vascular space invasion	0.109	0.062	0.127	0.029

SCC-Ag, squamous cell carcinoma-antigen; FIGO, International Federation of Gynecology and Obstetrics.

[a]An enzyme-immunoassay termed CYFRA 21-1, that measures serum fragments of cytokeratin -19.

Table 3. Univariate and multivariate analyses of various pretreatment factors for 5-year disease-free and overall survival in patients with squamous cell carcinoma.

	Disease-free survival				Overall survival			
	No. of events (%)	Univariate analysis	Multivariate analysis		No. of events (%)	Univariate analysis	Multivariate analysis	
		P	OR (95% CI)	*P*		*P*	OR (95% CI)	*P*
Age		0.270	-	-		0.016	0.016 (0.001-0.382)	0.011
< 50 yr	27 (12.7)				12 (5.6)			
≥ 50 yr	14 (7.1)				2 (1.0)			
FIGO stage		0.020	-	-		<0.001	-	-
IB	22 (8.0)				4 (1.5)			
II	14 (14.0)				5 (5.0)			
III-IV	5 (14.3)				5 (14.3)			
Tumor size		0.001	3.110 (1.588-6.093)	0.001		<0.001	8.497 (1.797-40.184)	0.007
≤4cm	15 (6.3)				2 (0.8)			
>4cm	26 (15.0)				12 (6.9)			
Pre-treatment SCC-Ag		0.165	-	-		<0.001	1.012 (1.000-1.024)	0.059
Pre-treatment CYFRA 21-1[a]		0.107	-	-		<0.001	1.086 (1.020.-1.157)	0.010

No., number; OR, odds ratio; FIGO, International Federation of Gynecology and Obstetrics; SCC-Ag, squamous cell carcinoma-antigen.

[a]An enzyme-immunoassay termed CYFRA 21-1, that measures serum fragments of cytokeratin-19.

Table 4 Univariate and multivariate analyses of various pretreatment factors for 5-year disease-free and overall survival in patients with non-squamous cell carcinoma

	Disease-free survival				Overall survival			
	No. of events (%)	Univariate analysis	Multivariate analysis		No. of events (%)	Univariate analysis	Multivariate analysis	
		P	OR (95% CI)	*P*		*P*	OR (95% CI)	*P*
Age		0.064	-	-		0.693	-	-
< 50 yr	5 (7.7)				4 (6.2)			
≥ 50 yr	6 (19.4)				3 (9.7)			
FIGO stage		<0.001	-	-		0.061	-	-
IB	6 (8.1)				4 (5.4)			
II	1 (6.7)				1 (6.7)			
III-IV	4 (57.1)				2 (28.6)			
Tumor size		0.271	-	-		0.499	-	-
≤4cm	5 (8.8)				3 (5.3)			
>4cm	6 (15.4)				4 (10.3)			
Pre-treatment SCC-Ag	-	0.002	-	-	-	0.019	-	-
Pre-treatment CYFRA 21-1[a]	-	<0.001	1.100 (1.047.-1.156)	<0.001	-	0.006	1.084 (1.024.-1.149)	0.006

No., number; OR, odds ratio; FIGO, International Federation of Gynecology and Obstetrics; SCC-Ag, squamous cell carcinoma-antigen.

[a]An enzyme-immunoassay termed CYFRA 21-1, that measures serum fragments of cytokeratin-19.

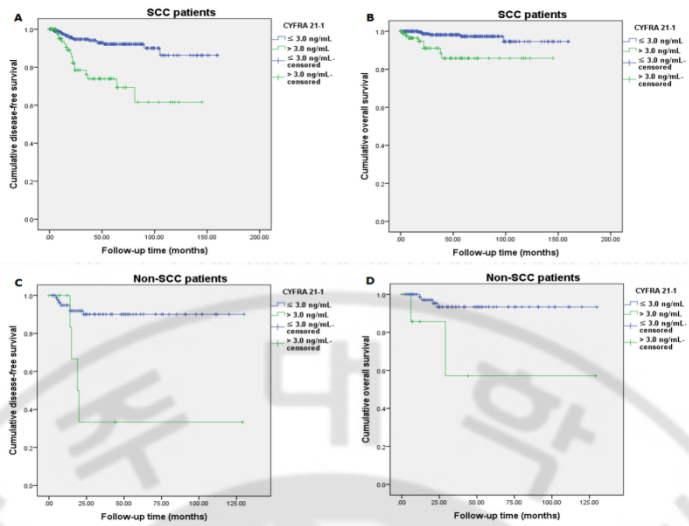

Fig. 1. 5-year disease-free survival and overall survival in patients with squamous cell carcinoma (A, B) and non-squqmous cell carcinoma (C, D) according to pretreatment CYFRA 21-1. SCC, squamous cell carcinoma; non-SCC, non-squamous cell carcinoma.

IV. DISCUSSION

Cervical cancer is the third most common malignant disease of women worldwide and the most common malignant disease afflicting women in many developing countries (Parkin et al., 2001; Jemal et al., 2011). In the previous studies, several authors have reported that serum tumor markers can assess the extent of disease, monitor the response to therapy, and may be of value in detecting early recurrence of tumor after treatment in the event of cervical cancer (Pras et al., 2002; Molina et al., 2005; Gadducci et al., 2008). SCC-Ag has been the best known tumor marker proposed for SCCs of the cervix until now (Duk et al., 1990; Montag, 1990; Farghaly, 1992; Duffy, 2004).

Increased levels of serum SCC-Ag was observed in 28~88% of cervical cancer patients. Furthermore, serum SCC-Ag is considered useful in the prognosis, early detection of recurrence, and treatment response (Scambia et al., 1991; Åvall-Lundqvist et al., 1992; Gadducci et al., 1992 , 1994; Sproston et al., 1995; Ngan et al., 1996; Duk et al., 1996; Bae et al., 1997; Bolger et al., 1997; Gaarenstroom et al., 1997, 2000; Yuan et al., 2001; Strauss et al., 2002; Pras et al., 2002; Molina et al., 2005; Yoon et al., 2007). It means that patients with increased serum SCC-Ag levels before treatment are associated with tumor size and the survival. In addition, consistent elevated serum SCC-Ag level after treatment is related to residual or recurrent disease. In view of its low sensitivity in the early stage of cervical cancer, however, SCC-Ag has not been suggested as a screening test. Moreover, some authors reported that pretreatment serum level of SCC-Ag has been found to correlate with tumor size, LN metastasis, stromal invasion, and LVSI (Åvall-Lundqvist et al., 1992;

Gadducci et al., 1994; Sproston et al., 1995; Ngan et al., 1996; Duk et al., 1996; Bae et al., 1997; Gaarenstroom et al., 2000; Yuan et al., 2001; Molina et al., 2003, 2005; Ogino et al., 2006), but in other reports it was not (Bonfrer et al., 1994; Tsai et al., 1995; Bonfrer et al., 1996; Suzuki et al., 2000; Puthucode-Easwaran et al., 2005). Furthermore, a normal SCC-Ag level does not exclude the presence of tumor and recurrence (Montag, 1990). Therefore, the clinical utility of pretreatment serum SCC-Ag is controversial. In this respect, finding new ideal serum tumor markers of recurrent cervical SCCs has become a frequent subject of investigation in the recent years.

In the present study, serum fragments of cytokeratin-19 can be measured by using the CYFRA 21-1 assay and this can be used as a tumor marker in cervical cancer and elevated CYFRA 21-1 levels have been found in 42–63% of patients with squamous cell cervical cancer. The sensitivity of CYFRA 21-1 was lower than that of SCC-Ag, but was also related to the tumor stage, tumor size, and depth of stromal invasion, LVSI, parametrial involvement and LN status. In addition, it was reported that combination with SCC-Ag may be more useful in predicting disease recurrence (Ferdeghini et al., 1993; Gadducci et al., 1994; Sproston et al., 1995; Gaarenstroom et al., 1997, 2000; Yuan et al., 2001; Pras et al., 2002; Strauss et al., 2002; Molina et al., 2005). However, clinical relevance of CYFRA 21-1 is still debated as with SCC-Ag.

Some authors reported that the prognostic value of pretreatment SCC-Ag level was unknown (Bonfrer et al., 1996; Bolger et al., 1997), but other authors had shown that pretreatment SCC-Ag level was related to DFS and OS (Å vall-Lundqvist et al., 1992; Sproston et al., 1995; Ngan et al., 1996; Duk et al., 1996; Bae et al., 1997; Hong et al., 1998;

Gaarenstroom et al., 2000; Yuan et al., 2001; Strauss et al., 2002; Molina et al., 2005). Duk et al. and Hong et al. reported that elevated SCC-Ag level is a factor of influencing the survival (Duk et al., 1996; Hong et al., 1998). Strauss et al. reported that the preoperative serum SCC-Ag level was an independent prognostic factor for both DFS and OS in patients with stage IA2-IIB squamous cell cervical cancer (Strauss et al., 2002). Until now, SCC-Ag was reported to be a significant prognostic factor in univariate and multivariate analysis. However, few data have been published regarding the use of CYFRA 21-1 as a tumor marker in cervical cancer. Fortunately, using univariate statistical analysis, some investigators found that pretreatment CYFRA 21-1 level was useful for predicting prognosis with cervical cancer patients (Gaarenstroom et al., 2000; Pras et al., 2002; Molina et al., 2005). Gaarenstroom et al. found that pretreatment elevated serum SCC-Ag and CYFRA 21-1 were obviously related to poor prognosis (Gaarenstroom et al., 2000). Molina et al. prospectively studied 156 cervical cancer patients and reported that pretreatment elevated levels of SCC-Ag and CYFRA 21-1 were associated with lower DFS and OS (Molina et al., 2005). Pras et al. reported that in a series of 114 patients who underwent RT or CCRT, post-treatment elevated serum CYFRA 21-1 was associated with residual tumor in 70% of the cases (Pras et al., 2002). However, they reported that multivariate analysis indicated that FIGO stage, tumor size, histologic grade, parametrial invasion, and LN status were independent prognostic factors, but not CYFRA 21-1. In summary, several studies concluded that SCC-Ag was an independent prognostic factor in multivariate analysis (Duk et al., 1996; Strauss et al., 2002). By contrast, CYFRA 21-1 was considered as a prognostic factor in univariate analysis, but not in multivariate analysis, which may be related to the small study population and different

distribution in early and late stages (Gaarenstroom et al., 2000; Molina et al., 2005). Hence, we conducted subgroup analyses according to the histologic subtype and then found that elevated CYFRA 21-1 were much more valuable than SCC-Ag.

To date, there has been no study on the relevance between CYFRA 21-1 and survival of cervical cancer in multivariate analysis. In order to evaluate the significance of CYFRA 21-1 which was considered by prognostic indicator, we reviewed the medical records of 506 cervical cancer patients. First, we studied in more detail regarding the relation between serum marker levels and clinico-pathologic variables in patients who underwent RH. This observation suggests that there were significant relationships between pretreatment SCC-Ag and CYFRA 21-1 levels and patient age, advanced FIGO stage, large tumor size, LN metastasis, deep stromal invasion, and LVSI. Notably, we also evaluated that elevated CYFRA 21-1 (r^2 =0.293, P<0.001; data not shown in Table) showing more meaningful correlation with FIGO stage than SCC-Ag (r^2 =0.234, P<0.001; data not shown in Table). Then we conducted subgroup analyses according to the histology type and concluded that pretreatment CYFRA 21-1 levels may be considered as a useful prognostic indicator in cervical cancer with reference to SCC-Ag. We recognized the inherent limitation of retrospective study and selection bias was also likely to affect the results. In addition, we admit that some patients with recurrence were lost to follow up during the follow up period. As a single-institution study, however, it is advantaged by the relatively large patient group and consistent treatment. To the best of my knowledge, our findings are the first report which had demonstrated the prognostic value of CYFRA 21-1 in multivariate analysis.

In conclusion, pretreatment CYFRA 21-1 levels may be considered as a useful

prognostic indicator in cervical cancer with reference to SCC-Ag.

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- 국문요약 -

자궁경부암환자의 치료전 혈청 CYFRA 21-1 레벨과 생존율의 상관관계: 506케이스의 다변량분석

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치료전 CYFRA 21-1 의 혈청치가 자궁경부암의 혈청종양표지물질로서 가장 널리 사용되고 있는 Squamous cell carcinoma antigen(SCC-Ag)와 더불어 유용한 예후 예측인자가 될 수 있는지 여부를 알아보고자 하였다. 본 연구에서는 광범위 자궁절제술 혹은 동시항암화학방사선요법 치료를 받은 506 명의 자궁경부암 환자들에 대한 후향적 연구를 하였다. 모든 환자들은 치료전 SCC-Ag 와 CYFRA 21-1 을 측정하였다. 치료전 각 예측인자가 생존율에 미치는 영향은 콕스 비례위험 모형을 사용하여 평가하였다. 그 결과, 광범위 자궁절제술을 시행 받은 환자에서 치료전 SCC-Ag/CYFRA 21-1 의 혈청치는 환자의 나이, 진행된 FIGO 병기, 큰 종양종괴, 림프절 전이 및 심부 기질 침윤 사이에 유의한 상관관계가 있었다. Cox 비례위험함수 모형을 이용한 다변량분석 결과 종양의 크기 > 4cm 는 편평상피암 환자의 무병생존율(OR, 3.110; [95% CI, 1.588-6.093], P=0.001) 및 전체 생존율 (OR, 8.497; [95% CI, 1.797-40.184], P=0.007) 을 예측하는 독립적인 예후인자인 반면에

치료전 CYFRA 21-1(P=0.010) 혈청치는 전체 생존율에 유의한 독립적인 영향을 미쳤다. 또한 치료전 CYFRA 21-1(p<0.001 and P=0.006) 혈청치는 비편평상피암 환자의 무병생존율 및 전체 생존율과 관련되는 유일한 독립적인 예측인자이었다. 저자들의 연구결과에 따르면 자궁경부암에서 치료전 CYFRA 21-1 혈청치는 SCC-Ag 와 더불어 유용한 예측인자로 사용할 수 있을 것으로 보인다.

핵심어: SCC-Ag, CYFRA 21-1, 자궁경부암, 생존율.