Kulak Burun Bogaz Ihtis Derg
2004;12(1-2):23-30

ORIGINAL ARTICLE

The significance of ferritin, lipid-associated sialic acid, CEA, squamous cell carcinoma (SCC) antigen, and CYFRA 21-1 levels in SCC of the head and neck

Baş-boyun yassı epitel hücreli (SCC) karsinomda ferritin, lipid ilişkili sialik asit, karsinoembriyonik antijen, SCC antijeni ve CYFRA 21-1 düzeyleri

Erdoğan İNAL, M.D., Meliha LAÇİN, M.D., Korhan ASAL, M.D., Alper CEYLAN, M.D., Ahmet KÖYBAŞIOĞLU, M.D., Fikret İLERİ, M.D., S. Sabri USLU, M.D.

Objectives: We investigated the value of some tumor markers in the diagnosis and treatment follow-up of squamous cell carcinoma of the head and neck.

Patients and Methods: Ferritin, lipid-associated sialic acid (LSA), carcinoembryonic antigen (CEA), squamous cell carcinoma (SCC) antigen and CYFRA 21-1 levels were determined in 28 patients with squamous cell carcinoma and in a control group of 20 patients with benign lesions of the head and neck. The measurements were made before treatment and in the first and third months of treatment.

Results: The sensitivity rates were as follows: 10.7% for ferritin, 89.3% for LSA, 21.4% for CEA, 42.9% for SCC antigen, and 14.3% for CYFRA 21-1. The specificity was 100% for all the markers. The sensitivity increased to 96.4% when CEA and LSA were used in combination. Declines in the levels after treatment were significant for ferritin, CEA, SCC antigen, and LSA. No significant relationship was found between the marker levels and lymph node metastasis, stage, and histologic differentiation of the tumors. Only ferritin and LSA levels were correlated with tumor size. Squamous cell carcinoma antigen was the only marker that manifested high levels in patients who developed locoregional recurrence and/or mortality.

Conclusion: Of the markers studied, LSA, CEA and SCC antigen may be of value in the evaluation of squamous cell carcinoma of the head and neck. Sensitivity and specificity rates may increase when they are used in combination.

Key Words: Carcinoma, squamous cell/blood; head and neck neoplasms/blood; tumor markers, biological/blood.

Amaç: Baş-boyun yassı epitel hücreli karsinomlarının tanı ve tedavi takibinde bazı tümör belirteçlerinin değeri araştırıldı.

Hastalar ve Yöntemler: Baş-boyun bölgesinde yassı epitel hücreli karsinom saptanan 28 hastada ve benign baş-boyun tümörlü 20 hastadan oluşan kontrol grubunda ferritin, lipid ilişkili sialik asit (LSA), karsinoembriyonik antijen (CEA), yassı epitel hücreli karsinom (SCC) antijeni ve CYFRA 21-1 düzeyleri tedavi öncesi ve tedavi sonrası birinci ve üçüncü aylarda olmak üzere ölçüldü.

Bulgular: Bu belirteçlerin duyarlılığı ferritin için %10.7, LSA için %89.3, CEA için %21.4, SCC antijeni için %42.9, CYFRA 21-1 için %14.3 bulundu. Tüm belirteçler için özgüllük %100 bulundu. Birlikte kullanıldığında, CEA ve LSA'nın duyarlılığı %96.4'e yükseldi. Tedavi sonrasında ferritin, CEA, SCC antijeni ve LSA düzeylerinde anlamlı düşüş görüldü. Araştırılan belirteçlerin düzeyleri ile lenf nodu metastazı, evre ve tümörün histolojik diferansiyasyonu arasında anlamlı ilişki saptanmadı. Sadece ferritin ve LSA düzeylerinin tümör boyutu ile ilişkili olduğu bulundu. Yassı hücreli karsinom antijeninin lokorejyonel nüks ve mortalite görülen olgularda yüksek seviyesini koruduğu izlendi.

Sonuç: İncelenen üç belirtecin (LSA, CEA ve SCC antijeni) baş-boyundaki yassı epitel hücreli karsinomları değerlendirmede önemli olduğu ve bunların birlikte kullanımı ile duyarlılık ve özgüllük değerlerinin yükselebileceği sonucuna varıldı.

Anahtar Sözcükler: Karsinom, yassı epitel hücreli/kan; baş-boyun neoplazileri/kan; tümör belirteci, biyolojik/kan.

◆ *Department of Otolaryngology, Medicine Faculty of Gazi University (Gazi Üniversitesi Tıp Fakültesi Kulak Burun Boğaz Hastalıkları Anabilim Dalı), Ankara, Turkey.*

◆ *Received - April 3, 2003 (Dergiye geliş tarihi - 3 Nisan 2003). Accepted for publication - September 25, 2003 (Yayın için kabul tarihi - 25 Eylül 2003).*

◆ *Correspondence (İletişim adresi): Dr. Erdoğan İnal. Turan Güneş Bulvarı, Ürdün Cad., Örmes Sitesi, No: 38/8, 06450 Oran, Ankara, Turkey. Tel: +90 312 - 468 38 34 Fax (Faks): +90 312 - 442 55 65 e-mail (e-posta): einal@gazi.edu.tr*

* *Presented at the 26th National Congress of Turkish Otorhinolaryngology, Head and Neck Surgery, September 22-26, 2001 (26. Ulusal Türk Otorinolarengoloji ve Baş-Boyun Cerrahisi Kongresi'nde sunulmuştur, 22-26 Eylül 2001) Antalya, Turkey.*

Early diagnosis, detection of recurrence or metastasis before the appearance of clinical symptoms and signs, and estimation of prognosis after treatment are very important for cancer patients; until today, several staging systems and radiologic methods have been found to be successful in this aspect.[1] Neoplastic cells usually affect molecular synthesis, resulting in changes in the levels of many substances in the cell membrane and extracellular fluid. These substances are called tumor markers. Those that may also increase in some benign diseases are nonspecific. Many tumor markers have been widely used in the diagnosis and follow-up of several cancers including carcinoma of the the colon, mammary gland, prostate and gonads.[2] In head and neck squamous cell carcinoma, second primary tumors are more frequent and the detection of recurrences is more difficult than other cancers. The clinical use of appropriate tumor markers may facilitate diagnosis and provide a more precise follow-up of these cancers.

Sialic acid is in the family of acetylated neuraminic acid derivatives and usually constitutes the terminal unreductable component in the carbohydrate chains of glycolipids and glycoproteins.[3] An elevation of the sialic acid level is probably related to an increase in the glycoprotein level in cancer patients. Some authors suggested that increased cell turnover and cell damage may also cause a rise in sialic acid levels. Sialic acid associated substances have been shown to be elevated in cancers of the mammary gland, lung, and neural tissue, in gynecologic and colorectal cancers, and in malignant melanoma.[2] However, elevated sialic acid levels have been found in some chronic diseases such as rheumatoid arthritis and cirrhosis, as well.[4]

Ferritin is an iron-binding major protein and plays a role in the storage of iron. Twenty different types of this isometric protein have been described. A more acidic type of isoferritin has been detected in cancer patients. Elevations in the level of blood ferritin have been reported in some hematologic malignancies; in cancers of the mammary gland, lung, liver, testis, and ovarian carcinomas, and in colorectal cancers.[5] In cancer patients, elevated serum ferritin levels have been attributed to changes in hematopoiesis and iron metabolism and to some nonspecific tissue damage. Some authors also postulated a direct secretion of ferritin from tumor cells.[6]

Carcinoembryonic antigen (CEA) is a protein-polysaccharide complex normally found in fetal liver, pancreas and intestinal tissues. Carcinoembryonic antigen was first reported by Gold and Freedman[7] in patients with colon cancer. It plays a role in immune response mechanism and metastasis in colorectal carcinomas. It has been reported to be elevated also in pancreas, liver, lung cancers, and in inflammatory intestinal diseases.[7]

Squamous cell carcinoma (SCC) antigen was first isolated from uterine cervix carcinoma patients in 1977 by Kato and Torigoe.[8] The nature and source of SCC antigen is not known exactly. However, expression of SCC antigen in squamous cell cancers has been reported.[8] Several studies investigated the significance of SCC antigen as a tumor marker in carcinomas of the lung, esophagus, anal region, and the head and neck.[8]

Intermediate filament proteins are major components of cellular skeleton. They are important as a marker of differentiation. Cytokeratins are the largest group of these filaments and they are specific to the epithelial cells. Twenty different types of cytokeratins have been identified. Depending on the grade of the differentiation, tumor cells create new subgroups of cytokeratins or lose original cytokeratin secretion.[9] Cytokeratin 19 (Ck-19) is expressed in the epithelium of buccal mucosa, tongue, floor of the mouth, vocal cords, and epiglottis. Two monoclonal antibodies have been developed to measure the soluble fragments of Ck-19 (CYFRA 21-1). Several studies evaluated the significance of CYFRA 21-1 especially in patients with squamous cell carcinoma of the lung.[10]

In this study, serum levels of ferritin, lipid-associated sialic acid (LSA), CEA, SCC antigen, and CYFRA 21-1 were measured in a group patients with squamous cell carcinoma of the head and neck and in a control group consisting of benign lesions of the head and neck. The levels of all markers were determined prior to the treatment, and in the first and third months following treatment. Additionally, correlations were sought between the levels of these markers and localization, size, stage, histologic differentiation of the tumor, and lymph node metastasis.

PATIENTS AND METHODS

Twenty-eight patients diagnosed as having squamous cell carcinoma of the head and neck in the Department of Otolaryngology and Head and Neck

Surgery of Gazi University Hospital were included. The study group consisted of 22 males and six females with a mean age of 56 years (range 29 to 78 years). The tumors were localized in the larynx (n=16; 12 supraglottic, 4 glottic), oral cavity (n=8), hypopharynx (n=2), nasal vestibule (n=1), and the maxillary sinus (n=1). The clinical staging of primary tumors according to the TNM system were stage 1 in six patients, stage 2 in six patients, stage 3 in eight patients, and stage 4 in eight patients. Twenty-six patients (92%) were smokers and six patients (22%) had a history of chronic alcohol consumption. Primary treatment was surgery in 13 patients, radiotherapy in five patients, chemotherapy in one patient, and a combination of radiotherapy and chemotherapy in one patient. Eight patients received radiation therapy postoperatively. After a follow-up of three months, complete response was observed in 23 cases, and partial response in two cases. Three patients died within three months following treatment. The measurements of serum tumor marker levels were performed in venous blood samples prior to the primary treatment, and one and three months after treatment.

Lipid-associated sialic acid levels were measured by the biochemical method developed by Katapodis and Stock[11] in 1980. Ferritin levels were measured with the use of the Immulite 2000 (DPC) kit (normal range, 28-365 ng/ml in males, 5-148 ng/ml in females) and CEA levels with the Immulite 2000 CEA (DPC) kit (abnormal >5 ng/ml). The measurements of CYFRA 21-1 were performed with the Elsa-Cyfra 21-1 kit (CIS Bio International/ORIS Group) with normal range being 0.3 to 3 ng/ml. Squamous cell carcinoma antigen was measured with the Imx SCC Kit (Abbott Laboratories/Japan) and normal range was accepted as 0 to 2 ng/ml.

The control group consisted of 20 patients (12 males, 8 females) with a mean age of 51 years (range 14 to 64 years), who had benign lesions of the head and neck. Both patient groups had a similar history of smoking and alcohol consumption.

For statistical analysis, the chi-square test, Student's t-test, Mann-Whitney U-test, and Kruskall-Wallis variant analysis were used. All data were analyzed using the SPSS 10.0 for Windows.

RESULTS

With respect to histologic differentiation, two tumors were poorly differentiated, seven were moderately differentiated, and 19 were well-differentiated.

Before the treatment, the mean values of all the tumor markers were significantly higher in cancer

TABLE I

COMPARASION OF TUMOR MARKER LEVELS BETWEEN THE STUDY AND CONTROL GROUPS

		Control group		Study group		
Tumor markers		Mean±SD	Median	Mean±SD	Median	*p*
Ferritin (ng/ml)	Before treatment	34±13	28	182±220	121	<0.001
	1st month			129±136	92	<0.001
	3rd month			126±147	46	<0.001
CYFRA 21-1 (ng/ml)	Before treatment	1.22±0.45	1.14	3.22±4.7	2.20	<0.05
	1st month			2.09±2.38	1.63	>0.05
	3rd month			1.87±1.42	1.56	<0.05
CEA (ng/ml)	Before treatment	1.14±0.53	1.09	3.50±3.71	2.31	<0.001
	1st month			2.32±2.23	1.58	>0.05
	3rd month			2.19±2.35	1.48	<0.05
SCC antigen (ng/ml)	Before treatment	0.92±0.30	0.90	2.36±1.74	1.60	<0.001
	1st month			1.40±0.98	1.20	<0.05
	3rd month			1.16±0.93	1.10	>0.05
LSA (mg/dl)	Before treatment	1.07±0.39	1.03	2.57±0.74	2.40	<0.001
	1st month			2.02±0.41	2.05	<0.001
	3rd month			1.86±0.49	1.77	<0.001

CEA: Carcinoembryonic antigen; SCC: Squamous cell carcinoma antigen; LSA: Lipid-associated sialic acid.

TABLE II

THE NUMBER OF PATIENTS WITH ELEVATED TUMOR MARKER LEVELS

Patient	CYFRA 21-1	Ferritin	CEA	SCC antigen	LSA	*Total*
n	3	4	6	12	25	28
%	10	14	21	42	89	100

patients compared to the control group ($p<0.05$ for CYFRA 21-1; $p<0.001$ for the rest). Following the treatment, their levels showed declines as shown in Table I. Compared to the control group, the mean levels of ferritin and LSA were significantly low in the first and third month of treatment ($p<0.001$).

The decreases in CYFRA 21-1 and CEA levels were not significant one month after the treatment ($p>0.05$); however, they became significantly low in the third month ($p<0.05$).

The level of SCC antigen significantly decreased in the first month of treatment ($p<0.05$); however, there was no significant difference in the third month ($p>0.05$).

Distribution of elevations with respect to the markers studied was as follows: CYFRA 21-1 was high in three patients (10%), ferritin in four patients (14%), CEA in six patients (21%), SCC antigen in 12 patients (42%), and LSA in 25 patients (89%) (Table II). In the control group, none of the patients exhibited elevated levels of tumor markers.

With respect to localization of the tumor, only CYFRA 21-1 showed significant difference, in that it was significantly low in patients with oral cavity cancer and glottic cancer ($p<0.001$).

When tumor size (T) was considered, it was found that only ferritin and LSA were significantly higher in T_3-T_4 tumors compared to T_1-T_2 tumors ($p<0.05$).

No significant relationships existed between the pretreatment levels of tumor markers and the stage of the tumor and lymph node metastasis ($p>0.05$; Table III, VI). Moreover, no positive correlation was observed between the marker levels and histologic differentiation of the tumor ($p>0.05$).

It was noted that CEA and CYFRA 21-1 levels were higher before treatment in patients who survived and did not develop any recurrence within the first three months of treatment (Table V).

DISCUSSION

Ferritin, as a tumor marker in squamous cell carcinoma of the head and neck, was first investigated by Veltri and Maxim[12] in a study including 113 patients with head and neck cancers, in which ferritin level was found as significantly elevated. In our study, the mean ferritin level was 34±13 ng/ml (median 28.9 ng/ml) in the control group and 182±220 ng/ml (median 121 ng/ml) in the study group and the difference was significant ($p<0.001$).

Vinzenz et al.[2] also reported significant elevations of ferritin in head and neck cancers, but they did not find any correlation between the stage of the tumor and ferritin levels. Maxim and Veltri,[5] in contrast, reported that the rise in the ferritin level was correlated with the stage of the tumor. In our study, pretreatment ferritin levels were significantly correlated with tumor size (T) ($p<0.05$), however, there

TABLE III

PRETREATMENT LEVELS OF SERUM TUMOR MARKERS WITH RESPECT TO THE STAGE OF THE TUMOR

	Stage 1-2		Stage 3-4		
Tumor markers	Mean±SD	Median	Mean±SD	Median	*p*
Ferritin (ng/ml)	133±192	66	227±241	206	>0.05
CYFRA 21-1 (ng/ml)	1.55±0.91	1.47	4.76±6.18	2.3	>0.05
CEA (ng/ml)	3.37±2.9	2.47	3.61±4.95	2.31	>0.05
SCC antigen (ng/ml)	1.96±1.49	1.40	2.73±1.93	3.10	>0.05
LSA (mg/dl)	2.44±0.86	2.24	2.67±0.63	2.57	>0.05

TABLE IV

PRETREATMENT LEVELS OF SERUM TUMOR MARKERS WITH RESPECT TO LYMPH NODE METASTASIS

	N_0		N+		
Tumor markers	Mean±SD	Median	Mean±SD	Median	*p*
Ferritin (ng/ml)	191±237	102	143±142	126	>0.05
CYFRA 21-1 (ng/ml)	3.17±5.1	1.85	3.45±2.77	2.30	>0.05
CEA (ng/ml)	3.88±4.07	2.42	1.98±0.64	2.31	>0.05
SCC antigen (ng/ml)	2.41±1.46	2.10	2.18±2.83	1.10	>0.05
LSA (mg/dl)	2.53±0.76	2.35	2.70±0.72	2.44	>0.05

was no correlation with lymph node metastasis and stage of the tumor (p>0.05).

It has been reported that ferritin levels become normal within 5 to 8 months after successful treatment, but in patients with a poor prognosis, the level of ferritin remain unchanged.[5] In our study, despite the shortness of the follow-up period, the level of ferritin underwent a significant progressive decline from the diagnosis to the third month of treatment (p<0.001). Nevertheless, there was no difference between the ferritin levels of patients with poor prognosis and good prognosis (p>0.05). Although higher ferritin levels were reported in poorly differentiated tumors,[13] we did not find any significant relationship between the histologic differentiation of the tumors and ferritin levels (p>0.05).

In squamous cell carcinoma of the head and neck, the value of ferritin as a tumor marker in the early diagnosis is low, because ferritin levels may be normal even in advanced stage cancers. In our study, elevated ferritin levels were observed in 14% of the patients, and this was not sufficient to differentiate cancer patients from the control group (p>0.05). However, the finding of a correlation between the tumor size and the ferritin level may increase the value of ferritin as a tumor marker. As reported in the literature, monitoring the tumor markers with serial measurements may be of value in the estimation of prognosis and detection of early

TABLE V

LEVELS OF SERUM TUMOR MARKERS WITH RESPECT TO PROGNOSIS WITHIN 3-MONTH FOLLOW-UP PERIOD

		Mortality/locoregional recurrence		Alive and no locoregional recurrence		
Tumor markers		Mean±SD	Median	Mean±SD	Median	*p*
Ferritin (ng/ml)	Before treatment	136±98	136	188±228	121	>0.05
	1st month	154±13	154	126±141	65	>0.05
	3rd month	315±49	315	109±141	42	>0.05
CYFRA 21-1 (ng/ml)	Before treatment	0.57±0.26	0.57	3.45±4.84	2.25	<0.001
	1st month	0.74±0.21	0.74	2.21±2.45	1.63	>0.05
	3rd month	2.35±1.2	2.35	1.83±1.46	1.56	>0.05
CEA (ng/ml)	Before treatment	1.36±0.98	1.36	3.68±3.81	2.44	<0.001
	1st month	1.26±0.79	1.26	2.41±2.29	1.58	>0.05
	3rd month	2.65±0.77	2.65	2.15±2.45	1.20	>0.05
SCC antigen (ng/ml)	Before treatment	2.35±2.05	2.35	2.36±1.77	1.60	>0.05
	1st month	1.40±0.28	1.40	1.40±1.03	1.20	<0.05
	3rd month	3.15±1.48	3.15	0.99±0.67	1.0	<0.05
LSA (mg/dl)	Before treatment	2.96±1.18	2.96	2.53±0.72	2.40	>0.05
	1st month	2.14±0.41	2.14	2.01±0.41	2.05	>0.05
	3rd month	2.05±0.21	2.05	1.84±0.51	1.74	>0.05

recurrence and metastasis.[5] In our study, this type of correlation was not observed as the study group was small and the follow-up period was short.

Lipid-associated sialic acid is a tumor marker which is elevated in all patients with squamous cell carcinoma of the head and neck. As it shows little variations in the measurements, it is convenient for clinical use as a tumor marker.[2] In our study, LSA levels were significantly higher in cancer patients compared to the control group.[14]

Some studies reported correlations between LSA levels and tumor size (T), stage of the tumor, lymph node metastasis, and distant metastasis.[15] In contrast, Dreyfus et al.[14] did not find any correlation between lymph node metastasis and the LSA level. Some authors suggested that localization of the tumor did not affect serum LSA levels.[16] In this study, LSA levels were significantly correlated with the tumor size (T) ($p<0.05$); however, no significant correlations were found with localization of the tumor, lymph node metastasis, or tumor stage ($p>0.05$).

Portoukalian et al.[17] reported a decline in the LSA level postoperatively due to the reduction of tumor bulk. In our study, a significant decline was also observed in the LSA level after the treatment ($p<0.001$). However, when pretreatment, the 1st and the 3rd month values of LSA were evaluated, no significant difference was found between patients with poor prognosis and good prognosis ($p>0.05$).

In this study, the sensitivity, specificity, and accuracy rates of LSA were 89.3%, 100%, and 93.8%, respectively. Klapan et al.[16] reported the preoperative sensitivity and specificity rates of LSA as 93-100% and 77-83%, respectively. Among the five tumor markers examined in this study, LSA had the highest preoperative sensitivity, suggesting that LSA might be the most appropriate tumor marker for the evaluation of head and neck cancers. In addition, some previous studies reported that LSA was a useful tumor marker in early diagnosis of recurrences and in monitoring treatment results.[16]

Squamous cell carcinoma antigen is a specific marker originally called as TA4. Fischbach et al.[18] reported elevated SCC antigen levels in 39% of patients with squamous cell carcinoma of the head and neck. We detected significantly higher SCC antigen levels in the study group compared to the control group ($p<0.001$), with 42% of the patients having elevated levels.

Dreyfuss et al.,[14] who found high levels of SCC antigen in 50% of the patients with T_4 tumors, suggested that SCC antigen levels were not affected by T and N status of the tumors.

In this study, pretreatment levels of SCC antigen were not correlated with the tumor size (T), lymph node metastasis, and the stage of the tumors ($p>0.05$). Eibling et al.[19] reported that tumor localization was associated with changes in SCC antigen levels. However, we did not find a significant difference in SCC antigen levels with respect to the localization of the tumors.

Squamous cell carcinoma antigen has been reported as a tumor marker with high specificity (70-90%), but low sensitivity (15-50%).[14] In our study, the specificity, sensitivity, and accuracy rates for SCC antigen were consistent with the literature, being 100%, 42.9%, and 75%, respectively.

Wollenberg et al.[20] reported higher pretreatment and post-treatment SCC antigen levels in patients with tumor recurrences. In this study, those who manifested a poor prognosis within the three-month follow-up period did not have significantly higher pretreatment SCC antigen levels ($p>0.05$). However, we found that SCC antigen was a significant marker for the differential diagnosis between benign and malignant lesions of the head and neck ($p<0.001$).

Silverman et al.[21] found that CEA levels were above 5 ng/ml in 36% of 439 patients with squamous cell carcinoma of the head and neck and reported a correlation with the stage of the tumors. They also found that CEA levels became normal after the resection of the tumors. In our study, pretreatment CEA levels were significantly high in the patient group ($p<0.001$) and increased CEA levels were detected in 21%; however, after the treatment a significant progressive decline was observed ($p<0.001$).

Some authors reported a correlation between the CEA level and the tumor size.[22] Compared to other cancers, the tumor size is usually smaller in squamous cell carcinoma of the head and neck; thus, increases in the CEA level is expected to be small.[23] In our study, CEA levels were not correlated with the tumor size and stage ($p>0.05$).

The prognostic value of CEA has been reported to be low.[24] Contrary to expectations, we found lower CEA levels in patients with a poor prognosis compared to those with a good prognosis ($p<0.05$) and the difference in CEA levels in the first and third month of the treatment were not significantly different ($p>0.05$). However, the short follow-up period in this study does not allow evaluations on the prognostic value of CEA.

Fischbach et al.[18] reported the sensitivity of CEA as 19.4%. In our study, the sensitivity and accuracy rates were 21.4% and 54.2%, respectively. On the other hand, CEA was significantly helpful in differentiating between cancer patients and the controls ($p<0.05$).

In view of these results, CEA seems to be a valuable tumor marker for the differential diagnosis of benign and malignant lesions of the head and neck. In addition, post-treatment declines in CEA levels may be a sign of adequate treatment and remission. As in the patients with squamous cell carcinoma of the head and neck, CEA levels were not elevated as much as that seen in gastrointestinal tumors; therefore, lower CEA levels should be accepted as significant. The use of CEA is limited to early diagnosis of cancers due to its low specificity and sensitivity. However, pre- and post-treatment evaluations of CEA levels may be useful to detect an occult disease and assess response to treatment.

Recently, the clinical use of cytokeratins as a tumor marker has become popular after the recognition of the role of cytokeratins in tumor biology. There are several studies reporting significant rises in the CYFRA 21-1 level in patients with squamous cell carcinoma of the head and neck.[23,25] However, some authors defined CYFRA 21-1 as an insufficient marker in squamous cell carcinoma of the head and neck.[26] Doweck et al.[27] reported the sensitivity of CYFRA 21-1 as 60% and found that its level was correlated with the stage of the tumor. In our study, the CYFRA 21-1 level was significantly high in cancer patients compared to the control group ($p<0.05$). However, the rise in the CYFRA 21-1 level was detected only in 10% of the patients with squamous cell carcinoma of the head and neck. The difference between the pre- and post-treatment values were not significant ($p>0.05$).

In several studies CYFRA 21-1 levels were significantly correlated with the stage of the tumor, lymph node metastasis, and distant metastasis.[25] In our study, we did not find any correlation with these parameters ($p>0.05$).

The sensitivity and accuracy rates for Cyfra 21-1 were found as 10.7% and 47.9%, respectively, and these were the lowest rates among five tumor markers studied.

All studies investigating the role of tumor markers in patients with squamous cell carcinoma of the head and neck showed that none of the tumor markers could be used alone in this cancer due to low sensitivity and specificity rates. In order to increase sensitivity and specificity rates, they were used in combination.[26,28] We also obtained a higher sensitivity rate (96%) by using LSA, SCC antigen, and CEA in combination. However, the use of LSA and CEA together also resulted in a sensitivity rate of 96% and an accuracy rate of 100%. The most reasonable and helpful clinical use seems to combine LSA and CEA in the diagnosis and follow-up of patients with squamous cell carcinoma of the head and neck.

In conclusion, LSA, CEA and SCC antigen were found to be significant tumor markers to evaluate squamous cell carcinoma of the head and neck. The clinical use of these three markers in combination will increase the sensitivity and specificity. However, as this is a preliminary study, further studies with larger series and long follow-up periods are necessary to clarify the clinical use of these tumor markers in squamous cell carcinoma of the head and neck.

REFERENCES

1. Schantz SP. Biologic markers, cellular differentiation, and metastatic head and neck cancer. Eur Arch Otorhinolaryngol 1993;250:424-8.
2. Vinzenz K, Schonthal E, Zekert F, Wunderer S. Diagnosis of head and neck carcinomas by means of immunological tumour markers (Beta-2-microglobulin, immunoglobulin E, ferritin, N-acetyl-neuraminic acid, phosphohexose-isomerase). J Craniomaxillofac Surg 1987;15:270-7.
3. Kiricuta I, Bojan O, Comes R, Cristian R. Significance of serum fucose, sialic acid, haptoglobine and phospholipids levels in the evolution and treatment of breast cancer. Arch Geschwulstforsch 1979;4:106-12.
4. Silver HK, Rangel DM, Morton DL. Serum sialic acid elevations in malignant melanoma patients. Cancer 1978;41:1497-9.
5. Maxim PE, Veltri RW. Serum ferritin as a tumor marker in patients with squamous cell carcinoma of the head and neck. Cancer 1986;57:305-11.
6. Papenhausen PR, Emeson EE, Croft CB, Borowiecki B.

Ferritin-bearing lymphocytes in patients with cancer. Cancer 1984;53:267-71.
7. Gold P, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med 1965;121:439-62.
8. Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. Cancer 1977;40:1621-8.
9. Coggi G, Dell'Orto P, Braidotti P, Coggi A, Viale G. Coexpression of intermediate filaments in normal and neoplastic human tissues: a reappraisal. Ultrastruct Pathol 1989;13:501-14.
10. Oremek GM, Siekmeier R, Zirker M, Kirsten R. The significance of Cyfra 21-1 in pneumological differential diagnosis. Lab Med 1994;18:100-4.
11. Katopodis N, Stock CC. Improved method to determine lipid bound sialic acid in plasma or serum. Res Commun Chem Pathol Pharmacol 1980;30:171-80.
12. Veltri RW, Maxim PE. Tumor immunity and tumor markers in head and neck cancer. In: Wolf GT, editor. Cancer treatment and research, head and neck oncology. 1st ed. Boston: Martin Nijhoff Publishers; 1984. p. 411-30.
13. Bhatavdekar JM, Vora HH, Goyal A, Shah NG, Karelia NH, Trivedi SN. Significance of ferritin as a marker in head and neck malignancies. Tumori 1987;73:59-63.
14. Dreyfuss AI, Clark JR, Andersen JW. Lipid-associated sialic acid, squamous cell carcinoma antigen, carcinoembryonic antigen, and lactic dehydrogenase levels as tumor markers in squamous cell carcinoma of the head and neck. Cancer 1992;70:2499-503.
15. Fischer F, Egg G. N-acetylneuraminic acid (sialic acid) as a tumor marker in head and neck cancers. HNO 1990;38:361-3. [Abstract]
16. Klapan I, Katic V, Culo F, Sabolovic D, Cuk V, Fumic K, et al. Lipid-bound sialic acid, prostaglandin E and histamine in head and neck cancer. Eur J Cancer 1993; 29A:839-45.
17. Portoukalian J, David MJ, Shen X, Richard M, Dubreuil C. Tumor size-dependent elevations of serum gangliosides in patients with head and neck carcinomas. Biochem Int 1989;18:759-65.
18. Fischbach W, Meyer T, Barthel K. Squamous cell carcinoma antigen in the diagnosis and treatment follow-up of oral and facial squamous cell carcinoma. Cancer 1990;65:1321-4.
19. Eibling DE, Johnson JT, Wagner RL, Su S. SCC-RIA in the diagnosis of squamous cell carcinoma of the head and neck. Laryngoscope 1989;99:117-24.
20. Wollenberg B, Jan V, Schmit UM, Hofmann K, Stieber P, Fateh-Moghadam A. CYFRA 21-1 is not superior to SCC antigen and CEA in head and neck squamous cell cancer. Anticancer Res 1996;16:3117-24.
21. Silverman NA, Alexander JC Jr, Chretien PB. CEA levels in head and neck cancer. Cancer 1976;37:2204-11.
22. Hoffmann J, Munz A, Krimmel M, Alfter G. Intraoperative and postoperative kinetics of serum tumor markers in patients with oral carcinoma. J Oral Maxillofac Surg 1998;56:1390-3.
23. Ogawa T, Tsurusako Y, Kimura N, Nishioka S, Akagi H, Nishizaki K, et al. Comparison of tumor markers in patients with squamous cell carcinoma of the head and neck. Acta Otolaryngol Suppl 1999;540:72-6.
24. Schroder M, Meyer T. CEA studies in squamous cell carcinomas of the head and neck. HNO 1986;34:334-42. [Abstract]
25. Niemann AM, Goeroegh T, Gottschlich S, Lippert BM, Werner JA. Cut-off value determination of CYFRA 21-1 for squamous cell carcinomas of the head and neck (SCCHN). Anticancer Res 1997;17:2859-60.
26. Ropka ME, Goodwin WJ, Levine PA, Sasaki CT, Kirchner JC, Cantrell RW. Effective head and neck tumor markers. The continuing quest. Arch Otolaryngol Head Neck Surg 1991;117:1011-4.
27. Doweck I, Barak M, Greenberg E, Uri N, Kellner J, Lurie M, et al. Cyfra 21-1. A new potential tumor marker for squamous cell carcinoma of head and neck. Arch Otolaryngol Head Neck Surg 1995;121:177-81.
28. Rassekh CH, Johnson JT, Eibling DE. Circulating markers in squamous cell carcinoma of the head and neck: a review. Eur J Cancer B Oral Oncol 1994;30B:23-8.