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HEAD AND NECK

CYFRA 21-1: a suitable tumor marker in patients with head and neck cutaneous squamous cell carcinoma?

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Abstract

Purpose The clinical significance of cytokeratin fraction 21-1 (CYFRA 21-1) for patients with head and neck cutaneous squamous cell carcinoma (CSCC) is unknown. Thus, the aim of the study was to evaluate the clinical value of CYFRA 21-1 in the context of treatment and follow-up for these patients.

Methods The clinical, histological and laboratory data of a total of 55 patients with the first diagnosis of head and neck cutaneous squamous cell carcinoma (T1–T4, N0–N2b, M0–1) between 2003 and 2017 were retrospectively analyzed. In 25 cases, the primary tumor could be treated successfully without residual or recurrent disease in the further course. The average follow-up period was 2.3 years. In all patients, pretherapeutic determination of CYFRA 21-1 was performed using the ECLIA test kit. The cut-off value was set at 3.3 ng/ml.

Results In 18 patients (32.7%), regional recurrence was found in the course of treatment. Distant metastases could be observed in two patients (3.6%). In these cases, no significant increase of CYFRA 21-1 blood concentration was detected at the time of recurrence/metastasis. At the time of the first diagnosis, the mean value of CYFRA 21-1 blood concentration was 2.4 ng/ml; and in cases of regional recurrence or distant metastases, the initial mean CYFRA 21-1 concentration was 2.0 ng/ml. There was no statistically significant relationship between CYFRA 21-1 blood concentration and analyzed tumor characteristics.

Conclusions According to current knowledge, the tumor marker CYFRA 21-1 is not clinically significant for treatment and follow-up of patients with head and neck CSCC.

Keywords CYFRA 21-1 · Tumor marker · Cutaneous squamous cell carcinoma · Head and neck cancer

Introduction

Non-melanoma skin cancer (NMSC) is the most common malignancy diagnosed in the western world with an increasing incidence [1]. In the United States, the number of patients has risen from 3.5 million in 2006 to 5.4 million in 2012 [2, 3]. Beside basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (CSCC) is the most common NMSC with an incidence of about 20% of all NMSC patients [4]. However, the exact epidemiology worldwide is still unknown because of the exclusion by large cancer registries, the low mortality rates, and the geographic variations in incidence rates [5]. Typical risk factors for the development of CSCC are sun exposure, increasing age, fair skin type, male sex, and smoking [6]. Furthermore, beta genus human papilloma virus (HPV) is supposed to play an important role as a cofactor in carcinogenesis of these tumors, which contributes to the increasing incidence of CSCC [7–9]. Due to the mentioned pathogenesis, up to 90% of CSCC are localized in the head and neck region [10]. Most CSCC are characterized by a good prognosis with a 3-year overall survival rate of 85–100% and can be easily treated in most cases [11]. However, a small group of

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patients characterized by a specific risk profile suffer from regional and distant metastases. In these cases, the prognosis decreases significantly with a 5-year survival rate of about 25–50% [12, 13]. Since the presence and extent of regional metastasis seems to have a high impact on the survival of the patients, an early diagnosis and therapy seem to be of utmost importance [13, 14].

Suitable tumor markers could be helpful to detect regional and distant tumor manifestation earlier, and thus improve the oncological outcome. CYFRA 21-1 is an established tumor marker for squamous cell carcinoma of the lung [15], which was first described in 1981 by Wu et al. [16]. CYFRA 21-1 is the serum soluble fragment of cytokeratin 19, which belongs to the acid type I keratins and weighs about 40 kDa [16]. Cytokeratin 19 is expressed by benign as well as malignant epithelium, with increased expression in the lower part of the aerodigestive tract. Thus, higher CYFRA 21-1 serum levels can be observed in lung cancer patients compared to patients with head and neck squamous cell carcinoma (HNSCC) [17]. CYFRA 21-1 is controversially discussed for the treatment of patients with HNSCC. In this context, various cut-off values have been proposed, varying from 1.0 ng/ml up to 3.3 ng/ml [18–20]. However, the results of previous studies revealed only a limited clinical relevance of CYFRA 21-1 for the diagnosis of HNSCC but seems to be useful in the follow-up period to detect regional or distant tumor recurrence [17, 21, 22]. Furthermore, there is general agreement about a significantly shorter overall and disease-free survival for patients with HNSCC and elevated CYFRA 21-1 serum levels [18, 19, 23]. However, up to now no studies have been conducted evaluating CYFRA 21-1 in the treatment of patients with CSCC of the head and neck region. Thus, the aim of the present study was to evaluate the clinical significance of CYFRA 21-1 as a tumor marker for CSCC of the head and neck region especially in cases of regional advanced or recurrent disease. Therefore, we analyzed the correlation of the CYFRA 21-1 serum concentration at initial diagnosis with several tumor characteristics, the overall and disease-free survival as well as the value of CYFRA 21-1 as a follow-up tumor marker for the identification of tumor recurrence.

Patients and methods

Inclusion criteria

Altogether, we retrospectively analyzed the data of 55 patients, who were treated between 2003 and 2017 for CSCC of the head and neck. Only patients with a histologically proven CSCC and at least one determination of CYFRA 21-1 serum level were included. Further exclusion criteria were a secondary tumor at the time of diagnosis or cancer of unknown primary (CUP).

A total of 55 patients (22 female and 33 male, average age: 85.3 years, range: 50–109 years) met the mentioned inclusion criteria. In Table 1 the clinical characteristics of the evaluated patients are summarized, including localization of the primary tumor, tumor stage, and disease progression.

Table 1 Patients and treatment characteristics ($n=55$)

Characteristics	No. of patients (%)
Gender	
Male	33 (60)
Female	22 (40)
Median age (range), years	85.3 (50–109)
Primary site	
Ear	17 (30.9)
Nose	13 (23.6)
Retroauricular	9 (16.4)
Cheek	8 (14.5)
Preauricular	3 (5.5)
Neck	2 (3.6)
Upper eyelid	1 (1.8)
Lower eyelid	1 (1.8)
Medial eye angle	1 (1.8)
T stage	
T1	20 (36.4)
T2	21 (38.2)
T3	9 (16.4)
T4	5 (9.1)
N stage	
N0	46 (83.6)
N1	2 (3.6)
N2a	3 (5.5)
N2b	4 (7.3)
M stage	
M0	51 (92.7)
M1	4 (7.3)
Tumor differentiation	
Good (G1)	4 (7.3)
Moderate (G2)	42 (76.4)
Poor (G3)	9 (16.4)
Regional recurrence	
Yes	18 (32.7)
No	37 (67.3)
Secondary tumors	
Yes	3 (5.5)
No	52 (94.5)
Distant metastases	
Yes	2 (3.6)
No	53 (96.4)

Diagnostics and tumor-staging

Clinical examination consisted of clinical inspection and palpation of the skin of the head and neck area, as wells as an endoscopic examination of the upper airways in the context of the ENT-specific examination. The assessment of the parotid and neck lymph nodes was performed by ultrasound in all cases. Computed tomography and magnetic resonance imaging were performed in cases of clinically suspected regional or distant metastases and advanced primary tumor. All patients were staged according to the TNM-classification by the International Union against Cancer (UICC) [24].

Treatment modalities

All patients with a curable CSCC of head and neck at the time of diagnosis underwent surgical treatment. Patients suffering from incurable tumors with evidence for distant metastasis received palliative radiotherapy. Patients with regional metastasis in the parotid gland upon initial diagnosis or during follow-up underwent either partial ($n=18$) or total parotidectomy (PE) ($n=4$) and selective neck dissection (SND) I–III depending on the extent of the metastasis. Patients with neck metastases underwent unilateral modified radical neck dissection (MRND). The type of PE (total PE, subtotal PE, lateral PE) was determined depending the extent of tumor invasion of the parotid gland. Accordingly, the type of ND [radical ND (RND), modified radical ND (MRND), selective ND (SND)] was determined, depending the lymph node status of the neck. Patients suffering from advanced primary tumors with close margin resection, residual disease, or regional metastasis received adjuvant radiotherapy.

Follow-up

Oncological aftercare implied clinical inspection and palpation of the skin in the head and neck area, as wells as endoscopic examination of the upper aerodigestive tract and sonographic imaging of the cervical lymph nodes. In a period of 2 years from the time of initial diagnosis follow-up examinations were performed every 4–8 weeks. The time intervals were subsequently extended to 3 months in the third, and 6 months in the fourth year after diagnosis. After five years annual follow-up examinations were performed. The mean follow-up time was 2.3 years (standard deviation 2.8 years) for the whole patient group. In patients with suspicion of local tumor recurrence, cervical lymph node metastasis or a secondary tumor, further diagnostics, including fine-needle aspiration cytology of suspicious neck nodes, magnetic resonance imaging (MRI) and computed tomography (CT) of the neck and the thorax were performed.

Measurement of CYFRA 21-1

In all patients, the CYFRA 21-1 concentration was measured at the time of first diagnosis. In 32 cases, further measurement of the CYFRA 21-1 serum concentration was performed after completion of surgical or adjuvant treatment, alternatively also during follow up, especially in cases of tumor recurrence. Venous blood samples (6 ml) were taken from the patients. Blood samples were allowed to clot, then centrifugated and preserved at − 80 °C until further processing. In all 55 patients, CYFRA 21-1 was measured with Enzymum-Test® Cyfra 21-1 [Roche Diagnostics, Rotkreuz, Switzerland] ECLIA test-kit. The two cytokeratin 19 specific antibodies KS 19-1 and BM 19-21 were used to detect CYFRA 21-1. The calculated CYFRA 21-1 concentration was expressed in ng/ml. According to the manufacturer`s specifications, we used a limit value of 3.3 ng/ml.

Statistical analysis

Analysis was performed with SPSS 25.0. Clinical and histological characteristics of the patients were evaluated by descriptive analysis. The analyzed clinical characteristics included age, sex, primary site, and a new disease progression after the end of treatment (local and regional recurrences, secondary tumors and distant metastasis). The analyzed tumor characteristics were the T, N, M stages and the histological grading. For evaluation of the link between CYFRA 21-1 and different tumor characteristics the nonparametric Jonckheere-Terpstra test was utilized. Statistical significance was assumed at a p value ≤ 0.05. The comparison of different records was illustrated by Box-plot diagrams. Kaplan–Meier curves were used to evaluate the disease-free and overall survival, while differences between the survival curves were compared by Log-rank test. At different cut-off points, paired-samples tests and Chi-square tests were used to analyze the value of CYFRA 21-1 as a follow-up marker.

Results

Treatment modalities

Altogether 53 (96.4%) patients underwent surgical intervention. After surgery, 9 (16.4%) patients received adjuvant radiotherapy. In 1 (1.8%) patient, simultaneous chemotherapy was carried out. In 2 (3.6%) patients, palliative radiotherapy instead of a surgical approach was performed due to distant metastasis at the time of diagnosis. In this study, 22 (40.0%) patients received PE [lateral PE: 13 (23.6%); subtotal PE: 5 (9.1%); total PE: 4 (7.3%)] and 24 (43.6%) patients received unilateral ND [SND: 15 (27.3%); MRND: 8 (14.6%); RND: 1 (1.8%)].

CYFRA 21-1 serum levels and TNM stage at initial diagnosis

Overall, the mean CYFRA 21-1 serum level at the time of diagnosis was 2.2 ng/ml (ranging from 0.5 to 15 ng/ml). In 13 (23.6%) patients, a serum level of ≥ 3.3 ng/ml was measured. Patients with a T1 tumor revealed a median CYFRA 21-1 serum concentration of 2.5 ng/ml and in cases of tumors classified T2 1.7 ng/ml. The median CYFRA 21-1 serum level for T3 tumors was 3.0 ng/ml and for T4 staged tumors 1.4 ng/ml. In this study, no significant correlation was found between the CYFRA 21-1 serum levels and the size of the primary tumor at the time of diagnosis ($p = 0.29$) (Fig. 1a).

In the present patient group, the highest median CYFRA 21-1 serum level (2.3 ng/ml) was observed in patients without lymph node metastasis (N0). All patients with lymph node metastasis, regardless of the stage, showed a lower median CYFRA 21-1 serum concentration (N1: 0.93 ng/ml; N2a: 1.1 ng/ml; N2b: 1.9 ng/ml). Thus, no significant correlation was found between CYFRA 21-1 and lymph node invasion at the time of diagnosis ($p = 0.40$) (Fig. 1b).

Patients with distant metastasis showed a lower median CYFRA 21-1 serum level (1.3 ng/ml) compared to patients without distant metastasis (2.3 ng/ml). Thus, no significant correlation was found between CYFRA 21-1 serum concentration and distant metastasis at the time of diagnosis ($p = 0.50$) (Fig. 1c).

CYFRA 21-1 serum level and histological tumor grading at initial diagnosis

For well-differentiated tumors (G1) the median CYFRA 21-1 serum concentration was 4.7 ng/ml, for moderate differentiated tumors (G2) 1.9 ng/ml, and for poorly differentiated tumors (G3) 2.3 ng/ml. No significant correlation was found between the CYFRA 21-1 value and the histological grading ($p = 0.40$) (Fig. 1d).

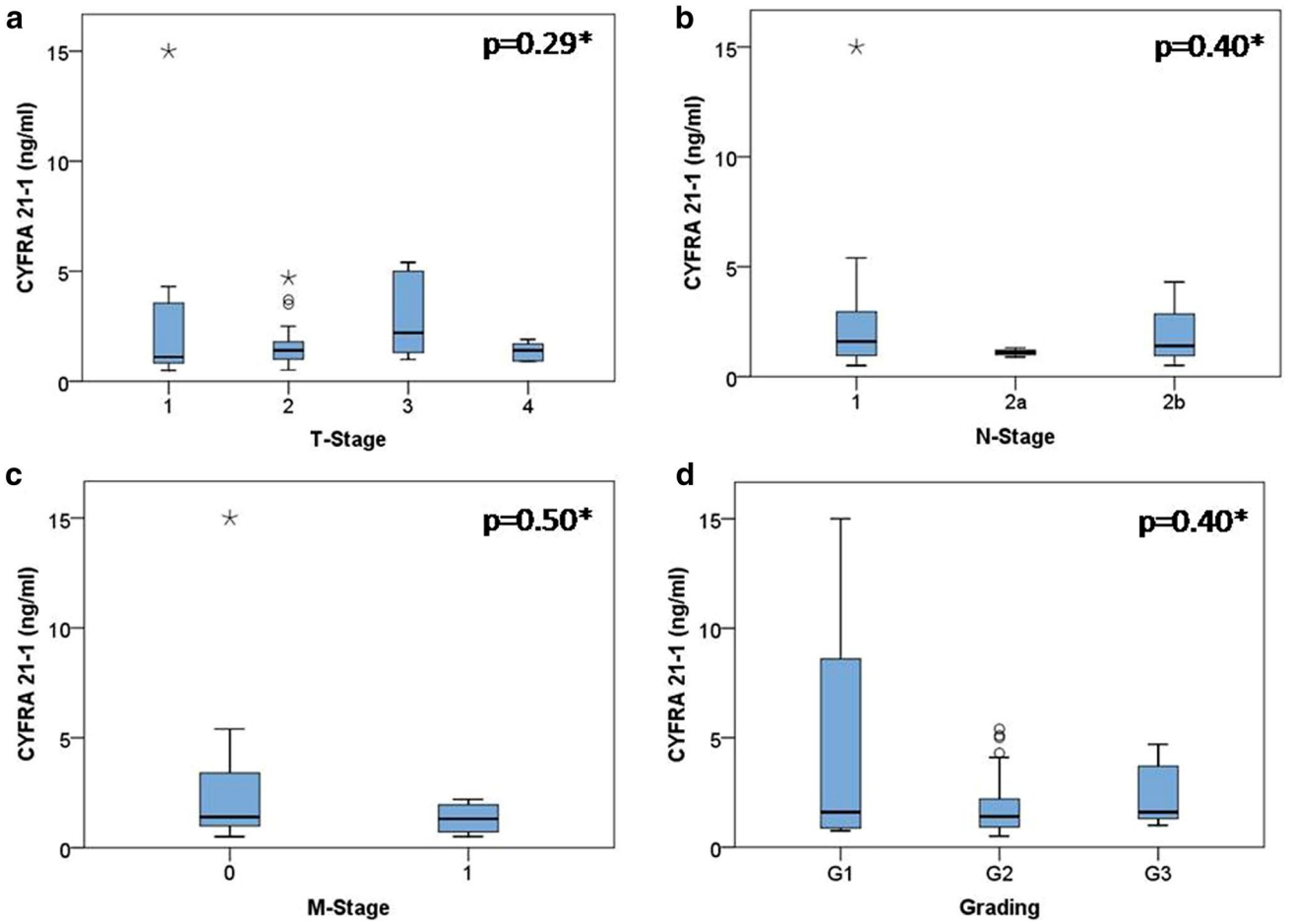

Fig. 1 Concentration of CYFRA 21-1 (ng/ml) at diagnosis as a function of T stage (**a**), N stage (**b**), M stage (**c**) and histological grading (**d**). *Jonckheere-Terpstra test

CYFRA 21-1 as a follow-up marker for CSCC

Residual tumor at the primary site ($n=5$), local tumor recurrence ($n=6$) or regional lymph node metastasis ($n=8$) were found in 19 patients. A total of 3 patients developed secondary tumors and 2 patients had distant metastases in the follow-up period. At the time of tumor recurrence, the mean CYFRA 21-1 serum concentration in patients was 1.8 ng/ml (0.7–6.9 ng/ml). A significant elevation of CYFRA 21-1 blood serum concentration could not be detected in these patients ($p=0.24$). Evaluated by Chi-square test, the CYFRA 21-1 serum concentration at time of first diagnosis was significantly lower in patients with tumor relapse in the further course of the disease, compared to patients without disease progression ($p=0.02$) (Fig. 2).

CYFRA 21-1 as a prognostic marker for overall and disease-free survival

A total of 5 (9.0%) patients died during the follow-up period. Only one of these patients had a CYFRA 21-1 serum concentration of ≥ 3.3 ng/ml at the time of diagnosis. 95.0% of the patients with CYFRA 21-1 values of ≤ 3.3 ng/ml and 92.3% of the patients with CYFRA 21-1 values of ≥ 3.3 ng/ml survived in the follow-up period. Statistical examination revealed no significant differences in the overall survival of both patient groups ($p=0.19$) (Fig. 3a).

A total of 19 (34.5%) patients suffered from disease progression in the follow-up period. All of these patients showed a CYFRA 21-1 value of ≤ 3.3 ng/ml at the time of diagnosis. Thus, 56.8% of the patients with a CYFRA 21-1 value of ≤ 3.3 ng/ml were clinically tumor-free compared to 100% of the patients with a CYFRA 21-1 blood concentration of ≥ 3.3 ng/ml. Statistical evaluation revealed no significant disease-free survival benefit for patients with a CYFRA 21-1 serum concentration below the cut-off value ($p=0.22$) (Fig. 3b).

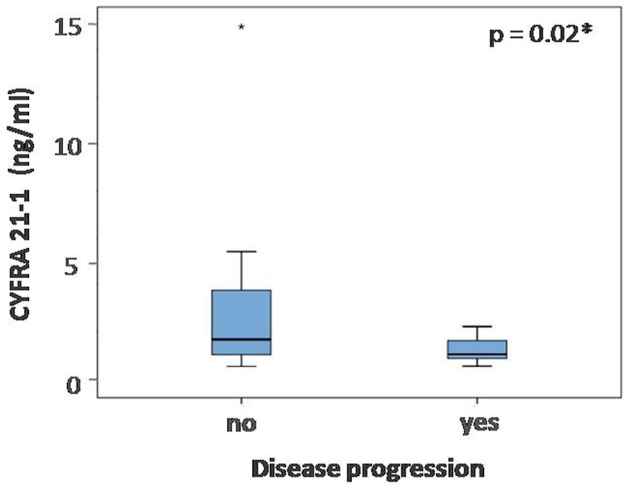

Fig. 2 Concentration of CYFRA 21-1 (ng/ml) at the time of diagnosis depending on disease progression. *Chi-square test

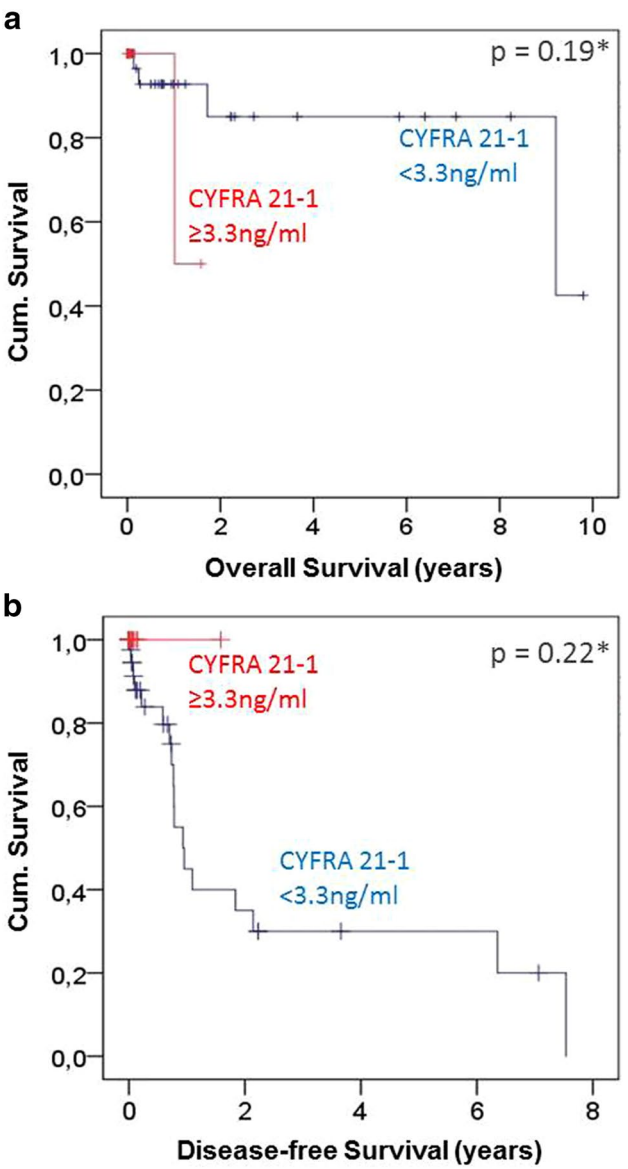

Fig. 3 Kaplan–Meier graphs for overall (**a**) and disease-free (**b**) survival. *Log-rank test

Discussion

CYFRA 21-1 is an established tumor marker in the treatment of pulmonary squamous cell carcinoma [15]. However, its value in the management of high risk advanced CSCC has not been analyzed so far. To the best of our knowledge, only one case report had been published analyzing CYFRA 21-1 as a tumor marker for CSCC [25]. In this case report, a

CYFRA 21-1 serum value of 33 ng/ml was determined in a patient with CSCC of the patient`s left shoulder staged cT3; cN2; cM1 at the time of diagnosis. After surgical treatment of the tumor, the serum level of CYFRA 21-1 significantly decreased to 5.0 ng/ml. The authors concluded that CYFRA 21-1 might be a useful marker for the diagnosis of poorly differentiated CSCC and an indicator for the clinical course of these patients.

Although there is no evidence for the diagnostic value of CYFRA 21-1 in the treatment of CSCC, several studies focused on this aspect regarding the treatment of patients with HNSCC. Some of these studies evaluated CYFRA 21-1 in an inhomogeneous group of patients, including CSCC patients, too [26]. However, due to several reasons, the results of previous studies analyzing CYFRA 21-1 for HNSCC patients have to be controversially discussed. Thus, beside tumor tissue, also healthy tissue may express CYFRA 21-1, which leads to a range of serum levels from 0.78 to 3.35 ng/ml even in healthy individuals [27–29]. Due to the varying serum concentrations of CYFRA 21-1 even in healthy subjects, it is difficult to find a suitable cut-off value for CYFRA 21-1. Furthermore, the expression of CYFRA 21-1 depends on the localization of the epithelium. In this context, CYFRA 21-1 expression in head and neck cancer is lower than in lung cancer. Additionally, some authors described that circulating CYFRA 21-1 might be influenced by the serum protein and the hematocrit values [22]. Therefore, a cut-off value of 3.3 ng/ml may be too high in the management of HNSCC patients [30, 31]. However, several previous studies on HNSCC set the cut-off value to 3.3 ng/ml [17, 32–34] to achieve high specificity. Thus, we used the same cut-off value of 3.3 ng/ml in the present study with only a small number of patients showing a higher CYFRA 21-1 serum level at the time of diagnosis. In contrast to the case report published by Ueda et al., which revealed a CYFRA 21-1 serum level of 33 ng/ml, we found a comparably low median CYFRA 21-1 concentration of only 2.2 ng/ml [25]. However, the high CYFRA 21-1 serum level and the significant decrease in the previous case report may be a result of the high primary tumor volume (16 × 10 × 5 cm). In the present study, the primary tumor stages were comparably low with T1 and T2 in 74.6% of the patients. Data from several previous studies on HNSCC indicate a correlation of the CYFRA 21-1 levels with the T and N stages of this tumor entity [18, 30, 35]. However, other studies revealed no correlation between CYFRA 21-1 and the T and N stages in patients with SCC of the oropharynx [22]. A further clinical trial with 830 HNSCC patients using a cut-off value of 3.3 ng/ml found a significant correlation between CYFRA 21-1 and the M stage [34]. However, we did not find any significant correlation between the CYFRA 21-1 serum level at the time of diagnosis and T, N as well as M stages in the present study on CSCC. These controversial results may be explained by various aspects. First of all, the present study included a comparably small number of patients, suffering from regional ($n = 9$) and distant metastases ($n = 4$). Thus, the tumor volume was comparably low and statistical differences may be underestimated. Furthermore, the CYFRA 21-1 serum levels depend on the expression of the tumor tissue, which may vary in each tumor [35]. Furthermore, the tumor localization in the head and neck region and even the subsite of an area might have an effect on the CYFRA 21-1 expression. If the expression of CYFRA 21-1 in the upper aerodigestive tract is lower than in the lung, the expression may also differ between the upper aerodigestive tract and the skin [30, 36]. Considering the results of the present study, the expression of CYFRA 21-1 in CSCC seems to be even lower than in the upper aerodigestive tract.

Besides the tumor stage, the grading of the primary tumor has been discussed to correlate with the CYFRA 21-1 concentration in HNSCC patients. In this context, Doweck et al. were the first to describe an inverse correlation between CYFRA 21-1 and the histological grading of the primary tumor in HNSCC patients [37], which was validated by the results of further studies [19]. However, some authors did not find any correlation between CYFRA levels and tumor grading in HNSCC patients [20, 22, 38]. Similarly, we found no statistical correlation in the present study. One explanation might be that the determination of histological differentiation of tumor cells neglects functional aspects and depends mainly on structural and morphological aspects. However, the expression of CYFRA 21-1 is based on functional aspects [39, 40]. Therefore, a correlation between the CYFRA 21-1 value and the histological differentiation should not be expected in any case.

Most CSCC are characterized by a good prognosis. However, some patients develop regional and distant metastasis after resection of the primary tumor and thus survival rates significantly decrease, similar to patients with HNSCC. In this context, several risk factors for developing regional metastases have been discussed in the literature. Primary tumor-specific risk factors encompass a tumor size of more than 1.5 cm, an infiltration depth of more than 4 mm, and low differentiation in tumor grading as well as perineural tumor invasion. Patient-specific risk factors include age of more than 70 years at diagnosis or immunosuppression [41, 42]. To detect a disease progression after initial treatment of the primary tumor, e.g. a suitable tumor marker would be helpful. In HNSCC, the clinical relevance of CYFRA 21-1 as a marker for tumor relapse in the follow-up is highly controversial. In a prospective study conducted by Wollenberg et al. with 257 patients, a low sensitivity of 18% and a specificity of 95% for CYFRA 21-1 was found using a cut-off value of 2.9 ng/ml [43]. In addition, Pradier et al. and Hoffmann-Fazel et al. did not consider CYFRA 21-1 to be an additional parameter for the identification of patients with

a risk to develop residual tumors after treatment, recurrent or progressive disease for HNSCC [33, 44]. However, other authors consider CYFRA 21-1 as a suitable tumor marker in HNSCC. Maas et al. and Deng et al. found a CYFRA 21-1 value above 3.3 ng/ml in 70.4% and 78.9% of their patients with a disease progression [20, 34]. In a clinical trial, Banal et al. also found a significant correlation between CYFRA 21-1 levels above 1.0 ng/ml and a tumor relapse [19]. In the present study, we found a significantly lower CYFRA 21-1 value for CSCC in cases of tumor relapse. Therefore, it has to be assumed that the CYFRA 21-1 serum concentration is not a suitable marker for tumor progression in patients with CSCC of head and neck, whereas CYFRA 21-1 might have more potential as a tumor marker in the upper aerodigestive tract. Beside the differences regarding the tumor localization, a further reason for these results might be the type of CYFRA 21-1 measurement. In this study, we used the newer and possibly more accurate ECLIA test kit instead of the ELISA test kit for CYFRA 21-1 determination.

In literature, the overall survival rates for patients with HNSCC and a CYFRA 21-1 value below 3.3 ng/ml seem to be superior compared to patients with a CYFRA 21-1 serum concentration above 3.3 ng/ml [23, 38]. Ceruse et al. confirmed these results with a lower cut-off value of 1.0 ng/ml [18]. The vast majority of patients analyzed in the study by Ceruse et al. were staged as UICC IV, therefore, the overall survival was generally shorter because of the advanced tumor stages. In the present study, no significant correlation between CYFRA 21-1 and the overall survival was found. One explanation might be that tumors localized at the skin generally express less CYFRA 21-1 than tumors of the upper aerodigestive tract. Another explanation might be that in other studies the CYFRA 21-1 concentration correlates with the TNM stage. In the present study, we found no correlation between CYFRA 21-1 and the TNM stage. Therefore, it must be questioned whether CYFRA 21-1 levels really correlates with the overall survival, or if the lower overall survival was an effect of advanced tumor stage that secondarily correlates with a higher CYFRA 21-1 serum concentration.

With respect to the relationship between CYFRA 21-1 and the disease-free survival rate of patients with HNSCC, there are consistent data in literature. The authors assume that patients with an elevated CYFRA 21-1 serum concentration have shorter disease-free survival than patients with low CYFRA 21-1 values. Studies by Ceruse et al. and Banal et al. revealed significant correlations in this context [18, 19]. Both authors used a low cut-off value of 1.9 ng/ml. Hsu et al. confirmed these findings with a higher cut-off value of 3.3 ng/ml for oral cavity carcinoma [23]. In the present study, we did not find a correlation between elevated CYFRA 21-1 concentrations and shorter disease-free survival in the analyzed patient population. The main reason might be a lower CYFRA 21-1 expression in the cutaneous tumor cells in cases of disease progression than in tumor relapses of the upper aerodigestive tract. The vast majority of tumors were staged as UICC stage IV in the clinical trials conducted by Ceruse et al. and Banal et al., while the majority of the analyzed tumors showed an earlier stage in the present study. The different results might further be explained by the development of tumor relapses in cases of occult metastases caused by advanced tumor stages, and, therefore, a shorter disease-free survival in advanced tumor stages.

Conclusion

To our knowledge, this is the first study evaluating the clinical significance of CYFRA 21-1 as a tumor marker for patients with CSCC of head and neck. Due to the retrospective setting of the study, there are some limitations; therefore, the assessment of the clinical impact of the findings in the present study on oncological results is limited. Analyzing the present data, so far no significant correlation of CYFRA 21-1 with any evaluated parameter was found. Furthermore, CYFRA 21-1 does not provide any improvement for detection of disease progression in CSCC. Therefore, CYFRA 21-1 does not seem to be a suitable follow-up tumor marker even in advanced cutaneous squamous cell carcinoma of the head and neck. Larger-scaled prospective studies are needed to confirm these results.

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Compliance with ethical standards

Conflict of interest The author declares that there is no competing interest.

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