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CYFRA 21-1 as a Prognostic Marker of Tumor Response to Radiation Alone or Combined With Chemotherapy in Patients With Carcinoma of Larynx or Hypopharynx.

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***Abstract* – Despite of relatively high rate of complete tumor responses after radiotherapy (RT) alone or in combination with chemotherapy (ChRT), locoregional relapse is a major reason of failure for patients with head and neck squamous cell carcinoma (HNC). If treatment failure is diagnosed early, salvage therapy could be possible. Such diagnosis is difficult due to the lack of early prognostic markers for discrimination between residual tumor and treatment-related changes shortly after treatment. The aim of the study was to evaluate clinical value of CYFRA 21-1 as a potential marker of early failure of radiotherapy in patients with laryngeal (LXC) or hypopharyngeal (HPC) cancer. Material and methods: Consecutive 93 patients with LXC (73%) and HPC (27%) were treated between 2009 and 2011 by RT alone (63%), or ChRT (37%). CYFRA 21-1 was estimated before (CYFRA 21-1_1) and at the end (CYFRA 21-1_2) of the treatment. Results: CYFRA 21-1_1 correlated with T and N stages. Median CYFRA 21-1_2 in patients with partial and with complete remission was 2.33 ng/ml, and 1.65 ng/ml, respectively (p=0.0001). Statistically significant differences in 3-year LRC (82% vs. 42%) and OS (57% vs. 40%) were observed between patients groups with CYFRA 21-1_2 <2 ng/ml and ≥ 2 ng/ml, respectively. In multivariate analysis CYFRA 21-1_2 remained significant prognostic factor for LRC (p=0,0003) and OS (p=0.01). Conclusions: CYFRA 21-1 assessed at the end of the RT or ChRT seems to be a prognostic marker for tumor response. Probability of persistent tumor is markedly higher in LXC and HPC patients with CYFRA 21-1 ≥ 2 ng/ml instantly after treatment.**

***Index Terms*—CYFRA 21-1, chemotherapy, laryngeal and hypopharyngeal cancer, radiotherapy.**

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I. Introduction

Radiotherapy (RT) alone or in combination with chemotherapy (ChRT) remains the main treatment for the most patients with cancer of larynx (LXC) and hypopharynx (HPC) due to similar cure rate as surgery and preservation of organ and function integrity [1]. However, locoregional relapse is still the major cause of treatment failure for those patients. Among patients with locoregionally advanced tumors 25-50% develop ultimately local or/and nodal recurrence [1] and next 20% patients present persisted residual mass at the site of primary tumor or metastatic nodes after the treatment completion. In most cases salvage therapy is still possible if treatment failure is diagnosed early enough . However, the differentiation between non-neoplastic and neoplastic change after RT is difficult especially shortly after treatment. Early detection of disease progression remains a challenging task mainly due to the lack of adequate early prognostic markers. CT, MRI or PET/CT routinely used in posttreatment locoregional assessment are best performed about 3 months after RT [2]. A delay in the detection of treatment failure has been shown to be deleterious to clinical outcome after RT [3].

CYFRA 21-1, a soluble fragment of cytokeratin 19, is an acidic subunit of the cytokeratin intermediate filament expressed by simple epithelia and their malignant counter-parts [4,5]. The CYFRA 21-1 test detects soluble fragments of cytokeratin 19 by means of two monoclonal antibodies directed against epitopes KS 19-1 and BM 19-21 [6]. CYFRA 21-1 is significantly elevated in patients with head and neck squamous cell carcinoma (HNC) with sensitivity and specificity in the range of 62 - 72% and 94 - 100%, respectively, considering various cut-off values (1 ng/ml; 1.3 ng/ml; 2.2 ng/ml; 3.3 ng/ml) [7,8,9,10,11]. Such range of cut-offs may be result of the assessments in groups of patients, without confounding to tumor sub-sites which may influence CYFRA 21-1 concentration[12]. Despite of this, CYFRA 21-1 appeared to be promising marker for patients with HNC, and may supplement staging of HNC before the treatment [7,8]. Moreover, some data showed that elevated CYFRA 21-1 few months after treatment indicated risk of recurrence [13,14]. However, information on the value of CYFRA 21-1 assessed directly after treatment completion is missing.

In this study we aimed to evaluate correlation between

CYFRA 21-1 analyzed instantly after the end of treatment and early treatment outcome in relatively homogenous group of patients with LXC and HPC who underwent RT or ChRT.

II. Materials and Methods

A. Patients

The retrospective study group consisted of consecutive 93 patients with histologically proven squamous cell carcinoma of LXC (73%) or HPC (27%). Patients were treated in Department of Radiation Oncology at Maria Skłodowska-Curie Memorial Cancer Center and the Institute of Oncology, Gliwice Branch, Poland, between January 2009 and February 2012. There were 19 women (20%) and 74 men (80%) in the average age of 60 years (range: 39 to 81 years). Stage of the cancer was determined by TNM scale (according to American Joint Committee of Cancer – AJCC, version 7). There were 7 (8%), 41 (44%), 28 (30%), T3 and 17 (18%) patients with T1, T2, T3 and T4 tumor stage, respectively, and 48 (52%), 6 (6%), 32 (34%), and 7 (8%) patients with N0, N1, N2 and N3 nodal stage of disease, respectively (no patients with distant metastases was included). Grading of histological tumor differentiation G1, G2 and G3 was assessed in 10%, 36% and 11% patients, respectively, in 43% of the patients G was not available. Most of the patients had LXC, the distribution between early (T1-2) and advanced (T3-4) tumors, as well as between N0 and N1-3 stages is almost half to half.

All patients were treated with RT alone or in combination with chemotherapy (ChT). ChT was given concomitantly with RT (ChRT) or before RT (IND). Four treatment subgroups were identified: IND followed by ChRT, IND followed by RT, ChRT and RT alone in 7%, 14%, 16% and 63% of patients, respectively. ChRT consisted of cisplatin, 100 mg/m2 given every 21 days over RT. Induction ChT consisted of docetaxel, cisplatin, 5-fluorouracil (TPF) or cisplatin and 5-fluorouracil (PF) given every 21 days, two or three times depending on treatment tolerance. Median total RT dose and overall radiotherapy treatment time were 70 Gy (range: 66-72 Gy) and 39 days (range: 36-93 days), respectively. The research protocol was approved by Ethical Committee of the Comprehensive Cancer Centre and all of participants signed informed consent before being enrolled into study group.

B. Biological material

Concentration of CYFRA 21-1 was determined in blood serum. Samples obtained after centrifugation at 3000 rotations/min for 10 min. at the temp. 40 C, were analyzed at the same day. Concentration of CYFRA 21-1 was detected by means of electrochemiluminescence immunoassay method, using the Roche Diagnostics reagent kits and COBAS e411 analyzer. Blood samples were taken twice: before treatment (CYFRA 21-1_1) and in the day of last fraction (CYFRA 21-1_2).

C. Statistics

In statistic overview of the results STATISTICA 9.1 (StatSoft) program was used. While interpreting the results median value was used. In the first part the study an analysis of the pretreatment prognostic factor was performed (age, sex, TNM classification) with the nonparametric Mann-Whitney test.

For the purpose of the study, patients were divided into 2 groups according to treatment results assessed over follow-up in mean of presence/absence of any signs of local, nodal or distant metastatic disease: patients with cured cancer disease (CCD) or with uncured cancer disease (UCD). Additionally, UCD group was divided on 2 subgroups: with persistent disease (PD, persistent primary or/and nodal tumor was presented at treatment completion and confirmed over follow-up) and recurrent disease (RD). Median values of markers for CCD, PD and RD were compared by nonparametric Kruskal-Wallis test. Wilcoxon test was used to compare markers concentration before and after treatment for CCD and UCD groups. The distribution of the treatment outcome was compared with Fisher exact test. The efficacy of CYFRA 21-1 as a marker for detect persistent tumour was evaluated with the aid of receiver operating characteristics (ROC) curve, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Locoregional control (LRC) was defined as lack of locoregional failure or locoregional recurrence. Overall survival (OS) was defined as the time from the end of treatment to death or last follow-up if they remained alive. Survival rates were calculated by the Kaplan–Meier method. Differences between survival rates were assessed by the log-rank statistic.

A multivariate Cox regression analysis included only variables that appeared prognostic in the univariate analysis and backward stepwise regression was used for optimization. P values smaller than 0.05 were considered significant. Submit your manuscript electronically for review.

III. Results

A. Correlation between CYFRA 21-1_1 and T, N, age and sex.

CYFRA 21-1_1 was significantly higher in patients with T3/T4 (p=0.04) or N+ (p=0.03) (Table 1). There was no correlation between CYFRA 21-1_1 and age or sex.

Table 1. Correlation between CYFRA 21-1_1 and T,N, age and gender

parameter	patients no.	CYFRA 21-1_1 ng/ml		
		median	range	p*
T stage				
T 1,2	48	1.77	0.73-5.31	0.04
T 3,4	45	2.30	0.78-10.97	
N stage				
N 0	48	1.87	0.73-4.35	0.03
N +	45	2.30	0.78-10.97	
age				
< 60	51	2.14	0.76-8.15	0.80
> 60	42	1.87	0.73-10.97	
sex				
male	74	1.95	0.73-10.97	0.38
female	19	2.19	1.02-6.2	

* *Mann-Whitney test*

B. Treatment results.

The median follow-up was 36 months (range: 6 - 70 months). CCD was observed in 58 (62%), UCD in 35 (38%) patients. Among UCD there were 31 patients (33% of all) with PD and 4 patients (5% of all) with RD. Local failure appeared as a persistent primary tumor (PPT) was presented in 27 patients, 19 of them had isolated PPT and 8 had PPT concomitant with persistent nodal tumor (PNT). PNT only was found in 4 patients. Recurrent primary tumor (RPT) was found in 3 patients and developed in the median time of 10 months after RT (range: 8-34 months), 1 RPT concomitant with recurrent nodal tumor (RNT) was found 16 months after RT. Distant metastases (DM) developed in the median time of 17 months (range: 6-40 months) and were found in 10 patients and in 4 of them it was the only reason of UCD. In two patients secondary primary tumor was diagnosed at 42 and 46 month after treatment. At the time of follow-up analysis 37 patients (40%) died.

C. Variation of CYFRA-21-1 in CCD and UCD groups

The ranges of CYFRA 21-1_1 and CYFRA 21-1_2 were: 0.73-10.97 ng/ml (mean 2.45 ng/ml, median 1.98 ng/ml) and 0.61-10.81 ng/ml (mean 2.21 ng/ml, median 2.00 ng/ml), respectively. Generally, CYFRA 21-1 during treatment decreased from median 2.04 ng/ml to median 1.65 ng/ml in CCD patients, but increased from median 1.91 ng/ml to median 2.25 ng/ml in UCD patients (Fig.1). This resulted in significantly higher CYFRA 21-1_2 for UCD comparing to CCD patients (median for CCD and UCD was 1.65 ng/m and 2.25 ng/ml, respectively, p=0.0011). CYFRA 21-1_2 was significantly higher in patients with PD. They had higher concentration of CYFRA 21-1_2 comparing to the patients with RD (Table 2). CYFRA 21-1_2 in patients with RD and in patients with CCD was similar. Only 5 patients in PD subgroup had CYFRA 21-1_2 concentration lower than 2.0 ng/ml (Table 3). Of interest, 4 patients from this group had no elevated CYFRA 21-1 also before treatment. To estimate CYFRA 21-1 as an instant prognosticator of treatment failure a ROC curve was used. The analysis was performed in comparison of patients with CCD and PD. Twenty six of 31 patients with PD had a CYFRA 21-1_2 of at least 2.00 ng/ml. This corresponds with sensitivity of 84%. In 58 patients with CCD, 39 had CYFRA 21-1_2 less than 2.00 ng/ml. Thus, the specificity was 67% with 57% of PPV and 88% of NPV (Table 3). Accuracy is measured by the area under the ROC curve (AUC). An area of 1 represents a perfect test, an area of 0.5 showed a lack of accuracy of marker. CYFRA 21-1_2 as a prognostic marker is shown by the AUC of 0.764 of the ROC curve with patients CCD and PD giving good discriminative ability *(Fig. 2)*. Sensitivity and specificity were calculated based on the median value of CYFRA 21-1_2 (2.00 ng/ml).

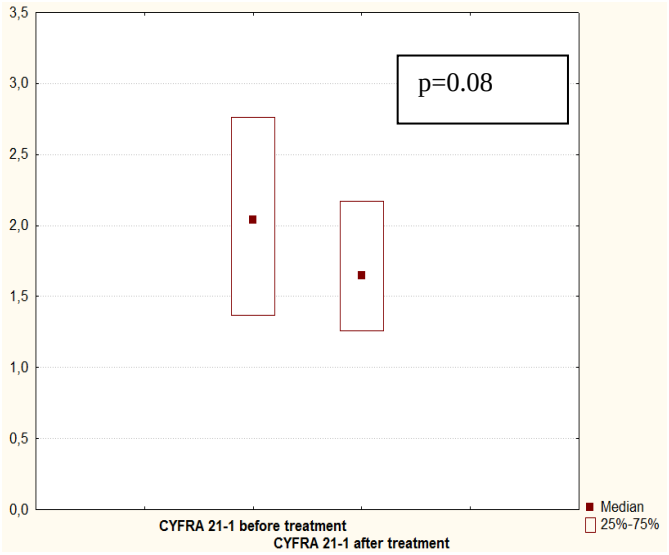

Fig. 1. A. The difference of CYFRA 21-1_1 and CYFRA 21-1_2 in CCD group.

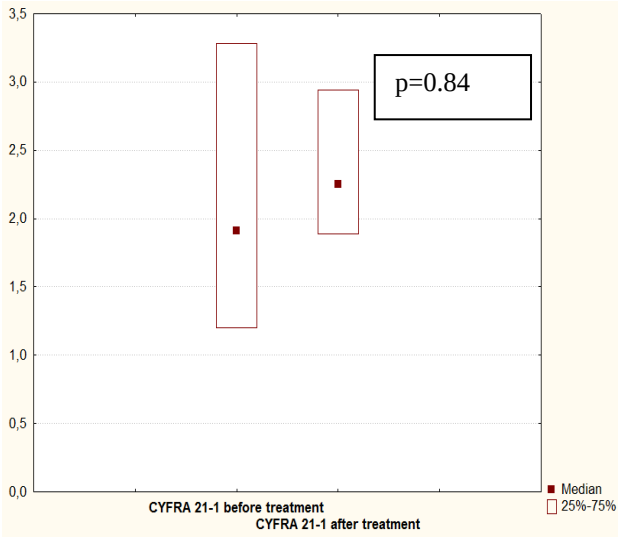

Fig. 1.B. The difference of CYFRA 21-1_1 and CYFRA 21-1_2 in UCD group.

Table 2. CYFRA 21-1_2 levels according treatment results

variable	median CYFRA 21-1_2 ng/ml	p*	p**
CCD	1.65		
PD	2.33	0.0001	
RD	1.27	0.6276	0.0105

** Kruskal-Wallis test*
p comparison between: CCD and PD; CCD and RD*
*p** comparison between PD and RD*

Table 3. Dependence of treatment outcome on median CYFRA 21-1_2

variable	CYFRA 21-1_2 <2.00 ng/ml	CYFRA 21-1_2 ≥2.00 ng/ml	p
CCD	39	19	0,00004
PD	5	26	

** Fisher test*

D. Prognostic value of CYFRA 21-1 for LRC.

In univariate analysis higher rate of LRC (p=0.00002) was found for patients with lower than 2.0 ng/ml CYFRA 21-1_2 *(Fig. 3).* Results were confirmed in multivariate analysis (Table 4) where patients with CYFRA 21-1_2 equal or above 2.00 ng/ml had 3.41 higher risk of locoregional failure (p=0.0003), what corresponded with 40% difference in 3-year LRC rate (82% vs 42%).

E. Prognostic value of CYFRA 21-1 for OS.

In univariate analysis higher rate of OS (p=0.004) was found for patients with lower than 2.0 ng/ml CYFRA 21-1_2 (Fig. 4). This was confirmed in multivariate analysis (Table 5) where patients with CYFRA 21-1_2 equal or above 2.00 ng/ml had 2.5 times higher risk of death (p=0.01), what corresponded with 17% difference in 3-year OS rate (57% vs 40%

Table 4. Factors influencing LRC ratio. Results of multivariate analysis

LRC	parameter	groups	p	RR	95% CI
	T	T3 / T4 T1 / T2	0.0105	2.4984	1.2386 – 5.0395
	CYFRA 21-1_2	≥2.00 ng/ml <2.00 ng/ml	0.0003	4.1111	1.8939 – 8.9240

** Results of Cox model prognosis analysis (RR – Relative Risk, 95% CI – 95% Confidence Interval)*

Table 5. Factors influencing OS ratio. Results of multivariate analysis

OS	parameter	groups	p	RR	95% CI
	T	T3 / T4 T1 / T2	0.022	2.205	1.121 - 4.337
	CYFRA 21-1_2	≥2.00 ng/ml <2.00 ng/ml	0.010	2.471	1.237 – 4.935

** Results of Cox model prognosis analysis (RR – Relative Risk, 95% CI – 95% Confidence Interval)*

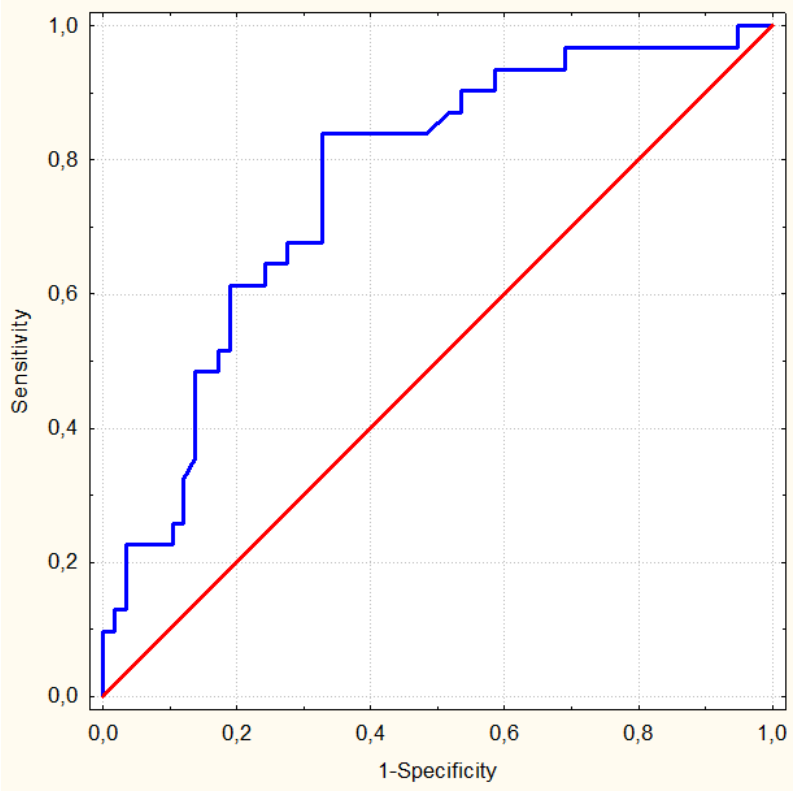

Fig. 2. Receiver operating characteristic (ROC) curve for CYFRA 21-1_2 to detect patients with persistent disease (PD). Area under curve (AUC) =0.76 (95% CI from 0.662 to 0.867)

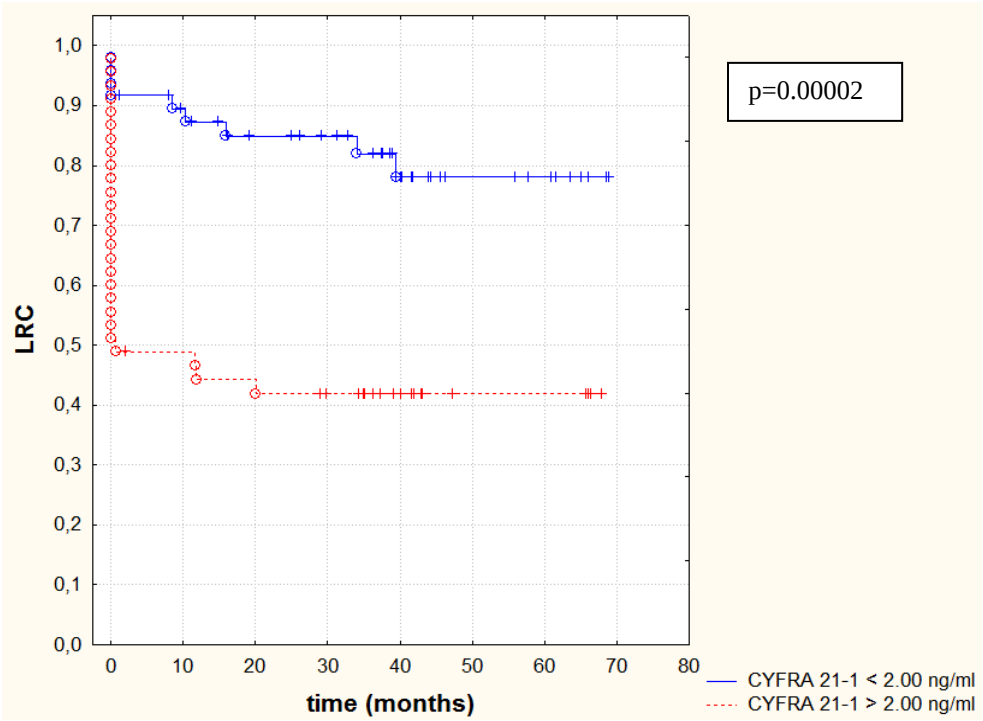

Fig. 3. LRC according to CYFRA 21-1₂

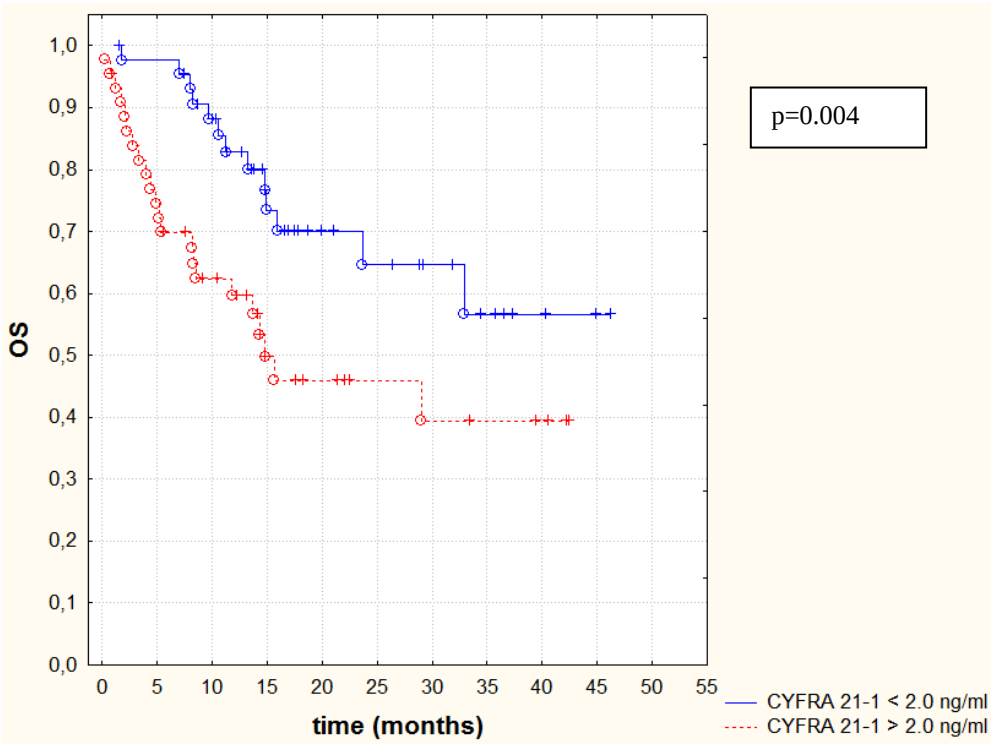

Fig. 4. OS according to CYFRA 21-1₂

IV. Discussion

Although many serum tumor markers have been evaluated for their clinical utility in HNC patients, their clinical benefit is unproven yet due to the low sensitivity. Among others also CYFRA 21-1 has been tested as a prognosticator of HNC treatment. A few studies have shown that initial (pretreatment) CYFRA 21-1 level is related to the stage of HNC being also highly sensitive and specific marker of locoregional recurrence or metastatic disease after treatment correlating with survival.

There is an opinion that CYFRA 21-1 is released into the bloodstream probably because of cell death, and therefore its level correlates very well with spontaneous, massive cellular necrosis what is typical for malignant disorders in advanced stage [15]. There are some data indicating that use of this marker as a diagnostic tool for patients with HNC is restricted because increase in CYFRA 21-1 levels in the serum is based on tumor burden rather than the presence of the disease [16].

Significant correlation between CYFRA 21-1_1 with tumor stage and lymph node involvement reported in this study is in concordance with some authors [7,8,12,16], yet others did not find such association [10,11]. Similarly to us, Banal et al. found that CYFRA 21-1 was correlated with tumor size after grouping T1/T2 vs T3/T4 [12]. These data suggest that CYFRA 21-1 may be considered as a marker of the tumor mass. Generally, CYFRA 21-1 decreases significantly after cytotoxic treatment of HNC. Some studies show that CYFRA 21-1 levels drop to below cut-off levels 24 hours after successful operation [15,16,17;18,]. On the other hand, Deng et al. have reported that HNC patients, who show local recurrence or distant metastasis within 1–6 months after surgery, had elevated CYFRA 21-1 already after treatment (such rapid cancer relapse after surgery may reflect uncomplete cytoreductive character of those operation) [8].

We have found that patients with LXC and HPC who were successful cured (CCD) by radiation with or without chemotherapy presented significantly lower levels of this marker immediately after RT than the patients who failed the treatment as a residual disease (Table 2). In addition, CCD patients had a significant decrease of the CYFRA 21-1 after RT, while for UCD patients CYFRA 21-1 did not decreased after RT *(Fig. 1).*

That lack of CYFRA 21-1 decrease after RT suggested a presence of persistent cancer cells which may turn into clinically detectable recurrence soon. Similar correlation was found by Alkotyfan et al. for patients with oropharyhngeal cancer where in cases of local tumor recurrence or distant metastasis a higher concentration of CYFRA 21-1 was measured than at the time of initial diagnosis. The median value for CYFRA 21-1 at the time of diagnosis and at the last measured value were 1.95 ng/ml and 4.6 ng/ml respectively. The median value for CYFRA 21-1 for those who were cured was approximately the same during follow-up and at the time of initial diagnosis (1.1 ng/ml) [11]. Al-Shagahin et al. found that for patients with LXC and HPC cancer in the group with locally residual disease and/or distant metastasis median values for CYFRA 21-1 at the time of diagnosis were 1.4 ng/ml, while that for the follow-up was 2.7 ng/ml and increased to 7.68 ng/ml for the last observed value. In both studies estimations of CYFRA 21-1 were performed 6-8 weeks after RT what was undoubtedly more close to the clinical diagnosis of residual disease [10].

Doweck et al. followed CYFRA 21-1 together with clinical status in 38 patients with various HNC origins for over 24 months (±10 months) Among 12 patients (32%), CYFRA 21-1 levels were elevated before and concomitantly with recurrent disease in 50% and 33% of patients, respectively. The time between elevation of the marker and diagnosis of clinical recurrence ranged from 0.7 to 7.5 months (mean: 4.1 month). Additionally the authors pointed out, that in several patients treated with RT who exhibited no clinical evidence of the cancer fluctuation of the CYFRA 21-1 levels was noted. [15]. Similar observation was done in our group of patients where 80% from patients with progressive disease who presented finally CYFRA 21-1 lower than 2 ng/ml had no elevated CYFRA 21-1 also before treatment. It may suggest that some tumors may not secrete CYFRA 21-1 at all.

Unlike our group, Doweck et al. based on patients with tumors of various HNC sites, histopathology and treatment modality. Author suggested that elevation of CYFRA 21-1 immediately after RT may be due to lasting process of tumor disintegration, not due to residual tumor. Our results shows however, that CYFRA 21-1 estimation at the end RT may reflect residual disease and indicate patients with high risk of failure before other diagnostic methods confirm the poor diagnosis.

It seems that an abrupt increase of CYFRA 21-1 during follow-up indicates disease progression in the individual patient, independently from the cut-off value. Maass et al. found that if CYFRA 21-1 increased above the threshold of 3.3 ng/ml and staging procedures were performed, tumor growth was found in 70% of such patients including distant metastases or local and neck recurrences [13]. Hoffmann-Fazel et al. reported that among those with distant metastases almost 90% had CYFRA 21-1 higher than 3.3 ng/ml [14].

Although a few studies have shown CYFRA 21-1 to be highly sensitive and specific markers, providing a valuable prognostic indicator for the detection of recurrent disease, not much data is available to test CYFRA 21-1 as an early marker of residual tumor. For detection of recurrent disease, most of the authors evaluated CYFRA 21-1 each 2-8 month after treatment (surgery or RT) [7,10,11,12] while we concentrated on CYFRA 21-1 evaluation in the day of last fraction of RT. Doweck et al. who follow up patients each month what seems to be most similar to our procedure, excluded from analysis those with progressive disease [15].

We believe that elevated level of CYFRA 21-1 at the end of RT may be of prognostic value indicating patients with high risk of failure due to residual disease. No clinically applicable markers are in practical use to diagnose such patients and to help differentiate between residual tumor mass from RT related changes in normal tissue. Repetitive MR or CT imagining, which are routinely performed, not allow for a reliable distinction between cancer and oedema, irradiation fibrosis or necrosis in most cases when residual mass remains shortly after RT [19]. The metabolic-anatomic information from FDG-PET/CT provides the most accurate

assessment of treatment response, but lower spatial resolution and problems with discriminating neoplastic processes from inflammation and tissue reaction make the interpretation of PET images confounding, especially in the early post-RT phase [20].

The clinical usefulness of CYFRA 21-1 as a marker of detection of persistent disease was confirmed by the AUC (0.733) of ROC curve revealing high sensitivity and specificity *(Fig. 2).*

Ceruse et al. assume that distant metastases must be carefully looked for in patients with high initial level of CYFRA 21-1 [7]. It has been reported previously that patients with high initial CYFRA 21-1 present significantly lower OS and DFS independently of other known prognostic factors [7]. To the best of our knowledge, our results showed for the first time that CYFRA 21-1 after RT is also significant prognostic value and its elevation above 2.00 ng/ml decreases OS ratio almost 2.5 times independently from tumor stage.

The study showed that CYFRA 21-1 measurement in blood provides a simple, non-invasive test for patients with laryngeal or hypopharyngeal cancer for high risk of failure due to residual disease.

V. CONCLUSION

CYFRA 21-1 assessed at the end of the RT or ChRT seems to be a prognostic marker for tumor response. Persistent, uncured tumor is very probable in patients with laryngeal or hypopharyngeal cancer with CYFRA 21-1 $\geq$ 2 ng/ml instantly after treatment.

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