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Original Scientific Paper

IS THERE A PROGNOSTIC ROLE OF FOCAL ADHESION KINASE AND CD8 IN SQUAMOUS CELL HEAD AND NECK CANCER TREATED WITH RADIOTHERAPY?

Vesna Bišof[1,2,3], Antonija Jakovčević[3,4], Anita Škrtić[3,5], Zoran Rakušić[1,3], Drago Prgomet[3,6] and Ivica Rak[3,7]

[1]Department of Oncology, Zagreb University Hospital Center, Zagreb, Croatia;
[2]School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia;
[3]School of Medicine, University of Zagreb, Zagreb, Croatia;
[4]Department of Pathology and Cytology, Zagreb University Hospital Center, Zagreb, Croatia;
[5]Department of Pathology and Cytology, Merkur University Hospital, Zagreb, Croatia;
[6]Department of Otorhinolaryngology and Head and Neck Surgery, Zagreb University Hospital Center, Zagreb, Croatia;
[7]Department of Otorhinolaryngology, Merkur University Hospital, Zagreb, Croatia

SUMMARY – The prevalence of relapses in advanced squamous cell head and neck cancer (SCHNC) is significant, and so is treatment morbidity. There is persistent need for reliable biomarkers in order to better personalize treatment. The purpose of the present study was to evaluate prognostic significance of focal adhesion kinase (FAK) and CD8 expression in human papillomavirus (HPV) negative SCHNC treated with radiotherapy. FAK and CD8 expression was evaluated by immunohistochemical staining. A total of 62 tissue samples were assessed. High expression of FAK was determined in 37.1% and high expression of CD8 in 25.8% of study patients. Patients with high expression of FAK had significantly more relapses than patients with low FAK expression (p=0.04). FAK and CD8 expression had no significant impact on overall survival (OS) (p=0.44 and p=0.48, respectively) and relapse free survival (RFS) (p=0.21 and p=0.31, respectively). However, patients with high expression of FAK and low expression of CD8 had the worst 5-year OS (38.7%) and 5-year RFS (44.3%). Patients with low expression of FAK had significantly less relapses. The prognostic role of FAK and CD8 expression in SCHNC patients treated with radiotherapy was not proven.

Key words: *Head and neck carcinoma; Focal adhesion kinase; CD8; Biomarker; Radiotherapy*

Introduction

Worldwide, head and neck cancer (HNC) accounts for more than 650,000 cases and 330,000 deaths annually[1]. In Europe according to the RARECARE project, all HNCs are considered rare[2]. The majority of them are squamous cell carcinomas with about 50% in advanced stage at the time of diagnosis. Radiotherapy plays an important role in the treatment, either applied postoperatively or as primary treatment with or without concomitant chemotherapy. However, locoregional

Correspondence to: *Vesna Bišof, MD, PhD*, Department of Oncology, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia
E-mail: vbisof@gmail.com

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recurrence occurs in up to 50% of patients after radiotherapy for advanced disease, and morbidity of the treatment is substantial[3-5]. Despite numerous studies conducted so far, only human papillomavirus (HPV) has been shown to be a significant biomarker of outcome in oropharyngeal cancers while other tumor sites of squamous cell HNC still lack such a biomarker[6]. As far as HPV negative oropharyngeal cancers and other squamous cell HNCs share similar etiologic, biologic and prognostic features, they are often explored together. Furthermore, it has recently been shown that overall survival (OS) for HNCs continues to decrease 5 years post-treatment even after stratification by p16 and smoking status[7]. Therefore, identification of reliable prognostic factors and targets for new therapies is important for better treatment tailoring.

Focal adhesion kinase (FAK) is a non-receptor protein encoded by the protein tyrosine kinase 2 (*PTK2*) gene. It is located in cellular structures called focal adhesions or sites of integrin clustering[8]. It has been shown that FAK can regulate cell proliferation, cell survival, cell migration, invasion, and epithelial-to-mesenchymal transition[8-10]. Besides, FAK is a regulator of endothelial cells, macrophage and fibroblast signaling in the tumor environment[9,10]. It has been shown that FAK can shuttle between the cytoplasm and the nucleus, and that it has a very important position in cell signal transduction[11]. Prognostic value of FAK has been studied in many solid tumors[12-15]. Results of a meta-analysis suggest worse OS in patients with high FAK expression in solid carcinomas but prognosis varies according to the cancer type[16]. Patients with FAK positive hypopharyngeal cancers treated with surgery displayed significantly worse disease specific survival (DSS) in the study by Omura *et al.*[17], whereas patients with laryngeal cancers and low FAK expression had better OS[18]. On the contrary, in the study by Canel *et al.*[19], although patients with supraglottic laryngeal carcinoma and high levels of FAK expression had poorer DSS, it did not reach statistical significance. Patients with oral carcinoma and low FAK expression had better OS in one study[20], whereas the results of another study were opposite[21]. Furthermore, several studies identified FAK as a biomarker of radioresistance in HNC cell lines[22,23]. Despite numerous studies performed in recent decades, the mechanisms underlying the activation and overexpression of FAK in HNC remain unclarified[24].

Cluster of differentiation 8 (CD8) is a transmembrane glycoprotein expressed mainly on the surface of cytotoxic T lymphocytes. Previous studies have shown that high expression of CD8 was associated with better prognosis in HNCs and a higher number of CD8 positive cells predicted better response to definitive chemoradiotherapy[25-29].

It has been shown that FAK family proteins integrate receptor-mediated signals that influence actin cytoskeletal rearrangement and effector T cell responses[30]. Besides, in the preclinical study, treatment of tumors with a FAK inhibitor resulted in an increase of CD8 positive T cells[31].

The relationship between FAK and CD8 expression in squamous cell HNCs is unknown as far as we know. As the results of prognostic value of FAK expression in HNCs are inconsistent, and taking into account its potential role as a biomarker of radioresistance, the purpose of the present study was to evaluate the impact of FAK and CD8 expression on OS and relapse free survival (RFS) in patients with squamous cell HNCs treated with radiotherapy. Considering that the treatment modality could potentially influence the outcome of treatment, we distinguished primary (PR) and adjuvant radiotherapy (AR) group. Therefore, the hypothesis of the present study was that high FAK and/or low CD8 expression pattern in HNC patients would be related to poorer OS and RFS.

Patients and Methods

Patients

Sixty-two patients with histologically confirmed HPV negative squamous cell HNCs treated with curative radiotherapy between 2011 and 2016 were retrospectively enrolled in the study. The following data were obtained from medical records: gender, age at the onset of the disease, stage according to TNM classification[32], type of therapy (postoperative radiotherapy, postoperative chemoradiotherapy, primary radiotherapy, primary chemoradiotherapy and primary radiotherapy with cetuximab). The indications for postoperative chemoradiotherapy were extracapsular spread and/or positive resection margins and/or pT4 stage and ≥4 positive lymph nodes. Primary chemoradiotherapy was performed in patients with locoregionally advanced disease

according to ESMO guidelines for a particular tumor localization[33,34]. High dose cisplatin (100 mg/m^2) was used concomitantly with radiotherapy, whereas cetuximab was used according to the study by Bonner *et al.*[3] after reimbursement 2014 in case of low value of creatinine clearance (≤50 mL/min) and/or significant comorbidity.

Patients with oropharyngeal cancer were treated with intensity modulated radiotherapy with simultaneous boost (IMRT-SIB), whereas in other tumor locations 3D-conformal radiotherapy (3D CRT) was applied. The dose to the gross tumor volume and positive lymph nodes in case of primary radiotherapy was 70 Gy in 35 fractions, 60 Gy for intermediate risk volume and 54 Gy for low risk volume. If IMRT-SIB was performed, dosages were as follows: 66 Gy in 30 fractions to the gross tumor volume and positive lymph nodes, 60 Gy in 30 fractions for intermediate risk volume, and 54 Gy in 30 fractions for low risk volume. The total dose to the high risk volume in the postoperative setting was 64-66 Gy (standard fractionation), 60 Gy to the intermediate risk volume, and 54 Gy to the low risk volume. The median follow-up period was 5.69 years. The study was done in accordance with the Helsinki Declaration of 1975, revised in 1983, and was approved by the Ethics Committee of the Zagreb University Hospital Center No. 02/21 AG.

Immunohistochemistry

The paraffin-embedded carcinoma tissue samples were fixed for 24 h in 10% buffered formalin immediately after resection, dehydrated in ethanol and embedded in paraffin, cut into 5 μm thin sections, and stained with a standard method (hematoxylin-eosin, H&E) for light microscope analysis. Histopathologically representative regions of tumor tissue and surrounding non-tumor tissue were defined and marked on H&E slides. For additional immunohistochemical staining, 3-4 μm thick cuts were used. The sections were deparaffinized with standard xylene and hydrated through graded alcohol series. The mouse monoclonal antibody clone OTI4A8 (formerly 4A8) anti-PTK2/FAK (catalog number TA506161, OriGene Technologies Inc., Rockville, USA) was used (1:150 dilution). Tissue sections were counterstained with hematoxylin. Positive control was lung carcinoma tissue according to the manufacturer. Negative controls with an omission of the antiserum from the primary incubation were also included. Immunostained samples were randomly reviewed and scored by two of the authors (A. J. and A. Š.). Immunostaining was scored based on the percentage of stained cells into 4 categories as follows: score 0 (0%), score 1 (1%-33%), score 2 (34%-66%), and score 3 (>66%), as previously described[20]. FAK positive immunohistochemical staining was observed in all analyzed tumor specimens with heterogeneous expression. Because of that, scores 1 and 2 were labelled as low expression, and score 3 as high expression.

Immunostaining for CD8 was performed with FLEX monoclonal mouse anti-human CD8, clone C8/144B (Dako Denmark A/S, code IR623). Tissue sections were counterstained with hematoxylin. Positive control was normal tissue of tonsil or spleen, while negative control was FLEX negative control mouse (code IR750). Scoring for tumor infiltrating lymphocytes (TILs) expression was conducted semiquantitatively through measuring the density of CD8 cells as previously described[25,26]. The median value of the total score was used as the cut-off point for separating low and high CD8 expression[25,26]. Median value of the total score of CD8 was 6.

Statistical analysis

In case of categorical data, comparison of baseline characteristics between the groups was tested with Pearson's χ^2 or Fisher exact test as appropriate, whereas in case of continuous data Wilcoxon-Mann-Whitney test was applied. The OS and RFS were estimated by the Kaplan-Meier method, and differences were assessed by the log-rank test. Both univariate and multivariate analyses were performed using the Cox proportional hazards model. All reported p values were two-sided, and $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed using the SAS statistical software.

Results

Twenty-three (37.1%) cases showed high FAK expression (i.e., score 3) while high CD8 positive staining was observed in 16 (25.8%) tumor samples. There were no statistically significant differences in the baseline clinical characteristics between the low and

Table 1. Correlations of focal adhesion kinase expression and clinicopathological characteristics of patients treated with radiotherapy

Characteristic		Low FAK / n=39 (62.90%)	High FAK / n=23 (37.10%)	p value
Age (yrs)	≤65 >65	24 (61.54) 15 (38.46)	16 (69.57) 7 (30.43)	0.57
Gender	Male Female	30 (76.92) 9 (23.08)	22 (95.65) 1 (4.35)	0.08
T stage	1-2 3-4	18 (46.15) 21 (53.85)	8 (34.78) 15 (65.22)	0.43
N stage	0 N+	12 (30.77) 27 (69.23)	7 (30.43) 16 (69.57)	1.00
Stage	1-2 3-4	6 (15.38) 33 (84.62)	4 (17.39) 19 (82.61)	1.00
Grade	1 2 3	5 (14.71) 19 (55.88) 10 (29.41)	4 (17.39) 13 (56.52) 6 (26.09)	0.94
Tumor site	Larynx Hypopharynx Oropharynx	23 (58.97) 13 (33.33) 3 (7.70)	11 (47.83) 8 (34.78) 4 (17.39)	0.46
Relapse	No Yes	30 (76.92) 9 (23.08)	12 (52.17) 11 (47.83)	**0.04**
CD8	Low High	27 (69.23) 12 (30.77)	19 (82.61) 4 (17.39)	0.37
Treatment modality	Primary RT Adjuvant RT	13 (33.33) 26 (66.67)	8 (34.78) 15 (65.22)	1.00

FAK = focal adhesion kinase; n = number; RT = radiotherapy

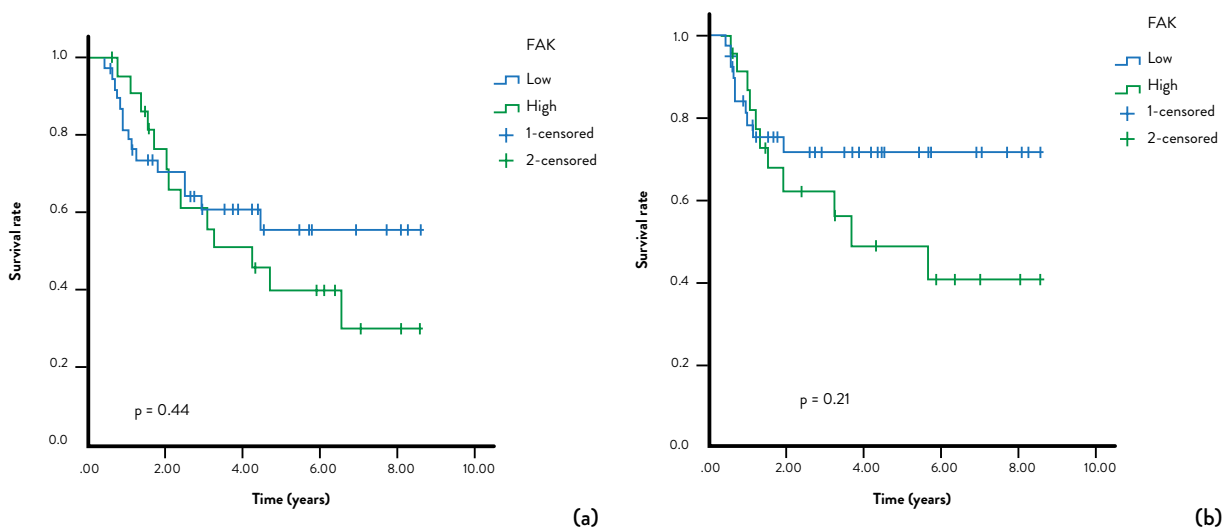

Fig. 1. Survival estimates according to expression of focal adhesion kinase: (a) overall survival;(b) relapse free survival.

Table 2. Correlations of CD8 expression and clinicopathological characteristics of patients treated with radiotherapy

	Characteristic	Low CD8 / n=46 (74.19%)	High CD8 / n=16 (25.81%)	p value
Age (yrs)	≤65 >65	29 (63.04) 17 (36.96)	11 (68.75) 5 (31.25)	0.75
Gender	Male Female	28 (82.61) 18 (17.39)	14 (87.50) 2 (12.50)	1.00
T stage	1-2 3-4	16 (34.78) 30 (65.22)	10 (62.50) 6 (37.50)	0.08
N stage	0 N+	17 (36.96) 29 (63.04)	2 (12.50) 14 (87.50)	0.11
Stage	1-2 3-4	8 (17.39) 38 (82.61)	2 (12.50) 14 (87.50)	1.00
Grade	1 2 3	7 (16.28) 24 (55.81) 12 (27.91)	2 (14.29) 8 (57.14) 4 (28.57)	0.98
Tumor site	Larynx Hypopharynx Oropharynx	23 (50.00) 18 (39.13) 5 (10.87)	11 (68.75) 3 (18.75) 2 (12.50)	0.33
Relapse	No Yes	30 (65.22) 16 (34.78)	12 (75.00) 4 (25.00)	0.55
FAK	Low High	27 (58.70) 19 (41.30)	12 (75.00) 4 (25.00)	0.34
Treatment modality	Primary RT Adjuvant RT	18 (39.13) 28 (60.87)	3 (18.75) 13 (81.25)	0.22

FAK = focal adhesion kinase; n = number; RT = radiotherapy

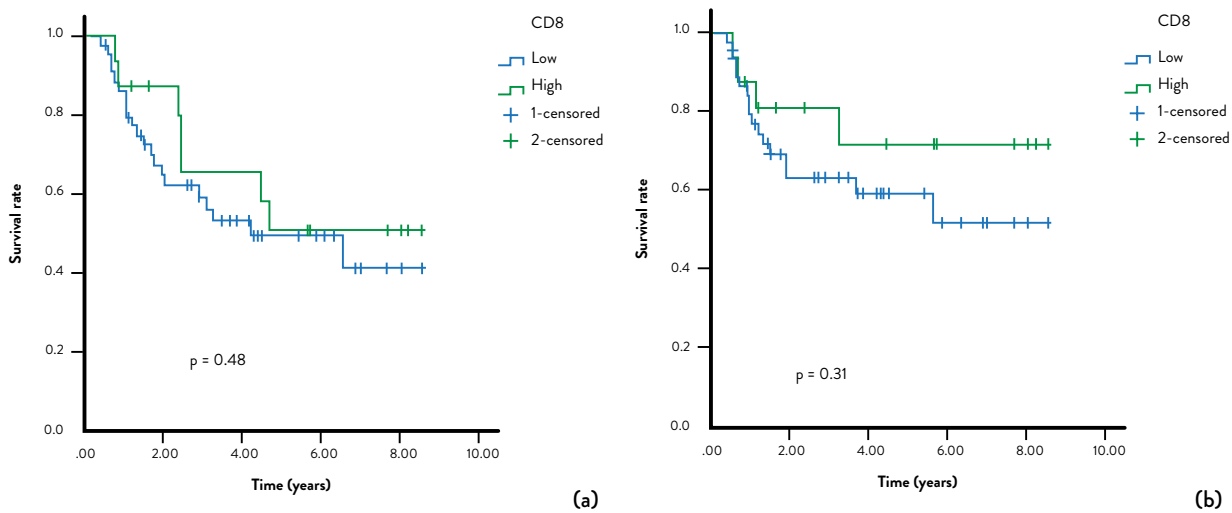

Fig. 2. Survival estimates according to expression of CD8: (a) overall survival; (b) relapse free survival.

high expression of FAK and CD8 groups (Tables 1 and 2), the only exception being the relation of FAK and relapse of the disease (Table 1). Patients with high FAK expression had twice as many relapses as those with low FAK expression (48% *vs*. 23%). There were 21 relapses in the whole patient cohort, i.e., 8 locoregional, 9 distant, and 4 both locoregional and distant. The median age at diagnosis of our 62 patients was 64 (range 35-85) years. The majority of patients (83.9%) had advanced disease (stage 3 and 4).

According to expectations, the distribution of low and high expression of FAK and CD8 did not differ between the two treatment groups. However, 57% of patients treated with PRT and only 24% of patients treated with ART were older than 65 years (p=0.034). Furthermore, grade 1 tumors and early stages of disease (T1-T2) were more frequent in the PRT group than in the ART group (p=0.007 and p=0.024, respectively). Almost all oropharyngeal cancers were treated with PRT (6 out of 7). Among the 41 patients treated with ART, there were 2 positive resection margins, 7 close resection margins (<5 mm), and 11 patients with pathologic extracapsular spreading. Concomitant chemotherapy was applied in 10 (47.61%) patients treated with PRT and 14 (34.15%) patients treated with ART. Only 3 patients from the PRT group received concomitant cetuximab. Furthermore, only one patient treated with PRT had subsequently to undergo surgery. Although the 5-year OS was 55.7% in the ART group and 32% in the PRT group, this difference was not statistically significant (p=0.14).

Kaplan-Meier survival analysis showed that FAK expression had no impact on OS and RFS (Fig. 1 a, b), although there was a tendency toward better OS and RFS in patients with low expression of FAK. The difference in CD8 expression had no significant impact on OS and RFS (Fig. 2 a, b). The cases with high expression of FAK and low expression of CD8 had

Table 3. Univariate analysis (Cox's proportional hazards model) of OS and RFS prognostic factors in head and neck cancer patients treated with radiotherapy

Variable		Univariate analysis					
		OS			RFS		
		HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age		1.08	1.03-1.13	**0.002**	1.04	0.99-1.10	0.11
Gender	Male Female	Ref. 1.60	0.61-4.22	0.342	1.07	0.32-3.65	0.910
Treatment modality	PR AR	Ref. 0.57	0.26-1.22	0.144	0.99	0.38-2.58	0.986
T stage	T1-T2 T3-T4	Ref. 1.26	0.87-1.84	0.223	1.56	0.98-2.47	0.059
N stage	N0 N+	Ref. 1.24	0.80-1.92	0.333	1.52	0.88-2.61	0.131
Grade	1 2-3	Ref. 1.80	0.54-6.01	0.342	1.19	0.35-4.10	0.781
FAK	Low High	Ref. 1.34	0.64-2.82	0.441	1.72	0.73-4.05	0.215
CD8	Low High	Ref. 0.73	0.31-1.73	0.478	0.57	0.19-1.71	0.318
Others	FAK high CD8 low	Ref. 1.54	0.72-3.29	0.267	2.11	0.89-4.98	0.088
Tumor site	Others Larynx	Ref. 0.41	0.19-0.89	**0.024**	0.32	0.13-0.81	**0.016**

FAK = focal adhesion kinase; OS = overall survival; RFS = relapse free survival; HR = hazard ratio; CI = confidence interval; PR = primary radiotherapy; AR = adjuvant radiotherapy; Ref. = reference

Table 4. Multivariate analysis (Cox's proportional hazards model) of OS and RFS prognostic factors in head and neck cancer patients treated with radiotherapy

	Variable	Multivariate analysis					
		OS			RFS		
		HR	95% CI	p value	HR	95% CI	p value
Age		1.06	1.00-1.13	**0.041**	1.04	0.98-1.11	0.226
Gender	Male Female	Ref. 1.77	0.53-5.96	0.357	1.28	0.31-5.22	0.735
Treatment modality	PR AR	Ref. 0.95	0.35-2.56	0.921	1.48	0.48-4.59	0.501
T stage	T1-T2 T3-T4	Ref. 1.60	0.62-4.10	0.332	1.88	0.58-6.15	0.294
N stage	N0 N+	Ref. 0.93	0.32-2.68	0.892	1.20	0.34-4.31	0.778
Grade	1 2-3	Ref. 1.57	0.44-5.59	0.488	0.71	0.19-0.70	0.617
FAK	Low High	Ref. 1.14	0.18-7.22	0.892	0.45	0.04-5.18	0.520
CD8	Low High	Ref. 1.19	0.28-5.16	0.815	2.05	0.33-12.53	0.439
Others	FAK high/CD8 low	Ref. 1.34	0.18-10.14	0.778	5.32	0.36-78.82	0.225
Tumor site	Others Larynx	Ref.0.37	0.14-0.98	**0.045**	0.33	0.10-1.02	0.055

FAK = focal adhesion kinase; OS = overall survival; RFS = relapse free survival; HR = hazard ratio; CI = confidence interval; PR = primary radiotherapy; AR =adjuvant radiotherapy; Ref. = reference

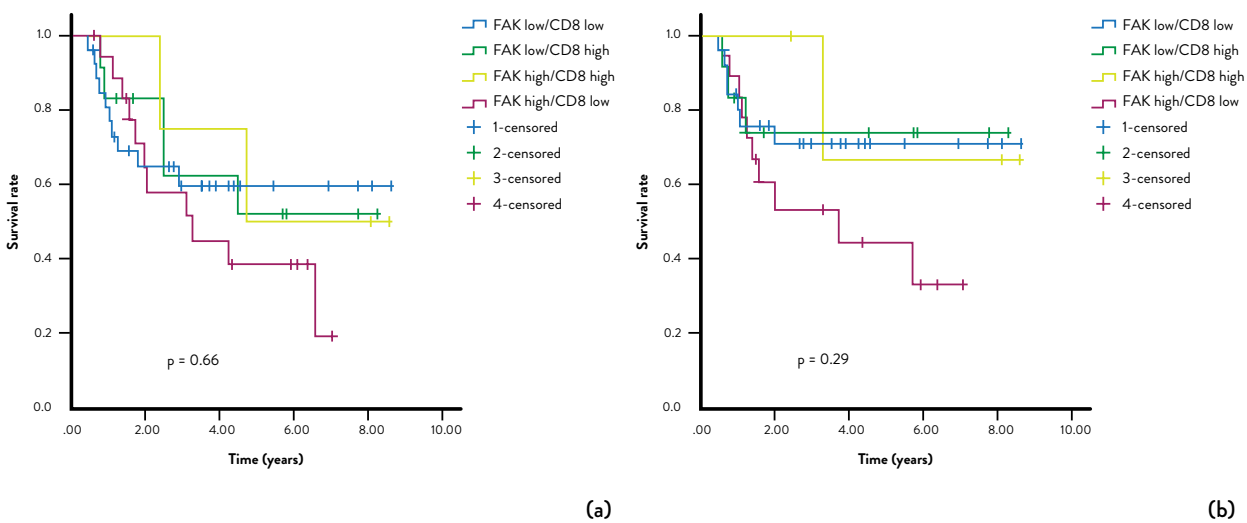

Fig. 3. Survival estimates according to expression of FAK and CD8:(a) overall survival; (b) relapse free survival.

the worst 5-year OS (38.7%) and 5-year RFS (44.3%) (Fig. 3 a, b).

However, age and tumor site were significant predictors of OS both on univariate and multivariate analyses (Tables 3 and 4). Furthermore, univariate analysis revealed that laryngeal localization was significantly related to a lower risk of relapse (Table 3).

Discussion

Radiotherapy is of a paramount importance along with surgery in the treatment of advanced HNCs but with substantial toxicity[4]. Therefore, investigations are underway to identify the potential biomarkers of response to radiotherapy, as well as prognostic biomarkers of treatment outcome[22,25,27,28]. Recently, it has been recognized that tumor microenvironment has important influence on treatment response and outcome besides complex tumor intracellular signaling pathways[6]. FAK is a multifunctional regulator of cell signaling within the tumor microenvironment and its expression in tumors has been linked to cancer growth, invasion and metastasis[9]. It has also a very important position in cell signal transduction[11]. On the other hand, CD8 positive cytotoxic T cell density has been shown as a potential biomarker in HNCs[26,27]. Besides, FAK in squamous cell carcinoma cells drives exhaustion of CD8 positive T cells[35]. Therefore, the aim of the present study was to evaluate the prognostic role of FAK and CD8 expression in patients with squamous cell HNCs treated with radiotherapy. We retrospectively analyzed patients with p16 negative carcinoma regardless of carcinoma localization due to their similar biology as previously shown[36].

It was previously demonstrated that median expression rate of FAK was 54% in human solid carcinomas[16]. In the present study, positive immunohistochemical staining was observed in all analyzed tumor specimens with high expression in 37.10% of tumor specimens. The percentage of positive FAK staining varied considerably among the studies not only for different tumor sites but also for different studied cohorts within the same tumor sites. Canel *et al.*[19] also found positive staining in all studied laryngeal tumor specimens with 62% of specimens having moderate to strong expression. Thus, 89.8% positive expression in oral carcinomas was reported in one study[20], 60% in another[36], and 66% in mobile tongue carcinomas[21]. Li *et al.*[18] showed 73% of positive laryngeal carcinomas and Omura *et al.*[17] 48% of positive hypopharyngeal carcinomas. In the present study, high CD8 expression was found in 25.81% of cases, which is consistent with the results reported by Balermpas *et al.*[25], although different results can be found[26,27].

The results of this study revealed no significant difference in baseline characteristics between the groups with high and low expression of FAK except for relapse of the disease. More relapses of the disease in the high FAK expression group are consistent with previously described function of FAK[9-11] and results of other studies[17,20,37]. However, in a retrospective study of HNC patients treated with primary radiation +/- chemotherapy, the expression of FAK was not associated with local control and distant metastasis[38]. Furthermore, results of the studies that report on the relationship between FAK expression and clinicopathological features have been somewhat inconsistent. It was found that FAK expression correlated with the stage[18,39], N status[18-20,39], grade[21], number of metastatic lymph nodes and incidence of distant metastases[17], T status and local recurrence[20].

In this study, no differences in clinicopathological features were found between the low and high CD8 expression groups. One possible explanation of this result is the inclusion of patients with more locoregionally advanced disease (83.9% stage 3-4, 69.4% N+ and 59.0% T3-4 stage) than in other studies[27,40]. It was shown that high CD8 expression was associated with oropharyngeal localization, early T stage and p16 status[26], no regional lymph node metastasis and no drinking[27], and N stage[26]. In the study by de Meulenaere *et al.*[40], CD8 expression correlated with age, early T stage, and lower grade.

The results of this study showed that patients with high expression of FAK and low expression of CD8 had the worst 5-year OS and RFS. It was previously shown that FAK regulated transcription of chemokines that drive recruitment of tumor-associated regulatory T cells, thereby creating a tumor suppressive microenvironment by inhibiting cytotoxic CD8+T cell activity[35].

The results of this study revealed a tendency towards better OS and RFS in the low FAK and high CD8 expression group. However, it should be noted that this relation was not statistically significant in

our study. Similar results were found in the study by Canel *et al.*[19]. They report poorer disease-specific survival (DSS) in patients with laryngeal carcinomas and high levels of FAK expression but it did not reach statistical significance. In addition, patients with decreased E-cadherin and increased FAK expression had reduced DSS[41]. Better OS was found in patients with negative FAK expression in laryngeal carcinoma[18] and oral carcinoma[20]. Omura *et al.*[17] found better DSS in patients with hypopharyngeal carcinomas and negative FAK expression. Although a meta-analysis revealed that FAK expression was associated with worse OS in squamous cell carcinoma, only two studies out of 30 studies in total conducted in head and neck carcinoma were included in analysis[16]. Theocharis *et al.*[21] did not find significant association of FAK expression with OS and disease-free survival in patients with mobile tongue squamous cell carcinomas. Therefore, results of the studies that investigated potential association between tumor FAK expression and treatment outcome are quite inconsistent. This can be partly explained by the fact that the mechanisms underlying the activation and overexpression of FAK in squamous cell HNC is still largely unclarified[24]. We do not know yet whether FAK plays a decisive role in the development and progression of squamous cell HNC or just performs in combination with other signaling pathways[24]. The limitations of this study which may have had an impact on the results were a low number of patients and the retrospective design.

In conclusion, according to the results of this study, FAK and CD8 expression did not prove significant relation with the survival outcome in patients with squamous cell HNC treated with radiotherapy although the tendency of such relation was clearly shown. The study also demonstrated the relation of high expression of FAK with more frequent relapses. The results obtained point to the need of further studies encompassing much larger samples of clinically homogeneous patients.

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Sažetak

IMAJU LI FOKALNA ADHEZIJSKA KINAZA I CD8 PROGNOSTIČKU ULOGU U PLANOCELULARNOM KARCINOMU GLAVE I VRATA LIJEČENOM RADIOTERAPIJOM?

V. Bišof, A. Jakovčević, A. Škrtić, Z. Rakušić, D. Prgomet i *I. Rak*

Učestalost recidiva kod uznapredovalog planocelularnog karcinoma glave i vrata (PKGV) je značajna kao i smrtnost nakon provedenog liječenja. Postoji stalna potreba za pouzdanim biomarkerima kako bi se bolje personaliziralo liječenje. Svrha ovog istraživanja bila je procijeniti prognostičko značenje ekspresije fokalne adhezijske kinaze (FAK) i CD8 u humanom papilomavirus negativnom PKGV liječenom radioterapijom. Ekspresija FAK-a i CD8 određena je imunohistokemijskim bojenjem. Ukupno su analizirana 62 uzorka tkiva. Visoka ekspresija FAK-a utvrđena je u 37,1% bolesnika, dok je visoka ekspresija CD8 utvrđena u 25,8% bolesnika. Bolesnici s visokom ekspresijom FAK-a imali su značajno više recidiva od bolesnika s niskom ekspresijom FAK-a (p=0,04). Ekspresija FAK-a i CD8 nije imala značajan utjecaj na ukupno preživljenje (OS) (p=0,44 i p=0,48) i preživljenje bez recidiva (RFS) (p=0,21 i p=0,31). Međutim, bolesnici s visokom ekspresijom FAK-a i niskom ekspresijom CD8 imali su najlošiji 5-godišnji OS (38,7%) i 5-godišnji RFS (44,3%). Bolesnici s niskom ekspresijom FAK-a imali su značajno manje recidiva. Ekspresija FAK-a i CD8 nije dokazala prognostičku ulogu u bolesnika s PKGV liječenima radioterapijom.

Ključne riječi: *Karcinom glave i vrata; Fokalna adhezijska kinaza; CD8; Biomarker; Radioterapija*