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Cancer testis antigen (PRAME) as an independent marker for survival in oral squamous cell carcinoma (OSCC)

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Abstract

Background: The objective was to assess the expression patterns of the cancer testis antigen PRAME, NY-ESO1, and SSX2 in oral squamous cell carcinoma (OSSC) and to correlate the expression with clinical and histopathological parameters including progression-free survival analysis.

Methods: The study variables of this retrospective cohort study ($n = 83$) included demographic data, histopathological data, and information on progression-free survival. PRAME expression patterns were rated based on immunohistochemistry on tissue microarrays (TMA). The survival rate was assessed by Kaplan–Meier method and Cox regression model. The primary predictor variable was defined as the expression of PRAME and the outcome variable was progression-free survival.

Results: Analysis of progression-free survival using Kaplan–Meier method showed that patients with positive expression of PRAME had lower probabilities of progression-free survival ($p < 0.001$). According to the Cox regression model, the level of PRAME expression had a considerable and significant independent influence on progression-free survival (positive PRAME expression increasing the hazards for a negative outcome by 285% in our sample; HR = 3.85, 95% CI: 1.45–10.2, $p = 0.007$). The expression of SSX2 ($n = 1$) and NY-ESO-1 ($n = 5$) in our samples was rare.

Conclusion: PRAME is expressed in OSCC and appears to be a suitable marker of progression-free survival, correlates with severe course, and may allow identification of high-risk patients with aggressive progression.

KEYWORDS
Cancer testis antigen, Immunohistochemistry, Oral squamous cell carcinoma, OSCC, PRAME

1 | INTRODUCTION

Oral squamous cell carcinoma (OSCC) has been reported to be the most common malignant neoplasm within the oral cavity and

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oropharyngeal region, frequent to metastasize to lymph nodes and of poor prognosis.[1,2] Assessment of a fitting therapeutical approach is commonly conducted by preoperative TNM staging according to the UICC together with imaging techniques such CT and MRI.[3] Due to high frequency of lymph node metastases of about 30% at the T1 stage, resection of the primary tumor as well as a cervical lymph node dissection is performed regardless of the T and/or N stage.[4] Nonetheless, occult nodal metastasis and disease recurrence resulting in poor overall survival remain a significant obstacle in patients' recovery. The TNM staging system, although widely used, does not consider the heterogeneity of OSCC and thus individual patient risk; therefore, prognosis-relevant biomarkers that better predict individual patient risk are needed.[5]

Cancer-testis antigens (CTA) are expressed in healthy germ cells and trophoblasts.[6] In healthy tissue, PRAME is only expressed in testis, ovaries, adrenals, and endometrium and was therefore categorized as cancer/testis antigen (CTA).[7] There have been several CTAs described as PRAME, MAGE, NY-ESO-1, SSX2, or BAGE. In different cancers, they are expressed in a divergent manner. After their identification in malignant melanoma, CTAs have been detected in carcinomas at various sites, including the lung, ovaries, urinary bladder, liver, and other organs. An important CTA with promising potential is the preferentially expressed antigen in melanoma (PRAME).[8]

First described in 1997, PRAME was shown to be overexpressed in melanoma cells indicating tumorigenic properties while also exhibiting a cytotoxic T-lymphocyte response.[7] To date, many other cancer entities of different tissue origin have been shown to express PRAME in high quantities such as in breast cancer, chronic leukemia, multiple myeloma, Hodgkin's lymphoma, non-small-cell lung carcinoma, ovarian cancer, in sarcomas such as synovial, lipo- and myxoid sarcomas as well as in head and neck squamous cell carcinoma.[9–11]

Other studies showed that PRAME may also be considered a tumor suppressor gene in case of cervical cancer[12] and acute myeloid and lymphoid leukemia.[13,14] As some studies come to contradictory results, a clearer understanding of PRAME needs to be achieved.

Its physiological function remains unclear. In 2005, Epping et al. demonstrated that PRAME acts as a retinoic acid receptor inhibitor in melanoma cells. Retinoic acid (RA) plays a key role for the proliferation arrest, differentiation, and apoptosis of various cell lines by inducing transcription of downstream genes. PRAME binds to the retinoic acid receptor (RAR), inhibiting its activation and therefore leading to dysregulated cell growth and development, explaining its oncogenic potential.[15]

Due to its limited expression profile in healthy tissue, its abundance in various cancer types, and antigenic properties, PRAME may be an ideal candidate biomarker and therapeutic target.[16] In this regard, Phase I and II clinical trials are currently ongoing in other entities.[17] PRAME expression has been extensively studied for various cancer types and is linked to poor prognosis and clinical outcomes.[18] The knowledge regarding the influence of PRAME on OSCC progression is limited. A reliable marker could restrict or extend the therapy based on individual prognosis and help estimate survival and progression on a molecular level.

The aim of this study was to investigate the correlation between the expression of PRAME, NY-ESO-1, and SSX2 with clinical and histopathological parameters including progression-free survival analysis.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

In a retrospective cohort study, the expression of PRAME and cancer staging were investigated in a sample of OSCC patients from the Department of Oral and Maxillofacial and Facial Plastic Surgery of the LMU, Munich, between January 1, 2010 and December 31, 2015. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[19] Due to the retrospective origin of the study, no informed consent was required from the patients.

2.2 | Inclusion and exclusion criteria

Patients over 18 years of age with the primary manifestation of OSCC who underwent curative surgical treatment with R0 resection were included and analyzed. The follow-up period was at least 60 months.

Patients were excluded from the study if they had a history of (i) head and neck malignancy prior to OSCC diagnosis, (ii) chemotherapy or antibody therapy, or (iii) head and neck radiation therapy.

2.3 | Study variables

The medical records of the patients were reviewed based on the pathological reports and analysis of immunohistochemical staining to determine the expression of PRAME, tumor size (T), occurrence of lymph node metastasis (N), distant metastasis (M), histological grading, age, gender, tumor recurrence, and progression-free survival. Tumor grading and staging were performed according to the criteria of the World Health Organization (WHO) classification of head and neck tumors and the 8th edition of the UICC TNM classification. The postoperative histopathological classification was the basis for determining the TNM stage in all patients. The primary predictor variable was defined as the expression of PRAME and the outcome variable was progression-free survival.

2.4 | Histopathology and tissue microarray construction immunohistochemistry

Tissue microarrays (TMAs) were assembled for analysis. For this purpose, representative tumor areas were marked on hematoxylin and eosin stain (H&E) slides of formalin-fixed and paraffin-embedded tumor specimens from all included patients according to standard procedures. Two punch biopsies of 0.6 mm were taken from the tumor core for each histologic specimen from the invasive front area. Samples from squamous cell carcinoma of the tonsils served as controls.

TABLE 1 Antibodies used for immunohistochemistry staining. ER2: epitope retrieval solution 2

Antigen	Product No.	Supplier	Clone	Dilution	Pre-Treatment
NY-ESO-1	SC-53869	Santa Cruz	E978	1:100	ER2
PRAME	ab219650	Abcam	EPR20330	1:1000	ER2
SSX2	AMAb91141	Atlas Antibodies	CL3202	1:3000	ER2

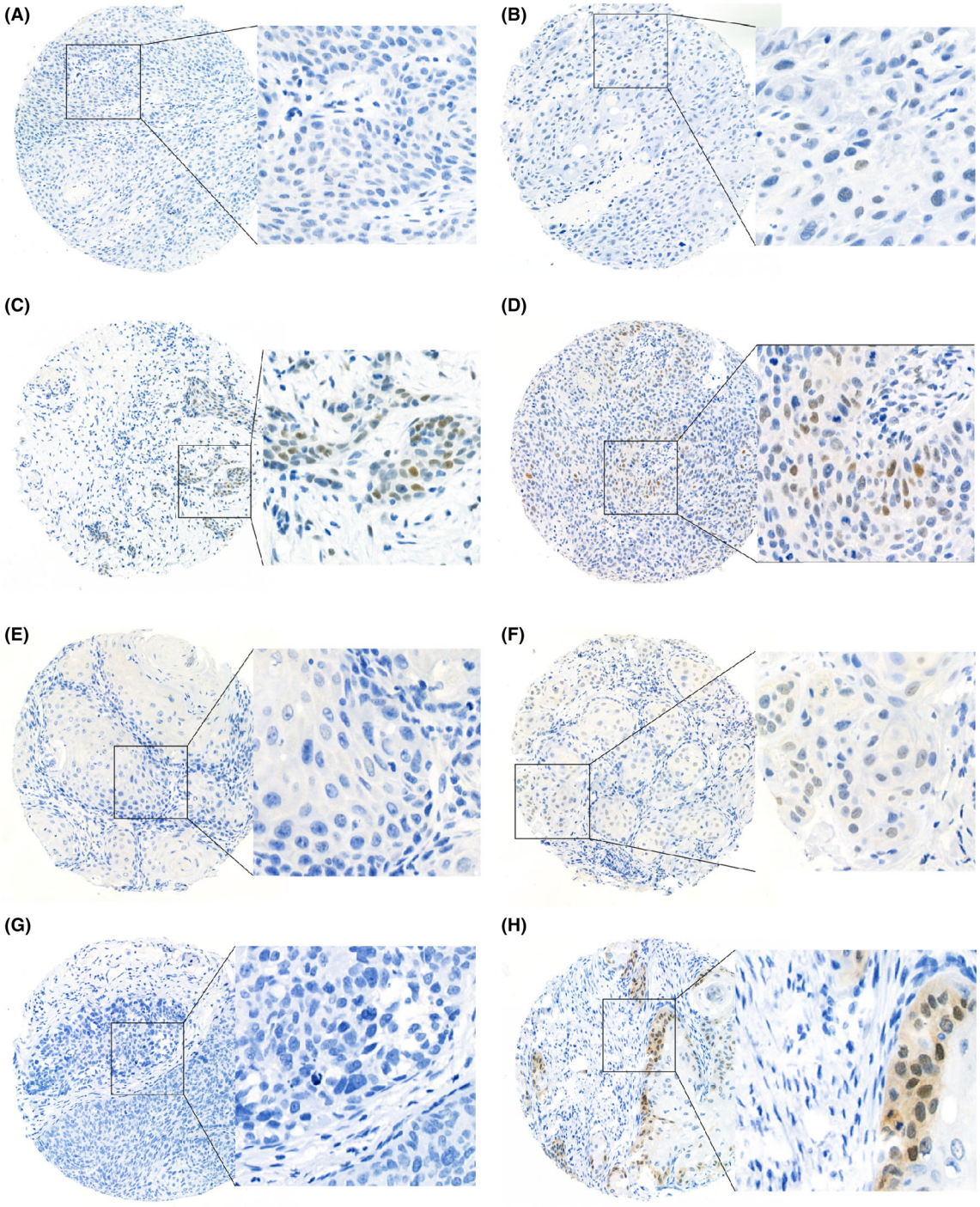

FIGURE 1 Tissue microarray stained for PRAME, NY-ESO-1, and SSX-2 representing immunoscoring. (A) negative PRAME expression; (B) low PRAME expression; (C) medium PRAME expression; (D) high PRAME expression; (E) negative NY-ESO-1 expression; (F) positive NY-ESO-1 expression; (G) negative SSX-2 expression; (F) positive SSX-2 expression; Whole punch Magnification 20×

2.5 | Immunohistochemistry

Immunohistochemical staining was performed on 5-μm TMA sections according to standard procedures. Antibodies against NY-ESO-1, PRAME, and SSX2 were obtained and used for analysis as described in Table 1. All tests were performed on an automated Leica Bond-3 staining platform (Leica). After heat-based antigen retrieval employing a high pH buffer (ER2, Leica), the primary carrier was applied. To detect the primary, a polymeric secondary kit (Refine, Leica) was used. Two investigators (TK & SH) performed the evaluation and semi-quantitative grading of all samples using a four-tier scale: 0, negative; 1, weak; 2, moderate; 3, strongly positive. For statistical analysis, the scale was reduced to a two-tier system (0 = low, versus 1/2/3 = positive) (Figure 1). The researchers assessing the TMAs were blinded to the clinical data.

2.6 | Statistical analysis

Patient characteristics are stratified by PRAME status. Low PRAME expression was defined as no staining on immunoassays and positive PRAME expression for patients with weak, moderate, or strong staining.

Survival curves (progression-free survival) for different PRAME status were created using the Kaplan–Meier method. A Cox proportional hazard model with age, gender, T stage, N stage, and grading as covariates was used to analyze whether positive PRAME expression

TABLE 2 Overview of patient characteristics, diagnostic and outcome variables for the study population

Characteristics	*N*	Overall, *N* = 83[a]	PRAME positive, *N* = 32[a]	PRAME negative, *N* = 51[a]	*p*-value[b]
Age of patient in years (at time of surgery)	83	64 (53, 78)	61 (48, 76)	66 (51, 80)	0.2
Gender	83				0.9
Female		33 (40%)	13 (41%)	20 (39%)	
Male		50 (60%)	19 (59%)	31 (61%)	
T	83				0.15
1		18 (22%)	3 (9.4%)	15 (29%)	
2		22 (27%)	9 (28%)	13 (25%)	
3		19 (23%)	10 (31%)	9 (18%)	
4		24 (29%)	10 (31%)	14 (27%)	
N	83				<0.001
0		44 (53%)	5 (16%)	39 (76%)	
1		17 (20%)	11(34%)	6 (12%)	
2		16 (19%)	12 (38%)	4 (7.8%)	
3		6 (7.2%)	4 (12%)	2 (3.9%)	
V	83				>0.9
0		82 (99%)	32 (100%)	50 (98%)	
1		1(1.2%)	0 (0%)	1(2.0%)	
L	83				0.012
0		76 (92%)	26 (81%)	50 (98%)	
1		7 (8.4%)	6 (19%)	1(2.0%)	
Pn	83				>0.9
0		78 (94%)	30 (94%)	48 (94%)	
1		5 (6.0%)	2 (6.2%)	3 (5.9%)	
M classification	83				>0.9
0		78 (94%)	30 (94%)	48 (94%)	
1		5 (6.0%)	2 (6.2%)	3 (5.9%)	
Grading	83				0.018
1		16 (19%)	9 (28%)	7 (14%)	
2		52 (63%)	14 (44%)	38 (75%)	
3		15 (18%)	9 (28%)	6 (12%)	
Depth of invasion	83	8.0 (4.0, 11.0)	9.0 (7.0, 12.2)	6.0 (4.0, 10.0)	0.013

[a]Median (IQR); *n* (%).

[b]Wilcoxon rank-sum test; Pearson's Chi-squared test; Fisher's exact test.

had an impact on progression-free survival after surgery. All statistical analyses were performed using R statistical software, version 4.0.3 (R Core Team, 2020, https://www.R-project.org/). Logistic regression models were computed with generalized linear models (GLM) using the binomial family and ordinal logistic regression models were computed with the polar function of the MASS package.[18]

3 | RESULTS

3.1 | Patient cohort and expression of cancer-testis antigens

This study included 83 patients (female $n = 33$, male $n = 50$; with a mean age of 61 ± 15 years) diagnosed with primary oral squamous cell carcinoma (OSCC). This cohort has already been investigated in another study regarding the expression of CD36.[20] The tumor was mostly localized in the alveolar process of the mandible ($n = 29/83$, 34.9%), followed by the floor of the mouth ($n = 19/83$; 22,9%) and then the anterior 2/3 of the tongue ($n = 15/83$; 18.1%), the hard palate and soft palate ($n = 8/83$; 9.6%), and finally, the alveolar process of the maxilla ($n = 12/83$; 14.5%).

Of the patients, 49% had limited disease stage (T1 and T2) and 52% were in the advanced disease stage (T3 and T4). Thirty-nine patients (46.2%) had histopathological evidence of cervical lymph node metastases (N1, N2, and N3), while five out of eighty-three patients (6%) presented with distant metastases. In terms of histopathological grading, OSCCs were found to be well-differentiated (G1) in 16 of 83 patients (19%), moderately differentiated (G2) in 52 of 83 patients (63%), and poorly differentiated (G3) in 15 of 83 patients (18%).

Strong PRAME expression in the specimen was seen in 32 of 83 patients (38.6%), strong NY-ESO-1 expression was evident in 5 of 83 patients (6.0%), and SSX-2 was evident in 1 of 83 patients (1.2%) (Table 1). Since NY-ESO-1 and SSX-2 were expressed in only a few cases, no further analysis of these markers was performed. Table 2 shows an overview of patient characteristics, diagnostic, and outcome variables.

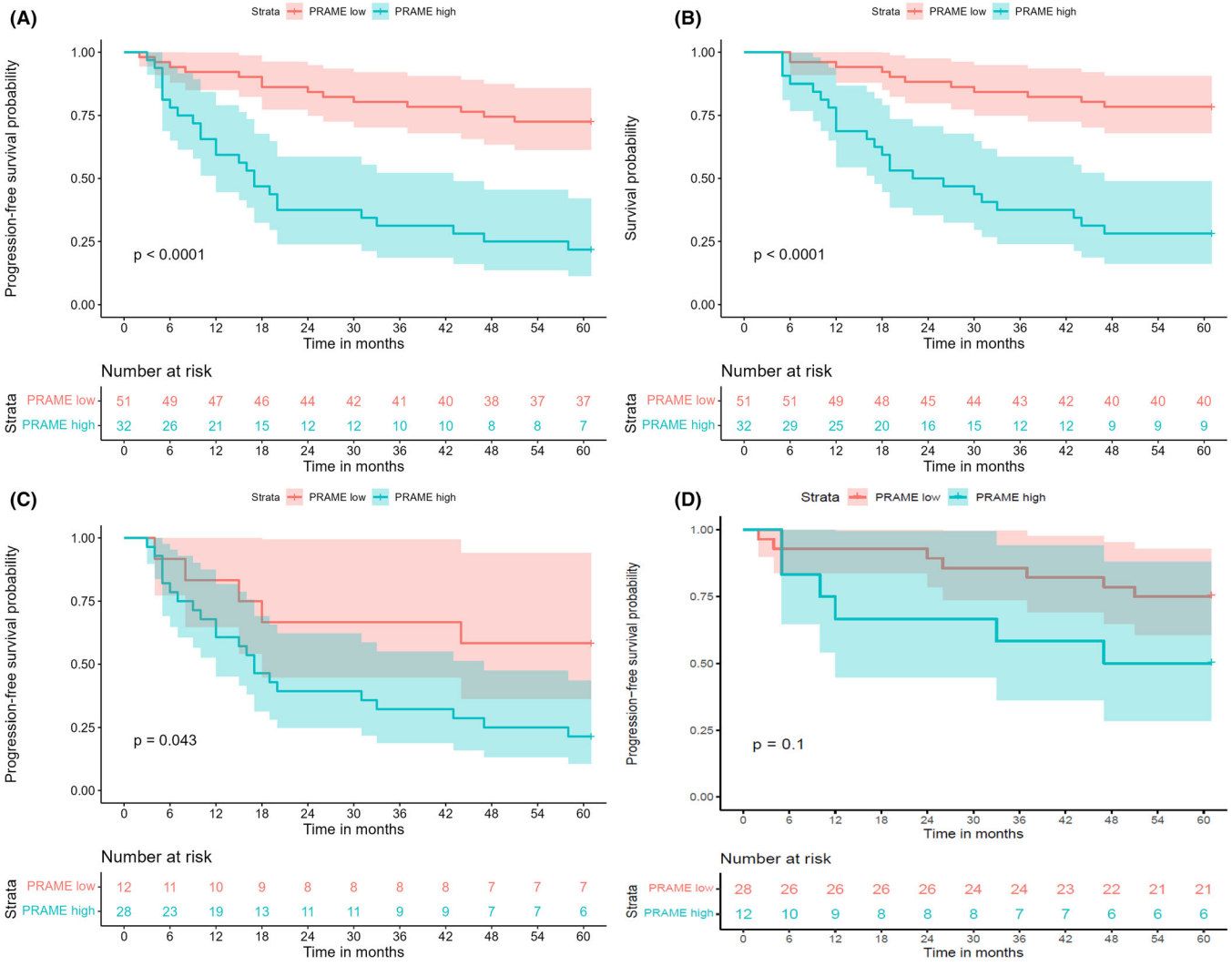

FIGURE 2 Kaplan–Meier survival curves. Progression-free survival of none vs. high PRAME expression. (A) Complete patient cohort progression-free survival ($n = 83$). (B) Complete patient cohort overall survival ($n = 83$). (C) Subgroup with N+ patients ($n = 40$). (D) Subgroup of patients with T1/T2 tumors ($n = 47$)

3.2 | Survival analysis, Kaplan–Meier method

Analysis of progression-free survival using Kaplan–Meier method showed that patients with positive expression of PRAME had a higher probability of an earlier relapse ($p < 0.001$) (Figure 2A). After 12 months of follow-up, 92,2% ($n = 47$ of 51) in the group with no PRAME expression were progression-free, whereas only 65,6% ($n = 21$ of 32) in the group with high PRAME expression had a positive outcome. After 24 months, the discrepancy of progression-free survival was even higher with 86,3% ($n = 44$ of 51) in the negative expression PRAME group and only 37,5% ($n = 12$ of 32) in the positive expression PRAME group. Finally, at the end of the follow-up time, 37 of 52 (72,5%) patients with low PRAME expression did not experience a recurrence and were alive, compared to only 7 of 32 (21,9%) of patients with positive PRAME expression. For comparison, the overall survival was also determined (Figure 2B). At the end of the follow-up time, $n = 9$ of 32 in the positive expression PRAME group and $n = 40$ of 51 in the negative expression group were alive.

Since N+ status is one of the most important prognostic factors in clinical practice, we investigated using the Kaplan–Meier method whether PRAME expression has an impact on progression-free survival in this subgroup. The analysis revealed that patients with positive expression of PRAME had lower probabilities of progression-free survival ($p = 0.043$) (Figure 2C).

Analysis of progression-free survival in the subgroup T1 and T2 tumors using the Kaplan–Meier curve showed that patients with positive expression of PRAME had lower probabilities of progression-free survival even though it was not significant, it might indicate a trend. ($p < 0.1$) (Figure 2D).

TABLE 3 Cox regression model for progression-free survival

Characteristics	HR	95% CI	*p*-value
PRAME			
Negative	–	–	
Positive	5.17	1.75, 15.3	0.003
Gender			
Female	–	–	
Male	2.85	1.21, 6.72	0.016
Age in years	1.04	1.02, 1.06	<0.001
T			
1	–	–	
2	1.49	0.42, 5.32	0.5
3	3.01	0.86, 10.6	0.086
4	2.09	0.51, 8.61	0.3
N			
0	–	–	
1	0.76	0.21, 2.76	0.7
2	2.16	0.68, 6.86	0.2
3	2.40	0.37, 15.7	0.4
V			
0	–	–	
1	1.77	0.13, 23.7	0.7
L			
0	–	–	
1	1.49	0.45, 4.90	0.5
Pn			
0	–	–	
1	3.62	0.98, 13.3	0.053
M classification			
0	–	–	
1	0.77	0.19, 3.18	0.7
Grading			
1	–	–	
2	1.13	0.35, 3.60	0.8
3	0.85	0.21, 3.41	0.8
Depth of invasion	1.00	0.90, 1.12	>0.9

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval.

3.3 | Survival analysis, Cox regression model

The Cox regression model included the predictors of age, gender, T, N, and grading. Adjusted to these covariates, the level of PRAME expression had a considerable and significant independent influence on progression-free survival (positive PRAME expression increasing the hazards for a negative outcome by 417% in our sample; HR = 5.17, 95% CI: 1.75–15.3, $p = 0.003$) (Table 3). Apart from the level of PRAME expression, only gender (males with a 2.85-fold risk compared to females; HR = 2.85, 95% CI: 1.21–6.72, $p = 0.016$) and age (every additional year of age increases the risk for recurrence or death by 5%; HR = 1.04, 95% CI: 1.02–1.06, $p < 0.001$) had a statistically significant independent influence on progression-free survival.

4 | DISCUSSION

The prognosis of OSCC has improved little in the past decades despite major advances in diagnosis and therapy. The limiting factors in terms of survival remain local recurrence and the occurrence of lymph node metastases.[21,22] In recent years, diverse biomarkers have been identified for OSCC of which, however, only a few are independent factors for survival. In the present study, the expression of PRAME, NY-ESO-1, and SSX2 and the correlation with clinical and pathological parameters were investigated.

PRAME was found to be expressed in 38.6% (32/83) of cases, whereas the expression of NY-ESO-1 occurred in only 6% (5/83) of the cases and SSX2 in only one case. In comparable studies examining head and neck cancers rather than isolated OSCC, PRAME expression varied between 50% and 66% in small patient collectives.[16,23] NY-ESO-1 expression was also rare at 7 %, and SSX2 was slightly more common, also at about 7 %.[23] However, it must be considered that the large group of head and neck carcinomas with its different entities differs

significantly from the OSCC group in terms of response to chemotherapy and radiation. Therefore, different marker expression is not surprising.

The expression of PRAME correlates significantly with higher grading, DOI, and the occurrence of lymph node metastases. There is no correlation with the T stage. This differs from the study of Figueiredo in which a higher T stage was associated with a positive PRAME expression.[24] However, many studies on other entities and on other markers show that there is often no correlation with the T stage and sometimes even an inverse correlation. This suggests that an increase in tumor mass does not necessarily lead to a higher expression of certain tumor markers. On the contrary, in some cases, the proportion of cells expressing markers is reduced.[3]

The log-rank analysis showed that progression-free survival is significantly reduced in cases with positive PRAME expression. Even with a pre-existing N+ status, the patient population with positive PRAME expression shows significantly worse progression-free survival, so it can be concluded that PRAME has a negative impact on progression-free survival regardless of N status.

Subsequent multivariate analysis showed that besides male gender and age, a positive PRAME expression is the only independent prognostic factor. Positive PRAME expression increased the risk by a factor of 5.17, male gender by a factor of 2.85, and age per year by a factor of 1.04. T status, N status, and grading were not independent prognostic factors. This may be due to the biological effects of PRAME, which seems to be a major cause of tumor malignancy and therefore determines TNM status and grading. The last two are therefore not independent prognostic factors.

Tumor markers must help provide a risk analysis that goes beyond the TNM and grading Scheme.[25] In this context, it must also be mentioned that so far tumor markers have not found their way into the daily clinical routine in OSCC.[26] A known problem is occult metastases, which cannot be visualized in the staging examination, but occur in 20%–40% of cases.[27] Especially T1 and T2 tumors are often misjudged regarding their risk. Survival in T1 and T2 tumors was found to be influenced by PRAME expression. The comparison shows a trend but is not significant due to the relatively small number of cases of T1 and T2 tumors. T1 and T2 tumors without PRAME expression might have a better prognosis, whereas T1 and T2 tumors with PRAME expression come along with a poor prognosis. This indicates that PRAME expression could help to identify patients at risk. In clinical trials, it is repeatedly discussed and investigated whether smaller tumors with a lower risk profile according to TNM and G status should be treated less radically.[28] The data presented here show that the PRAME status may be considered in such discussions and questions in the future, as this allows identifying high-risk patients with small tumors much more accurately.

The mechanism by which PRAME contributes to higher malignancy in different entities is not well understood. So far, it is known that PRAME suppresses the RA signaling pathway. The expression of PRAME in RA-sensitive cells allows them to escape RA-induced growth arrest, differentiation, and apoptosis.[15] This ability to suppress RA signaling may contribute to a positive selection of PRAME-overexpressing cells during oncogenesis, resulting in a higher malignant potential. Recently, though, PRAME has been shown to contribute to higher malignancy not only through the RA pathway, its nuclear localization has been linked to transcriptional regulation.[29] PRAME expression was also associated with a higher risk of metastasis and therefore connected to replicative immortality or stemness and invasion by promoting the epithelial-to-mesenchymal transition (EMT).[30] PRAME was linked to the promotion of CD44+ cancer-initiating cells as well.[16] In OSCC, higher CD44 expression by cancer cells has been shown to be associated with higher tumor budding activity at the invasion front, leading to poorer survival.[3]

PRAME could be of interest not just for individual prognosis and risk stratification, but also as a potential therapeutic target. It has been shown that PRAME has an immunogenic potential and leads to an increased number of tumors infiltrating lymphocytes.[31] Studies are currently investigating the effectiveness of PRAME-based cancer vaccines as well as therapeutic approaches based on CAR cells. Multi-tumor-associated antigen (TAA) vaccines, including PRAME as a target, resulted in a stable population of CD8+ T-Cells in some types of cancer in various tissue sites.[17] *Ex vivo* expansion of circulating autologous antigen-specific T-cells has also been shown to exhibit cytotoxic activity.[21] Genetically engineered T-cell receptor (TCR) T cells are also shown promising results in eradicating medulloblastoma cells.[22]

Several shortcomings of the study need to be discussed. The sample of our study is a selection of patients with severe course of head and neck tumors requiring surgical intervention. Besides, it is conceivable that tumors that are negative for PRAME in TMAs express it in other areas, and which may be more heterogeneous than it appears in TMAs. The relatively small cohort risks overestimate the effects of PRAME. The retrospective nature of the data reviewed carries the risk that confounders that are not possible remain undetected and have not been considered. Due to the retrospective design, potential complications and the impact of adjuvant therapy on progression-free survival cannot be clearly ascertained.

5 | CONCLUSION

PRAME appears to be a suitable prognosticator of progression-free survival, correlates with severe courses, and may allow the identification of high-risk patients with aggressive progression. PRAME may be synergistic to the TNM and grading scheme, which are not independent factors for survival when PRAME is included.

AUTHOR CONTRIBUTIONS

SH, FAP, and TK contributed to the study conception and design, data acquisition, analysis and interpretation, and to the writing and revision of the manuscript. RF, AJ, FF, NA, and PL contributed to data acquisition, analysis and interpretation, and to the revision of the manuscript. ME contributed to data analysis and interpretation, and to the revision of the manuscript. SO and MT contributed to the study conception and design, and to the writing and revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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