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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Overexpression of poliovirus receptor is associated with poor prognosis in head and neck squamous cell carcinoma patients

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Abstract

Purpose We aimed to investigate the prognostic value of multiple immune cell markers including programmed death-ligand 1 (PD-L1) and poliovirus receptor (PVR) in head and neck squamous cell carcinoma (HNSCC) using archival tumor tissues

Methods Patients diagnosed with HNSCC who have undergone surgical resection in 2005–2012 were included. Correlations between PVR and PD-L1 expression and patient characteristics were analyzed by analysis of variance. The Kaplan–Meier method and log-rank test were used to estimate survival. P values < 0.05 were considered statistically significant.

Results In total, 375 primary tumor tissues were analyzed using immunohistochemistry. High PVR expression was associated with a poor prognosis in terms of overall survival (OS) and recurrence-free survival (RFS), and tumors with high PVR expression were associated with a short OS. PD-L1 tumor expression did not have a prognostic impact on survival. Univariate analysis revealed that OS and RFS were affected by age and p16 and PVR expression; multivariate analysis revealed that age and p16 and PVR expression were the most important determinants of RFS.

Conclusion PVR overexpression is a poor prognostic factor in patients with HNSCC and co-targeting PVR and PD-L1 may be a promising therapeutic option that needs further investigation.

Keywords Squamous cell carcinoma of head and neck · Biomarkers · Programmed death-ligand · Poliovirus receptor

Introduction

Head and neck squamous cell carcinoma (HNSCC) often presents with advanced disease that is incurable and has poor prognosis. The median overall survival (OS) ranges from 6 to 9 months if the disease is recurrent or metastatic (Wiegand et al. 2015). The only targeted therapy that is approved in HNSCC is cetuximab, a monoclonal antibody of EGFR (Vermorken et al. 2008); however, there has been lack of new drug development until recently.

The recent development of immune checkpoint inhibitors has brought clinical practice changes, as results from clinical trials of pembrolizumab and nivolumab, both anti-PD-1 blockades, showed promising efficacy after failure of platinum-based therapy (Bauml et al. 2017; Ferris et al. 2016). However, the efficacy of anti-PD-1 monotherapy is modest, and the majority of patients do not show objective responses. Currently, a well-validated biomarker that predicts response to anti-PD-1 therapy is the PD-L1 expression on tumor cells (Herbst et al. 2014), but considering that the objective response rate is only about 20% in PD-L1 positive

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patients, better patient selection strategies are required and other mechanisms may limit the antitumor immune response within the tumors.

Besides PD-1 and CTLA-4, inhibitory receptors on tumor infiltrating lymphocytes (TILs) are functionally non-redundant, and work independently of each other. Inhibitory receptors involved in repressed T cell responses include B and T lymphocyte attenuator (BTLA), T cell immunoglobulin mucin domain 3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), V-domain immunoglobulin suppressor T cell activation (VISTA), and T cell immunoglobulin and ITM domain (TIGIT) (Anderson et al. 2016; Turnis et al. 2015). TIGIT constitutes a member of the poliovirus receptor (PVR)/nectin family, and the immunoglobulin superfamily, which is expressed on $CD4^+$, $CD8^+$, regulatory T cells, and NK cells. Known functions of TIGIT include the following: (1) inhibition of NK cell effector function, (2) suppression of costimulatory abilities of dendritic cells, and (3) suppression of $CD8^+$ T cell effector function and prevention of cancer cell elimination (Manieri et al. 2017). Upregulation or overexpression of PVR in tumor tissue may thus induce immune evasion, and lead to poor prognostic outcome in cancer patients. Ongoing clinical trials assessing the efficacy of anti-TIGIT monoclonal antibodies such as tiragolumab showed improved efficacy of the therapy when used in combination with atezolizumab in non-small cell lung cancer patients expressing PD-L1 (Delvys Rodriguez-Abreu et al. 2020). However, its clinical significance has not been elucidated in HNSCC patients yet.

In this study, we aimed to observe the expression of PVR in surgically resected HNSCC and to investigate the association between clinicopathological features and survival outcomes of these patients. In addition, we aimed to investigate the prognostic value of PVR in HNSCC, and to suggest how to best apply therapies by regulating immune responses.

Methods

Correlation analysis of immune checkpoint ligand and immune checkpoint receptor gene expression levels with survival using TCGA

To conduct a correlation analysis of immune checkpoint ligands (ICLs) and immune checkpoint receptors (ICRs), we collected RNA-sequencing data from the cancer genome atlas of HNSCC (TCGA-HNSCC) (Cancer Genome Atlas 2015). We used the normalized fragments per kilobase of transcript per million mapped reads (FPKM) values, and Spearman's correlations were calculated (Daniel 1990) for all pairs of 27 ICLs for integrative correlation analysis. For identifying ICL clusters with strong co-expression, hierarchical clustering was used to find the correlations for pairs of the 27 ICLs. Finally, we selected two clusters having no significant correlations between them. The patients from the TCGA dataset were categorized into four groups by high ($\geq$ 50th percentile, high) and low ($<$ 50th percentile, low) expression of the ICL gene, respectively. We used the Kaplan–Meier method to calculate the cumulative event (death) rate, and survival curves of each group were compared via the multivariate log-rank test with Tukey's post hoc correction (Dong et al. 2004).

Patients

HNSCC patients who received surgical resection between 2005 and 2012 at Severance Hospital were included. The inclusion criteria were as follows: (1) surgically resected HNSCC, (2) available tumor tissues and clinicopathological parameters, (3) no previous treatment including chemotherapy and radiotherapy, and (4) no distant metastasis. A total of 375 patients were examined for immune markers. As clinical parameters, primary tumor site, size, regional lymph node involvement, perineural invasion, and lymphovascular invasion were evaluated. Tumor staging followed the 7th American Joint Committee on Cancer (AJCC) TNM cancer classification system. An independent pathologist (S.O.Y.), blinded to the clinical data, examined all the tumor tissues. Pre-specified criteria were used to collect patients' medical records for evaluation of survival outcomes. Our study was approved by the Institutional Review Board of Severance Hospital and all patients had provided written informed consent.

Tissue microarray

Tissue microarrays (TMAs) were generated after representative tumor areas were confirmed under a microscope by selecting two to three areas per sample. We then collected tissue cores (3 mm in size) from the formalin-fixed paraffin-embedded (FFPE) blocks and established in paraffin blocks using a trephine. All TMA blocks contained tumor proportions of more than 50% on hematoxylin and eosin staining.

Immunohistochemistry

Immunohistochemistry (IHC) was conducted on 4-μm TMA tissue sections using a Ventana Bench Mark XT Autostainer (Ventana Medical Systems, Tucson, AZ, USA). Primary antibodies against the following antigens were used: PD-L1 (dilution 1:100; clone SP263; Ventana), PVR/CD155 (dilution 1:100; clone D8A5G; Cell Signaling, Danvers, MA, USA), CD8 (RTU; clone C8/144B; Dako, Glostrup) and p16 (RTU; Ventana).

PD-L1 positivity was defined as PD-L1 expression on $\geq$ 5% of tumor cells (Online Resource 1). PD-L1 high

vs. low was determined according to the cutoff of the mean value. TILs were quantitatively scored by measuring $CD8^+$ T cells according to previous methods (Balermpas et al. 2014, 2016). The frequency of infiltrating $CD8^+$ T cells was evaluated by examining five representative high-power fields under 400 × magnifications. Lymphocytes expressing CD8 were counted manually, and the cell counts were averaged. PVR was strongly expressed in the cytoplasm of skeletal muscle cells, and weakly to moderately expressed in part of endothelial cells. In other normal stromal cells within the tissue microenvironment, PVR expression was generally negligible (Online Resource 2). This expression pattern in normal stromal cells was used as internal control for PVR immunostaining. In tumor cells, PVR was expressed in the cytoplasmic membrane with variable intensity and percentage (Fig. 1). Therefore, PVR expression was scored according to the semiquantitative H-scoring with a range of 0–300. The dominant intensity score of membranous staining (0, no staining; 1, weak or barely detectable membranous staining; 2, distinct brown membranous staining; 3, strong dark brown membranous staining) was multiplied by the percentage of positive cell nuclei (0–100%). PVR expression was classified as high (23 < H-score) or low (H-score ≤ 23) on the basis of the mean value for overall cases. Samples were defined to be p16 positive when strong, diffuse nuclear and cytoplasmic staining was observed in more than 70% of tumor cells (Ang et al. 2010).

Statistical analysis

Overall survival (OS) was defined as the time from the initial diagnosis until death or the most recent follow-up. Recurrence-free survival (RFS) was defined as the time from surgery to initial tumor recurrence or death from any cause. The Kaplan–Meier method was used to estimate survival. A Cox regression model was used for univariate and multivariate analyses. The correlations between immune markers and clinical parameters were analyzed using the Chi-square test, Fisher's exact test, or analysis of variance. SPSS version 25.0 (IBM, USA) or R-3.6.1. was used for statistical analyses.

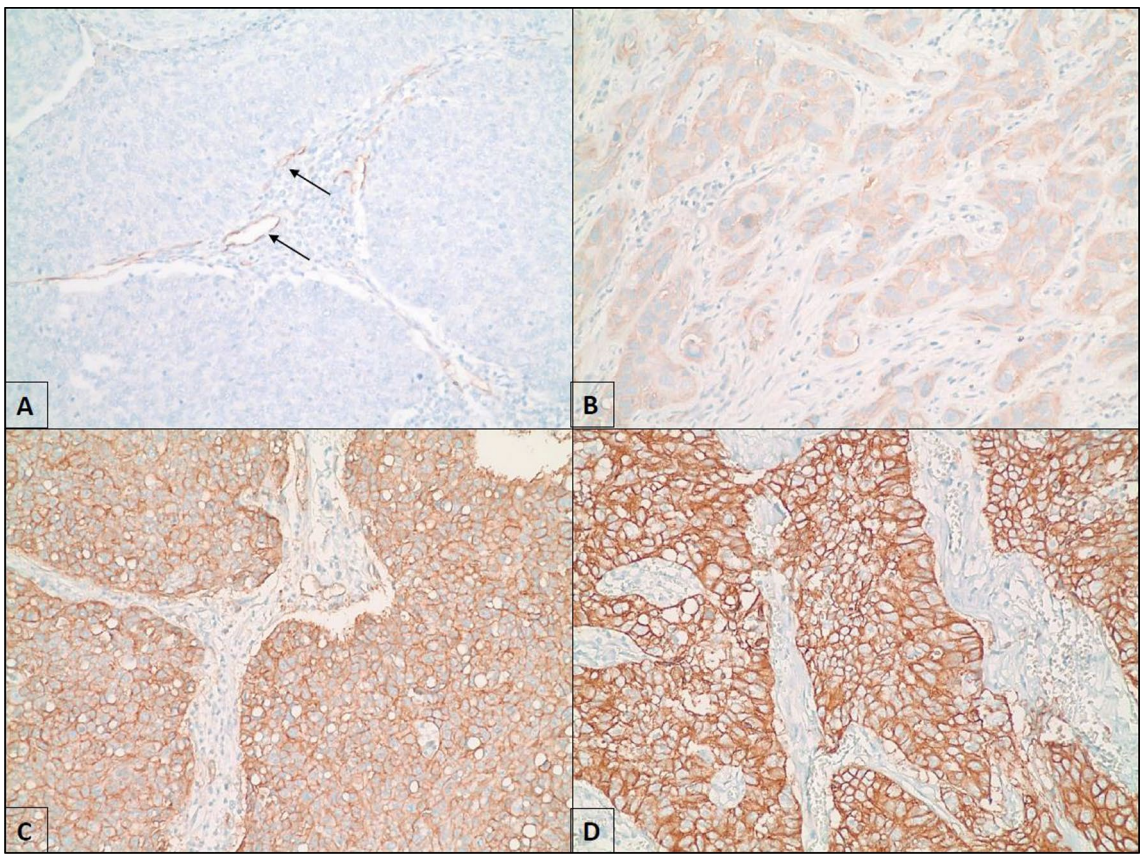

Fig. 1 Poliovirus receptor (PVR) expression on immunohistochemistry**.** PVR expression is varied according to intensity. **a** Intensity 0 **b** intensity 1 **c** intensity 2 **d** intensity 3. Thin arrows point the weak to moderate cytoplasmic expression of PVR in normal endothelial cells

Results

PVR is expressed regardless of PD-L1 expression in TCGA-HNSCC

To investigate the co-expression of ICLs, correlations between the expression levels of 27 ICLs were analyzed using the gene expression profiles extracted from TCGA-HNSCC RNA-seq data (Cancer Genome Atlas 2015). First, we analyzed the correlations among ICLs, and combined them into representative correlations using a previously described method (Hunter 1990). Clustering analysis showed that the PD-L1 (CD274) cluster was the largest (Fig. 2a, red box), including CD274 and 10 other ICLs (CD48/80/86, TIMD4, BTN2A2/3A1, VSIG4, TNFRSF14, PDCD1LG2, and LGALS9), and a PVR cluster, which includes PVR, CD276, and CD47, had no correlations with the ICLs of the CD274 cluster (Fig. 2a, blue box).

Next, patients were categorized into four groups according to the expression of CD274 and PVR: (1) high expression of CD274 and low expression of PVR (high/low); (2) low expression of CD274 and low expression of PVR (low/low); (3) high expression of CD274 and high expression of PVR (high/high); and (4) low expression of CD274 and high expression of PVR (low/high). We noted that the expression levels of PVR and CD274 were independent (Fig. 2b). In addition, we investigated the prognostic impact of CD274 and PVR by analyzing the survival difference between

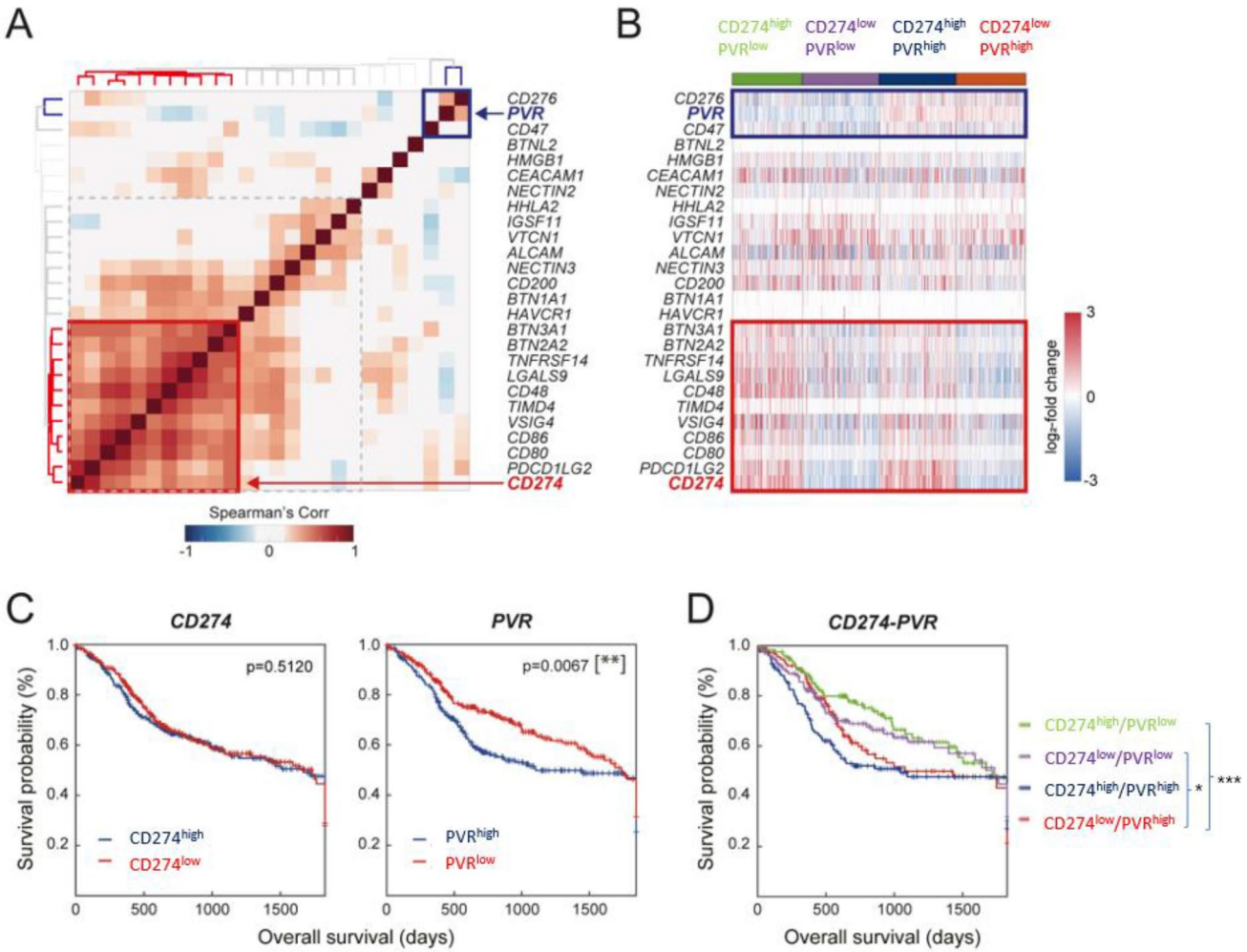

Fig. 2 Correlation analysis of immune checkpoint ligands and immune checkpoint receptor gene expression levels with survival using TCGA. **a** Correlations among immune checkpoint ligands and receptors in the TCGA-HNSCC datasets. **b** Patients categorized into four groups according to individual ICL expression: (1) high expression of CD274 and PVR (high/high); (2) low expression of CD274 and high expression of PVR (low/high); (3) high expression of CD274 and low expression of PVR (high/low); and (4) low expression of CD274 and PVR (low/low). **c** Comparison of overall survival according to CD274 high/low and PVR high/low. **d** Comparison of overall survival according to four patient groups

the patient groups with high (≥ 50th percentile) and low (< 50th percentile) levels of expression. High expression of CD274 was not associated with poor prognosis, while high expression of PVR rendered a significantly poorer prognosis (Fig. 2c). On the survival analysis, the high/high group reflected the worst prognosis, suggesting the possible additive effect of CD274 and PVR on the prognosis of these patients (Fig. 2d).

Baseline clinicopathological characteristics

A total of 375 patients' primary tumor tissues were investigated for analysis (Table 1). There was a predominance of males (74.4%) and patients under age 65 (72.3%). The most common primary site was the oral cavity (50.7%), followed by the oropharynx (31.2%), the larynx (10.4%), the hypopharynx (6.9%), and the nasal cavity (0.8%). According to the AJCC stage, stage 4 was most common (43.2%), and 40.8% of patients were current smokers. Regarding pathological aspects after surgery, resection margin was positive in 24.3%, lymphovascular invasion was positive in 19.7%, and perineural invasion was positive in 14.4% of patients. Immunohistochemical staining of p16 expression revealed that 41.6% of patients were positive.

Association of PVR expression and survival

We analyzed the association of prespecified markers and patient survival using Kaplan–Meier survival curves. As expected, p16 expression was associated with favorable survival, showing significantly prolonged OS and RFS (Fig. 3a, b). High PVR expression was associated with poor prognosis in patients, shown by inferior OS and RFS (both $P < 0.05$) (Fig. 3c, d). Patients with high and low PD-L1 expression showed similar OS and RFS (Fig. 3e, f), but when we compared PD-L1-positive vs. PD-L1-negative patients, RFS was significantly different among the two groups ($P = 0.0046$) (Online Resource 3A-B), whereas OS was not significantly different ($P = 0.307$).

Expression of PVR and PD-L1 in association with clinical characteristics

We compared the clinical characteristics of patients according to the degree of PVR or PD-L1 expression (Online Resource 4). Comparison of PVR^{low} vs. PVR^{high} patients revealed that P16 expression was more common in PVR^{low} group (50.2% vs. 31.5%, $P < 0.001$). Comparison of PD-$L1^{low}$ vs. PD-$L1^{high}$ patients showed a significantly more p16-positive patients in PD-$L1^{high}$ group (Online Resource 5). Next, we subdivided patients into four groups according to the degree of PVR and PD-L1 expression: (1) PD-$L1^{high}$/PVR^{low}, (2) PD-$L1^{low}$/PVR^{low}, (3) PD-$L1^{high}$/PVR^{high}, and (4) PD-$L1^{low}$/PVR^{high}, and compared their clinical characteristics and survival outcomes. The distribution of the four groups is shown in Online Resource 6. As shown in Online Resource 7, gender, primary sites, pN stage, smoking status, perineural invasion, and p16

Table 1 Baseline characteristics of patients

Clinical characteristics	Total $N = 375$
Age, years	
< 65 years	271 (72.3%)
≥ 65 years	104 (27.7%)
Gender	
Male	279 (74.4%)
Female	96 (25.6%)
Primary sites	
Oral cavity	190 (50.7%)
Oropharynx	117 (31.2%)
Larynx	39 (10.4%)
Hypopharynx	26 (6.9%)
Nasal cavity	3 (0.8%)
pT stage	
T1	162 (43.2%)
T2	145 (38.7%)
T3	26 (6.9%)
T4	42 (11.2%)
pN stage	
N0	166 (44.3%)
N1	68 (18.1%)
N2	138 (36.8%)
N3	3 (0.8%)
AJCC stage (7th)	
Stage 1	103 (27.5%)
Stage 2	43 (11.5%)
Stage 3	67 (17.9%)
Stage 4	162 (43.2%)
Smoking	
Never smoker	146 (38.9%)
Former smoker	76 (20.3%)
Current smoker	153 (40.8%)
Resection margin	
Positive	91 (24.3%)
Negative	284 (75.7%)
Lymphovascular invasion	
Yes	74 (19.7%)
No	301 (80.3%)
Perineural invasion	
Yes	54 (14.4%)
No	321 (85.6%)
p16 expression	
Yes	156 (41.6%)
No	218 (58.1%)

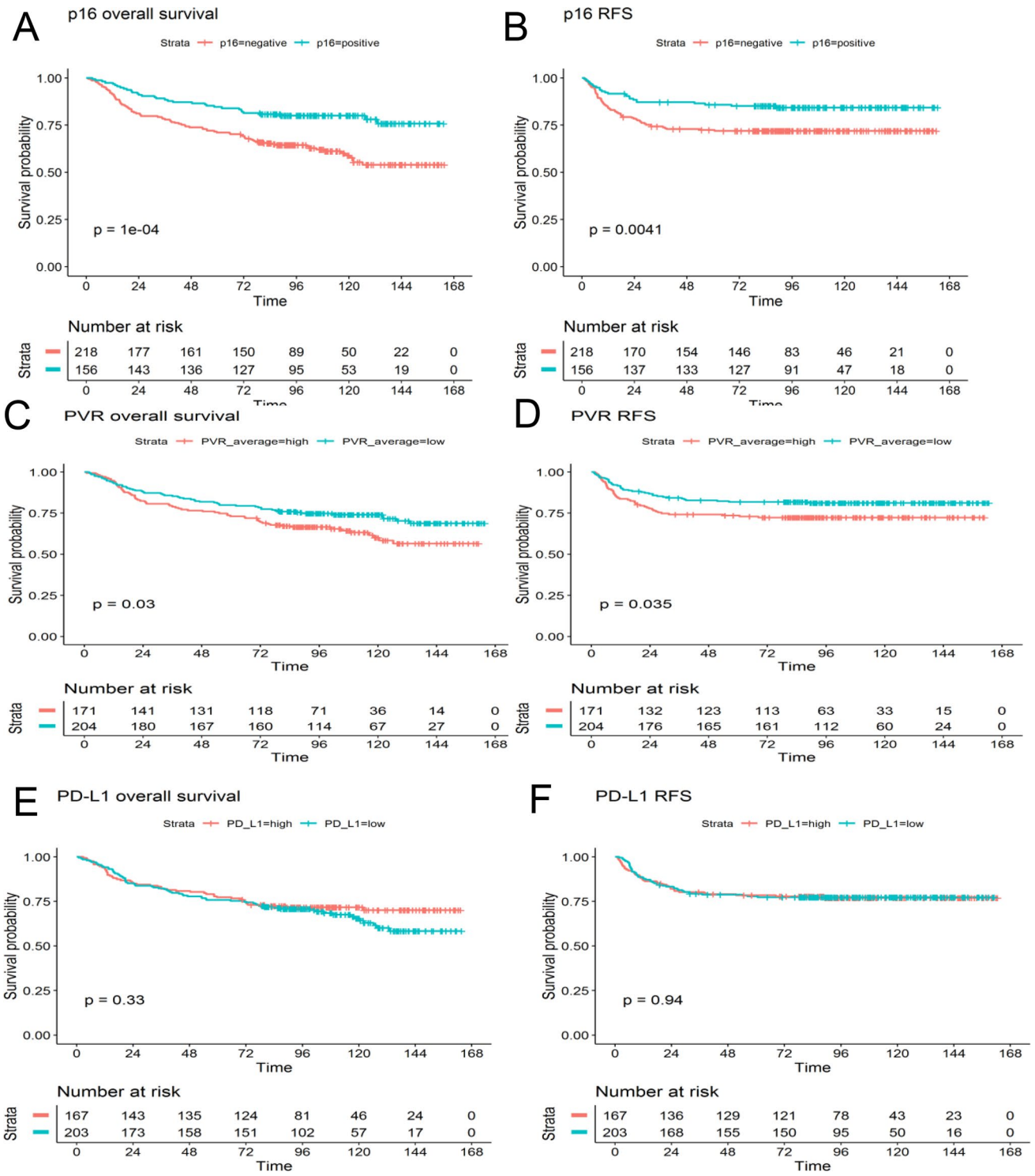

Fig. 3 Kaplan–Meier curves of overall survival (OS) and recurrence-free survival (RFS) according to different immune markers. **a** OS compared between p16 positive vs. negative ($P<0.0001$*). **b** RFS compared between p16 positive vs. negative ($P=0.0041$*). **c** OS compared between PVR high vs. PVR low ($P=0.03$*). **d** RFS compared between PVR high vs. PVR low ($P=0.035$*). **e** OS compared between PD-L1 high vs. PD-L1 low ($P=0.33$). **f** RFS compared between PD-L1 high vs. PD-L1 low ($P=0.94$). *PD-L1* programmed death-ligand 1; *PVR* poliovirus receptor

expression were significantly different between the four groups by ANOVA analysis. In addition, PD-L1^{low}/PVR^{low} group had more patients without nodal metastases when compared to PD-L1^{high}/PVR^{low} group, while perineural invasion was more common in PD-L1^{high}/PVR^{high} group when compared to PD-L1^{low}/PVR^{high} group. P16 expression positivity was significantly predominant in PD-L1^{high}/PVR ^{low} group. When we compared RFS and OS, the PD-L1^{high}/PVR^{high} group had the shortest RFS, but there was no statistically significant difference (Fig. 4a). We noted that the PD-L1^{high}/PVR^{high} group had significantly shorter OS compared to PD-L1^{high}/PVR^{low} group (Fig. 4b). We also examined the association of PVR and PD-L1 with stage, which is known important factor affecting survival. However, PVR and PD-L1 expression did not differ according to stage. In addition, correlation analyses between PD-L1, PVR and CD8 were performed, which revealed that CD8 and PD-L1 were significantly correlated (Pearson's correlation coefficient 0.393, $P < 0.0001$), while no correlation was seen between PD-L1 and PVR, PVR and CD8, and CD8 and PVR (data not shown). Next, we conducted separate analyses on oropharyngeal cancer patients only, comparing the prevalence of PVR and PD-L1 expression in association with p16 expression. We found that p16 expressing patients had significantly lower expression of PVR, as compared to p16-negative patients ($P < 0.001$) and p16 expressing patients had more PD-L1^{high} patients ($P = 0.001$) (Online Resource 8).

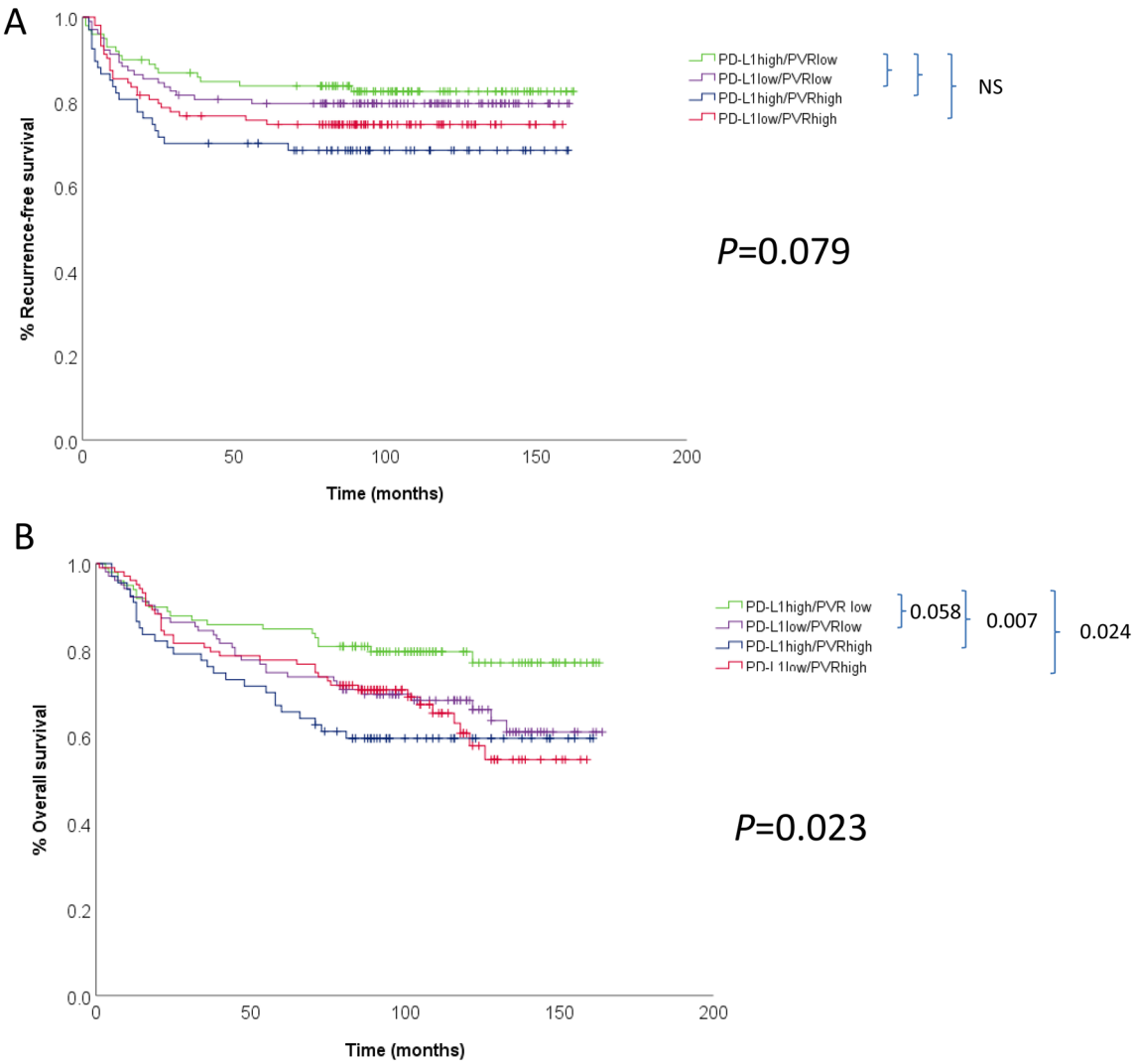

Fig. 4 Kaplan–Meier curves of overall survival (OS) and recurrence-free survival (RFS) according to four groups (Group 1: PD-L1^{high}/PVR^{low}, Group 2: PD-L1^{low}/PVR^{low}, Group 3: PD-L1^{high}/PVR^{high}, Group 4: PD-L1^{low}/PVR^{high}). **a** RFS compared between four groups ($P = 0.079$). **b** OS compared between four groups ($P = 0.023$). *PD-L1* programmed death-ligand 1; *PVR* poliovirus receptor

Univariate and multivariate analyses of factors affecting survival

We performed univariate and multivariate analyses to assess the factors affecting OS and RFS. On univariate analysis, higher age (≥ 65), negative p16 expression, higher stage (stage 3, 4), and higher PVR were associated with worse OS. On multivariate analysis, higher age, negative p16 expression, and higher stage remained significant (Online Resource 9). Regarding RFS, higher age, negative p16 expression, and higher PVR were associated with worse outcome on univariate analysis. Higher age, negative p16 expression, and higher PVR were independent risk factors of recurrence on multivariate analysis (Online Resource 10). PD-L1 status did not have a significant impact on either OS or RFS.

In addition, since we have previously reported that PD-L1 expression on immune cells beside tumor cells, was a favorable prognostic factor (Kim et al. 2016), we also investigated whether combined immune cell PD-L1 scoring with PVR expression could better predict prognosis (Online Resource 11). Interestingly, when we compared the effect of immune cell PD-L1 expression, we noted that there was a significant OS difference among IC^{high} vs. IC^{low} group among PVR^{low} group ($P = 0.006$). We did not find any notable difference in OS among IC^{high} vs. IC^{low} group among PVR^{high} group. Therefore, we can infer that presence of high PD-L1 expressing immune cells in tumor may predict more favorable outcome even among PVR^{low} group, which we previously defined as favorable prognostic group.

Discussion

With the advent of immunotherapy in the field of oncology, interests in immune markers have increased greatly. In this study, we comprehensively analyzed the immune-related markers in HNSCC tumors. $CD8^+$ TIL infiltration has been known to correlate with favorable prognosis in HNSCC patients (Kim et al. 2016), but we identified that PVR expression was also associated with poor prognosis in terms of both OS and RFS. PD-L1 expression on tumors did not have any prognostic impact on survival. In addition, both OS and RFS were significantly affected by age, p16 expression, and PVR expression, but multivariate analysis revealed that age and p16 expression were the most important determinants for both OS and RFS. Of note, our cohort contained non-oropharyngeal patients, in which the favorable prognostic role of p16 expression is less clear. Since not all patients had underwent p16 testing, the exact role of p16 in the prognosis of non-oropharyngeal patients still requires further research.

So far, the prognostic role of PD-L1 in HNSCC patients has been controversial. It was previously reported that PD-L1 expression detected by immunohistochemistry is not recommended to predict survival, but positive PD-L1 expression might predict better progression-free survival in advanced HNSCC (Yang et al. 2018). A recent analysis that evaluated PD-L1 expression on both tumor and immune cells identified that only PD-L1 expression on immune cells rendered a favorable prognostic impact in HNSCC patients (Kim et al. 2016). Therefore, PD-L1 as a single marker may not be reliable in predicting prognosis in HNSCC patients; however, combined analysis of multiple immune markers such as PD-1, CD3, CD8, and PVR may give a more comprehensive outlook of the prognosis.

High PVR expression was identified to be a poor prognostic factor of both OS and RFS. Likewise, a previous report also suggested that overexpression of PVR correlated with dismal prognosis in lung adenocarcinoma patients (Nakai et al. 2010), and multiple experimental studies have demonstrated that upregulation of PVR enhances proliferation, migration, and distant metastasis (Ikeda et al. 2004; Morimoto et al. 2008; Sloan et al. 2004). Very recently, Yao et al. reported that PVR expression was significantly associated with poor OS among HNSCC patients (Yao et al. 2020). Similarly, we have assessed PVR expression in a TCGA patient cohort, and have validated this at the protein level using a large number of surgically resected HNSCC tumor tissues. PVR binds to TIGIT, which then suppresses the antitumor immune response by limiting tumor infiltrating $CD8^+$ T cell functions (Li et al. 2014). A recent report suggested that blockade of the TIGIT-PVR axis increases immune reactivity, and thus targeting the TIGIT-PVR axis may be a future therapeutic option (Stamm et al. 2018). Similarly, blockade of TIGIT/CD155 signaling was shown to reverse T cell exhaustion and enhance antitumor immunity in HNSCC in vitro models (Wu et al. 2019). We also showed that $PD\text{-}L1^{high}/PVR^{low}$ showed superior RFS and OS, and that higher PVR expression was associated with worse OS. These findings suggest that blockade of PVR signaling may have an impact on antitumor immunity, and that co-blockade of PD-L1 and PVR may augment antitumor immunity. Likewise, a recent study identified that combination of PD-1 and TIGIT blockade reduced tumor growth in a preclinical glioblastoma model though modulations of both T cell and myeloid cell activities (Hung et al. 2018). A few early phase clinical trials using anti-TIGIT therapy alone or in combination with anti-PD-1 therapy are currently ongoing in advanced solid cancer patients. A recent phase 2 CITYSCAPE trial showed promising results by adding tiragolumab (anti-TIGIT) to Tecentriq (anti-PD-L1) in patients with advanced non-small cell lung cancer who express PD-L1 TPS of ≥ 50% (Rodriguez-Abreu et al. 2020). These results suggest that patient selection using predictive biomarkers is further required to improve the response to dual blockade.

Our study is limited due to its single-center, retrospective nature, and thus we cannot generalize our results. In addition, we cannot conclude whether various immune markers could predict response to immune checkpoint inhibitors, because our patients were not prospectively treated with anti-PD-1 or anti-PD-L1 antibodies. Further prospective analysis on the immune markers in relation to response to immune checkpoint inhibitors is warranted.

Conclusions

In conclusion, PVR overexpression was observed in HNSCC patients and was correlated with a poor prognosis, suggesting that co-targeting PD-L1 and PVR may be a novel therapeutic option.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-021-03531-8.

Author contributions Conceptualization, formal analysis, funding acquisition, and writing: SM LDHH, SH, SOY, and HRK. All the authors reviewed and edited the manuscript.

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Data availability Available.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Approved.

Consent to participate Consent.

Consent for publication Consent.

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