

Histological Heterogeneity of SLFN11 Expression and Its Association with Response to Carboplatin Plus Paclitaxel Therapy in Salivary Gland Cancer

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Abstract

Background:

Schlafen family member 11 (SLFN11) has emerged as a potential biomarker of sensitivity to DNA-damaging agents, including platinum compounds. However, its expression profile and clinical significance in salivary gland cancer (SGC) remain poorly understood. This study investigated the histological distribution of SLFN11 expression and its association with response to carboplatin plus paclitaxel (CBDCA + PTX) therapy in SGC.

Methods:

SLFN11 expression was assessed by immunohistochemistry using an H-score-based method. Associations between SLFN11 expression and histological grade or subtype were evaluated. In addition, treatment outcomes were analyzed in patients who received CBDCA + PTX as first-line systemic therapy for recurrent or metastatic disease. Objective response rate (ORR) was assessed according to RECIST version 1.1, and progression-free survival (PFS) was estimated using the Kaplan-Meier method.

Results:

SLFN11 expression demonstrated significant heterogeneity among histological subtypes and was enriched in high-grade tumors, particularly salivary duct carcinoma and squamous cell carcinoma. Seventeen patients treated with CBDCA + PTX were included in the efficacy analysis. In the overall cohort, ORR was numerically higher in the SLFN11-high group than in the SLFN11-low group (60% vs. 29%; odds ratio, 3.75). A similar tendency was observed in the non-adenoid cystic carcinoma (non-AdCC) subgroup (75% vs. 50%; odds ratio, 3.00). In contrast, PFS did not differ by SLFN11 expression status.

Conclusions:

SLFN11 expression varies substantially across histological subtypes of SGC and is enriched in high-grade tumors. SLFN11-high tumors showed numerically higher response rates to CBDCA + PTX therapy, suggesting that SLFN11 may serve as an exploratory biomarker of initial sensitivity to platinum-based chemotherapy, especially in non-AdCC.

Introduction

Salivary gland cancer (SGC) is a rare and heterogeneous group of tumors comprising diverse histological subtypes, for which no standard systemic therapy has been established. In recent years, molecular targeted therapies have been clinically introduced for selected subtypes, including human epidermal growth factor receptor 2 (HER2)-¹⁻³ and androgen receptor (AR)-targeted therapies⁴⁻⁶ for salivary duct carcinoma (SDC) and tropomyosin receptor kinase (TRK) inhibitors for secretory carcinoma^{7,8}. However, for tumors lacking these molecular targets, as well as for many other histological subtypes such as

adenoid cystic carcinoma (AdCC), effective systemic treatment options remain limited, and reliable therapeutic guidance has yet to be established.

Against this background, platinum-based cytotoxic chemotherapy has demonstrated modest efficacy in patients with recurrent or metastatic SGC. In particular, combination regimens consisting of cisplatin (CDDP) or carboplatin (CBDCA) with taxanes are widely used in clinical practice^{9–12}. However, therapeutic responses vary substantially among patients, and no reliable biomarker has been established to predict treatment efficacy.

SLFN11 is a molecule involved in the induction of cell death under conditions of DNA replication stress and has emerged as an important determinant of sensitivity to DNA-damaging agents, including platinum compounds and topoisomerase inhibitors^{13–15}. In several malignancies, SLFN11 expression has been reported to correlate with treatment response to these agents^{16–23}. However, within the head and neck field, previous investigations have been largely limited to squamous cell carcinoma (SCC)²⁴, and the expression profile and clinical significance of SLFN11 in SGC remain unclear.

Therefore, the present study aimed to clarify the distribution of SLFN11 expression across histological subtypes of SGC and investigate its association with treatment response to CBDCA plus paclitaxel (PTX) therapy, with the goal of exploring the potential utility of SLFN11 as a predictive biomarker for platinum-based chemotherapy.

Materials and methods

Patients

Patients with SGC who were treated at Hokkaido University Hospital between 2010 and 2025 were retrospectively enrolled in this study. Cases with archived tumor specimens available for immunohistochemical (IHC) analysis were included. Cases of SCC metastatic from other primary sites were excluded to avoid inclusion of non-salivary primary tumors. This study was approved by the institutional review board of Hokkaido University Hospital (No. 022–0389). Written informed consent was obtained from patients whenever possible; for patients who were lost to follow-up, an opt-out approach was adopted to provide an opportunity to decline participation in the study.

Immunohistochemical Staining and Evaluation of SLFN11

IHC staining for SLFN11 was performed on formalin-fixed, paraffin-embedded tissue specimens (Fig. 1). The primary antibody used was mouse monoclonal anti-SLFN11 antibody (D-2, #sc-515071, 200 µg/mL, Santa Cruz Biotechnology, Dallas, TX, USA). The anti-SLFN11 antibody was diluted at 1:500 in Tris-buffered saline containing 0.05% polyoxyethylene sorbitan monolaurate before use.

SLFN11 immunostaining was evaluated based on nuclear staining in tumor cells. Staining intensity was categorized as 0, negative; 1, weak; 2, moderate; and 3, strong. The percentage of tumor cells showing each staining intensity was estimated in 10% increments. The H-score was calculated using the following formula: $H\text{-score} = 1 \times \text{percentage of weakly stained cells} + 2 \times \text{percentage of moderately stained cells} + 3 \times \text{percentage of strongly stained cells}$. Accordingly, the H-score ranged from 0 to 300. The median H-score of the entire cohort was used as an exploratory cutoff, and tumors with an H-score of 40 or higher were defined as SLFN11-high, whereas those with an H-score below 40 were defined as SLFN11-low (Supplemental Fig. 1). Immunostaining was independently reviewed by two investigators (S.K. and S.H.) who were blinded to clinical outcomes, and discrepancies were resolved by consensus.

Carboplatin plus Paclitaxel Therapy

For patients with recurrent or metastatic SGC who were not eligible for HER2-targeted therapy, AR-targeted therapy, or TRK inhibitor therapy, CBDCA + PTX was generally selected as the first-line systemic treatment at our institution because of its favorable tolerability and convenience in the outpatient setting. PTX was administered at a dose of 200 mg/m² in combination with CBDCA at an area under the concentration-time curve (AUC) of 6 on day 1 of each 3-week cycle for up to six cycles.

Statistical Analysis

Continuous variables were expressed as median values with interquartile ranges (IQR) and compared using nonparametric statistical methods. The association between SLFN11 H-scores and histological grade (low-intermediate vs. high) was evaluated using the Mann-Whitney U test. Differences in SLFN11 H-scores among histological subtypes were initially assessed using the Kruskal-Wallis test. When the overall test was significant, post hoc pairwise comparisons were performed using the Mann-Whitney U test with Holm correction for multiple comparisons. Associations between SLFN11 expression status (high vs. low) and histological grade were evaluated using Fisher's exact test. The association between histological subtype and SLFN11 expression status was also evaluated using Fisher's exact test, followed by post hoc residual analysis using adjusted standardized residuals when the overall test was significant.

Objective response rate (ORR) was assessed according to RECIST version 1.1 based on investigator assessment and was defined as the proportion of patients who achieved complete response (CR) or partial response (PR). The association between ORR and SLFN11 expression status was assessed by calculating odds ratios with 95% confidence intervals (CIs).

Progression-free survival (PFS) was calculated from the date of treatment initiation to the date of radiological or clinical disease progression, appearance of new lesions, or death from any cause. Survival curves were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. All statistical analyses were performed using R software (version 4.5.2), and a two-sided p-value < 0.05 was considered statistically significant.

Results

Distribution of SLFN11 Expression by Histological Grade

The distribution of SLFN11 H-scores according to histological grade is shown in Figure 2A. High grade tumors demonstrated significantly higher SLFN11 expression levels than low-intermediate grade tumors. Consistent with this finding, analysis based on SLFN11 expression status revealed that the proportion of SLFN11-high tumors was significantly greater in high grade carcinomas than in low-intermediate grade carcinomas (Table 1).

Histological Subtype-Specific Patterns of SLFN11 Expression

Comparisons among the six most common histological subtypes demonstrated significant heterogeneity in SLFN11 expression by Kruskal-Wallis test (Figure 2B). Post hoc pairwise comparisons with Holm correction demonstrated significantly higher SLFN11 expression in SDC and SCC than in low-grade mucoepidermoid carcinoma (low-MEC).

Similarly, categorical analysis based on SLFN11 expression status demonstrated a significant association between histological subtype and SLFN11 expression status by Fisher's exact test. Residual analysis revealed that SDC showed a significantly higher proportion of SLFN11-high tumors, whereas low-MEC and Myoepithelial carcinoma (MyEC) demonstrated significantly lower proportions of SLFN11-high tumors (Table 1 and Supplementary Table 1).

Treatment Response to Carboplatin Plus Paclitaxel According to SLFN11 Expression

Seventeen patients who received CBDCA+PTX as first-line systemic therapy for recurrent or metastatic SGC were included in the response analysis (Table 2). Histological subtypes consisted of SDC (n = 7), AdCC (n = 5), SCC (n = 3), MyEC (n = 1), and carcinosarcoma (n = 1). Four patients had received no prior treatment. Among previously treated patients, surgery and radiotherapy had been performed in 10 and 12 patients, respectively, whereas no patients had received prior systemic therapy. Target lesions included the primary tumor in 4 patients, cervical lymph node lesions in 5 patients, and distant metastatic lesions in 14 patients.

In the overall cohort, patients with SLFN11-high tumors showed numerically higher ORRs than those with SLFN11-low tumors (60% [95% CI, 26–88] vs. 29% [95% CI, 4–71]; OR, 3.75 [95% CI, 0.47–29.8]). A similar numerical tendency was observed in the non-AdCC subgroup, in which the ORR was 75% (95% CI, 35–97) in the SLFN11-high group and 50% (95% CI, 7–93) in the SLFN11-low group (OR, 3.00 [95% CI, 0.24–37.7]) (Table 3). Consistent with these findings, waterfall plot analysis generally demonstrated greater

tumor shrinkage in SLFN11-high tumors (Figure 3). In contrast, no objective responses were observed in patients with AdCC regardless of SLFN11 expression status, including those with SLFN11-high tumors (Table 3).

Impact of SLFN11 Expression on Progression-Free Survival

A swimmer plot showing PFS in individual patients treated with CBDCA+PTX therapy is presented in Figure 4A. Responders generally showed relatively prolonged PFS; however, the impact of SLFN11 status on PFS varied substantially among individual cases. To minimize the influence of AdCC, which is generally characterized by slow tumor growth, swimmer plot analysis was additionally performed in the non-AdCC subgroup, demonstrating a similar trend (Supplementary Figure 2). Kaplan-Meier analysis demonstrated no significant differences in PFS between the SLFN11-high and SLFN11-low groups in either the overall cohort or the non-AdCC subgroup (Figure 4B and C).

Discussion

In the present study, we demonstrated the heterogeneity of SLFN11 expression across histological subtypes of SGC and investigated its association with the therapeutic efficacy of CBDCA + PTX therapy. SLFN11 expression was enriched in high-grade tumors, particularly SDC and SCC, suggesting that SLFN11 may reflect the biological aggressiveness of SGC. Furthermore, patients with SLFN11-high tumors showed numerically higher ORRs to CBDCA + PTX therapy, suggesting that SLFN11 expression may be associated with initial sensitivity to platinum-based chemotherapy. In contrast, no clear differences in PFS were observed according to SLFN11 expression status, suggesting a discrepancy between initial tumor shrinkage and durability of treatment response.

In this study, SLFN11 expression was elevated in high-grade SGCs, particularly in SDC and SCC. In MEC, SLFN11 expression was relatively low in low-grade tumors but comparatively high in high-grade tumors. Previous pan-cancer analyses have demonstrated substantial intertumoral variability in SLFN11 expression across different cancer types²⁵. Moreover, higher SLFN11 expression has been associated with higher tumor grade in several malignancies, including breast cancer, prostate cancer, and renal cell carcinoma^{26–28}. Our findings support the notion that SLFN11 expression may also correlate with biological aggressiveness in SGC.

Interestingly, SDC, which exhibited high SLFN11 expression in the present cohort, has also been reported to show relatively favorable responses to platinum-plus-taxane combination therapy. Previous studies have reported ORRs ranging from 39% to 90% in patients with recurrent or metastatic SDC treated with platinum-plus-taxane regimens, including CBDCA + PTX and CDDP plus docetaxel (DTX), which are generally higher than those observed in other SGC histologies^{9–12}. Taken together with the present findings, these observations raise the possibility that elevated SLFN11 expression may contribute to the relatively high platinum sensitivity observed in SDC. However, because SLFN11 expression was strongly

enriched in SDC, which is itself considered relatively sensitive to platinum-taxane chemotherapy, the observed association between SLFN11 expression and ORR may partly reflect histology-driven treatment sensitivity rather than an independent predictive effect of SLFN11 alone. Therefore, the present findings should be interpreted as hypothesis-generating, and further studies incorporating histology-adjusted analyses in larger cohorts are warranted to clarify the independent clinical significance of SLFN11 in SGC.

Despite the observed differences in ORR, no clear differences in PFS were identified according to SLFN11 expression status in this study. This tendency remained unchanged even after excluding AdCC, which is generally characterized by slow tumor growth kinetics. These findings suggest that SLFN11 may reflect “initial response” to DNA-damaging chemotherapy rather than long-term durability of treatment efficacy. In clinical practice, treatment outcomes are likely influenced by multiple additional factors, including intratumoral heterogeneity, activation of DNA repair pathways, acquired resistance mechanisms, and intrinsic tumor growth kinetics. Therefore, SLFN11 may be better interpreted as a complementary biomarker that helps predict initial treatment response, particularly in non-AdCC tumors, rather than as a definitive biomarker that fully determines platinum sensitivity in SGC.

Regarding AdCC, no objective responses to CBDCA + PTX therapy were observed in the present study, even among SLFN11-high cases. Previous studies have similarly reported poor response rates of 0–9% for CBDCA + PTX therapy in AdCC, consistent with our findings^{10,12}. In contrast, relatively favorable response rates of 23–60% have been reported for CDDP + DTX therapy in AdCC^{9,12}. This discrepancy may reflect differences in the DNA-damaging potency between CBDCA and CDDP, as well as the inherently low proliferative nature of AdCC. Accordingly, the predictive value of SLFN11 in AdCC may warrant re-evaluation in the context of more potent CDDP-based regimens.

Several limitations of this study should be acknowledged. First, the cutoff value defining SLFN11-high status remains inconsistent across previous reports, and no established cutoff has been validated in SGC. Therefore, the cutoff used in this study should be considered exploratory and requires validation in independent cohorts. Second, because SGC is a rare and histologically heterogeneous malignancy, the number of cases within each histological subtype was limited, reducing the statistical power of subtype-specific analyses. Third, this study evaluated only CBDCA-containing regimens, and the clinical significance of SLFN11 in CDDP-based therapy could not be assessed. Finally, this was a retrospective study with a relatively small sample size for evaluating platinum sensitivity. Accordingly, the present findings should be interpreted as exploratory and require validation in larger prospective studies.

In conclusion, SLFN11 expression varied substantially across histological subtypes of SGC and was enriched in high-grade tumors, particularly SDC and SCC. SLFN11-high tumors showed numerically higher response rates to CBDCA + PTX therapy, suggesting the potential utility of SLFN11 as an exploratory predictive biomarker of platinum sensitivity in SGC, especially in non-AdCC. Further large-scale prospective studies are warranted to validate the clinical utility of SLFN11 and to clarify its role in platinum-based treatment strategies for SGC.

Declarations

Ethics approval statement:

This study was approved by the institutional ethics committee (No. 022–0389).

Conflict of interest disclosure:

Satoshi Kano has received honoraria for lectures from Johnson & Johnson, Nippon Kayaku and Bayer, and research funds from Daiichi Sankyo. Nayuta Tsushima has received honoraria for lectures from Johnson & Johnson and Nikkiso. Yasushi Shimizu has received a research grant from MSD, and honoraria for lectures from Bristol-Myers Squibb, Eisai, Eli Lilly, MSD, and Ono Pharmaceutical. Akihiro Homma has received personal fees from Bristol Myers Squibb Japan, Eisai, MSD K.K, Ono Pharmaceutical, Sanofi, Eli Lilly Japan, Meiji Pharma, Otsuka Pharmaceutical Factory, GSK and m3.com outside the submitted work. Other authors have no conflicts of interest.

Author contributions:

S.K. and S.H. conceived and designed the study. S.K., J.T., N.T., H.I., H.I., M.K. and M.S. collected the data. S.K. performed the analysis. S.K. interpreted the data. S.K. drafted the manuscript. J.T., N.T., H.I., Y.S. and A.H. critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Data availability statement:

The datasets generated and/or analyzed during the study are available from the corresponding author upon reasonable request.

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Tables

Tables are available in the Supplementary Files section.

Figures

Figure 1

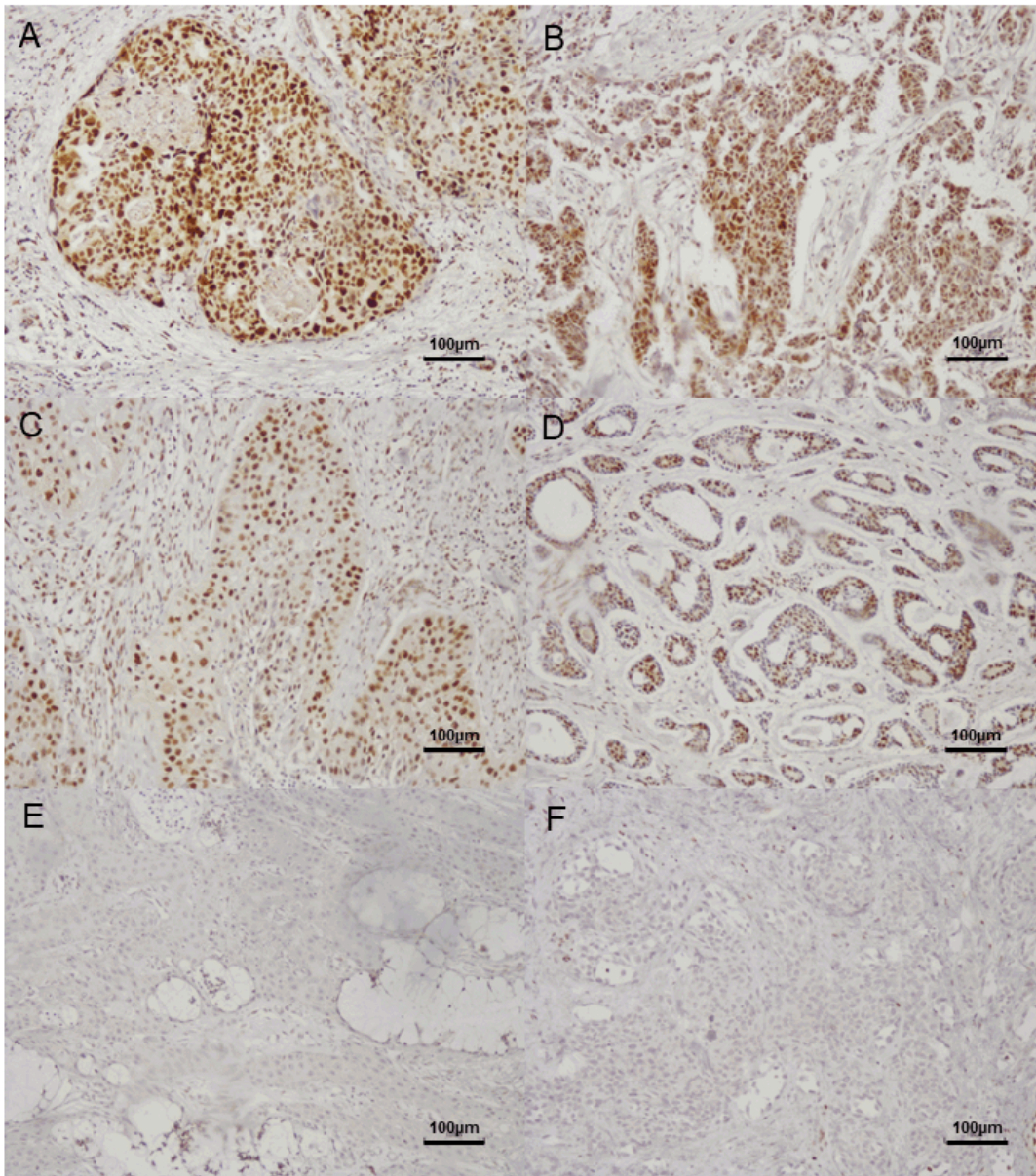


Figure 1

Representative immunohistochemical staining patterns of SLFN11 in salivary gland cancers.

Representative images demonstrating SLFN11 immunohistochemical expression across representative histological subtypes of salivary gland cancers. All images were obtained at $\times 200$ magnification. (A) Salivary duct carcinoma. (B) Squamous cell carcinoma. (C) High-grade mucoepidermoid carcinoma. (D) Adenoid cystic carcinoma. (E) Low-grade mucoepidermoid carcinoma. (F) Myoepithelial carcinoma.

Figure 2

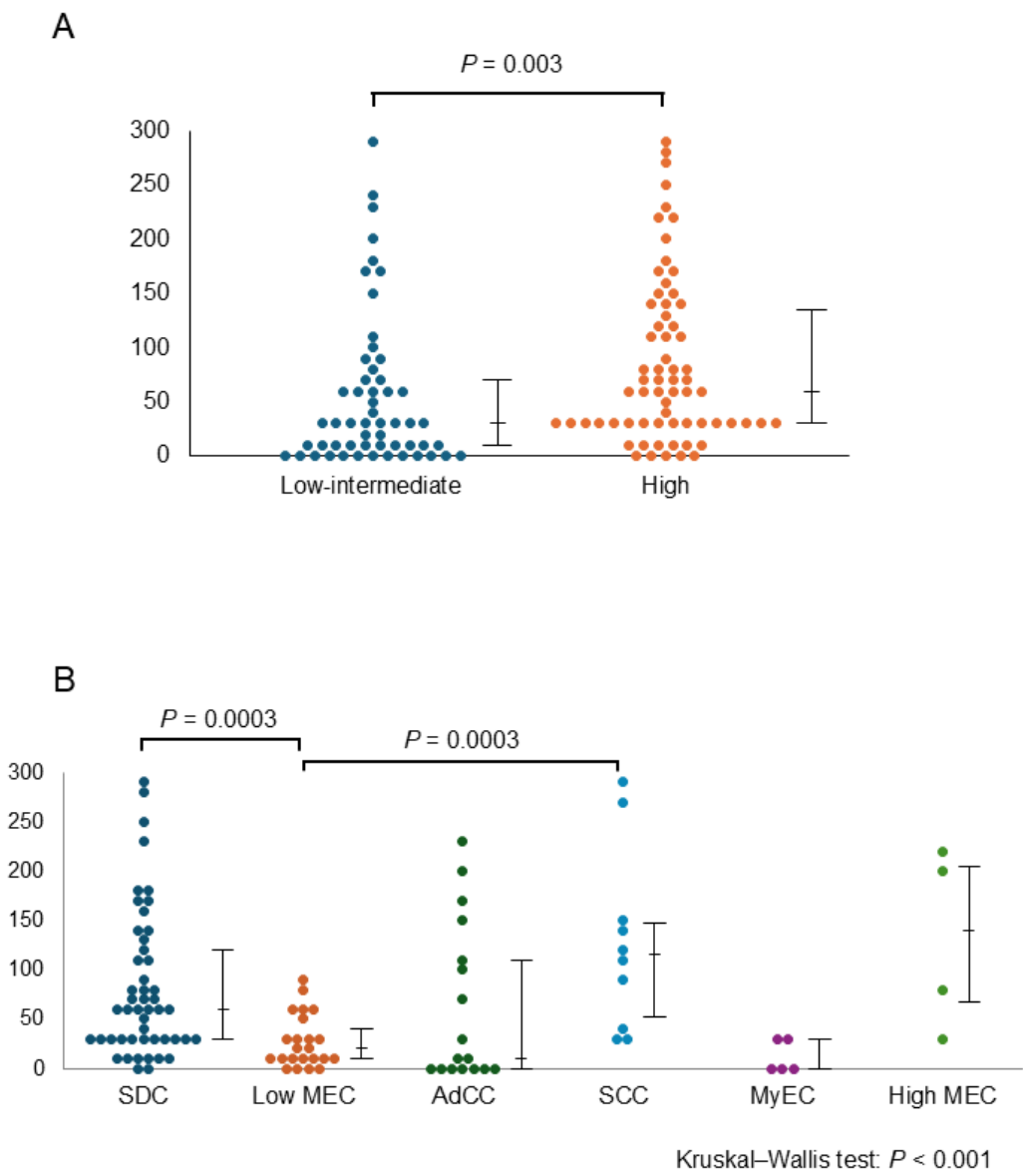


Figure 2

Association between SLFN11 expression and histological grade or subtype in salivary gland cancer.
(A) Comparison of SLFN11 H-scores between low/intermediate-grade and high-grade tumors. Statistical analyses were performed using the Mann-Whitney U test. (B) Comparison of SLFN11 H-scores among major histological subtypes of salivary gland cancer. Statistical analyses were performed using the

Each bar represents the best reduction from baseline in target lesions according to RECIST version 1.1. Bars are color-coded according to histological subtype. Asterisks indicate SLFN11-high tumors.

Figure 4

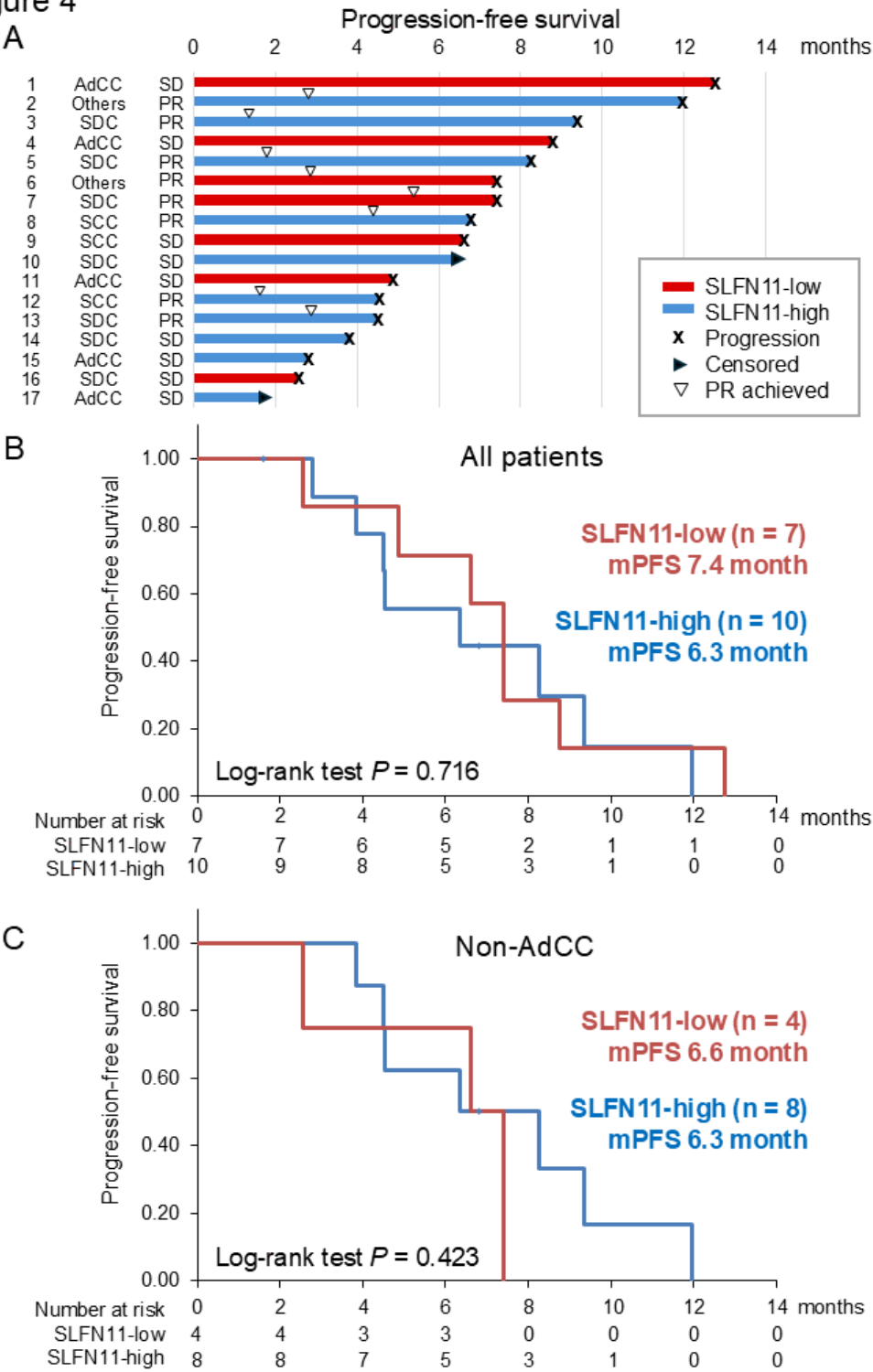


Figure 4

Association between SLFN11 expression and progression-free survival in patients treated with carboplatin plus paclitaxel therapy.

(A) Swimmer plot showing progression-free survival (PFS) according to SLFN11 expression status in all patients. Each bar represents an individual patient. Bar colors indicate SLFN11 expression status: red, SLFN11-low; blue, SLFN11-high. Patient number, histological subtype, and best overall response are shown on the left side of each bar. Symbols indicate achievement of partial response, disease progression or censoring status. (B) Kaplan-Meier curves for PFS stratified by SLFN11 expression status in the overall cohort. (C) Kaplan-Meier curves for PFS stratified by SLFN11 expression status in the non-adenoid cystic carcinoma cohort. *P* values were calculated using the log-rank test.

Supplementary Files

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