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Original Article

# Prognostic Significance of Tumor-infiltrating Lymphocytes and Anti-programmed Death-ligand 1 Therapy in Sinonasal Mucosal Melanoma: A 10-year Experience at a Single Institution

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## Abstract

***Background and objectives:*** Sinonasal mucosal melanoma (SNMM) is a rare aggressive malignancy that presents with dismal outcomes and a high metastatic propensity. The prognostic factors as well as therapeutic regimens remain largely unknown due to the rarity of SNMM. This study aimed to assess the characteristics of SNMM patients associated with a better prognosis. ***Methods:*** We performed an observational cross-sectional study to investigate the prognostic significance of tumor-infiltrating lymphocytes (TILs) and anti-programmed death-ligand 1 (PD-L1) therapy in 12 SNNM patients who were diagnosed at our institution and treated with anti-PD-L1 from 2011 to 2021. ***Results:*** Of the 12 cases, 5 (41.7%) patients displayed brisk TIL activity, while 7 patients (58.3%) had non-brisk TIL activity. The *BRAF* V600E mutation was not identified in any of the 12 cases by mutational analysis. The expression of PD-L1 was identified in 5 out of 10 SNMM cases (50%). Through analyzing the correlation between TILs and prognosis in 12 SNMM patients, we found that brisk TILs might be associated with a better prognosis compared with non-brisk TILs ($p$ = 0.036). ***Conclusions:*** Our results imply that awareness of the presence of brisk TILs and PD-L1 expression will provide guidance to clinicians for the treatment of SNMM.

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## Introduction

Mucosal melanoma is an unusual type of melanoma that involves multiple mucosal surfaces throughout the human body, including the sinonasal, oral, gastrointestinal, genitourinary, anorectal, and anogenital surfaces. In the region of the head and neck, sinonasal melanoma (SNMM) remains the most common subtype.[1] Because of late diagnosis at an advanced stage due to nonspecific symptoms, the five-year survival rate is no more than 30% in SNNM patients due to its high recurrence and metastatic potential.[2]

Although multiple therapeutic modalities have been implemented clinically, the outcomes of SNMM patients remain ominous. Importantly, the robust efficacy and unprecedented extension of patient survival following an anti-programmed death-ligand 1 (PD-L1) regimen have been demonstrated in numerous human cancer types, including non-small-cell lung cancer,[2,3] breast cancer,[4,5] and esophageal and gastric cancer[6–8] as well as in cutaneous melanoma.[9–12] Notably, through molecular testing, several independent studies have reported that PD-L1 is a molecular marker of mucosal melanoma, especially conjunctival melanoma.[13] In addition, PD-L1 expression has been demonstrated in both primary and metastatic malignant melanoma.[14–16] Moreover, according to multivariate analysis, PD-L1 overexpression has been revealed as an independent prognostic factor in melanoma patients.[17] However, the correlations between PD-L1 expression and prognosis of SNMM patients have not yet been elucidated.[18]

Tumor-infiltrating lymphocytes (TILs) are a type of immune cells that extravasate from the bloodstream and disseminate and colonize into the vicinity of cancer cells within the tumor microenvironment, and they predominantly consist of a diversity of lymphocytes.[19] The existence of TILs indicates that the immune network of the body can recognize abnormal tumor cells and mount an immune response against them. Furthermore, the critical role of TILs in immunotherapy has seized great momentum in recent years. TILs especially activate cytotoxic T cells, which can directly kill cancer cells, as well as recruit other immune cells by secreting a variety of cytokines.[20] In addition, TIL therapy has been demonstrated to improve the survival and outcomes in a number of human cancers,[21–23] including melanoma.[24,25] Notably, Amod and colleagues have reported that TIL therapy improved the therapeutic resistance and extended durable responses of tumor cells to anti-PD-L1 therapy by recruiting the TILs in the tumor microenvironment in anti-PD-L1 refractory patients

**Keywords:** Sinonasal mucosal melanoma; PD-L1 expression; Prognosis; Tumor-infiltrating lymphocytes.
**Abbreviations:** PD-L1, programmed death-ligand 1; SNMM, sinonasal mucosal melanoma; TILs, tumor-infiltrating lymphocytes.
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with metastatic melanoma.[26] These findings support the notion that TIL therapy may be used as an adjuvant strategy with immunotherapy.

Herein, we analyzed the TIL activity in 12 SNMM patients as well as determining whether brisk TILs or non-brisk TILs are associated with a better prognosis. Furthermore, PD-L1 expression was analyzed, and whether anti-PD-L1 therapy appeared to be associated with improved survival rates in SNMM patients was assessed. Taken together, our results can be used to identify a potential favorable prognostic marker as well as treatment for SNMM.

## Methods

### *Case collection*

The approval of the Institutional Review Board was obtained from the University of California, Irvine Medical Center to collect demographics, presentation of disease, clinicopathological information, treatment modalities, and survival time in 12 patients with SNMM. In addition, this study conformed to the ethical guidelines of the Helsinki Declaration (as revised in 2013). Since this study was a retrospective study using tissue collected for treatment and/or diagnostic purposes, the consent of the patients was waived.

### *Review and classification of PD-L1 analysis*

A pathologic review of all cases, including the biopsies and surgical excisions, was conducted by three pathologists; a comprehensive histopathological assessment of staging, evaluation for TILs, and PD-L1 expression determination by immunohistochemistry were performed.

The TIL scoring system was done based on a semiqualitative method according to the Protocol from the College of American Pathologists.[3] PD-L1 28-8 (OPDIVO) antibody was used to measure the expression of PD-L1 using immunohistochemistry. A reference range ≥1% was deemed positive, and a reference range <1% was considered negative.

### *Statistical analysis*

The statistical software R studio version 4.2.1 was adopted to conduct statistical analysis. The correlation of TILs with survival time was analyzed using the Kaplan–Meier method and the log-rank test.

## Results

The clinicopathological features, surgical procedure, therapeutic response, and survival time of all patients are summarized in Supplementary Table 1. Briefly, 12 patients with a median age of 70.0 years old (range: 53–96 years old) were included in this study. The mean tumor size was 3.5 cm (range: 0.8–6.3 cm), and they were previously untreated primary tumors that originated from the nasal cavity. Metastatic lesions were identified in 8/12 (67%) patients. During the course of follow-up, the recurrences and metastases were noted.

Out of the 12 patients, 7 patients presented a favorable response to the initial anti-PD-L1 therapy, and 5 patients had recurrence (did not respond to treatment). Three patients died, and eight patients had metastases during the course of follow-up. The median follow-up period was 18.1 months (mean: 22.4 months). More details regarding the therapeutic response, follow-up period, and status of recurrence and metastasis for each patient are listed in Supplementary Table 1.

Five out of 12 patients exhibited brisk TILs, while 7 patients had non-brisk TILs (58.3%) (Fig. 1). The well-established cutaneous melanoma-associated *BRAF* V600E mutation was not identified in any of the 12 cases by *BRAF* V600E melanoma mutational analysis. PD-L1 expression was further examined in 10 cases, and PD-L1 positivity (defined as ≥1%) was identified in 5/10 cases (50%). Through analyzing the correlation of TILs with the prognosis of the 12 SNMM patients using Kaplan–Meier analysis, it appeared that those with brisk TILs were associated with a better prognosis compared with those with non-brisk TILs ($p = 0.036$) (Fig. 2).

These findings imply that the presence of TILs and PD-L1 expression might represent a favorable prognostic marker in SNMM patients. Meanwhile, anti-PD-L1 therapy shows promise for improving the survival of SNMM patients with PD-L1 expression.

## Discussion

The primary findings of this study shed light on the prognostic significance of TILs in SNMM patients. Herein, we found that 41.7% of the SNMM patients presented with brisk TIL activity and that patients with brisk TILs might be associated with a better prognosis compared with those with non-brisk TILs ($p = 0.036$) in the limited number (12) of patients analyzed in the current study. In addition, PD-L1 expression was identified in 5/10 SNMM patients. These findings suggest that brisk TILs may be used as a potential prognostic marker in SNMM patients.

Although the expression and clinical significance of PD-L1 has been widely demonstrated in malignant skin melanoma,[14–16] the prognostic significance of PD-L1 expression in mucosal melanoma is still being debated. A study including 34 mucosal melanoma patients with the *BRAF* V600E mutation has shown that PD-L1 expression was positively correlated with a poor prognosis and that the absence of tumoral PD-L1 expression predicted a favorable response to conventional treatment and a better prognosis.[17] In contrast, Gadiot *et al*. have longitudinally analyzed 63 patients with stage III–IV mucosal melanoma (the *BRAF* mutation status is not mentioned) and found that there was no statistical significance between PD-L1 expression and overall survival.[16] These findings have propelled researchers to further investigate the prognostic significance of PD-L1 expression in mucosal melanoma patients in the following work. Although PD-L1 expression does not seem to be related to prognosis, the presence of PD-L1 expression has important clinical implications for the guidance of treatment for melanoma patients. In fact, Nivolumab plus Ipilimumab combination therapy dramatically improved the overall survival in advanced mucosal melanoma patients.[27] In the current study, our findings demonstrate that PD-L1 expression was identified in 50% of the patients analyzed (5/10 SNMM patients). Importantly, patients with anti-PD-L1 therapy appeared to show improved survival rates, although there was no significant correlation identified due to the limited number of cases analyzed in this study. This finding supports the idea that anti-PD-L1 immunotherapy might be a promising strategy for treating SNMM patients.

Several lines of evidence indicate the prognostic significance and therapeutic potential of TILs in numerous cancers. Interestingly, it seems that the specific role of TILs depends on the tumor subtype. The presence of TILs has been demonstrated to be significantly correlated with favorable outcomes in non-small cell lung cancer,[22] colorectal cancer,[28] hepatocellular carcinoma,[29] and ovarian cancer including melanoma.[24,25,30] In breast cancer, TILs predicted a favorable response to treatment and improved the survival rates of breast cancer patients with different subtypes,[31] suggesting

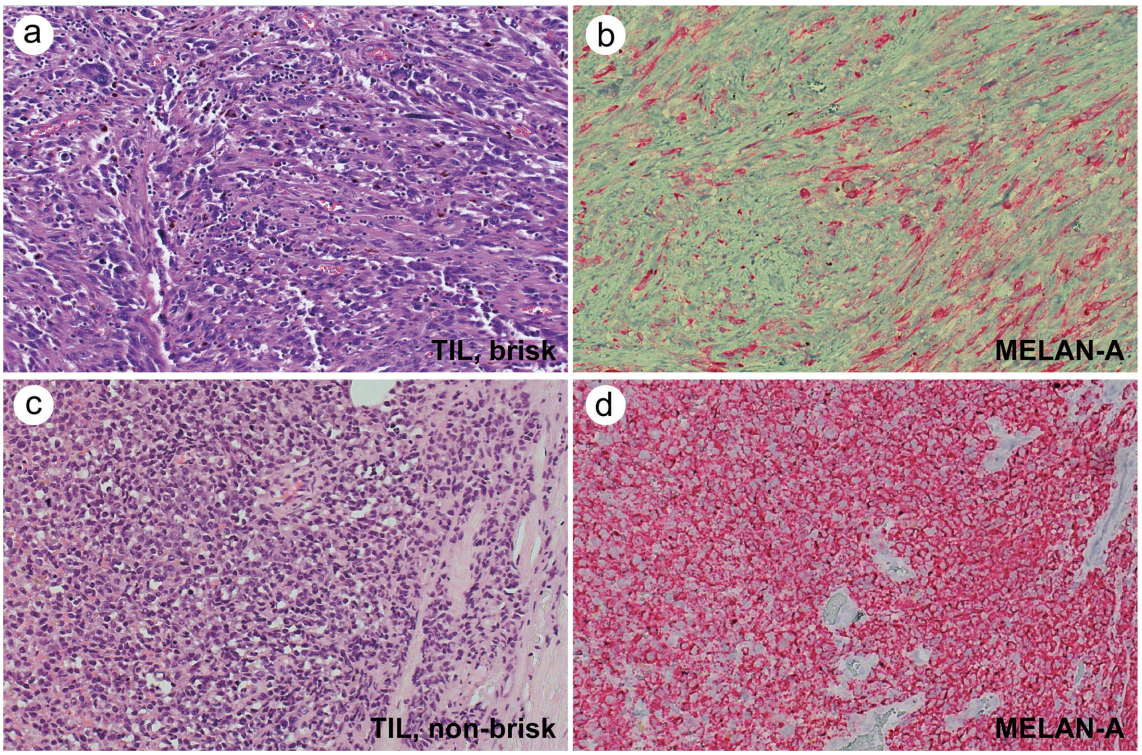


**Fig. 1. Immunohistochemistry.** (a) Representative hematoxylin and eosin staining of SNMM with brisk TILs, 40× magnification. (b) Representative immunohistochemical staining of MELAN-A in SNMM with brisk TILs, 40× magnification. (c) Representative hematoxylin and eosin staining of SNMM without brisk TILs (non-TILs), 40× magnification. (d) Representative immunohistochemical staining of MELAN-A in SNMM without brisk TILs (non-TILs), 40× magnification. SNMM, sinonasal mucosal melanoma; TILs, tumor-infiltrating lymphocytes.

that the specific role of TILs largely relies on the cancer subtype, in which the interaction between different immunological infiltrating cells and tumor cells may play a pivotal role. Consistently, our study showed that the presence of TILs was associated with better outcomes in SNMM patients, supporting the notion that TILs may play an antitumor role in SNMM. However, the specific functional role of TILs in SNMM is definitively worthy of in-depth investigations in the future.

Apart from the well-documented therapeutic efficacy of anti-PD-L1 therapy in different types of cancer,[32–34] including mucosal melanoma,[27] TIL therapy has emerged as a therapeutic strategy.[21–23,35] In mucosal melanoma, Rohaan *et al*. have reported that patients receiving TIL therapy presented a significantly better prognosis than those receiving chemotherapy.[36] In mucosal melanoma, Ledderose and colleagues have demonstrated that high densities of $CD3^+$ and $CD8^+$ TILs are strong positive prognostic biomarkers for the survival of SNMM patients.[37] Furthermore, the combination of TIL therapy and anti-PD-L1 therapy significantly improved drug resistance and prognosis in mucosal melanoma patients with a *BRAF* mutation.[17] Importantly in lung cancer patients, TIL treatment has been demonstrated to improve the resistance of tumor cells to anti-PD-L1 therapy;[38] this result also has been reported in metastatic skin melanoma patients.[26] These findings support the idea that TIL therapy alone or in combination with anti-PD-L1 presents a favorable therapeutic avenue for patients with mucosal melanoma. In the current study, our findings revealed that both the presence of TILs and anti-PD-L1 therapy seemed to be associated with better outcomes in SNMM patients, suggesting that this com-

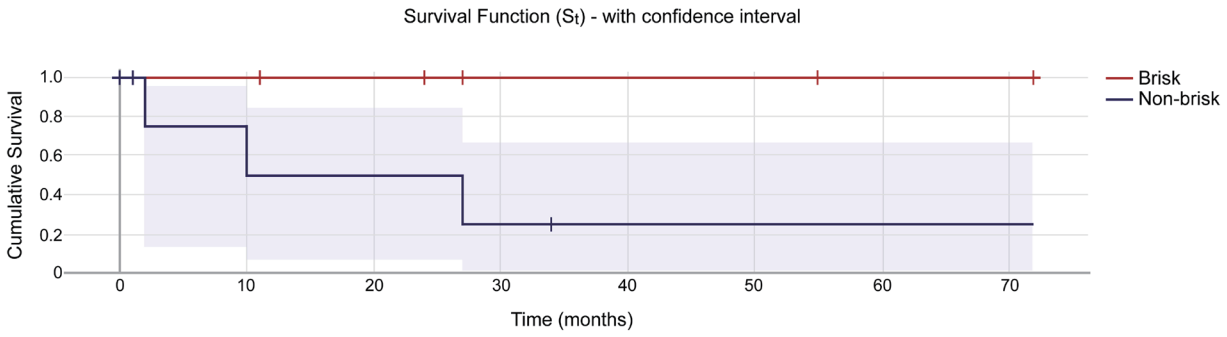


**Fig. 2. Kaplan–Meier analysis.** The presence of brisk tumor-infiltrating lymphocytes in sinonasal mucosal melanoma patients is associated with better overall survival (Log-Rank, $p = 0.036$).

bination of TILs and anti-PD-L1 therapy may be used as a treatment option for SNMM patients.

With advancements in molecular techniques, investigation of the molecular gene signature will facilitate the identification of novel driver genes in a variety of human cancers, including mucosal melanoma. A meta-analysis by Wang *et al*. has reported that *SF3B1* R625 codon mutations are unique to mucosal melanomas.[39] Furthermore, Mikkelsen and colleagues have explored the molecular profile of mucosal melanoma and found that apart from the *BRAF* mutation, *NRAS*, *KIT*, and *NF1* alterations were identified in non sun-exposed sites of mucosal melanomas.[40] These studies suggest that exploration of molecular alterations will reveal a novel pathogenesis of mucosal melanoma and be helpful in expanding the spectrum of prognostic and therapeutic targets in mucosal melanoma.

## Conclusions

Our study suggests that brisk TILs might serve as a potential prognostic factor in SNMM patients and that anti-PD-L1 therapy may be used as a potential therapeutic strategy in SNMM patients. Due to the limited number of patients included in the current study, further investigations regarding the prognostic significance of TILs and anti-PD-L1 therapy are warranted in prospective studies with a larger sample size.

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## Conflict of interest

This manuscript was submitted during Dr. Beverly Wang's term from January 2022 to December 2023 serving as an Advisory Board Member of *Journal of Clinical and Translational Pathology*. The authors have no other conflicts of interest to declare.

## Author contributions

Study concept (BW, JT), data collection (JT, SZ), data analysis (JT, DR), supervision of the study (BW), drafting of the manuscript (JT, DR), review and editing of the manuscript (BW, EK). All authors revised the manuscript critically and approved the version to be published.

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