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Immunohistochemical p16 expression in the prognosis of patients with sinonasal squamous cell carcinoma

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In sinonasal squamous cell carcinoma (SNSCC), the prognostic relevance of p16INK4a (p16) expression has been reported rarely. This study aims to examine the immunohistochemical expression of p16 and investigate the possibility of p16 as a prognostic factor for SNSCC. The medical records of 173 individuals with SNSCC between 2010 and 2022 were retrospectively reviewed. The researchers examined patients' demographics, p16 status, staging, tumor histological subtypes, treatment details, recurrence, metastasis, and survival outcomes. p16 was found in 22.0% (38/173) of SNSCC patients, and there was no difference between inverted papilloma-SNSCC (19.6%) and de novo SNSCC (23.0%). p16 status did not correlate with all the cases' age, gender, clinical stage, or therapy features. p16-positive patients had a considerably superior 5-year overall survival (OS) rate (80.7% vs. 57.5%, p=0.039) and a slight tendency in progression-free survival (PFS) rate (68.1% vs. 52.0%, p=0.15), except in stage T4b cases. In maxillary sinus lesions, p16-positive SNSCC had a better 5-year OS (87.4% vs. 49.2%, p=0.03) rate and PFS (79.1% vs. 40.7%, p=0.01) rate than p16-negative SNSCC. Among patients without skull base involvement (82.9% vs. 57.7%, p=0.037) or orbital invasion (86.9% vs. 57.3%, p=0.02), p16-positive SNSCC confers benefits in OS rates more than p16-negative SNSCC. Immunohistochemical p16 expression may be a predictive predictor in individuals with maxillary sinus SCC, non-T4b stage, without skull base involvement, and without orbital invasion.

Key words: p16INK4a; human papillomavirus (HPV); sinonasal squamous cell carcinoma; orbital invasion; skull base involvement

The most prevalent histologic subtype of all malignant sinonasal tumors is squamous cell carcinoma of the nasal and paranasal sinuses (SNSCC), which accounts for more than half of all cases. SNSCC is an uncommon tumor that may develop from *de novo* squamous cell carcinoma or in association with inverted papillomas (IPs). It was observed that 2–27% of IPs developed a malignant transition, with SNSCC being the most common [1, 2]. Human papillomavirus (HPV) infection has been extensively established as an etiological agent of oropharyngeal cancer during the last several years. It was shown that high-risk HPV might play a role in the pathogenesis of SNSCC, while low-risk HPV may be transcriptionally active in IPs [3]. Although there are rare reports in the literature on the fully established relationship between HPV status and SNSCC, emerging data suggest that HPV is a potential prognostic predictor for SNSCC.

Owing to a significant disparity in HPV detection rates, the exact impact of HPV on IP remains unclear. A meta-analysis comprising 19 studies found that there seemed to be a strong link between HPV infection and the malignant transformation of IPs [4]. HPV DNA was detected in 10.3% of IPs and 22.7% of IP-associated SNSCC, compared to 35.7% of SNSCC without an IP association relationship [5].

A study discovered that 53% (17/32) of SNSCC patients were HPV-positive by polymerase chain reaction, and HPV status had no impact on survival [6]. Despite this, HPV-positive patients were more prone to have local recurrence and metastasis. In contrast, a meta-analysis showed that patients with HPV-positive SNSCC had significantly superior 5-year overall survival (OS) (67.6%) compared with those with HPV-negative SNSCC (47.6%, p<0.01) and significantly better 2-year disease-free survival (81.7% vs. 55.8%, p<0.01) [7]. It was demonstrated that HPV status impacted survival; the 5-year survival rate for HPV-negative cancers was 26.4%, whereas the 5-year survival rate for HPV-positive tumors was 57.1% (p=0.002) [8].

The correlation between p16 overexpression and positive HPV status has been reported to be 69–100%. A retrospective investigation analyzed 49 cases of SNSCC and demonstrated a positive association between p16 and HPV; more importantly, disease-free survival for p16 positive (p16+) patients was considerably higher than for p16 negative (p16–) patients [9]. There was a study that reported a better prognosis in patients with p16+ SNSCC [10].

Using immunohistochemical assay for p16 protein was reported for detecting HPV-positive SNSCC [11]. However, immunohistochemical p16 staining for sinonasal malignancies is not a routine procedure. In this study, we attempted to investigate the frequency of p16 overexpression in SNSCC and discuss whether p16 may be a predictive factor for SNSCC patients.

Table 1. Patient characteristics in SNSCC (n=173).

Variables	p16 (–) No. (%)	p16 (+) No. (%)	p-value
Age (y)			
<60	67 (38.7)	25 (14.5)	0.08
≥60	68 (39.3)	13 (7.5)	
Gender			
Male	96 (55.5)	31 (17.9)	0.20
Female	39 (22.5)	7 (4.1)	
Tumor location			
Nasal	69 (39.9)	15 (8.7)	0.45
Maxillary sinus	49 (28.3)	17 (9.8)	
Ethmoid sinus	17 (9.8)	6 (3.5)	
Pathologic origin			
de novo SCC	94 (54.3)	28 (16.2)	0.63
IP-SCC	41 (23.7)	10 (5.8)	
T stage			
T1/2	19 (11.0)	2 (1.2)	0.07
T3/4a	82 (47.4)	23 (13.3)	
T4b	34 (19.6)	13 (7.5)	
Lymph node			
Negative	112 (64.7)	31 (17.9)	0.84
Positive	23 (13.3)	7 (4.1)	
Orbit involvement			
No	69 (39.9)	18 (10.4)	0.68
Yes	66 (38.2)	20 (11.5)	
Skull base involvement			
No	91(52.6)	22 (12.7)	0.28
Yes	44 (25.4)	16 (9.3)	
Chemotherapy			
No	46 (26.6)	9 (5.2)	0.22
Yes	89 (51.4)	29 (16.8)	
Treatment			
S+CRT	90 (52.0)	27 (15.6)	0.88
CRT+S	25 (14.5)	6 (3.5)	
CRT	20 (11.5)	5 (2.9)	

Abbreviations: SNSCC-sinonasal squamous cell carcinoma; IP-inverted papilloma; S-surgery; CRT-chemoradiotherapy

Patients and methods

Patient selection. One hundred and seventy-three unselected patients with sinonasal cancer between January 2010 and February 2022 were identified from our institution. The following data were examined and analyzed: patient demographics, p16 status, staging, tumor histological subtypes, treatment details, recurrence, metastasis, and survival outcomes. The 2017 American Joint Committee on Cancer staging criteria determined the tumor stage. Radiotherapy was used to treat all patients, comprising three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, and volumetric modulated arc therapy. Postoperative radiotherapy was performed as adjuvant therapy in 67.6% (117/173) of the cases. Preoperative radiotherapy combined surgery was used for 18.0% (31/173) of the patients. Furthermore, twenty-five patients (14.4%, 25/173) who declined surgery or were not surgical candidates accepted definitive radio(chemo)therapy. 68.2% (118/173) of the patients were delivered with radiochemotherapy. Our Institutional Review Board gave their approval to this project.

p16 immunohistochemical staining. Formalin-fixed and paraffin-embedded (FFPE) tumor tissues were stained with hematoxylin-eosin (H&E) according to the standard procedures. For immunohistochemical examination, the samples were sliced into four to five μm sections, and a primary monoclonal antibody anti-p16 (rabbit mAb, ab108349, Abcam, Cambridge, UK, 1:100) was used. Immunohistochemical staining for p16 was performed according to the manufacturer's instructions. The sample was considered positive for p16 if strong and diffuse nuclear and cytoplasmic staining was detected in ≥ 70% of the tumor cells [12]. Negative control was performed by omitting the primary antibody.

Statistical analysis. Statistical analyses were performed using IBM SPSS version 26.0 (IBM, Armonk, NY, USA) and GraphPad VR Prism 8.0 (GraphPad Software Inc., La Jolla, CA, USA). OS rates and PFS (progression-free survival) rates were computed by the Kaplan-Meier method and compared using the log-rank test. To establish statistical comparisons between two continuous variables, a student t-test was performed. The chi-square test was utilized to analyze the relationship between the categorical variables. A p-value of less than 0.05 was considered statistically significant in this study.

Results

Patient characteristics. Table 1 lists the patient and disease characteristics. One hundred twenty-seven males (73.4%) and 46 females (26.6%) were in the study group. The median age for all the cases in the present study was 58.0 years old (range 24–84 years). According to the pathological origin, there were 122 *de novo* SNSCC (70.5%) and fifty-one IP-SNSCC (29.5%). Tumors were found in the nasal cavity (48.6%, 84/173), the ethmoid sinus (13.3%, 23/173),

and the maxillary sinus (38.1%, 66/173). T1/T2 disease struck 21 patients (12.2%), T3/T4a disease struck 105 patients (60.7%), and T4b disease struck 47 cases (27.1%). Cervical lymph node metastasis at diagnosis was identified in 30 patients (17.4%). In all, seventeen patients (9.8%) were in stage I/II, thirty patients were in stage (17.4%) III, and one hundred and twenty-six patients were in stage IV (72.8%). Skull base involvement and orbital invasion were observed in 60 (34.7%) and 86 cases (49.7%). The median follow-up period for live patients was 25.0 months (range 1.8–137.7 months). Local recurrence or progression was discovered in 45 cases (26.0%) of the 173 cases, regional lymph node recurrence in 7 cases (4.0%), and distant metastasis in 17 cases (9.8%).

The relationship between p16 expression and patients' characteristics. Of the 173 patients who participated in this investigation, thirty-eight patients (22.0%) had p16 positive (p16+) evidence. The typical p16 expression feature in SNSCC is shown in Figure 1.

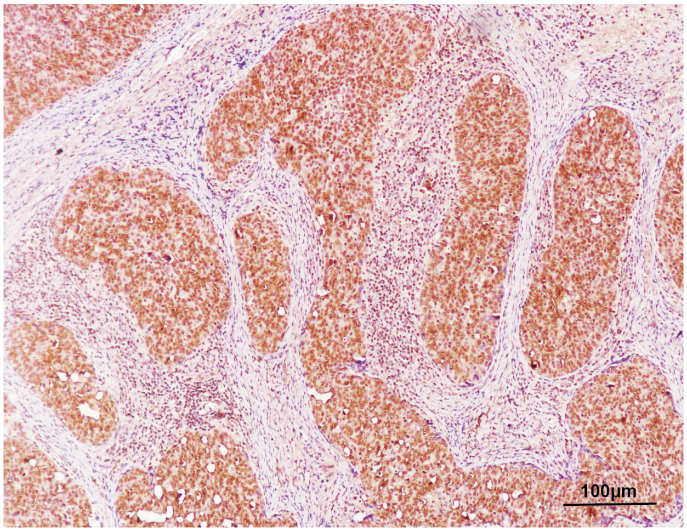

Figure 1. Representative images of immunohistochemical staining of sinonasal squamous cell carcinoma tissue: diffuse nuclear and cytoplasmic p16 expression (100×).

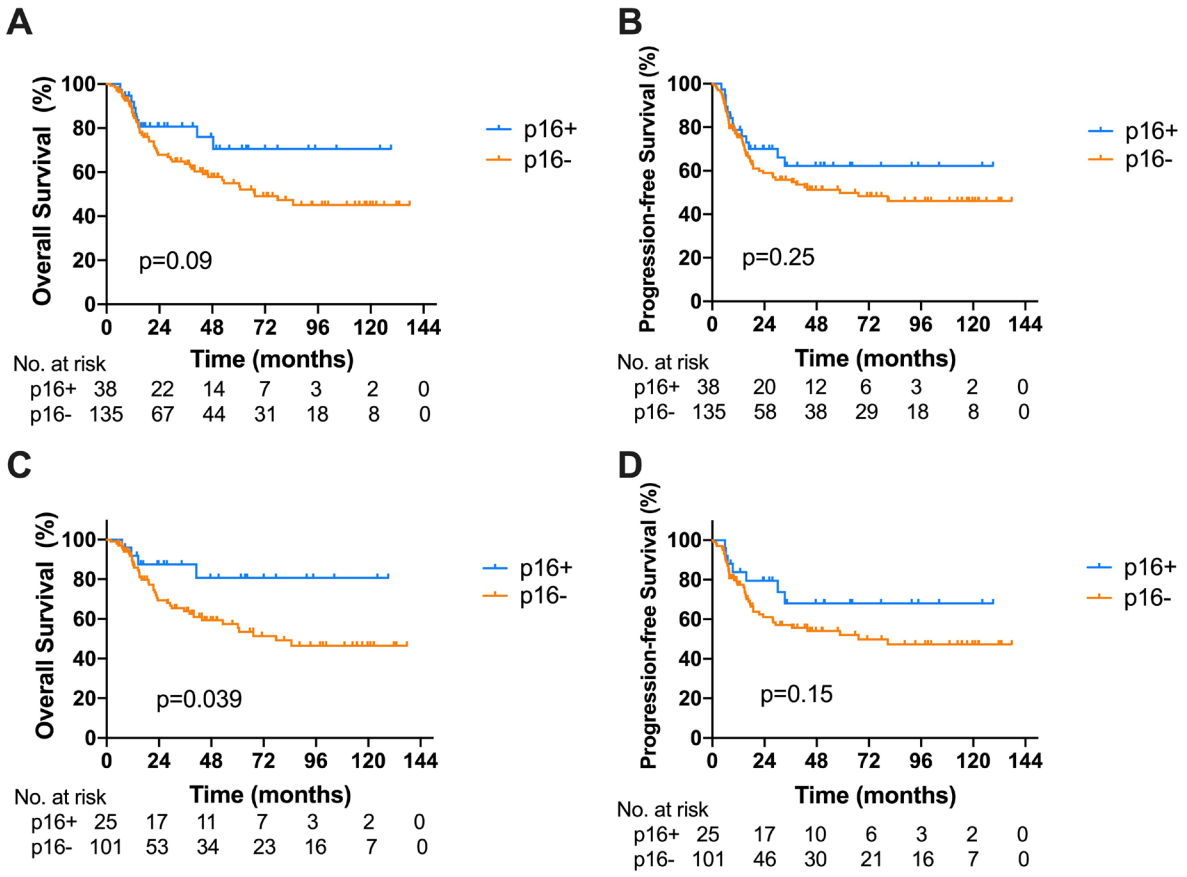

Figure 2. The Kaplan Meier analysis for 5-year overall survival (OS) rate and progression-free survival (PFS) rate in sinonasal squamous cell carcinoma (SNSCC). A, B) There was no significant difference in OS (70.5% vs. 54.9%, p=0.09) and PFS (62.2% vs. 49.8%, p=0.95) between p16+ group and p16- group in total 173 SNSCC. C, D) Except for T4b cases, the p16+ SNSCC patients showed a significantly better OS than the p16- cases (80.7% vs. 57.5%, p=0.039) and a slight improvement in PFS (68.1% vs. 52.0%, p=0.15).

Immunohistochemistry analysis identified p16+ tissues in ten IP-SNSCC patients (10/51, 19.6%) and twenty-eight *de novo* SNSCC patients (28/122, 23.0%), respectively. p16 status was unaffected by the tumor origin (χ^2=0.23, p=0.63).

There were no significant differences between the p16+ and p16– groups in age, gender, clinical stage, tumor site, and treatment characteristics in all the SNSCC patients. Additionally, 7 of 38 (18.4%) p16+ and 23 of 135 (17.0%) p16– patients had developed lymph node metastases, with no correlation between lymph node metastasis and p16 status (χ^2=0.04, p=0.84). Compared to p16+ cases, p16– patients did not show any difference in adjacent organ invasions, such as the orbital (χ^2=0.16, p=0.68) and the skull base (χ^2=1.19, p=0.28).

The impact of p16 expression on survivals in SNSCC. During the follow-up period, 62 patients died, including 53 patients (39.3%) in the p16– group, 9 patients (23.7%) in the p16+ group (χ^2=3.13, p=0.08). The mean time to death for the two groups was 24.8 months and 18.6 months, respectively, with no statistically significant difference (p=0.39). Local recurrence was not more likely in p16– patients (25.9%, 35/135) than in p16+ patients (26.3%, 10/38) (χ^2=0.002, p=0.96). In the p16– group, the meantime to local recurrence was 13.4 months, whereas, in the p16+ group, it was 13.1 months, with no statistical difference (p=0.39).

There was no significant difference in 5-year OS between the p16+ group and the p16– group (70.5% vs. 54.9%, HR=0.55, 95% CI=0.31–0.99, p=0.09), as well as PFS (62.2% vs. 49.8%, HR=0.71, 95% CI=0.41–1.21, p=0.25) in the whole SNSCC cohort. When the analyses were limited to patients with T1–T4a tumors, p16+ patients had a significantly superior 5-year OS (80.7% vs. 57.5%, HR=0.36, 95% CI=0.17–0.73, p=0.039), and a somewhat better in PFS (68.1% vs. 52.0%, HR=0.56, 95% CI=0.29–1.09, p=0.15) (Figure 2). In maxillary sinus lesions, p16+ SNSCC had superior 5-year OS (87.4% vs. 49.2%, HR=0.22, 95% CI=0.09–0.56, p=0.03) and PFS (79.1% vs. 40.7%, HR=0.25, 95% CI=0.11–0.57, p=0.01) than p16– SNSCC. For those patients without orbital invasion, p16+ patients conferred a better OS (86.9% vs. 57.3%, HR=0.22, 95% CI=0.10–0.52, p=0.02) and PFS (76.5% vs. 52.5%, HR=0.34, 95% CI=0.16–0.73, p=0.03). However, for those who had no skull base involvement, p16+ cases had better OS (82.9% vs. 57.7%, HR=0.31, 95% CI=0.14–0.66, p=0.037) but not PFS (72.7% vs. 52.7%, HR=0.45, 95% CI=0.22–0.92, p=0.08) (Figure 3).

Discussion

Since 1983, with the detection of HPV DNA in SNSCC, a growing number of studies have investigated HPV carcinogenesis in SNSCC as a possible etiological factor. HPV detection rates at SNSCC have varied widely, varying from 0 to 100%. The presence of HPV in sinonasal cancer and its prognostic significance, on the other hand, remains unclear. According to recent retrospective studies and meta-analyses, HPV-positive SNSCC was found in up to 30% of cases, regardless of the detection method [2]. Another meta-analysis of 1,449 cases showed that the total HPV prevalence was 25.5% in SNSCC, ranging from 25.5% to 31.7%, depending on the types of testing. The nasal cavity and ethmoids had the highest rate of 37.6%, while the maxillary, sphenoid, and frontal sinus had the lowest incidence of 15.1% [13]. It was reported that patients with HPV-positive tumors were younger than those with HPV-negative, and nasal cavity (49.4%) tumors were the most common [14]. In our cohort, there were no significant differences between p16+ cases and p16– cases in terms of age, gender, clinical stage, tumor site, or treatment features, in contrast to p16+ oropharyngeal malignancies with a variety of epidemiological factors [15, 16].

Many studies have assessed HPV genotypes in SNSCC, with HPV-16 and HPV-18 being the most common. High-risk HPV subtype infection has been associated with a higher incidence of malignant transformation from IP to SNSCC [17, 18]. The E6 and E7 oncoproteins boost oncogenic transformation in high-risk HPV subtypes by acting on the p53 and RB pathways, respectively, whereas the E5 oncoprotein is likely to play a crucial role in oncogenic transformation in low-risk HPV subtypes. p16, a tumor suppressor protein encoded by the CDKN2A gene (cyclin-dependent kinase inhibitor 2A), prevents typically damaged cells from proliferating by inhibiting the activation of Rb. As a result, using immunohistochemistry to detect p16 expression is a highly sensitive surrogate marker for high-risk HPV infection that is transcriptionally active [18].

In a retrospective analysis of data from the National Cancer Data Base, it was found that 31.5% of the SNSCC cases were HPV-positive [19]. HPV-positive SNSCC patients had a significantly higher 3-year OS rate (74.6%; 95% CI, 66.1–84.2%) than HPV-negative SNSCC patients (56.1%; 95% CI, 49.7–63.3%). Some investigators proposed that HPV infection played a minor role in SNSCC, and p16 immunostaining did not appear to be a valid surrogate marker for HPV [20]; however, whether p16 immunostaining could be a surrogate marker for SNSCC is worth being investigated.

To our knowledge, this is the most comprehensive study of p16 expression in immunohistochemistry as a predictor of SNSCC. p16 was discovered in 22.0% of SNSCC patients (38/173), with no difference between IP-SNSCC (19.6%) and *de novo* SNSCC (23.0%). When employed as a surrogate for transcriptionally active HPV, p16 staining is well consistent with HPV infectious status. Consequently, HPV DNA positivity and p16 positivity have a strong relationship [21].

Immunohistochemical p16 expression is thought of as a particularly sensitive surrogate marker in HPV-related oropharyngeal squamous cell carcinoma (OPSCC) [22–24]. In addition to OPSCC, immunohistochemical p16 expression has high sensitivity and specificity for detecting HPV infection in other squamous cell carcinomas of the head and neck [25]. However, whether p16 is a sensitive and specific surrogate marker of HPV infection for SNSCC has not been well

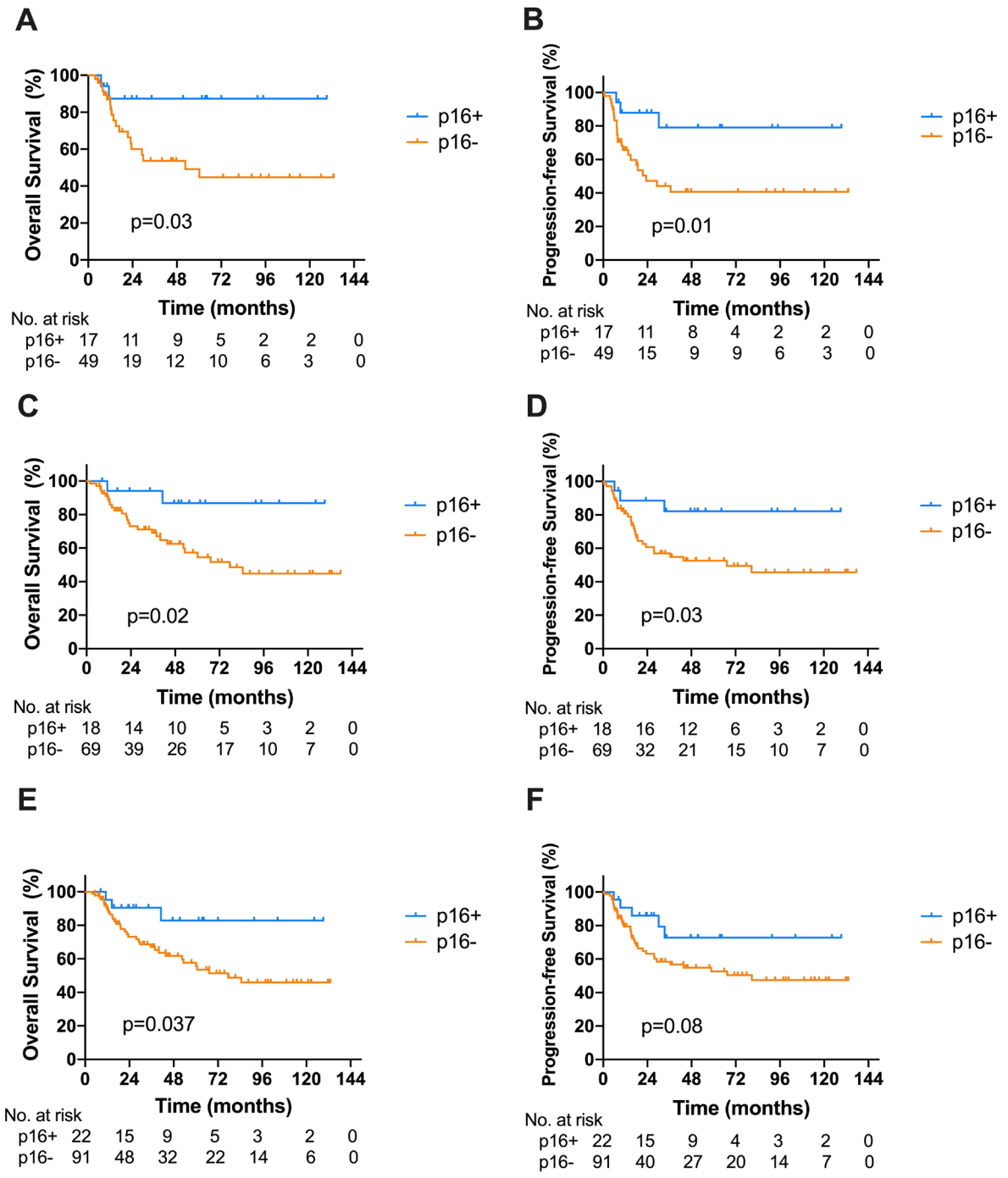

Figure 3. A, B) The Kaplan Meier analysis for 5-year overall survival (OS) rate and progression-free survival (PFS) rate in maxillary squamous cell carcinoma patients, p16+ patients showed a better OS (87.4% vs. 49.2%, p=0.03) and PFS (79.1% vs. 40.7%, p=0.01). C, D) P16+ patients conferred a better 5-year OS (86.9% vs. 57.3%, p=0.02,) and PFS (76.5% vs. 52.5%, p=0.03) for those patients without orbital invasion. E, F) For those who had no skull base involvement, p16+ status significantly correlated with a better OS (82.9% vs. 57.7%, p=0.037) but was not with PFS (72.7% vs. 52.7%, p=0.08).

established. One research reported that in 16 p16+ SNSCC patients, only 9 presented positively in site hybridization [26]. However, another study revealed HPV mRNA-positive sinonasal cancers displayed a significantly higher proportion of immunoreactivity for p16 than HPV-negative cancers [27]. In the whole SNSCC cohort, there was no significant difference between the p16+ groups and p16– groups in 5-year OS (70.5% vs. 54.9%, p=0.09) or PFS (62.2% vs. 49.8%, p=0.25).

These results were similar to those in that no prognostic value of p16 expression was observed for OS and PFS [26]. When stage T4b cases were excluded, p16+ patients showed significantly superior 5-year OS (80.7% vs. 57.5%, p=0.039) and a slight increase in PFS (68.1% vs. 52.0%, p=0.15). In reality, T4b SNSCC has a poor prognosis, and it is tough to improve it no matter how it is managed.

Before investigating the relationship between p16 status and SNSCC, it's worth emphasizing that we considered the TNM stage and other clinicopathologic factors. Compared with p16– SNSCC, p16+ SNSCC in maxillary sinus lesions showed better 5-year OS (87.4% vs. 49.2%, p=0.01) and PFS (79.1% vs. 40.7%, p=0.01). In a stratified analysis of patients with adjacent organ involvement, those without skull base or orbital invasion, patients with p16+ SNSCC had better OS than those with p16– cases. Complete surgical resection with postoperative radiotherapy is the standard of therapy for SNSCC, and it has been related to a greater OS rate [28, 29]. Negative surgical margins were difficult to achieve in individuals with orbital or skull base involvement to spare nearby vital organs. Patients with little organ involvement, on the other hand, had a wider range of radical treatment choices. After eliminating the poor predictive factors, it is more objective to investigate the relationship between p16 status and SNSCC prognosis.

This study has a few limitations. First, this is a retrospective review of a single institution. Second, we could not analyze the relationship between p16 and HPV in SNSCC due to a lack of HPV status testing. We are preparing to perform HPV RNA in situ hybridization on these groups and investigate the relationship between immunohistochemical p16 and HPV status in SNSCC to validate further findings of p16 as a biomarker. In addition, during more than a decade, the therapeutic approach evolved, which might cause some bias in the analysis. Despite these limitations, the findings of this study were in line with our expected hypotheses, and we were able to show a correlation between p16 expression and better prognosis in a specific subset of SNSCC patients. Further study that unifies patient status and treatment modality should be done to establish the utility of p16 expression in determining prognostic factors in SNSCC.

In conclusion, p16+ patients had a considerably superior 5-year overall survival rate and a slight increase in progression-free survival, except in stage T4b cases. In specific diseases such as maxillary sinus lesions, non-orbital invasion cases, or non-skull base involvement cases, p16+ SNSCC had a superior 5-year overall survival and progression-free survival than p16– SNSCC. Immunohistochemical p16 expression may be a predictive predictor in individuals with maxillary sinus SCC, not in the T4b stage, or without skull base involvement or orbital invasion.

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