



## Unusual cases of sinonasal malignancies: a letter to the editor on HPV-positive sinonasal squamous cell carcinomas

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### Introduction

This case series describes three unusual cases of human papillomavirus (HPV)-positive sinonasal squamous cell carcinomas (SNSCC). Moreover, the associated literature has been systematically reviewed. As HPV, especially high-risk types 16 and 18, has been considered a possible culprit in the development of SNSCC, studies have addressed the significance of HPV infection in SNSCC in particular [1–4]. A systematic review reported approximately 30% of SNSCCs being HPV positive – this both with and without association to inverted papilloma [5].

Symptoms of sinonasal malignancy are often quite unspecific, which often leads to diagnostic delay even with a classic presentation; in cases with unusual symptoms, clinical diagnosis may be rather challenging—as illustrated by the presented cases.

### Materials and methods

In April 2022, two authors (BBL and SS) systematically searched PubMed and Embase for articles in English using the following keywords: sinonasal carcinoma and sinonasal cancer combined with human papillomavirus, HPV, 'Papillomaviridae', and p16. See Supplementary for the detailed search strategy. We defined the research question according to the PICO (Patient, Interventions, Comparison, and Outcome) structure; all patients were diagnosed with SNSCC and were tested for HPV status. Regarding comparison, we compared the prognosis of HPV positive SNSCCs with HPV negative SNSCCs, and outcome was survival.

The study population for the case series consisted of three patients with HPV-positive SNSCC treated at the Department of Otorhinolaryngology, Head and Neck Surgery, and Audiology, Copenhagen University Hospital, Copenhagen, Denmark from 2010 to 2020. The SCC diagnosis was confirmed by morphology and immunohistochemical analysis;

HPV-related multiphenotypic sinonasal carcinoma (HMSC) cases were excluded.

HPV analysis was performed as part of the standard diagnostic workup testing for HPV DNA using HPV DNA PCR with general primers GP5+/6+ (GP5+: 50-TTTGTTACTGTGGTA GATACTAC-3'0; GP6+: 50-GAAAAATAAACTGTAAATCATATTC-3'0) and Platinum Taq DNA polymerase (Invitrogen, Naerum, Denmark) followed by inspection of PCR products by gel electrophoresis. Subsequently, genotyping was performed using next generation sequencing (NuGEN Technologies Inc., San Francisco, California) for sequencing on Illumina instruments as previously described [6] or by using the HPV chip assay (VisionArray® HPV Chip by Zytovision, Germany).

### Results

#### Systematic review

The Embase and PubMed search generated a total of 324 articles after removal of duplicates. Twenty-four articles met the inclusion criteria, as shown in Figure 1. The studies reported data on more than 4000 SNSCC patients. Study characteristics are shown in Table 1.

#### HVP and overall survival

Eighteen of the included studies ( $n = 3688$ ) reported on the occurrence of HPV in SNSCC and the association with OS [1,4,7–13,15,18–23,25,26]. Eleven of these studies ( $n = 3396$ ) reported improved survival in HPV-positive patients [1,7,8,12,13,15,18,20–23], whereas seven studies ( $n = 292$ ) did not find any statistically difference in survival rate [4,9–11,19,25,26]. Two of the studies ( $n = 108$ ) reported a trend towards better overall survival for the HPV positive SNSCCs, but did not find the correlation being statistically significant [4,11].

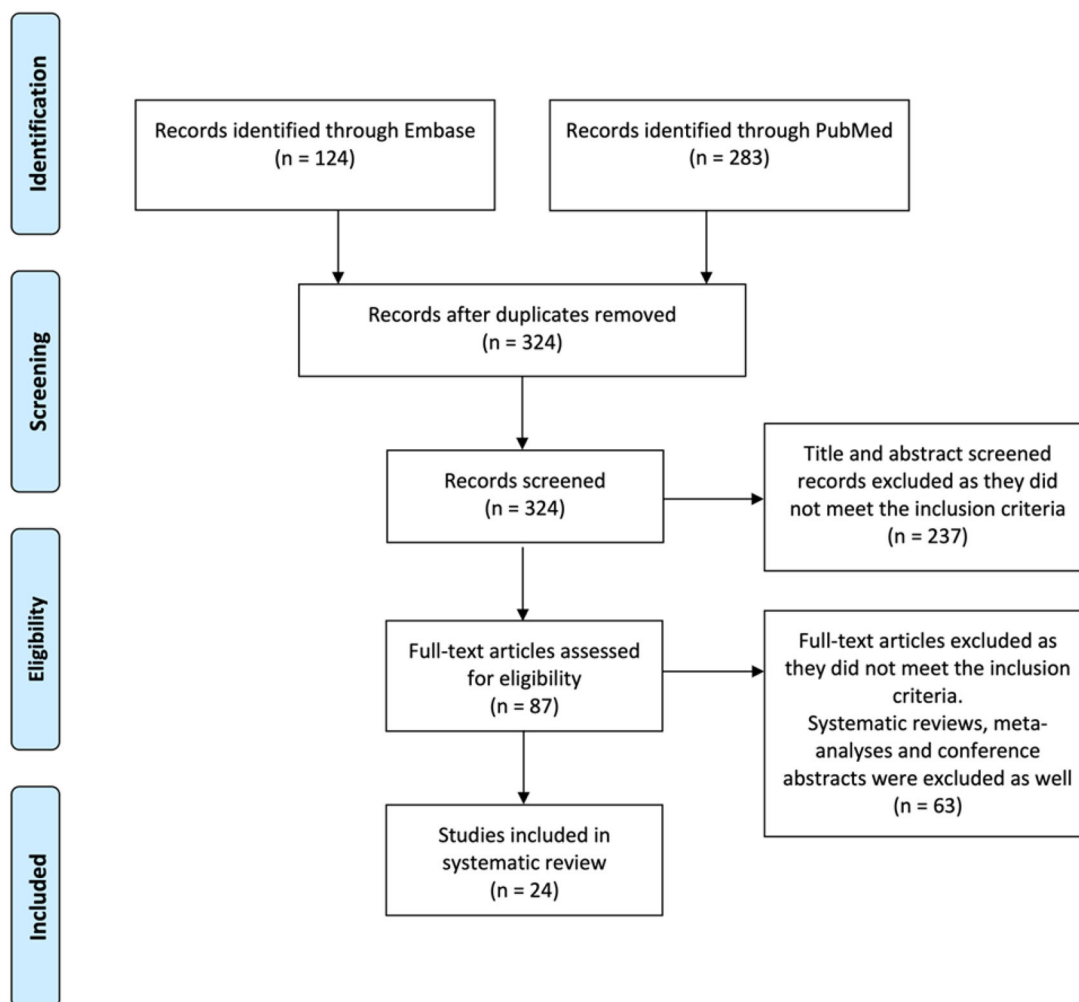


Figure 1. PRISMA Flowchart.

### HPV and p16

Eleven of the studies examined the role of p16 as a surrogate marker for HPV [4,8,10,13,14,16,17,20,24,27,28]. Six studies ( $n=475$ ) reported that p16 positivity was strongly associated with the presence of HPV DNA [8,10,13,17,20,28]. Svajdler et al. moreover, detected that sensitivity of transcriptionally-active HPV status, *via* p16 as a surrogate marker, was 62.5% and specificity was 92.3% [10]. In several small cohorts ( $n=139$ ), p16 was not found to be a reliable surrogate marker of HPV status in SNSCC [14,16,24,27].

### Case study

Three patients with HPV-positive SNSCC were included in this study as they had an unusual presentation and course of disease. The patients were seen and treated in accordance with the Danish fast track cancer program and consented to participate in this research report [29].

### Case 1 – cancer of unknown primary

A 57-year-old woman presented with an HPV16-positive head and neck cancer of unknown primary (CUP). The initial treatment of her CUP was left-sided-superficial parotidectomy revealing an intraparotid lymph node with non-

keratinizing squamous cell carcinoma (NKSCC) and no additional parotid pathology. Moreover, the surgical intervention comprised dissection of lymph nodes in levels II and III on the left side and bilateral tonsillectomy. Afterwards, resection of the lingual tonsils was performed using transoral robotic surgery (TORS). The primary tumour was not identified despite fluorodeoxyglucose-positron emission tomography (FDG-PET), computed tomography (CT) scan, and additional multiple biopsies from oro- and rhinopharynx.

Four years after the CUP diagnosis, the patient presented with nasal stenosis and ulceration on the left side of the nasal septum. Due to her history, an FDG-PET/CT was performed, and based on the findings a biopsy was obtained from the nasal ulceration. The latter demonstrated HPV-positive SNSCC, T1N0M0, containing the same HPV-type as her previous head and neck CUP. In agreement with our pathologists, the primary tumour was finally identified *i.e.* four years following her initial cancer diagnosis. Subsequently, a lateral alar rhinotomy, with resection of most of the nasal septum, was performed followed by local postoperative radiation therapy (RT).

The cancer recurred 15 months following the nasal surgery, suspected due to odontalgia, epistaxis and ulceration of the nose. Magnetic resonance imaging (MRI) and biopsies showed SCC involvement of the left side of the maxillary

**Table 1.** Study characteristics: inclusion period, source, and number of cases.

Authors (publication year, country)	Centre/data source(s)	Inclusion period	Cases, <i>n</i> <sup>a</sup>	WA, male patients	HPV and OS	p16 as surrogate marker
Al-Qurayshi et al. 2020, USA [7]*	National Cancer Database	2004–2015	537	63.1%	Correlation, <i>p</i> = 0.002	-
Alos et al. 2009, Spain [20]	Department of Pathology and treated at the Hospital Clinic, University of Barcelona	1981–2006	60	75%	Correlation, <i>p</i> = 0.0364	Sensitivity = 100% Specificity = 100%
Bishop et al. 2013, USA [27]	The surgical pathology archives of The Johns Hopkins Hospital	1995–2011	161	Not specified	-	97% of the HPV + tumours exhibited high p16 expression
Cabal et al. 2020, Spain [8]	Otolaryngology, Hospital Universitario central de Asturias	1989–2017	74	81.87%	No statistical correlation, unknown <i>p</i> -value	-
Cheung et al. 2010, Hong Kong [26]	Department of Ear, Nose & Throat, Pamela Youde Nethersole Eastern Hospital, Hong Kong	1995–2006	5	Not specified	-	No correlation between HPV + and p16+, <i>p</i> = 0.848
Chowdhury et al. 2017, USA [9]	Department of Otolaryngology, University of Kansas Medical Centre	1990–2015	26	73%	Correlation, <i>p</i> < 0.005	-
Cohen et al. 2019, USA [10]	University of Miami Department of Otolaryngology	2011–2017	47	60%	Correlation, unknown <i>p</i> -value	Sensitivity = 90% Specificity = 67%
Doescher et al. 2015, Germany [11]	Not specified	1994–2013	44	75%	No statistical correlation, <i>p</i> = 0.3	-
Hongo et al. 2021, Japan [12]	Kyushu University, Kyushu Cancer Centre, Hamanomachi Hospital, and Yamaguchi Red Cross Hospital	2003–2019	131	69.5%	Correlation, <i>p</i> = 0.0089	-
Hongo et al. 2021, Japan [13]	Kyushu University, Kyushu Cancer Centre, Hamanomachi Hospital, and Yamaguchi Red Cross Hospital	2003–2019	146	69.9%	Correlation, <i>p</i> = 0.0277	Sensitivity = 100% Specificity = 92.6% Positive predictive value = 52.4%
Hu et al. 2020, China [14]	The Eye and Ear, Nose & Throat Hospital of Fudan University	2010–2017	114	73.7%	-	Three HPV + cases out of 18 p16+
Jiromaru et al. 2020, Japan [15]	Kyushu University or Kyushu Cancer Centre	2003–2016	101	69.3%	Correlation, <i>p</i> = 0.0037	-
Jo et al. 2009, USA [16]	Department of Pathology, University of Virginia, Charlottesville	Not specified	4	Not specified	-	Three HPV + cases out of two p16+ cases
Kim et al. 2020, Korea [17]	Catholic Medical Centre hospitals, Seoul St. Mary's Hospital and Bucheon St. Mary's Hospital	2011–2019	27	Not specified	-	Sensitivity = 100%
Kılıc, et al. 2017, USA [1]*	National Cancer Database	2010–2014	770	64.9%	Correlation, <i>p</i> < 0.0001	-
Laco et al. 2015, Czech Republic [18]	The Fingerland Department of Pathology (University Hospital, Hradec Kralove, Czech Republic), Department of Pathology (General University Hospital, Prague, Czech Republic), and Department of Pathology (University Hospital, Olomouc, Czech Republic)	1995–2014	49	69.4%	No statistical correlation, <i>p</i> = 0.23	-
Larque et al. 2014, Spain [19]	Hospital Clinic, University of Barcelona, Villarroel, Barcelona, Spain	1985–2010	70	74.3%	Correlation, <i>p</i> = 0.028	-
Li et al. 2018, USA [20]*	National Cancer Database	2010–2014	Not specified	74%	No statistical correlation, unknown <i>p</i> -value	-
Markovic et al. 2020, USA [21]	The departmental database of Icahn School of Medicine at Mount Sinai, New York	2011–2018	32	65.6%	No statistical correlation, <i>p</i> = 0.17	-
Nishikawa et al. 2021, Japan [22]	Department of Head and Neck Surgery, Aichi Cancer Centre Hospital	2008–2019	90	77.7%	Correlation, unknown <i>p</i> -value	-
Oliver et al. 2020, USA [19]*	National Cancer Database	2010–2016	1418	64.7%	Correlation, <i>p</i> < 0.001	-
Svajdler et al. 2020, Czech Republic [23]	Louis Pasteur University Hospital in Košice, Slovakia and Faculty Hospital in Pilsen, Czech Republic and a large private pathology laboratory in Prešov, Slovakia	2002–2014	34	70.6%	No statistical correlation, <i>p</i> = 0.60	Sensitivity = 62.5% Specificity = 92.3%
		1990–2020	59	62.7%		

(continued)

Table 1. Continued.

Authors (publication year, country)	Centre/data source(s)	Inclusion period	Cases, n <sup>a</sup>	WA, male patients	HPV and OS	p16 as surrogate marker
Tendron et al. 2022, France [4]	Head and Neck Cancer Committee Database of Gustave Roussy Cancer Campus, Université Paris Saclay, Villejuif, France				No statistical correlation, $p = 0.06$	No prognostic value of p16 expression was observed for OS
Yamashita et al. 2015, Japan [24]	Not specified	Not specified	16	87.5%	-	p16+ overexpression identified in one of the four HPV+ cases

WA: weighted average; HPV: human papillomavirus; OS: overall survival.

<sup>a</sup>Only sinonasal squamous cell carcinoma cases were included.

\*Overlapping inclusion period from the National Cancer Database.

bone close to the nasal septum. Surgery was performed in October 2020 with radical resection of the palate and the maxillary bone from region +6 to 6+.

Six months later, FDG-PET/CT and biopsies showed recurrence of the cancer at T-site. The patient was treated with chemo- and immunotherapy. 18 months following the FDG-PET/CT, a new recurrence in the oral cavity (upper gum region +1 to +3) was identified. The patient is now in palliative treatment with chemo- and immunotherapy.

### Case 2 – multiple recurrences

A 63-year-old man was referred with a history of recurring painless left-sided epistaxis in 2009. Initial biopsy from the anterior part of the left side of the nasal septum contained a papillomatous tumour with carcinoma *in situ*. Subsequent biopsies demonstrated an HPV16- and p16-positive SNSCC, T1N0M0. Clinically, tumour invasion to the right side was visible and the patient was treated with radiotherapy (RT). A few months after RT, a rhinectomy was performed due to recurrence involving most of the nasal septum and the overlying skin.

During the following five years post RT, the patient had six minor recurrences in different sinonasal locations. These were all HPV-positive and treated surgically. At follow-up, seven months after the sixth recurrence, new biopsies containing SNSCC were obtained from the left lamina papyracea area close to a previously identified recurrence of the SCC. The tumour was surgically removed.

New recurrences close to the previous location were removed six months following the aforementioned surgery. New biopsies obtained at follow-up three months later, from areas close to the latter, showed HPV16-positive SCC. As it seemed that following the biopsies there was no visible tumour left, the patient declined further extensive surgery. At the subsequent examination one month later, no tumour or ulcer was visible.

In 2019, i.e. five years after the latest recurrence, the patient complained of irritation and bleeding from the nasal cavity. Biopsies confirmed a recurrence again at the lamina papyracea. Subsequent endoscopic surgery was performed, obtaining radicality. Currently, there is no sign of recurrence.

### Case 3 – HPV39

In a 51-year-old woman with enlarged cervical lymph nodes and a lymph node fine needle aspiration biopsy (FNA) containing SCC, an FDG-PET/CT scan demonstrated a focus in rhinopharynx with bilateral neck metastases. Biopsies from rhinopharynx and a resected cervical lymph node contained the same type of tumour, which were HPV39-positive. Treatment with three series of chemotherapy, followed by RT on T-site and weekly chemotherapy, was commenced.

Five years following this, a new primary tumour—an HPV39- and p16-positive SNSCC on the left side of the nasal septum reaching the ipsilateral ethmoidal cells—was diagnosed. Surgical resection of the tumour, as well as reconstruction of the external nose followed by post-operative RT, was performed.

Nineteen months later, recurrence was suspected due to an FDG-PET/CT showing PET-positive foci in the chin, left submental lymph node, and posterior left nasal cavity. Excision of the PET-positive tumour, lymph nodes, and initial T-site was performed, demonstrating HPV39-positive recurrence. Six months following the surgery, new biopsies of the right facial lymph node, level I, showed another recurrence, which was resected successfully. Currently, five years after, there is no sign of recurrence.

### Discussion

The current three cases illustrate a wide range of symptoms and disease course associated with HPV-positive SNSCC. As SNSCC is not a frequent disease, and because of the vague and unspecific symptoms associated with it, the clinical diagnosis can be difficult—even more so with uncommon symptoms [30]. This was clearly illustrated by the case of the patient previously treated for an HPV-positive CUP of the neck before the final diagnosis of the HPV-positive SNSCC. To the best of our knowledge, only one other case of SNSCC presenting as CUP has been described [31]. Lymph node metastases are not common at presentation of SNSCC; only around 10% present with nodal neck metastases, and in follow up, around 10% develop distant metastases (often alongside local recurrence) mostly those with higher tumour stages and tumour located in the maxillary sinus [30,32]. Interestingly, the primary lesion, in all our three cases, was

found in the nasal cavity. This demonstrates that HPV infection in the nasal cavity might be more frequent than previously expected [33].

All three included patients were diagnosed with multiple recurrence of their SNSCC. This demonstrates the importance of long-term systematic follow-up in patients with HPV-positive SNSCC, and how focus also should include other locations comprising neighbouring organs like nasopharynx. However, the result of an active and persistent therapy seems to have been justified.

The association between HPV and OPSCC, and the improved prognosis of the HPV-positive OPSCC patients compared with HPV-negative OPSCC, is well-established. Currently, the significance of HPV in SNSCC is still unclear, but the association is investigated [34–38]. Our review highlights that several studies indicate that HPV may play a role in the development of sinonasal cancer—particularly SNSCC [5,18,39–41]. In parallel with OPSCC, a positive prognostic value of HPV-positivity in SNSCC has been described. This was also reported as significant in eleven of our included studies [1,7,8,12,13,15,18,20–23]. Four of the enrolled studies reported on data from the National Cancer Database. As the data was extracted with overlapping time period, it is seen as a limitation to our review [1,18,22,25]. Whether the improved prognosis can be attributed in part to younger patients in the HPV-positive SNSCC patient group, remains to be explored [4,8].


## Conclusion

In conclusion, the cases described in this letter serve as reminders of the multifaceted symptoms of HPV-positive SNSCC, which should also be taken into consideration when usual workup fails to identify the primary tumour in a patient with CUP. Furthermore, the study demonstrates the importance of an awareness of HPV in SNSCC and systematic long-term follow-up along attention on new locations for recurrence. The general significance of HPV-positivity in SNSCC has not yet been determined - nor has the role of p16 overexpression in SNSCC, but our review indicates that patients with HPV-positive SNSCC may have a better survival than patients with HPV-negative SNSCC. Testing for HPV and p16 in the SNSCC is also recommended for future studies.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Data availability statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

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