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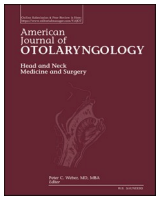

Surgical treatment of 186 sinonasal inverted papillomas and analysis of the immunohistochemical and molecular features associated with recurrences☆

Juan Ramón Gras-Cabrerizo [a,*], Maria Martel-Martin [b], Maria Casasayas-Plass [a], Katherina Kolanczak [c], Laura Lopez-Vilaró [d], Justyna Szafranska [d], Humbert Massegur-Solench [c], Xavier León-Vintró [c]

[a] Department of Otolaryngology/Head and Neck Surgery, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona and Corachán Clinic, Spain
[b] Department of Otolaryngology/Head and Neck Surgery, Hospital del Mar and Corachán Clinic, Barcelona, Spain
[c] Department of Otolaryngology/Head and Neck Surgery, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain
[d] Department of Anatomical Pathology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain

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ABSTRACT

Introduction: Inverted papillomas (IP) are benign epithelial tumors with a tendency to be locally invasive and with disposition to recur. The aim of our study is to present the results of IP treatment, considering pathological, immunohistochemical and molecular features of recurrence.

Material and methods: From 1978 to 2020, 186 sinonasal IPs surgeries corresponding to 152 patients were treated in our center. We performed a pathology evaluation of all the recurrent cases reviewing the histological diagnosis, the presence of mixed component other than IP, the koilocytic changes, the p16 over expression and HPV-DNA detection.

Results: Overall recurrence rate was 19 % (35/186). The 35 IP recurrences correspond to 22 patients, 9 of whom presented a single recurrence (single recurrence group) while 13 of them presented more than one recurrence (multi-recurrent group). Immunohistochemical analysis showed a higher percentage of p16 overexpression (54 % vs 33 % $p = 0.415$) and HPV-DNA presence (23 % vs 0 % $p = 0.240$) in the multi-recurrent group compared with single recurrence group. In addition, the revision showed more IP with exophytic papilloma focus (38 vs 22 % $p = 0.648$) and a higher proportion of IP with koilocytotic changes (61 % vs 22 % $p = 0.099$) in the multi-recurrent group. There is no significant difference between groups in our results.

Conclusion: The analysis of our patients may differentiate between two groups with recurrent papillomas. A single recurrence group where the cause of recurrence is probably an anatomical problem related to an incomplete resection, and a second pattern, the multi-recurrence group, where HPV infection may be the main cause of recurrence.

1. Introduction

Inverted papillomas are benign epithelial tumors with an incidence of 0.5 to 1.5 cases per 100,000 inhabitants per year [1,2]. The latest edition of the WHO classification of head and neck tumors confirmed the existence of the three previously described types of sinonasal papillomas, the inverted papilloma (IP), the exophytic papilloma (EP) and the oncocytic papilloma (OP), removing the eponym of Schneiderian for the IP [3]. IP and OP originate mostly from the lateral wall of the nasal fossa while EP originates more frequently from the anterior areas of the nasal septum. IPs are the most frequent, representing approximately 60 % of all papillomas. They are more frequent in males (3:1) and are usually diagnosed between the 5th and 6th decade of life. >95 % of cases are unilateral and have their origin preferentially in the ethmoid and/or lateral wall of the nasal fossa [4,5]. Their etiology is unknown, although for years the possible relationship with human papillomavirus (HPV) has been suggested in their pathogenesis. It is not clear whether the presence of HPV is a colonization or is actually an etiologic factor

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* Corresponding author at: Department of Otolaryngology/Head and Neck Surgery, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, C/ Mas Casanovas, 90, 08041 Barcelona, Spain.
E-mail address: jgras@santpau.cat (J.R. Gras-Cabrerizo).

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present in both recurrences and possible malignant transformations [6]. The current treatment for most IP is the endoscopic endonasal approach (EEA) with a recurrence rate according to the largest series ranging from 6 % to 25% [7–9]. The aim of our study was to present the results after treatment of IPs, considering pathological, immunohistochemical and molecular features of recurrence.

2. Material and methods

From 1978 to 2020, 186 sinonasal IPs surgeries corresponding to 152 patients were treated in our center. One patient had a bilateral IP (0.7 %). Seventy-seven percent of the patients (117/152) were male and 23 % (35/152) were female. The mean age of the patients at the time of diagnosis was 59 years, with a range between 16 and 84 years. Most patients (105/152) had no toxic habits. Seventy-three percent of cases were primary lesions (135/186) and 27 % were lesions previously treated (51/186) in other institutions. According to Krouse classification system [10], 26 lesions were classified as T1 (14%), 65 as T2 (35%), 89 as T3 (48%) and 6 lesions as T4 (3%).

Between 1978 and 89 most patients were treated with an external approach, while in the early 1990s EEA became the technique of choice for the vast majority of IPs treated in our center. Since 2005, in cases of involvement of the anterior or inferior wall of the maxillary sinus, in order to avoid a gingivolabial approach, we performed a medial maxillectomy preserving the inferior turbinate [11]. In cases where the lesion was massively affecting the mucosa of the anterior or lateral wall of the frontal sinus, especially if these were hyperpneumatized, EEA was complemented with an external approach.

Histologic slides of all the recurrent cases were reviewed by two pathologists. Immunohistochemical analysis of p16 expression was evaluated in all cases using a mouse monoclonal anti-p16INK4a antibody (clone JC2, Genova). The stain was labeled as positive when immunoexpression was present - either in the nucleus or cytoplasm - in ≥50 % of tumor cells. All samples were further tested for HPV DNA detection and genotyping using a Genomic PCR. The Chi-square or Fisher's exact test was used as needed to analyze local recurrences. The minimum follow-up time for patients was 2 years.

2.1. Ethics statement

The Institutional Review Board of Santa Creu i Sant Pau Hospital approved all protocols and procedures used. Data are available upon reasonable request.

3. Results

3.1. Total population

Sixty-seven percent (124/186) of the lesions originated in the ethmoid and/or lateral wall, 27 % in the maxillary sinus (51/186), 3 % (5/186) in the sphenoid sinus and in the remaining 3 % (6/186) another location was evident or the origin could not be clearly ascertained (one case in the inferior turbinate, two cases in the nasal septum, one case in the frontal sinus and two cases of probable multifocal origin).

An external approach was performed in 14 % of the lesions (21 lateral rhinotomies, 2 gingivolabial approaches and 4 craniofacial approaches). All patients who underwent lateral rhinotomy and gingivolabial approach were diagnosed and treated between 1987 and 1997. An EEA was performed in 159 lesions (86 %), 11 of which were associated with a gingivolabial approach. In the only case of IP originating in the frontal sinus, a Draf III frontal approach was performed. In 19 papillomas involving the maxillary sinus, the EEA included a resection and repositioning of the inferior turbinate technique.

3.2. Recurrences

Overall recurrence rate was 19 % (35/186), 13 % (17/135) in primary lesions and 35 % (18/51) in lesions previously treated in other centers. The percentage of recurrences according to Krouse classification was 7 % in T1 (2/26), 17 % in T2 (11/65), 20 % in T3 (18/89) and 66 % in T4 (4/6) ($p = 0.018$).

Three percent of the IPs were associated with carcinoma (6/186). Carcinomas diagnosed in the 80s and 90s were classified as infiltrating squamous cell carcinomas (1 synchronous lesion and 2 metachronous lesions). Those diagnosed after 2000 were described as carcinomas in situ, all of them observed simultaneously with the IP (synchronous).

Seventy-one percent of the recurrences (25/35) were located in the ethmoid and/or lateral wall, 23 % in the maxillary sinus (8/35) and 6 % in the sphenoid sinus (2/35). Table 1 shows the distribution of the number of recurrences according to its location and period of treatment.

The 35 IP recurrences correspond to 22 patients, 9 of whom presented a single recurrence (single recurrence group) while 13 of them presented more than one recurrence (multi-recurrent group). Table 2 shows the location of the first recurrence according to each group. In the multiple recurrence group, the initial tumors were in stage T3 in 6 out of 13 cases (46 %) and in stage T2 in another 6 out of 13 cases (46 %), with one case in stage T4.

Even though it was not statistically significant, immunohistochemical analysis (Table 3) showed a higher percentage of p16 overexpression (54 % vs 33 %) and HPV-DNA presence (23 % vs 0 %) in the multi-recurrent group compared to the single recurrent group. In addition, the revision showed more IPs with exophytic papilloma focus (38 % vs 22 %) and a higher proportion of IPs with koilocytotic changes (61 % vs 22 %) in the multi-recurrent group. Fig. 1. There is no significant difference between groups in our results.

4. Discussion

Currently, the EEA can successfully treat the vast majority of sinonasal IPs. In 2019 Peng et al. [12] published an extensive meta-analysis with >4000 patients showing a 13 % recurrence rate in the group of patients treated endoscopically versus 17 % in the group treated with external surgery. Bugter et al. [13] in a review of >1400 patients from contemporary series published recurrence rates of 11 % for endoscopic approaches, 18 % for external approaches and 12 % for combined approaches. Our results in patients treated with endoscopic surgery are consistent with the literature showing similar recurrence rate (17 %). On the opposite, our results show higher recurrence rate in external approaches. As described in a previous publication, most of our recurrences occurred in the 1970s and 1980s, when these lesions were diagnosed at more advanced stages than at present and were mostly treated with external approaches [14].

Recurrences are associated with several factors such as the presence of previous surgery, the location of the lesion, incomplete resection of the tumor or association with HPV. Probably the most important factor remains the incomplete resection of the tumor rather than the idiosyncrasy of the tumor itself. The presence of residual disease is related to the existence of a previous surgery where the presence of edema or polypoid lesions can be underestimated. In our study, the recurrence rate was clearly higher in the group of previously treated lesions compared to initial surgeries (35 % vs. 13 %). These differences are widely reported in the literature [12,15].

Table 1
Recurrences according to treatment period.

	1978–1999	2000–2020
Ethmoid, sphenoid and lateral wall	15 (93 %)	12 (63 %)
Maxillary sinus	1 (7 %)	7 (37 %)
Recurrences	16 (100 %)	19 (100 %)

Table 2
Location of the first recurrence according to single and multi-recurrence groups ($p = 0{,}609$).

	Single recurrence	Multi recurrence	Total
Ethmoid, sphenoid and lateral wall	6 (35 %)	11 (65 %)	17 (100 %)
Maxillary sinus	3 (60 %)	2 (40 %)	5 (100 %)

Table 3
Histological features, p16 overexpression and HPV-DNA detection and genotyping, according to the recurrence group. **EP: exophytic papilloma.*

	Single recurrence	Multi recurrence	Total	*P*-value
Mixed papilloma with an EP component	22 % (2/9)	38 % (5/13)	32 % (7/22)	0.648
Koilocytic changes	22 % (2/9)	61 % (8/13)	45 % (10/22)	0.099
p16 positivity	33 % (3/9)	54 % (7/13)	45 % (10/22)	0.415
HPV-DNA positivity	0 % (0/9)	23 % (3/13)	14 % (3/22)	0.240

The location of the papilloma determines the appearance of a possible recurrence. Although EEA is the technique of choice in the treatment of IP, there are unfavorable locations such as the anterior and inferior wall of the maxillary sinus or the lateral and superior wall of the frontal sinus. For this reason, some centers still perform external approaches or combined approaches with the endoscopic technique. As shown in Table 1, a change in the location of recurrences is evident with the incorporation of EEA. If we consider the year 2000 as a reference date in terms of the consolidation of endoscopic surgery in our center, we observe that the origin of recurrences decreased in the ethmoidal, sphenoidal and lateral wall regions from 93 % to 63 %, and increased in the maxillary sinus from 7 % to 37 %. One possible explanation is that in the 1980s–90s the gingivolabial approach, a commonly used technique, allowed extensive control of all the walls of the maxillary sinus. On the contrary, despite the significant advantages of EEA, an exclusively endoscopic approach to the maxillary sinus may present difficulties to access areas due to poor exposure, such as the anterior and inferior wall, particularly the alveolar recess. In order to avoid the use of an external approach, various endoscopic medial maxillectomies were described in the 1990s [10,16,17]. In our center, since 2005, IPs from the maxillary sinus have undergone a modified medial maxillectomy, preserving the inferior turbinate when it was not affected [11].

In a multivariate analysis, Lee et al. [18] identified frontal sinus invasion and the presence of bone involvement as prognostic factors in addition to incomplete resection of the lesion. Frontal sinus involvement both in its origin and extension is infrequent. In most cases the involvement of the frontal sinus has its origin in an invasion from the ethmoidal sinus and the bony walls are usually undamaged. In our database only one lesion originated in the frontal sinus and no recurrence had its origin in this location.

In agreement with other authors, we performed a combined endonasal and external approach when the anterior and/or lateral wall of the frontal sinus was affected, especially when the diameter between both walls was <1 cm; also, in cases with massive involvement of a lateral supraorbital cell or in cases with associated carcinoma [19].

The concept of radicality in the treatment of inverted papilloma, with excision of the tumor and drilling of the underlying bone, has changed in recent years [8]. IP is an epithelial tumor that invaginates

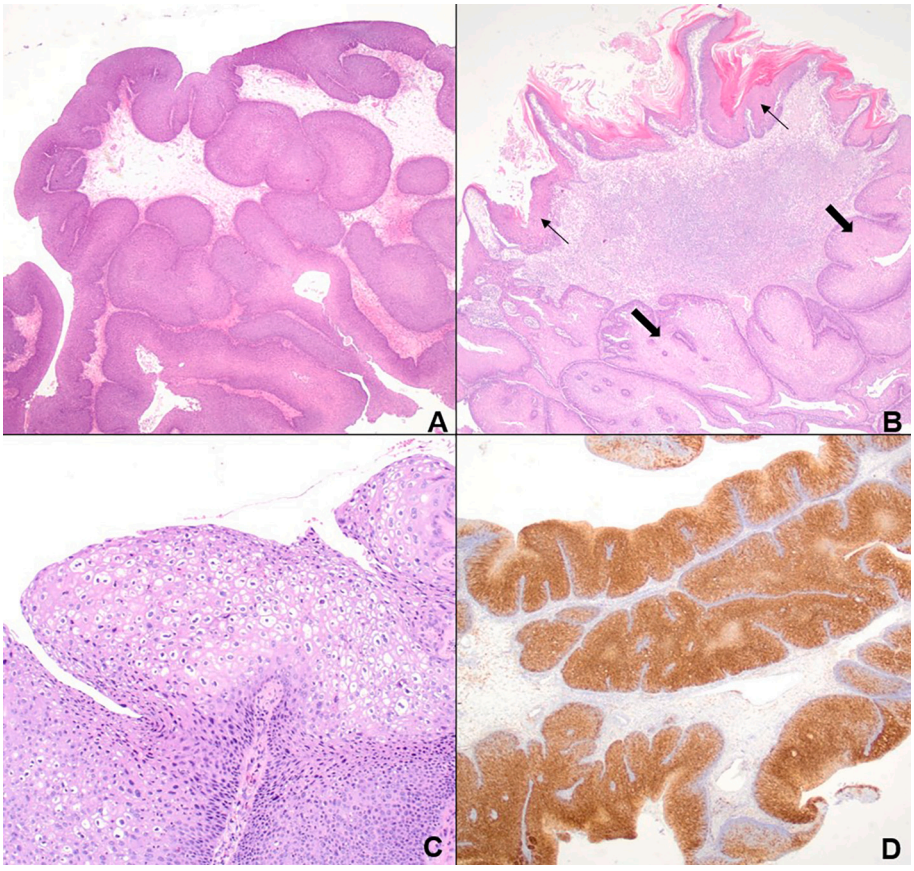

Fig. 1. A: Prominent downward endophytic growth of a conventional IP (H&E 20×). B: Exophytic component (fine arrow) in a multirecurrent IP (thick arrow) (H&E 20×). C: Severe koilocytic changes in a multirecurrent IP (H&E 100×). D: p16 overexpression in a conventional IP (IHQ 20×).

into the underlying stroma, preserving the basement membrane, and therefore does not invade cartilage or bone. In our experience, in the vast majority of cases, the papilloma has a unifocal origin and it is possible to identify the tumor's pedicle. We usually perform a wide excision of the underlying mucosa by subperiosteal dissection and if this is easily dissected, we do not perform bone drilling. In the case of finding anfractuosities in the bone, we drill the bone and leave it flat in order to be able to safely remove the mucosa.

Regarding HPV infection, the current knowledge does not support the hypothesis that the presence of HPV infection alone is sufficient for the development of an IP. The association between EP and low-grade HPV (6 and 11) has been demonstrated. In IP this relationship is contradictory and confusing. Some publications present percentages of association between HPV and IP higher than 50% [20]. On the other hand, recent studies show percentages below 10 %. Fulla M et al. found only 5 % of cases with HPV-DNA positive in 79 previously untreated IPs, and along the same lines Huan Wang et al. found only 6 % of patients with positive HPV-DNA [21–23]. These data suggest that HPV probably does not participate in the etiopathogenesis of IP but that the inflammation and metaplasia of the mucosa itself predispose to viral infection. In our series, a higher rate of p16 protein overexpression, EP foci and koilocytic changes was found in patients with multiple recurrences compared to patients with a single recurrence. As shown in Table 3, there is a differential pattern between the two groups that showed no statistical difference probably due to small samples. These findings may suggest that patients with multiple recurrences are more often associated with HPV infection.

Further support of this hypothesis is the different location affecting recurrences in the two groups. Recurrences in the maxillary sinus occur more frequently in patients with a single recurrence (67 %). Bearing in mind the anatomical peculiarities of the maxillary sinus previously mentioned, we can intuit that incomplete resection of the lesion is the cause of recurrence. In contrast, 65 % of recurrences in the multi-recurrence group are located in the lateral wall and/or ethmoid sinus, areas of better access with current approaches, suggesting a possible viral infection as a cause of recurrence.

The association between IP and malignant lesions is also controversial. Most studies suggest a rate of malignant transformation between 5 and 10 % of cases, almost always associated with squamous cell carcinoma. Re et al. [24] in a review of >3000 patients found an 8 % association between IP and squamous carcinoma. It is now suggested that this association is synchronous, i.e. they occur in the same lesion, rather than metachronous, where the malignant lesion develops in the resected area where the papilloma was previously present. In a meta-analysis published by Mirza et al. [25] in which they studied >3000 patients with IP, they found an association with a synchronic carcinoma in 7 % of cases and with a mechatronic carcinoma in 3.6 % of cases.

In our series, the percentage of association between carcinoma and IP has been progressively decreasing. In the last 20 years this association is 2 %, all of them being synchronous lesions with an pathological diagnosis of carcinoma in situ.

The higher proportion of infiltrating squamous cell carcinoma in patients diagnosed during the 80s and 90s is most likely due to overestimation of local component with expansive growth pattern. In agreement with our study, Viitasalo et al. [26] found only 0.7 % of papillomas associated with carcinoma. The future of this association will probably be clarified with the incorporation and analysis of new biological markers.

One of the limitations was the retrospective nature of the study and the fact that we only evaluated the immunohistochemical features in the recurrent cases, so the population studied was limited. Probably, comparing our results with a non-recurrent group is needed to confirm our findings.

5. Conclusion

The analysis of our patients may differentiate between two groups with recurrent papillomas. A single recurrence group where the cause of recurrence is probably an anatomical problem related to an incomplete resection, and a second pattern, the multi-recurrence group, where HPV infection may be the main cause of recurrence.

CRediT authorship contribution statement

Juan Ramón Gras-Cabrerizo: Investigation, Methodology, Writing – original draft. **Maria Martel-Martin:** Writing – review & editing. **Maria Casasayas-Plass:** Writing – review & editing. **Katherina Kolanczak:** Methodology. **Laura Lopez-Vilaró:** Investigation. **Justyna Szafranska:** Investigation. **Humbert Massegur-Solench:** Supervision. **Xavier León-Vintró:** Supervision.

Declaration of competing interest

The authors declare that there is no conflict of interest.

References

[1] Wang MJ, Noel JE. Etiology of sinonasal inverted papilloma: a narrative review. World J Otorhinolaryngol Head Neck Surg 2016;3(1):54–8.
[2] Hennessey PT, Reh DD. Chapter 9: benign sinonasal neoplasms. Am J Rhinol Allergy 2013;27(Suppl. 1):S31–4.
[3] Thompson LDR, Franchi A. New tumor entities in the 4th edition of the World Health Organization classification of head and neck tumors: nasal cavity, paranasal sinuses and skull base. Virchows Arch 2018;472(3):315–30.
[4] Hennessey PT, Reh DD. Chapter 9: benign sinonasal neoplasms. Am J Rhinol Allergy 2013;27(Suppl. 1):S31–4.
[5] Leoncini G, Zanetti L. The papillomas of the sinonasal tract. A comprehensive review. Pathologica 2017;109(1):31–4.
[6] Re M, Gioacchini FM, Bajraktari A, et al. Malignant transformation of sinonasal inverted papilloma and related genetic alterations: a systematic review. Eur Arch Otorhinolaryngol 2017;274(8):2991–3000.
[7] Busquets JM, Hwang PH. Endoscopic resection of sinonasal inverted papilloma: a meta-analysis. Otolaryngol Head Neck Surg 2006;134(3):476–82.
[8] Goudakos JK, Blioskas S, Nikolaou A, Vlachtsis K, Karkos P, Markou KD. Endoscopic resection of Sinonasal inverted papilloma: systematic review and Meta-analysis. Am J Rhinol Allergy 2018;32(3):167–74.
[9] Meng Y, Fang G, Wang X, et al. Origin site-based staging system of sinonasal inverted papilloma for application to endoscopic sinus surgery. Head Neck 2019;41(2):440–7.
[10] Krouse JH. Development of a staging system for inverted papilloma. Laryngoscope 2000;110(6):965–8.
[11] Gras-Cabrerizo JR, Massegur-Solench H, Pujol-Olmo A, Montserrat-Gili JR, Ademá-Alcover JM, Zarraonandia-Andraca I. Endoscopic medial maxillectomy with preservation of inferior turbinate: how do we do it? Eur Arch Otorhinolaryngol 2011;268(3):389–92.
[12] Peng R, Thamboo A, Choby G, Ma Y, Zhou B, Hwang PH. Outcomes of sinonasal inverted papilloma resection by surgical approach: an updated systematic review and meta-analysis. Int Forum Allergy Rhinol 2019;9(6):573–81.
[13] Bugter O, Monserez DA, van Zijl FVWJ, de Jong RJ Baatenburg, Hardillo JA. Surgical management of inverted papilloma; a single-center analysis of 247 patients with long follow-up. J Otolaryngol Head Neck Surg. 2017;46(1):67. Published 2017 Dec 20. doi:10.1186/s40463-017-0246-7.
[14] Gras-Cabrerizo JR, Montserrat-Gili JR, Massegur-Solench H, León-Vintró X, De Juan J, Fabra-Llopis JM. Management of sinonasal inverted papillomas and comparison of classification staging systems. Am J Rhinol Allergy 2010;24(1):66–9.
[15] Lisan Q, Laccourreye O, Bonfils P. Sinonasal inverted papilloma: risk factors for local recurrence after surgical resection. Ann Otol Rhinol Laryngol 2017;126(6):498–504.
[16] Sham CL, Woo JK, van Hasselt CA. Endoscopic resection of inverted papilloma of the nose and paranasal sinuses. J Laryngol Otol 1998;112(8):758–64.
[17] Sadeghi N, Al-Dhahri S, Manoukian JJ. Transnasal endoscopic medial maxillectomy for inverting papilloma. Laryngoscope 2003;113(4):749–53.
[18] Lee JJ, Roland LT, Licata JJ, et al. Morphologic, intraoperative, and histologic risk factors for sinonasal inverted papilloma recurrence. Laryngoscope 2020;130(3):590–6.
[19] Pietrobon G, Karligkiotis A, Turri-Zanoni M, et al. Surgical management of inverted papilloma involving the frontal sinus: a practical algorithm for treatment planning. Acta Otorhinolaryngol Ital 2019;39(1):28–39.
[20] Lin H, Lin D, Xiong XS. Roles of human papillomavirus infection and stathmin in the pathogenesis of sinonasal inverted papilloma. Head Neck 2016;38(2):220–4.

[21] Fulla M, Szafarowski T, Frias-Gomez J, et al. Human papillomavirus and factors associated with recurrence in sinonasal inverted papillomas from Poland and Spain head neck pathol 2020;14(3):758–67.
[22] Wang H, Zhai C, Liu J, Wang J, Sun X, Hu L, et al. Low prevalence of human papillomavirus infection in sinonasal inverted papilloma and oncocytic papilloma. Virchows Arch 2020;476(4):577–83.
[23] Justice JM, Davis KM, Saenz DA, Lanza DC. Evidence that human papillomavirus causes inverted papilloma is sparse. Int Forum Allergy Rhinol. 2014;4(12): 995–1001.
[24] Re M, Gioacchini FM, Bajraktari A, Tomasetti M, Kaleci S, Rubini C, et al. Malignant transformation of sinonasal inverted papilloma and related genetic alterations: a systematic review. Eur Arch Otorhinolaryngol 2017;274(8): 2991–3000.
[25] Mirza S, Bradley PJ, Acharya A, Stacey M, Jones NS. Sinonasal inverted papillomas: recurrence, and synchronous and metachronous malignancy. J Laryngol Otol 2007;121(9):857–64.
[26] Viitasalo S, Ilmarinen T, Aaltonen LM, Hagström J, Hytönen M, Hammarén-Malmi S, et al. Sinonasal inverted papilloma - malignant transformation and non-sinonasal malignancies. Laryngoscope 2022, Mar;133(3):506–11.