

An evaluation of factors which affect recurrence and malignancy of sinonasal papillomas

Evaluación de los factores que afectan la recurrencia y la malignidad de los papilomas sinasales

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Abstract

Objective: Sinonasal papillomas are rare benign tumors. They challenge otorhinolaryngologists due to their high recurrence rate and malignant transformation. The aim of this study was to investigate the clinical and demographic factors associated with recurrence and/or malignancy of sinonasal papillomas. **Methods:** This retrospective study included 49 patients who were operated on between 2014 and 2020. Clinical and demographic characteristics of the patients were retrieved from the patients' records. **Results:** The recurrence rate was determined to be 12.2% and the malignancy rate was 8.2%. Recurrence was significantly higher in females, the advanced stage (T3 and T4), and papillomas located in the maxillary sinus. The recurrence rate was significantly lower in patients treated with the endoscopic surgery. Factors affecting malignancy were the presence of dysplasia and extension out of the paranasal sinuses. **Conclusions:** The results of this study showed that the factors affecting recurrence were gender, papilloma stage, type of surgery performed, and whether the tumor extended to the paranasal sinuses.

Keywords: Sinonasal papilloma. Inverted papilloma. Paranasal sinus.

Resumen

Objetivo: Los papilomas sinasales son tumores benignos poco frecuentes. Suponen un reto para los otorrinolaringólogos por su elevada tasa de recurrencia y transformación maligna. Investigar los factores clínicos y demográficos asociados con la recurrencia y con la malignidad de los papilomas sinasales. **Métodos:** Estudio retrospectivo que incluyó 49 pacientes operados entre 2014 y 2020. Las características clínicas y demográficas se recuperaron de los registros de los pacientes. **Resultados:** Se determinó una tasa de recurrencia del 12.2% y una tasa de malignidad del 8.2%. La recurrencia fue significativamente mayor en las mujeres, en los estadios avanzados (T3 y T4) y en los papilomas localizados en el seno maxilar. La tasa de recidiva fue significativamente menor en los pacientes tratados con cirugía endoscópica. Los factores que afectaron a la malignidad fueron la presencia de displasia y la extensión fuera de los senos paranasales. **Conclusiones:** Los resultados de este estudio muestran que los factores que afectaron la recidiva fueron el sexo, el estadio del papiloma, el tipo de cirugía realizada y si el tumor se extendía a los senos paranasales.

Palabras clave: Papiloma sinasal. Papiloma invertido. Seno paranasal.

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Introduction

Sinonasal papillomas are benign tumors originating from the Schneiderian membrane of the nasal cavity and paranasal sinuses. There are three types of sinonasal papillomas; exophytic, oncocytic, and inverted, with the latter being the most common type. The most important features that distinguish inverted papilloma (IP) from other benign sinonasal tumors are; high recurrence, malignancy potential, and significant local bone erosion¹. The recurrence rate has been reported to be between 15% and 20%²⁻⁷. Recurrences usually occur within the first 3 years after incomplete excisions. IP may be histopathologically associated with varying degrees of dysplasia, carcinoma *in situ*, and squamous cell carcinoma (SCC)⁸. The malignancy rate has been reported to be approximately 1.9-27%⁹⁻¹³. Malignancy may coexist with the IP in the same lesion or may develop years after excision of the papilloma.

Many factors, including smoking, size of the papilloma, type of surgery, the presence of squamous hyperplasia, high hyperkeratosis, increased mitosis, HPV positivity, bilateral papilloma and localization of IP have been associated with recurrence or malignancy in the literature^{9,10,14}. In the majority of case series, the limited number of patients makes it difficult to draw reliable conclusions from these data, as sinonasal papillomas are rare and it can take many years to gather a large number of cases. Each institution should share their experiences to increase the number of the patients to be able to make an additional contribution to the literature on this subject. The aim of this study was to investigate the clinical and demographic factors associated with recurrence and/or malignancy in sinonasal papillomas. Furthermore, with the results obtained from this study, it was aimed to contribute to the pool of knowledge on this subject, which has many controversies and uncertainties.

Methods

The study was initiated following the approval of the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (Date: September 21, 2020, Number: 96/6). The study cohort included 61 patients who underwent surgery for sinonasal papilloma between 2014 and 2020. After the exclusion of 12 patients who were first operated on another center or who did not

have complete follow-up data, the analyses were completed with 49 patients. The parameters evaluated in this study were patient age, gender, smoking and alcohol consumption, follow-up time, type of surgery, papilloma side and localization of origin, the presence extranasal extension, the type and stage of the papilloma, and recurrence and malignancy rates. The Krouse Staging System¹⁵ was used for staging. The stage, localisation, origin, and invasion site of papillomas were determined according to the intraoperative findings and paranasal sinus tomography images.

The post-operative regular follow-up examinations included nasal endoscopic examination every 3 months in the 1st year, every 6 months in the 2nd year, and annually thereafter for up to 7 years. In the follow-up examinations, all cavities and sinuses were checked with straight and angled telescopes. In cases with suspicious lesions in the frontal sinus or in the anterior wall of the maxillary sinus, imaging was performed to view the areas that could not be seen with endoscopy. Patients with suspicious lesions identified in endoscopic examination underwent biopsies.

The Chi-square test was used in the statistical analysis. Parameters with a $p < 0.05$ were considered statistically significant.

Results

Demographic and clinical parameters of patients

The patients comprised 43 (87.8%) males and 6 (12.2%) females with a mean age of 48.96 ± 15.9 years (Range, 15-78 years) and a mean follow-up period of 39.16 ± 20.4 months (Range, 8-88 months). The demographic and clinical parameters of the patients are summarized in table 1.

Factors associated with recurrence

The overall recurrence rate of this cohort was 12.2%. The earliest time to recurrence was 9 months, and the latest was 72 months (Mean, 39.5 ± 21.6 months). All recurrences occurred in the same localisation as the original tumor. The relationships between the demographic and clinical parameters and recurrence are shown in table 2. Recurrence was observed in 7% of male and 50% of female patients. The difference between the gender in terms of recurrence rates was statistically significant ($p = 0.003$).

Table 1. Demographic and clinical parameters of patients

Parameters	Number of patients (%)
Age	
Mean $\pm$ standard deviation (SD)	48.96 $\pm$ 15.9
$\leq$ 45	16 (32.7)
$>$ 45	33 (67.3)
Gender	
Male	43 (87.8)
Female	6 (12.2)
Follow-up time (months)	
Min-Max	8-88
Mean $\pm$ SD	39.16 $\pm$ 20.4
Side of papilloma	
Right	34 (69.4)
Left	15 (30.6)
Type of papilloma	
Inverted	44 (89.8)
Non-inverted	5 (10.2)
Exophytic	5 (10.2)
Oncocytic	0
Originated site	
Paranasal sinus	27 (55.1)
Maxillary sinus	23 (46.9)
Frontal sinus	2 (4.1)
Sphenoid sinus	2 (4.1)
Ethmoid sinus	0
Nasal cavity	22 (44.9)
Lateral nasal wall	12 (24.5)
Middle turbinate	9 (18.4)
Inferior turbinate	1 (2)
Stage of papilloma	
Early (T1-T2)	18 (36.7)
T1	8 (16.3)
T2	10 (20.4)
Advanced (T3-T4)	31 (63.3)
T3	26 (53.1)
T4	5 (10.2)
Malign transformation	
Yes	4 (8.2)
No	45 (91.8)
Displasia	
Yes	5 (10.2)
No	44 (89.8)
Smoking	
Yes	20 (40.8)
No	29 (59.2)
Alcoholism	
Yes	3 (6.1)
No	46 (93.8)
Type of surgery	
Endoscopic	42 (85.7)
Open	0
Combine	7 (14.3)

Endoscopic surgery was performed on 42 (85.7%) patients, and 7 patients (14.3%) underwent combined surgery (Maxillary trocar, Caldwell Luc, and Bicoronal Forehead flap in 4, 2, and 1 patients, respectively). The recurrence rate in patients who underwent only endoscopic surgery was found to be significantly lower than those who underwent combined surgery ($p = 0.008$).

The sinonasal papillomas were separated into two groups according to localisation in the paranasal sinus or nasal cavity. The distribution of the sinonasal papillomas according to localisations is summarized in table 3. Sinonasal papillomas most commonly originated from the maxillary sinus in this cohort. Recurrence occurred in 6 of 27 patients (22.2%) with papilloma located in the paranasal sinus, and no recurrence was observed in any of the papillomas located in the nasal cavity. The difference between the two groups was statistically significant ($p = 0.018$). All the recurrences originated from the maxillary sinus.

In this study, the patients were evaluated in two groups. Those with Krouse stage T1 and T2, in which the papilloma is limited to the nasal cavity, ethmoid sinuses, and medial wall of maxillary sinus, were defined as early stage (Group 1). Patients with papilloma, which are more difficult to reach surgically, such as in the other walls of the maxillary sinus, sphenoid, and/or frontal sinuses (Krouse T3 and T4), were accepted as advanced stage (Group 2). Patients with malignancy and/or with extension out of the nasal cavity and paranasal sinus were also included in Group 2. The distribution of papilloma types according to the Krouse Staging System is shown in table 4. More than half of the patients were at the advanced stage (53.1% T3 and 10.2 % T4). All patients with recurrence were at T3 stage. There was a statistically significant difference between the two groups in terms of recurrence ($p = 0.046$). In five patients, the papilloma extended out of the nasal cavity and paranasal sinus. IP extended to the orbit in two of these patients, to the orbit and intracranial region in one patient, and to the parapharyngeal region in one patient. Another patient had an oroantral fistula stemming from IP invasion.

The study results showed that patient age, smoking and alcohol consumption, papilloma side and type, and the extension of sinonasal papilloma out of the nasal cavity and paranasal sinuses had no significant effect on recurrence ($p > 0.05$).

Table 2. The effects of demographic and clinical parameters of patients on recurrence

Parameters	Patients with Recurrence (number of patients [%])	Patients without recurrence (number of patients [%])	Total (number of patients [%])	p
Age Min-Max (mean±standard deviation)	16-59 (44.83 ± 15.2)	15-78 (49.53 ± 16)	15-78 (48.96 ± 15.9)	
≤ 45	2 (12.5)	14 (87.5)	16 (32.7)	0.97
> 45	4 (12.1)	29 (87.9)	33 (67.3)	
Side of papilloma				0.43
Right	5 (14.7)	29 (85.3)	34 (69.4)	
Left	1 (6.7)	14 (93.3)	15 (30.6)	
Gender				0.003*
Female	3 (50)	3 (50)	6 (12.2)	
Male	3 (7)	40 (93)	43 (87.8)	
Type of papilloma				0.38
Inverted	6 (13.6)	38 (86.4)	44 (89.8)	
Non-inverted	-	5 (100)	5 (10.2)	
Papilloma's originated site				0.018*
Intra-paranasal sinus	6 (22.2)	21 (77.8)	27 (55.1)	
Nasal cavity	-	22 (100)	22 (44.9)	
Extension out of the paranasal sinus				0.38
Yes	-	5 (100)	5 (10.2)	
No	6 (13.6)	38 (86.4)	44 (89.8)	
Stage of papilloma				0.046*
Early (T1-T2)	-	18 (100)	18 (36.7)	
Advanced (T3-T4)	6 (19.3)	25 (80.7)	31 (63.3)	
Smoking				0.63
Yes	3 (15)	17 (85)	20 (40.8)	
No	3 (10.3)	26 (89.7)	29 (59.2)	
Alcohol use				0.71
Yes	-	3 (100)	3 (6.1)	
No	6 (13)	40 (87)	46 (93.9)	
Type of surgery				0.008*
Endoscopic surgery	3 (7.1)	39 (92.9)	42 (85.7)	
Combined surgeries	3 (42.9)	4 (57.1)	7 (14.3)	

*p < 0.05, statistically significant values.

Table 3. Distribution of sinonasal papillomas according to originated site

Originated site	Number of patients (%)
Paranasal sinus	27 (55.1)
Maxillary sinus	23 (46.9)
Ethmoid sinus	-
Frontal sinus	2 (4.1)
Sphenoid sinus	2 (4.1)
Nasal cavity	22 (44.9)
Lateral nasal wall	12 (24.5)
Middle turbinate	9 (18.4)
Inferior turbinate	1 (2)

Factors associated with malignancy

The malignancy rate of this study was found to be 8.2% (4/49). All the patients who developed malignancy had inverted type and synchronous SCC. All patients with malignancy were male with a mean age of 54.75 years. All four patients with malignancy were treated with endoscopic surgery, and the follow-up time of these patients was 8, 22, 23, and 37 months, respectively. Recurrence was observed in only one patient with malignancy.

Of the 5 patients (40%) with dysplasia, malignancy was determined in 2 (40%). The malignancy rate of IP with dysplasia was significantly higher than that of IP without dysplasia (p = 0.006). The rate of malignancy

in IP extending out of the nasal cavity and paranasal sinuses was statistically significantly higher than in those without extension (3 of 5 patients, $p < 0.001$). In this cohort, no other parameters had any effect on malignancy.

Discussion

The overall recurrence rate in this study was 12.2% (6 of 49 patients), which was consistent with the literature. Some studies have reported significantly higher rates of recurrence¹⁶⁻¹⁸. The high rate of recurrence in one of these studies was explained by the fact that their hospital was a tertiary health-care center which treated more complex patients¹⁸. However, the development of recurrence in sinonasal papillomas is a multifactorial event and should not be attributed to a single factor. Factors such as the type of surgery applied, the surgeon's experience, the localization and stage of the papilloma, and the presence of residue may also affect recurrence. Many studies have been conducted on the recurrence and malignancy of sinonasal papillomas, but no consensus has been reached. In the current study, the factors with significant effect on the recurrence of sinonasal papillomas were determined to be; female gender, the stage and localization of the papilloma, and the type of surgery applied. Recurrence rates were found to be increased by a younger patient age and smoking according to Jardine et al.¹⁹, whereas Roh et al.²⁰ and Moon et al.²¹ reported that smoking, Suh et al.²² stated that female gender, and Katori et al.²³ that some histopathological features of papilloma (increased mitotic activity, hyperkeratosis, and the presence of squamous hyperplasia) increased recurrence. In other studies, residual papilloma tissue following surgery has also been blamed for recurrence^{10,24}.

In many studies, the recurrence rate in males has been reported to be higher than in females^{18,24}. In contrast, the recurrence rate in the current study was significantly higher in females than in males. Suh et al.²² also reported the relationship between recurrence and gender, with a recurrence rate in female patients of 50% (4 of 8 patients), similar to the current study. However, to be able to more clearly state that female gender increases recurrence, there is a need for further studies to be conducted with more female patients.

It has been reported that recurrence is more common in IP located in the frontal sinus, which is due to the difficulty in visualization of the sinus^{6,18,25-27}.

Recurrence in IP with frontal sinus localization has been reported to be 22.4%²⁸. In the two patients with frontal sinus localization in the current study, no recurrence developed. In some studies, it has been reported that maxillary sinus localisation increases recurrence^{7,29} and the results obtained in the current study were similar to those studies. In all the patients with recurrence, the IP was located in the maxillary sinus, and there was invasion of the anterior and lateral walls of the maxillary sinus. Just like the lateral wall of the frontal sinus, the anterior wall of the maxillary sinus is an area where papilloma can be overlooked, and residual tissue may remain. Although Caldwell-Luc and/or gingival trocar surgery was added to the endoscopic surgery in these cases; unfortunately, recurrence was still observed in some patients. In these cases, the inside of the sinus should be carefully checked with straight and angled telescopes to ensure that no residual tissue remains. The mucosa invaded by the papilloma should be curetted, and the bone tissue should be removed by drilling. When there is frontal sinus lateral wall invasion, it is difficult to reach this area with endoscopic surgery alone, so adding open surgeries such as bicoronal forehead flap and/or osteoplastic flap to the endoscopic surgery allows the papilloma to be removed without residue.

There are different opinions about the relationship between the stage of the IP and recurrence. Some studies have highlighted an association between recurrence and Krouse classification³⁰, while others have not^{4,5,7,17,24-26}. A meta-analysis revealed an increased risk of recurrence between Krouse T2 and T3 stages,³¹ and another study showed a significant relationship only between Krouse T4 stage and recurrence²¹. In most studies, the four stages have been compared with each other in terms of recurrence. In the current study, T1 and T2 stage papillomas, which are easier to reach surgically, were defined as early stage, and T3 and T4 stage papillomas, which are more difficult to reach, as advanced stage. Thus, it was aimed to compare 2 more homogeneous groups. The results showed that advanced-stage papillomas significantly increased recurrence.

In this cohort, the malignancy rate was observed to be 8.2% (4/49), which was consistent with the literature. All four patients had synchronous SCC, and no metachronous malignancy was observed during follow-up. Metachronous malignancy may develop many years after excision of the IP. Lesperance et al.³² described an average interval of 63 months between the onset of IP and the development of malignancy.



Figure 1. In the coronal paranasal sinus tomography, inverted papilloma + squamous cell carcinoma extending to the orbit by eroding the frontal sinus wall on the right side (the arrow shows erosion in frontal sinus wall).

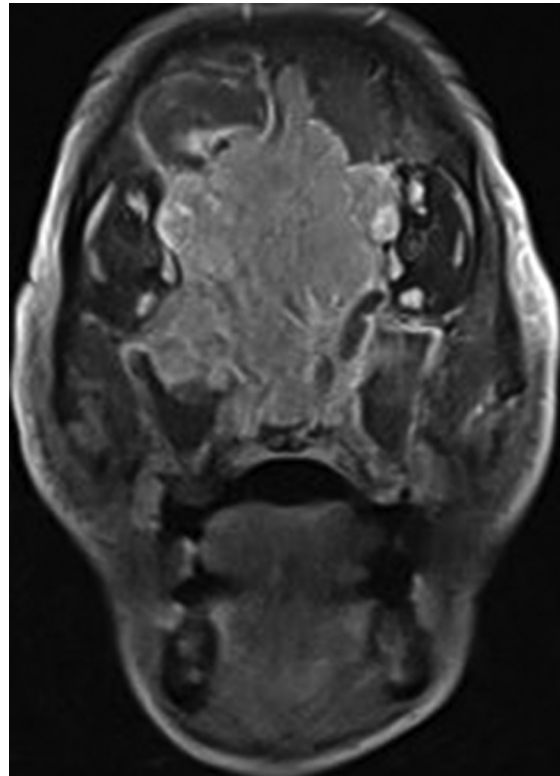


Figure 2. In the coronal paranasal sinus magnetic resonance T1 image, an inverted papilloma + squamous cell carcinoma that fills both nasal passages and all sinuses and extends to the orbit and intracranial area.

Another study showed that the development of metachronous malignancy occurred approximately 10 years after undergoing IP surgery³³. These data reveal the importance of long-term follow-up of patients with IP. Therefore, these patients should be checked at regular intervals, their complaints should be questioned, and endoscopic nasal examinations should be performed. If a suspicious mass is detected, radiological imaging should be performed and a biopsy should be taken.

Malignancy of IPs may present with different clinical scenarios. They may present with limited eye movements without a mass in the nasal passage and complaints of nasal congestion, as in one of the current study patients (Fig. 1). Or, as in the other patient, they may present with visual loss and loss of consciousness due to bilateral nasal mass that has invaded the orbit and intracranial area (Fig. 2). Clinicians must be alert to such cases.

Many factors affecting the malignancy of IPs have been reported. Hong et al. reported that smoking significantly affects malignancy³⁴. In a literature review, some biochemical and immunohistochemical markers

were found to play a role in malignant transformation¹³. In this cohort, the presence of dysplasia and invasion of papilloma outside the nasal cavity and paranasal sinus had a significant effect on malignancy in IPs. The rate of malignancy in IPs extending out of the paranasal sinus was significantly higher than those that did not. This result can be explained in 2 ways. First, papillomas that tend to extension outside the nasal cavity and the paranasal sinus are perhaps more aggressive and have higher malignant potential. The second reason may be the malignant and aggressive characteristics of the malignant tumor accompanying the IP. More research is needed of IPs that tend to invade to be able to predict which papillomas may behave more aggressively or become malignant.

For treatment of IPs, more experienced surgeons prefer the classical open surgery, whereas younger surgeons tend to perform endoscopic surgery²². In 2019, a meta-analysis stated that open surgeries are no longer the “gold standard” for surgery of IPs⁶. Goudakos et al.³⁵ stated that endoscopic surgery is the first choice for IPs, regardless of the stage of

Table 4. Distribution of papilloma types according to krouse staging system

Stage	Inverted (number of patients [%])	Exophytic (number of patients [%])	Oncocytic (number of patients [%])	Total (number of patients [%])
Early stage T1	8 (18.2%)	-	-	8 (16.3%)
T2	9 (20.4%)	1 (20%)	-	10 (20.4%)
Advanced stage T3	22 (50%)	4 (80%)	-	26 (53.1%)
T4	5 (11.4%)	-	-	5 (10.2%)
Total	44 (100%)	5 (100%)	0	49

papilloma. Endoscopic surgery provides better surgical results than open and combined surgeries³. In a meta-analysis by Peng et al., it was stated that the recurrence rate of the endoscopic surgery group was significantly lower compared to the open surgery group⁶. Bugter et al.¹⁷ also confirmed the superiority of endoscopic surgery over open and combine surgery. In the current cohort, 85.71% of the patients were treated with the endoscopic approach and 14.29% with combined surgery. Open surgery alone was not performed in any patient. It can be considered that every surgeon experienced in endoscopic sinus surgery can treat most patients with sinonasal papilloma, even malignant cases, with an endoscopic approach. Open surgeries can be added to the endoscopic approach, especially in cases that are difficult to reach endoscopically, such as localisation in the lateral wall of the frontal sinus, or anterior and lateral wall of the maxillary sinus. In appropriately selected patients, endoscopic surgery allows removal of the tumor without residue. In summary, endoscopic surgery; facilitates the treatment of sinonasal papillomas, decreases the complication and recurrence rates, shortens the hospitalization time, and accelerates post-operative recovery.

The present study had some limitations primarily that the retrospective nature of the study had a negative impact on the quantity and quality of the information, and this should be taken into account when interpreting the results. The number of patients was not very high. Because sinonasal papilloma is a rare disease and it takes a long time to gather a large case series. Further limitations could be said to be that the study was conducted in a single center and patients who had previously undergone surgery in another center were excluded. Therefore, there is a need for further studies with more patients to support the values that were found to be significant.

Conclusions

Although many factors affecting the recurrence of sinonasal papillomas have been identified, there is no definite consensus on this issue. In this study, the factors with a significant effect on recurrence were determined to be female gender, localization and stage of papilloma, and type of surgery. Factors affecting malignancy were the presence of dysplasia and extension out of the paranasal sinuses. Most sinonasal papillomas, including malignant cases, can be treated with endoscopic surgery regardless of stage. When necessary, open surgical approaches can be added to the endoscopic approach. Nevertheless, there is a need for more extensive research, especially molecular research, to further elucidate this complex issue.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary.

Declaration on the use of artificial intelligence.

The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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