# Inverted Papilloma: A Practical Approach to Diagnosis, Management, and Current Controversies

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## ABSTRACT

Inverted papilloma (IP) is an uncommon sinonasal malignancy primarily affecting middle-aged adults. It is characterized by locally aggressive behavior, a high recurrence rate, and a concerning potential for malignant transformation. The etiology of inverted papilloma remains unclear, although human papillomavirus (HPV) infection has been implicated in up to 40% of cases. Surgical intervention is the mainstay of treatment, with the approach (endoscopic versus external) dictated by the extent and characteristics of the tumor. Rigorous follow-up is mandatory to ensure early detection of local recurrence, which can manifest early or with a delayed presentation.

## KEY WORDS

*Human papillomavirus*, *Inverted papilloma, Surgical intervention*

## INTRODUCTION

Over the past centuries, our understanding of inverted papilloma (IP) has significantly evolved. Ward's initial description of a follicular tumor in the 19th century provided the foundation for Ringertz's landmark recognition of the inward growth pattern in 1938, leading to the coining of the now-standard term "inverted papilloma".[1] Hyams subsequently expanded the knowledge base by proposing a sub classification system in 1971.[2] The World Health Organization (WHO) then established a standardized histopathological classification in 1991, encompassing three distinct subtypes: inverted, exophytic, and oncocytic.[3] Notably, the term "Schneiderian papilloma" honors C. Victor Schneider, who described the ectodermal origin of the nasal mucosa in the 17th century.[4]

Inverted papilloma (IP) is a benign epithelial neoplasm arising from the sinonasal Schneiderian membrane. While uncommon, it presents diagnostic challenges due to its non-specific clinical presentation that can mimic other sinonasal disorders. This review article summarizes the current understanding of IP, including its epidemiology, diagnosis, treatment options, and future directions for research.

### Epidemiology

Inverted papillomas represent a small subset of sinonasal tumors, constituting only 0.5-4% of all such lesions.[3,4] Their annual incidence is estimated at 0.6-1.5 cases per 100,000 individuals, with a predilection for the fifth and sixth decades of life. Males exhibit a two to three-fold greater propensity for developing IP compared to females.[5-7] While the entire age spectrum can be affected, IP is rarely encountered in the pediatric population.[8]

### Etiology and Pathogenesis

The precise etiology of IP remains elusive.[9] Several potential contributing factors have been ex-plored, including chronic inflammatory processes, HPV infection, smoking habits, occupational and environmental exposures, cell cycle-related proteins, and angiogenic factors.[9,10]

Intriguingly, the presence of specific HPV DNA subtypes, particularly 6, 11, 16, and 18, has been correlated with an increased likelihood of both IP recurrence and malignant transfor-mation.[11] HPV types 16 and 18 seem to bear a stronger association with malignant transformation likely due to their effects on p53 and p21 and their involvement in oncogenesis.[11,12]

**Histopathology**

Inverted papillomas arise from the sinonasal epithelium, which originates from both the olfactory placode's neuroectoderm and the endodermal nasopharyngeal mucosa.[12] This intricate develop-mental origin likely underlies the spectrum of histological presentations observed in benign papil-lomas within this region.[12] Histologically, inverted papilloma (IP) is characterized by endophytic growth patterns with hyperplastic epithelial ribbons enclosed by basement membrane, infiltrating the underlying stroma. The epithelium is typically multilayered, composed of a mix of squamous and ciliated columnar cells with interspersed mucocytes.[13]

On molecular basis, IP is characterized by activating EGFR mutations, which are preserved even in case of malignant changes.[14]

**Anatomic Origin and Spread**

Inverted papillomas demonstrate a predilection for specific anatomical locations within the si-nonasal cavity. The lateral nasal wall, particularly in close proximity to the middle turbinate and posterior to the uncinate process, represents the most common origin site.[1,9,15] When considering the paranasal sinuses, the ethmoid and maxillary sinuses are demonstrably more vulnerable to IP compared to other paranasal structures.[16,17] The frontal sinus and, less frequently, the sphenoid sinus may occasionally harbor IP, typically as a result of direct extension from the adjacent eth-moid sinus.[17] Often the lesion extensively involves the multiple sites in 30% cases, making it dif-ficult to assess precisely its site of origin.

**Clinical Presentation and Diagnosis**

Inverted papilloma (IP) presents a diagnostic challenge due to its clinical mimicry of other si-nonasal disorders. Patients typically exhibit non-specific symptoms such as unilateral nasal ob-struction, rhinorrhea, epistaxis, and occasionally facial pain and hyposmia.[9,16,18] These overlapping presentations with sinonasal polyps, chronic rhinosinusitis, and even sinonasal carcinoma can sig-nificantly delay diagnosis.[19]

In advanced stages (40-60% of patients), a characteristic triad of facial asymmetry, a palpable or visible oral cavity mass, and an intranasal tumor may be present.[5] Additional symptoms can in-clude complete anosmia, epiphora, cheek numbness, and hyponasal speech. Orbital complications like proptosis can arise due to lamina papyracea erosion by the expanding of the tumor.[1]

Diagnostic nasal endoscopy usually showing a pale, polypoid lesion with a papillary appearance protruding from the middle meatus, which is sometimes made less obvious by the concomitant presence of inflammatory polyps. Therefore, the diagnosis hinges on biopsy, but false negatives can occur due to the presence of benign polyps within the nasal cavity.[19] Preoperative biopsies are essential to rule out malignancy.[19]

Computed tomography (CT) scans represent the gold standard for IP evaluation despite limita-tions.[20] Hallmark findings include bone remodeling manifesting as paranasal sinus calcifications, bony strut, focal hyperostosis and occasionally erosive or sclerotic changes.[19] Notably, localized hyperostosis on CT often corresponds to the tumor origin, aiding diagnosis and surgical planning by pinpointing the exact resection area for complete removal while minimizing unnecessary tissue manipulation.[21]

Magnetic resonance imaging (MRI) with gadolinium enhanced is the preferred modality for postoperative follow-up due to its characteristic streaky delineation with convoluted cerebriform patterns (CCP) on T2-weighted and contrast-enhanced T1-weighted images. This reflects the his-tologic arrangement of inverted papilloma characterized by the alternation of regular parallel folds made of a highly cellular metaplastic epithelium and of an underlying less cellular stroma. While MRI effectively differentiates the tumor from surrounding inflammation, it has limitations in distinguishing benign from malignant lesions.[20,22] Therefore, its primary role lies in detecting recurrent tumors.

In the postoperative setting, imaging studies such as MRI or CT scans are generally only warrant-ed when one of the following criteria is met: Limited access to a previously involved sinus due to scar tissue formation, persistence of clinical symptoms suggestive of ongoing pathology, histo-pathological confirmation of residual or recurrent disease.

Currently, no studies definitively compare the sensitivity and specificity of MRI and CT for pre-operative IP delineation.[20] The optimal diagnostic imaging modality remains under investigation.

**Treatment and Prognosis**

Surgery is the definitive treatment for the inverted papilloma. The different surgical approaches are as shown in table 1.[25,27-36]

Whatever be the surgical approach, the key concept for a radical resection is to dissect the in-volved mucosa in the sub periosteal plane and drill the underlying bone.[31,38]

Endoscopic sinus surgery (ESS) has emerged as the mainstay surgical approach for treating in-verted papilloma (IP), particularly endoscopic medial maxillectomy (EMM) for maxillary sinus lesions.[23] In select cases with a favorable pedicle on the anterior wall, a modified EMM technique can preserve the inferior turbinate and nasolacrimal duct (Tu

Na saving), potentially improving surgical visualization and reducing complication rates while achieving oncological control.[23]

ESS offers numerous advantages, including superior visualization, preservation of sinonasal phys-iology and mucociliary clearance, minimal external scarring, reduced surgical morbidity, and po-tentially lower recurrence rates compared to traditional open surgical techniques.[9]

However, ESS is contraindicated for IPs with significant skull base erosion, intracrani-al/intraorbital extension, substantial scar tissue from prior surgery, or specific cases involving con-current squamous cell carcinoma (SCC).[11]

Postoperative follow-up with endoscopic examinations is crucial. Postoperative surveillance is almost exclusively clinical. Regardless of the access selected, resection of inverted papillomas should lead to the creation of a largely marsupialized cavity that will allow wide access for endoscopic inspection during follow-up. A recommended regimen involves examinations every 3 months for the first 2 years, followed by biannual examinations for up to 5 years.[17] If recurrence is suspected, MRI scans and/or biopsies may be necessary for confirmation.[17]

Radiation therapy (RT) plays a limited role in IP treatment, primarily reserved for inverted papil-loma accompanied by SCC or inoperable cases. Data on RT for IP is scarce, with limited reports and small patient cohorts. While no universally accepted standard exists, most experts recommend RT for SCC/IP and for patients who are not surgical candidates.[3,10,18,24,25] The average ra-diation dose is around 56 Gy for post-surgical RT and 61 Gy for exclusive RT. Studies suggest superior 5-year survival rates for combined surgery and RT compared to either treatment alone in SCC/IP (84% vs. 41%, p = 0.006).[26]

**Table 1. Showing the surgical treatment approaches.**

| Anatomical site | Surgical approaches |
|---|---|
| Lateral wall of nasal cavity | Endonasal endoscopic approach |
| Septum | |
| Anterior or posterior ethmoid air cells | |
| Sphenoethmoid and sphenoidal spaces | |
| Maxillary sinus (medial, superior or posterior wall) | |
| Frontal space and frontal sinus (limited me-dial involvement) | |
| Lateral wall of frontal sinus | Endonasal endoscopic + frontal osteoplastic flap (e.g., bicoronal approach) |
| Maxillary sinus (anterior, inferior or lateral wall) | Endonasal endoscopic + Caldwell-Luc approach |
| Extrasinus extension Associated carcinoma | External (e.g., paralateronasal approach) |

**Recurrence**

The precise etiology of IP recurrence remains elusive.[26] Emerging evidence suggests a potential link between significant epithelial dysplasia within the tumor and an increased risk of recurrence and malignant transformation.[27] Recurrences within the first year are often attributed to residual tumor tissue from incomplete initial resection.[19]

Studies have reported variable recurrence rates based on tumor stage (Krouse classification): 0% for T1, 16% for T2, 25% for T3, and 60% for T4.[29] Incomplete tumor resection, inadequate surgical margin clearance, and tumors in anatomically complex locations are established risk factors for IP recurrence.[16,37] Li et al. observed a higher recurrence rate among patients with advanced-stage IP who underwent solely endoscopic surgery.[37] Additionally, their study of sphenoid sinus IP revealed a correlation between tumor attachment near the optic nerve and carotid artery with a 14.6% recurrence rate.[37] These findings emphasize the importance of meticulous tumor resection, particularly for IPs in challenging anatomical regions.

Endoscopic resection remains the mainstay of treatment for inverted papilloma, with studies re-porting recurrence rates below 10% in carefully selected cases.[31,39-41] However, meticulous surgical technique is paramount to minimize recurrence risk. Factors associated with increased recurrence include incomplete resection, advanced Krouse stage (particularly stage 3), recurrent dis-ease, smoking history, and the presence of dysplasia. Notably, dysplasia may independently triple the risk of recurrence. Unfortunately, the lack of a widely accepted staging system specific to inverted papilloma hinders robust comparisons of treatment outcomes across institutions.[41-43]

**Malignant Transformation**

Malignant transformation is observed in 5% to 15% of cases; synchronous occurrence is more frequent than metachronous. The vast majority of malignant tumors arising from inverted papil-lomas are squamous cell carcinomas, but other tumors such as sinonasal undifferentiated carci-nomas, mucoepidermoid carcinoma, and verrucous carcinoma may rarely occur.[44-46]

Interestingly, research suggests a potential association between HPV types 6/11 and 16/18 and IP harboring severe dysplasia or established SCC, leading to the hypothesis that HPV infection might be an early event in IP's malignant transformation.[47] Notably, patients with HPV-positive head and neck SCC often exhibit better clinical outcomes, possibly due to enhanced radiosensi-tivity and chemosensitivity.[7]

Currently, no dedicated SCC/IP classification system exists. The American Joint Committee on Cancer (AJCC) staging system is commonly used in clinical practice. However, for patients with a prior surgical history of IP, the accuracy of the AJCC system might be compromised due to its reliance

on preoperative imaging and surgical reports for disease stage assignment.[15]

Recent studies propose the localized absence of a characteristic convoluted cerebriform pattern (CCP) on MRI as a potential indicator of SCC coexistent with IP.[9]

**Knowledge Gaps**

Significant knowledge gaps persist regarding the molecular pathways driving malignant trans-formation of inverted papilloma (IP) to squamous cell carcinoma (SCC). Unveiling these mecha-nisms through focused research initiatives holds substantial promise for the development of novel biomarkers. These biomarkers could revolutionize the diagnostic landscape for sinonasal tumors by enabling more accurate identification, facilitating the development of targeted therapies, and ultimately improving patient outcomes. Furthermore, robust biomarkers could empower the im-plementation of effective screening strategies during initial patient presentations. This proactive approach would enable the early identification of individuals at high risk for malignant transfor-mation, allowing for timely intervention and potentially improving overall prognosis.

**Future Directions: Adjunctive Therapies**

While surgery remains the mainstay treatment for IP, the potential role of adjunctive therapies, particularly for aggressive HPV-related disease, warrants further investigation. Immunomodula-tory approaches, such as type I interferon, have shown promise in other HPV-associated malig-nancies. Interferon exerts its effect by inducing P53, a cytoplasmic protein that directly inhibits HPV DNA replication through interaction with the E1 protein of certain HPV strains.[48,49] In re-current respiratory papillomatosis, for example, both interferon and topical cidofovir have been shown to reduce recurrence rates.[50] The recently developed quadrivalent HPV vaccine, Gardasil, which offers protection against HPV types 6, 11, 16, and 18, holds promise as a potential preven-tive strategy. However, to date, no studies have explored the efficacy of these treatment modali-ties in the context of sinonasal inverted papilloma. Further research is necessary to determine the potential role of adjunctive therapies in managing HPV-positive IP and to evaluate the feasibility of HPV vaccination for preventing this subset of tumors.

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