Saudi Journal of Medicine and Public Health

https://saudijmph.com/index.php/pub

https://doi.org/10.64483/202522340

Pulmonary Papilloma: A Comprehensive Review

Mohammed Nuri Alqarrash [(1)] , Hassan Yousef Alharbi[(1)], Fatimah Ibrahim Alali[(1)] , Hassan Matuq Alrasheed [(2)] , Amnah Adnan Alghafli [(3)] , Fatimah Adnan Alghafli[(1)], Omamah Abbas Alabdullah[(1)], Ali Salman Al omaishi[(1)], Amnah Abdullah Alam [(4)] , Mansaur Essa AlHussain [(1)], Hawra Kazem Alghasham [(4)] , Jafar Sadiq Mohsen Alhababi[(1)], Zahra Wasel Ali Alothman[(1)], Maryam Ibrahim Hassan Alzuwayyid[(1)]

(1) Alomran general hospital,Ministry of Health, Saudi Arabia,
(2) Al Ahsa primary health care centers,Ministry of Health, Saudi Arabia,
(3) Aljafer General Hospital,Ministry of Health, Saudi Arabia,
(4) King Faisal General Hospital, Ministry of Health, Saudi Arabia

Abstract

Background: Pulmonary papillomas are rare benign papillary neoplasms of the respiratory tract, characterized by fibrovascular cores lined by epithelial cells. Despite their benign nature, they pose diagnostic challenges due to overlapping features with malignant lesions.

Aim: This review aims to provide a comprehensive synthesis of the etiology, epidemiology, pathophysiology, histopathology, clinical presentation, diagnostic strategies, and management of pulmonary papillomas.

Methods: A structured literature review was conducted, integrating data from epidemiological studies, histopathological analyses, and clinical reports to outline the spectrum of pulmonary papillomatous disease.

Results: Pulmonary papillomas encompass solitary papillomas, inflammatory polyps, and recurrent respiratory papillomatosis (RRP). HPV infection, particularly subtypes 6 and 11, is the predominant etiologic factor, while high-risk genotypes (16, 18) correlate with malignant transformation. RRP incidence is approximately 4 per 100,000 children and 2 per 100,000 adults, with pulmonary involvement in 8–9% of cases. Clinical presentation is often nonspecific, ranging from asymptomatic to obstructive symptoms and hemoptysis. Diagnosis relies on imaging, bronchoscopy, and histopathology. Management includes surgical excision, endoscopic removal, and emerging systemic therapies such as anti-VEGF and PD-1 inhibitors. Prognosis is favorable for solitary lesions but guarded in extensive RRP due to recurrence and rare malignant evolution.

Conclusion: Pulmonary papillomas, though uncommon, require multidisciplinary evaluation and vigilant follow-up to prevent misdiagnosis and manage recurrence. Advances in targeted and immunologic therapies offer promising adjuncts to conventional surgical approaches.

Keywords: Pulmonary papilloma, recurrent respiratory papillomatosis, HPV, bronchoscopy, antiangiogenic therapy, immunotherapy.

Introduction

Pulmonary papillomas are benign papillary neoplasms defined histologically by a fibrovascular core that is lined by epithelial covering, producing distinctive exophytic projections and a spectrum of clinical and morphological manifestations.[1] Although generally non-malignant in nature, their architectural pattern and variable epithelial lining can generate diagnostic uncertainty, particularly when radiologic or bronchoscopic appearances overlap with other endobronchial or peripheral pulmonary lesions. A clear conceptual framework for these tumors is therefore essential, not only to facilitate accurate recognition but also to guide appropriate therapeutic decision-making and follow-up in clinical practice. A structured appraisal of papillomatous lesions is commonly informed by the consideration of three principal categories, namely papillomatosis, inflammatory polyps, and solitary papilloma.[2] Viewing these entities collectively provides a more refined understanding of the broader group of papillomatous processes within the respiratory tract, clarifying both shared pathological features and important distinctions in etiology, distribution, and clinical behavior. This categorical approach supports clinicians and pathologists in interpreting endoscopic and histopathological findings, while also highlighting how differences among these lesions may influence symptom burden, recurrence risk, and overall patient management. Within this classification, solitary papillomas and inflammatory polyps are recognized as relatively infrequent diagnoses, whereas multiple papillomatosis represents the most commonly encountered form.[3] The clinical relevance of

*Corresponding author e-mail: malqarrash@moh.gov.sa (Mohammed Nuri Alqarrash).

Receive Date: 20 November 2025, Revise Date: 18 December 2025, Accept Date: 20 December 2025

papillomatosis is underscored by its comparatively higher frequency and its potential to present with a range of respiratory symptoms, sometimes mimicking alternative benign or malignant conditions. Consequently, comprehensive overviews of papillomatosis typically emphasize its epidemiology and clinical characteristics, as well as the diagnostic challenges that may arise during evaluation and the management strategies required to optimize outcomes and reduce morbidity.[3]

Etiology

The etiopathogenesis of multiple papillomatosis, widely referred to as recurrent respiratory papillomatosis, is most strongly linked to infection with human papillomavirus (HPV). Clinically, the disorder is defined by the tendency to develop recurrent benign papillomatous proliferations along the respiratory mucosa, with a predilection for the larynx and potential extension to the tracheobronchial tree, including the trachea and bronchi. In the vast majority of cases, HPV subtypes 6 and 11 are implicated, accounting for more than 90% of reported disease and generally exhibiting low oncogenic potential without a consistent predisposition to malignant transformation.[3] Nevertheless, the clinical severity, recurrence rate, and anatomic distribution of lesions can vary considerably between patients, indicating that viral characteristics alone do not fully account for the disease phenotype. Rather, heterogeneity within HPV 6 and 11 variants, together with host-related determinants—particularly the effectiveness and regulation of the immune response—appears to influence disease persistence and progression, shaping the overall clinical trajectory and therapeutic burden. In contrast to the typically low-risk HPV types associated with most cases, infection by other HPV subtypes carries greater oncogenic relevance. High-risk HPV genotypes, including 16, 18, and 31, have been associated with malignant transformation, especially in clinical contexts involving squamous cell papilloma and molecular alterations such as TP53 mutations.[4] These observations suggest a multifactorial mechanism in which viral oncogenicity interacts with host genomic instability to facilitate dysplastic evolution and, in a subset of cases, invasive carcinoma. In parallel, modifiable exposures may further amplify malignant potential. Smoking has been identified as an important risk factor for malignant transformation in squamous cell papilloma, with particular emphasis on its association in women, underscoring how carcinogenic inhalational exposures may synergize with HPV-driven epithelial change to accelerate neoplastic progression.[4]

Host immune competence is also a central determinant of susceptibility and clinical expression. Individuals with immunodeficiency states, including those living with HIV or other immune disorders, demonstrate increased vulnerability to HPV-related disease and may be predisposed to more extensive or recalcitrant forms of multiple papillomatosis. Impaired immune surveillance can permit viral persistence within the respiratory epithelium, thereby enabling repeated cycles of epithelial proliferation and recurrence. With regard to acquisition, HPV-related respiratory disease may be transmitted through oral-genital contact, reflecting mucosal exposure pathways, or acquired via vertical transmission during perinatal delivery from an infected mother, a route that has been recognized in the development of juvenile-onset disease. Inflammatory polyps, sometimes designated inflammatory pseudotumors, represent an etiologically distinct category in which inflammation is not merely a secondary finding but a defining pathogenic driver. This contrasts with lesions such as adenomatous polyps, in which primary epithelial dysplasia or abnormal proliferative growth predominates. Inflammatory polyps may arise as solitary or multiple papillary lesions, frequently in the setting of chronic respiratory infection, and some reports suggest a direct association between the infectious process and lesion development.[5] The contribution of immune dysregulation is also biologically plausible, as an exaggerated or aberrant immune reaction to infectious agents, inhaled particles, or other environmental stimuli can sustain chronic inflammation, leading to mucosal remodeling and eventual polyp formation. In selected cases, genetic factors may contribute, particularly when lesions are linked to specific genetic aberrations that may influence inflammatory signaling pathways or cellular proliferation.[6] Additionally, exposure to environmental irritants or toxins may perpetuate airway inflammation and thereby facilitate the emergence or persistence of inflammatory polyps, reinforcing the concept that both intrinsic immune factors and extrinsic exposures can converge to produce clinically appreciable lesions [5][6]. Solitary polyps are comparatively rare and appear to reflect heterogeneous etiologic influences. Reported associations include infectious triggers such as HPV as well as environmental exposures, notably smoking, indicating that even isolated lesions may arise from interactions between viral factors and chronic airway irritation.[2][7][8] Collectively, these etiologic patterns emphasize that pulmonary papillomatous and polypoid lesions do not represent a single-pathway disease spectrum; instead, they encompass viral, immune-mediated, genetic, and exposure-related mechanisms whose relative contributions vary by lesion subtype and patient context.

Epidemiology

Recurrent respiratory papillomatosis represents an uncommon but clinically significant disorder, with reported incidence rates varying according to age group and population characteristics. Epidemiological studies estimate an annual incidence of approximately 4 cases per 100,000 children and 2

cases per 100,000 adults.[9] These figures underscore the rarity of the condition while simultaneously highlighting its persistence across both pediatric and adult populations. Variability in reported incidence may reflect differences in diagnostic practices, access to specialized care, and regional surveillance methods, as well as true population-based differences in exposure and susceptibility to human papillomavirus (HPV). Age at disease onset and socioeconomic context appear to influence the observed epidemiological patterns. Higher incidence rates have been documented among individuals from lower socioeconomic backgrounds and among populations with lower levels of formal education.[10][11] These associations may be partially attributable to disparities in healthcare access, delayed diagnosis, or increased exposure to HPV through perinatal or behavioral pathways. Despite this association with disease occurrence, socioeconomic status has not been shown to correlate with disease severity or clinical aggressiveness, suggesting that while social determinants may influence risk of acquisition or recognition, they do not independently dictate disease progression or outcome. In parallel, the epidemiology of recurrent respiratory papillomatosis must be considered in the broader context of HPV prevalence. The prevalence of HPV infection among women has risen steadily, with estimates indicating an overall prevalence of approximately 26.8% in women aged 14 to 59 years and a peak prevalence of nearly 45% in those aged 20 to 24 years. These trends provide important background for understanding patterns of viral transmission and the potential reservoir for both juvenile- and adult-onset disease.

In adult populations, recurrent respiratory papillomatosis is more frequently encountered in men, who account for approximately 84% of laryngeal papilloma cases, with the highest incidence observed between 40 and 50 years of age and a secondary peak during the sixth decade of life.[12] This male predominance and bimodal age distribution may reflect differences in exposure, immune response, or hormonal and behavioral factors that influence susceptibility and disease expression. By contrast, papillomatous lesions of the lower airway and lung, including solitary papillomas and inflammatory polyps, are distinctly rare and together constitute less than 1% of all pulmonary neoplasms.[4] Their infrequency contributes to limited epidemiological characterization and poses challenges for early recognition and accurate diagnosis. Pulmonary involvement in the setting of HPV-associated recurrent respiratory papillomatosis remains an uncommon but clinically important manifestation, occurring in approximately 8% to 9% of affected individuals.[3] Such involvement is more commonly reported in pediatric patients and is often linked to vertical transmission during vaginal delivery from mothers with active genital HPV infection, particularly with HPV subtypes 6 and 11.[3] These epidemiological observations emphasize the heterogeneous distribution of disease across age groups and anatomical sites, reflecting the interplay between viral exposure routes, host susceptibility, and demographic factors in shaping the population-level burden of recurrent respiratory papillomatosis [3].

Pathophysiology

Papillomatous lesions of the respiratory tract may present as solitary or multiple nodules and exhibit diverse macroscopic configurations, including exophytic, sessile, or pedunculated growth patterns. These lesions most commonly arise within the larynx, reflecting the predilection of papillomatous disease for this anatomical site, but they may also involve adjacent structures such as the vocal cords, ventricular folds, subglottic region, and the laryngeal surface of the epiglottis. Although the larynx remains the primary site of involvement, recurrent respiratory papillomatosis is not confined to the upper airway and may extend along the entire respiratory tract, encompassing the tracheobronchial tree and, in rare instances, the pulmonary parenchyma. Among patients with laryngeal papilloma, distal airway involvement has been reported in approximately 2% to 5% of cases, whereas pulmonary parenchymal disease is observed in only about 1%, underscoring the relative infrequency but notable clinical significance of lower respiratory tract extension.[3][13] The fundamental pathogenic mechanism underlying papilloma formation is infection of the respiratory epithelium by human papillomavirus (HPV). The virus preferentially targets squamous epithelial cells and gains access to the basal layer of the epithelium through microscopic abrasions or disruptions of the mucosal surface. Once established within basal keratinocytes, HPV initiates a complex cascade of molecular events that promote viral persistence and epithelial proliferation. Viral oncoproteins interact with host cellular pathways, including activation of the epidermal growth factor receptor signaling axis and interference with tumor-suppressor mechanisms, thereby altering normal cell cycle regulation. These molecular disruptions drive increased cellular proliferation and abnormal differentiation, culminating in the formation of characteristic papillomatous projections. Morphologically, these lesions often assume a “cauliflower-like” appearance, particularly in recalcitrant reticular papillomatosis, and are frequently localized at the transitional zone between squamous epithelium and ciliated columnar respiratory epithelium, a region that appears especially susceptible to viral-mediated transformation.[14]

Genetic susceptibility further contributes to disease persistence and severity in selected patients. The genetic pathogenesis of recalcitrant reticular papillomatosis has been linked to mutations in key regulatory genes, including the tumor protein p53 gene (TP53), which plays a central role in genomic stability and apoptosis, and the interferon beta 1 gene (IFNB1), which is essential for antiviral immune responses.[15]

Alterations in these genes may impair effective viral clearance and enhance epithelial survival despite ongoing HPV infection, thereby promoting recurrent lesion formation. In addition to intrinsic genetic factors, host immune status is a critical determinant of disease expression. Recurrent respiratory papillomatosis has been described in individuals with immune-modulated conditions that predispose them to persistent viral infections, including patients with human immunodeficiency virus infection and other forms of immune deficiency.[16][17][18] In such settings, compromised immune surveillance allows continued viral replication and recurrent epithelial proliferation, contributing to aggressive or treatment-resistant disease courses. Angiogenesis represents another key component of papilloma pathophysiology. Vascular endothelial growth factor is strongly expressed within the epithelial membrane of respiratory papillomas and has been implicated as a major mediator of lesion growth and persistence.[19] The abundant expression of vascular endothelial growth factor receptors 1 and 2 on the endothelial cells of intralesional blood vessels further supports the role of angiogenic signaling in sustaining papillomatous tissue. This vascular proliferation not only facilitates lesion expansion but also provides a mechanistic rationale for the exploration of antiangiogenic therapies as potential treatment strategies. In parallel, immune evasion mechanisms contribute to the chronic and recurrent nature of the disease. Expression of the programmed cell death protein 1 pathway on papilloma cells reflects localized immunosuppression within the lesion microenvironment and suggests an additional layer of pathogenic complexity.[20] By attenuating effective T-lymphocyte–mediated immune responses, this checkpoint pathway may enable ongoing viral persistence and lesion recurrence. Consequently, therapeutic blockade of this pathway using monoclonal antibodies has emerged as a potential targeted approach, aiming to restore immune activity and interrupt the cycle of recurrence. Collectively, these molecular, genetic, immunologic, and angiogenic processes define the multifaceted pathophysiology of recurrent respiratory papillomatosis and account for its variable clinical behavior and therapeutic challenges [20].

Fig. 1: Pulmonary papilloma.

Histopathology

Pulmonary papillomas may present as either solitary lesions or multifocal nodules, with their gross and microscopic morphology reflecting both anatomic site and underlying clinicopathologic context. In recurrent respiratory papillomatosis, papillomatous nodules may assume an exophytic, sessile, or pedunculated configuration and are most frequently centered within the larynx, while commonly extending to contiguous structures including the vocal cords, ventricular folds, subglottic region, and the laryngeal aspect of the epiglottis. On macroscopic examination, these lesions typically appear polypoid, tan-white, and friable, projecting into the airway lumen and ranging from approximately 0.7 cm to as large as 9 cm, with a median size near 1.5 cm. Their intraluminal growth pattern is clinically relevant because progressive obstruction can promote post-obstructive phenomena in the distal airway, including bronchiectasis, mucus retention, and secondary obstructive alterations within the distal lung parenchyma. From a histological standpoint, pulmonary papillomas are generally composed of benign epithelial proliferations that tend to arise at transitional mucosal interfaces, particularly at junctions where ciliated respiratory epithelium meets squamous epithelium, a distribution that aligns with the known susceptibility of these zones to epithelial remodeling and viral-mediated proliferative change. Solitary papilloma represents a benign neoplasm arising from otherwise normal bronchial epithelium and has historically been subdivided on the basis of epithelial phenotype and stromal characteristics. Maxwell et al proposed a two-group classification.[21] In the first group, solitary papillomas are lined predominantly by columnar or cuboidal epithelium, with variable squamous metaplasia and generally minimal accompanying inflammation. In the second group, solitary squamous papillomas demonstrate a more conspicuous connective tissue stroma coupled with a stratified squamous epithelial lining. Although this dichotomous scheme has been influential, some authors contend that strict separation is of limited practical value because many lesions exhibit at least focal squamous metaplasia, resulting in histological overlap that challenges rigid categorization.[2] In routine diagnostic practice, therefore, emphasis is often placed on the integrated assessment of epithelial differentiation, stromal architecture, and cytologic features, rather than on absolute adherence to a binary framework.

Inflammatory polyps, by contrast, demonstrate a histologic pattern in which inflammation is a defining component rather than a secondary accompaniment. Microscopically, these polypoid lesions are lined by ciliated columnar epithelium and contain a fibrous tissue core that is infiltrated by inflammatory cells, reflecting their association with chronic mucosal irritation and

inflammatory remodeling. In broader terms, the microscopic appearance across papillomatous lesions is unified by the presence of a fibrovascular core and epithelial proliferation; in many cases, squamous epithelial lining may form lobulated proliferations, and within pulmonary parenchyma this can be accompanied by cavitation and necrotic change within alveolated tissue. Such findings underscore that, although papillomas are classically benign, their growth pattern and relationship to adjacent structures can produce complex secondary changes that may be misinterpreted radiologically or even histologically if limited tissue is available. Notwithstanding these shared features, the histopathological appearance varies substantially by subtype, and accurate classification depends on careful recognition of the defining epithelial and stromal patterns. Squamous cell papillomas are characterized by arborizing, delicate fibrovascular cores covered by stratified squamous epithelium. Exophytic lesions typically show orderly epithelial maturation, often with surface keratinization, and commonly demonstrate acanthosis and parakeratosis. While progression to squamous cell carcinoma is distinctly uncommon, malignant degeneration has been reported and may occur in association with TP53 mutations, reinforcing the need for attention to cytologic atypia and architectural disturbance when evaluating these lesions. In the context of solitary papillomas, classical cytopathic features suggestive of HPV infection—such as binucleation, nuclear wrinkling, and perinuclear halos—are present in fewer than 25% of cases, indicating that HPV-associated morphology is neither universal nor required for diagnosis. Nevertheless, additional atypical findings may be encountered, including dyskeratotic cells, enlarged atypical cells, and mitotic activity extending above the basal layer, features that heighten concern for dysplastic change. Dysplasia is graded according to the current World Health Organization classification into discrete, mild, and severe categories, providing a standardized framework for reporting and risk stratification. When papillomatous disease extends into the parenchyma, histologic patterns may include solid intra-alveolar nests of cytologically bland, non-keratinizing squamous cells or the development of large cystic spaces lined by similar epithelium, appearances that can complicate the distinction from other cystic or squamous proliferative lesions of the lung [21].

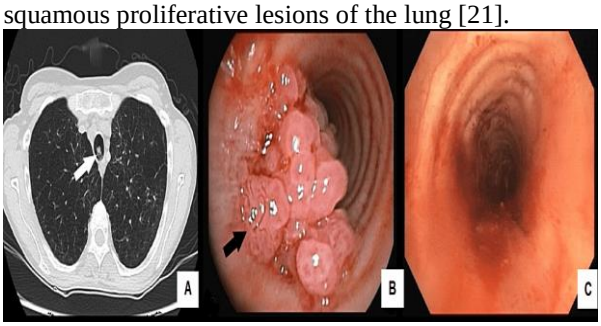

Fig. 2: Pulmonary Papilloma.

Glandular papillomas are defined by a fibrovascular core lined by pseudostratified or stratified columnar epithelium, which may form fine micropapillary tufts. The epithelial cells generally appear cytologically uniform, with eosinophilic cytoplasm and regular, round nuclei. Although focal clearing of the cytoplasm may be observed, significant nuclear atypia, necrosis, or abnormal mitotic figures are typically absent, and their presence should prompt reconsideration of the diagnosis or evaluation for an alternative neoplastic process. Mixed squamous and glandular papillomas exhibit combined features, with a predominance of glandular epithelium interspersed with squamous islands. In this mixed category, glandular atypia and necrosis are usually not identified, whereas squamous atypia may occasionally be present, necessitating thorough sampling to exclude dysplasia or early malignant transformation in the squamous component. At the molecular level, pulmonary papilloma has been associated with HPV 11 integration, which is regarded as tumorigenic and has been linked to gene duplication events and altered innate immune responses, providing a mechanistic basis for persistent epithelial proliferation and recurrence in a subset of cases.[3][12][17][22][23][24][25] These molecular associations complement histologic evaluation and may be particularly informative in diagnostically challenging circumstances or when clinical behavior is unexpectedly aggressive. From a practical diagnostic perspective, one of the most consequential challenges is distinguishing papilloma, particularly squamous papilloma with atypia, from squamous cell carcinoma when tissue is limited. Small biopsies may fail to capture the full architectural context, including the characteristic fibrovascular cores, the pattern of maturation, or the extent of invasion, thereby restricting definitive interpretation. For this reason, excisional resection is often required to establish a conclusive diagnosis, enabling comprehensive assessment of lesion architecture, epithelial-stromal relationships, and any features suggestive of malignant transformation [3][12][17][22][23][24][25].

History and Physical

The clinical presentation of pulmonary papillomas is often subtle and lacks pathognomonic features, rendering diagnosis challenging on the basis of history and physical examination alone.[1] Symptoms, when present, tend to be nonspecific and may overlap substantially with those of more common respiratory conditions. A significant proportion of cases, estimated at approximately 25%, are entirely asymptomatic and are identified incidentally during thoracic imaging performed for unrelated indications. In such circumstances, the absence of clinical manifestations underscores the indolent nature of many pulmonary papillomas and highlights the importance of radiologic vigilance and histopathologic confirmation to establish an accurate diagnosis. In an effort to better stratify disease burden and guide

clinical assessment, some centers have proposed a classification system that categorizes pulmonary papillomas into limited, moderate, and severe forms based on the extent of pulmonary involvement and the apparent aggressiveness of the lesions.[22] Within this framework, the limited type is defined by the presence of a solitary, sub-centimeter nodule, typically associated with minimal or no symptoms. In contrast, moderate and severe forms are characterized by multiple lesions, often cystic in nature and measuring several centimeters in diameter, which are more likely to produce clinically evident disease. This stratification provides a practical approach for correlating radiographic findings with symptom severity and potential risk of complications, although it does not replace individualized clinical judgment. When symptoms do occur, they most commonly reflect airway obstruction or irritation. Patients may report chronic cough or episodic wheezing, features that closely resemble those seen in solitary papilloma and that may lead to misdiagnosis as asthma or other obstructive airway diseases.[26] Such overlap is particularly problematic when wheezing is interpreted in isolation, without consideration of structural airway pathology. In addition to cough and wheeze, involvement of the larynx or proximal airway may result in hoarseness, stridor, and progressive dyspnea, reflecting mechanical narrowing of the airway lumen.[27] Recurrent respiratory infections are also frequently reported and are thought to arise from impaired airway clearance and localized obstruction, which predispose to mucus retention and secondary infection. Over time, repeated infections and chronic obstruction may contribute to structural airway damage and declining pulmonary function [26].

Certain patient populations appear to experience a more aggressive or symptomatic disease course. Individuals with underlying asthma, particularly those requiring daily inhaled corticosteroid therapy, have been reported to exhibit more pronounced clinical manifestations.[28] Although the precise mechanism remains incompletely understood, local immunomodulatory effects of corticosteroids may facilitate viral persistence or alter mucosal immune responses, thereby promoting lesion growth or recurrence. This observation underscores the importance of careful clinical evaluation in patients with refractory or atypical asthma symptoms, in whom alternative diagnoses such as pulmonary papilloma should be considered. On physical examination, findings are frequently limited and may be entirely unremarkable, especially in patients with small or peripherally located lesions. In symptomatic individuals, auscultation may reveal localized wheezing, diminished breath sounds, or crackles, depending on the degree and location of airway involvement. Stridor may be appreciated in cases with significant upper airway obstruction, while signs of respiratory distress may emerge in advanced disease. Importantly, these findings are not specific and must be interpreted in conjunction with imaging and endoscopic evaluation. The most severe clinical presentations of pulmonary papilloma include hemoptysis and the development of lung abscesses, both of which may necessitate urgent intervention. Hemoptysis may result from friable papillomatous tissue, associated bronchiectasis, or secondary infection, and its severity can range from mild blood-streaked sputum to life-threatening hemorrhage. In cases where hemoptysis is linked to bronchiectasis, bronchial artery embolization may be required to achieve hemostasis. However, the presence of hemoptysis in a patient with a history of smoking mandates thorough evaluation to exclude primary lung malignancy, given the potential for clinical and radiologic overlap.[29] In rare instances of uncontrolled bleeding or refractory disease, surgical pulmonary resection may be necessary to manage symptoms and prevent further complications [29]. Overall, the history and physical examination in pulmonary papilloma are characterized by variability and nonspecificity. While many patients remain asymptomatic, others present with a spectrum of obstructive and infectious symptoms that may evolve over time. Recognition of these clinical patterns, coupled with awareness of risk factors and severe presentations, is essential for timely diagnosis, appropriate intervention, and exclusion of malignant disease.

Evaluation

The diagnostic evaluation of pulmonary papillomas requires an integrated approach that combines clinical context, imaging characterization, endoscopic assessment, and histopathologic confirmation. Because clinical manifestations are frequently nonspecific and may overlap with common obstructive or infectious airway disorders, radiologic and bronchoscopic investigations typically provide the first substantive clues that prompt consideration of papillomatous disease. The diagnostic pathway is further shaped by the recognized heterogeneity of papillomas in their anatomic distribution, morphologic appearance, and potential for malignant transformation in selected contexts, all of which necessitate a careful and systematic evaluation strategy. Solitary papillomas most often present as centrally located endobronchial lesions, arising within major bronchi and producing intraluminal obstruction or irritative symptoms. Less commonly, they may be peripheral yet still demonstrate an endobronchial component, including rare presentations as plaque-like lesions.[26] This localization is clinically relevant because central lesions are more readily accessible to bronchoscopy, while peripheral or plaque-type lesions may require more nuanced imaging interpretation and targeted biopsy planning. In many cases, their endobronchial growth pattern explains the predominance of obstructive symptoms and the

frequent presence of post-obstructive complications, including atelectasis or recurrent infection, which may be evident on chest imaging and further reinforce the need for endoscopic evaluation [26].

Recurrent respiratory papillomatosis with pulmonary involvement introduces a broader and more complex imaging spectrum. Parenchymal disease can manifest as nodules or masses, with walls that may be smooth or irregular, and with variable thickness ranging from thin-walled to markedly thickened lesions. Cavitary nodules and cystic lesions may also be observed, again with overlapping wall characteristics that can mimic infectious cavities, inflammatory cysts, or cavitating malignancies. These parenchymal abnormalities have been reported to occur predominantly in the posterior regions of both lungs, a distributional tendency that may assist radiologists in pattern recognition when clinical suspicion is present. Importantly, the identification of concomitant hilar or mediastinal adenopathy should be interpreted as a potentially ominous sign, raising concern for malignant transformation rather than uncomplicated benign papillomatous disease.[30][31] This particular association underscores the critical need for nodal assessment when imaging findings suggest a deviation from the expected benign phenotype. Computed tomography remains the cornerstone imaging modality for characterizing airway and parenchymal involvement. CT findings described in pulmonary papillomatosis include endobronchial plaques and nodules, airway wall thickening, air-trapping, bronchiectasis, abscess formation, and even findings suggestive of foreign bodies, which may reflect secondary obstruction and retained secretions.[27][32][33][34] The diversity of CT features reflects the interplay between primary papillomatous growth and secondary airway sequelae, such as infection and bronchiectatic remodeling. In published series, solid nodules and cavitated nodules constitute the most frequent CT manifestations, accounting for more than 80% of reported pulmonary papilloma cases. These lesions may be scattered throughout the lungs and may exhibit distinctive patterns such as calcification, which can complicate differentiation from granulomatous disease or metastatic nodules depending on the clinical scenario.[3] By contrast, isolated intraparenchymal nodules occurring without any evidence of airway involvement are uncommon on CT, and their rarity may delay recognition when airway lesions are not simultaneously identified.[27] Accordingly, radiologic interpretation should be accompanied by careful inspection of the central and segmental airways to identify subtle endobronchial plaques or nodularity that may provide a unifying diagnostic explanation.

Although chest CT provides critical anatomic detail, neither CT nor positron emission tomography is considered highly sensitive or specific for definitive diagnosis of pulmonary papilloma. Nonetheless, both modalities can be valuable in procedural planning and risk stratification. PET imaging, in particular, may assist in identifying the most metabolically active or diagnostically informative lesion to target for biopsy, especially when malignant transformation is part of the differential diagnosis.[35] In addition, PET may reflect epithelial alterations on the papilloma surface, including metaplastic changes, which can manifest as increased uptake and thereby influence concern for dysplasia or early malignant evolution.[36] However, because inflammatory activity and infection can also produce avid uptake, PET findings must be interpreted cautiously and in conjunction with morphologic imaging and tissue diagnosis. Clinical suspicion should be heightened in specific patient populations, particularly those with severe, poorly controlled asthma who require ongoing inhaled corticosteroid therapy. Emerging evidence suggests an association between asthma and more aggressive phenotypes of recurrent respiratory papillomatosis. In a study of 90 patients diagnosed with recurrent respiratory papillomatosis (with ages at first diagnosis spanning 19 to 86 years), aggressive disease was observed in 57% of individuals with asthma compared with 16% among those without asthma ($P = .02$). Moreover, a markedly higher prevalence of aggressive disease was reported among corticosteroid users than non-users (80% versus 15%; $P = .004$).[28] While these findings support heightened clinical vigilance and a lower threshold for endoscopic assessment in such patients, the causal mechanisms remain insufficiently defined, and the available data do not yet permit definitive management recommendations solely on the basis of asthma status or corticosteroid exposure.[28]

Bronchoscopy remains a pivotal diagnostic modality for confirming solitary papilloma or recurrent respiratory papillomatosis. Endoscopic visualization may reveal characteristic endobronchial protuberances, papillomatous plaques, or obstructive lesions, and may also demonstrate secondary findings such as atelectasis due to airway occlusion. Nevertheless, procedural caution is essential, particularly when sampling laryngeal or central endobronchial lesions, because biopsies in these locations carry substantive risks of uncontrolled bleeding and airway compromise. These risks are amplified by the friable nature of papillomatous tissue and by the potential for rapid obstruction if hemorrhage or edema occurs in a narrowed airway lumen. Furthermore, because pulmonary papilloma lesions are often heterogeneous, small samples obtained via forceps biopsy may be inadequate for definitive classification and may fail to exclude dysplasia or invasive carcinoma. In selected cases, a core biopsy may still be insufficient, and excisional biopsy may be required to establish the diagnosis confidently, particularly when imaging features, clinical course, or PET uptake raise concern for malignant transformation. When immediate excision is not feasible or risk is judged excessive, serial imaging surveillance may be employed to monitor

lesion stability, though this approach must be individualized and balanced against the potential consequences of delayed diagnosis. Once tissue confirmation is achieved, further evaluation parallels that performed for other pulmonary neoplasms in situations where malignant transformation is suspected or cannot be excluded. Establishing histopathologic diagnosis is followed by staging to define disease extent and to assess for nodal involvement or distant spread, even though the primary lesion may be benign in many cases. Endobronchial ultrasound-guided bronchoscopy is particularly valuable for sampling mediastinal and hilar lymph nodes when adenopathy is present or when radiologic features suggest possible malignant evolution. In some circumstances, surgical staging may be required to obtain adequate tissue for definitive assessment.[37] Such staging is essential to inform management planning with curative intent, ensuring that therapeutic decisions are guided by accurate anatomic and pathologic delineation rather than by imaging impression alone.[37]

Treatment / Management

Therapeutic decision-making in pulmonary papilloma is inherently individualized and should be guided by lesion location, histopathologic subtype, baseline pulmonary reserve, and patient age, as these variables collectively determine procedural feasibility, anticipated morbidity, and long-term risk of recurrence or malignant transformation.[38] In practice, management spans a spectrum from curative local intervention for isolated endobronchial lesions to multimodal strategies for extensive disease, particularly when the pulmonary parenchyma is involved. Parenchymal dissemination, most often encountered in the context of recurrent respiratory papillomatosis, is consistently associated with less favorable outcomes, reflecting both the burden of multifocal airway obstruction and the difficulty of achieving durable local control. In such patients, the clinical course is more frequently complicated by progressive airway compromise and a heightened likelihood of requiring tracheostomy, a marker of advanced disease and significant functional impairment.[39] Because adult recurrent respiratory papillomatosis may be accompanied by substantial morbidity, a recognized risk of malignant transformation, and radiologic features that can resemble non-small cell lung cancer, some authors advocate a treatment posture that parallels the management principles applied to primary lung squamous cell carcinoma, particularly when parenchymal lesions are extensive or when malignant evolution is suspected [22]. This approach does not imply that all cases require oncologic therapy; rather, it underscores the need for rigorous staging, thorough tissue confirmation, and a low threshold for definitive resection when the differential includes invasive malignancy or when clinical behavior is atypically aggressive. In this setting, the goal is to avoid undertreatment of malignant disease while still acknowledging that many papillomatous lesions remain biologically benign.

For pulmonary papillomas diagnosed at early stages without evidence of metastasis, definitive local management most commonly involves surgical resection or endoscopic removal, with selection of technique determined by anatomic accessibility and the anticipated completeness of excision.[37] When lesions are endobronchial and well-circumscribed, bronchoscopic approaches may offer effective symptom relief and tissue diagnosis, whereas parenchymal disease or lesions with ambiguous malignant potential may require surgical resection to secure negative margins and enable full histologic assessment. Adjunct and alternative procedural modalities have been employed to reduce lesion burden and improve airway patency, including laryngeal microdebrider therapy, laser ablation, intralesional injection of the antiviral agent cidofovir, photodynamic therapy, cryotherapy, and subcutaneous interferon-alpha therapy.[40] (B3) These interventions are frequently applied in recurrent respiratory papillomatosis, where repeated procedures may be necessary because of the intrinsic tendency of HPV-associated lesions to recur and the practical limitations of achieving complete mucosal eradication. In recent years, systemic therapies have gained increasing attention, reflecting both advances in immuno-oncology and an improved understanding of the molecular microenvironment of papillomatous disease. Reports describing upregulation of programmed cell death protein 1 (PD-1) signaling within pulmonary papillomas provide a biologic rationale for immune checkpoint inhibition and suggest that anti–PD-1 agents such as nivolumab and pembrolizumab may have therapeutic potential in selected patients.[20][41] These observations are particularly relevant in refractory disease where repeated local procedures confer cumulative morbidity or fail to achieve durable control. While early experiences are encouraging, systemic immunotherapy requires careful patient selection and monitoring, given the possibility of immune-related adverse events and the current limitations of evidence in defining optimal indications, dosing, and duration for benign or borderline lesions.

Antiangiogenic therapy has also emerged as a prominent strategy, especially for aggressive recurrent respiratory papillomatosis. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, has been reported as a promising treatment with an acceptable safety profile in both adults and children.[42][6] Its mechanistic rationale is supported by evidence of VEGF involvement in papilloma pathogenesis, suggesting that inhibition of angiogenic signaling can disrupt the vascular support required for lesion growth and

persistence.[19] Clinically, systemic bevacizumab has been associated with meaningful prolongation of the interval between treatment initiation and the need for subsequent surgical intervention. In an observational period of approximately 22 months, more than half of treated patients reportedly did not require additional intervention, highlighting a potentially substantial reduction in procedural frequency and disease burden.[43] Notably, local injection of bevacizumab appears to yield less consistent benefit, limiting its applicability for many patients and reinforcing the need for larger, methodologically rigorous trials to clarify its true effectiveness, optimal administration route, and long-term outcomes. Pembrolizumab has similarly been described as a promising option, yet definitive conclusions await the final reporting of clinical trial results, which will be essential to establish efficacy and safety in a more generalizable manner.[44] Other pharmacologic strategies have been explored, including agents targeting inflammatory mediators and epithelial signaling pathways. Celecoxib has been proposed in some reports as a means to reduce prostaglandin production and potentially modulate EGER resistance; however, available evidence indicates that celecoxib has not demonstrated clinical effectiveness in treating pulmonary papilloma, illustrating the difficulty of translating mechanistic hypotheses into meaningful clinical benefit.45 Such findings emphasize the importance of controlled evaluation and discourage reliance on empiric therapies without supportive outcomes data.

From a prognostic standpoint, solitary papillomas that are completely removed surgically generally demonstrate excellent outcomes, with recurrences being uncommon. By contrast, recurrence rates are higher following endoscopic removal, with recurrence reported in approximately 20% of such cases, likely reflecting limitations in achieving complete excision and the potential for residual microscopic disease.[1][46] When resection is incomplete, recurrence is more likely, reinforcing the importance of procedural planning and adequate sampling. Malignant transformation is overall rare in squamous cell papillomas, yet vigilance remains warranted, particularly in cases with atypia, rapid growth, or concerning imaging findings.[1][46] Procedural safety considerations are also important: during laser therapy, precautions are necessary to reduce the risk of aerosolizing HPV DNA-containing particles, which may present an occupational hazard to healthcare staff if inhaled.[38] (B3) Preventive strategies, including HPV vaccination, are therefore viewed as promising for reducing the incidence of respiratory papillomatosis and, by extension, its pulmonary manifestations.[38] Given the possibility of pulmonary extension and the potential for delayed recognition, surveillance is a critical component of long-term management for patients at risk of pulmonary involvement. At present, there is no universally accepted consensus regarding the optimal monitoring strategy, reflecting gaps in evidence and variation in institutional practice. Nonetheless, expert recommendations have supported consideration of early baseline low-dose CT imaging of the chest for individuals with juvenile-onset recurrent respiratory papillomatosis, beginning at age 18 or earlier when additional risk factors are present, such as very early onset of disease, a history of tracheostomy, or the need for numerous surgical procedures.[22] Similar reasoning has been applied to adult-onset recurrent respiratory papillomatosis, in which obtaining baseline low-dose CT may assist with early detection of cysts, nodules, or parenchymal involvement. Where baseline imaging shows no evidence of pulmonary disease, periodic surveillance at approximately five-year intervals has been suggested, balancing radiation exposure against the need for longitudinal monitoring.[22] If incidental pulmonary nodules are identified, adherence to the updated Fleischner Society guidelines is recommended to ensure standardized risk-based follow-up and to avoid both over-investigation and missed malignancy.[47] Collectively, these treatment and surveillance principles reflect the evolving therapeutic landscape of pulmonary papilloma, in which procedural management remains foundational but is increasingly complemented by systemic targeted and immunologic strategies aimed at reducing recurrence, limiting morbidity, and improving long-term outcomes [45][46][47].

Differential Diagnosis

The differential diagnosis of pulmonary papillomas is clinically and pathologically consequential because these lesions may reproduce the symptoms, endobronchial appearance, and radiologic signatures of malignant or potentially malignant airway tumors. On clinical grounds, the most prominent considerations frequently include carcinoid tumor and squamous cell carcinoma, as both may present with cough, wheeze, hemoptysis, recurrent infection, or obstructive atelectasis, and both may form centrally located endobronchial masses. Radiologic evaluation may suggest an intraluminal lesion or proximal polypoid mass, but imaging alone is rarely decisive; therefore, microscopic examination remains indispensable to confirm papilloma and to exclude invasive malignancy. The diagnostic challenge is heightened by the possibility of secondary inflammatory change, squamous metaplasia, or focal atypia within papillomas, which can confound interpretation when biopsy material is limited. Within the spectrum of papillomatous lesions, squamous cell papilloma poses particular diagnostic difficulty because its principal histologic mimickers include inflammatory polyps and squamous cell carcinoma. Inflammatory polyps may display squamous metaplasia, especially in the setting of chronic irritation, but they fundamentally lack a true papillary architecture supported by a well-formed fibrovascular

core. Instead, inflammatory polyps are typically dominated by reactive mucosal changes, stromal edema or fibrosis, and a prominent inflammatory infiltrate. Recognition of the absence of an authentic papillary framework is therefore crucial when distinguishing an inflammatory lesion from a papillomatous neoplasm. Conversely, squamous cell carcinoma is defined by malignant epithelial proliferation with infiltrative growth, cytologic atypia, and architectural disarray. Histologically, it often forms nests and sheets of tumor cells that may demonstrate central keratinization with squamous pearls and may contain dyskeratotic cells. In cases where overt keratinization is not appreciable—particularly in small biopsies or in poorly differentiated tumors—immunohistochemistry can provide supportive evidence. Antibodies such as P63 and P40 are frequently valuable in identifying squamous differentiation, although they do not, in isolation, prove invasion; thus, their interpretation must be integrated with careful assessment of stromal invasion, cytologic atypia, mitotic activity, and necrosis [48].

The differential diagnosis of glandular papilloma similarly encompasses both benign and malignant entities, most notably primary pulmonary adenocarcinoma, metastatic adenocarcinoma, and other adenomas. Carcinomas generally demonstrate malignant cytologic features such as marked atypia, increased mitotic activity, and, critically, invasion through the basal lamina, thereby disrupting normal epithelial–stromal relationships. In addition, glandular papilloma is characterized by an epithelial composition that includes basal cells and may show ciliated and mucinous elements, a constellation that is typically absent in invasive adenocarcinoma.[3][48] From a structural perspective, adenocarcinomas classically form malignant glandular architectures and/or demonstrate mucin production, which serve as supportive features of carcinoma and are not typical attributes of pulmonary papillomas. Consequently, identification of invasion, loss of orderly epithelial maturation, and absence of the characteristic cellular constituents of glandular papilloma become central discriminators.[3][48] In diagnostically challenging scenarios—such as small bronchoscopic biopsies with crush artifact, surface ulceration, or limited representation of the papillary core—correlation with imaging, repeat sampling, or excisional resection may be required to achieve confident separation between papilloma and carcinoma [48].

Prognosis

Pulmonary papillomas are predominantly benign lesions and, when completely excised, are associated with a favorable prognosis and low rates of recurrence. The principal determinant of outcome in these cases is the adequacy of removal, as residual papillomatous tissue can serve as a nidus for local regrowth. Accordingly, recurrence is uncommon but remains possible when excision is incomplete or when lesions are multifocal and not amenable to total eradication. In most patients with isolated lesions, especially when surgical margins are clear, long-term outcomes are excellent and functional recovery is expected. Despite their overall benign nature, the prognostic profile of respiratory papillomas is complicated by the possibility of malignant transformation, which, although rare, becomes more clinically relevant in certain contexts. Malignant change has been reported more often in specific histopathologic patterns, particularly squamous cell papilloma, and risk appears to increase when pulmonary involvement is present, with some reports indicating an incidence as high as 16% in this subset.[39][49] This contrasts with isolated upper airway disease, in which malignant evolution is less frequently encountered. Importantly, recurrent respiratory papillomatosis carries a substantially higher risk of malignant transformation compared with isolated upper airway papillomatosis, with estimates suggesting a 32-fold increase in risk, emphasizing the need for sustained vigilance in patients with recurrent, extensive, or lower airway disease.[22] Prognosis in recurrent respiratory papillomatosis is therefore not determined solely by benign histology, but also by disease distribution, recurrence burden, and the cumulative effects of airway compromise and repeated interventions.

Several factors have been associated with an increased risk of malignant transformation and may, therefore, influence prognostic counseling and follow-up intensity. These include infection with high-risk HPV subtypes, particularly 16 and 18, smoking, prior radiotherapy, exposure to cytotoxic drugs, p53 gene mutation, and measures reflecting high disease activity such as elevated severity scores or increased activity of 2'-5'-oligoadenylate synthetase.[14][50] Although HPV subtypes 6 and 11 are generally regarded as low-risk, evidence suggests that they—especially subtype 11—may still be implicated in malignant transformation in a minority of cases.[51] The precise biological mechanism remains incompletely elucidated, but the oncogenic potential of HPV is commonly attributed to viral interference with cell-cycle regulation, which disrupts normal differentiation and can facilitate accumulation of genetic abnormalities over time. In addition, HPV-associated papillomas involving subtypes 16, 18, and 31 are recognized for their malignant potential, reinforcing the prognostic significance of viral subtype when known.[52] Clinically, laryngotracheal papillomatosis may extend into the lower respiratory tract in up to 5% of cases, and such spread may portend a more complex disease course requiring prolonged monitoring and, in some instances, more aggressive intervention.

Other Issues

Pulmonary papillomas occupy an important niche in thoracic pathology and respiratory medicine

because their rarity and protean imaging appearances can lead to diagnostic delay or misclassification as malignant disease. One of the most practical clinical lessons is that these lesions may closely mimic neoplasms such as carcinoid tumor and squamous cell carcinoma on radiological evaluation, particularly when they present as proximal polypoid masses or endobronchial lesions producing secondary airway obstruction. As a result, imaging should be regarded as an essential mapping tool rather than a definitive diagnostic modality, and microscopic confirmation remains mandatory to establish the diagnosis and to exclude invasive carcinoma. This principle is especially critical when clinical features such as hemoptysis, progressive airway compromise, or suspicious lymphadenopathy are present, as these findings can shift pretest probability toward malignancy. Another central point is that malignant transformation is uncommon overall and has been described in a small minority of cases, often cited as less than 2%, yet it is not uniformly distributed across subtypes.[1] Transformation is more frequently associated with squamous cell papillomas and appears to be enriched in patients with recurrent respiratory papillomatosis and pulmonary involvement. HPV infection plays a major etiologic and biologic role in many papillomatous lesions, particularly squamous papillomas, and knowledge of HPV subtype can meaningfully inform concern for dysplasia or malignant evolution when interpreted alongside histologic atypia and clinical behavior. Given these considerations, early surveillance and preventive strategies are frequently emphasized, especially in patients with recurrent disease, extensive airway involvement, or recognized risk factors such as smoking or high-risk HPV infection. The broader implication is that pulmonary papilloma should be approached as a benign diagnosis that nonetheless requires disciplined evaluation, adequate tissue sampling, and longitudinal vigilance tailored to risk.

Enhancing Healthcare Team Outcomes

Because pulmonary papillomas can span a range from incidental, easily resectable lesions to recurrent, multifocal disease with airway compromise, optimal outcomes depend on coordinated interprofessional management. Pulmonologists play a central role in initial evaluation, bronchoscopic diagnosis, and longitudinal surveillance, while thoracic surgeons and otolaryngologists contribute definitive procedural management, particularly when lesions involve the larynx, central airways, or pulmonary parenchyma requiring resection. Pathologists are essential in confirming the diagnosis, classifying subtype, and evaluating for dysplasia or malignant transformation, especially given the substantial overlap in clinical and radiologic appearance with malignant neoplasms. Pharmacists, particularly those with oncology expertise, become increasingly important when systemic or targeted therapies are considered, ensuring appropriate selection, dosing, and monitoring while accounting for drug–drug interactions and immune-related or vascular adverse effects. Nursing staff are indispensable in comprehensive assessment, monitoring respiratory status, identifying early signs of airway compromise or bleeding, and facilitating timely communication among specialties when clinical deterioration occurs. A shared understanding of presentation, diagnostic pitfalls, and management options across disciplines strengthens clinical decision-making and improves patient safety. Surgical excision is often the primary definitive intervention to minimize recurrence, yet adjuvant or alternative medical therapies may be appropriate in selecting patients, particularly those with recurrent respiratory papillomatosis or aggressive disease patterns. Because a small but meaningful risk of malignant transformation exists—especially in high-risk subgroups—structured follow-up with serial imaging and clinical reassessment is commonly recommended to detect progression early and to guide timely reintervention. Importantly, team-based care also improves the consistency of patient counseling regarding prognosis, recurrence risk, occupational precautions during aerosol-generating procedures, and the potential role of preventive measures such as HPV vaccination. In aggregate, integrating pulmonary medicine, surgery, otolaryngology, pathology, pharmacy, and nursing into a cohesive care pathway is essential for reducing morbidity, ensuring diagnostic accuracy, and optimizing long-term outcomes for patients with pulmonary papillomas [51].

Conclusion:

Pulmonary papillomas represent a rare but clinically significant entity within thoracic pathology. While most lesions are benign and amenable to complete surgical excision, their variable presentation and potential for malignant transformation—particularly in recurrent respiratory papillomatosis—necessitate careful diagnostic and therapeutic planning. The cornerstone of management remains accurate histopathologic confirmation, as imaging alone cannot reliably distinguish papillomas from malignant neoplasms. Multimodal strategies, including bronchoscopic removal, surgical resection, and adjunctive therapies such as laser ablation or intralesional antivirals, are frequently employed to achieve local control. Recent advances in systemic therapy, notably immune checkpoint inhibitors and antiangiogenic agents like bevacizumab, have expanded treatment options for aggressive or refractory disease, reducing procedural burden and improving quality of life. Despite these developments, recurrence remains a major challenge, underscoring the importance of structured surveillance and preventive measures such as HPV vaccination. Prognosis is excellent for solitary papillomas when completely excised, but more guarded in multifocal disease due to recurrence risk and rare malignant evolution. Ultimately, optimal outcomes depend on

early recognition, comprehensive evaluation, and coordinated interprofessional care, ensuring timely intervention and minimizing morbidity in this complex and heterogeneous condition.

References:

1. Brady P, McCreary C, O'Halloran KD, Gallagher C. Squamous Papilloma Causing Airway Obstruction During Conscious Sedation. Anesthesia progress. 2017 Fall:64(3):168-170. doi: 10.2344/anpr-64-03-07.
2. Miura H, Tsuchida T, Kawate N, Konaka C, Kato H, Ebihara Y. Asymptomatic solitary papilloma of the bronchus: review of occurrence in Japan. The European respiratory journal. 1993 Jul:6(7):1070-3
3. Fortes HR, von Ranke FM, Escuissato DL, Araujo Neto CA, Zanetti G, Hochhegger B, Souza CA, Marchiori E. Recurrent respiratory papillomatosis: A state-of-the-art review. Respiratory medicine. 2017 May:126():116-121. doi: 10.1016/j.rmed.2017.03.030.
4. Ding D, Yin G, Guo W, Huang Z. Analysis of lesion location and disease characteristics of pharyngeal and laryngeal papilloma in adult. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2023 Jan:280(1):289-295. doi: 10.1007/s00405-022-07575-5.
5. Argüelles M, Blanco I. Inflammatory bronchial polyps associated with asthma. Archives of internal medicine. 1983 Mar:143(3):570-1
6. Enrique OH, Eloy SH, Adrian TP, Perla V. Systemic bevacizumab as adjuvant therapy for recurrent respiratory papillomatosis in children: A series of three pediatric cases and literature review. American journal of otolaryngology. 2021 Sep-Oct:42(5):103126. doi: 10.1016/j.amjoto.2021.103126.
7. DRENNAN JM, DOUGLAS AC. SOLITARY PAPILLOMA OF A BRONCHUS. Journal of clinical pathology. 1965 Jul:18(4):401-2
8. ASHLEY DJ, DANINO EA, DAVIES HD. Bronchial polyps. Thorax. 1963 Mar:18(1):45-9
9. Reeves WC, Ruparelia SS, Swanson KI, Derkay CS, Marcus A, Unger ER. National registry for juvenile-onset recurrent respiratory papillomatosis. Archives of otolaryngology--head & neck surgery. 2003 Sep:129(9):976-82
10. Carifi M, Napolitano D, Morandi M, Dall'Olio D. Recurrent respiratory papillomatosis: current and future perspectives. Therapeutics and clinical risk management. 2015:11():731-8. doi: 10.2147/TCRM.S81825.
11. Venkatesan NN, Pine HS, Underbrink MP. Recurrent respiratory papillomatosis. Otolaryngologic clinics of North America. 2012 Jun:45(3):671-94, viii-ix. doi: 10.1016/j.otc.2012.03.006.
12. Yabuki K, Matsuyama A, Obara K, Takenaka M, Tanaka F, Nakatani Y, Hisaoka M. A unique case of a huge mixed squamous cell and glandular papilloma of non-endobronchial origin with a peripheral growth. Respiratory medicine case reports. 2018:24():108-112. doi: 10.1016/j.rmcr.2018.05.001.
13. Taliercio S, Cespedes M, Born H, Ruiz R, Roof S, Amin MR, Branski RC. Adult-onset recurrent respiratory papillomatosis: a review of disease pathogenesis and implications for patient counseling. JAMA otolaryngology--head & neck surgery. 2015 Jan:141(1):78-83. doi: 10.1001/jamaoto.2014.2826.
14. Fusconi M, Grasso M, Greco A, Gallo A, Campo F, Remacle M, Turchetta R, Pagliuca G, DE Vincentiis M. Recurrent respiratory papillomatosis by HPV: review of the literature and update on the use of cidofovir. Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale. 2014 Dec:34(6):375-81
15. Rady PL, Schnadig VJ, Weiss RL, Hughes TK, Tyring SK. Malignant transformation of recurrent respiratory papillomatosis associated with integrated human papillomavirus type 11 DNA and mutation of p53. The Laryngoscope. 1998 May:108(5):735-40
16. Lee JH, Smith RJ. Recurrent respiratory papillomatosis: pathogenesis to treatment. Current opinion in otolaryngology & head and neck surgery. 2005 Dec:13(6):354-9
17. Sievers C, Robbins Y, Bai K, Yang X, Clavijo PE, Friedman J, Sinkoe A, Norberg SM, Hinrichs C, Van Waes C, Allen CT. Comprehensive multiomic characterization of human papillomavirus-driven recurrent respiratory papillomatosis reveals distinct molecular subtypes. Communications biology. 2021 Dec 20:4(1):1416. doi: 10.1038/s42003-021-02942-0.
18. Gonçalves IC, Silva C, Gomes J, Xará S. Recurrent Respiratory Papillomatosis Presenting as Worsening Dyspnea in an HIV-infected Patient. Cureus. 2022 Dec:14(12):e32908. doi: 10.7759/cureus.32908.

19. Rahbar R, Vargas SO, Folkman J, McGill TJ, Healy GB, Tan X, Brown LF. Role of vascular endothelial growth factor-A in recurrent respiratory papillomatosis. The Annals of otology, rhinology, and laryngology. 2005 Apr:114(4):289-95
20. Ahn J, Bishop JA, Roden RBS, Allen CT, Best SRA. The PD-1 and PD-L1 pathway in recurrent respiratory papillomatosis. The Laryngoscope. 2018 Jan:128(1):E27-E32. doi: 10.1002/lary.26847.
21. Maxwell RJ, Gibbons JR, O'Hara MD. Solitary squamous papilloma of the bronchus. Thorax. 1985 Jan:40(1):68-71
22. Pai SI, Wasserman I, Ji YD, Gilman M, Hung YP, Faquin WC, Mino-Kenudson M, Muniappan A. Pulmonary manifestations of chronic HPV infection in patients with recurrent respiratory papillomatosis. The Lancet. Respiratory medicine. 2022 Oct:10(10):997-1008. doi: 10.1016/S2213-2600(22)00008-X.
23. . Histological typing of lung tumours. Tumori. 1981 Aug:67(4):253-72
24. Miyai K, Takeo H, Nakayama T, Obara K, Aida S, Sato K, Matsukuma S. Invasive form of ciliated muconodular papillary tumor of the lung: A case report and review of the literature. Pathology international. 2018 Sep:68(9):530-535. doi: 10.1111/pin.12708.
25. DeVoti JA, Rosenthal DW, Wu R, Abramson AL, Steinberg BM, Bonagura VR. Immune dysregulation and tumor-associated gene changes in recurrent respiratory papillomatosis: a paired microarray analysis. Molecular medicine (Cambridge, Mass.). 2008 Sep-Oct:14(9-10):608-17. doi: 10.2119/2008-00060.DeVoti.
26. Kim SR, Park JK, Park SJ, Min KH, Lee MH, Han HJ, Chung CR, Choi KH, Chung MJ, Lee YC. Solitary bronchial squamous papilloma presenting as a plaque-like lesion in a subject with asthma. American journal of respiratory and critical care medicine. 2011 Feb 15:183(4):555-6
27. Fortes HR, Ranke FMV, Escuissato DL, Araujo Neto CA, Zanetti G, Hochhegger B, Irion KL, Souza CA, Marchiori E. Laryngotracheobronchial papillomatosis: chest CT findings. Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia. 2017 Jul-Aug:43(4):259-263. doi: 10.1590/S1806-37562016000000351.
28. Robb PK Jr, Weinberger PM, Perakis H, Li A, Klein AM, Johns MM 3rd, Adkins LK, Postma GN. Association of asthma with clinically aggressive recurrent respiratory papillomatosis. Archives of otolaryngology--head & neck surgery. 2011 Apr:137(4):368-72. doi: 10.1001/archoto.2011.44.
29. Mitsumoto GL, Bernardi FDC, Paes JF, Villa LL, Mello B, Pozzan G. Juvenile-onset recurrent respiratory papillomatosis with pulmonary involvement and carcinomatous transformation. Autopsy & case reports. 2018 Jul-Sep:8(3):e2018035. doi: 10.4322/acr.2018.035.
30. Li YL, Wu MZ, Chai XM, Xu J. [CT findings of juvenile laryngeal papilloma spreading in bronchia and lung]. Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery. 2018 May:32(10):767-769. doi: 10.13201/j.issn.1001-1781.2018.10.010.
31. Kozu Y, Maniwa T, Ohde Y, Nakajima T. A solitary mixed squamous cell and glandular papilloma of the lung. Annals of thoracic and cardiovascular surgery : official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia. 2014:20 Suppl():625-8. doi: 10.5761/atcs.cr.13-00029.
32. Greene JG, Tassin L, Saberi A. Endobronchial epithelial papilloma associated with a foreign body. Chest. 1990 Jan:97(1):229-30
33. Miyoshi R, Menju T, Yoshizawa A, Date H. Expression of p16(Ink4a) in mixed squamous cell and glandular papilloma of the lung. Pathology international. 2017 Jun:67(6):306-310. doi: 10.1111/pin.12531.
34. Kim Y, Pierce CM, Robinson LA. Impact of viral presence in tumor on gene expression in non-small cell lung cancer. BMC cancer. 2018 Aug 22:18(1):843. doi: 10.1186/s12885-018-4748-0.
35. Tatci E, Gokcek A, Unsal E, Cimen F, Demirag F, Yazici S, Ozmen O. FDG PET/CT Findings of Recurrent Respiratory Papillomatosis With Malignant Degeneration in the Lung. Clinical nuclear medicine. 2015 Oct:40(10):802-4. doi: 10.1097/RLU.0000000000000895.
36. Lichtenberger JP 3rd, Biko DM, Carter BW, Pavio MA, Huppmann AR, Chung EM. Primary Lung Tumors in Children: Radiologic-Pathologic Correlation From the Radiologic Pathology Archives. Radiographics : a review publication of the Radiological Society of North America, Inc. 2018 Nov-Dec:38(7):2151-2172. doi: 10.1148/rg.2018180192.
37. Sakopoulos A, Kesler KA, Weisberger EC, Turrentine MW, Conces DJ Jr. Surgical management of pulmonary carcinoma secondary to recurrent respiratory papillomatosis. The Annals of thoracic surgery. 1995 Dec:60(6):1806-7

38. Harris K, Chalhoub M. Tracheal papillomatosis: what do we know so far? Chronic respiratory disease. 2011:8(4):233-5. doi: 10.1177/1479972311416381.
39. Yang Q, Li Y, Ma L, Xiao Y, Wang H, Ding Y, Hu R, Wang X, Meng L, Wang J, Xu W. Long-term Outcomes of Juvenile Onset Recurrent Respiratory Papillomatosis with Pulmonary Involvement. The Laryngoscope. 2021 Jul:131(7):EE2277-E2283. doi: 10.1002/lary.29376.
40. Adams AE, Steiner FA. Use of cryotherapy to treat obstructing papilloma of an accessory tracheal bronchus: case report. Journal of cardiothoracic surgery. 2022 Oct 22:17(1):273. doi: 10.1186/s13019-022-01977-6.
41. Creelan BC, Ahmad MU, Kaszuba FJ, Khalil FK, Welsh AW, Ozdemirli M, Grant NN, Subramaniam DS. Clinical Activity of Nivolumab for Human Papilloma Virus-Related Juvenile-Onset Recurrent Respiratory Papillomatosis. The oncologist. 2019 Jun:24(6):829-835. doi: 10.1634/theoncologist.2018-0505.
42. Ruiz R, Balamuth N, Javia LR, Zur KB. Systemic Bevacizumab Treatment for Recurrent Respiratory Papillomatosis: Long-Term Follow-Up. The Laryngoscope. 2022 Oct:132(10):2071-2075. doi: 10.1002/lary.30021.
43. Pogoda L, Ziylan F, Smeeing DPJ, Dikkers FG, Rinkel RNPM. Bevacizumab as treatment option for recurrent respiratory papillomatosis: a systematic review. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2022 Sep:279(9):4229-4240. doi: 10.1007/s00405-022-07388-6.
44. Cardoso Figueiredo M, Chantre-Justino M, Latini Ruback R, Pires de Mello P, Alves G, Helena Ornellas M. Clinical and treatment course of lung carcinoma from adult-onset recurrent respiratory papillomatosis with lung involvement: A case report. Oral oncology. 2021 Oct:121():105398. doi: 10.1016/j.oraloncology.2021.105398.
45. Limsukon A, Susanto I, Soo Hoo GW, Dubinett SM, Batra RK. Regression of recurrent respiratory papillomatosis with celecoxib and erlotinib combination therapy. Chest. 2009 Sep:136(3):924-926. doi: 10.1378/chest.08-2639.
46. Feng AN, Wu HY, Zhou Q, Sun Q, Fan XS, Zhang YF, Meng FQ. Solitary endobronchial papillomas with false impression of malignant transformation: report of two cases and review of the literature. International journal of clinical and experimental pathology. 2015:8(7):8607-12
47. Bueno J, Landeras L, Chung JH. Updated Fleischner Society Guidelines for Managing Incidental Pulmonary Nodules: Common Questions and Challenging Scenarios. Radiographics : a review publication of the Radiological Society of North America, Inc. 2018 Sep-Oct:38(5):1337-1350. doi: 10.1148/rg.2018180017.
48. Chuang HW, Liao JB, Chang HC, Wang JS, Lin SL, Hsieh PP. Ciliated muconodular papillary tumor of the lung: a newly defined peripheral pulmonary tumor with conspicuous mucin pool mimicking colloid adenocarcinoma: a case report and review of literature. Pathology international. 2014 Jul:64(7):352-7. doi: 10.1111/pin.12179.
49. Ahmed A, Shukla A, Hubbell N, Almujarkesh MK, LaBuda D, Ouchi T. Early Identification and Intervention in Malignant Transformation of Respiratory Papillomatosis. The American journal of case reports. 2023 Jan 10:24():e937665. doi: 10.12659/AJCR.937665.
50. Donne AJ, Hampson L, Homer JJ, Hampson IN. The role of HPV type in Recurrent Respiratory Papillomatosis. International journal of pediatric otorhinolaryngology. 2010 Jan:74(1):7-14. doi: 10.1016/j.ijporl.2009.09.004.
51. Goon P, Sonnex C, Jani P, Stanley M, Sudhoff H. Recurrent respiratory papillomatosis: an overview of current thinking and treatment. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2008 Feb:265(2):147-51
52. Stepp WH, Farzal Z, Kimple AJ, Ebert CS Jr, Senior BA, Zanation AM, Thorp BD. HPV in the malignant transformation of sinonasal inverted papillomas: A meta-analysis. International forum of allergy & rhinology. 2021 Oct:11(10):1461-1471. doi: 10.1002/alr.22810.