Review

Laryngeal Papillomatosis

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Review

Laryngeal Papillomatosis

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Abstract: Laryngeal papillomatosis and recurrent respiratory papillomatosis are caused by the human papillomavirus. It is characterized by papillomatous growths and is the most common benign disease of the larynx. Juvenile onset RRP is characterized by more aggressive disease compared to adult onset RRP. Patients often require frequent surgical procedures, with an increasing shift towards office-based treatment. A variety of surgical and adjuvant medical therapies are available with mixed responses. New targeted therapies and vaccines are currently under investigation as potential adjuncts in the management.

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1. Introduction

Recurrent Respiratory Papillomatosis (RRP), also referred to as Laryngeal Papillomatosis (LP) when primarily involving the larynx, is the most common benign neoplasm of the larynx [1]. It's caused by the Human Papilloma Virus (HPV), predominantly subtypes 6 and 11 [2, 3]. While RRP is a benign disease, it remains challenging to treat with significant morbidity due to its high recurrence rates [1]. The incidence in the United States has previously been estimated to be 4.3 per 100,000 children and 1.8 per 100,000 adults but has recently been shown to be declining as a consequence of the creation and subsequent expansion of HPV vaccination [1].

RRP exhibits a bimodal distribution classified as juvenile onset (J-RRP) and adult onset (A-RRP). Compared to A-RRP, J-RRP is typically characterized as a more aggressive disease with higher rates of recurrence, often requiring frequent surgical interventions. J-RRP is thought to arise from vertical transmission during childbirth from infected genital mucosa, while A-RRP arises from sexual transmission [1].

2. HPV

HPV comprises a family of small double-stranded DNA viruses that infect cutaneous and mucosal epithelium. Over 150 HPV types have been identified [4]. HPV types that infect cutaneous epithelium cause common skin warts, while HPV types that infect mucosal epithelium are further categorized as 'high risk' or 'low risk' based on oncogenic potential [4].

High-risk HPV types are implicated in the development of cervical cancer, as well as oropharyngeal and anogenital cancer. The high-risk types include HPV 16, 18, 31, 33, 45, 52, and 58, with HPV 16 and 18 accounting for about 66% of cervical cancers [5]. Low-risk HPV types include HPV 6 and 11, which more frequently cause low grade genital lesions, anogenital warts, and RRP [5]. HPV infection occurs at the basal lamina of epithelium and most infections are asymptomatic without any clinical manifestations. Despite the high incidence of infection, the majority resolve spontaneously in 1-2 years [5]. Those who develop persistent infections are most at risk for developing HPV related cervical, anogenital, or oropharyngeal cancers [4–6].

HPV is the most common sexually transmitted infection in both the United States and throughout the world. Prior to the introduction of the HPV vaccine, 79 million people were infected

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in the United States with about 14 million new infections per year. Almost half of these infections were in people aged 15 to 24 years old [6].

In 2006, the quadrivalent HPV vaccine was introduced in the United States. Data through 2018 revealed an 86% decrease in prevalence of HPV types 6, 11, 16, and 18 among females 14 to 19 years old, and a 71% decrease in females 20 to 24 years old. A 9 valent HPV vaccine was later introduced in 2014 [7, 8]. In the head and neck, 80% of oropharyngeal squamous cell carcinoma (OPSCC) is associated with HPV in the U.S. [9] . Between 1988 and 2004, HPV related OPSCC increased by 225%, while HPV-negative cancers declined 50% [10].

3. Laryngeal Papillomatosis

Clinical presentation of LP depends on the extent and location of the papillomatous growths. In children, the characteristic triad of symptoms includes dysphonia, stridor, and dyspnea [11]. J-RRP represents a distinct form of the disease in comparison to A-RRP. LP is typically more aggressive in children, more expensive to treat, and exhibits higher recurrence rates compared to adults [12, 13]. Specifically, children with aggressive disease require more frequent procedures and may be more likely to present with more distal disease, require tracheostomy, and experience complications [13–18]. It is important to note that adults can still present with aggressive disease. While there is no formal definition of what constitutes “aggressive” disease, a widely published definition includes 1 or more of the following: 10 or more total surgeries, 4 of more surgeries per year, distal spread to the trachea or beyond, or need for tracheostomy at any point [13–18].

HPV 11 is typically thought to be associated with greater risk of developing RRP and more severe presentations, which has been widely published [13, 15, 16, 19–22]. However, there is evidence that age of onset is a more relevant factor than HPV subtype [12, 18]. When controlling for age, HPV subtype was not strongly associated with disease severity and the findings were more suggestive that age at diagnosis was more predictive of disease severity. In patients who were diagnosed between ages 0-5 years, 80% experienced severe disease. In comparison, 60% of patients diagnosed between ages 5-10 years had severe disease, and 30% diagnosed after age 10 years had severe disease. The authors identified 5 years of age to be a critical age of diagnosis in predicting severe disease course [18].

It is unclear why children are more likely to present with aggressive disease. While J-RRP is strongly associated with perinatal HPV exposure, few infants who are exposed to or infected with HPV go on to acquire RRP [23, 24]. It is also currently unclear why some patients acquire RRP and others do not. Studies have explored the roles of genetic, immunologic, and degree of exposure in the development of RRP [22, 25].

The critical period for the development of the immune system in children is age 4-6 years old (Kovalenko). This coincides with the previously reported critical age at diagnosis for RRP that is associated with more severe disease [26]. Given HPV's opportunistic behavior (as evidenced by increased HPV-related disease in immunodeficiencies), an immature immune system may explain why younger age at diagnosis has been associated with more severe disease [22]. Regarding genetic factors, certain HLA class II genes are upregulated in RRP, while specific haplotypes are associated with increased susceptibility to severe disease [22].

Cases of malignant transformation are rare but have been reported [27–30]. Cases of malignant transformation in children were more likely to have pulmonary involvement and younger age of onset. In adults, dysplasia or malignant transformation was associated with older age of onset. Gender, smoking history, number of operations, and use of cidofovir were not associated with development of dysplasia or malignant transformation [30]. HPV type has not been shown to be correlated with malignant transformation [31]. The only significant risk factor for malignant transformation was LP without demonstrable HPV DNA, and thus HPV typing should strongly be considered for laryngeal disease [31].

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4. Transmission

Transmission of HPV in children has been suggested to occur via three mechanisms: vertical transmission between mother and newborn at birth via contact with genital mucosa, vertical transmission in utero, and horizontal transmission via the child's environment [22]. A large case control study of 3033 Danish infants showed that the risk of J-RRP was 231.4 times higher in children whose mothers had genital warts during pregnancy compared to those who whose mothers did not. This study also showed that the risk of RRP was doubled in spontaneous vaginal delivery lasting more than 10 hours [32].

While cesarian section has been shown to reduce transmission of viruses such as herpes simplex, Hepatitis B, and HIV, it is unclear if there is any role in preventing vertical transmission of HPV [33]. Vertical transmission may still occur in utero or postpartum even in cases of cesarian section, and can occur from sperm during fertilization [25, 34, 35]. Horizontal transmission may occur shortly after delivery through close physical contact with caregivers, relatives, and other environmental exposures that can transmit infection [22].

5. Management

The mainstay of treatment is the surgical removal of papillomas. Eradication of disease remains difficult due to the propensity of these papillomas to recur [36]. There are a variety of surgical modalities for ablating papillomas with the most widely used methods including laser, microdebrider, and coblation. Comparative studies have found no significant difference in recurrence trends between these modalities [37].

When addressing papillomas that involve the vocal fold, care must be taken to remain superficial to the vocal ligament [25]. A subepithelial injection or saline, epinephrine, or lidocaine into the superficial lamina propria can be utilized to protect the vocal ligament from damage. There is a significant risk of anterior web formation when treating bilateral sides of the anterior commissure and this can be staged to avoid this complication [25]. Whenever there is laryngeal involvement, it's critical to evaluate the trachea and mainstem bronchi to evaluate for distal spread of disease. Jet ventilation should be avoided if possible to prevent theoretical distal seeding of disease. A tracheostomy should also be avoided unless absolutely necessary to prevent papillomatous involvement of the stoma.

6. CO_2 Laser

The Carbon Dioxide (CO2) laser is commonly used for laryngological procedures. The wavelength of the CO2 laser is 10,600nm and is absorbed preferentially by water in soft tissues. The CO2 laser can be utilized to cut or ablate tissue [38]. It is imperative to adhere to proper laser safety protocols as airway fire is one of the most serious risks when using a laser. Different power settings and firing modes can be employed for a range of functions. 4-8 W with non-continuous firing allows for more precision when working at the vocal fold level and has a lower level of collateral damage [38].

7. Photo Angiolytic Lasers (KTP and TruBlue)

The potassium-titanyl-phosphate (KTP) laser has a wavelength of 532nm while the TruBlue (A.R.C. Laser GmbH) laser has a wavelength of 445 nm [39]. These are both considered photoangiolytic lasers that are absorbed preferentially by oxyhemoglobin, corresponding to a more selective ablation of highly vascularized tissues. The angiolytic nature of these lasers allow them to achieve better hemostatic control compared to other lasers [38, 40, 41]. However, these lasers can only be used as a fiber as opposed to the CO2 laser which has the option of either a fiber or use of a beam with micromanipulator. A lower energy setting with extended pulse width can be used to effectively

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coagulate papillomatous lesions and preserve the superficial lamina propria by reducing thermal injury [42].

8. Microdebrider

Powered laryngeal shavers have been shown to be a safe and effective modality for endoscopic treatment of RRP in adults and children when used appropriately [43–45]. Compared to laser, powered instruments avoid the risk of thermal injury and airway fire [46]. Various blade types and sizes are available. The Skimmer blade (Medtronic Xomed) can be used for more precise removal of papillomas near the vocal fold while the Tricut blade (Medtronic Xomed) can be used to remove more bulky lesions. Speed settings vary from 600 to 1,400 RPM, with slower speeds used for rapid removal of large lesions and faster speeds for more precision near normal mucosa [44]. Hemostasis is often achieved with application of epinephrine soaked pledgets [43, 44].

9. Coblator

Radiofrequency coblation (coblator) has become increasingly utilized in a variety of otolaryngological procedures [47–49]. It has been used safely and effectively in both adult and pediatric patients with extensive laryngeal papillomatosis [50, 51]. Benefits of radiofrequency coblation have been reported by some to include reduced blood loss, minimal damage to underlying tissues, decreased operation time, and greater time interval between additional procedures compared to laser ablation [52].

10. Office vs. OR

Management of LP has traditionally required surgical excision within the operating room. Due to its high recurrence rate, patients typically undergo frequent procedures to maintain airway patency and vocal quality. Office-based procedures provide an attractive alternative to the operating room, with the goal of saving costs, time, and avoiding the risks of general anesthesia. Office-based laser therapy has been reported as a safe and effective treatment that is well tolerated in unsedated patients [53–55].

Office-based laser treatment of LP is less costly than the operating room [56, 57]; however, these reports also found that patients required more frequent office-based treatments, which may reduce its cost-effectiveness [56, 58]. Not all patients are suitable candidates for office-based procedures, including those with severe disease burden or airway compromise. Appropriate patient selection based on expected tolerance is also an important consideration. Management in the operating room while under general anesthesia offers a more controlled environment and access to more specialized instruments. There is now more of a trend to treat patients in the OR when they originally present, with further treatment offered in the office to delay, sometime indefinitely, a repeat operation. Biopsies should be taken during a patient's first trip to the OR at a minimum, with consideration given for further biopsies at each successive surgery.

11. Medical Management

While the primary management of LP is surgical excision, adjuvant therapy is utilized to control the disease in up to 20% of patients [59]. There are no indications for when to use adjuvant therapies, but it is typically considered in cases where more frequent operative treatment is needed or if there is extralaryngeal involvement [60].

12. Cidofovir

Cidofovir is an antiviral agent that inhibits viral replication. It's a nucleotide analog that is incorporated into viral DNA and inhibits viral DNA polymerases [61]. It is FDA-approved for treatment of CMV retinitis in patients with AIDS but has been used off-label as an intravenous and

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intra-lesional adjuvant treatment for RRP since the 1990s. Initial studies evaluating its efficacy in treating RRP showed significant rates of disease remission with intralesional injections [62, 63]. Cidofovir has also been documented to reduce viral load and modified Derkay scores [64]. Many studies published since its initial use in treating RRP have demonstrated positive results with minimal side effects [60]. However, a randomized, double-blind, placebo-controlled study showed that there was no statistically significant difference in disease severity between those who received cidofovir compared to placebo [65]. A Cochrane review concluded that there is insufficient high-quality evidence to support the efficacy of intra-lesional cidofovir in the treatment of RRP [66].

Despite the widespread use of cidofovir in treating RRP, concerns regarding its risk of nephrotoxicity, neutropenia, and possible oncogenicity were raised. In animal studies, cidofovir was found to be carcinogenic and teratogenic [67]. Current reports do not show evidence of long-term nephrotoxicity, neutropenia, or the development of dysplasia or malignancy related to the use of intralesional cidofovir [60, 68].

13. Bevacizumab

Bevacizumab is a humanized monoclonal antibody that inhibits angiogenesis by blocking vascular endothelial growth factor A (VEGF-A) [69]. VEGF-A mRNA is highly expressed in RRP tissue samples compared to unaffected tissue, implicating its role in the disease process [70]. Initial case reports showed dramatic responses with systemic therapy in both adult and pediatric patients [71–73]. More recent systematic reviews suggest that intralesional and systemic bevacizumab is effective in decreasing disease burden and the need for frequent surgical intervention in adults and children [69, 74, 75]. Systemic administration is particularly well-suited for lesions that involve the tracheobronchial tree and are more difficult to access for surgical excision [60]. While bevacizumab has been shown to be well tolerated with minimal adverse effects, boxed warnings suggest an increased risk of gastrointestinal perforation, impaired wound healing, and hemorrhage [74, 76].

14. HPV Vaccine

In 2006 the quadrivalent HPV vaccination was first made available to the public targeting HPV types 6, 11, 16, and 18. In 2015 a 9 valent vaccine was released targeting additional types 31, 33, 45, 52, and 58. The HPV vaccine has also been proposed as potentially having a therapeutic effect in the treatment of RRP [77] . Theories suggested that both antibody- and cell-mediated immune responses may decrease the risk of recurrence and reinfection by inhibiting latent HPV in the surgical site [78, 79]. A 2019 meta-analysis found that use of the HPV vaccine as an adjuvant treatment for RRP reduced the number of surgical procedures [80]. There are currently multiple active clinical trials investigating new therapeutic vaccines with the primary purpose of treating of those with LP.

15. Viral Vaporization

With the rise in HPV-related diseases came a growing concern for the risk of transmitting HPV to providers during surgical procedures in which viral particles may be vaporized as a result of electrocautery or laser ablation of HPV infected tissues [81]. There is increasing evidence that ablative procedures disperse HPV DNA particles into the environment [82, 83]; however, the infectivity of HPV DNA particles in ablative plumes is unclear. Infectivity of laser plumes containing viral particles has been demonstrated with bovine papillomavirus (BPV) in animal models [84, 85]. Some data suggests increased rates of HPV DNA in samples taken from providers performing laser treatment of warts, yet the rates remained comparable to that of the general population [81, 86]. In a series of 12 patients with laryngeal papillomatosis treated with KTP laser, HPV virus was undetectable by PCR on the laser fibers used to treat them [87]. The available evidence demonstrates that HPV DNA can be dispersed during ablative procedures using laser and electrocautery with uncertain infectious potential. Providers are thus at theoretical greater risk of HPV exposure and best practice includes utilizing N95 masks and smoke evacuation systems to minimize risk [82].

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16. Future Directions

An ongoing Phase 1/2 trial is evaluating DNA plasmid vaccines targeting E6 and E7 proteins of HPV 6 and 11 (INO-3107 – Inovio Pharmeceutical, Inc.) NCT04398433 [88]. Interim results have shown a decrease in the number of surgical interventions required compared to the year prior to administration, decreased severity, and durable cellular response against HPV 6 and 11 [89].

Immunotherapies utilizing monoclonal antibodies that target the programmed death 1 (PD-1) and ligand (PD-L1) pathway have been used to treat advanced HPV-mediated head and neck cancer [90]. The PD-1/PD-L1 pathway has shown activity in RRP [91, 92] Nivolumab is a monoclonal antibody targeting the PD-1 receptor; it was used to treat two adult patients with recurrent J-RRP [93]. One patient experienced remission after 9 months of treatment. The second patient had a mixed response characterized by improvement in laryngeal disease, while some pulmonary lesions shrank, and others grew [93]. A phase II trial evaluated avelumab, a monoclonal antibody targeting PD-L1 [94]. The results showed improvement in laryngeal disease across all 12 patients, but pulmonary disease did not respond [94].

HIV protease inhibitors have demonstrated activity against HPV-mediated cervical carcinoma in-vitro, with lopinavir being the most effective one identified [95]. A study of patients with cervical HPV positive high grade squamous intraepithelial lesions (HSIL) treated with topical lopinavir/ritonavir showed no dysplasia in 63% of patients after 12 weeks of treatment [96]. RNA interference targeting E7 has also shown activity against cervical carcinoma in vitro via upregulation of p53 and retinoblastoma (Rb) protein, providing potential targeted gene therapy for HPV-mediated disease [97]. These potential therapies have demonstrated activity against HPV-mediated disease and may have potential in treating RRP in the future.

17. Conclusions

RRP is the most common benign disease of the larynx, caused by HPV. It's notoriously challenging to treat due to its tendency to recur. Two distinct forms are recognized based on age of diagnosis, with J-RRP representing more aggressive disease. The mainstay of management is surgical excision with many different modalities utilized according to surgeon preference. Patients typically require frequent surgical procedures, and office-based laser treatment is useful in delaying repeat trips to the operating room in appropriately selected patients. Many adjuvant treatments are available with mixed responses but may be particularly suited for patients with distal disease that is not easily accessible for resection. Ongoing trials are exploring new vaccine strategies and targeted therapies that have the potential to improve control of LP in the future.

References

1. Derkay, C. S.; Wiatrak, B. Recurrent Respiratory Papillomatosis: A Review. *Laryngoscope*, **2008**, *118* (7), 1236–1247. https://doi.org/10.1097/MLG.0b013e31816a7135.
2. Benedict, J. J.; Derkay, C. S. Recurrent Respiratory Papillomatosis: A 2020 Perspective. *Laryngoscope Investig Otolaryngol*, **2021**, *6* (2), 340–345. https://doi.org/10.1002/lio2.545.
3. Donne, A. J.; Hampson, L.; Homer, J. J.; Hampson, I. N. The Role of HPV Type in Recurrent Respiratory Papillomatosis. *Int J Pediatr Otorhinolaryngol*, **2010**, *74* (1), 7–14. https://doi.org/10.1016/j.ijporl.2009.09.004.
4. Doorbar, J.; Quint, W.; Banks, L.; Bravo, I. G.; Stoler, M.; Broker, T. R.; Stanley, M. A. The Biology and Life-Cycle of Human Papillomaviruses. *Vaccine*, **2012**, *30*, F55–F70. https://doi.org/10.1016/j.vaccine.2012.06.083.
5. Elissa Meites, M. M.; Julianne Gee, M.; Elizabeth Unger, P. M.; Lauri Markowitz, M. Human Papillomavirus.
6. Satterwhite, C. L.; Torrone, E.; Meites, E.; Dunne, E. F.; Mahajan, R.; Ocfemia, M. C. B.; Su, J.; Xu, F.; Weinstock, H. Sexually Transmitted Infections Among US Women and Men. *Sex Transm Dis*, **2013**, *40* (3), 187–193. https://doi.org/10.1097/OLQ.0b013e318286bb53.
7. Rosenblum, H. G.; Lewis, R. M.; Gargano, J. W.; Querec, T. D.; Unger, E. R.; Markowitz, L. E. Declines in Prevalence of Human Papillomavirus Vaccine-Type Infection Among Females after Introduction of

 doi:10.20944/preprints202412.2345.v1

Vaccine — United States, 2003–2018. *MMWR Morb Mortal Wkly Rep*, **2021**, *70* (12), 415–420. https://doi.org/10.15585/mmwr.mm7012a2.

8. Emiko Petrosky, M.; Joseph A. Bocchini Jr, M.; Susan Hariri, P.; Harrell Chesson, P.; C. Robinette Curtis, M.; Mona Saraiya, M.; Elizabeth R. Unger, P. M.; Lauri E. Markowitz, M. *Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices*; 2015.
9. Gribb, J. P.; Wheelock, J. H.; Park, E. S. Human Papilloma Virus (HPV) and the Current State of Oropharyngeal Cancer Prevention and Treatment. *Dela J Public Health*, **2023**, *9* (1), 26–28. https://doi.org/10.32481/djph.2023.04.008.
10. Chaturvedi, A. K.; Engels, E. A.; Pfeiffer, R. M.; Hernandez, B. Y.; Xiao, W.; Kim, E.; Jiang, B.; Goodman, M. T.; Sibug-Saber, M.; Cozen, W.; et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *Journal of Clinical Oncology*, **2011**, *29* (32), 4294–4301. https://doi.org/10.1200/JCO.2011.36.4596.
11. Lepine, C.; Leboulanger, N.; Badoual, C. Juvenile Onset Recurrent Respiratory Papillomatosis: What Do We Know in 2024 ? *Tumour Virus Res*, **2024**, *17*, 200281. https://doi.org/10.1016/j.tvr.2024.200281.
12. Xi, Y.; Wang, H.; Wang, W.; Wang, X.; Zhang, J.; Zhao, J.; Wang, G.; Gui, J.; Ni, X. Risk Factors for Aggressive Recurrent Respiratory Papillomatosis in Chinese Juvenile Patients. *Acta Otolaryngol*, **2020**, *140* (9), 771–776. https://doi.org/10.1080/00016489.2020.1767804.
13. Doyle, D. J.; Gianoli, G. J.; Espinola, T.; Miller, R. H. Recurrent Respiratory Papillomatosis: Juvenile versus Adult Forms. *Laryngoscope*, **1994**, *104* (5), 523–527. https://doi.org/10.1002/lary.5541040503.
14. Omland, T.; Akre, H.; Lie, K. A.; Jebsen, P.; Sandvik, L.; Brøndbo, K. Risk Factors for Aggressive Recurrent Respiratory Papillomatosis in Adults and Juveniles. *PLoS One*, **2014**, *9* (11), e113584. https://doi.org/10.1371/journal.pone.0113584.
15. Derkay, C. S. Task Force on Recurrent Respiratory Papillomas: A Preliminary Report. *Archives of Otolaryngology - Head and Neck Surgery*, **1995**, *121* (12), 1386–1391. https://doi.org/10.1001/archotol.1995.01890120044008.
16. Armstrong, L. R.; Derkay, C. S.; Reeves, W. C. Initial Results From the National Registry for Juvenile-Onset Recurrent Respiratory Papillomatosis. *Arch Otolaryngol Head Neck Surg*, **1999**, *125* (7), 743. https://doi.org/10.1001/archotol.125.7.743.
17. Draganov, P.; Todorov, S.; Todorov, I.; Karchev, T.; Kalvatchev, Z. Identification of HPV DNA in Patients with Juvenile-Onset Recurrent Respiratory Papillomatosis Using SYBR® Green Real-Time PCR. *Int J Pediatr Otorhinolaryngol*, **2006**, *70* (3), 469–473. https://doi.org/10.1016/j.ijporl.2005.07.018.
18. Buchinsky, F. J.; Valentino, W. L.; Ruszkay, N.; Powell, E.; Derkay, C. S.; Seedat, R. Y.; Uloza, V.; Dikkers, F. G.; Tunkel, D. E.; Choi, S. S.; et al. Age at Diagnosis, but Not HPV Type, Is Strongly Associated with Clinical Course in Recurrent Respiratory Papillomatosis. *PLoS One*, **2019**, *14* (6), e0216697. https://doi.org/10.1371/journal.pone.0216697.
19. Niyibizi, J.; Rodier, C.; Wassef, M.; Trottier, H. Risk Factors for the Development and Severity of Juvenile-Onset Recurrent Respiratory Papillomatosis: A Systematic Review. *Int J Pediatr Otorhinolaryngol*, **2014**, *78* (2), 186–197. https://doi.org/10.1016/j.ijporl.2013.11.036.
20. Campisi, P.; Hawkes, M.; RN, K. S. The Epidemiology of Juvenile Onset Recurrent Respiratory Papillomatosis Derived from a Population Level National Database. *Laryngoscope*, **2010**, *120* (6), 1233–1245. https://doi.org/10.1002/lary.20901.
21. Lépine, C.; Voron, T.; Berrebi, D.; Mandavit, M.; Nervo, M.; Outh-Gauer, S.; Péré, H.; Tournier, L.; Teissier, N.; Tartour, E.; et al. Juvenile-Onset Recurrent Respiratory Papillomatosis Aggressiveness: In Situ Study of the Level of Transcription of HPV E6 and E7. *Cancers (Basel)*, **2020**, *12* (10), 2836. https://doi.org/10.3390/cancers12102836.
22. Li, S.-L.; Wang, W.; Zhao, J.; Zhang, F.-Z.; Zhang, J.; Ni, X. A Review of the Risk Factors Associated with Juvenile-Onset Recurrent Respiratory Papillomatosis: Genetic, Immune and Clinical Aspects. *World Journal of Pediatrics*, **2022**, *18* (2), 75–82. https://doi.org/10.1007/s12519-021-00496-z.
23. Gerein, V.; Schmandt, S.; Babkina, N.; Barysik, N.; Coerdt, W.; Pfister, H. Human Papilloma Virus (HPV)-Associated Gynecological Alteration in Mothers of Children with Recurrent Respiratory Papillomatosis

 doi:10.20944/preprints202412.2345.v1

during Long-Term Observation. *Cancer Detect Prev*, **2007**, *31* (4), 276–281. https://doi.org/10.1016/j.cdp.2007.07.004.

24. Tenti, P. Perinatal Transmission of Human Papillomavirus from Gravidas with Latent Infections. *Obstetrics & Gynecology*, **1999**, *93* (4), 475–479. https://doi.org/10.1016/S0029-7844(98)00459-1.
25. Derkay, C. S. Recurrent Respiratory Papillomatosis. *Laryngoscope*, **2001**, *111* (1), 57–69. https://doi.org/10.1097/00005537-200101000-00011.
26. Qu, X.; Xiao, Y.; Ma, L.; Niu, Z.; Wang, J. High Recurrence Rate in Patients with Juvenile-Onset Respiratory Papillomatosis and Its Risk Factors. *European Archives of Oto-Rhino-Laryngology*, **2022**, *279* (8), 4061–4068. https://doi.org/10.1007/s00405-022-07390-y.
27. Ling, S.; Cheng, Y.; Yau, P. A.; Yim, C.; Kwan, H.; Mok, T. Recurrent Respiratory Papillomatosis (RRP) of Tracheobronchial Tree Presenting as Lung Collapse with Malignant Transformation after a Decade. *Respir Med Case Rep*, **2023**, *45*, 101904. https://doi.org/10.1016/j.rmcr.2023.101904.
28. Can, N. T.; Tretiakova, M. S.; Taxy, J. B. Natural History and Malignant Transformation in Recurrent Respiratory Papillomatosis: Human Papillomavirus (HPV), Dysplasia and an Autopsy Review. *Fetal Pediatr Pathol*, **2015**, *34* (2), 80–90. https://doi.org/10.3109/15513815.2014.968271.
29. Muhammad Fauzi, H. G.; Mohan Singh, A. S.; Abdul Rahim, S.; Chooi, L. L.; Ramasamy, V.; Mohamad Pakarul Razy, N. H.; Mohamad, I. Malignant Transformation of Juvenile Recurrent Respiratory Papillomatosis. *Gulf J Oncolog*, **2021**, *1* (36), 79–81.
30. Karatayli-Ozgursoy, S.; Bishop, J. A.; Hillel, A.; Akst, L.; Best, S. R. A. Risk Factors for Dysplasia in Recurrent Respiratory Papillomatosis in an Adult and Pediatric Population. *Annals of Otology, Rhinology & Laryngology*, **2016**, *125* (3), 235–241. https://doi.org/10.1177/0003489415608196.
31. Lee, L.; Cheng, A.; Fang, T.; Huang, C.; Liao, C.; Chang, J. T.; Li, H. High Incidence of Malignant Transformation of Laryngeal Papilloma in Taiwan. *Laryngoscope*, **2008**, *118* (1), 50–55. https://doi.org/10.1097/MLG.0b013e318155a288.
32. Silverberg, M. Condyloma in Pregnancy Is Strongly Predictive of Juvenile-Onset Recurrent Respiratory Papillomatosis. *Obstetrics & Gynecology*, **2003**, *101* (4), 645–652. https://doi.org/10.1016/S0029-7844(02)03081-8.
33. Winckworth, L. C.; Nichol, R. Question 2: Do Caesarean Sections Reduce the Maternal-Fetal Transmission Rate of Human Papillomavirus Infection? *Arch Dis Child*, **2010**, *95* (1), 70–73. https://doi.org/10.1136/adc.2009.171777.
34. LARSON, D. A.; DERKAY, C. S. Epidemiology of Recurrent Respiratory Papillomatosis. *APMIS*, **2010**, *118* (6–7), 450–454. https://doi.org/10.1111/j.1600-0463.2010.02619.x.
35. Lai, Y. M.; Yang, F. P.; Pao, C. C. Human Papillomavirus Deoxyribonucleic Acid and Ribonucleic Acid in Seminal Plasma and Sperm Cells. *Fertil Steril*, **1996**, *65* (5), 1026–1030.
36. Perkins, J. A.; Inglis, A. F.; Richardson, M. A. Iatrogenic Airway Stenosis With Recurrent Respiratory Papillomatosis. *Arch Otolaryngol Head Neck Surg*, **1998**, *124* (3), 281. https://doi.org/10.1001/archotol.124.3.281.
37. Liu, S.; Shao, J. Surgical Outcome of Different Surgical Modalities for Adult Recurrent Respiratory Papillomatosis. *Acta Otolaryngol*, **2023**, *143* (2), 196–200. https://doi.org/10.1080/00016489.2023.2169346.
38. Rosen, C. M. D.; Simpson, C. B. M. D. Principles of Laser Microlaryngoscopy. In *Operative Techniques in Laryngology*; Springer: Berlin, 2008; pp 85–89.
39. Hess, M. M.; Fleischer, S.; Ernstberger, M. New 445 Nm Blue Laser for Laryngeal Surgery Combines Photoangiolytic and Cutting Properties. *European Archives of Oto-Rhino-Laryngology*, **2018**, *275* (6), 1557–1567. https://doi.org/10.1007/s00405-018-4974-8.
40. Hock, K.; Kennedy, A.; Howell, R.; Friedman, A.; de Alarcon, A.; Khosla, S. Surgery and Adjuvant Therapy Improve Derkay Scores in Adult and Pediatric Respiratory Papillomatosis. *Laryngoscope*, **2022**, *132* (12), 2420–2426. https://doi.org/10.1002/lary.30042.
41. Hung, W.-C.; Lo, W.-C.; Fang, K.-M.; Cheng, P.-W.; Wang, C.-T. Longitudinal Voice Outcomes Following Serial Potassium Titanyl Phosphate Laser Procedures for Recurrent Respiratory Papillomatosis. *Annals of Otology, Rhinology & Laryngology*, **2021**, *130* (4), 363–369. https://doi.org/10.1177/0003489420950374.

42. Burns, J. A.; Friedman, A. D.; Lutch, M. J.; Hillman, R. E.; Zeitels, S. M. Value and Utility of 532 Nanometre Pulsed Potassium-Titanyl-Phosphate Laser in Endoscopic Laryngeal Surgery. *J Laryngol Otol*, **2010**, *124* (4), 407–411. https://doi.org/10.1017/S0022215109991824.
43. Patel, R. S.; Mackenzie, K. Powered Laryngeal Shavers and Laryngeal Papillomatosis: A Preliminary Report. *Clin Otolaryngol Allied Sci*, **2000**, *25* (5), 358–360. https://doi.org/10.1046/j.1365-2273.2000.00389.x.
44. Patel, N.; Rowe, M.; Tunkel, D. Treatment of Recurrent Respiratory Papillomatosis in Children with the Microdebrider. *Annals of Otology, Rhinology & Laryngology*, **2003**, *112* (1), 7–10. https://doi.org/10.1177/000348940311200102.
45. El-Bitar, M. A.; Zalzal, G. H. Powered Instrumentation in the Treatment of Recurrent Respiratory Papillomatosis. *Arch Otolaryngol Head Neck Surg*, **2002**, *128* (4), 425. https://doi.org/10.1001/archotol.128.4.425.
46. Pasquale, K.; Wiatrak, B.; Woolley, A.; Lewis, L. Microdebrider Versus CO2 Laser Removal of Recurrent Respiratory Papillomas: A Prospective Analysis. *Laryngoscope*, **2003**, *113* (1), 139–143. https://doi.org/10.1097/00005537-200301000-00026.
47. Bortnick, D. P. Coblation: An Emerging Technology and New Technique for Soft-Tissue Surgery. *Plast Reconstr Surg*, **2001**, *107* (2), 614–615. https://doi.org/10.1097/00006534-200102000-00053.
48. Arya, A. K.; Donne, A.; Nigam, A. Double-blind Randomized Controlled Study of Coblation Tonsillotomy *versus* Coblation Tonsillectomy on Postoperative Pain in Children. *Clinical Otolaryngology*, **2005**, *30* (3), 226–229. https://doi.org/10.1111/j.1365-2273.2005.00970.x.
49. Atef, A.; Mosleh, M.; El Bosraty, H.; El Fatah, G. A.; Fathi, A. Bipolar Radiofrequency Volumetric Tissue Reduction of Inferior Turbinate: Does the Number of Treatment Sessions Influence the Final Outcome? *Am J Rhinol*, **2006**, *20* (1), 25–31. https://doi.org/10.1177/194589240602000105.
50. Timms, M. S.; Bruce, I. A.; Patel, N. K. Radiofrequency Ablation (Coblation): A Promising New Technique for Laryngeal Papillomata. *J Laryngol Otol*, **2007**, *121* (1), 28–30. https://doi.org/10.1017/S0022215106003069.
51. Rachmanidou, A.; Modayil, P. C. Coblation Resection of Paediatric Laryngeal Papilloma. *J Laryngol Otol*, **2011**, *125* (8), 873–876. https://doi.org/10.1017/S0022215111001253.
52. Hao, F.; Yue, L.; Yin, X.; Wang, X.; Shan, C. Low-Temperature Radiofrequency Coblation Reduces Treatment Interval and Post-Operative Pain of Laryngotracheal Recurrent Respiratory Papillomatosis. *Biosci Rep*, **2020**, *40* (5). https://doi.org/10.1042/BSR20192005.
53. Zeitels, S. M.; Burns, J. A.; Franco, R. A.; Hillman, R. E.; Dailey, S. H.; Anderson, R. R. Office-Based Treatment of Glottal Dysplasia and Papillomatosis with the 585-NM Pulsed Dye Laser and Local Anesthesia. *Annals of Otology, Rhinology & Laryngology*, **2004**, *113* (4), 265–276. https://doi.org/10.1177/000348940411300403.
54. Koufman, J. A.; Rees, C. J.; Frazier, W. D.; Kilpatrick, L. A.; Wright, S. C.; Halum, S. L.; Postma, G. N. Office-Based Laryngeal Laser Surgery: A Review of 443 Cases Using Three Wavelengths. *Otolaryngology–Head and Neck Surgery*, **2007**, *137* (1), 146–151. https://doi.org/10.1016/j.otohns.2007.02.041.
55. Filauro, M.; Vallin, A.; Sampieri, C.; Benzi, P.; Gabella, G.; De Vecchi, M.; Ioppi, A.; Mora, F.; Peretti, G. Recurrent Respiratory Papillomatosis: Comparing in-Office and Operating Room Treatments. *Acta Otorhinolaryngologica Italica*, **2024**, *44* (4), 233–241. https://doi.org/10.14639/0392-100X-N2951.
56. Miller, A. J.; Gardner, G. M. In-Office vs. Operating Room Procedures for Recurrent Respiratory Papillomatosis. *Ear Nose Throat J*, **2017**, *96* (4–5), E24–E28. https://doi.org/10.1177/0145561319889538.
57. Rees, C. J.; Postma, G. N.; Koufman, J. A. Cost Savings of Unsedated Office-Based Laser Surgery for Laryngeal Papillomas. *Annals of Otology, Rhinology & Laryngology*, **2007**, *116* (1), 45–48. https://doi.org/10.1177/000348940711600108.
58. Chen, S.; Connors, J.; Zhang, Y.; Wang, B.; Vieira, D.; Shapira-Galitz, Y.; Garber, D.; Amin, M. R. Recurrent Respiratory Papillomatosis Office versus Operating Room: Systematic Review and Meta-Analysis. *Annals of Otology, Rhinology & Laryngology*, **2021**, *130* (3), 234–244. https://doi.org/10.1177/0003489420949586.
59. Ivancic, R.; Iqbal, H.; deSilva, B.; Pan, Q.; Matrka, L. Current and Future Management of Recurrent Respiratory Papillomatosis. *Laryngoscope Investig Otolaryngol*, **2018**, *3* (1), 22–34. https://doi.org/10.1002/lio2.132.

60. Bertino, G.; Pedretti, F.; Mauramati, S.; Filauro, M.; Vallin, A.; Mora, F.; Crosetti, E.; Succo, G.; Peretti, G.; Benazzo, M. Recurrent Laryngeal Papillomatosis: Multimodal Therapeutic Strategies. Literature Review and Multicentre Retrospective Study. *Acta Otorhinolaryngologica Italica*, **2023**, *43* (2 (Suppl. 1)), S111–S122. https://doi.org/10.14639/0392-100X-suppl.1-43-2023-14.
61. Lea, A. P.; Bryson, H. M. Cidofovir. *Drugs*, **1996**, *52* (2), 225–230. https://doi.org/10.2165/00003495-199652020-00006.
62. Van Cutsem, E.; Janssens, J.; Rutgeerts, P.; Vantrappen, G.; Snoeck, R.; Van Ranst, M.; Fiten, P.; Opdenakker, G.; De Clercq, E.; Geboes, K. Successful Treatment of a Squamous Papilloma of the Hypopharynx-esophagus by Local Injections of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)Cytosine. *J Med Virol*, **1995**, *45* (2), 230–235. https://doi.org/10.1002/jmv.1890450221.
63. Snoeck, R.; Wellens, W.; Desloovere, C.; Ranst, M. Van; Naesens, L.; De Clercq, E.; Feenstra, L. Treatment of Severe Laryngeal Papillomatosis with Intralesional Injections of Cidofovir [(S)-1-(3-Hydroxy-2-Phosphonylmethoxypropyl)Cytosine]. *J Med Virol*, **1998**, *54* (3), 219–225. https://doi.org/10.1002/(SICI)1096-9071(199803)54:3<219::AID-JMV13>3.0.CO;2-C.
64. Mikolajczak, S.; Quante, G.; Weissenborn, S.; Wafaisade, A.; Wieland, U.; Lüers, J. C.; Klussmann, J. P.; Beutner, D. The Impact of Cidofovir Treatment on Viral Loads in Adult Recurrent Respiratory Papillomatosis. *European Archives of Oto-Rhino-Laryngology*, **2012**, *269* (12), 2543–2548. https://doi.org/10.1007/s00405-012-2103-7.
65. McMurray, J. S.; Connor, N.; Ford, C. N. Cidofovir Efficacy in Recurrent Respiratory Papillomatosis: A Randomized, Double-Blind, Placebo-Controlled Study. *Annals of Otology, Rhinology & Laryngology*, **2008**, *117* (7), 477–483. https://doi.org/10.1177/000348940811700702.
66. Chadha, N. K.; James, A. Adjuvant Antiviral Therapy for Recurrent Respiratory Papillomatosis. *Cochrane Database of Systematic Reviews*, **2012**, *2012* (12). https://doi.org/10.1002/14651858.CD005053.pub4.
67. Cidofovir Injection Solution Package Insert. Mylan Institutional LLC: Morgantown, WV April 2021.
68. Hoesli, R. C.; Thatcher, A. L.; Hogikyan, N. D.; Kupfer, R. A. Evaluation of Safety of Intralesional Cidofovir for Adjuvant Treatment of Recurrent Respiratory Papillomatosis. *JAMA Otolaryngology–Head & Neck Surgery*, **2020**, *146* (3), 231. https://doi.org/10.1001/jamaoto.2019.4029.
69. Ryan, M. A.; Leu, G. R.; Upchurch, P. A.; Tunkel, D. E.; Walsh, J. M.; Boss, E. F. Systemic Bevacizumab (Avastin) for Juvenile-Onset Recurrent Respiratory Papillomatosis: A Systematic Review. *Laryngoscope*, **2021**, *131* (5), 1138–1146. https://doi.org/10.1002/lary.29084.
70. Vargas, S. O.; Healy, G. B.; Rahbar, R.; Folkman, J.; Tan, X.; McGill, T. J.; Brown, L. F. Role of Vascular Endothelial Growth Factor–A in Recurrent Respiratory Papillomatosis. *Annals of Otology, Rhinology & Laryngology*, **2005**, *114* (4), 289–295. https://doi.org/10.1177/000348940511400407.
71. Nagel, S.; Busch, C.; Blankenburg, T.; Schütte, W. Behandlung Der Respiratorischen Papillomatose – Kasuistik Zur Systemischen Therapie Mit Bevacizumab. *Pneumologie*, **2009**, *63* (07), 387–389. https://doi.org/10.1055/s-0029-1214714.
72. MOHR, M.; SCHLIEMANN, C.; BIERMANN, C.; SCHMIDT, L.-H.; KESSLER, T.; SCHMIDT, J.; WIEBE, K.; MÜLLER, K.-M.; HOFFMANN, T. K.; GROLL, A. H.; et al. Rapid Response to Systemic Bevacizumab Therapy in Recurrent Respiratory Papillomatosis. *Oncol Lett*, **2014**, *8* (5), 1912–1918. https://doi.org/10.3892/ol.2014.2486.
73. Zur, K. B.; Fox, E. Bevacizumab Chemotherapy for Management of Pulmonary and Laryngotracheal Papillomatosis in a Child. *Laryngoscope*, **2017**, *127* (7), 1538–1542. https://doi.org/10.1002/lary.26450.
74. Gately, U. E.; Zhang, N.; Karle, W. E.; Lott, D. G. Adjuvant Intralesional Bevacizumab in Pediatric and Adult Populations With Recurrent Respiratory Papillomatosis: A Systematic Review. *Annals of Otology, Rhinology & Laryngology*, **2024**, *133* (10), 841–847. https://doi.org/10.1177/00034894241264388.
75. Pogoda, L.; Ziylan, F.; Smeeing, D. P. J.; Dikkers, F. G.; Rinkel, R. N. P. M. Bevacizumab as Treatment Option for Recurrent Respiratory Papillomatosis: A Systematic Review. *European Archives of Oto-Rhino-Laryngology*, **2022**, *279* (9), 4229–4240. https://doi.org/10.1007/s00405-022-07388-6.
76. Bevacizumab Solution for Intravenous Infusion Package Insert. Genentech, Inc.: San Francisco, CA May 2009.

77. Gallagher, T. Q.; Derkay, C. S. Pharmacotherapy of Recurrent Respiratory Papillomatosis: An Expert Opinion. *Expert Opin Pharmacother*, **2009**, *10* (4), 645–655. https://doi.org/10.1517/14656560902793530.
78. Makiyama, K.; Hirai, R.; Matsuzaki, H. Gardasil Vaccination for Recurrent Laryngeal Papillomatosis in Adult Men. *Journal of Voice*, **2017**, *31* (1), 104–106. https://doi.org/10.1016/j.jvoice.2016.01.008.
79. Kin Cho Goon, P.; Scholtz, L.; Sudhoff, H. Recurrent Respiratory Papillomatosis (RRP)–Time for a Reckoning? *Laryngoscope Investig Otolaryngol*, **2017**, *2* (4), 184–186. https://doi.org/10.1002/lio2.80.
80. Rosenberg, T.; Philipsen, B. B.; Mehlum, C. S.; Dyrvig, A.-K.; Wehberg, S.; Chirilă, M.; Godballe, C. Therapeutic Use of the Human Papillomavirus Vaccine on Recurrent Respiratory Papillomatosis: A Systematic Review and Meta-Analysis. *J Infect Dis*, **2019**, *219* (7), 1016–1025. https://doi.org/10.1093/infdis/jiy616.
81. Hu, X.; Zhou, Q.; Yu, J.; Wang, J.; Tu, Q.; Zhu, X. Prevalence of HPV Infections in Surgical Smoke Exposed Gynecologists. *Int Arch Occup Environ Health*, **2021**, *94* (1), 107–115. https://doi.org/10.1007/s00420-020-01568-9.
82. Cox, S. V.; Dobry, A. S.; Zachary, C. B.; Cohen, J. L. Laser Plume From Human Papillomavirus–Infected Tissue: A Systematic Review. *Dermatologic Surgery*, **2020**, *46* (12), 1676–1682. https://doi.org/10.1097/DSS.0000000000002757.
83. Palma, S.; Gnambs, T.; Crevenna, R.; Jordakieva, G. Airborne Human Papillomavirus (HPV) Transmission Risk during Ablation Procedures: A Systematic Review and Meta-Analysis. *Environ Res*, **2021**, *192*, 110437. https://doi.org/10.1016/j.envres.2020.110437.
84. Garden, J. M. Viral Disease Transmitted by Laser-Generated Plume (Aerosol). *Arch Dermatol*, **2002**, *138* (10), 1303. https://doi.org/10.1001/archderm.138.10.1303.
85. Garden, J. M.; O'Banion, M. K.; Shelnitz, L. S.; Pinski, K. S.; Bakus, A. D.; Reichmann, M. E.; Sundberg, J. P. Papillomavirus in the Vapor of Carbon Dioxide Laser-Treated Verrucae. *JAMA*, **1988**, *259* (8), 1199–1202.
86. Kofoed, K.; Norrbom, C.; Forslund, O.; Møller, C.; Frøding, L.; Pedersen, A.; Markauskas, A.; Blomberg, M.; Baumgartner-Nielsen, J.; Madsen, J.; et al. Low Prevalence of Oral and Nasal Human Papillomavirus in Employees Performing CO2-Laser Evaporation of Genital Warts or Loop Electrode Excision Procedure of Cervical Dysplasia. *Acta Dermato Venereologica*, **2015**, *95* (2), 173–176. https://doi.org/10.2340/00015555-1912.
87. Dodhia, S.; Baxter, P. C.; Ye, F.; Pitman, M. J. Investigation of the Presence of HPV on KTP Laser Fibers Following KTP Laser Treatment of Papilloma. *Laryngoscope*, **2018**, *128* (4), 926–928. https://doi.org/10.1002/lary.27018.
88. Inovio Pharmaceuticals. INO-3107 With Electroporation (EP) in Participants With HPV-6- and/ or HPV-11-Associated Recurrent Respiratory Papillomatosis (RRP).
89. Mau, T.; Amin, M. R.; Belafsky, P. C.; Best, S. R.; Friedman, A. D.; Klein, A. M.; Lott, D. G.; Paniello, R. C.; Pransky, S. M.; Saba, N. F.; et al. Interim Results of a Phase 1/2 Open-Label Study of INO-3107 for HPV-6 and/or HPV-11-Associated Recurrent Respiratory Papillomatosis. *Laryngoscope*, **2023**, *133* (11), 3087–3093. https://doi.org/10.1002/lary.30749.
90. Ferris, R. L.; Blumenschein, G.; Fayette, J.; Guigay, J.; Colevas, A. D.; Licitra, L.; Harrington, K.; Kasper, S.; Vokes, E. E.; Even, C.; et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *New England Journal of Medicine*, **2016**, *375* (19), 1856–1867. https://doi.org/10.1056/NEJMoa1602252.
91. Liu, T.; Greenberg, M.; Wentland, C.; Sepe, B.; Bowe, S.; Diercks, G.; Huynh, T.; Mino-Kenudson, M.; Schlegel, R.; Kodack, D.; et al. PD-L1 Expression and CD8+ Infiltration Shows Heterogeneity in Juvenile Recurrent Respiratory Papillomatosis. *Int J Pediatr Otorhinolaryngol*, **2017**, *95*, 133–138. https://doi.org/10.1016/j.ijporl.2017.02.022.
92. Ahn, J.; Bishop, J. A.; Roden, R. B. S.; Allen, C. T.; Best, S. R. A. The PD-1 and PD-L1 Pathway in Recurrent Respiratory Papillomatosis. *Laryngoscope*, **2018**, *128* (1). https://doi.org/10.1002/lary.26847.
93. Creelan, B. C.; Ahmad, M. U.; Kaszuba, F. J.; Khalil, F. K.; Welsh, A. W.; Ozdemirli, M.; Grant, N. N.; Subramaniam, D. S. Clinical Activity of Nivolumab for Human Papilloma Virus-Related Juvenile-Onset Recurrent Respiratory Papillomatosis. *Oncologist*, **2019**, *24* (6), 829–835. https://doi.org/10.1634/theoncologist.2018-0505.

 doi:10.20944/preprints202412.2345.v1

94. Allen, C. T.; Lee, S.; Norberg, S. M.; Kovalovsky, D.; Ye, H.; Clavijo, P. E.; Hu-Lieskovan, S.; Schlegel, R.; Schlom, J.; Strauss, J.; et al. Safety and Clinical Activity of PD-L1 Blockade in Patients with Aggressive Recurrent Respiratory Papillomatosis. *J Immunother Cancer*, **2019**, *7* (1), 119. https://doi.org/10.1186/s40425-019-0603-3.
95. Hampson, L.; Kitchener, H. C.; Hampson, I. N. Specific HIV Protease Inhibitors Inhibit the Ability of HPV16 E6 to Degrade P53 and Selectively Kill E6-Dependent Cervical Carcinoma Cells in Vitro. *Antivir Ther*, **2006**, *11* (6), 813–825.
96. Hampson, L.; Maranga, I. O.; Masinde, M. S.; Oliver, A. W.; Batman, G.; He, X.; Desai, M.; Okemwa, P. M.; Stringfellow, H.; Martin-Hirsch, P.; et al. A Single-Arm, Proof-Of-Concept Trial of Lopimune (Lopinavir/Ritonavir) as a Treatment for HPV-Related Pre-Invasive Cervical Disease. *PLoS One*, **2016**, *11* (1), e0147917. https://doi.org/10.1371/journal.pone.0147917.
97. Sima, N.; Wang, W.; Kong, D.; Deng, D.; Xu, Q.; Zhou, J.; Xu, G.; Meng, L.; Lu, Y.; Wang, S.; et al. RNA Interference against HPV16 E7 Oncogene Leads to Viral E6 and E7 Suppression in Cervical Cancer Cells and Apoptosis via Upregulation of Rb and P53. *Apoptosis*, **2008**, *13* (2), 273–281. https://doi.org/10.1007/s10495-007-0163-8.