Published in final edited form as:

Curr Otorhinolaryngol Rep. 2016 June ; 4(2): 90–98. doi:10.1007/s40136-016-0118-0.

Office-based Management of Recurrent Respiratory Papilloma

Kevin M. Motz¹ and Alexander T. Hillel¹

¹ Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins School of Medicine, 601 N. Caroline Street, JHOC 6th Floor, Baltimore, MD 21287, USA

Abstract

This review will highlight the indications and benefits of office-based therapy for recurrent respiratory papillomatosis (RRP) and discuss the utilization of photo-dynamic lasers and adjuvant medical therapy in office-based settings. Office-based management of RRP allows for more timely interventions, is preferred by the majority of patients, and negates the risk of general anesthesia. Current literature argues for the utilization of KTP laser over CO₂ laser for office-based treatment of RRP. Medical therapies for RRP are limited, but agents such as bevacizumab are promising and have been shown to reduce disease burden. Medical therapies that can induce disease remission are still needed. Office-based procedures save time and healthcare expenses compared to like procedures in the operating room. However, the increased frequency for office-based procedures predicts similar overall healthcare costs for office-based and OR laser excision of RRP. Office-based management of RRP is a feasible and well-tolerated strategy in appropriately selected patients with adequate local anesthesia.

Keywords

Recurrent respiratory papillomatosis; RRP; Human papillomavirus; HPV; Potassium titanyl phosphate laser; KTP laser; Bevacizumab; Office-based laryngology procedures

Introduction

Recurrent respiratory papillomatosis (RRP) is disease of benign squamous papilloma and the primary treatment is surgical. Prior to the advent and subsequent improvements in general anesthesia, endolaryngeal procedures for RRP were performed transorally, in awake patients, using mirror visualization [1]. As general anesthesia improved in the twentieth century, the surgical management of RRP transitioned to the operating room where direct laryngoscopy afforded better visualization and more complete removal of disease. However, over the past decade, advancements in fiber optics, channeled endoscopes, and laser technology have

Alexander T. Hillel ; Email: ahillel@jhmi.edu

Kevin M. Motz kmotz1@jhmi.edu

This article is part of the Topical Collection on *Recurrent Respiratory Papilloma*.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Kevin M. Motz and Dr. Alexander T. Hillel declare that they have no conflicts of interest.

Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

allowed for an increasing number of endolaryngeal procedures to be performed in a clinic setting. Now with the use of these improved endoscopic techniques and the incorporation of photodynamic lasers, the treatment of RRP is being delivered in an office-based setting to an unsedated patient. This technology coupled with new medical therapies continues to evolve the treatment paradigm for RRP.

The goal of this article is to review the etiology and demographics of RRP with focus on limitations of OR-based treatments. The implications of disease treatment on patient quality of life, voice outcomes, and health care associated costs will be examined, and the role office-based treatment has on improving these outcomes will be discussed. Finally, the techniques available for office-based treatment of RRP will be reviewed.

Pathophysiology, Demographics, and Presentation of RRP

RRP is a chronic viral disease characterized by the proliferation of benign squamous papilloma within the aerodigestive tract (Fig. 1a, b). RRP occurs in both children and adults and is caused by the human papillomavirus (HPV) types 6 and 11 [2, 3]. RRP represents the most common benign tumor in children and has a bimodal age distribution, typically affecting children under the age of five and adults in the third decade of life [4–6]. Given RRP's predilection for the larynx, it can produce dysphonia or even lead to airway compromise. Hoarseness is the most common presenting symptom of RRP followed by progressive stridor. The transmission of RRP in children is usually vertical and secondary to traversing the birth canal of an infected mother or from exposure to HPV in the amniotic fluid [7]. Active condyloma at the time of birth is the greatest risk factor for transmission and in those cases the transmission rate is 1/200–400 [7, 8]. The transmission of adult onset RRP is less clear. While RRP is not thought to be a sexual transmitted disease, oral sex is a risk factor for adult onset disease [9]. Additionally, re-activation of latent HPV infection is another possible cause of disease presentation [10]. Irrespective of the etiology, RRP, and the therapy necessitated for management are a source of significant morbidity for this patient population, and new innovative treatment strategies are needed.

Limitations of Operative Microlaryngoscopy

Operative microlaryngoscopy has been a long-standing and effective therapy for RRP, but its use is limited by the requirement for an operative suite and general anesthesia. The treatment goals for RRP focus on disease regression, airway maintenance, and the preservation of voice but can vary significantly based on disease severity and individual patient preference. To achieve and maintain these goals, serial procedures are often required and a reliance on operative microlaryngoscopy presents multiple barriers in providing this treatment. On average, a child presenting with RRP will require 4.4 procedures per year, and patients with severe disease can often require operative removal of papilloma every 4–6 weeks in order to maintain a patent airway [11, 12]. This need for repeated treatments increases the cumulative risk of general anesthesia. Recovery from general anesthesia translates into missed time from work or school and can have deleterious social and financial repercussions for the patient. This can influence patients to prioritize fewer operations, accepting the subsequent vocal deterioration. Additionally, each added procedure increases the potential for treatment associated morbidity and treatment-related vocal fold scar, which has been shown to

negatively impact voice quality, as well as VRQOL metrics and correlates to increased psychosocial morbidity [13]. Given this, there is a clear need for alternative treatment strategies for RRP. Therapeutic advancements that allow for effective disease treatment while reducing the treatment-related effects on patient morbidity, quality of life, and economic burden would be considered a step forward for the management of RRP.

Office-based Therapy Improves Quality of Life and Reduces Morbidity

Office-based therapies for RRP address some of the limitations of operative microlaryngoscopy, including improved patient quality of life and the maintenance of a consistent voice. Advancements in technology over the last 10 years have made office-based laryngeal surgery feasible for a range of procedures and have reduced the reliance on operative microlaryngoscopy (Table 1). Sophisticated fiber optics with distal chip technology, improved laser mechanics, and flexible channeled endoscopes have prompted the exploration of office-based surgery for RRP. This idea was pioneered and reintroduced as a management option for RRP by Dr. Steven Zeitels in 2004 and garnered widespread acceptance over the following decade [14•]. Office-based procedures for RRP decrease our dependence on general anesthesia and therefore can reduce OR-associated risks of papilloma excision. The decreased risk of surgery translates into earlier and more frequent treatments, and shifts the goals of treatment to not just maintaining airway patency but allows for patients to have a more consistent voice and improved quality of life [14•, 15].

The first case series that reintroduced unsedated office-based surgical management of RRP demonstrated that a 585-nm pulse-dye laser (PDL) could safely and effectively be used in an office-based setting for treatment of RRP or dysplasia [14•]. In this study, 93.9 % of patients were able to tolerate PDL laser treatment with 88 % of those patients, albeit a mixed cohort of dysplasia or RRP, having disease regression [50 % [14•]. While this original report commented that office-based therapy was thought to be less complete compared to similar microlaryngoscopic procedures, it touted that the disease threshold for office-based intervention was lower, and patients are able to receive treatment for disease severity that would otherwise be deferred [14•]. Furthermore, the reported improvements in tolerance, decreased time, and potential for cost savings compared to similar microlaryngoscopic procedures made office-based management of RRP an appealing option [15].

Office-based Management of RRP Reduces Overall Health Care Costs

In addition to improved patient tolerance, office-based treatment of RRP presents a potential overall health care savings incentive. In a time of health care reform focused on reducing waste, cost-effectiveness is a critical component needed for the acceptance of new treatment strategies. Multiple studies have described the associated cost savings of office-based laryngeal procedures, and in one study, savings of greater than \$5000 dollars were realized for every procedure performed in the office versus the operating room [16]. While these procedures are less costly, they are potentially less complete and there can be a compensatory increase in the frequency of procedures, such that overall costs may end up roughly even [16].

Concerning cost savings, it is important to recognize that the decrease in health care spending is often at the expense of the clinic secondary to reimbursements incompletely covering the associated costs of equipment, clinical staff, and laser fibers. This financial disincentive can result in fewer procedures being performed in the office [17]. To alleviate the financial constraints of office-based management of RRP, a change in designation of clinical space from “non-facility” to “facility” space may be beneficial, allowing for the addition of facility fee to cover associated costs of the procedure [18•]. Additionally, performing unsedated procedures for RRP in the endoscopy suite is another alternative that maintains the cost savings benefit of office-based procedures, does not produce a financial disincentive to the surgeon or clinic, and still removes the risks of anesthesia while improving physician efficiency [18•]. In all, many benefits from both a provider and patient perspective can be achieved from office-based management of RRP. However, these benefits depend on appropriate patient selection and the ability of the patient to tolerate the procedure so that adequate treatment can be delivered.

Patient Selection and Counseling for Office-based Laryngology Procedures

To improve the success of office-based management of RRP, careful deliberations should be had with each patient prior to attempting an unsedated procedure. Patient selection, counseling, and shared decision making is of critical importance in the success of office-based laryngeal surgery. This discussion should emphasize the nature of the procedure, the steps involved, and the risks, benefits, and alternatives. Informed consent should always be signed. Additionally, a patient's willingness to cooperate and anxiety should be assessed. Patients who are anxious and sensitive to diagnostic flexible laryngoscopy may be averse to unsedated procedures. Additionally, patients with a sensitive gag reflex may not tolerate an unsedated laryngeal procedure.

In addition to patient preference and tolerance, anatomic and disease-specific considerations must be assessed. Patients must have an adequate nasal passage to accommodate a larger channeled endoscope and/or be able to open their mouth sufficiently so instrumentation can be passed and manipulated. Patients with mild to moderate disease burden represent ideal candidates for office-based management (Fig. 1a). Additionally, the authors feel that a minimal amount of subglottic disease is not a contraindication for office-based treatment if the endoscope can achieve adequate access and visualization (Fig. 2). In contrast, cases where there is a high a burden of papilloma, airway compromise, or papilloma extending into the laryngeal ventricle are not ideal candidates for office-based procedures (Fig. 1b). While there is concern over elevated blood pressure, unsedated laryngology procedures remain a viable alternative for patients with comorbidities that increase the risk of general anesthesia (Fig. 3). Patients with systemic anticoagulation or coagulopathy should be carefully considered prior to office-based therapy. For carefully selected patients who are willing and cooperative, office-based surgery is an excellent option for the management of RRP.

Topical and Local Anesthesia for Office-based Laryngeal Procedures

The benefit of office-based laryngeal procedures is great in the hands of an experienced surgeon; however, these skills only go as far as one's ability to gain adequate local

anesthesia. The superior laryngeal nerve supplies sensory innervation to the supraglottis and glottis. In the majority of cases, appropriate laryngeal anesthesia can be obtained with the application of topical anesthetic agents. The modalities that can be used for delivery of topical anesthesia to the larynx are variable and often a reflection of physician preference. These methods include administration of 4 % lidocaine to the mucosa of the base of tongue, supraglottis, and glottis using a transtracheal approach, transorally with a curved cannula, or transnasally using the working channel port of the endoscope. Additionally, nebulized lidocaine can be administered prior to direct application to the surgical site. If 4 % lidocaine being used, its dose should typically should be capped at 5 mL (200 mg) but dosing may vary and should be calculated for every patient keeping in mind the maximum safe dose of 3 mg/kg [19]. Prior to transnasal procedures, it is important to assess nasal patency and provide local anesthesia and decongestant to the nasal cavity. All of the techniques mentioned are appropriate methods for achieving topical anesthesia and are equally tolerated by patients, and their use should be dictated by patient and physician comfort [20]. Additionally, if topical anesthesia provides inadequate comfort or cannot be achieved with a safe dosing protocol, additional local anesthesia can be achieved through a superior laryngeal nerve block as necessary [21].

Office-based Treatment Modalities for RRP

Laser Therapy—The introduction of laser technology for surgical management of RRP has evolved significantly and has improved the precision the of disease treatment. The introduction of the CO₂ laser as an operative instrument allowed for precise and hemostatic removal of papilloma [22]. While effective for disease treatment, the use of the continuous CO₂ laser in microlaryngoscopic cases had the potential for scarring of the SLP and webbing of the anterior commis-sure [22, 23]. Given these limitations, new technology which focuses on disease specificity and exploits the highly vascular nature of papilloma, led to the introduction of photodynamic lasers [24–26].

As stated earlier, unsedated office-based management of RRP was reintroduced using a photodynamic 585-nm PDL [14•]. The use of the PDL laser for treatment of RRP was adapted from its utilization in ablation of verrucous warts [27]. It was first established in microlaryngeal surgery and was quickly adapted for office-based procedures [14•, 28]. Photodynamic lasers offer disease-specific treatment for RRP by targeting the vascular system of papilloma through a wavelength specific for the absorption of oxyhemoglobin, which leads to coagulation of the underlying microcirculation of the papilloma [29]. Additionally, the specific wavelength and the pulsed delivery of energy limits damage to the surrounding tissue [30]. While the PDL had modest efficacy in the management of RRP, it has notable shortcomings that were magnified in office-based procedures. Specifically, the photodynamic properties of the laser were deemed unpredictable and required a very precise and consistent fiber to tissue distance, which in a conscious patient was difficult to maintain [30]. These technical features often resulted in bleeding secondary to non-uniform heating of blood vessels [29, 30]. Bleeding impairs visualization, and in the case of unsedated laryngeal procedures, stimulated patients to cough and move. Furthermore, blood absorbs the laser energy thus limiting its effect on the underlying papilloma.

Given these limitations of the 585-nm PDL, a shorter wavelength and longer pulsed 532-nm potassium titanyl phosphate (KTP) laser was trialed and subsequently, adopted for the management of RRP [29, 30]. The KTP laser is superior to the 585-nm PDL secondary to a more predictable photodynamic profile. The 532-nm wavelength is more preferential absorbed by oxyhemoglobin, and the increased pulse length allows for more consistent intravascular coagulation, decreased bleeding, and less damage to surrounding epithelium [31, 32]. Additionally, the KTP laser is a solid-state device making it more mechanically sound and less prone to mechanical failure. Given its superiority to the PDL, the KTP laser has gained significant popularity for the treatment of RRP in micro-laryngeal and office-based surgery and now represents the preferred laser treatment modality for office-based management of RRP.

Adjuvant Medical Therapy—Medical therapies for the treatment of RRP have been investigated and their use in office-based procedures has been described. While surgery therapy remains the mainstay of treatment, it is not curative, and repetitive procedures are still necessitated. Given the added risk of each additional procedure, medical therapies modifying the disease course are of high value. The antiviral agent Cidofovir (Vistide) and the antiangiogenic agent Bevacizumab (Avastin) have received much attention as potential adjuvant therapies for RRP. Given that these therapies are not curative, the goal of their use is to slow disease progression and limit the number of procedures.

Intralesional Cidofovir: Given the viral etiology of RRP antiviral therapy has been of interest. Cidofovir, an acyclic nucleoside phosphonate that inhibits viral DNA replication by inhibition of DNA polymerase, has been commonly utilized. Cidofovir has a broad range of activity against DNA viruses, including HPV. Investigations of the mechanism of action of cidofovir in HPV-related disease are unclear. However, it is proposed that Cidofovir functions by incorporating itself into genomic DNA causing genetic instability and leads to apoptosis [33]. Its selectivity for HPV-positive cells is hypothesized to be related to decreased cell cycle regulation and DNA repair mechanisms in HPV-infected cells leaving the HPV-infected cells more susceptible to cidofovir-induced apoptosis [34].

Cidofovir use as a sublesional injection for the treatment of RRP was first introduced in 1998 [35]. There have been multiple case series and retrospective studies evaluating cidofovir's efficacy and safety in both the adult and pediatric RRP populations. Many of these studies have demonstrated promising results showing increased rates of remission, decreased disease severity scores, and a reduction in the number of procedures needed [35–37]. Conversely, the only randomized control trial evaluating the efficacy of cidofovir compared to placebo for the treatment of RRP did not demonstrate a significant difference in treatment [38]. Additionally, concerns over potential-negative side effects exist. While rare when used intralesion-ally, nephrotoxicity and neutropenia are potential side effects of cidofovir. Additionally, reports of increased rates of dysplastic change and malignant degeneration in papilloma treated with cidofovir has been a concern; however, these this has failed to be substantiated [38–40]. Finally, reports of long-term vocal fold scarring resulting in intractable hoarseness have been presented and some feel that this is an underreported side effect of intralesional cidofovir [41]. While cidofovir may be administered as part of

office-based therapy, we feel the lack of evidence of its efficacy combined with its risks leave no role for cidofovir in office-based management of RRP.

Intralesional Bevacizumab (Avastin): The dense microcirculatory system found within papilloma represents a potential target for medical treatment of RRP and is the target of intralesional bevacizumab. Given the role of vascular endothelial growth factor (VEGF) in angiogenesis and its increased expression in papilloma, this pathway represents an attractive target for medical therapy [42]. Bevacizumab is a humanized monoclonal antibody specific for VEGF that acts to block interaction with its target receptor. Bevacizumab has been used as systemic therapy for adjuvant treatment of malignant neoplasms, as well as locally for angiogenic disease of the eye [43, 44]. Bevacizumab was introduced for off-label use in the management of RRP in 2009. A cohort of 10 patients receiving office-based therapy for RRP with a prior history photoangiolytic treatment, underwent adjuvant sublesional injection of bevacizumab at a dose of 5–10 mg every 4–6 weeks. This administration resulted in a 90 % reduction in recurrence and a 40 % clinical resolution rate at 8–10 weeks. Additionally, only two (of 10) patients required continued photoangiolytic therapy; the others were maintained on bevacizumab injection alone [41]. Further studies, prospective in nature, have continued to demonstrate similar results of adjuvant intralesional bevacizumab [45••].

The initial studies of intralesional bevacizumab appeared promising; however, safety profiles and standard dosing schedules were incomplete. To address this, Best et al. followed 43 patients undergoing 100 consecutive high dose (range 15–88 mg) sublesional bevacizumab injections for the treatment of RRP, 83 of them being office-based administrations. Serum chemistries and hematology were followed after each injection in a group of 18 patients. The remaining 25 patients were reviewed in a retrospective fashion for indications of potential complications. At the conclusion, no significant physiological, hematological, or local adverse reactions were identified in either group indicating that intralesional administered of bevacizumab is safe even at higher dosing [46].

The above information suggest that bevacizumab injection is an effective adjuvant to KTP laser therapy for the treatment of RRP and is capable of decreasing disease severity and the reducing the number of required procedures. While the data support the use of adjuvant bevacizumab no distinct guidelines exist on when to initiate its use. However, these authors feel if disease severity cannot be controlled and necessitates four or more procedures per year, the addition of bevacizumab should be considered. Finally, the off-label use of bevacizumab for the management of RRP must be clearly explained as part of informed consent [47].

The HPV Vaccination and RRP: Vaccination against HPV has become commonplace for the prevention of cervical cancer. The quadrivalent vaccine, gardasil, has immunogenicity against the HPV-6 and HPV-11 strains which are implicated in the pathogenesis of RRP. While not technically an office-based procedure, HPV vaccination against those particular strains has been proposed to be protective against the development of RRP and that routine vaccination will reduce the incidence [48]. Interestingly, recent studies have investigated the vaccines potential as a treatment modality for patients already suffering from RRP. In this

study, it was demonstrated that the vaccination could increase antibody titers against the HPV-6 and 11 to levels higher than that with native infection alone [49]. In a retrospective study that investigates the addition of Gardasil during treatment of RRP, patients experience longer intervals between surgery and 40 % experienced complete remission [50]. While data supporting the use of HPV vaccination for the treatment of RRP is nearly absent, the topic does merit discussion and future investigations.

Conclusions

RRP represents a challenging and often unremitting disease that requires multiple procedures to maintain airway patency and intelligible voice. Surgery is the primary treatment strategy and recent advances in flexible laryngoscopy and laser technology have allowed for a return to office-based procedures that were performed prior to the advent of general anesthesia. Surgical care of RRP may now be conducted safely and effectively in an unsedated patient therefore removing the risk and morbidity of general anesthesia. Additionally, photodynamic lasers, such as the 532 nm KTP laser that allow for targeted therapy, can be safely and effectively used in a clinic-based setting. Therapies such as bevacizumab, which focus on disease-specific pathways and can be easily administered in an office-based setting, serve as promising adjuvant therapies to surgical intervention. In all, the transition to unsedated office-based management of RRP has allowed for decreased health care costs, improved patient quality of life, and improved physician efficiency.

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Elsberg, L. Laryngoscopic surgery illustrated in the treatment of morbid growths within the larynx. Collins; Philadelphia: 1866.
2. Bennett RS, Powell KR. Human papillomaviruses: associations between laryngeal papillomas and genital warts. *Pediatr Infect Dis J*. 1987; 6(3):229–32. [PubMed: 3033592]
3. Mounts P, Shah KV, Kashima H. Viral etiology of juvenile- and adult-onset squamous papilloma of the larynx. *Proc Natl Acad Sci USA*. 1982; 79(17):5425–9. [PubMed: 6291043]
4. Morgan AH, Zitsch RP. Recurrent respiratory papillomatosis in children: a retrospective study of management and complications. *Ear Nose Throat J*. 1986; 65(9):19–28. [PubMed: 3769839]
5. Shykhon M, Kuo M, Pearman K. Recurrent respiratory papillomatosis. *Clin Otolaryngol Allied Sci*. 2002; 27(4):237–43. [PubMed: 12169123]
6. Derkay CS. Task force on recurrent respiratory papillomas: a preliminary report. *Arch Otolaryngol Head Neck Surg*. 1995; 121(12):1386–91. [PubMed: 7488368]
7. Shah KV, Stern WF, Shah FK, Bishai D, Kashima HK. Risk factors for juvenile onset recurrent respiratory papillomatosis. *Pediatr Infect Dis J*. 1998; 17(5):372–6. [PubMed: 9613648]
8. Silverberg M. Condyloma in pregnancy is strongly predictive of Juvenile-Onset recurrent respiratory papillomatosis. *Obstet Gynecol*. 2003; 101(4):645–52. [PubMed: 12681865]
9. Kashima HK, Shah F, Lyles A, Glackin R, Muhammad N, Turner L, et al. A comparison of risk factors in Juvenile-Onset and adult-onset recurrent respiratory papillomatosis. *Laryngoscope*. 1992; 102(1):9–13. [PubMed: 1309932]

10. Kocjan BJ, Gale N, Hocevar Boltezar I, Seme K, Fujs Komlos K, Hosnjak L, et al. Identical human papillomavirus (HPV) genomic variants persist in recurrent respiratory papillomatosis for up to 22 years. *J Infect Dis.* 2013; 207(4):583–7. [PubMed: 23204170]
11. Armstrong LR, Derkay CS, Reeves WC. Initial results from the national registry for juvenile-onset recurrent respiratory papillomatosis. RRP task force. *Arch Otolaryngol Head Neck Surg.* 1999; 125(7):743–8. [PubMed: 10406310]
12. Bishai D, Kashima H, Shah K. The cost of juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg.* 2000; 126(8):935–9. [PubMed: 10922223]
13. Chadha NK, Allegro J, Barton M, Hawkes M, Harlock H, Campisi P. The quality of life and health utility burden of recurrent respiratory papillomatosis in children. *Otolaryngol-Head Neck Surg.* 2010; 143(5):685–90. [PubMed: 20974340]
14. Zeitels SM, Franco RA, Dailey SH, Burns JA, Hillman RE, Anderson RR. Office-based treatment of glottal dysplasia and papillomatosis with the 585-nm pulsed dye laser and local anesthesia. *Ann Otol Rhinol Laryngol.* 2004; 113(4):265–76. [PubMed: 15112968] [This is the first study reporting the feasibility and efficacy of office-based therapy in the management of RRP. In this study 77 of 82 procedures were tolerated and able to be completed, and that 50 % disease involution was achieved in 88 % (68/77) of those cases.]
15. Rees C, Halum S, Wijewickrama R, Koufman J, Postma G. Patient tolerance of in-office pulsed dye laser treatments to the upper aerodigestive tract. *Otolaryngol Head Neck Surg.* 2006; 134(6): 1023–7. [PubMed: 16730550]
16. Rees CJ, Postma GN, Koufman JA. Cost savings of unsedated office-based laser surgery for laryngeal papillomas. *Ann Otol Rhinol Laryngol.* 2007; 116(1):45–8. [PubMed: 17305277]
17. Kuo CY, Halum SL. Office-based laser surgery of the larynx: cost-effective treatment at the office's expense. *Otolaryngol-Head Neck Surg.* 2012; 146(5):769–73. [PubMed: 22261492]
18. Hillel AT, Ochsner MC, Johns MM 3rd, Klein AM. A cost and time analysis of laryngology procedures in the endoscopy suite versus the operating room. *Laryngoscope.* 2015 doi:10.1002/lary.25653. [This study demonstrates an innovative solution for addressing the financial disincentive of office-based laryngeal procedures. The use of the endoscopy suite or the redesignation of “unregulated” clinical space to “regulated” space can remove the financial burden of unsedated laryngeal procedures while maintaining the overall cost savings touted for office-based procedures.]
19. Wang SX, Simpson CB. Anesthesia for office procedures. *Otolaryngol Clin North Am.* 2013; 46(1):13–9. [PubMed: 23177401]
20. Gadkaree SK, Best SR, Walker C, Akst LM, Hillel AT. Patient tolerance of transoral versus percutaneous thyrohyoid office-based injection laryngoplasty: a case-controlled study of forty-one patients. *Clin Otolaryngol.* 2015; 40(6):717–21. [PubMed: 25865128]
21. Sulica L, Blitzer A. Anesthesia for laryngeal surgery in the office. *Laryngoscope.* 2000; 110(10 Pt 1):1777–9. [PubMed: 11037843]
22. Dedo HH, Yu KCY. CO₂ laser treatment in 244 patients with respiratory papillomas. *Laryngoscope.* 2001; 111(9):1639–44. [PubMed: 11568620]
23. Ossoff RH, Werkhaven JA, Dere H. Soft-tissue complications of laser surgery for recurrent respiratory papillomatosis. *Laryngoscope.* 1991; 101(11):1162–6. [PubMed: 1943417]
24. Hartnick CJ, Boseley ME, Franco RA, Cunningham MJ, Pransky S. Efficacy of treating children with anterior commissure and true vocal fold respiratory papilloma with the 585-nm pulsed-dye laser. *Arch Otolaryngol Head Neck Surg.* 2007; 133(2):127–30. [PubMed: 17309979]
25. McMillan, K.; Pankratov, MM.; Wang, Z.; Bottrill, I.; Rebeiz, EE.; Shapshay, SM. Anderson, RR., editor. [2015 Dec 10] Atraumatic laser treatment for laryngeal papillomatosis.; 1994. p. 104-10. Available from: <http://proceedings.spiedigitallibrary.org/proceeding.aspx?articleid=950870>
26. Mcmillan K, Shapshay SM, McGilligan JA, Wang Z, Rebeiz EE. A 585-nanometer pulsed dye laser treatment of laryngeal papillomas: preliminary report. *Laryngoscope.* 1998; 108(7):968–72. [PubMed: 9665240]
27. Franco RA, Zeitels SM, Farinelli WA, Anderson RR. 585-nm pulsed dye laser treatment of glottal papillomatosis. *Ann Otol Rhinol Laryngol.* 2002; 111(6):486–92. [PubMed: 12090703]

28. Tan OT, Hurwitz RM, Stafford TJ. Pulsed dye laser treatment of recalcitrant verrucae: a preliminary report. *Lasers Surg Med.* 1993; 13(1):127–37. [PubMed: 8426521]
29. Anderson RR, Parrish JA. Microvasculature can be selectively damaged using dye lasers: a basic theory and experimental evidence in human skin. *Lasers Surg Med.* 1981; 1(3):263–76. [PubMed: 7341895]
30. Zeitels SM, Akst LM, Burns JA, Hillman RE, Broadhurst MS, Anderson RR. Pulsed angiolytic laser treatment of ectasias and varices in singers. *Ann Otol Rhinol Laryngol.* 2006; 115(8):571–80. [PubMed: 16944655]
- 31•. Zeitels SM, Akst LM, Burns JA, Hillman RE, Broadhurst MS, Anderson RR. Office-based 532-nm pulsed KTP laser treatment of glottal papillomatosis and dysplasia. *Ann Otol Rhinol Laryngol.* 2006; 115(9):679–85. [PubMed: 17044539] [This study demonstrates the safety and efficacy of office-based utilization of the KTP laser for RRP. The KTP laser has a better photodynamic profile compared to that of the PDL laser.]
32. Broadhurst MS, Akst LM, Burns JA, Kobler JB, Heaton JT, Anderson RR, et al. Effects of 532 nm pulsed-KTP laser parameters on vessel ablation in the avian chorioallantoic membrane: implications for vocal fold mucosa. *Laryngoscope.* 2007; 117(2):220–5. [PubMed: 17204988]
33. Andrei G, Snoeck R, Schols D, De Clercq E. Induction of apoptosis by cidofovir in human papillomavirus (HPV)-positive cells. *Oncol Res.* 2000; 12(9–10):397–408. [PubMed: 11697818]
34. De Schutter T, Andrei G, Topalis D, Naesens L, Snoeck R. Cidofovir selectivity is based on the different response of normal and cancer cells to DNA damage. *BMC Med Genomics.* 2013; 6:18. [PubMed: 23702334]
35. Pransky SM, Magit AE, Kearns DB, Kang DR, Duncan NO. Intralesional cidofovir for recurrent respiratory papillomatosis in children. *Arch Otolaryngol Head Neck Surg.* 1999; 125(10):1143–8. [PubMed: 10522508]
36. Fusconi M, Grasso M, Greco A, Gallo A, Campo F, Remacle M, et al. Recurrent respiratory papillomatosis by HPV: review of the literature and update on the use of cidofovir. *Acta Otorhinolaryngol Ital.* 2014; 34(6):375–81. [PubMed: 25762828]
37. Grasso M, Remacle M, Bachy V, Van Der Vorst S, Lawson G. Use of cidofovir in HPV patients with recurrent respiratory papillomatosis. *Eur Arch Otorhinolaryngol.* 2014; 271(11):2983–90. [PubMed: 24756616]
38. McMurray JS, Connor N, Ford CN. Cidofovir efficacy in recurrent respiratory papillomatosis: a randomized, double-blind, placebo-controlled study. *Ann Otol Rhinol Laryngol.* 2008; 117(7):477–83. [PubMed: 18700421]
39. Wemer RD, Lee JH, Hoffman HT, Robinson RA, Smith RJH. Case of progressive dysplasia concomitant with intralesional cidofovir administration for recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol.* 2005; 114(11):836–9. [PubMed: 16358603]
40. Broekema FI, Dikkers FG. Side-effects of cidofovir in the treatment of recurrent respiratory papillomatosis. *Eur Arch Otorhinolaryngol.* 2008; 265(8):871–9. [PubMed: 18458927]
41. Zeitels SM, Lopez-Guerra G, Burns JA, Lutch M, Friedman AM, Hillman RE. Microlaryngoscopic and office-based injection of bevacizumab (Avastin) to enhance 532-nm pulsed KTP laser treatment of glottal papillomatosis. *Ann Otol Rhinol Laryngol Suppl.* 2009; 201:1–13. [PubMed: 19845188]
42. Rahbar R, Vargas SO, Folkman J, McGill TJ, Healy GB, Tan X, et al. Role of vascular endothelial growth factor-A in recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol.* 2005; 114(4):289–95. [PubMed: 15895784]
43. Lynch SS, Cheng CM. Bevacizumab for neovascular ocular diseases. *Ann Pharmacother.* 2007; 41(4):614–25. [PubMed: 17355998]
44. Keating GM. Bevacizumab: a review of its use in advanced cancer. *Drugs.* 2014; 74(16):1891–925. [PubMed: 25315029]
- 45•. Zeitels SM, Barbu AM, Landau-Zemer T, Lopez-Guerra G, Burns JA, Friedman AD, et al. Local injection of bevacizumab (avastin) and angiolytic KTP laser treatment of recurrent respiratory papillomatosis of the vocal folds: a prospective study. *Ann Otol Rhinol Laryngol.* 2011; 120(10):627–34. [PubMed: 22097147] [This study, prospective in nature, demonstrates that the addition of intralesional bevacizumab to KTP laser therapy enhances disease involution compared to KTP

laser therapy alone, and that in 16 of 17 cases the combination of KTP laser and adjuvant bevacizumab had improved disease regression compared to KTP laser alone.]

46. Best SR, Friedman AD, Landau-Zemer T, Barbu AM, Burns JA, Freeman MW, et al. Safety and dosing of bevacizumab (avastin) for the treatment of recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol*. 2012; 121(9):587–93. [PubMed: 23012897]
47. Sidell DR, Nassar M, Cotton RT, Zeitels SM, de Alarcon A. High-dose sublesional bevacizumab (avastin) for pediatric recurrent respiratory papillomatosis. *Ann Otol Rhinol Laryngol*. 2014; 123(3):214–21. [PubMed: 24633948]
48. Peng S, Best SR, Hung C-F, Loyo M, Lyford-Pike S, Flint PW, et al. Characterization of human papillomavirus type 11-specific immune responses in a preclinical model. *Laryngoscope*. 2010; 120(3):504–10. [PubMed: 20025042]
49. Villa LL, Ault KA, Giuliano AR, Costa RLR, Petta CA, Andrade RP, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16, and 18. *Vaccine*. 2006; 24(27–28):5571–83. [PubMed: 16753240]
50. Young DL, Moore MM, Halstead LA. The use of the quadrivalent human papillomavirus vaccine (gardasil) as adjuvant therapy in the treatment of recurrent respiratory papilloma. *J Voice*. 2015; 29(2):223–9. [PubMed: 25619468]

Fig. 1.

Variation in the extent of papilloma burden. Flexible laryngoscopic view demonstrating two cases of RRP with differences in disease severity. **(a)** A view of a small amount of papilloma limited to the right true vocal fold that could be addressed with an office-based treatment. This contrasts with a flexible laryngoscopic view of a patient with extensive disease burden and airway compromise **(b)** that would be better addressed in the operating room

Fig. 2.
Subglottic papilloma. A panel of images demonstrating a papilloma in the subglottis that was amendable to office-based laser therapy

Fig. 3.

Endoscopic series of KTP laser ablation of a right aryepiglottic papilloma. Treatment series from a 45-year-old male with a history of morbid obesity, significant cardiac disease with recent placement of 2 cardiac stents, and a chief complaint of right-sided odynophagia. Although the right aryepiglottic fold papilloma was large (**a**), an in office laser procedure was feasible (**b**). At the conclusion of the office-based KTP treatment (**c**), a small amount of residual papilloma was present, which resolved completely by follow-up at 3 weeks (**d**)

Table 1

Summary of recent impact studies for office-based management of RRP

Study	Study characteristics	Conclusions
Feasibility of office-based laryngeal laser therapy for RRP		
Zeitels et al. [14*]	Prospective Study of 51 patients (82 cases)	Office-based laryngeal laser therapy is feasible and tolerated in the majority of patients and is capable of effective disease management
Office-based KTP laser versus pulse-dye laser for laryngeal procedures		
Zeitels et al. [31**]	Prospective study of 48 patients (72 cases)	The 532-nm pulsed KTP laser was superior to the PDL laser secondary to its photodynamic profile, increased pulse length, and improved durability
Office-based adjuvant intralesional bevacizumab for treatment of RRP		
Zeitels et al. [45**]	Prospective study of 20 patients	Local bevacizumab injection was an effective adjuvant to KTP laser ablation compared to control injection
Cost analysis of office-based procedures		
Hillel et al. [18*]	Retrospective review of billing information	Office-based laryngology procedures are considered cost savings but often at the expense of the clinic if space is considered "unregulated." This cost savings can still be realized without putting financial constraints on the clinic if done in the endoscopy suite