

Contemporary Management of Laryngeal Papilloma in Adults and Children

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Occurring in children and adults, recurrent respiratory papillomatosis (RRP) is the most common neoplasm in humans. Although benign, malignant transformation of these human papillomavirus (HPV)-associated lesions is well documented, but rare. More commonly, RRP can be life threatening because of airway obstruction from growth and proliferation of the papilloma lesions.

RRP typically presents as hoarseness, although more advanced cases manifest with stridor and respiratory distress. The disease most commonly occurs on the true vocal folds. Treatment has focused on removal of obstructing lesions, with additional ablation of the root of the papilloma in hope of preventing regrowth. Since the popularization of the carbon dioxide (CO₂) laser for laryngeal surgery in the 1970s, repeated laser ablation has been the mainstay of therapy; some pediatric patients have undergone suspension microlaryngoscopy with laser treatment monthly or even more frequently. There is a high rate of recidivism because lesions regrow at the sites of ablation, and others develop in previously seemingly uninvolved areas. Thus, although some investigators have had limited success at keeping the lesions controlled through regular repeat surgeries, it is generally accepted that laser treatment, along with other surgical techniques (cold excision, use of a microdebrider), usually is not curative [1–9]. In the last 30 years, more attention has been directed toward adjuvant treatments, which range

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from systemic immune modulators to locally injected antivirals, in patients who have localized or disseminated disease. Successful long-term eradication of RRP lesions is unreliable, but there has been some improvement in reducing the number and frequency of procedures that require general anesthesia through the use of adjuvant treatments and in-office procedures.

Epidemiology

The true incidence and prevalence of RRP are unknown, most likely because of the lag between the onset of hoarseness or voice change and definitive diagnosis. In 1995, based on a survey of otolaryngologists in the United States, the Task Force on RRP reported a projected total of 3623 new cases and 9015 active cases of adult RRP, and a projected total of 2354 new cases and 5970 active cases of pediatric RRP [10]. Significantly more surgical procedures were performed on the pediatric population than on adults (16,597 versus 9284), at more than twice the cost (\$109 million versus \$42 million). The Task Force data were extrapolated to estimate an RRP prevalence of 4.3 per 100,000 children and 1.8 per 100,000 adults in the United States [10]. This was comparable to studies that were conducted in the state of Virginia (4 per 100,000 children and 1 per 100,000 adults) [10], and in Denmark (3.84 per 100,000 population) [11].

There are two clinically distinct forms of RRP: juvenile onset and adult onset [12]. Juvenile-onset RRP (JORRP) is diagnosed most commonly between 2 and 4 years of age [13] (1 day is the youngest documented age at diagnosis [10]); 75% of diagnoses are made before the fifth birthday [14]. JORRP is equally common in boys and girls who are younger than 12 years of age, and is generally more aggressive than adult-onset RRP (AORRP). Similarly, within the pediatric population, JORRP tends to be more aggressive the earlier it presents. Children who were diagnosed with RRP before the age of 3 years had 3.56 times the chance of undergoing more than four surgeries, and were at twice the risk for having more than two anatomic sites involved with lesions, when compared with children who were diagnosed with JORRP after 3 years of age [11]. AORRP is diagnosed most commonly between the ages of 20 and 40 years (84 years is the oldest documented age at diagnosis [10]), has a slight male predilection, and is overall less common than JORRP. Although the aggressive form of RRP is more common in children, it can occur in adults [12].

Human papillomavirus

With more than 90 subtypes identified, and after decades as the suspected etiology behind RRP, HPV-6 and -11 were confirmed as the causative agents for RRP in the 1990s using viral probes. The virus is a small, nonenveloped, icosahedral capsid virus that contains a 7900–base pair–long, double-stranded circular DNA. HPV enters cells at the basal layer of epithelium

and elaborates RNA to produce viral proteins. HPV has been found consistently in the epithelium of papilloma lesions and adjacent normal appearing tissue; this explains the ability of the virus to cause recurrent disease, despite apparent surgical eradication of lesions. Viral subtype also seems to predict severity of disease; children who are infected with HPV-11 frequently have more aggressive airway obstruction and greater need for tracheotomy [15]. Forty-five percent of respondents to a 2002 survey of the American Society of Pediatric Otolaryngologists (ASPO) reported routinely obtaining HPV subtyping at initial biopsy [16]. This number may be high compared with the overall percentage of otolaryngologists who subtype for HPV when evaluating airway lesions that are suspicious for RRP, given the cost of subtyping. A better understanding of the epidemiology and relationship of HPV subtype to disease severity would result from routine HPV subtyping; however, the direct benefit to individual patients has not been established.

Risk factors

HPV-6 and -11 also are the most common subtypes in cervical condylomata acuminata, and multiple investigators noted an association between mothers who had genital HPV infection and the incidence of RRP [17–21]. In different series, from 50% to 70% of patients who had JORRP were born to mothers who had genital warts during pregnancy or childbirth. Kashima and colleagues [22] found that 72% of 26 patients who had JORRP versus 36% of 33 patients who had AORRP had the clinical triad of: (1) being the firstborn, (2) being delivered vaginally, and (3) being born to a teenaged mother; this triad has been observed by other investigators. Patients who had AORRP also were more likely than controls to have more lifetime sexual partners and a higher frequency of oral sex. The presence of HPV in the genital tract of women of child-bearing age is believed to be at least 25% worldwide; clinical infection of pregnant women in the United States is between 1.5% and 5% [10,14,23,24]. These data predict a much higher incidence of RRP than that which has been found. Shah and colleagues [23] estimated that only 1 in 400 children who are born to mothers who have active condylomata contracts RRP. HLA class I and II genotyping on 56 white and 14 black patients who had RRP showed an increased frequency of HLA-DRB1*0102 in white patients; this suggested that this allele predisposes patients to RRP [25]. In the same study, other HLA alleles were enriched in the patients who had RRP, which suggested their possible role in determining disease severity. Other risk factors, which have yet to be elucidated, must account for an individual's susceptibility to RRP. Finally, although the numbers are small, RRP has been identified in children and adults who have HIV or congenital immunodeficiencies, or who are medically immunosuppressed after organ transplantation [10]. These risk factors may be anecdotal; however, they could be important in

elucidating the pathophysiology of RRP because the host-immune response obviously is decreased in these cases.

Clinical presentation and evaluation

Because of the variable aggressiveness of RRP, as well as the diverse number of airway sites that can be involved, patients present with a range of symptoms and physical examination findings. Subtle voice changes over long periods of time may go unnoticed by many adult patients, and never progress to frank hoarseness, dysphonia, or dyspnea. Children who have RRP may be misdiagnosed. They often present with symptoms of hoarseness, stridor, and respiratory distress after diagnosis and treatment of recurrent croup, worsening asthma, or severe bronchitis have been unsuccessful. RRP should be considered in any patient of any age who presents with hoarseness, voice change, and shortness of breath, and especially in young children who have feeding difficulties, failure to thrive, recurrent pneumonia, or dysphagia. Careful history taking can help “place” RRP in a differential diagnosis for other laryngeal lesions. Slowly progressive hoarseness without risk factors for other airway lesions, especially in patients who have parental histories of genital condylomata, should raise suspicion for RRP [12].

Contemporary evaluation of patients begins with physical examination, with the utmost attention being paid to general appearance and the overall integrity of the patient’s airway. If the patient’s airway is stable, the examination should include flexible nasopharyngolaryngoscopy or rigid videostroboscopy to define, if any, the nature, extent, and severity of airway pathology. This will be achievable in most patients, with some challenge posed by young, school-aged children (~4–9 years old) who may require general anesthesia and direct laryngoscopy for laryngeal evaluation. Conversely, patients who have noisy breathing (stridor), who appear anxious or air hungry, with or without the use of accessory breathing muscles, require immediate attention in a “safe” setting where support staff and airway equipment are available. Most often, this is an operating room setting with a full complement of laryngoscopes, bronchoscopes, endotracheal tubes, a tracheotomy set, and a team of anesthesiologists, nurses, and operating room staff that is familiar with complex airway cases. In the hospital setting, an acute airway may need to be evaluated in the ICU setting, in which case the aforementioned equipment and personnel should be available.

Diagnosis

Generally, the diagnosis of RRP is a clinical one that is based on the gross appearance of the airway lesions, and is confirmed by histopathology. Lesions of the anterior nasal passages, oral cavity, and oropharynx can be seen readily on examination. Indirect mirror laryngoscopy can be used to

identify supraglottic and glottic lesions, but clinicians rely heavily on flexible nasopharyngolaryngoscopy for identification and description of most lesions. Most patients who have an upper airway lesion require suspension microlaryngoscopy under general anesthesia to evaluate fully the extent of the lesion and obtain a biopsy; however, select adult patients may tolerate biopsy in the office setting with local anesthesia.

RRP has a predilection for anatomic sites that are junctions between squamous and ciliated epithelium, and thus, follow a predictable pattern of distribution. The growth pattern of papillomas, the recurrence rate, and the remission rate, however, are unpredictable. In general, papillomas occur most commonly on the limen vestibuli, the nasopharyngeal surface of the soft palate, the midzone of the laryngeal surface of the epiglottis, the upper and lower margins of the ventricle, the under surface of the vocal folds, the carina, and at bronchial spurs [12,26]. Grossly, papillomas are pink or white, sessile or exophytic lesions, pedunculated or broad based, with small, frondlike projections (Fig. 1). Multiple clusters of papilloma can be seen at one or more sites in the airway; RRP also can manifest as a carpet of papillomatous epithelium over a wide distribution (Fig. 2). Under magnification, as in suspension microlaryngoscopy, punctate vasculature is evident over the surface of papillomas. Histologically, RRP is composed of multiple fingerlike projections of nonkeratinized stratified squamous epithelium overlying a vascularized core of connective tissue stroma (Fig. 3) [12,14]. The basal epithelium can be normal to hyperplastic, and cellular differentiation can be normal or abnormal with variable expression and production of keratins [14]. Generally, mitotic figures are limited to the basal layer. Lesions rarely undergo malignant degeneration; however, the papilloma virus is oncogenic and varying degrees of atypia are common.

Treatment

The goal of treating RRP is to remove as much disease as possible to improve or maintain respiratory function, while preserving laryngeal function.



Fig. 1. Isolated papilloma of the left anterior true vocal fold.

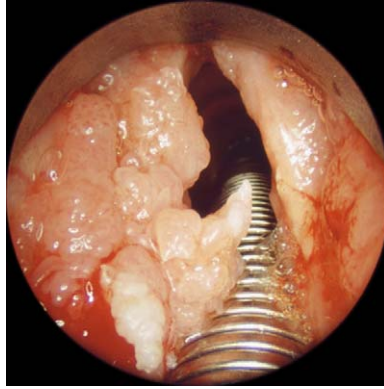


Fig. 2. Diffuse papillomatous epithelium over bilateral true and false vocal folds and left ventricle.

This is particularly important in approaching RRP of the glottis and subglottis, because overaggressive ablation of disease can result in severe scarring. Historically, the mainstay of RRP treatment has been primary resection of lesions under general anesthesia. Some patients who have mild to moderately aggressive disease are treated adequately with only a few procedures; however, many pediatric patients require multiple procedures in their lifetime, often on the order of 8 to 12 per year. With the risk of general anesthesia, most clinicians work closely with patients to maximize the time between procedures, using either respiratory or phonatory compromise as a barometer by which to gauge the timing of procedures. In recent years, with the development of other

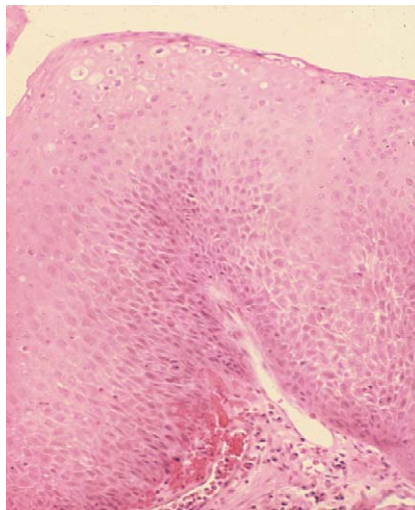


Fig. 3. Central fibrovascular core with overlying fingerlike projection of nonkeratinized stratified squamous epithelium (hematoxylin-eosin preparation).

primary and adjuvant treatments, many laryngologists are treating their adult patients at shorter intervals in the office under local anesthesia, and thus avoiding frequent general anesthetics.

Treatment modalities available to the modern otolaryngologist and discussed below include: cold excision, CO₂ laser ablation, pulsed dye laser (PDL) ablation, cidofovir, α -interferon, indole-3-carbinol (I3C), and photodynamic therapy (PDT).

Primary treatment modalities

Techniques of RRP surgical resection have evolved remarkably in the last 30 years. Likewise, as new modalities have emerged, otolaryngologists' preferences for, and use of, various options have changed; however, no mode of primary treatment for RRP has been able to eradicate the disease. Thus, even with the use of combined techniques, patients generally undergo multiple procedures to control disease, because a cure has not been found. RRP has proven to be a chronic disease.

Cold excision and carbon dioxide laser ablation

Before the 1970s and the implementation of the CO₂ laser, cold excision of papillomas to debulk disease was the mainstay of treatment. Phonomicrosurgical techniques that place more emphasis on preservation of normal tissue are used today, and have been enhanced by the development of microflap and subepithelial injection techniques, and by the use of larger binocular laryngoscopes. Generally, these techniques are best applied to localized, minor disease and are not indicated for diffuse laryngeal disease.

The development of the CO₂ laser in the 1970s was an important milestone for the treatment of RRP. Used with suspension microlaryngoscopy, the CO₂ laser permits precise ablation of lesions and excellent hemostasis. With a wavelength of 10,600 nm, the CO₂ laser converts light into thermal energy, and targets water in treated tissues, which results in tissue destruction by vaporization. The laser can be used in a defocused mode to debulk massive RRP, and then switched to a focused spot size to ablate residual RRP in areas in which minimal damage to laryngeal structures is desired (ie, the phonatory producing areas, the commissures, and the subglottis) [12]. CO₂ laser operative technique is described at length in the literature [12,14,27]. A particularly effective technique for the laser removal of sessile papillomatous growth has been our "laser brush technique." The laser is used at the lowest wattage setting to permit vaporization of tissue, usually 2 to 3 W. The time exposure is 1 second and the spot size diameter is 300 μ m (0.3 mm). The laser is applied in "brush strokes" in an anterior to posterior direction to the broad surface of the papillomas, which causes some superficial vaporization and carbonization of the surface. The depth of penetration is superficial. The carbonization is removed with open microsuctions or with the use of a small, saline-soaked neurosurgical patty ("the

brush”) and suction. Under the operating microscope at 16× magnification, the depth of removal can be detected easily. The laser is used in brush strokes to remove the next layer of papillomas in a similar manner until the uninvolved submucosa is identified. Because papillomas only involve the mucosa, this layered approach with microhemostasis from the laser and occasional use of topical adrenaline is effective and safe. In 1995, the Task Force on RRP reported that 92% of respondents to their survey preferred the CO₂ laser for initial treatment of RRP; the remaining 8% favored suspension microlaryngoscopy with cold excision [10].

Despite the excellent results that are obtained with the CO₂ laser, its drawbacks are significant. Inappropriate choice of power settings and time exposure or overaggressive use of the laser can result in thermal damage to tissues that are deep or adjacent to the papilloma. Consequences in the endolarynx can be severe, and include acute and chronic glottic edema with airway compromise, vocal fold scarring, and poor voice [12]. Damage to surrounding normal airway tissue also increases its susceptibility to viral particle implantation and subsequent mucosal seeding of RRP [12,26]. In order to balance the goals of obtaining adequate control of disease and minimizing tissue damage and scarring, many surgeons resort to performing frequent procedures on their patients. With this practice come the attendant risks of general anesthesia, and with operating theatre expenses, add to the overall high cost of caring for RRP patients.

585-nm Pulsed dye laser therapy

With concern for the significant cumulative risk of soft tissue complications from CO₂ laser ablation that patients who have RRP often face, in 1994, McMillan and colleagues [28] proposed 585-nm PDL treatment as a minimally traumatic alternative. Subsequent *in vivo* studies using a canine model demonstrated that PDL irradiation of normal laryngeal tissue produced vascular destruction without acute or delayed disruption of epithelium, laryngeal atrophy, or fibrosis [28,29]. Based on reports that PDL may cause regression of HPV-induced cutaneous lesions, and the safety of PDL in canine larynges, a pilot study was launched in patients who had RRP [30]; complete regression of lesions was demonstrated within 1 month of treatment without adverse consequences. Other studies have shown the PDL to be useful in minimizing RRP burden without the scarring that is associated with CO₂ laser ablation [31,32]. This advantage is attributed to the unique wavelength of the PDL, which causes photoablation of vasculature that nourishes the papillomata, with minimal thermal conductivity into surrounding tissues. The chromophore for the PDL is oxyhemoglobin in erythrocytes, which is targeted selectively during treatment, and, on irradiation, extravasates from the supporting vasculature into the papilloma stroma. This results in a dark purpura that is apparent during treatment, and is used as a treatment end point (Fig. 4). The oxyhemoglobin targeting is selective, and water is not vaporized as in treatment with CO₂ laser. Thus,

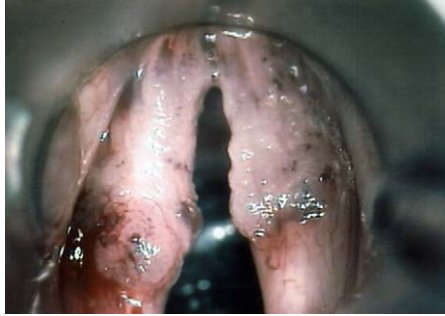


Fig. 4. Appearance of glottic papilloma after treatment with 585-nm PDL laser. Note the dark purpura which results from the extravasation of oxyhemoglobin from the fibrovascular core into the papilloma stroma.

the surface mucosa is preserved during PDL treatment; this prevents the development of raw surfaces that are vulnerable to metaplasia, scarring, and implantation of viral particles. If the PDL is used at higher power settings, there can be thermal damage to the surrounding tissues. The laser should be used at power settings that cause photovascular ablation and not tissue destruction or vaporization. Franco and colleagues [32] used a Photogenica V 585-nm PDL (Cynosure Inc., Chelmsford, Massachusetts) at 450- μ s pulse width, 5 J per pulse maximum output of 1 Hz, 1-mm fiber, 1- to 2-mm spot size, and 38 to 255 J/cm² fluence. We reported results using a Model SPTL-1A 585-nm PDL (Candela Corporation, Wayland, Massachusetts) at 300- to 500- μ s pulse width, 1-mm fiber with 2.7-mm spot size or 600- μ m silica fiber in a flexible nasolaryngoscope with 3-mm spot size, and 6 to 10 J/cm² fluences with one to five pulses per area treated [31]. The higher fluence of energy destroys the papilloma using thermal energy beyond the wavelength-selective approach on blood vessels. The surgeon needs to take care to limit thermal effects to avoid collateral tissue damage.

One drawback to PDL is that it is not effective on large, bulky lesions; best results have been seen on sessile lesions [31,32]. This implies that large lesions may be treated best initially with the CO₂ laser, cold excision, or microdebrider, before the base or anterior commissure is treated with PDL. This also implies that more frequent follow-up procedures may be necessary to control RRP with PDL; however, because it can be used under local anesthesia in an outpatient setting, the cost savings and anesthesia risk reduction are significant. The authors predict that PDL will be used more frequently in the outpatient setting, and possibly supplant CO₂ laser ablation as the primary mode for follow-up surgical management of adult patients who have RRP.

Microdebridement

In 1999, Myer and colleagues [33] reported the first experience with a laryngeal microresector system for treating RRP. Powered instrumentation

for sinus surgery was adapted for use in the larynx (Xomed, Inc., Jacksonville, Florida), and has evolved in the last 5 years to include longer, thinner, angled oscillating blades that incorporate suction and irrigation. This allows surgeons to resect papillomas with one hand, while manipulating lesions as needed with the other hand under suspension microlaryngoscopy. Other investigators use the microdebrider and a hand-held telescope connected to a video monitor. By 2004, 53% of APSO member responders to a web-based survey on RRP management preferred the microdebrider for surgical removal of lesions (versus 42% who preferred the CO₂ laser) [16]. Proponents of the microdebrider cite several advantages over the CO₂ laser, including a less expensive equipment charge, less personnel-intensive, no thermal trauma, and less risk to operating room staff (ie, no exposure to laser plume, nor risk of ocular injury) [33]. There also is no risk of airway fire, which is ever present when using the CO₂ laser. In a retrospective review of 18 patients who were younger than of 18 years of age who were treated at two institutions with CO₂ laser and microdebrider techniques, Patel and colleagues [34] reported a significantly shorter operative time for the microdebrider (mean times 32.4 minutes versus 59.2 minutes). The microdebrider seems to be particularly effective for bulky exophytic disease; however, the device should be used with caution for the sessile growth pattern of papillomas. There is some danger of extending the depth of resection deep into the submucosa or muscle, and causing scarring and loss of phonatory function. In addition, there is no hemostasis with use of the debrider, which impairs visualization of the depth of resection.

Adjuvant treatments

Although surgery remains the mainstay of treatment for RRP, adjuvant treatments have an important place in patient management. Between 2001 and 2004, the reported use of adjuvant treatments in pediatric patients increased from 10% to 22% [14,16]. Clinical guidelines for instituting adjuvant therapy have not been developed; however, the most common criteria in the literature are patients who require more than four surgical procedures in 1 year, spread of disease to multiple distal sites, or rapid regrowth of lesions with airway compromise [14,16]. The most common adjuvant therapy was systemic α -interferon [14], until the emergence and adoption of intralesional cidofovir [16]. Other therapies that are used in addition to surgery, and under study, are I3C and PDT. Acyclovir, isotretinoin, methotrexate, and ribavirin have been used, but are not used widely today. Heat shock protein (Hsp) E7 is a novel adjuvant that showed promising results in a phase II trial, and warranted a confirmatory phase III trial.

Cidofovir

Cidofovir [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine] is a nucleoside analog (Gilead Sciences, Inc., Foster City, California) that is

approved by the U.S. Food and Drug Administration for intravenous use to treat cytomegalovirus retinitis in patients who have AIDS [35]. Although not approved for topical or intralesional use, cidofovir has been used to treat several cutaneous and mucosal viral lesions [2–5,7–9,11–13,35–37]. The first report of successful intralesional use of cidofovir for RRP was by Van Cutsem and colleagues [7] in 1995. The investigators successfully treated a 69-year-old patient's hypopharyngeal and esophageal papillomas through direct injection of cidofovir into the papillomas. Three years later, in 1998, Snoeck and colleagues [2] reported the successful treatment of 16 of 17 patients who had severe laryngeal papillomatosis by intralesional injection of cidofovir in various volumes of 2.5 mg/mL at 2-week intervals. Following this report, in 1998 the authors began the use of cidofovir for recurrent respiratory papillomatosis through intralesional injections of the medication diluted to 2.5 mg/mL as reported by Snoeck and colleagues [2]. Our observed success was largely good, but not in all patients. Other surgeons were having the same clinical results, because reports began to emerge of combining cidofovir with other treatments, and of increasing the concentration of cidofovir in the injection. Cidofovir comes from the manufacturer at a concentration of 75 mg/mL; however, physicians typically have reported significant dilutions of the medication before intralesional injection. Following the literature, the authors have doubled the concentration of cidofovir that they use to 5.0 mg/mL, although other surgeons have begun to use higher concentrations (7.5–10 mg/mL). Co and Woo [38] reported their initial experience with serial office-based intralesional injections of cidofovir in awake patients using concentrations of 7.5 mg/mL concentrations. Woo now routinely uses concentrations of 20 mg/mL (personal communication, 2005).

The potential for renal toxicity of systemic (intravenous) cidofovir has been well documented [39], and Bienvenu and colleagues [36] reported a case of acute renal failure that was induced by topical cidofovir. Few prospective studies have been conducted on the local toxicity of intralaryngeal cidofovir [40]. Chhetri and colleagues [40] published the first report on local effects of intralaryngeal cidofovir injection in a canine model. The study found dose-dependent injury to the vocalis muscle after 12 injections at 2-week intervals. Endomysial edema resolved in the groups that received low dosages (0 and 2.5 mg), it resolved partially in the groups that received intermediate dosages (5 and 10 mg) with superficial residual damage; permanent, full-thickness necrosis, atrophy, and fibrosis was found in the groups that received high dosages (20 and 37.5 mg), after an additional 6-month observation period. Spiegel and colleagues [41] reported the first evaluation of the local effects of cidofovir injection on cartilage using a rabbit model. After evaluating the gross and histologic effects of local perichondrial injection of cidofovir into 96 1-cm² sections of rabbit auricles (24 each of 0 mg/mL, 5 mg/mL, 25 mg/mL, and undiluted 75 mg/mL), they concluded that delayed skin changes or histopathologic change in the cartilage may be

expected at approximately one third of sites injected. Although there was a statistical likelihood for increased local change after cidofovir injection, there was no correlation of severity with injected dose.

Cidofovir has come to the forefront of adjuvant treatments for RRP in the last 10 years. Direct intralesional injection of cidofovir has found increasingly widespread use as a primary treatment for RRP in children and adults [2–8]. Multiple investigators have shown that cidofovir for RRP markedly decreases the frequency and severity of local disease recurrence. Ideally, the medication would work in a single setting to eliminate papillomatous lesions; however, clinical experience suggests that repeated injections are necessary. No prospective randomized study has been done on the effectiveness of dose and repetition. Most important, cidofovir does not offer a cure for RRP. Further research on its toxic effects and most effective dose likely will unfold in the next decade.

α -Interferon

In 1981, Haglund and colleagues [42] reported the first results of using human leukocyte interferon in seven patients who had RRP. This uncontrolled study was encouraging and led to multiple other studies that demonstrated positive early results with interferon therapy, primarily in the reduction of disease severity. Most series also showed recurrence of disease on continued treatment, as well as a rebound phenomenon—or increased severity of disease—on withdrawal of therapy [42–51]. At best, complete response rates vary from 30% to 60%. In 1988, Healy and colleagues [52], conducted a multicenter, randomized, clinical trial that recruited 123 patients. They were assigned to receive surgery or surgery and interferon over 1 year, and were followed for 1 year; the initial benefit of interferon therapy was not sustained over time.

Nonetheless, interferon therapy had an important place in the treatment of patients who have severe RRP that requires multiple surgeries. In 1995, the Task Force on RRP survey revealed that 9% of pediatric patients, and 1% of adult patients had been treated with interferon [10]. By 2004, the ASPO survey showed a marked decline of interferon use to 4% of pediatric patients who had RRP [16]. In this report, Schraff and colleagues [16] noted the availability and parallel increase in the use of other adjuvant treatments, especially cidofovir, as one possible reason for the decrease in interferon therapy. Additionally, the use of alternative adjuvants may reflect concern over the undesirable side effects of interferon, which include fever, nausea, vomiting, malaise, renal and hepatic dysfunction, growth retardation (even if temporary), and spastic diplegia. The authors have used interferon in occasional adult patients who had extremely aggressive disease with good results; however, the risks of interferon's side effects often outweigh the benefits of therapy.

Indole-3-carbinol

I3C is found in cruciferous vegetables (cabbage, cauliflower, broccoli, brussels sprouts), and is a potent inducer of the cytochrome P-450

metabolism of estrogen, which results in 2-hydroxylation of estradiol. Estrogen increases HPV gene expression. In the oxidation and hydroxylation of estrogen, different relative levels of 2-hydroxyestrone (2-OHE1) and 16 α -hydroxyestrone (16 α -OHE1) are associated with a higher or lower risk for developing hormone-dependent tumors and epithelial cell hyperproliferation. Higher 2-OHE1/16 α -OHE1 ratios, as increased by I3C, decrease the likelihood of papilloma formation because hyperproliferation of epithelial cells is not induced [53].

I3C inhibited the development of papillomas in HPV-infected laryngeal tissue that was transplanted into immunocompromised nude mice [53]. Based on their successful treatment of a 30-month-old girl who required nine surgeries in 6 months to control aggressive RRP with daily dietary supplementation with cabbage juice [54], Rosen and colleagues [55] conducted an open-label, phase I prospective trial of chemically pure I3C in 18 patients. I3C was well tolerated without major complications or severe side effects. A few patients experienced transient nausea and dysequilibrium. There was no adverse effect on pediatric growth patterns. None of the patients had accelerated growth of their papillomas. Mean follow-up was 14.6 months, during which time 6 patients had a complete response to I3C, with no growth of their papillomas; 6 had partial response, with significantly slowed growth; and 6 had no change in the growth rate of their RPP. Similar results of 33% complete responses, 30% partial responses, and 36% no response to I3C were reported by Rosen and Bryson [56] in a larger, long-term series of 33 patients who were followed over a mean of 5 years; in this study, adults had a better overall response to I3C than did children.

I3C is a promising adjunctive treatment for RRP that is easy to administer, has few side effects, and offers good results to at least one third of patients. Further clinical trials are warranted with larger numbers of patients, especially in the pediatric population.

Photodynamic therapy

Described in the early 1900s, PDT has been used to destroy neoplasms by light activation of a photosensitive dye that selectively concentrates in tumor cells. Vascular and tumor destruction result from the vascular stasis that occurs with the in situ generation of singlet oxygen by laser activation of the photosensitizer [57]. In 1986, Shikowitz and colleagues [58] reported the first effective use of PDT on virally induced cutaneous papillomas in an animal model. Abramson and colleagues [59,60] next established the safety parameters of PDT in the canine larynx—by demonstrating the effects of increasing light intensities at 630 nm—then began trials in human subjects [60]. Combined, studies by these investigators at Long-Island Jewish Medical Center demonstrated that PDT was an effective therapy for RRP when used with dihematoporphyrinether (DHE), which has a predilection for highly vascular tissue, and decreased RRP growth rates by 50% [57–61]. Light-dose effect studies did not show significant changes in response rates

with increased light intensities [57]; however, a greater decrease in papilloma growth rate was seen in patients who received 4.25 mg/kg DHE (versus 3.25 mg/kg DHE) 48 to 72 hours before photoactivation with the optimal 50 J/cm² argon-pumped dye laser light. Despite good clinical response to this regimen at 3 years, HPV-DNA persisted in tissue biopsies [61].

The main side effect of using DHE for PDT is the 6- to 12-week increased photosensitivity; mild to severe sunburn results from exposure to natural UV and indoor fluorescent light if precautions are not taken. This prompted a search for alternative photosensitizers, and resulted in the study of PDT with meso-tetra (hydroxyphenyl) chlorin (m-THPC), because of its better tissue selectivity and shorter washout time [62]. The study showed a delayed response in most patients, and an initial transient increase in disease severity in many patients. Recurrences occurred in the patients who were followed for 3 to 5 years, but at rates that generally were less than the pretreatment recurrence rates. Latent HPV-DNA was not eliminated with m-THPC treatment. m-THPC was not compared with DHE in this study, so comparative conclusions cannot be made.

Heat shock protein E7: a novel therapy

HspE7 is a recombinant fusion protein that covalently links the C terminus of 638 amino acids from Hsp65 (derived from *Mycobacterium bovis* bacille Calmette-Guérin) with the E7 protein of HPV-16. Nonclinical studies demonstrate the activity of the fusion protein in vivo and in vitro, but also show that its individual components are not active when given alone or as mixtures. Goldstone and colleagues [63] showed that subcutaneous administration of HspE7 in an animal model generated an E7-specific, cell-mediated and humoral immune response. Chu and colleagues [64] showed that HspE7 induces dose-dependent regression of the epithelial cell-derived murine tumor, TC-1, which expresses HPV-16 E7. Based on these and other studies that suggest that HspE7 is cross-reactive for HPV types other than HPV-16, Derkay and colleagues [65] conducted an open-label, single-arm intervention study at eight medical centers on the clinical effects of subcutaneous HspE7. Fourteen female and thirteen male immune-competent patients between the ages of 2 and 18 years—all with histologically proven RRP that required at least four surgical procedures in the 12 months before enrollment, and 7 who had pulmonary disease—were recruited for the study. None of the participants had received adjuvant therapy for RRP within 30 days, nor had they received immunotherapy within 9 months of starting the study. After a baseline debulking surgery, each patient received three monthly subcutaneous injections of HspE7, 500 µg, over 60 days. The primary end point was the length of the interval between the initial debulking surgery and the first debulking surgery that was required in the posttreatment period. This was compared with the median intersurgical interval of the four surgeries before study enrollment. Study results showed a marked positive effect of HspE7 on the number of surgeries required. The first

posttreatment intersurgical interval increased 93% over the pretreatment interval for the overall population. There also was a statistically significant increase in the median of all posttreatment intersurgical intervals over a 60-week follow-up, which indicated a sustained effect of HspE7. Incidentally, the effect was more pronounced in female patients than in male patients. Finally, based on the laryngoscopic staging and severity score that was developed for, and used in, the study, HspE7 also reduced the lesion growth rate. Generally, HspE7 was well tolerated. The study reported that a high proportion of participants experienced transient injection site reactions of mild to moderate severity.

HspE7 is being studied under the guidance of the U.S. Food and Drug Administration; a phase III pivotal trial seemed to be warranted by these results. HspE7 offers the benefit of a more systemic approach to RRP than does intralesional cidofovir, without the adverse side effects of interferon, and it can be administered in an outpatient setting. Although HspE7 is unlikely to offer a cure for RRP, it may reveal itself as the treatment that is most effective in keeping the disease in check.

Tracheotomy

The Task Force on RRP reported the need for tracheotomy in 6% of adult patients and 14% of pediatric patients [10]. Children who required a tracheotomy were diagnosed with RRP at a younger age than were those who did not require a tracheotomy (2.7 years versus 3.9 years) [66]. These rates are similar to those that were reported by Lindeberg and Elbrond [67] for Danish patients who had RRP (4% of adults and 14% of children). Cole and colleagues [68] reported that 21% of 58 pediatric patients who were treated over 10 years needed a tracheotomy. The need for tracheotomy arises when disease has progressed to the point of causing respiratory distress that is due to significant airway obstruction, above or below the glottis. Regardless of the incidence of tracheotomy, most investigators agree that the procedure should be avoided if possible, because of its association with distal tracheal spread, which is believed to be caused by the interruption that is made in respiratory epithelium and the creation of a new squamociliary epithelial junction. For the same reason, decannulation after tracheotomy should occur as soon as possible, with emphasis on achieving disease control by way of endoscopic procedures, and a goal of preventing extralaryngeal spread.

Prognostic factors and quality of life issues

As the basic science and clinical communities have continued to expand and evaluate treatment options for RRP in the last 20 years, new emphasis has been placed on identifying prognostic factors that might influence the aggressiveness of treatment that is warranted. Similarly, in the current era

of economically oriented medical practice and patient-centered research, the cost of RRP to patients and society has gained more attention.

Age at onset is a well-established factor in predicting the severity of RRP. Epidemiologic studies in Denmark and the United States have shown that patients whose disease manifests before the age of 5 years require more surgical interventions, and undergo adjuvant therapy and tracheotomy more frequently than do patients whose disease occurs at older than 5 years, given the higher rate of tracheal and pulmonary extension in these younger patients [10–12,69].

HPV viral type has been of focal interest in evaluating the aggressiveness of RRP since its confirmation as the etiologic agent in RRP in the 1990s. With the establishment of HPV-6 and -11 as the most common types identified in airway lesions, several retrospective studies attempted to correlate viral type with disease aggressiveness. Early evidence was conflicting, and HPV-6 and -11 each was identified as the more aggressive viral type, or as equally aggressive [70–72]. More recently, Wiatrak and colleagues' [15] longitudinal prospective study of 73 patients who had JORRP demonstrated that patients who were infected with HPV-11 had more aggressive disease than did those who were infected with HPV-6, as evidenced by higher disease severity scores, need for more frequent surgical interventions, greater requirement for adjuvant therapy, higher incidence of tracheal and pulmonary disease, and greater need for tracheotomy. Gerein and colleagues [73] conducted a multicenter prospective study of 42 patients who had RRP who were treated with α -interferon. HPV-11 was associated with poorer response to therapy, and greater incidence of pulmonary spread and malignant transformation than was HPV-6. Taken with other retrospective studies, it seems that HPV-11 is the more aggressive viral subtype in RRP; however, the clinician's ability to perform viral typing, and the influence of identifying viral type on successful treatment is not well established.

In addition to predictors of severe disease, predictors of remission may help clinicians to counsel patients and their families during the course of RRP management. Few studies have addressed factors that may predict remission, and "remission" itself is not defined universally. Data on 165 new cases from the national registry for JORRP were analyzed by Ruparelia and colleagues [74] in search of factors that lead to remission—defined in that study as no surgical procedures needed for at least 1 year. The only factor that was predictive of remission was older age at diagnosis, with the maximum probability of remission being 44.2% at 3.6 years of age. The hazards of remission increased by 1.13 for every 1 year in age at diagnosis. Patients who underwent fewer than four procedures in the year after diagnosis also were more likely to experience remission than were those who required more than four surgical procedures in the year after diagnosis. Factors that were evaluated, but were not associated with remission, included adjuvant drug therapy in the first year of diagnosis, nonwhite race, and gender. Although patients who have AORRP can have an aggressive form of the disease, in

general, they undergo fewer lifetime surgical procedures than do patients who have JORRP; this may imply a higher rate of remission in patients who have adult-onset disease. Again, however, there is a paucity of literature on remission rates in adult patients. Given that RRP is more likely to recur in respiratory mucosa that undergoes metaplasia or injury, recurrence may be more likely in smokers and patients who have reflux disease. Future research is required to establish control of reflux and smoking cessation/nonsmoking as predictors of remission.

In 1995, the Task Force on RRP estimated that the annual cost of surgical procedures for RRP was more than \$150 million in the United States. With inflation alone, this figure must have grown over the last 10 years, and does not include the cost of adjuvant treatments and in-office procedures which are growing in popularity. The toll that RRP takes on patients and their families is well known among clinicians who care for them; however, studies on the cost to patients and caregivers in the way of time out of work and school, limitation of occupation/disability, transportation, and home care have not been published. Bishai and colleagues [75] assessed the medical costs and number of quality-adjusted life years (QALYs) for a statistical patient who had JORRP in 1997. Annual costs for this statistical case were nearly \$58,000 (range, \$32,000–\$94,000), with a lifetime cost of \$202,000 (range, \$62,000–\$474,000), and included the surgery-associated costs of hospital stay, physician fees, and outpatient visits. The burden of QALYs was estimated at 0.31 QALY per year of disease (range, 0.10–0.96 QALY per year of JORRP). This correlated to a lifetime loss of 2.01 QALY for a single case of JORRP (range, 1/28–4.61 total QALYs). The investigators speculated on the cost-effectiveness of offering women who had visible condylomata an elective cesarean section in an effort to attempt to prevent new cases of JORRP. There is not enough prospective evidence to support a policy that promotes this practice; however, analyzing the economics of such policies likely will play a greater role in the continued research on RRP prevention and treatment.

Several patient questionnaires were developed in the 1990s to assess the impact of various voice problems on the individual, including the voice-related quality of life instrument, and the voice handicap index, which addresses the social impact of dysphonia of any cause [76–78]. To monitor the burden of disease, Hill and colleagues [79] developed a questionnaire that is specific to RRP, and issued it with an established, generic multi-item health questionnaire (the United Kingdom Short Form–36; SF-36) to 36 patients who had RRP. Twenty-six patients responded; all had lower scores on the SF-36 than did controls, particularly in the domains of pain, physical limitation, and energy/vitality. Results from the RRP questionnaire identified 22 symptoms that patients who had RRP also were more likely to suffer than were controls (eg, difficulty speaking in noisy environments/for more than 15 minutes/on the phone, difficulty shouting/singing, or difficulty with depression/fatigue/sore throat). Responsiveness

of the questionnaires to change in disease burden was not assessed. Despite its limitations and the lengthiness of the questionnaire, the study again reflects the increased interest in developing instruments that consistently measure the impact of RRP on patients' quality of life. Lindman and colleagues [80] similarly highlighted the need to develop means of longitudinally evaluating quality of life issues for children who have RRP. Identifying issues that are most important and burdensome to patients will direct clinicians in their treatment of, and research on, the disease.

New frontiers: updates in pathophysiology

Along with persistent efforts to improve RRP management, the last decade yielded a surge of interest and work in the realm of molecular biology that focused on defining the pathophysiology of RRP. Investigators questioned the roles of cellular immunity, cell cycle regulatory proteins, angiogenesis, and host-susceptibility factors in the development and persistence of RRP. Most studies are of small caliber—involving fewer than 25 patients—and most have not been reproduced. These numbers are not surprising given the small number of patients that is affected by RRP; but they do point to the need for large, multicenter efforts in the future.

Four areas of research are discussed below. All of them seek to identify specific molecular entities that are involved in RRP and that potentially can be targeted in novel treatments.

RRP is known to arise in immune-suppressed patients—including those who HIV, transplant recipients who are on immune suppressive drugs, and others who have congenital immune deficiencies—and in otherwise healthy patients. Because the defense against viral infections is mediated by T helper 1 (Th1) cells, and involves the interaction between Th1 cells and tissue antigen-presenting cells (APCs), which produces interleukin (IL)-2 as a critical messenger in the cytokine cascade that ensues, Snowden and colleagues [81] identified serum levels of IL-2 and the APC-Th1 cell upregulated IL-2 receptor (IL-2R) as plausible markers of immune activity to evaluate in patients who had RRP. Serum levels of IL-2 and IL-2R were determined by ELISA in samples from 15 children who had RRP and 10 control subjects. Serum IL-2 and IL-2R levels were significantly lower in patients who had papilloma. Among patients who had RRP, those who had more aggressive disease were significantly younger than were those who had less aggressive disease, and they had higher levels of serum IL-2 and IL-2R (although they were lower than in normal controls). The investigators concluded that these data support an aberrant cell-mediated immune response in children who have RRP, and they are undertaking a multicenter study to corroborate their findings in a larger population.

Given the apparent unregulated neoplastic growth of papillomas in RRP, Poetker and colleagues [82] looked at the possible role of apoptosis and its

dysregulation in this disease process. The expression of several proapoptotic and antiapoptotic factors were studied. Particular attention was paid to survivin, a cell cycle-regulated antiapoptotic factor that is expressed in normally developing fetal tissues and many tumors and premalignant lesions, but rarely in normal differentiated tissues. The effects of HPV infection on apoptosis and the expression of apoptotic factors is unknown; however, this group found that the mean protein expression of survivin was nearly fivefold greater in RRP papillomas that were taken from 11 RRP specimens than in five normal laryngeal tissue specimens that were tested ($14.2\% \pm 2.5\%$ versus $3.0\% \pm 0.8\%$ of normalized ribosomal protein L32, $P = .003$). Protein levels of survivin were completely absent by Western blot analysis in the normal laryngeal tissue, whereas survivin was found in the papilloma samples. This differential expression of survivin in RRP samples may represent the dysregulation of apoptosis by certain factors in patients who are infected with HPV, and could be targeted by novel treatments in the future.

Vascular endothelial growth factor (VEGF)-A exerts a variety of effects on vascular endothelium and is known to play a role, with its endothelial receptors, in several nonneoplastic processes that involve angiogenesis. Overexpression of VEGF-A also has been demonstrated in several neoplasms. Rahbar and colleagues [83] investigated whether VEGF-A could be a factor in the pathogenesis of RRP. In a retrospective study of 12 patients who had RRP, formalin-fixed papilloma specimens and samples of larynx tissue from five normal autopsy specimens were examined for the presence of mRNA for VEGF-A and vascular endothelial growth factor receptors (VEGFR)-1 and -2. VEGF-A mRNA was expressed strongly in the epithelium of papillomas of all 12 patients who had RRP, and VEGFR-1 and -2 mRNA were expressed strongly in the vascular endothelium of the fibrovascular cores of the papillomas. Conversely, the control samples showed no expression of VEGF-A mRNA or VEGFR-1 or -2 mRNA. With the knowledge that tumor growth was suppressed by the inhibition of VEGF-A or its receptors in several experimental models, Rahbar and colleagues [83] entertain the possibility of suppressing these factors to treat RRP.

Finally, perhaps the largest undertaking to understand the pathophysiology of RRP is described by Buchinsky and colleagues [84] as the Multicenter Initiative Seeking Critical Genes in Respiratory Papillomatosis. Twenty-one hospitals are aiming to recruit 400 patients and their parents through a collaboration between the RRP Task Force and the Center for Genomic Sciences at Allegheny-Singer Research Institute in Pittsburgh. The investigators postulate that susceptibility to RRP is encoded genetically, because millions of neonates are exposed to RRP during vaginal delivery, but few develop the disease. The objective is to determine the host genes that govern susceptibility to RRP by conducting a genome-wide association study on family triads of patients who have RRP and their parents. Data from the human genome project will be used to identify alleles that are over- and undertransmitted

from parents to their offspring who are affected by RRP. Blood specimens will be collected from each person in the triad, the DNA will be extracted, each genotype will be determined, and that of the patient who has RRP will be compared with those of his/her parents. RRP biopsy specimens for each patient also will undergo HPV typing. It is hoped that defining the genes that govern host susceptibility to RRP will enhance our understanding of the disease and host-viral interactions in general.

Summary

As has been the case for decades, clinicians and scientists continue to struggle with the treatment of RRP. They are seeking new and better management strategies, while striving to identify the risk factors for acquiring RRP and predictors of disease severity and disease remission. RRP remains a “predictably unpredictable disease” with a varying natural history that makes the study of various effective therapies difficult. The surgeon remains charged to use the tools and techniques that work best for him or her in caring for patients who have RRP, to maximize disease control, and to minimize collateral damage to normal tissues and function. The creation of the RRP Task Force and the initiation of several multicenter studies reflect the increased collaborative nature of the work that is being done to understand RRP. New efforts in the last decade have focused on assessing the economic and social costs of RRP, and on eliciting the pathophysiology of the disease on a molecular level. These new areas of interest will blossom over the next half century. In time, novel treatments that target specific protein modulators of RRP will be developed as the genetics of host susceptibility to RRP are revealed.

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