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Head and Neck section

Recurrent laryngeal papillomatosis: multimodal therapeutic strategies. Literature review and multicentre retrospective study

La papillomatosi laringea ricorrente: strategie terapeutiche multimodali. Revisione della letteratura e analisi retrospettiva multicentrica

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SUMMARY

Objectives. Recurrent respiratory papillomatosis (RRP) is a benign, rare disease caused by Human Papilloma Virus (HPV) that can be divided into juvenile and adult forms. The course of the disease is variable, but is usually more aggressive in the juvenile form. The standard surgical treatment is represented by CO_2 laser resection, although photoangiolytic lasers represent a valid alternative. Adjuvant therapies have been proposed for disease control in case of frequent surgical resections or spreading into the lower airways. In recent years, the development of immunotherapy led to the use of bevacizumab either intratumorally or intravenously, but the most promising therapeutic development is represented by HPV vaccination. This paper aims to present a narrative review of the literature and the experience of three different University Centres in the treatment of RRP.

Methods. A retrospective analysis of the clinical charts of all patients affected by laryngeal papillomatosis and treated in three different University Centres between 2002 and 2022 was performed. The following parameters were collected: sex, age at first evaluation, sites of larynx involved, HPV type, type of first surgical treatment, presence and number of recurrences, surgical treatment of recurrences, adjuvant therapies, side effects and status at last follow-up.

Results. Seventy-eight patients were available for evaluation. Of these, 88% had adult onset RRP (Ao-RRP) and 12% juvenile onset RRP (Jo-RRP). The glottis was the most frequently involved subsite; all patients were submitted to surgical resection with CO_2 laser under general anaesthesia. Recurrences appeared in 79% of the patients, the patients who did not recur were all adults. The mean number of recurrences was 9 (range 1-110). Recurrences were more frequent in children (M = 20; range 2-110) than adults (M = 5; range 1-21). Thirty-two (52%) of the 62 patients who recurred were re-treated with CO_2 laser under general anaesthesia, while office-based treatment with a photoangiolytic laser was preferred in the remaining 30 (48%) patients. Adjuvant treatments were applied in 26 patients. The analysis of the course of the disease showed that in the 9 patients with Jo-RRP, 6 (67%) were free of lesions at the last follow-up, while the other 3 (33%) had papillomas. Of the 69 patients with Ao-RRP, 53 (77%) were alive and free of disease at the last visit, 14 (21%) were alive with disease, 1 (1%) was lost at follow-up and 1 (1%) died for other disease. Severe side effects were not observed except for 2 patients, who developed posterior glottic stenosis.

Conclusions. Our results confirmed the literature review. RRP is a potentially aggressive disease, especially in juvenile onset. Surgical resection is still first-line treatment, but in case of multiple recurrences the use of adjuvant therapies must be taken into consideration.

KEY WORDS: recurrent respiratory papillomatosis, laser surgery, cidofovir, bevacizumab, vaccine, HPV infection

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RIASSUNTO

Obiettivi. *La papillomatosi recidivante delle vie respiratorie è una rara patologia benigna causata dal Papilloma virus umano (HPV) e può essere suddivisa in una forma giovanile ed una dell'adulto. Il decorso della malattia è variabile, di solito più aggressivo nella forma giovanile. Il trattamento chirurgico standard è rappresentato dalla resezione con laser CO_2, anche se i laser fotoangiolitici possono rappresentare una valida alternativa. L'utilizzo di terapie adiuvanti è stato proposto per il controllo della malattia nei casi che richiedono trattamenti chirurgici frequenti o che tendono a diffondere nelle vie respiratorie inferiore. L'alfa-interferon è stato uno dei primi farmaci ad essere utilizzati, seguito dal cidofovir. Negli ultimi anni, lo sviluppo dell'immunoterapia ha condotto all'utilizzo del bevacizumab sia per somministrazione intralesionale o sistemica, ma lo sviluppo terapeutico più promettente è rappresentato dalla vaccinazione anti HPV. Lo scopo di questo lavoro è di presentare una revisione della letteratura e l'esperienza di tre differenti Centri Universitari nel trattamento della papillomatosi recidivante delle vie respiratorie.*

Metodi. *È stata condotta un'analisi retrospettiva sulle cartelle cliniche dei pazienti affetti da papillomatosi laringea e trattati in tre differenti Centri Universitari tra il 2002 e il 2022. Sono stati analizzati i seguenti parametri: sesso, età alla prima visita, siti laringei coinvolti, sierotipi di HPV, tipologia del primo trattamento chirurgico, presenza e numero di recidive, trattamento chirurgico delle recidive, terapie adiuvanti, effetti collaterali e status all'ultimo follow-up.*

Risultati. *Settantotto pazienti sono stati selezionati per lo studio. Di questi, l'88% presentava papillomatosi dell'adulto (Ao-RRP) e il 12% una forma giovanile (Jo-RRP). La glottide è risultata la sottosede più coinvolta; tutti i pazienti sono stati sottoposti a chirurgia con laser CO_2 in anestesia generale. Recidive sono state osservate nel 79% dei pazienti, i pazienti che non hanno mostrato recidive erano tutti adulti. Il numero medio di recidive è stato di 9 (range 1-110). Le recidive sono risultate più frequenti nei bambini (M = 20; range 2-110); rispetto agli adulti (M = 5; range 1-21). Il 52% dei 62 pazienti con recidiva è stato ritrattato con laser CO_2 laser in anestesia generale, mentre nell'altro 48% dei pazienti è stata scelta una procedura ambulatoriale con un laser fotoangiolitico. Terapie adiuvanti sono state impiegate in 26 pazienti. L'analisi del decorso della malattia ha rivelato che nei 9 pazienti con papillomatosi giovanile, 6 (67%) erano liberi da malattia all'ultimo follow-up, mentre gli altri 3 (33%) avevano ancora papillomi. Dei 69 pazienti con papillomatosi dell'adulto, 53 (77%) erano liberi da malattia all'ultima visita; 14 (21%) presentavano ancora papillomi; 1 (1%) è stato perso al follow-up e 1 (1%) è morto per altra malattia. Effetti collaterali severi sono stati riscontrati solo in 2 pazienti che hanno sviluppato una stenosi glottica posteriore.*

Conclusioni. *I risultati hanno confermato quelli della revisione della letteratura. La papillomatosi respiratoria ricorrente è una malattia potenzialmente aggressiva, specie nell'insorgenza giovanile. La resezione chirurgica è ancora il trattamento di prima linea, ma in caso di multiple recidive è necessario prendere in considerazione l'uso di terapie adiuvanti.*

PAROLE CHIAVE: *papillomatosi respiratoria ricorrente, chirurgia laser, cidofovir, bevacizumab, vaccino, infezione da HPV*

Introduction

Recurrent respiratory papillomatosis (RRP) is the term used to describe infection of the upper aerodigestive tract by Human Papilloma Virus (HPV). HPV 6 and 11 are responsible for more than 90% of RRP cases [1]. HPV 16 and 18 are high-risk subtypes, with the potential for malignant transformation, which occurs in less than 1% of juvenile RRP cases [2].

Although papillomas can arise anywhere in the tract, the larynx is the most affected organ. A bimodal age of distribution is characteristic, with young adults or young children affected. Juvenile RPP (Jo-RRP) has a more aggressive and recurring course with a high risk of extension to the lower respiratory tract. The adult RRP (Ao-RRP) is mostly located at the glottic level with the occurrence of dysphonia as the main symptom. Because of this unpredictable course, knowledge and management of RRP is essential to any otolaryngologist [3].

Epidemiology

The incidence and prevalence of RRP are not well defined. It is estimated that Jo-RRP is present in 4.3 per 100,000 children and 1.8 per 100,000 adults in the United States [4]. The prevalence of the disease is variable depending on the age of presentation, country and socioeconomic status [3].

Jo-RRP usually develops before the age of 12 years, with 75% of cases diagnosed before the age of 5 and with no difference in sex. It is more aggressive than the adult type and is more active the earlier it appears in life. In this case, the risk of obstructing and descending lesions in the lower respiratory tract is very high. It is estimated that the appearance before the age of 3 is associated with a 3.6-fold higher risk of more than 4 surgical procedures and to 2-fold higher risk of multiple anatomic sites being affected [5].

Ao-RRP occurs after the age of 12; the peak of incidence is between 20-40 years, with males being more affected. The disease is less active, and the anterior part of the glottis is the most frequently involved site [5]. It has been reported that the average number of surgeries in the first five years of diagnosis is 5.1 per year, decreasing to 0.1 per year after 15 years [6,7].

Human papilloma virus

In 1923, Ullman first confirmed the presence of an infectious agent in laryngeal papillomas, but it was only in the 1980s that RRP was confirmed to contain HPV-DNA [3].

HPV 6 and 11 account for most cases of RRP and type 11 is responsible for the most aggressive clinical course, followed by type 6. Types 16, 18, 31, and 33 have also been

rarely detected, and their presence is linked to a major risk of malignant transformation [3,5].

It is widely accepted that HPV infection is limited to the basal cells of the stratified epithelium. In the cervix uteri, the squamous columnar junction is the most common site for development of condylomas. The larynx also has a similar junction, namely the squamous ciliary junction (lSCJ) between the stratified squamous epithelium and pseudostratified ciliated columnar epithelium. Laryngeal papillomas often develop at sites with lSCJ and are characterised by a fibrovascular core of connective tissue covered by stratified squamous epithelium [4]. However, the laryngeal papilloma often appears on any site of the laryngeal mucosa that is not covered by genuine stratified epithelium, especially in the juvenile onset form. This is because both stratified squamous epithelium and pseudostratified respiratory epithelium express p63 and integrin-a6, proteins which are necessary for infection and replication of HPV [8]. Furthermore, it is known that repeated surgical procedures to eliminate papillomas, inducing a squamous metaplasia of the ciliated epithelium, and increasing the number of subsites exposed to viral infection [8].

It remains unclear why only a small fraction of HPV-exposed individuals develop RRP and why still fewer develop a severe course of the disease [3].

Different studies have demonstrated that patients with RRP are unable to produce an effective HPV-specific T-cell immune response, present abnormal expression of IL-10 and IFN-g and a downregulation of the transporter associated with antigen presentation (TAP-1) [3,9]. These alterations are more severe in Jo-RRP because of the immaturity of the immune-system and could explain the more severe course of the disease in children [9].

The main reservoir of HPV 6 and 11 is the anogenital tract and HPV is the most common sexually transmitted disease. The prevalence of HPV is increasing in the female population, in women aged 14 to 59 years is 26.8% and in women between 20-24 years is nearly 45%. These percentages increase when factors such as education, poverty index and number of sexual partners are taken into consideration [3,5].

Vertical mother-to-child transmission during passage through the birth canal is the main way of infection for Jo-RRP. The risk is increased in young primipara mothers because of a higher viral load and prolonged labour. Therefore, not all children born from HPV-positive mothers with genital condylomata develop respiratory papillomatosis. Other factors seem to be important: patient immunity, timing, length and volume of virus exposure, local traumas (intubation, extra-oesophageal reflux). Moreover, neonates may become infected before birth through transplacental transmission [3,5].

HPV in Ao-RRP is sexually transmitted, and patients with Ao-RRP have significantly more lifetime sex partners and a higher frequency of oral sex than nonaffected adult controls [10].

Clinical findings

Juvenile and adult RRP differ in terms of clinical presentation, progression, and severity of the disease. Despite being infected before or during birth, most children do not manifest any symptoms of RRP immediately [3]. Because the larynx is the most common site of infection, hoarseness is the first symptom in most paediatric patients. However, this finding is frequently associated with asthma, allergy, laryngitis and nodules of the vocal cords, so that it is only when stridor appears that laryngeal papillomatosis is considered. Usually, the mean time between the first clinical findings and the diagnosis is about 1 year [3,5]. Jo-RRP is mostly diagnosed between 2 and 4 years of age even if 75% of the juvenile patients with RRP are diagnosed by age 5 years [3,11].

Thirty percent of the affected children present extralaryngeal spread of disease; the oral cavity is the most common site, followed by trachea, bronchi, and oesophagus. Rarely, the larynx is not affected despite the presence of lower respiratory tract disease [3,11].

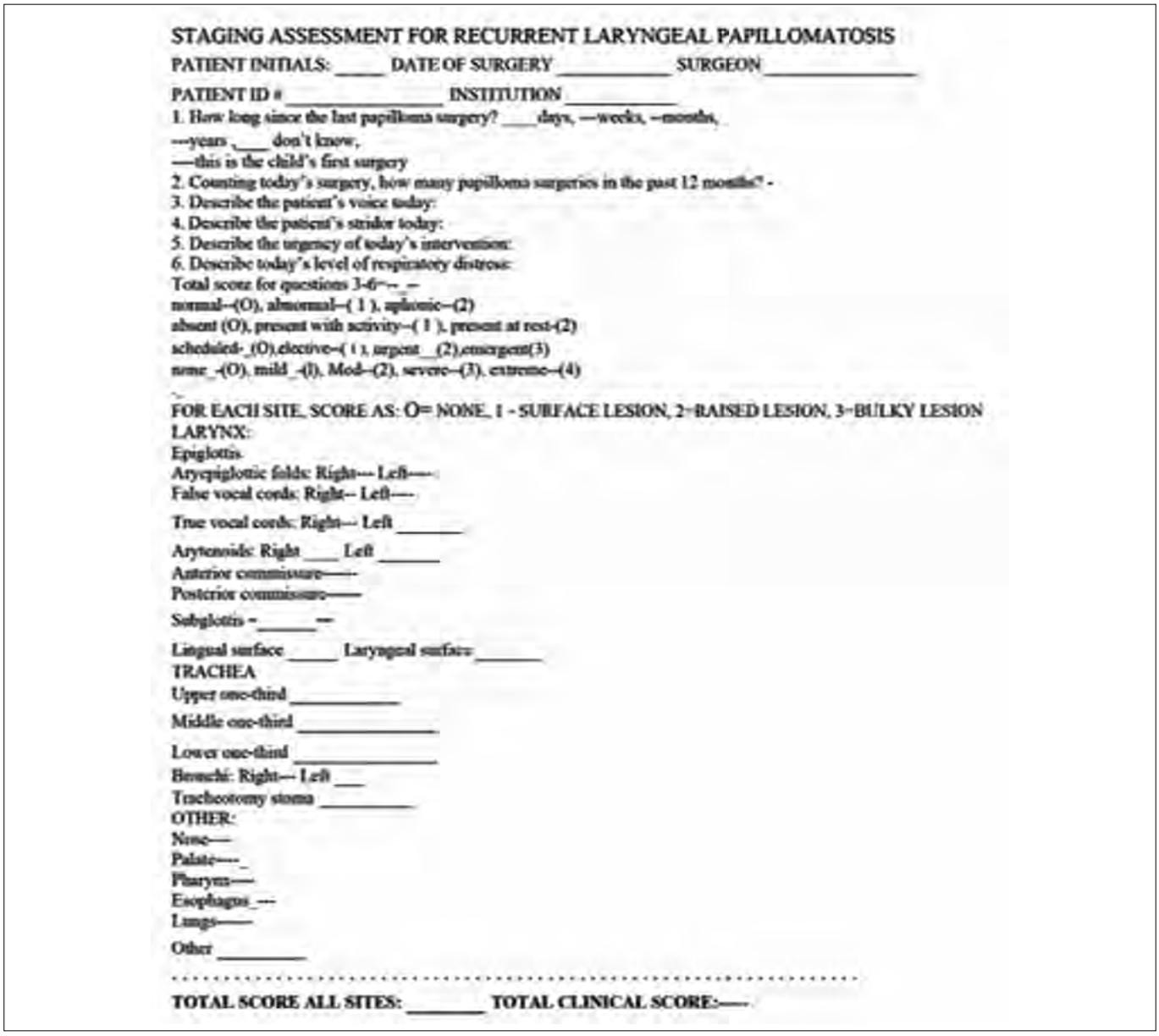
Dysphonia is the first symptom in adults because of the predominant involvement of the glottis. Dyspnea is rarely observed when treatments are available [5].

Clinical course

The clinical course of RRP can vary. Some patients show an aggressive disease which requires frequent surgery to prevent airway obstruction; others show a progressive and spontaneous remission, but in many cases the course remains unpredictable [3].

There is no unanimous and rigorous definition of the severity of the RRP. This depends on the degree of dysphonia, the consequences at the level of communication, social and professional integration, and the frequency of surgical procedures necessary for disease control [5]. Recurrent dysphonia, especially that related to the surgical treatments, can have a negative impact on the personal, social, and professional life of patients.

A severity scale, the Derkay Staging System, is used in the literature to quantify the severity of the RPP and is based on the laryngeal structures involved (Fig. 1) [12]. Derkay's score is composed of a for-site score and a clinical score. The for-site score takes into account the amount of disease (0: none; 1: surface; 2: raised; 3: bulky) in the dif-



STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

PATIENT INITIALS: _____ DATE OF SURGERY _____ SURGEON _____

PATIENT ID # _____ INSTITUTION _____

1. How long since the last papilloma surgery? ____days, —weeks, –months,
---years ,____ don't know,
—this is the child's first surgery
2. Counting today's surgery, how many papilloma surgeries in the past 12 months? -
3. Describe the patient's voice today:
4. Describe the patient's stridor today:
5. Describe the urgency of today's intervention:
6. Describe today's level of respiratory distress:
Total score for questions 3-6=-_-
normal--(O), abnormal--(1), aphonic--(2)
absent (O), present with activity--(1), present at rest-(2)
scheduled-_(O),elective--(1), urgent__(2),emergent(3)
none_-(O), mild_-(l), Mod--(2), severe--(3), extreme--(4)

FOR EACH SITE, SCORE AS: O= NONE, 1 - SURFACE LESION, 2=RAISED LESION, 3=BULKY LESION

LARYNX:
Epiglottis
Aryepiglottic folds: Right--- Left----
False vocal cords: Right-- Left----
True vocal cords: Right--- Left _____
Arytenoids: Right ____ Left _____
Anterior commissure----
Posterior commissure----
Subglottis =_____—
Lingual surface _____ Laryngeal surface _____
TRACHEA
Upper one-third _____
Middle one-third _____
Lower one-third _____
Bronchi: Right--- Left ___
Tracheotomy stoma _____
OTHER:
Nose—
Palate—_
Pharynx—
Esophagus_—
Lungs—
Other _____

TOTAL SCORE ALL SITES: _____ TOTAL CLINICAL SCORE:—

Figure 1. The Derkay Staging System [12].

ferent laryngeal and extra-laryngeal subsites. The clinical score takes into consideration voice quality, presence of stridor, urgency of intervention and presence of respiratory distress [12].

The risk of spreading into the subglottis or the trachea is rare but tremendously increased by a tracheotomy or prolonged intubation. Pulmonary involvement is the most aggressive course of the disease and can lead to complete pulmonary failure by destruction of the lung parenchyma with a higher risk of malignant transformation [3]. This rare presentation accounts for less than 1% of RRP and is usually associated with HPV-11 infection [3].

Diagnosis

Fibreoptic examination of the larynx with normal white light is the first-line endoscopy in the diagnosis of laryngeal diseases. Nevertheless, in many cases, this examination does not allow to precisely recognise the peculiar findings and satellite foci of RRP, so the ultimate diagnosis must be verified by histology [13].

For this reason, in recent years new endoscopic techniques such as Narrow Band Imaging (NBI), iScan, autofluorescence, contact endoscopy and optical coherence tomography have been developed to give deeper insight into the

biological properties of lesions, ensuring both a high rate of true positive biopsies and a reduction in unnecessary biopsies [13].

In particular, NBI allows for better distinction between benign and malignant lesions because it allows us to study the laryngeal mucosal and submucosal vascular patterns and to detect any vascular changes or neoangiogenesis [14]. In 2010, Ni et al. proposed a classification of laryngeal lesions based on changes in intraepithelial papillary capillary loops (IPCL) patterns: benign lesions have type I-III patterns, are pre-cancerous and suspected malignant type IV and malignant type Va, b, c [15]. In the literature, the sensitivity, specificity, and accuracy of NBI in detecting malignant lesions are > 95% [14]; however, this diagnostic tool has one main limitation: laryngeal papillomatosis. In fact, laryngeal papillomatosis shows the same IPCL type V pattern of laryngeal cancer [16]. In 2015, the European Laryngological Society (ELS) published another classification of laryngeal vascular changes to better distinguish the difference between laryngeal papillomatosis and cancer [17]. According to this classification, lesions with longitudinal vessels are benign, while lesions with IPCL can be typical for both papillomatosis and laryngeal cancer. The difference between them is the angle of the turning point of the vessel: laryngeal papillomatosis usually has wide-angled turning points, whereas cancer lesions have narrow-angled turning points [17]. However, these features are not easily visible, so that high expertise of the otolaryngologist and practice with high-quality equipment are mandatory [18]. In experienced hands, NBI is extremely useful in the diagnosis of untreated lesions in the pre-operatory and intra-operative setting, and even during follow-up, improving the detection of multifocal foci of disease that are otherwise not visible under white light [13].

Treatment modalities

The standard care for the management of RRP is surgical resection. The surgery must be aimed to provide an adequate vocal outcome, preserving as much as possible the integrity of the underlying anatomical structures and maintaining airway patency [1,19], while avoiding any iatrogenic complications. Aggressive resection must not be the goal, as injury to the surrounding mucosal surface can increase expression of HPV dormant in nearby cells [19]. Moreover, wide resection in single-stage is absolutely contraindicated for laryngeal lesions located in the anterior or posterior commissure; in these sites, double-stage procedures or subtotal resections are required to avoid webbing and scarring that can determine permanent dysphonia or airway obstruction [19]. As an alternative, thanks to the recent introduction of office-based treatment of RRP, it has been possible to treat bulky lesions involving the entire glottis under general anaesthesia, leaving small residual commissural or para-commissural ones and treat them, after the complete healing process, in office under local anaesthesia.

In patients with very aggressive disease, an additional goal is to prevent distal spreading to the lower respiratory tract. Tracheotomy must be reserved only for very severe cases at risk of airway obstruction, providing an additional risk for colonisation and distal spread of RRP [19]. The advent of new ventilation technique with small catheters, such as the Tritube of Evone system by Ventinova, allows, even in cases of lesions obstructing the airways, safe intubation thu avoiding tracheotomy and trachea-bronchial viral spreading [20].

Different surgical techniques have evolved in the management of RRP, moving from cold instruments and microdebriders to different types of lasers [1,19].

Lasers

There are two different categories of lasers: ablative/cutting lasers such as CO_2 and thulium lasers, which target water, and photoangiolytic lasers, such as pulsed-dye (PDL), potassium-titanyl-phosphate (KTP) lasers and True-Blue laser, which target haemoglobin [2,19].

The CO_2 laser quickly gained popularity to treat RRP since the 1960s because of its fine cutting and coagulating ability, but repeated surgical sessions may result in fibrosis, scar formation, loss of the elastic properties of the mucosa of the vocal cords and voice impairment [21].

Conversely, photoangiolytic lasers precisely target haemoglobin in highly vascularised papillomas and may have a better haemostatic effect than the CO_2 laser [19,21]. In particular, KTP laser wavelength is more strongly absorbed by haemoglobin, resulting in greater coagulation and less tissue damage [19]. It has been demonstrated that the application of KTP laser in laryngeal microsurgery seems to guarantee better accuracy and precision surgery, less tissue damage, shorter hospital stays and lower rate of recurrences than the CO_2 laser; nevertheless, there is still a major limitation on its widespread use because KTP laser equipment is more expensive than CO_2 lasers [21].

Microdebrider

Microdebriders have gained popularity due to the speed they provide in removing bulky papillomas and the absence of thermal effects. They are often used in combination with a laser: the microdebrider removes the bulk of the papilloma while lasers provide the haemostatic effect and treat the sessile lesions [19].

In-office lasers procedures

In-office lasers procedures, usually performed with KTP or PDL lasers, and the newly introduced true-blue laser [2,20,22], have offered an alternative to the traditional management under general anaesthesia. The glass fibre laser is inserted into the working channel of the video endoscope, thereby reducing costs and hospital stays, while giving the possibility to treat even small lesions that are not suitable for treatment under general anaesthesia [2,21,23]. This allows patients to maintain a better voice-related quality of life, moving the treatment goal from airway patency to a better and permanent quality of voice.

In general, the procedures are safe and well tolerated in adult patients who have received adequate local anaesthesia (5% lidocaine or 5% neobucaine). However, they are not an option for every patient; patients with bulky or extended lesions or with inadequate tolerance to the videoendoscope are poor candidates. Awake procedures are also not suitable in children[19].

In general, adult patients with a new diagnosis of laryngeal papillomatosis should first be treated under general anaesthesia to allow for disease evaluation, biopsies and removal of bulky and disseminated lesions. Subsequent procedures can be performed in the office according to the extent of disease, patient tolerance and surgeon skills [19].

In addition, there is evidence for the possibility to perform in-office intralesional administration of cidofovir or bevacizumab after laser procedures [24,25].

Adjuvant therapies

Although surgery is the main treatment modality for RRP, it has been estimated that 20% of patients require some form of adjuvant therapy to control the disease [19]. Although there is no specific indication for the use of adjuvant treatment, it is widely considered when the need for surgical debridement is frequent (more than 4 to 6 procedures/year) or if the lesions begin spreading beyond the larynx [26].

Interferon

Alpha-interferon was one of the first adjuvant treatments adopted at the beginning of the 1980s. It is a cytokine that binds to specific cell receptors and modifies the immune response with an anti-proliferative and anti-viral effect. It has been used in either intralesional or intramuscular routes of administration. The efficacy of intramuscular use is dose-dependent, suspension of the treatment is associated with rebound effects, and the sustained response is inadequate[11]. Moreover, side effects, especially hepatotoxicity and toxicity on the nervous system, were severe in some cases. For these reasons, its use was progressively abandoned [26].

Pegylated interferon alpha2a is the novel counterpart. It has improved half-life and pharmacokinetics; side effects are less severe, but still present during long-term treatment, so that it is rarely used due to emergence of other drugs with fewer local and systemic side effects, such as cidofovir and bevacizumab [19].

Antiviral agents and cidofovir

Antiviral drugs used in the treatment of RRP include acyclovir, ribavirin and cidofovir [11].

The efficacy of acyclovir and ribavirin was tested in the 1990s in a few case series and seemed to be linked to the presence of viral co-infections (herpes simplex, cytomegalovirus, or Epstein-Barr virus). These clinical studies are insufficient to conclude for a beneficial effect of these drugs [5,11].

The introduction of cidofovir for the management of the RRP since the late 1990s resulted in a great improvement in the control of the disease [5]. Cidofovir is a cytosine nucleotide analogue. Once converted in the active form, it is incorporated into DNA and exerts its toxicity in the Herpes Virus and Papilloma virus families. Its systemic use is approved for treatment of CMV retinitis in HIV patients, Herpes Simplex, Herpes Zoster and Epstein-Barr infections in immune-compromised patients. Systemic treatment is associated with neutropenia and nephrotoxicity [26]. The intralesional off-label use has been adopted for the treatment of genital HPV or RRP. The antiviral effect is dose-dependent, but there are no clear protocols for dose, concentration, and frequency of administration [27].

Even if many studies have reported significant response rates with almost no side effects (Tab. I) [28-36], in 2012 a Cochrane review of clinical trials comparing intralesional use of cidofovir *vs* placebo after surgical debulking found that there was no significant difference in disease control in the two groups after 12 months of follow-up and concluded that there was insufficient evidence to support the efficacy of antiviral agents as adjuvant therapy in the management of RRP [37].

Moreover, in January 2011, a communication provided by the manufacturer of cidofovir addressed very serious side effects concerning its off-label use. The warning included reports on nephrotoxicity, neutropenia, oncogenicity and even some fatalities. The manufacturer did not specify the severity of the reported complications, the off-label indication of the drug, or its way of administration or concentration dosage; nonehteless, it decided to withdraw the drug from all non-USA countries [38].

As this was a general warning, it was inconclusive whether this would account for its use in RRP [38]. For this reason, the European Laryngological Society initiated a research project

Table I. Summary of cidofovir in reviewed clinical trials.

Study	Year	Number of patients	Median age (years)	Pre-treat mean Derkay score	Pre-treat surgical rate (surgery per year)	Post-treat mean Derkay score	Post-treat surgical rate (surgery per year)	HPV type	Mean concentration (mg/ml)	Results and conclusions
Ablanedo-Terrazas et al. [28]	2022	4, 1 Jo	17	23.5	3.4	0.5	0		5	Decrease in the Derkay severity score with IL cidofovir
		3 Ao								
Jackowska et al. [29]	2019	42	30		8 (mean of procedures before cidofovir)		2.5 (mean of procedures after cidofovir)			Treatment with intraepithelial cidofovir injections and CO_2 laser debulking can lead to a nearly normal voice. 22 complete remissions. 20 partial remissions
		3 Jo								
		39 Ao								
McMurray et al. [30]	2008	19	32	13.2		2.7			0.3-5	Cidofovir demonstrate a reduction in severity index score
		3 Jo								
		16 Ao								
Naiman et al. [31]	2006	17	4	7.67 (CR)		0 (CR)			5-7.5	12 complete remissions. 5 partial remissions
		17 Jo		9.75 (PR)		4.25 (PR)				
Chung et al. [32]	2006	11	7	13.7	7.4	2.6	6.9		5	The effectiveness of cidofovir as an adjuvant treatment for RRP remains unproven, but the possibility of some therapeutic effect is modestly suggested. 5 complete remissions. 6 partial remissions
		11 Jo								
Peyton Shirley et al. [33]	2004	11	2	11.9				HPV 11	5-7.5	Cidofovir is a useful tool adjunctive therapy in RRP. Significant response 27%, partial response 18%, no response 55%
		11 Jo						HPV 6		
Chhetri et al. [34]	2003	5		9.2		1		HPV 11	5	A scheduled protocol for the treatment of Jo-RRP with cidofovir, with increasing interval between treatments, is effective in controlling this disease
		5 Jo						HPV 6		
Bielamowicz et al. [35]	2002	13	48	10	2.15	0	0	HPV 11	4.17-6.25	Intralesional injection of cidofovir is an excellent treatment option with limited local and systemic toxicities. The long-term remission rates for patients with respiratory papilloma are unknown
		13 Ao						HPV 6		
Pransky et al. [36]	2000	10	7	19.6	19 (mean of procedures before cidofovir)	12.7	2.2 (mean of procedures after cidofovir)	HPV 11		Cidofovir therapy is an effective and beneficial treatment
		10 Jo						HPV 6		

Jo: Juvenile onset; Ao: Adult onset; CR: Complete Response; PR: Partial Response.

on the side effects of off-label use of cidofovir in RRP patients [39]. A newsletter and editorial were written to recruit otorhinolaryngologists who treated RRP patients with intralesional cidofovir. All participating centers received a questionnaire and a retrospective case file report. Sixteen hospitals from 11 countries worldwide submitted 635 RRP patients, of whom 275 were treated with cidofovir. There were no significant differences in neutropenia or renal dysfunction before and after cidofovir. There was no significant difference in upper airway and tracheal malignancies between the cidofovir and non-cidofovir groups. No clinical evidence was found for long-term nephrotoxicity, neutropenia, or laryngeal malignancies after the administration of intralesional cidofovir in RRP patients [38]. Nevertheless, drug import is now allowed only for authorised use for clinical trials.

Table II. Summary of bevacizumab in reviewed clinical trials.

Study	Year	Number of patients	Median age (years)	Pre-treat mean Derkay score	Pre-treat surgical rate (surgery per year)	Post-treat mean Derkay score	Post-treat surgical rate (surgery per year)	HPV type	Dose of bevacizumab (mg)	Results and conclusions
Albanedo Terrazas et al. [28]	2022	6	20	9	1	1.5	0		25 mg/ml	Decrease of Derkay scores but no statistical significance
		2 Jo								
		4 Ao								
Rogers et al. [45]	2013	10	8	19	8	13	4	HPV 11	2.5 mg/ml (0.5 ml)	Bevacizumab may indeed limit the number of surgical procedures required per year and increase the duration between procedures in patients with aggressive RRP, while simultaneously improving voice outcomes
		7 Jo						HPV 6		
		3 Ao								
Best et al. [46]	2012	43	48							Higher doses of bevacizumab are relatively safe in adult patients
		43 Ao								
Zeitels et al. [24]	2011	20	Range (18-60)						7.5-12.5 mg	3 complete responses, 16 partial responses with less disease in treated vocal fold, 1 more disease in the treated vocal fold. Treating RRP by coupling the antiangiogenetic agent bevacizumab with KTP laser photoangiolysis is synergistic

Jo: Juvenile onset; Ao: Adult onset.

Bevacizumab

Bevacizumab is a recombinant monoclonal humanised antibody that blocks angiogenesis by inhibiting human vascular endothelial growth factor A (VEGF-A) and by preventing the activation of its receptor (VEGF-R) [19]. Rahbar et al. conducted a retrospective study to determine the role of VEGF-A in the pathogenesis of RRP patients [40]. Strong expression of VEGF-A mRNA was noted in the squamous epithelium of RRP patients, and strong expression of VEGFR-1 and VEGFR-2 were noted in the endothelial cells of the papilloma blood vessels [40]. These observations provided the rationale to evaluate the use of bevacizumab in RRP. The predominant effect of bevacizumab in RRP is modulation of vasculature and not the induction of apoptosis, and stronger effects are seen coupling the use of this drug with photoangiolytic lasers, especially KTP [40].

Bevacizumab can be administered both intravenously and intralesionally. Intravenous use is indicated for patients with non-accessible bronchial lesions, lung parenchyma involvement, papillomas of the paranasal sinuses, or for patients at high risk for voice mutilation by interventional therapies [41]. The approved dose is 5-15 mg/kg every 2-3 weeks in adults and 5-10 mg/kg every 2-4 weeks in children [42,43].

Intralesional use is indicated for recurrent laryngeal manifestations of the disease. The approved dose is 7.5-12.5 mg at 25 mg/ml [44].

Table II summarises the results of bevacizumab in clinical trials [24,28,45,46].

Other adjuvant treatments

Other compounds have been proposed in small case series for the management of RRP, such as celecoxib, indole-3-carbinol, anti-reflux drugs, PD-1 inhibitors, and gefitinib. Unfortunately, no clinical trials are yet available to assess the actual efficacy of these adjuvant treatments.

Vaccines

The most promising development in the treatment of RRP is HPV vaccination. The quadrivalent HPV vaccine (Gardasil) is active against HPV type 6, 11, 16 and 18, and has been used in different adult and juvenile case series to manage RRP with promising results in terms of increased

interval between surgeries or decreased recurrence [47,48]. Moreover, quadrivalent vaccination in RRP patients with HPV DNA positivity and zero or low anti-HPV antibodies increases both anti-HPV 6 and anti-HPV 11 antibodies [49].
Therefore, the greatest hope lies in prophylactic vaccination of pre-adolescent boys and girls. It is expected that widespread vaccination of pre-adolescents will decrease HPV genital wart acquisition and, as a secondary effect, will reduce the incidence of laryngeal infections to newborns via vertical HPV transmission and, in turn, reduce the incidence of juvenile and overall RRP [50].

Personal series

Methods

We conducted a retrospective analysis of the clinical charts of all the patients affected by laryngeal papillomatosis and treated in three different University Centres between 2002 and 2022.
Demographic results are reported in Table III. Seventy-eight patients (54 males and 24 females) were available for evaluation. The mean age was 43 years (range 0-82); of these, 88% had adult onset RRP (Ao-RRP) and 12% juvenile onset RRP (Jo-RRP). Data regarding the subtypes of HPV were present only in 11 cases and HPV 6 was the most frequent subtype detected.
The following parameters were collected: sex, age at first evaluation, sites of the larynx involved, HPV types, type of the first surgical treatment, presence and number of recurrences, surgical treatment of recurrences, adjuvant therapies, side effects and status at last follow-up.
The high number of variables related to the patient and disease as well as the heterogeneity of the cohort does not permit statistical analysis.

Table III. Demographic characteristics (n = 78).

Sex	M	54 (69%)
	F	24 (31%)
Age	Mean	43 years
	Range	0-82 years
	< 12 years	9 (12%)
	> 12 years	69 (88%)
Site	Glottis	59 (76%)
	Supraglottis	5 (6%)
	Glottis + supraglottis	5 (6%)
	Glottis + supraglottis + subglottis	3 (4%)
	Glottis + subglottis	2 (3%)
	Larynx +trachea	3 (4%)
	Trachea	1 (1%)
HPV	Determined	11 (14%)
	HPV 6	4
	HPV 16	2
	HPV 18	1
	HPV 31	1
	HPV 44	1
	HPV 45	1
	HPV 51	1
	HPV 50	1
	Undetermined	67 (86%)

Results

The glottis was the most often involved subsite (76% as a unique localisation); spreading to supraglottis, subglottis or trachea was observed in 13 patients. In 2 cases, the lesion affected only the supraglottis and in 1 case the trachea.
All patients were submitted to surgery under general anaesthesia with CO_2 laser combined with microdebrider in case of bulky and obstructing lesions at first diagnosis (Tab. IV). Recurrences appeared in 79% of patients, and the 16 patients (21%) who did not recur were all adults. Overall, the mean number of recurrences was 9 (range 1-110). Recurrences were more frequent in children (M = 20; range 2-110) than adults (M = 5; range 1-21).
Thirty-two (52%) of the 62 patients who recurred were re-treated with CO_2 laser under general anaesthesia, while office-based treatment with a photoangiolytic laser was preferred in the other 30 (48%) patients.
Adjuvant treatments were applied in 26 patients (Tab. IV). Intralesional alfa-interferon was administered in 8% of cases; these patients were all adults and were treated between 2003 and 2013. Bevacizumab was the preferred compound administered since 2005, both intralesional or systemic, alone or in combination with quadrivalent vaccine (Tab. IV).
The analysis of the course of the disease showed that in the 9 patients with Jo-RRP, 6 (67%) were free of lesions at the last follow-up, while the other 3 (33%) had papillomas. These were the most severe cases with 8, 34 and 110 recurrences, respectively. Of the 69 patients with Ao-RRP, 53 (77%) were alive and free of disease at the last visit (16 with no recurrences and 37 with recurrences), 14 (21%) were alive with disease; 1 (1%) was lost at follow-up and 1 (1%) died for other disease.
Severe side effects were not observed except for 2 patients, with 110 and 7 recurrences respectively, who developed posterior glottic stenosis. Only 1 patient underwent malignant transformation of the lesions. Some degree of dysphonia was observed in 9 patients.

Table IV. Treatment data.

First surgical treatment	CO_2 laser	78 (100%)	
Recurrences	Yes	62 (79%)	9 < 12 yrs 53 > 12 yrs
	No	16 (21%)	all adults
	Overall mean n. of recurrences	9	
	Overall range	1-110	
	Mean n. of recurrences < 12 yrs	20	
	Range < 12 yrs	2-110	
	Mean n. of recurrences >12 yrs	5	
	Range > 12 yrs	1-21	
Surgical treatment for recurrences	CO_2 laser	32 (52%)	
	Office based blu laser	30 (48%)	
Adjuvant treatments for recurrences	IL-IFN	5 (8%)	5 adults
	Sy Bevacizumab	10 (16%)	8 adults + 2 children
	Vaccine	6 (10%)	4 adults + 2 children
	Sy Bevacizumab + Vaccine	4 (6%)	3 adults + 1 children
	IL + Sy Bevacizumab + Vaccine	1 (2%)	1 child
	None	36 (58%)	

IL: Intralesional; IFN: Interferon; Sy: Systemic.

Conclusions

RRP is a chronic disease that is difficult to treat because of the unpredictability of its recurrences and aggressiveness. HPV infection drives local immune dysfunction, but it is still unclear why some patients experience a more severe disease than others, especially in the juvenile onset form [19]. Currently, primary management of RRP is surgical resection of lesions by cold instrumentation such as the microdebrider, or photoangiolytic and CO_2 lasers. The choice between the treatment under general anaesthesia and in-office procedures is based on the lesion's size and localisation and the patient's compliance. In case of frequent recurrences, treatments under local anaesthesia are better tolerated by the patient, thus improving adherence to the follow-up protocol.

The principles of surgical therapy in RRP have been well stated by Bergler et al. [11]. According to these authors, surgery must be considered as relief of symptoms, and rarely a definitive cure.

Surgical trauma may induce new papilloma growth and consequentially any damage to healthy mucosa must be avoided whenever possible. There is no need to treat all the lesions in one treatment session and extensive resections of the anterior and posterior commissures must be avoided because of the risk of glottic stenosis. Even in case of compromised patency of the airway, tracheotomy should be postponed as long as possible to avoid the spread of the disease to the trachea; in case of tracheotomy cannulation, the time must be as short as possible [11].

When surgical treatment requires more than 4 procedures per year, or in case of extensive or aggressive disease with airway compromise, adjuvant pharmacological therapies must be considered. IFN-alfa was the first compound used to increase the immune response in RRP patients with good results, also confirmed in our experience, but its systemic side effects limited its use and research moved toward intralesional or systemic cidofovir and recently to intralesional or systemic bevacizumab.

However, additional studies on the interaction between the low-risk types of HPV and the immune system are necessary to develop novel immunomodulatory molecules to better manage RRP patients [11].

HPV vaccination has shown therapeutic benefit, but, due to the low incidence of RRP, multicentre clinical trials are

still required to assess the efficacy of the HPV vaccines in reducing the recurrence rate of the disease. Routine prophylactic HPV vaccination in pre-adolescent children is expected to decrease the HPV genital warts and, as a secondary effect, to decrease the incidence of RRP by reducing the vertical transmission of HPV to newborns.

Recently, emerging office-based procedures represent a valid adjunctive therapeutic option to carefully follow these patients, minimising the side effects and lack of the adherence to cure due to the multiple treatments under general anaesthesia. Moreover, the routine utilisation of bioendoscopic techniques in the pre- and intra-operative settings allows better and earlier detection of recurrences, thereby increasing the possibility to perform a customised and limited resection.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

GB: designed the study, performed literature search, analysed the data and wrote the paper; FP collected the data, analysed the data and performed literature search; MV, EC, AV, FM collected the data; SM, GS, GP, MB contributed to paper revision. All the authors read and approved the final version of the manuscript.

Ethical consideration

Not applicable.

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