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ORIGINAL ARTICLE

Retrospective analysis of laser vs other therapeutic modalities for laryngeal papillomatosis: European multicenter study

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Summary

Purpose: *Laryngeal papillomatosis can be an aggressive and potentially life-threatening disease, affecting both children and adults. Local excision is the gold standard of treatment, but recurrences are frequently inevitable. The purpose of this study was to present the experience of three institutions with different therapeutic modalities and discuss them in relation with the relevant literature.*

Methods: *Sixty patients underwent papilloma resection during the last decade in three institutions (Homburg/Saar and Marburg, Germany and Athens,Greece). Patient data were retrospectively analyzed for therapeutic modalities applied, rate of complications and synechia formation, necessary operations and need for tracheostomy.*

Results: *Carbon dioxide laser therapy was the most common modality applied alone or combined with other treatment modalities. No major complication was observed, while glottic synechia was the most common minor complication in 5 (8.3%) patients. Of the patient cohort 55.6% required reoperation, while no patient required tracheostomy.*

Conclusions: *Surgical debulking with or without adjuvant treatment remains the mainstay of treatment, which mainly aims to reduce the number and frequency of recurrences since no definitive curative therapy is known so far.*

Key words: *CO2-Laser, cold instruments, debulking, HPV vaccination, papillomatosis*

Introduction

Laryngeal papillomas are the most common tumors of the larynx [1]. They are benign epithelial tumors induced by human papilloma virus (HPV) types 1 and 6 [2], but their malignant transformation is possible [3-5]. While in children papillomas affect predominantly the vocal cords, with increasing age the supra- infraglottic regions and the trachea are more frequently affected [1]. Respiratory papillomatosis can sometimes regress spontaneously, but often runs a protracted course requiring multiple endolaryngeal procedures to maintain a sufficient airway [3]. Due to papilloma's ability to recur, a wide range of therapeutic modalities have been applied to mainly prolong the disease free interval, ranging from the traditional use of cold instruments [5], CO2 laser [5-7], microdebrider [7], photodynamic therapy (PDT) [8], cidofovir [4,9-10], interferon-α (IFN-α) [11], up to the newly introduced vaccines [12].

Herein, we present the experience in treating laryngeal papillomatosis in three institutions over a period of 10 years.

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Methods

Patients

The data of 60 consecutive patients with laryngeal papillomatosis treated during the last 10 years at the Department of Otolaryngology, Head and Neck Surgery, University Clinic of Homburg, Germany (15 patients), at the Department of Otolaryngology, Head and Neck Surgery, Evangelismos Hospital, Athens, Greece (14 patients), and at the Department of Otolaryngology, Head and Neck Surgery, University Clinic of Marburg, Germany (31 patients) were retrospectively analyzed. Endpoints examined included therapeutic regimes, rate of complications and synechiae formation, necessary reoperations and need for tracheostomy. Thirteen patients had received previous treatment in the form of laser (9 patients), cold instruments excision (4 patients) or combined laser and cold instruments surgery (2 patients). Two of these 13 patients were already treated with laser and cold instruments in different therapeutic sessions. One of these patients had already undergone 16 procedures, 12 by means of laser and 4 with the aid of cold instruments. Two patients had already undergone a temporary tracheostomy. Patients enrolled in this study had a minimum follow-up of 1 year (range 12-120 months, median 63 months). In this study it was not examined if a new operation was necessary due to recurrence, due to residuum or as part of a multistep operative procedure so that every new operation was described as reoperation.

Surgical technique

After papillomas exposition using a Kleinsasser microlaryngoscope (Figure 1a), removal was performed by means of vaporization with the CO2 laser alone (37 patients), with the aid of cold instruments as monotherapy (30 patients) or with CO2 laser and cold instruments combination (8 patients), regarding treatment in 60 patients during their whole follow up. Eleven patients were treated with 2, while two with 3 different therapeutic regimes during their observation time. In some patients an application of PDT (4 patients), cidofovir (4 patients), INF-α (3 patients), mitomycin (2 patients), or HPV vaccination (1 patient) was performed as adjuvant procedure (Table 1).

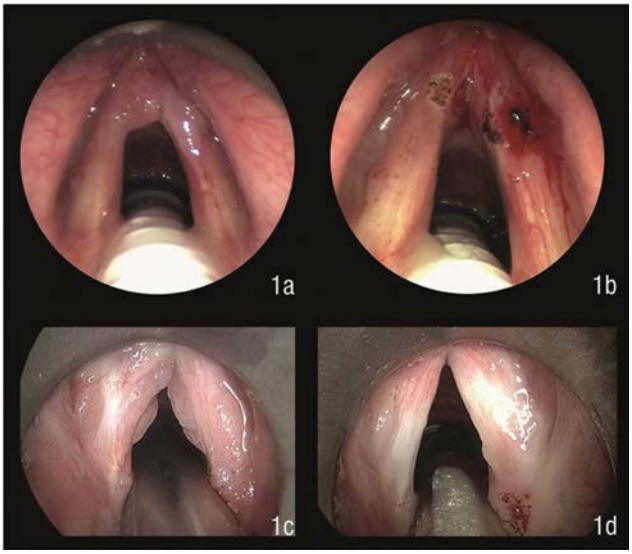

Figure 1. A and **C:** Endoscopic view of the papillomatous lesions. **B**: Endoscopic view after debulking of the lesions. **D:** Endoscopic view in recurrence-free interval.

Table 1. Selected treatment modalities in 60 patients with laryngeal papillomatosis

Therapeutic modalities	*Number of patients who received this therapy initially and during follow-up*
Laser (as monotherapy and in combined mode)	45
Cold dissection (as monotherapy and in combined mode)	38
Photodynamic therapy	4
Cidofovir	4
INF-A	3
Mitomycin	2
HPV vaccination	1

In case of CO2 laser treatment, a power of 1-4W was used to resect/vaporize the papillomas. Smoke evacuators were used, since laser smoke or plume can contain HPV active viral DNA, endangering thus the operating personel. Carbonization rests were then removed with the aid of a neurosurgical cotton wool. In case of papillomas of both vocal cords treatment was not performed on both sides simultaneously to avoid postoperative synechiae. For patients that underwent excision with the aid of cold instruments, bouchaeyer or kleinsasser microlaryngeal instrumentation were used for meticulous papilloma removal. In both cases of CO2 laser application combined with surgery by means of cold instruments, excessive tissue resection was avoided, since this can lead to increased risk of stenosis or webbing (Figure 1b).

In patients receiving PDT, hematoporphyrin derivative (6 mg/kg) was given intravenously 48 to 72 hrs prior to surgery. Cidofovir injections were given to the areas previously cleaned mechanically or with the laser. Single-drug dose ranged from 1 to 3 ml (1ml=5mg), while the average was 2 ml. INF-α was applied in the form of Roferon A 3Mio IE 1xday s.c.

In one case with glottic synechia due to repeated previous operations *alio loco*, and in a patient where the papillomas of the anterior commissure were resected, mitomycin C (0.4 mg/ml) was applied topically on the anterior commissure for 4 min. One child was vaccinated with three doses of the quadrivalent prophylactic HPV vaccine Gardasil® (Sanofi Pasteur MSD) after one treatment with cold instruments and was in follow up for one year after treatment; the child is recurrence-free until now.

After operation completion the patients were not allowed to speak for 3-5 days.

Results

There were 41 male and 19 female patients. Patient age ranged between 2 and 77 years (median 52) with a mean age of 50.2±19.39 years. These 60 patients underwent a total number of 194 operations (3.2 per patient). None of the patients presented with a major life-threatening complication. The most common minor complication was a synechia of the anterior commissure in 5 patients, which in 3 cases produced no symptoms and could only be observed with the aid of the microlaryngoscope, while in 2 cases a CO2 laser transection was performed. None of the patients required tracheostomy. Repeat operations were carried out in 56.6% of the patients (34/60). No significant difference was noticed in repeat operation rate between the two larger patient groups, the one treated with CO2 alone and the other treated with cold instruments alone. One patient required 15 reoperations during 91 months of observation time. During the first year of follow-up 31 patients (51.6%) did not require reoperation, 12 required one (20%), 9 two (15%), 3 required three reoperations (5%) while 5 patients required more than 3 reoperations (8.3%) (Figure 2). The reoperation free-interval interval in the patients that required a new operation ranged between 1 and 101 months (median 7.2). Malignant transformation was observed in 4 out of the 60 patients (6.6%). Three underwent laryngectomy, while in one case a patient not willing to undergo an operation was treated by means of primary radiotherapy.

In our study data for HPV status were available for 29 patients. HPV was positive in 25 patients (type 6 – 25 patients, type 11 – 20 patients, type 16 – 1 patient) and negative in 4 patients.

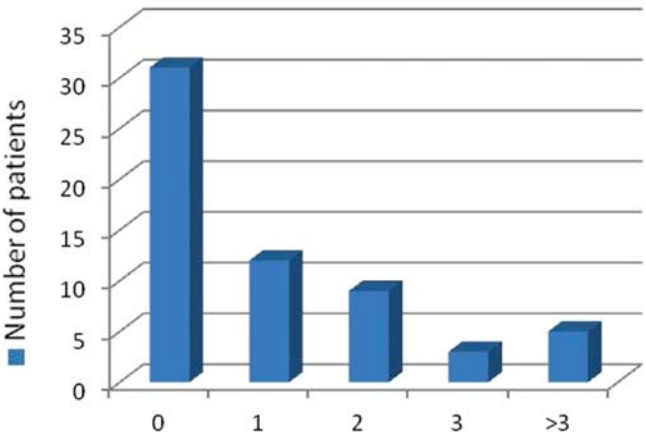

Figure 2. Reoperations during the first year after therapy.

Discussion

The main goal of surgery in case of laryngeal papillomatosis is to remove the disease, while at the same time preserving normal laryngeal anatomic structures and function [13]. To achieve this goal a plethora of treatment concepts have been proposed [4-13].

"Conventional surgery" by means of cold instruments has been described either as monotherapy or versus laser surgery [3,4]. In the study of Mahnke et al. [4] 95 patients with laryngeal papillomatosis were divided into groups according to therapy type (group 1 - patients treated with cold instruments only, group 2 - patients treated with laser only, group 3 – patients treated with combination of cold instruments and laser). The authors found no significant difference of the recurrence rates between patients treated with laser or cold instruments. This report fits to our own experience presented here.

Laser therapy has a wide range of applications in the field of ENT surgery [14], with CO2 being the workhorse in larynx surgery. In a study [5] that presented the authors' experience with CO2 laser on 244 patients with respiratory papillomatosis (RP), laser excisions of RPs every 2 months achieved "remission" of disease (no visible RP on indirect or often direct laryngoscopy 2 months after last removal) in 37% of the patients, "clearance" of the disease process (no RP clinically apparent for 3 years after last removal) in 6%, and "cure" (no clinical recurrence for 5 years after last removal) in 17% of the patients. Common complications include glottis synechias, tracheal stenosis, scarred larynx due to recurrent disease and high number of necessary mechanical and laser interventions [1,5]. We observed that 5 patients presented a minor complication in the form of synechia of the anterior commissure. No life threating complication was observed and only 3 patients (5.4%) after laser surgery as monotherapy presented a glottis web. We didn`t observe a higher incidence of synechia formation using cold instruments. Our strict limitation of working only along one vocal cord with treatment of the other vocal cord after a time interval might be an explanation for this observation. Despite protecting the opposite vocal cord with moistened surgical sponge, a lesion

of the opposite vocal cord had not been prevented in the 3 patients avoiding synechia formation. Disadvantages of CO2 laser include the expensive use of laser and risks like collateral damage to local tissue and laser injuries to the surgeon.

PDT has also shown to be an effective therapy for papillomavirus infections of the larynx. In a study of Feye and Kastenbauer [8] in 12 patients, PDT laser therapy was performed 48 hrs after intravenous application of hematoporphyrin derivative. After PDT the endolaryngeal mucosa had reepithelized in all patients with no signs of residual disease. No synechia of the anterior commissure was observed. Side effects of PDT include hypersensitive skin reactions, local edema, liver-toxicity and nausea [8]. In our study no PDT side effects were encountered.

The role of cidofovir has also been examined [4]. Derkay et al. [9] conducted an online survey distributed to laryngeal surgeons internationally, in which 74 surgeons who had previously used cidofovir, reported their experience with 1,248 patients. The authors concluded that intralesional cidofovir may be initiated if surgical debulking is required every 2 to 3 months. In another study [10], which retrospectively analyzed the data of 635 patients with recurrent respiratory papillomatosis, of whom 275 received cidofovir, no clinical evidence was reported for more long-term nephrotoxicity, neutropenia or laryngeal malignancies after intralesional cidofovir administration. In our study, no patient treated with cidofovir injections after laser ablation presented with the above mentioned complications.

Interferon A has also displayed a positive role in the scene of papillomatosis treatment following surgery. In a national study in Cuba, 169 patients with laryngeal papillomatosis were included. In these patients intramuscular IFN alpha-2b was administered after surgical removal of the lesions. Seventy-three percent (118) of the patients concluded the treatment without lesions, while the rest showed a significant reduction in the number and size of lesions. In this study high percentage of adverse effects was documented, especially fever in 59% of the patients [11].

Mitomycin C has proven efficacy in preventing anterior glottic stenosis (AGS) after transoral microresection of glottic lesions involving the anterior commissure (AC) [15,16]. In the study of Benamansour et al. [16] 18 patients with anterior glottis webs underwent CO2 laser section of the web, mitomycin application and temporary silastic stent placement. After a mean follow up of 48.4 months none of the patients had laryngeal web recurrence. In our study none of the patients treated with mitomycin required a reoperation during follow-up.

Emerging vaccination allows primary prevention against HPV induced papillomatosis. Hočevar-Boltežar [12] performed HPV vaccination on 11 patients with recurrent respiratory papillomatosis that led to complete response in 1 patient, partial response in 7 and no response in 3 patients. The mean interval between surgical procedures was 271.2 days before the vaccination and 537.4 days after it, while the mean number of surgeries per year was 2.16 before the vaccination and 0.93 after it. In our study a 2 year-old child was treated by means of a 4-valent vaccine and showed no sign of recurrence during 12 months of follow-up.

Tracheostomy should be avoided, if possible, in patients with laryngeal papillomatosis, since it can lead to papilloma dissemination to the trachea or even to the bronchii [17]. However, in some cases of massive juvenile papillomatosis, a trachestomy can be necessary [18]. In our study no patient needed tracheostomy during follow-up.

HPV, especially types 6 and 11 (HPV-6 and HPV-11), have been implicated in cases of recurrent respiratory papillomatosis [19], but types 16 and 18 (HPV-16 and HPV-18) have been also occasionally identified [20]. In our study HPV was positive in 25 of the available 29 patients.

Due to absence of a curative therapy for laryngeal papillomatosis up to date, operative revision or revisions are usually inevitable [1,4,5]. In the study of Rehberg and Kleinsasser [3] a patient was treated 34 times endoscopically within 15 years. In our analysis a patient received a maximum of 16 sessions of treatment. In different studies malignant transformation frequency can range between 1.6% and 12.3%. In our study 4 patients (6.6%) developed a squamous cell carcinoma during follow-up.

Conclusion

Up until today, no known curative method is available for laryngeal papillomatosis. Laser therapy combined with adjuvant therapy in the form of PDT, cidofovir or interferon can prolong the patient disease-free intervals, reducing the risk for tracheostomy. Vaccination against HPV-induced papillomatosis has shown encouraging results in recent case reports and studies with few patient

numbers. Multicenter studies examining HPV vaccination regimes are necessary to evaluate this promising method for laryngeal papillomatosis therapy.

Conflict of interest

The authors declare that they have no conflict of interest.

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