Chapter 19
Recurrent respiratory papillomatosis treated with laser surgery and intra-lesion bevacizumab (Avastin®) injection.
Characteristics of mucosal glottic wave analyzed with HSDP, kymography, regional FFT & red-color pattern

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Abstract

Recurrent respiratory papillomatosis (RRP) is a devastating disorder, especially in a professional voice user. The mainstay of treatment is based on immaculate serial removal of regrowing papillomas, usually with a laser. Repetitive laser excisions can cause significant scarring and webbing. The risks of post-operative sequela are exponentially increased with anterior location of papilloma clusters. The resultant dysphonia is not amenable to physiological voice therapy protocols. Additional or adjunctive treatments are eagerly sought by patients to avoid complications. Many of these treatments remain unproven. Recently, bevacizumab (Avastin®) has been advocated as potentially useful. Consequently, we report a case treated with potassium titanyl phosphate (KTP) lasering of papillomas with adjunctive intra-lesional bevacizumab injections. Current outcome of the case is analyzed with both traditional laryngovideostroboscopy (LVS) and High Speed Digital Phonoscopy (HSDP).

Keywords: papilloma, bevacizumab, Avastin®, laser surgery, HSDP, LVS, professional voice user, kymography, P-FFT, RCA

Introduction

RRP of the vocal folds (VF) is a devastating disease usually requiring long-term repeated, meticulous surgical removals. The high recurrence rates are associated with staggering costs and often lead to post-operative scarring of the VF, resulting in different types of dysphonia [1-3]. To improve surgical outcomes and to reduce the potential risk of scarring, medical therapies are often given concurrently [4-9]. These therapies have included: α-interferon given intravenously, intra-lesional Cidofivir injections, vaccines to DNA viruses and mumps, oral indole 3-carbinaol, Cimetidine, proton pump inhibitors, or Celecoxib & Erlotinib combination therapy.

The most current medical therapy includes adjuvant intra-lesional bevacizumab (Avastin®) injection coupled with the use of 532-nm pulsed KTP laser [10]. Also, an adjuvant Gardasil® injection protocol coupled with CO2 laser removal has been introduced [11-12]. Ironically, to date, all these adjuvant therapies produce disappointing or marginal improvement [12]. The basic surgical debulking techniques are often effective when
aggressive, but may result in tissue scarring and webbing, reducing the mucosal wave in a devastating complication for the professional voice user [1-2, 4, 11]. This is specifically a negative outcome for a professional voice user.

Hoping to improve laser surgical results in a professional singer, our patient elected to couple bevacizumab intra-lesional injections with pulsed KTP lasering of the lesions. The hope was to reduce the size of recurrences (and resultant amount of lasering), reduce the frequency of recurrences, and even induce complete remissions. To objectively verify the results we used LVS with acoustics and advanced HSDP technology followed by analysis of the obtained images. This plan, utilizing an unproven investigational medication and the most advanced diagnostic imaging technology available, is of significant potential value to evaluate these treatments, specifically in a professional voice user very concerned about voice outcome.

Case report

Approximately four years ago, the lead singer of an alternative rock/hip-hop band was involved in an altercation in which he was choked. He noted a resulting loss of upper vocal range and occasional voice breaks. After three months he sought medical consultation and was initially told he had a VF nodule. Subsequent referral to our Voice Disorder Clinic (Kaiser Permanente, Oakland, CA, USA) led to a provisional diagnosis of RRP (Figure 1).

This diagnosis was confirmed by the ensuing microdirect laryngoscopy (MDL) biopsy and KTP laser removal of the papillomas. Subsequently, he has had five additional laser procedures performed at intervals of three, five, three, four, and two months. The last three procedures were accompanied by submucosal VF injection of bevacizumab (Avastin®) in a dose of approximately one ml of 25-mg/ml solution. This solution was injected under the location of papilloma removal and in the areas of anterior commissure involvement. Since his last MDL, he has remained disease free for 40 months.

While trying to maintain a full performance schedule, he subjectively reports a slight loss of vocal power especially in his habitual fundamental frequency (F0). At regular intervals, including postoperative visits, he underwent routine LVS studies as previously described [11]. In addition, he was also examined using the Kay-Pentax High-Speed Imaging system (Model 9710, Montvale, NJ, USA) when this became available to us. A 90° transoral rigid scope inserted without topical anesthesia was used to record images at 2000 f/s with 512 x 512 image resolution. We obtained transoral visual images of the glottis during production of the most comfortable sustained F0 production. F0 levels above the most comfortable pitch levels were not examined as the patient reported his comfortable and lower pitch levels were more troublesome than higher pitches when singing.
The collected data comprising 8000 consecutive frames was subjected to subsequent detailed analysis including kymography, point FFT, and red-color analysis.

**Results**

**Visual inspection**

Visual inspection of the glottis area either by conventional LVS or by HSDP did not show any visible papilloma clusters as shown in Figure 2 (last exam was carried out in January 2014). This means that he was free of the visible disease for 40 months post last Avastin® treatment.

Characteristics of the mucosal wave were observed in both exams, but glottal area wave function was calculated exclusively from the HSDP and details of voice initiation and termination were observed only in the HSDP recordings.

Visual inspection suggested asymmetrical mucosal wave documented by both LVS and HSDP systems, but HSDP provided objective documentation of vibratory phase differences and gave more detailed assessment of specific areas of the VF with reduced mucosal wave amplitude on the right VF. Additionally, while glottic competence with full VF approximation was noted on traditional LVS, HSDP revealed a subtle lack of full contact between the VF.

![Figure 2](image.jpg)

**Figure 2.** No visible papilloma clusters in LVS (A) or HSDP (B).

**Kymography**

Kymography analyzes VF motion by extracting a time sequence of single scan lines from consecutive frames of video recordings of the VF. Kymography provides analysis of aperiodicity, left-to-right VF asymmetry, cycle-to-cycle variability, and frequency & phase differences between the VF. Kymographic analysis was performed using four areas of segmentation of which three corresponded to the location of the papilloma at the previous surgery and the fourth location corresponded to the posterior portion of the vibrating VF (Figure 3).

Results showed only mild out of phase vibratory activity with mildly reduced amplitude of the mucosal wave in the anterior portion of the glottis, the area with highest preoperative concentration of the papilloma clusters.
Figure 3. Kymographic analysis showing reduced amplitude of the glottic cycle on the right true VF; differences in frequency are negligible.

Point FFT analysis

Point FFT analysis (Figure 4) showed reduction in F0 in the area of the last operating field vis a vis non-affected areas.

Figure 4. Point FFT analysis showed only minimal differences between the vibratory activity of the left and right (operated upon) VF.

Red-color analysis

Red-color analysis was performed (Figure 5) since normal laryngeal mucosa shows as light tissue and affected tissue (i.e., papilloma) correlates with increased vascularization showing predominance of red tint. No appreciable differences were noted between the operated and non-operated field, though the operated area was more “red” than the non-operated area.
Summary and conclusions

We do not have sufficient data to claim efficacy of bevacizumab (Avastin®) in the treatment of RRP of the larynx. Following six serial surgeries with the final three procedures combined with intra-lesion bevacizumab injections, his disease free interval has extended to 40 months with no recurrence noted on recent exam (October 2015) with LVS and HSDP.

Moreover, HSDP showed minimal and acoustically insignificant asymmetry in the vibratory pattern within and between the operated and non-operated portions of the VF. This is a rewarding outcome, especially given his prolonged disease free interval and preserved singing voice. This case also demonstrates the trials and tribulations of caring for a professional vocalist afflicted with this chronic and potentially devastating condition. We will continue to follow him closely to ensure early detection of recurrent disease.

Note: Since this work we have had an opportunity to evaluate the efficacy of Avastin® in an additional four patients and we noted a high variability of efficacy. This will be discussed in future work.

References