Management Strategies for Skull Base Inverted Papilloma

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Abstract
Objective. Inverted papilloma attached to the ventral skull base presents a surgical dilemma because surgical removal of the bony pedicle is critical to decrease risk of recurrence. The objective of this study is to evaluate the effectiveness of endoscopic management of skull base inverted papilloma.

Study Design. Case series with planned data collection.

Setting. Tertiary medical center.

Subjects. Patients with skull base inverted papilloma.

Methods. Over 7 years, 49 patients with skull base inverted papilloma were referred for surgical resection. Demographics, operative technique, pathology, complications, recurrence, and postoperative follow-up were evaluated.

Results. Average age at presentation was 57 years. Twenty-six patients (53%) had prior attempts at resection elsewhere, and 5 had squamous cell carcinoma (SCCA) arising in an inverted papilloma. Six patients (12%) suffered major complications, including skull base osteomyelitis in 2 previously irradiated patients, cerebrospinal fluid leak with pneumocephalus (n = 1), meningitis (n = 1), invasive fungal sinusitis (n = 1), and cerebrovascular accident (n = 1). The mean disease-free interval was 29 months (range, 10-78 months). One patient with SCCA recurred in the nasopharynx (overall 2% recurrence rate). He is disease-free 3 years following endoscopic nasopharyngectomy. Three patients with SCCA had endoscopic resection of the skull base, while 1 subject with inverted papilloma pedicled on the superior orbital roof had an osteoplastic flap in conjunction with a Draf III procedure. All others received endoscopic resection.

Conclusions. Removal of the bony pedicle resulted in excellent local control of skull base inverted papillomas. Our experience demonstrates that disease eradication with limited morbidity is attainable with this approach.

Keywords
inverted papilloma, endoscopic, skull base, ventral

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Inverted papilloma (IP) is a benign, locally aggressive neoplasm that usually arises in the nasal cavity. As there is a 5% to 20% risk of malignant transformation and up to a 50% risk of recurrence, management can be challenging.1-4 The goals of surgery are to provide sufficient exposure for complete resection, allow an unobstructed view for postoperative surveillance, and minimize postoperative morbidity.1,2,5 Historically, techniques for managing skull base disease included procedures requiring external incisions, such as craniofacial resection with lateral rhinotomy (or midfacial degloving).

The development of endoscopic approaches to the sinuses and skull base has revolutionized surgical management of IP. Several authors have reported convincing data for this approach, with decreased morbidity and complication rates and equivalent recurrence rates as compared with traditional open approaches.5-9 However, given the rarity of skull base involvement, there are insufficient data regarding the optimal approach to IPs pedicled at the ventral skull base, particularly with regard to adequate excision margins. To date, published reports pertaining to management of skull base IP consist primarily of case reports, although several studies detail the success of endoscopic management of IP involving the sphenoid and frontal sinuses.10-16

Histologic studies have suggested that benign sinonasal disease has a rapid propensity for invasion once adjacent to the ventral skull base.17 Coupled with a high recurrence rate, this observation has fueled debate regarding the proper management of the bone underlying the attachment at the

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ventral skull base. In light of the aggressive nature of IP once pedicled at the bony skull base, as well as empiric data supporting successful disease eradication with removal of the bony pedicle, we elected to perform this routinely in our patients. The objectives of the current study are to evaluate outcomes related to resection of skull base IPs with removal of the bony pedicle and describe strategies for IPs pedicled at the ventral skull base.

**Methods**

Over a 7-year period, 49 patients underwent surgical management of histologically confirmed IP with a pedicle involving the ventral skull base. The Institutional Review Board at the University of Alabama at Birmingham approved the prospective collection of data involving these subjects. A single otolaryngologist performed surgical resection, and postoperative evaluation, including endoscopy, was performed at regular intervals. Demographic data were recorded upon patient enrollment, with clinical data including site of skull base involvement and stage of disease recorded at time of surgery. Patients were staged according to the Krouse staging system. Data regarding demographics, histopathology, surgical management, recurrence, and complications were collected prospectively. Analyses for the current study were performed on data collected from January 2008 to May 2015.

**Results**

Demographic and clinical data are presented in Table 1. The average age at presentation was 57 years old. Patients were predominantly male (73%), and advanced-stage disease was common, with 33 patients (67%) presenting with T3 or T4 disease. Twenty-six patients (53%) had prior attempts at resection elsewhere, and 5 had squamous cell carcinoma (SCCA) arising in an IP (10%). The most common site of skull base attachment was the ethmoid roof, although multiple sites were often involved. Complications were recorded in 6 individuals (12%), with skull base osteomyelitis noted in 2 patients who had previously received radiation. One patient each sustained postoperative cerebrospinal fluid (CSF) leak with pneumocephalus, meningitis, invasive fungal sinusitis, and cerebrovascular accident. The mean disease-free interval was 29 months (range, 10-78 months). Nasopharyngeal recurrence was noted in 1 patient with SCCA (overall 2% recurrence rate) who has been disease free 3.5 years following resection. No recurrences were identified within the surgical margins of the mucosa surrounding the pedicle were cleared in all cases. The pedicle was cauterized, and the underlying tissue drilled down to paper-thin bone or dura. The only variance in technique was with histologically confirmed SCCA. Of the 5 patients with SCCA, 3 had endoscopic composite resection of the skull base (bone + dura) rather than drilling of the pedicle. The other 2 subjects had focal microinvasive carcinoma where the diagnosis of SCCA was determined in the final pathology specimen. Further skull base composite resection and radiation treatment were discussed. One patient elected to have postoperative adjuvant radiation treatment, while the other refused any further intervention. In those with composite resection, reconstruction was performed with porcine small intestine submucosal grafts (Biodesign; Cook Medical, Bloomington, Indiana) as underlay with nasoseptal flap overlay in 2 cases and with Biodesign underlay/overlay in the third individual due to loss of the septum from tumor infiltration. The only adjunct open procedure required in the entire series was an osteoplastic flap that was performed in conjunction with a Draf III procedure. In this subject, the IP was pedicled partly on the superior orbital roof (Figure 2).

**Discussion**

Ventral skull base IP is a manifestation of advanced disease. Open excision has historically been preferred in this scenario, but endoscopic resection has recently emerged as the preferable technique. Our series is the largest consecutive series of skull base IP patients in whom endoscopic resection was the primary intervention. Despite a complex patient population, including 53% who had prior attempts at resection, no recurrences were identified within the surgical

| Table 1. Demographic and Clinical Data. |
|-------------------------------|----------------------------------|
| Characteristic               | n (%)                           |
| Age, y, mean (range)         | 57.4 (29-85)                    |
| Sex                          |                                 |
| Male                         | 36 (73)                         |
| Female                       | 13 (27)                         |
| Side                         |                                 |
| Right                        | 28 (57)                         |
| Left                         | 21 (43)                         |
| T classification             |                                 |
| T2                           | 16 (33)                         |
| T3                           | 25 (51)                         |
| T4                           | 8 (16)                          |
| Primary                      | 23 (47)                         |
| Recurrent                    | 26 (53)                         |
| Site of skull base attachment\(\text{a}\) |                                 |
| Ethmoid roof                 | 38 (76)                         |
| Posterior table              | 12 (24)                         |
| Planum sphenoidale           | 8 (16)                          |
| Cribriform                   | 5 (8)                           |

\(\text{a}\)Values presented in n (%) unless indicated otherwise.

Patients can have multiple sites of skull base attachment.
field, although 1 patient with SCCA did have recurrence at a noncontiguous site. The low recurrence rate noted in the current series of patients should be considered a result of meticulous technique focused on removing the bony pedicle with frozen section control of margins.

Although histologic data and clinical experience have long suggested a role for aggressive bone removal in management of IP, a lack of convincing clinical data and concerns regarding the morbidity of removing the bony skull base have provided significant controversy regarding this technique. In a study conducted by Chiu et al, histopathologic evidence was presented demonstrating bony invasion in all IP resection specimens. Bony resection has become standard in resection of IP at typical subsites such as the lateral nasal wall; therefore, this technique is standard in our management at the skull base and orbital wall as well. The primary difference between orbital wall and skull base management is related to the difference in the ease of bone removal. In case of orbital wall involvement, the bone is thinned if necessary with the drill but then manually removed completely. Dura is usually exposed in small areas of the skull base, but paper-thin bone is left in most of the field as support. Similar to skull base involvement, we do not violate the periorbita unless there is SCCA involvement where periorbita is resected as a deep margin.

Although there was no clear trend among the recorded complications, several unique occurrences deserve mention. Of the 5 patients in whom SCCA was detected, 3 sustained major complications. Two of these patients developed osteomyelitis/osteonecrosis of the skull base following radiation therapy. The third developed a CSF leak with pneumocephalus following reconstruction. As is well described, radiation-induced tissue hypoxia and fibrosis impair wound healing. This phenomenon is particularly evident in head and neck subsites such as the mandible and temporal bone. The development of osteomyelitis/necrosis in these patients was attributable to relative local ischemia secondary to irradiation and the need for aggressive resection given the presence of SCCA. Both these patients recovered with extended antibiotic therapy. The third patient developed pneumocephalus/CSF leak several days after removal of packing at the first clinic visit. Upon return to the operating room, nasoseptal flap dehiscence was noted at the anterior portion of the skull base repair. The flap was repositioned, and the patient subsequently recovered without sequelae.
One individual in the study developed invasive fungal sinusitis. Although this disease is primarily seen in immunocompromised individuals, he was immunocompetent prior to his initial surgical biopsies. Due to massive concomitant nasal polyposis, the decision was made to place him on extended prednisone treatment for 6 weeks prior to surgery to assist with identification of the pedicle (Figure 3). Following surgical removal, he developed severe pain and immobility in his left eye at 5 days postoperatively. Emergent evaluation identified black, necrotic tissue within the left surgical field and orbital wall. It was discovered upon admission that he had developed diabetes mellitus with serum blood glucose >400 mg/dL. He was diagnosed with mucormycosis on histology and ultimately required frontal craniotomy, left orbital exenteration, serial debridement, and long-term topical, intravenous, and oral antifungal therapy. Aggressive control of his blood glucose was initiated at admission, and he required insulin for several months postoperatively managed by an endocrinologist. The development of invasive fungal disease in this case was attributed to prednisone-induced uncontrolled diabetes in combination with devitalized tissue as a result of the surgery, which provided a nidus for fungal invasion. This is the first reported instance of invasive fungal disease in the management of skull base IP, but overall the risk in immunocompetent individuals should still be considered low.

The second infectious complication occurred in a patient with a portion of his IP attached at the posterior cribriform plate. Attachment in the cribriform area was unusual in the current series. Three patients had SCCA and received composite resections, while only 2 others with IP had cribriform involvement. Because of our aggressive approach, we generally anticipate a CSF leak through the olfactory fila and do not consider this a complication if it occurs. In this case, there was a small leak identified following cauterization and drilling. A small free graft was placed, and the patient was discharged the next day on amoxicillin/clavulanate. Intraoperative cultures were positive for Klebsiella pneumoniae, which was the noted agent in his meningitis. There was no postoperative leak, so it was assumed that inoculation occurred during surgery and was subsequently not covered adequately with the antibiotic. Of note, concomitant infection is relatively common with IPs secondary to long-standing obstruction. If purulence is visualized in clinic, we culture prior to surgery for postoperative antibiotic planning purposes.

Our final major complication was a patient with hypotension and mental status changes after awakening form anesthesia. She was found to have a small temporal stroke on magnetic resonance image scan. Neurology was consulted, which recommended keeping her mildly hypertensive for 2 days to improve cerebral perfusion. Mental status returned to baseline with no permanent deficits.

**Conclusion**

Skull base IP is a rare and complex disease. Limiting recurrence mandates an aggressive approach, which must be balanced against the risk of central nervous system and local complications. Data from the current study demonstrate that removal of the bony pedicle is essential for disease eradication and can be performed safely.

**Author Contributions**

Jessica W. Grayson, analysis of data, Interpretation of data, drafting/revising, final approval, accountable for content; Sunny S. Khichi, assist in manuscript, analysis of data, drafting/revision, accountable for content; Do-Yeon Cho, acquisition of data, revising manuscript, final approval, accountable for content; Kristen O. Riley, acquisition of data, revising manuscript, final approval, accountable for content; Bradford A. Woodworth, acquisition of data, interpretation of data, revisions of manuscript, final approval, accountable for content.

**Disclosures**

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