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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Ενδοκράνια κι ενδοκογχική επέκταση ανεστραμμένων θηλωμάτων: θεραπευτικές στρατηγικές

Intracranial and intraorbital extension of inverted papillomas: Treatment strategies

ΔΗΜΗΤΡΙΟΣ ΣΠΙΝΟΣ

ΑΘΗΝΑ

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ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ

ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ του Μεταπτυχιακού Φοιτητή

Δημητρίου Σπίνου

Εξεταστική Επιτροπή

- Χρίστος Γεωργάλας, Επιβλέπων
- Γεώργιος Στράντζαλης
- Μαρία Πιάγκου

Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε από την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της .....για την αξιολόγηση και εξέταση τ... υποψηφίου κ... ....., συνεδρίασε σήμερα ...../…../…....

Η Επιτροπή **διαπίστωσε** ότι η Διπλωματική Εργασία τ... Κ... .....

Με τίτλο *Intracranial and intraorbital extension of inverted papillomas: Treatment strategies* , είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη. Η εξεταστική επιτροπή αφού έλαβε υπ' όψη το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή στον παραπάνω Μεταπτυχιακό Φοιτητή την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's).

Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους....., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ....., και για τον βαθμό «ΚΑΛΩΣ» ψήφους ..... Κατά συνέπεια, απονέμεται ο βαθμός «.....».

Τα Μέλη της Εξεταστικής Επιτροπής

....., Επιβλέπων (Υπογραφή)

....., (Υπογραφή)

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Summary

Introducion: Sinonasal inverted papillomas (IP) are benign tumors of the nasal cavity of ectodermal origin. Although they have a relatively low incidence, these are tumors of high interest for the otorhinolaryncologists, as they present high recurrence rates (12-20%) and a lifetime malignant transformation risk of 10%. Furthermore, they tend to extend to and invade neighbouring structures.

Aims: This thesis aims in presenting and analyzing prospectively collected data on a group of IP patients presenting with unique surgical challenges, namely those with IP extending intracranially/intraorbitally. It also aims in identifying all literature cases of patients presenting with IP extending intracranially/intraorbitally and in comparing surgical technique (endoscopic vs open surgery) in terms of recurrence rates.

Methods: Data on patient demographic characteristics, imaging, pathology, surgical technique and recurrences from a series of 14 patients with IP extending intracranially and/or intraorbitally were collected. A literature review (Pubmed) was conducted in order to identify and collect analogous data on all operated patients. Demographic, characteristics, number of previous operations and recurrence rates of endoscopically operated patients were compared to those with open surgeries.

Results: Our cohort of 14 endoscopically operated patients had a mean age ± standard deviation of 52.9 ± 11.6 and a male to female ratio of 10 to 4. Mean number of previous operations was 3.1 (range 0-16). Surgical technique and challenges were illustrated in 2 of 14 patients. Recurrence rate was 1 in 14 (7.1%). Literature searches identified twenty-eight patients (years 1981-2018) with IP extending intracranially and/or intraorbitally that were operated using an endoscopic (N= 6) or open technique (N=20). Mean age and male:female ratio did not differ between open or

endoscopically operated patients. The present series included a significantly higher ($p<0.01$) number of revision cases compared to previous endoscopic resection cases found in the literature. A trend for lower recurrence rates in endoscopically operated patients (5%) compared to those with open surgeries (20%) was apparent, but did not reach statistical significance.

Discussion and Conclusions: Patients with IP extending intracranially and/or intraorbitally represent a rare patient cohort that commonly undergoes multiple operations/revisions. Recent endoscopic techniques as illustrated in the present thesis are likely to maximize thorough excision by removing the pedicle of the tumor with high precision while minimizing surgical morbidity by reducing the structures resected to the absolute minimum. Moreover, correct planning and creation of the surgical field is non-negotiable for the complete excision of the tumor. A trend for lower recurrence rates in endoscopically operated patients compared to open surgery is consistent with salient literature. Future studies on larger patient cohorts are warranted to support the superior efficacy of the endoscopic technique in patients with IP extending intracranially and/or intraorbitally.

Key words: Inverted papilloma, skull base, orbit, endoscopic surgery

Περίληψη

Εισαγωγή: Τα ανεστραμμένα θηλώματα (ΑΘ) είναι καλοήθεις όγκοι της ρινικής κοιλότητας εξωδερμικής προέλευσης. Παρόλο που έχουν σχετικά χαμηλή επίπτωση, πρόκειται για όγκους ενδιαφέροντος για τους ωτορινολαρυγγολόγους, καθώς παρουσιάζουν υψηλά ποσοστά υποτροπών (12-20%) κι έναν κίνδυνο κακοήθους εξαλλαγής της τάξεως του 10%. Επιπλέον, τείνουν να επεκτείνονται και να διεισδύουν σε γειτονικές δομές.

Στόχοι: Η παρούσα διπλωματική εργασία στοχεύει στην παρουσίαση κι ανάλυση προοπτικά συλλεχθέντων δεδομένων μιας ομάδας ασθενών με ΑΘ που εκτείνονται ενδοκράνια/ ενδοκογχικά και που παρουσιάζουν μοναδικές χειρουργικές προκλήσεις, Επίσης, στοχεύει στον εντοπισμό όλων των περιστατικών ασθενών της βιβλιογραφίας που παρουσιάζουν ΑΘ που εκτείνονται ενδοκράνια/ ενδοκογχικά και στην σύγκριση χειρουργικής τεχνικής (ενδοσκοπικής έναντι ανοιχτής χειρουργικής επέμβασης) με γνώμονα τα ποσοστά υποτροπής.

Μέθοδοι: Συλλέχθηκαν δεδομένα για τα δημογραφικά χαρακτηριστικά των ασθενών, την απεικόνιση, την ιστολογία των όγκων, τη χειρουργική τεχνική και τις υποτροπές από μια σειρά 14 ασθενών με ΑΘ που εκτείνονται ενδοκράνια/ ενδοκογχικά. Μια βιβλιογραφική ανασκόπηση (Pubmed) διεξήχθη προκειμένου να εντοπιστούν και να συλλεχθούν ανάλογα δεδομένα για όλους τους ανάλογους ασθενείς της βιβλιογραφίας. Τα δημογραφικά χαρακτηριστικά, ο αριθμός των προηγούμενων χειρουργείων και τα ποσοστά υποτροπής των ενδοσκοπικά χειρουργημένων ασθενών συγκρίθηκαν με εκείνα των ανοικτών χειρουργικών επεμβάσεων.

Αποτελέσματα: Η ομάδα των 14 ενδοσκοπικά χειρουργημένων ασθενών είχε μέση ηλικία 52,9 ± SD 11,6 και αναλογία ανδρών προς γυναικών 10 προς 4. Ο μέσος αριθμός προηγούμενων εγχειρήσεων ήταν 3,1 (εύρος 0-16). Η χειρουργική τεχνική που ακολουθήθηκε σε αυτή τη σειρά κι οι δυσκολίες που αντιμετωπίστηκαν περιεγράφηκαν σε 2 από τους 14 ασθενείς. Το ποσοστό υποτροπής ήταν 1 στα 14 (7,1%) περιστατικά. Η βιβλιογραφική αναζήτηση ανέδειξε είκοσι-οκτώ ασθενείς (έτη 1981-2018) με ΑΘ που εκτείνονται ενδοκράνια/ ενδοκογχικά, εκ των οποίων 6 χειρουργήθηκαν ενδοσκοπικά και 20 ανοικτά. Η μέση ηλικία και ο λόγος ανδρών: γυναικών δεν διέφεραν μεταξύ ασθενών χειρουργημένων ανοικτά ή ενδοσκοπικά. Η παρούσα σειρά περιλαμβάνει έναν στατιστικά σημαντικό αριθμό ($p < 0,01$) προηγουμένως χειρουργημένων ασθενών σε σχέση με παλαιότερα περιστατικά ενδοσκοπικής εκτομής που βρέθηκαν στη βιβλιογραφία. Η τάση για χαμηλότερα ποσοστά υποτροπής σε ασθενείς χειρουργημένων ενδοσκοπικά (5%) σε σχέση με εκείνους που χειρουργήθηκαν ανοικτά (20%) ήταν εμφανής, αλλά όχι στατιστικά σημαντική.

Συζήτηση και συμπεράσματα: Οι ασθενείς με ΑΘ που εκτείνονται ενδοκράνια/ ενδοκογχικά αντιπροσωπεύουν μια σπάνια ομάδα ασθενών που συχνά υποβάλλεται σε πολλαπλές χειρουργικές επεμβάσεις. Οι νεότερες ενδοσκοπικές τεχνικές, όπως περιγράφονται στην παρούσα διατριβή, είναι πιθανό να μεγιστοποιήσουν την ακριβή εκτομή του όγκου, ελαττώνοντας τις δομές που αφαιρούνται στις απολύτως αναγκαίες και τα ακρωτηριαστικά χειρουργεία, ελαχιστοποιώντας τη μετεγχειρητική νοσηρότητα. Επιπλέον, ο σωστός σχεδιασμός του χειρουργικού πεδίου είναι αδιαπραγμάτευτο βήμα για την ορθή πλήρη εκτομή του όγκου. Η τάση για χαμηλότερα ποσοστά υποτροπής σε ενδοσκοπικά χειρουργημένους ασθενείς σε σύγκριση με την ανοικτή χειρουργική τεχνική παρατηρείται και στην σχετική

βιβλιογραφία. Οι μελλοντικές μελέτες με μεγαλύτερες ομάδες ασθενών σίγουρα θα επιβεβαιώσουν την ανώτερη αποτελεσματικότητα της ενδοσκοπικής τεχνικής.

Λέξεις-κλειδιά: Ανεστραμμένο θήλωμα, βάση κρανίου, οφθαλμικός κόγχος, ενδοσκοπική χειρουργική επέμβαση

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List of Abbreviations

acf: anterior cranial fossa

crib: cribriform plate

CSF: cerebrospinal fluid

edu: extradural

er: ethmoid roof

fs: frontal sinus

idu: intradural

IP: inverted papilloma

lp: lamina papyracea

nv: nasal vestibule

oa: ophthalmic artery

OCR: opticocarotid recess

onc: optic nerve canal

orb: orbit

pcc: paraclival carotid artery

pf: pterygopalatine fossa

ps: planum sphenoidale

psc: parasellar carotid artery

ss: sphenoid sinus

vnc: vidian nerve canal

Introduction

Sinonasal inverted papillomas (IP) are benign tumors of the nasal cavity of ectodermal origin, described for the first time by Ward in 1854. (Ward, 1854) The low incidence of 0.2 to 1.5 new cases a year per 100,000 people contributes to less than 5% of the sinonasal tumors, making them some of the rarer neoplasms of the nose and paranasal sinuses (Re et al., 2017; Scheel et al., 2015). Despite their small numbers, rhinologists have developed a keen interest in IPs, as they tend to expand locally aggressively (Lund et al., 2010) and have recurrence rates after surgical excision, ranging between 12% and 20% (Busquets and Hwang, 2006; Peng et al., 2019). The introduction of endoscopic techniques has been associated with a reduction of recurrence rates, as indicated by recent meta – analyses (Busquets and Hwang, 2006; Peng et al., 2019). It has been postulated that surgical technique is related to recurrence, incomplete resection thus being associated with persistent cases. (Attlmayr et al., 2017) These features of IP, coupled with a high potential for malignant transformation – between 3.4% and 9.7% - render proper management challenging. (Grayson et al., 2016; Wood and Casiano, 2012) However sufficient exposure and complete excision can be challenging, especially in the case of IP invading adjacent structures such as the orbit and the skull base. Such extensive papillomas pose significant challenges to their surgical management and may demand the use of multiple, novel techniques. The inclusion of the endoscope in our everyday practice, offered less invasive alternatives for the resection of such tumors, resulting in reduced morbidity compared to the traditional open approaches (Bathma et al., 2011; Castelnuovo et al., 2010). Although the use of endoscopic techniques for the resection of IPs is widely accepted, the available literature is not so clear regarding papillomas extending intracranially / intraorbitally, as there is only a small number of

case series and reports relating to such tumors (Grayson et al., 2016; Karligkiotis et al., 2016; Suh et al., 2015; Thaler et al., 1999).

The present thesis aims in presenting and analyzing prospectively collected data on a group of IP patients presenting with unique surgical challenges, namely those with IP extending intracranially/intraorbitally. It also aims in identifying all literature cases of patients presenting with IP extending intracranially/intraorbitally and in comparing surgical technique (endoscopic vs open surgery) in terms of recurrence rates.

Methods

Data collection

Out of a total of 53 patients, fourteen patients, ten males, underwent endoscopic surgical resection for IP with attachment to the skull base and intracranial and/or infraorbital extension by the senior author, over a period of 5 years (2014-2019). Twelve of fourteen cases were revision cases; their previous operation(s) being performed in other hospitals. All patients underwent thin slice (<1mm) computed tomography and magnetic resonance imaging with contrast. These radiological studies were subsequently reconstructed in 3 planes by the senior author and assessed meticulously for extent and depth of attachment and involvement of adjacent tissues (orbit including periorbita, orbital fat and muscles, cribriform plate, lateral lamella, carotid and optic nerve canals etc, CT angiography was performed when the internal carotid was involved, Imaging (MRI-CT) revealed the involvement of the skull base and orbit in each case and histological confirmation of IP was acquired for each patient separately. Demographic data was recorded based on history taken from each patient upon admission. Date of operation, time from 1st diagnosis, follow-ups, as well as revisions –if any- were prospectively collected. Details of the surgical technique and anatomical structures resected were collected from the digital operation notes of these patients. Consent was received from these patients and the Committee of the "MSc in Applied Neuroanatomy" of National and Kapodistrian University of Athens reviewed and approved the collection of their data and its use in this case series.

Furthermore, a review of the English literature for all cases of IP attached to the skull base and/or the orbit was performed, as well as invading the aforementioned

structures. We searched Pubmed using keywords including –but not limited to- the terms "inverted papilloma, schneiderian inverted papilloma, schneiderian papilloma, orbit, skull base, cribriform plate, carotid artery, opticocarotid recess, endoscopy, endoscopic surgery". Data was collected concerning demographics, recurrence, anatomical structures affected and surgical technique. We took steps to guarantee that all duplicate cases were excluded. We considered eligible all cases where the areas of attachment and / or invasion of skull base or orbit were clearly documented, as opposed to the papilloma simply abutting or in contact with the orbit and skull skull base. When site of attachment or intracranial/intraorbital invasion were not clearly stated, these cases were not deemed eligible. We did not include cases with no data on their follow up. All cases with malignant transformation or in situ carcinoma were excluded. All statistical analysis was done with IBM SPSS 25 software.

Preoperative workup

Prior to surgery all our patients underwent meticulous imaging using sinus protocols. Inverted papillomas (IP) attached to the skull base or the orbit require thin-slice CT scanning and T1- weighted MRI scanning with contrast. An important feature we need to identify is the osteitis sign, as it is a strong indicator of the site of origin and thus attachment of the lesion. Although the Krouse staging system (Krouse, 2000) is widely accepted, it provides little assistance in planning a complete excision of IP. Like most staging systems, it refers to the anatomical subsites (frontal sinus, sphenoid sinus etc) occupied by the papilloma; however, primary papillomas grow in an exophtic, non-invasive way and as a result, only their site of attachment matters: once this has been dealt with, the remainder of the papilloma is easily removed and does not impact on the extent of surgery. As we will present in greater detail later in this

study, treatment of IPs requires a radical excision of the pedicle attached to the bone at their site of origin. Complete removal is almost always feasible, following the oncological principles of piecemeal removal until the demonstration of pedicle and attachment. We can thus safely say that the location of the osteitis provides us with greater details of the possible extent of the surgical procedure, compared to simply the structures involved in the disease.

Another important consideration while preparing for the surgical resection is the early inclusion of computer-aided surgical navigation. IPs related to the skull base and the orbit are challenging, thus making navigation an essential tool for the proper excision. Furthermore, it is important to bear in mind that these patients usually suffer from multiple recurrences. An astounding 85% of the cases in this series are revisions, which means normal anatomy of the area is heavily altered and advanced imaging techniques are assisting us in being thorough in the surgical cleaning of the area, while remaining safe for our patients

Surgical Technique

All the patients were operated under general anaesthesia. Topical phenylephire was sprayed in the patient's nose before induction and then 1:10:000 topical adrenaline solution was applied with ribbon gauzes in the nasal cavity for vasoconstriction. In this case series all the 14 patients were treated via endoscopic- intranasal resection techniques. The principles of endoscopic skull base surgery were applied in all of our cases: A binostril approach was used in almost all cases allowing for bimanual instrumentation and the use of three or four hands techniques. In cases of papillomas involving the sphenoid and middle cranial fossa, a posterior septectomy and wide bilateral sphenoidectomy was performed to allow for wide visualization and

contralateral bimanual access (with the assistant holding the endoscope). For the same reasons, in all the cases of IP involving the posterior table or posterior wall of frontal sinus, a Draf III technique was employed for the unification of the two frontal sinuses and use of contralateral nostril for bimanual lateral access.

Intraoperatively, the pedicle of the IP was identified and, if required for better exposure, the mass of papilloma, debulked -without removing the mucosa- in order to identify the site of origin. Upon identification, the involved bone was drilled with rough diamond burr and removed. Specifically, the cribriform plate and the periorbita were completely excised when the IP was attached to/invaded them. The involved mucosa, was excised with clear margins. When the tumor was extending to neighboring structures as a space-occupying lesion, without truly invading said structures, involved mucosa in contact but not invaded by the papilloma was preserved.

The specifics of the drill shaft and the electrocautery used depended on the anatomic area the IP was attached to. For frontal sinus, anterior ethmoids and lateral maxillary sinus, angled shafts of 45 to 70 degrees were deployed. For manipulations in the medial orbital wall, posterior ethmoids and sphenoid sinus we opted for 15 degrees diamond drills. A 30 degrees endoscope was used in most cases, as we feel it offers the advantage of "viewing around the corner" without causing any disorientation that arises from the use of more angled endoscopes. However, in cases involving extreme lateral frontal sinus, we found the use of 45 and even 70 degrees useful, while operating in the sphenoid sinus, we preferred the use of the 0 degree endoscope.

For complex cases involving sensitive anatomical structures –intraorbital components, periorbita, OCR or the carotid artery- micro intsruments, (curretes, scissors and

elevators) from the endoscopic skull base set were used for tumor excision. Furthermore, the "Two-nostrils-four–hands" technique was used in the aforementioned cases, which provided an unimpeded view to the surgeon and an optimal surgical field for subtle manoeuvres.

Results

Fourteen patients were selected as part of this series amongst the cases operated by the senior author between 2014 and 2019. They were ten males and four females with an average age of 52.9 and range 29 to 68 years, at the time of surgery. Most of our patients had been operated before elsewhere, twelve out of fourteen being revision cases. Notably, five of our cases had undergone more than two revisions, by the time we operated on them. Mean number of previous operations was 3.1 (range 0-16). Mean follow up time was 27.9 months and ranged between 6 to 68 months. Our follow-up protocol includes endoscopy every two months for the first year, every 4 months for next two years, every 6 months for years 4 and 5 and yearly endoscopy subsequently. An important note is that we excluded from this study all patients who were found with, or developed later an IP related squamous cell carcinoma. Cases with local foci of malignancy and in situ carcinoma were also excluded.

An important aspect of the surgical challenge of these cases is not just the structures involved by the neoplasm, but mostly the sites of attachment and origin. These will affect both our excision decisions and the techniques employed. Thus, using imaging studies and throughout the operation we need to identify them and protect the underlying structures. As far as patient individual details, we present our findings in Table I. Overall, four patients had attachment to the sphenoid sinus' walls related to the skull base- either planum sphenoidale or lateral walls or sella- without any attachment to the carotid artery. Another three patients presented with attachments to the opticocarotid recess (OCR), immediately involving the paraclival and parasellar parts of the carotid. Four patients' site of attachment was the anterior skull base-

either the ethmoid roof or the cribriform plate, and two originated from the posterior table of the frontal sinus. Amongst these patients, three were presented with multiple sites of origin, being attached to the orbital wall or the lamina papyracea, in addition to their other site of origin.

Table I

Patient No	Age	Sex	Primary/Recurrent	Side	Structures Invaded	Follow-up (months)	Recurrence
1	59	male	3rd revision	bilateral	lateral wall of ss, pcc	45	No
2	47	female	8th revision	bilateral	nv, left and right orb, ps, crib, idu	8	Yes
3	66	male	2nd revision	right	fs, lp, orb	20	No
4	43	male	2nd revision	right	lp, er, orb	11	No
5	68	male	2nd revision	right	lateral wall of ss, onc, oa, ocr, pcc, psc	8	No
6	59	female	3rd revision	right	lateral recess of ss, ps, ocr, pcc, psc, vnc	6	No
7	43	male	3rd revision	right	fs, lp, orb	6	No
8	64	female	Primary	left	pf, pcc, vnc	36	No
9	60	male	1st revision	bilateral	crib, orb, acf	68	No
10	52	male	2nd revision	right	crib, acf	11	No
11	54	male	1st revision	right	lateral wall of ss, onc, ocr, pcc	49	No
12	59	male	16th revision	bilateral	lateral wall of ss, ps, lp	56	No
13	37	female	1st revision	bilateral	fs, crib, lp	43	No
14	29	male	Primary	bilateral	crib	24	No

Another important feature of these patients' disease is the invasion of the intra-cranial and intra-orbital space. Nine of our patients presented with extended disease invading the orbit trapping or involving the periorbita and/or optic nerve. Another four of our

patients' disease involved the bony carotid canal within the sphenoid or the clivus; in three cases the IP was attached to it, whereas in the other patient's case, it had eroded the bony carotid canal,encroaching but not invading the artery iteslf.

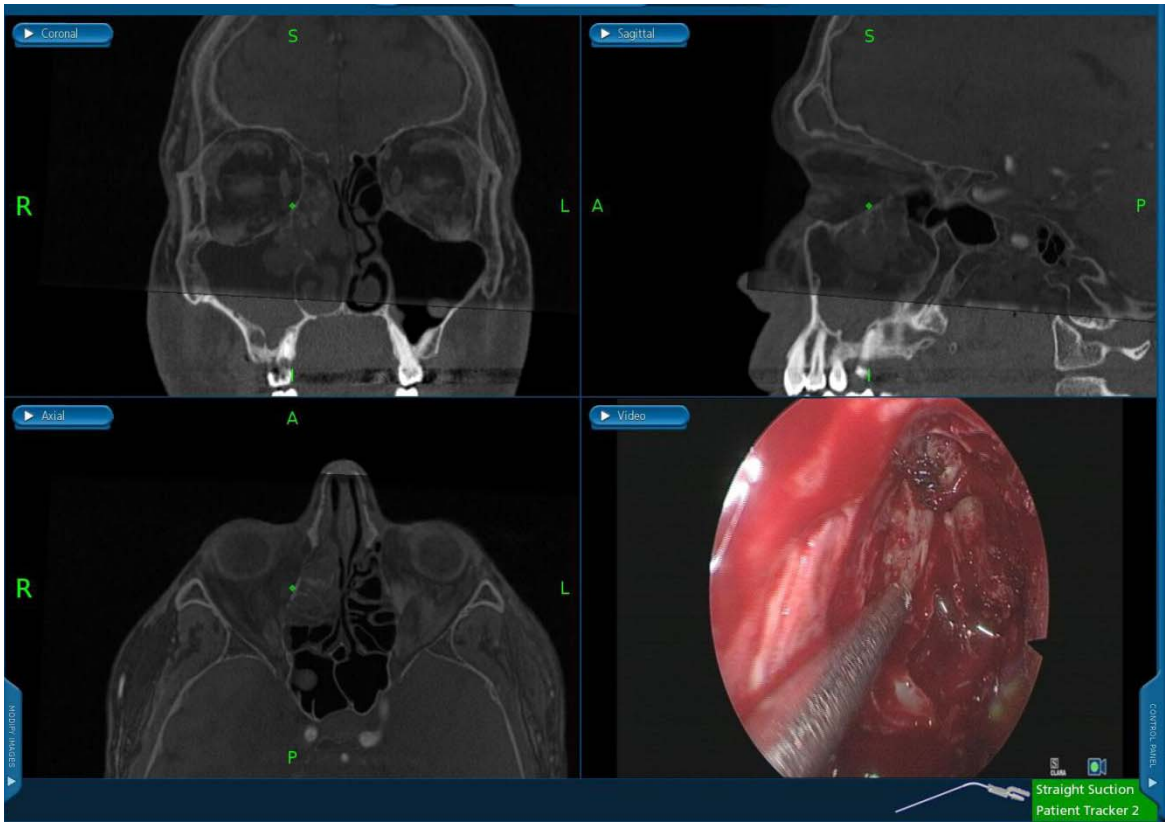
As far as complications are concerned, we did not face any cases of CSF leak or orbital bleeding. There were no cases of major haemorrhage or post-operative meningitis. However, one of our patients did develop a postoperative mucocele in the right orbit, which was subsequently drained in the outpatients, through the wide open Draf 3 neoostium. During the follow up period, one recurrence was observed: This was in a patient operated a total of 8 times previously over a period of 20 years. The IP was invading the intra-dura space in Patient 2 and an extended dissection of this area was needed. However, the patient refused the operation offered.

We will describe in greater detail, two of our cases which presented great surgical challenges and illustrate clearly the need of the aforementioned steps we took during the preparation of our surgical field.

Case 1

An otherwise fit 66-years-old gentleman, arrived into our care with a history of a persisting IP, having had his first operation 14 years ago. When he was first examined in our outpatient, his right nasal cavity was completely occupied by the lesion. Imaging studies revealed the tumor invading the skull base, eroding lamina papyracea and completely obstructing the frontal sinus. The site of attachment (osteitis sign) was seen at the medial orbital wall, in an area of erosion and new bone formation of the lamina papyracea. An endonasal endoscopic approach including a frontal sinus

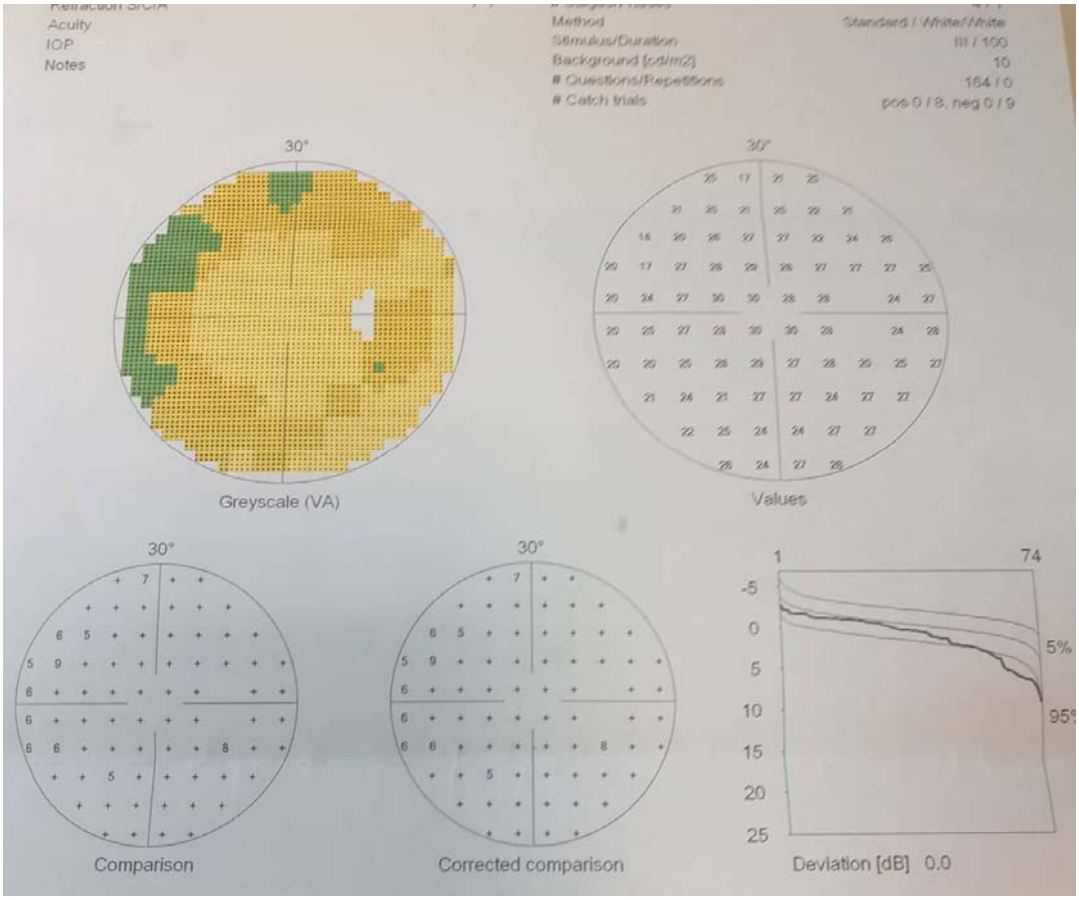
drillout (Draf III) for the resection of the IP with neuro-navigation was then decided as the best course of action. The right side was completely obstructed by the peduncle of the IP. The uncinate process of the ethmoid was excised and an endoscopic medial antrostomy was conducted, revealing a mucus-filled maxillary antrum. The approach to the tumor was centripetal - from uninvolved areas towards the area of attachment: To that effect, a bilateral wide sphenoidectomy was performed, an anterior and posterior ethmoidectomy defining the postero-superior limits of the tumor The frontal recess was identified, the two frontal sinuses unified with a Draf III technique. The site of origin of the IP was confirmed, as identified preoperatively, (Pic1). Part of the lamina papyracea was thickened and heavily affected by osteitis and was thus removed, revealing the underlying periorbita. The remaining lamina was then drilled with a diamond burr and cauterized to guarantee no residual disease on the site of origin. The challenge of not traumatizing the periorbita and the extraoccular muscles was tackled due to the wide surgical field achieved by the Draf III resection previously, allowing for a four-hands-technique resection. The mucosal tissue isolated earlier was used on the anterior wall of the frontal sinus, along with a silicone sheet and absorbable sponge nasostent. The silicone sheet was scheduled to get removed the 10^{th} post-operative day. Biopsies were sent from samples of the main peduncle, as well as its extensions to the periorbita and frontal sinus. No major bleeding or other complications whatsoever were observed. No injury of the periorbita was noted. The patient was discharged from the hospital the day after the operation, healing well.



Pic 1: Intra-operative imaging of IP invading lamina papyracea

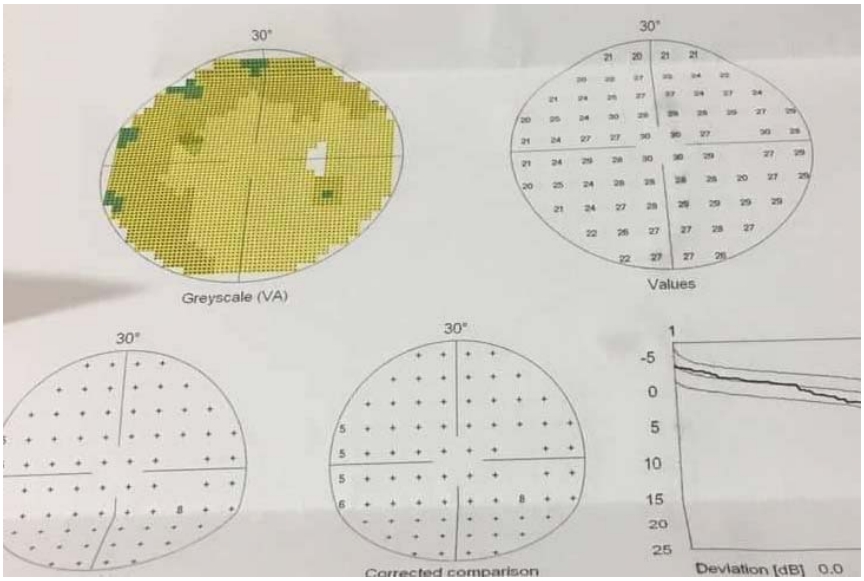
Case 2

A 68-years-old gentleman arrived at our hospital with the second recurrence of IP in the area of the sphenoid sinus and the lateral recess of the sphenoid. He had first been operated about ten years ago, presenting with a first recurrence almost seven ago. Pre-operative imaging studies revealed the IP originating from the opticocarotid recess (OCR) extending into the optic canal. Ophthalmologist's examination revealed that his visual fields were affected (Pic2,3).

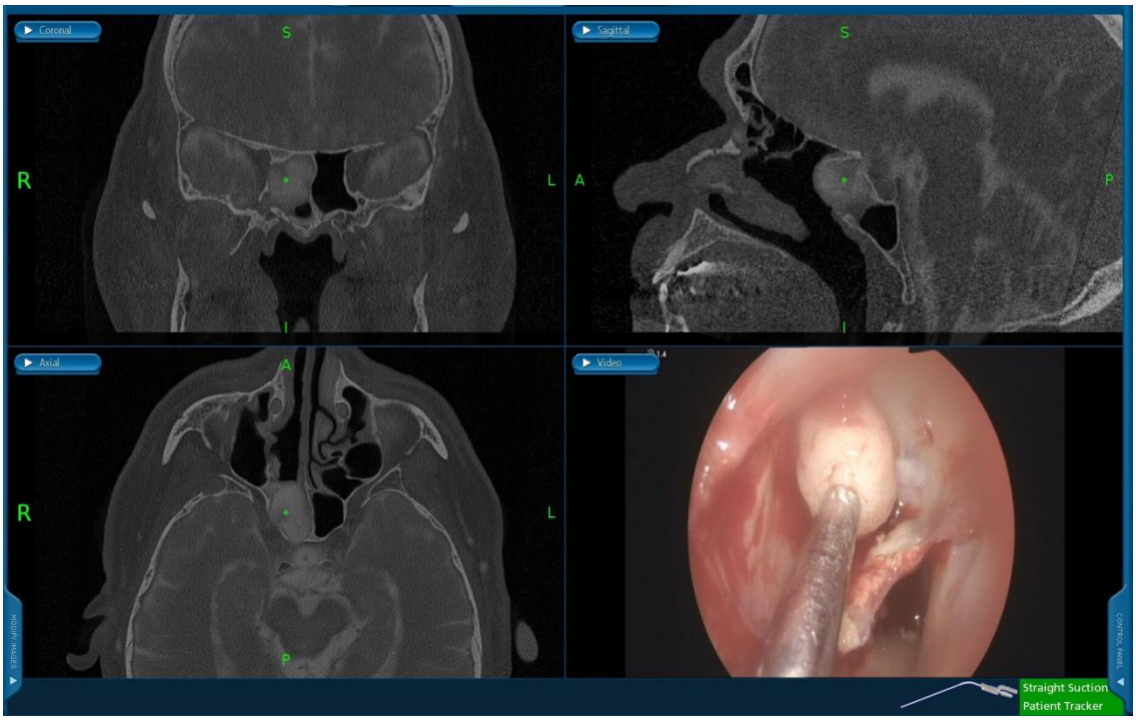


Pic 2: Pre-operative visual fields assessment (part A)

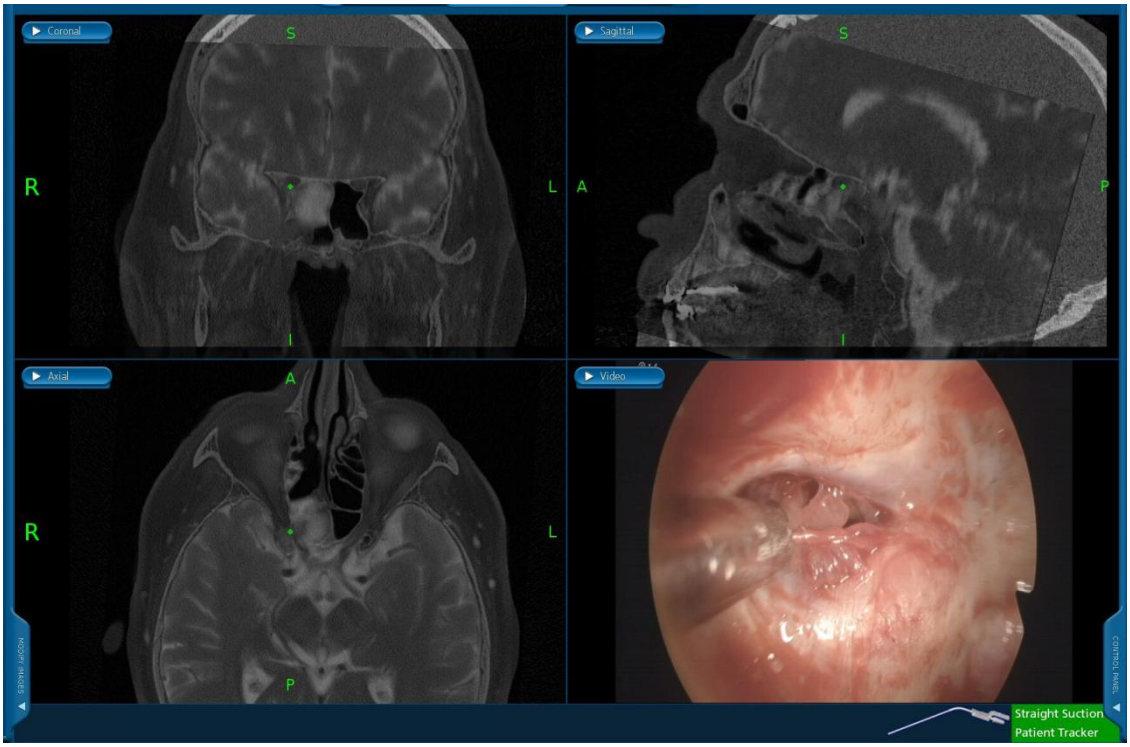
He was fit for the operation and thus an endonasal endoscopic resection of the IP with the assistance of neuro-navigation was considered at the best of his benefits. Using a straight shaft drill, both sphenoid sinuses were opened, by removing the anterior wall of the sphenoid and the posterior part of the septum, as well as the lower half of the middle turbinates bilaterally. A mucocele full of mucopus was identified within the right sphenoid sinus (Pic4). Next, the structures surrounding the OCR were resected and the attachment of the IP to it was identified (Pic5). The bony walls of both the carotid artery and the optic nerve were eroded by the disease. Using Doppler, the course of the carotid was identified, and all but a small piece of bone with residual disease was removed. Again the wide surgical field allowed for us to view around the corner of the lesion, as well as use the four-hands-technique for detailed resection of the tumour afferent to the carotid artery. It was decided that the complete removal of the IP from the OCR was impossible without compromising the patient's safety. The IP was then completely excised from the area of the lateral recess of the sphenoid between the carotid and the vidian nerve. He had an uncomplicated post-operative course without any cerebrospinal fluid (CSF) leaks or signs of infection and was safely discharged the next day from the operation. At 6 weeks following surgery, a new visual fields exam showed a significant improvement



Pic 3: Pre-operative visual fields assessment (part B)



Pic 4: Intra-operative image of mucocele filling the right sphenoid sinus



Pic 5: Intra-operative image of IP invading the OCR

In the relevant literature, 28 individual cases were identified with adequate follow-up details and evidence of skull base/orbit attachment or invasion. Eighteen patients were male and ten were female. They were from 23 to 92 years old with a mean age of 56.2 ±16.9. Seventeen cases were previously operated, while five patients suffered at least one recurrence of their inverted papilloma. We present in detail their demographic data, follow up and recurrence, as well as the structures invaded by the IP in Table II.

	Table II									
Author	**Age**	**Sex**	**Primary/Recurrent**	**Intracranial extension**	**Intraorbital extension**	**Cranial Nerve Involvement**	**Carotid Involvement**	**Follow-up (months)**	**Resection of the extension**	**Post-operative recurrence**
(Fakhri et al., 2005)	51	male	Primary	✓			✓	30	endoscopic	−
(Fakhri et al., 2005)	60	male	Primary				✓	79	endoscopic	−
(Hardy et al., 2015)	60	male	Primary		✓			13	open	−
(Albathi et al., 2018)	75	male	Primary		✓			15	endoscopic	−
(Albathi et al., 2018)	87	male	1st revision		✓			7	endoscopic	−
(Walijee et al., 2015)	69	male	1st revision		✓			15	open	−
(Gendeh et al., 2007)	54	male	Primary	✓				5	endoscopic	−
(Strojan et al., 2013)	69	male	Primary	✓		✓		24	open	−
(Gomez et al., 2000)	40	male	4th revision	✓				246	open	−
(Gomez et al., 2000)	32	female	1st revision		✓			96	open	−
(Gomez et al., 2000)	84	female	1st revision		✓			17	radiotherapy	+
(Miller et al., 1996)	42	female	1st revision	✓	✓	✓		36	open	−
(Vural et al., 1999)	51	female	2nd revision	✓	✓			2	open	+
(Vural et al., 1999)	44	female	4th revision	✓				96	open	+

(Bajaj and Pushker, 2002)	33	male	3rd revision		✓			6	open	−
(Wright et al., 2011)	32	male	Primary	✓	✓			12	open	−
(Myers et al., 1981)	66	female	Primary		✓			36	open	−
(Dolgin et al., 1992)	23	female	3rd revision	✓	✓			10	open	+
(Vrabec, 1994)	62	male	1st revision	✓				37	open	−
(Vrabec, 1994)	54	male	1st revision		✓			87	open	−
(Vrabec, 1994)	59	female	1st revision		✓			14	open	−
(Vrabec, 1994)	72	male	4th revision		✓			24	open	−
(Vrabec, 1994)	38	male	1st revision		✓			90	open	−
(Peterson and Heim, 1991)	92	female	Primary	✓				9	no	−
(Lewis et al., 1989)	52	female	Primary	✓	✓			72	open	−
(McCary et al., 1994)	58	male	1st revision		✓			49	open	−
(Christensen and Smith, 1986)	60	male	1st revision		✓			48	open	+
(Kodama et al., 2012)	55	male	Primary		✓			24	endoscopic	−

The mean age ± standard deviation (SD) of our population was 52.9 ±11.6 compared to a mean of 63.7 ±14.3 in the cases endoscopically resected in the literature. Applying T-test on these two populations revealed no statistical significance (p=0.09) in this observed difference. Regarding the sex of our patients 10 out of 14 were male, while all 6 of the patients reported in literature having undergone endoscopic resection of IP were male. Applying Fisher's exact test, as the criteria for chi-square were not met, we calculated p=0.27, which is suggestive of statistically unimportant difference. Thus we grouped together the patients of the present study and all the endoscopic approach cases from the literature for further comparison with the open resection cases. The mean age ± SD of the endoscopic resection cases was 56.1 ± 13.1, while the mean age ± SD of the open resection cases was 50.8 ± 14.1. Using T-test on these groups, no statistically significant difference was revealed (p=0.23), suggesting that age was not a selection bias affecting the strategy of treatment. Furthermore, in endoscopy group, a male to female ratio of 16:4 was observed, compared to 12:8 in open resection group, a statistically insignificant difference in sex distribution, according to Fisher's exact test (p=0.3).

Regarding previous operations, we first compared our series to the endoscopic cases of the literature. Twelve out of fourteen (85.7%) patients were previously operated before arriving under our care, whereas all six of the endoscopic cases in the literature were primary cases. Thus, our series had a significantly higher rate of reoperations compared to the literature cohort (Fisher's exact test, $p<0.01$). This result suggests a selection bias in the endoscopic resection cases found in the literature compared to the cases of the present series. In the sum of the endoscopic cases, 12 out of 20 (60%) were revision cases compared to 15 out of 20 (75%) in the open approach group, a difference without any statistical significance according to chi-square test (p=0.31).

The follow-up in our series was 27.9±20.4 months compared to a follow-up of 26.7±25 in the endoscopic cases of the literature. Applying a T-test this difference is insignificant (p=0.9). Comparing the follow-up of all the endoscopic cases to all the open approach cases we observe a mean follow-up of 27.6±21.9 months for the former compared to 50.7±54.4 months for the later. This difference was stark albeit non-significant (p=0.08). Moreover, we studied and compared the recurrence rates in this series to the endoscopy cases in the literature, as well as the recurrence rates in the clustered endoscopic resection cases group to the open resection cases group. We reported a single recurrence in our series of fourteen cases (7.1%), whereas not a single recurrence was observed in the 6 endoscopy cases of the literature; a statistically insignificant difference (p=1) according to fisher's exact test. Thus, the cumulative recurrence rate in endoscopic resection cases group was 1:20 (5%) compared to a recurrence rate of 4:20 (20%). This difference in recurrence rates of endoscopic vs open resection cases was notable albeit insignificant (p=0.34 in Fisher's exact test).

Discussion

Our 14 patients were treated via endoscopic- intranasal resection techniques. Furthermore, piecemeal resection of IP was not found inferior as far as tumour control is concerned compared to en bloc excision (Bathma et al., 2011; Castelnuovo et al., 2010; Peng et al., 2019). Some of the features of endoscopy leading to those results are probably related to the ability to magnify, as well as the excellent illumination of the surgical field and the ability to view around the corner (Busquets and Hwang, 2006). The location of the disease in the frontal sinus has traditionally been a limitation to the use of endoscopic techniques. However the development of efficient instruments and the greater experience earned by the sinus surgeons led to transnasal excisions even in the far lateral portion of the frontal sinus and/or in the supraorbital recess (Karligkiotis et al., 2015).

In order to deliver a proper oncological resection via endoscopic approaches, there are principles to be followed in all cases: impeccable visualization and unobstructed instrumentation are required. A common pattern observed in some of our patients who had undergone multiple previous operations in the area of the sphenoid, was that the previous surgeons tried to be minimally invasive, using a uni-nostril approach for the sinus. We would like to underline the importance of the binostril approach in these cases, as only in that way are our instruments capable of reaching all the walls of the spenoid and are we able to perform all the required manoeuvres for the excision, using three or four hands techniques. Furthermore, wide exposure – as provided by wide sphenoidectomy and removal of the rostrum of the sphenoid in cases of sphenoid and cribriform plate, frontal sinus drillout and unification via a Draf III technique for the excision of IPs attached to the posterior table or posterior wall of the frontal sinus and anterior skull base.

It is well documented that the most common site of origin of the IP is the maxillary sinus (Tong et al., 2019). However, a wide maxillary antrostomy along with tumour debulking could potentially mislead us in missing the true site of origin if located elsewhere. The pedicle targeted surgery allows for less invasive dissection of the areas the IP expands to, while we achieve radical excision of the cradle of the tumour itself. However, given that a malignancy is always part of our differential we need a definitive diagnosis before initiating a less invasive operation. Multiple biopsies of the tumour are recommended to be collected pre-operatively, in order to safeguard that there is no focal malignant transformation (Landsberg et al., 2008). Despite osteitis sign being a useful tool in preparing for the operation (Yousuf and Wright, 2007), the site of attachment needs to be confirmed endoscopically intra-operatively. Furthermore, from our experience, for patients who have undergone multiple operations, it is hard to distinguish the bone remodeling at the site of IP origin from the scar tissue and remodeling of the sinuses due to the previous operations, in CT and MRI studies. Careful debulking with a microdebrider will most of the time allow us to pinpoint the locus of tumour infiltration. This only stresses the point we raised before, of the need for the surgical team to prepare their surgical field appropriately for easy visualization and instrumentation of the affected areas. Finally, meticulous surgical excision of the site of attachment is vital – and that should include all involved tissue, whether this is periorbita, cribriform plate or dura.

As shown by the findings of the present study and those in previous cohorts (Table II), patients with IP attached to the skull base are patients that commonly undergo several operations. Specifically, in the literature we observe that 64% of the documented cases that presented with intracranial or intraorbital invasion concerned revision cases. This highlights either inadequate technique during the primary surgery,

resulting in recurrence and tumour seeding. Thus, adequate excision of the tumor the first time is of paramount importance. Close to the site of attachment, inflammatory bony reaction leads to loss of lamellar bone and the production of new immature bone. The process leads to the entrapment of affected mucosa into small crevices. This embedded mucosa epithelium should also be removed during the IP excision, as it will become the locus of future recurrences (Chiu et al., 2006). Proper surgical excision of the IP thus means not only drilling off the affected bone superficially, but with care going deeper that the affected periosteum and also cauterizing the mucosa in close proximity. This way, is the risk of residual disease kept to a bare minimum. This means our resection should be radical –whenever this is possible- according to oncological principles. Both the invasive nature of IPs- despite them being histologically benign- as well as their potential of malignant transformation, calls for removal of the involved bone and drilling and cauterization of the margins of the pedicle. This series consists of a limited number of patients and cannot contribute to a statistically important difference as far as recurrence rates are concerned. Despite this, using the pedicle-oriented surgical excision technique, we report of a drastically reduced recurrence ratio compared to the one found in the literature. Further series and meta-analyses will be needed to actually support this finding and its significance for future surgical decisions in planning the excision of IP.

The aforementioned technique is only possible due to the evolution in the surgical instruments during the last years. Angled scopes, curved debriders and endonasal drills, as well as a plethora of sophisticated graspers, microscissors and curettes of variable sizes and angles allow us to work with precision in inaccessible areas, such as the extreme lateral of frontal sinus (Pagella et al., 2014). Regarding the sphenoid sinus surgery and resection in close proximity to the internal carotid, the “two nostrils

four hands" technique (Castelnuovo et al., 2006), is in our view ideal for subtle manipulation of these structures. Further information drawn from the pre-operative CT which can be pivotal regarding the resection of IPs in proximity to the carotid concerns the integrity of the carotid canal. If the bony canal of paraclival and parasellar carotid has been invaded, we might be forced to be less radical in our excision, leaving a small part of the IP behind, in order to protect the IC from injury. For the IPs invading the lamina papyracea, an investigation should be made during the operation for the integrity of the periorbita. If no signs of invasion are found, using a Freer, the IP is carefully detached from the structures adjacent to the lamina along with the lamina itself, leaving the periorbita intact and no reconstruction is to be undertaken. However, in case of frank invasion, periorbita should be removed and periorbital fat needs to be cauterized. Silicone sheets may be used to support the orbital structures and provide a substrate for fibrosis. They are removed during the post-operative follow-up on the 10^{th} day. Last but not least, in case of meningeal invasion, after the resection of the dura, the surrounding tissue is cauterized and the defect restored using the three-layer method (Geyik et al., 2016). In our series, using this technique we appear to have avoided the post-operative complication of CSF leak.

Pre-operative imaging is of paramount importance when treating inverted papillomas. Both CT and MRI complementary help us to evaluate the extent and origin of disease. Inflammatory changes on the affected bone may vary, but periosteal thickening seems to be a common finding in various studies (Chiu et al., 2006; Yousuf and Wright, 2007). Periosteal thickening appeared in all the cases of the above study in the deep margin. These histopathologic conditions impact on the radiographic imaging. We can use CT imaging to locate the presence of osteitis, thus predicting the site of

attachment of the IP. Nevertheless, CT cannot distinguish the IP margins from adjacent soft tissue, such as mucosa and retained secretions. CT can be pivotal for diagnostic purposes, as the lobulated margin of IPs has been reported as a characteristic finding on CT (Savy et al., 2000). MRI on the other hand cannot provide detailed data on sinus walls destruction, but tumour invasion in dura- carotid-orbit are handily recognizable. Optimal modality is T1 weighted sequence before and after gadolinium administration with sinus protocol, using fat suppression. T2 weighted sequence can act complementary to differentiate the IP from secretions and secondary mucoceles. Dura or periorbita infiltration is easily demonstrated by these imaging techniques, allowing us to properly design our surgical steps and pinpoint the excision targets.

As our current strategy for treating IPs concerns the pedicle of the tumour, its extension to the sinuses and nasopharynx has little effect on the surgical decisions. In fact, the term "extent of disease" may be misleading, as it is in fact space occupation instead of frank invasion. We tried to isolate the cases from the literature concerning frank invasion of the skull base, however a severe limitation in our study is that most authors use the Krouse system for describing their cases of IP. In this endoscopic era, space-occupation has little predictive value for the treatment or follow-up of our patients. Some efforts have been made for a new classification system to be created which would provide greater insight for the planning of endoscopic resection of IP (Dragonetti et al., 2011). We believe for the time being, a classification system using the site of attachment, as revealed from the CT and resection may be needed for the endoscopic surgeons to be able to develop common criteria for classification and surgical excision planning.

It can be postulated that the extension of IP to the structures discussed in this thesis is facilitated by the entrapment of residual mucosal foci due to partial previous excision of the primary disease. In the previous cases using endoscopic resection techniques found in the literature (Table II) a significant selection bias was observed in the form of all the patients being primary cases. Via this series we would like to illustrate that the endoscopic surgery arsenal of tools and techniques provides a safe means of treatment revision cases too. Twelve out of fourteen of our patients had been previously operated in other hospitals. Despite the surgical challenges we only had a single recurrence, supporting that endoscopic resection is the optimum treatment for IP, including in this specific group of patients with intracranial/intraorbital extension of IP.

Although the open approach for IP resection offers excellent exposure and the direct excision of the tumour en bloc, the most recent meta-analysis (Peng et al., 2019) supported significantly reduced recurrence rates for the endoscopic compared to the open resection. These results, along with the well-established reduced morbidity and hospitalization that endoscopic techniques offer (Larget et al., 2015), shapes the endoscopic resection as being the ideal option for IP treatment. While the present findings do not provide evidence for statistically significant differences, they suggest reduced recurrence rates in patients with IP extending intracranially and/or intraorbitally treated via endoscopic resection (5%) using novel resection and field exploration strategies compared to open resection techniques (20%).

Furthermore, piecemeal resection of IP was not found inferior as far as tumour control is concerned compared to en bloc excision (Bathma et al., 2011; Castelnuovo et al., 2010; Peng et al., 2019). Some of the features of endoscopy leading to those results are probably related to the ability to magnify, as well as the excellent illumination of

the surgical field and the ability to view around the corner (Busquets and Hwang, 2006). The location of the disease in the frontal sinus has traditionally been a limitation to the use of endoscopic techniques. However the development of efficient instruments and the greater experience earned by the sinus surgeons led to transnasal excisions even in the far lateral portion of the frontal sinus and/or in the supraorbital recess (Karligkiotis et al., 2015).

Limitations

This case series consists of strictly selected cases representing a very specific population. This led to a rather limited number of cases being included. Another limitation of this study concerns the review of the literature. Although steps were taken to include all the patients with IP attached to the skull base and/or orbit, it was impossible to actually include them all. Several authors did not provide clear evidence of attachment, while others did not offer sufficient individual patient data, leading to these cases being excluded from our literature review.

Conclusions

Patients with IP extending intracranially and/or intraorbitally represent a rare patient cohort that commonly undergoes multiple operations/revisions. Recent endoscopic techniques as illustrated in the present thesis are likely to maximize thorough excision by removing the pedicle of the tumor with high precision while minimizing surgical morbidity by reducing the structures resected to the absolute minimum. Moreover, correct planning and creation of the surgical field is non-negotiable for the complete excision of the tumor. A trend for lower recurrence rates in endoscopically operated patients compared to open surgery is consistent with salient literature. Future studies on larger patient cohorts are warranted to support the superior efficacy of the endoscopic technique in patients with IP extending intracranially and/or intraorbitally.

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Appendix I

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