Dissertation

Subjective and Objective Assessment of Novel Adjuncts and Quality of Life in Endoscopic Transsphenoidal Skull Base Surgery

submitted by

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Good Scientific Practice".

Peter Valentin Tomazic
Graz, April 2021

Disclosures

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Table of Contents

Abbreviations

CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CSF	cerebrospinal fluid
CT	computed tomography
ENT	Ear, nose and throat
FESS	Functional endoscopic sinus surgery
IFN-gamma	interferon gamma
IL	interleukin
MR	magnetic resonance imaging
OCR	optico-carotid recess
PETC	piezoelectric endoscopic craniotomies
SD	standard deviation
TGF-ß	transforming growth factor beta
TONES	transorbital neuroendoscopic surgery
TSLP	thymic stimulating lymphoid protein
VAS	visual analogue scale

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Abstract (English)

Introduction: In the last decades functional endoscopic sinus and skull base surgery has become the gold standard to approach this anatomically challenging region. Many advanced approaches have come up in the past years and technological advances have brought more safety to surgeons and patients when it comes to complications and comorbidities. The biggest advances lie in imaging and development of high resolution cameras as well as delicate instruments to allow minimal invasive surgery. This study aims to evaluate the feasibility and outcomes of novel 3D endoscopy as well as novel piezoelectric techniques to approach lesions at skull base.
Material and Methods: The study comprises to parts. In the first part 15 patients have prospectively been enrolled for endoscopic skull base surgery where PETC has been applied. Following parameters were evaluated: age, diagnosis, size of the adenoma, success of piezoelectric surgery (yes/no) if an intact bone flap could be dissected, state of the dura after harvested bone flap, size of the bone flap, time for surgery and time for piezo application, intra- and postoperative complications, pre- and postoperative visual analogue score (VAS) for nasal blockage, post-nasal drip and smell.
For part two 20 patients were prospectively enrolled undergoing FESS where operated sides were randomized to wither 2D and 3D. A questionnaire was filled out by the surgeon evaluating usability and imaging qualities of the respective technology, as well as time needed for surgery.
Results: Part one: In all patients (N=15) piezoelectric an intact bone flap could be harvested successfully and the dura remained intact. The mean size of the bone flap was 55.9 mm^2 (SD: 20.1) which was sufficient in all cases. Mean time for piezoelectric craniotomy to harvest the bone flap and expose the dura was 4 min 22 sec (SD: 165 sec). Mean total time for surgery was 90 minutes (SD: 22.8 min) which was significantly (p=0.002) lower compared to our standard surgical procedures (mean: 112 minutes, SD: 82.8 min). Postoperative VAS did not deteriorate significantly apart from smell. Part two: Both techniques were successful without any complications. 3D is superior to 2D in depth perception, anatomical detail recognition and 3D effect.
Conclusion: PETC is safe and effective enabling the surgeon to naturally reconstruct the skull base after endoscopic approaches where earlier bone had to be removed harboring the potential of CSF leaks. 3D technology is excellent for teaching and potentially reducing intraoperative complications since critical anatomic structures can be identified better and thus protected.

Abstract (German)

Einleitung: In den letzten Jahrzehnten ist die funktionelle endoskopische Nasennebenhöhlen- und Schädelbasischirurgie zum Goldstandard geworden. In den letzten Jahren sind viele Innovationen entstanden, und der technologische Fortschritt hat Chirurgen und Patienten mehr Sicherheit gegen Komplikationen und Komorbiditäten gebracht. Die größten Fortschritte liegen in der Entwicklung von hochauflösenden Kameras sowie empfindlichen Instrumenten für diese minimalinvasiven Operationen. Diese Studie analysiert die Anwendbarkeit der neuen 3D-Endoskopie sowie Ergebnisse piezoelektrischer Techniken zur Operation von Läsionen an der Schädelbasis.

Material und Methoden: Die Studie besteht aus 2 Teilen. Im ersten Teil wurden 15 Patienten prospektiv für eine endoskopische Schädelbasisoperation eingeschlossen, bei der PETC angewendet wurde. Folgende Parameter wurden bewertet: Alter, Diagnose, Größe des Adenoms, Erfolg der piezoelektrischen Operation (ja / nein), wenn ein intakter Knochendeckel präpariert werden konnte, Zustand der Dura nach dem Heben des Knochendeckels, Größe des Knochendeckels, Zeit für die Operation und Zeit für die Piezoanwendung, intra- und postoperative Komplikationen, prä- und postoperativer visueller Analog-Score (VAS) für behinderte Nasenatmung, postnasaler Sekretion und Geruch.

Für den zweiten Teil wurden prospektiv 20 Patienten einer FESS unterzogen, bei der die operierten Seiten zu 2D oder 3D randomisiert wurden. Der Chirurg füllte einen Fragebogen aus, in dem die Anwendbarkeit und die Bildqualität der jeweiligen Technologie sowie die für die Operation benötigte Zeit analysiert wurden.

Ergebnisse: Erster Teil: Bei allen piezoelektrischen Patienten (N = 15) konnte ein intakter Knochendeckel erfolgreich präpariert werden und die Dura blieb intakt. Die mittlere Größe des Knochenlappens betrug 55,9 mm^2 (SD: 20,1), was in allen Fällen ausreichend war. Die durchschnittliche Zeit für die piezoelektrische Kraniotomie, um den Knochendeckel zu entnehmen und die Dura freizulegen, betrug 4 Minuten und 22 Sekunden (SD: 165 Sekunden). Die durchschnittliche Gesamtzeit für die Operation betrug 90 Minuten (SD: 22,8 Minuten), was im Vergleich zu unserem Standardverfahren (Mittelwert: 112 Minuten, SD: 82,8 Minuten) signifikant ($p = 0{,}002$) niedriger war. Der postoperative VAS verschlechterte sich abgesehen vom Geruch nicht signifikant. Teil zwei: Beide Techniken sind ohne Komplikationen anwendbar. 3D ist 2D in Bezug auf Tiefenwahrnehmung/-schärfe, anatomische Detailerkennung und 3D-Effekt überlegen.

Schlussfolgerung: PETC ist sicher und effektiv und ermöglicht es dem Chirurgen, die Schädelbasis nach endoskopischen OPs, bei denen früherer Knochen entfernt werden musste, auf natürliche Weise zu rekonstruieren. Die 3D-Technologie eignet sich hervorragend zur chirurgischen Ausbildung und zur potenziellen Reduzierung intraoperativer Komplikationen, da kritische anatomische Strukturen besser identifiziert und geschützt werden können.

1. Introduction

Since the 1970's functional endoscopic sinus surgery (FESS) has become the gold-standard in the treatment of inflammatory and neoplastic diseases of the nose and paranasal sinuses [1,2]. Among other centers the Department of Otorhinolaryngology at the Medical University of Graz pioneered this technique and spread its knowledge around the globe. This minimal invasive approach replaced open approaches or microscopic approaches which were less functional and had worse outcomes. With the new technique the natural sinus outflow tracts are re-established and ventilation and drainage leads to the cure of most inflammatory sinus disease like chronic rhinosinusitis without nasal polyps [3]. In the last 20 years, the use of the endoscope and the interdisciplinary cooperation between ear, nose and throat (ENT) and neurosurgery have become increasingly important. From today's perspective, endoscopic access to the pituitary gland has also become the gold standard. The minimal invasive access and use of natural body cavities, in this case the nose, has become established in the long term.

A quick look into the past shows that the endoscope was also discovered in neurosurgery around the turn of the century. Walter E. Dandy (1886-1946) first attempted to excise the choroid plexus under direct endoscopic view in a hydrocephalic patient, however apart from contemporary reports, no scientific publications exist about this. The neuroendoscopic method was then abandoned in neurosurgery in the 1970s and 1980s due to the lack of success and the establishment of the microscope. The three-dimensional view of the microscope, the possibility of perfect illumination and the magnification of the surgical field put the endoscope into a minor role compared to the open, traditional neurosurgical access routes. The limitation of microscope, however, remained the view "around the corner" within the surgical field. In the 1960's, Guiot et al. [4] described the advantages of using the endoscope in their work on the exploration of the transsphenoidal access route to the pituitary gland. This point in time can be described as the birth of endoscopic transsphenoidal surgery. The direct, panoramic view into the operating cavity resulted in a significant improvement in safety and the quality of the operation. Appuzzo et al. [5] contributed significantly to the establishment of this method in 1977. Nevertheless, it was not until the 1990's that the endoscope found wider acceptance in skull base surgery. Jho et al. [6] described the purely endoscopic method using the 4-hand technique.

After increasing experience in endoscopic pituitary surgery, the indications gradually expanded to include craniopharyngiomas, tuberculum sellae meningiomas and other sellar and supra- or parasellar lesions [7]. These so-called midline approaches subsequently made access to the anterior skull base possible ranging from the frontal recess or the lower frontal sinus wall to the back and down to the craniocervical junction and the first two cervical vertebrae. Malignant tumors such as esthesioneuroblastomas and advanced carcinomas of the paranasal sinuses were also increasingly operated in this way, which was previously considered impossible [8]. Two major developments occurred in parallel to the novel surgical approaches which were the ability to navigate intraoperatively and to use new closure techniques to reconstruct the skull base after removing the respective lesions, in order to permanently close a CSF leak [8].

In the area of intraoperative navigation, an electromagnetic system is mostly used which offers the possibility of fusion between computed tomography and magnetic resonance tomography. The advantage of electromagnetic systems lies in the design of the instruments, which are much smaller than optical instruments due to coils which are only around a millimeter in size. Since there is little space in the nostrils and surgery is usually carried out using a four-hand technique with three instruments and an endoscope, this design has enormous advantages. Furthermore, the coil for detecting the instruments is located in their tip so that they can be bent if necessary without having to be re-registered or even replaced by curved instruments. This property complements the essential advantage of endoscopes that allow a view "around the corner", which is not possible with microscopes. Recent developments make it possible to use “augmented reality” access paths to the sinuses to be drawn preoperatively on the navigation device, which are then overlaid with the endoscopic image, thus making it easier to find the access. Another aspect of this software is to mark or measure critical structures such as the internal carotid artery or the optic nerve in on the CT and / or MR preoperatively. If one approaches these structures with a navigated instrument and / or the navigated endoscope, the system warns the surgeon acoustically or optically. This can be very useful in anatomically confusing situations.

The endoscopic access to, for example, large tumors at skull base makes it necessary to open or partially resect the dura mater. The resulting defects and iatrogenic CSF leaks must be permanently closed. The development of a variety of techniques makes this possible through the endoscopic route. A wide range of materials are used, which can be autologous or heterologous. In most centers, autologous materials such as fascia lata or temporalis are used. In the case of very large defects, various vascularized mucosal flaps have been described - the best known of these is the Hadad flap [9] - which revolutionized endoscopic skull base surgery and further reduced the limitation of access due to the resulting defect. Additional aids such as fibrin glue and absorbable materials to fix and support the grafts are used [10]. Navigation-based measurement tools are also used for more precise planning of the grafts. With this software, the defect can be measured, so that the graft can be cut more precisely to fit shape and size.

Another new development are endoscopic piezoelectric devices with which you can cut bone at skull base and harvest flaps instead of removing the bone entirely. This bone flap can be reinserted after the lesion has been removed, which naturally reconstructs the skull base [11]. The increasing experience in endoscopic skull base surgery led beyond the midline access to lateral accesses into the pterygopalatine fossa, infratemporal fossa and even into the orbit [12]. Access through the orbit into the middle cranial fossa became known as TONES: transorbital neuroendoscopic surgery [13]. Here, similar to the nose, the orbit is used as an access corridor to remove e.g. meningiomas of the middle fossa endoscopically. Since the endoscope is the optical tool for visualisation of the surgical field, developments are pursued to improve resolution and color quality of the cameras. The newest developments are three-dimensional endoscopes to overcome the deficit of a 2D field which was the primary criticisms against endoscopic approaches by surgeons using microscope [14].

1.2 Aims of this study

The study comprised two parts: Part one analyses the feasibility and outcome of novel piezoelectric endoscopic craniotomies (PETC). This technique allows to harvest bone flaps endoscopically as compared to external craniotomies. With this technique a nature-like reconstruction of skull base and the major complication of postoperative CSF-leaks may be significantly reduced. Moreover, less hemostyptic material is used which should improve the postoperative nasal quality of life.

In part two the second innovation in endoscopic sinus and skull base surgery –three dimensional (3D) endoscopy is analysed regarding its feasibility and advantages compared to standard 2D endoscopy.

1.3 Endoscopic anatomy of the inner nose

The common nasal cavity is a space divided into two halves by the nasal septum, starting anterior at the nostrils via the nasal vestibule and ending posteriorly at the choana separating it from the nasopharynx.

Each half of the nasal cavity has a medial and a lateral wall, a floor and a roof. The lateral wall is narrowed by the protruding turbinates (Conchae nasales).

The roof is formed anteriorly by the frontal bone, then by the lamina cribrosa of the ethmoid bone and in the back by parts of the sphenoid bone [15].

The olfactory filaments (Fila olfactoria) pass through the lamina cribrosa to the olfactory bulb. Here the bone is very thin and there is a close relationship between the nasal cavity, the anterior cranial fossa (fossa cranii anterior) and the frontal lobe, where endoscopic access to e.g. olfactory groove meningeomas is possible [16].

The floor of the nasal cavity is formed in the anterior two thirds by the palatal processes of the maxilla (processus palatini maxillae) and then in the posterior third by the horizontal processes of the palatine bone (laminae horizontales ossis palatini). These bones meet transversely at the transverse palatine suture and in the midline at the median palatine suture and form the anterior nasal spine in the median front and the posterior nasal spine in the back. The nasal septum rides on the respective nasal crest of the two bones. The floor of the nasal cavity is also the roof of the oral cavity, which explains the close topographical relationship between the two anatomic regions.

The medial wall comprises the nasal septum and separates the two nasal cavities from each other. The septum consists of cartilaginous and bony parts. At the point where bone and cartilage meet, there is often a small protrusion called the septal tubercle. The bones involved are the ethmoid bone with its perpendicular plate at the top and the vomer at the bottom.

The lower edge of the vomer sits on the crista nasalis and the upper edge has a connection to the sphenoid body and its rostrum via its alae. The rear edge is set vertically and separates the choanae from each other. In endoscopic transnasal approaches the vomer is unharmed to guarantee optimal airflow in the posterior nose [17].

The edges of the perpendicular plate of the ethmoid are connected to the rostrum of the body of the sphenoid bone at the back, superiorly to the lamina cribrosa and anteriorly to the nasal portion of the frontal bone and the nasal bone.

The cartilaginous septum completes the nasal septum between the bony parts and may extend posteriorly as far as the sphenoid rostrum. This most superior and posterior parts are resected in endoscopic transspenoidal approaches to reach and open the anterior sphenoid sinus wall.
The nasal cavity opens posteriorly into the nasopharynx through the choanae. As a result, the posterior wall is incomplete except for its cranial part, which is provided by the body of the sphenoid bone. Each choana is roughly shaped like an egg. Thus, they are wider at the base than at the top. The boundaries of the choanae are the vomer medially, inferiorly the lamina horizontalis ossis palatini, laterally the lamina medialis processus pterygoidiei, above and laterally the processus vaginalis of the latter and above medially the ala of the vomer [15]. In case of a choanal atresia endoscopic access to the choana is granted by an inferior medial route posteriorly.
The lateral wall has the most complicated structure. Here, the turbinates (Conchae nasales) protrude into the nasal cavity. They narrow the nasal cavity in such a way that a continuous cavity - from the floor to the roof - is only present medially near the septum: the common nasal meatus.

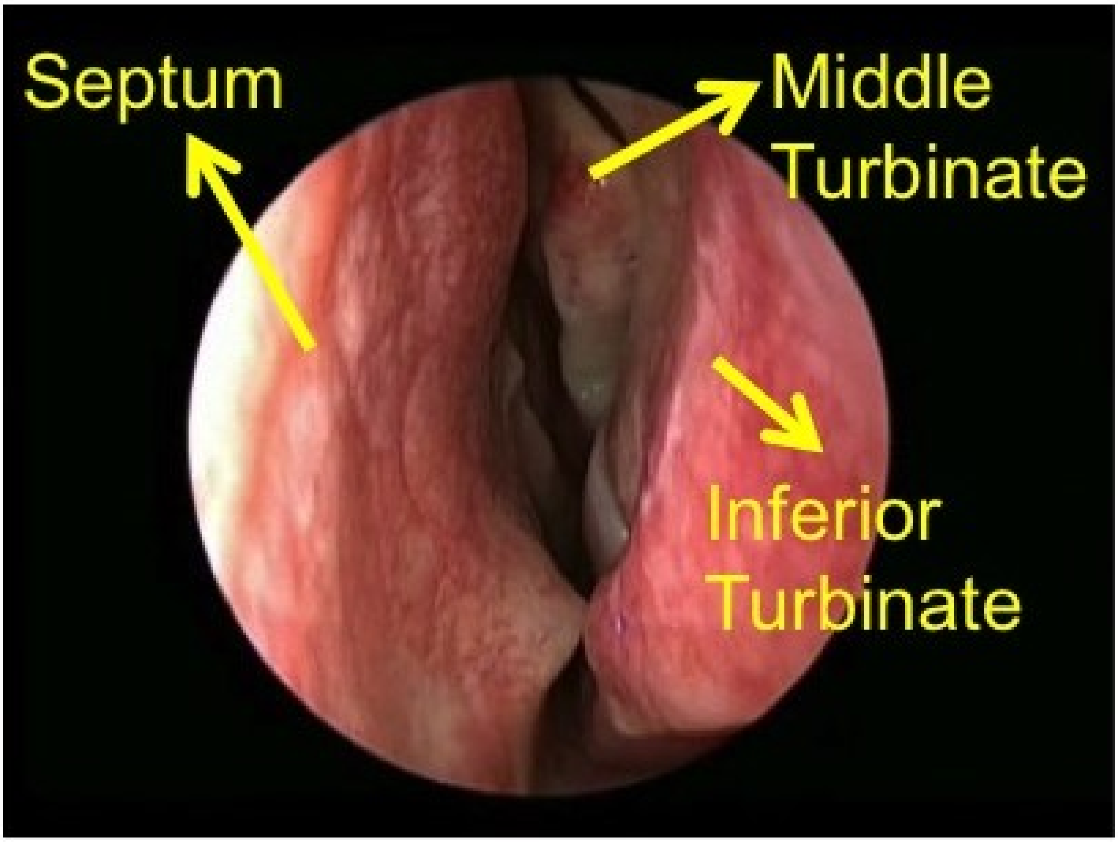

Figure 1: Endoscopic view into a left nasal cavity showing important structures like the nasal septum, the middle- and inferior turbinates.

Of the conchae nasales, the inferior turbinate is formed as an independent bone and the middle and superior turbinate as parts of the ethmoid bone. A small supreme nasal concha can also be located above superior turbinate.

Under each of the turbinates there is a meatus nasi inferior, medius, superior and possibly also a meatus nasi supremus respectively.

If you remove the turbinates, you can see the bones that make up the lateral nasal wall. These are thin lamellas that do not form a complete wall. The medial surface of the nasal bone can be seen in the upper and anterior part. The processus frontalis of the maxilla joins the nasal bone posterior and inferior followed by the small lacrimal bone (os lacrimale). The lower part of the lateral nasal wall is formed by a bony lamella of the maxilla. This separates the nasal cavity from the maxillary sinus and forms its maxillary sinus hiatus which, however, is narrowed by neighboring bony processes. Above and laterally, the lamina papyracea of the ethmoid bone delimits the nasal cavity. It carries the ethmoid cells (ethmoid sinus) and the middle and superior (possibly supreme) turbinate. If the ethmoid is removed endoscopic access to the orbit and inner orbital structures can be achieved [18]. In the back, the palatine bone with its maxillary lamina and the pterygoid process with its medial lamina complete the confinement of the lateral nasal wall.

Since the lateral nasal wall is not completely closed off by bone, there are openings and niches that are only covered by mucosa. These are the hiatus semilunaris, which leads into the ethmoid infundibulum, from which the maxillary sinus and some of the anterior ethmoid cells can be accessed endoscopically [15]. Underneath the hiatus semilunaris are the nasal fontanelles that lead into the maxillary sinus. Finally, behind the middle turbinate, there is the sphenopalatine foramen, which is bordered by the sphenoid and orbital processes of the maxillary lamina of the palatine bone and the body of the sphenoid bone. The sphenopalatine artery enters the nasal cavity through the sphenopalatine foramen.

The hiatus semilunaris is a half-moon-shaped crevice created by protruding bones. The ethmoid bulla protrudes from above and is an extensively pneumatized anterior ethmoidal cell. The lower border is formed by the posterior edge of the uncinate process of the ethmoid bone. This is a thin, sickle-shaped bony process of the ethmoid bone, the curvature of which, runs from superior-anteriorly to posterior-inferiorly. In endoscopic transethmoidal approaches this is the first structure to be dissected in order to reach the ethmoidal cavity [1,2].

The shape of the turbinates creates spaces under neath them that are known as nasal passages (meatus nasi). The meatus nasi are named after the turbinate they belong to: Meatus nasi inferior, medius, superior and possibly supreme.

The inferior nasal meatus (meatus nasi inferior) is bounded laterally by the lateral nasal wall and separated from the maxillary sinus. Its roof and its lateral boundary are the inferior turbinate.

The lacrimal duct (ductus nasolacrimalis) opens into the lower nasal passage about one centimeter behind the head of the inferior turbinate. At the point where the nasal passage breaks through the mucous membrane, there is a fold, the so-called Hasner's valve.

Contrary to its name, it does not serve to close the duct, but it does mark the location of its opening.

The middle nasal meatus is delimited above and medially by the middle turbinate. The middle turbinate is frequently pneumatized and is then referred to as concha bullosa. The turbinate is fixed to the bone via its basal lamella. This changes its orientation in space from ventral to dorsal and can thus be divided into three sections.

In the anterior third it is strictly vertical and sagittal and inserts at the base of the skull at the angle between the horizontal and lateral lamina cribrosa. This is where the stability of the middle turbinate is lowest. In the middle third, the basal lamella turns laterally to insert into the lamina papyracea. From then on it moves caudally and appears almost frontally. In the back third it turns and runs horizontally to form the roof of the middle nasal meatus. The frontal portion of the basal lamella forms the boundary between the cellulae ethmoidales anteriores et posteriores. The anterior ethmoid cells open into the middle nasal meatus anterior inferior to this border. The lateral wall of the middle nasal passage shows complex relationships, since it is not entirely formed by bone everywhere, but is only partially covered by mucous membrane. This lies over "crevices" which are limited by thin bone lamellae. These "gaps" are the two nasal fontanelles in the lower part of the lateral wall (see above).

Above that is another fissure, the hiatus semilunaris. This crescent-shaped gap lies between the uncinate process below and the ethmoid bulla above (see above). It leads to the ethmoid infundibulum. In order to clearly differentiate between the hiatus semilunaris and the ethmoid infundibulum, it should be noted that the former is a two-dimensional gap that leads into a three-dimensional space, namely into the ethmoid infundibulum.

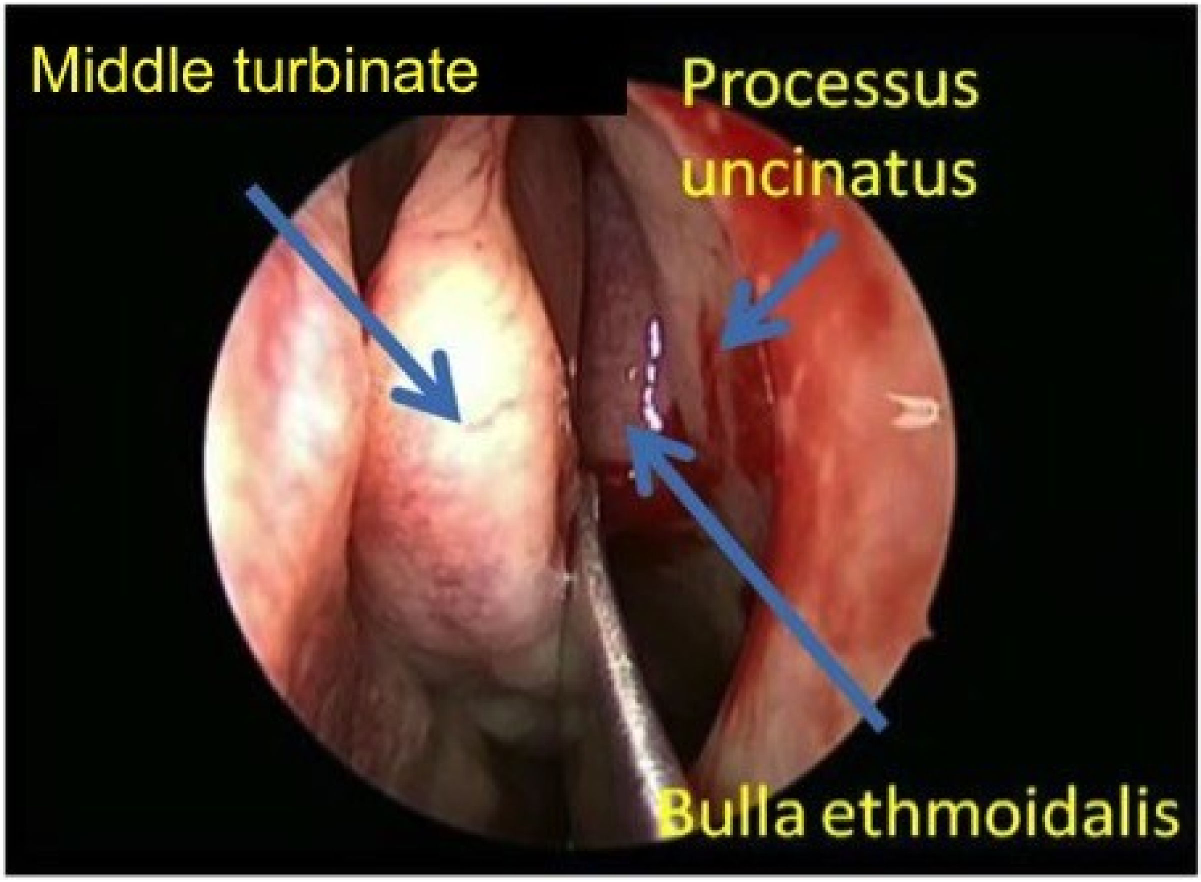

Figure 2: Endoscopic view into the middle meatus showing the uncinate process and the ethmoidal bulla. The middle meatus is the most important access into the ethmoidal infundibulum and the ethmoid sinus for endoscopic sinus surgery.

The hiatus semilunaris could therefore be called the “gateway” to the ethmoid infundibulum in endoscopic sinus surgery.

The ethmoid infundibulum is delineated medially by the uncinate process and mucosa. Its posterior wall is the anterior wall of the ethmoid bulla. The largest part of the infundibulum is bounded laterally by the lamina papyracea of the ethmoid bone, which forms the medial orbital wall.

The anterior wall ends blindly at an acute angle, where the uncinate process attaches to the lateral nasal wall in an arched aspect on its way back and down. Therefore, the infundibulum appears "v" -shaped on the horizontal section. The maxillary sinus opens into the ethmoid infundibulum.

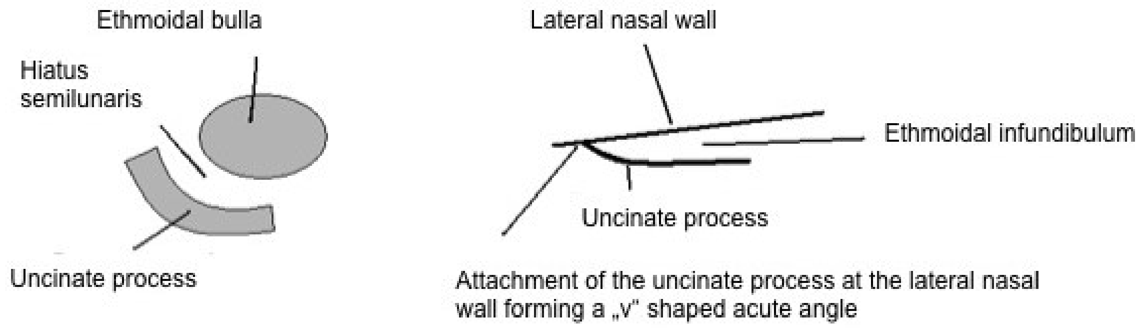

Figure 3: Anatomic relationships of the ethmoidal infundibulum seen from a lateral view (left panel) and above (right panel).

If the cranial aspect the uncinate process is attached at skull base, the frontal sinus also opens into the infundibulum via the frontal recess that precedes it. A bony nasofrontal duct does not exist and thus the opening of the frontal sinus into the ethmoidal infundibulum should be referred to as frontal outflow tract [15]. If the uncinate process bends cranially and medially and attaches to the middle turbinate, the frontal sinus also drains into the ethmoid infundibulum via its frontal recess.
The third constellation would be that the uncinate process bends laterally with an attachment to the lamina papyracea. Then the ethmoid infundibulum would end cranially in the so-called terminal recess and the frontal sinus would open medially from it - via the frontal recess - into the middle nasal meatus.

The superior nasal meatus (meatus nasi superior) is bounded by the lateral nasal wall and the superior turbinate. The posterior ethmoid cells (sinus ethmoidales posteriores) open into it. If there is no supreme turbinate the sphenoethmoidal recessus immediately is below the roof of the nasal cavity and posteriorly to the superior nasal turbinate. It is bounded superior by the lamina cribrosa, posteriorly by the anterior wall of the sphenoid sinus and below and in front by the superior nasal turbinate. In this region the opening of the sphenoidal sinus is located, which leads into the sphenoid sinus. This is the most important landmark for the endoscopic endonasal transsphenoidal approach to skull base [8,19].

1.4 Endoscopic anatomy of the paranasal sinuses

The paranasal sinuses comprise 3 large paired sinuses: The maxillary sinus, the frontal sinus and the sphenoidal sinus. Between the orbits lie the paired ethmoid sinuses that are composed of thin bony lamellas. They are divided into an anterior ethmoid and a posterior ethmoid sinus by the frontal portion of the ground lamella of the middle turbinate. In endoscopic sinus surgery the lamellas are dissected to gain access to the large sinuses and also allow ventilation and drainage and medication like nasal sprays to reach further into the cavities. In order to reach skull base in endoscopic skull base surgery the ethmoid lamellas are dissected as well as parts of the septum.

The ethmoid sinuses are an irregular system of mucous membrane-lined, pneumatized spaces that completely fill the ethmoid bone. They are only separated from each other by thin bony lamellae. A distinction is made between anterior and posterior ethmoid cells. Those cells whose mucous membrane is supplied by the anterior ethmoid artery, which open into the middle nasal meatus or the ethmoid infundibulum and lie in front of the frontal portion of the basal lamella of the middle turbinate belong to the anterior ethmoid sinus.

Those cells whose mucous membrane is supplied by the posterior ethmoid artery, which open into the upper (if present, uppermost) nasal meatus and lie behind the frontal portion of the basal lamella belong to the posterior ethmoid sinus [15,20,21].

The ethmoidal lamellae also from the middle and superior nasal turbinates. The ethmoid bulla, which protrudes against the ethmoid infundibulum, is also an ethmoid cell. Laterally, the ethmoidal cavity is confined by the papyraceous lamina. The roof is formed by the frontal bone, which lies over the cells. They are bounded posteriorly by the sphenoid bone. Medially, the ethmoidal lamellae are in topographical relationship to the olfactory fossa and the cribriform plate. Depending on its depth skull base injuries and CSF leaks are potential complications in sinus surgery, in skull base surgery however the access to anterior skull base lesions like esthesioneuroblastomas or olfactory groove meningiomas lies here [22,23].

The anterior ethmoidal artery, which normally runs in the orbitocranial canal, can cross the ethmoid cells here on its way to the intracranial region. Computed tomographic images provide information about the relationship between the ethmoid roof and the lamina cribrosa and possibly the course of the anterior ethmoid artery. Particular caution is required here during surgical interventions on the ethmoid bone. In continuation with the vertical lamina cribrosa lies the insertion of the middle turbinate. Due to the topographical proximity of the ethmoid cells to the orbit, an ethmoid cell can advance into the orbital floor in the case of pronounced pneumatization. These cells are called Haller's cells. Since the orbital floor is also the roof of the maxillary sinus, pronounced Haller's cells can obstruct the entrance to the maxillary sinus and lead to secondary maxillary sinusitis [24] .

The sphenoid bone represents the posterior border of the ethmoid sinus and can be accessed via that route. However, there is a possibility that the posterior ethmoid cells may develop laterally and even cranially to the sphenoid sinus.

These cells are called sphenoethmoid cells (Onodi cells), which can come into close anatomic proximity to the optic nerve and the internal carotid artery. The optic canal can even be completely surrounded by an Onodi cell. An attempt to surgically penetrate the posterior wall of the Onodi cell in the direction of the sphenoid sinus would, with high probability, injure the optic nerve. Thus, instruments should be directed inferior/medially to gain access.

The maxillary sinus is the largest sinus in humans. It lies in the maxilla and communicates with the nasal cavity through its natural ostium. In the maxillary sinus we distinguish a floor, a roof, a lateral and medial wall, a rounded posterior wall and an anterior wall. The shape of the maxillary sinus can be compared to a three-sided prism. The base of the prism is the floor of the maxillary sinus, the facies alveolaris. The roof of the prism corresponds to the orbital facies of the maxillary sinus and is thus the floor of the orbit. The lateral wall of the maxillary sinus points towards to zygoma. The medial wall of the maxillary sinus (facies nasalis) is the lateral nasal wall. The posterior wall of the maxillary sinus lies in the angle between the medial and lateral side of the prism. It is rounded and corresponds to the tuber maxillae (Facies tuberalis). It bulges into the infratemporal fossa - with its important nerves and vessels. The fossa can be reached here via the maxillary sinus in extended endoscopic approaches [25]. Opposite the facies tuberalis lies the anterior wall of the maxillary sinus. From the outside you can see the fossa canina (Facies fossae caninae). The maxillary sinus can be accessed from the outside via its lateral and lower quadrants.

The floor of the maxillary sinus borders the alveolar process of the maxilla and can also pneumatize it and form an additional recess. Here the maxillary sinus is in close contact with the roots of the second premolar and the first molar.

On the one hand, infections or fungal contamination of the respective root can ascend here into the maxillary sinus, on the other hand, so-called oroantral fistulas arise during tooth extractions because of the thin bone, which often even has dehiscences [26]. The roof of the maxillary sinus corresponds to the orbital floor. Here, the infraorbital nerve runs in the infraorbital canal, with its vessels that sensibly supply parts of the face. The lateral wall of the sinus is related to the proc. zygomaticus and can also pneumatize it as a recessus zygomaticus.
The medial wall of the sinus borders the nasal cavity. In its upper half we can see the natural ostium of the sinus. The maxillary sinus communicates with the nasal cavity through this opening over the ethmoid infundibulum [15].

The frontal sinus is located in the frontal bone (Os frontale) and is separated from the opposite cavity by a septum. The shape of the sinus and its size can vary. Due to the bony ridges protruding into the sinus it can have several niches. A frontal section distinguishes between a front wall, a posterior wall and a floor. The anterior wall of the sinus projects, depending on its extent, onto an area that can traced laterally from the root of the nose over the superciliary arc. The posterior wall borders the anterior cranial fossa with the frontal lobe of the brain. The floor separates the sinus from the nasal cavity medially. Here, its outflow tract is located. Laterally, the floor borders the orbital roof.
However, there is the possibility that the orbital roof is pneumatized in the dorsal direction starting from the sinus. In this case there are two layers of bone between the orbit and the anterior cranial fossa, namely the actual skull base and the roof of the orbit [27,28].

The sphenoid sinus (sinus sphenoidalis) is located in the body of the sphenoid bone (corpus ossis sphenoidalis). It is a paired sinus divided into two by an irregularly formed septum (septum sinuum sphenoidalium). The sphenoid sinus is the most posterior sinus. It has a topographical relationship to the nasal cavity, the nasopharynx and the interior of the skull.
The optic chiasm and pituitary gland lie above its roof. The cavernous sinuses are located laterally. Due to these topographical relationships of the sphenoid sinus, surgical interventions on the pituitary gland and beyond are possible in this way [29].
The development of the sphenoid sinus begins after birth from a dorsal recess of the sphenoidal concha. Pneumatization lasts from the age of six to the end of the growth period.
Depending on the extent of the sphenoid sinus, a distinction is made between small conchal, presellar and large sellar and postsellar types. The postsellar type is the most common.

In the conchal type there is a small cavity between the anterior wall of the body of the sphenoid bone and the pituitary pit, which, however, is not reached.
The presellar type extends from the anterior wall of the body of the sphenoid bone to the anterior wall of the pituitary fossa and extends caudally to the roof of the nasopharynx.
The sellar type extends dorsally to a vertical line that can be drawn through the anterior wall of the dorsum sellae. Finally, the postsellar type extends beyond this and pneumatizes the dorsum sellae.
The larger the sphenoid sinus, the wider access it offers during operations; on the other hand, important neighboring structures such as the optic nerve or the internal carotid artery are at risk during surgery which makes their identification and excellent imaging quality mandatory. The shape of the sphenoid sinus has six walls and can be compared to a cube.
The sphenoid sinuses on each side are separated from each other by the intersphenoidal septum which is also the medial wall. In most cases the septum is not oriented strictly median and vertical. Most of the time, one sphenoid sinus gains size at the expense of the other. The septa are often curved and can be configured in an “S” or “C” shape. There are also often secondary septa that subdivide the sinus irregularly. Due to the fact that there are various forms of septa, these must not be considered landmarks in surgical interventions, especially if there are significant deviations from the midline and the septum is inserted laterally in the area of the optic canal or the carotid.
With strong pneumatization in the median, anterior and lower directions, the sphenoid sinus can extend over the rostrum ossis sphenoidalis between the vomer and into the septum nasi forming a septal recess.
As a variant, the midline of the sphenoid sinus can be traversed by a median craniopharyngeal canal. It represents a non-obliterated connection between the epipharynx and the sellar region, through which the adenohypophysis migrates cranially out of Rathke's pouch during embryonic development. Therefore, the canal may contain ectopic pituitary tissue and meninges .
The anterior wall of the sphenoid sinus harbors its opening/ostium. It is made up of the body of the sphenoid bone and the sphenoidal concha.
The sphenoid sinus ostium is most often located in the top quarter of the anterior wall. In about 70% of the cases, the ostium is rounded and measures 2.43 mm in diameter. It is 14.6mm (8.9-23.1mm) from the anterior wall of the hypophyseal fossa. The ostium opens into the sphenoethmoid recess of the nasal cavity. If the endoscope is moved along an imaginary line between the anterior nasal spine and the middle of the middle turbinate, the ostium of the sphenoid sinus is reached. The length of this imaginary line is approximately 6 - 7cm [30].

With extensive pneumatization, the sphenoid sinus forms recesses in the neighboring structures. In this way, the sinus can extend from the anterior wall into the ethmoid bone. This bulge is known as the ethmoid recess, which can extend further to the orbit and even to the maxillary sinus.
If one tries to reach the maxillary sinus via the ethmoid bone (transethmoidal access route to the sphenoid sinus), one has to pay attention to the presence of Onodi cells. The sphenoid sinus is then not, as usual, behind the posterior ethmoid cell but, in relation to the Onodi cell, located medially and inferiorly.
These cells can have different configurations depending on their topographical relationship between the sphenoid sinus and the canal or optic nerve.
All Onodi cells have in common that they surround the optic canal from below, above and medially, which, per definition, additionally to the topographical relationship with the sphenoid sinus, distinguishes the Onodi cell from a normal posterior ethmoid cell. The anterior section of the floor of the sphenoid sinus forms the roof of the choanae. In the posterior part it borders the epipharynx and forms its roof. As a variant, two recesses of the sphenoid sinus can develop laterally from the floor. The expansion known as the palatine recess pneumatizes the orbital process of the palatine bone. The second bulge of the sphenoid sinus extends laterally into the orbital facies of the great wing of the sphenoid. It is called the inferior lateral recess. This extension rarely extends to the round and oval foramina. In extreme cases, the sphenoid sinus expands to the petrous apex. Here, cholesterol granulomas of the apex can be drained surgically through an endoscopic transsphenoidal approach [31,32]
The sphenoid sinus can extend laterally and below into the pterygoid process. This bay is known as the pterygoid recess.
The pterygoid canal is closely related to the floor of the sphenoid sinus. In 38% it is below the level of the sphenoid sinus, in 34% in its level and in 18% within the cavity. If the canal is at the level of the sinus floor or if it runs intrasphenoidally, its bone cover can be dehiscent. In this case, during surgical interventions on the sphenoid sinus, care should be taken to avoid any damage to the nerves that run through the canal (Nervi canalis pterygoidei or Vidian nerve) [33].
The posterior wall of the sphenoid sinus is part of the body of the sphenoid bone in the upper section and part of the clivus in the lower part, depending on its extent. This is why the connection between the sphenoid and occipital bones also lies here.

If the sphenoid sinus extends far into the clivus, one speaks of a posterior recess. The sphenoid sinus can pneumatize the posterior clinoid process posteriorly and upwards. This bulge is called the posterior superior recess.
The lateral wall of the sinus is entirely provided by the sphenoid bone. Its proximity to important structures like the cavernous sinus and the internal carotid artery makes it particularly important.

The cavernous sinus is a venous cerebral sinus surrounded by the dura mater. The sphenoparietal sinus and the ophthalmic vein open into it from the front. The cavernous sinus receives its drainage through the superior and inferior petrosal sinus that emerge from its posterior wall. The cavernous sinuses on both sides are connected by intercavernous sinuses, which run through the sella turcica in front of and behind the pituitary gland. They form a venous ring around the pituitary gland.
The sinus is traversed by connective tissue trabeculae and it appears to be divided into individual caverns, which is where its name arose from.
The internal carotid artery and cranial nerves run through the sinus. A frontal section through the sinus can be used to distinguish three walls: a roof, a lateral and a medial wall. All walls are made of dura mater which fuse at the bottom in a “v” shape.
The lower part of the medial wall borders the side wall of the sphenoid sinus. With severe pneumatization of the sphenoid sinus it can be very thin. In the upper half, the medial wall of the cavernous sinus borders the pituitary gland.
The roof of the sinus is set horizontally and is at right angles to the side walls. It separates the sinus from the middle fossa.
On its way through the cavernous sinus from caudal to cranial, the internal carotid artery shows different courses. Its course can best be described in the side view. The curves in the artery are called the carotid siphon. Depending on the number and characteristics of the curves, the siphon can be U-, S- or W-shaped. However, there are also more stretched courses of the carotid. The carotid artery is stabilized in the sinus by the connective tissue trabeculae inserting into it.
The lateral wall, in which important nerves run, separates the cavernous sinus from the middle fossa and the temporal lobe. From cranial to caudal, these are the following nerves: the oculomotor nerve (III), the trochlear nerve (IV), the ophthalmic nerve (V / 1) and the maxillary nerve (V / 2). The abducens nerve (VI) runs very caudally through the sinus lateral to the internal carotid artery. Except for the abducens nerve, which runs laterally next to the internal

carotid artery, the above-mentioned nerves lie in the side wall of the sinus and are surrounded by the dura mater.

The sequence in which these nerves exit the brain stem is reflected inside the sinus.

The oculomotor nerve enters the wall of the cavernous sinus laterally to the posterior clinoid process, runs alongside of it to reach the orbit through the superior orbital fissure [34].

The trochlear nerve enters the cerebellar tentorium before the sinus and thus runs a longer route through the dura mater. It also passes through the superior orbital fissure into the orbit, where it is crossed by the oculomotor nerve. There is a possibility that the oculomotor nerve may enter the dura of the sinus a little higher and then run into its roof. Then the trochlear nerve is also higher, in the angle between the lateral wall and the roof of the cavernous sinus.

The ophthalmic and maxillary nerves enter the dura of the cavernous sinus after their emergence from the trigeminal ganglion Meckeli and pass through it covered by a thin dural layer. The ophthalmic nerve enters the orbit through the superior orbital fissure. Here, the oculomotor nerve and the trochlear nerve approach it from above. The maxillary nerve leaves the cranial cavity through the foramen rotundum to enter the pterygopalatine fossa.

Finally, the abducens nerve runs through the cavernous sinus laterally next to the internal carotid artery in order to reach the orbit also via the superior orbital fissure. It enters the cavernous sinus at the apex of the temporal bone [35,36].

The trigeminal ganglion Meckeli lies lateral and dorsal to the cavernous sinus.

Depending on the width of the sphenoid sinus, the structures next to it bulge into its side wall and are visible from the inside.
From top to bottom, these are the optic canal, the internal carotid artery, and the maxillary nerve (V2). The pterygoid canal is still projecting on the floor of the sinus.
The optico-carotid recess (OCR) is located between the prominence of the optic nerve canal and the internal carotid artery [37].
The entire course of the internal carotid artery can be seen through the cavernous sinus on the side wall of the sphenoid sinus.

Figure 4: Endoscopic view into a right sphenoid sinus with *carotid artery and **optic nerve which protrude into the sinus as bulges and surround the ***optico-carotid recess.

The optic nerve and internal carotid artery must be identified during surgical interventions on the pituitary gland, as the opening of the pituitary fossa occurs medial to these key structures. The roof of the sphenoid sinus is indented by the hypophysial fossa or sella, making it higher in the front than in the back. The concavity of the sella creates a pit called the hypophysial fossa in which the pituitary gland lies. The surgical window to the pituitary gland and beyond is created on the anterior wall of the sella.

The sella region is part of the middle cranial fossa and comprises the following structures: the planum sphenoidale, the sella turcica ("Turkish saddle"), the pituitary gland, which lies in the fossa hypophysialis of the sella turcica, and the cavernous sinuses on both sides of the sella. The sphenoid sinus is located under the sella or pituitary gland and between the cavernous sinuses.

The sphenoidal plain is a thin plate of bone that forms the anterior roof of the sphenoid sinus. It is initially set horizontally and makes a slight caudal kink on the sphenoid limbus. On this sloping part it shows a notch, the sulcus praechiasmaticus. The sphenoid planum then runs more horizontally again and merges at the sellae tubercle at a 90 ° angle caudally into the sella turcica. On the sides the planum sphenoidale runs out into the processus clinoidei medii. The optic chiasm can lie in the prechiasmatic sulcus, although this name is then misleading. In most cases, the chiasm lies in front of the pituitary stalk (pituitary infundibulum). The sella turcica forms about half of the roof of the sphenoid sinus. It has a front and a rear wall and a floor. These walls merge into one another in a rounded manner and form a semicircle at the sagittal section that resembles a saddle.

The anterior wall is almost vertical and begins at the sellae tubercle, which forms the boundary between the planum sphenoidale and the sella. It then merges into the bottom of the sella, which is concave. The floor rises dorsally and forms the dorsum sellae. In contrast, to the anterior wall of the sella, the dorsum consists of solid bone and is part of the clivus. The dorsum sellae ends in the posterior clinoid process.

The following structures are found in the sella as standard variants: a sella spur, sellar bone bridges, a craniopharyngeal canal and a pituitary cistern which are not relevant in endoscopic transsphenoidal approaches [38].

1.4.1 Function of the nose and paranasal sinuses

The paranasal sinuses arise as protuberances of the main nasal cavity through bone resorption and pneumatization. The osteoclasts located in the mucous membrane or in the periosteum are responsible for the osseous resorption process.

Since the mucous membrane of the main nasal cavity develops into the sinuses, the mucosa of the paranasal sinuses is a continuation of the nasal mucous membrane. This also explains the common and similar reaction to exogenous noxae.

The paranasal sinuses maintain a connection to the main nasal cavity via their natural ostia or outflow tracts. The ventilation of the sinuses and the transport of secretions out of them take place through these openings. If these ostia are obstructed, e.g. due to inflammatory swelling of the nasal mucosa, the transport of secretions is inhibited, the cleaning function is impaired and finally, secondary sinus infection occurs.

The healthy sinuses are drained by the active transport of secretions from the ciliated epithelium. The epithelium of the paranasal sinuses is a multilayer, columnar ciliated epithelium, which is firmly fused with the periosteum of the skull and is thinner than the mucous membrane of the main nasal cavity [39].

The sinus mucus is continuously produced by seromucosal glands and intraepithelial goblet cells. It is configured in such a way that it consists of a viscous gel layer on the surface and a serous sol layer which lies underneath.

The cilia of the ciliated epithelium beat synchronously in the transverse and metachronous direction in the longitudinal direction with a frequency of 8 to 20 beats per second. This mucociliary transport ensures the flow of secretions and the cleaning (mucociliary clearance) of the sinuses [40].

The stroke of the cilia is divided into a fast phase and a slower recovery phase. Only during the former do the cilia briefly touch the gel layer. The rest of the time they are only in contact with the sol layer. In the fast stroke phase, the kinetic energy of the cilia is transferred to the mucus and the gel phase is moved like a carpet over the sol phase. Due to the surface tension, the mucous layer remains coherent.

The production of the mucus is mainly regulated parasympathetically. The nerve fibers reach the glands via the major petrosal nerve and the pterygopalatine ganglion where they switch. The corresponding nucleus is the nucleus salivatorius superior. The sympathetic innervation is given by the carotid plexus and the deep petrosal nerve, which connects to the major petrosal nerve in the pterygoid canal. The sympathetic fibers originate from the lateral horn (cornu laterale) of the spinal cord. The relationship between the sol and gel layers is also essential. With increasing viscosity and thickening of the sol phase, the cilia come into intensive contact with the gel phase. This disrupts their beat rhythm and they are too weak to transport the mucus. Apart from deviations from these parameters, the mucociliary transport is also impaired by other noxae such as cigarette smoke, dry air, medication (e.g. parasympatholytics) and foreign bodies.

Obstructions (e.g. swelling of the mucous membrane) in the area of the ostia also lead to an up-regulation of secretions. The viscous gel phase accumulates at the ostium and cannot be transported out. Impairments of the secretion flow favor the contact of the mucous membrane with allergens, viruses and bacteria, which in turn damage the mucous membrane and hinder the mucociliary transport [3,41].

The flow of secretions from the sinuses is always directed towards their natural ostia. Accessory ostia can occur in the maxillary sinus are ignored and bypassed. The mucus moves over these ostia like a carpet and covers it without entirely leaving the maxillary sinus. Parts of the mucus circulates between the natural and accessory ostium and gives the patient the feeling of a blocked nose and postnasal drip. Thus, it is important to unify these ostia surgically to prevent the circulation phenomenon. The natural ostium of the maxillary sinus is always tilted and can be identified that way. A better optical depth may facilitate the correct identification. In the worst case the surgeon creates an additional accessory ostium in the fontanelle and the problem persists in the so-called missed ostium phenomenon.

Furthermore, small mucosal lesions are easily bridged as long as the force of the cilia is sufficient and the gel layer is cohesive.

If two opposing mucosal surfaces come into contact, there is a synergy between both sides and the transport is not impaired. However, if there is greater pressure on the ciliary epithelium, such as inflammatory swelling, the transport is disturbed. This is why during FESS narrow anatomic passages are removed for regular mucus transport. If too much mucosa was removed the contrary happens and excessive scarring or synechiae would again hamper the transport. The correct identification of lamellae especially those opposing each other could prevent this problem. Here again, a better depth perception for the surgeon could be of great advantage.

Furthermore, neuropeptides such as substance P should also be involved in the regulation of secretion production [42].

Under normal circumstances, secretion transport and production are never interrupted. The maxillary sinus renews its mucus every 20 to 30 minutes.

The best conditions for unhindered transport are: good blood circulation, a temperature of approx. 33 ° C, good ventilation / humidification and a pH between 7 and 8 [43].

1.5 Standard endoscopic technique for paranasal sinus and skull base surgery

1.5.1 Approaches to the paranasal sinuses

The most common reason to indicate FESS is chronic rhinosinusitis (CRS). Generally spoken, this disesase can be divided into two phenotypes: chronic rhinosinusitis with (CRSwNP) and without nasal polyps (CRSsNP). The prevalence of this disease in Europe is around 10% with regional fluctuations from 6.9 to 27.1% [44]. In comparison, around 2.2% of Austrians have had a heart attack in their lifetime and around 5% suffer from diabetes that deserves treatment. According to the European guidelines of the European Rhinological Society (EPOS) one speaks of chronic sinusitis if the disease lasts longer than 12 weeks and has at least two of the following symptoms: nasal congestion, runny nose, Face pain / pressure or decreased odor [3].
For diagnosis, one of the symptoms must be either a stuffy nose or a runny nose. The diagnosis is made on the basis of a detailed medical history, clinical symptoms, nasal endoscopy or is made using computed tomography (CT). The CT shows what is known as a “white-out”: shading of the sinuses of different degrees, from peripheral swelling to complete opacification of all sinuses. In the past, there was a clinical distinction between two forms of CRS: those with nasal polyps (CRSwNP) and those without nasal polyps (CRSsNP). Cystic fibrosis or Kartagener's syndrome with dyskinesia of the cilia of the nasal mucous membrane are among the diseases that clinically present the picture of CRSwNP, but must be differentiated from them. With CRSsNP, tight anatomical conditions in the area of the drainage system of the paranasal sinuses often lead to chronic (recurrent) inflammation of the nasal mucosa. If the administration of nasal steroids for at least 1 month with / without nasal rinsing does not bring any improvement, the CRSsNP is usually treated by endoscopic sinus surgery, in which the drainage paths of the sinuses are widened. The principle of surgery is to restore the natural excretory ducts and openings - as far as possible - in a functional and minimally invasive manner. As a first step the uncinate process is dissected to open the ethmoidal indundibulum. Then the ethmoidal bulla is resected and the frontal portion of the basal lamella of the middle turbinate is seen whose penetration leads into the posterior ethmoid. The ethmoidal lamellae are resected until skull base and orbital wall (papyraceous lamina) are exposed. The anterior wall of the sphenoid sinus is displayed and penetrated in an inferior/medial fashion not to run into optic nerve and/or carotid artery. Skull base is then followed anteriorly and the frontal recess is dissected and the frontal outflow tract opened in order to ventilate and drain the sinus.

From the ethmoidal infundibulum and behind the former uncinate process the natural maxillary sinus ostium is exposed and enlarged if needed.

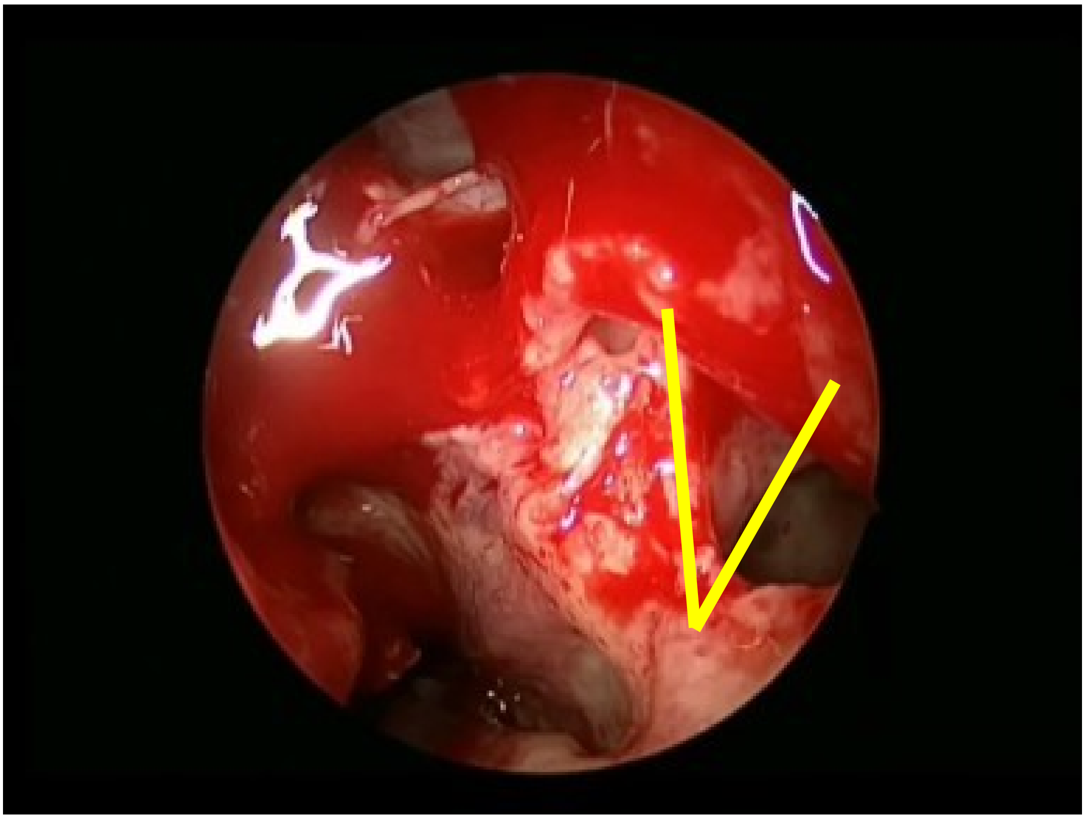

Figure 5: View onto the natural maxillary sinus ostium (on the left) after resection of the uncinate process and bulla (infundibulotomy). The yellow bars indicated that the natural ostium is always tilted from superior lateral to inferior medial and never strictly sagittal.

Because of the close dissection to critical structures an optimal optical quality of the endoscope and camera are mandatory to avoid complications. Because of the 2D, image depth cannot be visualized but is mostly determined by haptic feedback. Particularly, the niches in the ethmoid adjacent to the orbit as as well as the anatomic structures in the sphenoid (OCR) could better be identified in a 3D setting which is the aim of this study.

Due to the intervention in the anatomy and opening of the natural ventilation and drainage pathways of the sinuses, this form of CRS can be mostly cured. Follow-up treatment with nasal rinses or administration of nasal steroid sprays can be carried out after the operation. In most cases, a final result can be expected after about 1-3 months and nasal steroids and nasal rinses can then be discontinued at the latest. In some forms, the underlying mechanism is more complex and involves increased remodeling of the mucosa and submucosa. This inflammation is Th1-mediated and dominated by neutrophils. Cytokines such as IFN-γ and TGF-β are also involved. In individual cases, the follow-up treatment can be extended or the success rate reduced and a revision may be necessary. With these revisions, there can be a maximum expansion of the access routes, although the mucous membrane and important structures such as the turbinates should be spared. In addition to this and anatomical causes, there are also simpler forms of CRSsNP with a trigger such as an infected tooth of the so-called odontogenic sinusitis (especially the maxillary sinus affected), the presence of a fungal ball (usually Aspergillus) or a reactive (single) polyp such as the antrochoanal polyp, which arises from the maxillary sinus. Eliminating the cause then leads to the healing of the sinusitis.

Chronic sinusitis with polyps (CRSwNP), on the other hand, is a complex, systemic immunological disease, the cause of which is still not clear [45]. If topical and / or systemic therapy does not lead to improvement for at least 1 month and / or deterioration occurs again after discontinuation, especially of systemic steroids, an operation is indicated. From a clinical point of view, however, recurrences occur very frequently (around> 50% in some studies) even after surgical rehabilitation of the adrenal cavity (including removal of the polypoid nasal mucosa), which in turn must be treated with drugs and surgically Although important factors such as recurrent (viral) inflammation, environmental pollutants, immunological reactions including allergies, asthma, expression of epithelial and subepithelial inflammation mediators, tissue eosinophilia, staphylococcal colonization, etc., which seem to contribute to the development of CRSwNP, are still a single trigger not known. In contrast to CRSsNP, around 75% of those affected in Europe are Th2-mediated inflammation in which a large number of cytokines such as IL-4, -5 and -13 play a role. Recently, the epithelium itself was discovered to play an important role and attention has been paid to other mediators such as IL-33 and TSLP. This underlines the complexity of this disease and the importance of its endotypes (at least 10 different ones have been described for sinusitis), which repeatedly leads to the discovery of new metabolic processes and deviations from the pure phenotypes, which only differentiate between the presence of polyps as diverse as the disease is, this clinical picture also requires a multimodal therapy concept. It is important to inform the patient that - if necessary - functional, endoscopic sinus surgery (FESS) does not cure the disease and that permanent improvement cannot be guaranteed.

1.5.2 Approaches to the skull base

Contrary to the paranasal sinuses the purpose of approaches to skull base is not to gain access to the sinuses for inflammatory diseases but to use them as well as the nasal cavity as “highway” to the skull base. Here the most common indication are pituitary adenomas followed my craniopharyngeomas and meningeomas [7]. These complex interventions are usually performed in a 4-handed technique were ENT and neurosurgeons work together throughout the operation. The task of the ENT surgeon is to create a transnasal, transsphenoidal access route to the pituitary gland. The ENT surgeon looks into the patient's left nasal cavity with an 0° endoscope to find the natural ostium of the sphenoid sinus. This is achieved by guiding the endoscope along an imaginary line that connects the anterior nasal spine with the middle of the concha nasalis media. The angle between the nasal floor and the endoscope shaft is approximately 30 °.

The surgical field lies in the common nasal meatus and the sphenoethmoid recess. The turbinates, the nasal passages and the ethmoid bone remain untouched.

If the turbinates obstruct the view and / or the path to the sphenoid sinus, they can be moved laterally with the help of a freer elevator.

After the sphenoid sinus ostium has been found, adrenaline swabs are inserted here to reduce the swelling of the mucous membrane and achieve good vasoconstriction. The same procedure is then carried out on the opposite side.

After removing the swabs, the natural sphenoid sinus ostium is expanded with a circular punch. The ostium is first widened medially in the direction of the septum and then in the caudal direction. This can lead to bleeding, as branches of the sphenopalatine artery run here. To avoid damage to the arteries a mucosal flap including the vessels is created and deflected. After the ostium has been sufficiently expanded, the same steps are done on the opposite side.

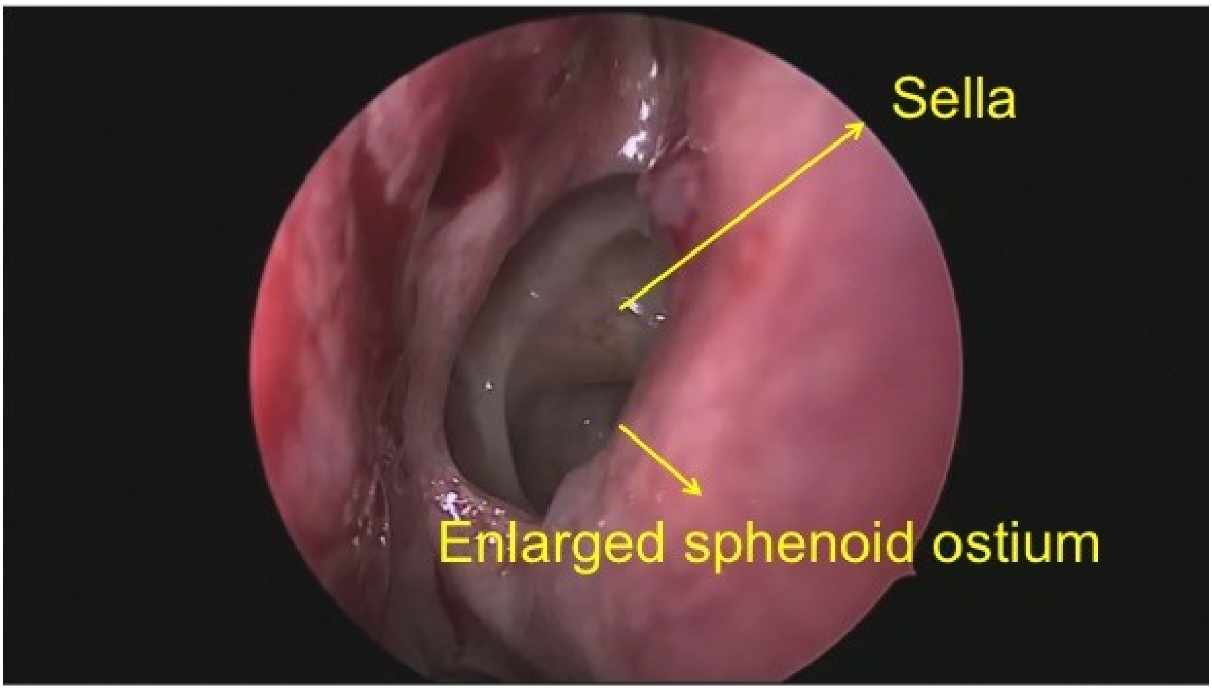

Figure 6: Endoscopic paraseptal view into the sphenoid sinus with the sella (and clivus below) via the enlarged natural sphenoid ostium on the right.

After the sphenoid sinus ostia have been enlarged on both sides, the nasal septum is incised with a sickle knife in its superior and posterior part (ethmoidal part) without damage to the vomer to maintain normal airflow within the nose. The incision is usually made about an inch in front of the sphenoid rostrum at the level of the enlarged sphenoid sinus ostia.

The septum is incised with a sickle knife and cut with the cut surface parallel to the septum, first cranially and then caudally. You can now look through the opening into the patient's left nasal cavity. The septum is resected from here with a cutting instrument in the direction of the sphenoid rostrum.

To widen the septum window, additional instruments such as side cutters, back-biters or punches according to Hayek can be used.

The aim is to create a large access to the sphenoid sinus that offers enough space to then remove the adenoma using the four-handed technique. This is achieved by removing the sphenoid rostrum and resecting the bone cranially in the direction of the planum sphenoidale and caudally to the floor of the sphenoid sinus. The sphenoid planum merges with the hypophysial fossa at the sphenoid tubercle. This is a danger zone because the dura of the sella diaphragm inserts into the tuberculum sellae and if it is injured it can lead to CSF fistulas.

After removing the anterior wall of the sphenoid sinus, one gains a good overview of the sphenoid sinus, the intersphenoidal septum and - with appropriate expansion - also of the

protrusion of the sella floor caused by the tumor. The bulges of the internal carotid artery and the optic nerve as well as the optico-carotid recess should also be found.
The next step is to remove the intersphenoidal septum down to the floor of the sella. This is done with cutting instruments. After a free access to the sella floor has been created, the neurosurgeon opens the sella floor. This is usually done with cutting instruments. Then the tumor is removed with diverse grasping, cutting and aspirating instruments. If the bone is too thick chisels or even drills need to be applied. In case of superior extension of the tumor or transplanum approaches in cases of meningeomas the dura is incised to gain access to the lesion iatrogenically causing a CSF-leak. Since the sella and skull base bone had been removed it cannot be used for reconstruction of the skull base. Thus, the aim of this study is to evaluate piezoelectric techniques where bone is preserved and can be used for nature-like reconstruction of skull base with potential reduction of postoperative CSF-leaks.

1.5.3 Indications for approaches to skull base: pituitary adenomas

Pathological changes in the pituitary gland cause under-function (hypopituitarism) or over-function (hyperpituitarism). The disease then manifests itself due to decreased or increased hormone release and their effects. In most cases, the over-functions are benign hormone-producing adenomas of the pituitary gland. If the peripheral endocrine gland fails (e.g. st.p. thyroidectomy), increased plasma hormone levels are found due to the lack of negative feedback.
Increased hormonal activity of the pituitary is almost always due to a hormone-producing adenoma. Pituitary adenomas account for 85% of all skull base lesions operated at the Department of General ORL, Head and Neck Surgery at the Medical University of Graz. Less commonly is a disorder of the hypothalamus with increased secretion of releasing hormones. At 10-15%, adenomas are among the most common intracranial tumors. An adenoma with the size of <10mm is called a microadenoma and a size> 10mm is called a macroadenoma [29].
The tumors can usually be clearly demarcated from healthy parenchyma. A capsule is rarely formed [46]. If so gentle dissection around the adenoma and along the capsule should be attempted for an in-toto resection.

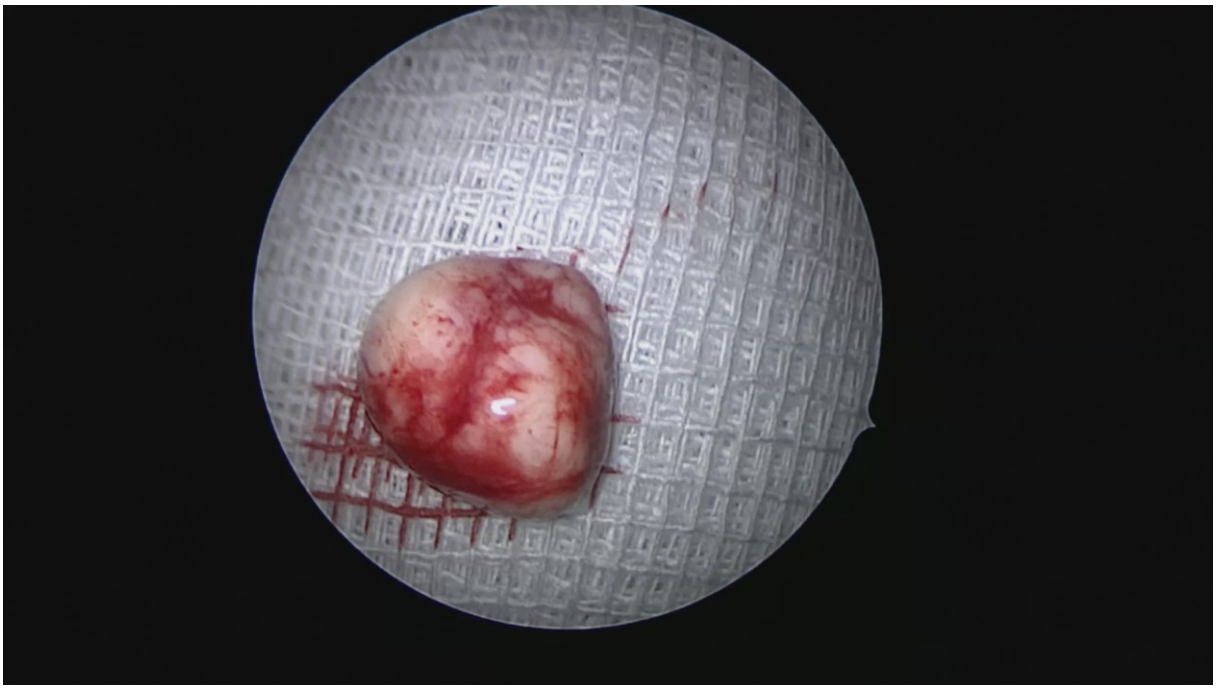

Figure 7: Rare case of an encapsulated pituitary microadenoma with in-toto resection.

Their surface is red-brownish in color, lobulated and their consistency is soft. Large adenomas often show ischemic necrosis and pseudocysts. The remaining parenchyma of the pituitary gland is normal, compressed (partial hypopituitarism) or completely destroyed (panhypopituitarism), depending on the size of the adenoma. Pressure on the pituitary stalk can also result in partial hypopituitarism.

Aggressively growing adenomas can widen the sella (CT), the clinoid processes erode or grow into the surrounding structures (cavernous sinus, sphenoid sinus, hypothalamus). In case of eroded bone in the sella floor the dura may be exposed or the bone is thin such as there is no bone flap to be harvested.

When the optic chiasm is under pressure from an adenoma this results in heteronymous bitemporal hemianopsia. There is rarely an increase in intracranial pressure due to compression of the 3rd ventricle. In addition to these local manifestations, depending on the hormone produced, generalized symptoms can also be seen as a result of the action of the respective hormone [47].

1.5.4 Complications of endoscopic sinus and skull base surgery

The main complications include cerebrospinal fluid leaks, injury to vessels, and injury to nerves. CSF-leaks in sinus surgery result mainly from injury to the cribriform plate. Here, the bone is thinnest and the middle turbinate is attached. On the way to the frontal sinus if instruments are oriented too far medially this thin bone and dura can be penetrated [22]. For skull base surgery the sella diaphragm is a weak area within the dura.

A predilection site for this is the planum sphenoidale, which merges into the fossa hypophysialis at the sella tubercle. The diaphragm inserts into the tubercle and can be injured in the case of excessive resection of the sphenoid rostrum or curettage in this area. The CT images provide information about the expansion of the tumor in this area and the thickness of the bone. Small CSF-leaks are usually closed by putting restorable collagen packing in surgical cavity. If the situation is unclear or a high-pressure leak occurs, the application of a lumbar drainage is recommended. Larger CSF-leaks must be treated surgically. This is done with a fascia lata graft from the thigh, fat plugs, local mucosa flaps or nasoseptal flaps [8].

Bleeding occurs when the blood vessels in the operating area are damaged. Branches of the sphenopalatine artery run along the sphenoid rostrum. If the sphenoid sinus ostium is enlarged, these branches can be injured. Bleeding from these branches or excessive oozing bleeding of the mucous membrane can be treated with an electrocautery. In case of an anticipated nasoseptal flap these vessels need to be spared by creating a small mucosal flap which is deflected inferiorly in order not to compromise the flaps vasculature [48].

The intercavernous sinuses, which connect the two cavernous sinuses, run across the sella. In the case of large adenomas, these are mostly obliterated by tumor compression and there is little risk of bleeding. However, if bleeding does occur, it is stopped postoperatively by intrasellar pressure.

Life-threatening bleeding occurs when the internal carotid artery is injured. Using the CT and MR images, the course, the position in relation to the surgical field and the relationship to the tumor should be studied preoperatively. Intraoperatively, with the help of the navigation system, the position of the instruments in relation to the artery can be determined in order to maintain the necessary safety distance or to identify the course of the vessel. In case of carotid injury bleeding packing is not possible in an open skull base since the blood would run intracranially. Interventional radiology must be in stand by. As temporary measure crushed muscle form the neck could be placed over the damaged carotid to stop the bleeding until interventional radiology is ready [49].

Nerve lesions in this area affect the optic nerve and the cranial nerves running in the cavernous sinus.

As with the carotid artery, imaging and navigation can be used to determine the location of the optic nerve and avoid injury. As a general rule lesions expanding lateral to the optic nerve must not be addressed by a transnasal endoscopic approach.

The nerves running in the cavernous sinus are particularly at risk during parasellar expansion of the adenoma and infiltrative growth.

1.6 Novel adjuncts in endoscopic sinus and skull base surgery

Two technical aspects in endoscopic sinus and skull base surgery are essential for successful procedures: instrumentation and visualization. Here, the most important innovations take place to develop the possibilities for accesses and safety further. The most recent advances have been made in piezoelectric techniques and high resolution 4K 3D camera systems. For piezoelectric techniques the Department of General ORL, Head and Neck Surgery pioneered the development of specialized tips with which endonasal craniotomies are possible [11]. With this instruments bone can be spared and flaps can be created where earlier the bone had to be cut or drilled away and its resulting loss lead to reconstruction at skull base refraining from a natural bony barrier which as missed abutment may lead to postoperative CSF-leaks.
With regard to enhanced imaging techniques the 3D technology offers a natural three-dimensional view of the surgical field. Contrary to 2D –which was the major criticism by microscope users in the early endoscopic era- a better depth perception and identification of structures were postulated. These aspects should improve teaching young surgeons and provide more safety for advances surgeon avoiding to run into critical endonasal structures with subsequent complications.

1.6.1 Piezoelectric effect and application for surgery

The Piezoelectric effect is used because of material asymmetry that converts electric energy into physical deformation. If pressure is applied on organic materials movement is stimulated in the dipole moment and a flow of charges when crystals are aligned generating vibrations in the material which disintegrates it. The organic piezoelectric effects in the human body are due to asymmetry in biological molecules [50]. Proteins in the body mainly exert the piezoelectric effect. Amino acids which are the building blocks of proteins contain dipoles in their polar groups which then are set in movement and reorientation of the charge that exerts stress and vibration. Collagen, elastin and keratin belong to connective tissue where the effect is used. Collagen fibers –which are the main component of bone- are rearranged by piezoeffect because there is an intrinsic piezoelectric heterogeneity within the fibre coinciding with the periodic variation of gap and overlap regions [51].

Thus, in surgery, piezoelectric devices, are used to cut bone by micromovements of the oscillating device that are transferred into the mineral tissue without damage to soft tissues like dura mater of the brain. Classical instruments such as a chisels, hammers or rotating saws and drills are more invasive not only destroying the bone but also damaging the soft tissues around and underneath it. Hard tissues, such as mineralized bones are disintegrated by frequencies of 25–39 kHz, whereas neurovascular structures are cut at frequencies higher than 50 kHz. There are no macrovibrations that cause discomfort to the patient or disturb / harm the surrounding tissue [52]. The tip oscillates in a linear direction, and covers a distance of 60–200 μm [53].

1.6.2 Three dimensional endoscopy

The introduction of endoscopy transformed visualization of the surgical field, allowing minimally invasive surgery contrary to previously major open approaches with related comorbidities. These were either performed with indirect light sources or microscopes which both provided binocular vision, depth perception and consequently the accurate recognition and management of relevant structures which endoscopes did not. Experienced endoscopic surgeons overcome lack of depth perception using visual and haptic feedback, as well as detailed knowledge of anatomy [54]. Three-dimensional (3D) endoscopy has been introduced to functional endoscopic sinus surgery (FESS) with the aim to provide real-time depth perception that should improve surgical outcomes and reduce complications. Depth perception is permitted by the interpretation of intuitive clues and stereopsis. Stereopsis is the perception of depth produced by the reception of visual stimuli from both eyes which is integrated in the neocortex in the optical centre of the occipital lobe. Stereoscopic vision permits better visualization of curvature and texture of structures, which is important in the sinuses and skull base with its delicate and also irregular shaped structures bulging into the surgical field. The currently developed technology uses mainly dual chip-on-the-tip scopes in which two video chips create two digital images that are projected onto a screen. Polarizing eye-glasses project a different image to each eye which are “put together” in the brain [14,55]. A disadvantage is that the use of polarizing screens and glasses may cause discomfort to the surgeon from nausea to vertigo. Moreover, since some screens filter around 75% of light out a dark background environment is required which of course hampers the overall OR team in fulfilling their tasks. These are the major ergonomic shortcomings of 3D endoscopic technology which need to be thoroughly evaluated to allow improvements in further development [56].

2. Material and Methods

2.1 Patients

For part one of the study fifteen patients (7 male and 8 female) were enrolled in this study with a mean age at surgery was 50 years (SD: 16.6). All patients were referred to our department for pituitary surgery and were enrolled in this study if an endoscopic transnasal approach was indicated with the following inclusion criteria: age >18 years, no other significant co-morbidities, no participation in other studies and intact bone at the sella (determined through preoperative CT).
All patients were operated via a transnasal endoscopic approach using piezoelectric surgery (Synthes Gmbh Piezoelectric System, Satelec, Merignac cedex, France, CE 0459) to harvest bone flaps to access the sella and for later reconstruction. This was possible without breaking the bone, which was repositioned after the intervention and covered by mucosa. The mucosa was dissected off the sella and placed laterally before opening the bone. A mucosal or periosteal bridge (with only the bone thinned out by the piezotome) was preserved serving as a "swinging door" to preserve the vessels supplying the bone. The dura was not injured by the piezoelectric osteotome. The loss of bone in the incision lines (<1 mm) was minimal. Throughout the procedure excellent endoscopic visualization could be achieved as constant irrigation to allow the piezoeffect had an additional cleansing effect of the endoscope lens. Both, the suction and the piezoelectric device could be maneuvered by the neurosurgeon with enough space for manipulations intranasally while the ENT surgeon was guiding the endoscope. No limitations regarding maneuverability were experienced and surgical freedom was not impaired as long as the endoscope's lens remained clean.

For part two of the study 20 patients diagnosed with chronic rhinosinusitis without polyps (primary, diffuse non Type 2 CRS) without prior surgery but refractory to conservative treatment were included according to EPOS2020 [3]. Following inclusion criteria were applied: age >18 years, no previous sinus operations, bilateral disease, no severe comorbidities such as bleeding disorders of systemic diseases. A bilateral FESS procedure was performed, one side with the 2D-endoscopic technique, the other side with the 3D-endoscopic technique which was randomized by means of an electronic randomization programme. One side was performed with the standard KARL STORZ 2D/HD endoscopic camera whereas the other side is operated with the new 3D endoscopic camera devices (TIPCAM®1 S 3D, 30°, 4 mm; TIPCAM®1 S 3D, 0°, 4mm, Karl Storz GmbH).

2.2 Parameters evaluated

For part one following parameters were evaluated: age, diagnosis, size of the adenoma (maximum diameter in centimeters), success of piezoelectric surgery (yes/no) if an intact bone flap
could be dissected, state of the dura after harvested bone flap, size of the bone flap (in square millimetres), time for surgery and time for piezo application, intra- and postoperative complications, pre- and postoperative visual analogue
score (VAS) for nasal blockage, post-nasal drip and smell. The size of the bone flap (in mm^2) was determined with electromagnetic navigation (shape tool by Fiagon, Berlin, Germany). All patients were followed up 3 months after surgery with VAS scores, clinical examination, nasal endoscopy and CT scan to evaluate
bony recovery. Postoperative VAS was scored from 0 (best) to 10 (worst). Bone structure of the skull base was evaluated on postoperative CTs by a three-staged score:
1: complete bony recovery with intact sella floor
2: partial bony recovery with small detectable defects
3: no bony recovery with major decalcified defect.

For part two a questionnaire was completed by the surgeon judging the subjective impression of visualisation and handling after surgery. Moreover, the time of duration for the procedure using the 2D-endoscope and the 3D-endoscope was measured per side.

3D Endoscopy compared to 2D Endoscopy in Functional Endoscopic Sinus Surgery

Reference: 2D HD Endoscope = 3 points
Rate on a scale of 1-5 (1 = much worse, 2 = worse, 3 = equal, 4 = better, 5 = much better)

	Ethmoid Sinus	Maxillary Sinus	Sphenoid Sinus	Frontal Sinus
Imaging				
Recognition of Details / Anatomical Understanding				
Color Brilliance				
Illumination				
Image Distortion				
Size of Field				
Depth Perception				
Fogging				
3D Effect				
Usability				
Intraoperative Handling of the Camera / Efficiency of Surgical Movements				
Ergonomics / Changing of Endoscopes				
Weight of Endoscopes / Camera				
Nausea				
Dizziness				
Headache				
Positioning of Endoscope (angled View)				
Time for preoperative Preparation				
Conflict with Instruments				
Lens cleaning Effort				
Time for Preparation 2D				
Time for Preparation 3D				

Figure 8: Questionnaire about feasibility of 3D endoscopy evaluating imaging and usability.

The questionnaire comprised 20 questions with an ordinal scale from 1-5 where 1 meant that 3D was much worse than 2D and 5 meant that 3D was much better than 2D.

2.3 Statistics

Statistical evaluation was performed using IBM SPSS Statistics 22, Armonk, NY: IBM Corp. All values are presented as means and standard deviation (SD), ranges and percentages. Wilcoxon test was applied to test pre- and postoperative differences in VAS scores. Student t-test was used to calculate time for surgery. Mann-Whitney-U test was used for imaging and usability scores. A P-value of <0.05 was considered statistically significant.

2.4. Ethical statement

The institutional review board of the Medical University of Graz approved the study: Approval number 27-090 ex 14/15 (part one) and 29-619 ex 16/17 (part two). Informed consent was obtained from all patients.

3. Results

3.1 Part one

All patients were diagnosed with a pituitary adenoma with a mean size of 1.9cm (SD: 0.6). In all patients (N=15) piezoelectric an intact bone flap could be harvested successfully and the dura remained intact. The mean size of the bone flap was 55.9 mm^2 (SD: 20.1) which was sufficient in all cases. Mean time for piezoelectric craniotomy to harvest the bone flap and expose the dura was 4 min 22 sec (SD: 165 sec). Mean total time for surgery was 90 minutes (SD: 22.8 min) which was significantly (p=0.002) lower compared to our standard surgical procedures (mean: 112 minutes, SD: 82.8 min).
After the removal of the adenoma Spongostan® for hemostasis was placed into the sella. In 14 patients the dural flap was replaced, the bone flap was reinserted and fixed with autologous fibrin glue Vivostat®, without any additional resorbable material or packing inside the nose. In one patient (with microadenoma) stronger bleeding form the cavernous sinus occurred, thus the bone flap had to be additionally fixed with Oxicell®. Two iatrogenic CSF-leaks occurred intraoperatively because of far suprasellar extension of the adenoma, one was fixed with Tachoseal® the other one with fascia lata. No postoperative CSF-leaks occurred.
Upon follow-up (3 months after surgery) nasal endoscopy revealed normal mucosa and re-epithelialisation of the sella floor and anterior wall of the sella in 13 cases. One case was lost to follow-up and one case showed crusting and remnants from resorbable material after intraoperative fixation of cavernous sinus bleeding. In 12/14 patients a stage 1 status of the bone flap could be seen upon CT which means complete bony recovery with intact sella floor
Postoperative VAS scores for nasal blockage and post nasal drip were not significantly different comparing pre- to postoperative status. VAS for smell was significantly higher.

	N	%
Stage 1	12	86
Stage 2	2	14
Stage 3	0	0

Table 1: Stages of bone flap status 3 months postoperatively.

	preoperative		postoperative		p-value
	mean	SD	mean	SD	
VAS nasal comfort	0.17	0.58	0.33	1.15	n.s.
VAS post nasal drip	0.15	0.55	1.08	2.36	n.s.
VAS smell	0.07	0.27	1.21	1.81	0.046

Table 2: pre- and postoperative VAS scores and level of significance.

3.2 Part two

In 20 patients the mean overall score for imaging properties was 3.22 (SD: 0.46) with a slight preference for 3D endoscopy. For usability properties the mean overall score was 2.91 (SD: 0.1) with a slight preference for 2D endoscopy. In detail 3D endoscopy scored best in depth perception (mean: 3.6) followed by 3D effect (mean: 3.4) and recognition of anatomic details as regards imaging properties (Figure 9).

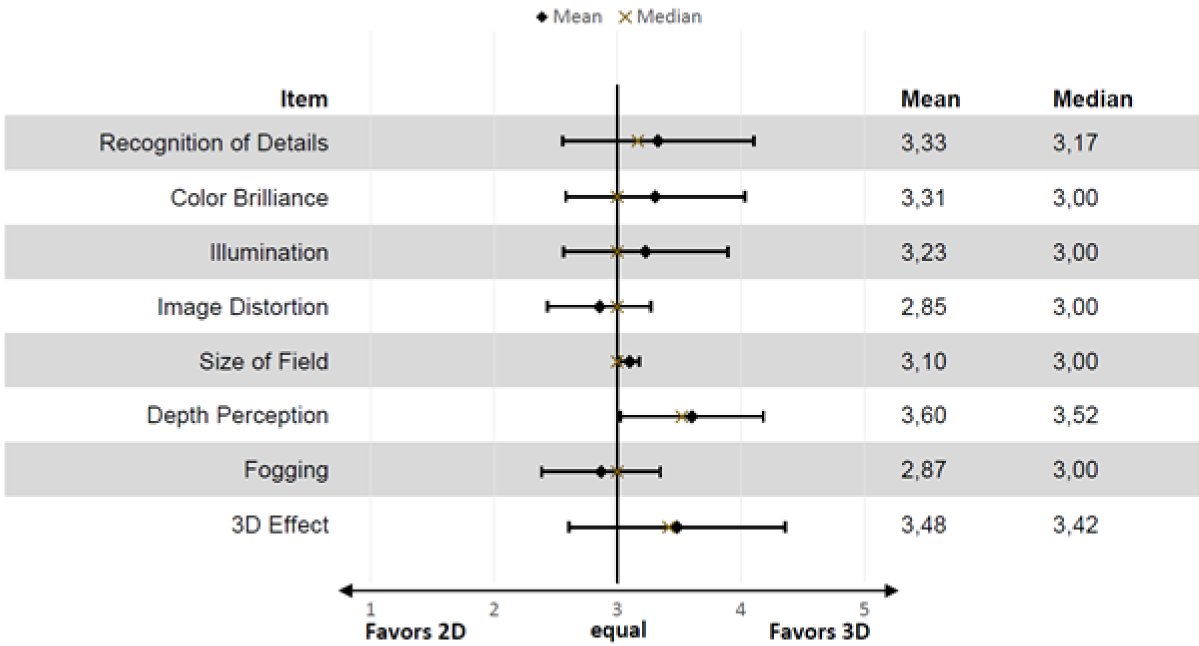

Figure 9: Modified forest plot indicating the detailed scores for imaging properties comparing 2D to 3D endoscopy where a score of 3 meant equal performance.

When analyzing the imaging properties for all sinus separately the ethmoid sinus scored best with a mean depth perception score of 3.95, 3D effect of 4.0 and recognition of details of 4.1 (Table 3 a and b). Contrary, the maxillary sinus scores worst with a mean score of 2.8, 2.6 and 2.3 respectively for the three correlating features.

Imaging property	**Mean**	**SD**
Recognition of Details	4.1053	.99413
Color Brilliance	3.6316	.76089
Illumination	3.2632	.45241
Image Distortion	2.8421	.68825
Size of Field	3.1053	.31530
Depth Perception	3.9474	.97032
Fogging	3.0526	.62126
3D Effect	4.0000	1.20185

Table 3a: Detailed imaging properties for the ethmoid sinus.

Imaging property	Mean	SD
Recognition of Details	2.3333	.76696
Color Brilliance	2.8333	.70711
Illumination	3.1111	.47140
Image Distortion	2.8333	.51450
Size of Field	3.1111	.32338
Depth Perception	2.8333	.51450
Fogging	2.8889	.47140
3D Effect	2.6667	.76696

Table 3b: Detailed imaging properties for the maxillary sinus.

In detail 3D endoscopy only scored better in weight of the endoscope (mean: 3.28, SD: 0.44) analyzing usability properties. 2D was superior in positioning the endoscope, nausea and lens cleaning effort (Figure 10).

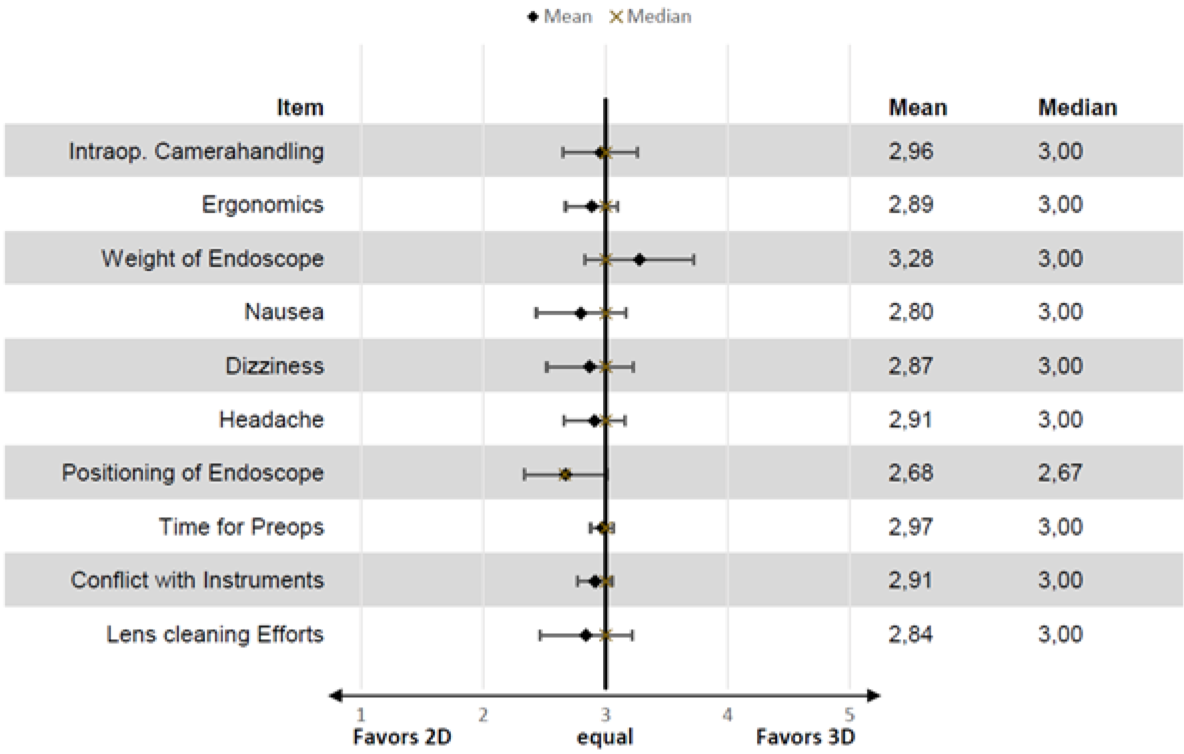

Figure 10: Modified forest plot indicating the detailed scores for imaging properties comparing 2D to 3D endoscopy where a score of 3 meant equal performance.

The mean duration of surgery was 16.4 (SD: 7.4) minutes for 2D and 13.1 (SD: 6.1) minutes for 3D ($p<0.05$). When time was adjusted per sinus operated mean time for 2D was 6.25 (SD: 3.45) minutes and 4.96 (SD: 2.68) for 3D. Adjusted time was analyzed since not in every single patient (N=20) all sinuses were operated/approached and surgery was tailored according to pathology and affected sinuses.

4. Discussion

Phillip Bozzini invented the endoscope in 1806. It looked like tea can and was made out of metal. The funnel of the “can” was a thin tube that was inserted into the body, the handle also had a hole to look through and the light was provided by a candle where fumes drained superior through a “chimney”. This first endoscopic device was used for cystoscopy and later stimulated other inventions for endoscopy of other organs. The biggest challenge was the light source which with candle light naturally is limited and later electric light bulbs were used creating heat which gave large discomfort to the patient. It was in the 1950’s that Hopkins and Storz came together to combine their technologies: a cold light fountain with glass rod fibres illuminated by an extracorporal light source and a rigid endoscope long and thin enough to be placed inside the nose [57].

The idea of nasal endoscopy was picked up by Walter Messerklinger in Graz who found out that mucus transport inside the sinuses followed a genetically determined pathway and is – under healthy conditions- always directed towards the sinuses natural ostia or outflow tracts. With the endoscope he was able to visualize the important drainage pathways and saw that obstructions there lead to subsequent inflammation [58]. Since these obstructions were mainly due to opposing mucosal surfaces inside the crucial zones like the ostiomeatal complex (OMC), a region in the ethmoidal infundibulum where frontal, maxillary and anterior ethmoid sinuses drain, the surgical removal of certain lamellae would relief these obstructions and guarantee ventilation and drainage of the adjacent sinus. The development of delicate instruments that would fit inside the nose in addition to angled scopes that made a view around the corner possible lead to the development of FESS that followed the principles of minimally invasive surgery only removing obstructing anatomic structures but leaving the mucosa as functional organ of the nose intact. The combination of that technique together with the growing knowledge about sinus drainage anatomy furthermore preserved the natural outflow tracts refraining from creating mega openings into the sinuses routinely that were dysfunctional [1,2,21].

Before FESS, access to the maxillary sinus was either created by inferior meatal punctures to drain e.g. abscesses or external approaches via the canine fossa named after Caldwell Luc [59]. For inferior meatal punctures the primary success rate was satisfying after pus was drained, however the mucus passed the artificially created opening and re-infections were possible. For Caldwell Luc approaches a bone window was created in the maxillary bone’s anterior wall (the

canine fossa) or a puncture was performed. Complications of that approach were that since the mucosa was stripped entirely the sinus was dysfunctional and even obliterated. It also led to osteomyelitis of the jaw and potential deformities of the cheek or numbness of the latter [60].
For the frontal sinus external osteoplastic operations were applied where the sinus was opened through a trans-eyebrow approach. The sinus was cleared from mucosa and in some cases obliterated or even cranialized (Riedel, Janssen-Ritter, Uffen-Orde approaches). For inflammatory sinus disease these techniques were very radical leading to similar complications as for open maxillary sinus approaches. For trauma cases or extended approaches particularly in tumor surgery they still have a place in sinus surgery and can even be combined with endoscopic approaches [61]. For the ethmoid sinus or even sphenoid sinus transnasal or transseptal microscopic approaches were used –even in pituitary surgery- leaving limited space and vision. Moreover, an angled view could not be provided by the microscope [62]. Despite comparable results the endoscopic approach gained more and more importance over the microscopic approach to the pituitary gland and is today considered the gold standard. With the advent of pituitary surgery via an endoscopic transsphenoidal route the continuous cooperation between ENT and neurosurgery as well as the four-handed technique became increasingly popular. This lead to advanced approaches where not only pituitary adenomas but craniopharyngeomas, meningeomas and other midline tumors inclusive of esthesioneuroblastomas were approached [63-65]. Subsequently lateral lesions in the infratemporal fossa or even inside the orbit were removed via the nose [13,18,25,66]. The predominant success of the endoscope was due to the larger visual field with the possibility of angulated vision around the corner and the minimal invasive character of the approaches compared to open transcranial approaches with osteomyelitis, brain retraction and tearing of neural fibres.
Especially in midline-lesions the (entire) anterior skull base can be exposed and to gain access to the tumor the dura mater is incised or even resected leading to iatrogenic CSF-leaks which have to be closed in order to prevent ascending meningitis and/or encephalitis. Thus, the development of reconstructive techniques were necessary [67]. The preliminary CSF-leak rate was around 9% but ranging up to 40% in some studies [68]. At the early stages leaks were repaired by fascial grafts (e.g. fascia lata) in combination with fat-plugs and mucosal flaps in combination with hemostyptic material and fibrin glue. The techniques varied from combined underlay-overlay techniques to purely overlays depending on the anatomic situation. The majority of grafts were autologous. The problem was the missing abutment at skull base, the possibility to fix the grafts and the healing in since they were not vascularized and connective

tissue and vessels need a certain amount of time to grow into the grafts to provide definite fixation [8].

To overcome the problem of devascularisation and unphysiological mucosal covering, Hadad et al. postulated a revolutionary concept that would become known as the "Hadad-flap" [9]. Here the entire sepal mucosa, preferably on one side, can be dissected off the septal bone and cartilage in a posterior direction with preservation of a mucosal stalk at the inferior circumference of the natural sphenoid ostium containing branches from the sphenopalatine artery that feed the sepal mucosa. With this flap one has vascularized tissue that attached faster to underlying bone building a stable layer. Since the entire septal mucosa and even parts of the nasal floor and inferior lateral nasal wall can be harvested the flap can be designed to be large enough to cover the posterior inferior table of the frontal sinus reaching to as far as the sphenoid sinus and clivus. The flap not necessarily requires an overlay fascia that may even hamper the collagen fiber ingrowth and can be fixed with resorbable material. Nevertheless, its fixation relies on adhesion and pressure from the material below and cannot be stitched to its bed. With a gradual closure technique depending on size and localization of the defect the overall postoperative CSF-leak rate could be lowered to 1.6% [69]. Albeit being a superior technique the Hadad-flap has limitations: It is an advanced technique that is difficult to perform in inexperienced hands. Furthermore, if there is a malignant tumor at the midline it can infiltrate the nasal septum which –for oncologic margins- must be resected and thus the flap is lost. Furthermore, in recurrences the mucosa may be harmed after potential radiation therapy which also hampers a proper dissection and creation of the Hadad-flap. Lastly, there may be size defects or pre-existing septal perforations. A potential complication of the flap itself is its mucosal stalk. If it is torqued during surgery or too much pressure is applied by the hemostyptic material the flap may (partially) necrotize, retract and lead to a recurring leak. This may also happen if the blood pressure, coagulation or viscosity if the blood changes due to post-anesthesia or intensive care stay which also decreases its viability [69].

Despite the advances in closure techniques for endoscopic transnasal skull base approaches one problem remains namely that the bone at skull base is lost. A nature-like reconstruction as in transcranial approaches where the bone is re-positioned after the removal of the lesion is not possible. The bone would serve as additional abutment for the underlay and if regrown is a potentially more stable graft then mucosal/fascial grafts alone. With the currently available instruments thus far a bone flap creation was not possible. Chisles, punches or drills are too bulky and cuts are too big for a sufficiently stable bone graft where the bone is very delicate. In a mouse model Yang et al. showed that piezosurgery provides faster and better healing of bone defects than conventional burs [70]. To overcome the problem of bone loss or bone resorption a piezoelectric device with specialized endoscopic tips was developed at the Department of General ORL, Head and Neck Surgery at Graz [52].

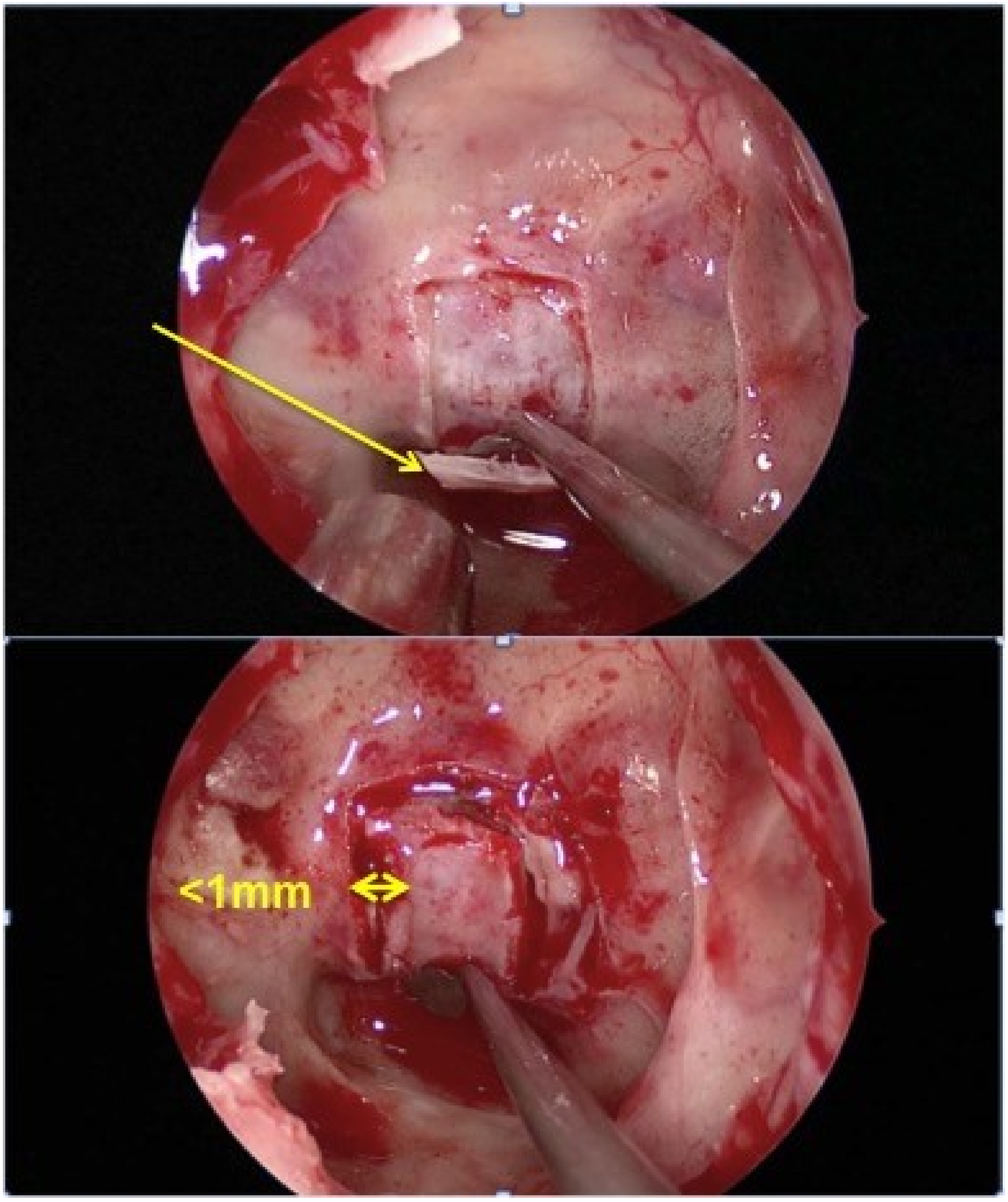

Figure 11: Piezoelectric technique used to create a bone flap (upper panel, arrow) in the sella floor with subsequent reposition and minimal bone loss at the incision lines (lower panel).

PETC is commonly used in maxillofacial surgery, rhinoplasty, neurosurgery and orthopaedics [71,72]. The problem for transnasal approaches was that the tips were too short. The novel endoscopic tip allows micromovements between 60 and 200μm/s and is targeted in a 90∘ angle to the surface of the bone which makes movements inside the nasal cavity and sinuses possible.

In a cadaveric model this technique created sufficiently large bone flaps for sellar approaches ($1cm^2$) and transplanum/transtubercular approaches ($-5cm^2$) [52]. The incisions lines of the bone flap margins were <1mm and the underlying dura was unharmed. We wanted to analyse if the bone flap was stable after 3 months of surgery and whether it was resorbed or healed in which it did in 89% of cases.

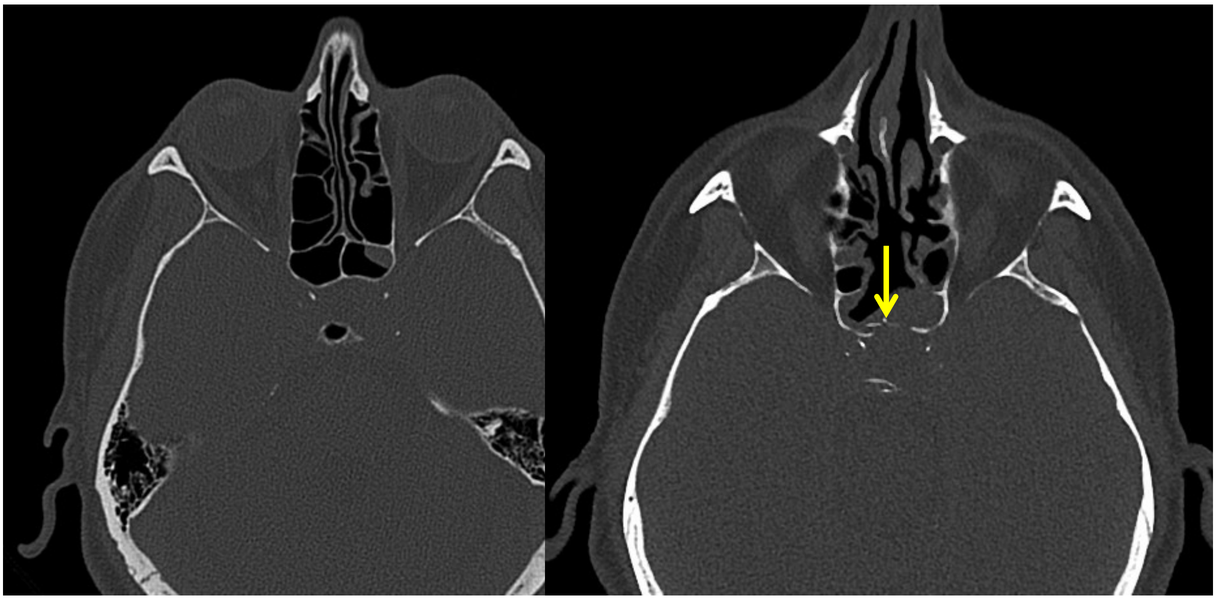

Figure 12: Pre- (left) and postoperative (right) CT scan (axial plane) showing that the bone flap partially healed in after 3 months (yellow arrow).

Moreover, no CSF-leak occurred postoperative in 15 patients. A second hypotheses tested was that due to the abutment the bone flap created at skull base little to no hemostyptic material apart from autologous fibrin glue was needed to fix the grafts in situ [73] which would improve patients comfort postoperatively. This was evaluated by VAS scores pre- and postoperatively and endoscopic evaluation. Normal mucosa without crusting or remnant material was found in 93% and VAS score did not differ significantly postoperatively as regards nasal comfort and postnasal drip.

Figure 13: Endoscopic view onto the sella 3 months postoperatively, the mucosa has clearly healed and only a minor crust remains centrally, upon palpation the anterior sella wall was intact.

Only sense of smell deteriorated which cannot be attributed to the technique or the approach since the olfactory mucosa was untouched. This may be due to the postoperative swelling of the turbinates and less air passing to the olfactory cleft. Hong et al. [74] reported a similar finding in their study were postoperative sense of smell decreased by 1.12 points compared to 1.4 in the present study on a VAS score (0-100, here values are presented by a factor 10 to be compared to the present study). Rioja et al. [75] reported long-term outcomes of endoscopic endonasal approaches for skull base surgery reporting mainly outcomes of SNOT-22 questionnaires. Particularly for expanded approaches long-term quality of life was significantly reduced for smell, nasal discharge and function. Another clear advantage was the significantly reduced surgical time for the approach (mean 90 vs. 112 minutes).

Regardless of the indication for endoscopic approaches be it for sinonasal disease or skull base lesions the most important issue is excellent visualization. The development of endoscopic techniques of the sinuses and the anterior skull base came along with the debate about the superiority of endoscopic vs. microscopic techniques [8,76]. Nevertheless, endoscopic transnasal techniques have become the gold standard for approaches to the sinuses and anterior skull base and studies that still compare both techniques show similar outcomes [62].

The biggest argument for the microscope was the 3 dimensional image of the surgical field. The stereoscopic vision made the surgical field more realistic and especially in complex neurovascular anatomic situation the topographic relationship in a three dimensional space and the recognition of it during surgery is indispensible for a complication free intervention. The biggest breakthrough for endoscopic sinus surgery were the functionally better results of FESS compared to open approaches with patients being particularly happy with cosmetic and functional outcomes and the avoidance of reconstruction of sinus walls [77].

Since neurosurgeons had a long tradition in microscopic pituitary surgery the necessity of switching to endoscopic approaches was not seen in the beginning. Moreover, the instrumentation was designed for microscopic approaches, neurosurgeons were not used to sticky mucosa and blurring vision of mucus and blood running over the endoscope as well as the different perspective in addition to the missing stereoscopic vision.

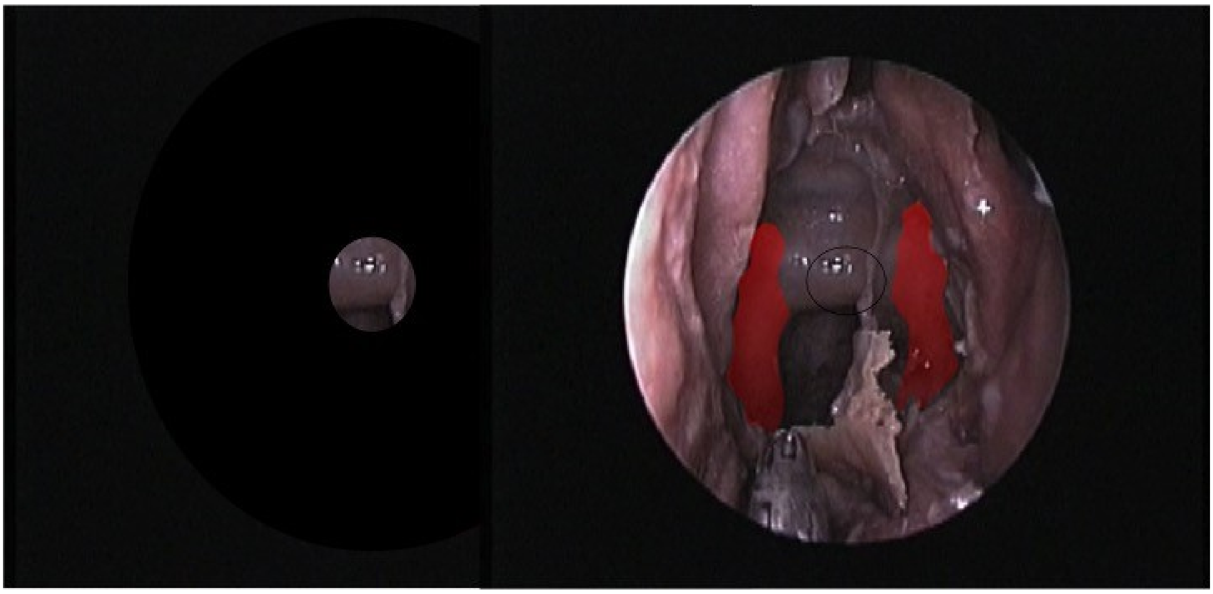

Figure 14: Microscopic (left) surgical field compared to endoscopic (right) field, the red areas indicate both carotid arteries and the black circle the frame of microscopic vision.

Here, the striking experience in favor of the endoscope was made because of the wider view and optical field by angled scopes and direct visualization of the anticipated area without a long optical canal through specula. What remained for skull base as well as sinus surgery was the absence of a 3D vision.

Recently, digital 3D endoscopes have been developed to also overcome this shortcoming of endoscopic approaches. For skull base surgery particularly depth perception was a clear advantage of the novel 3D technique [14,55,78]. For sinus surgery itself little is published about the feasibility of 3D techniques. In 2015 Ogino-Nishimura et al. [79] analysed various approaches in 5 cadavers and compared 2D to 3D techniques. In their study, they did not use a chip-on-the tip endoscope but combined two endoscopes and overlapped the images which –as in chip techniques- were separately presented to the single eye by polarizing glasses. On five cadavers various surgical approaches were simulated comparing 2D to 3D, including septoplasty, full house FESS (all sinuses opened), extended sphenoidotomy with exposure of the carotid artery, frontal sinusotomy, orbital decompression and pituitary surgery. They evaluated the accessibility of the surgical field and image quality. Despite the minor quality of the resolution (1920x540 pixels) compared to the present technology and the wider diameter of the two-scope 3D device (4.7 vs 4mm) they concluded that 3D offered a more precise anatomical understanding especially of the posterior paranasal sinus structures. This finding is very important since the crucial neurovascular structures are located in this area. In a well pneumatised sphenoid sinus the carotid artery, the optic nerve, the maxillary nerve and the vidian nerve bulge into the sinus lumen.

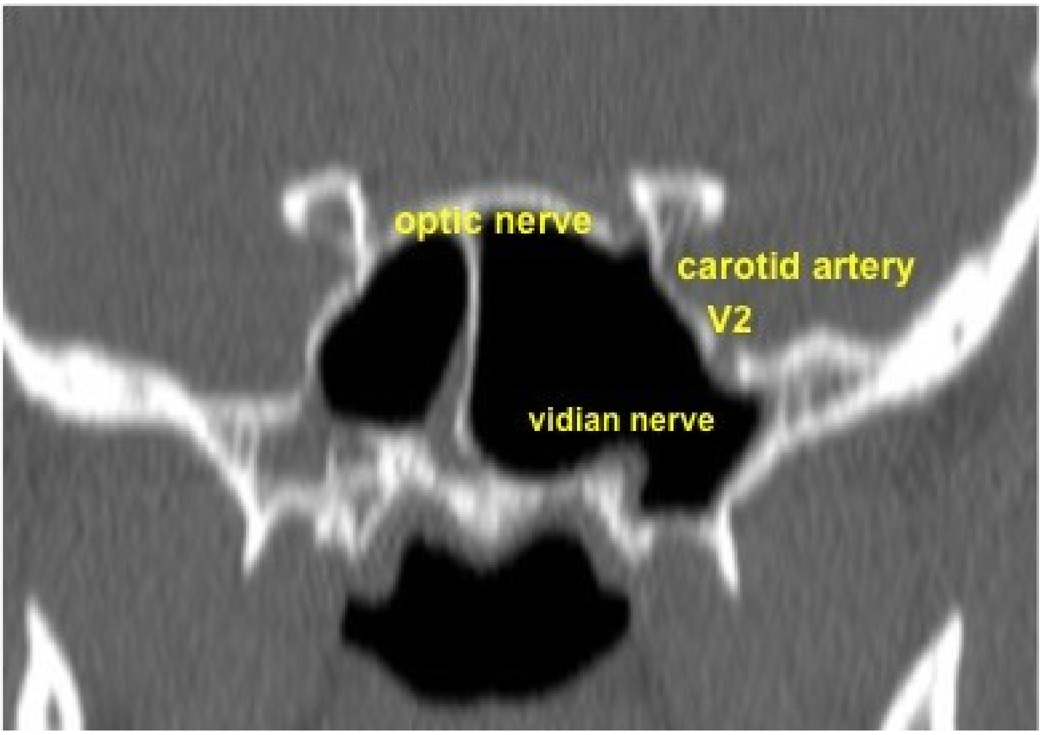

Figure 15: Detailed sphenoid sinus anatomy on a CT with important neurovascular structures.

The more the sinus is pneumatised the less thick the bony canals are which can lead to fatal consequences like internal carotid artery bleeding or blindness when punching into the optic nerve. Here, the distances and the anterior posterior depth and orientation of the canals are better identified in a 3D image. The haptic feedback that experiences surgeons rely on may be fatal in very thin or even demineralized carotid artery canals. In the maxillary sinus the critical structure is the infraorbital nerve running in its roof and is thus not at great risk to be damaged. The important vessels like the maxillary artery are well protected inside the infratemporal fossa and penetrating the posterior maxillary sinus wall is unlikely. The sphenopalatine artery is at risk in its foramen which is in close topographical relationship to the posterior end of the middle turbinate and despite cutting into it is not recommended unless for tumor surgery or cautery in case of posterior epistaxis opening it accidentally does not cause as severe a bleeding as running into the internal carotid artery would [49,80]. In the frontal sinus itself there are no critical structures unless one penetrated the posterior wall into the anterior cranial fossa.

In the present study which, as of today, is the first two analyze the feasibility of 3D endoscopy we focus on imaging and handling aspects of both systems (2D and 3D) from KARL STORZ and answered questionnaires after each surgery. Prior to surgery the side was randomized to either technology to avoid interindividual bias through different anatomic situations. As expected 3D showed a better score in 3D effect.

As in other reported studies recognition of details and depth perception was superior in 3D than in 2D. Only in the maxillary sinus recognition of details was slightly better in 2D. This may be due to the fact the maxillary sinus is best evaluated with angled scopes and the 3D technology only allows digital rotation thus far whereas standard scopes can be rotated against the camera along their longitudinal axis. Because of the digital rotation effect without rotation of the lens the imaging quality may be lower than in 4K endoscopes.

The sphenoid sinus showed a high score (mean: 3.88) in depth perception which is relevant for endoscopic sinus surgery as well as skull base surgery given the anatomic vicinity of both optic nerves and carotid arteries, the latter often ending in fatal bleeding [49,80]. In the usability scores 2D was better in all aspects but weight of the endoscopes and user-friendliness. The design of the 3D endoscopes is such that the camera and the scope itself come in one piece. The chip technology allows a slimmer design compared to lens systems and lies more comfortably in the surgeons' hand. A disadvantage is the handling especially the need to continuously wear 3D glasses. This may cause discomfort at the ear because they are not custom made which is true for long surgeries. Moreover, the necessity to accommodate to the 3D effect and to keep a certain position of the head in relation to the monitor may cause nausea, dizziness, vertigo and even neck stiffness. These problems may possibly be overcome by better design of the polarizing glasses. Another point was the extra effort in lens cleaning and the easier fogging of one of the lenses and the hitherto worsening of image quality. This is attributed to the two chip and thus two lens technology where if one lens becomes dirty e.g. by mucus running over it the 3D effects vanishes and the optical quality deteriorates. Here, lens cleaning devices would help which are already available in standard 2D endoscopy [81].

For angled vision two scopes (a 0° and 30°) are the minimum requirements for standard endoscopic surgery. In 2D the surgeon can easily change the scope and plug it to the camera whereas the one-piece 3D scopes need to be plugged into the camera console by a non-sterile OR assistant. Despite the lower weight and slim design another disadvantage is that the scope and camera are in a single piece so in angled endoscopy you either need two scopes for upward and sideward view or you digitally change the orientation of the scope which deteriorated the image quality. The illumination and color brilliance was generally better in 2D than 3D because of the chip depending on digital resolution and in 2D the image is transferred to the camera through optical lenses which require less light and colors are displayed more naturally. Through ongoing miniaturization advances the chips will definitely provide an equal resolution with equal illumination in the future.

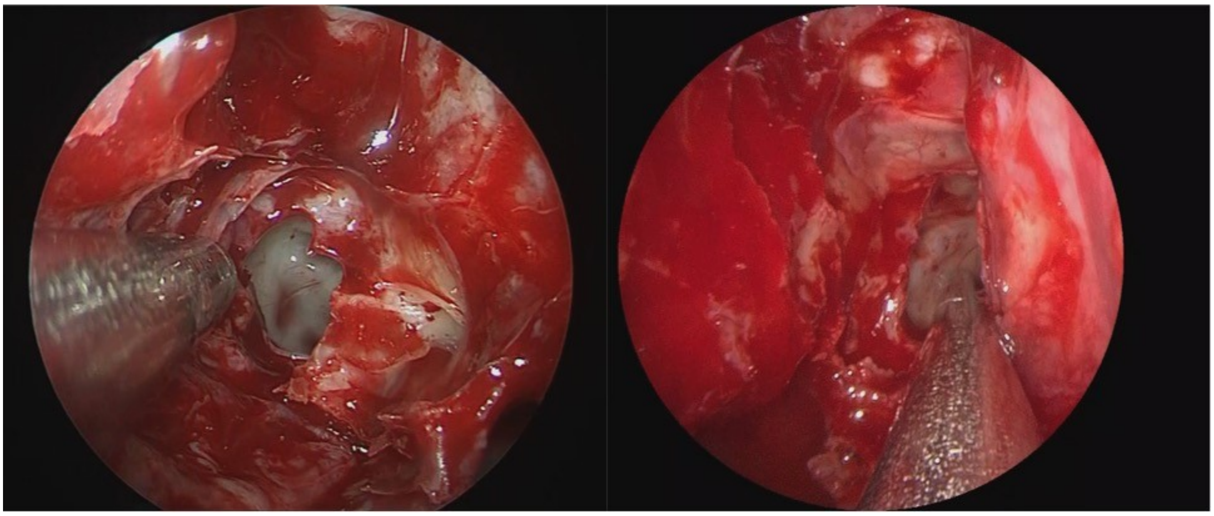

Figure 16: 2D (left) compared to 3D (right) with respect to illumination and color brilliance in the same patient, side and localization.

We were also interested in duration for surgery. Here, significant differences could be seen comparing the two systems where 3D was slightly “faster”. This has to be seen in the light of the surgeon performing the intervention since there may be a steeper learning curve in younger surgeons who adapt faster to the new technology than experienced surgeons who have optimized their technique with 2D endoscopy [82].

The biggest advantage of 3D thus lies in anatomical details and depth perception. Here, especially for teaching purposes 3D is a useful tool to better explain the topographical relation to critical anatomical structures within the paranasal sinus system. To date endoscopic techniques are mainly told by cadaver dissection courses and observation of live surgeries. Some studies exist proposing simulators since cadaveric specimen are not available to many centers and/or are expensive. In augmented reality or virtual reality some simulators show good training opportunities but can never compensate for cadavers. The problem of availability of cadavers had been tried to solve by 3D printing or generation of models through other techniques [83-86]. Here again the problem of high costs arises.

Integrating 3D technology in teaching during cadaver demonstration dissection and live surgery could enhance the faster understanding of the complex endoscopic anatomy. The topographical relationship of structures and especially the distance between them on a z-axis are better demonstrated in a 3D environment.

This coincides with another issue of 3D implementation since experienced surgeons are used to 2D and accommodated to its shortcomings as regards stereoscopy. In our multicenter study we looked at outcomes between younger and senior surgeons and found out that there was no difference in scoring, both groups accommodated fast to the technology and we did not see a learning curve since the new technology was adapted to fast. Nevertheless, if future generations are trained with 3D from the beginning the questions of usability may disappear.

5. Conclusion

Endoscopic sinus and skull base surgery has become the gold-standard over the past decades. In addition to development of novel approaches inherently came technological advances. The three major pillars of these innovations are visualization, instrumentation and navigation. For visualization the most recent developments are made in 3D endoscopy. This field solves the last criticism surgeons still using microscopic approaches since the stereoscopic vision missing in standard endoscopes can now be provided. We proved that this technology is superior in depth perception and anatomic detail recognition. The critical structures in the sinuses and skull base can better be identified and put in correlation with spatial orientation. This will lead to reduced complication for the experienced surgeon and faster learning for the novice. The future will provide better ergonomics and color brilliance as miniaturization progresses. Most probably in conjunction with navigation tools augmented reality will be embedded as standard so preoperatively designed pathways to the sinuses, alarms or haptic feedback when near critical structures and mechanically enhanced angled vision will be the further development of current 3D technologies.

For instrumentation the piezoelectric system offers the possibility to –for the first time- perform endonasal craniotomies instead of craniectomies. With this the bone is preserved and a natural reconstruction of skull base can be achieved leading to more patient comfort since packing materials can be reduced and to less complications particularly CSF-leaks. In the near future endonasal cranio-fix devices may be developed to fix the bone flap to the surrounding skull base so a n optimal abutment is achieved. These devices must be designed to fit into the nose and the fixation pellets must be resorbable to avoid a second intervention.

Once piezoelectric tips are further developed in different sizes and angulation there is a high potential to avoid drilling inside the nose which grants better postoperative healing outcomes since the bone is less traumatized and potential tears of dura and lacerations of vessels can be avoided since the piezo effect only works on mineral tissues.

Taken together these technologies allow interventions to be safer, enhance surgeons' confidence and provide better outcomes for the patients

References

1. Stammberger H. Endoscopic endonasal surgery--concepts in treatment of recurring rhinosinusitis. Part I. Anatomic and pathophysiologic considerations. Otolaryngology -- Head and Neck Surgery 1986;94:143–7.

2. Stammberger H. Endoscopic endonasal surgery--concepts in treatment of recurring rhinosinusitis. Part II. Surgical technique. Otolaryngology -- Head and Neck Surgery 1986;94:147–56.

3. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology 2020;58:1–464.

4. Guiot G, Derome P. [Surgical approaches to hypophyseal adenomas]. Rev Otoneuroophtalmol 1974;46:337–46.

5. Apuzzo ML, Heifetz MD, Weiss MH, Kurze T. Neurosurgical endoscopy using the side-viewing telescope. Journal of Neurosurgery 1977;46:398–400.

6. Jho HD, Carrau RL, Ko Y, Daly MA. Endoscopic pituitary surgery: an early experience. Surg Neurol 1997;47:213–22–discussion222–3.

7. Kurschel S, Gellner V, Clarici G, Braun H, Stammberger H, Mokry M. Endoscopic rhino-neurosurgical approach for non-adenomatous sellar and skull base lesions. Rhinology 2011;49:64–73.

8. Lund VJ, Stammberger H, Nicolai P, Castelnuovo P, Beal T, Beham A, et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. Rhinology.Supplement 2010;(22):1–143.

9. Hadad G, Bassagasteguy L, Carrau RL, Mataza JC, Kassam A, Snyderman CH, et al. A Novel Reconstructive Technique After Endoscopic Expanded Endonasal Approaches: Vascular Pedicle Nasoseptal Flap. The Laryngoscope 2006;116:1882–6.

10. Tomazic PV, Edlinger S, Gellner V, Koele W, Gerstenberger C, Braun H, et al. Vivostat(R): an autologous fibrin sealant as useful adjunct in endoscopic transnasal CSF-leak repair. Eur Arch Otorhinolaryngol 2015;272:1423–7.

11. Tomazic PV, Gellner V, Koele W, Hammer GP, Braun EM, Gerstenberger C, et al. Feasibility of piezoelectric endoscopic transsphenoidal craniotomy: a cadaveric study. BioMed research international 2014;2014:341876.

12. Tomazic PV, Stammberger H, Habermann W, Gerstenberger C, Braun H, Gellner V, et al. Intraoperative medialization of medial rectus muscle as a new endoscopic technique for approaching intraconal lesions. Am J Rhinol Allergy 2011;25:363–7.

13. Moe KS, Bergeron CM, Ellenbogen RG. Transorbital neuroendoscopic surgery. Neurosurgery 2010;67:ons16–28.

14. Altieri R, Tardivo V, Pacca P, Pennacchietti V, Penner F, Garbossa D, et al. 3D HD Endoscopy in Skull Base Surgery: From Darkness to Light. Surg Technol Int 2016;29:359–65.

15. Lund VJ, Stammberger H, Fokkens WJ, Beale T, Bernal-Sprekelsen M, Eloy P, et al. European position paper on the anatomical terminology of the internal nose and paranasal sinuses. Rhinology.Supplement 2014;(24):1–34.

16. Gellner V, Tomazic PV. Limits of the endoscopic transnasal transtubercular approach. J Neurosurg Sci 2018;62:297–300.

17. Cappabianca P, Cavallo LM, Colao A, Del Basso De Caro M, Esposito F, Cirillo S, et al. Endoscopic endonasal transsphenoidal approach: outcome analysis of 100 consecutive procedures. Minimally invasive neurosurgery : MIN 2002;45:193–200.

18. Tomazic PV, Stammberger H, Habermann W, Gerstenberger C, Braun H, Gellner V, et al. Intraoperative medialization of medial rectus muscle as a new endoscopic technique for approaching intraconal lesions. Am J Rhinol Allergy 2011;25:363–7.

19. Cavallo LM, Messina A, Cappabianca P, Esposito F, de Divitiis E, Gardner P, et al. Endoscopic endonasal surgery of the midline skull base: anatomical study and clinical considerations. 2005.

20. Stammberger H, Posawetz W. Functional endoscopic sinus surgery. Concept, indications and results of the Messerklinger technique. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 1990;247:63–76.

21. Stammberger H. Functional Endoscopic Sinus Surgery. Philadelphia, Pennsylvania: B.C. Decker; 1991.

22. Kainz J, Stammberger H. Danger areas of the posterior rhinobasis. An endoscopic and anatomical-surgical study. Acta Otolaryngol 1992;112:852–61.

23. Preti A, Mozzanica F, Gera R, Gallo S, Zocchi J, Bandi F, et al. Horizontal lateral lamella as a risk factor for iatrogenic cerebrospinal fluid leak. Clinical retrospective evaluation of 24 cases. Rhinology 2018;56:358–63.

24. Kainz J, Braun H, Genser P. [Haller's cells: morphologic evaluation and clinico-surgical relevance]. Laryngorhinootologie 1993;72:599–604.

25. Snyderman CH, Pant H, Carrau RL, Prevedello D, Gardner P, Kassam AB. What are the limits of endoscopic sinus surgery?: the expanded endonasal approach to the skull base. Keio J Med 2009;58:152–60.

26. Tomazic PV, Dostal E, Magyar M, Lang-Loidolt D, Wolf A, Koele W, et al. Potential correlations of dentogenic factors to the development of clinically verified fungus balls: A retrospective computed tomography-based analysis. Laryngoscope 2016;126:39–43.

27. Sommer F, Hoffmann TK, Harter L, Döscher J, Kleiner S, Lindemann J, et al. Incidence of anatomical variations according to the International Frontal Sinus Anatomy Classification (IFAC) and their coincidence with radiological sings of opacification. Eur Arch Otorhinolaryngol 2019;276:3139–46.

28. Leunig A, Sommer B, Betz CS, Sommer F. Surgical anatomy of the frontal recess--is

there a benefit in multiplanar CT-reconstruction? Rhinology 2008;46:188–94.

29. Sethi DS, Leong JL. Endoscopic pituitary surgery. Otolaryngologic Clinics of NA 2006;39:563–83–x.

30. Lang J. Hypophyseal region--anatomy of the operative approaches. Neurosurg Rev 1985;8:93–124.

31. Tomazic PV, Nemetz U, Koele W, Walch C, Braun EM, Hammer GP, et al. Cholesterol granulomas of the petrous apex; endonasal endoscopic approach. B-Ent 2013;9:263–7.

32. Kingdom TT, Delgaudio JM. Endoscopic approach to lesions of the sphenoid sinus, orbital apex, and clivus. American Journal of Otolaryngology--Head and Neck Medicine and Surgery 2003;24:317–22.

33. Wu SW, Chen WL, Chen WL, Chen MK. Transnasal endoscopic resection of vidian nerve schwannoma accompanied by sphenoid mucopyocele and oculomotor palsy: a case report. B-Ent 2012;8:207–11.

34. Sharma A, Rieth GE, Tanenbaum JE, Williams JS, Ota N, Chakravarthi S, et al. A morphometric survey of the parasellar region in more than 2700 skulls: emphasis on the middle clinoid process variants and implications in endoscopic and microsurgical approaches. J. Neurosurg. 2017;:1–11.

35. Jittapiromsak P, Sabuncuoglu H, Deshmukh P, McDougall CG, Spetzler RF, Preul MC. Anatomical relationships of intracavernous internal carotid artery to intracavernous neural structures. Skull Base 2010;20:327–36.

36. Hoogendijk CF, Pretorius E. Cavernous sinus anatomy as a basis for interpretation of the clinical picture and radiological investigations in a case of Entomophthorales infection. Clin Anat 2006;19:535–9.

37. Andrianakis A, Tomazic PV, Wolf A, Anderhuber F, Gerstenberger C, Pilsl U, et al. Optico-carotid recess and anterior clinoid process pneumatization â€" proposal for a novel classiï¬cation and uniï¬ed terminology: an anatomic and radiologic study. Rhinology 2019;57:444–50.

38. Kulwin C, Schwartz TH, Cohen-Gadol AA. Endoscopic extended transsphenoidal resection of tuberculum sellae meningiomas: nuances of neurosurgical technique. Neurosurgical Focus 2013;35:E6.

39. Baraniuk JN, Clauw D, Yuta A, Ali M, Gaumond E, Upadhyayula N, et al. Nasal secretion analysis in allergic rhinitis, cystic fibrosis, and nonallergic fibromyalgia/chronic fatigue syndrome subjects. Am J Rhinol 1998;12:435–40.

40. Antunes MB, Cohen NA. Mucociliary clearance--a critical upper airway host defense mechanism and methods of assessment. Current Opinion in Allergy and Clinical Immunology 2007;7:5–10.

41. Voynow JA, Rubin BK. Mucins, mucus, and sputum. Chest 2009;135:505–12.

42. Tonnesen P, Hindberg I, Schaffalitzky de Muckadell OB, Mygind N. Effect of nasal

allergen challenge on serotonin, substance P and vasoactive intestinal peptide in plasma and nasal secretions. Allergy 1988;43:310–7.

43. Williams OW, Sharafkhaneh A, Kim V, Dickey BF, Evans CM. Airway mucus: From production to secretion. Am. J. Respir. Cell Mol. Biol. 2006;34:527–36.

44. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA²LEN study. Allergy 2011;66:1216–23.

45. Tomassen P, Vandeplas G, Van Zele T, Cardell L-O, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J. Allergy Clin. Immunol. 2016;137:1449–1456.e4.

46. Prevedello DM, Ebner FH, de Lara D, Ditzel Filho L, Otto BA, Carrau RL. Extracapsular dissection technique with the cotton swab for pituitary adenomas through an endoscopic endonasal approach -- how I do it. Acta Neurochir (Wien) 2013;155:1629–32.

47. Santiago-Andres Y, Golan M, Fiordelisio T. Functional Pituitary Networks in Vertebrates. Front Endocrinol (Lausanne) 2020;11:619352.

48. Kassam AB, Thomas A, Carrau RL, Snyderman CH, Vescan A, Prevedello D, et al. Endoscopic reconstruction of the cranial base using a pedicled nasoseptal flap. Neurosurgery 2008;63:ONS44–52–discussionONS52–3.

49. Koitschev A, Simon C, Löwenheim H, Naegele T, Ernemann U. Management and outcome after internal carotid artery laceration during surgery of the paranasal sinuses. Acta Otolaryngol 2006;126:730–8.

50. Shamos MH, Lavine LS. Piezoelectricity as a fundamental property of biological tissues. Nature 1967;213:267–9.

51. Minary-Jolandan M, Yu M-F. Uncovering nanoscale electromechanical heterogeneity in the subfibrillar structure of collagen fibrils responsible for the piezoelectricity of bone. ACS Nano 2009;3:1859–63.

52. Tomazic PV, Gellner V, Koele W, Hammer GP, Braun EM, Gerstenberger C, et al. Feasibility of piezoelectric endoscopic transsphenoidal craniotomy: a cadaveric study. BioMed research international 2014;2014:341876.

53. Kotrikova B, Wirtz R, Krempien R, Blank J, Eggers G, Samiotis A, et al. Piezosurgery--a new safe technique in cranial osteoplasty? International journal of oral and maxillofacial surgery 2006;35:461–5.

54. Cote M, Kalra R, Wilson T, Orlandi RR, Couldwell WT. Surgical fidelity: comparing the microscope and the endoscope. Acta Neurochir (Wien) 2013;155:2299–303.

55. Kari E, Oyesiku NM, Dadashev V, Wise SK. Comparison of traditional 2-dimensional endoscopic pituitary surgery with new 3-dimensional endoscopic technology: intraoperative and early postoperative factors. Int Forum Allergy Rhinol 2012;2:2–8.

56. Raheja A, Kalra R, Couldwell WT. Three-Dimensional Versus Two-Dimensional

Neuroendoscopy: A Preclinical Laboratory Study. WNEU 2016;92:378–85.

57. Bickerton R, Nassimizadeh A-K, Ahmed S. Three-dimensional endoscopy: The future of nasoendoscopic training. Laryngoscope 2019;129:1280–5.

58. Messerklinger W. [Endoscopy of the nose]. Monatsschr Ohrenheilkd Laryngorhinol 1970;104:451–6.

59. Bernstein L. The Caldwell-Luc operation. Otolaryngologic Clinics of NA 1971;4:69–77.

60. Low WK. Complications of the Caldwell-Luc operation and how to avoid them. Aust N Z J Surg 1995;65:582–4.

61. Weber R, Draf W, Kratzsch B, Hosemann W, Schaefer SD. Modern concepts of frontal sinus surgery. The Laryngoscope 2001;111:137–46.

62. Pablo A, Sofia B, Maximiliano T, Patricia FD, Alvaro C, Claudio Y, et al. Endoscopic versus Microscopic Pituitary Adenoma Surgery: A Single-center Study. Neurol India 2019;67:1015–21.

63. Ceylan S, Koc K, Anik I. Extended endoscopic approaches for midline skull-base lesions. Neurosurg Rev 2009;32:309–19–discussion318–9.

64. Cappabianca P, Cavallo LM, Esposito F, de Divitiis O, Messina A, de Divitiis E. Extended endoscopic endonasal approach to the midline skull base: the evolving role of transsphenoidal surgery. Adv Tech Stand Neurosurg 2008;33:151–99.

65. Kassam AB, Gardner PA, Snyderman CH, Carrau RL, Mintz AH, Prevedello DM. Expanded endonasal approach, a fully endoscopic transnasal approach for the resection of midline suprasellar craniopharyngiomas: a new classification based on the infundibulum. Journal of Neurosurgery 2008;108:715–28.

66. Mishra A. Transorbital approach to infratemporal fossa: novel technique. The Journal of laryngology and otology 2011;125:638–42.

67. Kassam A, Carrau RL, Snyderman CH, Gardner P, Mintz A. Evolution of reconstructive techniques following endoscopic expanded endonasal approaches. Neurosurgical Focus 2005;19:E8.

68. Borg A, Kirkman MA, Choi D. Endoscopic endonasal anterior skull base surgery: a systematic review of complications over the past 65 years. WNEU 2016;95:383–91.

69. Conger A, Zhao F, Wang X, Eisenberg A, Griffiths C, Esposito F, et al. Evolution of the graded repair of CSF leaks and skull base defects in endonasal endoscopic tumor surgery: trends in repair failure and meningitis rates in 509 patients. Journal of Neurosurgery 2018;130:861–75.

70. Yang B-E, Girod S. Efficacy of bone healing in calvarial defects using piezoelectric surgical instruments. J Craniofac Surg 2014;25:149–53.

71. Gleizal A, Bera JC, Lavandier B, Beziat JL. Piezoelectric osteotomy: a new technique for bone surgery-advantages in craniofacial surgery. Childs Nerv Syst 2007;23:509–13.

72. Gonzalez-Lagunas J, Mareque J. Calvarial bone harvesting with piezoelectric device. The Journal of craniofacial surgery 2007;18:1395–6.

73. Tomazic PV, Edlinger S, Gellner V, Koele W, Gerstenberger C, Braun H, et al. Vivostat: an autologous fibrin sealant as useful adjunct in endoscopic transnasal CSF-leak repair. Eur Arch Otorhinolaryngol 2014;

74. Hong SD, Nam DH, Kong DS, Kim HY, Chung SK, Dhong H-J. Endoscopic Modified Transseptal Transsphenoidal Approach for Maximal Preservation of Sinonasal Quality of Life and Olfaction. WNEU 2016;87:162–9.

75. Rioja E, Bernal-Sprekelsen M, Enriquez K, Enseñat J, Valero R, de Notaris M, et al. Long-term outcomes of endoscopic endonasal approach for skull base surgery: a prospective study. Eur Arch Otorhinolaryngol 2015;:1–9.

76. Muskens IS, Briceno V, Ouwehand TL, Castlen JP, Gormley WB, Aglio LS, et al. The endoscopic endonasal approach is not superior to the microscopic transcranial approach for anterior skull base meningiomas-a meta-analysis. Acta Neurochir (Wien) 2018;160:59–75.

77. Dova S, Karkos PD, Constantinidis J. Reconstruction of frontal defects with calvarial grafts. Rhinology 2018;56:297–302.

78. Zaidi HA, Zehri A, Smith TR, Nakaji P, Laws ER. Efficacy of Three-Dimensional Endoscopy for Ventral Skull Base Pathology: A Systematic Review of the Literature. WNEU 2016;86:419–31.

79. Ogino-Nishimura E, Nakagawa T, Sakamoto T, Ito J. Efficacy of three-dimensional endoscopy in endonasal surgery. Auris Nasus Larynx 2015;42:203–7.

80. AlQahtani A, Castelnuovo P, Nicolai P, Prevedello DM, Locatelli D, Carrau RL. Injury of the Internal Carotid Artery During Endoscopic Skull Base Surgery: Prevention and Management Protocol. Otolaryngol. Clin. North Am. 2016;49:237–52.

81. Kuroda R, Nakajima T, Yamaguchi T, Watanabe E. A New Irrigation System (Endosplash) for a Rigid Endoscope in Trans-sphenoidal Endoscopic Surgery. Neurol Med Chir (Tokyo) 2016;56:409–15.

82. Tomazic PV, Sommer F, Treccosti A, Briner HR, Leunig A. 3D endoscopy shows enhanced anatomical details and depth perception vs 2D: a multicentre study. Eur Arch Otorhinolaryngol 2020;1–6.

83. Varshney R, Frenkiel S, Nguyen LHP, Young M, Del Maestro R, Zeitouni A, et al. Development of the McGill simulator for endoscopic sinus surgery: a new high-fidelity virtual reality simulator for endoscopic sinus surgery. Am J Rhinol Allergy 2014;28:330–4.

84. Wiet GJ, Yagel R, Stredney D, Schmalbrock P, Sessanna DJ, Kurzion Y, et al. A volumetric approach to virtual simulation of functional endoscopic sinus surgery. Stud Health Technol Inform 1997;39:167–79.

85. Dharmawardana N, Ruthenbeck G, Woods C, Elmiyeh B, Diment L, Ooi EH, et al. Validation of virtual-reality-based simulations for endoscopic sinus surgery. Clin

Otolaryngol 2015;40:569–79.

86. Arora A, Lau LYM, Awad Z, Darzi A, Singh A, Tolley N. Virtual reality simulation training in Otolaryngology. Int J Surg 2014;12:87–94.