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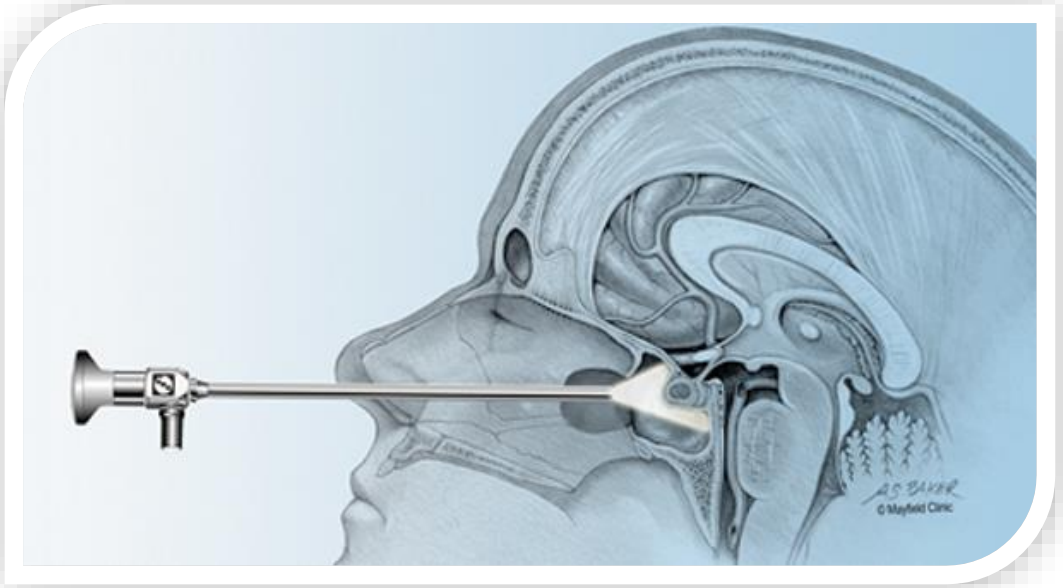

VALIDATION OF ENDOSCOPIC ENDONASAL SKULL BASE SURGERY QUESTIONNAIRE

END OF TERM PROJECT

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Look for knowledge. Follow your instinct

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ABSTRACT

Background: Nowadays most of pathologies of skull base are treated by endoscopic endonasal approach. This technique have comparable outcomes with the microscopic approach, less complications than external approach, and a hospital stay reduction. Quality of life assessment in patients with skull base tumors is important because of the complexity of surgery and associated significant morbidity. Multiple instruments have to be used to assess the quality of life of these patients because of a lack of a single ideal metric to measure symptom and endoscopic morbidity.

Objectives: The aim of this study is to create and validate a new questionnaire of quality of life to assess the quality of life of patients operated by endoscopic endonasal approach for the extirpation of skull base tumors, and to use it as a tool to assess the stability of quality of life of these patients.

Methods: The study will be a creation and validation of a quality of life questionnaire performed at Clínica Teknon and Hospital de la Santa Creu i Sant Pau. Relevant questions will be generated from a review of literature and interviews with health professionals, surgeons, patients and caregivers. The pool of questions will be reduced using a likert-type response scale to patients that have already been operated, and using standard psychometric criteria. Using a factor analysis the domains will be identified. Using a non-probabilistic consecutive sampling, 35 patients will be recruited in order to assess reliability and validity of the questionnaire. The internal consistency will be assessed using Cronbach α value and reliability using test-retest reliability. The validity of the construct will be assessed by testing if the clinical variable of the patient influences his quality of life domain score as hypothesized. Once created and validated, the questionnaire will be used prospectively to evaluate the stability of quality of life during 24 months to each of 35 patients that will be recruited from another non-probabilistic consecutive sampling.

Final Goals: This unique and site-specific instrument would assess the quality of life of this patients more quickly and efficiently, would help to investigate possible predictors of functional outcome after surgery, and may help to guide the selection of optimal therapy, type of surgical approach, and reconstruction method and to implement measures that improve perioperative care of patient that dsire a fast functional and emotional recovery.

Key Words: Quality of Life, questionnaires, endoscopic endonasal approach, skull base tumors.

LYST OF ACRONYMS

ASBQ	Anterior Skull Base Questionnaire
CAS	Computer-aided Surgery
CEIC	Comisión Ética para la Investigación Médica
CSF	Cerebrospinal Fluid
CT	Computed Tomography
ICC	Intraclass correlation coefficient
MMSE	Minimental State Examination
MRI	Magnetic Resonance Imaging
SNOT 20	20 Item Sinonasal Outcome Test
SNOT 22	22 Item Sinonasal Outcome Test
QOL	Quality of Life
SF-36	Short Form 36 Health Survey

INTRODUCTION

ANATOMIC RELATIONSHIP

To understand the history and evolution of the endoscopic endonasal skull base surgery is mandatory to understand the close relationship of the anatomic regions in this particular area. The anterior skull base is directly related with the sinus cavities and the nasal fossae structures as well as the orbit and it muscles, nerves and vessels. The pathology, either inflammatory or tumours, may spread from the nose and sinuses to the skull base and, inversely, the pituitary and brain tumours may affect the nose and sinus structures and cavities. Is for this reason that during centuries the surgeons has tried to reach the skull base using the natural cavities to improve the results with the minimum aggressiveness on the external structures avoiding unnecessary deformities and mutilations. During the last century has appeared new tools that has allowed the dreams of the ancient surgeons come true.

Figure 1. Egyptian scalpel and curette used to remove the brain tissue for mummification procedure.

Figure 2.Egyptian sarcophagus used for mummification procedure

HISTORY OF ENDONASAL TUMOR SURGERY

The endonasal endoscopic approach to the skull base has undergone a fast development in the last years. It can be explained by a better knowledge of the anatomical regions, the new image studies and navigation systems, the development of new surgical techniques and reconstruction materials, and also through interdisciplinary collaboration among different specialties.

Endoscopic endonasal tumor surgery has been developed from the interactions of the field of rhinology and skull base surgery. Major advances like the introduction of microscopic and endoscopic visualization tools and techniques, the improvements of radiology, and finally the use of powered instrumentation and intraoperative image guidance has increased the benefits of endonasal tumor surgery**.**

ORIGINS OF SINUS SURGERY

Egyptians were among the first to remove brain tissue transnassally as a part of mummification procedure. Then, Leonardo da Vinci (1452-1519), Andreas Vesalius (1514-1564), Giovanni Filippo Ingrassia (1510-1580), Nathaniel Highmore (1651), Zuckerkandl (1882) provided a detailed description of nasal and paranasal sinuses. The Zukerkandl text "Anatomy of the nose and of its pneumatic attachments" (1) became the standard reference book (2).

In 1660, C.V. Schneider concluded that the nasal mucus is not produced by the brain, but by the mucosa of paranasal sinuses (3). Consequently, multiple approaches were described to access these secretions. Several procedures were described to reach the maxillary sinuses and, eventually, Caldwell (1893) and Luc (1897) from USA and France, separately, described a surgery that included the opening of maxillary sinus through the canine fossa. This technique remained the gold standard option during decades to access maxillary sinus (4).

Intranasal Ethmoid Surgery with the unaided eye had limitations and operative dangers and made the procedure controversial. Killian (1900) (5), Halle (1906) (6), Mosher (1912) (7) and others have been considered the founders of endonasal ethmoid sinus surgery but the lack of endoscopic tools limited the technique and sometimes was abandoned for long periods of time (2).

In this pre-antibiotic and pre-endoscopic era that kind of surgery had a high incidence of complications such as meningitis and encephalitis, and for this reason from 1920 to 1980 most rhinologists used the external approach to access paranasal sinuses. (2).

The surgery was revolutionized with the introduction of microscope and with rode-lens endoscope. In 1958 Heermann introduced the microscope in endonasal sinus surgery (4). Then the introduction of self-retracting speculum made easier to do bimanual techniques. Hirschmann (1903) (8) was the first to introduce a true endoscope to explore the nose and the sinuses. After, the development of rod lens endoscopes by Harold Horace Hopkins was added

to the “cold light” technology, allowed to have a high image quality and a new knowledge of the physiology, pathology and, consequently, the perfection of medical and surgical treatment (9).

ENDOSCOPIC ENDONASAL SINUS SURGERY

After the Heermann report on intranasal surgery with the use of binocular microscope, most of surgeons have developed new tools and procedures: Prades (Spain 1971), Bagatella and Mazzoni (Italy 1980) (10), Draf (Germany 1982) (11), but the developing of endoscopes with a smaller diameter, higher illumination, and improved resolution motivated to some of them to switch to endoscope for functional studies of nasal and paranasal sinus mucosa. Terrier and Friedrich (Switzerland 1985) (12), Messerklinger (13) and Stammberger (Austria 1985) (14) are considered the fathers of the Endoscopic Sinus Surgery. This technique has been introduced in most countries and popularized by Kennedy in USA (1985), Wigand and Hosemann in Germany (1986) (15), Massegur and Ademà in Spain (1991) (16) among others all around the world and nowadays is considered the gold standard for the surgical treatment of the nose and paranasal sinuses pathology (17).

DEVELOPMENT OF ENDONASAL ONCOLOGIC AND SKULL BASE SURGERY

During the first years of development of endoscopic endonasal sinus surgery, the indications were mainly inflammatory diseases and tumors were considered as contraindications for this approach. With the improvement of the quality of the images and the surgical material, benign tumours, such as inverted papillomas, and, eventually, malignant tumours have become new indications with the same recurrence rate as external approach (18). With the development of the technique over the last 20 years most surgeons have accepted, after strong controversies, that the endonasal approach is adequate for the extirpation of all kind tumours into the oncological rules.

Once the idea of the endonasal approach for benign tumors was accepted, some authors began to present their experience with malignant tumors (19). The changing concept of the “piecemeal” removal versus “in bloc” removal from the oncological point of view, has changed the perception of this kind of surgery in malignant tumors. In some cases this surgery produces the same or superior results if we compare the traditional external approach with the minimal invasive technique. However, nowadays the traditional technique is not obsolete because it is used for large tumors that cannot be removed with endonasal approach and, sometimes, a

combined approach (endocopic and external) is used to achieve better oncologic results with a close control of all the safe margins.

ENDOSCOPIC ENDONASAL SKULL BASE SURGERY

The first endonasal approaches for skull base tumors were the trans-septal trans-sphenoidal microsurgery under optical control with microscope, and until recently was considered the standard procedure for pituitary tumors.

In 1995 appeared interdisciplinary (neurosurgeons plus otorhinolaryngolgists) groups of endoscopic skull base surgery that used endonasal endoscopic approaches to access the pituitary gland to remove adenomas or macroadenomas (20,21) *(see Figure 3 and 4).* And with the development of the endonasal approach the entire ventral skull base could be accessed with this minimally invasive approach, and with oncological outcomes that were comparable with the traditional techniques (22), and with less morbidity (23). Amin Kassam and Ricardo Carrau developed this technique in USA with outstanding results (24,25). E Pasquini and G Frank (italy) (26), H Stammberger (Austria), H Massegur and B Oliver (Spain) (27) *(See Figure 5)* had contributed to spread this technology all around the world to reach the category of "gold standard " technique for most skull base tumors.

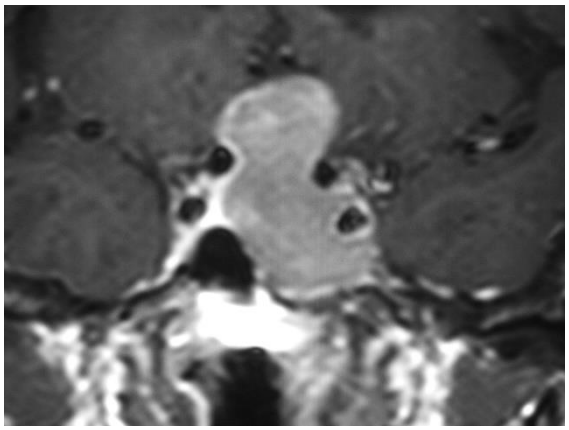

Figure 3. MRI (coronal view) of a macroadenoma with suprasellar and left cavernous sinus invasion

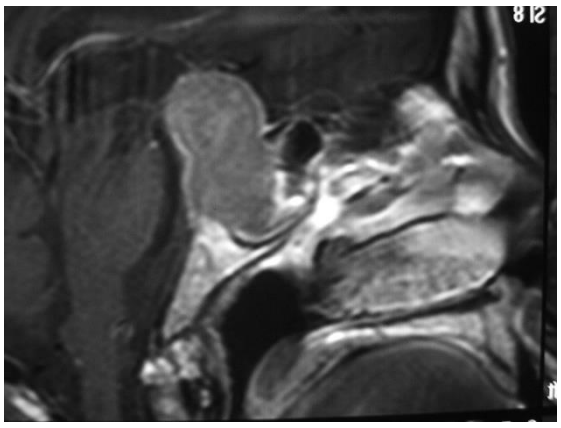

Figure 4. MRI (sagital view) of a macroadenoma with a suprasellar and left cavernous sinus invasion

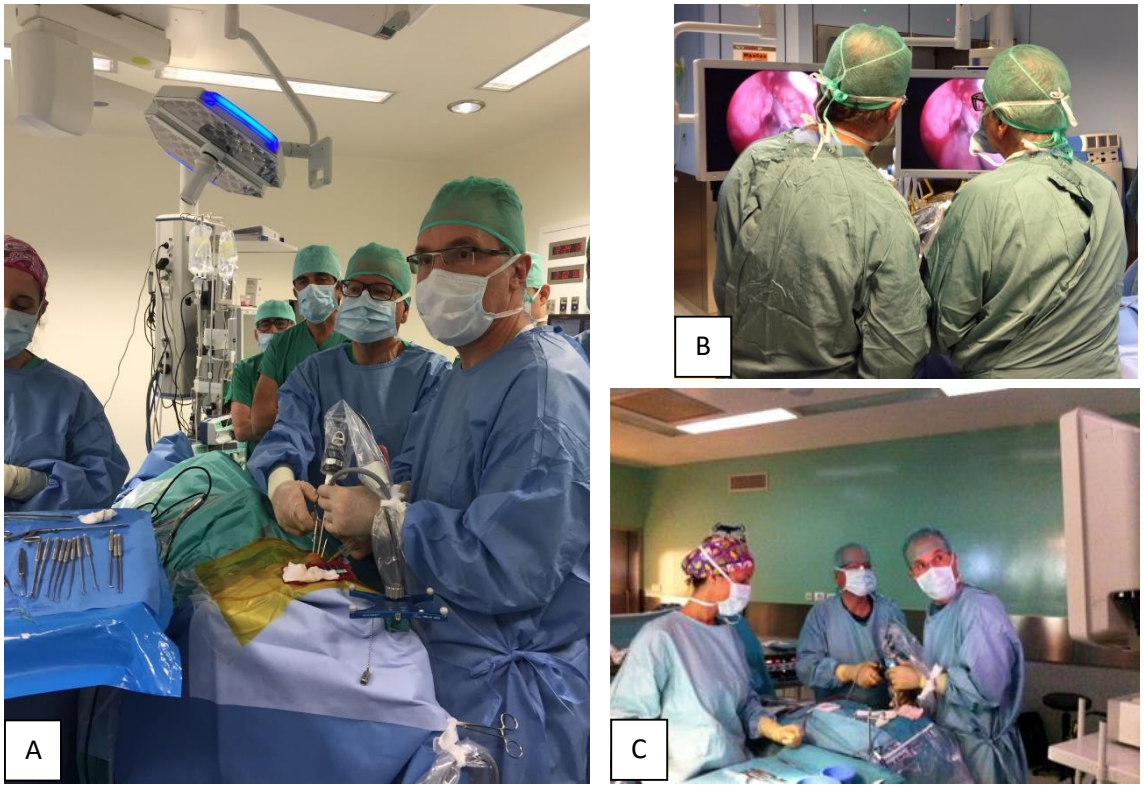

Figure 5. A,B,C. Neurosurgeon-ORL team working together doing the 4 hand endoscopic technique on a case of skull base tumor.

Nowadays most of pathologies of the skull base are treated by endoscopic endonasal "4 hands" technique with the collaboration of otolaryngologists and neurosurgeons (23,28).

In most centres the first endoscopic endonasal approach has been done for the pituitary gland adenomas, and then they have taken enough experience to treat another kind of pathologies. The only condition is that the pathology must be located medially to the neurovascular axis of the skull base (23). It is mandatory to follow a learning curve, from basic endoscopic procedures to the most challenging, to achieve the best results avoiding undesired complications.

The results obtained with this technique are comparable with the results of microscopic approach in the treatment of pituitary adenomas, minimising iatrogenic damage, from the neurosurgical point of view, and even improving results in some locations, such as the suprasellar and parasellar regions *(See Figure 5 and 6)*. Comparing with the external approaches, major complication rates (death, intracranial haemorrhage, ophtalmoplegia, loss of visual acuity, CSF (cerebrospinal fluid) leak, and diabetes insipidus) were not significantly different, minor complications (anosmia, synechiae, deviated septum, nasal anaesthesia, lip anaesthesia, postoperative epistaxis, intraoperative CSF leak) are significantly reduced, the use of prophylactic lumbar drainage decreased, and there is an hospital stay reduction. Endoscopic endonasal approach provides a better exposure of the sella and the parasellar area, giving the opportunity of making a major resection of the pituitary skull base tumours under direct visual control “around the corner” (29).

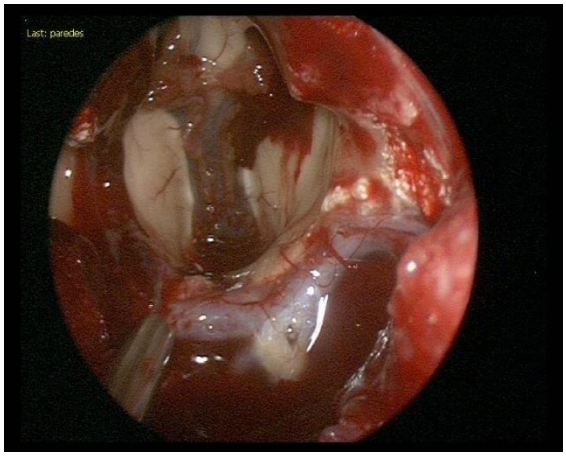

Figure 6. Intraoperatory endoscopic endonasal view of the 3th Ventricle with Monroe foramina after a cordoma resection.

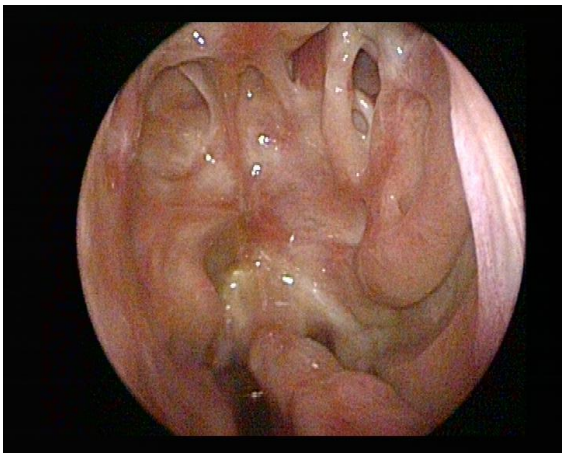

Figure 7. Endoscopic view of the nasal fossa 1 year postoperative after a skull base reconstruction with a mucoperichondrical flap.

This technique is the gold standard to treat the CSF leak of the anterior skull base, and also for the majority of benign lesions of the fossa and the paranasal sinuses such as inverted papillomas, fibrosseous lesions or vascular lesions (23).

The improvement of the reconstruction techniques for large defects of the skull base with flaps instead of free grafts has promoted the increasing indications for endoscopic endonasal approaches with a better quality-of-life and less morbidity (23).

RADIOLOGICAL TOOLS

The skull base surgery would not be developed without the development of Computed Tomography (CT), magnetic resonance imaging (MRI), and angiography. In 1980 W. Draf suggested the use of routine preoperative CT scans to plan endoscopic sinus surgery, and now this is a systematic and mandatory preoperative evaluation for the surgery of chronic sinusitis (30), and is used for evaluation and surgery planning of sinonasal tumors. In the mid of the 1980 appears, parallel to CT, the first reports of MRI used for sinonasal tumors (31), and in the following decades it became the routine method pre-surgery to plan it *(See figure 7 and 8).*

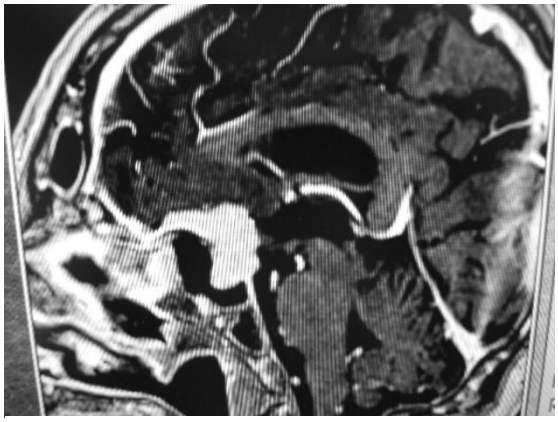

Figure 7. MRI (sagittal view) of a suprasellar meningioma affecting planum sphenoidale and right cavernous sinus.

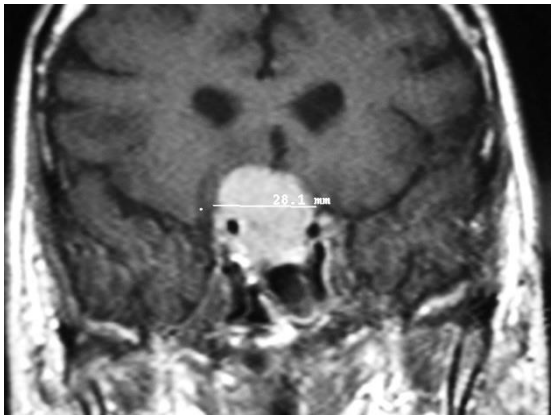

Figure 8. MRI (coronal view) of a suprasellar meningioma affecting planum sphenoidale and right cavernous sinus.

The development of angiography and its interventions such as embolization has improve the management of tumors with high vascularization like angiofibromas.

SOFT TISSUE SHAVERS OR MICRODEBRIDERS, ULTRASOUND DEBRIDERS, MICRODOPPLER

Orthopedics surgeons have used soft-tissue shavers or microdebriders for many years, but it was in 1996, when Setliff and Parsons use a soft-tissue shaver in endoscopic sinus surgery. This kind of tools have been adapted for endonasal surgery with continuous irrigation-aspiration, several angulations to reach the frontal sinus and bipolar energy to control bleeding (32). The ultrasounds debriders allow to reduce the tumor from the inside to the surface of tumor and remove sorrounding tissues under precise visual control. The microdoppler is a useful tool to precise locate the vessels in the surgical field that can be masked by the tumor. All these tools have helped to develop more and more this kind of surgery and to reduce morbidity and to improve the postsurgical quality of life of the patients.

IMAGE AND NAVIGATION

The improvement of the quality of the images until the 3D technology has contributed to facilitate the work of the surgeon giving a more accurate vision of the surgical field and the minor details in it.

Image-guidance systems were first used in neurosurgery but it has been beneficial to use in endoscopic sinus surgery (33). They were called "Computer-aided surgery", and the first one was introduced in 1986. It provided real-time information about the location of surgical instruments, gave information about the localization of the tumor and neighbour structures and it helped the surgeon to avoid or to control complicated areas such as the orbit or the brain. *(Figure 9 and 10)*

Figure 9. Skull base with image guidance (navigation).

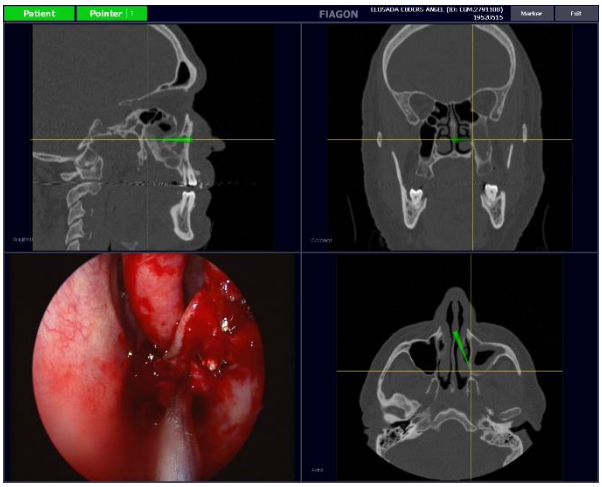

Figure 10. Skull base with image guidance (navigation).

QUALITY OF LIFE

The final aim of all medical and surgical improvements are always to obtain the best benefits for the patient in terms of cure of the pathology but, mainly, on the quality of life (QOL) after the treatment.

WHO defines Quality of Life as "*individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's*

physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment"(34), and it is needed to improve treatment modalities, facilitate the return to patient's daily function, and accelerate the return to normal life. In the case of surgery, the estimation of QOL outcomes can guide the surgeon to think which is the most appropriate surgical approach for the patient, and may influence the decision to treat and determine the type of treatment based on the current condition of the patient and future expectations (35). A detailed understanding of all the aspects that can affect the quality of life of the patient may help the surgeon to improve his management and assessment, and identify specific impediments as possible during follow-up, and specifically medical interventions in patients with increased medical risk (36).

QOL assessment is an important outcome measure in patients with skull base considering the complexity of surgery and associated significant morbidity. To assess the QOL of endoscopic skull base surgery, nasal morbidity has to be considered, these includes nasal crusting, nasal discharge, anosmia and nasal obstruction (37). Several questionnaires and tools have to be used to assess because of a lack of a single ideal metric to measure symptom and endoscopic morbidity, and that is a bias for real results (38).

The stability of QOL following the first months after surgery is not well established. Some authors say that during the 6 months after surgery there is a gradual improvement in QOL measures, while beyond this period of time there is no significant change reported (39). While other authors say that there's an improvement in the overall QOL score between 6 to 24 months after surgery compare with 3 to 6 months after surgery (35).

QUALITY OF LIFE QUESTIONNARIES

For a valid interpretation and application of QOL for a particular diagnosis or treatment, a validated site-specific multidimensional instrument and appropriate administration should be used (40). A site-specific multidimensional instrument has some advantages over commonly scales as Karnofsky scale, which is an overall measure of patient and not site-specific (41). Some QOL instruments that can be used to assess QOL outcomes following skull base surgery are showed in Table 1. The best instruments to measure QOL are 1. Reliable, with consistent and reproducible results even a change of conditions; 2. Valid, covering all the range of topics relevant to the condition with established measures; 3. Responsive, being sensitive in detecting change (42).

Quality of Life Instruments	Measure
Karnofsky performance Status Scale (41)	Assesses functional status of cancer patients; not site-specific, not multidimensional
Short Form Health Survey Questionnaire (SF-36) (43)	Multidimensional, not site-specific
Modified questionnaire from Woertgen (44)	Multidimensional. Not Site-specific
Anterior Skull Base questionnaire (45)	Multidimensional and site-specific.
Sinonasal Outcome Test (SNOT-22) (46)	Site specific for endoscopic endonasal skull base surgery
Sinonasal Outcome Test (SNOT-20) (47)	Site specific for endoscopic endonasal skull base surgery

Table1. QOL instruments used to assess QOL outcomes of skull base surgery

An ideal specifically quality-of-life endoscopic endonasal approach for skull base tumors questionnaire should be performed using SF-36 (Short Form 36) health survey questionnaire (as a general quality-of-life questionnaire), SNOT-22 (22 Item Sinonasal Outcome Test) (to evaluate the sinonasal morbidity), and cancer-specific ASBQ (Anterior Skull Base Questionnaire) (for the skull base morbidity) as base to perform the new questionnaire. These are discussed in detail bellow.

SF-36

The SF-36 Health Survey is a multi-purpose, short-form health survey which contains 36 questions. It is a generic measure of health status as opposed to one that targets specific age, disease or treatment group. It can assess health of general and specific populations, differentiate the health benefits of a wide range of treatments researching the cost-effectiveness of a treatment, and screening individual patients (43,48,49).

The limitations of SF-36 are:

- It does not take into consideration a sleep variable
- It has a low response rate in >65 population

The taxonomy has three levels: 1. Items; 2. Eight scales have 2-10 items each one; 3. Two summary measures that have 8 scales. *(See Annex 1)*

Three scales (Physical functioning, Role physical, Bodily Pain) are more correlated and contribute most to the scoring of the Physical Component Summary measure. The mental component are more correlated with Mental Health, Role-Emotional, and Social Functioning scales, and these 3

contribute most to the score of Mental Health Summary measure. The three scales that are not mentioned before have correlations with both Summary measures (49) *(See Annex 2).*

SNOT-22

The Sinonasal Outcome Test (SNOT-22) is a disease-specific health related quality of life instrument for use in chronic sinusitis, polyposis and also used to measure the outcome of a surgical intervention. It is a modification of a pre-existing questionnaire, the SNOT-20. Two additional measures were added to SNOT-20, nasal blockage and loss of sense of taste and smell (46).

This questionnaire comprises 22 questions evaluating four specific domains, including rhinologic, ear/facial, sleep, and psychological function. The SNOT-22 is scored on an (0-6) ordinal scale, with "0" representing "no problem" and "6" representing "problem as bad as it can be". The range of SNOT-22 goes from 0 to 110, lower scores means a better health-related quality of life (46).

The SNOT-22 could be a guide for making decision such as a consent for surgery if the surgeon think that it could improve the patient's symptom (46).

It could be used for endoscopic endonasal approach to evaluate the patient's sinus symptoms with another QOL questionnaires, such as anterior skull base questionnaire (ASBQ) due to lack of a single medical measure for this approach (38) *(See Annex 3).*

ASBQ

The anterior skull base QOL questionnaire is a cancer-specific multidimensional instrument for QOL assessment in patients undergoing anterior skull base surgery. The principal objective of this instrument is to evaluate QOL of a patient and with it, to promote the restoration of the function of a patient and his return to normal life (45).

The questionnaire has 35 questions and they are grouped into six relevant QOL domains:

- Performance (six items): This questions are about performance in general, at work, at home, participation in social activities, communication with people, and the effect of health on performance. In this domain older patients, malignant tumors, the ones that have received radiation therapy, people with comorbidity, or who underwent extensive surgery have lower scores than patients without these conditions

- Physical function (seven items): This domain involve patient's physical functioning, as to lean and stand, to walk, to climb stairs, and to conduct activities of daily life. Patients with the same clinical conditions that were explained before have lower scores than people without it.
- Vitality (seven items): the questions are about the energy and vitality of the patients.
- Pain (three items): The set of three questions are about the degree of pain that the patient suffers.
- Influence on emotions (five items): This domain is about the emotional impact of the disease on the patient. Patients with the clinical conditions explained before have lower scores than patients without it.
- Specific symptoms (seven items): This domain covers aspects of symptoms like taste, smell, appearance, epiphora, nasal secretions, and visual disturbances. Patients with the clinical conditions said before have lower scores at this domain too (45).

The questionnaire can be administered by mail or by a trained interviewer (45) *(See Annex 4).*

JUSTIFICATION

Nowadays most of pathologies of the skull base are treated by endoscopic endonasal approach with the collaboration of otolaryngologists and neurosurgeons. It has comparable results with the microscopic approach and even better results in suprasellar and parasellar regions. Compared with the external approach the number of major rate complications are the same, but endoscopic endonasal approach decreases the number of minor complications and there is a hospital stay reduction (23).

To assess the QOL of patients operated by endoscopic endonasal approach some instruments have to be used, such as SNOT-22, ASBQ (38). Given the lack of a single ideal metric to measure symptom and endoscopic morbidity, a new test of quality of life specific for endoscopic endonasal skull base surgery, that could provide complementary information to guide patient care, should be validated.

The Postoperative QOL has not been assessed using a unique and site-specific instrument for this approach, so the new endoscopic endonasal skull base quality of life questionnaire will be a

tool to investigate the stability of QOL during 24 months after surgery with the aim to evaluate the recovery time of patients.

HYPOTHESIS

Considering that the aim of the study is to validate a QOL questionnaire and there is no dependent and independent variables, there is not a formal hypothesis to test.

OBJECTIVES

Primary objective: To develop and to validate a unique site-specific endoscopic endonasal skull base surgery quality of life questionnaire for the extirpation of skull base tumors.

Secondary objective: To use the new quality of life questionnaire as a tool to assess the Stability of QOL who underwent endoscopic endonasal approach for resection of skull base tumors.

METHODOLOGY

STUDY DESIGN

The aim of the study is to create and to validate a quality of life questionnaire for endoscopic endonasal approach for the extirpation of skull base tumors that will be performed with the patients treated by the multidisciplinary teams of Clínica Teknon, composed by Dr. Humbert Massegur and Dr. Bartolomé Oliver; and Hospital de la Santa Creu i Sant Pau of Barcelona, composed by Dr. Juan Ramón Gras, Dr. Joan Ramón Montserrat, Dr. Pere Tresserres and Dr. Fernando Muñoz.

STUDY POPULATION

There are 3 populations in the study.

A population of surgically treated patients for skull base tumors will be selected to perform a retrospective study to elucidate the questions that may be included or rejected for the final endoscopic skull base questionnaire.

Another population of the study are patients that will be operated by endoscopic endonasal approach to remove skull base tumors that will be used to assess reliability and validity of the questionnaire.

The final population of the study are patients that will be operated by endoscopic endonasal approach to remove skull base tumors that will be used to assess the stability of quality of life.

INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria to participate in the study are:

- Patients operated by endoscopic endonasal approach for the extirpation of skull base tumors.

The exclusion criteria that not permit to participate in the study are:

- Subjects with moderate to severe cognitive impairment that will be evaluated using the Mini mental Test (MMSE) ≤17/30 *(see Annex 5).*
- Subjects with severe hearing impairment.
- Subjects with receptive aphasia.
- Subjects unable to speak.

SAMPLE PROTOCOL

SAMPLE SELECTION

Sample 1: A first selection will be retrospective with patients that have been operated on Clínica Teknon and Hospital de la Santa Creu i Sant Pau in a first part for the instrument development due to make an assessment of the items through a Likert type response scale, with the aim to add new ones to prepare the questionnaire before assessing reliability and validity.

Sample 2: A non-probabilistic consecutive sampling method will be used. The patients will be recruited during their attendance in the neurosurgical department of Clínica Teknon and Hospital de la Santa Creu i Sant Pau, with the aim of assessing reliability and validity of the questionnaire.

Sample 3: After the construction and the validation of the new questionnaire, a new non-probabilistic consecutive sampling method will be used to assess the stability of QOL after the construction of the new questionnaire.

All participants will be revised to fulfil the inclusion criteria and none of the exclusion criteria stated above, and will be informed about the purpose of the study and will be invited to read and sign the information sheet and informed consent *(see Annex 6)*. They only will be included in the study if they sign and agree with the conditions.

SAMPLE SIZE

To calculate the sample size the power calculator GRANMO® will be used.

An estimation of 35 patients will be necessary to enter at the study if we take into account that a minimum intraclass correlation coefficient of 0.7 of test-retest reliability would be necessary according to previous data published (43,45,46) and taking care that it has been estimated a follow-up losses tax of 10% and a type 1 error of 5%.

DATA COLLECTION

An independent trained physician will conduct all the interviews to avoid any bias that could stem from surgeon-patient interaction.

INSTRUMENT DEVELOPMENT

A review of literature will be used to perform the new questionnaire. A pool of questions related to general QOL (Short Form-36), anterior skull base tumors (cancer-specific ASBQ), and finally sinonasal morbidity (SNOT-22) will be reviewed. Some additional questions will be included to cover symptoms, specifically associated with endoscopic endonasal surgery morbidity taken from interviews with health professionals, surgeons, patients and caregivers.

A number of questions will be constructed after the review of literature and the interviews that will detect the differences in QOL between the preoperative and postoperative periods in this specific surgery.

35 subjects recruited retrospectively that have been operated by endoscopic endonasal approach for the extirpation of a skull base tumor will be selected and asked to rate each of the questions on a six-point Likert-type response scale for its relative importance to their own QOL (number 1 indicates that there is no relation with their QOL and number 6 indicates a great relation), and they will propose new questions that could be important to their own QOL and there won't be in the questions that will be performed. The questions that will be rated with 1 or 2 on a 6 point scale will be deleted from the questionnaire.

DATA ANALYSIS

The data will be analyzed using IBM SPSS® for Windows®

A first factor analysis with Varimax rotation (it determines the relationship of the factors to each other. It simplifies all the set of items classifying them in domains that are independent to each other) will be performed to identify potential domains of QOL. Once the domains were created, we will use the Spearman correlation coefficient to determine if the questions of each domain contribute significantly to it, the once that will be <0. 45 will be dropped. At this stage, another Varimax rotation will be performed in the reduced questionnaire to confirm all the domains.

RELIABILITY

Two types of reliability will be assessed: internal consistency and test-retest reliability. The internal consistency is the way individual items relate to each other, it reflects the homogeneity of items in the scale. The internal consistency of each domain will be evaluated using the Cronbach α value (it calculates the average of correlations between all the items in the measure), and the ones with poor internal consistency will be deleted (if it is <0. 70).

Test-retest reliability measures the stability of an instrument over time with repeated testing. It can be measured by administering the instrument to respondents on two different occasions and examining the correlation between scores using an intraclass correlation coefficient (ICC) (the ICC will be used because the same results in the score of the instrument will be needed in the two occasions). The ICC should be 0. 70 or more. Test-retest reliability will be used to random selected respondents and repeating it after 2 weeks, or repeating the test to the selected patients after two or three days.

VALIDITY

The validity indicates if the instrument appears to be assessing the desired qualities.

If it's known that, for example, old age, perioperative radiotherapy, malignancy, or comorbidity are negative predictive factors (39), the validity of the construct could be assessed by testing if the clinical variable of the patient influenced his or her quality of life as we have hypothesized. So our population will be divided in four groups: age (60 years or older), malignant or benign tumor, presence of perioperative radiotherapy, and patients with additional illness. Then comparisons will be made between the punctuation of the test and the categorical groups using the t-student or Mann-Whitney test depending on whether the distribution is normal or not.

STABILITY OF QOL

With the new quality of life questionnaire, the stability of QOL following the first months after surgery is an important issue in the study.

Considering that the stability of QOL after surgery is not clear (35,39), the QOL scores of 35 patients will be assessed with the new QOL questionnaire at month 3, month 6, month 12 and month 24 of each patient to set the stability of QOL after the extirpation of a skull base tumor by endoscopic endonasal approach.

ETHICAL ASPECTS

The research protocol will be presented to both *Comisión de Ética para la Investigación Médica* (CEIC) located in Clínica Teknon and Hospital de la Santa Creu I Sant Pau of Barcelona before the study is initiated.

The main investigators and collaborators guarantee that the study will be conducted in accordance to the human rights and the ethical considerations gathered in the World Medical Association Declaration of Helsinki of *"Ethical Principle for Medical Research Involving Human Subjects revised in 2013".*

No patient information will be used without their previous consent. At the time of admission, study information and purposes will be explained to each patient and they will be invited to sign the informed consent. To maintain the confidentiality and data security, no names, postcodes,

addresses, birth dates or other numbers will be collected. The security of data will be ensured on locked network which only will be accessible for the principal responsible researchers of the project. According to the national and international laws regarding patient's autonomy, the study will be governed by:

- *Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal.*
- *Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.*

The authors have to declare that they have no conflicts of interest.

STRENGHT AND LIMITATIONS

As any study design, there are different limitations that may interfere in the proper study performance and their final results. These can be classified in biases, study design and sample limitations.

BIASES

Taking into account the biases of selection, the people that will be asked to enter to the study and the people that will not enter because they do not want to participate, will make mandatory to describe their characteristics because a bias of selection can be produced.

Regarding to information biases, a detection biases can be produced if the physician who make the interviews insists at the questions that he/she hopes that will be altered. To try to avoid this information bias a well trained physician interviewer should collect all the information.

The information collected could not be representative if all the interviews are not done by the same interviewer. This bias could be avoid if all the interviews are done by the same trained physician interviewer.

Another bias of information may occur due to the easy way that people have to access to the information via internet. This can develop a situation where the population will not be honest when they will have to answer the questions from a questionnaire.

If all the people that will be operated by endonasal endoscopic approach for an anterior skull base tumor are included in the study, an information bias can be produced if the patient included has a moderate or a severe cognitive impairment, a hearing impairment or is unable to speak. Even a caregiver could be used as a proxie for the estimation of QOL (50), the subjects with these characteristics will be excluded.

The kind of tumor treated must be homogeneous and/or divided in different categories depending on the anatomical areas affected.

To avoid the Howthrone effect the interviews will be done by a unique trained physician interviewer.

To avoid information bias at Likert type response scale and at all the items of the new questionnaire, pair answers will be used instead of odd to avoid that the subject response is going to be the middle when they don't know certainly what to response.

When the information from Hospital de la Santa Creu i Sant Pau will be collected an error due to the surgeons that make the intervention could be done because not all the operations are carried out by the same surgeons. However in Clínica Teknon all the surgical interventions are carried out by the same team.

Finally, confusion variables will be avoided in the instrument development, concretely when Validity is evaluated.

STUDY DESIGN

In this study is important to consider a key factor: the loss of patients due to the lost to follow-up. It is an important factor because most of subjects that will enter to the study, especially the ones from Clínica Teknon, are patients from another regions that have more probabilities to be lost to follow-up. It will be avoided encouraging the physicians to use motivational interviewing in order to engage patients to the study, and those from other regions will be asked if they want to continue participating in the study via telephone survey or via mail.

Concerning the time of the study, we assume that the duration will be long, but not for it more expensive. The duration of the construction of the questionnaire is approximately 2 years, but due to the study of stability of QOL, the duration increases.

SAMPLE LIMITATIONS

A Sample limitation that can be found is about culture and socioeconomical level of the patient. The population of Hospital de la Santa Creu i Sant Pau will not be the same as the population of Clínica Teknon. The population of Clínica Teknon probably have a higher cultural and socioeconomical status (because is a private center) and maybe their answers to questions could be different than the population of Hospital de la Santa Creu i Sant Pau.

The ideal situation would be that the population that will rate the questions with a likert-type respond scale, the ones that will be used to assess reliability and validity, and the ones that will be evaluated to assess the stability of QOL would be the same, but it is impossible to reach. Trying to avoid a bit this limitation the three populations will be composed by 35 patients.

STRENGHT POINTS

Although the duration of the study is long, that do not imply an increase of the cost. The increase of the study is only for stability of QOL, it will be important to investigate the duration of the symptoms after surgery using only a tool that will be specific for this approach.

The cost of the study will not be high considering that the majority will be the salary of statician and the interviewer.

The patients that will enter to the study will not suffer any intervention and will only be asked to answer a series of specific questions. This will not suppose a nuisance for the patients and will reduce the cost of the study.

WORKING PLAN

The Study will be performed in 70 months and it will be composed of 5 phases with different objectives and activities in each part. The outline of the study and plan proposed and the activities that will be done are described in detail bellow:

Phase 1: Study setting-up and coordination (6 months)

- **Study setting-up**: During this period of time, the investigator and co-workers will make a literature review and, propose objectives and hypothesis, develop a methodology and a draft of the protocol design. (1st month)

- **First informative meeting**: When the draft of the protocol design has been made, it will be presented to the collaborators and they will agree with an execution plan and organization. The main investigator will manage the participation of the two centres during this phase. (2nd month)
- **Final project design and writing**. (3rd month)
- **Protocol revision and approval**: The protocol will be presented to CEIC for its revision and approval. (4th month)
- **Second informative meeting:** Once the protocol had been approved by the CEIC, the main investigator will organize some sessions with all implicated professionals (otorhinolaryngologists and neurosurgeons) in which the interviewer that will carry out the interviews will be selected and trained. This session will be used to homogenize and agree a standardized method of action. (5th to 6th month)

Phase 2: Review of questionnaires, interviews, participant's recruitment and data collection (15 months)

- **Review of questionnaires**: A review of ASBQ, SNOT-22 and SF-36 will be done and some questions will be selected. (7th month)
- **Interviews**: Another questions will be included from the interviews of professionals, patients and caregivers. (8th to 9th month)
- **Data collection from retrospective search**: 35 patients that have been operated during the previous year will be asked to answer questions from a likert-type response scale to remove the ones with lowest punctuations, and will propose new questions. (10th to 12th month)
- **Participant's recruitment and data collection**: this part will last from 9 months and it will consist in the recruitment of patients with the desired inclusion criteria. During the first visit, the informed consent will be facilitated to the patients. Once operated, the required information will be collected. (12th to 21st month)

Phase 3: Data Analysis, 2nd participant's recruitment and collection of Stability of QOL data. (36 months)

- **Data analysis**: A statistician will take all collected data and will proceed to analyze it with a specific statistical program with the aim of define the domains that will have the questionnaire and to measure the validity and reliability. (22nd to 25th month)
- **2nd Participant's recruitment**: This part will last from 9 months and it will be a recruitment of patients with the desired inclusion criteria for the study of Stability of

QOL. During the first visit, the informed consent will be facilitated to the patients. (26th to 35th month)

- **Collection of Stability of QOL data**: With the new questionnaire, a collection data about the stability of QOL with the new questionnaire will be collected during 24 months after each surgery. (29th to 60th month)

Phase 4: Results interpretation and final report elaboration (5 months)

- **Results interpretation**: With the statistical data obtained, the investigators will analyze and discuss about the collected data. (26th to 28th month and 61st to 63rd month)
- **Final report writing**. (63rd to 64th month)

Phase 5: Results publication and dissemination. (4 months)

- **Results publication:** The results will be presented to specific national and international conferences and meetings. (65th to 67th month)
- **Final report dissemination:** The final report will be submitted to scientific journals to be published. 68th to 70th month)

STUDY CHRONOGRAM

	2017	2018	2019	2020	2021	2022
PHASE 1: STUDY SETTING UP AND COORDINATION						
Study Setting up						
First informative meeting						
Final project design and writing						
Protocol revision and approval						
Second informative meeting						
PHASE 2: REVIEW OF QUESTIONNAIRES, INTERVIEWS, PARTICIPANT'S RECRUITMENT AND DATA COLLECTION						
Review of questionnaires						
Interviews						
Data Collection from retrospective search						
Participants recruitment and data collection						
PHASE 3: DATA ANALYSIS, 2ND PARTICIPANT'S RECRUITMENT AND COLLECTION OF STABILITY OF QOL DATA						
Data analysis						
2nd Participant's recruitment						
Collection of stability of QOL data						
PHASE 4: RESULTS INTERPRETATION AND FINAL REPORT ELABORATION						
Results interpretation						
Final report writing						
PHASE 5: RESULTS PUBLICATION AND DISSEMINATION						
Results publication						
Final report dissemination						

BUDGET

COST	UNIT COST	UNITS, MONTHS OR HOURS	TOTAL
PERSONEEL			
STATICIAN	35€	120 hours	4200€
INTERVIEWER	45€	250 hours	11250€
PUBLICATION AND DIFFUSION COSTS			
Article publication and diffusion			1200€
OTHER JUSTIFIED COSTS			
Questionnaire and informed consent print	0,15€	500 units	75€
Mobile phone charges	25€	70 months	1750€
TOTAL			**18475€**

The cost of the surgery is not included in budget because it takes part of the patient treatment.

The interviewer will be a unique trained physician that will assume all the interviews.

The MMSE is available for free in clinical practice.

PROJECT RELEVANCE

In recent years we are seeing an increase of endoscopic approaches over external approaches, and the extirpation of skull base tumors is not an exception. Endoscopic endonasal approach for the extirpation of skull base tumors has reach the category of “gold standard” technique for most skull base tumors. Furthermore, this technique improves the outcomes of the tumor extirpation and the quality of life of patients.

To assess the quality of life of these patients, multiple instruments have to be used. So the aim of this project is to create and validate a new unique and site-specific instrument that could assess the quality of life of this patients more quickly and efficiently, could help to investigate possible predictors of functional outcome after surgery, and may help to guide the selection of optimal therapy, type of surgical approach, and reconstruction method and to implement measures that improve perioperative care of the patient that desire a fast functional and emotional recovery.

However, we have to be aware of the limitations of a quality of life questionnaires; they may not be truly centred on patient, because they impose standardised domains derived from the population as a whole (they have a lack of external validity), and may restrict the choice of a patient symptoms to report, their real feeling of a symptom. In that case their scores may be difficult to interpret (51). Another point to consider is that a minimum number of questions must have the maximum reliability as possible so, accordingly, with increased patient numbers, prospective study design, and pretreatment evaluation, longitudinal and multicenter studies would enable to improve the new quality of life questionnaire and, thus, to improve assessment of QOL.

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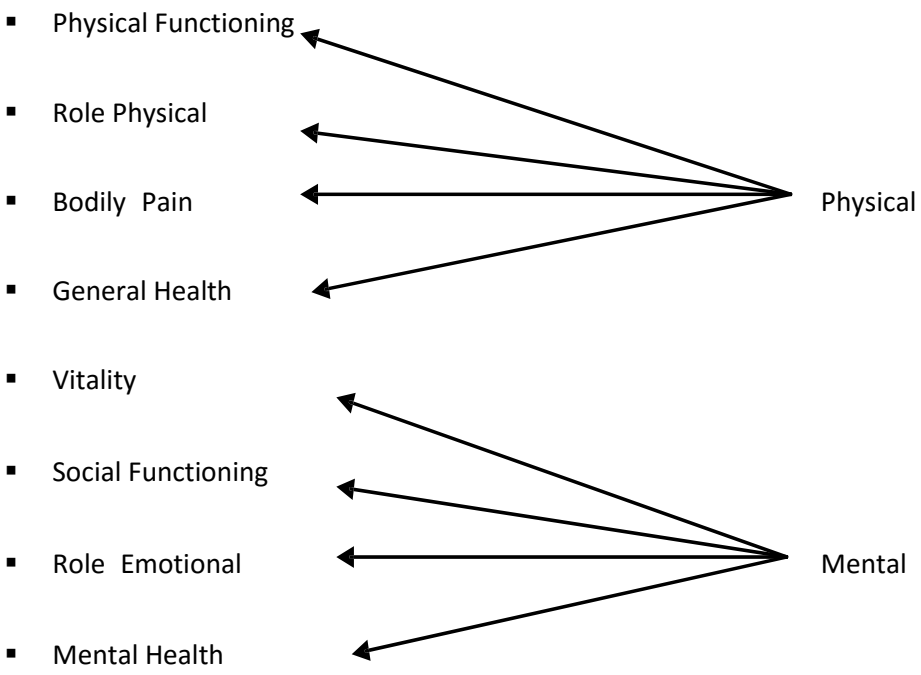
* It is indispensable to mention these articles considering the relevancy of these authors in relation to the history of endoscopic endonasal skull base surgery.

ANNEXES

ANNEX 1: TAXONOMY OF SF-36



ANNEX 2. THE SF-36 HEALTH SURVEY **SF36 Health Survey**

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)

- Excellent ☐
- Very Good ☐
- Good ☐
- Fair ☐
- Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)

- Much better than one year ago ☐
- Somewhat better now than one year ago ☐
- About the same as one year ago ☐
- Somewhat worse now than one year ago ☐
- Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	**Yes, Limited A Lot**	**Yes, Limited A Little**	**Not Limited At All**
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	(Please circle one number on each line.)	**Yes**	**No**
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	**Yes**	**No**
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

ANNEX 3. THE SNOT-22

SINO-NASAL OUTCOME TEST (SNOT-22) COPYRIGHT NOTICE

I.D.:_____ **SINO-NASAL OUTCOME TEST (SNOT-22)** DATE:_____

Below you will find a list of symptoms and social/emotional consequences of your rhinosinusitis. We would like to know more about these problems and would appreciate your answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems as they have been over the past two weeks. Thank you for your participation. Do not hesitate to ask for assistance if necessary.

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	**0**	**1**	**2**	**3**	**4**	**5**		○
2. Nasal Blockage	**0**	**1**	**2**	**3**	**4**	**5**		○
3. Sneezing	**0**	**1**	**2**	**3**	**4**	**5**		○
4. Runny nose	**0**	**1**	**2**	**3**	**4**	**5**		○
5. Cough	**0**	**1**	**2**	**3**	**4**	**5**		○
6. Post-nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
7. Thick nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
8. Ear fullness	**0**	**1**	**2**	**3**	**4**	**5**		○
9. Dizziness	**0**	**1**	**2**	**3**	**4**	**5**		○
10. Ear pain	**0**	**1**	**2**	**3**	**4**	**5**		○
11. Facial pain/pressure	**0**	**1**	**2**	**3**	**4**	**5**		○
12. Decreased Sense of Smell/Taste	**0**	**1**	**2**	**3**	**4**	**5**		○
13. Difficulty falling asleep	**0**	**1**	**2**	**3**	**4**	**5**		○
14. Wake up at night	**0**	**1**	**2**	**3**	**4**	**5**		○
15. Lack of a good night's sleep	**0**	**1**	**2**	**3**	**4**	**5**		○
16. Wake up tired	**0**	**1**	**2**	**3**	**4**	**5**		○
17. Fatigue	**0**	**1**	**2**	**3**	**4**	**5**		○
18. Reduced productivity	**0**	**1**	**2**	**3**	**4**	**5**		○
19. Reduced concentration	**0**	**1**	**2**	**3**	**4**	**5**		○
20. Frustrated/restless/irritable	**0**	**1**	**2**	**3**	**4**	**5**		○
21. Sad	**0**	**1**	**2**	**3**	**4**	**5**		○
22. Embarrassed	**0**	**1**	**2**	**3**	**4**	**5**		○

2. Please mark the most important items affecting your health (maximum of 5 items)_____

ANNEX 4. THE ANTERIOR SKULL BASE QUESTIONNAIRE

The anterior skull base questionnaire

Below is a list of statements that other people with your illness have said are important. By circling one number per item, please indicate how true each statement has been for you.

1. How would you define your general performance?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

2. How would you define your performance at work?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

3. How would you define your performance at home?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

4. During the past 4 weeks, how much did you participate in social activities?

Very much	Quite a bit	Moderately	A little bit	Not at all
5	4	3	2	1

5. How would you define your communication with people?

Excellent	Very good	Good	Fair	Poor
5	4	3	2	1

6. During the past 4 weeks, how much did your health interfere with your performance?

Extremely	Quite a bit	Moderately	A little bit	Not at all
1	2	3	4	5

How well do you perform the following activities (please refer to questions 7–10)?

7. Climbing stairs

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

8. Leaning and standing

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

9. Walking for around 100 meters

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

10. Walking for around 10 meters

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

11. During the past 4 weeks, how frequently did you stay in bed during the day?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

12. How would you define your ability to carry out routine activities?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

13. During the past 4 weeks, how much has your health affected your activity?

Extremely	Quite a bit	Moderately	A little bit	Not at all
1	2	3	4	5

14. During the past 4 weeks, did you feel physically weak or strong?

Very weak	Quite weak	Neither strong nor weak	Quite strong	Very strong
1	2	3	4	5

15. During the past 4 weeks, how frequently did you feel tired?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

16. How much did you accomplish during the last 4 weeks?

Nothing at all	A little bit	Moderately	Quite a bit	Quite a lot
1	2	3	4	5

17. During the past 4 weeks, did you feel depressed or happy?

Very much depressed	A bit depressed	Neither depressed nor happy	A bit happy	Very much happy
1	2	3	4	5

Below is a list of statements that other people with your illness have said are important. By circling one number per item, please indicate how true each statement has been for you.

18. How would you define your motivation to perform various activities?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

19. During the past 4 weeks, how frequently did you feel energetic?

None of the time	A little of the time	Some of the time	Most of the time	All of the time
1	2	3	4	5

20. How would you define your relations with your partner?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

21. During the past 4 weeks, how frequently did you experience pain?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

22. During the past 4 weeks, how much did pain interfere with your ability to perform?

Extremely	Quite a bit	Moderately	A little bit	Not at all
1	2	3	4	5

23. During the past 4 weeks, how frequently did you have to take painkillers?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

24. During the past 4 weeks, how frequently did you feel tense and nervous?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

25. During the past 4 weeks, how frequently did you have a problem falling asleep?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

26. During the past 4 weeks, how frequently did you feel worried?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

27. During the past 4 weeks, how frequently did you feel relaxed or calm?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
1	2	3	4	5

28. How would you define your financial or economic status?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

29. How would you define your appetite?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

30. How would you define your sense of taste?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

31. How would you define your sense of smell?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

32. How would you define your appearance?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

33. How would you define the extent of your nasal secretions?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

34. How would you define your eye secretions and tears?

Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

35. How would you define your eyesight?

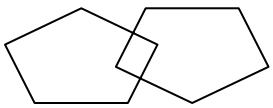
Poor	Fair	Good	Very good	Excellent
1	2	3	4	5

ANNEX 5. THE MINI-MENTAL STATE EXAMINATION

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: ***Ask the questions in the order listed. Score one point for each correct response within each question or activity.***

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

Instructions for administration and scoring of the MMSE

Orientation (10 points):

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

Registration (3 points):

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

Attention and Calculation (5 points):

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):

- Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
- Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.
- Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

(Folstein, Folstein & McHugh, 1975)

Interpretation of the MMSE

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Sources:

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- Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. *Hosp Pract*. 1987;22(1A):99, 103, 106, 110.
- Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922-935.

DOCUMENTO INFORMATIVO SOBRE LA CONSULTA OTORRINOLARINGOLÓGICA

Nombre y apellidos: .....

Edad: ..... D.N.I.: ..... Nº historia clínica: .....

Diagnóstico del proceso: ..... Fecha: .....

Médico informante: ..... Nº Colegiado: .....

La Otorrinolaringología es una especialidad que se ocupa de la atención de diversos órganos de la cara, el cráneo, y el cuello. Por lo general, estos suelen ser muy sensibles en el curso de su exploración. Su especialista tiene la experiencia suficiente y posee los recursos técnicos adecuados para atenderle de la manera más apropiada. No obstante, a lo largo de la consulta puedan surgir diversas incidencias que debe de conocer:

Los instrumentos que utilizamos son, muchas veces, metálicos. Aún manejados con el máximo cuidado, estos instrumentos pueden rozar la superficie de los órganos examinados produciendo la lógica molestia y, excepcionalmente, la aparición de una pequeña hemorragia. Si bien su especialista le atenderá con la mayor habilidad, en ocasiones, la aparición de las mencionadas molestias es inevitable.

También, cabe la posibilidad de que precise instilar en las fosas nasales, la garganta o el oído diversas substancias, tales como un anestésico local, vaselina, etc. por lo que, si es alérgico o no tolera bien alguna medicina, debe de advertirlo con anterioridad.

En general, la garganta es una zona delicada de explorar ya que, en ocasiones, el paciente puede tolerar mal la mencionada exploración y sufrir náuseas. Entienda que su especialista intentará evitarle cualquier molestia pero, en ocasiones, ello resulta difícil. Procure estar relajado y con la confianza de que no sufrirá ningún daño innecesario. Para el examen de la garganta se utiliza un depresor de lengua. Accidentalmente el depresor podría producir alguna pequeña lesión, rozaduras o excoriaciones que podrían justificar pequeñas hemorragias

A criterio del especialista que le atiende pueda requerir la exploración con un endoscopio -aparato que permite una mejor iluminación y control de determinadas zonas de su organismo- por lo que, si existe alguna anomalía anatómica que pueda dificultar dichas maniobras, debe advertirlo con anterioridad. Además, el endoscopio sufre un proceso de desinfección muy riguroso por lo que, incluso con un esmerado lavado, puede resultar irritante. Dependiendo de las molestias secundarias, pueda ser conveniente lavar su nariz, o realizar gárgaras con suero fisiológico, durante unos días.

En el caso concreto del oído, si existiera una perforación timpánica o alguna otra lesión que conozca, debe de advertirlo con anterioridad para que su especialista pueda atenderle de la manera más adecuada.

En general, todas estas cavidades –la nariz,la garganta, el oído, etc.- pueden contener pequeñas costras, formaciones de piel, secreciones, acúmulos de cerumen, objetos extraños, sustancias diversas, taponamientos quirúrgicos, etc. que deben de ser retirados. Las técnicas de extracción son muy diferentes en dependencia de distintas circunstancias. Si bien su especialista le atenderá con el máximo cuidado, durante estas maniobras podrían producirse pequeñas lesiones, tales como pequeños desgarros timpánicos, heridas en la nariz o la garganta, etc.

Por último, su atención puede requerir la realización inmediata de pequeños gestos terapéuticos, tales como el taponamiento nasal, la cauterización de pequeñas zonas sangrantes, etc. Su especialista le informará en concreto de cada una de ellas y de los detalles que le puedan interesar.

Además, el estudio de diversas enfermedades, tales como el vértigo, la congestión nasal, la alergia, etc. pueden requerir la reproducción de dichas situaciones, para su mejor estudio. En el caso del paciente vertiginoso, a pesar del máximo cuidado, a lo largo de su exploración pueden producirse situaciones de inestabilidad o caídas accidentales.

Por último, durante su consulta, el médico pueda necesitar una gran cantidad de información relativa a su salud o a consultas anteriores realizadas con otros especialistas. No oculte ningún dato sobre su caso, otras enfermedades, hábitos o régimen de vida, que pudieran ser relevantes, a los médicos que le atienden. Además, el médico pueda requerir tomar las muestras biológicas que considere necesarias para el estudio de su proceso, así como las imágenes precisas o las muestras de voz para la adecuada documentación del caso. Como norma general, entienda que **la intención del médico es la de ayudarle** por lo que debe de colaborar activamente con él, en el curso de su trabajo. No dude en formular las preguntas o exponer las dudas que puedan surgir a lo largo de su exploración o tratamiento.