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Olfactory Function Following Endoscopic Endonasal Skull Base Surgery: Clinical and Histological Outcomes

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1. **Objectives**:
   Primary Outcome: To compare the olfactory function before and after endoscopic skull base surgeries for all skull base pathology cases.

   Secondary Outcomes:
   - To validate olfactory sparing approaches
   - To obtain data to audit outcomes of treatment of skull base pathologies
   - To determine the degree of disability

2. Introduction

2.1 Overview

This is a prospective study including all patients undergoing standard of care endonasal skull base surgery at The Ohio State University Wexner Medical Center. We will evaluate the olfactory function using a standardized test, The University of Pennsylvania Smell Identification Test (UPSIT). Each patient will have the UPSIT administered as part of standard of care before surgery and at six month post-surgery. As part of the research, each patient will also have the UPSIT administered at one, three, and twelve months post-operatively. Results will be correlated with the type of surgical approach and other factors that may alter olfaction.

Standard of care intraoperative measurements of the olfactory area (before and after harvesting of nasoseptal flaps, which may include part of the olfactory epithelium) will be obtained and compared with human cadaveric studies. We will use a sterile acetate sheet with a printed grid to obtain precise measurements. During harvesting, a sample from the most superior aspect of the nasoseptal flap will be obtained for immunohistochemical study to confirm the absence or presence of olfactory epithelium.

Patients who develop anosmia after surgery will be offered a standard of care biopsy of the olfactory area to try to ascertain the presence or absence of neural degeneration. We hypothesize that the olfactory epithelium is at risk during endoscopic endonasal skull base surgery and that olfactory dysfunction increases with the extent of surgery. Pre- and post-operative evaluation of olfaction is essential to ascertain the true incidence of this problem and to tailor the endoscopic endonasal skull base surgery in such a way that we achieve complete removal of the pathology or correction of the pathology while preserving the sense of the smell. By conducting this study, we will be able to spare this area in more effective ways.

2.2 Background and Rationale

Advances in endoscopic endonasal skull base surgery over the past several years have increased the survival rate for patients with skull base pathologies; however, these patients may develop significant morbidity following intervention. Serious complications include cerebrospinal leaks, which may lead to meningitis or intracranial abscess; therefore, reconstruction of the defect, achieving a complete separation of the cranial cavity from the sinonasal tract is critical. Adoption of the vascularized nasoseptal flap resulted in a reliable and reproducible reconstructive technique that led to a significant decrease in the incidence of postoperative CSF leaks. Unfortunately, this flap may prolong operative time, increase intraoperative and postoperative bleeding, and cause sinonasal morbidities such as nasal crusting, nasal obstruction, and olfactory dysfunction.

Identifying the adverse long-term effects of treatment becomes increasingly important as patients try to resume previous activities and an independent lifestyle. The measurement of functional states and health-related quality of life issues are at the forefront of medicine and have become necessary measures of functional outcome following the treatment of a variety of medical and surgical disorders. Although the World Health Organization has long defined health as not only the absence of disease, but as ‘‘complete physical, mental, and social well-being,’’ reports of surgical outcomes for patients with skull base lesions have often been limited to length of survival or the presence or absence of disease. More recently, there has been greater recognition of the importance and feasibility of including quality of life (QOL) indexes as an additional clinical end. Although there is no universally accepted definition for QOL, it is generally agreed that QOL is a multidimensional construct encompassing patient perception of overall well-being. It is necessary to differentiate QOL from symptom assessment, as the perceived impact of a given symptom may vary significantly between individuals and over time.

Anosmia and hyposmia may result after skull base surgery; either because of involvement of the olfactory epithelium by the pathology or due to injury by the surgical approach. Olfactory dysfunction has a negative effect on the overall quality of life. Nonetheless, research addressing olfactory function in regards to endoscopic skull base surgery and its correlation to the tailoring of the approach to preserve olfactory function is sparse.

Smell identification tests exploit a variety of qualitatively distinct odorants and set concentrations of stimuli. The more sophisticated of these tests derive from test measurement theory and focus on the comparative ability of individuals to identify odors. The 40-item University of Pennsylvania Smell Identification Test (UPSIT), known commercially as the Smell Identification (SIT) was the first of such tests to capitalize on this process. This test asks the subject to smell an odor and then identify the smell from a list of forced-choice alternatives. This paradigm is surprisingly reliable (test-retest reliability coefficients for the UPSIT are commonly on the order of 0.95 [Doty et al., 1985]) perhaps because linking an odor to a given object or locale appears to be a quintessential function of the olfactory system.

Measurement of olfactory function pre-operatively compared to post-operative results will open novel venues to evaluate modifications of the vascular flaps for skull base reconstruction.

3. Eligibility Criteria

3.1 Inclusion Criteria

1. Patients presenting with skull base pathologies requiring endonasal surgery (i.e. tumors, inflammatory process, fractures, defects, etc.) at The Ohio State University Wexner Medical Center (OSUWMC)
2. 18 years or older
3. Able to obtain informed consent from the patient
4. Negative serum pregnancy test for women of childbearing potential

3.2 Exclusion Criteria

1. Patients presenting with a skull base pathology that does not require endonasal surgery
2. Inability to obtain informed consent from the patient
3. Patient will be unable to return to clinic at specific follow-up times
4. Pregnant or nursing
5. Prisoners

4. Study Procedures

4.1 Study Design

This is prospective study evaluating olfactory function by administering the standard of care UPSIT (smell identification test) preoperatively and repeated at 6 months (±30 days) after surgery. As part of this research, the UPSIT will be repeated at 1 (±30 days), 3 (±30 days), and 12 months (±90 days) after surgery. All patients will also be asked to answer two questionnaires: the ASK Nasal -12 (Appendix 1) and the Skull Base Inventory (SBI) (Appendix 2) before the surgery and at one, three, six and twelve months postoperatively as part of the research portion of this study. If surveys and/or UPSIT smell test cannot be completed during the follow-up visit (i.e. due to time constraints) the surveys and/or UPSIT

smell test and a self-addressed stamped envelope will be mailed to the participants. Additionally, the surveys can be emailed to the participants, if they prefer, and are comfortable providing their email address. The data obtained from all UPSIT and questionnaire time points will be analyzed for this study.

4.2 Data Collection

Coded data will be recorded and will be accessible only to the research team. Only the Principal Investigator will have access to the code key.

A REDCap database will be used to collect the data. Data collected will include:

- Patient demographics
  a. Age
  b. Gender
- Occupation
- Habits
- History of prior nasal or maxillofacial trauma, surgery or radiotherapy
- History of allergies or bronchial asthma
- Underlying diseases that may affect the healing process
- Nasal symptoms
- Primary diagnosis
- Radiological data will also be collected for these patients. This will include CT scan and MRI results as clinically indicated.

The following surgical data will be collected from the patient's medical record:

- Operative approach with detailed information about the extent of the approach
- Type of flaps
- Ligation of the ethmoidal arteries
- Technique for flap harvesting
- Measurement of the olfactory area (total and spared)

The following histopathological data will be collected:

- Type of pathology
- Margins

The following immunohistochemical data will be collected:

- Result of biopsy of superior aspect of the flap
- Result of biopsy taken from the olfactory region in the nose in patient with post-operative anosmia. If it showed degenerative olfactory neurons, it proved that the olfactory area was not spared during surgery.

Symptoms such as change in smell, bleeding, CSF leak, change in vision will be collected as part of the follow-up data at post-operative months one, three, six, and twelve.

4.3 Statistical Analysis

Continuous patient demographic, surgical, histopathological and immunohistochemical data will be summarized numerically (mean, standard deviation, range) and graphically (box plots). Categorical data will be summarized and presented as frequencies (percent). Linear mixed models will be fit to assess the relationship of clinical and demographic characteristics with changes in the main longitudinal outcome of olfactory function as measured using UPSIT over time. Linear mixed models take into account the correlated nature of the data within study participants over time. Relationships between demographic and clinical data and the secondary outcomes will be assessed using linear mixed models (Longitudinal continuous outcomes), logistic regression (dichotomous secondary outcomes), or linear regression (continuous secondary outcomes at a single time point) where appropriate.

5. References

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