Impairment of Olfaction and Mucociliary Clearance After Expanded Endonasal Approach Using Vascularized Septal Flap Reconstruction for Skull Base Tumors

BACKGROUND: Endoscopic skull base surgery is now the preferred treatment option to remove skull base tumors.

OBJECTIVE: To evaluate the patient’s sense of smell and mucociliary clearance time (MCT) after skull base surgery.

METHODS: Patients with pituitary adenoma underwent a transnasal transsphenoidal endoscopic approach (TTEA group, n = 36), whereas patients with other benign parasellar tumors underwent an expanded endonasal approach (EEA group, n = 14) with a vascularized septal flap. Assessment of symptoms (Visual Analogue Scale), olfactometry (Barcelona Smell Test, BAST-24), and MCT (saccharin test) were performed before and 3 months after surgery.

RESULTS: Before surgery, patients reported poorer BAST-24 scores on detection, identification, and forced choice than the healthy population, but both study groups had similar sinonasal symptoms, BAST-24, and MCT scores. After surgery, no changes in symptom scores (Visual Analogue Scale) were observed except for the loss of smell (26.7 ± 30.5 mm, P < .05) and posterior nasal discharge (29.7 ± 30.3 mm, P < .05) compared with baseline (5.2 ± 11.3, 19.1 ± 25.3, respectively). EEA patients reported higher loss of smell and posterior nasal discharge compared with TTEA. TTEA and EEA groups had similar scores on postoperative BAST-24. After surgery, however, patients showed prolonged saccharin test (15.6 ± 10.8 min, P < .05) compared with baseline (8.4 ± 4.4 min). In addition, EEA patients reported longer MCT than TTEA patients.

CONCLUSION: EEA but not TTEA has a short-term (3 months) negative impact on patient’s olfaction and mucociliary clearance. Patients should be informed about smell loss as a consequence of skull base surgery to prevent legal claims. Likewise, further research and some modifications on reconstruction flaps are encouraged to avoid damaging the olfactory neuroepithelium.

KEY WORDS: Mucociliary clearance, Olfaction, Pituitary adenoma, Sinonasal symptoms, Skull base, Smell test

The transnasal transsphenoidal endoscopic approach (TTEA) to the sella turcica and the expanded endonasal approach (EEA) to the skull base are techniques that have undergone much development over the past several years. To reduce the high rate of cerebrospinal fluid leaks, a broad vascularized septal flap (VSF) based on the posterior nasoseptal artery has been formally described for closure of skull base defects and to provide a healthy nasal microenvironment. Recent advances in the treatment of skull base tumors have had a major positive impact on the long-term survival of patients. Likewise, transnasal surgery has the potential to impair normal physiological processes, including olfaction, and consequently can negatively impact the patient’s quality of life.

ABBREVIATIONS: BAST-24, Barcelona Smell Test; EEA, expanded endonasal approach; ESS, endoscopic sinus surgery; MCT, mucociliary clearance time; TTEA, transnasal transsphenoidal endoscopic approach; UPSIT, University of Pennsylvania Smell Identification Test; VAS, Visual Analogue Scale; VSF, vascularized septal flap

© Congress of Neurological Surgeons. Unauthorized reproduction of this article is prohibited.
The olfactory neuroepithelium is located in the upper recesses of the nasal cavities within the cribriform plate and sectors of the superior turbinate, middle turbinate, and septum. Loss of olfaction can result in hazardous events such as cooking-related accidents, the inability to detect fires or gas leaks, or ingestion of rotting food or toxic substances. Nevertheless, EEA might increase the damage to olfactory neuroepithelium owing to middle turbinate resection and VSF reconstruction. Nasal morbidity such as crusting and discharge are the most common postoperative symptoms following TTEA or EEA especially after VSF. Denuded mucosal surfaces, resulting from harvesting the VSF, are usually left to heal by secondary intention, prolonging postoperative septal remucosalization, which promotes nasal crust formation.

Mucociliary clearance time (MCT) is the key defense mechanism in the upper airways, because the removal of debris-laden mucus in the sinuses completely depends on MCT. So far, the way in which the nasal MCT is regulated remains unknown. Ciliary beat frequency and physical properties of the mucus layer are important factors that influence MCT effectiveness. MCT can be affected by environmental heat, moisture, trauma, smoking, viral infections, chronic rhinosinusitis, allergic rhinitis, adenoid hypertrophy, septum deviation, surgery, cystic fibrosis, chronic bronchitis, and asthma.

Given that the approach requires resection of structures with known contributions to sense of smell and mucociliary transport, the goal of this study was to determine whether the expanded surgical approach had any effect on sinonasal symptoms, olfaction, and MCT. To our knowledge, this is the first prospective study to evaluate olfactory outcomes and MCT in EEA with VSF reconstruction for benign tumors in comparison with standard pituitary surgical approaches.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Patients older than 18 years with pituitary or skull base tumors were included in this study. Patients with chronic rhinosinusitis and/or nasal polyposis, allergic rhinitis, intranasal drug abusers, nasal surgery, and past history of preexisting subjective smell disturbance were excluded.

Study Population

Sixty-two patients diagnosed with pituitary or skull base tumors and scheduled to undergo surgery between 2009 and 2011 were enrolled in this prospective study. Twelve patients were excluded from this study for different reasons: reoperation (n = 4), malignancies (n = 5), nasal polyposis (n = 2), and previous anosmia (n = 1). Finally, 50 patients met the inclusion criteria (66% female, mean age 47.7 ± 15.5 years, ranging from 22 to 82 years). Patients with pituitary adenoma (TTEA group, n = 36), with either functioning (n = 23) (growth hormone-secreting, n = 9; adrenocorticotropic hormone-secreting, n = 6; and prolactin-secreting surgically treated, n = 8) or nonfunctioning (n = 13) adenoma, underwent tumor resection by TTEA and middle turbinate preservation, whereas patients with other benign parasellar tumors underwent EEA with VSF reconstruction (EEA group, n = 14: macroadenoma = 3, meningioma = 4, craniopharyngioma = 3, Rathke cleft cyst = 1, chordoma = 3). The EEA group included 9 left-sided and 5 right-sided VSFs depending on septum deviation and tumor localization. VSF was performed by using low-power cutting cautery, with care being taken to leave 1 cm below the cribriform plate along the flap length to preserve olfactory neuroepithelium. Nasal endoscopy was performed by the same otorhinolaryngologist for all patients before and after surgery to ensure consistency in the evaluation of mucosa aspect, crusting, synchiae formation, and remucosalization. The Ethics Committee of Hospital Clínic de Barcelona approved the study, and signed informed consent was obtained from all patients.

Study Design

Assessment of sinonasal symptoms (Visual Analogue Scale, VAS), sense of smell (Barcelona Smell Test, BAST-24), and MCT (saccharin test) were performed on all patients before and 3 months after surgery. Ohashi et al. reported that complete recovery of the nasal mucosa after trauma may occur after a postoperative period of 5 days if basal cells and basement membrane remain intact. When the entire nasal mucosa was mechanically damaged, regenerative stratified epithelium covered the defect in 1 week, new ciliated cells appeared in 3 weeks, and complete regeneration was observed at 6 weeks. Furthermore, Günzel and Huhn reported that prolonged MCT was normalized 3 months after septoplasty. Based on these findings, the authors decided to wait at least 3 months for full recovery of nasal mucosa to evaluate postoperative symptoms, sense of smell, and nasal MCT.

Surgical Procedures

Transnasal Transsphenoidal Endoscopic Approach

The middle turbinate was gently deflected laterally to allow posterior access. The nasal mucosa overlying the anterior sphenoid wall and vomer was cauterized before the sphenoid sinus was opened. After wide removal of the anterior wall of the sphenoid sinus, the mucosa of the sinus was removed to prevent postoperative bleeding and late mucocele formation. The dura of the sella was adequately exposed to remove the tumor. A vascularized flap was not used, and postoperative nasal packing was not routinely used.

Expanded Endonasal Approach

Middle turbinectomy was usually performed in the majority of patients, and resection of the posterior third of the superior turbinate was needed, in some cases, to improve accessibility to the tumor. The posterior part of the septum was then drilled out, and a wide sphenoidotomy and ethmoidectomy were later performed to identify anatomical landmarks within the sphenoid bone. In fact, the exposure through an extended approach was “tailored” depending on surgical pathway, type, tumor size and shape, and relationship with the surrounding neurovascular structures. The anatomical limits of the surgical box were definitively established by using the micro-Doppler probe and the intraoperative navigation system.

The VSF was designed according to the size and shape of the anticipated defect. Two parallel incisions using a cutting cautery on a low-power setting were performed following the sagittal plane of the septum. One
incision followed the maxillary crest and nasal floor, whereas a parallel incision followed a line 1 cm below the superior aspect of the septum (olfactory sulcus). These parallel incisions were joined anteriorly by a vertical incision. Posteriorly, the superior incision was extended laterally to cross the rostrum of the sphenoid sinus. The inferior incision extended following the edge of the posterior septum and, then, laterally crossing the posterior choana just below the floor of the sphenoid sinus. The elevation of the mucoperichondrium and mucoperiosteum proceeded in an anterior to posterior direction while the neurovascular pedicle was preserved. We usually store the flap in the nasopharynx or maxillary sinus depending on the tumor localization.

Reconstruction was key to prevent complications mostly related to postoperative cerebrospinal fluid leakage. One single large layer of dural substitute was positioned in the extradural space between the dura and the surrounding bone to provide a watertight closure. Then the vascularized mucosal flap was used to cover the skull base reconstruction and the previously denuded surrounding bone. Anterior nasal packing was maintained 24 to 48 hours after surgery.

Study Outcomes

Sinonasal Symptoms

Patients were asked to evaluate sinonasal symptoms (nasal obstruction, facial pain or pressure, anterior and posterior discharge, sneezing, itching, and smell loss) by using the VAS (0-100 mm). The disease severity classification of the European Position Paper on Rhinosinusitis was used to score VAS smell loss (mm) (0 = no smell change, 0-30 = mild hyposmia, 31-70 = moderate hyposmia, >70 = severe hyposmia).^13^

Barcelona Smell Test

Twenty-four odors are used in the BAST-24: (a) 20 odors to assess the first cranial nerve (olfactory): banana, gasoline, lemon, rose, onion, smoked, anise, coconut, vanilla, melon, mandarin, bitter almond, pineapple, cheese, strawberry, mushroom, eucalyptol, clove, turpentine, and peach; and (b) 4 odors to assess the fifth cranial nerve (trigeminal): formol, vinegar, ammonia, and mustard. After being exposed for 5 seconds to an odorant, patients were asked to answer a number of questions: (1) to test smell detection, “Did you smell anything?”; (2) to test smell identification, “Did you recognize this odor?”; and (3) to test smell forced choice, “Which of these four odors did you smell?” The healthy control group consisted of 100 age-sex–matched healthy volunteers without subjective olfactory disturbance or nasosinusal disease, and with a mean age of 42 ± 16 years (ranging from 21 to 85 years).^14^ The control group belonged to the same geographic area and socioeconomic class as the patient population.

Mucociliary Clearance Time

The nasal MCT was studied by using the method described by Anderson et al.^15^ The method is simple, noninvasive, and economical, and it yields reproducible results. MCT was done at normal room temperature, and patients were told to sit comfortably with their heads in a slightly extended position. Patients were told not to bend forward and not to sniff, inhale, or exhale forcefully and to avoid nasal manipulation during the test. At first, nasal secretions were aspirated and then a 1 mm particle of saccharin was placed on the floor of the nose about 1 cm posterior to the anterior end of the inferior turbinate. The time in minutes required by the individual to perceive the sweet taste was noted. The patients were asked to report any change in taste and were not told that they would perceive a sweet taste. A previous study demonstrated that, in patients without septum deviation, MCT was similar on both sides. However, concave-side septal mucosa seems to impair mucociliary transport, presumably owing to ciliary loss, increased inflammation, and decreased density of the seromucous glands.~16~ For these reasons, the nasoseptal flap was obtained from the wider nasal cavity, including the nasal floor mucosa, and the MCT test was performed on the same side of the septal flap.

Statistical Analysis

The data are presented as mean ± standard deviation. Student t test was used to compare outcomes with those of the healthy population and between TTEA and EEA groups. Pearson correlation coefficients were used to examine the association between the loss of smell by using BAST-24 and sex, age, nasal symptoms, and MCT. A P value of less than .05 was considered statistically significant.

RESULTS

Panhypopituitarism was preoperatively present in 3/36 patients (8.3%) and in 4 additional patients (12.1%) as a consequence of surgery (one or more pituitary deficiencies). At the latest follow-up revision after surgery, most of the patients with nonfunctioning tumors (12/13) and most of the patients with acromegaly (8/9) experienced complete remission. All patients with Cushing disease also presented hormonal resolution. No further negative effect of panhypopituitarism or hypothyroidism on olfactory function was observed.

Mean time to septum remucosalization for the EEA group with VSF was 87 ± 14 days, and the mean time to absence of crustings was longer (99 ± 16 days; range, 75-121 days, P < .05) than the TTEA group (45 ± 13 days; range, 32-78 days). Mild synchieae without subjective breathing difficulties was present in 8% postoperatively, with no significant differences between both groups. No further effects of sex or age on study scores were found.

Sinonasal Symptoms

At baseline, patients reported mild sinonasal symptoms with no differences between EEA and TTEA groups or between functioning and nonfunctioning adenomas (Table 1). After surgery, all patients showed similar VAS symptom scores, with the exception of smell loss and posterior nasal discharge.

Before surgery, moderate-to-severe smell loss (VAS > 30 mm) was reported in 6% of the TTEA and 0% of the EEA group. After surgery, 23% of TTEA and 50% of EEA patients reported moderate-to-severe smell loss. Patients showed a poorer sense of smell after surgery compared with baseline, with EEA patients reporting a higher smell loss in comparison with the TTEA group (Figure 1).

Before surgery, moderate-to-severe posterior nasal discharge (VAS > 30 mm) was reported in 8% of the TTEA and 7% of the EEA group. After surgery, moderate-to-severe posterior nasal discharge was present in 27% of the TTEA group and 65% of the EEA group after surgery. EEA patients reported more posterior nasal discharge in comparison with the TTEA group (Figure 2).
No significant differences were observed on sense of smell and posterior discharge by VAS between functioning and nonfunctioning adenoma.

No significant correlation was found between nasal obstruction and MCT or BAST-24.

Barcelona Smell Test

At baseline, patients from both study groups, with no differences between them on BAST-24, reported poorer scores on smell detection (95.2 ± 9.5%, P < .01), identification (23.1 ± 22.3%, P < .001), and forced choice (25.2 ± 26.6%, P < .001) than the healthy general population (99.2 ± 1.5%, 54.7 ± 4.9%, 72.2 ± 6.8%, respectively). After surgery, patients showed no significant changes in smell detection (94.2 ± 9.9%), identification (20.9 ± 20.2%), and forced choice (61.5 ± 19.9%) in comparison with baseline. In addition, no significant differences were found between EEA and TTEA groups (Figure 3) or between functioning and nonfunctioning adenoma on BAST-24 outcomes after surgery (Table 2).

However, there was a significant correlation between the self-reported loss of smell and detection score by BAST-24 (R: 0.46; P < .05), showing that VAS is more sensitive to changes than subjective olfactometry (BAST-24).

Mucociliary Clearance Time

At baseline, no significant differences on the saccharin test were found between TTEA and EEA groups (Figure 4). After surgery, however, all patients showed longer MCT (P < .01) than at baseline. In addition, patients from the EEA group reported a longer MCT (P < .01) than the TTEA group as well as more crusting and posterior nasal discharge. No differences on MCT between functioning and nonfunctioning adenoma were observed either before (9.3 ± 3.5 min, 7.9 ± 5.4 min) or after (11.4 ± 8.4 min, 14.6 ± 5.7 min, respectively) surgery.

Study Limitations

The main limitations of the study are (1) although the small sample of EEA patients made it difficult to draw strong conclusions,
this novel study does reveal important insights focusing on postoperative MCT and olfaction alterations; (2) the studied group was heterogeneous, including patients with all types of adenomas and skull base tumors; (3) BAST-24 does not incorporate the Odor Detection Threshold test, which could also be useful to measure olfactory acuity; and (4) although the present study is limited to 3 months postoperative follow-up, a longer follow-up will be done and data analyzed.

DISCUSSION

The main findings of our study are as follows: EEA but not TTEA has a short-term (3 months) negative impact on patients’ MCT and loss of smell as measured by VAS but not by olfactometry (BAST-24). EEA patients reported more nasal discharge. This could be due to VSF and long crusting time. Functioning tumors had no further negative effect on sense of smell and MCT in comparison with nonfunctioning tumors.

Sinonasal symptoms following endoscopic sinus surgery (ESS) have been studied extensively in chronic rhinosinusitis. Olfactory function measured by Sniffin’ Sticks test improved significantly 3.5 months after surgery in those patients who received ESS, but no significant increase was found in patients treated with nasal septum surgery. These results may not apply to endoscopic skull base surgery because of the use of more aggressive techniques and the absence of inflammatory mucosa. de Almeida et al17 demonstrated that nasal crusting (98%) and discharge (46%) were the most common postoperative symptoms, with longer times for complex cases but not for patients with VSF or fat grafts. The majority of patients experienced no change in the sense of smell; only 7.9% had a decrease in the ability to smell after surgery.

Many previous studies relied on self-reporting of olfactory deficits, and no objective measures were used to determine olfactory function. Kennedy et al18 showed that the sublabial transseptal transphenoidal approach resulted in olfactory changes in 1.5% to 12% of patients, likely because of injury to the cartilaginous septum and inflammation of the olfactory cleft. Ikeda et al19 similarly demonstrated an objective decrease of olfactory function in 12% of patients undergoing the sublabial transseptal approach. Zada et al20 retrospectively reported a moderate-to-severe impairment of olfaction in 9% of patients after microscopic TTEA. Dusick et al21 retrospectively showed that 10.4% of patients reported a moderate-to-severe impairment of olfaction. Higgins et al22 mentioned a 2% to 12% incidence of

![Figure 3](image-url)

**FIGURE 3.** The effect of surgery on the loss of smell with the use of the Barcelona Smell Test. Effect of transnasal transphenoidal endoscopic approach (TTEA) in comparison with the expanded endonasal approach (EEA). Open columns, before surgery; filled columns, after surgery.

**TABLE 2.** Sense of Smell Scores by Visual Analogue Scale (0-100 mm) and BAST-24 Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Smell Loss (VAS, mm)</th>
<th>Barcelona Smell Test (BAST-24)</th>
<th>Detection, %</th>
<th>Identification, %</th>
<th>Forced Choice, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfunctioning adenoma (n = 13)</td>
<td>4.9 ± 1.7</td>
<td>97.0 ± 6.3</td>
<td>25.5 ± 20.2</td>
<td>49.5 ± 12.6</td>
<td></td>
</tr>
<tr>
<td>Functioning adenoma (n = 23)</td>
<td>6.2 ± 1.1</td>
<td>93.7 ± 11.2</td>
<td>24.3 ± 27.8</td>
<td>55.3 ± 24.3</td>
<td></td>
</tr>
<tr>
<td><strong>3 months after surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfunctioning adenoma (n = 13)</td>
<td>26.5 ± 35.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>94.5 ± 11.3</td>
<td>14.5 ± 11.3</td>
<td>61.1 ± 25.7</td>
<td></td>
</tr>
<tr>
<td>Functioning adenoma (n = 23)</td>
<td>24.6 ± 29.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92.7 ± 10.4</td>
<td>30 ± 24.4</td>
<td>64.1 ± 16.3</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>BAST-24, Barcelona Smell Test; VAS, Visual Analogue Scale.

<sup>b</sup>P < .05 between baseline and 3 months after surgery.
anosmia and hyposmia in patients treated by the transseptal approach. Koren et al. found hyposmia and anosmia in 10% of patients who had undergone TTEA. Tan and Jones reported 4% of patients with hyposmia. Our study reported 12% of anosmia, in line with other studies (VAS > 70). In addition, our study demonstrated that VAS is more sensitive to smell changes than subjective olfactometry (BAST-24) as we have previously reported in patients with persistent allergic rhinitis.

Only 2 studies have investigated the effect of endoscopic skull base surgery on olfaction by using subjective olfactometry. Harta et al. studied 45 patients after endoscopic pituitary tumor resection with the use of the University of Pennsylvania Smell Identification Test (UPSIT). A transient difference was found between preoperative and 1-month UPSIT scores. At 3 months, no clinically significant difference was found on repeat olfactory testing. They concluded that, although the transnasal endoscopic approach to the sella removes structures known to contribute to olfactory function, it has no clinically significant effect on olfaction. In this study, the impact of VSF on olfaction was not investigated. Rotenberg et al. studied 17 patients with pituitary tumors after TTEA and VSF. With the use of UPSIT, all patients were tested as being hyposmic 6 months postoperatively, and all of them reported olfactory loss. Although this study had a small sample size and no non-VSF group was included, it raised the question as to whether there is any value in raising a VSF for all cases of pituitary surgery. Our results partially agree with those of Rotenberg, although we only performed VSF for EEA and not for pituitary surgery.

Another study investigated the impact of microsurgery on the sense of smell. Actor et al. retrospectively analyzed 96 patients who underwent transnasal transphenoidal microsurgery. Olfactory performance was assessed by using the Sniffin’ Sticks test and/or the Zürcher Geruchstest. After surgery, 49% of patients improved, 35% deteriorated, and 16% presented with unchanged olfactory performance.

Mucociliary transport is the physiological process that depends on the number of cilia and the beat frequency. To our knowledge, no further studies have investigated the impact of VSF on MCT. Different studies have concluded that septoplasty improves reduced MCT and that the effect of nasal surgery on nasal mucociliary activity may be more accurately evaluated in the third rather than in the first postoperative month. David et al. reported that, if septoplasty surgery is successfully performed, nasal MCT significantly improves. They also found that there is no significant difference in MCT between the obstructed nasal cavity and the opposite side of the deviated septum. Shone et al. showed that MCT in nasal cavity improved after septoplasty and ESS for nasal polyposis. Studies with septal perforation patients elicited that the regeneration duration of a total layer injury of the nasal mucosa continues up to 3 months. Recently, Caicedo-Granados et al. described an innovative technique that improves the remucosalization of the VSF donor site with a local contralateral septal mucosal flap. Patients also reported less nasal crusting and better nasal airflow.

As a result, we have recently included the possibility of permanent changes in smell to the standard informed consent for these procedures when informing patients scheduled to undergo expanded endoscopic skull base surgery.

Further research on olfactory neuroepithelium and modifications on reconstruction flaps should be encouraged to prevent smell loss and alteration of mucociliary transport. The superior nasal septum incorporates part of the olfactory innervation system, so preservation of most of the cephalic strip of septal mucosa may preserve the olfactory epithelium and its function. Our group is currently investigating the impact of a modified Hadad flap with the use of a superior incision 2 to 2.5 cm below the olfactory sulcus (using microscissors instead of electrocautery) while lateralizing the inferior incision toward the inferior meatus. Thus, a large flap is obtained without damaging the olfactory neuroepithelium.

CONCLUSION

To our knowledge, this is the first study to investigate the effect of skull base surgery by using VSF on olfaction and MCT in comparison with standard surgical pituitary approaches. Expanded skull base surgery with VSF reconstruction has a short-term (3 months) negative impact on patients’ olfaction and MCT. In addition, patients undergoing EEA with VSF reported more nasal discharge and longer crusting time. Functioning tumors have no further negative effect on MCT and loss of smell than nonfunctioning tumors. Patients should be informed about smell loss as a consequence of endoscopic skull base surgery to prevent future legal claims. Likewise, further research and some modifications on reconstruction flaps are encouraged to avoid damaging the olfactory neuroepithelium.

Disclosures

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article. This study was presented as an oral presentation at the European Rhinologic Society meeting, Toulouse, France, June 17 to 21, 2012.
REFERENCES


