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Olfactory Outcomes After Endoscopic Skull Base Surgery: A Systematic Review and Meta-analysis

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Objectives: Determine the effect of endoscopic skull base surgery (ESBS) on long-term olfactory outcomes after surgery.

Methods: An English-language search was conducted using the Cochrane, MEDLINE, Scopus, and Embase databases from January 2000 to October 2017 for adult patients undergoing ESBS with subjective and objective olfactory outcomes. Two authors independently examined articles to identify those meeting inclusion criteria. Studies examining objective olfactory outcomes after ESBS were included in the meta-analysis. A random-effects meta-analysis of patients undergoing sellar and parasellar ESBS was conducted to compare preoperative and postoperative olfactory outcomes using the University of Pennsylvania Smell Identification Test (UPSIT) and Cross-Cultural Smell Identification Test (CCSIT).

Results: Among 339 eligible articles, 29 articles met inclusion criteria. Twenty-five of these focused on sellar and parasellar tumors. Individual articles not meeting criteria for meta-analysis were qualitatively reported. Meta-analysis showed there was no difference in preoperative and postoperative olfactory function after sellar and parasellar ESBS based on the UPSIT (five studies, mean difference [MD] = 1.03; 95% CI: 1.93; P = .50) and the CCST (three studies, MD = −0.77; 95% CI: −3.03, 1.49; P = .50). A pooled overall meta-analysis revealed similar results (eight studies, effect size = −0.30; 95% CI: −0.79, 0.18; P = .22). However, heterogeneity for all meta-analyses was high (I² > 95%, P < .01), suggesting significant variation in the included studies.

Conclusions: Based on published objective olfactory outcomes after sellar and parasellar ESBS, there was no significant difference between preoperative and postoperative olfaction. Further prospective studies using validated objective measures of olfaction are required to improve our understanding on this subject.

Key Words: Olfaction, smell, anterior skull base, pituitary, endoscopic skull base, transclival, trans sphenoid, transnasal, transcribriform, expanded endonasal approach, systematic review, meta-analysis, chordoma.

Level of Evidence: 2a

INTRODUCTION

Olfaction plays an essential role not just in smell, but also in the formation of emotion and memory. Olfactory dysfunction can have a profound impact on quality of life and mental health, with strong associations to depression. Olfaction is thus an important consideration in endoscopic skull base surgery (ESBS), which often puts normosmic patients at risk for smell loss. With the ever-increasing role of ESBS in the management of anterior skull base lesions, postoperative olfactory outcomes have become of great interest to both patients and clinicians.

Loss of smell after ESBS can theoretically be due to direct trauma, inflammatory changes, or obstruction. Pressure or damage to the olfactory neuroepithelium may cause a transient or permanent loss. From the chronic rhinosinusitis literature, it is known that inflammatory changes in the olfactory mucosa and degree of nasal obstruction may both play a role in hyposmia. A systematic review and meta-analysis in the chronic rhinosinusitis population showed that endoscopic sinus surgery leads to improvements in subjective and objective measures of olfaction.

ESBS patients differ from chronic rhinosinusitis patients in that they presumably have lower rates of olfactory dysfunction and sinonasal morbidity prior to surgery. Thus, it is important to examine the ESBS cohort as a distinct group of patients. A few prior prospective and retrospective studies have examined subjective and objective olfactory outcomes in ESBS patients, all with conflicting results. Prior reviews summarizing olfactory function before and after ESBS have been limited, and no consensus has been reached regarding the effects of ESBS on olfaction.

As early as 2011, de Almeida et al. performed an evidence-based review looking at quality of life outcomes after ESBS. However, aggregate olfaction data were not specifically discussed, and the authors identified this as a future area for research. Similarly, Awad et al. examined sinonasal...
morbidity after ESBS, but not specifically olfactory dysfunction. More recently, Thompson et al., Patel et al., and Greig et al. all summarized key studies on olfactory outcomes after ESBS, but these were not comprehensive systematic reviews, and they did not perform a meta-analysis.5,6,19

To date, no systemic review with meta-analysis has been performed to examine objective olfactory function after ESBS. Barriers to meta-analysis include potential differences in surgical technique, tumor histology, and olfactory testing. The goals of this study were to determine the effects of ESBS on long-term olfactory outcomes after surgery. To accomplish this, we aimed to perform a comprehensive systematic review and a focused meta-analysis. To minimize heterogeneity in the meta-analysis, this portion of the study was limited to only sellar and parasellar tumors with reported objective, validated measurements of olfaction.

METHODS

Systematic Search Strategy and Study Selection

Study protocol was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. An experienced librarian conducted a comprehensive search of several databases with input from the study’s principle investigator. Databases were searched from inception to October 11, 2017 and included Ovid MEDLINE, OVID Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. Key words included but were not limited to “skull base,” “endoscopic,” and “olfaction”/“smell.” Only English-language articles were included.

Identified publications then underwent independent review by two separate investigators (L.X.Y., C.M.L.). Both reviewers conducted title and abstract review to screen articles for exclusion. Articles were excluded if they involved 1) studies on endoscopic endonasal surgery without skull base involvement; 2) case series, reviews, and basic science studies with no quantifiable clinical outcomes; 3) anatomic studies and surgical technique reports with no quantifiable clinical outcomes; 4) procedures not exclusively performed endoscopically; and 5) clinical studies on ESBS with no olfactory outcomes. Study investigators (L.X.Y., C.M.L., G.C.) also conducted a supplemental manual search of bibliographies of included articles.

After exclusion criteria were applied and the manual search was conducted, all remaining articles underwent full-text review for eligibility. Three independent reviewers participated in full-text review (L.X.Y., C.M.L., C.L.P.). Additional studies were excluded because they contained 1) duplicate cohorts, 2) no olfactory outcomes as assessed by tests or questionnaires, and 3) microscopic as opposed to ESBS surgical outcomes. A PRISMA flowchart summarizing identification, screening, eligibility, and inclusion criteria is presented in Figure 1.

Study Selection for Meta-analysis

All included studies, regardless of anatomic site of pathology, were qualitatively summarized. For the meta-analysis, we chose to further focus our selection criteria by limiting it to patients undergoing ESBS for sellar/parasellar pathologies. This provided greater homogeneity in tumor pathology, surgical technique, and extent of surgical dissection. In addition, it allowed for focus on an anatomic site that likely had less direct impact on olfaction, as opposed to areas such as the cribriform plate or olfactory groove. All types of skull base reconstruction were included in the meta-analysis, including nasoseptal flaps (NSFs) and rescue flaps. NSFs (Hadad-Bassagasteguy flaps) are defined as vascular pedicled mucosal flaps of the nasal septum based on the nasoseptal artery, as described by Hadad et al.20 Rescue flaps were defined by Rivera-Serrano et al. and include superior septal incision similar to an NSF, but no anterior or inferior incisions.21

To ensure greater validity in olfactory outcomes, only studies using objective, validated measures of olfaction were included. We excluded studies using only subjective patient-reported measurements of olfaction, such as a visual analog scale (VAS). We also excluded uncommon instruments used in only single studies. Final validated, objective, olfactory instruments included in the meta-analysis included the University of Pennsylvania Smell Identification Test (UPSIT) and Cross-Cultural Smell Identification Test (CCSIT). The UPSIT is a well-validated, widely used, objective, psychophysical test of olfaction.22 It is sensitive to age, gender, and diseases known to affect olfaction.23 Olfaction is measured on a scale from 0 to 40, with 40 being the highest score.23 The CCSIT is a shortened form of the UPSIT that includes selected items familiar to North American, European, South American, and Asian cultures.24 A score of 12 on the CCSIT is the highest score. The normosmia ranges of both scores depend on the gender and age of the test taker.

Meta-analysis

Pre- and postoperative olfactory outcomes, along with sample size, were extracted from the studies included in meta-analysis. Olfactory outcomes were summarized using means and standard deviations.

For unpoled meta-analysis of the UPSIT and the CCSIT, a random-effects model was utilized, with mean difference and the standard error of the mean difference as model inputs. The standard error of the mean difference was calculated according to the Cochrane Handbook for Systematic Reviews of Interventions,25 which defines it as:

$$\sqrt{SD_{pre}^2 + SD_{post}^2 - 2 \times r \times SD_{pre} \times SD_{post}}$$

where $r$ is the correlation coefficient between pre- and postoperative olfaction scores. As is common with matched retrospective studies, a correlation coefficient $r$ was not reported in any of the studies included in the meta-analysis. Thus, a correlation coefficient of 0.6 was estimated based on methods provided in the Cochrane handbook.25

For pooled meta-analysis, a random-effects model was also utilized; Cohen’s $d$ and its standard error were used to describe the effect size and its variance. This was calculated according to established formulas for pre- and posttreatment matched studies.26 The $I^2$ statistic was used to evaluate for
heterogeneity. A sensitivity analysis was conducted for both the unpooled and pooled meta-analyses, using a range of 0.3 to 0.9 as the correlation coefficient \( r \) between pre- and postoperative olfaction scores. All analysis was performed in Microsoft Excel (Microsoft, Redmond, WA) and Stata 12 (StataCorp, College Station, TX).

**Bias Assessment**

Assessment for risk of bias was performed using the Newcastle-Ottawa Quality Assessment Scale tool for cohort studies\(^27\) and the Cochrane Collaboration tool for assessing bias in randomized controlled trials (RCTs).\(^28\) These bias assessment tools are aimed to gauge the amount that a difference in outcome can be attributed to the intervention.

**RESULTS**

**Study Selection**

Five hundred one articles were found via the initial librarian-led systematic database search. After removal of duplicates, 339 articles were considered for our systematic review. Sixty-six articles underwent independent full-text review, and 29 articles were included for qualitative analysis (Fig. 1, Tables I–III). All references to significant differences in the qualitative analysis refer to statistical significance, as measured and defined by the original study authors.

Four studies focused on patients undergoing ESBS for pathologies of the entire skull base, whereas 25 studies focused specifically on sellar and parasellar pathologies. Of these 25 studies, seven studies reported predominantly subjective outcomes measures, whereas the remaining reported some kind of objective outcome. Of the objective outcome measures reported, six studies reported UPSIT outcomes, and eight studies reported CCSIT outcomes. The remaining studies reported a variety of uncommon objective tests of olfaction. After further exclusion of duplicate cohorts and studies with missing summary statistics, five studies using the UPSIT and three studies using the CCSIT were included in individual and pooled meta-analysis. A brief summary of all 29 articles included in our systematic review can be found in Tables I through III.
Qualitative Summary

Studies Not Exclusively Involving the Sella/Parasellar Area. Four studies included patients who underwent surgery of entire skull base, including the cribiform plate (Table I). Due to the suspected effects that heterogeneity of tumor location and type could have on olfaction outcomes, these studies were excluded from the meta-analysis. They are described below.

Dolci et al. found that 10 of 41 patients had signs of hyposmia or anosmia after ESBS.29 However, no preoperative scores or statistical comparisons were taken, some patients had olfactory groove tumors, and follow-up time was variable. Tajudeen et al. focused exclusively on the feasibility of smell preservation after endoscopic unilateral resection of esthesioneuroblastoma, and showed that eight out of 14 patients were able to preserve some olfaction on UPSIT testing after surgery.30 Upadhyay and colleagues looked at olfactory outcomes in all patients undergoing NSF, and found that NSF was associated with a short-term deficit in the UPSIT at 6 weeks, but returned to baseline by 6 months.31 Patients undergoing ESBS with rescue flaps had no changes in olfaction.31 Finally, Bedrosian et al. examined postoperative olfactory outcomes after ESBS using the Anterior Skull Base Questionnaire, which contains a single question on sense of smell. The authors showed a significant deficit in olfaction at 3 weeks postoperatively, that steadily recovered after 6 months of follow-up.32

Subjective Measures of Olfaction Following ESBS for Sellar/Parasellar Pathologies. Seven studies from the systematic review focused on subjective olfactory outcomes after ESBS for sellar/parasellar pathologies (Table II). Many of these studies utilized the 22-item Sino-Nasal Outcome Test (SNOT-22), which is popular due to its reliability, validity, and ease for the patient.33 Studies were only included in the qualitative analysis if authors independently reported answers to the sense of smell/taste question on the SNOT-22.

Zimmer et al. compared pre- and postoperative SNOT-22 scores in patients undergoing ESBS for pituitary adenomas without NSFs, specifically examining answers to the question regarding sense of smell/taste. They noted a significant worsening in olfaction at 1 month postoperatively, which recovered to baseline by 3 months.34 Wang et al. prospectively followed a similar cohort of patients with the General Nasal Patient Inventory. They also found a significant transient change in the sense of smell, which went on to recover back to baseline after 3 months.35

A few studies focused on SNOT-22 outcomes in the setting of raising NSFs or rescue flaps for skull base reconstruction during ESBS. Hanson et al. showed no significant postoperative differences the visual analog scale (VAS) of smell in patients undergoing NSF reconstruction.36 Jalessi et al. compared NSF reconstructions in ESBS to other types of fat or fascial grafts. They did find a transient deficit in postoperative olfaction at 1 month, but this was only in the NSF group, and it went on to return to baseline by 3 months.37 In contrast, Kim et al. utilized bilateral rescue flaps for skull base reconstruction as opposed to NSF, and did find a significant worsening in subjective olfaction measured using a study-specific VAS.38

Two other studies using a VAS also found significant deficits in smell after ESBS. Rioja et al. found significant worsening of olfaction as measured by the VAS in both transphenoidal endoscopic and expanded endonasal approaches to the sella and parasellar space.38 However, they found no difference between preoperative and postoperative olfaction using objective testing with the Barcelona Smell Test (BAST-24).38 A group led by Kim used a VAS to assess a specific binosorial, four-handed transphenoidal approach practiced at their institution, and also found a significant worsening of olfaction as measured by their VAS.39

Objective Measurements of Olfaction in the Sella/Parasellar Not Included in the Meta-analysis. Four studies focused on objective olfactory outcomes after ESBS in the sella, but were not included in the meta-analysis.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Type of Study</th>
<th>Total No.</th>
<th>Primary Comparison</th>
<th>Measure of Olfaction</th>
<th>Septal Flap?</th>
<th>Tumor Type</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedrosian et al.</td>
<td>PC</td>
<td>85</td>
<td>Pre- vs. postoperative</td>
<td>ASBQ (single question on sense of smell)</td>
<td>NSF in some</td>
<td>Variety</td>
<td>Short-term (at 3 weeks) significant decrease in smell, but recovered in the long term (after 6 months)</td>
</tr>
<tr>
<td>Dolci et al. (2017)</td>
<td>RCS</td>
<td>41</td>
<td>NA</td>
<td>CCCRC</td>
<td>All NSF</td>
<td>Pituitary adenomas, meningiomas, others</td>
<td>10 of 41 patients had signs of hyposmia or anosmia postoperatively</td>
</tr>
<tr>
<td>Tajudeen et al.</td>
<td>RCS</td>
<td>14</td>
<td>NA</td>
<td>UPSIT</td>
<td>All NSF</td>
<td>ONB</td>
<td>6/14 patients had residual smell, 2 patients had almost normal smell</td>
</tr>
<tr>
<td>Upadhyay et al.</td>
<td>PC</td>
<td>42</td>
<td>Pre- vs. postoperative, NSF vs. bilateral rescue flap</td>
<td>UPSIT</td>
<td>NSF or bilateral rescue flap</td>
<td>Pituitary adenomas, RCCs, meningiomas, others</td>
<td>UPSIT significantly decreased at 6 weeks in the NSF group, but returned by 6 months; no changes in UPSIT in the rescue flap group</td>
</tr>
</tbody>
</table>

ASBQ = Anterior Skull Base Questionnaire; CCCRC = Connecticut Chemosensory Clinical Research Center; NA = not applicable; NSF = nasoseptal flap; ONB = olfactory neuroblastoma; PC = prospective cohort; RCC = Rathke’s cleft cyst; RCS = retrospective case series; UPSIT = University of Pennsylvania Smell Identification Test.
in either group. Soyka et al. explored monorhinal olfaction and found no significant changes in postoperative olfactory function in their cohort, but did not report any ranges or standard deviations.

Two studies used the Sniffin' Sticks test to assess olfactory outcomes after ESBS. Schluter et al. aimed to evaluate the effect of rhino-septal splints after ESBS on olfaction, and found no significant changes in postoperative olfactory function in either group. Soyka et al. explored monorhinal olfaction after raising an NSF during ESBS of the sella. They found no significant decrease in olfactory function observed on the flap donor side of the nose compared to the contralateral side. The authors did not find this to be clinically relevant unless patients had preexisting single-sided olfactory loss prior to ESBS.

Quantitative Analysis/Meta-analysis

Of the studies reporting UPSIT outcomes, five of six reported adequate summary statistics in the original article necessary for meta-analysis input and were included in the final analysis (Table III). Rotenberg et al. described a significant decrease in the UPSIT at 6 months after surgery in their cohort, but did not report any ranges or standard deviations for their cohort, making the study ineligible for meta-analysis. The five studies included in the meta-analysis reported pre- and postoperative UPSIT scores on 140 patients after ESBS. Postoperative follow-up testing for these patients ranged from 1 month to 6 months. Meta-analysis results from the UPSIT are displayed in the forest plot in Figure 2. There was no significant difference in the pre- and postoperative UPSIT scores after ESBS for sellar/parasellar pathologies (mean difference = −1.03, 95% confidence interval [CI]: −3.98, 1.93, P = .50).

Of the studies reporting CCSIT outcomes, two studies did not report adequate summary statistics for meta-analysis. These two excluded studies were both from Kim et al., and showed that ESBS was associated with significant changes in nasal cavity dimensions, but these anatomic changes did not correlate with changes in olfaction. In addition, multiple studies showed overlapping cohorts from the same study.
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Type of Study</th>
<th>Total No.</th>
<th>Primary Comparison</th>
<th>Measure of Olfaction</th>
<th>Septal Flap?</th>
<th>Tumor Type</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscellaneous objective outcomes</td>
<td></td>
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</tr>
<tr>
<td>Griffiths et al. (2014)</td>
<td>RCS</td>
<td>35</td>
<td>Pre- vs. postoperative,</td>
<td>BSIT</td>
<td>All unilateral or bilateral rescue flaps</td>
<td>Pituitary adenomas, Rathke’s cleft cysts, others</td>
<td>No significant postoperative changes in the BSIT</td>
</tr>
<tr>
<td>Kahilogullari et al. (2013)</td>
<td>PC</td>
<td>50</td>
<td>Endoscopic vs. microscopic</td>
<td>Smell diskettes</td>
<td>No</td>
<td>Pituitary adenomas, Rathke’s cleft cysts, others</td>
<td>Significantly better postoperative olfaction in the endoscopic group</td>
</tr>
<tr>
<td>Schluter et al. (2016)</td>
<td>RC</td>
<td>49</td>
<td>Rhino-septal splints vs. no splints</td>
<td>Sniffin’ Sticks</td>
<td>No</td>
<td>Pituitary adenomas, Rathke’s cleft cysts, others</td>
<td>No significant changes in postoperative olfaction in either group</td>
</tr>
<tr>
<td>Soyka et al. (2017)</td>
<td>RCS</td>
<td>18</td>
<td>Pre- vs. postoperative</td>
<td>Sniffin’ Sticks</td>
<td>All unilateral NSF</td>
<td>Pituitary adenomas, others</td>
<td>Significant decrease in olfactory function on the flap donor side compared to the contralateral side</td>
</tr>
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<td></td>
<td></td>
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<tr>
<td>UPSIT</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Chaaban et al. (2015)</td>
<td>PC</td>
<td>18</td>
<td>Pre- vs. postoperative,</td>
<td>UPSIT</td>
<td>NSF in some</td>
<td>Pituitary adenomas</td>
<td>No postoperative changes in UPSIT, regardless if NSF was used</td>
</tr>
<tr>
<td>Hart et al. (2010)</td>
<td>PCS</td>
<td>57</td>
<td>Pre- vs. postoperative,</td>
<td>UPSIT</td>
<td>No</td>
<td>Pituitary adenomas, Rathke’s cleft cysts</td>
<td>Transient significant decrease in UPSIT at 1 month, recovered with no changes in the UPSIT at 3 months</td>
</tr>
<tr>
<td>Harvey et al. (2015)</td>
<td>PCS</td>
<td>40</td>
<td>Pre- vs. postoperative</td>
<td>UPSIT</td>
<td>All modified NSF</td>
<td>Pituitary adenomas, others</td>
<td>No difference in the UPSIT postoperatively</td>
</tr>
<tr>
<td>Rotenberg et al. (2011)</td>
<td>PC</td>
<td>17</td>
<td>Pre- vs. postoperative</td>
<td>UPSIT</td>
<td>All NSF</td>
<td>Pituitary adenomas</td>
<td>Significant decrease in the UPSIT at 6 months postoperatively</td>
</tr>
<tr>
<td>Sowerby et al. (2013)</td>
<td>PCS</td>
<td>22</td>
<td>Pre- vs. postoperative</td>
<td>UPSIT</td>
<td>Face-of-sphenoid flap sacrificing middle turbinate</td>
<td>Pituitary adenomas, Rathke’s cleft cysts</td>
<td>No significant postoperative changes in the UPSIT at 1-2 months postoperatively</td>
</tr>
<tr>
<td>Tam et al. (2013)</td>
<td>RCT</td>
<td>20</td>
<td>NSF vs. no NSF</td>
<td>UPSIT</td>
<td>NSF vs. no NSF</td>
<td>Pituitary adenomas</td>
<td>Significantly decreased UPSIT at 6 months in both groups, worse olfactory deficit in those with NSF</td>
</tr>
<tr>
<td>CCSIT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong et al. (2014)</td>
<td>RCS</td>
<td>49</td>
<td>Cold knife vs. cautery for the rescue flap incision</td>
<td>CCSIT, VAS</td>
<td>All nasoseptal rescue flaps</td>
<td>Pituitary adenomas</td>
<td>No overall significant postoperative decrease in CCSIT, but worse olfaction in the cautery group compared to cold knife</td>
</tr>
<tr>
<td>Kim et al. (2016)</td>
<td>RCS</td>
<td>119</td>
<td>Pre- vs. postoperative</td>
<td>CCSIT, CCCRC</td>
<td>All bilateral rescue flaps</td>
<td>Pituitary adenomas</td>
<td>Significant increase in nasal passage dimensions postoperatively, but no correlation with olfaction</td>
</tr>
<tr>
<td>Kim et al. (2016)</td>
<td>RCS</td>
<td>92</td>
<td>Pre- vs. postoperative</td>
<td>CCSIT, CCCRC</td>
<td>All bilateral rescue flaps</td>
<td>Pituitary adenomas, Rathke’s cleft cysts, others</td>
<td>Significant increase in nasal passage volumes postoperatively, but no correlation with olfaction</td>
</tr>
<tr>
<td>Kim et al. (2017)</td>
<td>RCS</td>
<td>535</td>
<td>Pre- vs. postoperative</td>
<td>CCSIT, CCCRC, VAS</td>
<td>Bilateral rescue flaps in most</td>
<td>Pituitary adenomas, Rathke’s cleft cysts, others</td>
<td>Significant decrease in the CCSIT, CCCRC, and VAS at 6 months postoperatively</td>
</tr>
<tr>
<td>Kim et al. (2013)</td>
<td>PC</td>
<td>15</td>
<td>Pre- vs. postoperative, cold knife vs. cautery for the NSF incision</td>
<td>CCSIT, BTT</td>
<td>All NSF</td>
<td>Pituitary adenomas</td>
<td>No significant postoperative differences in olfaction at 6 months in either group</td>
</tr>
</tbody>
</table>

*Study was excluded from the meta-analysis due to insufficient data.

BSIT = Brief Smell Identification Test; BTT = Butanol Threshold Test; CCCRC = Connecticut Chemosensory Clinical Research Center; CCSIT = Cross-Cultural Smell Identification Test; NSF = nasoseptal flap; PC = prospective cohort; PCS = prospective case series; RC = retrospective cohort; RCS = retrospective case series; RCT = randomized controlled trial; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.
study group, and thus three additional studies were excluded. Only the studies with the most comprehensive cohort were included in the meta-analysis. In the end, three of eight studies using CCSIT were included for meta-analysis (Table III) reporting CCSIT scores on 599 patients after ESBS. Olfactory follow-up for these patients ranged from 3 to 6 months. Meta-analysis results from the CCSIT are displayed in the forest plot in Figure 3. There was no significant difference in the pre- and postoperative CCSIT scores after ESBS for sellar/parasellar pathologies (mean difference = −0.77, 95% CI: −3.03, 1.49, \(P = .50\)).

Pooled meta-analysis results using both the UPSIT and the CCSIT are displayed in the forest plot in Figure 4. Overall, there was no significant difference between pre- and postoperative objective olfactory outcomes after ESBS for sellar/parasellar pathologies. The overall effect size was −0.30, suggesting a small overall postoperative decrease in olfaction. However, this change was not significant (\(P = .22\)).

Heterogeneity was high for all three meta-analyses (\(I^2 > 95\%\), \(P < .01\) for all), suggesting significant variation in the included studies. Sensitivity analysis was performed on all three meta-analysis models. Because an \(r\) value of 0.6 was assumed as the correlation coefficient between pre- and postoperative olfactory scores, a wider range was selected for sensitivity analysis. Utilizing an \(r\) range of 0.3 to 0.9 had no effect on the overall results of all three meta-analyses; there was still no significant difference found between pre- and postoperative olfactory outcomes for the UPSIT, CCSIT, and the pooled meta-analysis.

**DISCUSSION**

This study is the first systematic review and meta-analysis focusing on olfactory outcomes after ESBS. We found 29 studies reporting quantifiable olfactory outcomes after ESBS, using either subjective or objective outcome measures. A qualitative analysis was conducted. We then conducted a meta-analysis that focused on objective olfactory outcomes after ESBS for sellar/parasellar tumors. Notably, on meta-analysis, we found no significant difference between pre- and long-term postoperative olfaction, as measured by the UPSIT and CCSIT.

The qualitative analysis was divided into three portions. The first focused on studies that examined ESBS sites not confined to the sella/parasella (Table I). Most of these studies found no differences in long-term objective\(^3\) or subjective\(^3\) olfaction after ESBS, with the exception of ESBS for esthesioneuroblastomas.\(^3\) Next, we focused on

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### Table III

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Sample Size</th>
<th>Mean Difference (95%CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaaban 2015</td>
<td>18</td>
<td>−0.80 (−3.39, 2.39)</td>
<td>17.08</td>
</tr>
<tr>
<td>Hart 2010</td>
<td>45</td>
<td>1.20 (0.08, 2.32)</td>
<td>20.69</td>
</tr>
<tr>
<td>Tam 2013</td>
<td>20</td>
<td>−5.45 (−6.30, 4.60)</td>
<td>20.95</td>
</tr>
<tr>
<td>Sowerby 2013</td>
<td>17</td>
<td>0.30 (−0.87, 1.47)</td>
<td>20.64</td>
</tr>
<tr>
<td>Harvey 2015</td>
<td>40</td>
<td>−0.28 (−1.44, 0.88)</td>
<td>20.64</td>
</tr>
<tr>
<td>Overall ((I^2 = 96.6%, p = 0.000))</td>
<td></td>
<td>−1.03 (−3.98, 1.93)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.

---

### Table IV

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Sample Size</th>
<th>Mean Difference (95%CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim 2017</td>
<td>536</td>
<td>−0.77 (−3.01, −2.54)</td>
<td>30.73</td>
</tr>
<tr>
<td>Kim 2013</td>
<td>15</td>
<td>0.47 (−0.21, 1.15)</td>
<td>32.85</td>
</tr>
<tr>
<td>Hong 2014</td>
<td>49</td>
<td>0.02 (−0.42, 0.46)</td>
<td>33.43</td>
</tr>
<tr>
<td>Overall ((I^2 = 98.8%, p = 0.000))</td>
<td></td>
<td>−0.77 (−3.03, 1.49)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
studies of subjective olfaction after ESBS in the sella/parasella (Table II). Again, four of the seven studies found no long-term (beyond 3 months) postoperative changes in subjective olfaction.15,26,36 Three studies found significantly worse postoperative olfaction using a subjective VAS.37–39 Of note, however, studies reporting outcomes using a VAS often showed inconsistencies in both the magnitude and directionality of the scale that is actually adopted and given to patients (i.e., 0–10 on the VAS, with 10 being worst smell vs. 0–100 on the VAS, with 100 being the best smell). Ultimately, the study-specific VAS remains an unvalidated measurement of subjective olfaction with unknown correlations to patient quality of life. In the Rioja et al. study, differences in postoperative olfaction on the VAS could not be validated objectively using the BAST-24 test.38 As such, it is difficult to draw any definitive or cohesive conclusions regarding subjective olfaction outcomes based on the VAS.

Of the studies focusing on objective olfactory outcomes after ESBS in the sella/parasella (Table III), only three found differences in postoperative olfaction after ESBS.14,46,47 Reasons for the discrepancy observed in those three studies could be differences in technique or biases in pre- and postoperative patient counseling, the latter of which may affect patient self-confidence when taking the olfaction test. Importantly, as our overall meta-analysis showed, when all studies are considered, there is no statically significant difference in overall pre- and postoperative olfaction on objective testing after ESBS. Although the lack of statistical significance may be due to the inadequate power of studies included in the meta-analysis, even a statistically significant change of −1.03 on the UPSIT and −0.77 on the CCSIT would be unlikely to be clinically significant. Previous studies have defined the minimal clinically important difference of both scores to be about a 10% change in the UPSIT and a change of 1 on the CCSIT.13,46,48

Results from studies that compare olfaction outcomes with or without harvesting of NSF have been conflicting. A previous comment by Greig et al. suggested that NSF elevation likely leads to impairment in objective measures of olfaction, whereas ESBS without elevation of NSF only leads to transient reduction in olfaction. Based on our more comprehensive review and meta-analysis, we do not believe that there is enough evidence to support the former statement. Unfortunately, we could not extract enough patient-specific data from studies to conduct a formal meta-analysis comparing NSF versus no NSF in postoperative olfaction. We agree with the authors’ opinion that NSF elevation in sellar and parasellar ESBS can be avoided in patients at lower risk of cerebrospinal fluid leak to minimize overall postoperative sinonasal morbidity.

We do recognize that ESBS may lead to transient reductions in olfaction. Several studies in our review showed that there may be transient deficits in objective7,31 and subjective15,26,36 olfaction at about 1 to 3 months after surgery, which recovered by approximately 6 months. This finding is also supported by several studies not included in our qualitative review due to lack of olfaction-specific data. Gallagher et al. showed that patient-reported sinonasal morbidity after ESBS improved after 4 weeks.39 de Almeida et al.17 and Pant et al.50 suggested that most sinonasal symptoms take 3 to 4 months to resolve. Based on this literature, we agree that reevaluation at 6 months seems a reasonable interval for follow-up to capture the majority of patients who have return of olfactory function. This interval of temporary olfaction dysfunction is not only important to future study designs, but also to clinicians seeking comprehensive informed consent and appropriate follow-up intervals for their patients. Fortunately, as our meta-analysis showed, these transient olfactory deficits are not likely to carry on in the long term.

Our study is not without limitations. The objective olfactory instruments used in this study, although widely used and well validated, tests only suprathreshold olfaction. Thus, a lack of olfactory deficit on tests such as the UPSIT does not preclude the possibility of subtler threshold-level olfactory dysfunction. The UPSIT and CCSIT also cannot be viewed in the online issue, which is available at www.laryngoscope.com.
recognize unilateral olfactory decline, as both nostrils are tested simultaneously. This study also has limitations common to all meta-analyses, including publication biases and the inclusion of low-quality studies. We recognize that publication bias may exist. Some negative results may not ever reach publication. On the other hand, surgeons may be biased to publish more negative results, as these may support a positive surgical outcome. Either way, the literature represented in this systematic review may not be reflective of overall surgical outcomes for ESBS. Our Newcastle-Ottawa and Cochrane Collaborative (Table IV) bias assessments show that moderately high quality studies were included in the meta-analysis. Other measures taken in our methods to strengthen the reliability of our conclusions include application of a sensitivity analysis on our meta-analyses results.

Another important factor limiting our review was heterogeneity of surgical technique within and between studies. We did not control for these differences in technique when considering the overall effect of ESBS on olfaction. Some surgeons and studies utilize an NSF, whereas those who do not may utilize rescue flaps in unilateral or bilateral fashion. In those who do utilize an NSF, variations also exist in the use of cold knife or electrocautery to make the superior limb incision. However, we believe that including a variety of surgical techniques offers a more realistic reflection of actual practices. There were also differences in tumor pathology and the methods by which olfaction was tested. We did our best to minimize the heterogeneity in these studies by grouping our qualitative analysis and meta-analysis by location of pathology and instruments of olfactory measurement. We also attempted minimize the effect that heterogeneity would have on our meta-analysis conclusions by using a random-effects model, similar to prior studies in this field. Nonetheless, we recognize that there is a high degree of heterogeneity in our meta-analysis.

The heterogeneity displayed in our review shows that additional carefully designed, multi-institutional prospective studies are needed in the literature. These future studies should rigorously collect data on tumor size, location, surgical, and reconstructive techniques, and utilize comprehensive validated measures of olfaction. We recommend large sample sizes and consistency of variables in future studies, which will help future aggregate reviews to have more homogeneous data. Given the expanding and routine role of ESBS in the management of sellar pathology and anterior skull base lesions, knowledge of postoperative olfactory outcomes is essential for a skull base surgeon’s consultation with their patients.

CONCLUSION

Based on current published evidence, there is no significant difference between preoperative and long-term postoperative olfaction in patients undergoing ESBS for sellar and parasellar pathologies, as measured by the UPSIT and CCSIT. These findings may impact pre- and postoperative patient counseling. Further prospective studies using validated objective measures of olfaction are required to improve our understanding on the subject.

BIBLIOGRAPHY
