



# Olfactory function in patients after transsphenoidal surgery for pituitary adenomas—a short review

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## Abstract

Olfaction is an important sensory input that obviously affects many daily activities. However, olfactory dysfunction (hyposmia and anosmia) leads to a pronounced decrease in quality of life. Surprisingly, little attention has been paid to olfactory changes after transsphenoidal surgery for pituitary tumors. In this review, we summarize current knowledge of the effects of transsphenoidal pituitary surgery on olfaction and compare different surgical techniques. Based on selected studies, the endoscopic approach, in comparison with the microscopic approach, seems to be superior in terms of preservation of olfactory function, although the quality of data from these studies is generally poor. The best results were observed when the endoscopic approach was used without harvesting of the nasoseptal flap.

**Keywords** Olfaction · Pituitary adenoma · Transsphenoidal approach · Endoscopic surgery · Microscopic surgery · Skull base

## Introduction

Olfaction is an important sensory input that affects several everyday activities, such as detection of hazards and food. Olfactory dysfunction (hyposmia and anosmia) leads to a significant decrease in quality of life (QoL), especially regarding food intake, safety, personal hygiene, and sexual function [4]. Depression is diagnosed more frequently in patients with olfactory dysfunction. Two causes of this dysfunction have been proposed. First, decreased QoL may lead to depression, and second, olfactory loss per se affects the brain's functioning, especially emotional control. A potential mechanism is reduced neuronal input from the olfactory nerve via the amygdala into the limbic circuit [4].

Endonasal operations may affect olfaction as demonstrated in studies conducted by otorhinolaryngologists [30]. Despite that neurosurgeons have used the

transsphenoidal route to pituitary lesions since Harvey Cushing, little attention has been paid to the “collateral damage” caused on the route to the sella turcica. A probable reason for this might be that neurosurgeons have mainly focused on removing intracranial tumors, with nasal morbidity being a less important concern. However, a paradigm shift in recent decades has made the patient's functional outcome more important and thus olfactory function after transsphenoidal surgery for pituitary adenoma is now being investigated.

In this review, we summarize current knowledge of the effects of transsphenoidal pituitary surgery on olfaction and compare different surgical techniques.

## Methods

The PubMed, Scopus, and Web of Science databases were searched for The Boolean search term pituitary adenoma AND (transnasal OR endonasal) AND (smell OR olfaction OR olfactory). The search was performed on 12.1.2018, with restriction to the English language but without limitation on the publication date. The present authors checked and selected all articles according to the inclusion and exclusion criteria (see below). References from each of the studies included in the review were checked for the identification of additional, relevant studies for systematic review.

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#### Inclusion criteria:

- original research article
- case series of predominantly patients with pituitary adenoma
- case series that examined olfaction using subjective/objective olfactometry before and after surgery
- case series of adult patients

#### Exclusion criteria:

- olfactory assessment using questionnaires, visual analogue scales or one question only
- extended endonasal approach for mixed skull base lesions
- insufficient data to determine type of olfactory examination

The search was done independently by two of the present authors (MM and DN). Figure 1 shows a PRISMA flow diagram created according to the PRISMA statement [24].

### Data extraction

For each study, we determined the number of patients who underwent surgery, the olfactometry test used, results of the olfactometry analyses, surgical approach, use of nasoseptal flap, and type of nasoseptal flap. Results of the olfactometry measurements were determined as early postoperative olfactory dysfunction (< 3 months) and late postoperative olfactory dysfunction ( $\geq$  3 months).

### Results

Our search resulted in 49 articles of which 41 met all inclusion criteria. Altogether, eight articles were excluded: review articles ( $n = 3$ ), position papers ( $n = 2$ ), letter to the editor ( $n = 1$ ), historical article ( $n = 1$ ), and case report ( $n = 1$ ). Afterwards, full texts were assessed for eligibility. This procedure led to an additional 30 papers being excluded: olfactory assessment using questionnaires, visual analogue scales, or a simple question only ( $n = 23$ ), other diagnosis than pituitary adenoma ( $n = 5$ ) and duplicated data ( $n = 2$ ). This left 11 studies to be reviewed. However, a cross-reference search of these studies disclosed that another nine studies were eligible for the review. Thus, the final sample included 20 articles that matched our inclusion criteria [1–3, 6, 10, 12–19, 22, 26–29, 31, 32]. Hong et al. published three papers with overlapping patient populations [14–16]. Based on the full text of articles, we included patient groups that were unique to each paper. Kim et al. also published three

papers with overlapping patient populations [20–22]. We included only the latest paper from 2017 [22], which comprised patients from previous studies as well. Results are summarized in Table 1.

Only one study was a randomized controlled trial (RCT) [29]. There were 14 prospective cohort studies and five retrospective studies.

Different olfaction tests were used in the 20 articles: the Small Diskettes Olfaction Test (SDOT), University of Pennsylvania Smell Identification Test (UPSIT), Cross-Cultural Smell Identification Test (CC-SIT), Butanol Threshold Test (BTT), T & T olfactometer, Barcelona Smell Test-24 (BAST-24), Connecticut Chemosensory Clinical Research Center test (CCCRC), and Brief Smell Identification Test (BSIT).

There were 1197 patients in the studies examined. In six studies, olfaction deficits less than 3 months after surgery were investigated: in four studies, deficits were disclosed and in two studies deficits were not disclosed. Dysfunction after 3 months after surgery and later was assessed in 23 cohorts: deficits were disclosed in 10 studies and not disclosed in 13 studies.

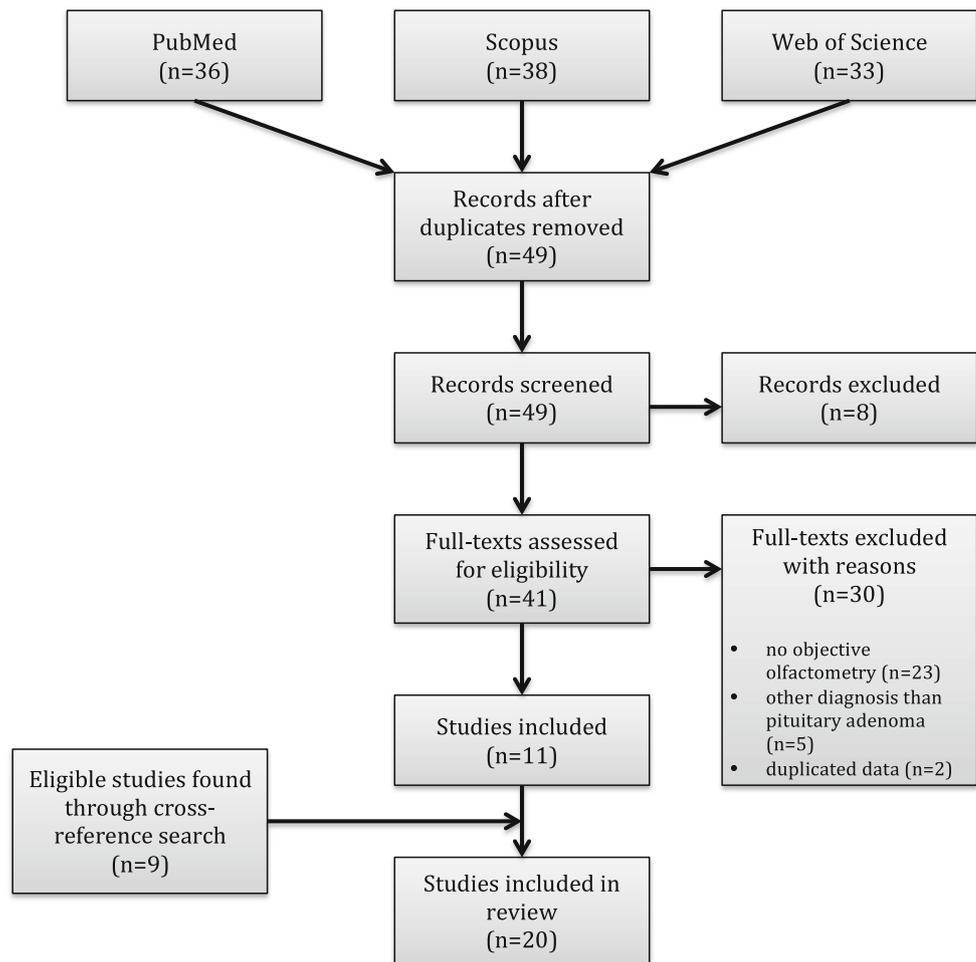
Only two of ten studies found dysfunction of olfaction when the endoscopic approach without the nasoseptal flap or the modified rescue flap was performed. Using the endoscopic approach with the nasoseptal flap, five of nine studies found olfaction dysfunction.

Two studies compared different techniques of harvesting the nasoseptal flap. Some authors prefer using the cold knife over electrocautery when raising the nasoseptal flap. The reasoning is that the cold knife technique is supposed to cause less thermic damage to the adjacent olfactory mucosa. Neither Hong et al. nor Kim et al. noted any difference between different flap harvesting techniques [14, 19].

Finally, three of five studies reported olfaction dysfunction when applying the microscopic approach. Only two studies directly compared the endoscopic and microscopic approaches [15, 18]. Kahilogullari et al. observed a significantly worse outcome in patients in the microscopic group. Hong et al. found a slightly (though statistically insignificant) worse outcome in olfactory function in microscopic group using a subjective olfactometry test [15].

We also extracted numbers of patients with postoperative olfaction dysfunction in different studies. In some studies, authors provided only results of olfactory score by groups and did not provide categorial data about individual patients. Therefore, we were able to analyze 604 patients from 19 studies only. The rate of olfaction dysfunction (either moderate or severe or anosmia) was as follows: 3% in endoscopic group without a flap, 14.4% in endoscopic group with a flap and 39.7% microscopic group. Results are summarized in Table 2.

**Fig. 1** PRISMA flow diagram created according to the PRISMA statement



## Discussion

### Olfactory mucosa and surgical considerations

Two of the main factors that might cause olfactory dysfunction following transsphenoidal surgery are direct damage to the olfactory mucosa and obstruction of airflow to the olfactory mucosa.

Functional mature olfactory receptor neurons are present at the roof of the nasal cavity, the anterior and medium part of the middle turbinate, the dorsoposterior part of the septum, the superior turbinate, and the middle turbinate anteriorly. Escada et al. described the lower limit of the olfactory mucosa at the upper and middle turbinates and the confronting nasal septum approximately 15 mm from the base of the skull [7]. The olfactory mucosa extends to a lower level than the sphenoid ostium.

Postoperative obstruction of airflow towards the olfactory mucosa might be due to anatomical changes in the nasal cavity during surgery. Dutten et al. investigated the effect of middle turbinate suture conchopexy during

endoscopic sinus surgery on olfactory function and found no impairment after the procedure [5].

In the first weeks after surgery healing of mucosa takes place, early postoperative crusting may be observed in some cases. Mucosal regeneration is complete in approximately 6 weeks, but return of ciliary function takes about 3 months [31]. Study by Sowerby et al. analyzed only early results [27]. All the other studies either analyzed the results after  $\geq 3$  months or analyzed early results and results  $\geq 3$  months after surgery.

### Smell testing

Patient's self-perception of olfactory function has been found to be unreliable [23]. To quantify and qualify the human sense of smell, several types of olfactometry have been developed, including the subjective qualitative olfactometry, subjective semiquantitative olfactometry (odor threshold determination), and objective olfactometry.

The subjective qualitative olfactometry focuses on odor determination (identification). In subjective qualitative

**Table 1** Studies on olfactory function in patients after transsphenoidal surgery for pituitary adenomas

Author	Year	Design	Patients	Olfactometry results			Surgical approach	Nasoseptal flap
				Test used	Dysfunction			
					(< 3 M)	(≥ 3 M)		
Ikeda et al.	1999	Prosp. cohort	25	T&T olfactometer	–	Y	Microscopic transseptal	–
Hart et al.	2010	Prosp. cohort	45	UPSIT	Y	N	Endoscopic	–
Actor et al.	2010	Retrospective	96	SniffSt/SDOT	–	N	Microscopic transnasal	–
Rotenberg et al.	2011	Prosp. cohort	17	UPSIT	–	Y	Endoscopic	Unilateral HB
Alobid et al.	2013	Prosp. cohort	36	BAST-24	–	N	Endoscopic	–
Kahilogullari et al.	2013	Prosp. cohort	25	SDOT	Y	N	Endoscopic	–
		Prosp. cohort	25	SDOT	Y	Y	Microscopic transseptal	–
Tam et al.	2013	RCT	10	UPSIT	–	Y	Endoscopic	Unilateral HB
		RCT	10	UPSIT	–	Y	Endoscopic	–
Sowerby et al.	2013	Prosp. cohort	22	UPSIT	N	–	Endoscopic	HB (only 4 pts)
Kim et al.	2013	Case-control	15	CC-SIT, BTT	–	N	Endoscopic	unilateral HB
Hong et al.	2014	Prosp. cohort	49	CC-SIT	–	N	Endoscopic	bilateral rescue
Griffiths et al.	2014	Retrospective	35	BSIT	–	N	Endoscopic	bilateral rescue
Hong et al.	2015	Prosp. cohort	20	CC-SIT, BTT	–	N	Microscopic transseptal	–
Chaaban et al.	2015	Prosp. cohort	18	UPSIT	–	N	Endoscopic	HB (only 6 pts)
Harvey et al.	2015	Prosp. cohort	40	UPSIT	–	N	Endoscopic	unilateral modified HB
Wang et al.	2015	Prosp. cohort	53	T&T olfactometer	Y	Y	Microscopic transseptal	–
Hong et al.	2016	Prosp. cohort	51	CC-SIT	–	N	Modified endoscopic	–
Kim et al.	2017	Retrospective	77	CC-SIT, CCCRC	–	Y	Endoscopic	Bilateral HB
		Retrospective	135	CC-SIT, CCCRC	–	Y	Endoscopic	Bilateral HB and rescue
		Retrospective	323	CC-SIT, CCCRC	–	Y	Endoscopic	bilateral Rescue
Upadhyay et al.	2017	Prosp. cohort	35	UPSIT	N	N	Endoscopic	bilateral Rescue
Soyka et al.	2017	Retrospective	18	SniffSt	–	Y	Endoscopic	unilateral HB
Eordogh et al.	2017	Retrospective	17	SDOT	–	N	Modified endoscopic	–

*UPSIT* University of Pennsylvania Smell Identification Test, *SDOT* the Small Diskettes Olfaction Test, *SniffSt* Sniff Sticks, *BAST-24* Barcelona Smell Test-24, *CC-SIT* Cross-Cultural Smell Identification Test, *BTT* Butanol Threshold Test (BTT), *CCRC* Connecticut Chemosensory Clinical Research Center test, *BSIT* Brief Smell Identification Test, *HB* Hadad-Bassagasteguy nasoseptal flap

olfactometry, the patient is exposed to suprathreshold stimulus, with the task of identifying the odor. Numerous substances were used for the sniffing olfactometry test.

In subjective semiquantitative olfactometry (odor threshold determination), patient is exposed to successively more concentrated samples until the odor is detected.

The objective olfactometry is based on the registration of a cortical electric potential after an odor event (electroolfactography, EOG). This method is based on EEG registration during olfaction, i.e., is not based on patient's answers. A flow olfactometer is an instrument for the creation of well-defined, reproducible smell stimuli in the nose without tactile or thermal stimulation of the olfaction mucosa. Different odors are used to facilitate the odor event (e.g., amyl acetate). The event intervals range from 30 to 45 s.

### Microscopic transsphenoidal surgery

Microscopic transsphenoidal surgery of the sella turcica was a gold standard for many decades. Five studies fulfilled the inclusion criteria of this review paper. Three of these studies

reported long-term olfactory dysfunction. Altogether, 39.7% of patients suffered olfaction dysfunction.

Different modifications of the microscopic transsphenoidal technique were applied (four series used the transseptal approach and one the transnasal approach). The transnasal paraseptal approach, with the incision of the septal mucosa, became more popular in the last two decades. Griffith and Veerapen popularized the direct route for the microscopic transsphenoidal approach [9].

### Endoscopic transsphenoidal surgery

Endoscopic pituitary surgery has gained popularity because of better panoramic visualization and is less invasive. In this review, we evaluated 16 papers that included 978 patients who underwent endoscopic pituitary surgery. This surgical technique varied among the studies, especially regarding the use of the nasoseptal flap and type of nasoseptal flap (see below and 2). Considering only those studies that used the endoscopic approach without any nasoseptal flap, only one of six reported worsened olfactory function after surgery.

**Table 2** Studies where individual data on patients' decline of olfaction were available: endoscopic group, endoscopic group with flap and microscopic group

Technique	Author	Patients	Olfactory dysfunction (no. of patients)	Olfactory dysfunction (%)
Endoscopic	Hart et al. 2010	45	0	
	Kahilogullari et al. 2013	25	0	
	Tam et al. 2013	10	4	
	Hong et al. 2014	49	0	
	Griffiths et al. 2014	35	1	
	Hong et al. 2016	51	2	
	Eordogh et al. 2017	17	1	
	Upadhyay et al. 2017	35	0	
	All endoscopic studies	267	8	3%
	Endoscopic with flap	Rotenberg et al. 2011	17	6
Tam et al. 2013		10	4	
Kim et al. 2013		15	1	
Chaaban et al. 2015		18	1	
Harvey et al. 2015		40	1	
Soyka et al. 2017		18	4	
All endoscopic studies with flap		118	17	14.4%
Microscopic	Ikedo et al. 1999	25	3	
	Actor et al. 2010	96	34	
	Kahilogullari et al. 2013	25	18	
	Hong et al. 2015	20	0	
	Wang et al. 2015	53	32	
	All microscopic studies	219	87	39.7%

This study group that showed worsened olfactory function after the surgery consisted of only 10 patients, but it is the only RCT in the present review [29].

Significant postoperative olfaction decline was observed in 3% of patients.

### Comparison of microscopic and endoscopic surgery

Only two studies directly compared the endoscopic and microscopic approaches [15, 18]. Kahilogullari et al. examined 25 patients who were operated endoscopically and 25 patients who underwent microscopic transseptal surgery [18]. The authors observed a significantly worse outcome in patients in the microscopic group: 20% of the patients were anosmic and 52% hyposmic 6 months after surgery. In the endoscopic group, 8% of the patients suffered from transient hyposmia and all patients improved 6 months post-surgery. In addition, patients in the microscopic group presented with significantly more postoperative synechia. In the other study, Hong et al. compared 35 patients operated endoscopically and 20 patients

operated using the microscopic transseptal approach. The patients in the microscopic group showed a slightly (though statistically insignificant) worse outcome in olfactory function using a subjective olfactometry test [15].

One can only speculate why the incidence of hyposmia seems to be higher in microscopic technique. The speculum, typically used in microscopic technique, may apply an unbalanced force at the posterior olfactory groove and displace the bony septum laterally to the contralateral side of the dissection [18]. This may cause laceration of the submucosal layers. The blades push and press on the superior nasal conchae as well. The mucosal damage on both surfaces induces synechia formation, which may lead to deterioration of olfaction.

### Middle turbinate resection

Resection of the middle turbinate in endoscopic surgical treatment is sometimes used to improve access to the skull base [2]. In the standard transsphenoidal approach to pituitary adenoma resection of the middle turbinate is not necessary and

usually lateralization is sufficient. Olfactory mucosa is present on the upper part of the middle turbinate and its resection may lead to changes in airflow patterns in the nasal cavity [8]. In the present review, only one study described unilateral middle turbinate resection using the standard transsphenoidal approach. The authors of this study did not find a significant postoperative decrease of olfactory function in their patient group [27].

### Nasoseptal flap

To prevent postoperative leak, a technique of harvesting nasoseptal flap that covers defects in the skull base has been developed. Two basic types of nasoseptal flaps have been used in our reviewed studies: the Hadad-Bassagasteguy (HB) and the rescue flap. The HB flap is a vascularized mucoperichondrial and mucoperiosteal axial pattern flap based on the posterior branch of the sphenopalatine artery [11]. The rescue flap, described by Rivera-Serrane et al., consists of partially harvesting only the most superior and posterior aspect of the flap to protect its pedicle and provide access to the sphenoid face during surgery. The rescue flap can be harvested at the end of the procedure if needed. This technique might minimize septum donor site morbidity for those patients without intraoperative CSF leaks [25].

Six studies used no flap, four the rescue flap, and nine the HB flap. Only one study—although the largest of the four that used the rescue flap—reported a decrease in olfactory function. In contrast, five of the nine studies that used the HB flap reported a decrease in olfactory function. One RCT compared olfactory outcome in 10 patients who underwent endoscopic transsphenoidal surgery with harvesting of the HB nasoseptal flap with 10 control patients [29]. The authors found a decrease in olfactory function in both the HB flap and control group, but the HB flap group fared significantly worse than the controls. It is important to mention that the rate of postoperative olfaction dysfunction was higher in cases when flap was harvested (14.4%) compared to cases without any flap (3%).

There is no difference whether the cold knife or electrocautery is used for raising the nasoseptal flap [14]. [19].

### Conclusion

Olfactory outcome after transsphenoidal surgery has been a neglected area of study. In the past two decades, however, interest in this area has increased and several prospective cohort trials and one RCT have been conducted. Data on this topic are heterogenous and provide only a low level of evidence.

From our review, the endoscopic approach appears to be superior regarding preservation of olfactory outcome when

compared with the microscopic approach. The best results were obtained when the endoscopic approach was performed without harvesting of the nasoseptal flap. The effect of middle turbinate resection on olfaction was not rigorously examined. In conclusion, we recommend using an endoscopic approach without routine harvesting of the nasoseptal flap for pituitary adenomas with low risk of CSF leak.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** Ethical approval is not needed for this type of review.

**Informed consent** Informed consent is not needed for this type of review.

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